Preface to the Third Edition

In the more than 20 years since we conceptualized and outlined the first edition of the Handbook of Clinical Child Neuropsychology, much has changed in our field yet much has remained the same. There have been great strides in understanding both normal and pathognomic development of neural structures that have led us to greater depths of understanding the brain–behavior relationships in children. It seems that advances in neurobiology and related neurosciences continue to add impetus to the need for emphasizing the role of the brain in many forms of psychopathology that were once considered solely the domain of psychodynamics and behaviorism. We have implored the authors of this third edition to take careful note of the science that underlies the practice of clinical child neuropsychology and to integrate these advances wherever possible into the updates of their chapters as well as considering them in the chapters that are new to this volume. At the same time that our depth of understanding of brain–behavior relationships has improved, many of the methodological and statistical problems that have plagued research in the field remain. We continue to provide chapters on these issues in an attempt to improve research and research outcomes in the discipline in addition to providing chapters that give guidance to current best practices for the workhorse practitioner.

Unfortunately, one of the things that has not changed in our field is the presence of a dearth of qualified pediatric and child clinical neuropsychologists. While there are more qualified child practitioners now than ever before, children remain underserved. Every year, without fail, since the National Institute of Mental Health began issuing a list of underserved populations within the United States, children have appeared in the top 10 of all underserved populations. Our hope is that by continuing to provide information on current practice, science, and thought about the practice of clinical child neuropsychology in a common location, we will continue to foster the development of the field and perhaps attract additional practitioners to obtain expertise with children.

In this third edition, updates of chapters from the second edition appear along with a variety of new chapters that present information on topics that have become more salient over the several decades we have toiled over this handbook. Those familiar with prior editions will note new works by Sam Goldstein and Adam Schwebach on the Neuropsychological Basis of Learning Disabilities; Antolin Llorente on the Neuropsychological Assessment of Spanish-Speaking Children and Youth; Arthur MacNeill Horton, Jr. and Arthur MacNeill Horton, III on the Child Clinical Neuropsychology of Drug Abuse; Sam Goldstein and Kordell Kennemer on Neuropsychological Aspects of ADHD; Robert McCaffrey, Julie Horwitz and Julie Lynch on Child Forensic Neuropsychology; Priscilla Bade-White, John Obrzut, and Philip Randall on Neuropsychological Aspects of Pervasive Developmental and Autism Spectrum Disorders; and Jack Naglieri, Cara Conway, and Sam Goldstein on Using the PASS Theory in Neuropsychological Assessment. We consider these to be central/main stream efforts that are central to understanding the field of clinical child neuropsychology and the broadening role of child practitioners in our discipline. As a strong example of the latter, Joan Mayfield's chapter on the role of the pediatric neuropsychologists in coma is a seminal work in the guidance it provides the child practitioner.

As we have noted in prior volumes, there are many individuals to whom we must express our appreciation and without whom this work could not have been completed. As the publishing industry has consolidated, this handbook has moved across publishers. We greatly appreciate the efforts of Sharon

Panulla and Janice Stern, of Springer, for continuing to appreciate the need for this volume as well as their guidance and ultimately bringing it to fruition at its new home. We also cannot forget Eliot Werner, our original editor from Plenum Publishing Company (now absorbed under the Springer umbrella), who had sufficient faith in us as well as the development of child clinical neuropsychology as a discipline to risk publishing a large, comprehensive handbook originally in this field. The dedication and efforts of all of our chapter authors are acknowledged and sincerely appreciated. Without their hard work and careful thought, this handbook would be a shallow effort on our part. Elaine wishes to express her gratitude to her family, David, Emma, and Leif for their support and encouragement. Cecil continues to note and appreciate Julia's contributions to his efforts not only through her confidence, emotional support, and companionship, but through her willingness to engage him in discussions particularly of the applicability of our science to the day-to-day problems of the clinical practitioner, of which she remains a superb example.

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Development of the Child's Brain and Behavior

BRYAN KOLB AND BRYAN D. FANTIE

Introduction

Perhaps the central issue in neuropsychology over the past 100 years has been the question of how psychological functions are represented in the brain. At the turn of the century, the debate was largely whether or not functions were actually localized in the cortex. Although today this is no longer a subject of major discussion, the general problem of determining *what* is localized in the cortex remains. One way to examine this issue is to look at the way function and structure emerge in the developing child.

As we look historically at the consideration of structure–function relationships in development, we are struck by the reluctance of researchers to engage in such analyses. Indeed, although Freud and Piaget were trained in biology, both carefully avoided inclusion of brain development in their theories of psychological development. It is likely that one major impediment to such theorists was an absence of biological data about developmental neuroscience (Segalowitz & Rose-Krasnor, 1992).

The development of structure–function relationships can be examined in three basic ways. First, we can look at the structural development of the nervous system and correlate it with the emergence of specific behaviors. Initially this approach seems ideal, as the development of both the nervous system and behavior is orderly and consistent across individuals. Unfortunately, it is not as simple as it appears.

The nervous system matures in a relatively unremitting way, unfolding to the dictates of time. Behavioral change, on the other hand, is often more highly dependent on environmental factors. Thus, the degree of damage caused by sensory deprivation is largely determined by *when* it occurs during an animal's life (Hubel & Wiesel, 1970). In contrast, whether or not someone can ice-skate will be more easily predicted when one knows if the person was raised in Canada or Brazil. In addition, age-related neural changes are seldom immediately observable in vivo so it is extraordinarily difficult to correlate structural and functional variables directly. Furthermore, hypotheses regarding brain devel pment are hard to verify, especially because the human nervous system cannot be manipulated during development. Nevertheless, despite these impediments, this approach is still possible.

The second way to examine morphological and psychological development is to scrutinize behavior and then make inferences about neural maturation. For example, we might study the emergence of distinct cognitive stages carefully, as Piaget (1952) and his followers have done, and then predict what alterations must have occurred in the nervous system to account for

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the behavioral change. This approach has not been widely used, largely because psychologists most interested in human development have not been very interested in brain function and many behaviors considered important to child development may not be related directly to neural growth. Nevertheless, this approach is promising and has been pursued actively by Gibson (1977).

There is a tendency to emphasize school-related skills as the most important for study in child neuropsychology. This is not surprising, given the lasting impact that educational success can have on one's entire life, professionally, socially, and, in terms of confidence and self-esteem, personally. In modern Western industrialized countries, the vast majority of a child's waking time is spent in school. Because of the sequential and cumulative nature of most of this type of learning, any impediment can result in a child being left with a widening academic gap between themselves and peers, a gap which, in the age of social promotion, can easily become insurmountable. Many types of childhood learning disabilities are likely related to abnormalities in neural development although this may not always be the case. We must remember that the human brain did not evolve in a classroom. In fact, the neural underpinnings of some learning disabilities may not actually be abnormal in anything other than the statistical sense of the term, and do not represent a true pathology of any kind; good news we hope given the large number of people who seem to receive the "learning disabled" diagnosis.

In light of the fact that, until fairly recently, only a very small proportion of the population was literate, it seems clear that reading, unlike spoken language, could not have been the result of direct evolutionary pressure on humans as a species. Therefore, the capacity to read is probably something akin to what Stephen Jay Gould and Richard Lewontin (1979) would call a "spandrel." Spandrels are traits that, themselves, "have no adaptive tale to tell, but reflect structural constraints imposed by an organism's development or by its quirky evolutionary history," (Dennett, 1995). So humans having the capacity to learn to read most likely came about as a sort of by-product of having developed other cognitive abilities. Therefore, although differences in the facility in learning to read might often be the direct result of the type and configuration of the neural structures one has, these differences may be the result of the normal variance in neuroanatomy that would not have any noticeable effect if one lived in a time or place where reading had not the preeminence as it does in our culture.

Albeit, reading is a very important function, especially for children, and it is essential that clinical neuropsychologists who work with children consider how variance across cognitive domains will affect how a child will fare in school. For the purpose of understanding how developmental neural changes underlie cognitive development, however, it might be better to look at more basic, elemental processes that likely map more closely on the functional neural architecture Thus, the basic functions that are related to neural development may not be found easily by studying scholastic behaviors such as reading. Rather, the neural mechanisms underlying reading ability may best be understood by examining fundamental visuospatial or visuomotor skills, which serve as components of higher-level, more complex cognitive behaviors such as reading.

The third way to study neural structure–function relationships is to relate brain malfunction to behavioral disorders. This method, which is prevalent in research dealing with adults, is difficult to apply to the developing brain. The major problem is that the function of a specific neural area may change over time. For instance, Goldman (1974) found that although juvenile rhesus monkeys that had sustained frontal cortex lesions in infancy could solve tasks sensitive to frontal lobe damage in adults, they subsequently lost this ability as they matured. This result can be interpreted as showing that some other structure, probably the striatum, initially controlled the behaviors necessary for the successful performance of the tasks. Through the natural course of development, this function is eventually transferred to the frontal cortex as the original structure takes some other role in the production of behavior. Because, in this case, the frontal cortex was damaged, it was unable to assume the function when required and the task could not be fulfilled. Therefore, because the association of functions and brain sites that is applicable at one age may be inappropriate at other ages, there is not just one form of the immature brain.

The plasticity of the immature brain poses another problem to inferring structure–function relations from malfunction in the developing nervous system. Brain damage occurring in infants may produce very different behavioral effects than in adults because early injury has also altered fundamental brain organization. The trauma does not affect the function of only the brain areas that are damaged directly. It also disrupts other neuroanatomical sites and circuitry appearing later, the subsequent normal development of which was dependent upon the intact structure and function of the regions damaged.

For example, Rasmussen and Milner (1977) showed that if neonatal speech zones, usually found in the left cerebral hemisphere, are damaged, language may develop in the right cerebral hemisphere. Similar damage at 5 years of age may cause the speech zones to move within the left hemisphere. In both cases, language would then occupy space normally serving other functions. The chronic behavioral loss would manifest itself in some other cognitive function, such as spatial orientation, even though the damage can be shown to have been in the cortical site that normally subserves language functions. Identical lesions could result in very different deficits depending on the age at which the damage occurred. Such effects do not occur in the adult.

