Early caregiving experiences play a central role in shaping corticolimbic development and emotional learning and regulation. Given dynamic changes in corticolimbic maturation, the effects of caregiving experiences are likely to depend on the developmental timing of exposure. Cross-species evidence has identified timing-related differences in the effects of caregiving adversity. However, the extent to which developmental differences in associations between caregiving adversity and corticolimbic circuitry align with a sensitive period model has remained unclear. Converging evidence from studies of caregiver deprivation points to a sensitive period for caregiving influences on corticolimbic circuitry and emotional development during infancy. By contrast, differential associations between maltreatment and corticolimbic circuitry at specific ages in childhood and adolescence may reflect experience-dependent mechanisms of plasticity. Delineating sensitive periods of development and the precise experience-related mechanisms by which caregiving experiences influence corticolimbic development is essential for refining conceptual models and understanding risk and resilience following early adversity.

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A rich cross-species literature has begun to identify the effects of caregiving experiences on corticolimbic circuitry and emotional behavior. Given marked changes in species-expected inputs and neuroplasticity across development, caregiving experiences are likely to differentially shape behavior during infancy, childhood, and adolescence [2–4]. However, much remains unknown about precise experience-related mechanisms and whether developmental differences in the effects of caregiving experiences reflect sensitive periods [5]. Identifying specific timing-related effects of caregiving experiences and differentiating between experience-expectant and experience-dependent mechanisms is key to advancing conceptual models of caregiving environments and corticolimbic development.

Sensitive periods of development
During a sensitive period of heightened neuroplasticity, a specific environmental input has a particularly strong influence on a specific brain circuit, and plasticity is limited following this window [6,7]. Importantly, sensitive periods are characterized by experience-expectant learning and are thought to reflect neural preparation to encode species-expected environmental stimuli [8]. Recent years have witnessed transformative discoveries of the molecular triggers (e.g., excitatory-inhibitory balance) and brakes (e.g., perineuronal nets, myelin) that control the onset and closure of sensitive periods, as well as the insight that sensitive period processes are themselves malleable [7]. Unlike experience-expectant plasticity, which tends to occur early in development, experience-dependent plasticity occurs in response to individual experiences (which are not necessarily species-expected) and facilitates learning throughout development [8]. The current review aims to apply a critical lens to existing research on caregiving effects on corticolimbic development to begin to delineate which developmental differences in caregiving influences may align with a sensitive period model and experience-expectant versus experience-dependent plasticity.

Caregiving and corticolimbic development
Decades of research have demonstrated the robust links between caregiving and offspring emotional behavior [9], with a growing literature focused on neurobiological mechanisms. Cross-species evidence has demonstrated that early caregiving experiences have particularly strong effects on corticolimbic circuitry involved in learning about salient aspects of the environment and regulating emotion. Connections between regions such
as the medial prefrontal cortex (mPFC), amygdala, and hippocampus, which play a key role in regulating emotion and guiding biologically relevant learning [10], may be especially impacted by adversity due to their dense innervation with glucocorticoid receptors and the developmental timing of circuit maturation [11]. Whereas prefrontal regions and their connections with limbic structures undergo protracted development, the amygdala matures relatively earlier and may be particularly sensitive to the early social environment [12]. Though these connections undergo marked changes across development [13,14], functional connectivity at rest is already evident between the amygdala and regions such as ventromedial prefrontal cortex (vmPFC) in infancy [15]. Moreover, amygdala-mPFC functional connectivity at rest among newborns is associated with negative affect at six months of age [16] and with behavioral inhibition at two years of age [17]. Environmental influences on corticolimbic circuitry in early life may play an active role in shaping longer-term neural and behavioral phenotypes. For example, neural co-activations induced via experiences with caregivers may ‘entrain’ the system during a highly plastic time in ways that shape intrinsic corticolimbic architecture and affective behaviors [18–20]. Moreover, the early sensitivity of the amygdala to environmental inputs may directly guide mPFC function and connectivity [20] and influence later-developing aspects of broader cortico-subcortical circuitry through developmental cascades [21].

