

Gee, D. G. (2016). Sensitive periods of emotion regulation: Influences of parental care on frontoamygdala circuitry and plasticity. In H. J. V. Rutherford & L. C. Mayes (Eds.), *Maternal brain plasticity: Preclinical and human research and implications for intervention*. *New Directions for Child and Adolescent Development*, 153, 87–110.

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Sensitive Periods of Emotion Regulation: Influences of Parental Care on Frontoamygdala Circuitry and Plasticity

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Abstract

Early caregiving experiences play a central role in shaping emotional development, stress physiology, and refinement of limbic circuitry. Converging evidence across species delineates a sensitive period of heightened neuroplasticity when frontoamygdala circuitry is especially amenable to caregiver inputs early in life. During this period, parental buffering regulates emotional behaviors and stress physiology as emotion regulation circuitry continues to mature. By contrast, disorganized or poor quality caregiving has profound and lasting consequences on the maturation of frontoamygdala circuitry essential for emotion regulation, even following termination of this early life stressor (e.g., adoption from orphanage). This article highlights how interactions between caregiving experiences and the biological state of the developing brain have broad implications for long-term health. © 2016 Wiley Periodicals, Inc.

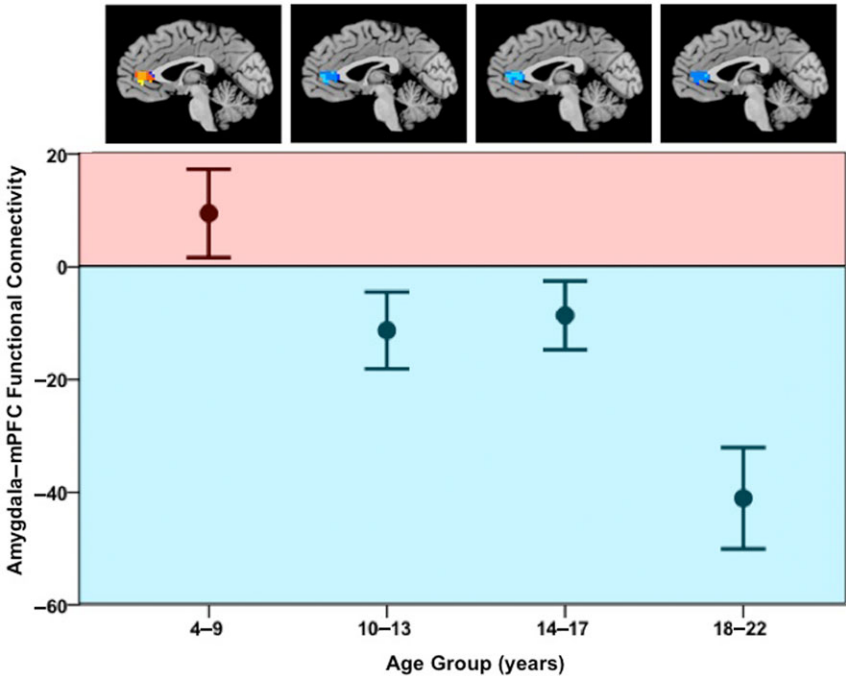
Early experiences have a profound influence on the developing brain and behavior, with early environments shaping neuroaffective trajectories and long-term adult phenotypes of emotional behavior. Across a long evolutionary history, environmental stability has led to caregiving being one of the strongest species-expected experiences for altricial species early in life. The parent-child relationship is critical to emotional well-being across development (Levine, 2001; Ainsworth, 1969; Bowlby, 1982), and the absence of parental care is one of the most potent stressors for an infant (Bick & Nelson, 2016; Rincón-Cortés & Sullivan, 2014; Tottenham, 2012; Tottenham & Sheridan, 2009). Strong evidence across species suggests that caregivers affect mental health and emotional behavior by influencing the neurobiology underlying emotion regulation (Callaghan & Tottenham, 2015; Tottenham, 2015). Given dynamic changes in neuroplasticity across development, caregiving experiences are likely to interact with the typical course of brain development such that parents influence offspring emotional functioning in unique ways at different developmental stages (Gee & Casey, 2015). Thus, studies of early and long-term follow-up are essential for delineating sensitive windows of emotional development and how parental care modulates this development differently across the lifespan.

Sensitive Periods and Development of Frontoamygdala Circuitry

Typical brain development is marked by dynamic changes that have broad implications for how early experiences shape brain maturation and long-term behavioral outcomes. Sensitive periods occur when the developing brain is especially open to environmental restructuring (Andersen, 2003; Hensch, 2005; Knudsen, 2004; Rice & Barone, 2000). During these periods of heightened neuroplasticity (i.e., when capacity for change and formation or remodeling of neuronal connections is greatest), environmental stimuli can lead to a series of developmental cascades that ultimately influence behavioral phenotypes across the lifespan in both positive and negative ways (Davidson & McEwen, 2012; Masten & Cicchetti, 2010). Thus, developmental phases of heightened plasticity may render the brain especially vulnerable to disrupted parental care but also create developmentally unique opportunities when the system is especially amenable to parental buffering or intervention. While sensitive periods have been more commonly identified for sensory modalities such as visual or auditory systems, emerging evidence in nonhuman animals points to a sensitive period for socioemotional development involving stress and anxiety (reviewed in Cameron, 2001; Hensch, 2004; Moriceau & Sullivan, 2006; Yang, Lin, & Hensch, 2012). The effects of parental buffering and parental deprivation on socioemotional behavioral and neural development extend this evidence to humans.

