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Authors
Short, AK
Bolton, JL
Baram, TZ

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CHAPTER

12

Mechanisms by which early-life experiences promote enduring stress resilience or vulnerability

Annabel K. Short[1,2], *Jessica L. Bolton*[1,2], *Tallie Z. Baram*[1,2]

[1]Department of Anatomy/Neurobiology, University of California-Irvine, Irvine, CA, United States; [2]Department of Pediatrics, University of California-Irvine, Irvine, CA, United States

Introduction

A predisposition to emotional and cognitive disorders originates early in life (Kessler et al., 2005; Insel, 2009). The concepts of gene-environment interaction, and the importance of early-life experience for resilience or vulnerability to mental illness, have been demonstrated in both preclinical rodent studies and clinical studies in human populations (Insel, 2009; Bale et al., 2010; Gunnar, 2010; Fox et al., 2010; Juul et al., 2011; Bale, 2015). Resilience is defined as an active and adaptive biological, psychological, and social response to an event that may otherwise impair one's normal function (Dudley et al. 2011; Russo et al., 2012). Vulnerability is the susceptibility of an individual to a disorder and is often related (in addition to genetics) to early experiences. Resilience or vulnerability to a stressor tends to be regulated by molecular, cellular, synaptic, and finally, behavioral changes that determine the level of coping and normal function. Early-life experiences that contribute to resilience or vulnerability may consist of stimuli from the general environment (poverty, wealth, war). Notably, in view of the crucial importance of interaction/attachment with the primary caretaker for survival (Bowlby, 1950), there is compelling evidence to suggest that sensory signals from the primary caretaker during the neonatal period are vital in determining an individual's vulnerability or resilience to cognitive and emotional disorders later in life (Meaney and Szyf, 2005; Fenoglio et al., 2006; Lupien et al., 2009; Korosi, 2009; Fox et al., 2010; van Hasselt et al., 2012; Wang et al., 2014). Thus, early-life adversity/stress, as well as beneficial early-life experiences, may be "filtered" by the mother and conveyed to the infant via altered maternal signals.

Stress Resilience
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There is now a large body of evidence in humans associating early-life adversity with emotional and cognitive disorders later in life. These publications range from epidemiological studies of famine or war (Brown et al., 1995; Eriksson et al., 2014) to prospective, cross-sectional, and case-control analyses (e.g., Bremner et al., 1993; Kaplan et al., 2001). To elucidate both direct causal and mechanistic relationships between early-life experiences and outcomes later in life, rodent models have been utilized. A variety of prenatal and postnatal manipulations have been employed in these studies (Molet et al., 2014; Walker et al., 2017). Studies inducing early-life stress are associated with negative emotional consequences, including behaviors that typically signify depression, anxiety, and social isolation. The consequences of early-life (prenatal as well as postnatal) stress on emotional and social behaviors have been a subject of several recent reviews (Lucassen et al., 2013; van Bodegom et al., 2017; Walker et al., 2017). Although not as widely studied, manipulations that result in a more positive early-life environment are associated with increased learning and memory, and decreased anxiety-like phenotypes (Weaver et al., 2004; Fenoglio et al., 2006; Champagne, 2008; Korosi, 2009; Korosi et al., 2010).

The type and severity of early-life perturbations determine their consequences. In humans, this effect is highlighted in studies of institutionally raised children. These studies show chronic impoverished care was associated with cognitive and emotional problems. However, the associated consequences were somewhat reversed by fostering into more positive environments, thus highlighting the importance of early interaction with a primary caregiver (Fenoglio et al. 2005, 2006; Gunnar, 2010; Chen et al., 2012; Wang et al., 2014). Abnormal patterns of maternal care, ranging from unpredictable neglect to inconsistency and lack of sensitivity, can be a major cause of early-life stress (Fenoglio et al., 2005; Bota and Swanson, 2007). This is in contrast to repeated, predictable barrages of maternal care. To study early-life experiences, animal models have aimed to recapitulate these conditions by manipulating maternal interactions with the developing individual.

