The Stress Acceleration Hypothesis: effects of early-life adversity on emotion circuits and behavior

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The importance of early experiences for mental health across the lifespan is well recognized. In particular, there is a strong association between adverse caregiving experiences and mental illness. However, relative to studies assessing outcomes in adults, there are far fewer studies assessing the earlier emerging manifestations of caregiving adversity during development. This lack of developmental research limits an understanding of the mechanisms that link adversity with mental illness. Adoption of a developmental approach to research in this field will yield greater insights into the factors that tie adversity to poor emotion function across a lifespan. In this review, we focus on recent findings that have used a developmental approach in the examination of mental health and early adversity. These studies are notable in that, across numerous species, they converge on the idea that early adversity leads to accelerated maturation of emotion circuits in the brain and in the behaviors supported by these regions. We propose that these 'stress acceleration' effects are evidence of early system adaptation.

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Introduction

It has long been recognized that early experiences establish the foundation for life long mental health. Arguably the most important of these early experiences is the ongoing parent–child relationship. Indeed, being born into and brought up within a stable home can be a powerful factor contributing to mental wellbeing [(e.g., 1)]. However, the opposite is also true; dysfunctional early caregiving (such as neglect, parental mental illness, and familial violence) is strongly associated with mental illness, accounting for up to 45% of child-onset, and 32% of adult-onset mental health disorders (including anxiety, mood and psychotic disorders) [2,3]. While the relationship between early experiences of adversity and mental illness is often observed, the mechanisms linking these experiences are not well articulated. Hence, understanding how early experiences get 'under the skin' to influence an individual across his/her lifespan is one of the central goals of research in the affective neurosciences.

One predominant perspective on the link between early adversity and mental illness is that such early experiences impair brain function, as children with histories of adversity reliably perform more poorly on tests of language and cognition [4–6]. However, numerous theories now predict that, rather than leading to general deficits or delays, adversity may in fact lead to a reprioritization of developmental strategy away from a neotenous state (which favors a slow developmental pace and prolonged childhood [7]) and toward more adult-like functioning within fear/stress-related domains [8••,9–13]. For example, many theories operating within an evolutionary biology framework (including Life History Theory, Psychosocial Acceleration Hypothesis, Child Development Theory, and the Adaptive Calibration Model) posit that our evolutionary history selected for plasticity in developmental trajectories, such that early experiences could program the length of childhood and the age of pubertal transition [9,10,12,13]. Specifically, these theories suggest that slower developmental strategies would be advantageous in conditions of low stress, allowing the individual to absorb information from the social and family environment early in life that may increase survival and parenting skills before transitioning into the reproductive stage of development. By contrast, faster developmental strategies allowing for earlier reproduction are proposed to increase reproductive success and fitness in contexts of adversity where long-term survival is uncertain. Indeed, in support of these theories, there is considerable evidence demonstrating that the age of pubertal maturation is negatively associated with levels of stress in the early environment (e.g., reviewed in [9]).

The frameworks discussed above are persuasive in their description of accelerated patterns of development as adaptations to contexts of early adversity (as opposed to traditional views that stress diminishes functionality). However, the mechanisms behind how such altered trajectories are related to the higher rates of mental illness seen in adversity-exposed populations remain elusive. The fact that caregiving adversity is associated with both accelerated development of emotion behavior/neurobiology, as

well as increased risk for mental illness compellingly suggests that the two outcomes may be mechanistically related. Our goal in the current paper is to provide a neurobiological framework (the Stress Acceleration Hypothesis) within which to conceptualize such stress-induced accelerations, particularly those that occur within stress and fear systems. Using this framework, we then consider whether the early changes in trajectories of affective neurocircuitry are associated with later emergences of mental health disorders. Although these links have yet to be established within a single study over developmental time, the theory attempts to provide a mechanistic link between early adversity and mental illness (e.g., depression, anxiety) that is established in the literature [2]. We begin the paper by reviewing behavioral, then neural, studies of stress acceleration effects on fear systems, before putting forward the Stress Acceleration Hypothesis and discussing how accelerated outcomes may be mechanistically linked to mental health/illness.

