



Early life stress and neural development: Implications for understanding the developmental effects of COVID-19

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Abstract

Chronic and/or extreme stress in childhood, often referred to as early life stress, is associated with a wide range of long-term effects on development. Given this, the COVID-19 pandemic has led to concern about how stress due to the pandemic will affect children's development and mental health. Although early life stress has been linked to altered functioning of a number of neural and biological systems, there is a wide range of variability in children's outcomes. The mechanisms that influence these individual differences are still not well understood. In the past, studies of stress in childhood focused on the type of events that children encountered in their lives. We conducted a review of the literature to formulate a new perspective on the effects of early life stress on development. This new, topological model, may increase understanding of the potential effects of the COVID-19 pandemic on children's development. This model is oriented on children's perceptions of their environment and their social relationships, rather than specific events. These factors influence central and peripheral nervous system development, changing how children interpret, adapt, and respond to potentially stressful events, with implications for children's mental and physical health outcomes.

Keywords Stress · Development · Adversity · Predictability · Safety · COVID-19

The outbreak of a global pandemic associated with COVID-19 has brought to the forefront the question of how stress influences children's developmental outcomes. Potential sources of stress related to the pandemic include fear of illness or death of family and friends due to exposure to COVID-19, economic instability due to job loss and the economic recession, school and work closures, and lack of consistency in policies designed to mitigate the effects of the pandemic. All of these potential sources of stress can disrupt typical family dynamics (Gassman-Pines & Gennetian, 2020). We already see evidence that the COVID-19 pandemic, particularly job and income loss, is associated with more harsh parenting behaviors (Kalil et al., 2020) and increased risk for maltreatment (Lawson et al., 2020), as well as increased risk for behavioral issues in children (Patrick et al., 2020). The potential for stress during the pandemic is intensified by existing inequalities:

low income and minority communities have been disproportionately affected by both the health and economic consequences of the pandemic, having higher death and COVID-19 case rates, decreased access to virtual learning environments, and increased food insecurity (Ahmed et al., 2020; Armitage & Nellums, 2020). Chronic and/or severe stress during early childhood, referred to as early life stress, can have long-lasting consequences for development (Pechtel & Pizzagalli, 2011; Pollak, 2015). Given this, there has rightfully been concern about how the pandemic will affect children's development (Crawley et al., 2020; Prime et al., 2020). We discuss how research examining the bio-behavioral effects of early life stress can inform our understanding of the potential consequences of the COVID-19 pandemic on children's health.

The term stress refers to the psychological response elicited when an individual perceives themselves to be under threat or challenge. Stress is generally beneficial, producing a range of behavioral and physiological changes designed to address the perceived threat. However, extended activation of stress response systems can have negative physical and mental health outcomes (McEwen, 2017b; Sapolsky, 2015). A key aspect of stress is that stress responses are elicited by an individual's

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perception of something as stressful rather than the events to which they are exposed. This means variability in individuals' perceptions of stress is an integral contributor to individual differences in psychological and physiological stress responses (Brosschot, 2017; Peters et al., 2017).

Historically, research on stress and child development has tended to focus on the types of external events children encounter, such as war exposure, abuse, neglect, or food insecurity. More recently, researchers have started to incorporate a role for children's perceptions of their environments as a way to better understand the effects of stress (Allwood et al., 2017; Danese & Widom, 2020). While somewhat mixed (Negri, 2020), this research, along with that in adults and nonhuman animals suggesting that perceptions are critical in shaping experiences of stress, indicates a need for conceptualizations of early life stress that do not rely solely on events. A new approach, termed "topological," reframes consideration of how early life stress might affect biological stress response mechanisms by emphasizing how children understand and interpret what is happening to them (Figure 1; Smith & Pollak, 2020). In this approach, it is not the type or category of an event to which a child is exposed that is meaningful, but rather how various factors influence how an event or environment is perceived and interpreted by the child. This means that when examining the potential effects of the COVID-19 pandemic on development, it is important to examine factors that may be shift how children perceive and interpret the pandemic alongside specific potential stressors, such as economic strain and parental job loss.

