HHS Public Access

Author manuscript

Curr Top Behav Neurosci. Author manuscript; available in PMC 2018 August 21.

Published in final edited form as:

Curr Top Behav Neurosci. 2018 ; 38: 117–136. doi:10.1007/7854_2016_42.

Neurobiological programming of early life stress: Functional development of amygdala-prefrontal circuitry and vulnerability for stress-related psychopathology

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Abstract

Early adverse experiences are associated with heighted vulnerability for stress-related psychopathology across the lifespan. While extensive work has investigated the effects of early adversity on neurobiology in adulthood, developmental approaches can provide further insight on the neurobiological mechanisms that link early experiences and long-term mental health outcomes. In the current review, we discuss the role of emotion regulation circuitry implicated in stress-related psychopathology from a developmental and transdiagnostic perspective. We highlight converging evidence suggesting that multiple forms of early adverse experiences impact the functional development of amygdala-prefrontal circuitry. Next, we discuss how adversity-induced alterations in amygdala-prefrontal development are associated with symptoms of emotion dysregulation and psychopathology. Additionally, we discuss potential mechanisms through which protective factors may buffer the effects of early adversity on amygdala-prefrontal development to confer more adaptive long-term outcomes. Finally, we consider limitations of the existing literature and make suggestions for future longitudinal and translational research that can better elucidate the mechanisms linking early adversity, neurobiology and emotional phenotypes. Together, these findings may provide further insight into the neuro-developmental mechanisms underlying the emergence of adversity-related emotional disorders and facilitate the development of targeted interventions that can ameliorate risk for psychopathology in youth exposed to early life stress.

Keywords

Early Life Stress; Amygdala; Prefrontal Cortex; Child/Adolescent Development; Psychopathology

1 Introduction

Early life stress (ELS) is associated with higher incidence of mental health problems across the lifespan, accounting for 29% of health disorders worldwide (Green et al., 2010; Kessler et al., 2005, 2010). Multiple forms of postnatal adversities confer vulnerability for stress-related psychopathology, including maltreatment, neglect, parental stress or psychopathology, trauma, family conflict, poverty-related stressors and institutionalized care

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(Essex et al., 2011; Humphreys et al., 2015; Lansford et al., 2014, Kessler et al. 2010). Although these adverse exposures often occur during infancy and/or childhood, emotional difficulties often continue to persist throughout development, with three quarters of stress-related mental health diagnoses made by the age of 24 (Kessler et al., 2005; Merikangas et al., 2010). Given the robust epidemiological evidence linking ELS with long-lasting emotional difficulties, it is important to identify the neurobiological mechanisms through which early experiences "get under the skin" to increase risk for psychopathology.

Developmental mechanisms of adaptation play an important role in understanding the long-term links between ELS and mental health outcomes in adulthood. According to the Dynamic Systems Theory, development is experience-driven, emerging via interactions with the environment that unfold over time (Smith & Thelen, 2003). In the context of ELS, several developmental theories (Barker's hypothesis, Developmental Origins Theory, Adaptive Recalibration model, Experiential Canalization) emphasize the role of adaptation in response to adversity, such that the organism develops in order to promote survival in the expected environment (Barker, 2007; Blair & Raver, 2012; Del Giudice, Ellis, & Shirtcliff, 2011; Wadhwa, Buss, Entringer, & Swanson, 2010). Similarly, the Stress-Acceleration Hypothesis posits that neurobiological changes in response to early adverse experiences are adaptive in the short-term, but may have long-term trade-offs in the functional integrity of neuro-affective circuitry and heighten vulnerability for maladaptive mental health outcomes later in life (Callaghan & Tottenham, 2016).

In line with this developmental perspective, the current review will discuss how early adverse experiences influence neuro-affective development to confer risk for stress-related emotion dysregulation. We will delineate how the amygdala-prefrontal circuit, implicated in threat-reactivity and emotion regulation, appears to be particularly sensitive to the effects of stress during early life. The current paper focuses on the functional development of amygdala-prefrontal circuitry, as stress-induced changes in structural development have been reviewed elsewhere (Tottenham & Sheridan, 2009). Specifically, we will highlight converging evidence suggesting that multiple forms of ELS are characterized by similar functional phenotypes of neuro-affective circuitry across development: (1) heightened amygdala reactivity and (2) altered amygdala-prefrontal connectivity. Next, we will discuss how developmental changes in amygdala-prefrontal circuitry predict individual differences in symptoms of stress-related psychopathology. Finally, we will discuss potential protective factors that may buffer the effects of stress on neuro-affective development to confer more resilient long-term trajectories. Given that ELS increases risk across several, often comorbid psychiatric disorders (De Bellis et al., 2001; Kessler et al., 2010), this paper will focus on the neurobiology of emotion dysregulation from a transdiagnostic and dimensional perspective.

2 Target Neural Circuitry: Amygdala and Prefrontal Cortex

2.1 The Role of Amygdala-Prefrontal Circuitry in Emotion Regulation

Robust translational and clinical research has linked amygdala-prefrontal circuitry with symptoms of emotion dysregulation (Hariri & Holmes, 2015). In adults, regulatory connections between amygdala and prefrontal cortex are critically implicated in learning and

responding to emotional cues in the environment (Davis & Whalen, 2001; Kim, Hamlin, & Richardson, 2009). The amygdala is involved in detecting salient information in the environment to initiate physiological responses to potential threat (Davis & Whalen, 2001). Top-down recruitment of medial prefrontal regions regulate amygdala reactivity to facilitate extinction learning (Milad, Rauch, Pitman, & Quirk, 2006; Phelps & LeDoux, 2005) whereas dorsolateral prefrontal regions implicated in more effortful processes, like cognitive reappraisal, modulate amygdala reactivity during emotion regulation (Buhle et al., 2013). Functional alterations of amygdala reactivity and amygdala-prefrontal connectivity have been identified in patients with internalizing and stress-related disorders, including anxiety, depression and PTSD (Etkin et al., 2004; Koenigs & Grafman, 2009; Murray, Wise, & Drevets, 2011). In the Research Domain Criteria (RDoC) recently outlined by the National Institutes of Mental Health (Morris & Cuthbert, 2012), amygdala-prefrontal circuitry has been implicated in the psychological constructs of fear and sustained threat, highlighting its role in the neurobiological underpinnings of transdiagnostic dimensions of threat-reactivity and emotion regulation (Dillon et al., 2015).

In humans, amygdala-prefrontal circuitry undergoes protracted development, with age-related changes observed across childhood, adolescence and young adulthood. Several studies have observed heightened amygdala reactivity in response to emotionally salient cues in younger ages (Gee, Humphreys, et al., 2013; Guyer et al., 2008; Hwang et al., 2014; Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014; Vink et al., 2014). As amygdala reactivity declines with increasing age (Decety et al., 2012; Gee, Humphreys, et al., 2013; Guyer et al., 2008; Hwang et al., 2014; Swartz et al., 2014; Vink et al., 2014), the functional integrity of amygdala-mPFC circuitry continues to strengthen into young adulthood (Gabard-Durnam et al., 2014). Importantly, age-related changes in amygdala reactivity and/or connectivity with the prefrontal cortex during cognitive reappraisal tasks correspond to the maturation of emotion regulation abilities across development (Dougherty, Blankenship, Spechler, Padmala, & Pessoa, 2015; McRae et al., 2012; Silvers, Shu, Hubbard, Weber, & Ochsner, 2015). Pediatric disorders of anxiety, depression and PTSD are characterized by heightened amygdala reactivity and atypical amygdala-prefrontal connectivity during emotion processing tasks (Gaffrey et al., 2011; Garrett et al., 2012; Pagliaccio et al., 2012; Pine, Guyer, & Leibenluft, 2008; Roy et al., 2013; Wolf & Herringa, 2016). Moreover, altered patterns of age-related changes in amygdala-prefrontal connectivity have been shown in a cross-sectional sample of anxious youth and young adults (Kujawa et al., 2016) suggesting that deviations from the normative trajectory of amygdala-prefrontal development are associated with symptoms of emotional dysregulation in clinical samples.

