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Effects of early life stress on amygdala and striatal development

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ABSTRACT

Species-expected caregiving early in life is critical for the normative development and regulation of emotional behavior, the ability to effectively evaluate affective stimuli in the environment, and the ability to sustain social relationships. Severe psychosocial stressors early in life (early life stress; ELS) in the form of the absence of species expected caregiving (i.e., caregiver deprivation), can drastically impact one's social and emotional success, leading to the onset of internalizing illness later in life. Development of the amygdala and striatum, two key regions supporting affective valuation and learning, is significantly affected by ELS, and their altered developmental trajectories have important implications for cognitive, behavioral and socioemotional development. However, an understanding of the impact of ELS on the development of functional interactions between these regions and subsequent behavioral effects is lacking. In this review, we highlight the roles of the amygdala and striatum in affective valuation and learning in maturity and across development. We discuss their function separately as well as their interaction. We highlight evidence across species characterizing how ELS induced changes in the development of the amygdala and striatum mediate subsequent behavioral changes associated with internalizing illness, positing a particular import of the effect of ELS on their interaction.

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1. Introduction

The ability to navigate the world is dependent upon evaluating affective stimuli in terms of their relative danger/safety and their potential for reward (e.g., appraising someone as trustworthy, avoiding unhealthy foods). While extensive research indicates that affective valuation relies heavily on the amygdala and ventral striatum in adulthood, early life may be a time during which such processes are critical for learning environmental contingencies and understanding how to interact with the world. A robust literature highlights important normative structural and functional changes in the amygdala and striatum during the early years of life (i.e., childhood, adolescence), which facilitate approach and avoidance behaviors. One key factor in the normative development of affective valuation is a stable rearing environment characterized by the presence of species expected caregiver availability (Tottenham, 2012). Caregivers provide developing organisms not only a means by which to meet basic survival needs, but they also provide a regulatory base from which to explore and learn about the world (Hofer, 2006).

Across species, severe psychosocial stressors early in life (early life stress; ELS), particularly in the form of the *absence* of species expected caregiving (i.e., caregiver deprivation) can profoundly influence affective valuation and the establishment of stable relationships with caregivers and others. Caregiver deprivation is frequently associated with a host of developmental concerns, including the onset of both internalizing (anxiety and depressive disorders) and externalizing behaviors (e.g., impulsivity, conduct disorders) later in life (Ellis et al., 2004; Zeanah et al., 2009). These behavioral phenotypes critically involve alterations in the ability to evaluate and appropriately respond to rewarding/aversive stimuli, suggesting that ELS induces alterations in the functional development of the amygdala and striatum. In this review we will examine the effects of ELS on neural and socio-affective development, largely from on the perspective of caregiver deprivation. We propose that the association between ELS and subsequent behavioral consequences associated with internalizing illness are mediated by changes effected on amygdala and striatal function and their interaction. We will begin by operationalizing ELS and its downstream behavioral consequences. We will next detail anatomical and functional considerations of the amygdala and ventral striatum in maturely developed organisms, with respect to their role in affective valuation, with a particular spotlight on examining their interaction. Next we will review extant findings on the normative structural and functional development of these structures. We will then highlight the role of ELS in the structural and functional development of these regions and related behavioral effects. We will conclude with a proposal for how ELS may affect amygdala-striatal interactions and discuss limitations and future directions for the field.

A recent framework for conceptualizing ELS posits that adverse early experiences fall along dimensions of threat and deprivation (McLaughlin et al., 2014; Sheridan and McLaughlin, 2014). Here, threat is conceptualized as an atypical experience posing a direct physical danger to a developing organism (e.g., physical/sexual abuse), whereas deprivation is operationalized as the absence of expected social, cognitive and affective environmental inputs and enrichment during development (e.g., neglect). Consideration of the nature of adversities experienced is an important step forward in the field. We would add that caregiver deprivation (i.e., emotional neglect or institutional care) also poses a direct threat to a (semi-)altricial organism's survival: caregiver deprivation involves a lack of protection from outside threats and a lack/absence of physiological and affective regulation from a caregiver. Caregiver deprivation can take many forms across species––e.g., removing a maternal figure from a nest, rearing in isolation from the rest of a group, or institutionalization in humans (i.e., being reared in orphanage care). We will focus largely on ELS in the form of caregiver deprivation in this review, because it allows for the ability to draw parallels across non-human and human literatures.

ELS is often associated with the development of a host of cognitive, social and affective deficits, which precede the development of mental illness later in life (Gee and Casey, 2015; Green et al., 2010; Gunnar and Quevedo, 2007; Masten and Cicchetti, 2010). Most frequently, caregiver deprivation is linked with the development of social withdrawal, poor regulatory abilities, and higher risk for internalizing illness such as depression and anhedonia, anxiety disorders, as well as externalizing disorders and behavioral problems (Conti et al., 2012; Corcoran et al., 2012; Ellis et al., 2004; Gee and Casey, 2015; Gunnar and Quevedo, 2007; Lupien et al., 2009; Pechtel and Pizzagalli, 2011; Romeo et al., 2003; Sánchez et al., 2001; Tottenham and Sheridan, 2009; Zeanah et al., 2009). The link between caregiver deprivation and downstream mental health consequences may be mediated by ELS induced changes in the functional development of the amygdala and striatum and their interaction, both of which undergo massive change throughout childhood and adolescence, lending them to be plastic and subject to environmental influence (Gee and Casey, 2015; Masten and Cicchetti, 2010).

2. Amygdala and striatum: anatomical considerations

The amygdala and striatum are two subcortical structures critical for affective valuation and learning across species. The amygdala is comprised of approximately thirteen nuclei and subnuclei (rodents: LeDoux, 2000 non-human primates: Pitkänen and Amaral, 1998; Pitkänen et al., 1997). The basolateral complex of the amygdala (the lateral nucleus, basal nucleus, accessory basal nucleus; BLA) and the central nucleus (CeA) are most often implicated in affective valuation, and relay information regarding associations between environmental stimuli and potential outcomes to connected regions (LeDoux, 2000; Pitkänen et al., 1997). The BLA receives sensory input from thalamic nuclei, auditory and sensory cortices as well as the hippocampus, and provides both direct and indirect signals to the central nucleus of the amygdala (Pitkänen et al., 1997). The majority of BLA neurons are excitatory glutamatergic cells which project to other amygdala nuclei including the CeA, the ventral hippocampus (anterior in humans), prefrontal cortex and importantly, to the ventral striatum (nucleus accumbens (NAcc)). The CeA is the major output structure of the amygdala, containing primarily inhibitory GABAergic neurons and controls autonomic responses to incentive-laden stimuli (Davis and Whalen, 2001; Phelps and LeDoux, 2005).

The striatum is the primary input region of the basal ganglia (Delgado, 2007) and receives input from a host of prefrontal cortical and subcortical structures including orbitofrontal cortex (OFC), ventromedial PFC (vmPFC), portions of anterior cingulate cortex (ACC), the hippocampus, and importantly, the amygdala (Alexander et al., 1986; Haber and Behrens, 2014; Haber and Knutson, 2010; Middleton and Strick, 2000; Pennartz et al., 2011; Sesack and Grace, 2010). The striatum can be segregated along a dorsal-ventral divide (though see Voorn et al., 2004) The dorsal striatum is comprised of the caudate nucleus and the putamen, whereas the ventral striatum is comprised of the nucleus accumbens (consisting of medial (core) and lateral (shell) divisions), and ventral portions of the caudate nucleus and putamen (Delgado, 2007; Haber and Knutson,