Behavioral studies demonstrating stress acceleration effects

While the development of emotional learning and emotion regulation has been investigated for some time in rodent studies (e.g., [14]), there are far fewer examples of research explicitly investigating the interaction between rearing environments and the maturation of emotion learning in any species. Interestingly, those studies that have focused on that interaction report that rearing adversity has significant consequences for two forms of emotion learning with clear clinical implications — fear conditioning and extinction. In the first studies to investigate the effects of rearing adversity on fear learning, standard-reared infant pups were compared to pups raised in an impoverished home cage with reduced nesting material [15]. This impoverished environment affects maternal behaviors, leading to fragmented care, and often, pup maltreatment [16]. When the non-stressed pups were later exposed to threat conditioning (odor-shock pairings) as infants (i.e., on postnatal day [P] 10), they exhibited an age appropriate paradoxical approach response toward to the shock-paired odor (a behavior consistent with attachment). By P12, a developmental transition occurs whereby non-stressed pups begin to exhibit avoidance responses to shock-associated odors. Critically, that behavioral transition from odor approach to odor avoidance occurred much earlier in development if pups had been exposed to rearing adversity (reduced nesting material), suggesting that rearing adversity accelerated the developmental trajectory of threat responses displayed toward learned aversive stimuli [15].

While the studies just described examined the effect of rearing adversity on the *expression* of threat behavior to conditioned aversive cues, other studies have reported that early life adversity also affects the *retention* of such conditioned associations. For example, rats exposed to aversive

early rearing (involving either maternal-separation, repeated foot-shock, hypothermia, or restraint) before explicit fear conditioning in infancy exhibited longer lasting fear associations than their non-stressed peers ([17,18], see [46] for a review). Indeed, evidence also exists for accelerated development of appetitive memory retention (e.g., [17]), but extensive review of this evidence is beyond the scope of the review. Enhanced retention for multiple conditioned associations in young animals is particularly noteworthy, as memory in early life is typically characterized by very rapid forgetting — a phenomenon known as infantile amnesia (see [19], for a review). Hence, it appears that early adversity accelerated the trajectory of memory development beyond the period of infantile amnesia, allowing for adult-like memory retention in infancy.

Inhibitory learning too appears to develop faster following early exposure to stress. While fear inhibition (i.e., extinction) of learned fear responses appears to be relatively 'adult-like' in early life, relapse behavior following extinction develops more gradually, becoming apparent only at post-weaning ages (see [20], for a review). In rats exposed to maternal separation rearing, however, or those reared by a mother treated with the stress hormone corticosterone, the developmental trajectory of extinction-relapse was shifted to the left [21–23]. In other words, stressed rats began to exhibit contextually mediated relapse (i.e., renewal and reinstatement) of extinguished fear as early as infancy. Importantly, context mediation of fear extinction is known to involve interactions between the medial prefrontal cortex (mPFC) and amygdala (for reviews see [24,25]) — neural interactions that are not involved in extinction under typical rearing conditions in infancy (for a review see [20,45•]). This brings up the intriguing possibility that early adversity leads to premature development of neural circuits involved in mature forms of emotional responding — particularly amygdala–mPFC interactions, possibly via stress prematurely activating these structures. Indeed, there is now a growing body of evidence in humans and rodents (reviewed in the next section) suggesting that this is true.

In sum, the behavioral literature suggests that emotional development in individuals exposed to early adversity, especially parental deprivation, appears to be fast-tracked, such that independent forms of emotion regulation (i.e., not parent regulated) occur earlier in development. Broadly defined, these data fit with many of the theories that use the evolutionary-biology framework by suggesting that individual developmental trajectories respond to environmental context is ways that may confer a survival advantage to that individual. More specifically, however, these data fit with the stress-acceleration framework by demonstrating how mature forms of emotion learning and expression emerge following adversities known to impact the stress response system — parental deprivation. The impact of such adversity on the neural

regions involved in stress and emotion is reviewed in the next section.

