



Influences of early-life stress on frontolimbic circuitry: Harnessing a dimensional approach to elucidate the effects of heterogeneity in stress exposure

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Abstract

Early-life stress confers profound and lasting risk for developing cognitive, social, emotional, and physical health problems. The effects of stress on the developing brain contribute to this risk, with frontolimbic circuitry particularly susceptible to early experiences, possibly due to its innervation with glucocorticoid receptors and the timing of frontolimbic circuit maturation. To date, the majority of studies on stress and frontolimbic circuitry have employed a categorical approach, comparing stress-exposed versus non-stress-exposed youth. However, there is vast heterogeneity in the nature of stress exposure and in outcomes. Recent forays into understanding the psychobiological effects of stress have employed a dimensional approach focused on experiential, environmental, and temporal factors that influence the association between stress and subsequent vulnerability. This review highlights empirical findings that inform a dimensional approach to understanding the effects of stress on frontolimbic circuitry. We identify the timing, type, severity, controllability, and predictability of stress, and the degree to which a caregiver is involved, as specific features of stress that may play a substantial role in differential outcomes. We propose a framework for the effects of these features of stress on frontolimbic development that may partially determine how heterogeneity in stress exposure influences this circuitry and, ultimately, mental health.

KEYWORDS

adolescence, adversity, brain development, childhood, early-life stress, infancy, mental health

1 | INTRODUCTION

A 2-year-old child is pulled from her mother's arms by border patrol officers. She watches as her mother is handcuffed and taken away while she is loaded into a van to be taken to a detention center. At the detention center, her care is infrequent and unreliable. She does not know if or when she will see her mother again. A 5-year-old watches as her neighbor is fatally shot. Between the ages of seven and sixteen, a young boy witnesses his mother experience severe domestic violence, roughly three to four times per week, with the worst event occurring at age eight.

Due to their exposure to early-life stress, each of these children is at increased risk for alterations in brain development and the emergence of internalizing and externalizing disorders, both in childhood and later in life. However, there is substantial heterogeneity across these exposures. It is possible that these stressors will differentially shape a child's brain development and long-term mental health. Moreover, symptom presentations may differ based on the stressor, and therapeutic approaches may need to be tailored to address these varied presentations. Importantly, the links between specific aspects of stress exposure and neurodevelopment and the

extent to which heterogeneity in stress exposure can inform prevention and intervention remain elusive.

Foundational research has demonstrated the profound and lasting consequences of early-life stress, but common methodological approaches have precluded a more nuanced understanding of the effects of specific features of stress. Researchers have often grouped children with a broad range of stressful experiences into a single “stress-exposed” sample (e.g., De Bellis et al., 1999) or examined individuals exposed to a single type of stress (e.g., individuals universally exposed to parental deprivation in institutionalized care settings; e.g., Tottenham et al., 2010; Zeanah et al., 2003). Due to the fact that multiple forms of stress have been integrated into one group or a single type of stress has been studied, it has been difficult to determine how specific features of stress may confer risk or resilience for long-term outcomes. Even within studies that have examined responses to a single type of stress (e.g., parental deprivation), the heterogeneity in exposure likely obscures important associations between features of stress exposure and neurobiological outcomes. To take exposure to institutionalized care as an example, children with this shared experience have been exposed to a wide range of different stressors (Csaky, 2009). Children included in post-institutionalized care samples have been placed into institutionalized care under varying circumstances, such as abuse, neglect, or death of a caregiver. Adding further complexity, some children who experienced institutionalized care were exposed to chronic trauma throughout childhood while others were exposed to a single event. As is evidenced by this example, past research on the effects of stress on frontolimbic circuitry has been limited in its ability to elucidate pathways between specific features of exposure and neurobiological outcomes. Overall, though, these approaches have afforded the field a valuable understanding of the broad architecture of the effects of early-life stress on the brain and behavior. This research has shown that frontolimbic circuitry is susceptible to the effects of early-life stress and that alterations in this circuitry likely contribute to the increased risk for psychopathology following stress (VanTieghem & Tottenham, 2018).

Building upon this work, researchers have advocated for using more multilevel, multivariate approaches to understand the complexity of stressful experiences and their effects on child development (e.g., Cicchetti & Toth, 1995; McCoy, 2013; Pynoos, Steinberg, & Piacentini, 1999). For example, recent studies examining the effects of stress exposure on the developing brain employ a dimensional approach (as opposed to categorizing individuals as exposed or not exposed to early-life stress), highlighting specific features of stress exposure that may differentially affect neural structure and function. These studies emphasize the importance of experiential (e.g., severity), environmental (e.g., type), and timing-related features (e.g., age of onset) (Belsky, Schlomer, & Ellis, 2012; Cameron, 2001; Edmiston et al., 2011; Gee & Casey, 2015; Lupien, McEwen, Gunnar, & Heim, 2009; McLaughlin, Sheridan, & Lambert, 2014; Miller et al., 2018; Peña, Nestler, & Bagot, 2019; Sheridan, Peverill, Finn, & McLaughlin, 2017; Tottenham & Sheridan, 2009; Úbeda-Contreras, Marín-Blasco,

Nadal, & Armario, 2018; Zhu et al., 2019) on the association between stress exposure and subsequent vulnerability across multiple domains of functioning in both human and animal models.

The following review highlights empirical contributions that inform a dimensional approach to understanding the effects of stress on neurodevelopment. We specifically focus on frontolimbic circuitry given the substantial evidence of the impact of stress on this circuitry and the importance of this circuitry for emotion regulation and long-term mental health. First, we briefly highlight decades of research that have observed robust changes in frontolimbic circuitry following stress across species. Grounded in this literature, second, we identify features including the timing, type, severity, controllability, and predictability of stress exposure, as well as the degree to which a caregiver is involved in stress exposure, as key dimensions to be considered in research on early-life stress and frontolimbic circuitry. Finally, we propose a framework for further testing how heterogeneity in these specific features of stress exposure and their interactions influence frontolimbic development.

2 | EFFECTS OF STRESS ON THE DEVELOPMENT OF FRONTOLIMBIC CIRCUITRY

Prior to reviewing empirical findings on specific dimensions of stress exposure, we briefly summarize the extant literature detailing the effects of stress on the development of frontolimbic circuitry, which has primarily taken a categorical approach to delineating differences between stress-exposed and non-stress-exposed individuals. Animal studies provide converging evidence for the susceptibility of amygdala–prefrontal–hippocampal circuitry to environmental stress, which may be due to the dense innervation of these structures with glucocorticoid receptors (De Kloet, Vreugdenhil, Oitzl, & Joëls, 1998; Honkaniemi et al., 1992; Lupien et al., 2009; Plotsky et al., 2005; Wang et al., 2014; Woolley, Gould, & McEwen, 1990) and the specific timing of frontolimbic circuit maturation (see Tottenham & Sheridan, 2009 and Gee & Casey, 2015 for review). Chronic stress is associated with increased dendritic arborization and spine density of the amygdala (Mitra, Jadhav, McEwen, Vyas, & Chattarji, 2005; Vyas, Bernal, & Chattarji, 2003; Vyas, Mitra, Rao, & Chattarji, 2002), and conversely, with atrophy in regions implicated in downregulating the stress response, such as the medial prefrontal cortex (mPFC) and the hippocampus (Magarinos, Verdugo, & McEwen, 1997; Radley, Arias, & Sawchenko, 2006; Vyas et al., 2002). Animal models of early-life stress, such as maternal separation and abusive maternal care, demonstrate that early-life stress also affects connectivity of frontolimbic circuitry (Eiland & Romeo, 2013; Ishikawa, Nishimura, & Ishikawa, 2015; Malter Cohen et al., 2013; Rainekei, Cortés, Belnoue, & Sullivan, 2012). For example, stress exposure is associated with alterations in the development of projections between the amygdala and prefrontal cortex (PFC), which are in

turn associated with long-term alterations in frontolimbic circuitry in adult rats (Eiland & Romeo, 2013; Ishikawa et al., 2015).