We point out the pitfalls in developmental neuropsychology not to discourage the study of the child's brain, but to caution that what follows in this chapter must be considered in light of these problems. We shall summarize research on neocortical development using each of the three approaches outlined above. We begin by considering the anatomical development of the cerebral cortex. We then consider functional development and try to draw correlations between the emergence of particular behaviors and neural development. Finally, we examine factors affecting brain development.

Anatomical Development of the Child's Brain

The process of brain growth can be understood by considering the composition of the nervous system. The cortex is a laminated structure of approximately six layers made up of neurons and glial cells. Some glial cells in the brain, called oligodendrocytes, insulate certain portions of many neurons by wrapping around them. Other glial cells, mainly astrocytes and microcytes, are thought to perform basic maintenance and support functions for neighboring neurons. Neurons receive input from other neurons across tiny spaces known as synaptic gaps through processes called dendrites while sending output to other neurons via processes called axons. Cortical neurons exchange information with other cortical neurons as well as with neurons located in subcortical structures. Additionally, the many projections each neuron usually receives from other neurons often use different chemical substances to transmit information. Basically, these chemicals excite or inhibit the activity of the target cell, and it is the net total of these influences that determines whether or not the neuron fires. The successful development of the brain into a properly functioning, integrated organ requires that each component first be formed and then be correctly interrelated with the others.

The development of the different components of the nervous system can be categorized into distinct phases, illustrated in Figure 1. These include (1) the birth of neurons (neurogenesis), (2) the migration of neurons to their correct location, (3) the differentiation of neurons into different types and their subsequent maturation of connections, and (4) the pruning back of connections and cells themselves. Each of these stages is dependent on the production of specific molecules that act to facilitate the respective process. These molecules include various growth factors, hormones, and specific proteins that act as a sort of traffic signal for cells or their processes to follow. We will consider the development processes in turn.

Neural Generation

The human brain follows a general pattern of development, beginning as a neural tube and gradually acquiring the features of the adult brain (illustrated in Figure 2), that is typical of all mammals. The basic neural tube surrounds a single ventricle where cells are generated along the ventricular wall and then migrate out to their proper location. In humans, approximately 10^9 cells are required to eventually form the mature neocortex of a single cerebral hemisphere (Rakic, 1975). During development, the cortex

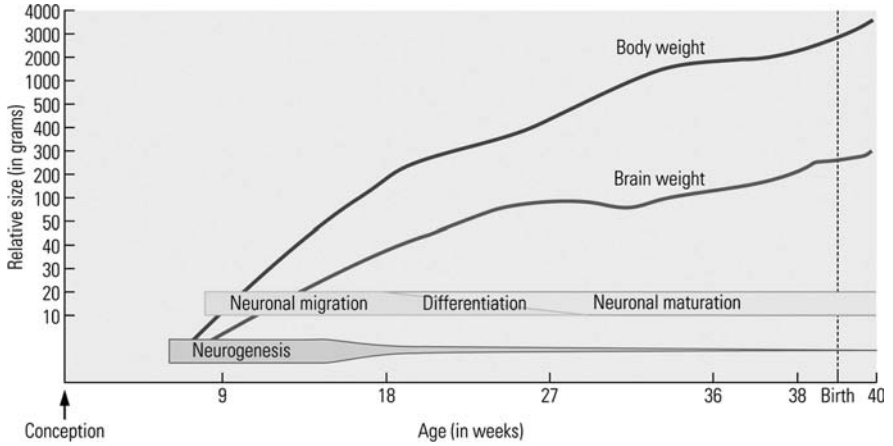

FIGURE 1. Stages of brain development.

is composed of four embryonic regions: the ventricular, marginal, intermediate, and subventrical zones (as illustrated in Figure 3). These zones are transient features uniquely related to early development for each either disappears or becomes transformed so that they are no longer identifiable in the adult nervous system.

Sidman and Rakic (1973) combined the extensive studies of Poliakov (1949, 1961, 1965) with their own observations to produce a

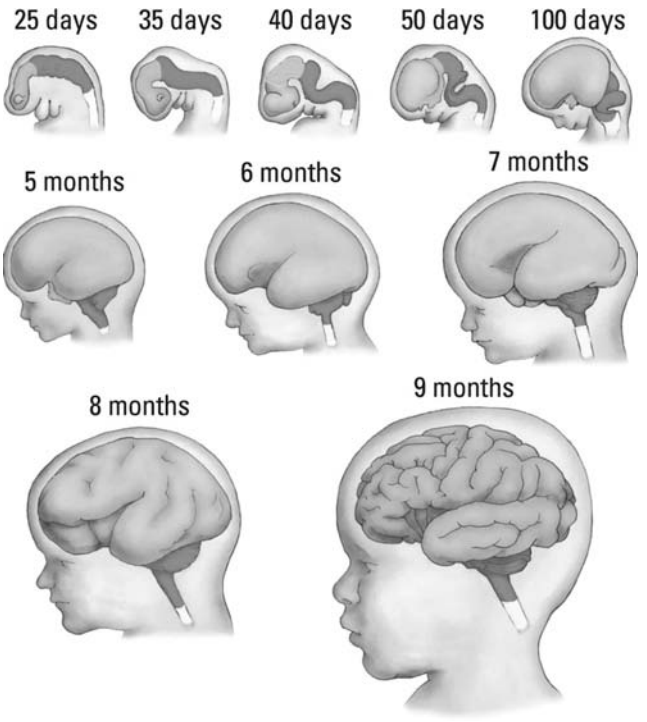

FIGURE 2. Prenatal development of the human brain showing a series of embryonic and fetal stages. (Adapted from Cowan, 1979.)

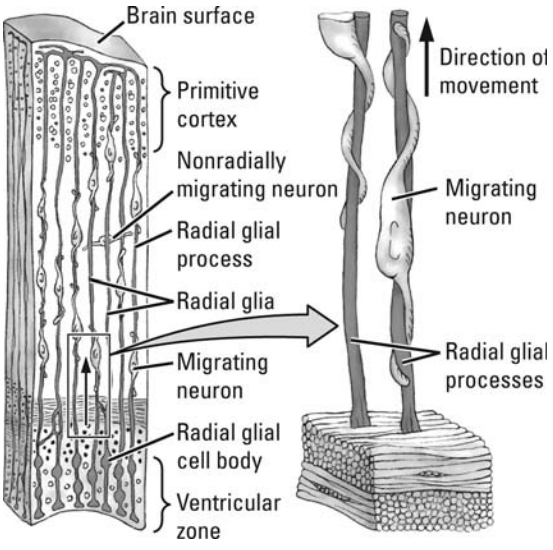

FIGURE 3. Schematic representations of the pattern of neural migration along the radial glial cells (after Rakic, 1981). Migrating neurons leave the ventricular and subventricular zones and travel to more superficial layers. En route they pass through the deeper neurons, which are already in place.

summary of the timing and phases of cortical development in humans. There is some disagreement over how long cells destined for the cortex divide and migrate in the human, but most cortical cell proliferation appears to be complete by the middle of gestation, although, at this stage, the cortex by no means appears like that of an adult. Cell migration may still proceed for some months after this time, possibly continuing postnatally, and the cortical lamination continues to develop and differentiate until after birth.

One curious feature of cortical development is that it progresses in an "inside-out" progression. Neurons destined to form layer VI form first, followed in sequence by layers V to II. Marin-Padilla (1970, 1988) studied the sequential lamination of the human motor cortex in ontogenesis and found that by the fifth embryonic month, cortical layers V and VI are visible, although not yet completely mature. Over the ensuing months, the remaining layers develop (as summarized in Table 1). Thus, we see that successive waves of neurons pass earlier-arriving neurons to assume progressively more superficial positions. A second curious feature of brain development is that the cortex overproduces neurons, which are later lost through normal cell death. Layer IV in the motor cortex is a particularly clear example of this because cells that are visible there in the seventh month and at birth later degenerate, leaving an agranular layer.

As might be predicted, the precise timing of the development and migration of cells to different cytoarchitectonic regions varies with the particular area in question. For example, Rakic (1976) showed that while the ventricular zone is producing layer IV cells for area 17, the neighboring ventricular zone is generating layer III cells that will migrate to area 18. Thus, at any given moment during cortical ontogenesis, cells migrating from the ventricular zone are destined for different regions and layers of the cortex. One implication of this phenomenon is that

TABLE 1. Sequential Lamination of the Human Motor Cortex in Ontogenesis[a,b]

	Cortical layers						
			III				
Case	I	II	Upper	Lower	IV	V	VI
5-month fetus	++	0	0	0	0	+	+
7-month fetus	++−+++	+	+	+−++	+	++	++
7½-month fetus	+++−++++	++	++	++−+++	++	+++	+++
Newborn infant	++++	+++	+++	++++	++++	++++	++++
2½-month-old infant	++++	+++	++++	++++	Very thin	++++	++++
8-month-old infant	++++	+++	++++	++++	Agranular	++++	++++

[a] From Marin-Padilla (1970)
[b] Key: 0, unrecognizable; +, immature; ++, developing; +++, established; ++++, fully developed.

events that might affect the fetus during cortical development, like the presence of a toxic agent such as heavy metals, will affect different cytoarchitectonic zones differently. For example, prenatal exposure to methylmercury can produce dendritic spine dysgenesis in the pyramidal neurons of the somatosensory cortex of rats (Stoltenburg-Didinger & Markwort, 1990). Furthermore, because specific populations of cells are migrating at different times to any given cortical laminae, it implies that toxic agents, or other environmental events, could perturb the development of a specific population of cells to a particular cytoarchitectonic area.

Finally, we must mention that there has been recent controversy over the presence of neurogenesis in the adult brain. There is agreement that neurogenesis continues in the hippocampus and olfactory bulb, but although neurogenesis has been reported in the neocortex, striatum, amygdala, and substantia nigra, the latter findings have been difficult to replicate consistently in the undamaged brain (for a review, see Gould, 2007).

