CHAPTER 3

Neurobiology of Fetal and Infant Development

Implications for Infant Mental Health

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Contemporary models of human development emphasize complex, dynamic interactions between genetic predispositions and environmental pressures at all stages from conception to maturity. Theoretical frameworks such as Bronfenbrenner's *ecological systems theory,* for instance, situate development within multiple life contexts shaping child trajectories (Bronfenbrenner, 1979). Recent scientific advances, meanwhile, have shed light on molecular mechanisms underpinning the emergence of developmental phenotype from a complex interplay of genotype and environment. Work on epigenetics, for instance, elucidates how environmental exposures can leave durable chemical signatures on DNA and surrounding molecules to influence gene expression. In the field of neurobiology, substantial research has elucidated mechanisms of "neural plasticity," or the capacity of neural tissues to change in response to environmental exposures. Evidence of heightened neural plasticity during early development helps explain the profound susceptibility of cognitive, behavioral, emotional, and health outcomes to fetal and infant exposures.

In this chapter, we provide a selective review of some of the ways in which environment and genes interact to shape child brain and behavioral development, with a particular focus on the neurobiology of infant mental health. We begin by providing an overview of prenatal and early postnatal brain development and organization. Next, we describe our current understanding of how environmental influences impact neurodevelopment, focusing on what is known about neurobiological mechanisms of early brain plasticity. To delve deeper into the mental health implications of neural plasticity, we consider the case of individuals exposed to substantial early psychosocial adversity—experiences such as prenatal maternal psychological stress or depression, child abuse or neglect, parental psychopathology, and depriving institutional care. We explore what is known about the neurobiological mechanisms by which such adverse early exposures shape developmental outcomes and mental health in infancy and beyond.

Throughout our discussions, we emphasize literature drawing on measures of neurobiological functioning and structure. Techniques discussed include electroencephalography (EEG), which uses small sensors placed on the scalp surface to measure the synchronous activation of large numbers of neurons, thus assessing characteristics such as brain maturity and specialization. Other important techniques include magnetic resonance imaging (MRI), which uses magnetic fields to elucidate brain structure or function with better spatial resolution. We also draw on important insights from animal models, emphasizing the significance of these

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findings for our understanding of human neurodevelopment.

To close the chapter, we explore factors thought to underpin differential susceptibility to early environmental adversity across individuals. Here, we consider why some individuals exposed to early social risk factors are spared serious neurodevelopmental sequelae. We consider how insights into neurobiological mechanisms underpinning differential responses to the environment can be leveraged to promote "resilient" outcomes in infant mental health. We finally consider priorities for future research, including ongoing efforts to develop enhanced interventions informed by neuroscientific evidence.

Brain Development

The human brain develops over a protracted period of time, beginning to form just a few weeks after conception and not reaching adult maturity until approximately the third decade of life (Somerville, 2016). A relatively similar functional and structural brain organization arises for all humans experiencing a typical developmental trajectory. The organization of this system has its inception in the formation of the neural tube, comprising both motor and sensory cells, with a basic orientation situating sensory inputs on the tube's dorsal face and motor outputs on its ventral surface. This organization is maintained across the course of development, with a similar sensory–motor distribution in the spinal cord and, to some extent, the cerebral cortex. Specifically, because the ventral surface of the neural tube forms the more anterior parts of the brain, the sensory–motor organization occurs again in the brain roughly along the anterior–posterior axis. Each human brain has several sulci (inner folds) and gyri (outer portions of the folds) that are similar across individuals. These major sulci and gyri provide guides to identify lobes of the brain (see Figure 3.1), with lobes, in turn, providing the coarsest organization by which regions of the brain, serving particular functional roles, are typically identified.

Embryonic Origins of Neurodevelopment

As noted, human brain development spans the first weeks after conception into the third de-

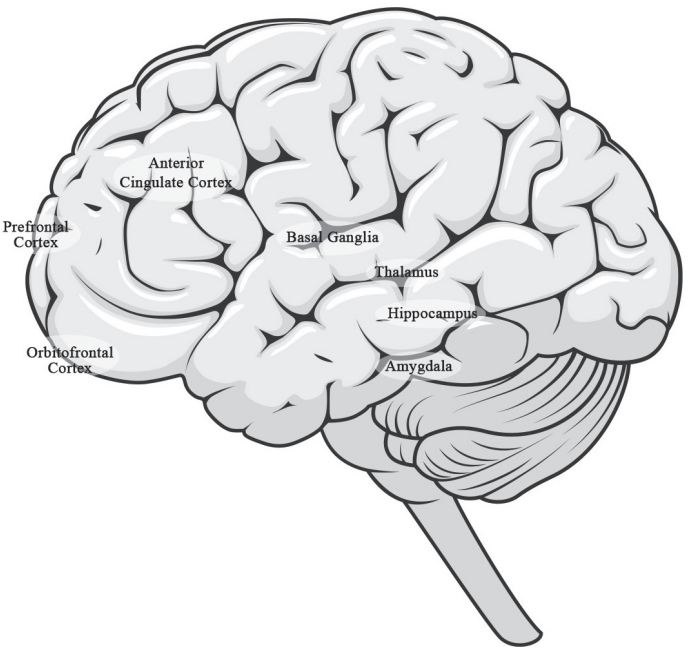

FIGURE 3.1. Adult brain organization. This figure illustrates the target of developmental growth by showing some key structures contributing to adult brain organization.

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cade of life (or beyond).* Immediately after conception, the diploid zygote begins dividing rapidly, and by the first week after conception forms a mass of about 100 unstructured cells known as the *blastocyst*. The blastocyst next begins to organize structurally; the center becomes the *embryoblast,* which will give rise to the embryo itself, and the outer portion becomes the *trophoblast,* giving rise to all supporting tissues including the amniotic sac, placenta, and umbilical cord. Over subsequent weeks, the cells comprising the future embryo undergo another organizational transformation, forming three germ layers: the *endoderm* (inner layer), *mesoderm* (middle layer), and *ectoderm* (outer layer). The central nervous system (brain and spinal cord) and peripheral nervous system both form from the ectodermal germ layer, as do the meningeal membranes covering the brain and spinal cord, as well as the epidermis, mammary glands, pituitary gland, and subcutaneous glands.

Once the basic germ layers have formed, the first major stage of brain development, *neural induction,* begins with formation of the primitive neural tube. The chemical agents principally responsible for the transformation of ectodermal progenitor cells into nervous system tissue are called *transforming growth factors* (Muñoz-Sanjuán & Brivanlou, 2002). As progenitor cells in the ectoderm multiply, a surface initially forms, known as the *neural plate*. Next, a groove forms along the plate's longitudinal axis, as seen in the illustration in Figure 3.2. This groove gradually begins to fold over onto itself to form a tube, beginning to close on day 22 of gestation (Keith, 1948) and if all goes well, closing completely by day 26 (Sidman & Rakic, 1982). Primitive neural cells (*neuroblasts*) inside the tube go on to make up the central nervous system (CNS), with the rostral portion of the tube giving rise to the brain and the caudal portion giving rise to the spinal cord. This process of neural tube formation and differentiation of regions that will give rise to different CNS structures is called *neurulation* (for a review of neural induction and neurulation, see Lumsden & Kintner, 2008). Cells trapped outside the tube and below the ectodermal wall, termed "neural crest cells," go on to form the autonomic nervous system, the components of the nervous system regulating unconscious basic functions such as respiration, heart rate, circulation, and digestion.

Once the tube itself is closed, the neuroblasts initiate a phase of particularly rapid proliferation into new neurons ("neurogenesis"), generally beginning in the fifth gestational week and peaking between the third and fourth months (Volpe, 2000; for review, see Bronner-Fraser & Hatten, 2008). During peak proliferation, it is estimated that several hundred thousand new nerve cells are generated each minute (Brown, Keynes, & Lumsden, 2001; for an excellent tutorial on cell proliferation, see McConnell, 1995).