2.2 Plasticity of Amygdala-PFC Circuitry in Early Life

Converging evidence across species suggests that amygdala-prefrontal circuitry is highly sensitive to environmental inputs, particularly during early life (Callaghan, Sullivan, Howell, & Tottenham, 2014). The amygdala is heavily innervated by glucocorticoid receptors (Avishai-Eliner, Yi, & Baram, 1996), with the highest peak in Corticotrophin Releasing Hormone (CRH) receptor density during the first few postnatal weeks (Avishai-Eliner et al., 1996). Stress exposure during early life results in increased mRNA expression of CRH in the amygdala in rodents (Hatalski, Guirguis, & Baram, 2012). Importantly, the functional

development of the amygdala is tightly linked to Hypothalamic–Pituitary-Adrenal (HPA) axis function, such that increases in cortisol are associated with the developmental onset of amygdala reactivity and fear learning in rodents (Moriceau, Wilson, Levine, & Sullivan, 2006).

Several animal models of ELS (e.g. abusive maternal care, maternal separation, chronic restraint stress, and odor-shock conditioning) have shown that that early adverse environments have enduring effects on amygdala structure and function (Eiland, Ramroop, Hill, Manley, & McEwen, 2012; Malter Cohen et al., 2013; Raineki, Cortés, Belnoue, & Sullivan, 2012). Moreover, regulatory connections between amygdala and prefrontal cortex are highly susceptible to environmental influences during early life in rodent models. For example, chronic stress exposure during the juvenile stage causes dendritic atrophy in the prefrontal cortex (PFC; Eiland et al. 2012) and alters the emergence of amygdala projections to the PFC, resulting in long-term imbalance of amygdala-prefrontal circuit function in adult rats (Ishikawa, Nishimura, & Ishikawa, 2015). In light of these findings, amygdala-prefrontal development may play an important role in the neurobiological etiology of emotion dysregulation in humans following ELS.

3 Effects of ELS on Amygdala-PFC Circuitry in Humans

When examining the effects of ELS on neurobiological development in humans, there are two important considerations that delineate the state of current research. First, aside from notable exceptions in which there is known timing and duration of adverse exposures (i.e. adoption from institutionalized care), many forms of ELS are chronic in nature, making it difficult to delineate the effects of stressors during specific time points across development (reviewed in Tottenham & Sheridan, 2009). Given cross-species evidence suggesting that amygdala development is most sensitive to environmental input early in life (Callaghan et al., 2014), the current review focuses on adverse experiences that occur during infancy and/or childhood. Second, recent theoretical frameworks have suggested that certain dimensions of adverse experiences (e.g. threat vs. deprivation) may have differential effects on neurobiological development (McLaughlin, Sheridan, & Lambert, 2014). Although early adversities are often complex exposures comprised of multiple dimensions of experience (e.g. abuse and neglect; Arata, Langhinrichsen-Rohling, Bowers, & O'Brien, 2007), many forms of ELS are considered threatening to children's physical or emotional well-being (McLaughlin et al., 2014). In the current review, we focus on research examining threat-related alterations in neuro-affective development following exposure to ELS. Specifically, we present converging evidence suggesting that amygdala-prefrontal circuitry, implicated in threat-reactivity and emotion regulation, is a common neurobiological target impacted by multiple forms of early adverse experiences.

3.1 Effects of ELS on Amygdala Reactivity

In adults, heightened amygdala reactivity to emotional cues has been identified across several domains of ELS reported retrospectively, including maltreatment (Dannlowski et al., 2013; van Harmelen et al., 2013) emotional neglect (Bogdan, Williamson, & Hariri, 2012; White et al., 2012) and lower perceived social status (Gianaros et al., 2008). Recent

prospective longitudinal studies have corroborated these effects, showing that cumulative childhood stressors associated with low socioeconomic status have lasting effects on amygdala function in adulthood (Evans et al., 2016; Javanbakht et al., 2015). For example, childhood poverty has been associated with increased amygdala reactivity to negative relative to positive emotional cues in adulthood (Javanbakht et al., 2015). In the same prospective cohort, cumulative risk exposure associated with childhood poverty was directly related to higher amygdala reactivity to neutral facial expressions, suggesting that stress-related increases in amygdala reactivity may not be specific to threat-related stimuli, also extends to neutral socio-emotional cues (Evans et al., 2015).

In accordance with studies in adult ELS samples, children and adolescents with a history of early adversity also show enhanced amygdala reactivity to emotional stimuli. Previously institutionalized (PI) youth with a history of institutional care exhibit heightened amygdala reactivity to threat-related facial expressions across childhood and adolescence (Gee, Gabard-Durnam, et al., 2013; Maheu et al., 2010; Tottenham et al., 2011). Similarly, increased amygdala response to negative emotional stimuli has been identified in children and adolescents with prior exposure to maltreatment (McCrory et al., 2013; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015), traumatic events (Marusak, Martin, Etkin, & Thomason, 2014), and family violence (McCrory et al., 2011). Moreover, greater levels of stressful life events have been associated with longitudinal increases in threat-related amygdala reactivity during adolescence, suggesting that heightened amygdala reactivity may represent a neural marker of previous stress exposure (Johnna R Swartz, Williamson, & Hariri, 2015). Importantly, McCrory et al. (2013) found that children with earlier onset of maltreatment exposure showed higher levels of amygdala reactivity to pre-attentively presented emotional stimuli, suggesting a relationship between the timing of stress exposure onset and degree of amygdala reactivity. However, further research is needed to delineate whether stress-induced increases in amygdala reactivity are primarily driven by the developmental timing (i.e. age of onset) or the duration (i.e. chronic versus acute) of adverse experiences.

3.2 Effects of ELS on Amygdala-PFC Connectivity

In addition to heightened amygdala-reactivity, ELS has also been characterized by altered functional connectivity of the amygdala with prefrontal regions. Although the valence (i.e. positive or negative) and regional specificity (i.e. dorsolateral or medial regions of PFC) of amygdala-prefrontal connectivity findings are task-dependent and often vary across studies, ELS has been consistently associated with atypical connectivity patterns relative to non-stressed control groups. In a prospective study, young adults with a history of childhood maltreatment showed atypical connectivity between the amygdala and inferior frontal gyrus when processing threat-related emotional stimuli (Jedd et al., 2015). Childhood poverty has also been associated with alterations of amygdala-prefrontal connectivity in adulthood, such that lower family income during childhood is associated with reduced amygdala-ventrolateral PFC (vlPFC) connectivity during cognitive reappraisal (Kim et al., 2013). Importantly, cumulative stress exposure mediated the effects of family income on vlPFC recruitment during reappraisal, suggesting that associations between childhood poverty and prefrontal dysregulation are driven by effects of chronic stress (Kim et al., 2013). Together,

these findings suggest that heightened emotional reactivity following ELS may emerge from impaired top-down prefrontal regulation of amygdala reactivity in response to emotional cues.

Given that ELS is associated with atypical amygdala-prefrontal function in adulthood, recent research has examined how these adversity-induced changes emerge across development. In a cross-sectional study from early childhood to late adolescence, PI youth showed an atypical trajectory of age-related changes in threat-related amygdala-mPFC connectivity relative to comparison youth, such that PI youth exhibited more mature (i.e. adult-like) connectivity at younger ages (Gee, Gabard-Durnam, et al., 2013). Youth with trauma exposure also show atypical amygdala-prefrontal function in response to emotional distractors, with weaker negative connectivity between the amygdala and perigenual ACC (pgACC) relative to comparison youth (Marusak et al., 2014). Moreover, the strength of amygdala-pgACC connectivity predicted performance on the emotional conflict task, suggesting that impaired regulation of emotional distractors in trauma-exposed youth may be related to altered circuit function (Marusak et al., 2014). Similarly, PTSD youth exhibit weaker amygdala-dACC connectivity and atypical age-related changes in amygdala-mPFC connectivity in response to threat-related stimuli (Wolf & Herringa, 2016). Importantly, the youth diagnosed with PTSD in this sample were exposed to a wide range of early adverse experiences (e.g. trauma, abuse, neglect; Wolf & Herringa, 2016), suggesting evidence of equifinality with regard to neuro-affective phenotypes following exposure to different forms of ELS (Cicchetti & Rogosch, 1996).