Cell Migration

Because cortical cells are born distal to the cortical plate and must migrate there, one can ask how this occurs, particularly as cells traveling to the outer layers must traverse the cells and fibers of the inner layers. In a series of elegant studies, Rakic (1972, 1975, 1981, 1984) showed that neurons migrate to the appropriate laminae within the cortex along specialized filaments, known as radial glial fibers, which span the fetal cerebral wall at early ages. These radial glial cells originate in the ventricular zone and extend outward to the cortical plate. As the cortex develops, thickens, and sulci begin to appear, the radial glial fibers stretch and curve, guiding the migrating neurons to their correct location (see Figure 3). Interestingly, prenatal exposure to gamma radiation or alcohol during particular windows of vulnerability can either halt migration prematurely, or prolong it abnormally, respectively (Hicks, Damato, & Lowe 1959; Miller, 1986), thus causing an extensive disruption of brain function and structure by interfering with a single developmental process.

Axonal Development

As cells migrate along the radial glial fibers, they begin to develop axons that run to subcortical areas, other cortical areas, or across the midline as commissural fibers. The rate of axon development is extremely rapid, apparently on the order of 1 mm/day. In addition to axons of cortical cells growing out, axons from the thalamus enter the cortex after the principal cortical target cells complete their migrations and assume the appropriate positions within the developing cortical plate (Rakic, 1976).

Dendritic Development

Two processes occur during development of the dendrite: dendritic arborization and spine growth. The dendrites begin as individual processes protruding from the cell body. Later, they develop increasingly complex extensions, looking much like the branches of trees in winter. Spines are little appendages, resembling thorns on a rose stem that begin to appear in the seventh intrauterine month (Poliakov, 1961). Before birth, they are observed only on the biggest neurons (mainly those found in layer V). After birth, they can also be found on other neurons where they spread and densely cover the dendritic surface. Although dendritic development begins prenatally in the human, it continues for a long time postnatally. In laboratory animals, the development of both dendritic branches and spines has been shown to be influenced dramatically by environmental stimulation (Greenough, 1976), a phenomenon that is probably very important in relation to the human child's development. In addition, it is now clear that dendritic development is also affected by gonadal hormones, leading to the development of a male or female cerebral structure (Juraska, 1990). The influence of gonadal hormones is not limited to birth but continues into adulthood and may play an important role in the processes related to aging (Stewart & Kolb, 1994). In contrast to the development of axons, dendritic growth usually commences after the cell reaches its final position in the cortex and proceeds at a relatively slow rate, on the order of micrometers per day. The disparate developmental rates of axons and dendrite are important because the faster-growing axon can contact its target cell before the dendritic processes of that cell are

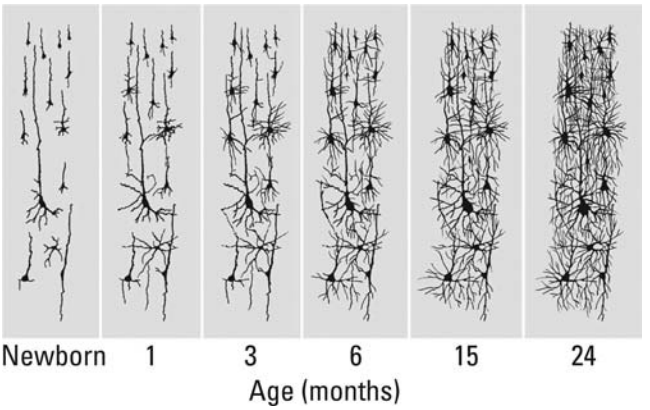

FIGURE 4. Postnatal development of human cerebral cortex around Broca's area as taken from camera lucida drawings of Golgi-Cox preparations (from Conel, 1939–1967)

elaborated, suggesting that the axon may play a role in dendritic differentiation (Berry, 1982). The morphological changes associated with dendritic growth in the frontal cortex are illustrated in Figure 4.

Synaptic Development

The mechanism that controls synapse formation is one of the major mysteries of developmental neurobiology, largely because synapses are perceptible only by electron microscopy, which does not allow direct observation of their sequence of development in living tissue. The onset of synaptogenesis is abrupt, and the appearance of synapses in any particular area is remarkably rapid although neurons may be juxtaposed for days before they actually make synaptic connections. Synapses usually form between the axon of one neuron and the dendrites, cell body, axons, or established synapses of other cells. Because synaptogenesis begins before neurogenesis is complete, neurons migrating to the superficial layers of the cortex must bypass cortical neurons on which synapses have already formed or are in the process of forming.

Although little is known about the details of synaptic development in humans, Bourgeois (2001) outlined five distinct phases of synapse formation in the cerebral cortex of primates, as illustrated in Figure 5 for the macaque. The first two phases take place in early embryonic life and are characterized by the generation of low-density synapses. The synapses formed in phases 1 and 2 differ in their origin, but both groups are believed to be generated independently of experience.

The number of synapses grows rapidly in phase 3, with the peak in the macaque at about 40,000 synapses per second. This phase begins before birth and continues until nearly 2 years of age in humans. Phase 4 is characterized by an initial plateau in synapse number followed by a rapid elimination of synapses that continues through puberty. Phase 5 is characterized by another plateau in synapse number through middle age followed by a drop in senescence.

The first developmental period of synapse reduction is dramatic, falling to 50% of the number present at age 2. And just as synapses can be formed very rapidly during development, they may be lost at a rate of as many as 100,000 per second in adolescence. It should not surprise us that teenagers are so moody when their brains are undergoing such rapid changes in organization.

In phases 3 and 4, the development (and elimination) of synapses is influenced by experience-expectant and experience-dependent mechanisms. Experience-expectant means that the synaptic development depends on the presence of certain sensory experiences. For example, in the visual cortex, the synapses depend on exposure to features such as line orientation, color, and movement. The general pattern of

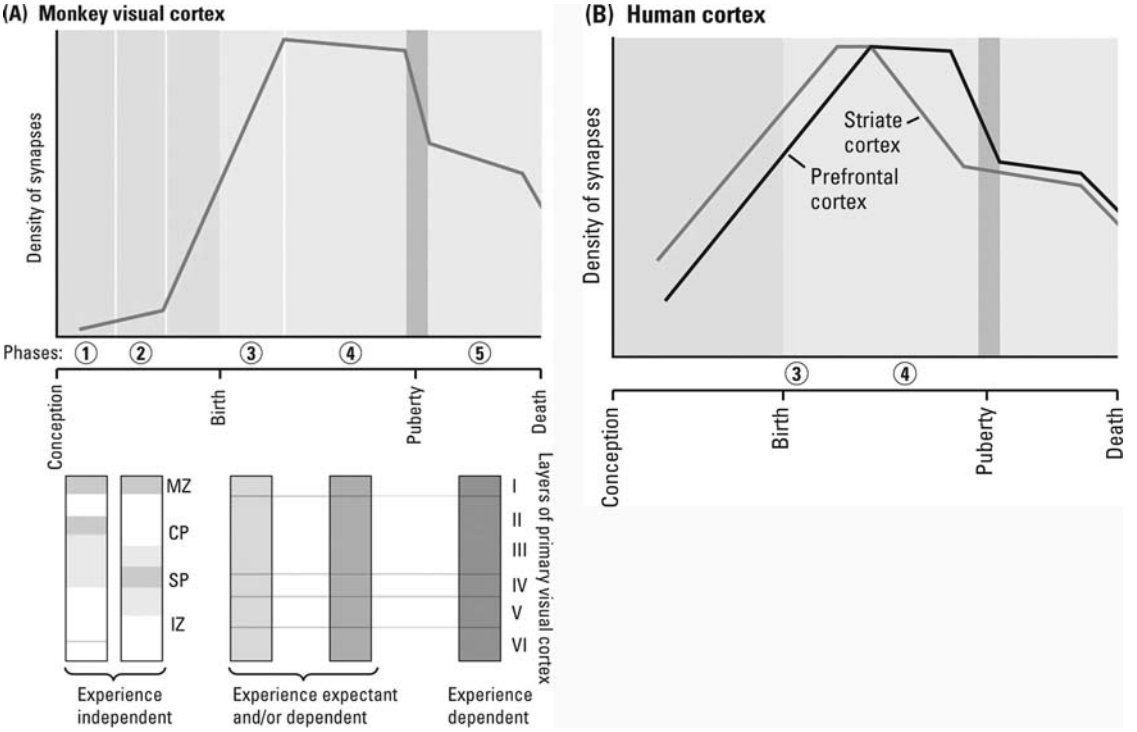

FIGURE 5. (A) Phases of synapse formation and pruning. Five different phases of synaptogenesis are identified between conception and death. The shading in the *vertical bars* indicates the areas of synapse formation during each phase. (B) Changes in the relative density of synapses in the visual cortex and prefrontal cortex as a function of days after conception. (After Bourgeois, 2001; Huttenlocher, 1984, 1990)

these synapses is presumed to be common to all members of a species—provided the individual members receive the appropriate experience. Experience-dependent refers to the generation of synapses that are unique to the individual. For example, in the visual system, these synapses can correspond to the learning of specific visual information such as the features of a particular face.

It is interesting that the synaptic density of infants appears to exceed that of adults, for it has generally been assumed that a larger number, or a greater density, of synapses implies a higher functional capacity. Evidence of decreasing synaptic density coincident with increasing cognitive skill is thus intriguing, especially because high numbers of synapses have been found in certain cases of mental retardation (Cragg, 1975). It is not surprising that intellectual ability cannot be predicted merely by its relation to the quantity of some anatomical feature, such as synapses, and it is almost certain that the process involved in reducing synaptic density often represents some sort of qualitative refinement.

Glial Development

The differentiation and growth of neurons, which are generally produced before their associated glia, appear to play some role in stimulating the growth and proliferation of glial cells, but the mechanisms are unknown (Jacobsen, 1978). In contrast to neurons, which only relatively recently have been shown to continue to be born in very restricted brain areas, glial cells continue to proliferate throughout life.

Myelin Development

Myelination is the process by which the glial cells of the nervous system begin to surround axons and provide them with insulation.

Although nerves can become functional before they are myelinated, many researchers in the 1920s and 1930s assumed that neurons only reach adult functional levels after myelination is complete (Flechsig, 1920). This notion now appears to be an oversimplification but is, nonetheless, useful as a rough index of cerebral maturation. In contrast to other aspects of cortical development, myelin appears late, at a time when cellular proliferation and migration are virtually complete. The primary sensory and motor areas begin to myelinate just before term, whereas the frontal and parietal association areas, the last to myelinate, begin postnatally and continue until about age 15 years or, sometimes, even later. Because different regions of the cortex myelinate at different times, and myelination begins in the lower layers of each cortical area and gradually spreads upward, the upper layers of the motor and primary sensory areas are myelinating at the same time that the lower areas of some association areas are just beginning to myelinate.