Emotional behavior and related frontoamygdala circuitry undergo many changes across infancy, childhood, and adolescence. Evidence across species highlights regionally specific neurodevelopmental trajectories, with the amygdala maturing earlier than the prefrontal cortex (PFC) (Chareyron, Lavenex, Amaral, & Lavenex, 2012; Lenroot & Giedd, 2006; Machado & Bachevalier, 2003; Payne Machado, Bliwise, & Bachevalier, 2010). Sensitive periods may occur during periods of rapid change (Lupien, McEwen, Gunnar, & Heim, 2009), corresponding to the early structural development of the amygdala. The amygdala also has a high density of glucocorticoid receptors (Honkaniemi et al., 1992; Wang et al., 2014), which have been linked to amygdala-mediated effects of stress (e.g., Lee, Schulkin, & Davis, 1994; Arnett et al., 2015). Due to these cellular properties and substantial changes early in life, the amygdala may be especially susceptible to early environmental influences (Lupien, McEwen, Gunnar, & Heim, 2009; Plotsky et al., 2005; Sabatini et al., 2007) and more resistant to recovery following early adversity (Ganzel, Casey, Glover, Voss, & Temple, 2007; Lupien et al., 2011; Malter Cohen et al., 2013). In normative development, children show robust amygdala reactivity to fearful faces and other emotional stimuli, with reactivity typically decreasing following childhood (Decety, Michalska, & Kinzler, 2012; Gee, Humphreys et al., 2013; Silvers, Shu, Hubbard, Weber, & Ochsner, 2014; Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014; Vink, Derks, Hoogendam, Hillegers, & Kahn, 2014; but see Hare et al., 2008, which suggests differential developmental trajectories depending on task demands and emotional context). This heightened amygdala reactivity parallels excessive normative childhood fears, such as separation anxiety (Gee, Humphreys et al., 2013). The reciprocal connections between the amygdala and medial PFC (mPFC) that support effective emotion regulation and fear extinction in healthy adults (e.g., Kim, Somerville, Johnstone, Alexander, & Whalen, 2003; Phelps, Delgado, Nearing, & LeDoux, 2004) show protracted development throughout childhood and adolescence both functionally (Decety, Michalska, & Kinzler, 2012; Gabard-Durnam et al., 2014; Gee, Humphreys et al., 2013; Perlman & Pelphrey, 2011; Vink et al., 2014) and structurally (Lebel et al., 2012; Swartz et al., 2014). Excessive fears decline with age, which is mediated by a developmental switch in frontoamygdala connectivity (Gee, Humphreys et al., 2013). Children show positive functional connectivity, whereas negative functional connectivity emerges around the transition to adolescence, consistent with an increasingly regulatory circuit (Gee, Humphreys et al., 2013b; Figure 6.1). Similarly, stronger negative functional connectivity (Silvers et al., 2014) and increased mPFC recruitment (McRae et al., 2012) parallel improvements in emotion regulation with age. Further highlighting normative changes in frontoamygdala circuitry, whereas the amygdala appears to be central to fear learning early in life, a more complex circuit including the mPFC and hippocampus becomes involved across development (Britton et al., 2013; Livneh & Paz, 2012; McCallum, Kim, & Richardson, 2010;

Figure 6.1. Developmental switch in frontoamygdala connectivity (adapted from Gee, Humphreys et al., 2013). A developmental switch from positive to negative functional connectivity between the amygdala and mPFC was observed during the transition from childhood to adolescence in typically developing youth. Younger children displayed positive functional connectivity, which became more strongly negative from adolescence to young adulthood.



Pattwell et al., 2012). Given the substantial changes in fear learning and emotion regulation circuitry following childhood, research has increasingly focused on how emotion regulation occurs early in development as frontoamygdala circuitry is continuing to mature.

Impact of Parental Buffering on Emotional Reactivity and Frontoamygdala Circuitry

Decades of research have demonstrated that parental care has strong and lasting effects on emotional functioning. The parent-child relationship is central to many theories of development (e.g., Ainsworth, 1969; Baumrind, 1966; Bowlby, 1982), and parenting affects behavioral and brain development across species (e.g., Callaghan, Sullivan, Howell, & Tottenham, 2014; Howell et al., 2013; Moriceau & Sullivan, 2006; Romeo et al., 2003;

Plotsky et al., 2005; Tottenham et al., 2010, 2011). Parents have key regulatory effects on offspring emotional behavior, physiology, and stress reactivity (Gunnar & Donzella, 2002; Hofer, 1994; McCoy & Masters, 1985), a phenomenon termed parental buffering (Hostinar, Sullivan, & Gunnar, 2014). Cross-species studies have provided increasing insight into the neurobiological mechanisms underlying parental buffering, as frontoamygdala circuitry is highly conserved across species and the infant-caregiver relationship is critical for survival in all altricial species (Callaghan et al., 2014). In addition, these studies allow for greater control over the timing and administration of parental care while also controlling for genetic and environmental background.

