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Stress and the Adolescent Brain: Amygdala-Prefrontal Cortex Circuitry and Ventral Striatum as Developmental Targets

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Abstract

Adolescence is a time in development when significant changes occur in affective neurobiology. These changes provide a prolonged period of plasticity to prepare the individual for independence. However, they also render the system highly vulnerable to the effects of environmental stress exposures. Here, we review the human literature on the associations between stress-exposure and developmental changes in amygdala, prefrontal cortex, and ventral striatal dopaminergic systems during the adolescent period. Despite the vast differences in types of adverse exposures presented in his review, these neurobiological systems appear consistently vulnerable to stress experienced during development, providing putative mechanisms to explain why affective processes that emerge during adolescence are particularly sensitive to environmental influences.

Keywords

Human; Adolescence; Stress; Amygdala; Prefrontal Cortex; Ventral Striatum

Humans have one of the slowest rates of brain development of all species, taking years to reach maturity (Thompson & Nelson, 2011). On the one hand, this protracted development can be quite costly to the species, placing tremendous energy demands on parents and lengthening the period of time that offspring remain dependent on another member of the species. However, it has been argued that this long developmental period is in fact adaptive for the human species (Bjorklund, 1997; Tottenham, 2014). A developmental period that has been particularly elongated through evolution is adolescence (Thompson & Nelson, 2011). One of the adaptive values of a long adolescent period is a prolonged period of developmental plasticity. Thus, adolescence is a time of immense learning about the environment, in particular the social environment (Blakemore, 2008). However, this benefit of increased plasticity also renders developing neurobiology vulnerable to stressors that happen during development. Indeed, stressors incurred during development have different

effects on brain function than if they are incurred in adulthood (Birn, Patriat, Phillips, Germain, & Herringa, 2014). Because of continued brain development extending into adolescence, this period is both a time when sensitivity to new environmental exposures (Casey et al., 2010; Somerville & Casey, 2010), particularly non-familial social stimuli, is high and when large individual differences in affective behaviors can be first observed (Casey, Pattwell, Glatt, & Lee, 2013; Gee & Casey, 2015). This review will discuss functional changes in human brain development and their intersections with psychosocial stressors.

A Foreword on Stress and Adolescence

Stress is commonly defined as any environmental challenge that threatens the well-being of an organism (McEwen & Gianaros, 2011). The "environment" is a powerful agent of developmental change, but it is also very challenging to measure in humans. This problem becomes magnified when trying to assess and quantify exposure to stressors in the environment. Stressors in the environment can vary by type, degree, frequency, number, age of exposure, and duration since exposure (see Tottenham & Sheridan, 2010). Moreover, stressors during development can be challenging to ascertain because of reliance on retrospective reporting (Widom & Sherpard, 1996) as well as caregivers' or adolescent's reluctance or inability to report on stress exposure. More importantly for consideration of adolescent stress is defining the temporal parameters of the stress exposure in question. For illustration, imagine three different adolescents who are participating in stress research, all with three different patterns of stress exposures, as illustrated in Figure 1. There is first the case of *developmentally chronic* stress (top row), with stress-related behavioral and brain phenotypes measured in adolescence. The second would be a history of traumatic stress that was *preadolescent-limited* (e.g., to infancy or childhood), with stress-related behavioral and brain phenotypes measured in adolescence (middle row). The third would be current traumatic stress that is *limited to adolescence* and measured in adolescence (bottom row). The latter, adolescent limited stress, is very rare in the human literature and much more common in the animal literature, which unlike human research can control the timing of stress exposure. There are several possible reasons for this discrepancy; it could be that developmentally chronic stress is the most frequently occurring type of stress experience; alternatively, it is plausible that adolescent limited traumatic stress (in the absence of prior significant stress) is quite frequent, but perhaps more challenging to identify as research samples. As will be described, there are a handful of studies that have examined adolescent limited stressors, but these acute stressors tend to be milder daily stressors, rather than traumas. Moreover, it is typically challenging to distinguish with great precision which of these three types of developmental stress is being assessed in human studies.

Importantly, these three different types of stress histories can be associated with very different effects on brain development. For these reasons, it is critical to find convergence with animal models (e.g., see Romeo, Patel, Pham, & So, in press, this issue), which can much more precisely define and control the developmental timing of stressors. These cross species endeavors have identified significant concordance across rodent models of laboratory stress and findings in human adolescents who experience real-world stress (Callaghan, Sullivan, Howell, & Tottenham, 2014; Malter Cohen et al., 2013). These animal

models complement human studies of adolescent stress, and therefore offer important translational value providing highly controlled information about developmental mechanisms.

The period of adolescence is especially important to consider when examining the effects of stress on neurobiology, whether it is living with a history of stress or experiencing concurrent stress. As reviewed elsewhere (Andersen & Teicher, 2008; Callaghan & Tottenham, 2016; Tottenham, 2014; Tottenham & Sheridan, 2010), stress exposures during development can have very different effects, and sometimes more potent effects, on the brain than when those exposures occur in adulthood. There are several reasons for differences from adults. First, there is the rapid brain development and increased plasticity of developing systems relative to the adult. Secondly, the developing brain is rich with stress hormone receptors (e.g., corticotropin releasing factor), even more so than in the adult (Avishai-Eliner, Yi, & Baram, 1996). Thirdly, the nature of brain developmental change is hierarchical, and therefore environmentally-induced alterations will not only impact stress-sensitive regions but also the development of the targets to which they will later project. However, it is less clear how individual periods *within* development (i.e., infancy versus childhood versus adolescence) result in differential outcomes on human brain development. There are studies suggesting that prolonged trauma during infancy can have the most profound effects on brain function (Cowell, Cicchetti, Rogosch, & Toth, 2015). On the other hand, retrospective reporting on recalled age of stress exposure has indicated later ages (e.g., early childhood or transition to adolescence) may be a sensitive period for volumetric development of subcortical neural regions (Anderson et al., 2008; Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014). Most likely, the age of greatest impact will vary by domain of functioning. The human literature on developmental timing effects is much more limited than the animal literature for the reasons mentioned above, and probably the most conservative approach at this time is to appreciate that stressors during development have a profound, and usually different or greater, impact on brain function and to leverage translation across the animal literature (see Romeo et al., in press, this issue), which can much more easily control temporal factors associated with stress.

