Early Adversity and Development: Parsing Heterogeneity and Identifying Pathways of Risk and Resilience

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Adversity early in life is common and is a major risk factor for the onset of psychopathology. Delineating the neurodevelopmental pathways by which early adversity affects mental health is critical for early risk identification and targeted treatment approaches. A rapidly growing cross-species literature has facilitated advances in identifying the mechanisms linking adversity with psychopathology, specific dimensions of adversity and timing-related factors that differentially relate to outcomes, and protective factors that buffer against the effects of adversity. Yet, vast complexity and heterogeneity in early environments and neurodevelopmental trajectories contribute to the challenges of understanding risk and resilience in the context of early adversity. In this overview, the author highlights progress in four major areas—mechanisms, heterogeneity, developmental timing, and protective factors; synthesizes key challenges; and provides recommendations for future research that can facilitate progress in the field. Translation across species and ongoing refinement of conceptual models have strong potential to inform prevention and intervention strategies that can reduce the immense burden of psychopathology associated with early adversity.

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Adversities that occur early in life, such as maltreatment, exposure to violence, and poverty, are common and can have profound and lasting influences on mental health. Between one-half and two-thirds of youths experience at least one form of adversity or traumatic event prior to adulthood (1–4), and childhood adversity is estimated to play a role in one in three psychiatric disorders in adulthood (4). Youths exposed to adversity are at increased risk for a broad range of internalizing and externalizing problems, including anxiety, depression, posttraumatic stress disorder (PTSD), disruptive behavior disorders, and substance use disorders (2, 4–7). Moreover, early adversity is experienced at higher rates by minoritized communities (8), contributing to mental health disparities (9). Delineating the neurobiological pathways by which early adversity leads to psychopathology is critical for targeted treatment approaches and early risk identification. While research to date in both animals and humans has provided major scientific advances in delineating these pathways, the current state of the science lacks the specificity and mechanistic insight that is essential for reducing the immense burden of psychopathology. In this overview, I review progress and gaps in four promising areas of research, highlight key challenges, and provide recommendations for future directions to advance the field.

MECHANISMS: IDENTIFYING PATHWAYS LINKING EARLY ADVERSITY WITH MENTAL HEALTH

A growing body of research has examined behavioral, cognitive, and neurobiological processes that may explain the robust association between early adversity and risk for psychiatric disorders. Cross-species evidence has demonstrated that early adversity has particularly strong effects on stress physiology (10–12) and corticolimbic neural circuity (13–15) involved in learning about salient aspects of the environment and regulating emotion (16). Indeed, youths exposed to early adversity show alterations in hypothalamic-pituitary-adrenal (HPA) axis function (10, 11, 17, 18) and in both the structure and function of the medial prefrontal cortex (mPFC), amygdala, and hippocampus and their connections (13, 19–23). Connections between these regions may be especially affected by adversity because of their dense expression of glucocorticoid receptors (14, 24–27) and the developmental timing of circuit maturation (14, 15, 28). 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 (29, 30). Environmental influences on corticolimbic circuitry in early life may play an active role in shaping longer-term neural and behavioral phenotypes, including future responding to adversity. In addition to increasing risk for psychopathology during development, early adversity increases risk of psychopathology following subsequent adversity exposure (31, 32). Emerging evidence suggests that alterations in hippocampal-fronto-amygdala circuitry also underlie effects of stress sensitization (33, 34). Collectively, these studies highlight a central role of corticolimbic circuitry in mediating the effects of early adversity on risk for psychopathology.

Early adversity is also associated with alterations in large-scale brain networks that support cognitive and affective functions (19, 20, 35), such as the salience network involved in detection of behaviorally relevant stimuli (36–40), the fronto-parietal network involved in cognitive control (41–46), and the frontostriatal network involved in reward processing (47–53). Paralleling these neural differences, youths exposed to adversity show alterations across a range of domains, including emotion regulation, reward processing, social information processing, and associative learning (20, 54, 55). Despite the potential for resilience and change during development, the effects of adversity can persist long after the adversity ends, and some of the same behavioral and neural alterations have been observed in adults who report exposure to early adversity (21, 56, 57). Given the transdiagnostic nature of disruptions in cognitive control and affective functions, these alterations provide plausible pathways from early adversity to a range of internalizing and externalizing disorders.

