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Toward Understanding How Early-Life Stress Reprograms Cognitive and Emotional Brain Networks

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Vulnerability to emotional disorders including depression derives from interactions between genes and environment, especially during sensitive developmental periods. Adverse early-life experiences provoke the release and modify the expression of several stress mediators and neurotransmitters within specific brain regions. The interaction of these mediators with developing neurons and neuronal networks may lead to long-lasting structural and functional alterations associated with cognitive and emotional consequences. Although a vast body of work has linked quantitative and qualitative aspects of stress to adolescent and adult outcomes, a number of questions are unclear. What distinguishes 'normal' from pathologic or toxic stress? How are the effects of stress transformed into structural and functional changes in individual neurons and neuronal networks? Which ones are affected? We review these questions in the context of established and emerging studies. We introduce a novel concept regarding the origin of toxic early-life stress, stating that it may derive from specific patterns of environmental signals, especially those derived from the mother or caretaker. Fragmented and unpredictable patterns of maternal care behaviors induce a profound chronic stress. The aberrant patterns and rhythms of early-life sensory input might also directly and adversely influence the maturation of cognitive and emotional brain circuits, in analogy to visual and auditory brain systems. Thus, unpredictable, stress-provoking early-life experiences may influence adolescent cognitive and emotional outcomes by disrupting the maturation of the underlying brain networks. Comprehensive approaches and multiple levels of analysis are required to probe the protean consequences of early-life adversity on the developing brain. These involve integrated human and animal-model studies, and approaches ranging from *in vivo* imaging to novel neuroanatomical, molecular, epigenomic, and computational methodologies. Because early-life adversity is a powerful determinant of subsequent vulnerabilities to emotional and cognitive pathologies, understanding the underlying processes will have profound implications for the world's current and future children.

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CONCEPTUAL FRAMEWORK (INTRODUCTION)

Brain maturation involves multiple dynamic processes that are regulated both by genetic factors and environmental input (Huttenlocher and Dabholkar, 1997; Caspi *et al*, 2003; Levitt, 2003; Gluckman *et al*, 2008; Martin *et al*, 2009; Krishnan and Nestler, 2010). Although some of these processes are complete at birth, the early postnatal brain is far from maturity and continues to undergo significant developmental processes; these processes include axonal and dendritic growth, synaptic stabilization, and synaptic pruning (Bale *et al*, 2010; Regev and Baram, 2014; Hoeijmakers *et al*, 2015). The perinatal period therefore represents a critical stage of development, rendering the brain particularly vulnerable to organizing (and disorganizing) environmental influences. Indeed, when stress is experienced during this critical early-life period, its impact on brain function can be long-lasting or even permanent, compared with the typically transient effects of stress on the adult brain (Everson-Rose *et al*, 2003; Wilson *et al*, 2005; van Os *et al*, 2010; Provençal and Binder, 2015). Decades of research in the neuroscience and neuroendocrine fields have therefore focused on identifying the mechanisms by which early-life stress regulates brain development. In mammals, including humans, monkeys, and rodents, maternal input has perhaps the most significant influence on the type of environment experienced during development (Bowlby, 1950; Seay, 1962; Baram *et al*, 2012; Rincón-Cortés and Sullivan, 2014; Kundakovic and Champagne, 2015). In accordance, most animal models of early-life stress have targeted maternal interaction, disturbing either the quantity or quality of maternal care early in life

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(for recent reviews, see Molet *et al*, 2014; Nishi *et al*, 2014). Such models have become widely adopted, and from this vast literature it is clear that the ultimate outcome of early-life stress depends on several aspects of the 'stressful' experience: its timing, quality, severity, and duration. Developmental stress may have long-lasting consequences for the structure and function of several brain networks, ultimately modulating the output of multiple emotional, social, and cognitive behaviors. Because mental and neurocognitive illnesses most commonly commence early in life (Kessler *et al*, 2005; NIH Workgroup, 2009), improved understanding of cognitive and mental illnesses requires knowledge of the type of early-life events that influence cognitive and emotional outcomes, and of the diverse mechanisms by which these influences take place.

