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Early-life Social Adversity and Developmental Processes in Nonhuman Primates

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Abstract

Most primate species produce offspring that are altricial and highly dependent upon caregivers. As a consequence, a host of developmental trajectories can be dramatically altered by variation in early experiences. We review the impact of early social experiences (in both experimental models and natural contexts) on developmental profiles in three species of nonhuman primates: marmosets, squirrel monkeys, and macaques. Graded exposure to early-life social adversity (ELSA) produces short- to long-term effects on multiple developmental outcomes, including affect, social behavior, cognitive and attentional processes, and in the neural substrates that underlie these sociobehavioral traits.

Introduction

It is scientific and biomedical dogma that exposure to adverse early environments leads to a host of altered biological and behavioral processes, many of which can place organisms at risk for lifetime dysfunction and disease. Given the delayed neurological development and the extensive reliance on caregivers early in life, primates represent a taxon in which the absence of, unpredictability in, and even subtle variation, in early caregiving would be expected to leave neural and behavioral fingerprints on a host of developmental outcomes. We will compare the outcomes of experimental models of early-life social adversity (ELSA) vs. natural variation in ELSA to understand the relative utility of such models in psychiatric and evolutionary research. In this review, we focus on recent findings from nonhuman primates that characterize the ways in which ELSA profoundly shapes subsequent social behavior, emotional processing, and cognition, and alters the neural substrates for the canalization of these traits.

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Conflict of interest statement

Nothing declared.

Models of early life social adversity in nonhuman primates

Three approaches are utilized to evaluate the impact of ELSA on developmental outcomes in nonhuman primates. The first involves chronic rearing of offspring in suboptimal rearing environments (SOR) that depart from species-typical norms (e.g., rearing in a nursery vs. rearing with the mother; variable foraging demand on mothers). The second approach exposes young primates to unpredictable short-term separations (STS) from caregivers. The third approach takes advantage of normative variation (NV) in early interactions with caregivers. These strategies are characterized in Table 1. Sufficient data for review are available on three taxa of primates – macaques (*Macaca* spp.), squirrel monkeys (*Saimiri sciureus*), and marmosets (*Callithrix* spp.), and important features of social structure and early offspring care in these species are highlighted in Box 1. Below we review the impact of ELSA on six major developmental outcomes.

Developmental Outcomes

Affective Behavior

Affective behavior encompasses emotional responses, including distress, fear, and anxiety. Though affective behavior also encompasses positive emotional states, the extant literature focuses primarily on the effects of ELSA on negative affect. Defining and assessing affective behavior in primates is complex and must take into account species-typical behavior. For instance, anxiety behavior is characterized by yawning and scratching in rhesus [1], dorsal contact levels and food consumption in squirrel monkeys [2], and heightened locomotion and contact calling in infant marmosets [3]. ELSA has been implicated in affective expression in nonhuman primates both in infancy and in adulthood. Macaques reared in sub-optimal mother-only conditions show higher fear and anxiety responses to a stress-inducing challenge than those from rearing conditions in which multiple adults and peers are present [1]. These affective responses, also characterized by pronounced behavioral inhibition, in SOR-exposed macaques persist well into adulthood [4]. Some behavioral effects of ELSA may not be long lasting, as macaques that experienced STS as infants displayed normative behavioral reactivity when placed in short-term social isolation as adults [5]. ELSA alters distress behavior and vocalizations in both macaques and marmosets. Adolescent macaques exposed to ELSA exhibit enhanced responses to an acoustic startle test and elevated rates of contact calling during social separation, indicating higher levels of anxiety and fear [6,7]. Similarly, marmoset infants exposed to STS demonstrate altered rates of distress vocalizations and enhanced anxiety behavior in both homecare interactions and during social separations [3,8]. Increased rates of distress calls are also observed in infant macaques that experienced abuse compared to infants who were not abused [9]. Despite the increased anxiety phenotype exhibited by ELSA-exposed animals in social contexts, ELSA may lead to decreased distress and increased novelty seeking in non-social contexts. Macaques exposed to SOR showed lower levels of distress during a developmental assessment compared to control animals [10]. Squirrel monkeys exposed to STS and macaques that experienced early life abuse showed increased exploratory behavior in the context of novel objects and environments [2,11,12]. These findings suggest that some benefits may derive from ELSA, such as increased resistance to

the stress of novel nonsocial situations. The increased emotionality observed in social contexts following ELSA suggests that poor early life social experiences modify the perception of social environments, thereby altering behavioral response patterns. Fear, anxiety and distress behaviors follow similar trajectories in primates exposed to ELSA, suggesting a generalized shift in affective processing.

