Chapter 3
Development in the CNS

Neuronal development proceeds in an orderly fashion during development of the embryo and fetus. There are certain stages of development that are consistent across individuals during gestation. Following birth, changes in the brain are related to genetics, biology, and environmental stimulation. This chapter will provide an overview of development pre- and postnatally, and discuss challenges that develop due to environmental aspects (stress, substance abuse, toxins, etc.).

Prenatal Course

The fastest rate of brain growth occurs prenatally, when it is estimated that every minute 250,000 brain cells are formed through mitosis (Papalia & Olds, 1992). The increase in the number of cell bodies occurs most rapidly between 25 and 40 weeks gestation (Ivry, & Mangun, 2002). The human brain develops in orderly stages, beginning in the neural tube at 25 days gestation and, though not fully mature, assumes adult features at birth. Finally, this chapter provides information about genetic, environmental, and psychosocial differences that can affect brain development. In pediatric neuropsychology the assessment almost always includes the caretakers and the family unit. Providing services to children requires enlisting the family in treatment and support. The spinal cord, the brain stem, and a large portion of the forebrain are developed at 40 weeks gestation, while the cerebellum has maximum growth by the time of birth and during the first year. Six neuronal layers make up the cytoarchitectonic structure of the cerebral cortex (Kolb & Whishaw, 2003). These layers develop differentially during gestation and through the first year of life. These cortical layers develop in an inside-out fashion, where neurons move into specific regions and are passed by later migrating layers. These layers migrate into various regions, forming the structural organization of the cortex (Kolb & Whishaw, 2003).

While neurons proliferate and migrate to different cytoarchitectonic regions during various prenatal stages, numerous factors can interrupt this process. Environmental toxins (e.g., alcohol and drugs) pose a particular threat to the migration process and, depending on the time and stage of fetal development, different brain regions can be impaired causing significant cognitive and behavioral deficits later in life. These areas of concern are discussed later in this chapter.

Proliferation and Cell Migration

Cell migration is largely defined at birth, and the time and place of migration appear to be regulated by physical as well as chemical processes (Carlson, 2007). The developmental process is marked by an intricate neuron-glial interaction, where neurons are guided along radial glial fibers to their proper location. The migration process occurs rapidly, and several cortical layers appear visible during the fifth month of fetal development (Kolb & Whishaw, 2003). The cortex begins to thicken and shows signs of developing sulci during this period. The

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sulci develop early, with the longitudinal fissure apparent at 10 weeks, the lateral sulcus at 14 weeks, the parieto-occipital sulcus at 14 weeks, and the central sulcus at 20 weeks gestational age (Carlson, 2007). Within six months of inception, neurons are genetically programmed to proliferate so that the proper number of cells is available.

During the neonatal and postnatal periods neurons also differentiate and migrate into genetically predetermined regions of the brain. Aberrant neuronal development can cause cell to migrate to the wrong locations or cause neurons to make inappropriate synaptic connections. For example, it has been suggested that schizophrenia results from abnormal neuronal connections where mesocortical regions (dopaminergic systems) fail to connect to frontal cortical regions (Buchsbaum et al., 2006). Cell death occurs during these early developmental stages because more neurons are generated than are necessary; thus, strategic or "selective cell death" appears critical in the developing fetal brain (Gazzaniga et al., 2002) with approximately 25–33 percent of neurons in the developing brain being pruned back during the process of neuronal proliferation and migration. Brodal (2004) suggests that as many as 50 percent of motor neurons in the spinal cord are eliminated. It has been hypothesized that neurons compete for a limited amount of the "trophic substance" that keeps the cells alive, so that only a portion of fetal neurons can survive (Brodal, 2004). Neurodevelopmental disorders caused by abnormal cell proliferation, migration, or cell death can have a significant impact on a child's cognitive, behavioral, and psychosocial potential. The impact of these neurodevelopmental anomalies is reviewed in later chapters.

Axon and Synaptic Formations

Once they reach their destination, neurons continue to develop and differentiate. Axons appear to follow or to "grow along" other pioneer axons with high concentrations of chemicals that seem to set the course or direction of growth (Gazzaniga et al., 2002). Brodal (2004) suggests that axons may recognize their developmental path as a result of "chemoaffinity" between the axon terminals and target neurons. Further, chemical markers may be present only in specific phases of development and then may disappear to ensure selective contact with target neurons. The peripheral nervous system is known to have specific protein nerve growth factor (NGF) that stimulates the outward movement of axons, so that axons grow into these regions and away from areas without NGF. Brodal (2004) suggests that other proteins such as brain-derived neurotrophic factor (BDNF) may play a similar function in the brain. Axons grow at a rapid rate, while cells are still migrating, and cross to form pathways that connect the hemispheres. The anterior commissure which connects the frontal lobes first appears at about three months' gestation, while the corpus callosum (a major bundle of fibers that connects the hemispheres) develops at a slower rate (Brodal, 2004). The hippocampal commissure appears after three months' gestation, followed by the appearance of another set of fibers that eventually develop into the corpus callosum. The corpus callosurn continues to develop postnatally and is fairly well formed by five years of age (Witelson, 1989).

Dendritic and spine growth (visible at about seven months' gestation) occurs at a slower rate than axon development and usually starts after cells have reached their final destination. Dendritic development continues postnatally and is affected by environmental stimulation after birth. Synaptic development is less understood, although synapses have been observed during the fifth month of fetal development (Carlson, 2007). The relationship between synaptic density and cognitive abilities may be an inverse one, because synaptic density appears to decrease with age. Whereas synaptic density was once thought to be indicative of increased functional abilities, the reduction of synapses may be related to efficiency and refinement of function in some qualitative sense (Gazzaniga et al., Ivry, & Mangun, 2002).