Stress Acceleration

While a wealth of studies have demonstrated the effects of early adversity on the brain and stress response systems, a growing literature suggests that early adversity affects the timing or pace of neurobiological development itself (58–61). Life history theory posits that early experiences shape developmental trajectories to meet the environmental demands that individuals are likely to encounter—in the context of a harsh early environment, accelerated pubertal development could be adaptive to prioritize opportunities for reproduction (62, 63). Building on work on life history strategies, predictive adaptive response models suggest that early adversity accelerates biological aging across multiple domains (64, 65). Supporting these ideas, there is cross-species evidence of acceleration in pubertal tempo (66–71), which may be triggered by alterations in endocrine function (17, 66, 72), and cellular aging (73–77) following adversity.

In terms of neurodevelopment, the stress acceleration hypothesis suggests that early adversity leads to precocious maturation of corticolimbic circuitry and behaviors governed by this circuitry, fostering greater capacity for independent regulation of stress and emotion in the absence of a stable, nurturing environment (58). Early adversity has been associated with accelerated maturation of corticolimbic circuitry in both rodents (78–80) and humans (81–86). However, other studies have found evidence of delay or a lack of differences in developmental timing following adversity (59). Recent evidence suggests that some acceleration effects may be specific to corticolimbic circuitry and not to other brain networks (83) and may vary as a function of adversity-related factors. Indeed, a study from Keding and colleagues in this issue of the *Journal* (87) found that exposure to abuse was associated with delayed structural maturation that was specific to emotion-related neural circuitry, whereas neglect was associated with a more distributed pattern of accelerated structural maturation in female youths.

Although much remains unknown about the function and long-term correlates of shifts in developmental timing, earlier maturation may represent an ontogenetic adaptation (58, 62, 82, 88). Recent work demonstrating acceleration of ventromedial prefrontal cortex (vmPFC)–amygdala connectivity following early adversity found that the more mature pattern of connectivity was associated with slower telomere shortening and slower pubertal tempo (84), suggesting protective neural system effects in the context of accelerated cellular aging following early adversity. Paralleling these findings, children exposed to caregiver deprivation who showed a more mature pattern of vmPFC-amygdala connectivity displayed lower separation anxiety (82), consistent with evidence that stronger inverse amygdala-mPFC functional connectivity is associated with lower internalizing symptoms among youths exposed to early adversity (89). At the same time, there are likely to be long-term consequences of precocious maturation. Future research that examines longer-term effects of accelerated development, tests whether neural findings of acceleration are specific to corticolimbic circuitry, and further examines how developmental timing may converge or diverge across different biological domains will help to provide a more comprehensive understanding of the influences of early adversity on the timing of maturation.

HETEROGENEITY: DIMENSIONAL MODELS OF EARLY ADVERSITY

Despite vast heterogeneity in the nature of early adversity and in developmental outcomes, existing studies have often taken one of several approaches that may obscure meaningful variability. A common study design compares an adversity-exposed group to a non-adversity-exposed group, with the adversity-exposed group comprising individuals exposed to a broad range of adverse experiences (90), or comprising individuals exposed to a single type of adversity (91, 92) without comparison to other types of adversity (13). Another dominant approach has conceptualized adversity in terms of cumulative risk, modeling a continuous measure of adversity exposure as the number of categories of adversity to which an individual has been exposed (93). While such research has contributed foundational knowledge to the

field, approaches that focus on specific elements of adversity exposure have the potential to identify key factors that moderate the effects of adversity and to more precisely parse variability in outcomes (13, 88, 94–98). Parsing such variability may be essential for identifying mechanisms and facilitating targeted intervention approaches.

Unpredictability

A robust cross-species literature demonstrates that unpredictability is one important dimension of adversity (88, 99–101), particularly in the context of caregivers' behaviors. Early caregiving cues, such as the contingency of caregiver responsivity to infants, form the basis of children's expectations of the environment and are foundational to cognitive and affective development (102, 103) and the development of secure attachment relationships (104). In studies of rodents that manipulate the degree of predictability in maternal care via fragmented care models, rodent pups exposed to unpredictable care show disruption in cognitive and affective processes (99, 101, 105). Alterations in corticolimbic circuitry may underlie these disruptions, as rodents exposed to unpredictable maternal signals exhibit altered amygdala-mPFC connectivity (106), greater amygdala activity (56), and altered corticolimbic interactions that have been associated with anhedonia (107–110).