In addition to changes in task-elicited functional connectivity, ELS has also been associated with weaker resting-state amygdala-prefrontal connectivity across developmental stages, suggesting that early adversity has long-lasting impacts on the functional integrity of emotion regulation circuitry. In adults, self-reported history of childhood trauma is associated with weaker resting-state connectivity between amygdala and pregenual ACC (pgACC; Fan et al., 2014). Similarly, adolescents who experienced childhood maltreatment (Herringa et al., 2013) and youth with history of trauma exposure (Thomason et al., 2015) show weaker amygdala-subgenual anterior cingulate cortex (sgACC) connectivity at rest. In a younger cohort of children and young adolescents, higher levels of cumulative stress during childhood predicted weaker amygdala-ACC connectivity (Pagliaccio et al., 2015). Importantly, ELS-induced changes in amygdala connectivity may be identifiable as early as infancy. At 6 months of age, family stress, as defined by high levels of interparental conflict, is associated altered patterns of resting-state amygdala connectivity with posterior cingulate cortex, a regional hub of the default mode network (Graham, Pfeifer, Fisher, Carpenter, & Fair, 2015). Although further research is needed to delineate how early alterations in amygdala connectivity influence longitudinal neuro-affective development, these findings highlight the potential role of amygdala connectivity as a neurobiological marker for stress vulnerability as early as the first year of life (Graham et al., 2014).

4 Amygdala-PFC Circuitry and Individual Differences in Psychopathology Following ELS

In the previous section, we presented evidence suggesting that there is some degree of equifinality in neurobiological development following ELS (Cicchetti & Rogosch, 1996), such that different types of early adverse experiences have converging effects on the development of emotion regulation circuitry, resulting in atypical amygdala-prefrontal circuit function. However, there is also evidence of multifinality, such that there is wide heterogeneity in long-term mental health outcomes following ELS (Cicchetti & Rogosch, 1996). For example, similar adverse experiences (e.g. institutional care) confer risk for multiple types of psychopathology across individuals (De Bellis et al., 2001; Humphreys et al., 2015; Cicchetti & Rogosch, 1996). In the context of developmental theory (Adaptive Calibration, Experiential Canalization, Stress Acceleration), environmentally driven changes in neurobiology represent an ontogenetic response to adversity, and may confer adaptive or maladaptive behavioral outcomes in specific domains or contexts across development (Blair & Raver, 2012; Callaghan & Tottenham, 2016; Del Giudice et al., 2011; Wadhwa et al., 2010). Given the heterogeneity in mental health outcomes associated with ELS, it is important to consider how individual trajectories of neuro-affective development predict risk or resilience following exposure to early adversity. The following discussion will review recent evidence linking adversity-induced changes in amygdala-prefrontal function with individual differences in psychopathology (i.e. anxiety, depression, PTSD).

4.1 Amygdala Reactivity and Psychopathology

Individual differences in amygdala reactivity predict dimensional measures of emotional functioning in both typically developing and stress-exposed youth. In typical children and adolescents, increased amygdala reactivity to sad facial expressions predicts level of concurrent internalizing symptoms (Swartz et al., 2014) and depressive symptoms (Pagliaccio, Luby, Luking, Belden, & Barch, 2014). Youth with trauma exposure and post-traumatic stress symptoms have shown greater amygdala reactivity to emotional facial expressions relative to non-exposed youth (Garrett et al., 2012) although there are mixed findings (Crozier, Wang, Huettel, & De Bellis, 2014; Wolf & Herringa, 2016). A recent study examined the interaction of early trauma exposure and psychiatric status on amygdala reactivity to emotional stimuli during childhood (Suzuki et al., 2014). Amygdala response varied as a function of both early trauma and concurrent levels of psychopathology, such that children with trauma exposure and current diagnosis of Major Depressive Disorder (MDD) exhibited the greatest levels of amygdala reactivity (Suzuki et al., 2014). Moreover, recent evidence suggests that heightened amygdala reactivity predicts long-term increases in negative affect in both healthy and depressed preschool children (Gaffrey, Barch, & Luby, 2016). Together, these studies suggest that amygdala reactivity may represent a neural marker for current and/or future levels of stress-related psychopathology during childhood and adolescence. However, further longitudinal studies are needed to delineate the specific effects of different types of stressors on amygdala reactivity phenotypes and long-term mental health outcomes.

4.2 Longitudinal Studies of Amygdala-PFC Connectivity and Psychopathology

Recent longitudinal findings also suggest that atypical amygdala-prefrontal connectivity may represent a neurobiological risk factor for the emergence of psychopathology following ELS. In adolescents with a history of childhood maltreatment, the strength of resting-state amygdala-sgACC connectivity mediated the relationship between maltreatment exposure and internalizing symptoms, such that weaker amygdala-sgACC connectivity conferred higher levels of anxiety and depressive symptoms (Herringa et al., 2013). In a recent study of cumulative childhood stress, Pagliaccio et al. (2015) examined the relationship between resting-state amygdala-ACC connectivity and longitudinal assessments of internalizing psychopathology in children. Similar to Herringa et al. (2013), weaker amygdala-ACC connectivity mediated the effect of stressful and traumatic life events on current symptoms of anxiety. Moreover, amygdala-prefrontal connectivity and concurrent symptom levels were both significant predictors of anxiety symptoms one year later, providing longitudinal evidence that stress-related changes in the functional integrity of amygdala-prefrontal circuitry confer vulnerability for future stress-related psychopathology (Pagliaccio et al., 2015).

Given that amygdala functional development is tightly linked to the HPA axis (Moriceau & Sullivan, 2006), cortisol reactivity may play an important role in the developmental cascade linking neuro-affective changes to long-term mental health outcomes following ELS. In a long-term prospective study, Burghy et al. (2012) examined the effects of cumulative maternal stress on cortisol levels during childhood and resting-state amygdala-prefrontal connectivity in late adolescence. Greater levels of maternal stress during the first year of life were associated with heightened baseline cortisol levels during childhood, suggesting a dose-dependent response in the HPA axis response to ELS (Burghy et al., 2012). Although maternal stress did not directly predict amygdala-ventromedial PFC (vmPFC) connectivity, higher childhood baseline cortisol levels were associated with altered resting-state amygdala-vmPFC connectivity in adolescent females. Moreover, the strength of amygdala-vmPFC connectivity mediated the relationship between heightened cortisol and symptoms of depression and anxiety in adolescent females, albeit in different directions. Specifically, weaker amygdala-vmPFC connectivity predicted greater symptoms of anxiety, while stronger connectivity predicted greater symptoms of depression, suggesting that divergent trajectories of amygdala-prefrontal development following ELS confer risk for different forms of internalizing psychopathology. Overall, this study provides longitudinal evidence across multiple-levels of analysis that stress-related changes in HPA-axis regulation are associated with atypical amygdala-prefrontal connectivity and heightened vulnerability for internalizing psychopathology following ELS.

4.3 Cross-sectional Studies of Amygdala-PFC Connectivity and Psychopathology

Cross-sectional studies have examined the effects of ELS on age-related changes in the developmental trajectory of amygdala-prefrontal circuit function. PI youth with a history of orphanage care showed atypical age-related changes in task-elicited amygdala-mPFC connectivity in response to fearful faces (Gee, Gabard-Durnam, et al., 2013). In typically developing youth, children showed more positive amygdala-mPFC connectivity, whereas adolescents showed negative amygdala-mPFC connectivity. However, PI children showed

more mature (i.e. negative) connectivity at earlier ages relative to age-matched comparisons. In line with previous literature (Burghy et al., 2012), cortisol levels mediated the relationship between ELS and amygdala-mPFC connectivity, supporting the role of the HPA axis in stress-related changes in neuro-affective development (Gee, Gabard-Durnam, et al., 2013). Importantly, amygdala-mPFC connectivity predicted current levels of psychopathology in the PI group, such that more mature connectivity conferred lower levels of anxiety. In the context of the Stress-Acceleration model (Callaghan & Tottenham, 2016), these findings suggest that earlier functional maturation of this circuitry may represent an adaptive response to previous stress exposure that reduces vulnerability for emotion dysregulation. However, given the cross-sectional nature of this study, further longitudinal research is needed to delineate whether these early stress-induced adaptations predict risk or resilience in the long-term.