TABLE 2. Neocortical Neurotransmitters[a]

Transmitter type	Cell location
Afferents	
Norepinephrine	Locus coeruleus
Dopamine	Substantia nigra A10
Serotonin	Raphe
Acetylcholine	Globus pallidus magnocellular
Intrinsic	
GABA	Aspinous stellate (all layers)
Neuropeptides (somatostatin, neuropeptide Y, vasoactive intestinal polypeptide, cholecystokinin)	Aspinous bipolar stellates
Efferents	
Glutamate	Pyramidal cells (layer V corticostriatal)

[a]After Coyle (1982).

Neurochemical Development

Chemical neurotransmitters serve as the primary means of interneuronal communication, yet virtually nothing is known about the neurochemical development of the human cortex. Although there are numerous studies of neurotransmitter development in the rat, knowledge about the relationships among transmitters in the adult neocortex is still limited, and the most completely described neurochemical systems make only a modest contribution to the overall synaptic activity of the neocortex (see Table 2). There are, however, some developmental studies using nonhuman primates that are worth reviewing as the human brain is likely to be similar (see also Parnavelas, Papadopoulos, & Cavanagh, 1988).

Goldman-Rakic and Brown (1981, 1982) investigated the regional distribution of catecholamines in rhesus monkeys ranging in age from newborns to young adults. Their overall findings were that although monoaminergic systems are present in the cortex at birth, these networks continue to develop for years. Catecholamine development varies greatly between different cortical regions, and the most striking postnatal increases in content were observed in the frontal and parietal association areas. Perhaps most interesting was their observation that catecholamine development (especially that of the monoamines) parallels functional development in the prefrontal cortex over the first 2–3 years of life. These data support the suggestion that catecholamines may play an important role in the development of functional activity in the frontal cortex and likely affect the morphological development of various neuronal processes such as dendritic fields.

Postnatal Brain Development

After birth, the brain does not grow uniformly but rather tends to increase its mass during irregular periods commonly called growth spurts. In his analysis of brain/body weight ratios, Epstein (1978, 1979) found consistent spurts in brain growth at 3–10 months, accounting for an increase of 30% in brain weight by the age of 1½ years, as well as between ages 2 and 4, 6 and 8, 10 and 12, and 14 and 16+ years. The increments in brain weight were about 5–10% over each 2-year period. This expansion takes place without a concurrent increase in neuronal proliferation and is unlikely to be accounted for by increases in the number of glial cells. Rather, it most likely results from the growth of dendritic processes and myelination. Such an increase in cortical complexity would be expected to

correlate with increased complexity in behavioral functions, and it could be predicted that there would be significant, and perhaps qualitative, changes in cognitive function during each growth spurt. It may be significant that the first four brain growth stages coincide with the classically given ages of onset of the four main stages of intelligence development described by Piaget. We return to this later.

Cell Death

One of the most intriguing stages in brain development is cell death. Consider the following analogy. If one wanted to make a statue, it would be possible to do so either by starting with grains of sand and glueing them together to form the desired shape or by starting with a block of stone and chiseling the unwanted pieces away. The brain uses both the procedures but relies mainly on the latter to achieve the "final" form. We have already described how the brain creates the block to be sculpted, by generating an overabundance of neurons and connections. The "chisel" in the brain could be of several forms including genetic signal, environmental stimulation, gonadal hormones, stress, and so on. Similarly, the same processes are likely to affect the development of dendrites, axons, and synapses. Cell death does not end in infancy but continues well into adulthood (Bartzokis Beckson, Po, Nuechterlein, & Mintz, 2001). The possibility that environmental events may alter the brain by influencing cell death is intriguing because it implies a permanence to at least some effects of early experience.

One example of the effect of environmental stimulation on brain development comes from the work of Werker and Tees (1992). They studied the ability of infants to discriminate phonemes taken from widely disparate languages such as English, Hindi, and Salish. Their results showed that infants can discriminate speech sounds of different languages without previous experience, but there is a decline in this ability, over the first year of life, as a function of specific language experience. One might speculate that neurons in the auditory system that are not stimulated early in life may somehow be selected against and die, although there are other explanations.

Not only is there cell death during development but there is also a process of pruning

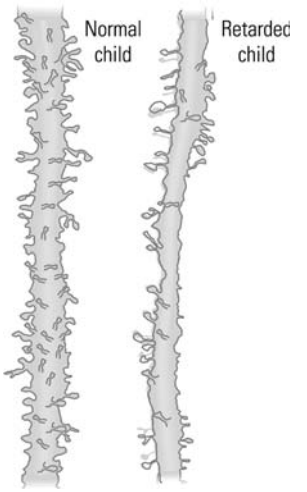

FIGURE 6. Camera lucida representations of Golgi preparations showing typical dendritic segments of medium-sized pyramidal neurons. *Left*: Example of apical segment from a normal 7-year-old child (accident case). *Right*: Example of apical segment from a 12-year-old profoundly retarded child. (After Purpura, 1974.)

synapses, as mentioned earlier. Recall that there is synapse elimination in the frontal lobe until adolescence (Figure 6). Thus, it seems likely that just as the nervous system uses the block-and-chisel method for choosing neurons, a similar process is used for selecting neuronal connections. The difference, however, is that it seems reasonable to expect that the brain could replace pruned connections later in life whereas the replacement of lost neurons is much less likely.

Imaging Studies of Brain Development

MRI and fMRI techniques are revolutionizing the study of human brain development. Early studies of gray-matter volumes showed that whereas a decline in gray-matter volume beginning around 6–7 years of age continues through adolescence, white matter volumes increase over the same time frame.

Gogtay et al. (2004) quantified the changes in gray-matter density at specific cortical points by using serial MRI scans of children followed over a 10-year period. The general finding was a shifting pattern of gray-matter loss, which presumably reflects neuron and synaptic pruning,

beginning in the dorsal parietal and sensorimotor regions and spreading laterally, caudally, and rostrally. The first regions to mature are primary cortical regions involved in basic sensory and motor functions. Parietal regions involved in space and language mature around puberty (age 11–13 years). Tertiary cortical areas such as the prefrontal cortex begin to mature last in late adolescence and continue well beyond.

Cortical Function at Birth

The extreme paucity of behavioral skill in the newborn leads to the notion that, shortly after birth, the cortex has not yet begun to function. Thus, the cortically injured infant was once thought to be indistinguishable from the normal child at birth (Peiper, 1963). Several lines of evidence suggest that the cortex is indeed functioning, although not like the adult brain. It is now known that cortically hemiplegic infants can be distinguished from normal babies on the basis of muscle tone (Gibson, 1977) and cortically damaged infants may also have abnormal sleep–waking cycles and abnormal cries (Robinson, 1966). There are also several measures of electrical activity that imply cortical activity is present at birth. EEG activity can be recorded from the fetal brain (Bergstrom, 1969), and epileptic seizures of cortical origin can occur in the neonate (Caveness, 1969). Perhaps the most compelling evidence of early cortical activity comes from the extensive work of Purpura (Purpura, 1976, 1982). In his study of cortical activity in premature human infants, Purpura took advantage of the fact that between 26 and 34 weeks of gestation, cortical pyramidal cells in primary visual cortex undergo significant growth and branching. These changes are associated with corresponding maturational changes in the electrophysiological characteristics of the visual evoked potentials (VEPs) in preterm infants. Although, even at birth, the VEPs are not identical to those of adults, they are present and indicate that at least primary visual cortex is functioning in some capacity.

Chugani and Phelps (1986) studied glucose utilization in the brain of infants using positron emission tomography. Their results showed that in infants 5 weeks of age or younger, glucose utilization, which can be taken as a crude measure of neural activity, was highest in the sensorimotor cortex, a result that is in accordance with anatomical evidence that this is the most mature cortical region at birth. By 3 months of age, glucose metabolism had increased in most other cortical regions, with subsequent increases in frontal and posterior association cortex occurring by 8 months. Thus, by about 8–9 months there is evidence of activity throughout the cerebral cortex, although it continues to change in the years to come.

Over the past decade, there has been an explosion of work on cognitive function in the developing brain including sensory functions (especially audition and vision), memory, face processing, spatial ability, and attention. The details of this work are beyond this chapter, but a recent volume summarizes much of this work (Nelson & Luciana, 2008).

Abnormal Development of the Child's Brain

We have seen that the anatomical development of the child's brain consists of the proliferation and migration of cells, the growth of axons and dendrites, synapse formation and loss, myelin growth, and so on. These processes begin early in embryonic development and continue until late adolescence. In view of the complexity of the cortex and its prolonged development, it is reasonable to expect that normal cortical development could be disrupted by any number of events. These include abnormalities in the normal genetic program of neural growth, the influences of exogenous factors such as psychoactive drugs (e.g., nicotine, antidepressants), toxic substances, or brain trauma, and nutritional or other environmental circumstances (e.g., maternal stress). We do not propose to discuss all of these possibilities, but will confine our discussion to those events that are most likely to be important to the neuropsychologist, namely abnormal neural differentiation and early brain damage.