The nature of stressors can vary dramatically across adolescents. What is perhaps most striking across the human literature is that despite the vast differences between the nature of adverse experiences to which adolescents might be exposed, such as parental neglect/deprivation, abuse, community violence, and natural disasters, there are nonetheless common developmental outcomes observed across studies. Most commonly, adolescents with a history of stress exposure are at elevated risk for dysregulated affect, and this core feature gives rise to a wide range of psychosocial challenges, including anxiety, depression, personality disorders, externalizing problems, and eating disorders (Dvir, Ford, Hill, & Frazier, 2014). This review focuses on the current literature examining the underlying neural correlates of dysregulated affect in adolescence, which to date has largely focused on alterations in prefrontal cortex (PFC), amygdala, and ventral striatum. There are other regions that are certainly impacted by stress in adolescence (e.g., the hippocampus; cerebellum); however, for the scope of this paper, we focused on the amygdala, ventral striatum, and PFC since the function of these regions have received the most empirical attention in affective/motivational processes during adolescence.

In development, the increasing ability to regulate affect relies heavily on dynamic interactions between the amygdala, PFC, and striatum (Ernst et al., 2005; Hare, Tottenham, Davidson, Glover, & Casey, 2005; Somerville, Hare, & Casey, 2011; Somerville, Jones, & Casey, 2010). Broadly defined, both the amygdala and the ventral striatum are involved in affective associative learning. Research has shown that the amygdala and the ventral striatum exhibit responsivity to both positive (appetitive) and negative (aversive) stimuli (Paton, Belova, Morrison, & Salzman, 2006). However, there are also differences that have been noted in the literature. For example, the amygdala is typically implicated in identifying highly salient emotional stimuli and serving as an attentional gate for associative learning (e.g., Pearce & Hall, 1980). The ventral striatum is more likely to be implicated in reward-based learning, computing a prediction error based on anticipated outcomes (Li, Schiller, Schoenbaum, Phelps, & Daw, 2011; Schultz, Dayan, & Montague, 1997). Models of affective behavior posit that the organization between PFC, amygdala, and ventral striatum allows for the dynamic coordination of emotional learning and responding through Pavlovian and instrumental processes that link emotion to action.

The PFC is an association area that coordinates and regulates information throughout the brain. The amygdala has strong bidirectional projections with the PFC (Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003), while the ventral striatum receives unidirectional projections from the amygdala and PFC, including excitatory projections that facilitate reward learning (Stuber et al., 2011), and sends indirect projections back to the PFC (Cardinal, Parkinson, Hall, & Everitt, 2002; Casey, 2015; Cho, Ernst, & Fudge, 2013). The strong connectivity from the amygdala to the ventral striatum (Cho et al., 2013) has been observed during human development starting as early as early childhood as measured by resting state functional connectivity (Fareri et al., 2015). However, what will be clear in this review is that to date, the functional significance of these amygdala-ventral striatum connections has not been thoroughly examined in human development, and much of the extant human developmental work has approached the function of these two regions in parallel rather than in coordination. We anticipate that understanding these connections will provide important information not only about typical adolescent affective behaviors, but also the impact of stress exposures in adolescents. However, current research on the development of these regions has already provided much insight into how environmental stress influences adolescent behavior and brain development, which will be reviewed below.

Although significant brain development occurs well before the start of adolescence, there are notable changes during adolescence, particularly in stress sensitive affective and cognitive systems. Moreover, adolescence is marked by increased stress and heightened stress reactivity, compared to children and adults (Dahl & Gunnar, 2009; Dorn, Dahl, Woodward, & Biro, 2006). For example, the hypothalamic-pituitary-adrenal (HPA) axis, which is one of the major stress axes in humans and produces cortisol, and undergoes tremendous change with the transition to adolescence (Adam, 2006; Netherton, Goodyer, Tamplin, & Herbert, 2004), both in basal levels as well as in response to laboratory stressors (e.g. public speaking), to a novel social stressor (e.g. peer rejection), and to academic stressors (Klimes-Dougan, Hastings, Granger, Usher, & Zahn-Waxler, 2001; Knutsson et al., 1997; Stroud, Papandonatos, Williamson, & Dahl, 2004). In fact, Gunnar and colleagues (2009) show nonlinear patterns of heightened basal HPA activity and greater stress reactivity to a stressor

across development, with adolescents showing the most robust effects compared to children and young adults. There are many reasons for this change. First, there is an intimate association between the activity of the HPA axis and the hypothalamic-pituitary-gonadal axis, which is responsible for pubertal elevations in testosterone and estrogen (Dismukes, Shirtcliff, Hanson, & Pollak, 2015). Secondly, the HPA axis is particularly sensitive to social challenges, which may increase dramatically with adolescence (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009). Thirdly, there is mounting evidence from both rodent and human research to suggest that the transition to adolescence represents a time when HPA axis undergoes dramatic change. For example, the HPA axis exhibits a significant gain in reactivity following puberty. This change is especially important to understand for adolescents with a history of stress; pre-pubertally, previously-institutionalized adolescents exhibit flattened morning cortisol production, possibly reflecting a down-regulation of "cortisol as a counter-regulatory response to prolonged periods of elevated cortisol" (Quevedo, Johnson, Loman, Lafavor, & Gunnar, 2012). However, previously-institutionalized adolescents in mid- to late-puberty do not show this flattening (Gunnar et al., 2009; Hostinar, Johnson, & Gunnar, 2015; Quevedo et al., 2012; Romeo, 2010). These findings have led to the conclusion that "puberty probably allows the reprogramming of the HPA axis" (Gunnar et al., 2009). This transition occurs in parallel with large developments in subcortical and cortical neural regions, like the amygdala, PFC, and ventral striatum, whose activity is highly modulated by cortisol and related stress hormones, because circulating cortisol can easily pass through the blood-brain barrier and readily interacts with amygdala-PFC circuitry (Avishai-Eliner et al., 1996; Moriceau, Roth, Okotoghaide, & Sullivan, 2004) and also with the ventral striatum (Graf et al., 2013). This confluence of developmental changes may increase the susceptibility of adolescents to environmental stressors (developmentally chronic, pre-adolescent limited, or adolescent limited).