Atypical amygdala-prefrontal functioning has also been identified in a cross-sectional study of PTSD youth with a history of early adversity (Wolf & Herringa, 2016). Specifically, threat-related connectivity between the amygdala and dACC/dmPFC predicted severity of avoidant symptoms in PTSD youth. Moreover, they identified altered patterns of age-related connectivity phenotypes in the PTSD group, such that amygdala-vmPFC connectivity increased with age in typically developing youth, but decreased with age in PTSD youth (Wolf & Herringa, 2016). Similar to Gee et al. (2013), children with PTSD showed more mature amygdala-vmPFC connectivity, suggesting that stronger connectivity may represent a developmental adaptation to compensate for heightened emotional reactivity following ELS. However, adolescents with PTSD showed less mature amygdala-vmPFC connectivity relative to age-matched comparisons, indicating that early adaptations in response to adversity may result in trade-offs in the long-term function this circuitry. Although it is possible that exposure to traumatic events at earlier vs. later stages of development (i.e. childhood vs. adolescence) may differentially alter neuro-affective development, there were no reported effects of duration-since-exposure of adversity, nor the length of PTSD diagnosis on amygdala-vmPFC connectivity in this study (Wolf & Herringa, 2016). Although the observed age-related changes in amygdala-vmPFC connectivity were not directly associated with PTSD symptoms, these findings highlight the importance of examining developmental trajectories when considering the effects of ELS on amygdala-prefrontal function and emotional disorders.

5 Protective Factors and Neuro-Affective Development Following ELS

Although ELS is associated with a higher incidence of stress-related psychopathology, many individuals exposed to early adversity do not develop clinical disorders (McGloin & Widom, 2001). Moreover, individuals with history of ELS may show difficulties in specific domains of socio-emotional functioning (e.g. anxiety), but show competence in other domains (e.g. social skills; Masten, 2004). A broad literature on resilience has identified factors at both the individual level (e.g. cognitive factors), and environmental level (e.g. family, community) that contribute to individual differences in mental health and well-being following ELS (Jaffee, Caspi, Moffitt, Polo-Tomás, & Taylor, 2007; Masten, 2004). Given the evidence of multifinality following ELS, it is important to identify how protective factors influence neurobiological development to reduce risk for stress-related psychopathology (Cicchetti &

Blender, 2006;. McLaughlin, 2016). For the purposes of the current review, we will focus on protective factors of the social environment that may ameliorate the effects of ELS on neuro-affective development via social buffering.

In behavioral studies, quality caregiving and family stability have been consistently shown to promote more resilient long-term outcomes following exposure to early adversity (reviewed in Afifi & MacMillan, 2011). For example, in the Bucharest Early Intervention Project (BEIP), youth with stable foster-care placements following institutional care showed lower levels of internalizing symptoms during early adolescence relative to those who experienced disruptions in foster care (Humphreys et al., 2015). Importantly, the two groups did not differ in the amount of time spent in institutional care or psychiatric history at age 4, suggesting that the observed difference in adolescent levels of psychopathology occurred as a function of caregiver stability, as opposed to earlier levels of trauma exposure or psychopathology (Humphreys et al., 2015). Similarly, longitudinal studies of childhood maltreatment have shown that family-level protective factors, such as caregiving stability (DuMont, Widom, & Czaja, 2007), perceived parental care (Collishaw et al., 2007), and parental warmth (Miller-Graff, Cater, Howell, & Graham-Bermann, 2016) are associated with reduced risk for future psychopathology. Together, these findings suggest that positive and stable caregiving is associated with lower levels of emotional problems following multiple forms of early adverse experiences.

In light of strong evidence linking caregiver support and mental health outcomes, ample research has focused on identifying the neurobiological mechanisms underlying these social-buffering effects (Hennessy, Kaiser, & Sachser, 2009; Kikusui, Winslow, & Mori, 2006). Evidence across species has shown that caregivers regulate emotional and neurobiological development (reviewed in Callaghan et al., 2014). In rodent pups, maternal presence has transient effects on cortisol release and amygdala function, such that maternal presence blocks stress reactivity and fear learning during the early stage of rat pup development (Moriceau & Sullivan, 2006). Similar social buffering effects have been identified in humans; parent availability reduces cortisol response to social stress (Hostinar, Johnson, & Gunnar, 2014) and enhances emotion regulation abilities in children (Gee et al., 2014). Moreover, parental stimuli can induce transient changes in functional connectivity of amygdala-mPFC circuitry, and these neurobiological changes predict the degree of parental buffering of children's emotion regulation abilities (Gee et al. 2014). Together, these findings provide a plausible neurobiological mechanism through which caregivers can directly influence neuro-affective functioning during development.

Despite robust evidence of social buffering effects during typical neuro-affective development, no evidence to date has examined these effects on emotion regulation circuitry in youth with history of ELS. However, recent behavioral evidence suggests that interventions such as high-quality foster-care may promote healthy emotional development in youth with a history of early institutional caregiving (Troller-Renfree, McDermott, Nelson, Zeanah, & Fox, 2015). In the BEIP study, children with earlier placement into high-quality foster care showed greater attention bias to positive stimuli relative to children who experienced prolonged institutional rearing and typically developing children (Troller-Renfree et al., 2015). Importantly, positive attention bias in foster care youth predicted lower

externalizing symptoms at age 8 and lower internalizing problems at age 12, suggesting that positivity-bias following early foster-care placement is associated with improved socioemotional functioning in the long-term (Troller-Renfree et al., 2015; Troller-renfree et al., 2016). However, a recent study of internationally adopted PI children and adolescents found that parental presence during a social stress task had no greater regulatory effect on cortisol reactivity relative to stranger presence, suggesting that social buffering mechanisms may exert differential effects on stress-related neurobiology depending on prior social experiences (Hostinar, Johnson, & Gunnar, 2015). Moreover, animal models have shown that social buffering effects are diminished following atypical caregiving experiences (i.e. nursery rearing; reviewed in Kikusui, Winslow, & Mori, 2006). As such, further research is needed to investigate potential mechanisms through which protective factors such as positive parenting behaviors may be able to recalibrate the developmental trajectory of neuro-affective circuitry, and whether they exert effects over and above the effects of ELS to protect against future risk for stress-related psychopathology.

6 Limitations and Future Directions

While the current review focused on common phenotypes of neuro-affective circuitry associated with ELS, there are several directions of future research that will advance our understanding of how early adversity and protective factors influence neurobiological development and subsequent mental health outcomes following ELS. First, there is limited research examining the effects of timing and chronicity of stressors on neuro-affective functional development. Recent studies examining structural brain development have identified differential effects of adversity on amygdala volume depending on age of exposure (Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014; Tottenham & Sheridan, 2009), and there is preliminary evidence linking the age of maltreatment exposure to degree of amygdala reactivity during childhood (McCrory et al., 2013). However, the complexity and chronicity of adverse experiences in the majority of human studies makes it challenging to differentiate whether stress-related effects on amygdala-prefrontal development occur as a function of the duration or timing of the stress exposure. Although international adoption studies can provide insight into the effects of ELS (e.g. institutional care) that occurs during a discrete developmental window, there may be limitations in its generalizability. These limitations highlight the important role of preclinical studies that use animal models of ELS. While there will always be the ethical limitations in studying stress exposure in humans, animal studies can experimentally manipulate age of onset, chronicity, and severity of ELS to allow for greater conclusions of causality. Moreover, translational research can provide more precise examination of the underlying neurobiological mechanisms associated with early adverse experiences that cannot be accessed through human neuroimaging studies.

Second, recent theoretical frameworks have emphasized importance of examining specific dimensions of early adverse experiences, such as threat and neglect, and how they influence different aspects of neurobiological development (McLaughlin et al., 2014). Although the current review focused specifically on threat-related alterations in amygdala-prefrontal circuitry, other dimensions of early experience may target different neural circuits (e.g. cortico-striatal circuitry) and neuro-cognitive domains (e.g. reward learning, executive functions; Goff & Tottenham, 2014; McLaughlin et al., 2014). Further longitudinal research

is needed to compare how certain dimensions of adverse experiences differentially alter neurobiological circuitry to confer risk for specific domains of psychopathology.