It is here worth noting that until one to two decades ago, neurogenesis was thought to occur exclusively in the prenatal period, with a few notable exceptions, such as the olfactory bulb. However, new techniques have made it clear that postnatal neurogenesis from stem cell precursors occurs in additional brain regions in humans (Deng, Aimone, & Gage, 2010; Gage, 2000; Yuan, Li, Ding, & Arias-Carrion, 2014; Zhao, Deng, & Gage, 2008), nonhuman primates (Bernier, Bedard, Vinet, Levesque, & Parent, 2002; Gould, Beylin, Tanapat, Reeves, & Shors, 1999; Kornack & Rakic, 1999), rodents (Gould et al., 1999; Wang et al., 2011), and some other mammals (Ming & Song, 2011) well into adulthood. While debate continues regarding which specific regions experience postnatal neurogenesis, consensus has emerged that the dentate gyrus of the hippocampus is one such region (Spalding et al., 2013). Interestingly, postnatally derived cells in the dentate gyrus and other areas of the cortex may differ from prenatally derived cells, for example, appearing morphologically normal but having a relatively short half-life (Gould, Vail, Wagers, & Gross, 2001).

Of relevance to this chapter, it appears that experience influences the addition of postnatally derived neurons (e.g., Gould et al., 1999; Kohman & Rhodes, 2013). For example, not only the mass but also the number of cells in the rodent dentate gyrus increases when rats are placed in so-called "enriched" contexts (marked by demands on learning and memory), or in environments that encourage voluntary running (Deng et al., 2010). In contrast, stress in adulthood (e.g., the presence of threaten-

*The question of when brain development formally ends is hotly debated. Based on MRI, the structure of the adult brain appears to be in place by the third decade of life. However, as Somerville (2016) has recently noted, there is considerable remodeling beyond that period, making it difficult to draw any precise conclusions about when brain *development* ends and adult development begins.

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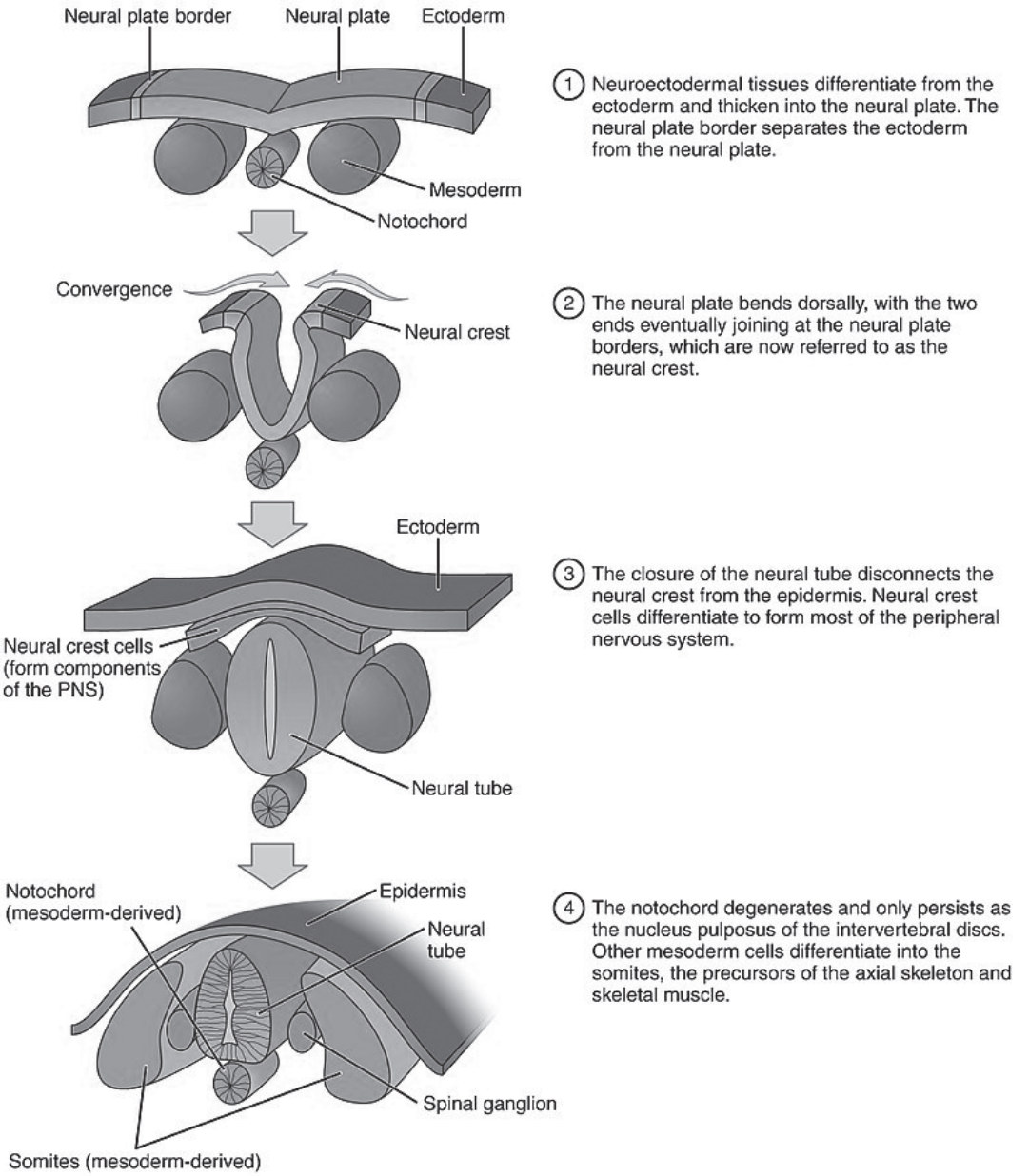

FIGURE 3.2. The process of neurulation. This figure illustrates the process whereby the primitive neural plate (derived from the outer portion of the embryonic ectodermal wall) first thickens (due to cell proliferation) and then folds over onto itself (Panels 1 and 2). Once the neural tube is formed, closure initiates from both the top (rostral) and bottom (caudal) ends. Cells trapped inside the tube give rise to the central nervous system (brain and spinal cord), whereas those trapped between the outside of the tube and the ectodermal wall give rise to the autonomic nervous system (Panels 3 and 4). From Wikimedia Commons. Retrieved from *https://commons.wikimedia.org/w/index.php?title=File:2912_Neurulation-02.jpg&oldid=288810384.*

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ing odors, such as the smell of a fox) appears to down-regulate neurogenesis in the dentate gyrus. Interestingly, if these same rats are then newly placed in enriched environments, subsequent upregulation of neurogenesis occurs in the hippocampal area previously impacted by stress (Gould, 2003). Considering effects of *early* experiences specifically, it appears that stress in infancy may impact later potential for hippocampal neurogenesis. In one study, rats exposed to a pharmacological glucocorticoid (mimicking the body's principal stress hormone) on postnatal day 6 produced fewer of the neural stem cells necessary for later hippocampal neurogenesis, and showed corresponding alterations in cognitive and emotional functioning in adulthood (Ortega-Martínez, 2015). Also relevant to mental health, robust postnatal hippocampal neurogenesis may buffer effects of stress on depressive behavior (Snyder, Soumier, Brewer, Pickel, & Cameron, 2011), and may be important for antidepressant efficacy (Perera et al., 2011; Schoenfeld & Cameron, 2015).

Returning to the process of prenatal development, let us next consider the period after rapid prenatal neurogenesis. Between the time when the neural tube closes (around the 26th day of gestation) and the sixth week, rapidly proliferating neuroblasts generate three organizational regions—the forebrain, midbrain, and hindbrain—that will give rise to the brain's five vesicles. At the top of the tube, the forebrain, or *prosencephalon,* will go on to form the *telencephalon* (the progenitor structure for the cerebral hemispheres and basal ganglia) and *diencephalon* (forming the hypothalamus and thalamus). The midbrain remains as the *mesencephalon,* and below that the hindbrain will give rise to the *metecephalon* (pons and cerebellum) and the *myelencephalon* (medulla). The rest of the neural tube forms the spinal cord.

