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Symposium

Neurocognitive Development of Motivated Behavior: Dynamic Changes across Childhood and Adolescence

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The ability to anticipate and respond appropriately to the challenges and opportunities present in our environments is critical for adaptive behavior. Recent methodological innovations have led to substantial advances in our understanding of the neurocircuitry supporting such motivated behavior in adulthood. However, the neural circuits and cognitive processes that enable threat- and reward-motivated behavior undergo substantive changes over the course of development, and these changes are less well understood. In this article, we highlight recent research in human and animal models demonstrating how developmental changes in prefrontal-subcortical neural circuits give rise to corresponding changes in the processing of threats and rewards from infancy to adulthood. We discuss how these developmental trajectories are altered by experiential factors, such as early-life stress, and highlight the relevance of this research for understanding the developmental onset and treatment of psychiatric disorders characterized by dysregulation of motivated behavior.

Key words: **motivation; threat; reward; development; early life stress; prefrontal cortex; dopamine**

Introduction

The past decades have seen a surge in research on the neurocircuitry supporting motivated behavior in adulthood. Convergent findings across species suggest that dynamic interaction between the prefrontal cortex (PFC) and subcortical regions, including the amygdala, hippocampus, and striatum, plays a central role in learning to predict potential threats and rewards and determining how to respond to such environmental challenges (Phelps and LeDoux, 2005; Haber and Knutson, 2010; Stuber et al., 2011; Namburi et al., 2015; Beyeler et al., 2016; Burgos-Robles et al., 2017). At the same time, a convergent literature has elucidated pronounced changes in the structure and function of these circuits from childhood to adulthood (Murty et al., 2016; Casey et al., 2017), highlighting the protracted development of structural connections between the PFC and subcortical regions (Barnea-Goraly et al., 2005; Lebel et al., 2012; Simmonds et al., 2014; Achterberg et al., 2016), as well as shifting functional dynamics within this circuitry (Gee et al., 2013b; Betzel et al., 2014; Swartz et al., 2014; Fareri et al., 2015; Jalbrzikowski et al., 2017). These findings are consistent with the marked changes in motivated learning and decision-making that occur across development; however, to date, we have only a provisional understanding of how these behavioral changes relate to developmental changes in the brain.

In this review, we present recent research that has begun to elucidate both neural and cognitive mechanisms that give rise to shifts in threat and reward processing from childhood to adulthood. Building on an extensive literature on aversive conditioning and extinction in humans and animal models in adulthood, we first discuss how the neurocognitive processes that underpin threat prediction and reactive behavioral responses to anticipated threats change over the course of development. In light of extensive evidence for the central role of dopamine (DA) in the modulation of many facets of reward processing, we next discuss how developmental changes in the dopaminergic system across adolescence might relate to changes in reward-motivated behavior during this developmental period (Fig. 1). The threats an individual may face and the experiences that they deem rewarding will vary as a function of developmental stage, as well as across individuals. Just as motivated behavior may shift to meet the needs of a particular developmental challenge, alterations in the species-expected environment may demand adaptations in motivated behavior. In the third section of this review, we emphasize how changes in motivated behavior over the course of development may represent experience-dependent adaptations to the demands of one's environment or developmental stage, and discuss how atypical experiences (e.g., exposure to early-life stress) might alter the normative developmental trajectory of motivated