In addition to protective factors of the social environment, genetic factors play an important role in moderating risk for emotional psychopathology following ELS (Heim & Binder, 2012; Uher & McGuffin, 2008). For example, genetic polymorphisms in neuroplasticity genes (e.g. BDNF) have been associated with ELS-related changes in neurobiological development and emotion regulation (Casey et al., 2009). More recent work has shown that cumulative risk profiles across several HPA-related genetic alleles moderate the association between amygdala-prefrontal connectivity and anxiety symptoms in children exposed to stressful life events (Pagliaccio et al., 2015). Importantly, genetic factors are often correlated with variability in the early environment in human studies, representing a significant challenge for researchers to differentiate the effects of genetics (e.g. parent psychopathology) from the effects of ELS (e.g. family conflict). This can include studies of adoption and foster-care cohorts, as children who display more emotional difficulties at a young age may experience greater disruptions in family placements (Scarr & Mccartney, 1983). Despite these potential confounds, not all individuals with genetic predispositions (e.g. family history of psychopathology) will develop an emotional disorder, and emerging research suggests that environmentally-induced epigenetic modifications in gene expression also predict vulnerability for psychopathology (Swartz, Hariri, & Williamson, 2016). For example, low socioeconomic status has been associated with longitudinal increases in promotor methylation of the sertonin transporter gene during adolescence (Swartz, Hariri, & Williamson, 2016). Importantly, these epigenetic changes were associated with enhanced threat-related amygdala reactivity, which in turn predicted longitudinal increases in depressive symptoms in adolescents with a family history of depression (Swartz et al., 2016). These findings emphasize the critical role of early experiences on the developmental trajectories of neuro-affective circuitry and risk for stress-related psychopathology.

7 Conclusion

In summary, emerging research has begun to identify the developmental pathways through which early adverse experiences alter emotion regulation circuitry to increase risk for stress-related psychopathology. However, little is known regarding the differential effects of adversity on amygdala-prefrontal function during different developmental stages (i.e. infancy, childhood, adolescence) and different dimensions of exposure (i.e. maltreatment vs. neglect). Further research delineating the effects of timing and type of adversities, as well as their interplay with genetic and epigenetic factors, is needed to advance our understanding of the neuro-developmental mechanisms implicated in vulnerability for psychopathology following ELS. This research will be facilitated by the incorporation of translational studies that directly compare human studies with animal models of ELS to provide further insight into the mechanisms underlying the link between early experiences and neuro-affective development. By applying a dimensional and developmental framework to future research, we can also begin to elucidate how and when protective factors can buffer the effects of ELS on neurobiological development to mitigate long-term risk for psychopathology. Ultimately, such research will be informative for developing policies and targeted interventions to improve mental health outcomes for individuals who have experienced early adversity.

References

Afifi TO, MacMillan HL. Resilience following child maltreatment: A review of protective factors. Canadian Journal of Psychiatry. 2011 May.56:266–272. 10.1016/0145-2134(96)00062-2 10.1017/S0954579409000480 10.1016/S0145-2134(03)00104-2. DOI: 10.1016/j.chiabu.2005.11.015 [PubMed: 21586192]

Arata CM, Langhinrichsen-Rohling J, Bowers D, O'Brien N. Differential correlates of multi-type maltreatment among urban youth. Child Abuse & Neglect. 2007; 31(4):393–415. DOI: 10.1016/j.chiabu.2006.09.006 [PubMed: 17412420]

Avishai-Eliner S, Yi SJ, Baram TZ. Developmental profile of messenger RNA for the corticotropin-releasing hormone receptor in the rat limbic system. Brain Research. Developmental Brain Research. 1996; 91(2):159–63. http://doi.org/0165380695001581 [pii]. [PubMed: 8852365]

Barker DJP. The origins of the developmental origins theory. Journal of Internal Medicine. 2007; 261(5):412–417. DOI: 10.1111/j.1365-2796.2007.01809.x [PubMed: 17444880]

Blair C, Raver CC. Child development in the context of adversity: Experiential canalization of brain and behavior. American Psychologist. 2012; 67(4):309–318. DOI: 10.1037/a0027493 [PubMed: 22390355]

Bogdan R, Williamson DE, Hariri AR. Mineralocorticoid receptor Iso/Val (rs5522) genotype moderates the association between previous childhood emotional neglect and amygdala reactivity. American Journal of Psychiatry. 2012; 169:515–522. DOI: 10.1176/appi.ajp.2011.11060855 [PubMed: 22407082]

Buhle JT, Silvers JaWager TD, Lopez R, Onyemekwu C, Kober H, … Ochsner KN. Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies; Cerebral Cortex (New York, NY: 1991). 2013. 1–10. (Gross 1998)

Burghy CaStodola DE, Ruttle PL, Molloy EK, Armstrong JM, Oler Ja… Birn RM. Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. Nature Neuroscience. 2012; 15(12):1736–41. DOI: 10.1038/nn.3257 [PubMed: 23143517]

Callaghan BL, Sullivan RM, Howell B, Tottenham N. The international society for developmental psychobiology Sackler symposium: Early adversity and the maturation of emotion circuits-A cross-species analysis. Developmental Psychobiology. 2014; 56(8):1635–1650. DOI: 10.1002/dev.21260 [PubMed: 25290865]

Callaghan BL, Tottenham N. The Stress Acceleration Hypothesis: Effects of early-life adversity on emotion circuits and behavior. Current Opinion in Behavioral Sciences. 2016; 7:76–81. DOI: 10.1016/j.cobeha.2015.11.018 [PubMed: 29644262]

Casey BJ, Glatt CE, Tottenham N, Soliman F, Bath K, Amso D, … Lee FS. Brain-derived neurotrophic factor as a model system for examining gene by environment interactions across development. Neuroscience. 2009; 164(1):108–20. DOI: 10.1016/j.neuroscience.2009.03.081 [PubMed: 19358879]

Cicchetti D, Blender JA. A multiple-levels-of-analysis perspective on resilience: Implications for the developing brain, neural plasticity, and preventive interventions. Annals of the New York Academy of Sciences. 2006; 1094:248–258. DOI: 10.1196/annals.1376.029 [PubMed: 17347356]

Cicchetti D, Rogosch FA. Equifinality and multifinality in developmental psychopathology. Development and Psychopathology. 1996; 8:597–600. Retrieved from file://localhost/Users/lornaquandt/Documents/Papers/2007/Unknown/2007-3.pdf\npapers://4f210845-804c-495f-b761-84503ca2694d/Paper/p757.

Collishaw S, Pickles A, Messer J, Rutter M, Shearer C, Maughan B. Resilience to adult psychopathology following childhood maltreatment: Evidence from a community sample. Child Abuse & Neglect. 2007; 31(3):211–229. DOI: 10.1016/j.chiabu.2007.02.004 [PubMed: 17399786]

Crozier JC, Wang L, Huettel Sa, De Bellis MD. Neural correlates of cognitive and affective processing in maltreated youth with posttraumatic stress symptoms: Does gender matter? Development and Psychopathology. 2014; 26(2):491–513. DOI: 10.1017/S095457941400008X [PubMed: 24621958]

Dannlowski U, Kugel H, Huber F, Stuhrmann A, Redlich R, Grotegerd D, … Suslow T. Childhood maltreatment is associated with an automatic negative emotion processing bias in the amygdala. Human Brain Mapping. 2013; 34(11):2899–909. DOI: 10.1002/hbm.22112 [PubMed: 22696400]

Davis M, Whalen PJ. The amygdala: vigilance and emotion. Molecular Psychiatry. 2001; 6(1):13–34. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11244481. [PubMed: 11244481]

De Bellis MD, Broussard ER, Herring DJ, Wexler S, Moritz G, Benitez JG. Psychiatric co-morbidity in caregivers and children involved in maltreatment: A pilot research study with policy implications. Child Abuse and Neglect. 2001; 25(7):923–944. DOI: 10.1016/S0145-2134(01)00247-2 [PubMed: 11523869]

Decety J, Michalska KJ, Kinzler KD. The contribution of emotion and cognition to moral sensitivity: A neurodevelopmental study. Cerebral Cortex. 2012; 22(1):209–220. DOI: 10.1093/cercor/bhr111 [PubMed: 21616985]

Del Giudice M, Ellis BJ, Shirtcliff EA. Neuroscience and Biobehavioral Reviews The Adaptive Calibration Model of stress responsivity. Neuroscience and Biobehavioral Reviews. 2011; 35(7):1562–1592. DOI: 10.1016/j.neubiorev.2010.11.007 [PubMed: 21145350]

