Adolescence and Reward: Making Sense of Neural and Behavioral Changes Amid the Chaos

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Introduction

Adolescence is a time of significant neural and behavioral change with remarkable development in social, emotional, and cognitive skills. It is also a time of increased exploration and risk-taking (e.g., drug use). Many of these changes are thought to result from increased reward value coupled with an underdeveloped inhibitory control, and thus, a hypersensitivity to reward. Perturbations during adolescence can alter the developmental trajectory of the brain, resulting in long-term alterations in reward-associated behaviors. This review highlights recent developments in our understanding of how neural circuits, pubertal hormones, and environmental factors contribute to typical adolescent reward-associated behaviors, with a particular focus on sex differences, the medial prefrontal cortex, social reward, social isolation, and drug use. This research has only begun to elucidate the contributions of the many neural, endocrine, and environmental changes to heightened reward sensitivity and increased vulnerability to mental health disorders that characterize this life stage.

Adolescence can be both an exciting and a tumultuous time. It comprises the formative years during which individuals reach sexual maturity and develop the social, emotional, and cognitive skills needed as they move toward independence and adulthood (Spear, 2000). It is a time of increased exploration, but this exploration often includes increased sensation seeking and the initiation of drug use (Steinberg, 2004; Lipari and Jean-Francois, 2013), which could contribute to the high percentage of preventable deaths among teens (Minino, 2010). It is also a time of increased vulnerability to stress and the emergence of several psychiatric and behavioral disorders (e.g., schizophrenia, depression, and eating disorders) (Kessler et al., 2005). Hence, research into the neurobiological underpinnings of adolescence is important for providing a basic understanding of normative social, emotional, reproductive, and cognitive development as well as the prevention and treatment of health risks and disorders that characterize this life stage.

The prevailing theory underlying adolescent vulnerability to psychiatric disorders proposes a developmental mismatch in accumbal-driven sensation seeking (risk-taking) and prefrontal inhibition of impulsivity (Casey and Jones, 2010). It is thought that this mismatch leads to a greater sensitivity to rewarding stimuli and may explain adolescents' increased vulnerability to drugs of abuse and stress, mentioned above (Casey and Jones, 2010). Sex differences in vulnerability to psychiatric disorders emerge during adolescence, as do important sex differences in the types of disorders displayed by males and females. For example, males are seemingly more vulnerable to externalizing disorders (e.g., bipolar disorder and attention deficit hyperactivity disorder), whereas females are more susceptible to internalizing disorders (e.g., depression and anxiety). Although it is difficult to disentangle how social structures contribute to these vulnerabilities, it is critical to acknowledge that social and biological variables likely act in concert to produce such outcomes. There are striking sex differences in adolescent development, including in the timing of puberty and neural development. These may give rise to sex differences in the vulnerability to psychiatric disorders. Therefore, forming a concrete understanding of these developmental differences is critical for advancing sex-specific treatment strategies for vulnerable populations.

The reorganization of the reward circuitry during adolescence is one factor that is integral to both adolescent development and increased vulnerability to disease (Luciana, 2013; Doremus-Fitzwater and Spear, 2016). This process is driven by complex interactions among neural pathways, endocrine axes, and environmental stimuli to produce a functional mesocorticolimbic reward system in adulthood. Hence, it is imperative to determine how these factors act independently and in concert to shape the mesocorticolimbic reward circuitry during adolescence. This review highlights research on interactions between the mesocorticolimbic dopamine (DA) system, pubertal hormones, and environmental perturbations (drug use and social stress) and their effects on cognitive and social adolescent development.

Puberty-Dependent and Puberty-Independent Adolescent Development

"Puberty" and "adolescence" both refer to the transition from childhood to adulthood, but these terms are not equivalent. Puberty is reserved for physiological and behavioral changes associated with the attainment of reproductive competence (e.g., activation of the hypothalamic-pituitary-gonadal [HPG] axis, appearance of secondary sex characteristics, and onset of sexual interest and mating behaviors), all of which are sexually dimorphic. Adolescence is a broader term that includes puberty as well as nonreproductive traits (e.g., social, emotional, and cognitive development).