Stress is a signal indicating a potential or perceived threat (Calabrese *et al,* 2007; Joëls and Baram, 2009; Ulrich-Lai and Herman, 2009; McEwen and Gianaros, 2011). Stress is ubiquitous and has high biological significance because it enables rapid, delayed, and often enduring adaptive processes to changing circumstances (Calabrese *et al*, 2007; Joëls and Baram, 2009; McEwen and Gianaros, 2011). Accordingly, the central nervous system is equipped with several sensing mechanisms to identify stress, as well as processes to respond to stressful signals and be modified by them. Cognitive brain networks, including those centered on the hippocampus and prefrontal cortex regions involved in emotional processes, such as amygdala and the nucleus accumbens, as well as network involved in social behaviors, appear to be particularly vulnerable to the effects of stress (Kim and Diamond, 2002; Joëls and Baram, 2009; Lupien *et al*, 2009; Malter Cohen *et al*, 2013; Sandi and Haller, 2015). Important parameters that govern the effects of stress on brain functions include the context and nature of the stress (Zoladz and Diamond, 2008; Joëls and Baram, 2009; McEwen and Gianaros, 2011; Schwabe *et al*, 2011). Stress is not a unitary entity, but a spectrum of signals that vary both in severity and in duration. Mild or short-lasting stress often enhances memory and decision making by augmenting synaptic plasticity, perhaps reflecting the adaptive importance of remembering threatening or dangerous circumstances (Joëls and Baram, 2009; McEwen and Gianaros, 2011). However, these same mechanisms, when activated intensely or for a prolonged period, may provoke detrimental effects (McEwen and Gianaros, 2011; Maras *et al*, 2014). In the mature human and rodent, chronic stress often exerts adverse effects on cognitive functions including memory (Kim and Diamond, 2002; McEwen and Gianaros, 2011; Schwabe *et al*, 2011).

WHAT GENERATES STRESS EARLY IN LIFE? ARE THE CONSEQUENCES A RESULT OF THE STRESS OR OF THE PROVOKING SIGNALS?

Because of the immaturity of both the 'stress system' and the developing brain, environmental signals that might generate stress in the adult, such as restraint, may not be stressful to the neonate (Levine, 1957; Yi and Baram, 1994; Sullivan *et al*, 2003). The age-specificity of stress-provoking stimuli has contributed to the concept of a 'stress hypo-responsive period' (see box). A large body of work has since discovered that the developing brain responds to age-specific stress in an age-specific manner, with profound, enduring consequences.

In addition, it was initially assumed that the neonatal period represented generally stable, unidirectional processes of brain development, so that the effects of stress across this period were consistent and cumulative. This assumption has turned out to be largely inaccurate, because even within the early postnatal period, the type and magnitude of stress-induced changes can vary markedly according to precisely when the stress occurs. This notion has been directly tested by studies using a single 24-h maternal separation (van Oers *et al*, 1998a, b). For example, a 24-h separation during postnatal days 3–4 leads to a hyper-responsivity to stress later in life, whereas the same procedure just days later (postnatal days 7–8 or 11–12) results in a hypo-responsive stress system. Similar differences have been extended to learning and memory outcomes: maternal separation on postnatal day 3 impairs active avoidance and conditioned freezing, whereas the same stress on postnatal day 9 improves performance in these tasks. These data suggest that the epoch of early postnatal-life comprises complex and overlapping developmental processes, and these may drastically influence the consequences of any experiences or environmental perturbations (Avishai-Eliner *et al*, 2002).

In addition, the nature of the perturbations that lead to early-life stress seems to govern its consequences. In humans, chronic early-life stress has both physical and emotional components, and the emotional aspects are dominant. In large part, a majority of human early-life stress stems from abnormal patterns of maternal care varying from neglect to inconsistency and lack of sensitivity (Bowlby, 1950; Nelson *et al*, 2011; Sheridan, McLaughlin, 2014). Complete absence of maternal care results in catastrophic consequences on cognitive and emotional development as found in the studies of orphanage-raised children (Nelson *et al*, 2011; Hostinar and Gunnar, 2013). To study early-life stress, several rodent models have attempted to recapitulate these conditions by manipulating maternal–pup interactions.