Neural studies demonstrating stress acceleration effects

Some of the first studies to investigate the effect of early adversity on the neural circuits involved in fear learning and extinction focused on the amygdala. Critically, across many species it was shown that rearing adversity had dramatic effects of amygdala structure and function that appear to indicate accelerated development. In terms of amygdala function, previous studies have shown that stress leads to precocious involvement of the amygdala in fear learning. For example, the transition from approach to avoidance responses to shock-paired odors that occurs across typical rat development is paralleled by a change in amygdala involvement in threat conditioning [15]. Critically, early adversity accelerated not only the behavioral responses to conditioning (i.e., from approach to avoidance), but also the involvement of the amygdala, such that after stress, odor-shock learning in infancy elicited precocious avoidance and amygdala activation [15]. In terms of structural development following stress, studies in juvenile rodents have shown that stress leads to precocious myelination of axons in the basolateral amygdala [26] and studies in humans have shown that maternal deprivation in early in life (i.e., previous institutionalization; PI) is associated with atypically large amygdala volumes in children (5–16 years) that appeared to reflect earlier structural maturation [27]. Similarly, 10-year-old children exposed to maternal depression since birth had larger amygdale than same aged peers without depressed mothers [28]. Also, high rates of childhood adversity were associated with a larger (i.e., more mature) left amygdala volume in early adolescence (mean age 12.64 years) [29•]. However, some studies have also reported smaller amygdala volumes following adversity (e.g., abuse, institutional neglect) in adolescents (mean age 11–12 years) [30,31] and in preschoolers (3–6 years) [32]. Hence, further studies are required to determine the precise manner in which different adversities may affect amygdala volume across development.

In addition to affecting structural and functional development of the amygdala, the emotion center of the brain, rearing adversity is also know to affect the development of neural regions that can regulate amygdala activity — the mPFC and hippocampus. For example, studies in humans have shown that parental deprivation accelerates the functional development of the mPFC in children, such that amygdala–mPFC interactions are more adult-like following deprivation experiences [33••]. Specifically, previous studies across typical development had shown that functional connectivity between amygdala and mPFC changes from being positive in childhood (6–10 years), to becoming negative in adolescence and adulthood (11–17 years) [34]. That switch in connectivity

valence occurred earlier following previous institutionalization, such that the negative connectivity pattern was evident already in childhood in the previously institutionalized group [34]. Critically, within the previously institutionalized group, those exhibiting the more mature pattern of connectivity appeared to have less anxiety than those with the immature pattern, suggesting that early maturation of amygdala–mPFC functional connectivity may confer emotion regulation advantages, at least in the short-term. Although fear learning and extinction have not been explicitly assessed in the PI youths, one might speculate, based on the neural acceleration patterns reported, that emotion-learning behaviors might also look more 'adult-like' in this group. Interestingly, studies that have examined structural changes in the prefrontal cortex following adversity have often reported smaller volumes in children (11–12 years) [30,31], demonstrating a possible dissociation of the effects of stress on structural and functional development (i.e., accelerated functional maturation, possibly at the cost of impaired structural integrity).

In terms of the hippocampus, it appears that rearing adversity may have differing effects on structural and functional development. For example, numerous studies have reported that children and adolescents (3–12 years) exposed to neglect, abuse, conditions of poverty and depressive maternal symptomatology from birth had similar or smaller hippocampal volumes to typically reared children/adolescents [28,32,35]. By contrast, studies in rodents have shown that the experience of early social isolation causes an early transition in the molecular signaling cascade for long-term potentiation (LTP) in the hippocampal CA1 region in infancy [36]. Importantly, LTP is the cellular substrate underlying learning and memory, and hippocampal CA1 activity is known to be particularly involved in learning contextual associations [37]. Hence, although effects of early adversity on hippocampal structure appear to involve reduced volume (that may indicate delayed development or even damage), the cellular mechanisms supporting adult-like emotion learning, as well as the emergence of numerous forms of learning known to rely on hippocampal function (i.e., contextual conditioning, contextually mediated renewal of extinguished aversions [21,22,38]) do appear to be developmentally accelerated by stress.

Similar to the behavioral data demonstrating 'acceleration' phenotypes following early adversity, the neural data just discussed also supports the idea that development is faster paced following adversity. Specifically, brain regions important for detecting and responding to stress and threat (the amygdala, prefrontal cortex, and hippocampus) all appear to be more mature (either functionally and/or structurally) following adversity. The fact that adversity in the rearing environment has been linked to both accelerated developmental patterns as well as

mental illness across numerous literatures provides strong initial support for the proposal that a mechanistic link exists between the two processes. In the next section we discuss our hypothesis that the accelerated developmental patterns are causal in creating mental health risk.