The COVID-19 pandemic is characterized by a number of aspects that have the potential to result in chronic, extreme perceptions of stress for many individuals. Changing and

inconsistent messaging from public health officials and policy makers along with abrupt changes in policies tied to the COVID-19 pandemic—moving in and out of stay at home orders and lockdowns, schools closing, reopening, and closing again, and piecemeal mask policies that lack enforcement—all have the potential to increase feelings of uncertainty and unpredictability associated with the pandemic. Additionally, social distancing policies and workplace and school closures can increase feelings of social isolation, which could exacerbate perceptions of stress linked to the pandemic. Evidence suggests that both children and adults are experiencing increases in stress, perceived social isolation, depression, and anxiety related to the pandemic (Lee et al., 2020; Li & Wang, 2020; Tull et al., 2020). However, there has been a range of variability in how stressful and isolating individuals find the pandemic (Ellis et al., 2020; Sutin et al., 2020). Taking an approach towards stress that incorporates a role for children's perceptions of the pandemic in influencing their experiences of stress can aid with understanding why children may be differently affected by the COVID-19 pandemic. In this manuscript, we apply a topological approach to examine potential effects of the COVID-19 pandemic on children's development, reviewing the role of perceptions of predictability and safety, particularly perceptions of safety related to having strong, supportive social relationships, in shaping children's responses to stress.

Early life stress and development: A brief overview

To date, early life stress, as measured by children's event exposures, has been linked to consistent patterns of effects

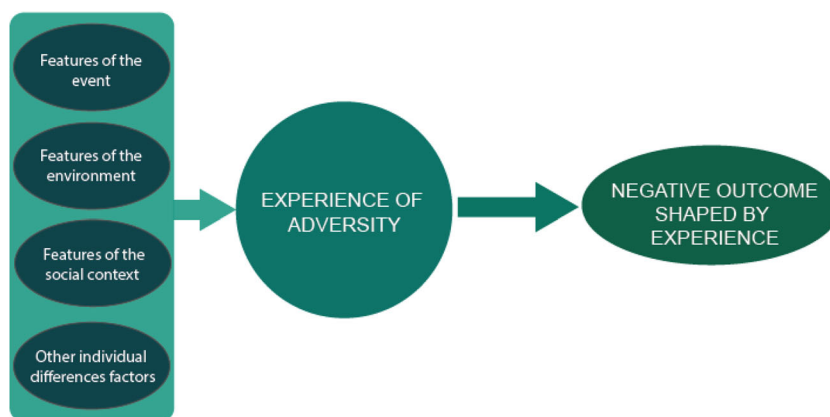


Fig. 1. Topological approach for conceptualizing early adversity (figure adapted from Smith & Pollak, 2020). Factors or dimensions surrounding the potentially adverse events children are exposed to contribute to the child's experience, which then activates relevant bio-behavioral responses to those circumstances. Meaningful factors might include features of the event (e.g., intensity, chronicity, developmental timing); features of the environment (e.g., predictability, contingency, controllability); and features of the child's social context (e.g., presence of safety,

social support), as well as other individual differences factors, such as genetics, temperament, or previous life history. In the context of the COVID-19 pandemic, this suggests that children's outcomes will not be determined solely by their existing environment. Instead, they will likely be more influenced by factors related to features, such as predictability, controllability, and safety, that shape how children make meaning of the pandemic

on neural development. Indeed, early life stress is associated with altered functioning of the hypothalamic pituitary adrenal (HPA) axis, autonomic nervous system, and immune system (Alkon et al., 2014; Danese & Lewis, 2017; Koss & Gunnar, 2017; Loman & Gunnar, 2010). These systems are critical to facilitating motivated psychological and behavioral responses to the environment, particularly environmental threats and challenges (Berntson & Cacioppo, 2004; B. S. McEwen, 2019b). The effects of early life stress on peripheral stress response systems are thought to be a result of altered neural plasticity in circuits integral to stress responses, including the prefrontal cortex (PFC), hippocampus, amygdala, and striatal circuits (Fareri & Tottenham, 2016; C. A. McEwen & McEwen, 2017). Many of these changes have been hypothesized to represent adaptive responses to environments of high threat, which become problematic within the broader social context (Boyce & Ellis, 2005; Obradović et al., 2016). However, there also is a wide range of variation in children's outcomes after exposure to early life stress (Hostinar & Gunnar, 2013b; Palacios-Barrios & Hanson, 2019). We understand relatively little about what drives this variability (Smith & Pollak, 2020). This suggests a need for alternative approaches aimed at examining the bio-behavioral effects of childhood stress that are not solely focused on children's event exposure.