The degree of predictability of maternal care influences long-lasting cognitive and emotional resilience or vulnerability

Experimental model studies, in conjunction with human studies, have found that maternal input is the most significant environmental experience during development (Bowlby, 1950; Baram et al., 2012; Kundakovic and Champagne, 2015). Thus, most animal models of early-life stress have manipulated maternal interaction, disrupting either the quantity or quality of maternal care early in life (see Molet et al., 2014; Walker et al., 2017; van Bodegom et al., 2017 for recent reviews).

Studying early-life experiences experimentally

Disrupted maternal care

Some of the earliest and most informative translational work on early-life stress associated with disrupted maternal care has been performed in nonhuman primates. These models have the advantage of modeling the development of complex psychiatric disorders. Initial nonhuman primate studies were the first to demonstrate the association of intact

maternal-infant interactions with appropriate development of cognitive and emotional phenotypes (Mason and Harlow, 1958). In addition to these studies of disrupted maternal care, a model of physical separation in nonhuman primates has been used. With this approach, Sanchez and colleagues associated adverse early-life experience with altered development of the stress response. This abnormal development resulted in emotional reactivity and manifested as poor maternal care when these infants reached adulthood and became mothers themselves (Maestripieri et al., 2006; Drury et al., 2017).

Due to the difficulties associated with nonhuman primate work, most studies of disrupted maternal care are performed in rodents. Although it is difficult to measure sophisticated cognitive and emotional disorders in rodents, appropriate testing and analyses yield tractable results when studying the developmental and behavioral outcomes of early-life stress. Given the similarities in the role of maternal care across species, and the significant parallelism of brain development especially the development of synaptic connectivity and brain circuits, rodents are a suitable model for studying the effects of maternal care–related stress on neuropsychiatric outcome.

Comparable with the maternal role in humans, the rodent dam is the primary source for nutrition and pup well-being. This includes providing protection and safety in the nest, which involves the communication of vital environmental signals from the dam to the pups (Levine, 1957; Eghbal-Ahmadi et al., 1999; Lucassen et al., 2013). Although removing the mother from the pup will effectively disrupt these signals, doing so for extended periods of time will lead to obvious physical stressors such as hypothermia and starvation. To overcome this, studies of disrupted maternal care may employ intermittent maternal separation, for variable lengths of time. This decreases the quantity of time available for maternal care in addition to causing a repeated stress (Millstein and Holmes, 2007). These approaches have been widely employed in the field and have provided an understanding of how directly decreasing maternal care influences early development and outcomes later in life. Yet, these approaches have yielded variable results (Shalev and Kafkafi, 2002; Aisa et al., 2007; Hill et al., 2014). Furthermore, adverse conditions that are commonly experienced by human infants and children include situations such as severe poverty, famine, war, maternal drug abuse, where the child is with the mother and receiving maternal signals. Because of the overwhelming importance of maternal signals, including their nature and patterns, there is a rationale to study early-life adversity in the presence of the mother. To recapitulate poverty in the presence of the mother, a now prevalent approach uses manipulations of the home cage while both the dam and pups are present. During postnatal days (P)2–9, nesting and bedding materials are limited (LBN) (Gilles et al., 1996; Molet et al., 2014; Naninck et al., 2015), and this manipulation reliably and reproducibly causes fragmented and unpredictable maternal behaviors toward the pups (Molet et al., 2016a). This is likely because the impoverished environment induces stress in the dams (Ivy et al., 2008). Notably, the duration or quality of the nurturing behaviors of the dams is minimally altered: it is the patterns of maternal care that are disrupted (Ivy et al., 2008; Rice et al., 2008; Molet et al., 2016a; Walker et al., 2017). This fragmented maternal care causes chronic, unpredictable, and uncontrollable "emotional stress" in the pups (Gilles et al., 1996; Ivy et al., 2008; Rice et al., 2008; Moriceau et al., 2009; Wang et al., 2011; Molet et al., 2014; Naninck et al., 2015). The pups' stress is apparent in persistent elevation of plasma corticosterone and adrenal hypertrophy, which is associated with emotional and cognitive vulnerabilities in adulthood (Brunson et al., 2005;