The stress acceleration hypothesis

The studies discussed above converge on the finding that, across species, early life caregiving stress prematurely activates and accelerates the maturation of various neural structures, functional profiles, and molecular compositions, in brain regions important for emotion expression, and associative learning and memory. We propose that accelerated phenotypes emerge because stress experienced early in life may prematurely activate the core circuitry of emotional learning and reactivity [11]. That is, the acceleration of limbic development following early stress may rely on an activity-dependent process. Importantly, we hypothesize that this accelerated development, while meeting immediate emotional demands (i.e., emotional regulation in parental absence), may have long-term consequences on circuit integrity and functioning by altering developmental plasticity. This adaptation may increase the vulnerability of the individual to developing fear-related psychopathology in adulthood. Indeed, decreased plasticity in adulthood between amygdala and prefrontal regions has recently been shown to increase the risk for an anxious phenotype in a rodent model [39]. Taken together, the argument follows that prematurely terminating the plasticity afforded by a developmental sensitive period for emotional behaviors may have significant consequences on emotion regulation abilities in adulthood.

At a behavioral level, we argue that this accelerated maturation may reflect a reprioritization of developmental trajectories in favor of emotional systems, and associative learning and memory, in ways that confer a survival advantage to the developing offspring. Specifically, it may be adaptive to move from a state of parent-regulation to self-regulation earlier in environments characterized by absent or inconsistent parental care. Put another way, the quantity and quality of parental care may act as an environmental signal for the pace of offspring maturation within circumscribed emotion systems [8••,40••].

Consistent with an adaptation interpretation, it has been shown that an accelerated amygdala–mPFC phenotype following parental deprivation was associated with less anxiety during childhood [33••]. However, whether that short-term benefit is maintained across time, and whether there are costs associated with early emotion system maturation, remain relatively unknown. Importantly, a long childhood period has been proposed as critical for the development and practice of behavioral skills and strategies during play that can later be used to aid survival and reproduction [41]. Also, a prolonged period of cortical

development is associated with greater general intelligence [42]. In terms of emotion circuitry, we have recently suggested that a period of immaturity is required so that parent-assisted emotion regulation can help mold the circuitry into its stable adult state [40••]. In this hypothesis, early termination of the immature period would shift the circuit into a stable state of function before it had acquired the characteristics needed for adequate self-regulatory control. In support of this hypothesis, evidence now exists in rodents demonstrating that the emotion circuitry of young individuals is less responsive to environmental regulation following early adversity [15]. Hence, although early emergence of self-regulation may be advantageous in contexts of parental absence, there are likely numerous costs to this developmental trajectory. Further research is required to understand how such latent vulnerabilities may become manifest, both at the time of the stressor as well as later in development.

Conclusion

The studies discussed in this review strongly suggest that accelerated development of emotion behaviors and circuits is a core outcome following the experience of rearing adversity. We suggest that such accelerated development may have implications for the integrity of emotion circuits and emotion regulation later in life. It remains possible that these neural adaptations are in fact indicators of longer-term mental health resilience — a solid understanding of these adaptations continues to be investigated. However, findings from several literatures suggest that anxiety is a common long-term outcome associated with 'growing up' quickly [43], an example being the increased risk for internalizing disorders in adults with a history of exhibiting early parentification behaviors due to having parents that were unable to provide optimal parenting [44]. The veracity of the model proposed in this paper will require very long-term follow-up data to fully address.

Although a comprehensive review of the mechanisms behind these acceleration effects are outside the scope of the current review, evolutionary-biology theories and data on pubertal development following adversity would indicate that both stress and sex hormones are likely to play a role. Future studies aimed at understanding the biological and psychological pathways that lead to acceleration of emotional development following rearing adversity will have a large impact on the treatment and prevention of mental illness. Although this review focused largely on cross-sectional studies, the use of longitudinal designs in future studies should go a long way in elucidating the neurobiology of these stress-accelerated effects. Such designs will also be useful in determining whether accelerated brain development is predictive of psychopathology risk or resilience. We hope that the current paper can provide the scaffolding and motivation

for future research aimed at addressing stress effects on brain development.

Conflict of interest

The authors declare that they have no conflicts of interest to report.

Acknowledgments

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