Once the basic forebrain–midbrain–hindbrain structure has emerged, primitive neuroblasts and glioblasts (glial cell precursors) begin to migrate outward in a radial direction. In the rudimentary cerebral cortex, neuroblasts are guided to their target destination by *radial glial cells,* which essentially act as long tentacles upon which migrating neuroblasts attach (in the cerebellum, a different radial cell is used, the *Bergmann cell*; for discussion, see Komuro & Rakic, 1998). The neuroblast travels along the radial glial fiber to its target destination, where it then detaches and takes up its final location.

As wave after wave of neurons completes migration, eventually six layers (*laminae)* of the cortex form. Importantly, layers form in an inside-out fashion, such that the deepest layers of the cortex form first, followed progressively by more superficial layers. Thus, the oldest part of the cortex is also the deepest, and the newest is most superficial. Because neuroblasts migrate radially in a manner perpendicular to the cortical surface, columns of related cells also form. Many such columns are thought to subserve specific functions, such as "ocular dominance columns" providing organizational structure in the visual cortex. As a rule, cell migration concludes by about the sixth prenatal month, after which primitive neural cells undergo further differentiation and form more elaborately connected neural networks. Specifically, as neurons mature, they begin to develop processes (axons and dendrites) and then make connections (synapses) among themselves. In some parts of the brain, the axons of neurons become wrapped in myelin, serving to increase the speed of information conduction.

These last two events—*synaptogenesis* and *myelination*—follow variable developmental time courses in different brain regions. We know that sensory and motor regions begin to myelinate before birth and, for the most part, complete myelination within the first months or up to a year after birth. By contrast, the frontal lobe (particularly the prefrontal cortex) is probably not fully myelinated until close to adolescence or later (Lenroot & Giedd, 2006; for discussion of myelination, see Jernigan & Tallal, 1990; Nave & Werner, 2014; Raznahan, Greenstein, Raitano Lee, Clasen, & Giedd, 2012; Yakovlev & Lecours, 1967). With regards to synaptogenesis, we know broadly that (1) some brain regions form synapses before others and (2) all regions of the brain go through a period of synaptic overproduction followed by considerable pruning back of exuberant synapses to adult numbers. This pruning process is thought to enable environmental adaptation, forming brain structures functionally adapted to the organism's unique context. As for myelination, the time course of synaptic overproduction and pruning varies considerably across neural regions. Synapses in the visual areas of the brain, for instance, reach their peak of overproduction by about the fourth postnatal month, followed by gradual decline to adult numbers of synapses by approximately the end of the preschool period. The auditory region of the brain follows a simi-

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lar time course, although the peak and pruning phases occur slightly later (see Huttenlocher & Dabholkar, 1997). In other areas of the brain, however, synaptogenesis and pruning follow a much more extended time course. For instance, parts of the prefrontal cortex (e.g., middle frontal gyrus) do not reach peak synapse formation until closer to 1 year of age, and then show a much more gradual decline in numbers until at least adolescence (for review, see Huttenlocher, 1994). Further underscoring the protracted nature of both myelination and synaptic pruning in some areas, recent structural MRI evidence suggests that parts of the prefrontal cortex and some subcortical areas such as the basal ganglia and hippocampus may not attain adult levels of grey/white matter ratios until late adolescence to early adulthood (Lenroot & Giedd, 2006; Schmithorst & Yuan, 2010).

Summary

The core process of brain development begins within weeks of conception, and continues through the adolescent or young adult period; this process includes steps occurring at different times in in different brain regions. Broadly, the assembly of basic architecture occurs during the first two trimesters of fetal life, with the last trimester and the first few postnatal years reserved for marked changes in connectivity and function. The most prolonged changes occur in the wiring of the brain (synaptogenesis), in the fine-tuning of that wiring (pruning), and in making the brain work more efficiently (myelination). These latter processes involve dramatic, nonlinear changes from the preschool period through the end of adolescence and beyond.

Neural Plasticity

Neural plasticity refers broadly to the ability of neural tissues to change in response to environmental stimuli. It represents a core feature of brain development necessary for emergence of normative structure and function as the nervous system adapts to its environment. While the genetic code defines the universe of possible "instructions" for neural development in a given organism, the developmental environment shapes which instructions ultimately gain expression. Some neural plasticity persists throughout life, but the massive scale on which synapses are formed, eliminated, and reorganized during brain development allows for greatly enhanced neural responsiveness to environmental inputs in early life—a phenomenon we might refer to more specifically as "developmental plasticity" in neural systems. Such developmental plasticity has implications for diverse outcomes, including mental health.

The most classic examples of developmental plasticity occur in early sensory development. In sensory domains, it appears there may be critical periods for development. Although the terms are often used interchangeably, "sensitive periods" do differ from "critical periods" in fundamental ways. Knudsen (2004) has argued that the term "sensitive period" broadly describes a window of developmental time during which emergent neural structures and functions show heightened susceptibility to environmental input. If a key experience fails to occur during a sensitive period, it may be difficult, without tremendous effort, to redirect development along a typical trajectory; even then, function in the affected domain might still lag behind. "Critical periods," by contrast, are periods of time in which a needed environmental input *must* occur for normative development to proceed; lack of needed input results in irreversible changes in brain structure and/or function. Canonical demonstration of critical periods in sensory development were provided by Weisel and Hubel (1965, 1974), who demonstrated that "monocular deprivation" (removal of visual input to one eye) during discrete periods of postnatal development in studied mammalian species, including cats (Wiesel & Hubel, 1965) and monkeys (Wiesel & Hubel, 1974), produced irreversible reorganization of the visual cortex and functional blindness in the deprived eye—an effect absent in adults exposed to similar periods of deprivation. Similar evidence of persistent visual deficits following time-limited deprivation of normal visual input in infancy—though generally not in adulthood—has since been established in humans (for discussion, see Morishita & Hensch, 2008). Great inroads have recently been made in understanding the molecular cues and brakes that regulate critical periods, including how to lift such brakes (Hensch, 2004, 2005; Hensch & Bilimoria, 2012).

While animal development and some human sensory and perceptual processes may be marked by critical periods, it is thought that most human developmental domains are marked more commonly by sensitive periods. Here,

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the complexity of human neural systems may afford greater potential for spared circuits to compensate for compromised ones to preserve function, while the protracted nature of development allows for plasticity (and hence the possibility of some functional recovery) extending into later life (Knudsen, 2004). To consider an example of a human sensitive period, we know that starting around 6 months of age, an infant's ability to discriminate phonemes unique to unfamiliar languages declines dramatically (for reviews, see Werker, 2006; Werker & Vouloumanos, 2001). That said, the door does not shut completely on the potential to discriminate non-native contrasts at 6 months. For example, if infants are given additional experience with speech sounds in a non-native language before 12 months of age, discrimination of those phonemes is retained (Kuhl, Tsao, & Liu, 2003). A similar phenomenon occurs in the visual domain, specifically with regard to face processing. For instance, Pascalis, de Haan, and Nelson (2002) investigated facial discrimination among 6-month-olds, 9-month-olds, and adults. They found that individuals in these three age groups are all equally good at discriminating two human faces, but only 6-month-olds readily discriminate two monkey faces. However, if 6-month-olds are given a further 3 months of experience viewing monkey faces, they retain the ability to discriminate two monkey faces over time (Pascalis et al., 2005). Thus, as is the case with speech, face processing also appears to go through a developmentally sensitive period, although one that can be extended with specific experience.

Mechanisms of early neural plasticity may involve changes in response to environmental stimuli at multiple levels. For instance, changes may be physiological (e.g., the release of more neurotransmitters to compensate for cell death or damage), anatomical (e.g., dendritic branching and retraction, the formation and elimination of synaptic connections, or the extension of existing axons into the space vacated by axons that have been deleted due to injury), or metabolic (e.g., generation of new brain capillaries in response to the demand for oxygenated blood in an area being recruited for a new function). All these changes can occur at virtually any point in the life cycle, but they occur with particular frequency and intensity in early development.