Early synaptic redundancy and selective elimination of synapses in later development have been verified in PET studies (Caesar, 1983). The high levels of glucose metabolism recorded during the first year of life begin to decrease during the second year through adolescence. A process similar to selective cell death occurs to eliminate axon collaterals (Brodal, 2004). According to Brodal, this process is best understood in the study of the motor neurons that enervate

skeleton muscles. Whereas early stages of development are marked by the emergence of numerous neurons connecting to one muscle, multiple synapses are eliminated in later stages of development. Once motor neurons begin to send signals to the muscle, it appears that the process of synaptic elimination occurs. Brodal (2004) indicates that it is this process of synaptic elimination, once normal activity begins, that allows for precise neural connections. According to Brodal (2004), "meaningful" information rather than simple activity is a key factor in this process. The migration of cells may be disrupted by disorders in genetic programming or as a result of external disruption due to viral infections and disturbances to vascular circulation. Recent advances in brain imaging techniques are shedding new light on differences between genetic and acquired disorders that disrupt cell migration (Cody et al., 2005). Finally, synaptic networks become more elaborate in the postnatal period, where dendritic arborization increases in complexity (Brodal, 2004). In the third trimester the brain enters a major prenatal growth spurt, which continues postnatally until two years of age. Antenatal insults during the third trimester may result in cerebral palsy syndromes (Kolb & Whishaw, 2003)

Postnatal Course

An individual's full quota of neurons is reached by six months' gestational age, but postnatal development is marked by increased cortical complexity (Gilles & Gomez, 2005). In general, myelination increases brain weight from approximately 400 grams at birth to 850 grams at 11 months, to 1,100 grams at 36 months, to 1,350 to 1,410 grams at age 15, and continues to increase through age 60 (Gilles & Gomez, 2005). Four postnatal growth spurts have been found that correspond to Piaget's stages of cognitive development: from two to four years, from six to eight years, from 10 to 12 years, and from 14 to 16+ years (Kolb & Fantie, 1989). Although cognitive development follows time-lines similar to anatomical and physiological growth patterns, the manner in which environmental factors affect brain development through these growth spurts is an area that warrants further study.

Myelination is an important aspect in the brain's maturation. It first occurs in the primary sensory and motor cortices (prior to birth); the secondary areas of the basic senses myelinate within four months postnatally, while the myelination process begins postnatally in the frontal and parietal association regions and continues through the mid-20 s (Fredrik, Macoveanu, Olesen, Tegner, & Klingberg, 2007).

Myelination appears correlated to the development of and changes in visual, motor, social, and cognitive behaviors. Malnutrition, disease, injury, and inadequate stimulation can affect the myelination process, which in turn may affect the learning capacity of the individual. It may be that these environmental events affect the developing brain even more drastically than a more mature brain because they occur before the receptor sites for neurotransmitters are fully established. External medications may interfere with this process, affecting neurological and psychosocial development.

Gestation

The earliest stages of brain development are marked by rapid changes in the embryo. Within seven days of inception, two layers of tissue (the ectoderm and the endoderm) are present and, within nine days, a third layer (the mesoderm) develops and moves between the first two layers in a process referred to as neurulation. The ectoderm forms the neural groove, which in turn forms the neural tube. The process of neurulation is initiated in the first two weeks; embryonic tissue differentiates, forming the neural tube, and is completed by the fourth gestational week. During this process, embryonic tissues thicken, deepen, and close, forming the basic structures of the nervous system. Neurons and glial cells are formed on the outside wall of the neural tube, and the inside wall is covered with glial cells forming a canal that becomes filled with CSF. Throughout this course, neural tissues differentiate and migrate forming columns of spinal and cranial nerves that keep the organism alive. The cranial portion of the neural tube eventually develops into the brain, while the caudal portion becomes the spinal cord. Motor and sensory columns develop from separate

structures of the neural tube, and by the end of four weeks the neural tube closes.

Once the process of neurulation ends (4th week), three brain vesicles appear, forming the hindbrain, the midbrain, and the forebrain. These vesicles further differentiate into (1) diencephalon, which eventually forms the thalamus, hypothalamus, and epithalamus, and (2) the telencephalon, which forms the cerebral hemispheres. The lumina or cavities of the brain vesicles develop into the ventricular system, which can be compromised in various developmental or disease processes, such as hydrocephalus. The vesicles continue to develop into the major brain regions.

Although genetic factors map the nature and course of neuronal development, environmental factors have a significant influence on the developing nervous system. Brodal (2004) suggests that "use-dependent stimulation" is crucial during early stages of postnatal development. That is, the developing brain requires proper and adequate stimulation for optimal development. This aspect of neurodevelopment will be explored in later sections of this chapter.

The Development of Higher Cognitive Abilities

The relationship between cognitive-behavioral development and neuroanatomical development is relatively uncharted in young children, with two exceptions: motor and language functions. Changes in myelin formation in specific brain regions are correlated with increased complexity of functions and increased cognitive abilities in children from birth to five years of age. (See Table 3.1 for an overview of this interaction.)

Although there is an obvious interaction among developing brain structures, many of which are developing simultaneously, and behavioral changes, this relationship is highly variable. Brains are distinct in their individual cellular and neural growth patterns, but this process is affected by acculturation (Majovski, 1989) and chemical-environmental factors (Cook & Leventhal, 1992). Despite individual variations in this process, developmental trends in structural and behavioral interactions can be interpreted with these limitations in mind. The following sections address maturational processes in specific cortical regions. In some instances, sufficient research is not available to determine when structures are fully developed and how structural changes relate to cognitive development; however, there is sufficient evidence to suggest that meaningful patterns are emerging. The following review summarizes the current available research in this area.

Frontal Lobe Maturation

Conel (1939–1959) mapped postnatal frontal lobe development, showing rapid changes in density from birth until 15 months. Synaptic density increases until two years of age, when it is about 50 percent above that of adults, and decreases until about 16 years of age (Gazzaniga et al., Ivry, & Magnun, 2002). A decrease in the number of synapses in the frontal lobes may represent a "qualitative refinement" in the functional capacity of the neurons (Brodal, 2004). That is, cognitive complexity cannot be defined in simple quantitative terms, such as the number of synapses. These structural changes appear to correspond to the development of behaviors mediated by the frontal lobes, namely speech, executive, and emotional functions (see Table 3.1).