In humans, stress is similarly associated with structural differences in frontolimbic circuitry. Individuals exposed to early-life stress show differences in amygdala volume, though evidence has been mixed, with some studies showing larger volume (Heyn et al., 2018; Keding & Herringa, 2015; Mehta et al., 2009; Tottenham et al., 2010) and others showing smaller volume (Hanson, Nacewicz, et al., 2015; McLaughlin et al., 2016). Children exposed to stress also exhibit relatively decreased prefrontal, striatal, and hippocampal volumes compared to their non-stress exposed counterparts (Dannowski et al., 2012; Edmiston et al., 2011). Thus, findings in the human developmental literature generally correspond to cross-species observations of amygdala hypertrophy and atrophy of brain structures involved in top-down regulation of the fear response.

Paralleling these structural changes, children and adults with early-life stress exposure show functional alterations in frontolimbic circuitry (Weems, Russell, Neill, & McCurdy, 2019). Children and adults with histories of exposure to stress exhibit heightened amygdala reactivity to emotional and threat-related cues (Dannowski et al., 2013; Gee, Gabard-Durnam, et al., 2013; van Harmelen et al., 2013; Tottenham et al., 2011) and increased activation in the mPFC and ventrolateral PFC in response to emotional faces and tasks that require top-down control of amygdala activation (Ganzel, Kim, Gilmore, Tottenham, & Temple, 2013; Garrett et al., 2012; Godinez, McRae, Andrews-Hanna, Smolker, & Banich, 2016). Consistent with findings in rodents (e.g., Eiland, Ramroop, Hill, Manley, & McEwen, 2012), relative to non-stress exposed counterparts, early-life stress is also associated with alterations in frontolimbic interactions. Following stress exposure, individuals exhibit atypical patterns of amygdala functional connectivity with the PFC (Burghy et al., 2012), medial prefrontal gyrus (Jedd et al., 2015), dorsal anterior cingulate cortex (ACC) (Wolf & Herringa, 2016), pregenual cingulate (Fan et al., 2014; Marusak, Martin, Etkin, & Thomason, 2015), and subgenual cingulate (Herringa et al., 2013). Taken together, these findings suggest that early-life stress is associated with changes in both the structure and function of frontolimbic circuitry.

3 | IDENTIFYING DIMENSIONS OF STRESS EXPOSURE THAT MAY INFLUENCE FRONTOLIMBIC DEVELOPMENT

Building on the extant literature that has clearly documented the effect of early-life stress on frontolimbic circuitry, the current review focuses on dimensions of stress exposure for which there is an accumulation of empirical evidence suggesting the potential influence of a given feature on neurobiological outcomes in a developmental context. Each of these dimensions is first reviewed independently given sufficient evidence of its association with frontolimbic circuitry following stress. However, certain factors may not always be dissociable, and two or more dimensions may converge in specific instances (e.g., when a type of stress such as neglect is inherently

characterized by caregiver involvement). In our integrated framework that follows this section, we carefully consider interactions between dimensions. In addition, it must be noted that the following list of factors is not a comprehensive list. Additional important features such as cultural context, proximity to a stressful event, parental exposure to stress (and resulting expectations and beliefs about child development following stress), prenatal environments and exposure to stress in utero, as well as positive childhood experiences, genetic and epigenetic differences, child temperament, and other individual-level protective factors that counteract the potentially detrimental effects of stress are also likely to contribute to heterogeneity in neurobiological outcomes following early-life stress exposure. Although the task of relating specific individual- or exposure-level factors with neurobiological outcomes may appear intractable given the multivariate nature of early environments and complexity of development, clearly delineating the ways in which specific features of a given stress exposure may affect development is an important step in understanding this complex process. Here we chose to focus on specific features of stress exposure itself. As more research is conducted in these areas, the review and proposed framework are designed to accommodate a growing literature. Table 1 provides a summary of selected relevant evidence reviewed for each dimension of interest.

3.1 | Timing

Frontolimbic circuitry undergoes dynamic changes across the course of development (Casey, Heller, Gee, & Cohen, 2019; Gabard-Durnam et al., 2014; Gee et al., 2018; Gee, Humphreys, et al., 2013; Hare et al., 2008; Wu et al., 2016). As such, the specific state of the developing brain at the time of stress exposure likely impacts the short- and long-term repercussions of stress (Cameron, 2001; Eiland & Romeo, 2013; Lupien et al., 2009; Sabatini et al., 2007). Indeed, research to date highlights the role of developmental timing as a critical factor that may moderate the impact of stress on frontolimbic circuitry across species. For a detailed review on the impact of stress exposure that occurs during different developmental periods, see Gee & Casey (2015).

Various studies show differential effects of stress exposure on frontolimbic circuitry depending on the timing of stress exposure. Particularly compelling evidence on timing comes from the Bucharest Early Intervention Project (BEIP), a randomized controlled trial of children in institutional care that randomly assigned children to be placed in either foster care settings or to remain in institutionalized care settings (Nelson et al., 2007). Findings from the BEIP and other studies of institutionalized care suggest that parental deprivation occurring between 0 and 24 months, specifically, is especially detrimental for longer-term outcomes (Gunnar, Frenn, Wewerka, & Van Ryzin, 2009; McLaughlin et al., 2015; Rutter, 1998). These studies highlight potential sensitive periods during which stress exposure may have the strongest influences and emphasize the importance of considering the effects of stress on frontolimbic circuitry from

TABLE 1 Key findings reviewed for each dimension of interest, including how each dimension is typically assessed and study-specific results

Dimension of stress exposure	How dimension is typically assessed	General findings	References	Specific results
<i>Timing</i>	<ul style="list-style-type: none"> Retrospective report of age(s) at which event occurred Prospective documentation of events as they occur at specific ages Cut-off ages/ age ranges sometimes used (e.g., before age 3) 	<ul style="list-style-type: none"> Earlier age of onset associated with increased amygdala response Earlier age of onset associated with smaller hippocampus volume Later intervention associated with larger amygdala volume Early deprivation associated with early maturation of frontolimbic circuitry 	<p>Bath et al. (2016)</p> <p>De Bellis et al. (1999)</p> <p>De Bellis & Kuchibhatla (2006)</p> <p>Gee, Gabard-Durnam, et al. (2013)</p> <p>McCrary et al. (2013)</p> <p>Mehta et al. (2009)</p> <p>Tottenham et al. (2010)</p> <p>Tupler & De Bellis (2006)</p>	<p>In mice, fragmented maternal care was associated with early developmental shift from growth processes to maturation in hippocampus</p> <p>Earlier age of onset of maltreatment was associated with lower intracranial volume</p> <p>Earlier age of onset of maltreatment was associated with lower cerebellar volume</p> <p>Previously institutionalized children showed earlier development of mature pattern of amygdala-PFC connectivity, which was associated with reduced anxiety</p> <p>Earlier age of onset of emotional maltreatment and neglect was associated with increased reactivity in the amygdala for both angry and happy faces</p> <p>Longer period of previous institutionalization was associated with smaller volume of the left amygdala</p> <p>Later adoption from institutional care was associated with larger amygdala volume</p> <p>Earlier age of onset of maltreatment was associated with lower hippocampal volume</p>
<i>Severity</i>	<ul style="list-style-type: none"> Self- or parent-report ("subjective") ratings collected from reporter Interviewer ("objective") ratings less frequently collected at time of interview or in post-hoc review 	<ul style="list-style-type: none"> Mixed results regarding the association between severity of stress exposure and adult volumes of the amygdala and hippocampus Increased severity associated with increased adult amygdala-pregenual ACC connectivity Increased severity associated with increased amygdala-PCC and anterior medial PFC-PCC connectivity in infants 	<p>Dannowski et al. (2012)</p> <p>Fan et al. (2014)</p> <p>Graham et al. (2015)</p> <p>Pechtel et al. (2014)</p> <p>Veer et al. (2015)</p>	<p>Increased severity of self-reported childhood trauma exposure was associated with reduced gray matter volume in the hippocampus, insula, orbitofrontal cortex, anterior cingulate gyrus, and caudate</p> <p>Higher self-reported childhood exposure to emotional abuse was associated with reduced resting-state functional connectivity between the amygdala and pregenual ACC in adult males</p> <p>Increased postnatal interparental conflict was associated with increased amygdala-PCC and anterior medial PFC-PCC connectivity in infants</p> <p>Increased severity of early childhood maltreatment was associated with larger amygdala volume in adulthood</p> <p>Increased severity of childhood sexual abuse was associated with reduced amygdala volume in adulthood but unrelated to hippocampal volume</p>
<i>Type</i>	<ul style="list-style-type: none"> Endorsement of specific types of events either at individual event level (e.g., sexual abuse, physical abuse, neglect) or at category level (e.g., experience of threat vs. experience of deprivation) 	<ul style="list-style-type: none"> Different types of events have differing impact on white matter microstructure in frontostriatal tracts Reductions in PFC volume linked to specific types of stress Stronger negative amygdala-PFC connectivity in response to threat-related stress 	<p>Dennison et al. (2019)</p> <p>Edmiston et al. (2011)</p> <p>Kaiser et al. (2018)</p> <p>Pevevill et al. (2019)</p> <p>Sheridan et al. (2017)</p>	<p>Maternal deprivation, emotional deprivation, and exposure to trauma (i.e., child abuse and domestic violence) had distinct influences on the integrity of white matter microstructure in frontostriatal tracts</p> <p>Physical abuse, physical neglect, and emotional neglect were linked with distinct rostral prefrontal reductions</p> <p>Increased severity of threat-related early-life stress was associated with more strongly negative static amygdala-dorsolateral PFC resting-state functional connectivity and increased dynamic amygdala-rostral ACC dynamic resting-state functional connectivity</p> <p>Children exposed to physical, sexual, or emotional abuse showed increased negative vmPFC-amygdala task-related functional connectivity</p> <p>After adjusting for abuse, lower parental education was linked with inefficient recruitment of the parietal and prefrontal cortex in adolescents during high working memory load</p>