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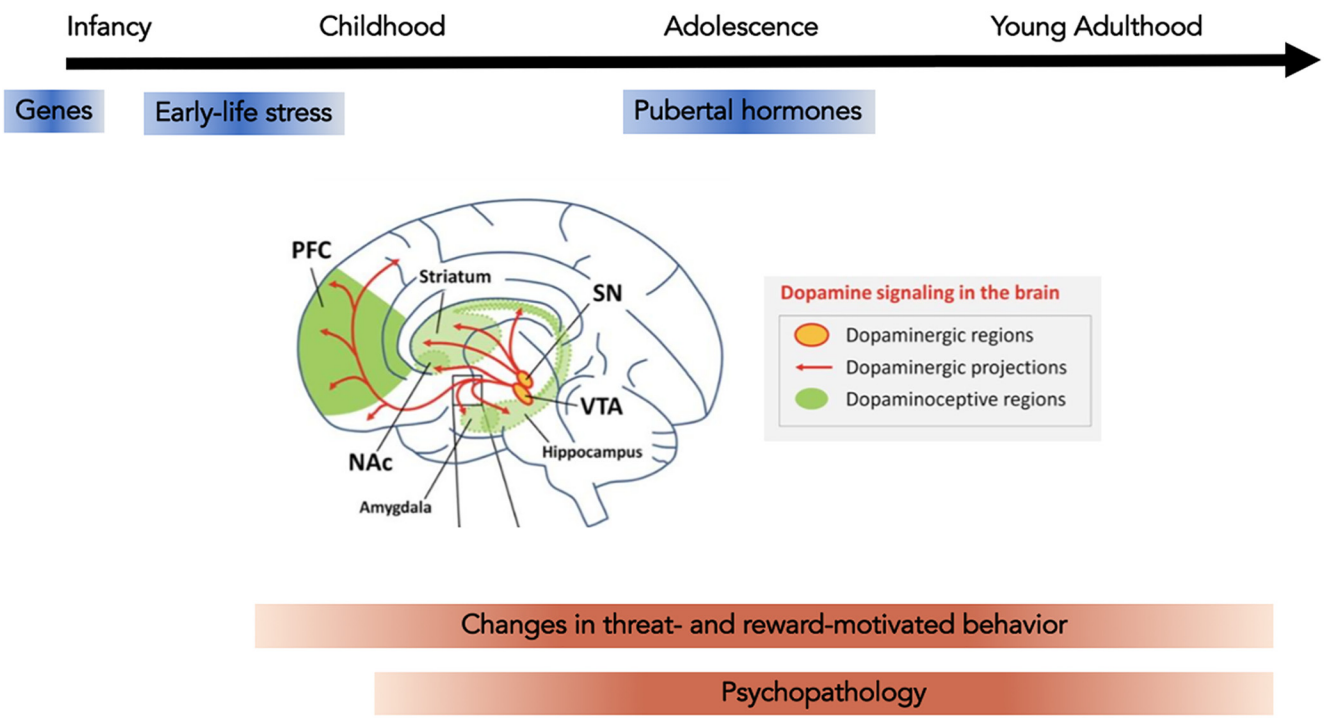

Figure 1. Neurocognitive development of motivated behavior. Prefrontal-subcortical circuitry and dopaminergic signaling undergo profound changes across childhood and adolescence (prefrontal cortex, PFC; nucleus accumbens, NAc; substantia nigra, SN; ventral tegmental area, VTA). These changes can interact with, and be influenced by, biological and environmental factors to alter trajectories of threat- and reward-motivated behavior in ways that alter risk for the emergence of psychopathology. Circuitry diagram adapted with permission from Sinclair et al. (2014).

behavior. Childhood and adolescence are periods of increased risk for psychiatric disorders (Kessler et al., 2007; Paus et al., 2008), the majority of which are characterized by core deficits in the ability to accurately anticipate and respond adaptively to potential threats and rewards. In the final section, we highlight how alterations in the normative trajectory of prefrontal-subcortical circuitry and motivated behavior may contribute to risk for psychiatric disorders at specific developmental stages and the implications of this research for optimizing clinical interventions during development.

Neurocircuitry of threat processing and its development

The ability to learn that cues or contexts signal potential threat, and to modify these learned associations as the environment changes, is critical for adaptive function. These abilities and their underlying neural mechanisms develop over time. Studies in rodents and humans have yielded a detailed model of the neurocircuitry underlying the acquisition and extinction of aversive learning in adulthood (Hartley and Phelps, 2010; Milad and Quirk, 2012). This work highlights the central role of the amygdala in acquisition, storage, and maintenance of aversive learning (Fanselow and LeDoux, 1999; Maren and Quirk, 2004), whereas extinction learning and retention involve dynamic interactions between the amygdala, the infralimbic (IL) and prelimbic (PL) regions of PFC, and the hippocampus (Maren and Quirk, 2004; Sierra-Mercado et al., 2011). Specifically, during adulthood, reciprocal connections between the amygdala and PL (for which the dorsal anterior cingulate is the proposed human homolog) drive the expression of conditioned responses to threat, and their reciprocal connections with the IL (for which the ventromedial PFC is the proposed human homolog) can inhibit the expression of conditioned responses to threat (Sotres-Bayon and Quirk, 2010). Mature rodents and humans show robust aversive learning, including avoidance, freezing, and elevated physiological reactivity to stimuli that have been paired with shock (e.g., Blanchard and Blanchard, 1969; Bolles and Collier, 1976). In adulthood, the extinction of conditioned responses is subject to relapse (i.e., the return of conditioned responding even after extinction) through renewal, reinstatement, and spontaneous recovery (e.g., Bouton, 2002). These forms of relapse indicate that, in mature animals, the aversive memory is not forgotten, even if the behavioral expression of fear has been attenuated.