Maternal presence directly affects amygdala function and threat learning during development in rodents. In early infancy, maternal presence maintains low levels of corticosterone and plays a key role in the stress hyporesponsive period (Moriceau & Sullivan, 2006). Prior to postnatal day (P)10 infants demonstrate approach behaviors toward an odor paired with a shock. This absence of avoidance learning is thought to facilitate attachment to the caregiver, necessary for survival, during a time when threat learning would be ecologically maladaptive (Perry & Sullivan, 2014). During the transitional sensitive period (P10–P15), maternal presence determines whether pups approach or avoid the odor paired with the shock. That is, pups continue to show approach behaviors if the mother is present, and thus suppressing corticosterone and blocking amygdala plasticity. However, corticosterone and amygdala activation increase if the mother is absent, instantiating threat learning and avoidance behaviors (Moriceau & Sullivan, 2006). Parental presence also buffers stress physiology and HPA axis reactivity in infant macaques (Levine, Johnson, & Gonzalez, 1985; Sanchez, 2006). Maternal presence, thus, buffers corticosterone and amygdala function to ensure early infant-caregiver attachment and mediates the onset of threat learning when it becomes adaptive for offspring to begin exploring the environment (Sullivan & Perry, 2015).

In humans, parents have strong buffering effects on children's emotional behavior and physiological reactivity. For example, parents suppress cortisol reactivity in children through physical presence and even facilitate the return of cortisol levels to baseline through a phone conversation immediately following a stressor (Gunnar & Donzella, 2002; Kertes et al., 2009; Seltzer, Prosofski, Ziegler, & Pollak, 2012). Further evidence shows parents can inhibit the acquisition of conditioned fears (Egliston & Rapee, 2007) and reduce existing fears (Simard, Nielsen, Tremblay, Boivin, & Montplaisir, 2008). In these ways, parental presence is a powerful regulator that influences emotional behaviors and what children learn about the environment.

Despite the importance of parental buffering for children's emotion regulation, less is known about its neurobiological mechanisms in humans. To test the hypothesis that parents regulate emotion in childhood by modulating frontoamygdala circuitry prior to the normative maturation of this

circuitry, we examined parental effects on amygdala reactivity, connectivity, and affective regulatory behavior (Gee et al., 2014). Children and adolescents performed an emotional go/no-go task of inhibitory control in an affective context twice, once in the presence of their mother and once in the presence of a stranger (friendly experimenter). During an fMRI scan, participants viewed faces of their mother and of a stranger. Whereas olfactory cues related to the mother are particularly salient in rodents, humans rely heavily on visual cues. Consistent with parental buffering of behavior, children showed better inhibitory control (fewer false alarms) when seated next to their mother than a stranger.

Importantly, the effect of maternal presence was specific to childhood and not to adolescence. Adolescents performed similarly on the task regardless of whether the mother or stranger was present. Children's amygdala reactivity was suppressed when viewing their mother's face compared with the stranger's face, and the mother's face physically induced a more regulatory pattern of negative amygdala-mPFC functional connectivity typically only observed at older ages (Figure 6.2). The parental buffering of frontoamygdala circuitry was not present in adolescents, who showed the typical pattern of functional connectivity and similar amygdala responding to both the mother's and stranger's faces. Together these findings suggest that during childhood, but not adolescence, parental stimuli elicit the recruitment of frontoamygdala function that is more typical of mature circuitry.

The more mature frontoamygdala profile in children in the presence of maternal cues was associated with individual differences in anxiety and attachment. Those children whose parents effectively buffered at the neural level also showed lower separation anxiety, reported that they were more likely to rely on their parent during a stressful time, and demonstrated better inhibitory control in their mother's presence (Gee et al., 2014). Though our study examined parental visual cues, similar effects have been shown in anxious youth whose parents were physically present during an fMRI scan (Conner et al., 2012). These findings suggest a potential neurobiological mechanism for the effects of parental buffering on emotional behavior such that parents may induce greater top-down mPFC regulation of the amygdala. Consistent with this idea, parental presence increases mPFC activity in both developing rodents (Bock, Riedel, & Braun, 2012) and macaques (Rilling et al., 2001).

Research in rodents, nonhuman primates, and humans shows robust evidence for a sensitive period of parental buffering effects, such that the developing organism is most open to parental shaping of frontoamygdala circuitry early in life. In rodents and nonhuman primates these effects are strongest in infancy, whereas they are evident during childhood but not adolescence (Gee et al., 2014; Hostinar, Johnson, Gunnar, 2015a) in humans. Though research has begun to examine the effects of parental cues on neural circuitry during human infancy (e.g., Graham, Fisher, & Pfeifer, 2013), future research is needed to fully characterize this period. The early

Figure 6.2. Parental buffering of frontoamygdala circuitry specific to childhood (adapted from Gee et al., 2014). (A) Presence of the maternal stimulus physically buffered right amygdala reactivity in children but not adolescents. Specifically, children showed lower activation of the right amygdala to their mother compared with a stranger. (B) Adolescents showed a pattern of negative amygdala–mPFC functional connectivity to both their mother and the stranger. In contrast, children exhibited the negative pattern of functional connectivity (typically only observed at older ages) to their mother but not the stranger.