What remains uncertain is what happens to circuits that are built early but then are *functionally* retracted—for instance, when the functional ability to discriminate non-native speech contrasts, intact at 6 months, largely recedes over the subsequent year. Are these circuits eliminated or do they lie dormant, capable of being recruited at a later date? Similarly, if the ability to discriminate two monkey faces is apparent at 6 months of age but lost by 12 months, has that circuit been erased entirely or might it simply lie dormant, with the potential for reactivation to enable specific functional capabilities later in life? For now, answers to these questions await additional research.

At a conceptual level, existing theoretical models provide additional insights into mechanisms of neural plasticity underpinning developmental sensitive periods (for general reviews, see Black, Jones, Nelson, & Greenough, 1998; Greenough & Black, 1992). Specifically, key models propose two broad mechanisms whereby experience influences formation of synapses. *Experience-expectant* development occurs when synaptic connections stably form after—and only after—some minimal experience has been obtained. The temporary and relatively unpatterned overproduction of synapses across brain regions provides for the structural substrate of "expectation." The assumption here is that synaptic contacts are initially transient and require some type of confirmation—specifically, via experience-mediated activation—for their continued survival. If such confirmation is not obtained, synapse retraction occurs based on a developmental schedule or competition from confirmed synapses. By contrast, *experience-dependent* development refers to a process unique to the individual, whereby idiosyncratic experiences influence brain development and function. The quintessential example of experience-dependent development is learning, something we are capable of doing throughout the lifespan. Experience-expectant development is therefore a time-limited function that, depending on experience, occurs during a sensitive or critical period of development. By contrast, experience-dependent development is less bounded within developmental time, occurring at any point in the life cycle. Of note, similar behavioral phenomena may be influenced by both types of processes: For example, the ability to *form* an attachment may reflect an experience-expectant process, whereas the *quality* of that attachment may reflect an experience-dependent process. Similarly, acquiring a language system generally may reflect an experience-expectant process, whereas surely

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acquiring a *vocabulary* may reflect an experience-dependent process.

Having established the concept of neural plasticity, we next consider its significance for infant mental health. Among individuals exposed to substantial psychosocial adversity in prenatal and postnatal life—experiences such as maternal stress and depression in gestation, child abuse and neglect, parental psychopathology, and depriving institutional care—we see that the mental health implications of neural plasticity are substantial. Research on such exposures suggests that sensitive period effects may play out not only in basic sensory and perceptual domains but also in the development of more complex capacities for emotion regulation, social cognition, reward processing, and executive functioning (e.g., Teicher & Samson, 2016). Changes in these domains based on early adverse social exposures can profoundly impact mental health, and highlight the "double-edged sword" of early neural plasticity. While necessary for normative brain development and lifelong adaptation, plasticity is not exclusively helpful to the organism. Neural cell death due to exposure to teratogens, such as alcohol, or lack of normal cell differentiation due to deprivation, for instance, show how susceptibility to environmental effects can lead to loss of neural functions. Similarly, individuals exposed to adverse early social environments may experience neurodevelopmental changes, leaving them more vulnerable to mental health problems both in early life and into adulthood. Experience, it has been said, "cuts both ways" (Nelson, 2005), as we highlight in ensuing discussions.

Implications of Developmental Plasticity for Mental Health: Early Adversity

In recent decades, important epidemiological findings have driven interest in the long-term effects of adverse psychosocial experiences during early developmental sensitive periods. Major population studies have shown, for instance, that cumulative early life exposure to experiences such as abuse and neglect, parental psychopathology, and family violence predicts lifelong outcomes in health and developmental domains. In the largest investigation of its kind, the Centers for Disease Control and Prevention (CDC)/Kaiser Permanente Adverse Childhood Experiences (ACE) Study linked such "childhood adversities" to risk of nearly every leading cause of adult mortality, including ischemic heart disease, cancers, lung and liver diseases, obesity, and diabetes, even after controlling for later life "adverse experiences" and factors such as socioeconomic status (Felitti et al., 1998). Effects of early social adversity were particularly significant for mental and behavioral health outcomes, which included risk of depression, substance addiction, and psychosis, as well as global ratings of psychological well-being (Anda et al., 2002; Edwards, Holden, Felitti, & Anda, 2003). Findings of effects of childhood adversity on risk for developing various psychopathologies have since been replicated in other large population studies (e.g., Bjorkenstam, Burstrom, Vinnerljung, & Kosidou, 2016), including some using prospective, longitudinal designs to strengthen evidence for predictive relationships between early adversity and later physical and mental health (e.g., Danese et al., 2009; Flaherty et al., 2013; Richards & Wadsworth, 2004). Such observations are thought to indicate that developmental plasticity and neurodevelopmental sensitive periods can augment the lifelong effects of the early social environment.

Since the initial publication of findings from epidemiological investigations, substantial scientific work has elucidated molecular mechanisms thought to underpin links between early adversity and later outcomes. This literature explores processes by which developmental adversity becomes "biologically embedded" in altered human physiology. While physiological changes can occur in a number of body systems (e.g., endocrine, metabolic, and immune), the remarkably plastic nature of the developing brain has situated neurodevelopmental disruption as a key driver of various systemic effects. In particular, central dysregulation of neuroendocrine stress reactivity may contribute substantially to later somatic and mental health problems. Yet neurodevelopmental changes after early social adversity extend far beyond disrupted stress reactivity, as we explore further below. Such alterations of neural development after early social adversity have substantial implications for infant mental health and can help explain how events beginning prenatally may potentiate psychopathology emerging many years later.

How, then, do adverse early social exposures interact with neural plasticity to drive outcomes? In the following section, we explore what has been learned to date from investigations of this question, focusing first on extensive work elucidating mechanisms of neuroendocrine stress

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dysregulation and broader neural changes. Our discussion draws substantially on animal models, which confer important advantages lending insight into human neurodevelopmental phenomena despite biological differences across species. Specifically, animal models enable the use of controlled experimental designs (e.g., intentional exposure to stressors, gene knockout approaches, and pharmacological manipulation of neurodevelopment) that would be unethical in human research, offering more robust demonstrations of causal relationships and mechanisms. Animal models also allow invasive sampling of neural tissue, including both CNS cells and fluids. Finally, animal models can approximate environmental exposures that may occur relatively rarely in human populations. Following insights gained in animal studies, replication of similar results in humans can support inferences about causal and mechanistic pathways that may be preserved across species. In the subsequent section, we examine such insights drawn from animal and human findings to explore what is known about the molecular mechanisms linking early social adversity to neurodevelopmental disruption, and about implications for infant mental health.

Neuroendocrine Stress Dysregulation after Early Adversity

The most extensively characterized pathway by which early social adversity is thought to disrupt neurodevelopment is via dysregulation of neuroendocrine stress reactivity (for a review, see McEwen, 2012). Early social adversity is thought to influence not only the physiological systems most directly involve in stress reactivity—namely, the hypothalamic–pituitary–adrenal (HPA) and autonomic axes (reviewed below)—but also central neural structures regulating these axes, including the hippocampus, amygdala, and prefrontal cortex (PFC). The hippocampus exerts broadly inhibitory control of amygdala-driven stress reactions, based, for instance, on past fear-learning processes and memory, while the PFC performs slower "top-down" cognitive reappraisal to modulate reactions (Doom & Gunnar, 2015; Heim & Binder, 2012).