Much of the research linking caregiving with emotional development comes from studies of severe caregiving adversity. Alterations of the HPA axis [22] and corticolimbic circuitry [23,24] appear to underlie effects of caregiving adversity on emotional learning [25] and regulation [26] and likely contribute to increased risk for mental health disorders. However, increasing evidence has also emerged linking normative variation in caregiving behavior with corticolimbic structure and function [27]. For example, during childhood, caregiver sensitivity is associated with amygdala volume and microstructure of the amygdala and hippocampus [28], and negative caregiving behavior is associated with amygdala activation and functional connectivity between the amygdala and superior parietal lobule [29]. In addition, caregiver control experienced during childhood is associated with amygdala activation and structural integrity of the uncinate fasciculus during young adulthood [30]. These studies further underscore the importance of caregiving in healthy brain development.

Developmental differences in the effects of caregiving on corticolimbic circuitry

Non-human animal work that allows for manipulating the timing of exposure shows that the effects of stress differ as a function of developmental timing [3]. Manipulating stress exposure is challenging in humans; however, naturalistic human studies of unfortunate events (e.g., institutionalized care) provide strong evidence for the importance of the timing of adversity. With its unique study design, the Bucharest Early Intervention Project has highlighted a potential sensitive period related to socioemotional development during the first two years of life. That is, youth who were exposed to caregiver deprivation via institutionalized care show more secure attachment, more normative stress responses, and more normative neurodevelopmental trajectories following placement into a foster care intervention prior to 24 months of age, relative to peers who were placed later [31]. These findings highlight infancy as a particularly important time for caregiving influences, as well as the potential for the identification of sensitive periods to inform interventions.

Consistent evidence has shown that the absence of stable, nurturing caregiving in the postnatal and infancy period disrupts corticolimbic development. Across species, early caregiver deprivation is associated with altered connectivity between the amygdala and mPFC in mice [32], rats [33], non-human primates [23], and humans [24]. It is possible that these findings reflect a sensitive period driven by experience-expectant mechanisms. Consistent with criteria for a sensitive period [7,34], infancy is a time of rapid and marked change in corticolimbic circuitry [35], and it is biologically plausible that this period is characterized by heightened neuroplasticity. There is also some specificity to the nature of the experience, the neural circuit affected, and the timing of the window during which caregiver deprivation has particularly strong effects [3]. However, evaluating sensitive period phenomena in human development is especially challenging, and additional research will be necessary to more rigorously assess all relevant criteria [5,34]. In particular, it is rare that longitudinal data are available to test whether effects of caregiver deprivation on corticolimbic circuitry persist into adulthood.

Although substantial evidence suggests that caregiving adversity has the strongest effects when experienced earlier in life [3,22,31], an alternative account suggests that risk may be highest when adversity occurs during specific windows that could occur later in childhood or adolescence. Studies examining variation in the timing of maltreatment have at times pointed to specific ages of exposure during childhood or adolescence at which effects on corticolimbic structure or function in adulthood are pronounced [36–38,39]. These studies highlight the complexity of interactions between developmental timing with the type of adversity exposure, sex, and regional specificity in the brain. For example, exposure to maltreatment between ages 10 and 11 is specifically related to amygdala volume in adulthood, relative to exposure at other ages during development [37], whereas sexual abuse at ages 3–5 and 11–13 is uniquely associated...
with hippocampal volume in adulthood [36]. Among men, hippocampal volume in adulthood is associated with neglect, but not abuse, prior to age 7. By contrast, hippocampal volume in women is associated with abuse, but not neglect, at ages 10–11 and 15–16 years [38]. However, it is not clear whether these developmental differences align with a sensitive period process, and experience-dependent mechanisms may better explain such age-related effects. As one example, maltreatment is unlikely to be a plausible type of species-expected stimuli at a specific developmental time [5]. Moreover, while these findings in adulthood may suggest non-linear peaks in risk throughout development, future studies during childhood and adolescence will be important for understanding more proximal corticobasal changes that may unfold across development.