Perceptions not events determine variability in stress responses

While the early childhood literature has tended to focus on whether children have been exposed to events deemed by researchers to be stressful or adverse, the vast majority of evidence with adults and nonhuman animals suggests that neural, physiological, and behavioral stress responses are not primarily influenced by the type of event to which an organism is exposed (Berntson & Cacioppo, 2004; McEwen & McEwen, 2012; Sapolsky, 2015). There is a range of variability in how both humans and nonhuman animals respond to the same type of stressor. Nonhuman animals demonstrate distinct behavioral responses to the same event, and this variability in behavior is tied to differential activation in the sympathetic adrenal-medullar, hypothalamic gonadal, and HPA systems (Buwalda et al., 1992; Korte et al., Korte et al., 1992, Korte et al., 1995; Veenema et al., 2003). Humans demonstrate similar variability in stress responses. This variability is observed in indices including cardiac autonomic responsivity (Berntson et al., 1994; Berntson & Cacioppo, 2004), immune reactivity (Cohen & Hamrick, 2003; Manuck et al., 1991), cortisol responses (Buchanan et al., 2006; Roy et al., 2001; Vedhara et al., 2000), and neural responses in the hippocampus and prefrontal cortex (Pruessner et al., 2008; Wager et al., 2009). These findings support the idea that the type of event or

environment to which an individual is exposed is not directly tied to a specific neurobiological response or outcome.

Given variation in stress responses does not appear to be attached to a particular environment or event, this raises the question of what does drive variability in stress responses. Evidence suggests that individuals' neurobiological stress responses and outcomes are more influenced by their perception of an event or environment as adverse (Brosschot et al., 2017; Goldstein & McEwen, 2002; Lazarus, 1990; McEwen, 2019a; Peters et al., 2017; Sapolsky, 2015). To illustrate, perceptions of controllability and predictability are two of the primary factors that influence whether a potential stressor is perceived as stressful (Bollini et al., 2004; Henry, 1992; Mormede et al., 1988; Muller, 2012). In humans, individual differences in perceptions of control have been linked to differential cortisol responses to acute laboratory stress, differences in brain volume, and differences in brain reactivity to stress in regions, including the hippocampus, amygdala, and prefrontal cortex (Harnett et al., 2015; Hashimoto et al., 2015; Pruessner et al., 2005). Other factors that influence how individuals interpret potential stressors include whether individuals perceive themselves to be in a safe or dangerous environment and their perceptions of their coping resources (Blascovich, 2008; Jamieson et al., 2018; Mendes et al., 2001).

This means that perceptions of stress, and associated neurobiological responses, can occur in the absence of any specific identifiable environmental event. Examples of this include rumination over previous experience or events, anxiety about future events, and feelings of loneliness and social isolation despite having social relationships available (Cacioppo et al., 2011; Hilt & Pollak, 2013; Ottaviani et al., 2016; Paulesu et al., 2010). Together this research indicates that any approach aimed at understanding individual differences in outcomes after stress exposure needs to incorporate the factors that shape individuals' perceptions and interpretations of their events. Additionally, it suggests that variability in individuals' responses to the COVID-19 pandemic will be linked to their perception of the pandemic.

Perception, childhood adversity, and the COVID-19 pandemic

Given the important role of perception in influencing variability in stress responses, it is unlikely that all children will respond to the COVID-19 pandemic in a similar manner. There are a wide range of factors that likely shape and modulate children's perceptions and interpretation of environmental adversity, including perceived control and predictability, perceived safety, genetics, timing, intensity, and chronicity of adversity, and gene by environment interactions, among many others (Hostinar & Gunnar, 2013a; McEwen & McEwen, 2017; Smith & Pollak, 2020). Given the high risk of

unpredictability and social isolation associated with the COVID-19 pandemic, we focused on recent research, which suggest integral roles for perceptions of predictability and safety, particularly perceived safety related to presence of sensitive and supportive social relationships, in shaping children's interpretations of their early environment.