(Continues)

TABLE 1 (Continued)

Dimension of stress exposure	How dimension is typically assessed	General findings	References	Specific results
<i>Control</i>	<ul style="list-style-type: none"> Self or parent report of experience of control during event 	<ul style="list-style-type: none"> Activation of the mPFC linked to the differentiation between controllable and uncontrollable stressors Amygdala-striatum connectivity linked to the differential effect of stressor controllability 	<p>Amat et al. (2008)</p> <p>Boeke et al. (2017)</p> <p>Kubala et al. (2012)</p>	<p>In rats, activation of the vmPFC during an uncontrollable stressor resulted in a behavioral response typical of response to a controllable stressor</p> <p>mPFC, striatum, and amygdala-striatum projections mediated the effect of control on decreased physiological reactivity to future stress</p> <p>In rats, exposure to an inescapable, but not an escapable, stressor activated the dorsal raphe nucleus, and lesions in the mPFC eliminated this effect</p>
<i>Predictability</i>	<ul style="list-style-type: none"> Self or parent report of experience of predictability during event Behavioral coding of maternal predictability during mother-child interactions 	<ul style="list-style-type: none"> Unpredictable caregiving associated with worsened performance on hippocampus-dependent tasks In mice, fragmented parental care linked with persistent alterations in amygdala circuitry 	<p>Brunson et al. (2005)</p> <p>Davis et al. (2017)</p> <p>Malter Cohen et al. (2013)</p>	<p>In rats, fragmented maternal care early in life led to late-onset, progressive dendritic atrophy and mossy fiber expansion in the hippocampus</p> <p>In humans and rats, exposure to unpredictable maternal sensory signals early in life was associated with worse performance on hippocampus-dependent cognitive tasks</p> <p>Early exposure to fragmented parental care was associated with emotion dysregulation in humans and with persistent alterations in amygdala circuitry and anxiety-like behavior in mice</p>
<i>Caregiver involvement</i>	<ul style="list-style-type: none"> Self or parent report of caregiver presence during or role in stress exposure 	<ul style="list-style-type: none"> Abuse perpetrated by a caregiver linked with reductions in PFC volume Prior institutionalization associated with heightened amygdala reactivity Later adoption linked with larger amygdala volume Previous institutionalization associated with earlier maturation of amygdala-PFC connectivity 	<p>Callaghan et al. (2019)</p> <p>Edmiston et al. (2011)</p> <p>Gee, Gabard-Durnam, et al. (2013)</p> <p>Malter Cohen et al. (2013)</p> <p>Mehta et al. (2009)</p> <p>Opendak et al. (2019)</p> <p>Tottenham et al. (2010)</p> <p>Tottenham et al. (2011)</p>	<p>Children who had previously experienced institutional care did not show the reductions in amygdala reactivity to parent cues exhibited by children in the comparison group</p> <p>Physical abuse, physical neglect, and emotional neglect perpetrated by caregivers were linked with distinct reductions in rostral PFC volume</p> <p>Previously institutionalized children showed earlier development of mature pattern of amygdala-PFC connectivity, which was associated with reduced anxiety within this maternally deprived group</p> <p>Early exposure to disorganized parental care was associated with emotion dysregulation in humans and with persistent alterations in amygdala circuitry and anxiety-like behavior in mice</p> <p>Longer period of previous institutionalization was associated with larger volume of the amygdala</p> <p>In rats exposed to early abuse, maternal presence did not lead to the expected reduction in mesolimbic dopamine engagement and blockage of threat learning</p> <p>Later adoption from institutional care was associated with larger amygdala volume</p> <p>Previously institutionalized children showed heightened amygdala reactivity to emotional cues</p>

Abbreviations: ACC, anterior cingulate cortex; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

a developmental perspective. In addition, several studies suggest that stress exposure may have particularly strong influences on longer-term amygdala structure when it occurs in late childhood and earlier adolescence, relative to late adolescence (Evans et al., 2016; Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014). For a comprehensive review of timing-specific effects of stress on amygdala development, see Tottenham & Sheridan (2009).

In addition to age of stress exposure, naturally occurring variability in the duration of exposure has allowed researchers to begin to test the long-term effects of chronic stress that occurs early in life. Within previously institutionalized populations, a longer length of stay in an institution (or later adoption) is associated with larger amygdala volumes years after the end of institutionalized care (Mehta et al., 2009; Tottenham et al., 2010), suggesting that

chronicity of stress has implications for neurobiological outcomes. Drawing from a broader sample of stress-exposed individuals, alterations in frontolimbic structure and function are also associated with the age at which stress onsets or with the duration of stress experienced (McCrary et al., 2013). Greater reductions in hippocampal volumes are associated with an earlier age of stress onset (Tupler & De Bellis, 2006). Although findings to date suggest that the cumulative number of years of exposure to a stressor is linearly related to the severity of neurobiological consequences, it remains difficult to dissociate the effects of an earlier age of onset from a longer duration of stress.

Despite recent progress in understanding how the timing of stress affects structural and functional changes in frontolimbic circuitry across development, identifying the more precise mechanisms linking early-life stress with long-term outcomes remains an important area of inquiry. One hypothesized mechanism suggests that stress exposure that occurs early in life may accelerate the timing of frontolimbic development (Callaghan & Tottenham, 2016b), consistent with broader theories suggesting that early-life stress accelerates biological aging (Belsky, 2019; Belsky, Steinberg, & Draper, 1991; Ellis, Figueredo, Brumbach, & Schlomer, 2009; Rickard, Frankenhuis, & Nettle, 2014). As one example, evidence from typically reared youth suggests a shift from positive amygdala-mPFC functional connectivity in childhood to negative amygdala-mPFC functional connectivity in adolescence, with this negative pattern being more consistent with mature regulation in this circuitry (Gee, Humphreys, et al., 2013). In contrast, post-institutionalized children and adolescents both exhibit a more mature pattern of negative amygdala-mPFC connectivity (Gee, Gabard-Durnam, et al., 2013), indicating the possibility of precocious maturation following early-life stress. This pattern of findings is consistent with rodent studies documenting accelerated development of frontolimbic circuitry in adverse caregiving environments (Bath, Manzano-Nieves, & Goodwill, 2016). Such acceleration may represent a shift in, or the premature closure of, a sensitive period that occurs in service of allowing individuals to adapt to an early harsh environment (Gee, Humphreys, et al., 2013); however, much remains unknown about the function of these changes in timing, and there are likely to be long-term consequences of such acceleration. Another potential mechanism underlying the timing-related effects of early-life stress exposure on development is stress sensitization, by which stress exposure during a certain phase of development may render individuals more vulnerable to subsequent stress exposure (Espejo et al., 2007). As one example, stress during childhood may be more strongly linked with poorer outcomes during adolescence when individuals have been exposed to severe caregiving-related stress in infancy, whereas stable and nurturing caregiving experiences during infancy may buffer against the consequences of later childhood stress (Wade et al., 2019). Further research is needed to delineate whether exposure to early-life stress sensitizes individuals to experience more detrimental neurobiological effects of later stress exposure.