Yet another way in which caregiving adversity may alter corticobasal development is by altering sensitive period processes themselves. In rodents, hippocampal and amygdala development, as well as some forms of emotional learning, are accelerated following early adversity [40–42]. In humans, evidence suggests that the timing of structural and functional corticobasal development may also be accelerated following adversity [24,43,44]. As one example, while viewing fearful faces, children who experienced caregiver deprivation exhibit more mature patterns of functional connectivity between the vmPFC and amygdala (i.e., negative task-based connectivity), which resemble those of adolescents and adults [24]. Across species these effects have been mediated by corticosterone levels (cortisol in humans) [24], suggesting that early caregiving adversity may prematurely stimulate the HPA axis in a way that contributes to precocious corticobasal and emotional development.

Such accelerated development may represent an ontogenetic adaptation in the context of an early harsh environment [45,46]. Consistent with this idea, children exposed to caregiver deprivation who show the more mature phenotype of vmPFC-amygdala connectivity also display lower separation anxiety [24]. These findings are in line with evidence that stronger inverse amygdala-mPFC functional connectivity is associated with lower internalizing symptoms among youth exposed to early family adversity [47] and that greater prefrontal control (specifically, superior frontal gyrus and dorsal anterior cingulate cortex) of amygdala reactivity during emotion regulation is associated with lower depressive symptoms following child maltreatment [48]. Moreover, recent work shows that the more mature pattern of vmPFC-amygdala connectivity is also associated with slower telomere shortening and pubertal tempo [49], which may further suggest protective effects in the context of evidence demonstrating accelerated cellular aging following early life adversity. However, there are likely to be long-term consequences of accelerated development. Such precocious maturation may signal a shift or premature termination of a sensitive period of caregiving influences, which could be associated with reduced plasticity. Future research will be important for understanding longer-term effects, testing whether neural findings are specific to corticobasal circuitry, and for further examining how developmental patterns of acceleration converge or diverge across different domains such as puberty, cellular aging, and neurodevelopment.

**Early caregiving influences on emotional learning and regulation**

Caregivers modulate offspring behavior in a number of domains related to affective behavior, including influencing what offspring learn and how they perceive the world around them. Encoding stable, reliable caregiver cues that are associated with safety during an early sensitive period (e.g., infancy) may be essential to the roles that caregivers play in modulating emotional learning and regulation later in development. Young offspring show a preference for cues related to their caregiver, even when those cues are inherently aversive. For example, rodent pups show approach behaviors toward an odor paired with a shock during a period when maternal presence maintains low levels of corticosterone and blocks amygdala plasticity [50]. Paralleling these findings in rodents, recent evidence demonstrates similar caregiver-related learning in humans. Specifically, young children were more likely to approach conditioned stimuli that were acquired in their caregiver’s presence and to avoid stimuli acquired in the caregiver’s absence [51]. This attraction to caregiver-related cues and absence of avoidance learning is thought to facilitate attachment early in life and ensure that the offspring stays close to their caregiver [52]. Critically, these effects depend on developmental stage. During a window from postnatal day (P)10 to P15, rodent pup behavior depends on maternal presence, such that pups continue to show approach behaviors if the mother is present. However, corticosterone and amygdala activation increase if the mother is absent, instantiating threat learning and avoidance behaviors [50], potentially to facilitate survival when offspring engage in exploration independently.