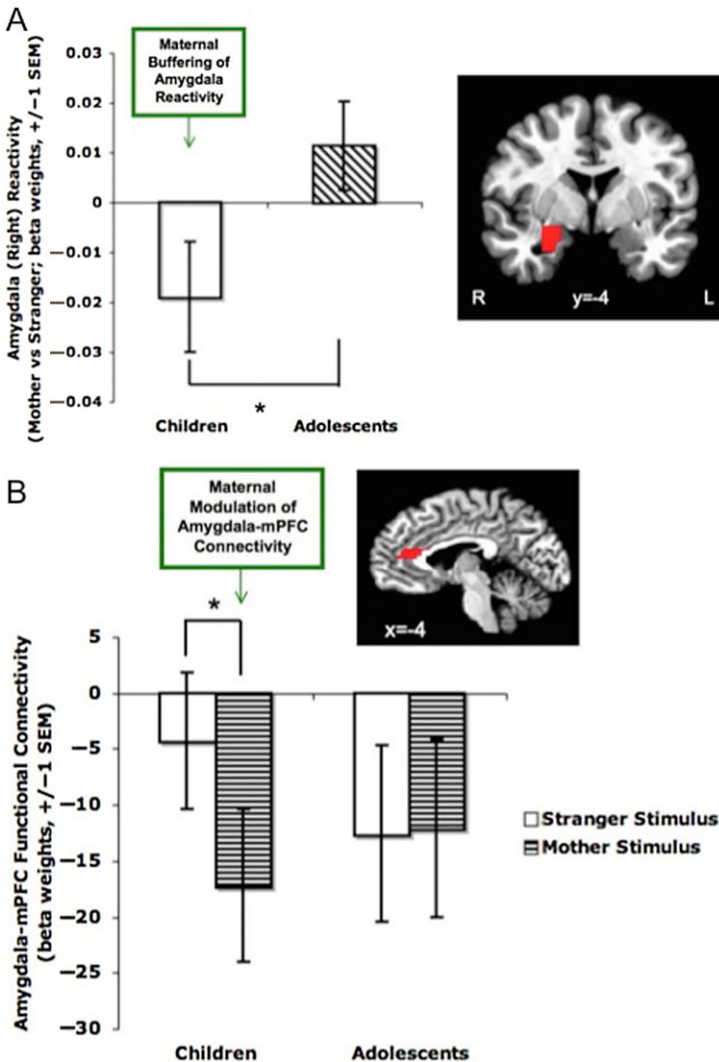
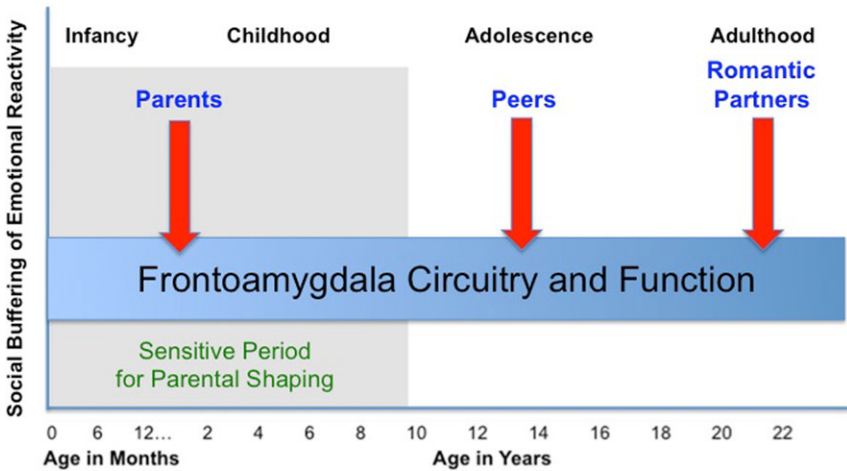


Figure 6.3. Social buffering of emotional reactivity across the lifespan. Parental buffering has unique regulatory effects on emotional reactivity during infancy (rodents) and childhood (humans). Social buffering continues across the lifespan, with different relationships serving a regulatory function at distinct developmental timepoints (e.g., peer influences in adolescence, partner influences in adulthood). Due to heightened plasticity to caregiving influences early in life, parental care is especially likely to play a strong role in shaping the development of frontoamygdala circuitry and function.



developmental stage when parental buffering is effective corresponds to a period of substantial changes in the amygdala (Tottenham, 2012), during which the system may be especially amenable to environmental influences (Sabatini et al., 2007; Lupien, McEwen, Gunnar, & Heim, 2009).