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Reproductive hormones, however, can have widespread effects, and the development of several nonreproductive adolescent traits can also be driven by activation of the HPG axis at puberty (puberty-dependent, e.g., ethanol intake, anxiety-related behaviors) (Primus and Kellogg, 1989, 1990; Vetter-O'Hagen and Spear, 2011). The physiological, anatomical, and temporal changes that differ between males and females can also lead to the emergence of sex differences during adolescence (Schulz et al., 2009a). Other adolescent traits, however, develop independently of HPG activation and merely coincide with pubertal development (puberty-independent, e.g., social play, aggression) (Whitsett, 1975; Smith et al., 1996; Wommack and Delville, 2007). Sex differences may also manifest in puberty-independent traits owing to organizational actions of perinatal hormones or direct actions of genes on the sex chromosomes (Arnold, 2017). This puberty-dependent versus puberty-independent distinction is important because many neuropsychiatric and behavioral disorders arise during adolescence, exhibit striking sex differences, and are impacted by pubertal hormones as well as nonpubertal factors (Fombonne, 2009; Graber, 2013; Trotman et al., 2013). Given that the mesocorticolimbic DA pathway is sexually dimorphic (Becker, 2009) and regulated by gonadal hormones in adults (Kuhn et al., 2010; Becker et al., 2012), a central question is whether adolescent development of reward-related behaviors and circuitry is puberty-dependent or puberty-independent.

Sex Differences in Reward and Reward-Related Circuitry

Studies in humans and laboratory animals generally support the notion that adolescents are more sensitive to reward than adults. This is behaviorally manifest in multiple ways, including elevated levels of sensation seeking and risk-taking, as well as reduced inhibitory control, which are all maximal during the early to mid-adolescent period (Burnett et al., 2010; Andrzejewski et al., 2011; Burton and Fletcher, 2012; Urosevic et al., 2012; Collado et al., 2014). In laboratory rodents, heightened reactivity to drug rewards has also been demonstrated (Doremus et al., 2005; Levin et al., 2007; Anker and Carroll, 2010), although this might depend on the drug or other procedural factors (Doremus-Fitzwater and Spear, 2016). When gender or sex is considered, an even more nuanced picture emerges. For example, compared with males, females have a relatively earlier and lower-magnitude peak in sensation seeking during mid-adolescence that is followed by a more rapid decline to stability by early adulthood (Shulman et al., 2015). In this comprehensive, longitudinal study, it was also demonstrated that impulse control improved steadily following early adolescence in both males and females, but males remained more impulsive than females through their mid-20s. In rats, compared with adults, male adolescents exhibit greater intake and motivation for palatable food that is either calorie dense (sweetened condensed milk) (Friemel et al., 2010) or calorie devoid (Marshall et al., 2017). However, this age-dependent difference in reward sensitivity was not apparent in female rats (Marshall et al., 2017). Using food-restricted rats trained to associate a tone with delivery of a sucrose solution, Hammerslag and Gulley (2014) found that the effects of age and sex were dependent on the characteristics of the behavior being measured. Specifically, females exhibited enhanced development of stimulus-directed behavior in that both adult and adolescent females acquired Pavlovian approach more quickly than males. Adolescents of both sexes, however, had weaker expression of goal-directed behavior (i.e., entries into the sucrose delivery trough) and were less sensitive to reward devaluation than adults.

Recent work has also highlighted gender and sex differences in neural development of reward-related brain circuits that may play an important role in these age and gender/sex differences in behavior. In the striatum, adolescent boys lag behind as they reach peak striatal volume at ~15 years of age compared with 12 years of age for girls (Raznahan et al., 2014). Structural development in the cortex also appears to be relatively delayed in boys compared with girls, although exceptions include a more rapid reduction in the thickness of the dorsolateral prefrontal cortex (PFC) in males (Raznahan et al., 2010). Many of these adolescent cortical changes are associated with adrenal and/or gonadal markers of pubertal maturation, often in a sex-dependent manner (Herting et al., 2017). In the rat medial prefrontal cortex (mPFC), there are significant decreases in neuron number (Markham et al., 2007), dendritic complexity (Koss et al., 2014), and synapse number (Drzewiecki et al., 2016) between adolescence and adulthood. At least some of these changes are more pronounced in females than in males and are closely linked to puberty onset (Willing and Juraska, 2015). However, in the core and shell regions of the nucleus accumbens (NAc), these "pruning" processes and the emergence of adult-like morphological features appear to occur much earlier and well before the onset of puberty (Tepper et al., 1998; Lee and Sawatari, 2011).