ELSA in the form of extreme maternal abuse alters the expression of affective behavior. Abused infant macaques display deficits in emotional expression such as the use of inappropriate vocalizations in response to contact and non-contact aggression [13]. Abused infants also exhibit high rates of distress vocalizations and anxiety-related behavior during normal social interactions, and in response to stressors and high-fear stimuli (animated toy accompanied by sounds) [11,14]. However, abused macaques show reduced anxiety-related behavior when exposed to low-fear or neutral stimuli (roll of tape) [11]. This differential response to low- and high-fear stimuli suggests that macaques that have experienced SOR have an altered system for threat assessment, with an increased threshold required to elicit a behavioral response relative to infants with normal developmental environments.

Social behavior

ELSA reduces competency in a wide domain of social interactions across developmental stages, beginning with the nature of interactions with caregivers. Both macaque and marmoset infants exposed to ELSA engage in abnormal interactions with caregivers. Infant macaques that experience higher levels of maternal abuse show lower levels of ventral-ventral contact with the mother, yet at the same time exhibit lower rates of breaking contact with their mothers [14]. Females that experienced abuse initiated contact at higher levels than nonabused females; however, this pattern was not observed in males that experienced ELSA [14]. Normal mother-infant social dynamics are altered in macaques exposed to STS – levels of mother-infant contact remain high at the developmental stage when normally-reared infants decrease maternal contact [7]. Marmosets that experienced STS spend more time in contact with their caregivers and more time in a nursing position on mothers compared to controls [8,15]. Despite increased rates of parental contact in the homecage, marmosets exposed to STS received decreased levels of paternal carrying after a social stressor [3].

ELSA has persistent effects on social behavior into adolescence and adulthood. Marmosets that experienced STS displayed decreased rates of social play [8,16]. While ELSA is associated with decreases in play behavior in macaques as well, levels of solitary play are higher as a consequence of ELSA [14]. Despite lower levels of social play, juvenile female macaques that experienced abuse spent *more* time in contact with infants [17]. In spite of this increased interest as juveniles, approximately 50% of females abused as infants (regardless of whether they were *born* to, or *cross-fostered* with, abusive mothers) abused their own infants, while nonabused females showed normal maternal care [18]. Long-term effects of ELSA are also observed in group-wide social dynamics. Macaques that experienced SOR have lower social dominance rankings than controls at both three and five years of age [19]. Though social dominance appears to be mediated by ELSA, rates of aggressive interactions in adolescent macaques appear to be unaffected by variation in early

life rearing experience [20]. Thus, lower social dominance in ELSA-exposed macaques may reflect generalized deficits in social skills, such as an inability to form and maintain social alliances.

Cognition

A hallmark of primate biology is cognitive complexity and flexibility, and ELSA can lead to differential effects on these processes, depending on the timing of the manipulation. In adult marmosets, simple visual discrimination performance is not affected by early adversity, but reversal learning, which requires suppressing or inhibiting previously rewarded responses, is impaired by STS [21,22]. Further, motivational components of learning and cognition are reduced by ELSA: marmosets reared under early STS give up sooner and receive fewer rewards in an operant task requiring increasing response:reinforcement ratios [21]. STS experienced later in postnatal life *enhances* behavioral inhibition in learning tasks in squirrel monkeys. Adults exposed to STS as infants performed better than controls on a food-reward task that required a shift from a well-learned response [23,24]. The inhibition of prepotent responses is mediated, in part, by activity in the prefrontal cortex (PFC), and ELSA exposure at varying stages of development may produce functional differences in the PFC (see **Neuroanatomy and function** below). Increased competency at tasks involving behavioral inhibition highlights a potential benefit of ELSA. Animals who have experienced early life stress may be better equipped to handle unpredictability or change later in life, since mild exposure to stress early in development increases both cognitive and social capability later in life [2,23].

Gene regulation and expression

ELSA certainly interacts with genomes and induces modifications in the epigenome to influence developmental outcomes [25]. Macaques that experience SOR and also carry a low-activity monoamine oxidase A polymorphism display increased anxiety responses relative to carriers of this allele that experience normative social environments [1]. ELSA has effects on the serotonergic system both through receptor expression and function. STS has differential regional effects on serotonin receptor mRNA expression in the ACC of marmosets, increasing expression in superficial laminae but decreasing expression in deep laminae [16]. Exposure to social adversity modifies two important signaling pathways that regulate SERT function in macaques. Macaques experiencing ELSA have lower hippocampal h3k4me3 expression (a marker of transcriptionally active genes) [26], and enhanced p38MAPK activity (a signaling molecule increasing SERT function), resulting in altered central serotonergic tone [27]. ELSA therefore produces long-term, perhaps lifetime changes in serotonin function.