Using EEG data to map brain activity, Thatcher (1996) suggests that there are "growth spurts" of cortical connections from the parietal, occipital, and temporal lobes to the frontal lobes. These growth spurts occur at three intervals: (1) from age 1.5 to 5 years; (2) from 5 to 10 years, and (3) from 10 to 14 years. After age 14 the frontal lobes develop at the same rate and continue until age 45. These corticocortical connections differ between hemispheres. The left hemisphere shows a developmental sequence of gradients involving anterior-posterior and lateral-mesial regions, with *lengthening* of connections between posterior sensory regions, and frontal areas, while the right hemisphere involves a *contraction* of long-distance frontal connections to posterior sensory areas. Thatcher (1996) suggests that the expansion of the left hemisphere is due to functional

Table 3.1 Myelination and cognitive development

Age	Visual/motor functions	Social/intellectual functions	Myelination
Birth	Sucking reflex, rooting, swallowing, Moro reflex, grasping, and blinking to light.		Motor root +++; sensory root ++; medial lemniscus ++; superior cerebellar peduncle ++; optic tract ++; optic radiation ±
6 weeks	Neck turning and extension when prone; regards mom's face; follows objects.	Smiles when played with.	Optic tract ++; optic radiation +; middle cerebellar peduncle; pyramidal tract+
3 months	Infantile grasp; volitional sucking; holds head up; turns to objects in visual field; may respond to sound.	Watches own hands.	Sensory root +++; optic trace & radiation +++; pyramidal tract ++; cingulum +; frontopontine tract +; middle cerebellar peduncle +; corpus callosum ±; reticular formation ±
6 months	Grasps with both hands; puts weight on forearms; rolls; supports weight on legs brief periods.	Laughs and shows pleasure. Makes primitive sounds. Smiles at self in mirror.	Medial lemniscus +++; superior cerebellar peduncle ++; middle cerebellar peduncle +; pyramidal tract ++; corpus callosum +; reticular formation +; association areas ±; acoustic radiation +
9 months	Sits and pulls self to sitting position; thumb–forefinger grasp; crawl.	Waves bye-bye; plays pat-a-cake; uses *Dada, Baba*; imitates.	Cingulum +++; formix ++; others as described
12 months	Releases objects. Cruises and walks with one hand held; plantar reflex flexor in 50%.	Uses 2–4 words with meaning; understands nouns; may kiss on request.	Medial lemniscus +++ pyramidal tract +++; fornix +++; corpus callosum +; intracortical neuropil ±; association areas ±; acoustic radiation ++
24 months	Walks up and down stairs; (two feet-step); bends and picks up object; turns knob; partially dresses; plantar reflex flexor 100%.	Uses 2–3 word sentences; uses *I, me*, and *you*; plays simple games; names 4–5 body parts; obeys simple commands.	Acoustic radiation +++ corpus callosum ++; association areas +; nonspecific thalamic radiation ++
36 months	Goes up stairs (one foot) pedals tricycle; dresses self fully except shoelaces, belts, and buttons; visual acuity 20/20/OU.	Asks numerous questions; says nursery rhymes; copies circles; plays with others.	Middle cerebellar peduncle +++
5 years	Skips; ties shoelaces; copies triangles; gives age.	Repeats 4 digits; names 4 colors.	Nonspecific thalamic radiation +++; reticular formation ++; corpus callosum +++; intracortical neuropil & association areas ++
Adult			Intracortical neuropil & association areas ++ to +++

Source: Adapted with permission "Development of the Child's Brain and Behavior" by B. Kolb and B. Fantie (1989), in C. R. Reynolds and E. R. Janzen, eds., *Handbook of Clinical Child Neuropsychology*, pp. 17–40. New York: Plenum Press.
Note: ± minimal amounts; + mild amounts; ++ moderate amounts; +++ heavy.

differentiation of new subsystems, whereas the contraction of the right hemisphere is the functional integration of previously existing subsystems. Thus, experience and stimulation play a direct role in the process of redefining and differentiating neuroanatomy.

Studies of changes in the brain over development using Magnetic Resonance Imaging (MRI) have

found differences not only by age but also by gender. Sowell, Trauner, Gamst and Jernigan (2002) found age-related increases in total brain volume as well as in white matter volume in a group of children aged 7–16. Differentiation in white matter was found during this period with increases in volume while gray matter was found to decrease in volume between childhood and adolescence. Cerebrospinal fluid (CSF) was found to show a 2 percent increase with age. Older participants had about 4 percent of the brain volume due to CSF, while younger participants had 2 percent of the total brain volume due to CSF. Additional age effects were found in the areas of the frontal lobe and anterior cingulate with increases in white matter volume in these regions. The caudate and thalamus were found to decrease in volume with age, which was gender-specific. Volumes of the caudate and putamen decreased with age for boys, but not for girls. Similarly, the cerebellum (the region of the brain responsible for fluid movement) was approximately 8 percent larger in boys. The putamen and globus pallidus (other areas deep in the brain and responsible for input of motor information) were also larger in males compared to females.

Male brains have been found to be approximately 7–10 percent larger in volume compared to females during childhood (Giedd, Castellanos, Rajapakse, Vaituzis & Rapoport, 1997; Giedd et al., 1996; Reiss, Abrams, Singer, Ross & Denckla, 1996; Sowell et al., 2002). When brain size was controlled, girls were found to show larger volumes in the gray matter of the temporal cortex, the caudate, thalamus, and regions deep inside the brain (i.e., hypothalamus). In a subsequent study, (Giedd et al., 1997) found that the amygdala (a structure involved in emotional processing) and the hippocampus (a structure involved in setting down memories) volumes increased for both genders with age. The amygdala was found to increase significantly more for males than females, while the hippocampus increased in volume more for females than for males.

Expressive Speech Functions

Scheibel (1990) examined dendritic structures in the frontal lobe to determine the relationship between functional speech abilities and cortical development. In a series of postmortem studies, electron microscopic techniques were applied to brain tissue taken from 17 subjects between the ages of three months and six years. Structural changes in dendritic growth patterns appear related to differences in language functions across the ages and are summarized as follows:

1. Initially, dendritic growth is greater in the right opercular region (motor speech area) than on the left at three months.
2. Dendritic systems on the left increase in higher order speech zones at six months and eventually surpass the right hemisphere.
3. The hemispheres develop in an uneven pattern for the next five years.
4. The dendritic system in the left hemisphere appears more complex by the age of six, and Broca's area resembles the development of adults at this age. Further, these structural changes appear related to differences in functional speech mechanisms present at each stage.