These aspects of adolescence provide a putative mechanism to explain the well-established findings that many mental illnesses associated with stress exposure emerge (or are first observed) during the adolescent period (Casey et al., 2013; Gee & Casey, 2015; Kessler et al., 2005). This paper will review the literature examining the associations between stressors and functional development of human subcortical-cortical circuitry during the adolescent period. Specifically, we will focus on amygdala-PFC circuitry and ventral striatal dopaminergic systems during adolescence. There were several motivations for this focus: the sensitivity of amygdala-PFC and ventral striatum to environmental stressors, particularly during adolescence; the significant developmental changes in amygdala-PFC and ventral striatum circuitry during the transitions into and out of the adolescent period; and the central role in amygdala-PFC and ventral striatum circuitry in individual differences in socio-affective behaviors that emerge during the transition into adolescence.

The goal of this review is to summarize what is currently known about stress during adolescence, how it impacts affective and motivational learning systems in adolescence, and how stress may exert neurobiological effects on circuitry that subserves these operations in the developing brain. There are, unfortunately, many types of stress exposures to which children and adolescents can be exposed, and each of these may be associated with stressor-unique effects on the brain (see Sheridan & McLaughlin, 2014). However, as will be discussed, there is nonetheless significant overlap across types of stress exposures on

subcortical regions like amygdala and ventral striatum. Because of their intimate association with the social environment, the amygdala-PFC and ventral striatal dopaminergic systems are particularly sensitive targets of stress in adolescence. We will start with a brief review of the effects of stress on amygdala-PFC circuitry followed by the literature on ventral striatal dopaminergic systems. Although there is strong interconnectivity of these regions with each other, the organization of this review follows the human developmental stress literature, which to date, has typically studied these systems separately.

Amygdala-PFC Circuitry Development

Adolescence is a developmental period characterized by large changes in affect regulation and its underlying neural correlates. In the healthy adult, connections between the amygdala and PFC comprise the core circuitry involved in negative affect generation and regulation (Kim, Loucks, et al., 2011; Lee, Heller, van Reekum, Nelson, & Davidson, 2012; Phan, Wager, Taylor, & Liberzon, 2002; Toyoda et al., 2011). The neurobiology of negative affect generation has been extensively and best characterized at the level of the amygdala, which mediates threat learning and vigilance (Davis & Whalen, 2001). The PFC sends projections to the amygdala that modulate amygdala reactivity (Milad & Quirk, 2002). These projections, depending on their source, can function to attenuate or potentiate (Senn et al., 2014) affective responding, and thus these connections are fundamental to mature affect regulation (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Delgado, Nearing, Ledoux, & Phelps, 2008; Monk, 2008).

However, amygdala-PFC connections are slow to develop. In rodents, long-range connections between the amygdala and medial PFC continue to develop well into adolescence (Cunningham, Bhattacharyya, & Benes, 2002; Johnson et al., 2016; Pattwell et al., 2016). In the human, this circuitry shows developmental changes across the first two decades of life. It has been posited that adolescence marks a new sensitive period for amygdala circuitry (Scherf, Smyth, & Delgado, 2013). Anatomically, there is considerable postnatal development in amygdala volume in infancy (Gilmore et al., 2012). Nonetheless, volumetric change continues to be observed into childhood and adolescence (Giedd et al., 1996; Uematsu et al., 2012). Some of these changes in volume correspond to pubertal change (Bramen et al., 2011; Goddings et al., 2014), suggesting that pubertal development is one important agent of developmental change in the amygdala during adolescence. Adolescence is a time of remarkable change in both functional and structural connections between the amygdala and PFC. Functional and structural connectivity between amygdala and PFC begins to exhibit adult-like patterns that serve regulatory function (Decety, Michalska, & Kinzler, 2012; Dougherty, Blankenship, Spechler, Padmala, & Pessoa, 2015; Gabard-Durnam et al., 2014; Gee, Humphreys, et al., 2013; Hare et al., 2008; Lebel et al., 2012; Perlman & Pelphrey, 2011; Silvers, Shu, Hubbard, Weber, & Ochsner, 2014; Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014; Vink, Derks, Hoogendam, Hillegers, & Kahn, 2014). These strengthening connections are developing at the same time that high amygdala reactivity to emotional stimuli (faces, scenes) is observed (Decety et al., 2012; Gee, Humphreys, et al., 2013; Guyer et al., 2008; Hare et al., 2008; Swartz et al., 2014; Vink et al., 2014). Different models have been developed to account for these findings (e.g., imbalance model, (Casey, Galvan, & Somerville, 2016); dual systems accounts, (Steinberg,

2010); triadic model, (Ernst, 2014)). Each of these models emphasizes the large changes and the continued development of limbic-cortical circuitry during adolescence. Although these changes allow for continued plasticity throughout adolescence, the instability associated with large age-related change increases the vulnerability of neural systems to be influenced by environmental stress (Lupien, McEwen, Gunnar, & Heim, 2009) as we will discuss in the next section.