Consistent with marked changes in prefrontal-subcortical circuitry, aversive learning undergoes substantial change across childhood and adolescence. Aversive conditioned responses are largely suppressed in young rat pups, before postnatal day (PND) 10 (Rudy and Cheatle, 1977), although the ability to feel pain and detect an aversive stimulus are both intact (Stehouwer and Campbell, 1978; Collier and Bolles, 1980; Emerich et al., 1985; Barr, 1995). Unlike avoidance or freezing behaviors observed in adults, pups exhibit approach behaviors toward odors that have been paired with a shock (Camp and Rudy, 1988; Sullivan et al., 2000). These findings have been taken to reflect a dominance of infant-caregiver attachment learning early in life (Landers and Sullivan, 2012), consistent with the role of maternal presence in suppressing rat pups' aversive learning until approximately PND 15 (Stanton et al., 1987; Suchecki et al., 1993; Moriceau and Sullivan, 2006). Following PND 10 and coinciding with the capacity for learning-induced synaptic plasticity in the amygdala, rats gain the ability to acquire aversive conditioned responses when not in the presence of the mother (Thompson et al., 2008; Landers and Sullivan, 2012). During the juvenile stage of development, although PL activity increases in response to aversive conditioned stimuli, inactivation of PL does not attenuate conditioned responding until adolescence (Monk, 2008; Chan et al., 2011; Li et al., 2012). Moreover, the inverse activity of PL and IL that is observed in adult aversive learning and regulation (Gilmartin

and McEchron, 2005; Corcoran and Quirk, 2007; Quirk and Mueller, 2008) emerges after the juvenile period (Kim et al., 2009).

In both humans and rodents, memories for aversive associations acquired during infancy (before PND 18 in rodents) are not as robust or persistent as those acquired later in life and are susceptible to forgetting through a process known as infantile amnesia (Campbell and Campbell, 1962; Campbell and Spear, 1972; Hayne, 2004; Kim and Richardson, 2007; Josselyn and Frankland, 2012; Li et al., 2014; Mullally and Maguire, 2014; Alberini and Travaglia, 2017). Moreover, during the juvenile stage, extinction learning is not subject to the forms of relapse typically observed in adults (renewal, reinstatement, and spontaneous recovery), suggesting that extinction learning during this stage may yield "unlearning" or erasure of the original aversive association (Yap and Richardson, 2007; Gogolla et al., 2009; Kim et al., 2009). The closing of this window for memory erasure through extinction coincides with changes in extracellular matrix chondroitin sulfate proteoglycans within the juvenile amygdala after which aversive memories are protected from erasure by perineuronal nets (Gogolla et al., 2009; Duvarci and Pare, 2014), as well as hippocampal-dependent changes mediating the closure of the window for infantile amnesia (Alberini and Travaglia, 2017).

During adolescence, aversive learning appears to be persistently retained and easily generalized (Morrow et al., 1969; Hefner and Holmes, 2007; McCallum et al., 2010; Kim et al., 2011; Pattwell et al., 2012; D. C. Johnson and Casey, 2015a; Baker et al., 2016). Adolescent rodents exhibit diminished extinction learning relative to younger and older individuals (McCallum et al., 2010; Kim et al., 2011; Pattwell et al., 2012), with impaired retention of extinction memory also apparent during adolescence in rats (McCallum et al., 2010; Kim et al., 2011; Baker and Richardson, 2015). Protracted development of prefrontal regions (PL and IL), which continues well into adolescence (Giedd et al., 1996, 1999; Cunningham et al., 2002; Gogtay et al., 2004; Casey et al., 2005; Chan et al., 2011), may limit the capacity for prefrontal regulation of the amygdala and hippocampus. Indeed, amygdala potentiation is observed following cued aversive conditioning during adolescence in mice (Pattwell et al., 2011; Saul et al., 2014). Interestingly, connectivity between the amygdala and PL is stronger in adolescence than in preadolescence or adulthood, marked by an increased number of axonal projections and a surge in dendritic spine formation in PL (Pattwell et al., 2016). As a result, a positive feedback loop may be maintained in this circuit that mediates the persistent expression of conditioned responses. Although the amygdala appears to be similarly involved in extinction across development, in rats, IL is not required for extinction before PND 21 (Kim et al., 2009). This suggests a change in the connectivity between amygdala and IL that emerges later in development (Arruda-Carvalho et al., 2017) to support adult-like, extinction learning. Moreover, bidirectional PL-amygdala synapses mature earlier than IL-amygdala synapses (Chan et al., 2011), and adolescent rodents exhibit blunted IL activity during extinction (Pattwell et al., 2012; Cruz et al., 2015), suggesting potential neurobiological mechanisms underlying the resistance of conditioned responses to extinction during adolescence.