In summary, both animal and human studies provide evidence for stress-related alterations in the structure and function of

frontolimbic regions, namely hypertrophy of the amygdala and atrophy of brain structures involved in top-down regulation of the amygdala, elevated amygdala reactivity and PFC activation, and atypical patterns of frontolimbic connectivity. To date, empirical studies assessing the effects of stress on the development of frontolimbic circuitry offer evidence for a linear association between cumulative duration of exposure and negative neurobiological outcomes, as well as for potential non-linear sensitive periods across development. Although the majority of research has focused on group differences between stress-exposed and non-stress-exposed youth, converging evidence across species suggests that within the stress-exposed group, the timing of stress exposure is meaningfully associated with alterations in frontolimbic development. Precocious maturation of frontolimbic circuitry may help the organism to reprioritize neurodevelopmental tasks in species-unexpected environments. Exposure to stress during specific developmental periods may render individuals more vulnerable to the effects of subsequent stress exposure.

Critical questions remain about the effects of developmental timing of stress exposure on frontolimbic circuitry. Future research that aims to dissociate the effects of chronic exposure and earlier age of exposure onset on frontolimbic circuitry will be necessary to establish whether there is a unique effect of chronicity on the developing brain. In addition, neurodevelopmental effects of stress exposure may be obscured by the fact that studies often assess these effects in mixed-age samples when the brain is changing dynamically. It is therefore difficult to dissociate effects of timing of stress exposure from the progressive nature of neurodevelopmental change (Heyn et al., 2018; Weems, Klabunde, Russell, Reiss, & Carrión, 2015). Conducting future research in single-age cohorts of children will be an important step in elucidating these effects.

Finally, timing is one feature that may be particularly important to consider in the context of other specific dimensions of stress. The interaction between timing and other features, such as the severity or type of stressor, may differentially confer risk or resilience for frontolimbic development (see sections below for initial work highlighting the importance of these interactions). Future research that takes into account the onset and duration of the stressor, as well as other features of that stress, will be poised to uncover the complex associations between stress and frontolimbic development.

3.2 | Severity

As an alternative approach to grouping individuals based on whether or not they were exposed to one or more stressful events, severity is frequently operationalized as either the number of stressful exposures or as a continuous score of severity of exposure to stress. Investigations of severity consistently suggest that more severe stress exposure (either in the form of a more severe single exposure, or of more cumulative exposure) has more detrimental effects on the developing brain.

With regard to brain volume, more severe reports of childhood maltreatment are linked with reduced gray matter volume in the hippocampus (Dannowski et al., 2012). Similarly, the severity of an

individual's exposure to a broad array of stress exposures ranging from exposure to domestic violence to physical and sexual abuse accounts for an estimated 27% of the variance in amygdala volume during childhood (Pechtel et al., 2014), and higher severity of childhood sexual abuse is associated with lower amygdala volume (Veer et al., 2015). In addition to volumetric differences that scale with severity of exposure, higher levels of exposure to early emotional abuse are associated with lower resting-state functional connectivity between the amygdala and the pregenual ACC (Fan et al., 2014). Among infants, more severe interparental conflict since birth is associated with greater connectivity of the posterior cingulate cortex with the mPFC and amygdala (Graham, Pfeifer, Fisher, Carpenter, & Fair, 2015). This work highlights the need for an increasing focus on network and circuit-based approaches to understand the effects of severity of stress exposure on the function and connectivity of frontolimbic circuitry.

The degree of severity of stress exposure in childhood also appears to have a lasting impact on structure and function of frontolimbic circuitry into adulthood. Exposure to more than two Adverse Childhood Experiences (ACEs; Felitti et al., 1998) is linked with smaller ACC and caudate nuclei volumes, but not with altered hippocampal volume, in adulthood, relative to adults without exposure to any ACEs (Cohen et al., 2006). On a continuous scale, these volumes are correlated with the total number of ACEs to which an individual was exposed (Cohen et al., 2006). Moreover, higher severity of childhood maltreatment is associated with elevated amygdala response to threat-related and sad facial expressions (Dannowski et al., 2012, 2013).

In summary, more severe childhood stress exposure is associated with reduced gray matter volumes in the limbic system and higher amygdala activation to negatively valenced emotional stimuli. However, little is known about the specific mechanisms by which more severe exposure confers greater risk for volumetric or activation-related changes in the brain. Additionally, it is unclear whether discrete instances of severe stress exposure affect brain development via differential pathways relative to more chronic exposure to severe stress. Future research that specifically examines the severity of stress exposure while controlling for other features of the stress may help to shed light on these remaining questions.

3.3 | Type

Early research on childhood stress often examined single types of stress in isolation or examined the effect of a cumulative number of stress exposures; however, more recent studies increasingly have compared the effects of specific subtypes of early-life stress to better understand how they might differentially influence frontolimbic development and behavior (e.g., Fujisawa et al., 2018; Teicher et al., 2018).

As one example, physical abuse, physical neglect, and emotional neglect have been differentially linked with alterations in gray matter volume within frontolimbic circuitry during adolescence (Edmiston et al., 2011). Physical abuse, physical neglect, and emotional neglect

are all associated with smaller rostral PFC volumes, whereas reduced gray matter volume in other regions (i.e., dorsolateral PFC, subgenual PFC, OFC, insula, striatum, amygdala, hippocampus, cerebellum) is specific to one or two of these subtypes of stressors, and sexual abuse and emotional abuse are not associated with any gray matter alterations. Similarly, research on white matter connectivity has identified differential associations with distinct types of stress, such that abuse (i.e., exposure to domestic violence and maltreatment) is associated with reduced white matter integrity in the external capsule, whereas other types of stressors (i.e., food insecurity and caregiver neglect) are associated with increased white matter integrity in the uncinate fasciculus among youth (Dennison et al., 2019). In addition to evidence for differential effects of abuse versus neglect and of subtypes of abuse on neural function (Blair et al., 2019), these findings provide examples of the differential impact of stress type on frontolimbic structural development.

Building on research on the effects of specific types of stress, an influential line of work has proposed a key distinction between stress exposure characterized by threat (i.e., involving the presence of harm) versus deprivation (i.e., involving the absence of expected cognitive or social inputs from the environment) (McLaughlin & Sheridan, 2016; McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014). Current theory posits that exposure to threat is associated with alterations in fear learning and emotion processing, whereas exposure to deprivation is associated with deficits in cognitive and executive functioning. Additionally, initial evidence suggests that experiences of threat versus deprivation may differentially influence neural development underlying these processes, though fewer studies have directly compared exposures characterized by these dimensions. Deprivation is associated with altered functional recruitment of the parietal cortex and PFC under high working memory load among adolescents, even when controlling for abuse (Sheridan et al., 2017). Threat-related stress exposure is often linked with alterations in prefrontal-amygdala interactions (Kaiser et al., 2018; Peverill, Sheridan, Busso, & McLaughlin, 2019), though these studies have not typically controlled for experiences of deprivation, making it difficult to assess the specificity of effects. Finally, altered fear learning and emotion regulation may be more closely associated with early exposures to threat, whereas deficits in cognitive control may be more strongly associated with early exposures to deprivation (Lambert, King, Monahan, & McLaughlin, 2017; Machlin, Miller, Snyder, McLaughlin, & Sheridan, 2019).

Additional studies examining effects of specific types of stress exposure on frontolimbic circuitry have highlighted important interactions between type and other factors such as sex or timing. For example, adult male hippocampal volume is associated with neglect, but not abuse, whereas female hippocampal volume is associated with abuse, but not neglect (Teicher et al., 2018). Demonstrating interactions between the type of stress and timing of exposure, a recent study found that physical maltreatment during childhood (ages 3–6) is linked with blunted amygdala response, whereas peer emotional abuse during adolescence (ages 13 and 15, specifically) is linked with increased amygdala response (Zhu et al., 2019).