As is the case in humans, maternal care has a critical role in rodent development. Beyond simply providing nutrition and safety in the nest, the dam is critical for providing important sensory signals and relaying environmental cues to the pups (Levine, 1957; Eghbal-Ahmadi *et al*, 1999; Champagne and Meaney, 2001; Lucassen *et al*, 2013). Maternal care has been well characterized in rodents and consists of several stereotyped behaviors, including nursing (arched back or low posture) and licking/grooming (Champagne *et al*, 2003). It follows that perturbation of dam–pup interactions has been viewed as a potent way to manipulate the early-life environment and provoke stress. Simply removing the dam for extended periods of time would lead to hypothermia and starvation, so that many

TABLE 1 Emotional Outcomes of CES Induced by Limited Bedding/Nesting Environment

CES period	Sex	Strain	Acute/long term	Outcomes	References
P 2–9	Male/female	Mice: C57BL/6 J	P 21, 29, 63 P 63	Enhanced anxiety-like behaviors in the novelty-induced hypophagia paradigm.	Malter Cohen *et al*, 2013
P 2–9	Male	Mice: 129S2/Sv x C57BL/6 J	3 months	Enhanced anxiety-like behaviors in OF and light-dark box tests.	Wang *et al*, 2012
P 2–9	Male	Rats: Wistar	P 60	Anxiety-like behaviors in EPM test.	Dalle Molle *et al*, 2012
P 2–9	Male	Rats: Sprague Dawley	P 45–60	Anhedonia-like behaviors in sucrose preference test and peer play.	Molet *et al*, 2015a
P 2–9	Male	Rats: Wistar	P 60	Increased anxiety in feeding tests, preference for comfort foods.	Machado *et al*, 2013
P 3–8	Both	Rats: Long-Evans	P 8	Disrupted social attachment behaviors.	Raineki *et al*, 2010
P 8–12	Both	Rats: Long-Evans	P 20, P 45	Impaired social behaviors. Depressive-like behaviors in FST.	Raineki *et al*, 2012

Abbreviations: CES, chronic early-life stress; EPM, elevated plus maze; FST, forced swim test; OF, open field; P, postnatal day.

models have used intermittent maternal deprivation, resulting in intermittent stress, with sometimes variable outcomes (Lehmann and Feldon, 2000; Milstein and Holmes, 2007). An alternative approach has been to provoke chronic, persistent changes in maternal nurturing behaviors by the use of cages with limited nesting and bedding material (Gilles *et al*, 1996; Molet *et al*, 2014; Naninck *et al*, 2015). This 'simulated poverty' induces stress in the dams (Ivy *et al*, 2008), and alters their behaviors (Ivy *et al*, 2008; Rice *et al*, 2008; Rincón-Cortés and Sullivan, 2014). This latter approach has provoked chronic unremitting stress in the pups (Gilles *et al*, 1996; Ivy *et al*, 2008; Rice *et al*, 2008; Moriceau *et al*, 2009; Raineki *et al*, 2010; Wang *et al*, 2011; Molet *et al*, 2014; Naninck *et al*, 2015). Notably, there is little evidence of physical stress of the pups, with no hypothermia and minimal weight changes (Molet *et al*, 2014). Thus, the early-life stress that is engendered seems to be a direct result of the fragmented, unpredictable sensory signals from the mothers (Moriceau *et al* 2009; Baram *et al*, 2012; Molet *et al*, 2014, 2015a). These seem to provoke chronic early-life stress, including persistent elevation of plasma corticosterone and adrenal hypertrophy (Gilles *et al*, 1996; Rice *et al*, 2008). Although all of these signs of stress dissipate rapidly when dams and pups are returned to routine cages, the chronic early-life stress promotes protean consequences on cognitive and emotional brain networks and functional outcomes (Tables 1 and 2), as well as brain development, stress sensitivity, and limbic network hyper-excitability (Huang, 2014; Dubé *et al*, 2015; Table 3).

EMOTIONAL AND SOCIAL CONSEQUENCES OF EARLY-LIFE EXPERIENCE VIA ALTERED STRESS NETWORKS

Hundreds of human studies over more than six decades have illustrated close statistical associations of early-life adversity and a variety of emotional problems. 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 (eg, Bremner *et al*, 1993; Kaplan *et al*, 2001). Although these associations are compelling, direct causality is difficult to infer in humans, and studies exist that challenge a direct or linear relationship of adversity and, for example, post-traumatic stress disorder (Pratchett and Yehuda, 2011). These difficulties have led to a large body of work using animal models. A variety of prenatal and postnatal stressors have been used in these studies, with a preponderance of studies finding 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 (eg, Sandi and Haller, 2015; Nishi *et al*, 2014). Here, we summarize in Table form the consequences of chronic early-life adversity provoked by abnormal maternal care in the limited bedding–nesting environment (Gilles *et al*, 1996; Molet *et al*, 2014), a model recently adopted and adapted by over 50 laboratories around the world (eg, Raineki *et al*, 2010; Wang *et al*, 2011; Bolton *et al*, 2013; Machado *et al*, 2013; Maniam *et al*, 2014; Kohl *et al*, 2015; Naninck *et al*, 2015; Table 1).