Rice et al., 2008; Molet et al., 2016b). These cognitive and emotional outcomes produced by the LBN approach have been reliably reproduced by numerous laboratories and multiple outcome measures (Moriceau et al., 2009; Roth et al., 2009; Dalle Molle et al., 2012; Raineki et al., 2012; Gunn et al., 2013; Malter Cohen et al., 2013; Naninck et al., 2015; Walker et al., 2017).

Augmented/predictable maternal care

Important biological phenomena run along a spectrum. If unpredictable maternal care provokes enduring vulnerability, then highly predictable patterns of maternal-derived sensory signals to the developing brain should promote cognitive and emotional resilience long-term.

Nurturing maternal care is typically quantified by licking and grooming behaviors. The handling paradigm (Levine, 1957; Plotsky and Meaney, 1993; Korosi, 2009) has been extensively used to modulate maternal licking and grooming quantity, as well as patterns. This involves a brief (15 min) daily separation of rat pups from the mother during the first weeks of life. The timing of these bouts of separation is crucial, and brief separations will promote increased, predictable sensory input to the pups upon reunion with their mothers (Liu et al., 1997; Fenoglio et al., 2006; Korosi et al., 2010). The recurrent predictable maternal signals lead to increased resilience to depressive-like behavior (Meaney and Szyf, 2005; Singh-Taylor et al., 2017) and improved learning and memory (Fenoglio et al., 2005). Notably, it is not simply the increase in maternal care that drives resilience. A single day of handling or irregular handling is insufficient to promote the molecular and behavioral outcomes (Fenoglio et al., 2006). Recurrent, predictable, repetitive brief separations (typically in the same circadian phase) seem to be required (Fenoglio et al., 2006; Karsten and Baram, 2013).

Cognitive and emotional outcomes of early-life experiences

The effects of early-life experiences on resilience or vulnerability in adulthood can be examined in rodents using standardized cognitive and emotional tests that are also translational to humans. Tests of emotional behavior such as the forced-swim test are used to identify depressive-like phenotypes in rodents, as when used in conjunction with routinely prescribed antidepressants, there is a reduction in depressive-like behaviors (Slattery and Cryan, 2012).

Measures of anxiety have relied on tests such as the open field and elevated-plus maze. Cognitive tests have typically involved memory and especially hippocampus-dependent spatial memory. Available standardized tests for this function include both the well-characterized Morris water maze and the object location memory test. The former involves stress/adversity in itself (forced swimming, cold water), whereas the object location relies on natural curiosity and is devoid of stress, as well as the potential confounding effect of early-life experience on stress-related behavior later in life. Thus, spatial memory tests are best when these considerations are included. An additional important caveat is that the large majority of studies have employed males, and many of the tests have been developed and standardized for males. Here, we note if reported studies and outcome pertain to females.

A spectrum of cognitive consequences of early-life experiences

Memory impairments have been the common outcome in rodents exposed to chronic early-life adversity. For example, in a rigorous and hippocampus-dependent test of object

location memory, an overt impairment in spatial memory was found as early as adolescence in rats reared for a week in the simulated poverty environment (LBN rats) (Molet et al., 2016b). A less rigorous memory task involving object recognition (OR) found comparable performance in LBN versus control adolescent rats during adolescence. However, an acute-stress "challenge" imposed 24 h prior to the test led to memory problems only in the LBN rats, thus unmasking a latent cognitive vulnerability (Molet et al., 2016b). The memory deficits after chronic early-life stress also progressed over the life span of LBN rats, so that deficits in OR memory emerged by middle age (Molet et al., 2016b). At this age, hippocampus-dependent memory deficits were also present using the Morris water maze task (Brunson et al., 2005; Ivy et al., 2010). These data, obtained in males, are intriguing, because the emergence of memory problems during middle age has been found in men experiencing early-life adversity in well-controlled epidemiological studies (Kaplan et al., 2001).

