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New insights into early-life stress and behavioral outcomes

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Abstract

Adverse early-life experiences, including various forms of early-life stress, have consistently been linked with vulnerability to cognitive and emotional disorders later in life. Understanding the mechanisms underlying the enduring consequences of early-life stress is an active area of research, because this knowledge is critical for developing potential interventions. Animal models of early-life stress typically rely on manipulating maternal/parental presence and care, because these are the major source of early-life experiences in humans. Diverse models have been created, and have resulted in a wealth of behavioral outcomes. Here we focus on recent findings highlighting early-life stress-induced behavioral disturbances, ranging from hippocampus-dependent memory deficits to problems with experiencing pleasure (anhedonia). The use of naturalistic animal models of chronic early-life stress provides insight into the spectrum of cognitive and emotional outcomes and enables probing the underlying mechanisms using molecular-, cellular-, and network-level approaches.

Introduction

Mental illnesses and cognitive disorders commence predominantly early in life [1,2], suggesting the need to explore events early on that predispose and contribute to disease onset. Epidemiological data indicate that various forms of early-life stress in humans can have life-long impacts, ranging from memory deficits and poor executive functioning [3–5] to more explicitly stress-related disorders such as depression, anxiety, and post-traumatic stress disorders [6–11]. Adverse early-life conditions, including poverty, loss of a parent, substance abuse by the mother or maternal depression, are consistently associated with vulnerability to various psychopathologies later in life [12–15]. Understanding the mechanisms for the enduring consequences of early-life stress on brain function has been an active area of neuroscience research, as this knowledge is critical for identifying clinically plausible therapeutic strategies. This review will focus on the behavioral outcomes of early-

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life stress, with a particular emphasis on new findings emerging within the past few years, and conclude with a unifying theory for how these profound changes may occur.

What is early-life stress?

The type and severity of the perturbations that cause early-life stress seem to govern its consequences. In humans, chronic early-life stress has both physical and emotional components, but the emotional aspects are dominant. Among the most influential studies of the effects of early-life stress are those of institutionally raised children, where chronic impoverished care was associated with cognitive and emotional problems [4,16]. Notably, the associated consequences were partially reversed by fostering, thus highlighting the importance of early-life care *per se* [4,16–19]. In large part, human early-life stress stems from abnormal patterns of maternal care, ranging from neglect to inconsistency and lack of sensitivity [18,20–22]. In order to study early-life stress, animal models have aimed to recapitulate these conditions by manipulating maternal interactions with offspring.

Modeling early-life stress

In mammals, including humans, monkeys and rodents, maternal input has perhaps the most significant influence on the environment experienced during development [20,22–25]. 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 [26,27] for recent reviews). Non-human primates, whose brains and sociality most closely resemble those of humans, have provided useful insights into the development of complex psychiatric disorders. The seminal work of Harlow and colleagues using maternally-isolated rhesus monkeys as a model was the first to demonstrate that maternal-infant interactions are required for normal cognitive and emotional development [23,28,29]. More recently, using a model of maternal maltreatment in rhesus monkeys, Sanchez and colleagues suggested that this adverse early-life experience affects the development of brain systems involved in stress responses, resulting in emotional reactivity and abusive parenting in adulthood [30,31]. Although primate models of early-life stress continue to provide important insights, the many practical and ethical concerns associated with the use of primates preclude their widespread use. The majority of early-life stress models, including the ones discussed here, employ rodents. Rodents are obviously incapable of reproducing the rich repertoire of human development and cognitive and emotional outcomes. Nevertheless, the major similarities in the role of maternal care, in the stress system, and the ready availability of cognitive and emotional tasks to probe behavior have rendered rodents a tractable model for studying the behavioral outcomes of early-life stress.