Though parental buffering effects appear specific to early life, social buffering continues with alternative relationships becoming prominent at distinct time points in development (Figure 6.3) (e.g., peer relationships during adolescence and romantic relationships during adulthood; Adams, Santo, & Bukowski, 2011; Calhoun et al., 2014; Coan, Schaefer, & Davidson, 2006; Ditzen et al., 2007; Terranova, Cirulli, & Laviola, 1999). However, parental scaffolding when frontoamygdala circuitry is highly plastic early in life is likely to be most influential in shaping the circuit and its long-term function (Tottenham, 2015). By physically inducing a mature state of frontoamygdala connectivity, parental presence leads to repeated coactivation of the amygdala and mPFC, which may be critical for long-term development of this circuit (Callaghan & Tottenham, 2015). Indeed, environmental experiences that coactivate regions within a circuit can shape

long-term changes in connectivity during adulthood (e.g., Harmelach, Premlinger, Wertman, & Malach, 2013). Given the influence of environmental experiences and heightened neuroplasticity during development, these effects are likely to be especially pronounced earlier in life. Recent developmental evidence in humans shows that task-based frontoamygdala connectivity predicts resting-state frontoamygdala connectivity two years later, suggesting that repeated coactivations early in development when the system is highly plastic may shape the more stable architecture of this circuit later in life (Gabard-Durnam et al., 2016). Over time, such neurobiological scaffolding may be a mechanism by which the external regulation provided by parents becomes internalized as older children transition to adolescence and beyond.

Impact of Parental Deprivation on the Development of Frontoamygdala Circuitry and Function

By contrast to the positive effects of parental buffering during typical development, parental deprivation during early life can have profound and lasting consequences. Early caregiving adversity is strongly associated with alterations of the HPA axis (e.g., Gee, Gabard-Durnam et al., 2013a; Gunnar, Frenn, Wewerka, & Van Ryzin, 2009; Koss, Hostinar, Donzella, & Gunnar, 2014; Moriceau, Raineki, Holman, Holman, & Sullivan, 2009; Sanchez, 2006) and frontoamygdala circuitry (e.g., Gee, Gabard-Durnam et al., 2013a; Hanson et al., 2015; Howell et al., 2013; Ono et al., 2008; Tottenham et al., 2010; Tottenham et al., 2011), increased anxiety (e.g., Gee, Gabard-Durnam et al., 2013a; Goff et al., 2013; Ono et al., 2008; Tottenham et al., 2010), and risk for psychopathology (e.g., Green et al., 2010; Zeanah et al., 2009). In rodents and nonhuman primates, caregiving adversity is typically studied using paradigms of maternal separation, maternal stress (e.g., via reduced nesting material), or naturally occurring maltreatment. In humans, one of the strongest models is parental deprivation that is experienced in institutionalized care followed by adoption into a stable home. Even in the best of circumstances, orphanage care is suboptimal and a potent stressor for an infant (Gunnar, Bruce, & Grotevant, 2000). Because chronic stress often follows early-life stress, drawing inferences about the developmental timing and effects of caregiving adversity in humans is challenging. However, this naturally occurring model provides a definitive endpoint to the adversity (date of adoption) and a stark contrast between the early stressful environment and the enriched family environment following adoption (Tottenham, 2015).

Substantial variability exists in developmental and long-term outcomes following institutionalized care, with some individuals thriving following adoption and others experiencing myriad negative consequences. Earlier adoption is consistently associated with better outcomes (e.g., Rutter, 1998;