Conversely, rats receiving predictable augmented maternal care had improved hippocampus-dependent cognitive function (Tang, 2001; Fenoglio et al., 2005; Lesuis et al., 2016). Together, these studies indicate that either naturally occurring or experimentally recurrent, predictable or enhanced sensory stimulation that pups receive from the dam improves hippocampus-dependent learning and memory later in life (Korosi and Baram, 2008).

Emotional consequences of early-life experience

A variety of emotional problems, based on rodent tasks considered indicative of depression or anxiety, have been reported after early-life stress (McEwen, 2003; Molet et al., 2014; Chen and Baram, 2016). Increased anxiety-like behaviors in the elevated-plus maze test were found later in adulthood (Dalle Molle et al., 2012, but see Molet et al., 2016a), Conversely, predictable barrages of maternal care early in life was related to decreased anxiety-like phenotypes in adult rats (Singh-Taylor et al., 2017).

Anhedonia, a reduced capacity to experience pleasure, which commonly heralds depression or schizophrenia in humans (Whitton et al., 2015), has been identified in rodents following perturbations of early-life experiences. Already during adolescence, anhedonia, apparent both as a significant reduction in sucrose preference and a reduction of peer play, was found in late-adolescent LBN rats (Molet et al., 2016a; Bolton et al., 2018). This anhedonia was not accompanied by overt anxiety-like behavior or depressive-like behavior. Adolescent anhedonia after early-life stress has since been confirmed in a separate LBN cohort in a different laboratory, as indicated by decreased consumption of palatable food (M&Ms) (Bolton et al., 2019). Furthermore, LBN rats self-administered lower levels of cocaine, consistent with a reduced hedonic set point (Bolton et al., 2019). These changes were shown to be selective to anhedonia, as early-life adversity did not affect other measures of addiction, such as sensitivity to self-administered cocaine dose; responding for cocaine under extinction conditions; or cocaine- or cue-induced reinstatement of cocaine seeking. Early-life adversity did not induce anxiety-like behavior or augmented locomotor response to acute cocaine. Together, these findings demonstrate enduring effects of early-life adversity on reward/pleasure-circuit function.

In contrast, rats that have been handled in the first week of a life, thus receiving recurrent barrages of maternal care signals, when given a similar task, had an increase in the consumption of palatable food, in the absence of an anxiety-like phenotype (Silveira et al., 2005).

Although the majority of emotional consequences of chronic early-life adversity have been negative, there is some evidence for positive outcomes following stressful experiences that are challenging but not overwhelming, so-called "stress inoculation" (Lyons, 2009). For example, Lyons and colleagues have demonstrated that exposure of newly weaned squirrel monkeys to brief intermittent maternal separations decreased subsequent anxiety and stress responsivity. This resilience to later stress did not seem to be maternally mediated or related to changes in maternal care, unlike the rodent models discussed above (Parker et al., 2006).

It is possible that some discrepancies reported on the emotional consequences of early-life stress may be due to inadvertent generation of recurrent, predictable bouts of maternal care, which may counteract or reverse the stress effects. For example, a recent powerful paper by Peña et al. (2017) did not find major emotional outcomes after early-life stress in the simulated poverty paradigm. Yet, in aiming to improve the approach, Peña et al. added daily maternal separations, which, upon the subsequent return of the dams to the cages, may have provided predictable, recurrent daily episodes of maternal tactile signals (licking) to the pups (Korosi et al., 2010; Singh-Taylor et al., 2015, 2017). Thus, the potential negative consequences of unpredictable and fragmented sensory signals from the mother in the LBN cages on the development of brain circuits were most likely mitigated by the predictable daily barrages of maternal care when the dams were returned to the cages. These variations highlight the complexities inherent in all of our experimental approaches to the human condition.