Following exposure to a stressor adequate to overcome inhibition, the "fast" autonomic axis evokes the canonical "fight-or-flight" reaction via sympathetic activation within a few seconds. The sympathetic response to stress is enacted quickly, in part via innervation of end organs, for instance, signaling cardiovascular structures to increase blood pressure and heart rate, and triggering rapid epinephrine and norepinephrine release from the adrenal medulla. The sympathetic response is coupled with reflex parasympathetic counterregulatory activation, such that responses are time-limited (Ulrich-Lai & Herman, 2009). The HPA axis, meanwhile, undergoes slower activation and produces a somewhat longer-lasting, though still self-limiting, response. In the case of the HPA axis, stress induces neurons in the paraventricular nucleus of the hypothalamus to secrete hormones including corticotropin-releasing factor (CRF), triggering the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH, in turn, triggers synthesis and secretion of glucocorticoids—principally cortisol in humans and corticosterone in some commonly studied animal species—from the adrenal cortex. In humans, peripheral cortisol elevation is detectable within about 30 minutes of stressor onset. Cortisol enacts broad homeostatic changes across multiple body systems, while exerting negative feedback on the HPA axis as a whole (Gunnar & Quevedo, 2007). Importantly, both autonomic and HPA stress responses are regulated centrally by corticolimbic structures (e.g., including CRF-releasing neurons in the amygdala), and by homeostatic centers in the hypothalamus and brainstem.

Abnormal stress reactivity stemming from early developmental disruption is thought to influence long-term risk of developing depression and other mental health disorders (Wilkinson & Goodyer, 2011), as well as numerous other pathologies associated with elevated "allostatic load," including cardiac, metabolic, and inflammatory diseases (McEwen & Gianaros, 2011). Dysregulation of the HPA axis has been studied more extensively than have autonomic changes, with abnormal diurnal cortisol rhythms or stress reactivity patterns being among the most consistent physiological correlates of prenatal, infant, and childhood social adversity in humans (Anacker, O'Donnell, & Meaney, 2014; Doom & Gunnar, 2015). Social adversities linked to HPA dysregulation include not only severe experiences such as child abuse and neglect but also more common exposures such as maternal depression in gestation and infancy (Essex, Klein, Cho, & Kalin, 2002).

Specific patterns of HPA axis changes linked to early adversity include both hyperreactiv-

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ity (Danese & McEwen, 2012; Lovallo, 2013) and hyporeactivity (Essex et al., 2013; Zilioli et al., 2016), observed variably in both adults and children. *Hyperreactivity* is considered potentially consistent with acquired insensitivity to cortisol's down-regulatory effects on the HPA axis, generating feedback failure. *Hyporeactivity,* meanwhile, may reflect exaggerated axis suppression or acquired glandular hyporesponsiveness. Importantly, HPA hyper- and hyporeactivity are both considered prototypical manifestations of elevated "allostatic load," and both predict stress-related diseases, including poorer mental health outcomes (Danese & McEwen, 2012; McEwen, 1998; Raison & Miller, 2003). Different patterns of HPA dysregulation are thought to reflect various factors, potentially including timing and type of exposure, the presence of concurrent psychopathology, and genetic differences (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001; Rao, Hammen, Ortiz, Chen, & Poland, 2008; Tyrka et al., 2009). Of note, preservation of HPA negative feedback mechanisms may be linked to adaptive outcomes. For instance, Heim and colleagues (2001) found increased ACTH response to laboratory stress among adult women exposed to childhood abuse compared to controls. However, only women who had experienced childhood abuse *and* suffered from current major depression showed corresponding excess cortisol response, while those without depression showed normal cortisol perhaps consistent with successful axis downregulation.

In elucidating not only patterns but also *mechanisms* of HPA axis changes, rodent models of gestational and infant stress have proven particularly useful. In rats, stressful experiences have been modeled in various ways. Approaches include *restraint stress,* or restraining movements of the dam (in the case of gestational stress models) or pup for periods of time each day (usually between 3 and 15 minutes), *water immersion,* in which rats are submerged in cold water, and *prolonged maternal separation*. Additional paradigms exploit naturally occurring differences in rat dam behaviors to model caregiving-related stress—namely, licking and grooming (LG) and arched-back nursing (ABN). Rat mothers can be classified as high- versus low-LG-ABN, with some evidence suggesting that low-LG-ABN behaviors may emerge in dams themselves exposed to stress during development or gestation (Champagne & Meaney, 2001). As in humans, rat models of stress in prenatal and early postnatal development produce consistent dysregulation of the HPA axis accompanied by phenotypic differences such as increased anxiety-like behaviors (Vallée et al., 1997). Offspring of low-LG-ABN dams show increased stress reactivity and neophobia—differences that persist in "cross-fostering" studies among biological offspring of high-LG-ABN dams raised by low-LG-ABN dams (Champagne, Francis, Mar, & Meaney, 2003; Champagne & Meaney, 2001).

Among key mechanistic pathways described in the previously mentioned models, it appears that low-LG-ABN caregiving produces lower serotonin turnover in the hippocampus, which in turn produces *hypermethylation* (a gene-silencing epigenetic change) in the promoter region of the gene for the glucocorticoid receptor (GR) for corticosterone (Anacker et al., 2014). The GR is preferentially involved in down-regulating the HPA axis such that decreased GR expression could mediate initial HPA hyperactivity. Hyperactivity, in turn, could persist into adulthood or generate compensatory changes leading to later hyporeactivity.

Similar findings have been replicated in humans. A key study found GR gene hypermethylation and decreased GR messenger RNA (mRNA) expression in hippocampal tissue of adult suicide victims exposed to early childhood abuse, but not of those without an abuse history (McGowan et al., 2009). The authors consider that such persistent epigenetic vestiges of early adversity in key regions such as the hippocampus may explain not only pathways of HPA dysregulation but also potentially the developmental origins of suicide and other mental health outcomes (McGowan et al., 2009; McGowan & Szyf, 2010). Additional epigenetic changes after early social adversity have been demonstrated in genes controlling expression or function of key HPA receptors (e.g., CRF receptor 1), signaling molecules (e.g., CRF, arginine/vasopressin, ACTH, and cortisol), neurotransmitters (e.g., gamma-aminobutyric acid, and glutamate), and other neuropeptides (e.g., brain-derived neurotrophic factor [BDNF]), particularly in the hippocampus and hypothalamus (McGowan & Roth, 2015). Such changes may have implications for neural signaling beyond the HPA axis as well. Durably altered serotonergic (Meaney & Szyf, 2005; St-Pierre, Laurent, King, & Vaillancourt, 2016) and glutaminergic (Maccari, Krugers, Morley-Fletcher, Szyf, & Brunton, 2014) signaling after exces-

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sive stress in early neurodevelopment is thought to explain some phenotypic changes relevant to mental health, such as increased anxiety-like behaviors.

Research on altered autonomic functioning after early social adversity has been relatively less extensive. Still, early adversity has been linked clearly to dysregulation of autonomic stress reactivity, including complex patterns of both sympathetic- and parasympathetic-predominant imbalance (Alkon, Wolff, & Boyce, 2012; El-Sheikh et al., 2009). As in the HPA axis, dysregulation patterns favoring either excessive (sympathetic-predominant) or diminished (parasympathetic-predominant) stress reactions represent characteristic manifestations of excess "allostatic load," with links to stress-related diseases, including depression (Alkon et al., 2012). Some suggest that directionality of autonomic dysregulation may relate to differences in outcomes. For instance, El-Sheikh and colleagues (2009) found that sympathetic activity was attenuated in children exposed to early abuse who developed antisocial behavior with callous–unemotional traits, but heightened in those developing antisocial behavior without callous–unemotional traits. Consistent with sensitive period effects, McLaughlin and colleagues (2015) found that children raised in depriving institutions (large orphanages) during infancy and randomized into a foster care intervention as toddlers showed normalization of aberrant sympathetic reactivity and vagal withdrawal to stress by time of follow-up in adolescence, though only if placement into foster care occurred before 24 months of age. Individuals initially randomized to remain in institutional care did not show this normalization, even though many were later placed in families, suggesting the importance of early intervention for autonomic recovery.

