Brain Development

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Summary and Keywords

The process of brain development begins shortly after conception and in humans takes decades to complete. Indeed, it has been argued that brain development occurs over the lifespan. A complex genetic blueprint provides the intricate details of the process of brain construction. Additional operational instructions that control gene and protein expression are derived from experience, and these operational instructions allow an individual to meet and uniquely adapt to the environmental demands they face. The science of epigenetics provides an explanation of how an individual's experience adds a layer of instruction to the existing DNA that ultimately controls the phenotypic expression of that individual and can contribute to gene and protein expression in their children, grandchildren, and ensuing generations. Experiences that contribute to alterations in gene expression include gonadal hormones, diet, toxic stress, microbiota, and positive nurturing relationships, to name but a few. There are seven phases of brain development and each phase is defined by timing and purpose. As the brain proceeds through these genetically predetermined steps, various experiences have the potential to alter its final form and behavioral output. Brain plasticity refers to the brain's ability to change in response to environmental cues or demands. Sensitive periods in brain development are times during which a part of the brain is particularly malleable and dependent on the occurrence of specific experiences in order for the brain to tune its connections and optimize its function. These periods open at different time points for various brain regions and the closing of a sensitive period is dependent on the development of inhibitory circuitry. Some experiences have negative consequences for brain development, whereas other experiences promote positive outcomes. It is the accumulation of these experiences that shape the brain and determine the behavioral outcomes for an individual.

Keywords: neurogenesis, synaptogenesis, cell migration, differentiation, myelination, epigenetic, synaptic pruning, apoptosis, plasticity, stress

Introduction

The multitude of precisely timed events that contribute to the development of the mammalian brain is nothing short of remarkable. This series of events, over a relatively short period of time, produces the cells that eventually comprise the brain. After the cells are

generated, they move to where they will become functionally integrated into neural circuits. Once they find their “correct” location, they assume their final fate and take on specific roles in shaping the underlying hardware that supports the behavior that the brain ultimately produces. Cell signaling, or the communication that occurs between cells, is responsible for the coordination of this myriad of events. Despite the relatively truncated period of time that is required to produce the majority of the neural cells that remain with an individual through their lifespan, the actual tuning and maturation of the brain and its circuitry extends through a significant portion of an individual’s lifespan. Regardless of the need for tight control on the circumstances that work together to build a brain, experience has an enormous influence on tuning the process. The science of epigenetics has given us a deeper understanding of the critical importance of experiences and how they contribute to brain outcomes. Perhaps even more astonishing is evidence that shows that prenatal and even preconception experiences of ancestors have the ability to shape both the connectivity of neural cells and ultimately their function in the brains of later generations. A difficulty arises in determining the endpoint of brain development. There are several markers of maturation that vary in their timing across brain regions; simply put, some brain regions mature faster than do others. In addition, brain plasticity is constantly remodeling areas in the brain in response to experience. These factors make it difficult to determine how long it takes the brain to reach full maturity.

Epigenetics and the Developing Brain

Epigenetics refers to the ability of experience to leave a message on top of the genetic code that can regulate how the DNA is read and how proteins are eventually expressed. These chemical messages on the chromatin can appear on the DNA as methyl groups, and on the histones as methylation, acetylation, or other kinds of chemical alterations. The chemical alterations serve to either increase or decrease expression of a gene and the protein that it codes for by increasing accessibility to the gene or restricting it. Typically, methylation of the DNA blocks gene expression whereas DNA demethylation promotes the expression of the gene. Non-coding RNAs (ncRNAS) can also block translation of messenger RNA (mRNA) into proteins. Perhaps the most impressive aspect of epigenetic changes is that they can be heritable (see Figure 1). Gene expression provides the foundation for brain development and because epigenetic messages control gene expression, they govern brain development by integrating environmental cues.

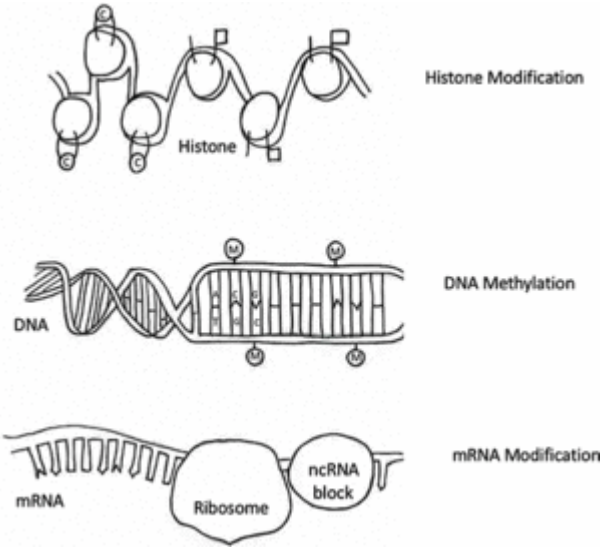

Figure 1. Epigenetic modifications. Environmental experiences have the potential to leave marks on top of the DNA to alter gene expression and protein production. Experiences can cause *Histone modification* by adding chemicals (methyl, acetyl, ubiquitin, or SUMOs—small ubiquitin-like modifiers) to the histone, thereby relaxing or tightening up the chromatin and altering access to the DNA. When access is restricted, the DNA cannot be transcribed into mRNA; when it is relaxed, mRNA transcription can proceed. *DNA methylation* involves adding a methyl group to the DNA at CpG (cytosine-guanine) sites. "A" stands for adenine and "T" stands for thymine. *mRNA modification* can occur when ncRNAs block messenger RNA translation into protein. After Kolb et al. (2016B, Figure 3.25).