Dillon DG, Rosso IM, Pechtel P, Killgore WDS, Rauch SL, Pizzagalli DA. responses and reward processing in anxiety and depression. 2015; 31(3):233–249. DOI: 10.1002/da.22202.Peril

Dougherty LR, Blankenship SL, Spechler Pa, Padmala S, Pessoa L. An fMRI Pilot Study of Cognitive Reappraisal in Children: Divergent Effects on Brain and Behavior. Journal of Psychopathology and Behavioral Assessment. 2015; 37(4):634–644. DOI: 10.1007/s10862-015-9492-z [PubMed: 26692636]

DuMont KA, Widom CS, Czaja SJ. Predictors of resilience in abused and neglected children grown-up: The role of individual and neighborhood characteristics. Child Abuse & Neglect. 2007; 31(3):255–274. DOI: 10.1016/j.chiabu.2005.11.015 [PubMed: 17386940]

Eiland L, Ramroop J, Hill MN, Manley J, McEwen BS. Chronic juvenile stress produces corticolimbic dendritic architectural remodeling and modulates emotional behavior in male and female rats. Psychoneuroendocrinology. 2012; 37(1):39–47. DOI: 10.1016/j.psyneuen.2011.04.015 [PubMed: 21658845]

Essex MJ, Shirtcliff Ea, Burk LR, Ruttle PL, Klein MH, Slattery MJ, … Armstrong JM. Influence of early life stress on later hypothalamic-pituitary-adrenal axis functioning and its covariation with mental health symptoms: a study of the allostatic process from childhood into adolescence. Development and Psychopathology. 2011; 23(4):1039–58. DOI: 10.1017/S0954579411000484 [PubMed: 22018080]

Etkin A, Klemenhagen KC, Dudman JT, Rogan MT, Hen R, Kandel ER, Hirsch J. Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. Neuron. 2004; 44(6):1043–55. DOI: 10.1016/j.neuron.2004.12.006 [PubMed: 15603746]

Evans GW, Swain JE, King AP, Wang X, Javanbakht A, Ho SS, … Liberzon I. Childhood Cumulative Risk Exposure and Adult Amygdala Volume and Function. Journal of Neuroscience Research. 2016; 94(6):535–43. DOI: 10.1002/jnr.23681 [PubMed: 26469872]

Fan Y, Herrera-Melendez AL, Pestke K, Feeser M, Aust S, Otte C, … Grimm S. Early life stress modulates amygdala-prefrontal functional connectivity: Implications for oxytocin effects. Human Brain Mapping. 2014; 35(10):5328–39. DOI: 10.1002/hbm.22553 [PubMed: 24862297]

Gabard-Durnam LJ, Flannery J, Goff B, Gee DG, Humphreys KL, Telzer E, … Tottenham N. The development of human amygdala functional connectivity at rest from 4 to 23 years: a cross-sectional study. NeuroImage. 2014; 95:193–207. DOI: 10.1016/j.neuroimage.2014.03.038 [PubMed: 24662579]

Gaffrey MS, Barch DM, Luby JL. Amygdala reactivity to sad faces in preschool children: An early neural marker of persistent negative affect. Developmental Cognitive Neuroscience. 2016; 17:94–100. DOI: 10.1016/j.dcn.2015.12.015 [PubMed: 26780113]

Gaffrey MS, Luby JL, Belden AC, Hirshberg JS, Volsch J, Barch DM. Association between depression severity and amygdala reactivity during sad face viewing in depressed preschoolers: An fMRI study. Journal of Affective Disorders. 2011; 129(1–3):364–370. DOI: 10.1016/j.jad.2010.08.031 [PubMed: 20869122]

Garrett AS, Carrion V, Kletter H, Karchemskiy A, Weems CF, Reiss A. Brain Activation To Facial Expressions in Youth With Ptsd Symptoms. Depression and Anxiety. 2012; 29(5):449–459. DOI: 10.1002/da.21892 [PubMed: 22553009]

Gee DG, Gabard-Durnam LJ, Flannery J, Goff B, Humphreys KL, Telzer EH, … Tottenham N. Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110(39): 15638–43. DOI: 10.1073/pnas.1307893110 [PubMed: 24019460]

Gee DG, Gabard-Durnam L, Telzer EH, Humphreys KL, Goff B, Shapiro M, … Tottenham N. Maternal Buffering of Human Amygdala-Prefrontal Circuitry During Childhood but Not During Adolescence. Psychological Science. 2014; 25(11):2067–2078. DOI: 10.1177/0956797614550878 [PubMed: 25280904]

Gee DG, Humphreys KL, Flannery J, Goff B, Telzer EH, Shapiro M, … Tottenham N. A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2013; 33(10): 4584–93. DOI: 10.1523/JNEUROSCI.3446-12.2013 [PubMed: 23467374]

Gianaros PJ, Horenstein Ja, Hariri AR, Sheu LK, Manuck SB, Matthews Ka, Cohen S. Potential neural embedding of parental social standing. Social Cognitive and Affective Neuroscience. 2008; 3(2): 91–96. DOI: 10.1093/scan/nsn003 [PubMed: 18594696]

Goff B, Tottenham N. Early-life adversity and adolescent depression: mechanisms involving the ventral striatum. CNS Spectrums. 2015; 20(4):337–45. DOI: 10.1017/S1092852914000674 [PubMed: 25511634]

Graham AM, Pfeifer JH, Fisher PA, Carpenter S, Fair DA. Early life stress is associated with default system integrity and emotionality during infancy. Journal of Child Psychology and Psychiatry. 2015; 56(11):1212–22. DOI: 10.1111/jcpp.12409 [PubMed: 25809052]

Graham AM, Pfeifer JH, Fisher Pa, Lin W, Gao W, Fair Da. The potential of infant fMRI research and the study of early life stress as a promising exemplar. Developmental Cognitive Neuroscience. 2014; 12:12–39. DOI: 10.1016/j.dcn.2014.09.005 [PubMed: 25459874]

Green JG, Mclaughlin Ka, Berglund Pa, Gruber MJ, Sampson Na, Zaslavsky AM, Kessler RC. Childhood Adversities and Adult Psychiatric Disorders in the National Comorbidity Survey Replication I. 2010; 67(2):113–123. DOI: 10.1001/archgenpsychiatry.2009.187

Guyer AE, Monk CS, McClure-Tone EB, Nelson EE, Roberson-Nay R, Adler AD, … Ernst M. A developmental examination of amygdala response to facial expressions. Journal of Cognitive Neuroscience. 2008; 20(9):1565–1582. DOI: 10.1162/jocn.2008.20114 [PubMed: 18345988]

Hariri AR, Holmes A. Finding translation in stress research. Nature Neuroscience. 2015; 18(10):1347–1352. DOI: 10.1038/nn.4111 [PubMed: 26404709]

Hatalski CG, Guirguis C, Baram TZ. Corticotropin releasing factor mRNA expression in the hypothalamic paraventricular nucleus and the central nucleus of the amygdala is modulated by repeated acute stress in the immature rat. Journal of Neuroendocrinology. 2012; 10(9):663–669.

Heim C, Binder EB. Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions, and epigenetics. Experimental Neurology. 2012; 233(1):102–11. DOI: 10.1016/j.expneurol.2011.10.032 [PubMed: 22101006]

Hennessy MB, Kaiser S, Sachser N. Social buffering of the stress response: Diversity, mechanisms, and functions. Frontiers in Neuroendocrinology. 2009; 30(4):470–482. DOI: 10.1016/j.yfrne.2009.06.001 [PubMed: 19545584]

Herringa RJ, Birn RM, Ruttle PL, Burghy CA, Stodola DE, Davidson RJ, Essex MJ. Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110(47):19119–24. DOI: 10.1073/pnas.1310766110 [PubMed: 24191026]

Hostinar CE, Johnson AE, Gunnar MR. Parent support is less effective in buffering cortisol stress reactivity for adolescents compared to children. Developmental Science. 2014; 2:281–297. DOI: 10.1111/desc.12195

Hostinar CE, Johnson AE, Gunnar MR. Early Social Deprivation and the Social Buffering of Cortisol Stress Responses in Late Childhood: An Experimental Study. 2015; 51(11):1597–1608.