In summary, there is mounting evidence that the type of stress exposure to which an individual is exposed is important for understanding specific neurobiological outcomes. However, in a substantial portion of youth, there is a high degree of co-occurrence among different types of adverse experiences (Dong et al., 2004; Finkelhor, Ormrod, & Turner, 2007; Green et al., 2010; McLaughlin et al., 2012). This co-occurrence makes it challenging to disentangle the long-term neurobiological effects of a single type of stress exposure on frontolimbic development. Future research comparing specific stressors to one another, as well as to poly-victimization via complex trauma, might be useful in identifying common and unique neurobiological outcomes associated with type of stress. Relatedly, central to the dissociation between threat versus deprivation, it is important to consider the effects of experiences that have elements of both threat and deprivation (e.g., witnessing domestic violence that results in removal of a primary caregiver from the home; dyadic parent-child exposure to an accident in which a caregiver dies). Future research will benefit from examining the complexity of stress subtypes and exposures with a mixture of characteristics. Finally, studies to date examining the impacts of specific types of stress on frontolimbic circuitry suggest important type-timing interactions that may be critical to understanding sensitive periods of risk. Therefore, continuing to promote multivariate approaches by assessing for multiple features of stress in a single study (e.g., type and timing) will improve the precision with which researchers can develop mechanistic conceptualizations of the specific impact of stress on neurobiological development.

3.4 | Control

Building on foundational theoretical work (Averill, 1973; Lefcourt, 1982; Maier & Seligman, 1976; Pervin, 1963), cross-species evidence suggests that having the ability to exert control over a stressor (i.e., controllability by altering the intensity, duration, onset, or termination of a stressful event) may play an important role in contributing to outcomes following early-life stress exposure. Research in both animals (Amat, Alekseev, Paul, Watkins, & Maier, 2010; Amat, Paul, Zarza, Watkins, & Maier, 2006; Maier & Watkins, 2005, 2010; Seligman & Maier, 1967; Weiss & Simson, 1986) and humans (Hartley, Gorun, Reddan, Ramirez, & Phelps, 2014) has shown that previous exposure to controllable stress may increase both plasticity in behavioral responses to subsequent stress as well as accessibility of more adaptive profiles of stress responding in multiple contexts related to stress exposure, fear learning, and social interaction. Relative to exposure to uncontrollable stress, evidence suggests that exposure to controllable stress may modulate such behavioral responding to subsequent stress through alterations in frontolimbic circuitry.

Animal research has provided foundational evidence for the idea that frontolimbic circuitry plays a key role in the effects of stressor controllability. In adult animals, the experience of controllable stress may determine future behavioral responses to

stress by blunting activation of the dorsal raphe nucleus (DRN) and 5HT1A activation via projections between the DRN and mPFC (Baratta et al., 2007; Kubala, Christianson, Kaufman, Watkins, & Maier, 2012), and in turn, the amygdala (Amat et al., 2006; Baratta et al., 2007; Baratta & Maier, 2019; Hartley et al., 2014; Liu, Tang, & Sanford, 2009). Exposure to controllable stress also may yield plasticity that enables subsequent stressors to more easily recruit the mPFC, promoting increased prefrontal regulation of the amygdala even when an individual does not have control over a subsequent stressor (Amat, Paul, Watkins, & Maier, 2008; Maier & Watkins, 2010). Projections between the lateral nucleus, basal nucleus of the amygdala, and striatum also appear to be central to aversively motivated action in rodents. Current theory posits that the direct, non-reciprocal projection from the basolateral amygdala to the ventral striatum transmits critical information about avoidance of an aversive stimulus (Ramirez, Moscarello, Ledoux, & Sears, 2015) and that connections between the prelimbic cortex and ventral striatum also mediate avoidance (Bravo-Rivera, Roman-Ortiz, Montesinos-Cartagena, & Quirk, 2015).

Consistent with findings in rodents, human studies suggest that control over a stressor modulates both short- and long-term responses to stress via alterations in frontolimbic circuitry. Initial investigations in adult humans highlight the centrality of the mPFC, striatum, and projections between the amygdala and the striatum in mediating the effect of control on reduced physiological reactivity to future stress (Boeke, Moscarello, LeDoux, Phelps, & Hartley, 2017). Recent human models propose that projections from the lateral to central amygdala facilitate reactive responses to threatening cues. In contrast, projections from the lateral amygdala to the basal amygdala and subsequent projections from basal amygdala to the ventral striatum and ventromedial prefrontal cortex (vmPFC) facilitate a more proactive response to threatening stimuli (Moscarello & Hartley, 2017). This distinction is also in line with evidence that functional synchronization of the mPFC, striatum, and amygdala predicts an individual's ability to successfully engage active coping behaviors in the face of the threat of shock (Collins, Mendelsohn, Cain, & Schiller, 2014). Finally, suggesting ecological validity and translation to contexts outside of the laboratory, individuals who showed increased activation of the vmPFC during exposure to uncontrollable stress report using active coping strategies to a greater degree in their daily lives (Sinha, Lacadie, Constable, & Seo, 2016). Taken together, these findings suggest that the experience of controllable stress may inoculate an individual against the harmful effects of subsequent exposure to stress through persistent modulation of frontolimbic neurocircuitry underlying stress reactivity.

In conclusion, studies of stressor controllability in rodents and human adults support the idea that experiencing control over a stressor may buffer against the negative effects of subsequent stress exposure. The ability to exert control over a stressor appears to moderate the effects of stress on frontolimbic circuitry, such that exposure to controllable stress facilitates adaptive coping and promotes long-term resilience. However, much remains

unknown about the mechanisms linking control to subsequent outcomes. It is possible that previous interactions with an environment characterized by high levels of control inform an individual's expectations of future control and may increase the deployment of adaptive coping strategies when an individual is presented with novel or uncertain environments (Averill, 1973; Lefcourt, 1982; Moscarello & Hartley, 2017). Future research could test the effects of control on individuals' cognitive, behavioral, and neural responses to stress to better understand the ways in which control may promote resilience during subsequent exposure to uncontrollable stress.

Finally, although the majority of research on control during stress exposure has been conducted in adult humans or animals, some evidence in rodents provides insight into the potential role of exposure to controllable stress during development. Rodents exposed to controllable stress during the period akin to adolescence show improved behavioral responses to stress in adulthood (Kubala et al., 2012). Thus, adolescence may be a period during which exposure to controllable stress has a stronger impact on later functioning, consistent with prior behavioral evidence of heightened active avoidance during adolescence (Bauer, 1978). Moreover, given that adolescence is characterized by dynamic changes in frontolimbic circuitry (Casey, Galván, & Somerville, 2016; Fareri et al., 2015; Gee, Humphreys, et al., 2013; Heller, Cohen, Dreyfuss, & Casey, 2016) that may mediate the effects of stressor controllability, research in humans would benefit from testing the effects of control over stress exposure during this unique developmental window. Furthermore, examining the interaction between control and other features of stress exposure during specific developmental stages may be particularly meaningful for identifying ways to leverage control to promote resilience. For example, contingent responding by caregivers during infancy may promote expectations of control (Gunnar, 1980; Lewis & Goldberg, 1968) in ways that shape stress responding and frontolimbic development later in life.

3.5 | Predictability

Based on a rich translational literature, the predictability of early-life environments has been proposed as an important influence on the development of frontolimbic circuitry and psychopathology (Baram et al., 2012). Several studies have examined basic forms of unpredictability by manipulating the predictability of a stressor (e.g., Schmitz et al., 2011). For example, unpredictable shock is associated with higher levels of a metabolite of norepinephrine in the hypothalamus, amygdala, and thalamus, as well as higher levels of plasma corticosterone, relative to predictable shock in rodents (Tsuda, Ida, Satoh, Tsujimaru, & Tanaka, 1989). The anterior insula, bed nucleus of the stria terminalis, and amygdala are activated in response to unpredictable aversive cues in adult humans (Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011; Andreatta et al., 2015; Shankman et al., 2014; Somerville et al., 2013), further suggesting that frontolimbic circuitry is involved in processing unpredictable cues.