Importantly, the consequences of early-life experiences are clearly further modulated later in life. In humans, fostering at 2 years or earlier clearly ameliorated the effects of institutionalization (Nelson et al., 2007). In rodents, enrichment (Bredy et al., 2003) or pharmacological manipulations (Ivy et al., 2010) at least partially reversed cognitive deficits promoted by early-life adversity. Understanding the basis of these consequences of early-life stress should enable targeted and logical interventions to improve lifelong outcomes.

Mechanisms by which early-life experiences elicit enduring changes in neuronal, circuit, and behavioral functions

How altered early-life experience promotes resilience or vulnerability to emotional and cognitive disorders in adulthood is yet to be fully elucidated. An attractive hypothesis is that, in analogy to the development of the visual and auditory brain circuits, early sensory signals from the mother alter synaptic development and pruning, thus influencing the maturation of brain networks involved in emotional and cognitive processing (Bogdan and Hariri, 2012; Burghy et al., 2012; Maras and Baram, 2012; Karsten and Baram, 2013; Singh-Taylor et al., 2015; Chen and Baram, 2016; Davis et al., 2017). Changes in synaptic connectivity, in turn, have recently been shown to influence epigenetic programs in stress-sensitive neurons (Singh-Taylor et al., 2017).

Stress-sensitive neurons in the hypothalamus are influenced by early-life stress as well as by augmented early-life experience

Early-life stress and fragmented maternal care have significant effects on the developing and adult stress response system. Abnormal maternal care in the simulated poverty environment provokes an increased number and function of excitatory synapses to stress-sensitive neurons in the hypothalamus (Gunn et al., 2013). In contrast, recurrent predictable maternal

signals reduce the number of excitatory synapses to corticotropin-releasing factor (CRF)–expressing cells in the paraventricular nucleus (PVN) of the hypothalamus (Korosi et al., 2010). Recent exciting data indicate that the change in synapse number and function is sufficient to turn on massive epigenetic/transcriptomic programs in the PVN CRF cells (Singh-Taylor et al., 2017). These changes include lifelong reduction in CRF expression in the PVN.

Reduced expression of CRF in the PVN is classically associated with reduced CRF release in response to stress throughout life. Thus, there is now a direct mechanistic connection between early-life experiences, development of circuitry of a key element of the stress system, and enduring epigenetic change in the level of expression and function of a stress hormone.

Notably, reduced or increased CRF expression and release influences the levels of circulating glucocorticoids, thus providing multiple pathways by which early-life stress or optimal experience will influence the brain long-term (Liu et al., 1997; Eghbal-Ahmadi et al., 1999; Korosi et al., 2010). Rodents, reared in LBN cages have elevated basal levels of serum corticosterone (Brunson et al., 2005; Rice et al., 2008). These changes are present immediately following the stress and may or may not persist into adulthood. Although there is also adrenal hypertrophy described in pups following LBN, these changes do not persist into adulthood (Gilles et al., 1996; Avishai-Eliner et al., 2001; Brunson et al., 2005; Ivy et al., 2008). Conversely, predictable maternal care is associated with decreased release of serum corticosterone in response to stress (Liu et al., 1997; Eghbal-Ahmadi et al., 1999; Meaney and Szyf, 2005; Singh-Taylor et al., 2017).