The mechanisms leading to these profound emotional changes are unclear. Abnormal maturation (Brunson *et al*, 2005; Bogdan and Hariri, 2012; Burghy *et al*, 2012; Maras and Baram, 2012) or rewiring of neuronal connectivity in the underlying brain networks (Karsten and Baram, 2013) have been proposed. The nature of these networks is not fully known, but they include amygdala-ventromedial prefrontal cortex circuitry implicated in the regulation of emotion (Burghy *et al*, 2012). Thus, abnormal maternal care and chronic early-life stress have been shown to result in increased number and function of excitatory synapses to stress-sensitive neurons in hypothalamus (Gunn *et al*, 2013), whereas reduced excitatory synapse number and function have been reported after augmented maternal care (Korosi *et al*, 2010). Increased excitatory input may sensitize the central components of the neuroendocrine stress system to subsequent stress, predisposing to stress-related emotional disorders. Other structural changes including stunting,

TABLE 2 Cognitive Outcomes of CES Induced by Limited Bedding/Nesting Environment

CES period	Sex	Strain	Acute/long term	Outcomes	References
P 1–7	Both	Rats: Long-Evans	P 7	Attachment learning deficits.	Moriceau *et al*, 2009
P 2–9	Male	Mice: C57BL/6 J	4–8 months	Memory impairments in MWM and NOR tests. No anxiety-like behavior in OF test.	Rice *et al*, 2008
P 2–9	Male	Mice: 129S2/Sv × C57BL/6 J	6 months	Memory impairments in MWM and Y-maze tests.	Wang *et al*, 2011
P 2–9	Male	Rats: Sprague-Dawley	10–12 months	Memory deficits in MWM and NOR tests.	Brunson *et al*, 2005; Ivy *et al*, 2010
P 2–9	Male	Mice	Adult	Abnormal learning and memory in several tasks.	Naninck *et al*, 2015
P 2–9	Male	Mice	P 45	Abnormal hippocampal learning and molecular signaling.	Wang *et al*, 2013
P 2–9	Male	Mice	Adult	Abnormal prefrontal cortex-dependent cognitive functions.	Yang *et al*, 2015

Abbreviations: CES, chronic early-life stress; MWM, Morris water maze; NOR, novel object recognition; OF, open field; P, postnatal day.

atrophy, or hypertrophy of dendritic structure and altered synapse number and function might take place in amygdala and hippocampus (Ivy *et al*, 2010). The resulting changes in intracellular signaling, potentially via calcium-dependent changes, might provide a signal for downstream gene expression effects, maintained via epigenetic alterations of the chromatin (Korosi *et al*, 2010; Hornung and Heim, 2014; Lewis and Olive, 2014; Turecki, 2014; Szyf, 2015).

COGNITIVE CONSEQUENCES OF EARLY-LIFE EXPERIENCE VIA DISRUPTION OF THE MATURATION OF HIPPOCAMPAL CIRCUITRY

The basis of the vulnerability of the developing brain to the adverse cognitive effects of early-life stress has been an area of intense research. This vulnerability results in large part from developmental processes that are still taking place during the early-life stress period. Here, we use the hippocampus as a salient example, emphasizing that cognitive functions involve a large set of behaviors enabled by complex and overlapping cortical and subcortical neuronal networks. In rodents, the organization of the hippocampal formation and the limbic circuit, involved in cognitive functions, takes place largely after birth, continuing through the first few weeks of life. In humans, the development of this circuit is characterized by a particularly prolonged trajectory, and refinement of cortical synapses and connectivity patterns continues for years into the adolescent period.