Research on predictability in early life has largely focused on the predictability of caregiver attention and action as a key feature associated with neurobiological responses to stress, with findings suggesting that environmental unpredictability (e.g., variable access to food resources) confers risk by altering maternal behavior (Rosenblum & Andrews, 1994; Rosenblum & Pully, 1984). Among rodents, exposure to fragmented care and higher rates of unpredictability in maternal cues are associated with cognitive and emotional dysfunction in pups (Baram et al., 2012; Brunson et al., 2005), which are likely driven by alterations in frontolimbic circuitry. Rodents exposed to unpredictable care show greater *c-Fos* expression in the basolateral amygdala, relative to animals raised in typical conditions (Malter Cohen et al., 2013). Altered frontolimbic interactions also appear to underlie anhedonia following unpredictable care (Bolton, Molet, et al., 2018; Bolton, Ruiz, et al., 2018; Molet et al., 2016; Risbrough et al., 2018). Among rodents previously exposed to unpredictable care, social play is associated with increased corticotropin-releasing hormone expression in the amygdala and increased structural connectivity between the amygdala and mPFC (Bolton, Molet, et al., 2018). Consistent with results of animal studies, unpredictability of maternal cues in humans during play with their 12-month-old infants (quantified by the number of transitions between different types of cues and modalities of interaction, e.g., visual, auditory, tactile) is associated with poorer cognitive outcomes in offspring, as compared to mothers who were more predictable during play (Davis et al., 2017). Though less is known about the potential effects of unpredictability early in life on frontolimbic development in humans, these findings suggest that frontolimbic circuitry may be influenced by early experiences characterized by unpredictability.

In conclusion, both animal and human studies suggest that exposure to unpredictable stress may exacerbate the effects of stress exposure on the development of frontolimbic circuitry and related neurocognitive outcomes. The majority of work in non-human animals and humans has focused either on manipulating the predictability of a stressor or on the predictability of caregiver cues. However, other types of stressors have the feature of unpredictability. For example, environmental unpredictability (in the form of variable availability of parental work, housing placement, and parental involvement in care) is associated with both parental behaviors toward offspring (e.g., maternal sensitivity) as well as offspring behaviors, including risk-taking in adolescence (Belsky et al., 2012). Yet, to our knowledge, there is no research on the impact of this type of unpredictable stress on frontolimbic development. Additionally, much like the type of stress, predictability may interact with the timing of stress in a significant way. Based on the salience of caregiving during infancy and early childhood, predictability of caregiver behavior may be most influential during these periods of development. Future research delineating the interaction between developmental stage and the unpredictability of stress exposure on frontolimbic development will be important for assessing key periods sensitive to the impact of these features.

3.6 | Caregiver involvement

The section above on predictability highlights the central role of caregiving relationships on neurobiological responses to stress. Most notably, the formation of caregiver attachments, even in contexts of stress, is critical to children's emotional and physical wellbeing, as well as survival (Bernstein & Freyd, 2014; Bowlby, 1969; Freyd, 1997). Rodent models have delineated a unique neural circuit central to attachment, which involves a hyperfunctioning locus coeruleus that releases norepinephrine and a hypofunctioning HPA axis (Landers & Sullivan, 2012; Perry & Sullivan, 2014). Rodent pups show a strong preference for cues associated with their mother, even when those cues are highly aversive, a mechanism that ensures the pup stays close to the mother (Moriceau & Sullivan, 2006). Similarly, recent parallel evidence in humans shows that young children approach conditioned stimuli learned in their parent's presence even when those stimuli are aversive (Tottenham, Shapiro, Flannery, Caldera, & Sullivan, 2019). Given the biologically preprogrammed need for attachment across species (Bowlby, 1969), the repercussions of a caregiver involved in a child's exposure to early-life stress, either through neglect or perpetration of abuse, may lead to significant disruptions in offspring development.

Many of the human studies examining the effects of caregiver involvement in early-life stress on offspring neurobiology focus on exposure to parental deprivation, which represents a critical deviation from species-expected caregiving. The BEIP has provided longitudinal data on the effects of early parental deprivation (Nelson et al., 2007), which is associated with alterations in frontolimbic circuitry. Children placed in institutionalized care exhibit larger amygdala volumes (Mehta et al., 2009; Tottenham et al., 2010) and amygdala hyperactivity (Gee, Gabard-Durnam, et al., 2013; Malter Cohen et al., 2013; Tottenham et al., 2011), compared with their never-institutionalized counterparts. Parental deprivation also alters the development of the HPA axis (Flannery et al., 2017; Gunnar et al., 2009; Gunnar, Morison, Chisholm, & Schuder, 2001; McLaughlin et al., 2015) and regulatory connections between the mPFC and amygdala (Gee, Gabard-Durnam, et al., 2013). These effects have been observed years following the experience of institutionalized care, highlighting the long-term effects of early parental deprivation on frontolimbic circuitry. Though parental deprivation also has more global effects on brain structure (McLaughlin, Sheridan, Winter, et al., 2014; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012), the observed alterations in frontolimbic circuitry may be more tightly associated with dysfunction in emotional reactivity and regulation following institutionalized care.

Studies of maltreatment (e.g., physical, sexual, and emotional abuse) represent another large body of research examining the effects of caregiver-related stressors. Childhood maltreatment is consistently associated with altered gray matter volume in regions including the amygdala and hippocampus (Edmiston et al., 2011; Hanson, Nacewicz, et al., 2015; McLaughlin et al., 2016; Morey, Haswell, Hooper, & De Bellis, 2016). The structure of key white matter tracts connecting the amygdala with prefrontal regions is also

disrupted following maltreatment, with evidence for lower structural integrity of the uncinate fasciculus among young adults previously exposed to maltreatment (Hanson, Knodt, Brigidi, & Hariri, 2015). Consistent with these structural alterations, individuals exposed to childhood maltreatment show disruptions in functional connectivity between the PFC and regions such as the hippocampus and amygdala (Herringa et al., 2013; Lambert, Sheridan, et al., 2017), as well as altered activation in the amygdala (Zhu et al., 2019) and hippocampus (Lange et al., 2019). Providing further evidence of the impact of caregiving-related maltreatment on subsequent emotional functioning, these changes in frontolimbic circuitry have been associated with alterations in processes such as threat generalization, emotion regulation, and fear learning.

One mechanism by which deviations from species-expected early caregiving may have adverse effects on frontolimbic circuitry is via disruption of parental regulation of emotions and stress reactivity (Callaghan et al., 2019; Opendak et al., 2019). Early caregiving relationships provide the structural framework from which children begin to forge their own representations of the world around them, and concepts about themselves, others, and how they relate to others (Bowlby, 1969; Sroufe, 2005). These early representations form the basis from which myriad developmental competencies emerge, including emotion regulation (Calkins & Hill, 2007; Tamis-LeMonda, Shannon, Cabrera, & Lamb, 2004; Thompson, 2014). A central role of the caregiver is to provide external regulation for an infant's emotions and to support development of intrinsic capacity for self-regulation (Hofer, 1978, 1994). Parental nurturance of infants (e.g., by responding sensitively to infant distress following a stressor; Bernard, Meade, & Dozier, 2013; Dozier, Roben, Caron, Hoye, & Bernard, 2018) and synchrony between children's bids and parental responses (Pratt, Singer, Kanat-Maymon, & Feldman, 2015) may be especially important aspects of parent-child interactions that regulate infants' emotional development. Emerging evidence across species has provided insight into the neurobiological mechanisms through which caregivers help to regulate emotion early in life. Caregiver presence suppresses amygdala reactivity and HPA axis-mediated stress responses in both rodents (Moriceau & Sullivan, 2006) and humans (Gee et al., 2014; Hostinar, Johnson, & Gunnar, 2015; see Tottenham, 2015 for a review). Notably, the potency of a caregiver's presence as a source of external regulation is diminished by adolescence (Gee et al., 2014; Hostinar, Sullivan, & Gunnar, 2014), suggesting that the effect of parental buffering may be developmentally specific. Thus, caregiver involvement in stress exposure is theorized to play a more detrimental role in shaping developmental trajectories for infants and young children, as opposed to adolescents or adults (Gee, 2016; Hofer & Sullivan, 2008; Tottenham, 2015).

