Chapter 4

The Developing Brain and Nervous System: Health and Risk

CHAPTER OUTLINE AND OVERVIEW

Measuring Brain Activity	*What are the current ways to study infant brain activity?*
Basic Structures of the Nervous System	*What are the two types of brain cells and how do they function? What are the main anatomical regions and physiological properties of the brain and nervous system?*
Prenatal and Infant Brain Development: A Critical Period	*Why is the prenatal and first three years of life a critical period for brain development? What parts of the brain and nervous system are developing the most rapidly during this period?*
Optimal and Non-Optimal Brain Development During Infancy	*What are the effects of the environment on brain development? What are the best ways to promote brain development in infancy?*

Brain development in the fetal and infancy periods is a new frontier of infancy research. **Developmental neuroscience** is the study of the developing brain and nervous system as it relates to psychological and behavioral functions such as moving, thinking, and feeling. In this chapter we will review the structure and function of the nervous system, including the brain. This is followed by a review of some of the developmental processes that explain why the fetus and infant are undergoing a critical period for brain development, meaning that the environments to which they are exposed during this period will have a lifetime impact on brain function. Finally, the impact of the environment on the developing brain is discussed, including understanding what types of environment are most conducive to healthy brain development. The primary references used in this chapter include publications related to the developing brain and nervous system (Ferre, Lopez, & Haggard, 2014; Fogel, 2013; Gao et al., 2016; Hodel , 2018; Keunen, Counsell & Benders, 2017 ; Mulkey & du Plessis, 2019; Stiles, Brown, Haist & Jernigan, 2015; Stiles et al., 2015).

MEASURING BRAIN ACTIVITY

The increased interest in the early development of the nervous system is partly due to the rise of new methods for monitoring brain activity that have allowed clinicians to diagnose abnormal brain function at younger ages. These methods have given researchers a new window on the neural processes that underlie normal behavioral development. **EEG** (electroencephalography) can be used to measure brain electrical activity on the surface of the scalp (Bernier, Calkins, & Bell, 2016). EEG measures brain electrical waves, where a higher amount of neural activity relates to increased EEG power. However, complex computations are required to ascertain where in the brain neural activity is originating (Hodel, 2018). **MEG**, magnetoencephalography, works in a similar way but uses magnetic fields rather than electrical activity. Both procedures provide detailed information on the timing of early brain activity. Similar to EEG, however, MEG cannot locate particular structures within the brain; however, it is less distorted by surrounding tissue (Lopes da Silva, 2013). This makes MEG useful for studying fetal brain activity on the surface of the mother's abdomen, through layers of maternal and fetal tissue (**fMEG**; Sheridan et al., 2010). This method has also been used to detect changes in brain activity that reveal learning in the fetal brain (Chapter 3). For example, fMEG has been used to document habituation in fetuses (in the third trimester) and newborns (Muenssinger et al., 2013).

There are also several methods that can track the locations of activated structures deep inside the brain. **MRI** (magnetic resonance imaging) and **fMRI** (functional magnetic resonance imaging) both utilize magnetic fields to image the infant brain. MRI produces a static image that can be used to detect differences in brain structure between different groups of infants (Hazlett et al., 2017). fMRI detects where blood is exchanging oxygen in the brain, an indicator of which brain regions are active. Thus fMRI can show changes in the infant brain over time; for example, when infants are asleep. Although MRI and fMRI require lying in complete stillness inside of a very noisy tube, studies with infants are conducted successfully utilizing these techniques (Gao et al., 2016; Hazlett et al., 2017; Keunen, Counsell, & Benders, 2017). A very useful technique for active babies is **fNIRS** (functional near infrared spectroscopy), which can also find the spatial location of activation from blood flow changes. This method uses infrared light that can pass through skin and other tissue and can be used with infants who can be sitting up or on the lap moving relatively freely (Emberson et al., 2017). Unlike fMRI, which requires special labs and expensive, heavy, stationary equipment, fNIRS probes easily fit over the head, do not

A child with an fNIRS probe.

Photo courtesy of the Princeton University Babylab, Sagi Jaffe-Dax.

require magnetic fields, and they are portable. Although fNIRS can only reach the upper layers of the cortex, the results compare well with adult fMRI data (Lloyd-Fox et al., 2014). PET (positron emission tomography) requires exposure to radioisotopes which can be detected in different regions of the brain that are active. Because of the radiation, it is not considered safe for research studies with infants. The main purpose of PET is to trace neurotransmitter activity (Grossman, 2013).

BASIC STRUCTURES OF THE NERVOUS SYSTEM

The Cells of the Nervous System: Neurons and Glia

Neurons are the information storage and transfer cells of the nervous system. *There are 86 billion (86,000,000,000) neurons in the adult human brain* (Voytek, 2013). Neurons process electrical and chemical information and transmit that information to other neurons. There are different types of neurons depending on their function in the nervous system, but they all have a similar structure, as shown in Figure 4.1. The cell body of the neurons code and transmit information in the form of electrochemical currents, called **action potentials**. Action potentials travel from the cell body along the **axons** to the axon terminals which can connect to other neurons. The axon transmits the cell's *action*.

The action potentials stimulate the production of neurochemicals at the junction between two neurons, the synapse. The **synapse** connects the axon terminals of the transmitting cell to the dendrites of the receiving cell, as shown in Figure 4.1. **Dendrites** (from the Greek word *dendron*, or tree) are the branching structures that receive information at the synapse from the axons of other neurons and transmit that information to the body of the connecting cell. Each neuron can connect to as many as 1,000 other neurons (more than 60 trillion interneuron connections!), creating a complicated and dynamic network that is responsible for sensing the environment and regulating thought, emotion, body function, and behavior, as well as creating the conscious experience of sensing and feeling the body, the self, and the external world.

Neurotransmitters. There are many types of neurochemicals exchanged between neurons that ultimately alter behavior and feeling states. In general, these chemicals produce either inhibition or arousal of brain function. **Serotonin**, for example, alters mood by creating a state of quiet alertness and feelings of well-being, but too little of it can lead to feelings of depression. Most drugs for treating depression increase serotonin levels. **Dopamine**, another common neurochemical, helps with control of attention and thought, feelings of pleasure and optimism, and regulation of movement. Too much dopamine can create thought disturbances like those found in schizophrenia, and too little may lead to movement disorders, such as Parkinson's disease. Other neurochemicals help or hinder vol-

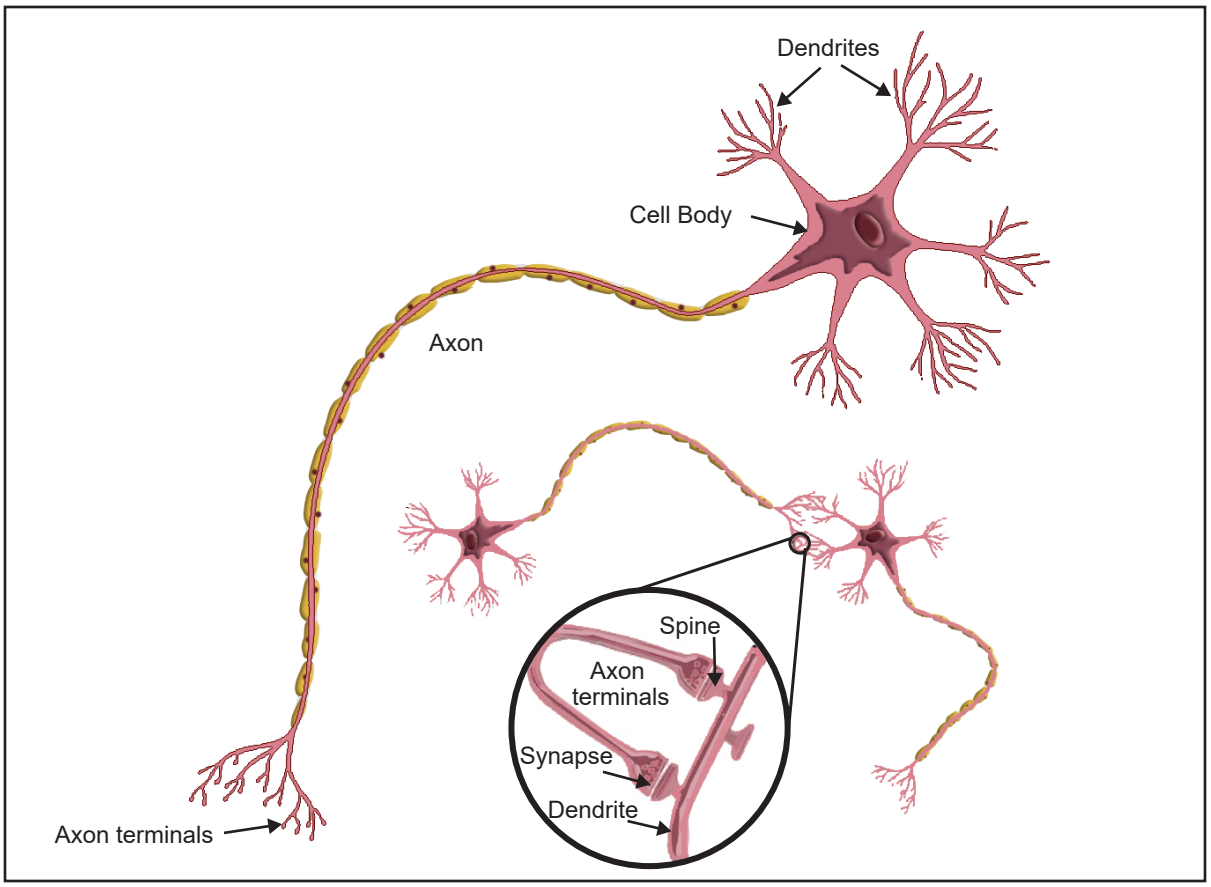

Figure 4.1 Brain Cells

Source: Adapted from Teylor and Chiaia, *A child's brain* (ed. M. Frank). New York: Haworth Press, 1984.

untary movements, sleep-wake cycles, sexuality and reproduction, the ability to form memories, emotional processing, and stress regulation.

Different types of neurons. Neurons are found all over the body, not only in the brain and spinal cord. **Afferent neurons** send signals from inside and outside the body to the brain, meaning that they transmit to the brain how things are *affecting* us. Far from the brain, the ends of afferent neurons contain specialized receptors. Receptors are found in the sense organs of the body and translate physical information into neurochemical information that can be sent to the spinal cord and brain for processing. Light, sound, pressure, and temperature, for example, are translated into neurochemical information by receptors in the eyes, ears, and skin. There are also receptors that sense the inner condition of the body including muscle stretch, balance and orientation in space, hunger, thirst, fatigue, itchiness, gut distension, sexual feelings, pleasure, and pain. These neurons related to the inner condition of the body form a crucial part of our sense of self.

The vast majority of neurons are in the spinal cord and brain. These **processor neurons** analyze the stream of afferent information coming from the receptors for the purpose of responding to these signals coming from outside and inside

the body. The brain's responses are then sent to efferent neurons which are directly connected to muscles that alter or *affect* internal and external behavior. **Efferent neurons** are found in the gut to regulate digestion, in the heart and blood vessels to regulate circulation, in the lungs and diaphragm for breathing, and in the muscles that regulate movement. For a newborn to get milk from a nipple, for example, many muscles in the head, neck, face, lips, jaw, throat, and gut need to be coordinated to allow for sucking, swallowing, and digesting. Tiny muscles behind the eyes allow the baby to look for the mother, and tiny muscles in the ears can tune hearing to the frequency range of human speech.

Glia. The other major group of cells in the nervous system is the **neuroglia**, or, more simply, **glia**. Like neurons, there are many different types of glia that serve different functions, all of which are especially important during fetal and infant brain development. Some glial cells provide oxygen and nutrients to the neurons via the bloodstream, and also remove waste products; these waste products include neurons that die due to lack of use. Other types of glial cells wrap around the axons to create a layer of insulation called **myelin**, a coating that improves the integrity and speed of conduction of electricity along the axon of the neuron. A final type of glial cell, the **radial glia**, provides a kind of scaffold of pathways along which neurons grow and migrate to their proper place within the brain during fetal development. Radial glia can help the infant brain to recover from injury (Jinnou et al., 2018). Radial glia hold neurons in place and are the origin of the term glia, which means "glue." Glia, however, do more than just glue neurons together, as we'll see when we return to the topic of brain development later in this chapter.