Speech during the first 6–12 months of age is characterized by affective communication patterns, which probably are related to dendritic growth in the right frontal regions (Scheibel, 1990). As the left frontal region develops the child's ability to understand syntax and more complex language forms improves. Development of dendritic processes in the language regions in the left hemisphere catches up to and eventually exceeds development in the right hemisphere corresponding to increases in the use and complexity of language skills. Some suggest that experience and functional differentiation go hand in hand and are necessary for further development.

Scheibel (1990) found that proximal and distal segments of the dendritic branches also differed depending on the hemisphere. Proximal segments (near the cell body) develop early, with distal segments (far) appearing later in development. Proximal segments are longer in the right hemisphere, with distal segments more pronounced in the left hemisphere. The proximal/distal ratio appears complementary, where proximal segments are longer in the absence of distal segments. The importance of distance from the cell body in determining the role of the dendritic processes is unknown. However,

Scheibel (l990) does suggest that distinct dendritic processes in the two hemispheres are probably related to functional differences between the two regions.

Executive Functions

Studies have also focused on the neurobehavioral correlates of frontal lobe development, specifically the emergence of "executive" functions (e.g., planning, flexibility, inhibition, and self-monitoring) that have been attributed to this area. Whereas prefrontal regions have been hypothesized to be involved primarily in executive functions, striatal regions also have been investigated (Castellanos et al., 1996; Semrud-Clikeman, Pliszka, Lancaster, & Liotti, 2006). Because there are rich connections between the frontal lobes and striatal regions (Semrud-Clikeman et al., 2006), it is reasonable to believe that these two areas are intimately involved in executive functions.

It has been strongly suggested that executive functions are subdivided between the dorsal frontal, lateral frontal, and orbital frontal anatomical regions. The dorsal frontal region may be responsible for determining how important a situation is; the lateral frontal is involved in determining if the selected action is worth the effort needed to obtain the result; and the orbital frontal is responsible for determining the social and situational appropriateness of actions. Thatcher (1991) suggests that the interaction of these three functionally relevant areas provides the behavior known as executive function.

In keeping with our transactional model, Denckla (2007) suggests that executive functions have two influences, one neuroanatomical and the other "psychodevelopmenta1," and that these influences not only interact, but also modify each other. For example, Denckla (2007) cites the example that construct validity of executive action is demonstrated by convergent (a child of X age can do this when he or she can do that) and divergent (a child of X age can do this, but not that) validity. Some suggest that the frontal lobes of children develop rather markedly between the ages of four and seven years, with steady but less dramatic increases from 12 years of age to adulthood (Luria, 1980). Others suggest that development of executive functioning begins in adolescence and continues up to about 24 years of age (Pennington, 1991). Still others suggest that the frontal lobes develop in cycles rather than with variable development between the hemispheres (Thatcher, 1996).

Experimental studies have shown that children do exhibit behaviors thought to be mediated by the frontal lobes much earlier than adolescence or adulthood. Similar to Denckla's (2007) convergent/divergent validity approach to executive functions, Becker, Isaac, and Hynd (1987) found age variation in skill attainment. Skills thought to be mediated by the frontal lobes were found to be mastered by 10- and 12-year-olds; these included the capability of inhibiting motor responses, remembering the temporal order of visual designs, using strategies for memory tasks, attending to relevant details and ignoring distractors, and employing verbal mediators to enhance performance. Six-year-olds had more difficulty inhibiting motor responses and remembering the temporal order of visual designs. There appeared to be a developmental shift for eight-year-olds, who were able to inhibit motor responses. While subjects at all age levels were able to verbalize directions, younger children, especially those under the age of eight, were not always able to inhibit perseverative responses.

Passler, Isaac, and Hynd (1985) also found that children progress through developmental stages showing mastery of some frontally mediated tasks at six and eight years, while other tasks were not even mastered at the age of 12. Six-year-olds gave flexible, correct responses for a verbal conflict task, but were unable to respond accurately to a nonverbal conflict task. Although eight-year-olds mastered both tasks and were also able to complete a perseveration task, they were unable to complete a series of drawings consistently or to respond correctly to verbal and nonverbal proactive inhibition tasks. Finally, even the 12-year-olds did not obtain full mastery of the verbal and nonverbal retroactive inhibition tasks.

Taken together these findings suggest that the greatest period of development for executive functions occurs between the ages of six and eight, with continued growth beyond the 12-year-old level for more complex tasks. Supporting these findings, children have been found to reach

adult levels of performance by 10 years of age on measures of cognitive flexibility (the Wisconsin Card Sorting Test), but did not reach adult levels of performance on a word fluency test even by the age of 17.

Emotional Functions

Models of the neuropsychological basis of emotions indicate that the frontal lobes play a central role in the processing of emotional responses (Semrud-Clikeman, 2007). The two hemispheres appear differentially involved in adults, with damage to the left hemisphere resulting in depression and catastrophic reactions; whereas damage to the right hemisphere results in inappropriate emotional reactions, including indifference or euphoria (Heilman, Blonder, Bowers, & Valenstein, 2003). Developmental patterns have documented that the left hemisphere may be more reactive to emotional stimuli in younger children (9 years of age) than adolescents (14 years of age) and adults (Davidson, 1994). As the right hemisphere matures, it has a modulating effect on the more reactive left hemisphere (Heilman, Watson, & Valenstein, 2003). Moreover, as the corpus callosum matures, the right hemisphere can inhibit or control the left hemisphere more effectively. Thus, depression in children and adults may be a function of underactivation of the frontal regions, or the right hemisphere may be overactivated. It may well be that it is the ratio of activation between the two hemispheres that is important rather than the level of activation of either one. Neurodevelopmental patterns may help to explain why depression seems to increase around puberty, which corresponds to the time when later-developing corpus callosal structures are becoming mature (Zaidel et al., 2003). The temporal lobes may also be important for the perception of emotions (e.g., facial or tonal), and differences between the anterior/posterior regions may be just as important as the right/left hemisphere differences in the control of emotions. For example, posterior regions of the temporal lobe are important for recognition of facial expressions while anterior regions may be implicated in understanding and recalling the labels for such expressions (Semrud-Clikeman, 2007).