In summary, empirical evidence supports the importance of considering caregiver involvement as a key dimension of stress exposure. Potentially due to disruptions in attachment relationships caused by caregiver-related adversity, stress involving caregivers has been shown to have a more deleterious effect than stress exposure that does not involve caregivers (D'Andrea, Ford, Stolbach, Spinazzola, & Kolk, 2012; van der Kolk, 2003). When stress is

characterized by involvement of a caregiver, either due to direct caregiver involvement (e.g., caregiver perpetration of abuse or neglect) or due to parent-child dyadic exposure to stress (e.g., shared violence victimization of mother and child), young children's attachment relationships with caregivers may be impaired and the strength of the caregiver as an effective buffer of stress reactivity may be compromised (Lieberman, 2004). As caregivers frequently play a central role in both experiences of deprivation (e.g., parental neglect, institutionalized care) and experiences of threat (e.g., maltreatment perpetrated by a caregiver), future research is needed to test whether exposure to parental deprivation (lack of species-expected input) and exposure to maltreatment perpetrated by a caregiver (species-atypical input) have divergent or convergent effects on the developing brain. Additionally, relative to children who have experienced non-caregiver-related adversity, children who have experienced caregiver-related adversity show increased risk-taking behaviors, aggression, dissociative symptoms, mood-related psychopathology, as well as difficulties with affect regulation, attention, and impulsivity (Cook et al., 2005; van der Kolk, 2003). In addition, children with stress exposure characterized by maladaptive family functioning are more likely to develop mental health problems, relative to children with childhood adversities not characterized by maladaptive family functioning (McLaughlin et al., 2010). Despite evidence for differential effects on behavioral outcomes, less is known about the impact of caregiver-related versus non-caregiver-related stress on frontolimbic circuitry. Future research directly comparing the effects of these stressors on frontolimbic circuitry would aid in the development of a nosology that distinguishes between stressors based on their impact on neurobiology. Finally, given the differential role of caregivers in children's lives throughout development, caregiver involvement in stress exposure may be particularly detrimental in infancy and early childhood. Future research quantifying the impact of caregiver involvement on shifts in neurobiology, and comparing this type of social category to others such as peers, will be useful in further delineating the impact of specific features on frontolimbic development.

4 | PROPOSING AN INTEGRATED NEURODEVELOPMENTAL FRAMEWORK

Frameworks of stress exposure to date have made foundational contributions to understanding the effects of specific features involved in stress exposure on development (Cicchetti & Toth, 1995; Gee & Casey, 2015; McCoy, 2013; Pynoos et al., 1999; Sheridan & McLaughlin, 2014). For example, Sheridan and McLaughlin (2014) have proposed a theoretical framework that details the differential psychobiological effects associated with threat and deprivation as two distinct types of stress exposure. Additional frameworks related to developmental timing of stress exposure (e.g., Gee & Casey, 2015; Tottenham & Sheridan, 2009) have outlined potentially divergent effects of stress exposure that occurs across development. However, existing frameworks have not captured the richness of the many features of stress exposure that may influence how a particular individual responds. For a framework to further advance our conceptualization of stress and frontolimbic development, it must address the ways in which specific dimensions of experience may interact with the biological state of the developing brain and, further, must consider differential trajectories resulting from variability in both the developmental state of the brain at a particular age of exposure and at a particular age of outcome assessment. The framework proposed here builds on this past theoretical work by offering an outline of multiple features—beyond a single dimension such as type or timing—that may moderate the association between stress exposure and frontolimbic development.

Integrating across the previously reviewed literature, we propose a set of dimensions of stress exposure that may predict unique variance in patterns of frontolimbic development across the life course (see Figure 1). The goal of this framework is to generate testable hypotheses and guide future research. Specifically, timing, severity, type, controllability, and predictability of stress exposure, as well as caregiver involvement in stress exposure, serve as potential moderators of the effects of stress on frontolimbic development. Given dynamic changes in frontolimbic circuitry across childhood and

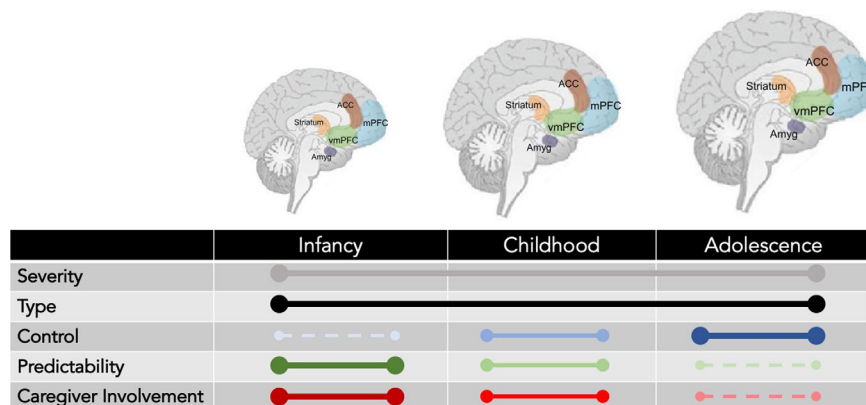


FIGURE 1 An integrative framework of dimensional effects of stress exposure on the development of frontolimbic circuitry. Lines that are thicker and darker represent stronger hypothesized influences on frontolimbic circuitry during a given developmental stage. ACC, anterior cingulate cortex; Amyg, amygdala; mPFC, medial prefrontal cortex; vmPFC, ventromedial prefrontal cortex. Brain image adapted from Macdonald, Goines, Novacek, & Kolk, (2016).

adolescence (Casey et al., 2019; Gee et al., 2018), the *timing* of stress exposure differentially impacts structure and function of frontolimbic circuitry. *Severity* of stress exposure is associated with alterations in both the structure and function of frontolimbic circuitry. Specific *types* of stress (e.g., abuse vs. neglect or physical abuse vs. sexual abuse) are associated with different frontolimbic outcomes, and current theory posits that exposures characterized by elements of threat versus deprivation may have differential effects on biological outcomes. Both animal and human studies provide evidence that experiencing *control* over a stressor may facilitate adaptive coping via changes in frontolimbic circuitry. Cross-species evidence further suggests that the degree of *predictability* involved in stress may moderate the effects of stress on frontolimbic circuitry. Finally, stress exposures involving *caregivers* (e.g., via abuse or neglect) are likely to be particularly detrimental for frontolimbic outcomes.

In addition to these features, the interactions among features are important to consider. Existing preliminary evidence highlights the interaction between *timing* and *control*, *predictability*, and *caregiver involvement* as important moderators of frontolimbic outcomes. In the current framework we propose potential developmental stages during which given dimensions of stress exposure may be especially salient. During infancy and early childhood, we expect that *predictability* of stress and *caregiver involvement* will be more strongly linked with frontolimbic development, relative to later childhood and adolescence. Although unpredictability of stress likely confers risk across the lifespan, existing research suggests it may have the strongest impact on frontolimbic development when it occurs during infancy and early childhood. Similarly, although caregiver involvement in exposure to stress is an important factor to consider across the lifespan, literature to date suggests that caregiver-absent or caregiver-perpetrated stress may be particularly detrimental in infancy and early childhood, likely due to the major role that caregivers play in establishing secure attachment with offspring and providing external regulation of emotion early in life (Callaghan & Tottenham, 2016a; Hostinar et al., 2015). During these early periods of life, offspring are particularly sensitive to predictability of parental behavior and caregivers' cues, which is important for healthy frontolimbic development and the development of secure attachment (Davis et al., 2017; Sroufe, 2005). During adolescence, we expect that *controllability* of stress will be more strongly related to frontolimbic development relative to control during childhood or adulthood. Cross-species empirical evidence suggests that related fronto-striatal-amygdala circuitry is distinct during adolescence in ways that may promote active coping via control (Casey et al., 2019; Heller et al., 2016). Although initial empirical evidence points to interactions with timing of stress exposure for specific types of stress (e.g., abuse vs. neglect) on specific outcomes (i.e., hippocampal volume) (Teicher et al., 2018), much remains to be explored about ways in which the impact of stress *type* might depend on developmental stage during which the stress occurs. Similarly, additional research will be needed to test whether there are developmentally-specific associations with *severity* of stress and frontolimbic outcomes.