Thus, although the effects of stress on adult cognitive functions such as memory are often reversible, stress that occurs early in life, though amenable to behavioral and pharmacological interventions (eg, Ivy *et al*, 2010; Shonkoff, 2011), can permanently alter these processes (Brunson *et al*, 2003). Focusing on chronic and/or severe early-life stress, long-lasting deficits, contextual fear conditioning (Guijarro *et al*, 2007; Kosten *et al*, 2007; Oomen *et al*, 2010) as well as in the Morris watermaze (Oitzl *et al*, 2000; Huot *et al*, 2002; Brunson *et al*, 2005; Uysal *et al*, 2005; Aisa *et al*, 2007; Rice *et al*, 2008; Ivy *et al*, 2010; Wang *et al*, 2012) have been found. Although these tests involve elements of stress and may therefore not be free of confounders, similar defects after early-life stress are found in object recognition (Brunson *et al*, 2005; Aisa *et al*, 2007; Kosten *et al*, 2007; Rice *et al*, 2008; Ivy *et al*, 2010; Hulshof *et al*, 2011) and object location (Molet *et al*, 2015b).

How might early-life stress impair memory and other cognitive functions? Early in life, stress may both interfere with the normal construction and maturation of cortical and hippocampal synaptic connections as well as promote their destruction (Kehoe and Bronzino, 1999; Brunson *et al*, 2005; Cui *et al*, 2006; Radley *et al*, 2008; Maras and Baram, 2012). In mature brain, stress induces structural changes that progress with the duration, severity, and developmental timing of the stress. Modifications of the synaptic machinery take place within minutes (Chen *et al*, 2008, 2013) and chronic stress leads to remodeling of dendritic branches (Kim and Diamond, 2002; McEwen, 2012). Dendritic integrity requires the presence of functional excitatory synapses, which are located primarily on dendritic spines (Bourne and Harris, 2008; Holtmaat and Svoboda, 2009; Kasai *et al*, 2010). Rapid, stress-induced dendritic spine loss has been found in the distribution of eventual dendritic atrophy in adult hippocampus (Pawlak *et al*, 2005; Diamond *et al*, 2006; Chen *et al*, 2008, 2013), suggesting that they are related. Importantly, the number and shape of synapse-bearing spines are dynamic (Bourne and Harris, 2008; Holtmaat and Svoboda, 2009; Kasai *et al*, 2010) and are regulated by factors including neurotransmitters, growth factors, and hormones that, in turn, are governed by environmental signals, including stress (Segal, 2010; Liston and Gan, 2011). Thus, a derangement of spine dynamics may provide a mechanism for stress-induced impairment of synaptic function, followed by dendritic loss and cognitive impairments.

After chronic early-life stress in rodents, impoverished dendritic trees and reduced hippocampal volume have been described (Brunson *et al*, 2005; Ivy *et al*, 2010; Molet *et al*,

TABLE 3 Structural, Functional and Gene Expression Changes Provoked by CES Induced by a Limited Bedding/Nesting Environment

CES period	Sex	Species/strain	Acute/long term	Outcomes	References
Stress system perturbations					
P 2–9	Both males	Rats: Sprague-Dawley mice: C57BL/6 J	P 9 only P 9; adult	Elevated basal corticosterone levels, higher adrenal weights.	Gilles *et al*, 1996; Avishai-Eliner *et al*, 2001a; Brunson *et al*, 2005; Rice *et al*, 2008
P 3–8	Both	Rats: Long-Evans	P 8	Elevated basal corticosterone levels.	Raineki *et al*, 2010
Structural and functional brain changes					
P 1–7	Both	Rats: Long-Evans	P 7	Amygdala-locus ceruleus-olfactory bulb network perturbations.	Moriceau *et al*, 2009
P 2–9	Both	Mice: C57BL/6 J × 129 Sv-SvJ	P 18–26	Enhanced glutamatergic drive onto CRH neurons of the hypothalamus. Astrocytic glutamate reuptake impairments.	Gunn *et al*, 2013
P 2–9	Male	Rats: Sprague-Dawley	10–12 months	Dendritic atrophy of CA1, CA3 pyramidal cells; mossy fiber sprouting. Synaptic plasticity defects in CA1, CA3.	Brunson *et al*, 2005 Ivy *et al*, 2010
P 2–9	Both	Rats: Sprague-Dawley	14–40 days	Hyper-excitability during chronic EEG recording, age specific-seizures (infantile spasm-like) in most; spontaneous seizures (epilepsy) in a minority.	Dube *et al*, 2015
P 3–8	Both	Rats: Long-Evans	P 8	Enhanced amygdala neural activity.	Raineki *et al*, 2010
P 8–12	Both	Rats: Long-Evans	P 45	Enhanced amygdala neural activity.	Raineki *et al*, 2012
Gene-expression changes					
P 2–9	Both	Rats: Sprague-Dawley	P 9	Transiently reduced CRH mRNA in PVN and CRF1 mRNA in hippocampal CA1, DG. Reduced CRH receptor binding in pituitary. Reduced GR mRNA expression in PVN and frontal cortex.	Avishai-Eliner *et al*, 2001
P 2–9	Male	Mice: C57BL/6 J	4–8 months	Reduced CRH mRNA expression in the PVN.	Rice *et al*, 2008
P 2–9	Male	Rats: Sprague-Dawley	10–12 months	Augmented CRH expression in the hippocampus.	Ivy *et al*, 2010
P 1–7	male	Rats: Long-Evans	Adult	Reduced BDNF expression in prefrontal cortex	Roth *et al*, 2009
P 2–9	Male	Mice: 129S2/Sv × C57BL/6 J	3 months	No change in CRH, arginine vasopressin in PVN, MR, GR in the hippocampus and CRH in central amygdala.	Wang *et al*, 2012
P 2–9	Both	Mice: C57BL/6 J × 129 Sv-SvJ	Adult	Upregulated CRH expression in the PVN.	Gunn *et al*, 2013
Structural and functional changes					
P 2–9	Male	Mice	Adult	Altered neurogenesis and survival of newborn cells.	Naninck *et al*, 2015
P 2–12	Male	Mice	P 26, P33, P68	Enhanced and aberrant amygdala activity.	Malter Cohen *et al*, 2013