Parietal Lobe Maturation

Although it is assumed that the sensory systems are functional prior to birth, very little is known about tactile-sensory development. Whereas evidence suggests that somesthetic senses are the first to develop embryonically, the course of development in infancy and early childhood is less understood. Proton magnetic resonance spectroscopy technology has been used to measure brain metabolism in order to determine regional differences in brain development from childhood into early adulthood (Hashimoto et al., 1995). There was a significant correlation between age and metabolic activity in the right parietal regions, suggesting rapid brain maturation in this region from one month up to the age of two or three years. The frontal regions showed less metabolic activation during the same time frame, suggesting slower development of these regions. The frontal lobes, dense with gray matter, are slower to myelinate and to form synaptic and dendritic connections than the more posterior brain regions.

The course of development for tactile perception has been most thoroughly researched for hemispheric asymmetries. Tactile form perception increases with age (from 8 to 12 years); children usually show a slight superiority in scores using their preferred hand (dominant hand), and scores on the non-preferred hand were much more variable than on the preferred (Baron, 2004). For the 12- to 14-year-old group, children show a more even range of scores and reach adult-like performance on these measures. Tactile finger localization develops more slowly, and most preschool children are unable to name or point to the finger that has been touched (Baron, 2004). This is a difficult task for most seven-year-old children, but by the age of nine few errors are present. When errors do appear, they occur more frequently on adjacent fingers (37.5%), which is four times higher than for adults. Thus, children respond differentially to tactile localization tests on the right and left hands, depending on the type of response mode required (Baron, 2004). Verbal responses seem to increase accuracy when identifying touch to the right hand, whereas nonverbal responses enhance accuracy with the left hand. Witelson and Pallie (1973) found that children do recognize nonsense forms better with the left hand, but recognition of letter shapes does not appear to have a right or left hand advantage.

Occipital Lobe Maturation

The visual system is slow to develop in humans. Myelination of the optic tract is moderately developed at six weeks of age, but is heavily developed by three months (Brodal, 2004). The myelination of the optic radiation is somewhat slower, with minimal development at three months of age and mild development at six weeks. However, heavy myelination occurs in the optic radiation at about the same time as the optic tract. Developmental trends in visual asymmetries have also been investigated in children. Kolb and Fantie (1989) found that the right hemisphere may be specialized for facial recognition in children as young as four years of age, and shows a steady increase in accuracy up to age five, with slower acceleration after this age. Kolb and Fantie hypothesize that the structural hardwire of the brain is sufficiently mature by age five and that further growth in accuracy is dependent on experience. While the six-year-old is adept at facial recognition, matching expressions to situations is not well developed until about 14 years of age. This finding implies that the later task may also require frontal lobe maturation as well as posterior cortical development.

Temporal Lobe Maturation

Developmental patterns have also been investigated for hemispheric asymmetry in the temporal lobes. Asymmetries of the temporal lobe appear to have some relationship between cortical maturation and the development of the corpus callosum (Brodal, 2004). There is sufficient evidence that the left planum temporale is larger than the right and that these differences are present at birth (Witelson & Kigar, 1988). This developmental course is likely related to functional differences between the two hemispheres in their ability to process information. Infants appear to discriminate speech sounds early on, as young as 1–4 months of age (Molfese & Molfese, 2002). Further, researchers have found functional lateralization of the left hemisphere for speech sounds in infants (Molfese & Molfese, 2002) and for music and non-speech sounds in the right hemisphere in infants. See Table 3.2 for a summary of developmental ages when asymmetry between the two hemispheres appears.

Rosen, Galaburda, and Sherman (1990) investigated the ontogeny of lateralization and have generated hypotheses about the mechanisms of asymmetry. In these studies, symmetry in the brain was found to be related to the size of the planum temporale in the right hemisphere. In brains with normal patterns of asymmetrical organization, there was a corresponding decrease in the size of the right hemisphere. This correspondence was not observed in brains that were symmetrical, as there was an abundance of neurons in the temporal regions of the right hemisphere. Further, the corpus callosum in symmetrical brains is larger than in those with normal patterns of asymmetry (Rosen et al., 1990). Rosen et al. (1990) hypothesize that this variation in volume is likely a result of "pruning" of the axons in the corpus callosum that takes place in early developmental stages. Asymmetry may be related to withdrawal of neurons in the corpus callosum, while ipsilateral connections are maintained. Numerous factors impinge upon normal brain development, affecting the manner in which neural systems function and how traits and behaviors are expressed. Genetic as well as environmental factors influence neurodevelopment. These factors will be reviewed briefly in the following sections.

How Genetic Factors Influence Development

Brain development appears to follow relatively fixed sequences of growth and changes in the biological processes that are genetically specified. Defects in the genetic program, intrauterine trauma (e.g., toxins), or other factors can result in serious malformations in brain size and structural organization. See Table 3.3 for a summary of these neurodevelopmental abnormalities.

Cell migration, axonal dendritic formation and growth, synaptic development, and myelination appear compromised. These neurodevelopmental anomalies produce a variety of functional/behavioral deficits, ranging from life-threatening to severely symptomatic to asymptomatic. While a

Table 3.2 Developmental milestones for functional asymmetry and cerebral Lateralization

Functions	Age	Hemisphere	Reference
Motor			
Thumb sucking, right hand preference	15-week fetus	Left	Hepper, Shahidullah, and White (1991)
Head turning[a]	Birth		
Reaching	4 months	Left	Young et al. (1983)
Passive holding		Right	
Moving pegs	3 years	Left	Annett(1985)
Finger tapping	3–5 years	Left	Ingram(1975)
Strength		Left	
Gestures		Left	
Auditory			
Syllables	21 hours	Left	Molfese and Molfese(1979)
Speech	>24 hours	Left	Hammer(1977)
White noise	>24 hours	Right	
Speech sounds	1 weeks–10 months	Left	Molfese, Freeman, and Palermo (1975)
Speech (CV)	22–140 days	Left	Entus(1977)
Music sounds	22–140 days	Right	
Conversational speech	6 months	Left	Gardiner and Walter (1977)
Name of child	5–12 months	Left	Barnet, Vicenti, and Campos (1974)
Visual			
Light flashes	2 weeks	Right	Hahn (1987)
Photography of Mom	4 months	Right	de Schonen, Gil de Diaz, and Mathivet (1986)
Patterns			
Global form	4–10 months	Right	Deruelle and de Schonen (1991)
Tactile			
Dichaptic	4–5 years	Right	Klein and Rosenfield (1980)
Emotions			
Approach expression to sugar H_2O	2 days	Left	Fox and Davidson (1986)
Facial expressivity	Infants	Right	Best and Queens (1989)
Happy facial expressions	10 months	Left	Davidson and Fox (1982)
Crying with separation from Mom	10 months	Right	Davidson and Fox (1989)
Discriminate	5–14 years	Right	Saxby and Bryden (1985)
Emotional faces			
Emotional tones	5–14 years	Right	Saxby and Bryden (1984)
Emotional reaction	9 years	Left	Davidson (1984)
to negative expression	12 years	Right	