In humans, unpredictability in parental cues—such as during play with 12-month-old infants (111)—and synchrony in infant-caregiver behavior (112) have similarly been associated with children's development. Greater unpredictability in broader environmental contexts, such as variability in housing, parental jobs, and parental involvement in care, is associated with risk-taking behavior in adolescence (100). One potential pathway by which broader environmental unpredictability (e.g., variable access to food resources) affects developmental outcomes is through alterations in caregiving behavior (100, 113, 114). Although neural correlates of unpredictability are harder to isolate and have been less explored in humans, recent evidence from a longitudinal study of parent-child dyads demonstrated that higher unpredictability of parental sensory signals at 6 and 12 months of age was associated with greater structural integrity of the uncinate fasciculus at ages 9–11 years, which was associated with episodic memory (115). Future research will be important to better understand the neurobiological correlates of unpredictability in humans and to continue to refine conceptual definitions and facilitate more precise measurement of environmental unpredictability (116).

Threat and Deprivation

Another influential approach draws a distinction between threat (i.e., adversity that involves significant potential for harm, such as abuse or violence) and deprivation (i.e., adversity characterized by the absence of an expected environmental input, such as cognitive or social stimulation, as in neglect or caregiver deprivation) (117, 118). Exposure to threat is associated with alterations in corticolimbic circuitry that include heightened amygdala activation to threat and lower amygdala, mPFC, and hippocampal volumes, with corresponding alterations in aversive learning and emotion processing (35, 119–125). By contrast, some evidence suggests that deprivation is more consistently associated with lower gray matter volumes and altered function in frontoparietal regions (41, 126), and with difficulties in executive functioning and language (127–131). However, deprivation in the form of previous institutionalization has also been associated with alterations in corticolimbic circuitry, including altered amygdala volume, amygdala-mPFC connectivity, and amygdala reactivity (82, 91, 132, 133), as well as alterations in aversive learning and emotion processing (86, 134, 135). In light of some inconsistent findings and challenges in modeling threat and deprivation (136, 137), ongoing research will be helpful to continue to inform how these elements may differentially influence development, including research that examines threat or deprivation while controlling for the other in the same study (130, 138–141). Taken together, various empirical and theoretical contributions to the field (13, 88, 94–97, 100, 137) highlight the value of delineating specific elements of early adversity to further advance knowledge of mechanisms and developmental trajectories.

TIMING: SENSITIVE PERIODS AND DEVELOPMENTAL EFFECTS

Given changes in neuroplasticity, and given that the neural circuitry sensitive to adversity undergoes dynamic changes from the prenatal period through young adulthood, the effects of adversity are likely to vary as a function of the developmental stage at which adversity occurs (13–15, 28, 142). Across species, evidence demonstrates that adversity that occurs early in life has particularly strong effects on neurobiological and psychiatric outcomes relative to adversity that occurs in adulthood (14, 143). Even during development, effects are likely to differ as a function of the specific timing of adversity exposure (e.g., infancy, early versus late childhood, early versus late adolescence, etc.). Animal work that allows for manipulating the timing of exposure shows that the effects of adversity differ as a function of developmental timing (14, 144). Manipulating adversity exposure is challenging in humans; however, naturalistic human studies of adversity provide converging evidence that outcomes depend on the timing of adversity (11, 21, 28, 94, 145–148).

Sensitive Periods

One important way in which the timing of adversity relates to developmental trajectories is through sensitive periods of heightened neuroplasticity, when a specific species-expected environmental input has a particularly strong influence on a specific brain circuit (149, 150). While sensitive-period phenomena are challenging to study in humans, the unique study design of the Bucharest Early Intervention Project (151) has provided insight into a potential sensitive period related to caregiving and socioemotional development

during the first 2 years of life. Findings suggest that youths 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 after 24 months of age (11, 152, 153). However, it remains unclear whether earlier placement into foster care is associated with more favorable outcomes because of a shorter duration of stress or because the stress may interact with plasticity, or both.

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 (154), rats (155), nonhuman primates (156), and humans (82). These findings may reflect a sensitive period driven by experience-expectant mechanisms. Consistent with criteria for a sensitive period (150, 157), it is likely that this period is marked by heightened neuroplasticity, and infancy is a time of rapid and substantial change in corticolimbic circuitry (158). There is also some specificity to the nature of the experience and the timing of the window during which caregiver deprivation seems to have particularly strong effects (14), although ongoing research will be important to test all relevant criteria (157, 159, 160). Future work will also provide critical insight into precisely what becomes biologically embedded during this period and how missed opportunities during this window may have cascading effects later in development (161).