Anatomical Structures of the Brain

The human brain can be divided into three basic regions: the brain stem, the limbic system, and the cortex. The **brainstem** is located in the back of the head where it joins the neck and is connected to the spinal cord. Input from the brainstem is important for regulating responses to stress (Myers, Schiemann, Franco-Villanueva & Herman, 2017). The lower brain stem, which is called the *medulla*, regulates heart rate and blood pressure. The top of the medulla is connected to the *midbrain* (associated with sleep-wake cycles and motor control) by the *pons* (which controls breathing and sensory relays). The *cerebellum* is a bulb-like formation connecting the brainstem and brain that controls movement coordination (see Figure 4.2). The brainstem contains the roots of the afferent and efferent neurons of the **autonomic nervous system** which is responsible for regulating respiration, heart rate, blood pressure, sucking, swallowing, digestion, and sleep-wake cycles. These autonomic nerves, the ones that control all the internal organs of the body, come directly from the brain stem and travel down the neck and into the chest and abdominal cavities.

The autonomic nervous system. The autonomic nervous system has two branches: sympathetic and parasympathetic. The **sympathetic nervous system** prepares the body for action by elevating heart rate, increasing metabolism and respiration rate, creating a state of active alertness and vigilance, and temporarily suppressing digestion. It is responsible for expending the energy reserves in the body. The **parasympathetic nervous system** allows the body to relax, slow down, rest, digest food and information, engage socially with others, learn, and grow. It is responsible for building and storing the body's energy resources. Both of these systems are active in early infancy, and babies—as well as adults—need a balance of arousal and rest for healthy development. Regulation of the autonomic nervous system, specifically vagal control of the heart, is associated with higher levels of emotional self-regulation and social skills (Porges & Furman, 2011). As we'll see later, too much arousal and stress—in the absence of times for relaxation and recovery—can impair the developing nervous system (McEwen, 2011).

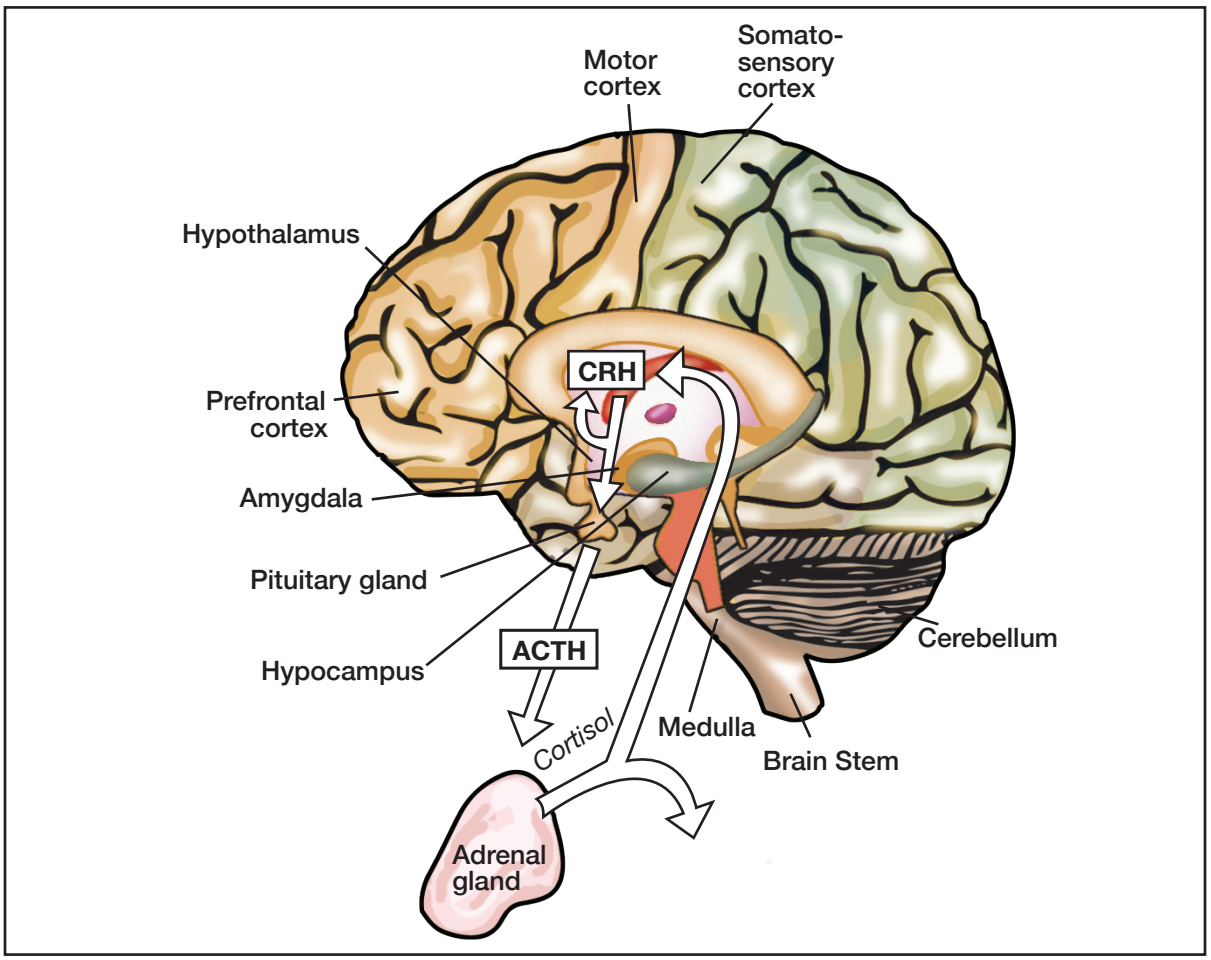

Figure 4.2 Brain structures that develop during infancy

The limbic system. The **limbic system** is located more or less in the center of the head, between the ears, and includes structures such as the amygdala, the hippocampus, the hypothalamus, and the pituitary gland (see Figures 4.2 and 4.3). This part of the brain is related to processes such as memory, regulation of states like sleeping and waking, breathing, temperature regulation, urinary and bowel control, emotion, and responses to stress vs. relaxation (Sokolowski & Corbin, 2012).

A number of structures within the limbic system are important for infant development. The **hippocampus** is a horseshoe-shaped structure (see Figure 4.3) that plays an important role in the formation of memories for events and sequences, known as **autobiographical memory**. Autobiographical memory is the ability to tell a story in words about oneself, and it does not begin until the third year of life and is underdeveloped until age five to seven (Bauer, 2015). The **amygdala** is a small bulb near the front end of the hippocampus (see Figure 4.3; amygdala means *almond* in Latin). There are two, a right and a left. The amygdala plays a role in the formation of emotional memories, especially those

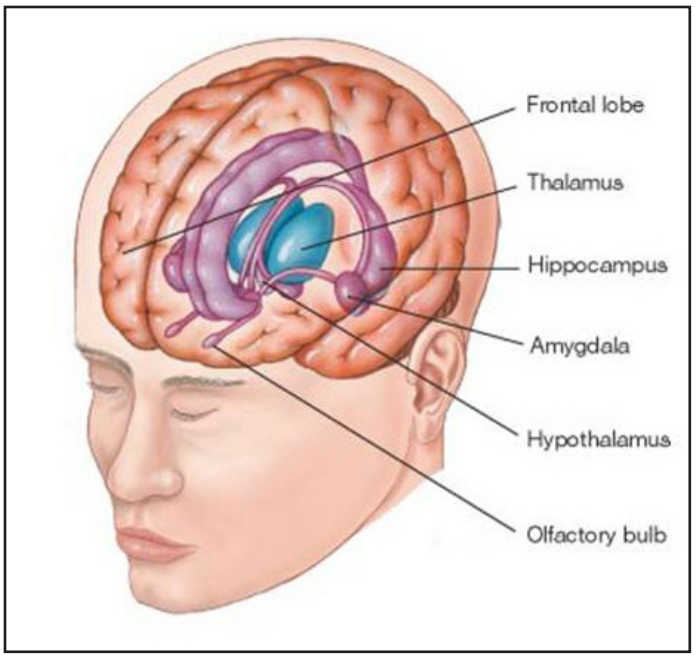

Figure 4.3 The limbic system of the inner brain.

related to fear and safety, and is functional at birth (Thomas et al., 2019).

The **hypothalamus** is a small structure in the lower-middle of the limbic system that links the brain to the endocrine (hormonal) system of the body via the pituitary gland and the blood stream. In response to stimulation coming from the body, the hypothalamus begins a cascade of hormones that activate the pituitary gland to release other hormones into the bloodstream. The **pituitary** is a hormone-producing endocrine gland. **Hormones** are neurochemicals that circulate in the bloodstream. Hormones can affect the regulation of body organs to activate digestion, sexual function, stress regulation and feelings of safety and comfort, milk production in nursing mothers, and cell growth throughout the body. By sending signals to the pituitary to secrete different hormones into the bloodstream, the hypothalamus also regulates the brainstem's responses to stress, body temperature, breathing and heart rate, hunger, thirst, and day-night rhythms. The hypothalamus, therefore, is very important in the early development of states of arousal (sleeping and waking), feeding (hunger and satiety), and self-regulation (calming distress) in the newborn period.

The HPA Axis. The hypothalamus, pituitary, and amygdala play a major role in the development of responses to stress and trauma, as explained below. When the amygdala senses threat or stress, it sends neurochemicals to the hypothalamus to activate the **HPA Axis,** the system by which threat/stress is translated into the release of hormones from the hypothalamus (via corticotropin-releasing hormone CRH) to the pituitary, from the pituitary (via adrenocorticotropin-releasing hormone ACTH) to the adrenal glands (located on top of each kidney, near the middle of the back), which results in the secretion of the hormone cortisol into the bloodstream (see Figure 4.2). **Cortisol** is a glucocorticoid steroid hormone and, as part of the sympathetic nervous system, prepares the body for action in response to stress. Cortisol—traveling via the bloodstream—also affects the neurons in the limbic system, where it heightens the formation of memories related to the stressful event, and

once that event has passed, slows down the production of cortisol via the HPA axis (Jiang, Tran, Madison, & Bakker, 2019).

Oxytocin. Hormones also play a role in regulating the autonomic nervous system to help us speed up or to slow down in response to events. The pituitary can also secrete the hormone **oxytocin** into the blood, which gives a feeling of warmth, comfort, and safety. Oxytocin is usually secreted when we are in close contact, or loving contact, or supportive touch, with another person (Uvnas-Moberg, Handlin, & Petersson, 2015). Oxytocin is associated with positive parenting behaviors, and oxytocin administered through the nose increases parental neural responses to infant crying and laughter (Feldman & Bakermans-Kranenburg, 2017). Administering oxytocin to fathers while they played with their infants corresponded with a subsequent increase in oxytocin in the infant, meaning that infant oxytocin levels can be increased without directly administering the drug (Weisman, Zagoory-Sharon, & Feldman, 2012). Oxytocin has been found to be directly related to empathy. In a study of youth from Israel and Palestine, two political groups currently at odds, youth had discussions with outgroup members and oxytocin levels increased after the discussion, but only in subjects who reported using perspective-taking, or empathizing with the outgroup member (Influs, Pratt, Masalha, Zagoory-Sharon, & Feldman, 2018).

Let's take breathing as one example of how this system works. The brain stem sends a signal—via the autonomic nervous system—to the lungs and diaphragm muscle to breathe in and out at a regular rhythm. The brain stem can also automatically adjust breathing to the level of physical exertion. The limbic system can override this simple automaticity of the brain stem, making us capable of further modulating that basic rhythm. Because of neural links between the amygdala and brainstem, we typically will hold our breath when feeling afraid, worried or anxious. We also typically relax our bodies and breathe a sigh of relief when we feel safe. The neural connections between the limbic system and brain stem function very rapidly to adjust breathing to the current physical and emotional demands (Masoaka, 2019).

The hormones that are released when feeling afraid (cortisol) or safe (oxytocin) further regulate the brainstem and body via the bloodstream. Hormones take more time to release and to dissipate, so they provide a longer term regulation of brainstem and body function. The limbic system functions automatically, like the brainstem, but it has more flexibility in regulating the body systems such as breathing in response to changing circumstances. The brainstem and the limbic system are the most functional areas of the brain at birth.

The cortex. Finally, the **cortex** (from the Latin word meaning the *bark* of a tree, Figure 4.4) is the outer layer of the brain. The cortex is the largest part of the human brain. It completely wraps around and covers the limbic system and forms synaptic connections with the limbic system. The cortex is divided into major anatomical regions called **lobes**. Starting at the back of the brain is the occipital lobe, which is where visual information is processed. The temporal lobes, one on each side of the brain and located just behind each ear, contain centers for auditory and speech processing. The temporal lobe also processes our sense of smell.