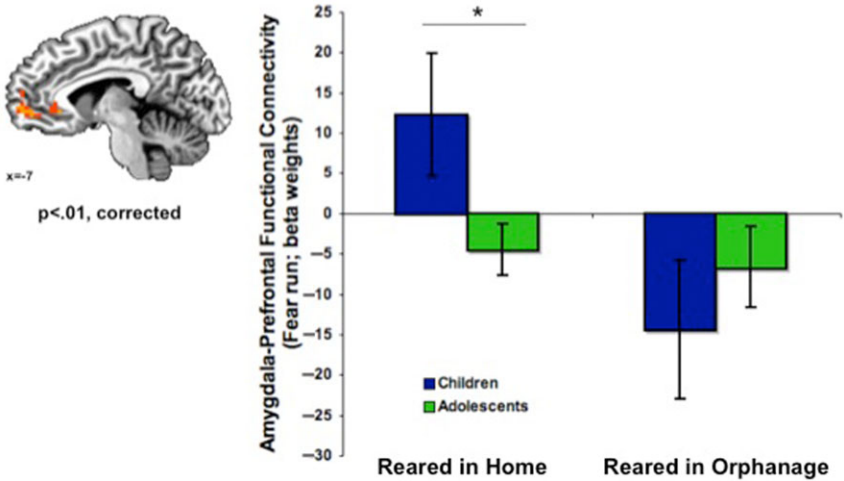
Tottenham et al., 2010). Due to its distinctive study design, the Bucharest Early Intervention Project has provided unique insight into the timing of these effects, highlighting a sensitive period of socioemotional development early in life. Previously institutionalized youth who were placed into a foster-care intervention prior to 24 months of age had better long-term outcomes including more secure attachment, more normative stress responses, and improved neurodevelopmental trajectories, compared with their peers who were placed later (Bos et al., 2011; McLaughlin, Fox, Zeanah, & Nelson, 2011; McLaughlin, Sheridan, Tibu, et al., 2015; Vanderwert, Marshall, Nelson, Zeanah, & Fox, 2010; Vanderwert, Zeanah, Fox, & Nelson, 2016). In addition, individual differences, the timing of adversity (Cameron, 2001; Sabatini et al., 2007), and the biological state of the developing brain at the time of stress (e.g., Schayek & Maroun, 2015; Gee & Casey, 2015) contribute to heterogeneous outcomes following parental deprivation. On average, children can show remarkable recovery in some domains of functioning (Nelson et al., 2007; Rutter, 1998). However, emotional functioning appears to be especially vulnerable to persistent effects of earlier parental deprivation, which may be due in part to the developmental timing and early plasticity of the amygdala (Sabatini et al., 2007). Children and adolescents who experienced parental deprivation during infancy display increased internalizing symptoms (Gee, Gabard-Durnam et al., 2013a; Goff et al., 2013; Tottenham et al., 2010), deficits in emotion regulation (Tottenham et al., 2011), increased behavioral freezing to fear stimuli (Stellern, Esposito, Mliner, Pears, & Gunnar, 2014), disrupted attachment to primary caregivers (O'Conner et al., 2003; Rutter, 1998), and dysregulated HPA function (Fries, Shirtcliff, & Pollak, 2008; Gee, Gabard-Durnam et al., 2013a; Gunnar et al., 2009; Koss, Hostinar, Donzella, & Gunnar, 2014). Disruptions in emotional functioning and anxiety have been linked with increased amygdala volume (Mehta et al., 2009; Tottenham et al., 2010) and reactivity (Gee, Gabard-Durnam et al., 2013a; Tottenham et al., 2011) in youth following parental deprivation.

To date, the precise neural mechanisms underlying difficulties in emotion regulation following parental deprivation have remained unclear. Cross-species evidence indicates that early parental deprivation leads to accelerated maturation of frontoamygdala circuitry and emotional learning (Callaghan et al., 2014). In rodents, caregiving adversity is associated with the early emergence of adult-like fear learning and related neural circuitry. Specifically, rodents exposed to fragmented maternal care exhibit increased amygdala reactivity and a premature transition from approach to avoidance behaviors following odor-shock conditioning (Moriceau et al., 2009; Moriceau & Sullivan, 2006). Prewaning rodents who experienced maternal separation also display the early emergence of persistent fear memories following cued fear conditioning and relapse following fear extinction, which contrast with the phenomenon of infantile amnesia that is typically observed early in development (Callaghan & Richardson, 2011, 2012;

Cowan, Callaghan, & Richardson, 2013). These effects are mediated by corticosterone, suggesting that disrupted maternal care acts on the developing fear system via early HPA stimulation. Maternal separation in mice is also associated with accelerated myelination in the amygdala (Ono et al., 2008). Together these findings suggest that rodents who experience early adverse caregiving undergo accelerated development of the fear system, which may serve as an ontogenetic adaptation by which the developing organism reprioritizes to cope with an environment lacking stable caregiving.

In humans, evidence supports the hypothesis that early parental deprivation accelerates frontoamygdala development. Individuals who experienced typical rearing conditions exhibit the “immature” pattern of positive amygdala-mPFC functional connectivity during childhood, with a developmental switch to negative functional connectivity around the transition to adolescence and continued strengthening of this neural phenotype into young adulthood (Gee, Humphreys et al., 2013b). However, children who experienced parental deprivation during infancy display the more mature pattern of negative amygdala-mPFC functional connectivity, such that their connectivity does not differ from that of adolescents (Gee, Gabard-Durnam et al., 2013a; Figure 6.4). Similar to findings in rodents, early frontoamygdala development was mediated by cortisol levels, suggesting that modifications of the HPA axis contribute to accelerated development. Though it is unclear whether heightened amygdala reactivity following parental deprivation (e.g., Gee, Gabard-Durnam et al., 2013a; Maheu et al., 2010; Tottenham et al., 2011) represents accelerated maturation, it may be that elevated amygdala reactivity instantiates the premature change in connectivity as an attempt to meet the heightened need for regulation. The early emergence of mature frontoamygdala functional connectivity following parental deprivation, such that young children already resemble adolescents and adults in their patterns of connectivity, indicates a major alteration in the normative trajectory of frontoamygdala development. Because participants scanned in this study were 6 to 17 years of age, it is unclear whether the typical period of positive frontoamygdala connectivity is accelerated in rate or shifted earlier in development and whether the changes following parental deprivation persist into adulthood. One possibility is that the premature emergence of the adult-like phenotype indicates a shift in or early closure of the sensitive period for environmental shaping of frontoamygdala circuitry via caregiving, consistent with findings in nonhuman animals of reduced structural and functional plasticity in frontolimbic circuitry following early maternal separation (e.g., Burton et al., 2007; Chatterjee et al., 2007; Chocyk et al., 2013; Eiland & McEwen, 2012; Law et al., 2009; Pusalkar et al., 2016). Future research will be necessary to test the hypothesis that accelerated development induced by parental deprivation limits plasticity or subsequent restructuring of frontoamygdala circuitry in humans.