Abnormal Neural Structure

In the event that either neurogenesis or neural migration is abnormal, one would expect gross abnormalities in cortical development. Clinically, a variety of conditions are recognized (Table 3), but little is known about the details of cell differentiation in these disorders. The major experimental study of disturbed migration in the cerebral cortex involves the reeler mouse

TABLE 3. Types of Abnormal Development

Type	Symptom
Anencephaly	Absence of cerebral hemispheres, diencephalon, and midbrain
Holoprosencephaly	Cortex forms as a single undifferentiated hemisphere
Lissencephaly	The brain fails to form sulci and gyri and corresponds to a 12-week embryo
Micropolygyria	Gyri are more numerous, smaller, and more poorly developed than normal
Macrogyria	Gyri are broader and less numerous than normal
Microencephaly	Development of the brain is rudimentary and the person has low-grade intelligence
Porencephaly	Symmetrical cavities in the cortex, where cortex and white matter should be
Heterotopia	Displaced islands of gray matter appear in the ventricular walls or white matter, caused by aborted cell migration
Agenesis of the corpus callosum	Complete or partial absence of the corpus callosum
Cerebellar agenesis	Portions of the cerebellum, basal ganglia, or spinal cord are absent or malformed

mutant. Caviness (Caviness, 1982; Caviness & Rakic, 1978; Caviness & Sidman, 1973) showed that in this animal the cortex is inverted relative to that of a normal mouse; the cells generated first lie nearest to the cortical surface and those generated last lie deepest. In addition, many of the pyramidal cells are abnormally oriented, in some cases with their major dendrites (the apical dendrites) oriented downward rather than upward as in the normal mouse. Despite their aberrant position, the cells develop connections as they would have had they been normally situated. Caviness and his colleagues studied the cortex of humans with various similar abnormalities, finding some of the same aberrant features (Caviness & Williams, 1979). Thus, in lissencephalic cortex, Williams, Ferrante, and Caviness (1975) found that cells failed to migrate into the appropriate layers and some cells were abnormally oriented, much as in the reeler mouse.

Injury and Brain Development

If the brain is damaged during development, it is reasonable to suppose that its development might be fundamentally altered. There are few studies of human brains with early lesions but there is a considerable literature from work with laboratory animals. In an extensive examination of monkeys with prenatal or perinatal frontal cortex injuries, Goldman-Rakic has shown a variety of changes in cortical development including abnormal gyral formation and abnormal corticostriatal connections (Goldman & Galkin, 1978; Goldman-Rakic, Isseroff, Schwartz, & Bugbee, 1983). Similarly, Kolb and his colleagues have found abnormal corticostriatal and subcorticocortical connections, abnormal myelination, altered cortical catecholamine distribution, thalamic shrinkage, reduced gliosis relative to animals with similar injuries in adulthood, and markedly thinner cortex following early frontal lesions in rats (for a review, see Kolb, 1995). The thin cortex appears to result both from a loss in the number of cortical cells and from a loss in dendritic arborization. In sum, there is good reason to presume that early damage to the human brain produces significant changes in cortical morphology that extend far beyond the boundaries of the tissue directly traumatized.

One of the clearest abnormalities in the developing human brain can be seen in studies comparing the brains of normal and profoundly retarded subjects. Golgi studies have shown abnormally long, thin spines on dendrites of cortical neurons in retarded children with no known genetic abnormality (Figure 6). The degree of abnormality is related to the severity of retardation. The dendritic abnormalities in retarded children are strikingly similar to those seen in rats with cortical injuries around the time of birth and may reflect similar etiologies.

One of the difficulties in applying the results of studies of laboratory animals to humans is the difficulty in equating the developmental age of the brain in different species. For example, when rats are born, their brain is very immature relative to the human brain, which is reflected in the fact that their eyes and ears are not open, and not functional. Cats are somewhat older

developmentally than rats but still are much less mature than humans. In contrast, at birth rhesus monkeys are more mature than humans. Thus, as we try to compare developmental ages we must not be overly impressed by the "birth day" but rather we need to focus on the developmental age of the brain. Looking at rats and humans, if we compare the state of cortical development and injury effects, it appears that newborn humans are roughly equivalent to 10-day-old rats; newborn rats are probably roughly equivalent to 8-month-old fetuses (Kolb, 1995). We must note, however, that other criteria will lead to somewhat different timetables (Clancy et al., 2007).

Behavioral Correlates of Brain Development

Two types of behavior have been extensively studied and correlated with anatomical development, namely motor behavior and language. We shall consider each separately and then consider the development of their asymmetrical representation in the cortex. Finally, we will discuss the behavior of children on standardized tests typically used by clinical neuropsychologists. We shall not attempt to be exhaustive in our coverage of each, but rather try to give a flavor of the findings to date.

Motor Systems

The development of locomotion in human infants is quite familiar to most of us. Infants are, at first, unable to move about independently, but eventually they learn to crawl and then to walk. The way in which other motor patterns develop is less obvious, but one has been described in an elegant study by Twitchell (1965) who documented the stages an infant passes through while acquiring the ability to reach out with one limb and bring objects toward itself. Before birth, the fetus's movements involve essentially the whole body. Shortly after birth the infant can flex all of the joints of an arm in such a way that it could scoop something toward its body, but it is not clear that this movement is executed independent of other body movements. Between 1 and 3 months it orients its hand toward, and gropes for, objects that have contacted it. Between 8 and 11 months it develops the "pincer grasp," using the index finger and thumb in opposition to each other. The development of the pincer grasp is extremely significant, because it allows the infant to make a very precise grasping movement that enables the manipulation of small objects. In summary, there is a sequential development of the grasping reaction: first scooping, then reaching and grasping with all fingers, then independent finger movements.

The fact that motor cortex lesions in adults abolish the grasp reaction with independent finger movements implies that there could be anatomical changes within the motor strip that correlate with the original development of the behavior. Although there are probably multiple changes occurring, especially in the development of dendritic arborizations, a correlation has been noted between myelin formation and the ability to grasp. In particular, the small motor fibers become myelinated at about the same time that reaching and grasping with the whole hand develop while the giant Betz cells of the motor cortex become myelinated at about the time the pincer grasp develops. These different types of motor fibers are thought to control arm and finger movements, respectively (Kolb and Whishaw, 1996).

The correlation between myelin development and motor behaviors can also be found in many other activities. Table 4 summarizes the development of a variety of behavioral patterns and myelin formation. It is difficult, of course, to be certain which correlations are meaningful, and, as we have noted, there are obviously many other anatomical changes occurring concurrently. Careful study of these data, however, does show some intriguing associations that warrant more detailed study.

Language Development

The onset of speech consists of a gradual appearance of generally well-circumscribed events that take place during the first 3 years of life (Tables 4 and 5). Language development is dependent not only on the development of appropriate perceptual abilities, such as the identification and categorization of speech sounds, but also on the development of motor capacities, especially those that control the lips and tongue. It therefore comes as little surprise that the precise movements of the lips and tongue needed for speech are fully developed well

TABLE 4. Summary of Postnatal Human Development[a]

Age	Visual and motor function	Average brain weight (g)[a]	Degree of myelination[b]
Birth	Reflex sucking, rooting, swallowing, and Moro reflexes; infantile grasping; blinks to light	350	Motor roots +++; sensory roots ++; medial lemniscus ++; superior cerebellar peduncle ++; optic tract ++; optic radiation ±
6 weeks	Extends and turns neck when prone; regards mother's face, follows objects	410	Optic tract ++; optic radiation +; middle cerebral peduncle ±; pyramidal tract +
3 months	Infantile grasp and suck modified by volition; keeps head above horizontal for long periods; turns to objects presented in visual field; may respond to sound	515	Sensory roots +++; optic tract and radiation +++; pyramidal tract ++; cingulum +; frontopontine tract +; middle cerebellar peduncle +; corpus callosum ±; reticular formation ±
6 months	Grasp objects with both hands, will place weight on forearms or hands when prone; rolls supine to prone; supports almost all weight on legs for very brief periods; sits briefly	660	Medial lemniscus +++; superior cerebellar peduncle +++; middle cerebellar peduncle ++; pyramidal tract ++; corpus callosum +; reticular formation +; associational areas ±; acoustic radiation +
9 months	Sits well and pulls self to sitting position; thumb–forefinger grasp; crawls	750	Cingulum +++; fornix ++; others as previously given
12 months	Able to release objects; cruises and walks with one hand held; plantar reflex flexor in 50% of children	925	Medial lemniscus +++; pyramidal tracts +++; frontopontine tract +++; fornix +++; corpus callosum +; intracortical neuropil ±; associational areas ±; acoustic radiation ++
24 months	Walks up and down stairs (two feet a step); bends over and picks up objects without falling; turns knob; can partially dress self; plantar reflex flexor in 100%	1065	Acoustic radiation +++; corpus callosum ++; associational areas +; nonspecific thalamic radiation ++
36 months	Goes up stairs (one foot a step); pedals tricycle; dresses fully except for shoelaces, belt, and buttons; visual acuity 20/20 OU	1140	Middle cerebellar peduncle +++
5 years	Skips; ties shoelaces; copies triangle; gives age correctly	1240	Nonspecific thalamic radiation +++; reticular formation ++; corpus callosum +++; intracortical neuropil and associational areas ++
Adult	–	1400	Intracortical neuropil and associational areas ++ to +++

[a]Source: Spreen, Tupper, Risser, Tuokko, & Edgell (1984).
[b]From Yakovlev and Lecours (1967). Estimates are made from their graphic data (±, minimal amounts; +, mild; ++, moderate; +++, heavy).

before the acquisition of finger and hand control.

The perceptual and motor processes necessary for language development are dependent on the maturation of the temporal and frontal lobes, which may be highly variable in developmental rate in some children. Thus, some children have a markedly delayed speech acquisition but later turn out to have normal intelligence and normal skeletal and gross motor development. For example, such children may not begin to speak in phrases until after age 4, in spite of an apparently normal environment and the absence of any obvious neurological signs that might suggest brain damage.