Abbreviations: BDNF, brain-derived neurotrophic factor; CA1 and CA3, cornum Ammonis regions of the hippocampus 1 and 3; CES, chronic early-life stress; CRH, corticotropin releasing hormone; CRH1, CRH receptor 1; DG, dentate gyrus; EEG, electroencephalography; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; P, postnatal day; PVN, paraventricular nucleus of hypothalamus.

2015b), and similar dendritic changes were found in the prefrontal cortex (Radley *et al*, 2008; Yang *et al*, 2015). In humans, chronic early-life stress such as rearing in orphanages promotes reduced volume of the cortex (especially prefrontal) as well as hippocampus and the latter correlates with stress duration (Hodel *et al*, 2015). The cortex is composed of several components including cell bodies, intercellular space, and branched dendritic tree. Indeed, the dendrites comprise ~42% of cortical volume (Paus, 2009). Therefore, in view of the correlated dendritic impoverishment and cellular volume loss in rodents, it is likely cortical, and hippocampal volume reduction in human adolescents and adults exposed to early-life adversity might derive from abnormal growth and branching of synapse-carrying neuronal dendrites. The reduced synaptic number in hippocampus and frontal cortex, in turn, may contribute to functional deficits (Brunson *et al*, 2005; Radley *et al*, 2008; Ivy *et al*, 2010; Schmidt *et al*, 2011; Maras and Baram, 2012).

This poor dendritic growth and branching and/or dendritic atrophy secondary to a loss of functional synapses on destroyed dendritic spines (Diamond *et al*, 2006; Chen *et al*, 2008; Lin and Koleske, 2010) may progress with age (Brunson *et al*, 2005; Ivy *et al*, 2010). Support for this possibility emerges from studies using transgenic mice (Wang *et al*, 2011, 2012). Specifically, mice with a conditional knockout of the *CRFR1* gene were resistant to the adult cognitive defects that follow chronic early-life stress. The early-life stress took place during the first postnatal week, prior to the repression of the CRFR1 receptor via a CaM Kinase II mechanism (the latter is expression commencing P5–10, with full maturation by P20; Wang *et al*, 2011). Thus, whereas CRFR1 receptors were still expressed during the first 10 days of life, the period of chronic stress, their elimination later in life was protective, suggesting that the cognitive deficits require progressive processes beyond the stress period. In addition, in wild-type