Amygdala-PFC Circuitry, Adolescence, and Developmentally Chronic/Pre-Adolescent Limited Stress

Across various types of traumatic stress exposures (e.g., parental neglect/deprivation, abuse, community violence, and natural disasters), alterations to amygdala function and amygdala functional connectivity to PFC during adolescence have been observed. These alterations correspond with the behavioral observations of increased fear reactivity (Fani et al., 2015), attentional biases towards threat (Fani et al., 2015; Troller-Renfree, McDermott, Nelson, Zeanah, & Fox, 2015) and difficulty with affect-related regulation (Tottenham et al., 2010) following significant stress exposure. What these exposures have in common is that they were experienced during a time of rapid brain development and are all threats to survival. The amygdala continues its development throughout adolescence, and its primary function is to gather information (both aversive and appetitive) that is important for survival. These aspects of the amygdala together with its abundance of HPA axis hormone receptors (Vazquez et al., 2006) position it well to be a target of these exposures.

Adverse caregiving is a significant early-life threat to the developing human, because of the absence of developmentally necessary regulation from the parent (see Tottenham, 2012 for review), and represents one of the earliest forms of psychological stress that a human can experience. One of the most highly replicable effects of caregiving adversity is amygdala hyperreactivity in response to emotional stimuli during adolescence (Garrett et al., 2012; Marusak, Martin, Etkin, & Thomason, 2015). Adolescents with a history of physical abuse and neglect (De Bellis & Hooper, 2012; McCrory et al., 2013) or exposure to family violence (McCrory et al., 2011) exhibit elevated amygdala reactivity in response to highly arousing emotional faces, even if they are presented preattentively (McCrory et al., 2013). This elevated amygdala reactivity to emotional faces has also been observed in adolescents who experience low parental warmth (Casement et al., 2014) or severe neglect and institutional care during infancy (Gee, Gabard-Durnam, et al., 2013; Maheu et al., 2010; Tottenham et al., 2011).

Significant stressors experienced later in development have also been associated with increased amygdala reactivity. In a group of healthy adolescents, the total number of stressors after the age of 4 years old was positively correlated with the magnitude of amygdala reactivity to emotional faces, suggesting the amygdala continues to be shaped by significantly stressful events beyond infancy and early childhood (Ganzel, Kim, Gilmore, Tottenham, & Temple, 2013). In a prospective study of adolescents, those who reported significant traumatic stress in the past year exhibited developmental increases in amygdala reactivity to emotional faces over a 2-year period, unlike those with low stress who exhibited age-related decreases. Moreover, those with significant traumatic stress were more likely to

exhibit an amygdala trajectory similar to adolescents with a significant familial risk for depression (Swartz, Williamson, & Hariri, 2015). These data suggest that amygdala hyperactivity in adolescence might be an important biomarker for mental illness associated with affect dysregulation (Swartz, Knodt, Radtke, & Hariri, 2015). In support of this interpretation, McLaughlin and colleagues (2014) had the rare opportunity to have obtained brain scans using functional magnetic resonance imaging (fMRI) from adolescents prior to the terrorist attack on the Boston Marathon. Following the attack, these researchers could predict post-traumatic stress disorder (PTSD) symptomology based on the magnitude of amygdala response in the initial scan.

Stress exposure is also associated with alterations in the development of connections between the amygdala and PFC regions during adolescence. One means of measuring functional connectivity is to employ resting state measures, which assay spontaneous regional interactions that occur when a subject is not performing an explicit task and provides an index of the integrity of a functional connection between regions of interest. Adolescents with a history of child maltreatment (Herringa et al., 2013) or trauma (Pagliaccio et al., 2015; Thomason et al., 2015) exhibit weaker connectivity between amygdala and PFC regions (Nooner et al., 2013), including regions in the medial PFC (mPFC). The nature of amygdala-mPFC resting state connectivity has implications for future mental health; in adulthood, weaker connectivity is associated with increased trait anxiety (Kim, Gee, Loucks, Davis, & Whalen, 2011). In adolescence, weaker amygdala-mPFC connectivity has been shown to mediate the associations between stress and anxiety symptoms (Pagliaccio et al., 2015) and PTSD symptoms (Cisler, Scott Steele, Smitherman, Lenow, & Kilts, 2013) suggesting that stress-induced alterations to amygdala-mPFC connectivity during adolescence may underlie emotional difficulties following stress exposures in development. In a more direct test of this hypothesis using a prospective design, Burghy and colleagues (2012) followed subjects from the age of 4 years old to 18 years old. In this study, stress experienced at 4 years old was associated with increased cortisol levels in childhood, which predicted altered functional connectivity between the amygdala and mPFC in adolescence. Amygdala-mPFC connectivity in adolescence was associated with anxiety and depression, although in different ways – amygdala-mPFC connectivity was negatively correlated with anxiety symptoms, but it was positively correlated with depression symptoms. These findings are important because they provide compelling evidence that developmental stress increases the risk for internalizing problems, and this association is mediated by alterations to amygdala-mPFC function during adolescence. This effect was only observed in females, suggesting a possible neurobiological basis for commonly observed sex differences in risk for internalizing problems (Nolen-Hoeksema, 1987).