Perceptions of predictability Predictability is defined as the degree to which accurate predictions can be made about future events based on current ones. Contingency, often characteristic of predictability, refers to the likelihood of one event or action being followed by another (Frankenhuis, 2016; Hasson, 2017). As stated previously, perceptions of control and predictability are two of the most critical factors shaping perceptions of stress (Peters et al., 2017; Sapolsky, 2004). This is especially relevant to the COVID-19 pandemic, because it has been accompanied by many factors that increase individuals' risk for high levels of perceived unpredictability and uncontrollability. Limited knowledge, especially early in the pandemic, about the virus and its transmission, along with conflicting and rapidly changing information and recommendations from elected and public health officials, all have the potential to contribute to high perceived unpredictability and uncontrollability. In the literature linking stress in early childhood to development predictability has been of increasing interest. Given this, we focused our discussion on how perceptions of predictability shape development and the implications this has for how children may respond to the COVID-19 pandemic. However, we recognize predictability and controllability are highly interrelated (Peters et al., 2017; Sapolsky, 2015) and likely both play important roles in influencing children's interpretations of their early environment and the COVID-19 pandemic.

A lack of predictability in the environment leads to perceptions of uncertainty, volatility, and uncontrollability, which can result in extended activation of stress response systems (Soltani & Izquierdo, 2019). This extended activation alters brain growth and architecture in regions, such as the PFC, amygdala, and hippocampus, which undermines stress regulation and coping (Peters et al., 2017). Parent-child relationships are stereotypically repetitive, highly predictable, and marked by contingent parental responses—adult caregivers reliably respond to infant cries, comfort a child who is hurt, and provide support to a child who is dysregulated (Fisher et al., 2016; Hallers-Haalboom et al., 2017). Lack of predictable and contingent input from caregivers affects children's expectations of the environment, leading to uncertainty and perceptions of a lack of control and vulnerability (Chen & Baram, 2016; Harms et al., 2018).

Indeed, evidence from nonhuman animals suggests that predictable and contingent parental responding plays an important role in shaping learning processes, particularly social learning (Baram et al., 2012; Risbrough et al., 2018; Zajac

et al., 2019). In rodents, variations in maternal care, measured via licking and grooming behaviors, have been associated with poorer learning and memory (Barha et al., 2007; Liu et al., 2000) and altered stress regulation (Champagne et al., 2008; Weaver et al., 2004). These effects appear to be dependent on changes in hippocampal (Champagne et al., 2008; Liu et al., 2000), prefrontal (Monroy et al., 2010; Zhang et al., 2005), and amygdala (Caldji et al., 1998; Fries et al., 2004) synaptic plasticity, areas that together play an important role in both stress responsivity and learning and memory (Eichenbaum, 2017; McEwen, 2017a). Variations in maternal care are linked to epigenetic changes in glucocorticoid receptors (Turecki & Meaney, 2016; Weaver et al., 2004) and alterations in both glucocorticoid and mineralocorticoid receptor expression (Champagne et al., 2008; van Hasselt et al., 2012). This is suggestive of changes in HPA functioning. Additionally, these changes appear to be driven by the type of maternal behavior to which pups are exposed. Cross-fostering infants of low-licking and grooming mothers with high-licking and grooming mothers appears to reverse some of these changes at the neural and behavioral levels (Liu et al., 2000; Weaver et al., 2004). Recent evidence suggests that these effects are not solely due to changes in amount of high-licking and grooming behaviors mothers exhibit towards their pups, but rather the predictability of these behaviors (Risbrough et al., 2018). More fragmented maternal behaviors are associated with greater alterations in stress response systems (Davis et al., 2017; Glynn & Baram, 2019).

While little research has attempted to directly assess predictability of the early environment in humans, growing evidence indicates that predictability of parental inputs contributes to children's outcomes above and beyond the types of inputs. Predictability of parental inputs (measured by calculating entropy rate for maternal auditory, visual, and tactile inputs during the parent-child interaction) demonstrates a stronger association with children's cognitive outcomes than the type of inputs (measured through coded maternal sensitivity, positive regard, and intrusiveness during a parent-child interaction) (Davis et al., 2017). Longitudinal research assessing early influences on adolescents' externalizing behaviors finds that unpredictability of the environment during childhood, quantified using changes in maternal employment, changes in residence, and changes in cohabitation, is associated with increased externalizing behaviors in adolescence. However, type of adversity (in this study, SES) is not (Doom et al., 2016).