Experiential factors clearly influence speech development (e.g., Werker & Tees, 1992) so it could be argued that language development is

TABLE 5. Summary of Postnatal Development of Basic Social and Language Functions[a]

Approximate age	Basic social and language functions
Birth	Comforted by sound of human voice; reflexive smile. Most common sounds are discomfort and hunger cries and vegetative sounds; by the end of first month the cries become differentiated; noncrying speech-like sounds usually during feeding
6 weeks	Makes eye contact with mother; spontaneous smile. Responds to human voice and being held by quieting; smiles when played with; makes cooing and pleasure noises; cries to gain assistance
2 months	Begins to distinguish different speech sounds; cooing becomes more guttural or "throaty"; seeing people causes excitement; unselective social smile
3 months	Discriminates between some individuals; recognizes mother; selective social smile; orients head to voices; makes a vocal response to others' speech; "babbling"—a phase characterized by the "spontaneous" production of sounds. Usually begins in month 2 or 3 and continues to months 12–15 or later although typically decreasing as echolalia increases
4 months	Selective attention to faces; prefers to look at happy rather than angry expressions; localizes to sounds; can discriminate individual faces; smiles at other babies; varies pitch of vocalizations; imitates tones
6 months	Laughs aloud; conveys pleasure and displeasure in prosody; smiles at self in mirror; "echolalia," the imitation of sounds made by others, usually beginning at months 4–7. Imitation of prosody occurs long before that of articulated speech segments; forms the dominant linguistic activity through the second year with decreasing importance, except during the acquisition of new words, until at least months 30–36
9 months	Waves bye-bye; plays patty-cake; makes distinct intonational patterns; social gestures
12 months	May kiss on request. Sentences, the long and progressive process of learning the symbolic significance of speech sounds enabling the capacity to understand and generate meaningful words and sentences; in most individuals maximum capacity is probably not achieved until the middle of the second decade or later; a 12-month-old may have a vocabulary of 5–10 words that will double in the following 6 months
24 months	"Vocabulary" can be approximately 200–300 words by the second year; names most common everyday objects; "morphological–syntactical"—most of child's utterances will be unitary, i.e., single, nonassociated linguistic units up to 18–24 months and occasionally later; next 5–6 years, at least, will be devoted to the acquisition of the complex, multistaged process of developing a mastery of a morphological–syntactical system
36 months	Has vocabulary of 900–1000 words; 3- to 4-word simple construction sentences (subject–verb); can follow two-step commands; curses
4 years	Has a vocabulary of more than 1500 words; asks numerous questions; sentences become more complex
5 years	The typical 5-year-old may have a vocabulary of approximately 1500–2200 words; discusses feelings; the average 5- to 7year-old will be expected to have acquired a slow but fluent ability to read; handwriting will also likely be slow; graphism, however, should be well differentiated and regular; competent "phonetic" writing; the mastery of the orthographic system can be expected to extend for several more years
6 years	Expressive vocabulary of about 2600 words; receptive vocabulary of 20,000–24,000 words; uses all parts of speech
Adult	Has vocabulary of 50,000+ words by age 12

[a]Adapted from Lecours (1975) and Owens (1984).

not so much dependent on the maturation of some neural structure as it is on some form of environmental stimulation. Although this is possible, it is unlikely that speech development is constrained exclusively by some environmental event. Indeed, it is a common observation by parents that children may have markedly different histories of language acquisition. Furthermore, there is no evidence that training infants will significantly speed up language acquisition. Thus, the emergence of speech and language habits is most easily accounted for by assuming that there are maturational changes within the brain. The difficulty is in specifying what these changes might be. Indeed, in view of the complexity of the neural control of language, it is futile to look for any specific growth process that might explain language acquisition.

Nonetheless, it would be instructive to know in what ways the cortex is different before the onset of language (age 2) and after the majority of language acquisition is completed (about age 12).

As we described earlier in our discussion of neural maturation, by 2 years of age there is little neocortical neural cell division and most cells have migrated to their final location in the cortical laminae. The major changes that occur between the ages of 2 and 12 years are in the interconnection of neurons, largely through a decrease in the total number of synapses as well as an increase in the complexity of their dendritic arborizations. The latter increase implies a reorganization of networks and almost certainly reflects the development of some new synapses. If one assumes that language acquisition requires the development of *functional* connections between neurons, much as hypothesized by Hebb (1949) in his concept of cell assemblies, then these changes in synaptic density and dendritic detail may be logical candidates as constraints on speech development. The postnatal changes in dendritic complexity within the speech areas are among the most impressive in the brain. As illustrated in Figure 5, the dendrites are simple at birth and develop slowly until about 15 months when the major dendrites are present. Between 15 and 24 months, there is a dramatic increase in the density of the neuropil. A similar observation can be made from examination of the cortex of the posterior speech zone. Given the correlation between language development and maturation of the language areas, we can infer that language development may be constrained, at least in part, by the maturation of these areas and that individual differences in language acquisition may be accounted for by differences in this neural development. Furthermore, given the known effect of environmental stimulation on dendritic development, we might also predict that those differences in language acquisition that have some environmental influence may do so by changing the maturational rate of the dendritic fields within these areas.

Cerebral Asymmetry

Just as the asymmetrical function of the adult's brain has been a focal point for neurological study, the development of asymmetry has been a focal point of developmental studies. As asymmetry is the subject of another chapter in this volume (see Kinsbourne, this volume), we shall consider this topic only briefly.

Most of the research with children that has been designed to demonstrate lateralization of function has emphasized the age at which asymmetry first appears (see Molfese & Segalowitz, 1988). Table 6 gives examples of a number of representative functions, which hemisphere usually shows the relative advantage, and earliest age of demonstrated asymmetry. A central theoretical issue is whether or not functions are disproportionately represented in the two hemispheres because they depend on certain anatomical asymmetries that develop independent of environmental stimulation. The fact that anatomical asymmetries can be observed in the cortex prenatally (Chi, Dooling, & Gilles, 1977; Wada, Clarke, & Hamm, 1975) and, therefore, exist before the expression of the behaviors implies that asymmetry is relatively innate. Nevertheless, several major problems arise when we try to correlate functional and anatomical asymmetry. First, the functions that are most lateralized in adults are not easily assessed in children. For example, it is extremely difficult, if not impossible, to determine handedness for writing in infants, unless, of course, one is willing to assume that some other indirect measure, such as hand strength, in this case, will serve as a reliable predictor. Second, hand preference, based on general use, appears to change several times during infancy in many children. In addition, correlations between function and anatomical asymmetry in adults are far from perfect. Although the left planum temporale is thought to be the posterior substrate of language functions, it is larger in only about 70% of right-handed people, whereas speech is lateralized to the left hemisphere in about 99% of right-handers. What then does a similar anatomical asymmetry in the fetal brain imply?

Development of Problem-Solving Ability

As each cortical layer within an area develops, it interacts with and modifies the function of the existing structure. Gibson (1977), therefore, suggested that behavior patterns would be

TABLE 6. Studies Showing Age of Asymmetry for Different Behaviors

System	Age	Dominance	Reference
Auditory			
Speech syllables	Preterm	Right ear	Molfese and Molfese (1980)
Music	22–140 days	Left ear	Entus (1977)
Phonemes	22–140 days	Right ear	Entus (1977)
Words	4 years	Right ear	Kimura (1963)
Environmental sounds	5–8 years	Left ear	Knox and Kimura (1970)
Visual			
Rhythmic visual stimuli	Newborn	Right	Crowell, Jones, Kapuniai, and Nakagawa (1973)
Face recognition	7–9 years	Left field	Marcel and Rajan (1975)
	6–13 years	Left field	Witelson (1977)
	9–10 years	None	Diamond and Carey (1977)
Somatosensory			
Dichhaptic recognition	All ages	Left	Witelson (1977)
Motor			
Stepping	<3 months	Right	Peters and Petrie (1979)
Head turning	Neonates	Right	Turkewitz (1977)
Grasp duration	1–4 months	Right	Caplan and Kinsbourne (1976)
Finger tapping	3–5 years	Right	Ingram (1975)
Strength	3–5 years	Right	Ingram (1975)
Gesturing	3–5 years	Right	Ingram (1975)
Head orientation	Neonates	Right	Michel (1981)

expected to emerge exactly in the manner described by Piaget (1952):

> Behavior patterns characteristic of different stages do not succeed each other in a linear way (those of a given stage disappearing at the time when those of the following one take form) but in the manner of the layers of a pyramid (upright and upside down), the new behavior patterns simply being added to the old ones to complete, correct or combine with them. (p. 329)

Thus, for example, because the deepest layers of the cortex myelinate first, and these are the efferent or output layers, one would expect to observe motor responses preceding the development of perceptual capacity. Indeed, according to Piaget, motor actions must come first, as motor actions provide data from which to build perceptions. The question to consider is just how well the stage of cognitive development coincides with changes in neural maturation. This is a difficult question that has not been studied extensively. Nevertheless, there is at least suggestive evidence that there may be a significant relationship between cortical development and the classical Piagetian stages. [We note that the Piagetian stages of cognitive development are a source of some debate, and there are several other conceptual schemes to describe the development of cognition in children (Carey, 1984). We will restrict our discussion to Piaget, however, because we wish merely to demonstrate the type of study that can be done and because we are unaware of any attempt to correlate other schemes of cognitive development to cortical maturation.]

Piaget was a biologist by training and considered the acquisition of knowledge and thought to be closely related to brain function. He proposed that cognitive development was a continual process and that the child's strategies for exploring the world were constantly changing. These changes were not simply a result of the acquisition of specific pieces of knowledge but rather, at some specifiable points in development, were fundamental changes in the organization of the child's strategies for learning about the world. Piaget identified four major stages of cognitive development: stage I, Sensorimotor, birth to 18 months; stage II, Preoperational or Symbolic, 18 months to 7 years; stage III, Concrete Operational, 7–11 years; and stage IV,

Formal Operational, 11+ years). In stage I, the infant learns to differentiate itself from the external world, learns that objects exist when not visible, and gains some appreciation of cause and effect. In stage II, the child begins to represent things with something else, such as drawing. Stage III is characterized by the child's ability to mentally manipulate concrete ideas such as dimensions of objects and the like. Finally, in stage IV, the child is able to reason in the abstract. Having identified the stages, the challenge for the neuropsychologist is to identify those changes in neural structure that might underlie these apparent qualitative changes in cognitive activity.

The first four brain growth stages described earlier coincide with the usual given ages of onset of the four main Piagetian stages (Epstein, 1979). A fifth stage of development, which would correlate with the fifth brain growth stage, was not described by Piaget but has been proposed by Arlin (1975). The concordance of brain growth and Piagetian stage is intriguing but, to date, remains too superficial and oversimplified. We need to know what neural events are contributing to brain growth and just where they are occurring. Little is known of this in children after 6 years of age, but the question remains important to the neuropsychologist seeking to understand the maturation of cortical operations. Gibson (1977) presented a detailed hypothetical analysis of stage I.