Timing-Related Effects of Adversity

Although considerable evidence indicates that adversity has the strongest effects when experienced earlier in life (10, 11, 14), risk could instead be highest when adversity occurs during specific windows of heightened plasticity that occur later in development. For example, corticolimbic circuitry undergoes substantial changes across childhood and adolescence (60, 162, 163). Particularly in the context of maltreatment, some studies have suggested pronounced effects of adversity on corticolimbic structure or function during childhood or adolescence (148, 164–166). These findings also highlight the complexity of interactions between developmental timing and the type of adversity exposure, sex, and regional specificity in the brain. For example, exposure to maltreatment at ages 10–11 was related to amygdala volume in adulthood, relative to exposure at other ages during development (148), whereas sexual abuse at ages 3–5 and 11–13 was associated with hippocampal volume in adulthood (164). In the functional domain, physical maltreatment during childhood (ages 3–6) was associated with blunted amygdala reactivity in adulthood, whereas peer emotional abuse during adolescence (ages 13 and 15) was linked with increased amygdala response in adulthood (166). While these studies in adulthood provide insight into nonlinear peaks in risk throughout development, future studies conducted during childhood and adolescence will be important for understanding more proximal changes in corticolimbic circuitry and psychopathology that may unfold during development.

PROTECTIVE FACTORS: CAREGIVER SUPPORT AND OPPORTUNITIES FOR RECALIBRATION

Despite the strong association between early adversity and mental health, not all youths exposed to adversity go on to develop psychiatric disorders. Delineating factors that promote resilience in the face of adversity and interactions between these resilience factors (167) is critical for identifying mechanistic targets for intervention, as well as for identifying youths at elevated risk. Stable, supportive caregiving is one of the strongest protective factors against psychopathology in the context of early adversity (168). Youths exposed to adversity who experience higher levels of caregiver support develop lower levels of symptomatology (169–171), and parenting behaviors are associated with children's symptoms of PTSD (172, 173).

A growing literature has provided increasing insight into the behavioral and neurobiological processes by which caregivers promote healthy development and resilience (174). For example, during childhood, caregiver sensitivity (i.e., the extent to which a caregiver is attuned and responsive to their child) is associated with amygdala volume and microstructure of the amygdala and hippocampus (175), and negative caregiving behavior is associated with amygdala activation and functional connectivity (176). In addition, caregiver control experienced during childhood is associated with amygdala activation and structural integrity of the uncinate fasciculus during young adulthood (177). In the context of adversity exposure, several studies have shown that caregiving support can buffer the effect of adversity on HPA axis function and corticolimbic networks involved in emotion regulation and executive control (178–180). Importantly, supportive caregiving is a modifiable target that can be strengthened through intervention. A randomized controlled trial of a supportive parenting intervention for families living in poverty showed that a longer duration of living in poverty during adolescence was associated with reduced amygdala and hippocampal volumes among young adults in the control condition (informational brochures), but not among young adults whose families participated in the Strong African American Families Program (181). Taken together, these findings indicate that supportive caregiving may buffer the risk of psychopathology following adversity by modulating corticolimbic circuitry, which can be targeted effectively through psychosocial intervention.

Caregiver Buffering

Caregivers play a central role in helping to regulate children's emotions and stress reactivity in the context of adversity (182–185). Recent research provides insight into the

neurobiological mechanisms that may underlie these effects. Paralleling evidence in rodents and macaques (186, 187), caregiver presence can buffer children's responses to stress by dampening cortisol reactivity (188) and amygdala reactivity (189). These findings suggest that caregivers may serve an external regulatory function while corticolimbic circuitry is still developing. Early biological embedding of safe and predictable caregiver-related cues during infancy may set the stage for caregivers, and eventually other attachment figures, to support regulation later in development (161, 190). Consistent with the idea that early experiences with caregivers may shape subsequent experiences of social buffering, early caregiving adversity is associated with weaker effects of caregiver buffering later in development across species (191–194). Although caregiver buffering of amygdala reactivity is weaker on average among youths previously exposed to caregiver deprivation, there is substantial variability in caregiver buffering following adversity. Among youths who experienced caregiving adversity, 40% show reduced amygdala reactivity to parental cues, and these youths exhibit lower anxiety up to 3 years later (191). These findings suggest that caregiver buffering of amygdala reactivity may promote resilience among youths at elevated risk of psychopathology following adversity.