Amygdala-PFC connectivity has also been examined in adolescence while participants are engaged in behavioral tasks. Connectivity measured during these manipulations offer an important complement to resting state measures because they index the coactivation of two regions that is elicited by a particular stimulus or behavioral demand. Across different types of stress exposures, task-based measures have demonstrated altered functional connectivity between the amygdala and PFC. For example, in response to viewing negative facial expressions, it has been shown that both trauma exposure (Wolf & Herringa, 2016) and a

history of early-institutional rearing (Gee, Gabard-Durnam, et al., 2013) is followed by greater inverse correlations between amygdala and mPFC. This pattern is more typical of healthy adults (e.g., Lee et al., 2012), suggesting an acceleration or temporary enhancement of function during development. The magnitude of these effects has been shown to be associated with avoidance behaviors (Wolf & Herringa, 2016). Whether these patterns of task-elicited connectivity reflect risk or resilience remains unclear – although further research is needed, one possible interpretation of altered connectivity is that it is an adaptation that helps the individual meet immediate emotion regulation needs, even if they are not optimal emotion regulation strategies in the long term (Callaghan & Tottenham, 2016); in support of this interpretation, the more adultlike patterns in amygdala-PFC regulatory connectivity in response to viewing fearful faces have been associated with lower current anxiety symptoms in previously-institutionalized youth (Gee, Gabard-Durnam, et al., 2013). Similarly, during an aversive learning paradigm, adolescents with a history of institutional care are more likely to exhibit adult-like patterns of amygdala functional connections with both ventral and dorsal medial PFC (Silvers et al., 2016). The dorsal region of medial PFC has been associated with more amplification of negative affect (Maier et al., 2012). This difference in both a regulatory region as well as an amplification region raises important questions about the relative balance between excitatory and inhibitory influences to and from the amygdala following stress exposure.

Tasks involving effortful emotion regulation have further revealed atypical amygdala-PFC functional connectivity in adolescence following stress exposure. Marusak and colleagues (2015) have shown that while performing an emotional conflict task that involves categorizing facial affect while ignoring an overlying emotion word, group differences related to trauma exposure emerged in amygdala and PFC regions (Marusak et al., 2015). Specifically, trauma-exposed youths exhibited amygdala-PFC connectivity patterns consistent with poor affect regulatory function. Correspondingly, the trauma exposed group also exhibited a failure to dampen amygdala reactivity and poorer regulatory skill. Cognitive reappraisal tasks (Ochsner et al., 2004) are another means of measuring emotion regulation skills, and they assess effortful attempts to dampen negative emotions elicited by negative images. During attempts to decrease responses to negative stimuli, maltreated adolescents were more likely to recruit prefrontal regulatory regions than controls to reach the same level of emotion regulation (McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015). Taken together, these task-based measures suggest that not only is amygdala reactivity altered by stress during adolescence, but also the nature of the communication between amygdala and prefrontal circuits is altered. These alterations may include adaptations for achieving the best possible affect regulation. It is possible that given the hierarchical nature of brain development and the early development of the amygdala, development of connectivity with prefrontal regions in adolescence depends very much on the earlier emerging function of the amygdala (as suggested by Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013). That is, stress-induced hyperreactivity of the amygdala may increase the risk for atypical connections with the PFC that can differ in nature, timing, or both.

Development of Ventral Striatal Dopaminergic Motivational Systems

In addition to large changes in amygdala-PFC circuitry, adolescence is a also developmental period characterized by significant changes in reward sensitivity, cognitive regulation and their neural correlates (Steinberg, 2005). The ventral striatum supports reward-related processes, such as reward based learning (Fiorillo, Tobler, & Schultz, 2003), through receipt of significant dopaminergic inputs from the ventral tegmental area and substantia nigra (Haber, 2011). The dopamine system, which undergoes significant maturation during adolescence (Andersen & Teicher, 2008, 2009; Rosenberg & Lewis, 1995; Spear, 2009), is also sensitive to the effects of stress. In adult rodents, acute stress induces increased extracellular levels of dopamine in the nucleus accumbens (Abercrombie, Keefe, Di Frischia, & Zigmond, 1989; Kalivas & Duffy, 1995; Ungless, Argilli, & Bonci, 2010), which is mediated through stress hormones (Kreek & Koob, 1998; Rouge-Pont, Deroche, Le Moal, & Piazza, 1998). Stress also increases firing rates (Anstrom & Woodward, 2005) and synaptic adaptation in dopamine neurons (Saal, Dong, Bonci, & Malenka, 2003) which is thought to amplify reward salience (Mather & Lighthall, 2012; Starcke & Brand, 2012). This section will review evidence suggesting that stress triggers motivational and reward seeking behavior.

Much insight on this topic has been gleaned from animal studies. Rodents in the juvenile period evince robust dopamine reactivity in stressful contexts. Postnatal stress in young rat pups leads to elevated levels of dopamine (Huppertz-Kessler, Poeschl, Hertel, Unsicker, & Schenkel, 2012). Juvenile versus adult rats show an enhanced stress response when exposed to cues of predation threat (Wright, Muir, & Perrot, 2012). Moreover, prenatal (Silvagni, Barros, Mura, Antonelli, & Carboni, 2008) and early life (Jezierski, Zehle, Bock, Braun, & Gruss, 2007) stress exposure leads to enhanced dopamine release and functional alterations of dopaminergic pathways in adolescence (Jezierski, Zehle, Bock, Braun, Gruss, 2007).

Stress-related alterations of dopamine release have also been demonstrated in adult humans (Starcke and Brand, 2012). Using positron emission tomography (PET), researchers have shown that a laboratory stressor increases dopamine release in the adult human brain (Scott, Heitzeg, Koeppe, Stohler, & Zubieta, 2006), which is correlated with higher cortisol levels (Pruessner, Champagne, Meaney, & Dagher, 2004), and that stress-induced cortisol levels were positively associated with amphetamine-induced dopamine release in the ventral striatum (Wand et al., 2007).

In humans as well, there are significant normative developmental changes ventral striatum during adolescence. Across many fMRI studies to date, researchers have shown significant changes in ventral striatal reactivity during adolescence. Most of these studies report that adolescents evince stronger activation of the ventral striatum in response to primary (Galván & McGlennen, 2013), secondary (Cohen et al., 2010; Galván et al., 2006; van Leijenhorst et al., 2010), and social rewards (Guyer et al., 2008; Telzer, Fuligni, Lieberman, & Galván, 2013) (Bjork et al., 2004). This increase in ventral striatum reactivity parallels the adolescent maturation of the dopamine system observed in animal models (Andersen & Teicher, 2008, 2009; Rosenberg & Lewis, 1995; Spear, 2009). These neural findings are paralleled by heightened reward sensitivity, risk taking and motivational behavior in adolescents as

compared to other age groups (see Galván, 2013 for review). Interestingly, environmental conditions have been found to exacerbate (Phuong & Galvan, in press) or diminish (Do & Galván, 2015) these effects, underscoring the malleability of the mesolimbic system during this crucial period of development.