Memory consequences of early-life stress and experiences—a hippocampal story

There is clear vulnerability or resilience accorded by early-life experience to hippocampus-dependent tasks. In rodents, early-life stress causes reduction in dorsal hippocampal volume associated with a reduction in dendritic arborization (Brunson et al., 2005; Ivy et al., 2010; Molet et al., 2016b). This is comparable with observations in humans. For example, children raised in orphanages have reduced hippocampal volume (Hodel et al., 2015). Rodent data allow speculation that reduced hippocampal volume in humans is also a result of a decrease in synaptic growth and branching of neuronal dendrites, contributing to the observed functional deficits (Brunson et al., 2005; Radley et al., 2008; Ivy et al., 2010; Maras and Baram, 2012; Chen and Baram, 2016). In addition to structural changes in the hippocampus of rodents following early-life stress, significant reduction in LTP has been observed, which progresses as the animal ages (Brunson et al., 2005). These structural and functional changes in the hippocampus following early-life stress are also associated with lasting molecular changes (Gilles et al., 1996; Avishai-Eliner et al., 2001; Bath et al., 2016). Both elevated plasma corticosteroids and enhanced CRF gene (*Crh)* expression in hippocampus (Ivy et al., 2010; Maras and Baram, 2012) might play a role in these hippocampal changes. Glucocorticoids powerfully modulate dendritic and synapse growth in hippocampus (Magarinõs and McEwen, 1995; Alfarez et al., 2009; Jafari et al., 2012; Liston et al., 2013), and chronic increases in CRF, via binding to local CRF receptors (Chen et al., 2013) impair dendritic branching and pruning early in life (Chen et al., 2004; Joëls and Baram, 2009).

In contrast to the adverse consequences of early-life stress, augmented maternal care may have beneficial influences on the hippocampus, and these also seem to progress with age. Aged rats that have undergone handling at an early age show less hippocampal cell loss when compared with control animals and maintain better cognitive function (Fenoglio et al., 2005).

Early-life experiences affect a number of brain systems

Early-life experiences provoke enduring changes in the expression of multiple molecules throughout the brain. This is likely mediated via large-scale transcriptional/epigenetic programs (Singh-Taylor et al., 2017; Peña et al., 2017; Gray et al., 2017).

Evidence for altered gene expression and function are found in anxiety-fear circuits, including the central nucleus of the amygdala (ACe), and bed nucleus of stria terminalis (BnST). In these regions, changes in *Crh* gene expression are an eloquent example of broad transcriptional change. In addition, the changes in *Crh* expression probably directly contribute to altered functional outcomes in behaviors subserved by the underlying circuits. For example, increased *Crh* expression has been found in amygdala (Dubé et al., 2015) already during adolescence after early-life stress; in contrast, high levels of predictable maternal care promote reduced *Crh* expression in the ACe (Fenoglio et al., 2004). Notably, the same experience promotes reduction of glucocorticoid receptor (GR) in ACe. As GR occupancy increases CRF expression in the amygdala (Makino et al., 1994), these findings support a coordinate effect of early-life experience on two mediators of the stress system. A second, intercalated circuit influenced by early-life experience encompasses the mesolimbic reward/pleasure circuit. As mentioned above, dysregulation of these systems has been observed following early-life stress. Mechanistically, social play, a pleasurable task, provoked Fos activation of CRF neurons within the ACe, in contrast to controls (Bolton et al., 2018). These findings suggest aberrant connectivity of pleasure/reward and fear/anxiety circuits. Importantly, knockdown of CRF expression in the ACe was sufficient to completely reverse the observed anhedonia in individual LBN rats, suggesting mechanistic roles for CRF-expressing neurons in the amygdala in the abnormal emotional function induced by early-life stress.

Aberrant patterns in Fos activation are apparent in LBN rats also following cocaine. The abnormal activation was found in other reward-related regions, such as the core of the nucleus accumbens (NAc) and the lateral habenula (LHb) (Bolton et al., 2019). This evidence for network disruptions following adverse early-life experiences is supported by high-resolution MRI studies. Tractography revealed increased tracts/streamlines connecting the amygdala to the medial prefrontal cortex in LBN rats (Bolton et al., 2018). Together, these results suggest that projections in both pleasure/reward- and anxiety/aversion-related circuits are enduringly altered because of early-life stress, which may have functional implications.

Although there is currently limited evidence for a role of augmented maternal care in pleasure and reward-seeking behavioral changes, there are reported changes in related brain regions. Fos mapping studies have suggested that the pathway of neuronal activation by repeated barrages of maternal care travels to the hypothalamic PVN via the ACe and BnST (Fenoglio et al., 2006). These high levels of neuronal activation result in robust and enduring suppression of *Crh* gene expression in these neurons (Fenoglio et al., 2006; Karsten and Baram, 2013), which further supports a role for the CRF neurons in the amygdala in resilience or vulnerabilities to emotional disorders in adulthood.