The Neurobiology of Brain Development

Cells of the Brain

Neurons are electrically active cells that form connections with other neurons and eventually work in concert to produce behaviors. Neurons have three functional subdivisions: (a) The soma or cell body is the core of the cell that contains the nucleus and machinery to synthesize proteins and deal with other critical cell functions. The soma integrates the information gathered by the dendrites and formulates how the cell will communicate with other neurons further along in the circuit. (b) The dendrites are branches that extend from the soma and function to collect information from other cells. Typically, many dendrites are associated with a single neuron. (c) The axon functions as the main information output of the neuron and is usually a single thin extension that leaves the base of the soma. Axons communicate with other neurons by releasing chemicals known as neurotransmitters.

Another group of cells that are derived from neural progenitors are glial cells, which provide support and sometimes regulate the neurons. Glial cells produced by radial glial cells are considered macroglia. Microglia differ from macroglia based on two characteristics: their size and their origin. Whereas macroglia originate from the neuroepithelial cells that arise from the innermost area of the neural tube, microglia are mesodermal in origin (from the middle layer of the trilaminar embryo). In addition, macroglia are larger cells than microglia. There are two types of macroglia; astrocytes and oligodendroglia. Astrocytes are cells that promote neuronal function by providing nutritional and structural support. Astrocytes contribute to the formation of the blood–brain barrier and repair and promote healing after injury. Oligodendroglia produce the myelin that forms around the axons of neurons as the brain matures (see Figure 2).

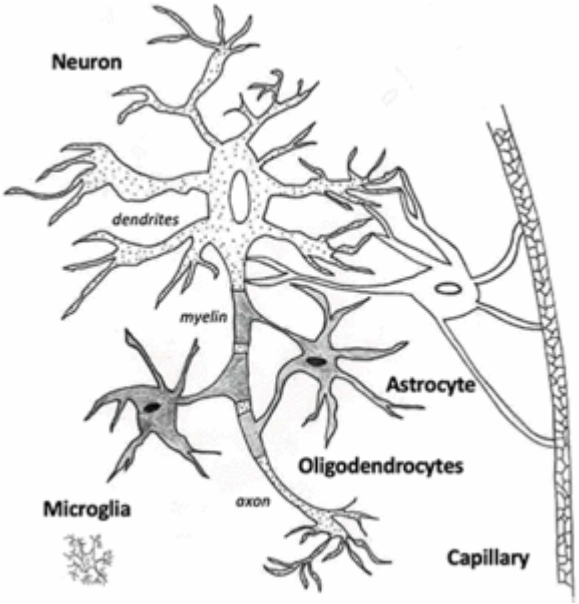

Figure 2. Cell types. There are many types of cells in the brain. Shown is a pyramidal neuron with dendrites and axon. The axon is myelinated by oligodendrocytes. An astrocyte is shown regulating transport of oxygen and nutrients from a capillary and supporting neuron function by providing components to assemble neurotransmitters, neurotransmitters themselves, or metabolic substrates to the adjacent neuron. A microglia cell is also depicted. Microglia provide immune support to the brain.

Microglia are a unique class of brain cells that are derived from yolk-sac primitive macrophage cells that remain in the brain until adulthood. They appear in the brain at about 5 ½ weeks gestation and regulate brain development in two key ways: immune defense and structural maintenance of the central nervous system (CNS). Microglia have a different morphology, an ameboid shape, in the prenatal and early postnatal period of brain development, unlike the “ramified” microglia that inhabit the adult brain. Although traditionally assigned the primary role of the immune cells of the brain, recent studies on microglia in the developmental period have revealed they engage in a number of diverse functions. Microglia have been shown to influence synaptic patterning, cell genesis in the

ventricular area, myelinogenesis in the corpus callosum, phagocytosis of cells in the proliferative zone and hippocampus, cell positioning and cell survival in the cerebral cortex, and axon dynamics in the striatum and corpus callosum (Lenz & Nelson, 2018). Much of this is accomplished by their ability to release diffusible molecules (i.e., vascular endothelial growth factor or VEGF 2) and to phagocytose brain elements (cells and synapses) that are weak, malfunctioning, or underused.

Phases of Brain Development

Ironically, the production of the human brain involves the interplay of processes that are both generative and degenerative. Generative processes include cell birth, migration, differentiation, maturation, synaptogenesis, and myelination. Degenerative processes also play a critical role in brain development and include the processes of cell death and synaptic pruning. The balance of these generative and degenerative processes gives rise to brain structures and connectivity and ultimately refines the physical architecture of the brain to maximize efficiency. There are seven phases of brain development that include: cell birth, cell migration, cell differentiation, cell maturation, synaptogenesis, cell death and synaptic pruning, and myelination (Kolb, Whishaw, & Teskey, 2016B, p. 252).

In humans, during the third week post-conception (Embryonic E; E13–E20), the process of gastrulation occurs during which the embryo forms a trilaminar structure that consists of the ectoderm (outer), mesoderm (middle), and endoderm (inner) germ layers. It is the ectodermal layer that later gives rise to the neuroepithelial cells (NECs) or neural stem cells that will eventually produce most of the cells found in the brain. After gastrulation, on E21 cells aggregate to form what is called the neural plate. On E22, the neural plate transforms into the neural groove which begins to fuse on E23 to form the neural tube. The inner cells of the neural tube form the CNS (brain and spinal cord) whereas the outer cells of the neural tube form the autonomic nervous system (Tierney & Nelson, 2009). The rostral portion of the neural tube closes first (E23–E26) and eventually forms the brain, and the caudal portion closes later (E28), eventually forming the spinal cord. Neural tube defects occur when a portion of the neural tube fails to close. If the failure to close occurs on the rostral portion of the tube, anencephaly, a condition wherein portions of the brain and skull fail to fully form, results. A baby born with anencephaly has sensory processing deficits and a failure to feel pain. Anencephalic infants usually die shortly after birth. Spina bifida is a condition that arises when a portion of the caudal neural tube fails to close. Varying degrees of motor impairments are seen in children with spina bifida depending on where the lesion in the spinal cord occurs, but for those most severely affected, paralysis can result. Neural tube defects are often associated with a lack of folic acid in the maternal diet but can arise from other genetic or environmental factors.