Ventral Striatum, Adolescence, and Developmentally Chronic/Pre-Adolescent Limited Stress

Like the amygdala and the PFC, the ventral striatum seems highly influenced by stress in adolescents. Young adults with a history of childhood stress exhibit blunted ventral striatal response when processing a monetary reward (Boecker et al., 2014; Hanson et al., 2016). Research in younger samples shows that this effect of stress on reward-related circuitry can emerge during adolescence. Adolescents with a history of institutional caregiving exhibit blunted ventral striatal response (Mehta et al., 2010). Specifically, at the group level, adolescents with a history of institutional care do not differentiate reward predicting cues of varying value (low, medium, high) in the ventral striatum, whereas control individuals showed greater responses to medium and high reward cues compared to low. Goff and colleagues (2012) showed that group differences in ventral striatal response to positive facial emotion between individuals with a history of institutional care and a typically-raised comparison group emerge first in adolescence. In this study, adolescence was also the time when depression symptoms increased significantly, and ventral striatum hypoactivity correlated with depressive symptomology in the adversity-exposed group (Goff et al., 2012). Research performed independently both Hanson et al. (2015) and Schneider et al. (2012) has shown that even less extreme forms of caregiving adversity (i.e., low maternal affiliation or emotional neglect) are associated with alterations in ventral striatal reactivity. Importantly, Hanson et al., (2015) showed that a history of emotional neglect was associated with decreased functional connectivity (perhaps even negative) between amygdala and ventral striatum in response to reward, providing a possible mechanism linking the elevated amygdala reactivity to blunted ventral striatum functioning in adolescents with a history of stress.

These findings of blunted ventral striatum responsivity during adolescence following early life stress might explain behavioral effects in reward-related paradigms often observed following stress exposures. The balloon analogue risk taking task (BART)(Lejuez et al., 2002) is a task that involves subjects' pumping up a virtual balloon that can grow larger with corresponding increasing reward but can potentially explode (if pumped too much) with a complete loss of rewards. It provides a measure of risk-taking under conditions of potential reward and has been associated with ventral striatal function in adults (Rao, Korczykowski, Pluta, Hoang, & Detre, 2008). Consistent with blunted ventral striatal reactivity described above, adolescents with a history of institutional caregiving exhibit less risk taking (i.e., they pump the balloon less) compared to same aged peers without a history of early adversity (Humphreys et al., 2015; Loman, Johnson, Quevedo, Lafavor, & Gunnar, 2014). Similarly, adolescents with a history of maltreatment and a diagnosis of depression are less like to select a risky choice (with high reward) during a two-choice decision-making task involving probabilistic monetary gains (Guyer et al., 2006). These findings are consistent with working models (e.g., Auerbach, Admon, & Pizzagalli, 2014; Goff & Tottenham, 2015),

which posit that early life stress may render the adolescent vulnerable to depression because of its effects on ventral striatal development during this sensitive time.

Adolescent-Specific Daily Stressors

There are many types of daily stressors that emerge during adolescence (Persike & Seiffge-Krenke, 2012) including family, academic (Arnett, 2002; Bynner, 2000), and peer (Eccles et al., 1993; Smetana, Campione-Barr, & Metzger, 2006) pressures. For example, demanding coursework and preparation for college placement often lead to increases in school related stress (McAndrew, Akande, Turner, & Sharma, 1998). Socially, adolescents frequently experience stressors in the domain of romantic relationships and peer networks (Hand & Furman, 2009; Kuttler & LaGreca, 2004). Also common is elevated stress associated with developing more intimate friendships while maintaining family relationships and establishing autonomy (Laursen & Collins, 1994; Nieder & Seiffge-Krenke, 2001). Ethnographic data demonstrates that these effects are observed globally, as adolescents from over 140 cultures report high feelings of stress in these domains (Schlegel, 2001). However, as noted in the foreword, there is limited research on acute effects of stress on adolescent neurobiological development in humans. We summarize here what has been found in research on the human adolescent amygdala, ventral striatum, and PFC in response to daily stressors.

Amygdala-PFC Circuitry—Based on adult findings, amygdala-PFC circuitry responds strongly and immediately to acute stressors (Oei et al., 2012; van Marle, Hermans, Qin, & Fernandez, 2010). These changes have been associated with acute administration of the stress hormone, glucocorticoids (Henckens, van Wingen, Joels, & Fernandez, 2010). Although there are no studies that have examined the effects of acute stress on amygdala-PFC circuit functioning during adolescence, the implications from the adult work provide strong motivation for the hypothesis that amygdala-PFC circuitry are highly reactive to environmental stressors. Moreover, significant and prolonged stressors during development might have even more pronounced effects on the long-term programming of these circuits.

Ventral Striatum—In adults, acute stress yields alterations in neural activation of mesolimbic-prefrontal circuitry, including the striatum, insula, thalamus, and prefrontal regions (Kogler et al., 2015; Pruessner et al., 2008), which may be due to the stress-related increases in dopamine release in ventral striatum (VS) and orbital frontal cortex (OFC) observed in animal models (Ungless, Argilli, & Bonci, 2010) and human positron emission tomography (PET) studies (Pruessner, Champagne, Meaney, & Dagher, 2004). Research shows that this enhanced dopamine release is magnified in individuals who also evince increased cortisol levels in response to psychosocial stressors (Pruessner et al., 2004). The behavioral consequences of these neurochemical and neural activation changes in response to stress include enhanced reward salience and greater reward-biased decisions (Porcelli & Delgado, 2009; Putman, Antypa, Crysovergi, & van der Does, 2010; Starcke & Brand, 2012).