The parietal lobes sit on top of each side of the brain, adjacent to the temporal and occipital lobes and include the sensory and motor cortices. These cortices are connected to the muscles and sense organs of the body via the spinal cord and afferent and efferent motor nerves. Unlike the autonomic nervous system in which the nerves to and from the internal organs come directly from the brain stem, the sensory and motor nerves come from regions of the spinal cord located near the muscles and sensory receptors. The nerves for the muscles and sense organs for touch and pressure in the hand and arm come from the upper part of the spinal cord;

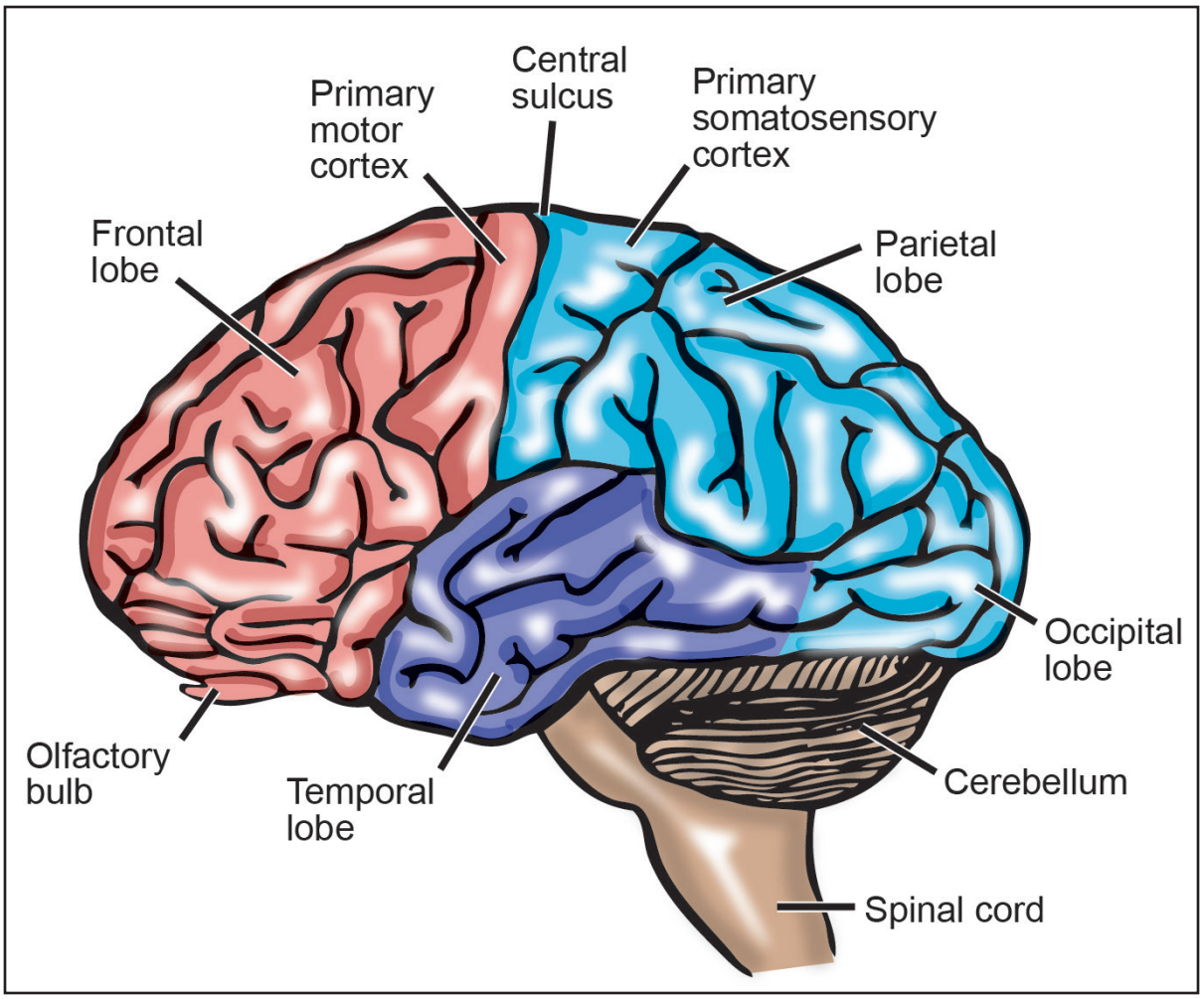

Figure 4.4 The functions of the major lobes of the brain's cortex.

those for the legs come from the lower parts of the spinal cord.

The parietal lobe is also a place where sensory and motor information from different parts of the body are integrated into a cohesive sense of our self in relation to the environment, called the **body schema** (Fogel, 2013). This includes our sense of movement and balance, our ability to locate particular parts of ourselves, to sense our body size and shape, and the awareness that our body has boundaries that separate us from other objects and bodies (Ferre, Lopez, & Haggard, 2014; Parkinson, Condon, & Jackson, 2010). The parietal lobes, sometimes in combination with the cerebellum at the base of the brain, allow us to integrate movement into a whole body functional pattern like reaching or walking, to sense our body's position in space, to tell the difference between our own movements and those of others, to feel the difference between touching ourselves and being touched by someone else, to distinguish our voice from voices of others,

and to know how to navigate safely as we move through the environment. As infants grow in their motor abilities over the first few years of life, this part of the brain is developing.

Another major anatomical area of the brain is the **insula** (or insular cortex, Figure 4.5). This is located underneath the temporal lobes, occupying a space between the temporal lobes and the limbic system. Related to the body schema which gives our sense of self in relation to the environment, the insula creates feelings of **interoception**, allowing us to *feel the inner condition of our bodies*, including the sense of hunger, thirst, itch, hot and cold, aches and soreness, pain, the need to urinate and defecate, and whether we are sick or healthy (Uddin, Nomi, Hebert-Saropian, Ghaziri, & Boucher, 2017). The insula plays a key role in social engagement and emotion. Dysfunction of the insula has been associated with symptoms of autism (Nomi, Molnar-Szakacs, & Uddin, 2019).

The frontal lobe (Figures 4.2 and 4.4) is located roughly above and behind the eyes. One important area of the frontal lobe is the prefrontal cortex. This is the most uniquely human part of our brain, which assists in reasoning, planning, organizing thoughts and behavior in adaptive ways, regulating emotions and urges, carrying out problem-solving, and making judgments. The prefrontal cortex also plays a role in inhibiting behavior, such as learning to wait for a meal instead of crying at the moment the infant

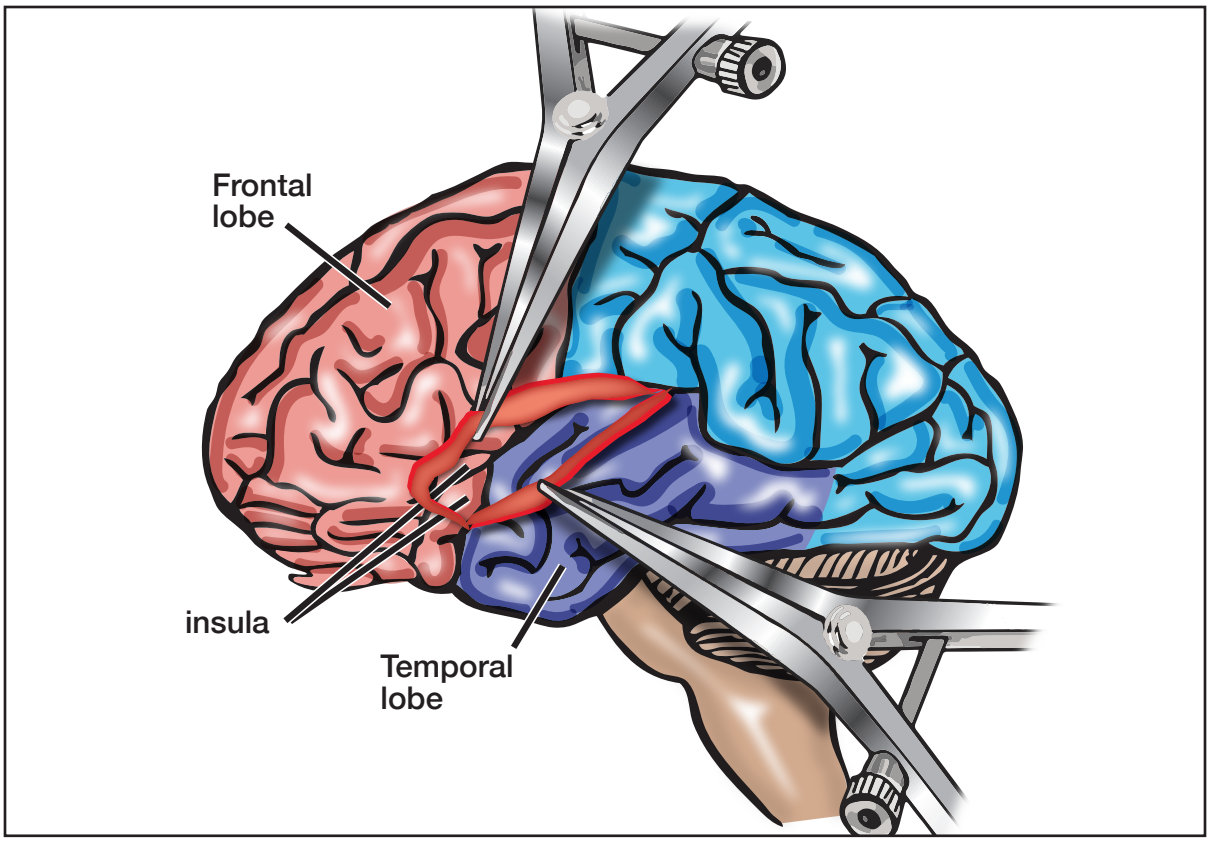

Figure 4.5 The insula, responsible for interoception, is located underneath the temporal lobes, occupying a space between the temporal lobes and the limbic system.

feels hunger (Rae, Hughes, Anderson, & Rowe, 2015). *The prefrontal cortex gives us the possibility of voluntarily (rather than automatically) regulating our body states and patterns of behavior*. Coming back to the example of breathing, the prefrontal cortex allows us to voluntarily hold our breath, such as when we swim underwater, or to voluntarily pace our breathing when we feel afraid.

The prefrontal cortex is composed of two areas, the medial prefrontal cortex (mPFC) and the lateral prefrontal cortex (lPFC). The mPFC connects to emotional processing areas such as the amygdala. hippocampus, and the sensory regions of the parietal lobes (Tottenham, 2017). The lPFC is connected to areas related to motor control (sitting still; Kramer et al., 2013). As early as the first month of life, the mPFC responds to infant-directed and emotional speech, pleasant smells, and a few months later to mutual gaze and familiar faces (Johnson, 2010). The mPFC responds to changes in serotonin, the neurotransmitter affecting mood, while the lPFC responds to dopamine, which regulates information and attention (Clos, Bunzeck, & Sommer, 2019; Puig & Gulledge, 2011). The lPFC responds to speech that is not directed to the infant and is not emotional, and to non-human objects (Grossman, 2013). The IPFC plays a role in holding objects in working memory and object permanence (Baird et al., 2002; Funahashi, 2017).

The two hemispheres. The brain is also divided into two halves, or hemispheres. The **right hemisphere** controls movements on the left side of the body (the right parietal cortex in particular). The right limbic sensory and prefrontal areas, as well as areas for hearing and vision (recognizing familiar faces), are where the majority of social and emotional activity is processed (Gainotti, 2019). These parts of the right hemisphere in particular undergo major developmental changes during the first two years of life when infants are discovering how to recognize the important people in their lives and to regulate their emotions and emotional attachments to those people.

The **left hemisphere** controls movements on the right side of the body. The left hemisphere prefrontal, parietal, and temporal cortices are more specialized for language (Reis, Dronkers, & Knight, 2016). In general, the right hemisphere is more holistic and emotional, creating impressions and the perception of larger patterns. The left is more analytic and rational, breaking down impressions and patterns into their component parts. The right hemisphere is more related to novelty and creativity that initially attracts our attention to some event, person, or object. After becoming more familiar, the left hemisphere takes over to organize and routinize the activity related to that situation (Rogers, 2019). The two hemispheres communicate via structural connections (called commissures), the largest of which is called the corpus callosum. The corpus callosum is larger in infants who go on to develop autism than in non-autistic control groups, but the insula appears to be smaller in older children and adults with autism (Wolff et al., 2015).

PRENATAL AND POSTNATAL INFANT BRAIN DEVELOPMENT

The period from the first weeks after conception through the postnatal age of three to four years is now understood to be critical for the development of the human brain. What happens to the individual during this approximately four-year period can determine whether the brain grows in a healthy and developmentally appropriate manner, or whether brain growth is compromised in some way. In this section, we'll review the basic ways in which normal brain development occurs. The next section covers optimal vs. non-optimal brain development, the factors that enhance or hinder brain growth.