As is the case in humans, maternal care plays a critical role in rodent development. The rodent dam is vital for not only providing nutrition and safety in the nest, but also providing important sensory signals and relaying environmental cues to the pups [32–35]. Simply removing the dam for extended periods of time would lead to hypothermia and starvation; thus, many models of early-life stress have used intermittent maternal separation (MS). This paradigm decreases the quantity of maternal care and results in intermittent stress [36,37]. Although MS models have provided a wealth of data on the effects of decreased maternal

interaction on pup development, some of the outcomes of this manipulation have been less consistent [38–42]. In addition, the paradigm may differ from relevant human conditions: When infants and children grow up in adverse conditions such as severe poverty, famine, war or with drug-abusing mothers, the stress is typically chronic rather than intermittent, and the mother is typically present and her behavior may be stress-provoking to the child [22,43–45].

A more recently emerging model involves provoking chronic changes in the quality of maternal care by the use of cages with limited nesting and bedding material (LBN) during postnatal days (P)2–9 [26,46,47]. This ‘simulated poverty’ induces stress in the dams [48], and profoundly alters maternal behaviors, such that they are fragmented and unpredictable [49,50]. Notably, the overall duration of maternal nurturing behaviors as well as their general quality (e.g., arched-back nursing) are little changed [24,48–50]. This approach has provoked chronic, unpredictable and uncontrollable “emotional stress” in the pups [26,46–49,51–53]. There is little evidence of physical stress in the pups, with no hypothermia and modest weight changes [26]. Thus, the early-life stress that is generated seems to be a direct effect of the fragmented, unpredictable sensory signals from the mothers [22,26,50,51], resulting in persistent elevation of plasma corticosterone and adrenal hypertrophy [46,49,54]. All of these signs of stress disappear after dams and pups are returned to routine cages on P10. Still, the experience in the LBN cages during this critical window results in long-lasting consequences on cognitive and emotional function. The LBN model has been found to provoke robust and generally reproducible cognitive and emotional outcomes, leading to its adoption by dozens of laboratories around the world [51–53,55–63]. Thus, this review will focus primarily on the LBN model and its behavioral outcomes. Notably, an obvious challenge for both human and animal-model studies of early-life stress and its life-long consequences is the presence of additional factors that might influence these outcomes, including genetics and individual differences in resilience/vulnerability. These are likely some of the factors promoting ambiguous or contradictory results in both human and animal-model studies.

Modeling the behavioral outcomes of early-life stress

The specific later-life consequences of early-life stress in humans are modeled in rodents using standardized cognitive and emotional tests that have been designed to optimize translation to the human condition. For example, rodent tests of depressive-like behavior, such as the forced-swim test (FST), have been validated to show improvement with human antidepressants [64]. Human cognitive function, though much more complex than in rodents, is subserved by areas of the brain that are homologous in the rodent: e.g., the Morris water maze memory task in rodents is analogous to spatial navigation and memory in humans and both are hippocampus-dependent [65]. Much research employing animal models has focused on hippocampus-dependent memory, because of the availability of standardized tests and well-characterized neural substrates, molecules and mechanisms. We describe some of these findings, and regret that space limitations prevent us from discussing executive functions and other prefrontal cortex-dependent behaviors in the context of early-life stress [66–68].

For any model of early-life stress, the detection of a behavioral outcome depends on several variables. The first set of variables pertains to the timing, nature and severity of the stress. Secondly, the age at which animals are tested, whether during adolescence, adulthood, or aging, can determine outcome. Third, the type and difficulty of the test that is used to measure behavioral outcomes is important. For example, a rigorous test such as object location memory (OL) might uncover subtle deficits not apparent in a less challenging test, such as object recognition memory (OR) [69]. These caveats are illustrated below.

A spectrum of cognitive consequences of chronic early-life stress

Diverse cognitive effects of early-life stress have been reported. For example, MS stress on postnatal day 9 has led to improved memory in the active avoidance test [70], whereas the same manipulation on postnatal day 4 has led to impaired memory in the same test [70]. This latter finding is more in line with the majority of the MS literature, which includes reports of impairments in the Morris Water maze test and OR [40,71]. There may be several possible bases for these divergent outcomes, including the potential that mild or predictable stress might be a positive experience [72]. More likely, these diverse results derive from mechanisms depending on the developmental timing of the separation [36].