Figure 6.4. Accelerated development of frontoamygdala functional connectivity following parental deprivation (adapted from Gee, Gabard-Durnam et al., 2013a). Left) A group by emotion interaction was observed in the mPFC, such that group differences emerged when participants viewed fearful faces. Right) Unlike comparison children who showed immature (positive) amygdala-mPFC connectivity, children with a history of early-life stress (previous institutionalized care) exhibited negative amygdala-mPFC coupling, such that the stressed children resembled adolescents. The results suggest an early closure of a sensitive period in frontoamygdala development following parental deprivation.



Potential Benefits and Consequences of Accelerated Development Following Parental Deprivation

Accelerated development of frontoamygdala circuitry may represent a short-term ontogenetic adaptation that facilitates independent survival in a species-unexpected caregiving environment. That is, accelerated frontoamygdala development and fear behaviors may have benefits in the absence of stable parental care (Callaghan et al., 2014; Callaghan & Tottenham, 2015; Gee, Gabard-Durnam et al., 2013a; Tottenham, 2015). For rodent pups lacking stable maternal care, adult-like fear retention and avoidance learning could contribute to effectively navigating an adverse environment and increase chances of survival (Rincón-Cortés & Sullivan, 2014). Though previously institutionalized youth displayed heightened anxiety relative to typically reared youth, individual differences emerged within the previously institutionalized group such that those who displayed the more mature pattern of negative amygdala-mPFC functional

connectivity had lower anxiety than their previously institutionalized same-aged peers with positive connectivity (Gee, Gabard-Durnam et al., 2013a). Thus, within a group that is at increased risk for anxiety due to early-life stress, accelerated development may confer some early benefit. Emerging evidence in humans suggests that some behavioral outcomes following early adversity may be adaptive given the unfavorable early environment and are consistent with expectations of the future environment based on these earlier experiences (Humphreys et al., 2015; Mittal, Griskevicius, Simpson, Sung, & Young, 2015). Some research even points to long-term adaptations in specific domains following altered caregiving (e.g., Zoicas & Neumann, 2016). Stress inoculation models suggest that mild stress (e.g., intermittent maternal separation) promotes resilience and better coping with environmental stressors later in life (Lyons & Parker, 2007). However, these models are likely to better approximate normative phasic changes in parental presence that characterize typical rearing (e.g., parents going to work and children attending school), which may be key to long-term “toning” of the system, than the severe parental deprivation experienced in institutionalized care (Callaghan & Tottenham, 2015).

Though accelerated maturation may provide short-term benefits in an environment that necessitates independent survival, it is unclear how long these benefits persist, and there are likely to be substantial consequences following premature termination of a sensitive period of openness to caregiving influences. Translational studies show that adult rodents who experienced early maternal separation exhibit the same behavioral phenotype of increased anxiety that has been identified in rodent pups following maternal separation (e.g., Caldji, Francis, Sharma, Plotsky, & Meaney, 2000; Nishi, Horii-Hayashi, & Sasagawa, 2014; Rincón-Cortés & Sullivan 2014; Sanchez, Ladd, & Plotsky, 2001), even in the absence of explicit memories of the stressor (Poulos et al., 2014). In humans, disruptions in emotional behavior and frontoamygdala circuitry exist years following the experience of institutionalized care (e.g., Gee, Gabard-Durnam et al., 2013a; Goff et al., 2013; Mehta et al., 2009; Tottenham et al., 2010, 2011; Zeanah et al., 2009), yet it is rare that studies have followed previously institutionalized youth into adolescence or adulthood. A cross-species examination of early disrupted maternal care in rodents that paralleled orphanage conditions provides unique insight into neural and behavioral phenotypes during adolescence and adulthood. Fear dysregulation (in this case, the inability to suppress fear responses in favor of goal-directed behavior) and amygdala hyperactivity persisted into adulthood following disrupted rearing, despite normative increases in prefrontal activation with age, suggesting consequences that last even beyond the termination of the stressful rearing condition and prefrontal maturation (Malter Cohen et al., 2013).