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Development of the PFC During Adolescence

The mPFC is a crucial regulator of reward-directed behaviors and likely contributes to cognitive development during adolescence. As a major component of the mesocorticolimbic DA pathway, the mPFC receives dopaminergic projections from the ventral tegmental area (VTA) and sends key glutamatergic projections to the NAc, a key integrator of reward processing (Albertin et al., 2000; McGinty and Grace, 2009; Hamel et al., 2017; Morrison et al., 2017). These regions form a larger circuitry (Fig. 1) that includes the basolateral amygdala (BLA) and ventral hippocampus (vHIP), among others. This circuit acts in concert to modulate dopaminergic and glutamatergic tone integrated by the NAc in response to salient stimuli. Loss or reduction of signaling within the PFC in humans has been associated with numerous psychiatric disorders, including anxiety and depression (Ressler and Mayberg, 2007) and substance use disorders (Volkow et al., 2010) in adulthood. Similar effects have been observed in rodent models in which exposure to stress or drugs of abuse can influence signaling between the PFC and NAc, resulting in addiction-related behaviors (MacAskill et al., 2014) or depressive-related behaviors (Covington et al., 2010; Vialou et al., 2014; Bagot et al., 2015). For example, repeated exposure to cocaine in adult mice decreases the PFC inputs to D1 DA receptor–containing medium spiny neurons in the NAc (MacAskill et al., 2014).

One of the most dramatic brain changes occurring during adolescence is the unfolding of DA connectivity in the mPFC. In contrast to DA projections to limbic regions (e.g., NAc) and cortical innervation of other monoamines (e.g., norepinephrine and serotonin) that reach adult density levels early in life (Coyle and Molliver, 1977; Levitt and Moore, 1979; Lidov et al., 1980; Benes et al., 2000; Diamond, 2002), DA projections to the mPFC do not fully mature until early adulthood (Kalsbeek et al., 1988; Benes et al., 2000; Manitt et al., 2011; Naneix et al., 2012). In rodent models of both sexes, the number of dopaminergic fibers in the mPFC increases linearly between the juvenile period (postnatal day [P] 25) and young adulthood, with the most prominent increases occurring between the late juvenile period and early adulthood (Naneix et al., 2012; Willing et al., 2017). Interestingly, this is not a rodent-specific phenomenon, as protracted mesocortical DA development occurs in nonhuman primates and most likely in humans (Rosenberg and Lewis, 1994; Lambe et al., 2000), paralleling cognitive maturation.

In addition to changes in dopaminergic projections in adolescence, changes in dopaminergic receptor expression are prevalent throughout the mesocorticolimbic system, which may underlie the altered sensitivity to rewarding stimuli. In the NAc and dorsal striatum of rats, DA D1 and D2 receptor expression peaks during adolescence (P40), then declines to reach adult levels at ~P80 (Andersen et

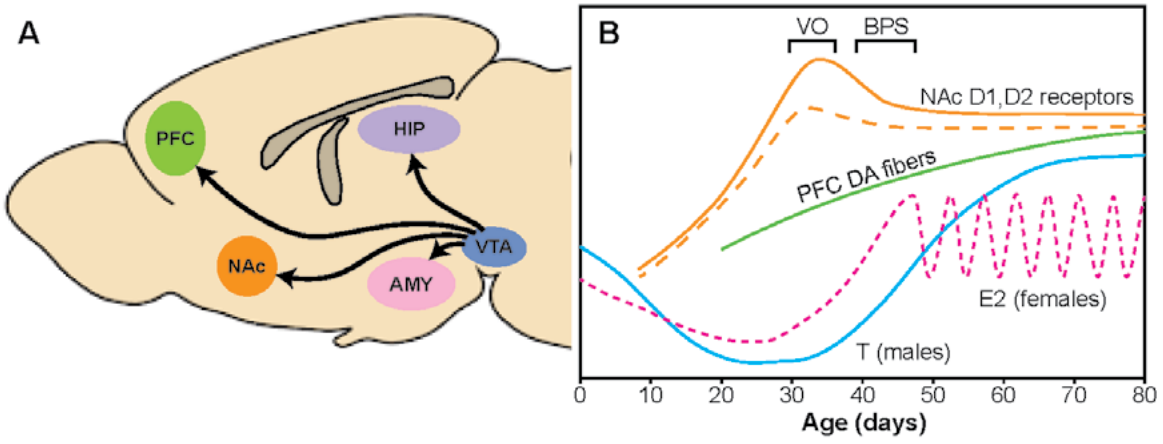

Figure 1. Adolescent development of the mesocorticolimbic DA pathway. ***A***, Major brain areas and projections of the mesocorticolimbic DA pathway. ***B***, Schematic of postnatal development of key c mponents of this pathway along with changes in gonadal steroid hormones and pubertal markers. Hashed lines, Data specific to females. Developmental patterns and markers are based on data from Tarazi and Baldessarini (2000) (NAc D1, D2 receptors); Naneix et al. (2012) and Willing et al. (2017) (PFC DA fibers); and Dohler and Wuttke (1975) and Vetter-O'Hagen and Spear (2012) (gonadal steroid concentrations and pubertal markers). VO, vaginal opening; BPS, balano-preputial separation, E2, estradiol; T, testosterone.