[a]Head turning correlated to same side as thumb sucking at birth.

number of these anomalies are related to defects in embryogenesis (dysplasias, agenesis of the corpus callosum, malformations of the cortex, etc.), both genetic and environmental factors appear to be causative factors. The extent to which other childhood and adolescent disorders, particularly dyslexia and schizophrenia, are genetically transmitted has been investigated. Developmental dyslexia has been the focus of studies demonstrating autosomal dominant (generation to generation) inheritance (Pennington, 2002). Volger, DeFries, and Decker (1984) found that less than half of persons with dyslexia have parents with a history of reading problems. According to Gilger, Hanebuth, Smith, and Pennington (1996), the genetic linkages will likely increase when cases of dyslexia resulting from injury or environmental damage are excluded from studies. Lubs et al. (1991) conclude that "developmental dyslexia is a heterogeneous group of disorders, some of which are inherited" (p. 74).

Malaspina, Quitkin, and Kaufman (1992) indicate that a number of other neuropsychiatric disorders of childhood and adolescence have a genetic component. Individuals with an affected relative

Table 3.3 Neurodevelopmental abnormalities associated with neurogenesis or abnormal neural migration

Abnormalities	Symptoms	Possible Causes
Size		
Micrencephaly	Brain is smaller than normal. Involves cognitive deficits, epilepsy.	Genetic, malnutrition, inflammatory diseases (e.g., rubella), radiation, maternal exposure to poisons
Megalencephaly	Brain is larger than normal. Intelligence ranges from subnormal to gifted, behavioral deficits.	Genetic
Abnormal tissue growth		
Holoprosencephaly	Hemispheres fail to develop. Single hemisphere or ventricle is present. Medical problems (e.g., apnea, cardiac) exists. Mental and motor retardation are present.	Neurotoxicity, genetic (trisomy 13–15)
Agenesis of corpus callosum	Corpus callosum fails to develop (partial or complete). Linguistic and intellectual deficits are present. Found with other neurological disorders (i.e., hydrocephaly, spina bifida).	Genetic
Cerebellar agnesis Cerebellum fails to develop		Genetic
Cortical malformations		
Lissencephaly	Sulci and gyri fail to develop. Found with agenesis of corpus callosum. Severe mental retardation, epilepsy. Early death.	Etiology unknown
Micropolygyria or polymicrogyria	Numerous small, and poorly formed gyri. Severe retardation to LD.	Intrauterine infections
Abnormalities with hydrocephaly		
Dandy-Walker malformation	Cerebellar malformations, with fourth ventricle enlargement. Other abnormalities (e.g., agenesis of corpus callosum).	Genetic
Abnormalities in neural tube and fusion		
Anencephaly	Hemispheres, diencephalon, and midbrain fail to develop.	Genetic
Hydranencephaly	Hemispheres fail to develop, CDF-filled cystic sac. Looks like hydrocephaly early. Appears normal at birth.	Umbilical cord strangulation. Vascular blockage, ischemia
Porencephaly	Large cystic lesion (bilateral). Mental retardation, epilepsy. Agenesis of temporal lobe. Early death.	Neonatal hemorrhaging following trauma, ischemia
Spina bifida	Neural tube fails to close. Skeletal, gastro-intestinal, cardiovascular, and pulmonary abnormalities, bulging dura mater.	Maternal fever, virus, hormonal imbalance, folic acid deficiency

Source: Adapted from G. W. Hynd and W. G. Willis, *Pediatric Neuropsychology*, Table 4.1, pp.73–77. Copyright © 1988 by Grune & Stratton, Orlando, Florida. Adapted by permission of The Psychological Corporation, Orlando, FL 32887.

seem to be at a higher risk of also developing some disorders, including a 45 percent morbid risk for dyslexia;, a 50 percent morbid risk for Gerstmann-Straussler syndrome (degenerative disease with motor signs and dementia), acute porphyna (motor neuropathy with psychiatric features), and myotonic dystrophy (motoric, intellectual, and psychiatric deterioration); a 25–50 percent risk for leukodystrophy (hyper- or hypotonicity with psychotic symptoms); a 25 percent risk for Lesch-Nyhan syndrome (spastic and movement disorders with retardation); a 24 percent risk for Wilson disease (liver disorder with neuropsychological symptoms); a 12.8 percent risk for schizophrenia; an 8 percent risk for bipolar disorders; a 4 percent risk for epilepsy, and, a 3.6 percent risk for Tourette syndrome (major behavioral disorder with motor and vocal tics). See Malaspina et al. (1992) for an

in-depth discussion of the epidemiology and genetic transmission of these and other neuropsychiatric disorders.

The specific abnormal gene(s) involved in these disorders are unknown; further, the role of environmental factors in the expression of these illnesses cannot be overlooked (Malaspina et al., 1992). Even when single autosomal genes are known, the exact nature or presentation of various disorders is unknown. Variable expression of neuropsychiatric disorders depends on a variety of factors, including age at onset of the illness. Further, it has been hypothesized that one genotype may result in multiple phenotypes or vice versa. The latter situation, where one phenotype arises from several genotypes, seems most likely for disorders with heterogeneous etiologies. For example, similar genetic inheritance seems to be present between schizophrenia and bipolar disorders. The critical point at this juncture is that the systematic linking of hereditary factors with environmental factors will likely be useful in advancing our understanding of childhood disorders. Given the importance of environmental and biological interactions for the expression of different types of behavior, it is important to briefly review this transactional aspect.