Cell Birth

The central-most portion of the neural tube gives rise to the ventricles and NECs form the cell layer around the ventricles called the ventricular zone. During neurulation, symmetric cell division of the NECs starts on E25 and results in a rapid expansion of the neural stem cell population by producing two daughter cells after each division; this continues to

E42. It is also during neurulation that a primitive map for the cellular organization of the brain emerges, and by E28 the nascent structures that become the forebrain, midbrain, and hindbrain are visible in the human embryo (Stiles & Jernigan, 2010). Proteins called morphogens that appear in NECs assist in spatial patterning by instructing cells to move in either the rostral or caudal direction and directing whether the cell should take a dorsal or ventral position in the brain. Just prior to neurogenesis, at about E42, the NECs start producing radial glial cells that extend their processes from the ventricular zone to the pial surface of the developing brain. The radial glial cells act as progenitors and give birth to both neurons and glia that are guided along them to their ultimate destination in the developing brain (Howard et al., 2008) . But at least three other types of progenitor cells also appear at this time: intermediate precursor cells (IPCs), short neural precursor cells (SNPs), and basal radial glial cells (bRGCs). All have the ability to produce neurons. The IPCs form the proliferative region known as the subventricular zone. IPCs undergo symmetrical divisions to self-renew but also produce pairs of post-mitotic neurons. SNPs produce neurons but they remain in the ventricular zone. The bRGCs inhabit the outermost region of the subventricular zone and they engage in self-renewal and production of neurons. At the end of neurogenesis, bRGCs, like RGCs, transform into progenitors that produce astrocytes.

It is important to note that in the postnatal period and extending throughout the lifespan, there are a few privileged brain regions that continue to produce neurons. The walls of the lateral ventricle are one such site. New cells generated here mostly migrate to the striatum but some find their way to the rostral migratory stream destined for the olfactory bulb. New cells arrive in the olfactory bulb throughout life and once they have migrated to their terminal position they assume their terminal fate. While most of the newly generated cells transform into inhibitory interneurons, some become periglomerular cells and the remainder, astrocytes. Continued neuronal production through the lifespan in the olfactory bulb may serve to influence olfactory circuitry by enhancing functional plasticity in these circuits (Lledo & Valley, 2016). The dentate gyrus of the hippocampus also appears to produce neurons throughout life but this issue is currently a topic that is hotly debated (Boldrini et al., 2018; Sorrells et al., 2018). Regardless of the debate, a number of studies show evidence of adult hippocampal neurogenesis (AHN), and it is thought that AHN may be reduced by chronic or toxic stress, and increased by exercise and treatment with antidepressants and selective serotonin reuptake inhibitors. It has been proposed that the anti-anxiety, antidepressant effect of these medications is linked to the production of new neurons in the hippocampal circuitry that replenish granule cells to their typical levels, thereby restoring normal hippocampal activity (Planchez, Surget, & Belzung, 2020).

Migration

Most cells migrate from the ventricular zone in the center of the developing brain and travel to their ultimate destination in the cortex. The cerebral cortex is a six-layered structure, and cells that leave the ventricular zone first are destined to arrive in the deepest cortical layers. These neurons lack a transcription factor, CUX-2. Cells that bear the

CUX-2 transcription factor migrate to the upper layers of the cerebral cortex and in doing so have to push through the neurons that have already taken up residence in the deeper layers (Franco & Müller, 2013). Thus, the cortex is considered to develop in an inside-out fashion, with the deepest layers established first followed by the outermost layers. Cajal-Retzius cells inhabit layer one of the developing cortex and provide a molecular signal called Reelin that acts as a stop signal for cells on the migratory quest to reach their correct final destination. Animals with Reelin deficiencies do not develop the typical laminar structure in the cortex. Disruption of the Reelin signaling cascade in humans often results in neurodevelopmental disorders such as schizophrenia, autism, bipolar disorder, and depression (Folsom & Fatemi, 2013).

Cells that are bound to become glial cells use multiple modes of migration that are ultimately determined by their final destination. Glial progenitors proliferate in the subventricular zone. Cells destined for dorsal positions in the brain migrate out in a radial fashion to the corpus callosum. They then either stay in the callosum or they continue to migrate along RGCs to their final position in the cortex. When cells have a lateral destination, they track white matter in a lateral direction and then follow RGCs to their targeted home.

Neurons are of two principal types: excitatory and inhibitory. Most excitatory neurons have a larger pyramidal shape and are considered pyramidal neurons. Excitatory neurons utilize neurotransmitters such as glutamate to communicate with other neurons and have dendritic spines extending from their dendrites. The dendritic spines provide points of contact with other neurons. Pyramidal neurons follow radial glial cells to reach their cortical destination and are considered to have migrated in a radial fashion. In contrast, inhibitory interneurons are typically stellate in form and do not bear the dendritic spines seen on excitatory neurons (see Figure 3). These interneurons do not originate in the ventricular region of the brain but rather come from the ventricular zone in an area of the ganglionic eminences and the preoptic area. The ganglionic eminences are three distinct transitory structures (lateral, medial, and caudal) that are located between the sites that later develop into the caudate nucleus and thalamus (Wonders & Anderson, 2006). The medial and caudal ganglionic eminences and the preoptic area give rise to the interneurons that inhabit the cerebral cortex. Interneurons reach their final destination by tangential migration guided by a series of tropic molecules that arise from local regions of the developing cortex (Stiles & Jernigan, 2010). The major neurotransmitter employed by inhibitory neurons is gamma aminobutyric acid (GABA). Inhibitory neurons serve in cortical networks to enhance efficiency of neuronal communication. In addition to this important role in modulating cortical processing, during development inhibitory neurons are also involved in regulation of neurogenesis and migration, and plasticity in cortical circuitry (Wonders & Anderson, 2006). These developmental functions of GABAergic interneurons appear to be related to the depolarizing or excitatory function of GABA during development rather than a hyperpolarizing or inhibitory function that GABAergic cells possess in the postnatal period. Indeed, it appears that the accumulation of an excessive number of chloride ions (Cl-) in immature inhibitory interneurons is responsible for the excitatory action of GABA. The reverse in GABA polarity from excitation to inhibition occurs shortly

after birth and is regulated by oxytocin receptors. Oxytocin released during birth interacts with oxytocin receptors that act directly on Cl- transporter proteins to effectively "flip" the GABA switch. Dysfunction in the oxytocin system that controls the GABA switch may contribute to developmental disorders such as autism.