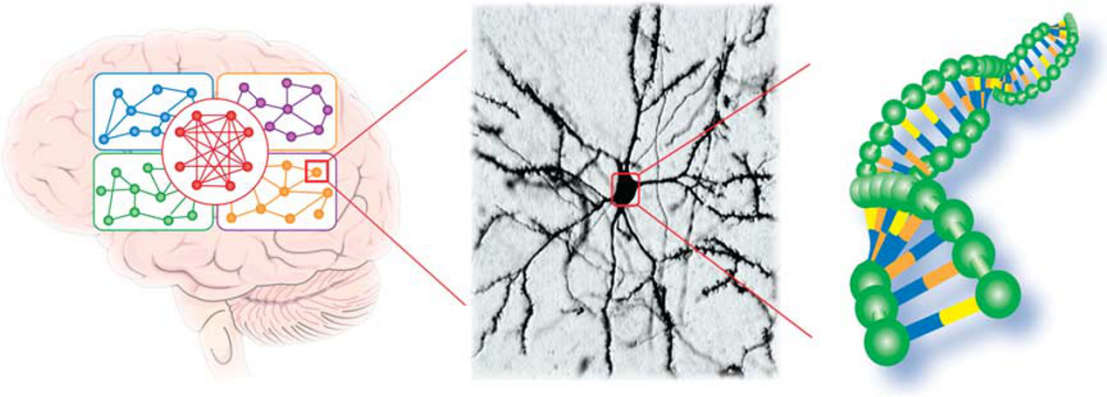

Figure 1. A schematic representation of the multiple levels of analysis that are required to appreciate the reprogramming of the brain by early-life experiences, including stress. Left: the brain is composed of a number of discrete yet overlapping and interacting networks. Center: neurons, the components of these networks, have a remarkable complexity of their structure, supporting profound functional complexity. Right: neuronal structure and function are governed by the repertoire of genes encoded by DNA, the regulated expression of these genes, and the orchestration of the location and function of the gene products in time and space.

mice and rats, a progressive emergence of cognitive problems and a progression of hippocampal dendritic injury support the idea that chronic early-life stress induces progressive functional and structural changes in the hippocampus. In contrast, a majority of the injury likely takes place within a 'critical' or 'sensitive' period early in life (Regev and Baram, 2014), because pharmacological interventions immediately following the early-stress period (Ivy *et al*, 2010) reversed the effect of such stress, whereas the same manipulation several months later had only a partial effect (Ivy *et al*, unpublished observations). Epidemiological studies in humans are also suggestive of a progressive injury: cognitive problems in individuals with surrogate markers of chronic stress during childhood emerge during middle age and are a risk factor for early dementia (Kaplan *et al*, 2001). In contrast, studies on children subjected to early-life emotional deprivation followed by environmental enrichment (Nelson *et al*, 2007; Hostinar and Gunnar, 2013) suggest that intervention beyond the first 2–3 years of life is less effective, supporting a sensitive or critical period for the major effects of early-life stress (Figure 1 in Regev and Baram, 2014). Abnormal development and progressive injury following early-life stress are not mutually exclusive, as impairments of cognitive functions over the lifetime may reflect cumulative effects of both early and continuing processes (McEwen 1999, 2012; Ulrich-Lai and Herman, 2009). Obviously, if the effects of early-life stress were to progress beyond the initial period, this would provide an important more protracted window for intervention.

THE TOOLBOX OF EARLY-LIFE STRESS

During stress, synapses in several brain regions are impacted by a cocktail of stress mediators with distinct and concerted actions and mechanisms. Glucocorticoids are the canonical stress hormones that are released peripherally in response to stress. They can have broad impacts on brain function (Drost *et al*, 2008; Ulrich-Lai and Herman, 2009; McEwen, 2012), including affecting neuronal structure such as dendritic arborization and the dynamics of dendritic spines (eg, Magariños and McEwen, 1995; Jafari *et al*, 2012; Liston *et al*, 2013). Thus, poor dendritic growth and branching may be a result of abnormal levels of glucocorticoids and their actions on cognate receptors (GR) (Alfarez *et al*, 2009; Liston and Gan, 2011). Alternatively, dendrites may atrophy, secondary to a loss of functional synapses on the destroyed dendritic spines (Lin and Koleske, 2010). In support of this idea, dendritic spines and novel mechanisms for these changes are emerging, including glucocorticoid receptor-mediated induction of actin-binding proteins (Liston and Gan, 2011).