Relative to cued conditioning, contextual conditioning in rodents emerges later in development (Rudy, 1992, 1993; McCallum et al., 2010; Pattwell et al., 2011; Schiffino et al., 2011; Jablonski et al., 2012; Akers et al., 2014). This developmental trajectory parallels the protracted maturation of the hippocampus (Raineki et al., 2010; Akers et al., 2014), consistent with its central role in the processing of contextual information (Maren et al., 2013). Despite intact contextual conditioning in preadolescents, freezing in a conditioned context is suppressed during adolescence (Pattwell et al., 2011). This developmental difference is likely due to a temporary inability to retrieve, rather to encode, the contextual aversive memory during adolescence because mice are able to retrieve and express the contextual aversive memory as they transition out of adolescence and into adulthood, coinciding with an increase in basal amygdala activity (Pattwell et al., 2011). Moreover, even previously consolidated aversive memories acquired during the juvenile period are temporarily suppressed during adolescence.

Research on aversive learning during human infancy and childhood has been more limited; however, consistent with evidence in rodents, humans exhibit substantial changes in aversive learning across development. Aversive learning has been observed soon after birth, with both infants (Wickens and Wickens, 1940; Ingram and Fitzgerald, 1974) and toddlers (Gao et al., 2010) exhibiting extinction and relapse effects. However, responding to aversive conditioned stimuli increases across childhood (Gao et al., 2010; Glenn et al., 2012; Jovanovic et al., 2014; Michalska et al., 2016) and differs between adolescents and adults (Lau et al., 2011), suggesting that the underlying aversive learning process continues to mature. As in rodents, the adolescent period in humans is marked by diminished extinction learning relative to younger and older individuals (Pattwell et al., 2012; D. C. Johnson and Casey, 2015b).

Consistent with changes in behavior, the neural circuitry underlying aversive learning in humans also undergoes developmental changes. The amygdala exhibits early structural (Humphrey, 1968; Giedd et al., 1996; Ulfig et al., 2003; Payne et al., 2010) and functional (Graham et al., 2016; Rogers et al., 2017; Gabard-Durnam et al., 2018) maturation; however, its functioning shifts across human development (Hare et al., 2008; Decety et al., 2012; Gee et al., 2013b; Swartz et al., 2014; Vink et al., 2014; Silvers et al., 2015). The amygdala responds differentially to threat cues as early as infancy in humans (Graham et al., 2013). Although aversive learning depends primarily on the amygdala early in life, a more complex circuit, including the hippocampus and PFC, supports aversive learning later in human development (Lau et al., 2011; Britton et al., 2013), consistent with a similar shift in rodents (Kim et al., 2009; Li et al., 2012). Moreover, the processes by which threat reactivity is regulated change by developmental stage. As with rodents, caregivers play a central role in suppressing threat reactivity early in life when regulatory connections are still maturing. Specifically, in humans, parental presence reduces the hypothalamic-pituitary-adrenal axis response and amygdala reactivity to stress during childhood (Gunnar and Donzella, 2002; Ahnert et al., 2004; Feldman et al., 2010; Seltzer et al., 2012; Gee et al., 2014; Hostinar et al., 2014), but not during adolescence (Gee et al., 2014; Hostinar et al., 2015). Despite diminished extinction learning in adolescence, longer-term reduction of conditioned responding is achieved when methods rely less on the PFC (e.g., extinction during memory reconsolidation, at which time a reactivated memory can be updated), than with PFC-dependent methods (e.g., extinction) (D. C. Johnson and Casey, 2015b). These findings correspond with continued development of connectivity between the hippocampus, amygdala, and PFC across childhood and adolescence in humans, both structurally (Lebel et al., 2012; Swartz et al., 2014; Gee et al., 2016) and functionally (Perlman and Pelphrey, 2011; Decety et al., 2012; Qin et al., 2012; Gee et al., 2013b; Gabard-Durnam et al., 2014; Vink et al., 2014; Jalbrzikowski et al., 2017).

While this section focused primarily on developmental changes in the acquisition and extinction of Pavlovian reactive

responses, a more recent literature in adult humans and animal models has begun to characterize the neurocognitive processes involved in the learning of threat-motivated instrumental actions that are effective at preventing aversive outcomes (LeDoux and Daw, 2018). Functional integration between the amygdala, striatum, and PFC appears to be critically involved in such active avoidance learning (Moscarello and LeDoux, 2013; Bravo-Rivera et al., 2014; Collins et al., 2014; Boeke et al., 2017; Diehl et al., 2018). An important area of future study will be to elucidate how changes within this circuitry modulate the learning and expression of threat-motivated instrumental actions across development.

Neurocircuitry of reward processing and its development

Convergent evidence in adult humans and animal models indicates a central role for the DA system in reward processing. DA neurons project broadly throughout the striatum, PFC, hippocampus, and the amygdala, and exhibit heterogeneity in receptor types and cotransmitters, conferring diverse mechanisms for influencing motivated behavior (Lammel et al., 2014; Hu, 2016). Consistent with this complex organization, DA has been implicated in a broad array of reward-related processes in adulthood, including learning the value of stimuli and actions (Schultz, 2015), determining how much time, effort, or risk-taking is warranted for a potential outcome (Salamone and Correa, 2012), and modulating memory for reward-associated events (Shohamy and Adcock, 2010).