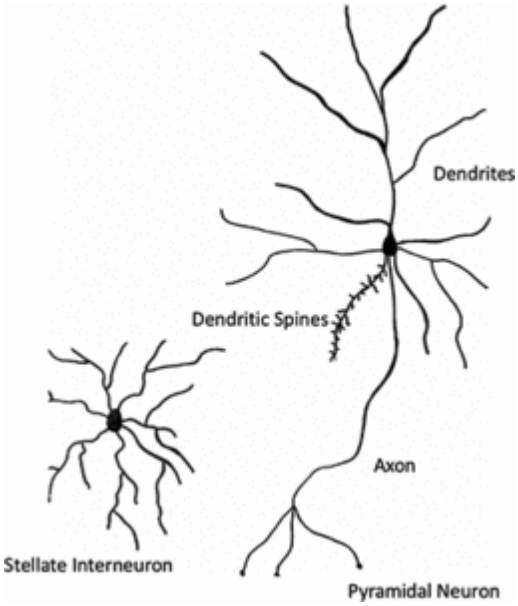

Figure 3. Neuronal types. A *pyramidal neuron* is named after the shape of its soma or cell body. Dendrites extend from the soma to gather information from other connected neurons. The site of connection, the synapse, is typically a dendritic spine. The pyramidal cell depicted has one branch with dendritic spines shown but these spines would be located on all dendrites of the neuron. A single axon extends from the base of the pyramidal-shaped cell body and can branch as shown to make contact with multiple other neurons. Pyramidal neurons are predominantly *excitatory*. Stellate means star shaped. The *stellate* shape is the form of most of the *inhibitory* interneurons in the brain.

Differentiation

The morphological and functional fate of a cell, that is, the type of brain cell it is destined to become, is determined by at least two types of patterning cues. Both spatial and temporal cues contribute to the process known as "patterning" during which cells transform into their final fully differentiated state. Spatial patterning occurs at the time of NEC production and determines not only where a cell will migrate to, but also what sort of cell it can transform into based on its location in the brain. Another type of patterning, temporal patterning, also plays a pivotal role in cell fate determination. Temporal patterning refers to the increasingly restricted possibilities of cell types that occur through progressive cell divisions of precursor cells. In addition to spatial and temporal patterning cues, cell fate is also determined by progenitor competence. As progenitor cells lose their competence to produce early born cell types, they gain competence to produce later born cell types. Thus, the production of particular cell types is restricted to particular windows of time. Post-mitotic cells have some degree of flexibility in their fate specification but this becomes more and more restricted as they age. The switch from producing neurons to glial cells also reflects an important transition in competence for neural progenitor cells such as NECs and radial glia. This is due in part to the highly methylated status of the glial fibrillary acidic protein (GFAP) promoter site in progenitors that are in their neurogenic

phase (Kohwi & Doe, 2013). Later demethylation of the GFAP promotor site allows the eventual production of the GFAP protein that is associated with astrocyte structure and function.

Maturation

Once neurons have reached their ultimate destination in the cortex and assumed their final cell fate, they mature by extending processes, dendrites and an axon, to facilitate communication with other cells. Dendrites are induced to elongate in order to provide potential sites of contact from presynaptic neurons. The axon terminal is guided to target cells by growth cones that enable the axon to detect potential viable connections. The extension of dendrites and axons allows the cell to achieve a fully functional state once synapses have been established. In the brain of a newborn, cells show limited dendritic arbor but by the time the baby reaches two years of age, dendritic branches and axonal connections have become abundant. This exuberant formation of cell processes is reflected in a two-year-old child’s remarkable ability to absorb new information and add new behaviors to their rapidly expanding repertoire.

Synaptogenesis

Synaptogenesis is the production of synapses between cells. A synapse is the functional site of cell–cell communication and is typically found between a presynaptic axon terminal and a postsynaptic dendrite. Information coming down the axon from the presynaptic cell has the potential to influence the output of the postsynaptic neuron based on the strength of the synaptic connection and where it is found on the postsynaptic cell. Synapses are of two general types: excitatory and inhibitory. Excitatory synapses have a wider synaptic cleft (the space between the pre- and postsynaptic terminals), round synaptic vesicles that contain neurotransmitters, a large active zone where neurotransmitters are released, and a dense network of proteins found on the postsynaptic side. Inhibitory synapses are characterized by a narrow synaptic cleft, flat synaptic vesicles, a smaller active zone, and sparse protein networks on the postsynaptic side. Most excitatory synapses are found on dendrites or their dendritic spines, whereas most inhibitory synapses are found on the cell body (Kolb et al., 2016B, p. 146). Experience drives synapse production and can induce dendritic spine production in areas of high cell–cell communication. Neurons can make thousands of synaptic connections with other cells but the ultimate number of connections appears to be, at least in part, regulated by the cortical area in which the cell resides. Posterior brain areas (i.e., visual regions of the cortex) have fewer connections than anterior areas of the brain; some areas of prefrontal cortex have upwards of 20X more connections than primary visual cortex (Elston, 2003).