However, glucocorticoids are only one of the molecular instruments impinging on synapses and dendritic spines during early-life stress. Neurotransmitters and neuropeptides, especially CRH, may contribute to both aberrant growth and/or exuberant pruning of dendrites and dendritic spines. In the case of CRH, the peptide is synthetized locally in the hippocampus, amygdala, bed nucleus of the stria terminalis, and cortex (Joëls and Baram, 2009). Increased CRH expression has been found in hippocampus (Ivy *et al*, 2010) and amygdala (Dube *et al*, 2015) after early-life stress. CRH is released during stress in several of brain regions as well as locus ceruleus (Rozendaal *et al*, 2002; Chen *et al*, 2004a; Van Bockstaele and Valentino, 2013). The peptide acts on CRH receptors within these regions (Chen *et al*, 2000, Van Pett *et al*, 2000; Refojo *et al*, 2011; Van Bockstaele and Valentino, 2013), and these receptors often reside on dendritic spines (Chen *et al*, 2004a, 2012). CRH has potent effects on dendritic spines and synapse integrity, effects that are mediated via actin remodeling (Chen *et al*, 2013), calcium-dependent calpain activation (Andres *et al*, 2013) and likely additional mechanisms. Chronic exposure to CRH may provoke dendritic stunting and atrophy (Chen *et al*, 2004b). Thus, abnormal, high levels of CRH may impair

dendritic arborization or contribute to dendritic pruning, perhaps in concert with glucocorticoid actions (Joëls and Baram, 2009).

CRUCIAL QUESTIONS AND FUTURE RESEARCH DIRECTIONS

The study of early-life stress provides a window into the understanding of normal adaptation, as well as the basis of resilience and vulnerability to emotional and cognitive disorders throughout life. Although much has been accomplished, several conceptual challenges remain. These include:

a. Identifying and defining genetic pre-dispositions to the impact of early-life stress. Although early-life adversity is a major risk factor for later pathology, there is a substantial variability in the outcome of early stress. What genetic (or epigenetic) factors impart vulnerability or resilience to the effects of early-life stress?
b. Identifying interactions between stress early in life and those stresses experienced later in life. Individuals exposed to early stress are likely to experience stress throughout their lifespan. How do early stressful experiences impact the consequences of stress experienced later in life? Are there other sensitive periods, such as adolescence, when the brain is particularly vulnerable to stress?
c. Elucidating the nature and underlying biology of sex-specific consequences of early-life stress. Human epidemiological data indicate that stress-related psychopathologies are more prevalent in females, yet there is a relative dearth of animal models studying how sex modulates vulnerability to the effects of early stress. How do genetic and hormonal sex differences contribute to sex-specific consequences of early-life stress?
d. Addressing the formidable issue of the generalization and translation of rodent studies to the human condition. Rodent models have proven extremely useful in describing the consequences of early-life stress on brain development and identifying mechanisms involved. However, it is crucial to exert care when applying these findings and theories back to the human condition.

Novel and exciting tools should enable addressing the conceptual above and the daunting-associated technical challenges. Transgenic mice with visible and controllable specific cell populations now offer tremendous opportunities for dissecting the roles of specific neurons and circuits. However, their use requires ascertainment of the specificity of these lines (Chen *et al*, 2015; Lammel *et al*, 2015). A clearer understanding of the roles of several individual stress mediators, including not only glucocorticoids but also CRH, other neuropeptides, and novel molecules, is emerging (Joëls and Baram, 2009). The individual and concerted actions of these mediators during sensitive postnatal periods should be probed, focusing on their effects on individual genes and neurons as well as on gene networks and ultimately brain networks that underlie normal and pathological functions.

THE CONCEPT OF THE 'STRESS HYPO-RESPONSIVE PERIOD'

Initial work on the ontogeny of the neuroendocrine stress response system indicated that the first 2 weeks of life in rodents (postnatal days 4–14 in rats; 1–12 in mice), the HPA system is relatively unresponsive to stress (termed the 'stress hypo-responsive period' or 'SHRP'). This characterization is based on low basal corticosterone levels, reduced sensitivity to CRH, and the apparent lack of a stress response to a variety of 'typical' stressors during this age. The SHRP likely reflects the still ongoing maturation of the HPA axis, and this reduction in HPA tone has been hypothesized to protect against the deleterious effects of glucocorticoids on brain development. Importantly, the initial concept of a SHRP has been proven to not fully represent the stress status of immature brains. In humans, stress responses to pain exist throughout the neonatal period. In rodents, immature pups have 300–400% increases in plasma corticosterone levels in response to age-appropriate stressors, that is, maternal separation or hypothermia. These hormonal responses are mediated by stress-induced activation of CRH release and associated with stress-induced enhancement of CRH expression in hypothalamic PVN neurons. Thus, rather than being unresponsive, the developing stress system seems to be tuned specifically to the types of stress that may be relevant to the early-life period.

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