The DA system also undergoes significant changes across development (Teicher et al., 1995; Galván, 2013; Spear, 2013). Although findings are somewhat mixed (Galván, 2013), evidence in rodents suggests that DA receptor binding and tonic DA concentrations within the striatum, a region centrally implicated in reward learning (Haber and Knutson, 2010), peak in adolescence (Tarazi et al., 1998; Badanich et al., 2006; Philpot et al., 2009). Corroborating these findings in animals, DA receptor density in the striatum is highest in postmortem adolescent human brains, relative to postmortem child and adult brains (Haycock et al., 2003), and adolescents exhibit greater striatal engagement during reward processing than children and adults in neuroimaging studies (Silverman et al., 2015). Notably, the adolescent peak in DA availability and reward-related activation is paralleled by typical adolescent behaviors, such as increased exploration, novelty-seeking, and risk-taking in both primates and rodents (Laviola et al., 2003; Spear, 2013), as well as changes in many laboratory measures of reward-related learning and decision-making (Hartley and Somerville, 2015). However, at present, we lack a clear mechanistic understanding of how developmental changes in DA signaling across adolescence alter reward processing.

The activity of DA neurons has been observed to closely approximate a reward prediction error (RPE) signal, a fundamental reward learning computation that encodes when rewards exceed or fall short of one's current expectation (Schultz et al., 1997). Striatal activity correlating with RPE signals has been observed from childhood onwards in several neuroimaging studies (Galvan et al., 2006; van den Bos et al., 2012; Keren et al., 2018). These signals likely support the early-developing ability to associate cues and actions with their reward values, which is evident from the earliest stages of postnatal development (Johanson and Hall, 1979). Although many studies have shown enhanced striatal responses to reward in adolescence (Silverman et al., 2015), and some find that RPE signals are specifically enhanced (Cohen et al., 2010) and associated with better learning performance (Peters and Crone, 2017) during this period, this pattern has not been observed consistently across reward learning tasks (van den Bos et al., 2012; Christakou et al., 2013). Thus, the significance of adolescents' increased striatal sensitivity to reward for learning remains unclear.

Dopaminergic networks extending beyond the striatum also contribute to reward processing. Bidirectional projections connect DA nuclei with the PFC and hippocampus, which enable DA signaling to be modulated by current goals and environmental features (e.g., novelty) to which the hippocampus and PFC are sensitive (Goto and Grace, 2005; Sesack and Grace, 2010). These connections between DA neurons with the PFC and hippocampus also facilitate functions, such as working memory, attention, and episodic memory (Seamans and Yang, 2004; Shohamy and Adcock, 2010). Projections from DA nuclei to the striatum can organize corticothalamic circuits (Haber, 2003), providing a mechanism by which reward signals can guide higher-order learning and decision-making (Balleine and O'Doherty, 2010; Botvinick, 2012). To date, the developmental trajectories of this broader circuitry remain poorly characterized. However, the hippocampus and PFC have protracted maturation into early adulthood (Giedd, 2004; Ghetti and Bunge, 2012) and exhibit changes in the excitation-inhibition balance during adolescence that suggest ongoing refinement of the function of these circuits (O'Donnell, 2010; Luna et al., 2015; Gomes et al., 2016).

Recent studies have begun to characterize the development of behaviors that require integration across these prefrontal-striatal-hippocampal circuits by administering more complex tasks that require learning more than simple reward associations. These studies suggest that the use of structured knowledge to explore or plan how best to obtain current or future rewards (van den Bos et al., 2015; Decker et al., 2016; Somerville et al., 2018), and the use of counterfactual reward information to guide choices (Palminteri et al., 2016), increase gradually from childhood into young adulthood. This gradual developmental emergence is consistent with evidence that these cognitive processes are PFC-dependent in adults (Daw et al., 2011; Badre et al., 2012; Donoso et al., 2014) and with the protracted development of prefrontal-subcortical connectivity (Casey et al., 2016).

Notably, other aspects of reward learning appear to be facilitated in adolescence relative to adulthood. A recent study found that adolescents showed better learning in a probabilistic reward learning task, and that their episodic memory for rewarding outcomes was related to heightened hippocampal RPE signals and greater functional connectivity between the hippocampus and the striatum during reward receipt (Davidow et al., 2016). This finding is consistent with recent suggestions that the functional development of the DA system during adolescence, through its projections to both the striatum and the hippocampus, may facilitate memory for reward-associated experiences during this period (Murty et al., 2016). These early studies provide burgeoning evidence of developmental changes in reward processing across multiple learning systems, and suggest that network integration between the striatum, PFC, and hippocampus across development contributes to these shifts in learning and decision-making. This work underscores the need for further research regarding the relationship between the myriad changes in adolescents' reward-motivated behavior and the function of these neural circuits, and examining the mediating role of DA systems.