Altered neural structure following early social adversity implicates one possible mechanism of altered autonomic reactivity. Gatt and colleagues (2009) used statistical models to suggest that complex gray-matter structural alterations in the amygdala, hippocampus, and lateral PFC after early-life adversity predicted alterations in autonomic reactivity mediating risk of depression, neuroticism, and/or anxiety, with the nature of structural and autonomic changes, as well as predicted symptomatology, moderated by polymorphisms in the *BDNF* gene. Still, much work remains to clarify relationships between neurostructural and autonomic changes.

It is also important to note that HPA and autonomic stress response systems share overlapping structural and molecular regulators, including shared central control by corticolimbic regions and common signaling molecules such as CRF. Thus, some mechanisms of change identified for HPA dysregulation likely have implications for autonomic functioning as well. Still, regulation of the two stress response axes is distinct, and any mechanistic overlap is likely to be complex and nonlinear. Further research is needed to explore pathways of autonomic disruption after early social stress.

Additional Neural Structural and Functional Changes after Early Stress

Far beyond altered stress reactivity, early social adversity predicts a broader array of neurodevelopmental changes, consistent with documented plasticity across diverse neural systems during early life. A large literature now links early-life social adversities such as abuse, neglect, maternal depression, stress, and caregiver deprivation to wide-ranging changes in brain structure and function (Bick & Nelson, 2016), while additional literature documents neural effects of psychosocial risk factors in the prenatal period (Graignic-Philippe, Dayan, Chokron, Jacquet, & Tordjman, 2014). Such findings are thought to have important implications for mental health (Nemeroff, 2016).

At the broadest anatomical level, exposure to serious social adversities during early development has been linked to decreases in total gray- and white-matter volumes, both in childhood and when measured later in adulthood (Bick & Nelson, 2016; Hart & Rubia, 2012; Teicher & Samson, 2016). Considering region-specific effects, frequently studied structures include the PFC, as well as the hippocampus and amygdala (McEwen, Nasca, & Gray, 2016)—"stress-sensitive" areas (containing high density of GRs) often targeted in "region of interest" investigations. Beyond roles in stress regulation discussed earlier, the PFC is a defining brain region for "higher order" human cognitive processes and top-down control of various other functions, while limbic structures such as the amygdala and hippocampus are important for consolidation of memories and learning, as well as emotion regulation. Adverse early social exposures including abuse, neglect, and depriving institutional care have been linked with reasonable consistency to volumetric de-

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creases in the PFC, as measured by structural MRI in both adults and children. Hippocampal volumetric decrease has been observed consistently in adults, though generally not in children, possibly suggesting latent effects on this slow-developing structure (Bick & Nelson, 2016). Complex structural changes in the amygdala include volumetric increase as well as decrease, with effects hypothesized to vary based on factors such as timing and type of social adversity (Tottenham & Sheridan, 2010). Beyond core "stress-sensitive" regions, additional volumetric changes have been observed on structural MRI in areas such as the corpus callosum, with evidence of decreased volumes in individuals exposed to childhood maltreatment. Similarly, in the anterior cingulate cortex, studies in adults exposed to early maltreatment have shown fairly consistent volumetric decrease (Bick & Nelson, 2016; Hart & Rubia, 2012; Teicher & Samson, 2016).

Shedding light on the significance of structural disruption, functional neuroimaging studies link exposure to early social adversities to compromise of core capacities such as emotion processing, fear modulation, reward processing, and executive functioning (e.g., cognitive control and flexibility, sustained attention, working memory) (Bick & Nelson, 2016). Further studies document deficits in learning and other dimensions of memory, with potential mediation of memory changes by hippocampal volume in some individuals exposed to early-life trauma (Mark et al., 2002). Repeated evidence of "timing effects" suggest that exposures in early infancy may exert preferentially greater effect on various neural functions, consistent with sensitive period physiology (Bick & Nelson, 2016; Nelson, Fox, & Zeanah, 2014).

Investigation of molecular mechanisms driving neurodevelopmental disruption again has focused substantially on effects of neuroendocrine stress mediators. The "neurotoxicity hypothesis" suggests that early excessive glucocorticoid elevation may kill or hinder growth of neurons, particularly in stress-sensitive regions. Glucocorticoid toxicity was initially explored in the hippocampus (e.g., Sapolsky, 2000) and has since been proposed in additional areas, including the PFC (reviewed in Ganguly & Brenhouse, 2015). Further research has implicated non-glucocorticoid stress mediators in neurotoxicity, including excitatory amino acids (e.g., glutamate, which is under partial control of adrenal stress mediators), inflammatory cytokines, and endogenous opioids (Danese & McEwen, 2012). Suggested mechanisms of neurotoxicity include excitotoxicity and oxidative stress. Of note, oxidative stress has also been linked to sensitive period disruption, which in turn is implicated in pathogenesis of both schizophrenia and autism (Do, Cuenod, & Hensch, 2015). Stress mediators are also thought to act through both epigenetic and nongenomic pathways to induce neuroplastic remodeling (McEwen, 2012), with evidence that cortisol may regulate key processes driving neural plasticity such as dendritic spine development and synaptic modulation (Liston & Gan, 2011). Analysis of CNS genetic expression changes after early adversity in animal models have used "gene ontogeny" approaches, identifying altered expression of genes involved in development of affective and social behavior, forebrain structuring, and in basic neural organizational mechanisms such as cell adhesion and closure of sensitive periods (Sarro, Sullivan, & Barr, 2014). In human studies, early adversity has been linked to genome-wide methylation changes, as well as specific effects on genes important for psychological health and general neural function, for instance, those encoding key neural signaling molecules (e.g., serotonin, glutamate, dopamine, catechol-*O*-methyltransferase, BDNF) (Essex et al., 2013).

Considering mental health effects specifically, neurodevelopmental changes induced by early adversity are thought to mediate increased risk of various psychopathologies, including major depressive disorder (Heim & Binder, 2012), posttraumatic stress disorder (PTSD) (McGowan, 2013), and addictions (Anda et al., 2002). Additional evidence suggests that neural structural alterations may increase vulnerability to later traumas. Gilbertson and colleagues (2002) found that hippocampal volumetric differences mediated vulnerability to later PTSD after trauma in adulthood. An additional study revealed evidence that altered neural structure may mediate effects of early abuse on the development of internalizing symptoms (Jensen et al., 2015). As noted, sensitive period disruption, such as that linked to oxidative stress, may also play a role in pathogenesis of autism and schizophrenia (Do et al., 2015; Hensch & Bilimoria, 2012). Altered reward-related activation in structures such as the nucleus accumbens and broader disruption of dopaminergic reward pathways by early social adversity, meanwhile, is proposed to generate increased risk of both

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addiction and depression (Ganguly & Brenhouse, 2015).

Effects of Early Deprivation: Studies of Institutionalized Children

Findings we discussed earlier suggest that excessive early stress can drive neurodevelopmental disruption and mental health risk. However, a distinct mechanistic pathway is also proposed that extends discussions of social "adversity" beyond stress alone. Specifically, it is thought that deprivation of needed or developmentally "expected" social and environmental stimuli can potentiate undesirable neurodevelopmental outcomes (Fox, Levitt, & Nelson, 2010). While effects of experiential deprivation during sensitive periods have been described most readily in sensory domains, the absence of key social inputs may similarly disrupt basic neurodevelopmental processes such as synapse confirmation. In the realm of social, emotional, and cognitive development, relevant inputs generally "expectable" for a developing child may include some minimal level of caregiver interaction, linguistic input, and some basic opportunities for learning in a varied physical environment. Deprivation of such inputs may represent an important, mechanistically distinct pathway by which early experience can hinder or derail neural development (for recent discussion, see Humphreys & Zeanah, 2015).