Cell Death and Synaptic Pruning

Neurons are overproduced in the developing brain. Although a newborn brain is only about a quarter of the size of an adult brain, their tiny brains contain roughly twice as many cells as are found in adulthood. Neurons that fail to make appropriate and useful connections are eliminated and as many as 50–70% of neurons initially produced fail to thrive (Stiles & Jernigan, 2010). This loss of cells is referred to as “neural Darwinism,” as

cells compete for resources (connections and survival factors) and only the “fittest” survive. Programmed cell death or apoptosis occurs naturally when a death signal is triggered and executioner caspases are activated within the cell. Cell death has been observed to occur at the time the neural tube closes and continues throughout the shaping of the brain. There are a number of triggers for programmed cell death. Executioner caspases can be activated by extrinsic death ligands or intrinsic signals such as DNA damage, loss of survival signals, overproduction of reactive oxygen species, or endoplasmic reticulum stress (Yamaguchi & Miura, 2015). Synaptic pruning occurs when synapses are weak, non-functional, or no longer used. Microglia phagocytose the remains of cells that have undergone programmed cell death and they strip away synapses that have been tagged for destruction. An intense period of synaptic pruning occurs in the early postnatal period at between one and two years of age and again in the juvenile period as the brain is preparing for the emergence of adult-like behaviors. It is estimated that 40–50% of synapses that are generated are eventually pruned away (Low & Cheng, 2006).

Myelination

Once axons reach their appropriate targets, they are wrapped in myelin produced by oligodendroglia. The myelin sheath facilitates the transfer of information from one cell to another by increasing the speed of neurotransmission. Myelin also provides physical support to the axon and the oligodendrocytes that produce myelin supply the axon with nutritional support (Stassart, Mobius, Nave, & Edgar, 2018). Cortical areas that mature earlier, that is, sensory and motor areas, show earlier myelination than association areas of the cortex that take longer to complete the maturation process. A study that compared the rates of myelination in chimpanzees and humans showed that while chimpanzees completed the myelination process at about the time of sexual maturity, in humans, myelination extended well into adulthood. The authors proposed that the extended period of maturation in the human brain allowed for the greater degree of cognitive development and cortical plasticity observed in humans (Miller et al., 2012). They also noted that the extended period of plasticity created a vulnerability to environmental insults in later maturing areas. A recent study of myelination in adolescents and young adults showed that delayed myelination in limbic association areas in the brain was associated with a higher risk for psychopathology and associated mental illness (Table 1; Vanes et al., 2019).

Table 1. Seven Phases of Brain Development: Timing, Process, and Purpose

Developmental Phase	**Timing**	**Process**	**Purpose**
1. Cell Birth	-Neurogenesis starts on E42 and is largely complete by the fourth month of pregnancy -Gliogenesis starts during the fourth month and continues throughout life	-Genesis of neurons and glia	-Produce cells to carry out brain function, i.e., "behavior"
2. Cell Migration	-Starts shortly after neurogenesis and continues for about six weeks	-Movement of cells to their final position	-Create functional areas in the brain
3. Cell Differentiation	-Begins shortly after cells are generated (~E42) and is completed once they reach their final destination	-Precursor cells transform to specified cell type	-Assume precisely defined roles
4. Cell Maturation	-Starts upon the cell achieving its final destination	-Growth of dendrites and axons	-Establish "incoming" and "outgoing" routes for communication
5. Synaptogenesis	-Starts *in utero* about 23 weeks post-conception -Peaks after first year of life	-Formation of cell to cell communication sites, i.e., synapses	-Create functional networks to support behavior

	- Continues through the lifespan as learning takes place		
6. Cell Death and Synaptic Pruning	-Cell death starts at E23 with the closure of the neural tube and continues -Peaks during adolescence -Continues through the lifespan	-Programmed cell death and stripping of non-functional or underused synapses	-Refine brain function -Increase efficiency
7. Myelination	-Begins in the fifth month of gestation -Continues well into the “thirties” in humans	-Formation of myelin sheath on axons connecting to other neurons	-Enhance speed of neurotransmission -Hallmark of cortical maturation

(*) Some privileged sites within the brain may have continued neurogenesis through the lifespan (i.e., dentate gyrus [Boldrini et al., 2018] and olfactory bulb [Durante et al., 2020]).

Development of Brain Systems

Throughout development, brain regions and their associated networks change and at any given developmental age, some show more advanced refinement than do others. For example, in newborns the occipital white matter develops before white matter in frontal areas, and central regions show advanced white matter development compared with peripheral areas. An imaging study of healthy human fetal brains between 18 and 39 weeks gestation has revealed differences in global and hemispheric brain growth (Andescavage et al., 2017). This study showed that the second half of pregnancy supported an increase in fetal cortical volume that was more than 20-fold and demonstrated that cortical volume change is exponential rather than linear. The greatest contributor to this volumetric change was attributed to increases in fetal white matter (22-fold increase) followed by an increase in cortical gray matter that showed a 21-fold increase in volume. The region of most rapid brain growth over the second and third trimesters was the cerebellum. Other work has demonstrated that the cerebellum continues to undergo rapid expansion (up to 240%) in the first postnatal year.

Primary motor and sensory areas are functional in the developing brain before association areas become elaborated and active. Immature forms of visual, sensorimotor, and auditory networks have been detected using rs_fMRI techniques as early as 30 weeks gestation. Studies of newborns using similar methodology have shown that primary motor and sensory networks are more extensively developed and localized than are areas that support higher cognitive functions. The restricted localization of primary networks in newborns reflects similar findings in adults (Thomason et al., 2015).

Although the reason our brains show lateralization of function remains speculative, it is generally thought that it confers efficiency and reduces the need for duplication in the space-limited brain. Language is a cognitive function that is lateralized and is typically found in the left hemisphere of right-handers and most left-handers. Surprisingly, differences in left and right hemispheric growth rates emerge in utero and result in greater gray matter volume in the left hemisphere as compared with the right. Similarly, the left cerebellar hemisphere was determined to be larger in mid-gestation but the right cerebellar hemisphere grows at a faster rate (Andescavage et al., 2017).