Biological and Environmental Factors

It has long been recognized that biogenetic (e.g., chromosomal abnormalities), environmental factors, (e.g., pre- and postnatal toxins and insults), and birth complications all affect the developing brain. Traumatic brain injury at an early age and a lack of environmental stimulation are also known to have long-term affects on optimal brain development. Prenatal and postnatal factors known to have an impact on the developing brain will be briefly reviewed.

Prenatal Risk Factors

With the advent of X-ray technology in the 1920s and 1930s, it became apparent that the developing fetus was susceptible to various environmental agents known as *teratogens*. Critical periods during the embryonic (second to eighth week of development) and the fetal stage (9th week to birth) appear particularly susceptible to exposure of teratogens. The central nervous system appears to be particularly vulnerable from the 5th week of embryonic development up to birth. The most detrimental environmental influences affecting neurodevelopment prenatally include alcohol, narcotics, pollutants, maternal disease, and malnutrition (Streissguth et al., 2004)

Maternal Stress, Nutrition, and Health Factors

In addition to numerous prenatal factors that place the developing child at risk for neurological complications, maternal stress, malnutrition, poor health, and age also play a role in the ultimate expression of these risk factors (van den Bergh, Mulder, Mennes & Glover, 2005). Extreme maternal stress is known to increase levels of stress in the fetus and has been associated with low birth weight babies and irritable, restless, colicky infants. Maternal stress may create vasoconstriction reducing circulation that ultimately produces fetal asphyxia, which is known to cause brain damage in the developing fetus. Some findings have indicated that prenatal stress may have long-term consequences with problems in coping and learning, particularly for males, and an increased incidence of mood disorders and schizophrenia (King, Laplante, & Joober, 2005; Mueller & Bale, 2007).

Maternal Nutrition

Nutritional deficiencies during the last three months of fetal life and during the first three months of infancy also can have severe effects on the developing brain, particularly seen as a decrease in the number of brain cells and brain weight (Walker, Thame, Chang, Bennett, & Forester, 2007). Although proper maternal nutrition can reverse infant mortality rates (Morton, 2006), the affects of pre- and postnatal malnutrition on the child's intellectual and behavioral development require additional study.

Maternal Health

Maternal health during pregnancy is generally monitored to ensure normal fetal development. Maternal hypotension may have an adverse affect on the fetal brain as it may result in circulation failures in the developing brain (Martens et al., 2003). Fibromyeline plaques or lesions form in cortical areas called "watershed regions." These ischemic-induced alterations, caused by a temporary loss of blood (perfusion), have been found in the brains of individuals with dyslexia (Duane, 1991).

Ischemia may also be induced by maternal or fetal autoimmune mechanisms. The extent to which these morphological variations are related to or contribute to reading disability will be explored in later chapters. The important point here is that maternal health directly affects the developing fetal brain. Glial cells and specific molecules that direct the migration of cells may be involved in such a way as to alter the cortical architecture of the child's brain (Duane, 1991).

Another maternal health factor that has known effects on the developing brain is rubella (German measles), which often results in deafness in babies if the mother contracts this disease in the first trimester of pregnancy. Eye and heart involvement are other likely outcomes if rubella occurs in the first eight weeks of pregnancy, whereas deafness is more likely to occur if the illness occurs between five and 15 weeks. Maternal herpes simplex 2 is also known to produce mental retardation and learning difficulties because this virus attacks the developing central nervous system of the fetus (Hutchinson & Sandall, 1995).

Concerns have recently been raised about the effects of acquired immune deficiency syndrome (AIDS) on the developing fetus. In the past birth defects including microcephaly as well facial deformities were found with mortality frequently present within five to eight months of symptom onset (Cotter & Potter, 2006). Prior to the new drug regimes, central nervous system involvement was found to be as high as 78–93 percent of children with human immunodeficiency virus (HIV), with signs of motor, visual-perceptual, language, and reasoning delays (Cotter & Potter, 2006; Suy et al., 2006).

Mothers who are likely to contract AIDS often come from high risk populations, including intravenous drug abusers, so other health factors may play a role in the manifestation of symptoms. The extent to which other psychosocial factors play a role in the long-term outcome for children with congenital HIV infection needs further study. When health, poverty, and psychological factors are controlled, infants born to teenagers and mothers over 35 do not appear to be at higher risk for complications (Cotter & Potter, 2006).

Maternal Alcohol Addiction

Heavy maternal alcohol consumption has serious consequences for the developing fetal brain, whereas the effects of drug addiction are less clear (Streissguth et al., 2004). Fetal alcohol syndrome (FAS) occurs frequently in infants born to alcohol-dependent mothers, and estimates suggest that 40,000 children are born with alcohol-related birth defects every year (Streissguth et al., 2004). Characteristic symptoms in children with FAS include pre- and postnatal growth delays; facial abnormalities (e.g., widely spaced eyes, shortened eyelids, small nose); mental retardation, and behavioral problems (e.g., hyperactivity and irritability). Central nervous system symptoms early in life include brain wave abnormalities, impaired sucking responses, and sleep problems, with attentional, behavioral, motor, and learning problems developing and continuing into later childhood (Streissguth et al., 2004). The developing fetal brain is highly susceptible to alcohol damage, and pregnant mothers are advised to eliminate alcohol consumption entirely (U.S. Surgeon General, 2005). Even moderate alcohol consumption (i.e., one to two drinks a day) in mothers who are breast-feeding can produce mild delays in motor development, including crawling and walking delays (Little, Anderson, Ervin, Worthington Roberts, & Clarren, 1989). Although not all children are equally affected, maternal alcohol consumption during pregnancy and lactation is definitely a risk factor, with deleterious affects on the developing brain.