Research in rodents suggests that these effects are a result of altered functioning in prefrontal-hippocampal-amygdala circuits. Unpredictable maternal inputs are associated with altered connectivity between the medial PFC and amygdala (Bolton et al., 2018) and decreased dendritic arborization in the hippocampus (Molet et al., 2016). These effects on prefrontal-amygdala-hippocampal circuits are apparent

beyond effects produced by types of maternal inputs. Additionally, the effects of predictability on neural circuits are linked to PTSD and depressive-like behaviors as well as deficits in learning (Risbrough et al., 2018). Together, this body of work suggests that variation in the predictability, stability, and/or degree of contingent responding of adult caregivers is a factor in shaping children's responses to adversity through alterations in prefrontal cortical and subcortical stress response circuits. It indicates that assessment of predictability of early environments has the potential to provide increased insight into individual differences in the neurobiological effects of early adversity on child development—variability that is not captured when focusing solely on types of adverse events. This also means that children's experiences of stress associated with the COVID-19 pandemic will be at least partially shaped by the extent to which the pandemic shifts their perceptions of predictability.

Perceptions of safety Throughout the COVID-19 pandemic, public health officials have recommended individuals and policy makers enforce social distancing measures aimed at limiting transmission of the virus. Depending on where an individual lives, these policies have included closing of nonessential businesses, school closures and limitations of in-person education, limiting the number of people outside a single household who can gather, and encouraging all individuals to stay at home and limit interaction with nonhousehold members as much as possible. In addition to being inconsistent and unpredictable (i.e., schools closing, reopening, and then closing again), these measures have the potential to increase the risk of children feeling socially isolated and lacking social support. In adults, having high-quality and supportive social relationships is associated with reduced perceptions of stress as well as dampened psychological and physiological responses to laboratory stress (for review see Eisenberger, 2013; Hawley & Capitano, 2015). These effects are thought to in part result from high-quality and supportive social relationships acting as a signal of safety (Beckes & Coan, 2011; Brosschot et al., 2017). Together this suggests social distancing measures implemented in response to the COVID-19 pandemic may alter children's experiences of stress associated with the pandemic by shifting perceptions of safety.

Increasingly, research supports a role for perceived safety in contributing to variations in children's responses to stress. Safety/security in early childhood has been characterized in a variety of different ways. Parental presence/adult "buffering," sensitivity, responsiveness, and support are all thought to be cues of safety (Brody et al., 2019; Gunnar et al., 2015). Lack of parental input, through isolation, maternal separation, neglect, or abusive parenting behaviors are all thought to represent cues of lack of safety (Callaghan & Tottenham, 2016; Sanchez et al., 2015). Cues of safety early in development play an important role in engaging the prefrontal circuits that

inhibit threat response circuits (Porges, 2015). This in turn will have implications for how children perceive and interact with their environment later in life (Grupe & Nitschke, 2013; Mobbs et al., 2007).

Indeed, evidence from nonhuman primate and rodent models supports this, finding that early parental presence plays an important role in inhibiting neurobiological threat response systems. Both rodent pups and infant primates demonstrate reduced glucocorticoid release and decreased amygdala activation in the presence of the mother (Sanchez et al., 2015; Sullivan & Opendak, 2018). However, in cases of abusive maternal rearing, maternal presence does not appear to exhibit buffering effects. Under these circumstances, rodent pups and primate infants demonstrate enhanced glucocorticoid responses to stress (Moriceau et al., 2009; Sanchez et al., 2015) along with alterations in both the structure and function of the amygdala and prefrontal cortex (Nephew et al., 2017; Rincón-Cortés & Sullivan, 2016; Spinelli et al., 2009). From this literature, it is clear parental presence, a salient early cue of safety, is important to supporting typical development of the neurobiological stress response systems.

There is evidence indicative of similar early regulatory effects of parental presence on the development of stress response systems in humans (Gunnar et al., 2015; Tottenham, 2015). Parallel to the rodent and primate literatures, parental presence has been demonstrated to dampen both cortisol (Hostinar et al., 2015; Seltzer et al., 2010) and amygdala reactivity (Gee et al., 2014) to stress in children. There also is evidence that disruptions of these early relationships, through maltreatment, is associated with altered prefrontal-amygdala connectivity (Fan et al., 2014). These changes in connectivity have been linked to children's risk for psychopathology (Gee et al., 2013; Herringa et al., 2016). It is difficult to establish causality from this type of correlational research (i.e., these effects could be a result of shared genetic factors between parent and child). However, this literature in combination with the animal research described above points to alterations of typical development of prefrontal-amygdala circuits in children lacking early cues of safety that have implications for their behaviors and mental health.