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al., 2000). In the PFC of male rats, there is also a selective decrease of cells expressing D1 receptors that project to the NAc between P44 and adulthood (Brenhouse et al., 2008). However, there may be important species differences in these receptor changes across adolescence (Pokinko et al., 2017), and little is known about sex differences in this developmental milestone.

Measures of functional connectivity in humans have further elucidated the widespread changes between the PFC and subcortical structures throughout adolescence, with some evidence suggesting that a relatively stable network connectivity state does not occur until at least the mid-20s (Dosenbach et al., 2010). The potential relevance of these changes for behavior is not fully understood, but decreases in the functional coupling between subregions of the PFC and the NAc have been linked to decreases in self-reported risky behavior across adolescence (Qu et al., 2015). Interestingly, studies of PFC activation in humans have revealed sex differences in function that go beyond what might be expected from the anatomical correlates. One such functional development is resting-state functional connectivity, which describes the degree of synchrony between two different brain regions or between nearby areas within a brain region. In the dorsolateral PFC, resting-state functional connectivity between the hemispheres tends to increase with age in males but decreases with age in females (Zuo et al., 2010).

These data demonstrate that the mesocorticolimbic DA pathway undergoes vast developmental changes during adolescence both in fiber projections to the PFC and in sensitivity to DA within the NAc, dorsal striatum, and PFC target areas through altered receptor expression. Some of these developmental changes seem to occur independently of the gonadal hormone surge associated with puberty (Andersen et al., 2000; Willing et al., 2017). Although tyrosine hydroxylase immunoreactivity in the PFC increases across adolescence, this increase does not appear to be associated with markers of pubertal status (Willing et al., 2017). Preventing the pubertal rise in gonadal hormones by gonadectomy on P28 does not alter the adolescent (P40) or adult (P80) levels of D1 or D2 receptor expression in the rat striatum (Andersen et al., 2000). Finally, many developmental changes occur before puberty (e.g., adult-like morphological features of striatal neurons) (Tepper et al., 1998; Lee and Sawatari, 2011). For many measures, more research is needed to answer this question. The influence of gonadal hormones on reward-associated behaviors and the mesocorticolimbic pathway in adults (Becker et al., 2012) suggests at least a modulatory role during adolescence, particularly with respect to the emergence of sex differences (Kuhn et al., 2010).

Pubertal Influences on mPFC Adolescent Development

Recent evidence suggests that, within the adolescent period, pubertal onset may be particularly critical in specific aspects of mPFC development and cognition. Previous work in rats has documented a reduction in mPFC volume between the juvenile and adult periods (Van Eden and Uylings, 1985), and this volumetric reduction may reflect a decrease in neuron number. Stereological quantification of the total number of neurons in the mPFC across adolescence revealed that the majority of neuronal losses occur during the period of pubertal onset, particularly in female rats (Willing and Juraska, 2015). Ovariectomy before puberty prevented these neuronal losses, further suggesting a role for pubertal hormones (Koss et al., 2015). Additionally, there are changes in dendritic complexity and synapse number in the mPFC during adolescence. Between P35 and P90, there is a reduction in dendritic spine density in both male and female rats (Koss et al., 2014). In a recent study, Drzewiecki et al. (2016) conducted an immunohistochemical analysis of synaptophysin as a marker for total synapse number in the mPFC in P25, P35, P45, P60, and P90 rats of both sexes. As expected, there was evidence for significant synaptic pruning during adolescence. Interestingly, a direct comparison of prepubertal versus postpubertal females at P35 and prepubertal versus postpubertal males at P45 (corresponding to the average age of pubertal onset) revealed that in both sexes, postpubertal animals had significantly fewer synapses than their prepubertal counterparts.