Prenatal Development

Stem cells. During the early embryonic period, cells are beginning to divide by mito-

sis (in which a cell divides into two identical copies) and to differentiate in their structure and function, as explained in Chapter 2. By the end of the third week following conception, the embryonic disc is composed of three different layers of stem cells: the endoderm, the mesoderm, and the ectoderm (see Chapter 2 and Figure 2.4). These terms are previously discussed in Chapter 2, but are further defined and expanded upon here. The **endoderm**, one of the earliest cell types to form in the embryo, causes the development of many internal organ systems of the body, such as the respiratory and gastrointestinal tracts, and their vital organs, including the thyroid, liver, pancreas, and bladder (Nowotschin, Hadjantonakis, & Campbell, 2019). The **mesoderm** facilitates key processes in the development of major tissues and organs in the embryo, such as the cardiovascular and musculoskeletal systems; in early development, it is also an important component of extraembryonic structures, including the placenta (Willey et al., 2006). The **ectoderm** creates the protective epidermis and the central nervous system, including the brain and spinal cord (Plouhinec et al., 2017). Thus, the skin, the largest and most sensitive sense organ in the body, grows out of the same layer of stem cells as the brain. In addition to comprising the nervous system, the stem cells in the ectoderm will also become the skin, nails, teeth, sweat glands, and sense organs.

Neurogenesis. During the first four prenatal months, new neurons and glial cells are created via mitosis in a process called **neurogenesis**. Although neurogenesis continues in small numbers throughout life, *virtually all of one's supply of neurons are produced during this period*. Neuronal stem cells, also called neuronal progenitor cells, migrate toward specific regions of the newly emerging head of the embryo. This migration is primarily guided by the radial glial cells, which provide the structural cells in the brain that hold the neurons in their place and create a pathway along which neurons grow and migrate. Cells that are not guided by radial glia are guided by chemical signals and by proteins on the surface of other cells (Purves et al., 2001).

During the migration process, the neuron's axons extend and send out neurochemicals that will find and create connections with the dendrites of other neurons. The axons lengthen and the cells migrate to form the distinctly different anatomical regions (reviewed in the previous section) of the brain that are also beginning to extend connections to different parts of the body (Valiente & Marin, 2010; Mason, 2009; Stiles & Jernigan, 2010). Once neurons reach their final destination in the brain and begin to make connections, they can no longer divide by mitosis (See Figure 4.6).

Synaptic pruning. After the fourth prenatal month, most of the brain's development occurs by making connections between cells and by "pruning," or selective death of unused neurons. Neurogenesis overproduces cells during the first four months of prenatal development, after which cells compete to see which are the strongest and most likely to survive. All neurons have an internal "suicide" program, meaning that the cell will die if it is not connected to other cells during development, if it does not get bathed in sufficient neurochemicals, or if it does not receive the appropriate epigenetic signals from the fetal environment to turn off the "suicide" genes. Cell death, known as apoptosis, appears to be a process that corrects errors in the early migration and neurogenesis phase of prenatal development, by weeding out poorly formed or weaker cells. By the time a baby is born, about 50 percent of their prenatal neurons have died (See Figure 4.6; Stiles & Jernigan, 2010). Neural Darwinism is the principle that strong neuronal connections survive while weak connections die off (Wilcox, 2018).

During the second half of the prenatal period (see Figure 4.6) brain development occurs primarily by **synaptogenesis**, the development of connections between neurons. The nervous system grows from the brain to the periphery of the

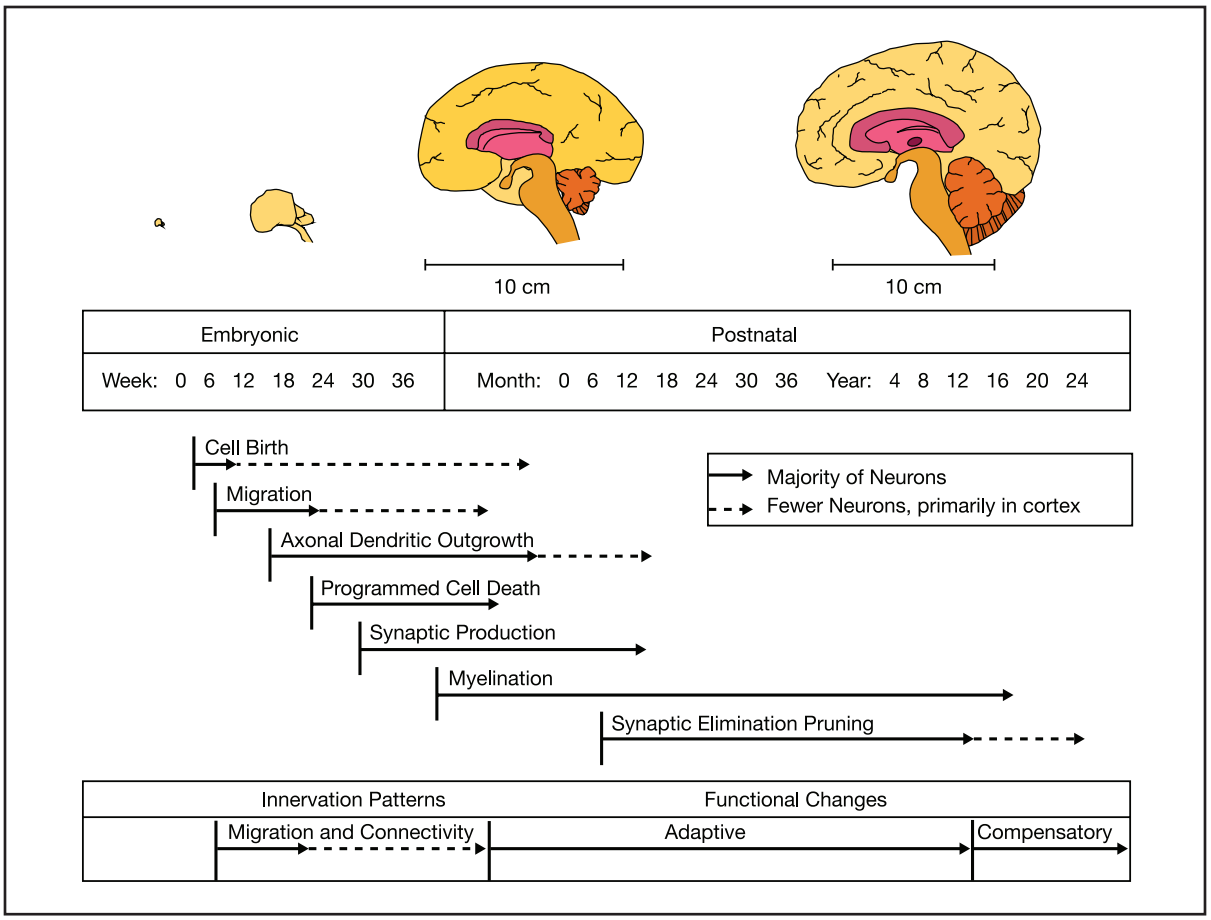

Figure 4.6 The major phases of brain development, especially the growth and migration of neurons and the development of synapses.
Source: Anderson, 2003.

body as cells that migrated to become part of the motor cortex, for example, synapse with cells in the the brain stem or spinal cord, and these cells synapse with cells in the periphery (the muscles, skin, internal organs, and sense organs) (Stiles et al., 2015). *The initial "wiring up" of the brain to the body is usually completed by 28 weeks*, which is when fetuses can begin to feel pain and generate movements under the control of the brain (See Chapter 2; Webb et al., 2001).

Myelination. In addition to lengthening and making connections during this period of prenatal development, the axons also become more efficient conductors by developing an insulation-like encasing of glial cells called **myelin**. Myelination improves the speed of electrical conduction along the axon by a factor of about three times. Myelination begins in the last few weeks before birth and grows rapidly during the first few postnatal months, but continues throughout life. Because of the rapid pace of myelination during this time period, one-month-olds process information about three times faster than newborns.

Postnatal Development

The postnatal development of the brain involves processes by which the networks between neurons become more complex, growing more dendrites and axon terminals and making an increasing number of synaptic connections and neurotransmitters (see Figure 4.7; Kolb & Gibb, 2011). In the prenatal period, an overproduction of neurons occurs via mitosis. Some of these neurons are pruned as those with weaker connections die. In the postnatal period, there is also an overproduction of synapses which are gradually pruned back so that stronger connections remain (Fair et al., 2009). By one year, the child's brain has 150 percent of the number of synapses as the adult's; this number begins to decline starting in the second year (Tau & Peterson, 2010). As a result, approximately 50 percent of the synaptic connections are lost as the child continues to grow (Stiles & Jernigan, 2010). Synaptic pruning is largely dependent on experience. The timing of pruning depends on which areas of the brain are undergoing rapid development. For example, pruning in the visual and auditory cortices is complete between the fourth and sixth year of life, while pruning in areas of higher function, such as areas involved in emotional regulation, are pruned throughout adolescence (Tierney & Nelson, 2009).

Figure 4.8 shows that synaptogenesis has an overproduction peak and then a decline, which has a similar shape in different areas of the brain. This figure also shows that some brain areas mature earlier than others. Because the shapes of the curves representing the number of synapses are similar, Figure 4.8 seems to suggest that there is steady growth and decline in the number of synapses over time. In actuality, synapses connect and disconnect as the person is engaging with the environment, over time scales of seconds, minutes, or hours (Newig, Gunther,

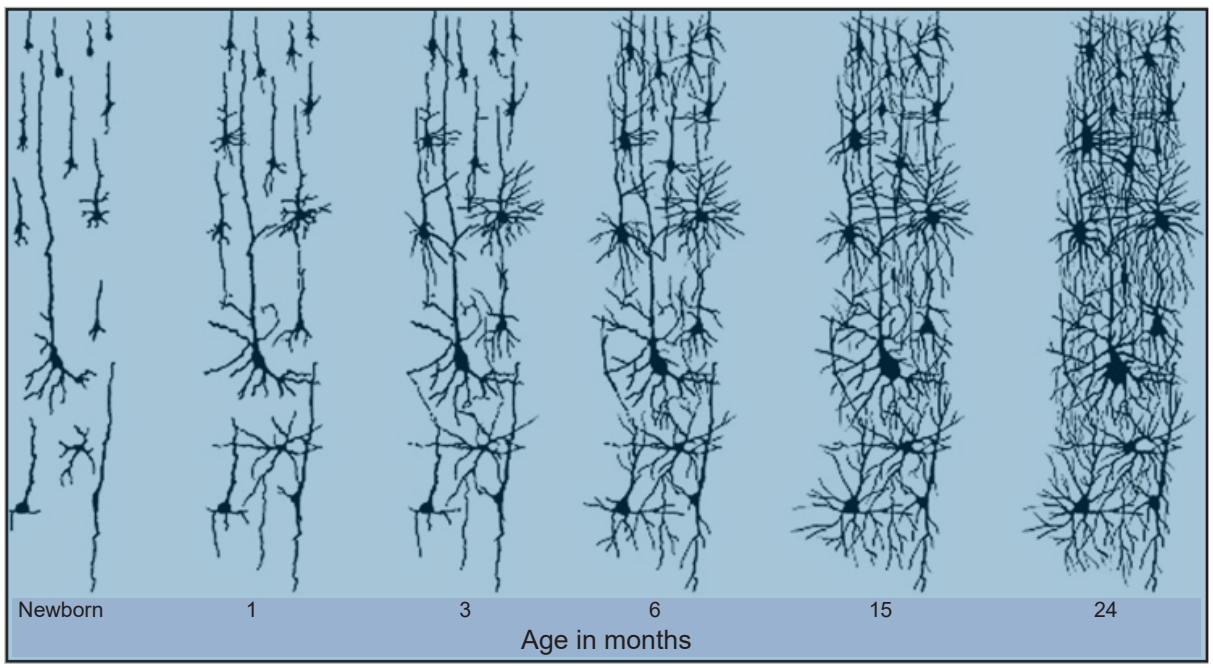

Figure 4.7 The development of neural networks via synaptogenesis.
Source: Webb et al., 2001.