Memory impairments have been the common outcome in rodents exposed to chronic early-life stress in the LBN paradigm. For example, in a rigorous and hippocampus-dependent test of OL memory, an overt impairment in spatial memory was found as early as adolescence in LBN rats [69]. A less rigorous memory task for OR found comparable performance in LBN vs. Control adolescent rats. However, an acute-stress “challenge” imposed 24 hours prior to the test led to memory problems only in the LBN rats, thus unmasking a latent cognitive vulnerability [69]. The memory deficits after chronic early-life stress also progressed over the lifespan of LBN rats, so that deficits in OR memory emerged by middle-age [69]. At this age, hippocampus-dependent memory deficits were also present using the Morris water maze task [54,73]. Timing of testing is thus an important factor in determining the cognitive outcomes of early-life stress.

Recent findings for emotional consequences of chronic early-life stress

A variety of emotional problems, based on rodent tasks considered indicative of depression or anxiety, have been reported after early-life stress [26,74–76]. More recently, anhedonia, a reduced capacity to experience pleasure which commonly heralds depression or schizophrenia in humans [77], has been identified following early-life stress. 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 [50]. This anhedonia was not accompanied in adolescent rats by overt anxiety-like behavior or depressive-like behavior. Increased anxiety-like behaviors in the elevated-plus maze test were found later in adulthood [55], but these were no longer found during middle-age (i.e., 12 months of age in rats) [78]. These effects of age on anxiety and other emotional outcomes are not surprising, because in humans, the emergence and waning of anxiety and depression are highly age-dependent [79,80].

Adolescent anhedonia after early-life stress has since been confirmed in a separate LBN cohort in a different laboratory, as indicated by decreased M&M consumption as well as reduced lever pressing for cocaine (S. Mahler, personal communication). Adolescent anhedonia after early-life MS has also been found by some authors [38,40], including one report of decreased cocaine self-administration [81], in accord with the attenuated drug-seeking in the LBN model. However, others reported increased or unchanged sucrose preference following MS [38–42].

The anxiety- and depression-like behaviors resulting from MS have been variable, ranging from increased anxiety in the elevated-plus maze test [55] and increased immobility in the FST [40] to no changes in either test [82,83]. For further details, the reader is referred to a recent review summarizing the emotional consequences of MS imposed at different developmental ages [26].

These differing results may be due to variation in the timing of the MS during development [84], as well as differences in the age of testing. The timing of the stress is important for emotional outcomes: Indeed for the LBN model, when it was imposed later during development, on P8–P12, increased immobility in the FST was reported during adolescence [60]. Furthermore, for all experimental models, the procedures employed for emotional testing (e.g., lighting during the elevated-plus maze test [85]) can affect the outcome. Accordingly, an effort should be made in the field to standardize behavioral testing procedures as much as possible, and recognize the importance of timing of developmental stress and of testing age when interpreting results.

Although the majority of emotional consequences of chronic early-life stress have been negative, there is some evidence for positive outcomes following stressful experiences that are challenging but not overwhelming, so-called “stress inoculation” [72]. 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 [86].

Conclusions

Stress has profound effects on the brain, manifesting as altered behavioral outcomes. This is especially true when the stress occurs during vulnerable developmental periods. Brain maturation involves multiple dynamic processes that are regulated both by genetic factors and environmental input [87–90]. Many of these processes continue during postnatal life. Although it is impossible to directly compare rodent and human brain development and their trajectories, there is excellent information about comparative development of specific brain regions across species. For example, hippocampal development in the full-term human neonate is similar to that of a P5–P7 rat [91], providing common context to studies targeting early-life stress and other manipulations.