Plasticity and Sensitive Periods in Brain Development

Brain plasticity is the ability of the brain to change in response to either internal or environmental cues. Three types of plasticity contribute to brain development: experience- independent, experience-expectant, and experience-dependent. While the genome contributes the foundational organization of brain development, connections are formed and refined by internal and external cues; this is an example of experience-independent plasticity. Experience-expectant plasticity is the tuning of the brain and its connections as a result of experiences generated by the environment. For instance, a newborn is considered a “citizen of the world” as it can distinguish sounds from all spoken languages, but by the age of about one year, children become “culture bound listeners” and can only distinguish the sounds of languages that were spoken to them (Kuhl, 2010). Experience-dependent plasticity refers to the brain’s ability to respond and adapt to environmental signals and demands; learning something new requires changes in the architecture of the brain to support that learning. Experience-dependent plasticity begins in the fetal period and extends through the lifespan (Kolb, Harker, & Gibb, 2016A).

Critical or sensitive periods in brain development refer to windows of opportunity that arise at different times for different brain systems during which experience is required to optimize performance. If the required experience is not provided during the sensitive period, it may be difficult if not impossible to retune the system later on. For example, the sensitive period for binocular vision is thought to occur between three and eight months of age. During this period, equal visual input from both eyes develops typical binocular vision. If, however, vision is occluded or limited from one eye, binocular vision will fail to develop in its usual form and the eye that provided input to the visual cortex becomes dominant. Thus, critical periods provide excellent examples of experience-expectant plas-

ticity. Recent work has demonstrated that the windows for critical periods are controlled by the maturation of GABAergic circuits that offset excitatory input with inhibition. In a sense, the critical period closes as “molecular brakes” dampen the plasticity response and alter the excitation/inhibition balance (Hensch, 2018).

Factors Influencing Brain Plasticity and Development

Sex Hormones

During gestation, gonadal hormones shape the developing body. Exposure to testosterone early in gestation masculinizes the fetus and the development of a penis and testes is initiated. In the absence of testosterone exposure, the fetus develops genitals that are characteristic of females. In humans, the SRY gene found on the Y chromosome is responsible for inducing the fetal testes, which become functional at seven weeks gestation. Testosterone differences occur in males and females through weeks 8–16 in gestation and then once again shortly after birth. During postnatal weeks 4–12 there is another surge in testosterone in boys over girls and this time frame is often referred to as “mini puberty.” These two high testosterone periods are responsible for organizational sex differences in the brain. Although some feminizing effects of estrogen have been demonstrated, organizational effects of steroidal hormones predominantly result from testosterone exposure. Later, high levels of testosterone in the pubertal and adult periods of life have activational effects on the architecture that has been established by early exposures. The male brain is larger than the female brain in the first few weeks of life and again in adulthood but the difference is not linear across the lifespan; it depends on the age at sampling. Many of the phases of brain development that proceed differently for males and females including cell birth, migration, cell death, synaptogenesis, and myelination are regulated by microglia. Males have many more microglia in multiple brain areas than are found in females, and these microglia have a more immature appearance, that is, ameboid morphology, than those seen in females. In the hippocampus, females have a higher rate of microglial initiated phagocytosis of progenitor cells, which may account for the known sex difference in hippocampal neurogenesis during development (Lenz & Nelson, 2018). The many observed sex differences in behavior suggest the existence of anatomical differences in the brain. Gender identity, sexual orientation, and child play all show large sex differences in their expression. For example, a high level of prenatal testosterone exposure is strongly correlated with a preference for play with vehicles over dolls. This sex-linked preference for play is typical of males but is also observed in girls with congenital adrenal hyperplasia who, as a result of this genetic disorder, experience elevated testosterone levels during gestation. Sex-linked differences also exist in psychiatric diagnoses. Males are more commonly diagnosed with autism spectrum, conduct, and attention deficit disorders, whereas females are more commonly diagnosed with eating disorders, anxiety, and depression. It is no surprise that sex differences in the brain occur as they are predicted by observed by sex differences in behavior. The big surprise is that the dif-

ferences observed in the brain are not large and appear to serve to make male and female brains function more alike (Hines, 2020). It is increasingly clear that sex hormones alone do not sufficiently account for sex and gender differences in brain and behavior. Hormones and environmental factors such as parental socialization and later self-socialization contribute to the complexity of the sex/gender issue and must be accounted for in order to master a better understanding of hormonal influences on brain development.

Stress

Stress is defined by Merriam Webster (N.D.) as “a physical, chemical, or emotional factor that causes bodily or mental tension and may be a factor in disease causation.” It is considered to be of two types: eustress is positive stress or stress that enables an individual to successfully overcome a challenging situation, and distress or toxic stress is a negative stress that arises from chronic or traumatic stress and compromises an individual’s ability to adapt to or overcome a stressful situation. It is well known that toxic stress has a profound influence on brain development and the timing of the stress, the amount of stress, and the sex of the individual experiencing the stress contribute to its impact (Gibb, Mychasiuk, Harker, & Kolb, 2013).

Prenatal Stress

Mothers who experience excessive distress during their pregnancy have infants who have reduced cortical gray matter in prefrontal cortex, premotor cortex, and medial and lateral temporal lobe (Buss, Davis, Muftuler, Head, & Sandman, 2010). These children show attention deficits and hyperactivity. It now appears that parental stress during the preconception period can also impact child brain and behavioral development. Animal models have demonstrated that paternal preconception stress alters brain and behavioral outcomes in offspring, particularly the males, and the effects are lifelong (Harker, Carroll, Raza, Kolb, & Gibb, 2018). Paternal effects seem to be mediated by alterations in sperm methylation patterns and microRNAs found in semen. Maternal preconception stress can also alter offspring brain and behavioral development but the effects appear less dramatic than those observed for males (Jenkins, Harker, & Gibb, 2018). Bowers and Yehuda (2020) document evidence of preconception trauma and extreme stress on humans. These exposures to preconception toxic stress predispose individuals to psychiatric disorders and other disease states but the mechanisms of intergenerational transmission of trauma is, as of yet, unavailable.