ELSA in nonhuman primates has also been associated with DNA methylation profiles in neural and peripheral tissues that have important implications for behavioral phenotypes. There is an interaction between rearing condition and methylation in the promoter region (5-HTTLPR) of the serotonin transporter gene: macaques that are exposed to SOR and have high levels of methylation in this region show increased stress reactivity [28]. SOR in macaques produces differential DNA methylation in promoter regions for more than 1,000 genes expressed in the PFC, including those regulating CNS development, immune function,

axonogenesis, and cellular responses to stress [29]. A recent comparative study examined ELSA-induced changes in genome-wide DNA methylation in peripheral lymphocytes in humans and macaques, and in rat PFC tissue. Common epigenetic changes among species were identified in the promoter region for five genes, one of which (*MORCI*) is strongly associated with major depressive disorder in humans [30]. Differential behavioral outcomes among individuals as a consequence of ELSA must therefore take into account genetic and epigenetic variation [9,10,20,31].

Neuroendocrinology and neurochemistry

Modification of HPA axis function is a common outcome of ELSA, and these changes can be broadly classified into (i) differences in baseline function and (ii) differential responses to stressors. Decreased baseline levels of cortisol (CORT) and/or adrenocorticotrophic hormone (ACTH) after exposure to ELSA have been observed in macaques [32,33], marmosets [3,8], and squirrel monkeys [2]. However, other studies have failed to find these differences [12,17,34,35]. Decreased baseline CORT levels may indicate a lower set point of the HPA stress axis in animals exposed to ELSA. STS has also been implicated in increased baseline norepinephrine levels [21], suggesting dual effects of ELSA on both the HPA axis and the sympathetic nervous system.

There are mixed findings regarding HPA responses to stressors in monkeys exposed to ELSA. Lower quality parental care has been associated with increased CORT levels after a stressor in marmosets [34] and female macaques [35], suggesting increased reactivity to a stressor. In contrast, higher quality parental behavior such as grooming and carrying by caregivers does *not* predict CORT responses in marmosets [34]. These findings imply that exposure to poor parental care alters HPA axis dynamics, while variation in more positive parent-infant interactions have little or no effect on this system. Increased rates of social play as juveniles may have a protective effect in stress-prone marmosets, since they exhibit decreased stress-induced CORT [36]. Interestingly, there may be sex differences in HPA response to stressors, as male macaques exposed to abuse had a lower CORT response to a stressor compared to non-abused males, while the opposite pattern (i.e., increased CORT response) was observed in abused females [35]. Female macaques [7] that experienced STS had higher CORT responses to social isolation than did control females or males exposed to either rearing condition, again suggesting that ELSA may have differential sex effects. In some model systems, ELSA has also been associated with reduced HPA responses to stressors: infant macaques exposed to SOR display lower CORT responses to standard stressors than controls [33]. Further, squirrel monkeys exposed to STS in infancy also have decreased stress-induced CORT responses after exposure to novel stimuli [2]; cf. [24]. However, marmosets and male macaques showed no STS-dependent difference in CORT levels after social separation [3,7,37] or exposure to a novel stimulus [37]. These differential effects of ELSA on hormonal responses to stressors may in part be related to differences in the nature of the stressor (acute or chronic), or to the degree and timing of early life adversity (length of separations, developmental timing). SOR reduces the responsiveness of the HPA axis in macaques to both dexamethasone-suppression and ACTH stimulation tests [33] and these neuroendocrine effects may be mediated by changes in glucocorticoid and mineralocorticoid receptor mRNA expression [38]. Together, these findings suggest ELSA

impacts HPA axis function by altering both central and peripheral regulatory processes [34,37].

Finally, ELSA alters long-term profiles of neurotransmitter metabolites in cerebrospinal fluid (CSF) throughout adolescence and adulthood. Differential early social environments particularly affect CSF levels of the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA). Adolescent and adult macaques exposed to ELSA have lower 5-HIAA titers, implying reduced serotonergic tone [26,39,40], cf. [41]. Modification of CSF levels as a consequence of ELSA for other monoamine metabolites and corticotropin-releasing hormone has also been documented [12,22,40,42]. As is the case for behavior, though, the effects of ELSA on neurotransmitter levels may depend upon allelic status in 5-HT relevant genes [42].