How the consequences of early-life experience are encoded long-term: transcriptional and epigenetic mechanisms

The critical importance of events taking place during sensitive developmental periods is their influence on developmental trajectories and hence their enduring effects (Russo et al., 2012;

Regev and Baram, 2014; Peña et al., 2017). In the context of early-life stress, this is clearly apparent from the ability of interventions, including pharmacological, to alter the course of these consequences if undertaken directly after the stress epoch (Bredy et al., 2003; Ivy et al., 2010). However, interventions several months later were ineffective in reversing the effects of early-life stress on hippocampal functions (Ivy et al., unpublished observations). There is also evidence for the crucial importance of the sensitive period in humans. Early-life stress is associated with an increased risk of dementia and cognitive problems in middle age (Kaplan et al., 2001; Nelson et al., 2007). Interventions were found only to be effective prior to the first 3 years of life, suggesting that mechanisms behind these behavioral changes decrease in plasticity over time (Nelson et al., 2007; Regev and Baram, 2014).

There is increasing evidence that the larger changes in brain circuit behavior induced by early-life stress may occur through molecular changes via epigenetic mechanisms. Commonly described epigenetic mechanisms include DNA methylation, histone modifications, and chromatin remodeling. Alterations to gene expression can occur via noncoding RNAs, which is often also regarded as an epigenetic mechanism.

Multiple studies in rodents have shown that aberrant maternal care, whether biological or fostered, will produce permanent changes in behavior and gene expression patterns (Roth et al., 2009). These changes in gene expression patterns have been associated with multiple epigenetic modifications both on a genome-wide level and to specific target genes (for a full review, see Kundakovic and Champagne, 2015). Although the majority of work has focused on the effects of early-life experiences on the hippocampus, there is also evidence for altered epigenetic states in the prefrontal cortex (Roth et al., 2009) and hypothalamus (Murgatroyd et al., 2009; Peña et al., 2013).

Weaver et al. (2004) were the first to link differences in maternal care to levels of GR promoter methylation. Analogous changes in methylation after early-life stress have been sought in humans (McGowan et al., 2009; Naumova et al., 2012; Suderman et al., 2014). Yet, it is unclear if DNA methylation, argued by Weaver to be a mechanism for lasting changes, is a cause or consequence of gene expression changes. Changes in gene expression in neuronal populations that drive the function of these neurons can be triggered and maintained via numerous mechanisms. Initiation of transcriptional changes is often secondary to transcription factors (Peña et al., 2017; Singh-Taylor et al., 2017), which might be activated in response to early-life sensory signals and/or changes in calcium entry to the cell resulting from changes in synaptic numbers (Chen et al., 2017). The mechanisms for stable changes in the chromatin that endure for life (and even transgenerationally, Chan et al., 2018) are complex. In addition to these epigenetic changes, there is also some evidence for a role for altered miRNA expression in encoding stress resilience or vulnerabilities from the early-life environment (Bai et al., 2012; Zhang et al., 2013), which may also be heritable across generations (Rodgers et al., 2013; Gapp et al., 2014; de Castro Barbosa et al., 2016; Short et al., 2016; Short et al., 2017). Histone modifications are also likely to play a role, and multiple histone modifications have been associated with differences in early-life experience (Weaver et al., 2004; Peña et al., 2017).