Development of Neuropsychological Test Performance

Neuropsychologists have developed an amazing array of tests since World War II with which to assess the behavior of patients with cortical injuries (e.g., Lezak, Howieson, Loring, Hannay, & Fischer, 2004). In principle, it is logical to suppose that if a test is sensitive to restricted cortical lesions in adults, and if a normal child performs poorly on such a test, it could then be inferred that the requisite cortical tissue is not yet functioning normally. This logic is seductive but is not without difficulties. First, the method assumes that tests will be sensitive to focal lesions: Few tests are. Second, a child may perform poorly on a test for many reasons. For example, a child may have difficulty with a verbal test because the speech areas are slow to develop or because he or she has an impoverished environment and has acquired only a limited vocabulary. Furthermore, just because a child does well on a test does not mean that the child's brain is solving the problem in the same manner as the adult brain. Indeed, there are examples of tests in which children do well, only to do more poorly the following year, followed later by improvement again. Thus, in their studies of facial recognition in children, Carey, Diamond, and Woods (1980) found that children improved in performance between ages 6 and 10, declined until age 14, and then attained adult levels by age 16. This result can be taken to imply that the younger children were solving the problem in a different manner than the older children and adults while, presumably, using different cortical tissues. In sum, although there are clear limitations to the inferences that can be made about the development of specific brain regions, we feel that much can be learned using this type of approach. We will illustrate this by focusing on our own studies using tasks that test frontal lobe function and the perception of faces and facial expression.

Frontal Lobe Tests

Segalowitz and Rose-Krasnor (1992) edited a special issue of *Brain and Cognition* that was devoted to the general premise that an understanding of cognitive development in children is dependent on understanding the role of the frontal lobe in development. Their argument is based on the idea that the frontal lobe plays a central role in generating cognitive strategies (as opposed to habits), evaluating those strategies, and monitoring both one's behaviors and the effects of one's behavior on other people. If their argument is correct, then an understanding of correlations between frontal lobe development and behavioral maturation is critical in developmental neuropsychology.

The idea that the frontal lobes play a special role in cognitive development is not new. Hebb (1949) speculated from his analyses of children with perinatal cerebral injuries that the frontal lobes were critical to cognitive development. In fact, Hebb believed that the frontal lobes played a more important role during development than in adulthood. More recently, Case (1992) has argued that between the ages of 1½ and

5 years, and again between the ages of 5 and 10 years, a sequence of changes take place in children's behavior that indicate a fundamental reorganization of their attentional and executive processes. Case correlates these functional changes with developmental changes in the frontal lobe (Stuss, 1992; Thatcher, 1992).

One way to investigate correlations between frontal lobe maturation and cognitive development is to study the behavior of children on tests performed poorly by people with acquired frontal lesions in adulthood. Two tests are especially sensitive to frontal lobe injury, namely the Wisconsin Card Sorting Test and the Chicago Word Fluency Test (Milner, 1964). In the first test, the subject is presented with four stimulus cards, bearing designs that differ in color, form, and number of elements. The subject's task is to sort the remaining cards into piles in front of one or another of the stimulus cards. The only help the subject is given is being told whether the choice is correct or incorrect. The test works on this principle: the correct solution is first to sort by color; once the subject has figured this out, the correct solution then becomes, without warning, to sort by form. Thus, the subject must now inhibit grouping the cards on the basis of color and shift to form. Once the subject has succeeded at sorting by form, the relevant feature again changes unexpectedly, this time to number of elements. This cycle of color, form, and number is repeated. The subject's score is the number of target categories completed after sorting 128 cards, and the task is terminated when all of the cards have been used or six categories have been completed, whichever comes first. Shifting strategies is particularly difficult for patients with left frontal lobe lesions.

In the second test, the subjects must write as many words as they can beginning with the letter "S" in 5 min. Following this, they must write as many four-letter words beginning with "C" as possible in 4 min and the final score is the total number of words generated. Frontal lobe patients do very poorly on this test. This deficit is not simply a problem of verbal ability, however, as frontal lobe patients perform at normal levels when asked to write the names of as many objects or animals as they can think of within a fixed time. We note that frontal lobe patients perform normally on many other tests as well. For example, on tests of visual recognition, which are performed poorly by patients with right posterior lesions, frontal lobe patients achieve normal levels of performance.

Kolb and Fantie (1989) tested children on the card sorting and verbal fluency tests and predicted that if the frontal lobes were slow to mature relative to other cortical areas, then children should reach adult levels very late, probably in adolescence on tests of frontal lobe function. In contrast, children should perform at adult levels much sooner on the tests performed normally by patients with frontal lobe lesions. This is indeed the case. Children perform poorly on all frontal lobe-sensitive tests when very young but improve as they develop. As predicted, performance on tests performed normally by adults with frontal lobe injuries improves more quickly, however, than performance on tests sensitive to frontal lobe injuries.

Frontal lobe patients are also notorious for their difficulties in social situations, although it is more difficult to quantify their behavior (Kolb & Whishaw, 2008). Kolb and Taylor (1981, 1990) showed that one way to analyze the unique frontal contributions to social interaction is to focus on the ability of frontal lobe patients to produce and recognize facial expressions. Kolb, Wilson, and Taylor (1992) gave children a series of tests of facial perception ranging from simple tests of facial recognition and closure to more complex tests in which facial expression had to be understood from the context of a cartoon. Children aged 5–6 years performed as well as normal adults on the tests of facial recognition but did not approach adult levels on the context-dependent facial perceptual tests until about age 14 years. Furthermore, in a small sample of adults with frontal lobe injuries in early childhood, we have shown abysmal performance on the context-related tests. This result is consistent with a series of case histories showing that children with frontal lobe injuries at the time of birth do not develop anything approaching normal strategies for coping with social situations (e.g., Ackerly, 1964; Eslinger & Damasio, 1985; Grattan & Eslinger, 1992).

Abnormal Brain Development and Behavior

Earlier we described abnormalities in neural migration that are probably found throughout the brain, but it is reasonable to

predict that there will be conditions in which such abnormalities might be restricted to relatively small zones of cortex. In fact, there is now reason to suppose that at least some forms of developmental dyslexia result from abnormal structural development. Drake (1968) examined the brain of a 12-year-old learning-disabled boy who died of cerebral hemorrhage. Autopsy showed that there were atypical gyral patterns in the parietal lobes, an atrophied corpus callosum, and neurons underlying the white matter that should have migrated to the cortex. More recently, Galaburda and his colleagues have reported analogous results from several dyslexic brains (Galaburda & Eidelberg, 1982; Galaburda & Kemper, 1979; Geschwind & Galaburda, 1985). Thus, in the brain of a 20-year-old male who previously had a reading disability despite average intelligence, they found an abnormal pattern of cytoarchitecture, especially in the posterior speech region of the temporal–parietal cortex. Although other details varied in these cases, the left posterior region was always abnormal. These abnormalities were believed to be the result of disordered neuronal migration and/or assembly. The right hemisphere was either completely or largely normal in all of these cases. Finally, Geschwind and Galaburda (1985) claimed to have evidence of similar anomalies in living dyslexic patients, with arteriovenous malformations in the left temporal region.

The finding of left temporal–parietal abnormality in dyslexics leads to the question of how these people, even as children, might perform on tests sensitive to focal cortical lesions. Few studies have compared dyslexic children directly to adults with left posterior lesions, but studies of dyslexic children have found behavioral deficits on tests that are particularly disrupted by left posterior lesions, including tests of short-term verbal memory, left/right differentiation, and verbal fluency (Sutherland, Kolb, Schoel, Whishaw, & Davies, 1982; Whishaw & Kolb, 1984). We must point out again that it is likely that not all children with learning disabilities have left posterior abnormalities. It would be interesting, however, to determine the correlation between neuropsychological test performance in learning-disabled children and the presence of left posterior abnormalities.

Early Brain Injury and Behavior

Perhaps the most dramatic evidence of recovery from brain injury comes from the observations that infants with damage to left-hemisphere language areas rarely have persistent aphasia. Indeed, shortly after he published his observations on the nature of aphasia from the left inferior frontal region in adults, Broca noted that children did not show long-lasting aphasia after similar injury, and he postulated that after injury to the left hemisphere language functions could shift to the right hemisphere (Broca, 1865). Barlow (1877) confirmed Broca's hypothesis in his investigation of a young boy who suffered a lesion of the left hemisphere, which led to only a transient speech disturbance, followed by a later lesion to the right hemisphere, which left the boy with a permanent loss of language. The simplest explanation of Broca's and Barlow's observations was that the developing brain was capable of functional reorganization that would allow development of relatively normal language abilities after injury to left-hemisphere language zones. Clinical studies over the next 100 years confirmed the general idea that the consequences of early focal lesions of the left hemisphere were minimal (e.g., Alajouanine & Lhermitte, 1965; Krashen, 1973; Lenneberg, 1967). In his comprehensive theory of language development, Lenneberg (1967) proposed that language-related processes in the left hemisphere developed rapidly from ages 2 to 5 years and then more slowly until puberty, by which time language development was complete. He reasoned that if brain damage occurred during the time of rapid development (up to 5 years), it would be possible to shift language functions to the intact right hemisphere, and there would be no chronic aphasia. By using Wada's sodium amobarbital procedure to determine the hemisphere mediating language, Rasmussen and Milner (1977) confirmed Lenneberg's speculation as they found that childhood injuries before 5 years of age allowed a shift in language processes to the right hemisphere. Injuries from about 6 to 10 years also allowed recovery from aphasia but this was sustained by a shift of language within the left hemisphere.

An additional important finding in the Rasmussen and Milner study was that many patients with injuries prior to age 5 had speech processes represented in both hemispheres.

Thus, if Broca's area was damaged, only those language-related functions subserved by Broca's area moved to the right hemisphere and, similarly, if only the posterior speech zone was damaged, only those processes moved to the right hemisphere. And, when both left frontal and temporal language areas were damaged, the functions of both regions shifted to the right hemisphere.

Given this clearly anomalous representation of speech in both hemispheres it would be surprising if there were not some type of disruption of nonlanguage functions, and, indeed, this is the case. For example, Woods and Teuber found that children with left-hemisphere injuries in the speech zones showed unexpected deficits in right-hemisphere functions as well as an overall drop in IQ (e.g., Woods, 1980; Woods & Teuber, 1973). Such results led to a reevaluation of the effects of early cortical injuries in children with a particular interest in looking at a broad range of cognitive functions, rather than just speech (e.g., Aram, 1988; Bates et al., 1997; Levin, Song, Chapman, & Howard, 2000; Stiles, 2000). The results of such studies make it clear that the advantages of having early, rather than later, cerebral injury may not be as great as once believed. In reviewing such results we can now reach the following conclusions.