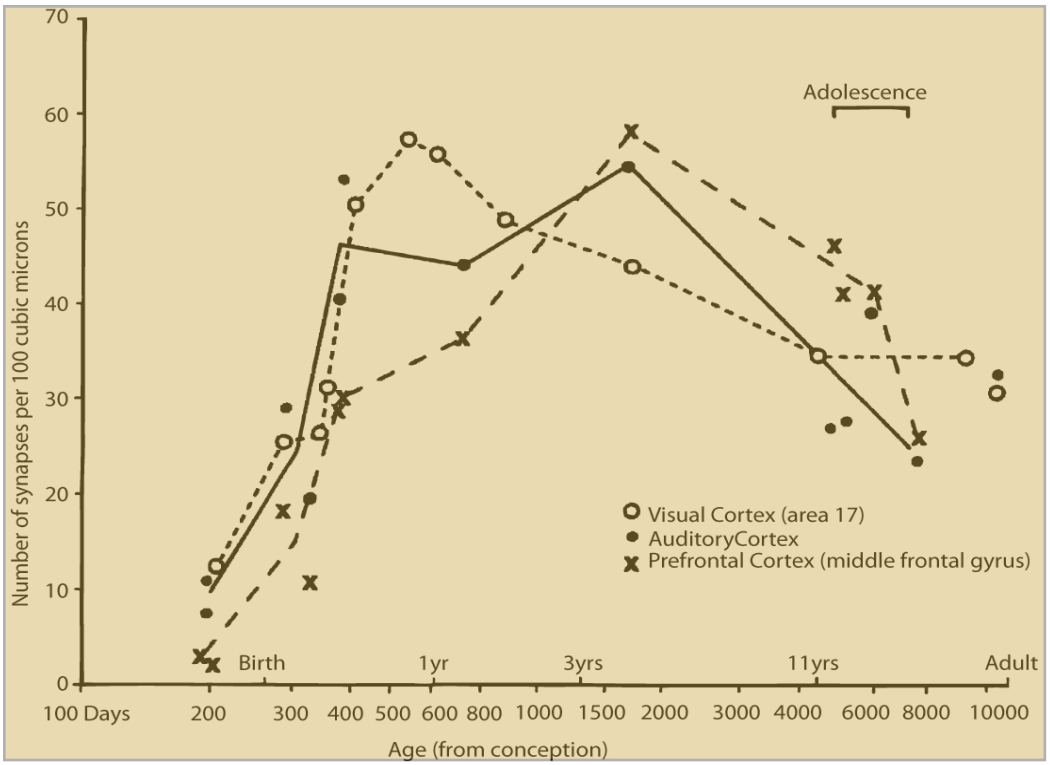

Figure 4.8 Developmental changes in synaptic density of the human brain

Source: Adapted from P. Huttenlocher & A. Dabhoklar, Regional differences in synaptogenesis in human cerebral cortex, 1997. *Journal of Comparative Neurology 4*, 387.

& Pahl-Wostl, 2010). Your synapses are probably doing this right now as you are trying to understand this chapter! The curves in Figure 4.8 relate to the total number of possible connections at any one time. Imagine a telephone network in which the number of calls peaks in the early evening. At any given time, however, millions of calls (connections between phones) are starting or ending. Like a telephone network, it appears that axons are sampling the space around them, "looking" for the best connections and "hanging up" on connections that they don't like (Stiles & Jernigan, 2010).

Back to Figure 4.8, note for example, that the auditory cortex develops earlier than the visual cortex. At birth, babies' hearing is better than their vision because they were exposed to sound prenatally, but not to light (see Chapter 5 on newborn sensory development). These sensory systems develop earlier than the prefrontal cortex, which is responsible for the regulation of emotion (waiting patiently for a meal instead of crying, for example). Sensory regions reach peak synaptic density during the first months of life, but the prefrontal cortex reaches its maximum number of synapses at 15 months of age or later. In fact, some regions of the prefrontal cortex do not reach peak synaptic density until early childhood (Hodel, 2018). Brain development, especially in the prefrontal regulatory areas, continues throughout life but at a slower pace than during infancy (Hedman et al., 2011).

Research also shows that the radial glial cells that grew prenatally to guide the migration

of neurons and their axons continue to function postnatally. Radial glial cells help to keep axons healthy with the right balance of neurochemicals, and they may even play an as yet unknown role in inter-neuron communication (Stiles & Jernigan, 2010). As we saw previously, two types of glial cells form the myelin coating around axons, *oligodendrocytes* in the central nervous system and *Schwann cells* in the peripheral nervous system. The neurochemical dopamine fosters the branching of dendrites and helps cells to synapse, and glia may play a role in this process (Kennedy & Elhers, 2011).

Experience and brain development. Neuromotor pathways and brain regions that were developed prenatally and are functional at birth—those that prepare the infant for survival—are called **experience expectant** because the brain appears to be ready and waiting for a specific type of environmental input (such as pain) for which a particular behavioral skill (such as crying) is best adapted. Many areas of the brain, on the other hand, do not have a specialized function at birth. Some cells and synapses have developed prenatally whose only purpose is to become ready to learn about a particular individual's postnatal experiences. These cells and connections are called **experience dependent**. In a "use it or lose it" fashion, as particular sensory and motor patterns are repeated in early development, specific experience-dependent synapses and cells are used more than others. The synapses that are used the most become strengthened, while those that are used the least eventually die (May, 2011; Scott & Monesson, 2010). For example, people who have musical experience have increased neuronal activity in the auditory and motor regions of their brains, as well as an increased number of synaptic connections in these areas (May, 2011).

In reality, all neurons and neural connections are experience dependent in the sense that they develop at some point in time with respect to the kind of environment in which the infant is exposed (Tau & Peterson, 2010). Cells and pathways that at birth are experience expectant were, at some time during prenatal development, made up of neuronal stem cells that were experience dependent. Recall that sucking, which is a well-established experience expectant pathway at birth, develops out of the tactile and motor experiences of the fetus (Chapter 2) and requires stimulation and repetition during the fetal period for the neural pathways to become strengthened into an experience expectant behavior at birth. All during development, as new actions are acquired, the neural pathways become more expectant of skill-specific information, which increases the skillfulness of the action.

These changes in cell and synapse development show that the brain's development is highly dependent on the individual's experiences (Fox, Levitt, & Johnson, 2010). The brain's construction tailors its development to the experiences of its owner. These neural developmental processes help us to understand how birth defects occur. Alcohol that the mother ingests during pregnancy limits the production of new axons and dendrites (Romero, Renau-Piqueras, Marin, & Estaban-Pretel, 2015), while lead exposure destroys myelin (Cecil et al., 2011). These conditions limit the number of experience expectant and experience dependent connections and cause information processing to be slower, making for a less adaptive, less intelligent individual. In the final section of this chapter, we'll discuss how different types of pre- and post-natal environments affect brain development.

Although all the cells of the cortex form prenatally, their connections with the limbic and brainstem regions have only begun to develop postnatally. The immaturity of the medial prefrontal cortex, to take one example, explains why the infant has some basic emotions like distress, but these emotions are not well regulated. Similarly, the basic reflexes of the newborn (sucking, swallowing, blinking, etc.) are semi-automatic and there is little voluntary control over movement at this age. Infants need

adults to help them calm down, to obtain food and other objects, and to stimulate them. For this reason, the way in which adults interact with infants plays a crucial role in how infants develop the connections between the cortex and the other areas. Adults, in other words, have a major influence on infant brain development.

There is a dynamic system of linkages between brain, experience, and behavior. And during the first few months after birth, infants experience stimuli of increasing intensity and complexity, and connections favoring those types of stimuli will be strengthened. By feedback from the brain to behavior, the window of sustained attention will widen. As sustained attention allows the infant to inspect and explore specific stimuli, feedback to the brain will correspondingly create connections that make those specific events more easily recognized on subsequent occasions (Stiles, Brown, Haist, & Jernigan, 2015; West & Greenberg, 2011; Hebb, 1949; Thelen & Smith, 1994).

Development of Functional Neural Networks

Although different anatomical structures are typically associated with particular functions, multiple structures work together as a network of synaptic connections to create organized behavior and body function (Johnson, Grossman, & Kadosh, 2009). There are four basic functional networks of the brain that are important to our understanding of infant development: (1) arousal, attention, and emotion (2) information processing and remembering, (3) regulation and executive function, and (4) self-awareness (Freides, 2001). Each of these functional networks goes through major developmental change during the prenatal and postnatal periods, and these changes correspond with changes in neuronal activity and anatomical structures.

Arousal, attention and emotion. This functional network regulates the sleep-wake cycle as well as cycles related to hunger, thirst, physical arousal during exercise and stress, and sexual-reproductive cycles in adolescents and adults. As we saw during prenatal development (Chapter 2), recognizable sleep-wake states—including REM sleep—do not emerge until the third fetal period, developing out of more primitive activity and rest cycles found in fetal period II. Newborns, as we'll see in a later chapter, can sleep up to 18 hours a day with frequent wakings (Waters, Suresh, & Nixon, 2013). The amount of time awake and alert increases with age as does the consistency of sleep periods. By the end of the first year, most but not all babies can sleep through the night. Also during the first year, infants undergo radical changes in feeding patterns as they shift from a liquid diet of milk to eating more solid foods.

The brain areas involved in these functions also shift developmentally. In the third fetal period and the first months of life, sleeping, waking, and feeding are primarily regulated by a network that connects the brain stem, the hypothalamus, and the spinal cord. This is one of the most primitive networks of the brain that is responsible for basic life functions and which does not require any voluntary control. This arousal and attention network expands with age in relation to developmental changes in the infant.

The duration of waking states expands in the postnatal period due to experience-dependent interactions between the infant and environment. The infant's attraction to faces and to colors in the first months of life, for example, leads to activation and synaptogenesis between the primitive brain stem-hypothalamus network with the parietal cortex (sensorimotor function and body schema), and the insular cortex (interoception of feelings of interest and enjoyment). This larger network provides the infant with more internal awareness of what it feels like to stay awake and engage with other people, which then allows the network to sustain increased waking times to "feed" the desire to engage with the environment.

Engaging with the environment, in turn, calls for some kind of orienting response and control of attention to something in the environment like a toy, the mother's face, or food. Infant orienting activates different regions of the parietal cortex that are responsible for linking sensory information (vision from the eyes and occipital lobe, sound from the ears and temporal lobes) to motor movements that create a behavioral orienting response such as turning the head or eyes to see or hear, or opening the mouth to orient to a nipple or spoon (Chica, Bartolomeo, & Valero-Cabre, 2011; Posner et al., 2011). Via positive feedback (see Chapter 1) within the orienting-arousal neural network, changes in states of arousal (longer waking times) are developed by increased skill in orienting, and better orienting is fostered by longer waking states.

Emotions also develop over the first years of life. The emotion of fear, for example, does not fully develop until the end of the first year, as fear of strangers and separation anxiety from the primary caregivers (Brooker et al., 2013). This is related to the developmental myelination of the amygdala and its connections to other brain networks, which becomes mature at the end of the first year. This is also the time when emotional attachments are forming. Experience dependent brain development that occurs during infant-caregiver interaction in the first year impacts the development of these pathways to the amygdala so that some infants are better able to be soothed by their caregivers than others (secure vs. insecure attachments; Braun, 2011).

Information processing and remembering. These brain networks for staying awake and paying attention are also connected into a larger network that includes the neurons that innervate sensory organs and the muscles that move the body. Speech and language processing, for example, are often said to be "located" in the temporal lobes. Studies of the brain, however, show that underlying linguistic ability is a complex network of connections between the temporal lobes, the parietal lobes which integrate sensory-auditory and motor function, and the sensorimotor areas that link directly to the auditory nerve and to the nerves that control the muscles of speech articulation in the mouth, lips, jaw, tongue, and throat (Bouchard et al., 2013; Homae et al., 2011). *This means that what infants and adults learn and remember in some way involves their whole body and not just the brain*. While there is currently a lot of interest in infant brain development, development occurs not only in the brain but in the relationship of the brain to the growing body. Therefore, network changes within the developing brain should be understood within the context of brain-body-behavior networks (Byrge, Sporns, & Smith, 2014).

Information processing, if it is to be efficient, requires learning and memory. Imagine that if every time you sat down to read this book, you had no memory of the previous times you read it. You would not get very far in your studies if this were the case. So, the nervous system evolved a way to encode, or remember, prior experiences to allow us to be more efficient in our actions, to go back to situations that made us feel good, and to avoid the ones that were unpleasant.

There are two basic kinds of memory: procedural-implicit and autobiographical-explicit, both of which will be reviewed in later chapters. **Autobiographical memory**, as noted earlier, is the ability to relate a story about a sequence of events in the past. This type of memory is not seen until infants are about three years old. This is because the hippocampus, which helps to organize information sequentially (stories have a beginning, middle, and end) does not become functional until that age. The hippocampus is part of the limbic system located under the interior surface of the temporal lobes.