Consistent with the effects of caregiver presence on corticosterone levels and amygdala plasticity in rodents, caregivers buffer stress physiology and HPA axis reactivity in infant macaques [53] and in humans [54]. Suggesting a potentially related mechanism by which caregivers modulate affective behavior early in life, during childhood, caregivers suppress amygdala reactivity and phasically induce a pattern of amygdala-mPFC functional connectivity that may be more strongly regulatory [55]. Paralleling this modulation of amygdala-mPFC circuitry, children also show enhanced regulatory behavior in an affective context in the presence of their mother compared with a stranger. The effects of caregivers on...
cortisol reactivity [54] as well as on regulatory behavior and amygdala-mPFC circuitry [55] are specific to childhood, and not adolescence. These findings suggest that caregivers may serve an external regulatory function while corticolimbic circuitry is still developing. With time and as this circuitry matures, reliance on external regulation may decrease as regulatory abilities become internalized to facilitate independent emotion regulation, and other major attachment figures such as close peers or romantic partners may take on an increasing role in social buffering [46,56] (Figure 1). In humans, caregiver presence has also been shown to increase discrimination between threat and safety cues during childhood, but not adolescence [57]. In these ways, caregivers play a central role in shaping what children learn about their environment and in regulating their behavior, particularly early in life. However, instead of caregiver effects on emotional learning and regulation during childhood reflecting a sensitive period itself, it may be that encoding reliable cues related to the support of caregivers earlier in life allows for those cues to exert these unique effects during childhood.

Consistent with this idea, increasing cross-species evidence suggests that early caregiving adversity disrupts the ways in which caregivers guide learning and buffer emotional reactivity in later stages of development. In rodents, infant maltreatment is associated with reduced effects of maternal presence on threat learning during infancy [58,59]. Interestingly, maltreatment during

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**Figure 1**

Caregiver influences on corticolimbic circuitry related to emotion regulation across development. Cross-species evidence suggests a sensitive period during infancy through which caregiving has particularly strong influences on corticolimbic development (including mPFC-amygdala connectivity) and longer-term emotional behavior. Caregivers regulate amygdala function during infancy (demonstrated in rodents, hypothesized in humans) and childhood (demonstrated in humans), and not in adolescence. The shift away from reliance on caregivers for extrinsic regulation may be accompanied by increased capacity for intrinsic emotion regulation around the transition to adolescence. Social buffering continues across the lifespan, with different primary attachment figures potentially serving a regulatory function at distinct developmental stages. Because of heightened plasticity to caregiving influences early in life, severe disruptions in caregiving during infancy may interfere with learning reliable, safe caregiver cues in a way that interferes with normative caregiver shaping of emotional learning and regulation later in development. Adapted with permission from Ref. Gee [46].
infancy has differential effects on maternal buffering during infancy versus adolescence. Whereas maltreatment completely disrupts maternal buffering at PN18, maternal buffering is present but weaker at PN28 [59]. In non-human primates, infant maltreatment is associated with weaker maternal buffering of stress-induced cortisol increases [60]. In humans, caregiver deprivation early in life interferes with caregiver buffering of amygdala reactivity during childhood [61]. However, effects are heterogeneous, such that approximately 40% of youth who experienced caregiver deprivation exhibit caregiver buffering, and those youth also experience steeper declines in separation anxiety over a period of three years. Thus, the ability to experience caregiver buffering of amygdala reactivity may enhance resilience within this group at elevated risk for anxiety. Taken together, these findings suggest that while caregiver buffering itself may not be consistent with a sensitive period phenomenon, caregiving adversity during a sensitive period in infancy may disrupt the encoding of stable, safe caregiver cues that are likely to be important for caregiver influences on emotional learning and regulation later in development.

**Future directions**

Despite a growing literature on developmental differences in the effects of caregiving on corticolimbic development, the experience-related mechanisms underlying these influences remain largely unknown. Ongoing research that evaluates which developmental differences are consistent with the criteria for a sensitive period will be essential to advancing conceptual models and understanding the mechanisms by which early caregiving experiences become biologically embedded to shape emotional development. It is rare that distinct models of experience-related mechanisms have been directly compared, and rigorously testing a sensitive period model in humans presents various challenges [5,62], including the complex and multifaceted nature of caregiving experiences, the protracted time needed to assess effects on mature function, and the inability to test for molecular regulators and direct markers of plasticity in humans. In addition, it is important to acknowledge that experience-expectant and experience-dependent learning are unlikely to be completely independent processes [8], and experience-related learning is unlikely to reflect a single process or model. In this regard, cross-species research will continue to be essential to testing hypotheses about sensitive periods [63], and bridging between formal modeling and empirical studies may offer powerful insights [62]. Further, study designs will need to incorporate precise measurement of timing of exposures and extend longitudinal follow-up to enhance the ability to test sensitive period models in human neurodevelopment.