Postnatal Stress

When the world discovered the extreme neglect experienced by Romanian orphans who had been raised in impoverished institutions, there was an outpouring of support and many of these children were adopted into loving families in the United Kingdom and North America. Although some of these orphans (now grown) seem remarkably unscathed by their experiences, most bear the consequences of early deprivation and neglect. It appeared that children adopted out by age six months showed the most remarkable recovery, whereas children adopted out at later stages of development had more

lasting negative outcomes. Children who spent more time in an orphanage had challenges in forming relationships, engaging with others, and had higher rates of social, emotional, and cognitive problems than other children. These issues seemed to be related to their inability to produce two particular molecules, arginine vasopressin and oxytocin (Wismer Fries, Ziegler, Kurian, Jacoris, & Pollack, 2005); both of these peptides are critical for the formation of social bonds and for regulating emotional behavior.

A study on the effects adverse childhood experiences (ACEs) on physical and mental health was undertaken in 1995–1997 by Kaiser Permanente and the Center for Disease Control. In this study, 17,000 adults received a questionnaire regarding their childhood experiences, with 10 indicators of adversities, and follow-up surveys regarding their current health status and behaviors (Felitti et al., 1998). This study was the first of its kind to detail the effects of traumatic stress on brain and behavioral development, and the results were shocking. Far more children experience traumatic stress than was previously thought and the long-term effects of those stressors is profound. Children who have three or more ACEs are known to have more difficulties in school. They are more likely to require special education, more likely to be suspended or expelled, score lower on standardized tests, and have poorer health. Remarkably, these children also show less brain lateralization. Adults who reported having experienced three or more ACEs are more likely to have low-wage jobs, if they are employed. Many are on social assistance because of chronic physical or mental health problems, or addictions. Based on the findings of the Romanian orphan studies and the ACEs studies, it is clear that we need to better understand how to control the responsivity of the stress system in order to improve developmental trajectories and brain function in trauma-exposed individuals. Taken together, these studies led to a greater appreciation of the impacts of early experience on brain development.

Diet

The foods that we eat not only provide the building blocks for the proteins, fats, and carbohydrates that are constituent parts of our bodies and brains, they also provide the basic substrates for assembling the neurochemicals that act as transmitters in our nervous system. The energy that the brain requires to fuel its operations also comes from our diet. Poor nutrition in childhood is associated with cognitive impairments later in life. The time during which the brain undergoes its most rapid development is also the time during which it is most vulnerable to inadequate nutrition. This period extends from about the beginning of the third trimester (24 weeks gestation) until two years of age. At the end of this period, the brain has achieved between 75 and 90% of its final adult volume. Many nutrients are important for the development of the brain but key nutritional elements during this period of rapid development include: protein, long chain polyunsaturated fatty acids, choline, iron, zinc, selenium, iodine, folate, and vitamin A. These nutrients support neuronal growth and function, and are also critical for glial cell function and survival. As one might predict, early nutritional deprivation reduces cell proliferation and decreases both neuronal and glial cell numbers, whereas later deprivation affects the developmental processes of differentiation, maturation, and synaptogenesis. These processes affect

neuronal complexity and the number of synapses that form between cells. Inadequate nutrition can have global effects on brain function, or it can affect specific circuits in the brain depending on the timing and the size of the deficit and the need for particular nutrients at particular times during development (Georgieff, 2007). There is an interesting relationship between stress and nutrition that is worth noting with respect to maternal food choices during pregnancy. The dynamics of hunger and satiety can be influenced by psychological stress and this can change eating patterns by influencing the amount and type of food that is chosen. A heightened stress response gives rise to what is known as “emotional eating.” Emotional eating favors high-sugar, high-fat food choices that serve to moderate the stress response. The stress response also interacts with a high-fat diet to trigger a proinflammatory response through the production of cytokines. Exposure to elevated cytokines increases the vulnerability of the developing offspring for neurodevelopmental disorders. Understanding how prenatal stress and nutrition interactions cause changes to metabolic, endocrine, and inflammatory processes in the developing brain would support clinical interventions aimed at mitigating their negative consequences (Lindsay, Buss, Wadhwa, & Entringer, 2018).

Microbiota

Any discussion of the contribution of nutrition necessitates the mention of the critical role of the gut microbiota in brain development. The gut microbiota is comprised of trillions of microbes and has been shown to take two to three years after birth to mature to a form resembling that seen in adulthood. Gut colonization is initially determined by the bacteria that reside in the amniotic fluid that the developing infant is immersed in and is further influenced by method of delivery (i.e., vaginal vs. caesarian section), by feeding practices such as breastfeeding versus formula, introduction of solid foods, day care attendance, illness, and exposure to antibiotics (Diaz Heijtz, 2016). The gut microbiota is important for harvesting energy and nutrients from ingested foods and it has been proposed that normal development of the gut microbiota is required to meet the metabolic demands of the developing brain during its rapid growth spurt and beyond (Goyal, Venkatesh, Milbrandt,Gordon, & Raichle, 2015). The microbiota produces compounds such as neurotransmitters that have the potential to influence both brain development and brain physiology. Studies have shown children with severe undernutrition have a gut microbiota that is immature compared with healthy age-matched controls who show typical growth phenotypes. Disruptions in the development of a normal gut microbiota may disrupt brain development or metabolism either globally or in specific neural circuits depending on the timing and nature of the disruptions. Processes affected by such disturbances include synapse formation or myelination. The coordinated development of both the brain and the gut microbiota may indicate that bidirectional signaling is important for their mutual normal maturation.