Additionally, in cases of maltreatment or adversity where children still receive high levels of support from their parents, the effects of adversity on prefrontal-amygdala circuits are mitigated. Adolescents living in poverty show altered connectivity in prefrontal cortical networks involved in executive functioning and emotion regulation, but not if they reported having high levels of parent support (Brody et al., 2019). Additionally, support provided by other adults or peers may diminish some of the bio-behavioral effects of adversity. Reported social support from family and friends is associated with reduced risk of psychopathology in children who experience maltreatment (McLafferty et al., 2018; van Harmelen et al., 2016). Children who report having more higher quality

peer relationships and adolescents who spend more time with their friends outside of school demonstrate reduced neural activation in circuits involved in pain processing to social rejection (Masten et al., 2012; Will et al., 2016). Adolescents who report lower levels of perceived social isolation also report decreased levels of perceived stress and reduced risk for depression, anxiety, and poor physical health (Harris et al., 2013; Ladd & Ettekal, 2013; Vanhalst et al., 2013). This suggests that, at least in humans, individuals outside of the parent-child relationship may be able to supplement these safety cues when they break down.

Consistently incorporating assessment of factors that represent early cues of safety, such as parental and peer support, when studying how children respond to early adversity, has the potential to greatly illuminate the neurobiological mechanisms through which negative environments shape development. Additionally, taking this type of approach can inform our understanding of individual variability in responses to the COVID-19 pandemic. Children may not necessarily experience increased isolation merely, because they are spending more time at home and less time at school. Rather, their perceptions of isolation and lack of support are going to vary based on the support they have at home from parents and other family members, their own relationships with parents and family members at home, and their access to relationships with other peers and adults. These perceptions likely will provide more insight into any long-term developmental effects of the pandemic.

Developmental effects of the COVID-19 pandemic: Informing policy

There has rightfully been a large amount of attention focused on how the stress associated with the pandemic will affect children's development long term and how to develop policies aimed at aiding those children at greatest risk for chronic or extreme stress associated with the pandemic (Dalton et al., 2020; Prime et al., 2020; Richtel, 2020). Indeed, the risk of experiencing the pandemic as a chronic and extreme stressor is especially high for children already in environments characterized by inequality and disparity (Gassman-Pines & Gennetian, 2020; Kalil et al., 2020). These are children for whom school and other extracurricular activities may represent some of the few predictable, reliable, and controllable aspects in their life where they have access to supportive relationships with peers and adults. Removing these structures not only increases these children's risk of experiencing the pandemic as a chronic, extreme stressor but has the potential to exacerbate the stress they are exposed in the home and deplete any available coping resources they may have. This in turn increases the risk for chronic, extended activation of

psychological, neural, and behavioral stress response systems and long-term negative physical and mental health outcomes.

Despite the COVID-19 pandemic increasing risk for chronic and extreme stress, the research we have reviewed above suggests that the pandemic and concomitant policies, such as school closures, are not necessarily going to equate to negative developmental outcomes for all children later in life. Instead, it indicates that the effects of such a population level event will be shaped by how children are perceiving and interpreting this event rather than the event itself. Indeed, recent research using a machine learning approach to examine what kinds of events typically characterized as stressors are associated with a range of academic and health outcomes found that no one event was particularly predictive of children's outcomes (Salganik et al., 2020). Additionally, reported exposure to child abuse or neglect has recently been demonstrated to more predictive of children's mental health outcomes than exposure identified through court reports (Danese & Widom, 2020). Given parental inputs of predictability and support seem particularly critical for shaping perceptions of stress, it is likely that, for children who are in a home environment in which parents are continuing to provide support, love, and affection and attempting to maintain consistency and predictability, the long-term effects of the pandemic on development may be buffered.