Although there has been much less research on the effects of concurrent adversity in adolescence (see Romeo et al., in press, this issue, for rodent studies), Casement and

colleagues (2014) examined the prospective associations between challenging social situations for girls at 11–12 years old and neural activation during anticipation of reward when they were 15 years old. There was a negative association between ventral striatum response and maternal warmth, suggesting at a minimum that the ventral striatum may respond quite differently to stressors that are experienced during the adolescent period. Galván and McGlennen (2012) used a daily diary approach to monitor and compare 14–17 year-old adolescents' daily stress to that of 18–21 year-old emerging adults. Results indicated that adolescent participants made more risky decisions during high stress relative to low stress, suggesting that stress impacts behavior in a similar, albeit more exaggerated, manner in adolescents relative to adults (Galván & McGlennen, 2012).

Similarly, Phuong and Galván (in press) used an ecological momentary assessment (EMA) approach to monitor adolescent participants' naturalistic stress for two weeks. Each participant visited the laboratory twice, once on a day when they endorsed a high level of daily stress and once on a day when they endorsed a low level of daily stress. This novel approach allowed for the examination of *within-person*, as well as developmental effects, thereby precluding potential confounds related to individual differences in laboratory-stress reactivity. At the lab, participants underwent fMRI scanning during a risky decision making task. The findings showed that adolescents (aged 14–17 years) made more risky choices than adults (ages 25–30 years) following a stressful day. This effect could not be explained by adolescents simply "being riskier" in general as there were no developmental differences following a self-reported minimally stressful day. The behavioral differences between adolescents and adults that emerged on stressful days were associated with developmental differences in neural recruitment as well. Adolescents showed less engagement of regions that have previously been associated with risk monitoring, including the orbital frontal cortex and insula, than adults (Phuong and Galván, in press). Adolescent girls also showed enhanced activation of the caudate, a region implicated in reward. In a follow-up study, the authors found that the relationship between insula response and risky behavior was exacerbated in individuals who reported regularly sleeping less than the 7 hours per night that is recommended by the National Sleep Foundation (Phuong and Galván, under review).

Prefrontal Cortex—The prefrontal cortex and its connections with subcortical regions is one of the latest to develop in the human brain, and therefore it is vulnerable to the effects of stressors during adolescence. Certainly, there is a rich literature in adults showing that acute stress negatively affects cognition (Janis, 1993; Keinan, 1987; Mather & Lighthall, 2012; Porcelli & Delgado, 2009; Preston, Buchanan, Stansfield, & Bechara, 2007), in learning, memory, decision and inhibition domains (Mather and Lighthall, 2012; Roozendaal, 2002; Sandi, 2013; Wolf, 2006). For instance, response inhibition performance in adult males is significantly impaired following acute stress (Scholz et al., 2009). Animal research has also found that rodents (Hennessy, Cohen, & Rosen, 1973; Micco, McEwen, & Shein, 1979) and monkeys exposed to stress-level cortisol treatments have impaired response inhibition (Lyons, Lopez, Yang, & Schatzberg, 2000), which is mediated via stress-induced atrophy of prefrontal neurons (Liston et al., 2006; Radley et al., 2004). These findings have been instrumental in establishing the mechanism by which acute stress can dysregulate cognition.

More recent research has focused on determining whether these stress effects on cognition and PFC extend to adolescent populations. Using the EMA approach described above, Rahdar and Galvan (2014) monitored adolescent participants' naturalistic stress for two weeks. Each participant visited the laboratory twice, once on a day when they endorsed a high level of daily stress and once on a day when they endorsed a low level of daily stress. At the lab, participants performed a Go/No-go task while undergoing fMRI to assess cognitive control and as a probe for prefrontal function. Behaviorally, all participants exhibited worse response inhibition under high, versus low, stress states, an effect that was significantly stronger in adolescents. At the neural level, there was a significant age by stress interaction, such that adolescents exhibited less recruitment of the dorsolateral prefrontal cortex (DLPFC) during inhibition under high-stress versus low-stress; adults evinced the opposite activation pattern in DLPFC. These data provide further support that the developing brain may be a more vulnerable target to the cognitive and neurobiological effects of stress (Rahdar & Galván, 2014).

Future Directions

Across several laboratories, samples, and paradigms, the human literature has demonstrated a strong association between stress-exposure and altered development of neuro-affective/motivational systems in adolescence. The effects of stress on affective, motivational, and cognitive systems during adolescence have largely been studied in parallel rather than in conjunction. However, it is becoming increasingly clear that the amygdala, PFC, and ventral striatum operate together during affective processes as they emerge during adolescence (see Casey et al., 2016; Ernst, 2014; Somerville, van den Bulk, & Skwara, 2014). Indeed, it is possible that direct stress-induced alterations in one region can produce cascading and indirect stress-alterations in the others. For example, stress-induced alterations to the early developing amygdala could have downstream effects as a result of unidirectional amygdala-ventral striatum projections (e.g., Cho et al., 2013) and the late development of the prefrontal cortex (e.g., Gee et al., 2013). This hypothesis requires longitudinal testing. Moreover, the nature of information represented by each region is less modular than distributed in the human. For example, the ventral striatum represents negatively valenced cues as well as positively valenced cues (Levita et al., 2009), and the amygdala is highly responsive to reward in addition to being sensitive to aversive cues (Murray, 2007). Computational modeling approaches with adult fMRI data have shown that the unique computations of the amygdala and ventral striatum work together to encode different parameters of environmental contingencies (Li et al., 2011). This approach, although not yet applied to data from developmental populations, might be a powerful one for understanding how stress influences adolescent brain function.