First considering insights from animal models, rats raised in "impoverished environments"—generally single-occupancy, closed-wall cages affording minimal social, cognitive, and sensory stimulation—develop reduced overall cortical depth and brain mass (Diamond, Rosenzweig, Bennett, Lindner, & Lyon, 1972). More recent animal models have investigated microstructural changes, demonstrating decreased dendritic spine density in PFC and hippocampal regions in rats exposed to social isolation in infancy (Silva-Gómez Rojas, Juárez, & Flores, 2003). Such findings are potentially consistent with globally decreased cortical thickness (McLaughlin et al., 2014) and reduced gray- and white-matter volume among children exposed to highly depriving institutional care in early infancy (Bick & Nelson, 2016). While tissue sampling requirements make it difficult to replicate histopathological findings from animal models, it is expected that cross-species preservation of core neurodevelopmental mechanisms such as synapse formation and pruning may make similar pathways relevant.

Insights into effects of early social-environmental deprivation on neurodevelopment and mental health in humans have been gleaned largely from studies of children raised in depriving institutions. While the term "institution" can apply to a range of settings, those thought to be most problematic, especially for young children, tend to be characterized by high child–caregiver ratios, routinized daily care regimens, limited social–emotional and cognitive stimulation, high staff turnover, and resultant limited opportunity for stable caregiver relationships (Berens & Nelson, 2015). Such settings include large orphanages prevalent in various countries, including some Soviet bloc states during and following the communist era.

Among studies of institutionalized children, the Bucharest Early Intervention Project (BEIP) has been particularly informative based on its longitudinal randomized controlled trial (RCT) design, which enables more robust demonstrations of causality than cohort or cross-sectional designs. The study began in 2000, with a group of infants and young toddlers who had lived virtually their entire lives in state institutions in Bucharest, Romania. It randomly assigned a subset of institutionalized children to be the first to benefit from a family care program (at the time, there was limited foster care in Romania), comprising the *foster care group*. Mean age at foster care placement was 22 months. Remaining children stayed initially in institutional care until further family placements became available, comprising the *care-as-usual group*; data were analyzed using an intention-to-treat design, and children moved into families as placements became available. Finally, a *never-institutionalized group* comprised control children living with their biological families in Bucharest (for details, see Zeanah et al., 2009). The study has since tracked numerous behavioral, neural, and biological markers of social–emotional functioning, cognitive ability, physical growth, and brain structure and function in these three groups for well over a decade (see Nelson et al., 2014, for a review of findings).

BEIP findings demonstrate broad developmental consequences of early institutional deprivation. At baseline, children in institutional care showed significant deficits compared to community controls in almost every functional domain studied. Mean developmental quotient (DQ), an infant analogue of intelligence quotient

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(IQ), was nearly two standard deviations lower at study outset among institutionalized children than among community controls (Smyke et al., 2007), with similarly large differences in rates of language and social impairment, poor physical growth, insecure and disorganized attachment, and a range of other negative outcomes. In follow-up, intervention effects—specifically, developmental improvement in the *foster care group* as opposed to the *care-as-usual* group—were seen in all functional domains previously mentioned (Nelson et al., 2014).

Various "timing effects" were also apparent, whereby children randomized into foster care prior to a particular age showed markedly greater improvement in specific domains. Specifically, timing effects were observed for risk of stereotopies, with mitigation of the effects of institutional care observed in children placed into foster care by 12 months of age (Bos, Zeanah, Smyke, Fox, & Nelson, 2010). More complete recovery of expressive and receptive language skills required family placement by age 15 months (Windsor et al., 2011), while mitigation of abnormal autonomic reactivity required placement by age 18 months (McLaughlin et al., 2015). Children placed by 24 months of age, finally, had more complete recovery in measures of cortisol reactivity (McLaughlin et al., 2015), attachment security (Smyke, Zeanah, Fox, Nelson, & Guthrie, 2010), IQ (Nelson et al., 2007), and EEG power (Vanderwert, Marshall, Nelson, Zeanah, & Fox, 2010). Such findings provide compelling evidence for sensitive period effects across multiple complex developmental domains.

Considering implications for mental health, again, BEIP findings are noteworthy. When assessed in follow-up at 54 months of age, children with a history of institutional care in infancy had higher rates of any psychiatric disorder than never-institutionalized community controls (53.2% vs. 22.0%). Among ever-institutionalized children, randomization into foster care was associated with better mental health—specifically, with decrease in internalizing disorders (anxiety and depression). Of the children initially randomized to remain in institutional care, 44.2% had internalizing disorders at 54 months, while the rate of internalizing disorders was only 22.0% among those randomized to foster care. Interestingly, significant reductions in "any psychiatric disorder" were seen only in girls in foster care. This gender difference may reflect, in part, the larger intervention effects on internalizing disorders, which were far more prevalent in girls. Differences in rates of behavior disorders—specifically, attention-deficit/hyperactivity disorder (ADHD) or oppositional defiant disorder (ODD)—were not statistically significant between the two ever-institutionalized groups, though higher than among community controls (Zeanah et al., 2009). Collectively, intervention effects in the setting of an RCT design here suggest that the early-care environment is causally related to psychopathology risk, and that the foster care intervention was more effective at reducing internalizing than externalizing disorders in these preschool children.

Stepping back from such findings, it is important to acknowledge that even studies of highly depriving environments such as large orphanages make it difficult to differentiate completely between effects of "deprivation" (i.e., changes driven by lack of input required for experience-expectant synaptic confirmation) and those of stress. A core challenge is that psychosocially depriving experiences, for instance, caregiver separation, tend to evoke concurrent stress reactions in young children (Doom & Gunnar, 2015). An alternative framing is that the absence of a "buffering" caregiver in settings of psychosocial deprivation may leave children less able to modulate stress reactivity and therefore more prone to harmful dysregulation. It therefore remains difficult to disaggregate what are likely to be concurrent, interacting, and overlapping mechanistic pathways of change. Even in animal models of deprivation, it is difficult to demonstrate, for instance, whether decreased density of synaptic connections after environmental deprivation represents failure of experience-expectant synapse confirmation versus glucocorticoid-mediated neurotoxicity or disrupted connectivity (as noted, glucocorticoids serve as core regulators of synaptic plasticity; Liston & Gan, 2011)—or, more likely, some interacting combination of both. Nevertheless, pervasive effects of institutional care in studies like the BEIP are quantitatively and qualitatively different than those observed among children exposed even to severe social stressors such as abuse. Effects of infant institutionalization extend beyond mental health to influence broader development parameters such as physical growth (despite consistently adequate nutrition), for example. Meanwhile, effects on functions such as IQ may be more profound and severe than typically seen in abused children (Nelson et al., 2007).

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Thus, though further work remains to be done, existing evidence is consistent with the idea that psychosocial deprivation imposes neurodevelopmental consequences that compound effects of early stress alone.

Summary

As demonstrated in preceding discussions, the developing brain can be profoundly influenced by early experience, including experiences of psychosocial stress and deprivation. We have emphasized the influence of early social "adversities" as a means to demonstrate the profound implications of developmental neuroplasticity for later mental health outcomes. We have presented evidence, beginning with rodent models, that excessive stress–response activation during fetal and infant life can substantially alter development of neuroendocrine axes and the developing brain more broadly. We further explored effects of psychosocial "deprivation" thought to disrupt "experience-expectant" developmental processes.

A broad conclusion is that structural characteristics and functional networks emerging from the interplay of genes and environment during fetal and infant life have the potential to influence outcomes over the life course, including mental health outcomes. Thus, interventions promoting supportive caregiving environments in the earliest months and years of life have the potential to promote resilience and to help children lay the foundation for lifelong mental and physical health—a theme we explore further in our closing section.

Differential Neurobiological Susceptibility to Adverse Environments

Having considered broad patterns of neurodevelopmental change, it is important that we also note remarkable diversity in outcomes among individuals exposed to serious early social adversity. Even after exposure to similar adverse experiences, some children experience substantial long-term developmental effects, while others seem relatively more developmentally spared. A large body of work has therefore explored why some children appear to fare better after serious developmental adversity, and what can be done to foster such "resilient" outcomes. Further reading is strongly suggested on this broad, important topic (e.g., Ellis, Essex, & Boyce, 2005; Lester, Masten, & McEwen, 2006), which we summarize briefly here.