Neuroanatomy and function

ELSA can produce long-term changes in neural circuits in regions that are relevant for the behavioral, cognitive and neuroendocrine differences. ELSA in macaques is associated with significant structural changes in the brain, including larger volumes of the anterior cingulate cortex (ACC) and dorsomedial prefrontal cortex (dmPFC) [41], reduced hippocampal and temporal gyri volume [43], and larger amygdala volume [11]. ELSA also selectively alters regional metabolic activity in the brain of macaques. Adults that experienced STS as infants showed an increase in glucose uptake in the orbitofrontal cortex (OFC) and superior temporal sulci, regions that are critical for decision-making, emotional regulation, and social behavior. STS was also associated with reduced glucose uptake in the hippocampus, a region associated with inhibitory control over the stress response [5].

Receptor distribution and gene expression in the brain, particularly those components involved in serotonin (5-HT) function, are altered by exposure to ELSA. The distribution of 5-HT binding, serotonin transporter (SERT) expression, and 5-HT_{1a} receptor binding in multiple brain regions are reduced in macaques for months to years as a consequence of SOR [44,45]. In females, however, SOR is associated with enhanced 5-HT_{1a} receptor density in the PFC [45].

Conclusions

Multiple models of ELSA in nonhuman primates have identified important and long-lasting modifications in behavioral, neuroendocrine, and neural endpoints, and these effects are summarized in Fig. 1. Interestingly, though rodent research has found many sex differences in response to ELSA, much of the primate literature fails to find these differential effects of sex. Furthermore, many studies have been conducted only on one sex [Males only: 4,6,20,26,29,42–44; Females only: 13,17,18,31,39]. Given the recent emphasis on the importance of sex as a biological variable in translational and clinical research at National Institutes of Health (NOT-OD-15-102; URL: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html>), future studies should explicitly assess the differential effect of ELSA on males and females.

The more extreme manipulations (SOR, STS) are clearly relevant for the etiology of psychiatric and behavioral disorders in humans, including depression, affective disorders,

and social dysfunction. A recent meta-analysis [46] of the lifelong effects of SOR in macaques highlights the persistence and penetrance of early social adversity, including increased lifetime frequency and severity of illnesses, a higher probability of developing atypical stereotypies, and an increased risk of being wounded in aggressive interaction. Models that utilize normative variation in early social experiences are relevant for identifying the origins and limits of phenotypic plasticity in response to differential early experience, and can explore the potential adaptive scenarios associated with the resulting phenotypic variants. Differences in the quality and quantity of early social interactions with caregivers may represent an important mechanism for programming brain and behavior for the social world that each organism will likely experience throughout their lifetime.

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Highlights

- Nonhuman primates are excellent models for the impact of social adversity on development
- Early social adversity enhances anxiety and impairs social function
- Multiple neurotransmitter systems are modulated as a consequence of early experience
- Social adversity produces lifetime changes in brain structure and function

Box 1**Species-specific social structure and offspring rearing styles in macaques, squirrel monkeys, and marmosets**

The three most common species for evaluating ELSA in nonhuman primates differ substantially in the nature of their social structure and, as a consequence, the social context in which offspring rearing occurs. Macaques reside in large multimale/multifemale groups, and female social relationships are organized along matriline. Offspring thus are exposed to mothers, close female kin, but do interact infrequently with adult males. While squirrel monkeys also live in large mixed-sex groups, these groups are sexually-segregated during the birth season and early life of infants; thus, infants interact primarily with mothers and other females. Marmoset monkeys live in extended family groups with minimal contact with non-kin individuals. Mothers, fathers, and older siblings all play a role in caregiving for offspring, and after the first two weeks of life, the majority of caregiving other than nursing is provided by fathers and siblings rather than mothers. primates.