The precise mechanisms underlying these long-term changes remain unclear, but one possibility is that early closure of a sensitive period limits opportunities for learning and adaptation later in life. The protracted

maturation that characterizes typical human neurodevelopment has evolutionary advantages for the developing organism and long-term outcomes (e.g., Shaw et al., 2006; Thompson-Schill, Ramskar, & Chryssikou, 2009). By contrast, abbreviated plasticity may increase rigidity of the system, consistent with evidence that early maternal separation reduces cognitive flexibility later in development (Lovic & Fleming, 2004; Thomas, Caporale, Wu, & Wilbrecht, 2016). What was once adaptive during parental deprivation is unlikely to be adaptive in the enriched and stable family environment that many youth experience following adoption. Environmental demands also change by developmental phase, and plasticity is likely necessary for meeting these new challenges (e.g., adolescence; Casey, Duhoux, & Malter Cohen, 2010). Such a mismatch with the environment or developmental stage may explain why previously institutionalized youth who undergo accelerated frontoamygdala development initially show less anxiety, but it is unclear how long those benefits persist, especially within a group at increased risk for psychiatric disorders in the long term. This appears especially true for accelerated development of the fear system, where the premature onset of adult-like fear learning could be maladaptive later in life. For example, persistent activation of fear circuitry in the absence of immediate threat has been linked with anxiety, hypervigilance, attentional bias to threat, and an impaired ability to distinguish between safety and danger, which are prominent features of anxiety disorders (e.g., Craske et al. 2009; Jovanovic, Kazama, Bachevalier, & Davis, 2012; McLaughlin, Sheridan, Gold, et al., in press; Roy et al., 2008). Though behaviors such as hypervigilance and attention to threat might benefit a developing organism navigating a harsh or unpredictable environment in the absence of parental care, these functions are less likely to be adaptive once the organism has achieved independence or is in a safe environment. Moreover, reduced frontoamygdala plasticity and parental deprivation may interfere with a child's ability to experience the typical benefits of parental buffering following adoption. Indeed, phasic regulation by parents requires plasticity of frontoamygdala circuitry (Callaghan & Tottenham, 2015). Cross-species evidence supports the hypothesis that maternal buffering during stress is less effective for juveniles who experienced early caregiving adversity (Fries, Shirtcliff, & Pollak, 2008; Hostinar, Johnson, & Gunnar, 2015b; Raineki, Lucion, & Weinberg, 2014), despite no differences in maternal behavior during the test of buffering (Sanchez, McCormack, & Howell, 2015). The hierarchical nature of neurodevelopment and sensitive periods, such that certain aspects of development must precede the maturation of others (Thelen, 2005), also indicates that shifts in the developmental timing of one circuit could have cascading effects on the organism's subsequent maturation (Hensch & Bilimoria, 2012). In these ways, the downstream effects of parental deprivation and resulting accelerated development may hinder later emotional functioning and contribute to the higher rates of psychiatric disorders observed in childhood and adolescence following early adverse rearing.

A growing literature on intervention following parental deprivation provides promise for ameliorating these long-term consequences (Bick & Nelson, 2016), and translational research in nonhuman animals has identified mechanisms of reopening sensitive windows of plasticity (Bavelier, Levi, Li, Dan, & Hensch, 2010; Hensch & Bilimoria, 2012) that may promote resilience following the premature termination of a sensitive period. Importantly, neural and behavioral changes can continue to be shaped by experiences across the lifespan even following sensitive periods. Environmental enrichment, such as care from a stable, nurturing family, is one way in which improved outcomes may be achieved following parental deprivation. Youth who were removed from institutionalized care and placed with foster families were less likely to have internalizing disorders than those who remained in institutionalized care (Zeanah et al., 2009). Environmental enrichment occurring proximally to the stressor has been shown to ameliorate consequences of maternal separation in animals (Francis, Diorio, Plotsky, & Meaney, 2002; Vivinnetto, Suarez, & Rivarola, 2013), and recent research shows that anxiety and amygdala hypertrophy previously induced by early maternal separation normalized following environmental enrichment provided during adulthood (Koe, Ashokan, & Mitra, 2016). These intriguing results suggest that environmental enrichment may be able to reverse negative consequences of parental deprivation much later in life. Though pharmacological interventions have remained less explored in humans, shifting the excitatory/inhibitory balance (e.g., with valproate or fluoxetine) in key neural circuits has been shown to increase plasticity in nonhuman animals (e.g., Bavelier et al., 2010; Gervain et al., 2013; Silingardi, Scali, Belluomini, & Pizzorusso, 2010). These promising directions may eventually provide insight into mechanisms of promoting resilience following early-life stress in humans.

Conclusions

Cross-species research on parental buffering and parental deprivation indicates a sensitive period early in life when frontolimbic circuitry is highly plastic and amenable to environmental caregiving influences. In typical rearing conditions, parents serve as a key source of phasic emotion regulation in childhood by modulating HPA and amygdala reactivity as frontoamygdala connections are continuing to mature, which may shape adulthood phenotypes of effective emotion regulation and related circuitry. Disruption of the parent-child relationship alters the course of frontoamygdala development and has longstanding behavioral and neural consequences. Emerging evidence suggests that accelerated development of frontoamygdala circuitry following parental deprivation serves as an ontogenetic adaptation to meet the needs of an unexpected adverse environment; however, premature closure of a sensitive period may increase risk for psychopathology by contributing to circuit stabilization that is no longer adaptive in later

developmental stages or environments. Understanding the neurobiological mechanisms underlying early caregiving influences and how they interact with the biological state of the developing brain will be critical for optimizing interventions and promoting resilience following early adversity.

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