Accumulating evidence suggests that pubertal hormones are also important modulators of adolescent reward processing. Indeed, several studies in humans have reported a positive relationship between pubertal testosterone and risk-taking (Forbes et al., 2010; Op de Macks et al., 2011; Cardoos et al., 2017) and impulsivity (Laube et al., 2017). Moreover, recent studies have found that activation in the ventral striatum was positively correlated

with salivary testosterone (Op de Macks et al., 2011; Braams et al., 2015), suggesting that there may be direct modulation of DA pathways by pubertal hormones. However, this hypothesis is only partially supported by findings in the animal literature. For instance, pubertal changes in gonadal hormones do not play a role in adolescent DA receptor overproduction (Andersen et al., 2002). Moreover, animal studies primarily identify the dorsal, not ventral, striatum as a key target of pubertal hormones (Matthews et al., 2013; Sinclair et al., 2014; Laube and van den Bos, 2016). In addition, these studies show that increases in pubertal hormones typically lead to a decrease in DA function (Stamford, 1989; Matthews et al., 2013; Purves-Tyson et al., 2014). Given the robust connectivity of the dorsal striatum to the PFC, it is possible that the influence of pubertal hormones on DA signaling specifically affects prefrontal influence over reward processing. Thus, while many details remain unclear, the extant animal literature suggests that pubertal hormones do impact the DA pathway. An important open question is how this hormonal modulation of DA in adolescence specifically influences reward processing and motivation.

Future research will be essential for establishing a mechanistic understanding of the ways in which specific developmental changes in prefrontal-striatal-hippocampal circuitry and DA signaling influence the changes in reward processing that characterize transitions from childhood to adulthood.

Effects of early-life stress on threat and reward processing

The early postnatal period sets the foundation for socioemotional and cognitive development. Elevated neuroplasticity renders the young brain exquisitely sensitive to environmental stimuli, such that early experiences can have lifelong effects on cortical-subcortical circuitry and behavior (McEwen, 2003; Hensch, 2005; Lupien et al., 2009; Shonkoff et al., 2012). Early in life, stable and responsive caregiving is one of the strongest species-expected experiences for altricial mammals (Tottenham, 2012). Caregiver-offspring relationships are essential for normative brain and behavioral development, rendering disruptions of early caregiving a profound stressor (Tottenham, 2012; Kok et al., 2015; McLaughlin et al., 2015; Bernier et al., 2016; Callaghan and Tottenham, 2016a; Gee, 2016). Even relatively brief alterations in caregiving have been associated with deleterious long-term physical and mental health outcomes (Heim and Nemeroff, 2001; Sánchez et al., 2001; Anda et al., 2006; Zeanah et al., 2009; Conti et al., 2012).

In humans, early-life adversity has been associated with myriad cognitive and socioemotional impairments, including reduced cognitive functioning (Nelson et al., 2007), delayed academic performance (Loman et al., 2009), alterations in associative learning (Hanson et al., 2017; Kamkar et al., 2017; Sheridan et al., 2018), and deficits in cognitive flexibility, working memory, and behavioral inhibition (Richards and Wadsworth, 2004; Bos et al., 2009; McDermott et al., 2012; Hanson et al., 2013; Harms et al., 2018). In the socioemotional domain, early-life stress is associated with social dysfunction, anxiety and depressive symptoms, and reduced ability to suppress attention to potential threat in favor of goal-directed behavior (Tottenham et al., 2010, 2011; Lawler et al., 2014; Burkholder et al., 2016; Krugers et al., 2017; Sheridan et al., 2018). These effects are mediated by altered patterns of neural structure, function, and connectivity in prefrontal-subcortical circuitry (Edmiston et al., 2011; Gee et al., 2013a; Hanson et al., 2013; Herringa et al., 2013; Bick et al., 2015; Thomason et al., 2015; Chen and Baram, 2016; Teicher et al., 2016; Fareri et al., 2017; Kaiser et al., 2018), which has a high density of glucocorticoid receptors (Woolley et al., 1990; Honkaniemi et al., 1992; De Kloet et al., 1998; Plotsky et al., 2005; Lupien et al., 2009; Wang et al., 2014). Changes in volume of the PFC, hippocampus, and amygdala have been identified following early-life stress (Mehta et al., 2009; Tottenham et al., 2010; van Harmelen et al., 2010; Luby et al., 2013; Hanson et al., 2015; Hodel et al., 2015; McLaughlin et al., 2016), and these alterations are associated with depression and anxiety symptoms (Vythilingam et al., 2002; Frodl et al., 2010; Tottenham et al., 2010; Bick et al., 2017). In parallel to structural changes, early-life stress drives altered patterns of brain activation, with evidence for hypoactivation in the PFC, hippocampus, and ventral striatum (Mehta et al., 2010; Goff et al., 2013; van Harmelen et al., 2014; Liberzon et al., 2015; Hanson et al., 2016), and hyperactivation in the amygdala (Tottenham et al., 2011; Gee et al., 2013a).

