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Sex Differences in the Developmental Neuroscience of Adolescent Substance Use Risk

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Abstract

Adolescence is a period associated with the initiation and escalation of substance use and is also a time during which substantial changes take place in neural development, personality and behavior. Although rates of substance use between adolescent girls and boys do not differ substantially, there is evidence for sex differences in underlying vulnerability pathways associated with the development of substance use disorder. Here we review sex differences in adolescent brain development and how these differences may contribute to different risk pathways between females and males that emerge during this developmental period. We also discuss methodological considerations in the study of sex differences in brain and behavior and their implications for interpretation. We close by highlighting promising areas for future work.

Introduction

Rates of substance use rise sharply throughout adolescence and peak in young adulthood [1,2]. While rates of past year substance use disorder (SUD) in 12–17 year olds are similar between females (4.5%) and males (4.0%), differences emerge in early adulthood, with higher rates of SUD in males aged 18 or older (10.1%), compared with females (5.7%)[3]. Likewise, sex differences in substance use are small to nonexistent in adolescents but by age 18 men drink more frequently, in larger quantities, and have greater rates of nicotine and marijuana use [4,5]. Therefore, sex differences in substance use vary by age with small differences in adolescence that increase in young adulthood. It is not clear whether this represents true developmental differences or “cohort effects” with current rates in adolescents reflecting changing cultural attitudes [6]: girls have historically had a lower prevalence of nicotine and marijuana use, but this difference has decreased over time [7,8]. Gendered behavior arises from a complex interaction of multiple influences including

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prevailing culture and social- and individual-level factors; these factors are profoundly different for boys and girls. In human research, it is rarely possible to "control for" the gendered environment and only examine biological sex [9]. We use the term sex in this review with the understanding that in humans it represents both biological sex and sociocultural influences.

Adolescence is not only associated with the initiation and escalation of substance use, but is also a time during which substantial changes in neural development, personality and behavior take place [10]. Models of adolescent brain development propose maturational changes that may contribute to normative increases in substance use during the teen years. However, these models do not explicitly consider sex differences. Although rates of substance use between adolescent girls and boys do not differ substantially, evidence indicates there are sex differences in underlying vulnerability pathways associated with SUD. Externalizing and internalizing problems often precede the initiation of substance use and are associated with a more severe and persistent course of SUD [11]. The externalizing pathway is characterized by rule-breaking, impulsivity, aggression, and sensation-seeking. Males generally show greater externalizing behavior than females [5]. In adolescent males, conduct and attention deficit hyperactivity disorders are most frequently cited as increasing SUD risk [reviewed in 6]. The internalizing pathway is characterized by negative affect, depression, and anxiety [11]. On average, females show greater internalizing behavior than males [12]. Sex differences in depression emerge in puberty with higher rates in females [6], and females have higher prevalence of comorbid depression or anxiety that typically predate SUD onset [13]. Thus, females are more likely to have an internalizing pathway and males more likely to have an externalizing pathway to SUD.

Next, we provide an overview of sex differences in adolescent brain development and discuss how they may contribute to divergent risk pathways (Figure 1). Due to the paucity of information available on sex differences in neurochemical pathways during adolescence in humans, the focus here is on brain structure and function (see [6] for a review of sex differences in neurochemical systems related to addiction in animal models and adult humans). We also consider the interpretation of sex differences in brain and behavior and their dependence upon study methods.

Developmental neuroscience and externalizing behaviors

The "imbalance model" of adolescent brain development proposes a tension between early development of bottom-up subcortical reward circuity, including the ventral striatum, and later-developing top-down prefrontal cortical control circuitry [14]. Normative risk-taking behaviors in adolescence, which include substance use, are believed to reflect high ventral striatum reactivity in the context of rewarding stimuli in absence of a prefrontal control system that can dampen the response [14]. This view is supported by recent research focusing on sensation-seeking, which is underpinned by subcortical motivation circuitry such as the ventral striatum, and impulsivity, which is mediated by cognitive control circuitry in the prefrontal cortex. Longitudinal work demonstrates a linear decrease in impulsivity across adolescence along with a curvilinear association between age and sensation-seeking, which peaks in middle adolescence [15], consistent with the predictions

of the imbalance model. Although this pattern holds for both females and males, there are key sex differences at the levels of both brain and behavior.

Prefrontal cortex development plateaus later in males than females although males have consistently greater volume and thickness [16,17]. Trajectories of functional connectivity between left and right dorsolateral prefrontal cortex also differ between females and males, with a pattern suggestive of earlier maturation in females [18]. In the ventral striatum, volumetric change follows a cubic trend (i.e., increasing, then decreasing) for males, but a linear (decreasing) trend for females [19]. Furthermore, functional neuroimaging has shown that adolescent females rely on frontal and striatal regions for inhibitory control more than males and these regions show significantly increased functional maturation in females [20].