These structural alterations within the mPFC are associated with changes in cognitive performance during adolescence, which also seem to depend on the timing of puberty. These differences in cognitive performance could reflect differences in reward processing. Indeed, substance use disorder is often described as maladaptive decision-making and reward learning. Given the importance of the entire PFC in reward learning, it follows that structural changes in adolescence result in altered cognitive performance and decision-making with regard to reward. Kanit et al. (2000) found that pubertal onset alters learning strategies in spatial memory tasks. However, there is a paucity of research that accounts for a potential role for puberty, particularly on mPFC-dependent

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tasks. Willing et al. (2016) have recently shown that pubertal onset leads to better performance on an mPFC-mediated cognitive flexibility component of a Morris water maze task in both male and female rats. Path length to the novel platform location was shorter in postpubertal males and females, and prepubertal animals spent a greater amount of time swimming in the quadrant where the platform was initially located, suggesting a deficit in cognitive flexibility that subsides after pubertal onset. In support of these findings, recent evidence suggests that pubertal hormones play a critical role in the maturation of the PFC in female mice. Gonadectomy before puberty blocked the adolescent increase in inhibitory neurotransmission, and prepubertal estradiol treatment accelerated the maturation of inhibitory tone in the PFC and advanced the increase in cognitive flexibility in females (Piekarski et al., 2017). Future studies are needed to determine whether these temporal associations with pubertal status reflect pubertal mechanisms or coincidental timing.

Development of Social Reward During Adolescence

The adolescent transition from childhood to adulthood requires a qualitative shift in the perception of rewarding social interactions (Spear, 2000). In humans, adolescence is characterized by increases in time spent with peers and changes in the quality of social interactions with family and peers (Larson et al., 1996). Adolescents rely on their contemporaries for social support and are increasingly reactive to treatment by their peers (Ladd et al., 2014). These social relationships influence the development and maintenance of maladaptive behaviors in adulthood (Patterson et al., 1992; Hankin et al., 1998). Indeed, peer influence is a strong predictor of adolescent depression (Thapar et al., 2012). This reorganization of social structure during adolescence is necessary for social species to develop appropriate behavioral strategies for survival in adulthood (Gopnik et al., 2017). A close association between adolescent social reorganization and puberty is thought to increase exposure to genetically distinct individuals when sexual behavior emerges, thereby decreasing the chance of inbreeding within a social group (Lawson Handley and Perrin, 2007).

As in humans, adolescent changes in social interactions and social structure are prevalent in rodents. Adolescent male rats place a greater value on peer-directed activities (Pellis and Pellis, 2017) and exhibit a greater preference for social stimuli in a conditioned place preference (CPP) test when compared with adults (Douglas et al., 2004; Yates et al., 2013) and females (Douglas et al., 2004; Weiss et al., 2015). However, this effect is most pronounced in socially isolated males. Additionally, a peer-paired chamber negates CPP induced by cocaine (Zernig et al., 2013) and amphetamine (Yates et al., 2013) in adolescent males but not in females (amphetamine only; Weiss et al., 2015). These data suggest that there are striking sex differences in sensitivity to social reward in adolescent rodents and that males display a greater sensitivity to social reward than females. These differences appear to be influenced by the pubertal hormonal surge and may result in long-term alterations in reward valence, as evidenced by the influence of prepubertal gonadectomy on reward-associated behaviors in both male rodents (Schulz et al., 2009b; Bell et al., 2013a,b) and female rodents (Perry et al., 2013). It is thought that adolescent-specific social experiences result in permanent neural and hormonal changes that coalesce in cognitive strategies that lead to effective coping in adulthood (Spear, 2000). Therefore, these observed sex differences in sensitivity to social reward may profoundly influence the neural circuitry involved in reward and the sex differences in reward-associated behavior seen in adulthood.

The limbic system is a known regulator of social interaction and social reward. In particular, the amygdala is critically important for the integration of emotional stimuli and regulates emotional and motivated behaviors (Wassum and Izquierdo, 2015). The BLA, in particular, has been studied extensively for its role in reward because it is thought to be important in assessing/assigning value to stimuli and is a key regulator of social interactions. Activation of the BLA reduces social interaction (Sanders and Shekhar, 1995), whereas inhibition of glutamatergic or GABAergic transmission within the BLA increases social interactions (Sajdyk and Shekhar, 1997; Paine et al., 2017). Recent evidence suggests that these behavioral effects are likely projection specific, as activating BLA-to-PFC projections decreases social behaviors in male mice (Felix-Ortiz et al., 2016). In addition to its reciprocal glutamatergic projections with the PFC, the BLA projects to the NAc and receives dopaminergic projections from the VTA (Wassum and Izquierdo, 2015). Although sex differences in development have yet to be studied, it is clear that each of these circuits develops at different stages in males (Bouwmeester et al., 2002a,b; Cunningham et al., 2002; Caballero et al., 2014; Wassum and Izquierdo, 2015; Arruda-Carvalho et al., 2017). For example, projections from the PFC to the BLA are established between P10 and