Opportunities for Recalibration

Just as periods of heightened plasticity can be associated with vulnerability, they also present opportunities for resilience. Recent evidence highlights the potential for adolescence to confer unique opportunities for recalibration of the HPA axis among youths exposed to early adversity who are later living in more favorable conditions. Children who were previously exposed to early caregiver deprivation via institutionalized care and later adopted into stable, supportive family environments show blunted cortisol reactivity to psychosocial stressors, and this effect can persist even years after adoption (10). However, they show increasing cortisol reactivity with pubertal development, such that their stress response did not differ from that of never-institutionalized youths following puberty (195, 196). These findings suggest that puberty may confer greater plasticity in the HPA axis, which facilitates recalibration to the current environment and the potential for heightened influences of supportive caregiving environments during this time. Future research that further examines the nature of an adolescent environment that facilitates recalibration, as well as the potential neural and behavioral consequences of pubertal recalibration (197), will be critical to inform translation to promote resilience.

CHALLENGES AND FUTURE DIRECTIONS IN THE STUDY OF EARLY ADVERSITY

Key Challenges

Research on early adversity has made considerable progress in delineating neurodevelopmental mechanisms underlying risk for psychiatric disorders, key timing and experiential factors that contribute to heterogeneity in exposure and outcomes, and protective factors that promote resilience. However, the field must confront several major barriers to continue advancing empirical knowledge and theory of early adversity.

One fascinating but challenging reality is the vast intricacy of the environment, the developing brain, and human behavior; there is much complexity and heterogeneity in adversity exposure itself and in neurodevelopmental and behavioral trajectories among youths exposed to adversity. Conceptual models have struggled to integrate burgeoning findings on the effects of early adversity on brain development and mental health. At the same time, in practice, empirically testing key predictions from complex conceptual models presents significant challenges. Because it would be unethical and infeasible to experimentally manipulate the nature or timing of adversity exposure in humans, the observational design of most studies in humans limits mechanistic insights and causal interpretations. Moreover, there is substantial chronicity and co-occurrence of adversities, and dimensions of adversity, in youths (2, 4, 198, 199), and such adversities occur in the context of an ever-shifting broader ecosystem (96, 200–202). Many studies have lacked the statistical power to examine complex higher-order interactions (e.g., of the timing and type of adversity) or to model risk factors that may be highly collinear (93, 137).

Measurement issues further hinder advances in the study of early adversity. Studies of early adversity often rely on retrospective self-report (203) of early experiences that are linked with measures of brain and behavioral functioning that are collected in adulthood (165). While recent evidence highlights the predictive validity and utility of self-reported measures of adversity, even when retrospective (204), this study design still precludes a developmental understanding of risk and resilience. In addition, most studies lack precise information about the developmental timing of adversity exposure or the depth of phenotyping that would be needed to test predictions from dominant conceptual models. Lastly, given that development and key processes relevant to adversity and mental health can unfold on the order of years, but also on a moment-to-moment basis, the optimal time frame for sampling to accurately model development may be practically impossible in humans.

Here, I highlight key themes for future research that will be essential to overcoming these challenges and fostering mechanistic insights and more precise prediction of mental health outcomes in the field.

Cross-Species Translation

Consistent with the foundational contributions of cross-species research to our current knowledge of early adversity (14, 56, 78, 205, 206), translational insights from research in animals will continue to be essential to mechanistic understanding of the links between early adversity and mental health. The ability to manipulate the type and

timing of risk and protective factors in animal models provides opportunities to test key predictions about development and the environment (207, 208). In particular, research in rodents and nonhuman primates can inform questions about sensitive periods of neuroplasticity and the neurobiological mechanisms that link adversity with developmental outcomes. Robust evidence across species has shown that neural and behavioral phenotypes following adversity result from a complex interplay between environmental, genetic, and epigenetic factors (209–212). Genetic predisposition plays an important role in developmental outcomes, with evidence that the effects of adversity depend in part on one's genotype. However, given the co-occurrence of early adversity with numerous genetic and environmental factors that affect children, caregivers, and family functioning, dissociating the contributions of heritable factors that co-occur with early adversity, relative to early adversity itself, presents a significant challenge (123). As one example, there is shared genetic vulnerability between children and parents, and the same heritable factors that contribute to a child's susceptibility to stress may contribute to their caregiver's behavior. While animal studies employing experimental designs have shown that adversity per se does play a causal role in developmental outcomes (123, 156, 213), much remains unknown about how a combination of adversity, genetic risk, and gene-environment interplay contributes to risk and resilience. Cross-species research has also increasingly demonstrated the role of epigenetic effects, such as regulation of gene expression, in linking early experiences with alterations in corticolimbic circuitry and behavior and will be central to mechanistic insights in this realm (214–218).