The transducing mechanisms that convert the experience of early-life stress to overt behavioral changes remain unclear. Abnormal maturation [54,92–94] or rewiring of neuronal

connectivity in the underlying brain networks [95] have been proposed. For example, 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 the hypothalamus [57], promoting vulnerability to future stress signals. In contrast, reduced excitatory synapse number and function has been reported after 'optimal' early-life experiences, such as augmented maternal care [96]. These changes in synaptic activity are sufficient to program long-term changes in neuronal gene expression, maintained via epigenetic alterations of the chromatin [97,98]. Thus, increased excitatory input early in life may sensitize the central components of the neuroendocrine stress system to subsequent stress, predisposing to stress-related emotional disorders. Other structural changes, including stunting, atrophy or hypertrophy of dendritic structure, and altered connectivity, might take place in the amygdala and hippocampus [73], as well as pleasure centers of the brain, contributing to widespread circuit-level dysfunction (Figure 1).

Recognizing the complexity of early-life stress and its long-term consequences allows for the generation of meaningful, novel approaches aiming to improve the human condition. Future work in the field must move beyond the traditional focus on the HPA axis to fully appreciate the vast array of behavioral outcomes and their network and mechanistic underpinnings [13,50,59,99–101]. Comprehensive approaches with multiple levels of analysis and integration of human and animal-model studies are required to probe the consequences of early-life adversity: understanding the underlying processes is a prerequisite for precise, individualized interventions to improve the outcomes of the world's current and future children.

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Highlights

- Early-life stress is linked with vulnerability to cognitive and emotional disorders.
- Naturalistic animal models of early-life stress are critical to identify mechanisms.
- Recent studies report outcomes ranging from hippocampus-dependent memory deficits to emotional consequences such as anhedonia and depression.

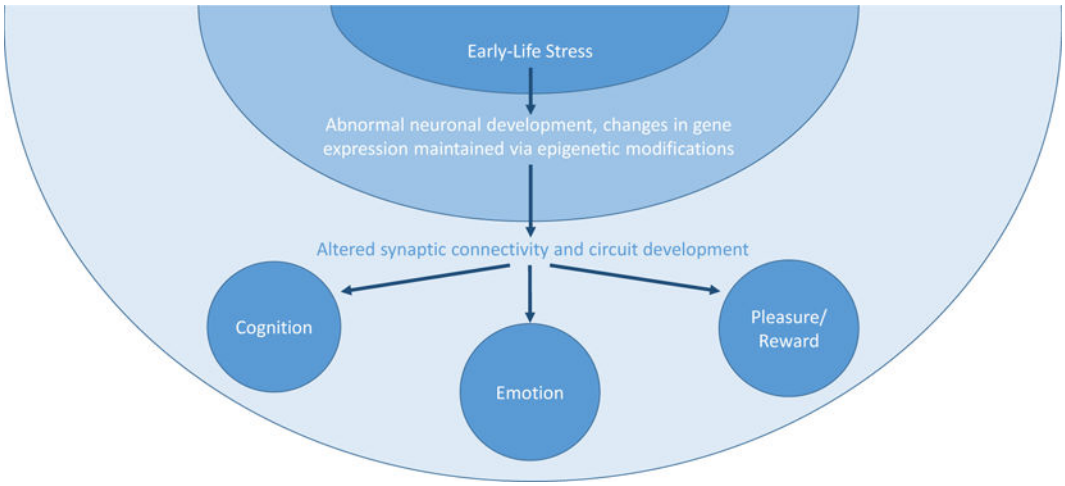

Figure 1.

A unifying theoretical framework for how early-life stress can induce long-term changes in behavior. The inciting event is the experience of early-life stress, represented in the first concentric circle. Early-life stress causes a cascade of changes acutely during the perinatal period that results in abnormal neuronal development and changes in gene expression, which are maintained long-term via epigenetic modifications of the chromatin (represented in the second concentric circle)[95,98,102]. 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 3 nodes within the third concentric circle) [78,93,103,104].