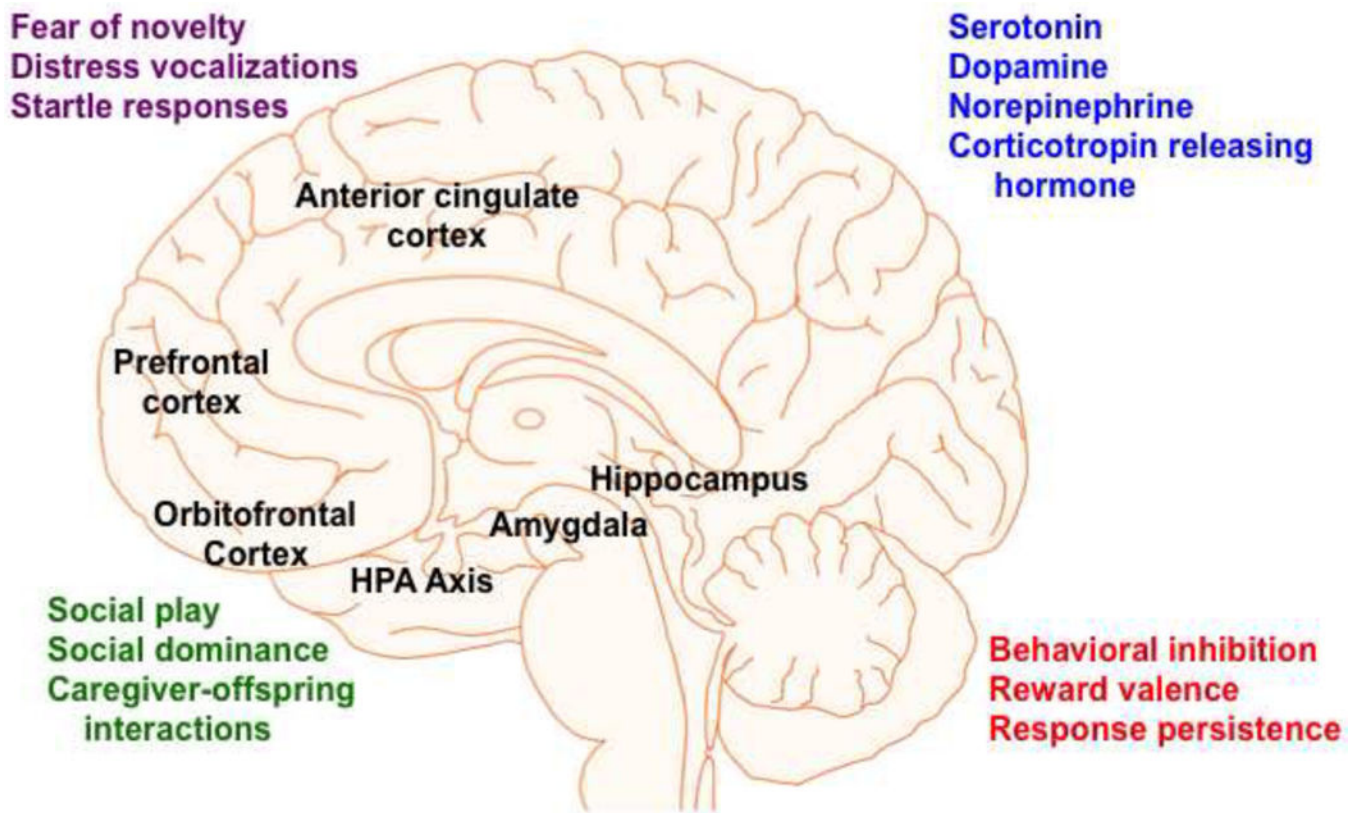


Figure 1.

Early-life social adversity (ELSA) in nonhuman primates has effects on multiple behavioral systems, neurotransmitter/neuroendocrine measures, and brain structure and function. Brain regions labeled with ^a indicate neuroanatomical volume differences between individuals exposed to ELSA and controls; ^b indicates differential functional effects between individuals exposed to ELSA and controls. Please refer to the text for details on the relationship between ELSA and endocrine and neurotransmitter function (**blue**). For social (**green**), affective (**purple**), and cognitive (**red**) outcomes, arrows characterize general patterns of ELSA on these measures.

Table 1

Methodological approaches for Early-life Social Adversity (ELSA) in nonhuman primates.

| Methodology | Approach ¹ | Description | Classification of Cited Studies |
|---|-----------------------|--|---|
| Suboptimal rearing (SOR) | Exp | Departure from species-typical rearing pattern throughout early development (e.g., social partners present during rearing; inducing changes in maternal care with enhanced foraging demands) | 1, 4, 6, 10, 19, 20, 26, 28, 29, 31, 32, 33, 41, 42, 43, 44, 45 |
| Short-term separation from caregivers (STS) | Exp | Intermittent and variable length of separation from caregivers during early development | 2, 3, 5, 7, 8, 12, 15, 16, 21, 22, 23, 24, 38 |
| Normative variation in early caregiving (NV) | Corr | Natural variation in early caregiving; ranges from extreme variation (e.g., infant abuse) to subtle variation (e.g., rates of infant rejection) | 9, 11, 13, 14, 17, 18, 27, 34, 35, 36, 39,40 |

¹Exp = Experimental; Corr = Correlational

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