Given ethical considerations that preclude the direct manipulation of the early childhood environment in humans, animal models have provided insight into the causal relationship between early-life stress and long-term behavioral, anatomical, neurochemical, and hormonal changes. Rodents exposed to early-life stress display similar behavioral phenotypes as those observed in humans, including alterations in cognitive functioning and responding to threat and reward. More specifically, rodent studies have demonstrated consequences of early-life stress that include deficits in working memory (Brenhouse and Andersen, 2011; Yang et al., 2015; Grassi-Oliveira et al., 2016), altered reward processing (Fuentes et al., 2018), reduced cognitive flexibility (Powell et al., 2015; Thomas et al., 2016), increased anxiety-like behavior (Kalinichev et al., 2002; Romeo et al., 2003), and altered social behavior (Kikusui and Mori, 2009).

As in humans, early-life stress in rodents leads to long-term changes in prefrontal-subcortical circuitry. Early-life stress or repeated stimulation of the hypothalamic-pituitary-adrenal-axis through pharmacological means is associated with diminished cell proliferation and increased cell death in the hippocampus (Gould et al., 1991a, b, 1992; Dachir et al., 1993; Cameron and Gould, 1994; Gould et al., 1997, 1998; Gage et al., 1998; Tanapat et al., 1998) and dendritic arbor atrophy and decreased dendritic spine plasticity in the hippocampus and PFC (Woolley et al., 1990; Watanabe et al., 1992; Magariños et al., 1998; Chen et al., 2008; Liston and Gan, 2011; Chen et al., 2013; Yang et al., 2015). Recent evidence suggests that early-life stress may alter the typical trajectory of adolescent PFC synapse overproduction and pruning (C. M. Johnson et al., 2016) to prematurely limit plasticity. In addition, several studies indicate reductions in PFC parvalbumin protein or cell labeling (Brenhouse and Andersen, 2011; Holland et al., 2014; Powell et al., 2015; Grassi-Oliveira et al., 2016), although results vary depending on the timing and duration of the stress paradigm, sex of the animal, and subregion of the PFC. Amygdala connectivity, structure, and function are also altered by early-life stress in rodents (Caldji et al., 2000; Sabatini et al., 2007; Malter Cohen et al., 2013; Yan et al., 2017; F. K. Johnson et al., 2018), yielding amygdala hyperactivity that persists even after termination of the stressor and the maturation of PFC, paralleling observations in humans (Malter Cohen et al., 2013).

Given evidence that early-life stress can shift the timing of prefrontal-subcortical development, the "stress acceleration hypothesis" posits that early-life stress leads to the accelerated development of neural and behavioral trajectories for aversive learning (e.g., Callaghan and Tottenham, 2016b). Rodents exposed to early-life stress exhibit accelerated development of the hippocampus (i.e., earlier maturation of parvalbumin interneurons, precocious synaptic development, and earlier onset of my-

elination) and earlier emergence of the inhibition of contextual conditioned responding (Bath et al., 2016). Similarly, early-life stress in rodents is followed by accelerated trajectories of cued conditioning (Sullivan et al., 2000; Moriceau et al., 2009; Callaghan and Richardson, 2011; Cowan et al., 2013) that have been associated with precocious engagement of the basolateral amygdala during the acquisition of aversive learning (Moriceau et al., 2004; Moriceau and Sullivan, 2006). Earlier structural maturation of the amygdala (Ono et al., 2008) and PFC (Muhammad et al., 2012) are also associated with early-life stress in rodents. In humans, early-life stress is followed by earlier emergence of adult-like functional connectivity between the amygdala and PFC (Gee et al., 2013a) and the recruitment of broader hippocampal-amygdala-PFC circuitry during aversive learning (Silvers et al., 2016). Paralleling findings in rodents (Moriceau et al., 2004, 2006), the earlier maturation of frontoamygdala circuitry in humans was mediated by cortisol levels (Gee et al., 2013a), suggesting that early-life stress may accelerate prefrontal-subcortical development via modifications of the hypothalamic-pituitary-adrenal axis (e.g., Ruttle et al., 2015). Changes in the timing of circuit maturation may confer initial benefits as an ontogenetic adaptation to meet the needs of the developing organism in an adverse environment (e.g., Gee et al., 2013a); however, there are likely to be long-term consequences of altered developmental timing. Moreover, much remains unknown about the nature of alterations in timing, such as whether they reflect acceleration to an adult-like state or premature closure of a sensitive period in development.