Cross-species translation in research on early adversity benefits from a relatively high degree of conservation of corticolimbic circuitry that is sensitive to adversity across species (219–221) and ongoing refinement of translational models of the early environment (56, 111, 222, 223). Progress will be greatly facilitated by meaningful cross-talk between researchers studying early adversity in humans and in animals (213, 224), including dialogues that inform translation both from animals to humans and from humans to animals, as well as direct collaborations (56, 111, 225–227).

Longitudinal Developmental Investigations

Some of the field's most pressing questions—including about the effects of adversity on the pace of brain development (e.g., stress acceleration) and about sensitive periods that may confer vulnerability but also offer opportunities for resilience (e.g., for pubertal recalibration)—involve developmental timing and trajectories. While cross-sectional designs require fewer resources and time, longitudinal designs that facilitate examination of within-person change over time (228) among youths exposed to adversity are necessary to more rigorously address these questions. Moreover, for many areas of inquiry, such longitudinal data need to be collected prior to adulthood and during specific windows of development in order to facilitate knowledge about how development unfolds. It would be impractical to draw inferences about the timing of a developmental process from neural and behavioral data collected in adulthood. As one example of the need for longitudinal developmental studies, much of the research providing evidence of acceleration of corticolimbic circuitry following adversity has been conducted cross-sectionally (81–83, 85, 86, 229). Longitudinal examinations will be important to reconcile inconsistent findings in this area (59), examine convergence or divergence in effects across different biological levels (e.g., corticolimbic circuitry, epigenetic aging, pubertal timing), and evaluate the extent to which acceleration may facilitate adaptation in the short term but be associated with consequences in the longer term.

"Big Data" and Collaboration

The inherent complexity of shifting environments and co-occurrence of different types of adversity (e.g., adversity characterized by varying degrees of threat, deprivation, or unpredictability) necessitate large sample sizes to ensure sufficient statistical power for complex modeling of higher-order interactions and change over time. Depending on the nature of adversity being studied, large sample sizes can also be required for adequately sampling youths with specific exposures. A growing number of large, collaborative cross-sectional or longitudinal big data studies exist that employ neuroimaging and assessments of the early environment and mental health among youths (230–242). These data sets can be orders of magnitude larger than traditional studies in human neuroscience (243) and increase the likelihood of identifying robust and reproducible findings related to the effects of early adversity, particularly with regard to phenotypic associations with brain development (244). At the same time, big data studies will not be able to address all important questions in this realm. The prevalence of some adversities will be too low in studies that did not ascertain youths based on exposure to adversity, and large-scale efforts are unlikely to have the capacity to collect in-depth assessments of adversity exposure at the level of precise developmental timing and dimensionality that can be prioritized in smaller-scale studies focused specifically on adversity. Thus, more general big data studies and studies that sample from specific populations (e.g., children who experienced maltreatment) or employ deeper phenotyping will provide complementary insights. In order to enhance statistical power for investigations with deeper phenotyping of early adversity, meta-analytic efforts focused on early adversity (e.g., via the Enhancing Neuro-Imaging Genetics Through Meta-Analysis consortium [245]) and multisite collaborations among researchers who have collected overlapping or harmonized measures of early adversity (19) will be essential to advancing knowledge. Leveraging large longitudinal studies to test and expand on existing hypotheses and age-related findings derived from smaller cross-sectional studies and, in turn, applying insights gained from big data

to more intensively investigate a specific phenomenon in smaller, investigator-led studies represent promising strategies for maximizing the value of complementary efforts in the field of early adversity and development.

Advanced Computational Approaches

Ongoing methodological advances will facilitate discovery about the mechanisms underlying the links between early adversity and mental health and the prediction of outcomes following adversity. Various conceptual approaches to early adversity have converged on the importance of parsing heterogeneity in the nature, timing, and experiential elements of adversity exposure and developmental outcomes to accelerate progress in identifying risk and mechanistic targets (13, 15, 21, 28, 88, 94, 95, 100, 117, 136). In addition to more traditional approaches that have been used to test predictions about a priori dimensions or timing of adversity, data-driven computational approaches may be particularly useful for identifying specific developmental windows associated with heightened risk or resilience (165, 166, 246) or for examining variability in exposure or outcomes to empirically derive key features of adversity exposure (247–249). As one example, a recent study applied similarity network fusion to large-scale environmental and brain imaging data from the Adolescent Brain Cognitive Development Study with the aim of decomposing heterogeneous associations between brain structure and specific aspects of the childhood environment (248). The findings identified subgroups of youths who displayed more homogeneous brain-environment associations, and this subtyping approach enhanced prediction of mental health symptoms (which was not possible without the subtyping). These findings suggest that it is possible to meaningfully parse heterogeneity in associations between the early environment and brain structure during development, and that doing so may enhance risk identification and facilitate mechanistic insights.