Before that, infants acquire **procedural memories** which are "ways of doing things." Procedural memories are basically an increased set of synaptic connections between various areas of the cortex with areas of the limbic system and brainstem, linking down to the efferent and afferent nerves going to and from muscles and

sense organs in the body, which become myelinated with use and experience doing a particular activity. Additionally, the basal ganglia and the cerebellum, both involved in the control of movement, are implicated in the creation of procedural memories (Finn et al., 2016). After a series of initially clumsy attempts to suck on a nipple or eat solid foods, babies' behavior becomes more skilled and efficient. Like riding a bike, once it is learned it is hard to forget it because the ability is "in" the cellular structure of nerves, sense organs, and muscle tissues. We don't have to think about it and, like riding a bike or singing a familiar song, information processing and remembering is a whole body experience, not just in the head.

Regulation and executive function. The growing ability to learn new skills requires a coordinated sequence of movements. For eating, this might be attaching to the nipple, sucking, and swallowing; or opening the mouth, waiting for a spoon, closing the mouth, tasting and chewing, then swallowing. For face-to-face interaction, infants need to visually orient to an adult, scan the face looking for where the eyes are directed and the adult's facial expression and voice, organize a response like a smile or coo, and then wait for the adult to do something else.

In the initial phases of learning a new skill, infants and adults use their orienting responses to focus on each particular part of the task. If, however, we continued to orient to every single component of a task, the task as a whole would take way too long to accomplish. We need, therefore, a mechanism for *inhibition* of the orienting reaction so that we can direct our attention to higher levels of processing that encompass a sequence of actions and sensations. We also need a means to have a *"working" or short-term memory* to remember each of the steps in the sequence, to *compare* our actions between different attempts at the same sequence, between one type of task and another, and between ourselves and another person.

Finally, we need to *regulate our emotions* so that we don't give up on learning something new in the face of complexity, distress, frustration, or fear (Best & Miller, 2010). Most of the neural basis for executive function comes from a network that includes all the prior networks along with their connections to the prefrontal cortex (regulation) and the insula (sense of self), which are the parts of the brain that mature the most slowly. One plateau of prefrontal development (Figure 4.8) occurs around the age of three years with the onset of language, autobiographical memory, and new forms of self-control that allow more sustained attention and autobiographical remembering. The second major growth and plateau of prefrontal function begins in adolescence and ends by 25 years (Selemon, 2013).

Depending on the person, it takes years to "grow out of," to regulate, the unruly urges and unwise risk-taking of adolescence via increased connections to the prefrontal cortex. Similarly, by age three or four years, infants have outgrown their earlier impatience, tantrums, and uncontrolled emotions and are better able to express their needs and understand other people. Links between the growing prefrontal cortex and the amygdala account for the emergence of more independent behavior and self-calming in the absence of direct adult support, an ability that emerges in the second and third years of life (Braun, 2011).

Even though there is a peak in the development of the prefrontal cortex at three to four years, even newborns have some prefrontal functions available (Brown & Jernigan, 2012). In early infancy, rudimentary prefrontal circuits help to regulate infant distress, often by soothing or distracting the infant from what was causing the distress. A lot of adult help is needed. Learning to eat solid foods, staying awake for longer periods, and many social and communicative skills that are acquired in the first three years, mostly with the help of adults, foster the development of prefrontal executive function. In

some way, adults serve as an "external" prefrontal cortex, filling in the gaps and providing assistance and emotional control when the infant or child cannot handle a situation. Interactions with other people around learning skills and dealing with emotions, particularly in attachment relationships, are therefore crucial to early brain development. Similarly, adolescents need a lot of parental guidance in learning to drive safely, managing their emotional urges, monitoring their use of the internet, and dealing with the ups and downs of peer relationship challenges.

Of all the executive functions in infancy, inhibition is perhaps the most important. Compromised inhibitory control in preschoolers is correlated with cognitive, behavioral and emotional problems later in life (Best & Miller, 2010). Interventions for school-age children that foster self-regulation have shown promising results for later school achievement and emotional stability (Shanker, 2013). One of the reasons that inhibition is important is because activation of the amygdala, which occurs when people are distressed or fearful, can dampen or shut down prefrontal regulatory functions.

We cannot really think clearly or act coherently when we are under stress or threat. This is because the amygdala activates the hypothalamus which then activates the sympathetic nervous system and promotes the secretion of cortisol which prepares the body to meet the stress or challenge (Herman et al., 2016). If the situation is overly stressful, emotional and cognitive executive inhibitory function is diminished in favor of immediate response to the stress. Fear also detaches us from our awareness of our own bodies by blocking the pathways to and from the insula and parietal cortex. Prefrontal inhibition of the amygdala, therefore, allows people greater access to their self-awareness and to more adaptive and regulated responses to the environment (Fogel, 2009; Likhtik & Paz, 2015).

Self-awareness. Most past research on the brain and nervous system has been devoted to how people respond to the environment, how we learn skills such as language and communication, how we regulate our emotional attachments, and how our sensory and motor skills adapt to environmental challenges. More recently, however, neuroscientists have discovered that there are major networks in the nervous system devoted almost entirely to sensing the inner condition of the body and mind (Lou, Changeux, & Rosenstand, 2017).

To move across a room, of course we need the motor skills of walking and postural control (it takes babies more than a year to learn how to walk), we need to identify the nature of the surface on which we are walking (flat or inclined, smooth or rough), and we need to have a sense of the objects in the room that we might have to avoid or step around (Hoch, Rachwani, & Adolph, 2019; Kretch & Adolph, 2017). This is all related to the way the brain and body respond to the challenges of the environment. We also, however, need to know where our own bodies are located with respect to those objects (body schema). We need to feel the differences in our muscles when we walk on different surfaces or when walking uphill or downhill (interoception). Interoception gives humans the ability to assess their own bodily states and the emotions associated with them. For example, someone who notices that their heart is beating fast may make the assessment that they are scared (Critchley & Garfinkel, 2017). In social situations, we need to sense the boundaries between ourselves and other people, where our body leaves off and another's begins, and to feel our own actions as different from those of another person.

All the other basic functions of the nervous system—arousal and attention, information processing and remembering, regulation and executive function—take months and even years to develop during infancy and childhood. Put in more concrete terms, infants develop their motor skills, perceptual abilities, social and language skills, emotional responses, and attachments to other people. As we engage with the world, our nervous system shifts and changes the way

it builds networks and connections for all these functions. The same is true for self-awareness.

As we'll see in this book, self-awareness goes through multiple developmental changes during infancy. The awareness of being a self, separate from others, does not begin until the end of the first year when infants begin to show separation anxiety, suggesting that they begin to perceive their mother or father as a separate person. It takes yet another year for infants to be able to recognize the image in the mirror as their own, and to begin to use words like *I*, *me*, and *mine*. Without a sense of self, people cannot comprehend how they affect others nor feel empathy for another person's feelings (Atkins, 2013).

OPTIMAL AND NON-OPTIMAL BRAIN DEVELOPMENT DURING INFANCY

Plasticity. One way to interpret the discussion in the previous section is that the human brain is not set at birth for all future experiences. On the contrary, what distinguishes humans from most other animals is the degree to which our brain has a talent for learning new skills and patterns. This begins in infancy and can continue through old age. **Neural plasticity** is the ability of the brain and nervous system to seek novelty, learn, and remember by continuing to alter the patterns of connections between neurons.

Brain development continues throughout our lives as we learn new things and adapt to changes in our environment. Brain development during gestation and infancy, however, is unique. The fetal and infant brain does not simply adapt to the environment. Rather, *the environment becomes permanently incorporated into the very structure of the brain* (Gao et al., 2019). This is because the basic structures and connections in the brain are actually forming during this period, and this explains why these early years of development are considered a critical period for brain development (see Chapter 1).

Let's suppose a normal teen or young adult does not get to attend college or high school. There is nothing to prevent that person from going back to school later in life, at least not from a neurological perspective. If they have the time, money, and motivation, it can be done. This is not the case for infants. If infants fail to get exposure to a loving parent or caregiver, this will affect the attachment patterns they form throughout the lifecycle. If they are not exposed to language in the first three years, they will never become fluent in any language.

Consider an individual who is blind at birth due to an eye defect. The blindness continues for the first few years of life, and then the person later has surgery to correct the eye defect. Even though this person now has visual signals traveling from the eye to the brain, he or she still cannot see the world as the rest of us see it. That's because the regions of the brain required to distinguish objects out of light and shadow develop during the first few years. It is not until 10 months of age that infants can recognize and clearly distinguish one object from another and view it as a separate and permanent entity. There are other instances of infants who are reared in orphanages with little adult attention, or those who are not exposed to appropriate language experience, who will develop severe impairments in social and linguistic function along with brain abnormalities (Juffer, van IJzendoorn, & Bakermans-Kranenburg, 2017; Nelson, 2007; Paterson et al., 2006).

For most humans with an intact brain, that brain retains a certain amount of plasticity throughout life. Appropriate educational and therapeutic experiences may be able to partially repair the effects of early deprivation. On the other hand, because the brain grows gradually, the infantile patterns of connection are never lost and a person who "recovers" from early deprivation may never be the same as one who never suffered from that experience. The prognosis for treatment and recovery depends upon the severity of the deprivation. The prenatal and infancy

period, in other words, builds the foundations on which later development can rest. Later experience can build certain kinds of processes but they will not be as strong or as adaptive as those built upon a more solid foundation (Fox, Levitt, & Nelson, 2010).

Effects of Prenatal and Infant Stress on Brain Development

Threat, stress and trauma. **Threat** is the sense of being in danger from outside of ourselves (e.g., another person or a collision with an object) or inside (e.g., a physical pain or feeling of anxiety). Threat can induce **stress.** During stress, the sympathetic nervous system mobilizes the body to respond to stress with either fight or flight, and the parasympathetic nervous system returns the body to its baseline, relaxed state. Stress occurs when the sympathetic nervous system is continuously activated without being counteracted by the parasympathetic nervous system (Won & Kim, 2016). **Trauma** is the condition that results from prolonged sympathetic activation and the resulting depletion of the body's resources and lack of time for recovery.

Stress is an important factor regulating individual differences in brain development. Its effects can begin before birth and continue throughout life. The evidence for the negative impact of stress and trauma is consistent across both human and animal studies. Basically, *every baby during their first two years of life comes to assess the world as either a safe or a threatening place*. This assessment is not made as a conscious choice, but rather a nonconscious evaluation by the autonomic nervous system that comes as a result of encountering and coping with difficult experiences in early life. This nonconscious evaluation of safety or threat is called **neuroception**, meaning that the autonomic nervous system (both the sympathetic and parasympathetic branches) makes the decision of how to respond and not the conscious mind (Devereaux, 2017; Porges, 2004).

Neuroception. There are three basic patterns of neuroception: immobilization, mobilization, and social engagement (Porges, 2004; Porges & Furman, 2011; see Table 4.1). Mobilization and immobilization are different types of responses to threat. With mobilization, there are two possibilities: fight or flight. These involve a high level of arousal shown in increased heart rate, blood flow, and faster breathing, all activated by the sympathetic nervous system (SNS). Because the body only has a limited amount of metabolic energy resources, this ongoing sympathetic activation is done at the expense of basic body functions such as digestion and immune system support. If we are mobilized too long, it will eventually compromise our physical and mental health.

Engagement with, attention to, and adaptive function with people and objects requires the ability to relax that is supported by the parasympathetic nervous system (PNS) which tends to decrease heart rate, slow breathing, and lower blood pressure. When we are relaxed and feeling safe, our cardiovascular, digestive and immune systems can work well and keep us healthy. Social and object engagement also require a balance between SNS and PNS activation, which allows us to stay alert and attentive (SNS) and at the same time able to relax and enjoy what we are doing (PNS).

Immobilization due to threat has two possibilities: freeze or faint. If we are not able to respond to stress and threat with mobilization, a more primitive and unmyelinated part of the PNS gets activated. Similar to normal PNS function, the body slows down toward relaxation. Immobilization, however, is an extreme form of PNS activation in which the body not only slows down but also shuts down, leading to a state of feigning death (fainting or sleep-like states), or "deer-in-the-headlights" frozen and unable to move or act. Immobilization is a last-resort survival response of the nervous system that has the effect of tuning out body awareness and pain.