Humphreys KL, Gleason MM, Drury SS, Miron D, Nelson CA, Fox NA, Zeanah CH. Effects of institutional rearing and foster care on psychopathology at age 12 years in Romania: follow-up of an open, randomised controlled trial. The Lancet Psychiatry. 2015; 2(7):625–34. DOI: 10.1016/S2215-0366(15)00095-4 [PubMed: 26303560]

Hwang S, White SF, Nolan ZT, Sinclair S, Blair RJR. Neurodevelopmental changes in the responsiveness of systems involved in top down attention and emotional responding. Neuropsychologia. 2014; 62:1–9. DOI: 10.1016/j.neuropsychologia.2014.08.003 [PubMed: 25019362]

Ishikawa J, Nishimura R, Ishikawa A. Early-life stress induces anxiety-like behaviors and activity imbalances in the medial prefrontal cortex and amygdala in adult rats. The European Journal of Neuroscience. 2015; 41(4):442–53. DOI: 10.1111/ejn.12825 [PubMed: 25581710]

Jaffee SR, Caspi A, Moffitt TE, Polo-Tomás M, Taylor A. Individual, family, and neighborhood factors distinguish resilient from non-resilient maltreated children: A cumulative stressors model. Child Abuse & Neglect. 2007; 31(3):231–253. DOI: 10.1016/j.chiabu.2006.03.011 [PubMed: 17395260]

Javanbakht A, King AP, Evans GW, Swain JE, Angstadt M, Phan KL, Liberzon I. Childhood Poverty Predicts Adult Amygdala and Frontal Activity and Connectivity in Response to Emotional Faces. Frontiers in Behavioral Neuroscience. 2015; 9(154)doi: 10.3389/fnbeh.2015.00154

Jedd K, Hunt RH, Cicchetti D, Hunt E, Cowell RA, Rogosch FA, … Thomas KM. Long-term consequences of childhood maltreatment: Altered amygdala functional connectivity. Development and Psychopathology. 2015; 27:1577–1589. DOI: 10.1017/S0954579415000954 [PubMed: 26535945]

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry2. 2005; 62(6):593–602. DOI: 10.1001/archpsyc.62.6.593

Kessler RC, McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, … Williams DR. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. The British Journal of Psychiatry. 2010; 197(5):378–385. DOI: 10.1192/bjp.bp.110.080499 [PubMed: 21037215]

Kikusui T, Winslow JT, Mori Y. Social buffering: Relief from stress and anxiety. Philosophical Transactions of the Royal Society B: Biological Sciences. 2006; 361(1476):2215–2228. DOI: 10.1098/rstb.2006.1941

Kim JH, Hamlin AS, Richardson R. Fear extinction across development: the involvement of the medial prefrontal cortex as assessed by temporary inactivation and immunohistochemistry. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2009; 29(35):10802–8. DOI: 10.1523/JNEUROSCI.0596-09.2009 [PubMed: 19726637]

Kim P, Evans GW, Angstadt M, Ho SS, Sripada CS, Swain JE. Effects of childhood poverty and chronic stress on emotion regulatory brain function in adulthood. PNAS. 2013; 110(46):18442–18447. DOI: 10.1073/pnas.1308240110/-/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1308240110 [PubMed: 24145409]

Koenigs M, Grafman J. Posttraumatic Stress Disorder: The Role of Medial Prefrontal Cortex and Amygdala. The Neuroscientist. 2009; 15(5):540–548. [PubMed: 19359671]

Kujawa A, Wu M, Klump H, Pine DS, Swain JE, Fitzgerald KD, … Phan KL. Altered Development of Amygdala-Anterior Cingulate Cortex Connectivity in Anxious Youth and Young Adults. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2016; 1(4):345–352. DOI: 10.1017/CBO9781107415324.004 [PubMed: 27525316]

Lansford JE, Dodge KA, Pettit GS, Bates JE, Crozier J, Kaplow J. A 12-Year Prospective Study of the Long-term Effects of Early Child Physical Maltreatment on Psychological, Behavioral, and Academic Problems in Adolescence. 2014; 156:824–830.

Maheu, Dozier M, Guyer AE, Mandell D, Peloso E, Poeth K, Jenness J. Preliminary study of medial temporal lobe function in youths with a history of caregiver deprivation and emotional neglect. Cog Affect Behav NEurosci. 2010; 10(1):34–49. DOI: 10.3758/CABN.10.1.34.A

Malter Cohen M, Jing D, Yang RR, Tottenham N, Lee FS, Casey BJ. Early-life stress has persistent effects on amygdala function and development in mice and humans. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110(45):18274–8. DOI: 10.1073/pnas.1310163110 [PubMed: 24145410]

Marusak HaMartin KR, Etkin A, Thomason ME. Childhood Trauma Exposure Disrupts the Automatic Regulation of Emotional Processing. Neuropsychopharmacology. 2014; 40(5):1250–1258. DOI: 10.1038/npp.2014.311

Masten AS. Regulatory processes, risk, and resilience in adolescent development. Annals of the New York Academy of Sciences. 2004; 1021:310–319. DOI: 10.1196/annals.1308.036 [PubMed: 15251901]

McCrory EJ, De Brito Sa, Kelly Pa, Bird G, Sebastian CL, Mechelli A, … Viding E. Amygdala activation in maltreated children during pre-attentive emotional processing. The British Journal of Psychiatry: The Journal of Mental Science. 2013; 202(4):269–76. DOI: 10.1192/bjp.bp.112.116624 [PubMed: 23470285]

McCrory EJ, De Brito Sa, Sebastian CL, Mechelli A, Bird G, Kelly Pa, Viding E. Heightened neural reactivity to threat in child victims of family violence. Current Biology: CB. 2011; 21(23):R947–8. DOI: 10.1016/j.cub.2011.10.015 [PubMed: 22153160]

McGloin JM, Widom CS. Resilience among abused and neglected children grown up. Development and Psychopathology. 2001; 13(4):1021–1038. DOI: 10.1017/S095457940100414X [PubMed: 11771905]

McLaughlin KaSheridan MaLambert HHK. Childhood Adversity and Neural Development: Deprivation and Threat as Distinct Dimensions of Early Experience. Neuroscience and Biobehavioral Reviews. 2014; 47:578–91. DOI: 10.1016/j.neubiorev.2014.10.012 [PubMed: 25454359]

McLaughlin KA. Future Directions in Childhood Adversity and Youth Psychopathology. Journal of Clinical Child & Adolescent Psychology. 2016; 45(3):361–82. DOI: 10.1080/15374416.2015.1110823 [PubMed: 26849071]

McLaughlin KaPeverill M, Gold AL, Alves S, Sheridan Ma. Child Maltreatment and Neural Systems Underlying Emotion Regulation. Journal of the American Academy of Child & Adolescent Psychiatry. 2015; 54(9):753–762. DOI: 10.1016/j.jaac.2015.06.010 [PubMed: 26299297]

McRae K, Gross JJ, Weber J, Robertson ER, Sokol-Hessner P, Ray RD, … Ochsner KN. The development of emotion regulation: an fMRI study of cognitive reappraisal in children, adolescents and young adults. Social Cognitive and Affective Neuroscience. 2012; 7(1):11–22. DOI: 10.1093/scan/nsr093 [PubMed: 22228751]

Merikangas KR, He J, Burstein M, Swanson SA, Avenevoli S, Cui L, … Swendsen J. Lifetime Prevalence of Mental Disorders in U.S. Adolescents: Results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A). Journal of the American Academy of Child & Adolescent Psychiatry. 2010; 49(10):980–989. DOI: 10.1016/j.jaac.2010.05.017 [PubMed: 20855043]

Milad MR, Rauch SL, Pitman RK, Quirk GJ. Fear extinction in rats: Implications for human brain imaging and anxiety disorders. 2006; 73:61–71. DOI: 10.1016/j.biopsycho.2006.01.008

Miller-Graff LE, Cater ÅK, Howell KH, Graham-Bermann SA. Parent-child warmth as a potential mediator of childhood exposure to intimate partner violence and positive adulthood functioning. Anxiety, Stress, and Coping. 2016; 29(3):259–273. DOI: 10.1080/10615806.2015.1028030