Advanced computational approaches will also provide novel insight into questions around developmental timing and plasticity. 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 (150). However, studying these processes in humans has been infeasible. A recent study (250) used a GABAergic benzodiazepine challenge to empirically generate a model of excitatory-inhibitory ratio based on multivariate patterns of functional connectivity in humans. The researchers then applied that model to a developmental sample of youths ages 8–22 and showed that the model predicted reductions in excitatory-inhibitory ratio during adolescence, which were specific to the association cortex and were related to psychopathology. The gradual reduction in the ratio of excitatory to inhibitory patterns with age that was observed in this study aligns with previous animal work on neurobiological mechanisms of sensitive periods (157, 251–253). These findings are consistent with the idea that adolescence is a sensitive period for the association cortex and represent a significant advance in the capacity to interrogate plasticity-related processes during human development.

Another significant analytic advance is the use of machine learning models of brain development to examine deviations from typical maturation. In this issue of the *Journal*, Keding and colleagues (87) leveraged a large multisite data set to examine maturational timing of gray matter volume related to adversity exposure and psychopathology among adolescent girls. They trained stacked generalizer machine learning models with gray matter volume estimates from whole-brain, emotion-related, and language-related circuit parcellations to predict chronological age in typically developing girls. These models generated brain age gap estimates (BrainAGEs) from gray matter volume of girls exposed to abuse or neglect and with internalizing disorders. Subsequent feature influence analyses interrogated which neural features contributed to adversity- and psychopathology-related differences in BrainAGE. Collectively, these studies highlight significant advances that have great promise in facilitating novel insights into the mechanisms underlying risk for adversity-related psychopathology in humans.

Refining Conceptual Models

Progress in understanding the effects of early adversity and mechanisms associated with risk and resilience, with the eventual goal of clinical translation, will rely on continual refinement of conceptual models. Theoretical approaches must grapple with the immense complexity of the developing brain, the environment, and behavior (254). A useful model of early adversity and neurodevelopment must account for the vast heterogeneity in outcomes and key concepts of equifinality (i.e., distinct early experiences leading to similar outcomes) and multifinality (i.e., similar early experiences leading to distinct outcomes) from developmental psychopathology (255, 256). In addition, while adversity is often conceptualized as influencing the brain and behavior (i.e., a unidirectional pathway), nuanced conceptualizations that facilitate empirical advances must account for the transactional nature of development. Developing youths are embedded within broader social contexts (96, 201, 202), and neural and behavioral alterations that follow adversity are not simply outcomes but also factors that reciprocally shape these contexts (212) and can alter the course of development (257).

While refinements and innovation in conceptual models could take many directions, several areas may be particularly fruitful for ongoing interplay between empirical research and conceptual refinement given the current state of the literature. First, dimensional models of adversity can flexibly allow for the incorporation of additional dimensions (13, 97) and will benefit from increased emphasis on the child's own perception and experience of any given event (136, 204, 258, 259). As one example, in addition to threat,

deprivation, and unpredictability (88, 98, 99), Cohodes and colleagues (13) have proposed a framework in which the effects of adversity on corticolimbic circuitry and mental health vary depending on the extent to which adversity is characterized by perceived controllability and caregiver involvement. Critically, building on a robust literature on the developmental timing of adversity (14, 15, 21, 28, 94), this framework emphasizes the importance of interactions between key experiential elements of adversity and the developmental timing of adversity exposure. Delineating when specific experiential elements 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 (13, 260).

Second, despite converging evidence that the effects of adversity can differ as a function of developmental timing of exposure, evaluation of which developmental differences fit the criteria for a sensitive period is rare (159, 261). Elucidating the experience-related mechanisms (262) underlying timing-related effects, as well as precisely what is biologically embedded during a given sensitive period, is essential to understanding the mechanisms by which early experiences shape neurobehavioral development (160, 161). Bridging insights from formal modeling (261) and empirical studies across species (263) may facilitate meaningful refinement of conceptual models of early adversity.