Taking a perception focused topological approach to understanding the effects of COVID-19 on development means that we should be careful about assuming which children are more or at less risk. As illustrated above, there are a plethora of factors not tied to specific events or environmental circumstances that will influence children's meaning making related to the pandemic. This also means there is ample opportunity for adults to buffer and intervene against the negative effects of pandemic related stress. At the same time, there are widening disparities related to economic and racial inequality, especially in the United States. These disparities do place a large proportion of families at significantly greater risk of chronic, extreme stress associated with the pandemic (Boyras & Legros, 2020; Fortuna et al., 2020). These also are the families that likely will have decreased access to any policies or interventions developed to aid families and parents in establishing supportive, predictable, and controllable environments (Araya et al., 2018; Lê Cook et al., 2017). Economic and racial inequality has already been linked to a range of differential outcomes for families during the pandemic. Low-income and minority communities have significantly higher cases and deaths from COVID-19, decreased participation of children in virtual learning environments, and many of these parents are having to choose between a job and income or childcare for young children (Ahmed et al., 2020; Armitage & Nellums, 2020; Chen et al., 2020). It is critical that opportunities for intervention take into consideration the significant disparities associated with inequality in the United States.

In implementing policies designed to provide economic and social support, through income supplements, rent moratoriums or assistance, and food aid programs, such as the Supplemental Nutrition Assistance Program (SNAP), it can be helpful for both researchers and policy makers to examine how these policies may shift how parents and children are perceiving and coping with their environments. Policies that both provide much needed economic relief along with alleviating feelings of uncontrollability, unpredictability, and lack of safety will likely have the most efficacy. Of particular interest are strategies that work to provide families with the resources to establish reliability and predictability at home to aid in management of stress. Exploring how parents' own stress about economic resources, meals, and potential job loss can be alleviated and finding new options, such as outdoor classrooms or activities in which social distancing can be maintained to continue to allow for peer interaction and engagement, likely can aid in supporting families and children during the pandemic. These all represent areas in which intervention could potentially help to shift children's perceptions of the pandemic towards those of safety rather than threat. Indeed, interventions that demonstrate the most efficacy for improving outcomes for children in high-stress environments are those that focus on the level of the family or both the family and school (Bakermans-Kranenburg et al., 2003; Finlon et al., 2015). Additionally, interventions designed to directly shift how individuals perceive and attend to information in their environments, such as cognitive behavioral therapy (Butler et al., 2006; Hofmann et al., 2012), may have utility. In sum, the long-term developmental outcomes of children related to the COVID-19 pandemic are likely not going to be uniform and will be linked to other factors that shift children's perceptions of stress and threat associated with the pandemic. Better understanding what and how those function can help support and aid children in coping with any stress related to the COVID-19 pandemic.

Conclusions

Under typical circumstances, early life stress has long-lasting and substantive consequences for development, making it a considerable public health and humanitarian problem. The COVID-19 pandemic has only exacerbated these issues, placing children and families already at risk of long-term psychological, behavioral, and health outcomes due to chronic or extreme stress at even greater risk—a risk that increases the longer the pandemic continues. An evidence-based approach towards identifying those children and families that may be most at risk of chronic and extreme experiences of stress related to the pandemic is critical to implementing policies designed to provide these families with effective tools and interventions to aid them in coping with stress. Key to this mission

is elucidating the neural, physiological, and behavioral mechanisms involved in individual differences in children's outcomes.

Because growing evidence suggests that individual differences in stress responses are not accounted for by the events to which children are exposed, it is imperative that we adopt alternative approaches towards understanding early life stress. Incorporating assessment of factors, including predictability, controllability, and perceived safety, that shift perceptions of stress has promise towards illuminating the underlying mechanisms supporting variability in children's responses to stress (Smith & Pollak, 2020). Taking this type of approach towards understanding childhood stress has the potential to greatly inform our understanding of why children respond to the COVID-19 pandemic differently and which children may be in most need of policy aid and intervention. It also can aid in policy-level interventions, as it may be possible to identify large groups of individuals who may be more likely to lack predictability or social support—i.e., low SES children whose parents are having to choose between employment and childcare. Additionally, it can more broadly illuminate our understanding of the bio-behavioral mechanism through which early environments influence development and why children end up in different places after experiencing similar events. A topological approach that is oriented around children's perceptions, rather than just the external stimuli they encounter in the world, can provide avenues through which to think differently about how to support and aid families and children struggling to cope with the pandemic. Longer-term, it can provide researchers and policy makers with better tools to address the important societal issues linked to experiences of stress early in life.

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