TABLE 4.1 Three Forms of Neuroconception
(SNS = Sympathetic Nervous System [Arousal]; PNS = Parasympathetic Nervous System [Relaxation])

Social World	*Type of Neuroception and the Related Nervous System*	*Characteristics*
Threatening	Immobilization Unmyelinated vagus PNS	Freezing, feigning death, behavioral shut-down, dissociation from the body
Threatening	Mobilization SNS	Fight or flight behavior, increased heart rate, slowed digestion and growth
Safe	Social engagement Balance between myelinated vagus PNS (relaxation) and SNS (arousal)	Relaxation, emotional engagement and regulation, appropriate challenges, growth

Source: Porges, 2004

Vagal tone and RSA. The PNS vagus nerve, the longest cranial nerve, connects to the heart and gut organs. When activated, it slows heart rate, acting like a brake on arousal. **Vagal tone**, the availability of a functionally myelinated vagal PNS that can help us relax in the face of stress, is measured by the ability of the heart to adjust its beat-to-beat frequency in the face of stress (Bagner et al., 2009). Respiratory sinus arrhythmia (RSA) is a way to measure vagal tone using an electrocardiogram (ECG). RSA is the degree to which heart rate is in synchrony with respiration, and the degree of RSA is thought to increase with cardiac vagal activity. One could think of RSA as the ability of breathing to calm us down. RSA varies inversely with heart rate, meaning that when heart rate is higher, RSA is lower. Low RSA is a psychophysiological marker of stress vulnerability; people exposed to chronic stress (people with PTSD, discussed below) have a significantly lower resting RSA than people who were not exposed to chronic stress (Campbell, Wisco, Silvia, & Gay, 2019). Low RSA is also associated with less ability to emotionally regulate oneself (Beauchaine & Bell, 2020). RSA was found to moderate the relationship between childhood adversity (e.g., stressful events, low-income, parental psychopathology) and adjustment (e.g., externalizing problems, internalizing problems, social competence; Klein, 2019). RSA grows over time and grows at a slower rate among infants who are later diagnosed with autism. The slow growth is most evident after 18 months of age, when symptoms typically begin to arise, and may be associated with challenging behaviors in children with autism (Sheinkopf et al., 2019).

The vagus nerve myelinates slowly over the first six months after birth, meaning that fetuses and young infants under six months do not have a vagal brake to modulate the effects on stress. In the first six months, infants need adult help to develop increased ability to digest food (solid foods are not typically given until sixmonths), to calm down when upset, and to have longer periods of social engagement with others. This means, on the one hand, that infants younger than six months need more protection from people around them to buffer the effects of stress, and on the other hand, that if this protection is not available, the effect of stress during this period is more likely to have lasting impairments of vagal tone leading to an impairment of the ability to regulate basic body function and manage stress (Porges & Furman, 2011).

Cortisol. Prolonged activation of the SNS and suppression of the PNS also activates the HPA axis (see above) resulting in the secretion of cortisol. Cortisol gives the body the energetic reserves it needs to respond to stress (fight or flight) and the energy and arousal levels that we

also need during normal engagement with the world. On the other hand, if stress is persistent, either prenatally from maternal stress or depression, or postnatally from lack of consistent and appropriate care and disturbances in social interaction, cortisol is overproduced because the infant's well-being is threatened.

In small amounts the body needs cortisol, and some cortisol is normally present during the waking day. In large amounts, however, cortisol is toxic to the brain and creates lasting changes that may persist over months and years, as shown in Table 4.2. As shown in the table, when cortisol returns to the brain via the bloodstream, it can alter structures by changing the epigenetic markers that influence cortisol receptors and neurotransmitters in the brain (Jiang et al., 2012; Braun, 2011; Murgatroyd & Spengler, 2011). The same processes also compromise the immune system, leading to higher prevalence of diseases in people who have experienced high levels of stress (Doom & Gunnar, 2015; Keunen, 2017; Schore, 2003; Miller & Chen, 2013).

PTSD. Because the hippocampus and amygdala are the two areas where memory is formed, cortisol not only changes the neurotransmitters and receptors as well as the connections between the limbic system and the rest of the brain, but cortisol also changes the way early experiences are remembered. Too much stress leads to a tendency to feel fear and threat in the future, even when the future situation is not necessarily fearful to an outside observer. It also leads to **post-traumatic stress disorder (PTSD)**, a decreasing ability of the individual to cope with the stress (mediated by the right prefrontal cortex) in appropriate ways, creating a person who is more likely to freeze (shut down and become unresponsive in severe cases), fight (tantrums, resistance, negativity), or flee (hide or withdraw) when they feel threatened. We will return to the topic of PTSD in later chapters, especially around the topics of infant attachment and infant mental health. Stress has a profound effect on the functionality of the immune system, and people with PTSD typically have higher inflammation levels due to an overactive immune system (Passos et al., 2015). Stress can alter the immune system of pregnant women, which can then impact the development of the fetus (Barrett, Sefair, & O'Connor, 2017). Additionally, stress during the neonatal period (birth to one month) is associated with the immune system of the infant, which can also lead to adverse developmental outcomes (Nist, Harrison, & Steward, 2018).

Prenatal and postnatal stress can occur because of maternal or paternal depression, anxiety, drug addiction, and PTSD, because of stressful life events (divorce and family strife, frequently changing residences, unsafe neighborhoods, crime, warfare and refugee migration, unemployment, natural disasters), poverty, nutritional deficits, and diseases. The risk for future impairment increases with the number of risk factors that occur (Robinson et al., 2011; Miller & Chen, 2013). The Adverse Childhood Experience (ACE) scale is utilized with children

TABLE 4.2 Effects of Stress on the Developing Brain
Stress, via the over-production of cortisol, changes how the brain develops

Amygdala	*Hippocampus*	*Prefrontal Cortex*
Increase in CORT receptors in amygdala leads to a bias to detect fear and anxiety, and creates a risk for PTSD and stress-related physical and mental illnesses	Decreased receptors for CORT in the hippocampus leads to decreases in the ability to self-regulate responses to stress, memory problems, overproduction of CORT, adrenal fatigue	Impaired cell growth decreases ability to self-regulate emotions and self-awareness, and impairs ability to form secure attachments

Source: (Eichenbaum & Cohen, 2001; Gunnar & Cheatham, 2003; Schore, 2003).

to assess how many major life stressors a child has experienced (Finkelhor, Shattuck, Turner, & Hamby, 2015).

Epigenetic changes. What are the consequences of these stress-induced alterations in the structure and neurochemical function of the brain during the prenatal and early infancy periods? Because the brain during this time period is sensitive to environmental influences, these effects can have serious consequences for later functioning. Outcomes can be serious, and in some cases, life-long. Because stress impairs the vagal-parasympathetic system responsible for calming, and dysregulates the HPA axis that changes key areas of the brain related to self-regulation, stress affects both mental and physical health. In fact, stress can engender epigenetic changes that alter patterns of DNA expression and cell development in the HPA axis, affecting responses to stress over the lifespan (Ellison, 2010).

Maternal cortisol can play different roles in prenatal brain development depending on the sex of the fetus. In boys, higher levels of maternal cortisol during pregnancy are linked to a weaker connection between a part of the cortex called the supramarginal gyrus (which interprets tactile sensory data and aids cognitive functions) and the amygdala (which facilitates the experiencing of emotions). In girls, higher levels of maternal cortisol during pregnancy are associated with stronger connections in the fetal brain between the amygdala and the supramarginal gyrus. Additionally, stronger neonatal amygdala connectivity in girls serves as the connecting or mediating link for the association between higher maternal cortisol and internalizing behaviors at two years old. This may help to explain why women have higher rates of internalizing psychiatric disorders (Graham et al., 2019).

DNA methylation, an important epigenetic mechanism, tends to inhibit gene activity, reduce DNA accessibility, and may even lead to the "silencing" of the gene (Szyf & Bick, 2013). DNA methylation also influences gene expression networks in the developing fetus and infant (Liu et al., 2016). Methylation of the genome is related to the developmental timing of adversity. Early exposure to adversity and stressors affects later DNA methylation patterns (Dunn et al., 2019). For example, prenatal depression and exposure to childhood abuse is linked to increased gene methylation that affects the neuroendocrine response to stress through what is called the glucocorticoid receptor gene. The action of this gene is related to greater cortisol reactivity in infancy. Additionally, caregiver relationships play an important role. Infants with insensitive, unreceptive mothers who were also depressed or anxious displayed higher baseline cortisol levels in comparison to their unexposed peers (Conradt et al., 2016).

Effects of early life stress. The list of effects of early stressors—mediated by these changes in the brain and nervous system—is long. The effects of cortisol on the prefrontal cortex predispose infants to later problems with executive function and self-control (Wagner et al., 2016; Beaver, Wright, & Delisi, 2007). Infants and children with harsh and controlling fathers tend to have higher levels of cortisol reactivity when faced with an emotional challenge. In fact, a father's negativity appears to alter a child's response to a stressful situation, and weaken the child's ability to regulate their response to stress in later years (Mills-Koonce et al., 2011). Toddlers who score low on measures of self-control are more likely to have physical health problems, substance abuse problems, problems with personal finances, and be arrested for criminal offenses (Bernier et al., 2010; Moffitt et al., 2011).

Infants who are likely to have been more stressed include infants whose mothers had higher levels of salivary cortisol during pregnancy or infants whose mothers had PTSD or elevated levels of anxiety. These infants were more likely to be born premature or at low birth weight, are less able to engage in social interaction, and have a compromised ability to control their emotions (Cherak et al, 2018; Enlow et al., 2011; Zietlow et al., 2019; Zijlmans et al, 2015).

Their motor and language development may also be delayed (Austin et al., 2017; Moss et al., 2017). Adverse effects continue during childhood and adulthood and may include cognitive and memory impairments, learning disabilities, ADHD, depression, anxiety, and poor school performance (Davis & Sandman, 2010; Ronald et al., 2010; Schetter, 2011). There is also a higher risk in later life for chronic diseases including cardiovascular, respiratory, and immune disorders including certain types of cancer as well as infant mortality (Cezar, Gomes, & Damatto, 2019; Class et al., 2013; Li et al., 2012; Marques et al., 2013; Rosa, Lee, & Wright, 2018). Early stress predisposes teens and adults to unhealthy lifestyles including substance abuse, aggressiveness and violent behavior, gambling, school failure, gang membership, unemployment, crime, incarceration, and poor parenting of their own children (Field & Diego, 2008; Hay et al., 2010).

Because the brain and nervous system affects the functioning of the entire body, adverse early experiences can have major impacts on both mental and physical health, and on education, work, and social behavior in later life. The evidence, as shown in Figure 4.9, points to alterations in epigenetic markers that may establish lifelong patterns of dysregulation vs. health in stress regulation, biochemistry, neurophysiology, immune function, and metabolism. Because the very biology of the individual is altered by early experience, some have called early brain development a kind of "programming" or "biological memory." While the immature fetus and infant is actually responding to stress in a way that enhances their survival from the stressors in the short-term, because of their immaturity these survival strategies can have extremely high long-term costs.

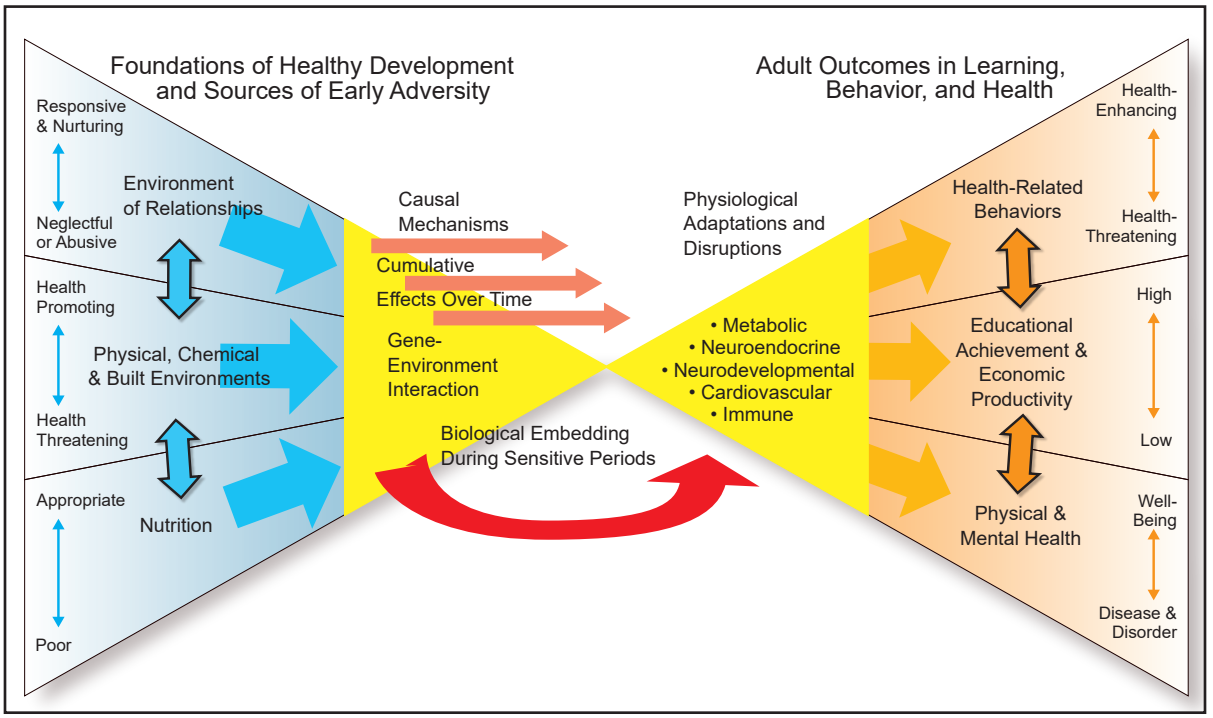

Figure 4.9 Multiple factors that influence the gene-environment interactions that set the stage for brain development. *Source*: Anderson, 2003

Benefits of stress. Some type of short-term stress is actually good for infants, children, and adults. Dealing with everyday frustrations, adapting to new experiences, waiting to get our needs met, and exploring an uncertain environment contribute to honing more adaptive responses and to the development of healthy prefrontal and executive function while still being able to regulate the effects of short term stress on the body. Long-term unresolved stress, not mediated by times of restoration and support, however, is toxic to the organism as well as the immune system, and can cause these more lasting and damaging effects (Dhabhar et al., 2010).