Considering factors moderating developmental and clinical effects of early adversity across individuals, underlying genetic variance is thought to play an important role. For instance, genetic polymorphisms have been linked to differential effects of childhood maltreatment on later risk of psychopathologies including depression, ADHD, and substance addiction (Nemeroff, 2016). Specific genes implicated include those encoding or regulating levels of key CNS receptors (e.g., for cortisol, CRF, oxytocin, and dopamine) and signaling molecules (e.g., serotonin, dopamine, and catecholamines). Importantly, for many of these gene–environment interactions, the presence of a higher-risk polymorphism alone is not sufficient to predict increased psychopathology but requires co-occurrence with adversity during early development to produce poorer outcomes (Heim & Binder, 2012; Nemeroff, 2016). Furthermore, some genetic variants, as in the case of the serotonin transporter-linked polymorphic region gene (*5-HTTPLR*), have been found to interact with early-life adversity to increase risk of not only psychopathology but also inflammatory dysregulation thought to drive broader health risks (Fredericks et al., 2010). Such findings suggest links between frequently co-occurring somatic and mental health problems in individuals exposed to developmental adversity.

Child sex and/or gender represent another moderating factor influencing effects of early adversity. For instance, complex differences in HPA and autonomic dysregulation among males versus females exposed to early adversity have been observed in animal and human models. Meanwhile, maternal versus paternal stress in early childhood has been linked to differential developmental effects on boys and girls, which researchers suggest may implicate socially embedded gender roles beyond biological sex alone (Essex et al., 2013). It should be noted here that most human studies have not allowed for differentiation between effect moderation by biological sex versus gender identity, and both genetic and social factors may contribute to effect moderation. Child sex and/or gender may also moderate some of the gene–environment interactions referenced earlier. For instance, in a meta-analysis, Kim-Cohen and colleagues (2006) found that a low-activity variant of the monoamine oxidase A gene

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(*MAOA*), important for metabolism of amine neurotransmitters (e.g., dopamine, norepinephrine, serotonin), conferred significantly greater increase in risk of mental health symptoms after exposure to childhood maltreatment among boys than among girls. Other studies have suggested that differing variants of *5-HTTLPR* may confer greater increase in depression risk when combined with early life stress among girls versus boys (Brummett et al., 2008).

Further work has focused on the broad influence of child "temperament" on the effects of early developmental experiences. "Temperament" here refers to stable, individual, trait-like profiles often present from early life, likely reflecting, in part, inherited tendencies. In particular, higher negative emotional reactivity or behavioral inhibition (a tendency to withdraw and display negative affect in response to novel people, places, and events) may alter effects of early adverse experience. For instance, children with high levels of behavioral inhibition or negative emotionality may be more vulnerable to HPA dysregulation under conditions of low-quality child care (Phillips, Fox, & Gunnar, 2011). Inhibited children also exhibit differential neural electrical activity, specifically, left frontal hypoactivation on EEG, a pattern similarly observed in depressed adults; this asymmetry may be further potentiated by the experience of environmental stress. Meanwhile, inhibited traits may increase longitudinal risk of affective symptomatology in general (Davidson, 1992, 1994), which could be exacerbated by adverse experiences.

Beyond child characteristics, an additional body of work has focused on the role of protective environmental factors in protecting infants and children from social adversity. A substantial literature suggests that having at least one stable, responsive caregiver (a "buffering caregiver") can substantially improve a child's resilience in the face of social adversity, including in very young infants. For instance, infants with a stable attachment figure show more attenuated and time-limited responses to acute stressors than those without secure attachments, particularly when in the physical presence of the attachment figure (Doom & Gunnar, 2015). HPA reactivity in early infancy is also found to mirror maternal reactivity when members of the mother–infant dyad are physically together, such that mothers with effective stress regulation can help buffer children from excess stress (Thompson & Trevathan, 2008). Secure attachment is also thought to mitigate effects of environmental stress by bolstering a child's self-perceived coping resources; caregivers may not only bolster infants' perceived safety in the face of threats but also foster learned coping skills over time (Gunnar, 1994). Such insights have been leveraged in interventions aiming to improve caregiver responsivity both among primary attachment figures and in nonfamily child care settings, with some evidence that caregiver-directed interventions can improve stress modulation and executive functioning to support resilience in adversity-exposed children (e.g., Greenberg, 2006).

Finally, as we have noted throughout, the specific nature of adverse social exposures, including type, intensity, timing, duration, and cumulative co-occurrence with other risks, can predict different outcomes. A key example of this moderation is the evidence of exposure "timing effects" in studies such as the BEIP, as well as investigations of child maltreatment (Bick & Nelson, 2016). The importance of co-occurrence of risks, meanwhile, is supported by epidemiological evidence. Specifically, large epidemiological studies show compelling "dose–response" relationships linking total number of early social risk factors to later psychopathologies, including depression and substance use disorders (Anda et al., 2002). Finally, considering effects of distinct exposures, some work has aimed to disaggregate effects of different forms of child maltreatment. For instance, one study involving over 500 subjects found that verbal abuse or witnessing domestic violence had greater effects on risk of later psychopathology than familial physical abuse, while cumulative exposure to more forms of abuse generally had a larger effect than the sum of component effects from abuse subtypes separately (Teicher, Samson, Polcari, & McGreenery, 2006). Additional work is needed to disaggregate effects of early adversities based on type and timing of exposure.

Conclusions

In this chapter, we have provided a framework for considering how research on the neurobiology of developmental plasticity can enhance our understanding of infant mental health. Even early in gestation, the embryonic and fetal brain can be influenced by exogenous factors, ranging from teratogens to maternal psychological

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stress. The extended temporal course of brain development, marked by initial overproduction of synapses and a subsequent lengthy phase of experience-driven retraction and elimination of connections, then leaves the brain susceptible to environmental influence over decades. The concentration of neurodevelopmental "sensitive periods" in early life, meanwhile, helps explain why events occurring in gestation and infancy appear to have such substantial implications for mental health over time. In particular, research on effects of early adversity suggests that excessive psychosocial stress and deprivation during early neurodevelopment can influence lifelong risk of various mental and physical health problems. Mechanisms of effect are thought to include dysregulation of neuroendocrine stress reactivity and other alterations of brain structure and function.

Broadly, our discussion suggests that interventions targeting the early social environment may have important impacts on infant mental health, laying the foundation for longer-term well-being. Relevant interventions, for instance, may aim to meet mental health needs of caregivers beginning in the prenatal period (or earlier), and to foster emergence of sensitive, stimulating caregiver–infant relationships. Achieving these goals requires not only direct support to parents but also consideration of the social-structural conditions in which families live. The need to consider structural context situates work to improve infant mental health in broader advocacy efforts. Relevant issues include promotion of policies for parental leave and affordable child care, family poverty alleviation, community and domestic violence reduction, initiatives combating social and economic exclusion and discrimination, immigration reforms protecting families, and efforts to improve foster care programs and bolster child protection.

In the realm of research, additional work needs to develop and enhance interventions based on neurobiological evidence. Improved research methods are needed to elucidate developmental effects of specific adverse exposures depending on their nature, social context, and developmental timing. Further work is under way to develop clinically applicable "biomarkers" of early adversity that may be used to identify at-risk children before the emergence of clinical pathology, and to track effects of interventions. The use of high-quality research designs, including prospective longitudinal studies and RCTs of interventions, will help to reduce bias in estimates of effect sizes linked to early exposures, and to strengthen evidence for predictive or causal pathways. In full, the insights afforded by neuroscience and molecular biology must be mobilized to help children, both by increasing their exposure to positive environmental influences and by preventing or buffering effects of serious adversity. As we hope we have made clear in this chapter, events in fetal and infant life can lay foundations supportive of mental health throughout the life course. It is our hope that clinical and basic science investigators, as well as practitioners, families, and patients, will continue to join forces, developing and improving evidence-based strategies for promotion of infant mental health.

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