Social Relationships

It has long been recognized that positive nurturing relationships between a caring adult and a developing child is a key factor in promoting healthy brain development. Attachment in mammals is typically considered between a mother and her offspring, but humans engage in allo-parenting wherein more than one adult takes a caregiving role with the infant. During the attachment process, the baby cries and the caregiver responds to the signal of the baby by addressing its needs. When this happens, the baby's needs are met and they learn to rely on their "attached" adult to meet their ongoing needs. This is called secure attachment and it is an important indicator of a positive bond between an infant and a parent/caregiver. In humans fathers, grandparents, caregivers, and even teachers can serve as secure attachment figures to children. Children who have a secure attachment with a nurturing caregiver have someone to turn to when they are feeling distressed, and this caring relationship buffers their stress and promotes development of the child's emotional regulation and executive function. Strong father attachment predicts lower externalizing and conduct problems, whereas secure mother attachment is associated with increased popularity and lower levels of antisocial behavior. Adolescent girls with secure father attachment are less likely to engage in sexual activity before age 16, have better self-esteem, and show increased participation in sports (Ranson & Urichuk, 2008). It has also been shown that father vocabulary predicts the child's vocabulary even though mothers are more likely to speak more to their children (Pancsofar & Vernon-Feagans, 2010).

In their book *The Irreducible Needs of Children*, Doctors Brazelton and Greenspan (2000) outline the seven needs of children: 7. Physical protection, safety, regulation; 6. Experiences tailored to individual differences; 5. Developmentally appropriate experiences; 4. Limit setting, structure, and expectations; 3. Stable, supportive communities and cultural continuity; 2. Protection of the future; and most importantly, the number 1 need is positive, nurturing relationships (see Figure 4).

Executive Function and Resiliency

Executive function (EF) is a group of skills supported by the prefrontal cortex that include working memory, cognitive flexibility, and behavioral inhibition. Family context has been shown to be an important predictor of executive function in children. Specifically, parents who display strong EF have children with stronger EF. In part, this relationship is mediated by parental engagement in EF-building activities with their children (Korucu, Litkowski, Purpura, & Schmitt, 2019). It is recognized that the EF skills displayed by a kindergarten student are a better predictor of their academic success than their IQ. An exciting aspect of EF is that it can be improved with training. In a recent study of preschool children (three to five years old), early childhood educators were trained on a series of games that were demonstrated to promote executive functions and were asked to incorporate these playful activities into their everyday programming. Children were tested prior to learning the games at the start of the academic year and then were tested again at the end of the term. Children who participated in the games with their teachers

showed significant improvements in their EF skills, whereas children whose teachers did not play the games with them did not show any EF gains (Coelho, Amatto, Halliwell, Gonzalez, & Gibb, 2020).

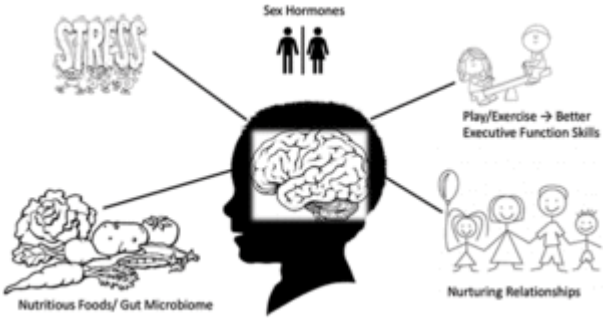

Figure 4. Factors influencing brain development. A myriad of factors influence the developing brain. Sex hormones affect brain structure and interact with other experiences to cause sex differences in behavioral output. Stress in both the prenatal and postnatal periods can have profoundly negative effects on the developing brain and can influence brain plasticity and behavior. Enduring positive and nurturing relationships are thought to be one of the most positive influences on brain development. Play promotes better executive function skills in children, which serves to bolster a child's resiliency, leading to improved developmental trajectories.

Strong executive function skills are associated with resiliency in children and adolescents. Resiliency is the ability to bounce back to normal after a stressful situation, a challenge, or toxic stress (adversity). Resiliency is not a trait, but rather is a state and is context dependent. A child in one situation may demonstrate resiliency but in another may show vulnerability and even stress intoxication. Children who show resilience develop it with practice, and the more opportunity they have to strengthen their resiliency skills, the less likely they are to be victimized by stress. Resilience develops as children are allowed to experience stressful situations while guided by supportive adults who buffer the stress and assist with resolving the situation with competency. Over time, children learn the skills and strategies that help them manage stressful situations with success. Resiliency in children is predicted by secure attachment with a caring adult(s), high childhood IQ, strong EF, and friendships.

As the profound negative sequalae of adversity during development become more apparent, and with the shocking number of adversities our children face during development, it becomes clear that we need to move toward teaching skills that promote resiliency in families, parents, and children. Adults need to provide supportive nurturing relationships and model good EF and resiliency in order for our children to achieve their optimal developmental potential by building healthy brains.

Conclusion

Brain development takes decades to complete and even the mature brain is constantly changing to meet the demands of life. The finished product relies on a balance of generative and degenerative processes to produce a brain that is uniquely attuned to our personal experiences and context. During the development of the brain, experience has a profound effect; positive experiences and/or relationships can produce a brain that is better able to manage life's challenges, whereas negative experiences and/or relationships can leave a brain incapable of meeting the demands of life. If adults can protect children from toxic stress and provide positive and nurturing support, they are sure to help a child achieve their full potential.

Abbreviations

VEGF
– vascular endothelial growth factor
E
– embryonic day
NECs
– neuroepithelial cells
GABA
– gamma aminobutyric acid
EF
– executive function

Further Reading

Websites

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Zero to Three, **Brain Development**

Centers for Disease Control and Prevention, **Early Brain Development and Health**

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