Drugs

Infant and fetal central nervous system signs have been shown to result from heavy maternal consumption of drugs during pregnancy, including marijuana,

cocaine, and heroin. Physical signs (i.e., low weight and premature infants), neurological complications, and central nervous system involvement (e.g., tremors and startles) have been found in infants born to mothers with high marijuana usage (Leech, Larkby, Day, & Day, 2006; Noland, Singer, Mehta, & Super, 2003). Cocaine use appears to affect blood flow into the placenta and may affect neurotransmitters in the fetal brain (Snow et al., 2004) Infants born to mothers who use cocaine are at risk for various complications, including spontaneous abortions, prematurity and low birth weight, small head size, and behavioral symptoms (lethargy, unresponsiveness, irritability, and a lack of alertness) (Snow et al., 2004). Leech et al. (2006) described the social interaction and play characteristics of children with intrauterine cocaine exposure. Drug-exposed toddlers were more disorganized, showed signs of abnormal play patterns, showed higher rates of depression and anxiety, and had trouble interacting with peers and adults. Dow-Edwards et al. (2006) also suggest that cognitive and behavioral problems in cocaine-exposed children may not be obvious until later childhood, when damage to frontal lobes and basal ganglia is evident. The long-term effects of cocaine use on the developing brain are difficult to differentiate from the effects of other environmental conditions that might accompany maternal drug use. However, mother-child and child-peer relationships are at risk because infants with symptoms previously described often have trouble with bonding and attachment. Maternal drug addiction may seriously interfere with the mother's ability to care for her infant properly.

Heroin addiction during pregnancy produces risk factors including high mortality rates, prematurity, malformations, and respiratory complications (Burns, Mattick, Lim, & Wallace, 2007) Infants display withdrawal symptoms at birth (tremors, vomiting, fevers, etc), and even though these decrease within months, mothers often have difficulty coping with the behavioral problems (i.e., irritability) that persist in heroin-exposed infants

Postnatal Risk Factors

Many of the prenatal risk factors mentioned previously (infant nutritional deficiencies, maternal stress, etc.) continue to have an effect on the developing brain in the postnatal period.

Nutritional Deficiencies

Although it is often difficult to isolate the effects of nutritional deficiencies from other socioeconomic complications, severe vitamin deficiencies have a direct influence on the developing brain (Lesage et al., 2006). Hypo- or hypervitaminosis A can lead to developmental and learning disabilities as well as problems with motor, balance, eye problems and mood and emotional disturbance (Marx, Naude, & Pretorius, 2006). Vitamin B depletion can produce neurologic symptoms including ataxia, loss of equilibrium, and impairment of righting reflexes. Neurons and the myelin sheath can be destroyed, moving from peripheral to central brain regions. Thus, numbness and other sensorimotor symptoms appear as early signs (e.g., tingling, muscle tenderness with mental confusion, and learning and memory problems appearing in later stages) (Yoshihiro et al., 2006). Vitamin B_{12} and folic acid deficiencies also have been implicated in structural changes in myelination. Further, low levels of folic acid caused by nutritional deficiencies in breast milk may delay the normal course of EEG development in infants. Other postnatal factors have been known to have long-standing effects on the developing brain, including birth complications, traumatic brain injury, exposure to environmental toxins, and lack of environmental stimulation. The way in which these factors affect the developing brain will be reviewed briefly.

Birth Complications

Birth complications during labor and delivery often produce neurological insults that have been associated with numerous childhood disorders, including psychiatric disorders (Akerman & Fischbein, 1991; Raine, 2002). Of particular concern are complications resulting in significant or prolonged loss of oxygen to the fetus. During the normal delivery process, contractions constrict the placenta and umbilical cord reducing the amount of oxygen to the fetus. In extreme situations, infants produce

elevated levels of stress hormones to counterbalance oxygen deprivation and to ensure an adequate blood supply during delivery. Neurological insults are known to follow extreme oxygen deprivation, so electronic fetal monitoring provides vital information about the fetal heartbeat and oxygen level.

A number of birth complications have been found in adults with psychotic symptoms that are consistent with schizophrenia, including long labor, breech presentation, abruptio placenta, neck knot of the umbilical cord, Apgar scores under six, vacuum extraction, meconium aspirated, large placenta infarcts, birth weight under 2,500 or above 4,000 grams, and hemolytic disease (Nasrallah, 1992; O'Reilly, Lane, Cernovsky, & O'Callaghan, 2001).

Environmental Toxins

Exposure to lead, even in low levels, can produce a variety of cognitive and behavioral problems in children (Freeman, 2007). Children with acute lead encephalopathy present severe symptoms, including seizures, lethargy, ataxia, nerve palsy, intracranial pressure, and death in some cases (25%) (Ris, Dietrich, Succop, Berger, & Bornschein, 2004). In about 20–40 percent of cases, children develop epilepsy, severe motor symptoms (hemiplegia and spasticity), and blindness. Inattention and hyperactivity are also known sequelae of lead exposure, although this relationship is not as strong in cases with lower level exposure (Wigg, 2001).

Environmental Stimulation

Postnatal stimulation is a critical factor affecting brain development and the child's capacity for learning. Although the infant appears genetically programmed for many abilities (e.g., sitting, walking, talking), the role of the environment can affect maturation rates in some areas (e.g., vision). Babies who are well-nourished, receive maternal attention and care, and are allowed physical freedom to practice and explore generally will show normal motor development. In extremely deficient environments (e.g., orphanages), motor delays have been documented.

Although infants are born with the ability to learn, learning occurs through experience. Language development, intellectual capacity, and social adaptations are influenced by the environment. The way mothers interact with, talk to, and respond to their infants affects their ability to develop into competent children. However, there appears to be interplay among these genetic-environmental influences. Children evoke differential responses from individuals in their environment depending on their behavior. These responses can reinforce original predispositions and result in more positive interactions with adult caretakers. Infants are highly responsive to attentive, warm, stimulating environments that encourage self-initiated efforts. Inadequate early environments can have a negative impact on a child's early development, but children can recover if they are placed in more responsive environments before the age of two years.

Summary

Neurodevelopmental investigations are beginning to explore how changes in brain structures are related to cognitive development, but this undertaking is far from complete. Further, this area of investigation should be viewed as exploratory and as an emerging field of study that no doubt will evolve with more research and better techniques of inquiry. The extent to which morphological differences are related to various behavioral deficits found in children with learning and reading deficits will be explored in more detail in subsequent chapters. How environmental factors interact with neurodevelopment and cognitive-behavioral development is also critical. Finally, this chapter provided information about genetic, environmental, and psychosocial differences that can affect brain development. In pediatric neuropsychology the assessment almost always includes the caretakers and the family unit. Providing services to children requires the family's participation in treatment and support. All neuropsychologists should understand the impact that family dynamics, family situations, and stresses present during gestation and childhood can have on a child's neurological development. To that end, this chapter sought to provide an overview

of some of the most important aspects of which to be cognizant when working with children and their parents.

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