How Can We Foster Healthy Brain and Bio-Behavioral Development for Infants?

How can we protect the fetus and infant from the undesirable effects of toxic stress? If the brain and physiology of the body can be so deeply impaired by unfortunate prenatal and infant experiences, can later more healthy, safe, and loving environments reverse the damage? How plastic is the brain?

Long-term effects of stress. Because the brain during this critical period (the period from the second half of gestation until the third birthday) is immature and sensitive, events in this period may affect the person for the rest of their life. The parts of the nervous system and the epigenetic processes that regulate the basic function of body and mind are informed by these early experiences to expect a certain kind of environment and to survive in that environment (Ellis & Del-Guidice, 2019). Even if a child has a genetic ability to be relatively resistant to stress, highly adverse environments with high levels of stress will override the genetic protective factors and create epigenetic markers that produce high levels of cortisol and subsequently affect brain development (Ouellet-Morin et al., 2008). If infants develop in very unsafe environments, they will retain the tendencies for hyper- and hypo-activation of the autonomic nervous system, even when their later environments are safer than those of their early years.

There is some room for hope, however, because each person develops in a different way and responds differently to the environment. While some infants exposed to toxic stress may never recover as adults and suffer from persistent heath and behavior problems, others will find ways to lead healthy and productive lives. It all depends on the severity of the original stress and on the supports and resources that may be available later in life. These effects can lower one's immunity to health issues later in life (including heart disease, strokes, and certain types of cancers) and alter cognitive functioning as well as inflammatory responses to stress, so a caring influence is crucial (Miller & Chen, 2013).

Infants who had been raised in poorly managed orphanages and who were severely deprived of social and linguistic input improved very little even after several years of receiving language enrichment programs. In other cases, however, it appears that the brain can recruit undamaged areas to serve similar functions as the damaged area, thus allowing the person to recover from early deprivation. New research suggests that different brain areas such as the hippocampus, which is linked to memory formation and the prefrontal cortex, which is involved in decision-making, actually can perform each other's functions to some degree (Rubin et al., 2017). Moreover, when an area of the brain such as the amygdala is non-functional, other areas can assist in memory formation (Poulus, Ponnusamy, Dong, & Fanselow, 2010). If stress that occurs prenatally and during the first year is followed by early intervention programs in preschool and day care during the second year, there is ample opportunity for full or partial recovery (Bick & Nelson, 2016; Blair & Raver, 2016; Novak & Morgan, 2019; Shavit, Friedman, Gal, & Vaknin, 2018).

Parental support and the effects of stress. Maternal warmth from a nurturing caregiver can serve as a buffer against the effects of prenatal stressors, such as poverty (Miller & Chen, 2013). Consider the following study. For a group of 125 women, fetal cortisol was sampled during amniocentesis. When the children were 17 months, those with high prenatal cortisol had shorter attention spans, fewer language skills, and fewer problem-solving skills but only if their attachment to their mothers was insecure. If they had a secure attachment to mothers, those with high prenatal cortisol showed no effects at 17 months. Thus, secure attachment with mothers completely eliminated the effects of prenatal stress (Bergman, Sarkar, Glover, & O'Connor, 2010). Other studies have shown that parental warmth, coupled with early intervention programs for families, can significantly reduce the risk of aggressive behavior in children who had early exposure to toxic stress (O'Neal et al., 2010). Similarly, infants at genetic risk for having lower vagal tone (lower adaptability of the ANS) and who had sensitive parenting during the first year, were no more likely to respond negatively to maternal separation at 12 months than infants who did not have a genetic risk factor. Infants with the risk factor had negative responses to separation only if their mothers were less sensitive to their needs during the first year (Propper et al., 2008).

In general, the effects of early experience have the potential to be alleviated when certain types of resources are present in the environment in later infancy and early childhood. Parental sensitivity, as shown by these studies, is one factor. Parents, being human, are better able to be sensitive to their infants if the parents themselves have opportunities to develop executive function and self-control, social support, openness to learning, and are not themselves overstressed or cognitively impaired. Thus, it is essential for parents to have strong support networks if they are to support their own and their children's resilience in recovery from trauma (Angley, Divney, Magriples, & Kershaw, 2015). On the child's side, in addition to parental support, having the ability to talk about their experiences, dreams, and fears, and having a community of support are all important factors in recovery (Quota et al., 2008; Sagi-Schwartz, 2008). The Case Report in this chapter reveals how these factors worked for one person who was three years old when an ethnic war engulfed the family and the country in which they lived.

In summary, the first three years of life is a critical period for brain development. When people think of brain development, they are most likely to think about cognitive development and the role of the cortex. Research shows, although development during infancy is crucial to successful cognitive functioning, infancy is not a relatively critical period for cortical and left-brain processes like reading, math, thinking, or musical ability. The development of these abilities accelerates after age three and continues throughout life. *Infancy is a critical period for the development of the limbic system, the insula, and the prefrontal parts of the brain—arousal, attention and emotion; information processing; regulation/executive function; and basic bodily self-awareness—which is fundamentally and crucially dependent upon the quality of sensitive caregiving, love, emotional sharing, and social engagement received and perceived by the infant*. As important as it is to expose infants to a cognitively stimulating environment, it is equally crucial to ensure that their environment is emotionally stimulating in a warm, positive manner and to provide the infant with the sense that the world is safe and secure.

Case Report
Recovering from War Trauma

The Case Reports in this book are based on undergraduate students' investigations into their own infant development, done in the form of a term project for classes one of us taught using previous editions of this book. This first case report is about the effects of early trauma, in this particular case, related to being in a war zone during the first three years of life. Here are excerpts in the student's own words.

> While we were moving from shelter to shelter, bombs went off in the distance and in close proximity. Gunshots were fired constantly, people around were crying and grabbing their family members, tanks fired shots, and soldiers yelled as their lives were lost. I used to close my eyes and hold my ears firmly with my hands any time a loud noise or bang came about. To this day, I will blink at any loud noise. Both of these situations resulted in unconscious long-term psychological effects. The scary part about my symptoms is that if I never researched my past trauma I would never have correlated my fear of dark and fear of loud noises with my war experience. However, after researching my question the reasons for these behaviors are unmistakably related to the war. I have trouble distinguishing my memories in terms of false or real. I shock my mother when I remember something from the war. I have flashbacks of shelters, the destruction of our home, and seeing myself in front of my home crying. These memories only come by from time to time, especially when my family and I are discussing the past.
>
> We lost our home due to grenades and tanks. We ended up as refugees in Germany, with no place to call home and no news of the whereabouts of other family members. We fought onward and made a life in Germany. A psychologist told my mother that I am at high risk for PTSD and need to avoid loud noises. PTSD (Post Traumatic Stress Disorder) impacts a lot of people who have gone through war trauma. My brother (who was nine at the time) was constantly shaking and blinking his eyes with fear and held a vengeance toward [those who attacked us]. My family had public anxiety due to trust issues after the war. They felt betrayed, but eventually gave trust to others impacted by the war and in the present day are living happy lives with healthy friendships. This explains why I must have had trust issues with others during my adolescence.I believe that the war has made me more susceptible to the emotions of my family in terms of feeling their grief. My weakness would be the inability to control my emotions when I am overwhelmed.
>
> My dad told me that I was a very cuddly baby and loved being touched. I was touched constantly by all relatives and friends and was frequently communicated to. Hugs came right at the door from my mom, dad, brother, and other relatives. I was a very calm and happy baby, this might be an additional explanation as to why I am sensitive and let my emotions and sensations out. I love being around others and being touched, which explains why I remember my mother tucking me to bed at night and touching my shoulder with her hand. I had a happy and healthy childhood (besides the war) and am capable of showing all of my emotions effectively. I have a resilience to stress and always look for positive outcomes. However, when I get overwhelmed I can explode with anger. This can be explained by the experiences I had during the war.

This report is a wonderful example of the research reviewed earlier. Even though the war experienced by this student at a young age has had lasting post-traumatic effects on the nervous system (lack of regulatory control in the face of stress, sensitivity to loud noises, etc.), this person had a loving and devoted family before, during, and after the war experience. They somehow managed to stay together as refugees in Germany before permanently resettling in the United States. All of these were protective factors that led, ultimately, to a more resilient nervous system and opportunities for continued healthy brain development.

SUMMARY

Measuring Brain Activity

- New methods have been developed to apply various neuroimaging modalities to studying the infant brain.
- EEG measures electrical activity and is temporally precise but not anatomically precise.
- Magnetoencephalography (MEG) is similar to EEG in that it is temporally but not spatially accurate. However, it utilizes magnetic fields instead of electricity MRI employs magnetic waves to detect anatomical structures in the brain (MRI) or changes in activity in these areas (fMRI). Infants are typically asleep when these methods are used.
- Functional Near-Infrared Spectroscopy (fNIRS) is a useful tool to use when babies are awake because it allows them to have a relatively free range of motion, using infrared light to detect changes in oxygenated hemoglobin on the surface of the cortex.

Basic Structures of the Nervous System

- Neurons are cells that receive, process, and transmit information throughout the nervous system.
- Glia are another type of cell in the nervous system that perform a variety of functions, including supporting, guiding, and insulating neurons.
- Synapses are the connections between neurons, typically between an axon terminal and a dendrite.
- Various neurochemicals affect our mood, cognition, and behavior.
- The major areas of the brain are the brain stem, limbic system, and cortex.
- The brain stem areas control autonomic nervous system functions, such as breathing, heart rate, blood pressure and digestion.
- Within the autonomic nervous system, the sympathetic nervous system works to expend energy and the parasympathetic nervous system works to build and restore energy.
- The limbic system processes emotions and memories as well as some body functions. Within the limbic system, the important structures during infancy are the hippocampus, amygdala, hypothalamus, and pituitary gland. The limbic system, along with the brainstem, is one of the most functional systems at birth.
- When the body is under stress, the hypothalamic-pituitary axis (HPA) causes the pituitary gland to secrete cortisol.
- The insula allows us to have the sense of interoception, allowing us to feel the inner conditions of our bodies.
- The prefrontal cortex connects limbic and cortical areas and is responsible for social and emotional regulation. The cortex involves thinking, reasoning, and judging.

Prenatal and Postnatal Infant Brain Development: A Critical Period

- The first three to four years of life are critical for brain development.
- The first stage of brain development is neurogenesis, the production and migration of neurons and glia during the first four prenatal months. Virtually all of one's lifetime supply of neurons are produced during this period.
- Most of the development of the brain after that time, both pre- and post-natal, is via making and pruning synaptic connections between neurons. The development

of connections between neurons is called synaptogenesis.

- Myelination begins in the last weeks leading up to birth, grows rapidly for the first few months, and continues to grow at a slower pace throughout life.
- Synaptic connections are dependent on the types of experiences and environments to which the infant is exposed.
- Neural networks control (1) arousal, attention and emotion; (2) information processing and remembering; (3) regulation and executive function; and (4) self-awareness.

Optimal and Non-Optimal Brain Development During Infancy

- Neural plasticity is the ability of the brain to learn and remember by rewiring its synaptic connections based on experience.
- Stress occurs when the parasympathetic nervous system is not able to counteract the effects of the sympathetic nervous system. Trauma results when there is prolonged activation of the sympathetic nervous system, which activates the hypothalamic-pituitary (HPA) axis and stimulates the release of cortisol.
- The idea that the autonomic nervous system responds unconsciously to stress, rather than the conscious mind, is called neuroception.
- Prenatally stressed infants as well as children who have experienced trauma during the first three years of life are at risk for adverse developmental effects.
- Infants are resilient and can recover from stress, perhaps aided by the plasticity of their developing brains.