Future research will be essential for elucidating the effects of specific dimensions of stress exposure on frontolimbic development. Based on the existing literature, the current framework identifies key dimensions that warrant consideration when assessing early-life histories of stress. Though initial empirical evidence suggests these features influence frontolimbic circuitry, findings regarding the specific nature of these effects (e.g., structural vs. functional effects; larger vs. smaller gray matter volume; increased vs. decreased activation or connectivity) has often been mixed, highlighting the need for more systematic study. In addition to testing the effects of these features of early-life stress, examining their interactions with developmental timing of stress exposure will be critical to delineating and more fully understanding sensitive periods during neurodevelopment. Notably, the majority of research examining developmental timing of stress and its interaction with other dimensions of stress in regard to frontolimbic circuitry has been conducted in adults. Though these findings have provided an important foundation, they preclude our understanding of how specific dimensions of stress exposure influence the unfolding of development, particularly given the hierarchical nature of brain development (Casey et al., 2019; Thelen, 2005) and developmental cascades across multiple systems following stress (Masten & Cicchetti, 2010; Teicher, Andersen, Polcari, Anderson, & Navalta, 2002). Thus, findings to date highlight both the complexity of developmental timing for processes of risk and resilience, as well as the need for studies that precisely assess timing of exposure across multiple domains of stress during development. Just as the timing of exposure matters, early-life stress may affect different outcomes in childhood versus adolescence (Raine et al., 2012; Rincón-Cortés & Sullivan, 2014; Tottenham & Sheridan, 2009). Finally, the current framework specifically focuses on the association between dimensions of stress exposure and frontolimbic circuitry. Future research systematically examining the relationships between these dimensions of stress exposure, frontolimbic development, and behavior will be essential to understanding heterogeneity in mental health outcomes following early-life stress.

Knowledge of how early-life stress shapes brain and behavioral development will provide translational targets to inform interventions designed to promote resilience among youth. As one example, knowledge of the developmental timing of stress exposure may help to optimize treatments based on the biological state of the developing brain. Sensitive periods may render the developing brain more vulnerable to the effects of stress but could also serve as windows of opportunity during which there is increased potential for positive adaptation or effective intervention (Gee & Casey, 2015). As frontolimbic circuitry changes markedly across childhood and adolescence, interventions based on the adult brain cannot simply be applied to youth. Instead, precisely targeting the developing brain is necessary to optimize interventions for specific stages of development such as childhood or adolescence (Lee, Anumagalla, Talluri, & Pavuluri, 2014). Similarly, treatment approaches could be meaningfully informed by other key dimensions of stress such as the type of stress that an individual experienced or the degree to which their caregiver was involved in the exposure. Moreover, some evidence suggests that, even with similar presentations of clinical symptoms, individuals exposed to

early-life stress differ in important ways from individuals not exposed to early-life stress (Klein et al., 2009; La Buissonnière-Ariza et al., 2019; Teicher & Samson, 2013). Clarifying the impact of unique features of early-life stress exposure is anticipated to have important implications for risk identification and efforts to tailor the timing and type of treatment for specific stressors, specific developmental stages, or specific individuals.

5 | METHODOLOGICAL SUGGESTIONS FOR FUTURE RESEARCH

Finally, we recommend several concrete methodological tactics to maximize the degree to which future research can meaningfully contribute to the proposed framework detailing the effects of specific dimensions of stress on the development of frontolimbic circuitry. The most commonly used interview- and questionnaire-based measures of early life stress typically only assess *type* (i.e., whether or not an individual has experienced specific isolated types of events) and few assess *timing* to a limited degree (e.g., by assessing the cumulative list of ages at which the event occurred; Steinberg et al., 2013; Teicher & Parigger, 2015). Future research focused on delineating the effects of early-life stress on both brain and behavior would benefit from employing dimensional measures of stress that capture the cumulative list of ages at which an event occurred, as well as the presence of key dimensions of interest at each age that a particular event occurred (e.g., whether an individual perceived control during an instance of witnessing domestic violence at age 5 versus at age 6). Although this type of data collection can be considerably time-consuming, this rich profile of an individual's stress history will allow for the examination of specific factors that may contribute to heterogeneity in neurobiological outcomes. In addition, it is important to note that the majority of studies assessing the effects of early-life stress on brain development employ retrospective accounts of stressful exposures across development, which have a low degree of reliability with prospective measures (Baldwin, Reuben, Newbury, & Danese, 2019). Although retrospective reports have contributed substantially to the evidence base for the effects of early-life adversity on outcomes across the lifespan, prospective accounts of each of the dimensional aspects of stress exposure (in conjunction with longitudinal collection of neuroimaging data) will facilitate the detection of signatures of specific elements of stress exposure earlier in life.

In order to test specific hypotheses related to the relative impact of isolated dimensions of stress exposure, data collection will need to harness the previously described measures with the goal of phenotyping specific differences between individuals (e.g., characterizing the age at which trauma exposure occurred within a sample of adults with early trauma exposure; delineating the degree to which a caregiver was involved in exposure among a group of individuals with childhood sexual abuse exposure). Given the time-consuming, clinically intensive, and costly nature of this data collection, establishing gold-standard batteries for trauma exposure across multiple

protocols will be a key step in aggregating sufficient data related to individual dimensions across larger samples. In addition, revisiting previously collected datasets with the goal of restructuring data to derive dimensions of interest may be particularly useful as protocols are adapted to more specifically assess dimensionality of stress exposure. Although an initial wave of research will likely focus on direct comparisons of features within specific factors of interest (e.g., comparing individuals with exposure at different developmental stages or with different types of exposure), future research should aim to examine interactions between the aforementioned features as is afforded by an increase in the richness of available measurement tools and datasets. Ensuring adequate statistical power to examine complex interactions between dimensions will further rely on incorporating key dimensions of stress exposure into the batteries of large-scale longitudinal studies of brain development (Hoffman et al., 2019). Finally, cross-species research will provide new insight into the effects of specific aspects of stress exposure, particularly given barriers to experimentally manipulating these dimensions in humans. Systematically testing the relative contributions of various dimensions of stress and their interactions with timing across development in animal studies (e.g., Peña et al., 2019), as well as collaborations examining parallel effects of stress across humans and animal models (e.g., Malter Cohen et al., 2013), will be essential for testing and building upon the hypotheses put forth in dimensional models of early-life stress.

6 | CONCLUSIONS

The extant literature has often heralded a message of universally detrimental neurobiological effects of exposure to stress. However, exposure to stress—even to the same type of stress—does not have a uniform effect on all individuals or on the same individual at different stages of development (Gabbay, Oatis, Silva, & Hirsch, 2004; Gee & Casey, 2015; Lupien et al., 2009). An estimated 70% of individuals have experienced a traumatic event that satisfies Criterion A of post-traumatic stress disorder in the Diagnostic Statistical Manual, but only 23% of these individuals go on to develop the full clinical presentation of the disorder (Breslau, Davis, Andreski, & Peterson, 1991; Kessler et al., 2017). Similarly, although there is a well-established link between exposure to stressful events and the development of psychopathology across development (e.g., Heim & Nemeroff, 2001), many individuals exposed to stress do not develop psychopathology. This phenomenon suggests that relying on a binary indicator of stress exposure may obscure understanding of which specific features of stress confer risk versus resilience. Further, this vast heterogeneity in outcomes underscores the importance of delineating the factors that may explain the multifinality of outcomes for individuals exposed to stress.

Studies of early-life stress and frontolimbic circuitry have traditionally investigated differences between stress-exposed versus non-stress-exposed individuals. Although decades of research using this categorical approach have identified a clear pathway from early-life stress to alterations in frontolimbic circuitry,

parsing the vast heterogeneity in stress exposure and subsequent outcomes is essential to enhancing risk identification and intervention. Specifically, identifying key dimensions that may moderate the impact of stress on frontolimbic development and further understanding how these dimensions operate and interact with each other will provide insight that can shape the ways in which we identify at-risk youth and tailor evidence-based treatments for specific individuals or profiles of stress exposure. In particular, delineating how specific features of stress exposure interact with the biological state of the developing brain has the potential to inform novel interventions based on sensitive periods of neurodevelopment. In the current framework, we propose key features of stress exposure that may differentially shape frontolimbic circuitry across development and call for future research to adopt a dimensional approach that can elucidate heterogeneity in outcomes following early-life stress and ultimately enhance the well-being of youth exposed to stress.

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CONFLICTS OF INTEREST

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