Moriceau S, Sullivan RM. Maternal presence serves as a switch between learning fear and attraction in infancy. Nature Neuroscience. 2006; 9(8):1004–6. DOI: 10.1038/nn1733 [PubMed: 16829957]

Moriceau S, Wilson Da, Levine S, Sullivan RM. Dual circuitry for odor-shock conditioning during infancy: corticosterone switches between fear and attraction via amygdala. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2006; 26(25):6737–48. DOI: 10.1523/JNEUROSCI.0499-06.2006 [PubMed: 16793881]

Morris SE, Cuthbert BN. State of the art. Dialogues in Clinical Neuroscience. 2012; 14:29–37. [PubMed: 22577302]

Murray EA, Wise SP, Drevets WC. Localization of Dysfunction in Major Depressive Disorder: Prefrontal Cortex and Amygdala. BPS. 2011; 69(12):e43–e54. DOI: 10.1016/j.biopsych.2010.09.041

Pagliaccio D, Luby J, Gaffrey M, Belden A, Botteron K, Gotlib IH, Barch DM. Anomalous functional brain activation following negative mood induction in children with pre-school onset major

depression. Developmental Cognitive Neuroscience. 2012; 2(2):256–267. DOI: 10.1016/j.dcn.2011.11.008 [PubMed: 22483075]

Pagliaccio D, Luby JL, Bogdan R, Agrawal A, Gaffrey MS, Belden AC, … Barch DM. Amygdala Functional Connectivity, HPA Axis Genetic Variation, and Life Stress in Children and Relations to Anxiety and Emotion Regulation. 2015; 124(4):817–833.

Pagliaccio D, Luby JL, Luking KR, Belden AC, Barch DM. Brain–behavior relationships in the experience and regulation of negative emotion in healthy children: Implications for risk for childhood depression. Development and Psychopathology. 2014; 26:1289–1303. http://doi.org/doi:10.1017/S0954579414001035. [PubMed: 25422962]

Pechtel P, Lyons-Ruth K, Anderson CM, Teicher MH. Sensitive periods of amygdala development: the role of maltreatment in preadolescence. NeuroImage. 2014; 97:236–44. DOI: 10.1016/j.neuroimage.2014.04.025 [PubMed: 24736182]

Phelps EaLeDoux JE. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron. 2005; 48(2):175–87. DOI: 10.1016/j.neuron.2005.09.025 [PubMed: 16242399]

Pine DS, Guyer AE, Leibenluft E. Functional Magnetic Resonance Imaging and Pediatric Anxiety. Journal of the American Academ. 2008; 47(11):1217–1221. DOI: 10.1097/CHI.0b013e318185dad0.FUNCTIONAL

Raineki C, Cortés MR, Belnoue L, Sullivan RM. Effects of early-life abuse differ across development: infant social behavior deficits are followed by adolescent depressive-like behaviors mediated by the amygdala. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2012; 32(22):7758–65. DOI: 10.1523/JNEUROSCI.5843-11.2012 [PubMed: 22649253]

Roy AK, Fudge JL, Kelly C, Perry JSa, Daniele T, Carlisi C, … Ernst M. Intrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2013; 52(3):290–299e2. DOI: 10.1016/j.jaac.2012.12.010 [PubMed: 23452685]

Scarr S, Mccartney K. How People Make Their Own Environments: A Theory of Genotype → Environment Effects Author (s): Sandra Scarr and Kathleen McCartney Published by: Wiley on behalf of the Society for Research in Child Development Stable URL: http://www.jstor.org/stable/. Child Development. 1983; 54(2):424–435. [PubMed: 6683622]

Silvers JaShu J, Hubbard AD, Weber J, Ochsner KN. Concurrent and lasting effects of emotion regulation on amygdala response in adolescence and young adulthood. Developmental Science. 2015; 18(5):771–84. DOI: 10.1111/desc.12260 [PubMed: 25439326]

Smith LB, Thelen E. Development as a dynamic system. Trends in Cognitive Sciences. 2003; 7(8):343–348. DOI: 10.1016/S1364-6613(03)00156-6 [PubMed: 12907229]

Suzuki H, Luby JL, Botteron KN, Dietrich R, McAvoy MP, Barch DM. Early life stress and trauma and enhanced limbic activation to emotionally valenced faces in depressed and healthy children. Journal of the American Academy of Child and Adolescent Psychiatry. 2014; 53(7):800–813e10. DOI: 10.1016/j.jaac.2014.04.013 [PubMed: 24954829]

Swartz JR, Carrasco M, Wiggins JL, Thomason ME, Monk CS. Age-related changes in the structure and function of prefrontal cortex-amygdala circuitry in children and adolescents: a multi-modal imaging approach. NeuroImage. 2014; 86:212–20. DOI: 10.1016/j.neuroimage.2013.08.018 [PubMed: 23959199]

Swartz JR, Hariri AR, Williamson DE. An epigenetic mechanism links socioeconomic status to changes in depression-related brain function in high-risk adolescents; Molecular Psychiatry. 2016 Apr. 1–6.

Swartz JR, Williamson DE, Hariri AR. Developmental Change in Amygdala Reactivity during Adolescence: Effects of Family History for Depression and Stressful Life Events. American Journal of Psychiatry. 2015; 172(3):276–283. DOI: 10.1176/appi.ajp.2014.14020195 [PubMed: 25526599]

Thomason ME, Marusak HA, Tocco MA, Vila AM, McGarragle O, Rosenberg DR. Altered amygdala connectivity in urban youth exposed to trauma. Social Cognitive and Affective Neuroscience. 2015; 10(11):1460–1468. DOI: 10.1093/scan/nsv030 [PubMed: 25836993]

Tottenham N, Hare Ta, Millner a, Gilhooly T, Zevin JD, Casey BJ. Elevated amygdala response to faces following early deprivation. Developmental Science. 2011; 14(2):190–204. DOI: 10.1111/j.1467-7687.2010.00971.x [PubMed: 21399712]

Tottenham N, Sheridan MA. A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. Frontiers in Human Neuroscience. 2009; 3:68.doi: 10.3389/neuro.09.068.2009 [PubMed: 20161700]

Troller-Renfree S, Mcdermott JM, Nelson CA, Zeanah CH, Fox NA. The effects of early foster care intervention on attention biases in previously institutionalized children in Romania. Developmental Science. 2015; 18(5):713–722. DOI: 10.1111/desc.12261 [PubMed: 25439678]

Troller-renfree S, Mclaughlin KA, Sheridan MA, Nelson CA, Zeanah CH, Fox NA. The benefits of a positive attention bias amongst children with a history of psychosocial deprivation. Biological Psychology. 2016.

Uher R, McGuffin P. The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: review and methodological analysis. Molecular Psychiatry. 2008; 13(2):131–146. DOI: 10.1038/sj.mp.4002067 [PubMed: 17700575]

van Harmelen AL, van Tol MJ, Demenescu LR, van der Wee NJa, Veltman DJ, Aleman A, … Elzinga BM. Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment. Social Cognitive and Affective Neuroscience. 2013; 8(4):362–9. DOI: 10.1093/scan/nss007 [PubMed: 22258799]

Vink M, Derks JM, Hoogendam JM, Hillegers M, Kahn RS. Functional differences in emotion processing during adolescence and early adulthood. NeuroImage. 2014; 91:70–6. DOI: 10.1016/j.neuroimage.2014.01.035 [PubMed: 24468408]

Wadhwa P, Buss C, Entringer S, Swanson M. Developmental Origins of Health and Disease: Brief history of the appraoch and current focus on epigenetic mechanisms. Semin Reprod Med. 2010; 27(5):358–368. DOI: 10.1055/s-0029-1237424.Developmental

White MG, Bogdan R, Fisher PM, Muñoz KE, Williamson DE, Hariri aR. FKBP5 and emotional neglect interact to predict individual differences in amygdala reactivity. Genes, Brain, and Behavior. 2012; 11(7):869–78. DOI: 10.1111/j.1601-183X.2012.00837.x

Wolf RC, Herringa RJ. Prefrontal-Amygdala Dysregulation to Threat in Pediatric Post-Traumatic Stress Disorder. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. 2016; 41(3):822–31. DOI: 10.1038/npp.2015.209 [PubMed: 26171717]