Lastly, research on developmental differences in caregiving effects has largely focused on timing-related factors in isolation. An important area for future research will be examining how timing-related factors (e.g., age of exposure, chronicity, duration) interact with key experiential dimensions of adversity, such as the extent to which adversity is characterized by threat versus deprivation [64], predictability [65], controllability, and/or caregiver involvement [for review, see Ref. 66**]. As one example, independent of severity, adversity perpetrated by a caregiver or adversity that involves dyadic caregiver/child exposure may have stronger or differential effects on corticolimbic development than adversity that does not involve a caregiver [67]. Further delineating how specific features of adversity differentially impact outcomes, and how those effects differ by developmental stage, could inform efforts to optimize risk identification based on developmental stage or the nature of adversity exposure.

**Conclusions**

Cross-species findings demonstrate that early caregiving experiences play a central role in shaping the development of learning and regulation in the affective domain. Adverse caregiving can alter corticolimbic development and normative processes such as caregiver buffering of amygdala reactivity, with lasting implications for emotional behavior and mental health. While increasing evidence demonstrates that caregiving influences depend on the timing of experiences, it is unclear under what circumstances earlier adversity is more consequential or whether there are windows of development throughout childhood and adolescence when caregiving adversity has the strongest effects. Moreover, much remains unknown about the experience-related mechanisms of plasticity that link early caregiving inputs with affective outcomes. Caregiver deprivation experienced during infancy has persistent effects on corticolimbic development and later caregiver buffering, which may reflect an early sensitive period for attachment and learning stable caregiver cues. Future research will be essential for testing whether developmental differences in caregiving influences may reflect experience-expectant or experience-dependent mechanisms, or influences on sensitive period timing itself. Refining conceptual models based on such knowledge has important implications for promoting resilience following early adversity and could be leveraged to enhance risk identification or tailor interventions based on factors such as developmental stage.

**Conflict of interest statement**

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


This study highlights the importance of developmental timing of adversity exposure, as well as how timing may interact with other key features of exposure such as the type of adversity. Specifically, the authors find that physical abuse experienced between ages 3−6 is associated with blunted amygdala reactivity in adulthood, whereas peer emotional abuse at ages 13 and 15 is associated with heightened amygdala reactivity in adulthood.


In this longitudinal study, the authors find that greater cumulative severity of early adversity is associated with stronger negative coupling between the amygdala and ventromedial prefrontal cortex. These findings are consistent with prior cross-sectional research (Gee et al. [14]) and may indicate accelerated neurodevelopment. Further, this study examined cellular aging and pubertal tempo, and findings suggest that frontolimbic changes following adversity may reflect a different developmental process.


Consistent with evidence in rodents, this study demonstrates that affective learning is shaped by caregivers early in human development. Specifically, young children showed greater behavioral approach to a conditioned stimulus that was acquired in their caregiver’s presence and avoidance of a conditioned stimulus acquired in their caregiver’s absence.


Building upon a rich cross-species literature on caregiver buffering, this study in rodents examined the effect of maltreatment on maternal buffering of threat learning. The authors find that maltreatment blocks maternal buffering of pups’ threat learning during infancy. The findings provide important insight into how the effects of early adversity differ depending on developmental stage. Specifically, the effect of maltreatment on buffering appears to differ during adolescence, such that maltreatment attenuates but does not block threat learning.


This study examined caregiver buffering of amygdala reactivity among children and adolescents previously exposed to parental deprivation. The authors find that severe caregiving-related adversity disrupts the normative process of caregiver buffering. However, a substantial proportion of youth exposed to parental deprivation do show caregiver buffering of amygdala reactivity, which is associated with lower risk of anxiety.


This review examines heterogeneity in early adversity and proposes a framework by which key dimensions of early adversity may differentially impact the development of frontolimbic circuitry. The authors particularly focus on the developmental timing of adversity exposure and how timing may interact with other factors such as caregiver involvement to influence outcomes.