Alterations in prefrontal-subcortical circuit development likely play an important mediating role in the pathway from early-life stress to later psychopathology (Green et al., 2010; Kessler et al., 2010). Importantly, behavioral and clinical phenotypes following early-life stress can vary across individuals and domains of functioning (e.g., Rutter and O'Connor, 2004). The nature of stress exposure (e.g., Sheridan and McLaughlin, 2014) and its timing relative to specific sensitive periods of neuroplasticity (e.g., Tottenham and Sheridan, 2009; Gee and Casey, 2015) may be critical determinants of long-term effects. Future research will be essential to delineate the dimensions of stress exposure and neurobiological and environmental factors that promote risk versus resilience following early-life stress.

Clinical implications

Deficits in motivated behavior are core features of psychiatric disorders, including depression, anxiety, bipolar disorder, schizophrenia, and substance use disorders. Each of these disorders is characterized by alterations in the capacity to appropriately predict and respond to threats or rewards in the environment (e.g., Dillon et al., 2014). Such deficits are consistent with observed abnormalities in prefrontal-subcortical circuitry across many forms of psychopathology (Rauch et al., 2003; Casey et al., 2007; Monk, 2008; Goldstein and Volkow, 2011; Arnsten and Rubia, 2012; Taylor et al., 2012; Brotman et al., 2014; Heller, 2016; J. A. Johnston et al., 2017) and with evidence that effective treatments act on this same circuitry (Goldapple et al., 2004; Ressler and Mayberg, 2007; Goldin et al., 2013).

The majority of psychiatric disorders emerge before adulthood (Kessler et al., 2007). Understanding neurodevelopmental changes in prefrontal-subcortical circuitry and their role in both the emergence of illness onset as well as treatment efficacy is critical to reducing the substantial burden of psychiatric disorders. The developing brain may be particularly vulnerable to certain forms of psychopathology at specific maturational stages. As one example, 1 in 5 adolescents has a psychiatric disorder that will persist into adulthood (Kessler et al., 2005). The confluence of neurodevelopmental state, hormonal changes and puberty, changes in stress reactivity (Romeo et al., 2006; Foilb et al., 2011), and increases in social demands may render adolescents particularly vulnerable to disruption in reward- or threat-motivated behavior (Ernst et al., 2009; Casey et al., 2016). Heightened sensitivity to rewards, increases in novelty-seeking, and enhanced exploratory behavior during adolescence are likely to serve adaptive functions, in part promoting transitions to adult roles. However, individual differences that predispose certain adolescents to vulnerability may interact with this developmental stage in ways that increase risk for disorders, such as substance use (e.g., Chambers et al., 2003), depression (e.g., Silberg et al., 1999), and anxiety (e.g., Gee et al., 2016).

The biological state of the brain at distinct developmental stages may have direct implications for optimizing treatments for these disorders in children and adolescents. Although the majority of treatments for youth are based on research in adults, pronounced changes during brain development suggest that mechanisms of illness and treatment are likely to vary across the lifespan (Lee et al., 2014). Integrating the neuroscience of the developing brain and motivated behavior with research on clinical interventions may enhance treatment outcomes during development. For example, in the domain of pediatric anxiety disorders, evidence-based treatments, such as cognitive-behavioral therapy and selective serotonin reuptake inhibitors, have proven effective (e.g., Walkup et al., 2008), yet recent studies highlight the need for enhanced clinical efficacy (e.g., Ginsburg et al., 2018). Protracted development of the regulatory connections between the PFC and amygdala may constrain mechanisms of anxiety reduction during childhood or adolescence (e.g., Pattwell et al., 2012), suggesting potential avenues to optimize interventions via approaches that are less dependent on the PFC (e.g., D. C. Johnson and Casey, 2015b). Future research that aims to optimize treatment based on the developing brain and state of threat- and reward-motivated behavior in childhood and adolescence may be especially useful for informing the timing and types of intervention that will be most effective at specific developmental stages.

In conclusion, dynamic changes in prefrontal-subcortical circuitry across childhood and adolescence support the development of motivated behavior. Unique developmental stages require individuals to flexibly respond and adapt to distinct environmental challenges and opportunities. Cross-species evidence demonstrates that experiential inputs actively shape the development of prefrontal-subcortical circuitry, and stress early in life can influence the structure, function, and maturational timing of this circuitry. Alterations in prefrontal-subcortical interactions likely contribute to deviations from the normative developmental trajectory of motivated behavior and confer risk for the myriad psychiatric disorders characterized by deficits in threat and reward processing. Future investigations that focus on elucidating brain-behavior relationships across development will be essential to understanding how prefrontal-subcortical maturation drives the development of motivated behavior and informing interventions that target deficits in threat- and reward-motivated behavior at specific developmental stages in psychopathology.

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