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P15 (Bouwmeester et al., 2002b; Arruda-Carvalho et al., 2017), but the reciprocal projections (BLA to PFC) are established a few days earlier (Bouwmeester et al., 2002b; Cunningham et al., 2002). The amygdalar circuit (including NAc, VTA, PFC, and vHIP) develops during the juvenile/early adolescent period, and synapses are established by the second or third postnatal week. Although projections within the amygdalar circuitry are established before adolescence, recent evidence suggests that the PFC-to-BLA projections undergo significant synaptic strengthening (as measured by the IPSC:EPSC ratio) on P30 (Arruda-Carvalho et al., 2017). Also, there are more PFC-to-BLA projections on P31 compared with P24 and P45 (Pattwell et al., 2016), suggesting that this time point in male adolescence may be a crucial developmental period for limbic structures. The BLA (Trezza et al., 2012; Achterberg et al., 2015) and extended amygdala (Meaney et al., 1981; Meaney and McEwen, 1986; Jessen et al., 2010) are both important regulators of social play, a prominent juvenile social behavior that may be sexually dimorphic (Veenema et al., 2013) and is important for social, emotional, and cognitive development (Pellegrini, 1988; Vanderschuren et al., 1997; van den Berg et al., 1999; Baarendse et al., 2013). Notably, the PFC-BLA synaptic development coincides with the developmental rise in this behavior (Panksepp, 1981). Finally, binding at oxytocin and vasopressin receptors (two social neuropeptides) peaks in the BLA and central amygdala during adolescence (P35) in both males and females (Smith et al., 2017). Given the known sex differences in social reward (Borland et al., 2018), it is imperative that future research determine whether there are sex differences in the development of BLA connectivity with the reward circuitry.

Brain areas outside the canonical reward-associated circuitry are also likely to play a role in sex differences in reward and motivation, particularly those that are hormone sensitive, sexually dimorphic, and send projections to brain areas of the mesocorticolimbic pathway. The medial amygdala (meAMY) is larger in males than in females (Hines et al., 1992; Kerchner et al., 1995). However, unlike most sexually dimorphic brain regions, sex differences in volume of subnuclei within the meAMY do not emerge until adolescence, and the pubertal testosterone surge in males contributes to the organization of this sex difference (De Lorme et al., 2012). This change in meAMY structure co-occurs with changes in rewarding sociosexual behaviors that are in part regulated by it (De Lorme et al., 2012). Additionally, the meAMY is sensitive to stress in adolescence in a sex-dependent manner. For example, adolescent stress demasculinizes the meAMY: meAMY volume and cell number are decreased in males stressed during adolescence compared with their control counterparts, and these stressed males are less efficient at mating (Cooke et al., 2000). Collectively, this literature suggests that the meAMY contributes to the development, initiation, and maintenance of sex differences in reward and motivation. Additionally, the emergence of many sex differences in meAMY during adolescence is affected by social cues and could be crucial for the manifestation of sex differences in motivation and reward in adulthood.

Conclusions

The factors contributing to adolescent reward are many, and we are only beginning to understand the complex interactions among neural networks, endocrine axes, and environmental cues that direct the development of a functioning male- and female-typical mesocorticolimbic reward circuit. The many behavioral changes and neuroendocrine interactions may seem chaotic, but it is clear that adolescent development is a highly regulated and coordinated process. In this review, we have highlighted a few overarching themes that are beginning to emerge from the chaos: (1) There are notable sex differences in adolescent development that might underlie sexually dimorphic reward-associated behaviors in adulthood. (2) The mesocorticolimbic pathway is critical for adolescent changes in social reward and reward learning. (3) Reorganization of the reward circuitry, particularly the PFC, during adolescence relies on social interactions, pubertal hormones, as well as nonpubertal processes. (4) Adolescent reward circuitry is highly vulnerable to social stress and drugs of abuse. Further research is necessary for a comprehensive understanding of the factors that regulate the development of the mesocorticolimbic pathway, those that lead to increased vulnerability to disruption, and how this process drives developmental changes in motivation and reward. This research would benefit from the use of multiple approaches and models to disentangle the neural, endocrine, and environmental influences on adolescent reward. Together, these investigations will provide valuable insight into sex-specific psychiatric and behavioral disorders that arise during adolescence and could lead to novel avenues for treatment and prevention.

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