Lastly, while adversity-related alterations in neurobiology or behavior are often framed as detrimental, alternative perspectives highlight the adaptive nature of some phenotypes following adversity (58, 82, 264–267). That is, such ontogenetic adaptations may bolster the ability to cope with or survive in a harsh and unpredictable environment (62, 262, 266, 268). A more nuanced understanding of the neurobiological and behavioral effects of adversity during development is critical to a more comprehensive conceptualization of early adversity, as well as to promoting resilience and adaptive behavior in the face of future adversity. Reevaluating "deficit models" and carefully considering frameworks that emphasize adaptation and even areas of increased strength following adversity (e.g., "hidden talents") (269, 270) could both stimulate important scientific discoveries and shift the often dominant narrative of deficits that can contribute to stigma of youths exposed to adversity (29, 271).

Translation to Intervention

Building on progress in identifying mechanisms linking early adversity with mental health, translating such knowledge to inform intervention and prevention strategies for youths exposed to adversity is a critical goal for the field. Although existing evidence-based treatments can be highly effective for youths who develop psychopathology following adversity (272–276), a substantial proportion of youths do not sufficiently benefit from existing treatments (277). Moreover, there is great need to enhance prevention strategies that can be employed following adversity and prior to the development of psychopathology. Even with similar clinical presentations, some evidence suggests that individuals exposed to early adversity differ in important ways from individuals not exposed to early adversity (278–280), further highlighting the importance of efforts to optimize treatments for youths exposed to adversity.

Continual advances in research on early adversity can inform prevention and intervention strategies in several key ways. First, cross-species research can specifically delineate the timing of sensitive periods, which may render the developing brain more vulnerable to the effects of adversity but also provide enhanced opportunities for positive change through intervention (28). Corticolimbic circuitry and related functions such as fear learning and emotion regulation, which are altered following adversity, undergo dynamic changes across development (281–285). Thus, youths with adversity-related psychopathology may benefit from interventions that are specifically optimized based on the biological state of the developing brain (260, 286, 287). Second, building on conceptual models that emphasize key experiential elements of adversity exposure, as well as their interaction with developmental timing, may represent a powerful approach to optimizing interventions for a given individual based on factors such as the individual's developmental stage or a profile of adversity exposure (13). Third, knowledge of the mechanisms underlying risk for psychopathology following early adversity will be important for identifying modifiable processes that can be targeted in treatment. As one example, consistent evidence has linked early adversity with alterations in threat-related social information processing biases, heightened emotional reactivity and difficulties with emotion regulation, and disruptions in reward processing, all of which are associated with specific targets for intervention (288). By contrast, less is known about adversity-related alterations in emotional learning (86, 121, 122, 289). Given that emotional learning undergoes marked changes during development (60, 290–292) and is the target of many well-established interventions (293, 294), ongoing research on learning-related processes following adversity may be particularly useful for fostering progress in clinical translation (288). Lastly, enhancing caregiver support, a well-established protective factor in the context of adversity, provides another important target for intervention and is already a central component of many interventions (295, 296). Future investigations of the specific mechanisms by which interventions can facilitate the recovery of caregiver capacities for regulation following missed opportunities for predictable, safe caregiver cues during an early sensitive period may be particularly helpful for informing intervention strategies for youths exposed to early adversity (161). Taken together, these areas for future research highlight the need to enhance the efficacy of interventions for youths exposed to adversity and the potential for

precision medicine approaches that tailor interventions based on the developmental timing or specific features of adversity exposure.

CONCLUSIONS

Exposure to early adversity is a potent risk factor for psychopathology. Cross-species investigations have facilitated substantial progress in delineating neurodevelopmental mechanisms associated with risk and resilience following early adversity. However, the vast complexity and heterogeneity in early environments and in developmental trajectories following adversity present challenges to achieving mechanistic insight and effective clinical translation. An overview of the current state of the field points to the importance of longitudinal investigation in large developmental samples, coupled with deeper phenotyping of the early environment in youths exposed to adversity, and the potential for advanced computational approaches to parse heterogeneity and provide novel insight into sensitive periods. Ongoing refinement of conceptual models that incorporates insights from cross-species research and developmental psychopathology will be essential to future progress and translation to enhance risk identification and optimize interventions for youths exposed to adversity.

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