1. *Children show significant sparing or recovery of language functions after early injury to known language areas, but these functions are not normal*. For example, Bates and colleagues (e.g., Bates & Thal, 1991; Bates et al., 1997; Reilly, Bates, & Marchman, 1998) provided detailed longitudinal descriptions of language impairment and development in a population of children with perinatal focal lesions. These children have delayed language development, but by kindergarten age most of these children have caught up in their lexical and syntactic abilities. Nonetheless, the children still have continuing linguistic impairments. Importantly, in contrast to adults with focal lesions of the language areas, the site of the lesion in the left hemisphere of children does not affect the pattern of linguistic deficits: the pattern of deficits is uniform across the lesion population. There was, however, a difference in the severity of deficits associated with different foci of damage because children with left temporal injuries had more severe deficits than children with other injuries.

2. *Perinatal lesions of either the left or right hemisphere produce significant language deficits during development*, a result that is quite different from what occurs in adults. In fact, Bates and colleagues (1997) found that depending on the language measure, early right-hemisphere lesions can produce greater receptive language impairments up to age 5 years than comparable early left-hemisphere lesions. This result is surprising and could be explained, in part, by suggesting that, if left-hemisphere language functions can shift to the right hemisphere, then perhaps some nonverbal functions can shift to the left hemisphere, which could lead to some disruption of normal language development.

3. *Children with focal right- or left-hemisphere injury show deficits in spatial processing, but like language functions, the spatial functions improve as the children develop*. Stiles and her colleagues (e.g., Akshoomoff et al., 2002; Stiles et al., 2005; Stiles Trauner, Engle, & Nass, 1997) followed a group of children with lesions (largely caused by stroke) incurred by 6 months of age and found deficits in visuospatial processing as early as children could be tested. The deficits abated over development and by puberty the deficits were markedly attenuated relative to children (or adults) with later injuries. One key point in the studies of Stiles is that the deficits observed in children are qualitatively similar to those seen in adults with similar focal lesions. This finding contrasts with the effects of early lesions on language functions (see above).

4. *The outcome from focal and diffuse lesions in early childhood is very different*. In an extensive series of studies of children with closed head injuries, Levin and his colleagues (e.g., Levin et al., 1996; 2000) have found that verbal and sensorimotor skills are more impaired in young children following severe closed head injuries than in older children sustaining comparable injuries. It appears that whereas functional outcome after focal lesions may be best if the injury is perinatal, diffuse damage at a similar age leads to a very poor functional outcome.

5. *Recovery from early cortical injury is task specific*. As we have noted, the best evidence of functional recovery or sparing after early injury can be seen in the domain of language. Compensation is not as extensive for nonlanguage functions, however. For example, in general, nonverbal functions are usually impaired after

early lesions, regardless of the location of the lesion (Carlsson & Hugdahl, 2000; LeVere, Gray-Silva, & Le Vere, 1988; Nass, de Coudres-Peterson, & Koch, 1989). Teuber (1975) argued that nonverbal deficits occur after left-hemisphere lesions because the shift of language to the right hemisphere "crowds" the right hemisphere, compromising the normal right-hemisphere functions (see also Satz, Strauss, Hunter, & Wada, 1994; Strauss, Satz, & Wada, 1990). And, of course, damage to the right hemisphere impairs nonverbal functions because that is the function of the right hemisphere.

But the task-specific nature of recovery can be seen in motor behaviors as well. Children with congenital hemiplegia show recovery of language functions but the hemiplegia remains (e.g., Carlsson & Hugdahl, 2000). Similarly, B. Kolb and B. Milner (unpublished) studied patients with early lesions of the language regions of the left temporal lobe who were shown by sodium amobarbital testing to have language functions represented in both hemispheres (that is, the posterior speech zone but not the anterior speech zone shifted to the right hemisphere). These patients later all had their damaged left temporal lobe removed for the relief of intractable seizures. In contrast to patients with similar removals, but with normal left-hemisphere speech representation, those patients with anomalous speech representation showed deficits on a task of copying sequences of arm movements, a deficit normally seen only in patients with left frontal or parietal injuries (Kolb & Milner, 1981). Thus, these patients paid a price for their good language functions but, in contrast to Teuber's suggestion that shifting language can interfere with right-hemisphere functions, in this case, it interfered with a left-hemisphere function.

6. *Deficits from perinatal lesions may not emerge until many years later*. Because infants have poorly developed perceptual, cognitive, and motor functions, it is often not possible to assess the effects of early injury until late childhood or even puberty. For example, Banich Cohen-Levine, Kim, and Huttenlocher (1990) studied the development of performance on two subtests of the Wechsler Intelligence Scale for Children, namely vocabulary and block design, in children with congenital cerebral injuries. They found that at 6 years of age there were no differences in performance, but as the children aged, significant deficits emerged in the brain-injured children relative to age-matched controls. Given that many cognitive functions, and especially frontal lobe functions, are not mature until well into puberty (e.g., Kolb & Fantie, 1989; Kolb et al., 1992), it should not be surprising if some of the effects of frontal lobe injuries might not appear for over a decade after an infant injury, a result that was first noted by Hebb (1949).

7. *General intelligence is compromised by early cerebral injuries, and especially if there is a seizure disorder*. Although not all children with early brain injuries have general intelligence scores that fall below average, as a general rule of thumb, children with injuries in the first year (e.g., Riva & Cazzaniga, 1986) or children with a persistent seizure disorder (Vargha-Khadem & Polkey, 1992) have compromised IQs. This effect on IQ occurs even after perinatal frontal lobe lesions, lesions that do not normally affect IQ in adults with frontal injuries (Hebb, 1949; Kolb & Fantie, 1989).

8. *There is far less recovery from bilateral versus unilateral injuries*. One curious, but consistent, finding is that children with restricted bilateral injuries often have a worse functional outcome than children with a complete hemisphere removed. For example, children with complete removal of the left hemisphere usually show a shift of language functions to the right hemisphere. Vargha-Khadem, Watters, and O'Gorman (1985) found that even small lesions of the right hemisphere appear to be capable of blocking the shift of speech from the left to the right hemisphere in children with perinatal injuries to the speech zones of the left hemisphere, which resulted in severe and persisting language deficits. This effect of the right-hemisphere lesion is present even if the injury is well beyond the homologous language zones in the right hemisphere.

9. *Descending motor pathways can be reorganized following early damage and this reorganization may be functionally significant*. Using both functional magnetic resonance imaging (fMRI) and somatosensory evoked potentials (SEP), Holloway and colleagues (2000) investigated the sensorimotor functions of patients with childhood hemispherectomies. Many of these patients showed SEP in the normal hemisphere when the nerves of the limb opposite the

excised hemisphere were stimulated. Similarly, fMRI showed that for at least some of the patients, passive movement of the same limb produced activation in a region of somatosensory cortex in the normal hemisphere. The responses to the hand ipsilateral to the normal hemisphere must occur because direct ipsilateral pathways run from the normal hemisphere to the affected limb.

Similar conclusions have been made in studies showing that when patients with congenital hemiplegia move the hand opposite the intact hemisphere, they commonly show mirror movements of the hemiplegic hand (e.g., Farmer, Harrison, Ingram, Stephens 1991). Carr (2000) used transcranial magnetic stimulation to induce electromyographically measured movements in a group of 32 congenitally hemiplegic patients. Sixty-four percent of these patients showed EMG activity in the hemiplegic limb when the ipsilateral hemisphere was stimulated. No such movements were seen in control subjects or the other patients. All but two of the patients with anomalous ipsilateral pathways had prenatal injuries, whereas the lesions in the remaining patients were all postnatal, a result that suggests that age at injury may be critical in the development of functionally significant anomalous corticospinal pathways.

10. *The effects of early injury vary with age.* We have seen several clues that precise age at injury may be critical in predicting functional outcome, which leads us to several generalizations. First, prenatal lesions are more likely to lead to the development of functional ipsilateral motor pathways than lesions after birth, although the formation of such pathways is possible following postnatal injuries, especially in cases of hemispherectomy. The removal of most (or all) of a hemisphere may be important because large lesions alone, such as seen in congenital hemiplegia or cerebral palsy, appear unlikely to produce anomalous corticospinal pathways. Second, language appears to be the most plastic function if the brain is injured after birth, and the time course of this plasticity appears to be much longer than for other functions, lasting up to 10 years of age. The special plasticity of language functions may be related to its recent phylogenetic development and/or to the prolonged ontogenetic development of language functions in children. Third, although small focal lesions in the first few months of age do not appear to affect general cognitive functioning (i.e., IQ), as a rule of thumb lesions in the first year produce greater impairments in IQ than those occurring later. This appears to be especially true of frontal lobe lesions, a result that led Hebb (1949) to conclude that the earlier frontal lobe injury occurred in children, the worse the effect was on cognitive functioning.

Conclusion

The process of brain maturation is long, lasting at least into early adulthood. We have approached the problem of assessing the nature of functional localization in the cortex by examining the way in which structure and behavior emerge in the developing child. Neurons, the elementary components of the brain, are born, migrate, and, as their processes elaborate, establish connectional relationships with other neurons. Behavioral and cognitive capacities follow a similar sequence of development from the rudimentary to the complex. Structure–function relationships can be inferred by matching the developmental timetables of brain anatomy and physiology with those of behavior. In addition, we have demonstrated that neuropsychological tests that are sensitive to focal cortical damage in adults can be used to assess whether certain areas have reached functional maturity in normal, developing children. Furthermore, by studying the abnormal development of the brain and behavior, we may make inferences regarding the importance of particular developmental events on behavior.

The study of anatomical and behavioral development of the brain of the child is admittedly far from complete. However, we believe that the data obtained to date are beginning to answer the questions about the nature of the brain of the child. The continued study of developmental neuropsychology promises to change our understanding of the biological bases of the development of human behavior.

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