Implications for mental health: Research Domain Criteria Framework

There are significant mental health implications for delineating the adolescent processes that are affected by developmental stress. Identifying the mechanisms targeted by exposure to stress and how they are affected during adolescence is central to understanding the developmental emergence of mental illnesses (e.g., anxiety and depression) within the Research Domain Criteria (RDoC) framework (see Kozak & Cuthbert, 2016, for discussion).

For example, the affective dimensions of negative affect and positive affect and the cognitive constructs of cognitive control and working memory are all at risk for alteration by stress and all contribute to diagnoses of anxiety and depression. By identifying which dimensions are more or less affected by particular types of stress exposures at different levels of analysis, including brain circuitry, behavior physiology, environment, and development, we may have more power to predict mental health course with greater specificity for an individual. However, development is highly dynamic, which presents additional challenges, as well as opportunities, to understanding the emergence of mental health problems within an RDoC framework (Casey, Oliveri, & Insel, 2014). Knowledge of normative developmental changes in the brain and how they interact with timing of stress exposures and the timing of phenotypic manifestation is necessary for a more complete understanding of the pathophysiology and etiology of mental illness. These domains of functioning will also each have its own developmental timeline, and they will interact with each other during development; thus interactions between dimensions should be considered across infancy, childhood, and adolescence. The significant changes that occur during the transitions into and during adolescence, both at the level of neurobiology and environment, render adolescence a vulnerable period for stress-related alterations to the mechanisms that underlie affective processes. Moreover, future work that continues to characterize how adolescent brain development is influenced by environmental stressors can also provide insight into the mechanisms for recovery and adaptation.

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Highlights

- Adolescent changes in affective neurobiology increases vulnerability to stressors
- Amygdala, prefrontal cortex, and ventral striatum are consistent targets of stress
- Potential mechanisms for affect dysregulation that emerges in adolescence

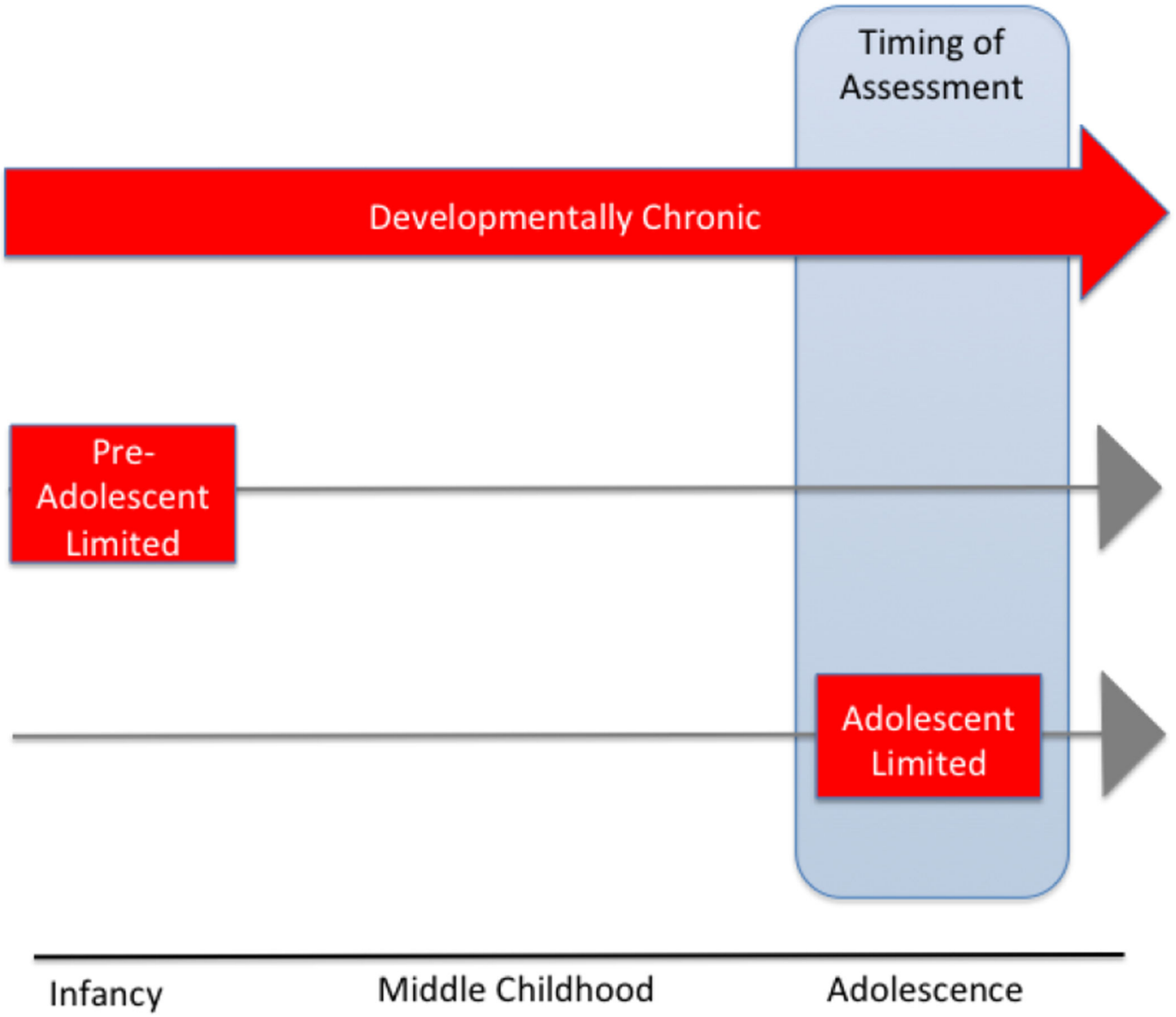

Figure 1.

Different Chronicities of Adolescent Stress. (Top row) *Developmentally chronic* stress occurs chronically throughout development. (Middle row) *Preadolescent-limited (to infancy* or *childhood*) is comprised of a history of traumatic stress. (Bottom row) *Adolescent limited* describes current traumatic stress that is limited to adolescence.