These types of chromatin modifications follow both early-life adversity (see above) and beneficial early-life experiences. Repressive histone modifications were recently observed after augmented early-life experience (Singh-Taylor et al., 2017). In this instance, large-scale epigenetic changes were initiated by increases in the function of a transcriptional repressor, NRSF. Later in life, NRSF binding to target genes was no longer observed. Rather, there

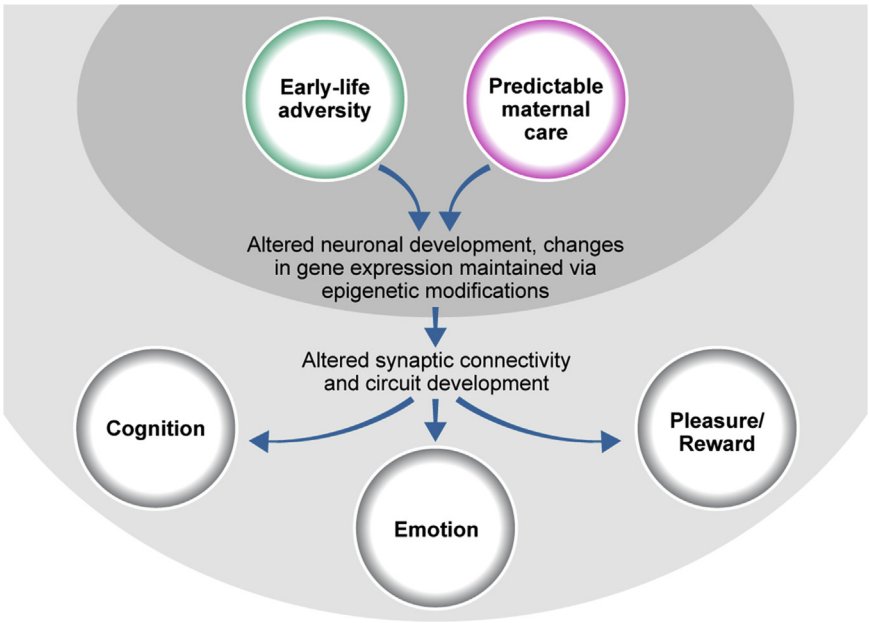

FIGURE 12.1 A unifying theoretical framework for how early-life experiences can induce long-term changes in behavior. The inciting event is the experience of early-life adversity (green) or repeated, predictable barrages of maternal care (pink), represented in the overlapping circles. Changes in early-life experiences cause a cascade of changes acutely during the perinatal period that results in altered neuronal development and changes in gene expression, which are maintained long-term via epigenetic modifications of the chromatin (represented in the dark grey inner concentric circle). These molecular- and cellular-level changes build upon each other to create altered synaptic connectivity and circuit development at the level of the network, ultimately resulting in the observed alterations in cognition, emotion, and pleasure/reward (represented by the three nodes within the light grey outer concentric circle). *Adapted from Bolton, J.L., Molet, J., Ivy, A., Baram, T.Z., 2017. New insights into early-life stress and behavioral outcomes. Current Opinion in Behavioral Sciences 14, 133–139 with permission.*

were increases in histone modifications associated with repression of these target genes, including *Crh* (Singh-Taylor et al., 2017). These results suggest a transition of epigenetic states across the life span in response to changes in the early-life experiences.

Conclusions

Early-life experiences modulate risk and resilience to stress-related emotional and cognitive disorders in adulthood. The mechanisms by which experiences during the sensitive developmental period early in life translate into enduring molecular, cellular circuit, and behavioral phenotypes are emerging (Fig. 12.1). This chapter reviews available knowledge. It proposes a unified mechanistic scenario, where patterns of sensory input from the mother influence the number and function of synapses onto stress-sensitive neurons (in analogy to similar processes in visual and auditory systems). Synapse changes regulate transcriptional and epigenetic programming in distinct neuronal populations, which modulate how these

neurons wire together into circuits and the levels of expression of numerous genes. Together, the altered circuitry and altered neuronal behavior in response to future stimuli promote a phenotype of resilience or vulnerability to stressful signals throughout life—and perhaps across generations.

This framework requires much additional work to affirm or refute. However, it provides a common mechanistic understanding for the enduring consequences of both adverse and beneficial early-life experiences, leading to resilience and vulnerability, respectively, to stress-related emotional and cognitive disorders.

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