The consequences of these brain differences have not been directly investigated, but behavioral studies provide insight. For example, males have lower levels of impulse control and higher levels of sensation-seeking than females, but females reach peak levels of sensation-seeking earlier than males and decline more rapidly thereafter [21]. Furthermore, the decrease in impulsivity is more gradual in males than females. This may have important implications for sex differences in substance use as it has been shown that a slower decline in impulsivity is associated with a more rapid increase in alcohol, marijuana and tobacco use [22]. Furthermore, externalizing behavior problems have been associated with poor prefrontal control [23], so sex differences in prefrontal development and downstream effects on impulsivity may contribute to sex differences in SUD vulnerability.

Trajectories of sensation-seeking, however, are not strongly associated with substance use escalation [22]. Progression in drug use is predicted by an imbalance resulting from heightened reward-seeking and weak executive control whereas heightened reward-seeking balanced by strong executive control is associated with drug experimentation, but not progression [24]. Thus, experimentation with substances may be related to a tendency to seek out rewarding experiences stemming from reward-related circuitry whereas persistent, compulsive use characterizing addiction may be more closely linked to acting without planning or consideration of consequences, stemming from prefrontal circuity. It is possible, then, that normative increases in reward system responsivity during adolescence may account for comparable levels of substance use in girls and boys, whereas greater impulsivity and protracted development of inhibitory control in males may account for greater rates of SUD emerging later in development.

Developmental neuroscience and internalizing behaviors

The triadic model is another influential theory of brain development [25]. It is consistent with the imbalance model with regard to motivated behavior, but also considers the normative increases in emotional intensity and lability that occur in adolescence. Specifically, it proposes that emotional lability reflects heightened emotional responding centered in the amygdala during adolescence due to poor prefrontal cortex modulation [25]. Although this is rarely discussed in relation to SUD risk, it is directly relevant to sex differences in the internalizing vulnerability pathway. Adolescent girls are more likely than boys to endorse coping with negative emotions as a rationale for drinking alcohol [26] and

differences in the development of amygdala may affect vulnerability to anxiety and depression. For example, males have greater peak amygdala volume, but they reach this peak later in puberty than females [19]. Larger amygdala volume has been correlated with poorer emotional control in female, but not male, adolescents [27], suggesting that amygdala development may have a larger effect on emotional behavior in females [28].

Adolescent males and females also have different patterns of amygdala functional connectivity, with females exhibiting greater integration between posterior cortex and amygdala regions involved in socio-affective processing [29]. Sex differences in activation patterns across adolescence have also been found, with one study reporting decreasing activity with age in the left amygdala in response to emotional (fearful) faces in females but not males [30] and another reporting decreasing activity in the right amygdala with age to negatively-valenced words in males but not females [31]. These seemingly conflicting reports are difficult to interpret—they suggest a role for lateralization and context (i.e., task demands) in sex differences in emotional processes.

Sex differences in vulnerability to stress may also play an important role in the internalizing pathway. Adolescent girls, but not boys, who abuse alcohol tend to have experienced a high-level of stressful life events [32,33]. Furthermore, interpersonal stress and its cortisol response are more strongly linked to internalizing symptoms in adolescent girls than boys [34]. The prefrontal cortex and amygdala are particularly sensitive to the effects of stress [35]. Females who experienced early life stress had higher cortisol levels in childhood and less connectivity between the amygdala and prefrontal cortex in adolescence, which was associated with greater symptoms of anxiety [36], suggesting that girls are more likely to suffer lasting neural effects of early stress.

The current state of sex differences research in the developmental neuroscience of adolescent SUD

None of the structural imaging studies reported above directly investigated functional consequences of sex differences in the context of SUD vulnerability. A more direct way to understand brain-behavior relationships is through functional neuroimaging techniques such as fMRI. Some sex differences have been reported in healthy adolescents during inhibitory control and emotion processing fMRI studies, as reviewed above, but sample sizes are relatively small, and the tasks and analysis methods differ across studies, which hampers generalizability [37]. One review of fMRI studies comparing reward-related activation between adolescents and adults noted that the majority of studies lack the power to examine sex differences [38]. Furthermore, studies specifically documenting neuro-functional links between age-related sex differences and SUD risk are limited. A recent review of fMRI studies of SUD risk in adolescents found that only 6 of the 18 studies reported analyses of sex and 4 of these were post-hoc analyses in small sample sizes [39].

There has been a recent policy shift at the NIH calling for increased attention to sex in research. This will undoubtedly result in a much-needed increase in research into sex differences in brain functional development and associations with emerging psychopathology, including SUD. However, without appropriate attention to methodological

considerations and a framework to interpret differences – as well as similarities – there will be minimal benefit to our understanding [40].

Interpreting sex differences in the developmental neuroscience of adolescent SUD

The interpretation of sex differences largely depends on methodological features of the studies in which the differences were found. When there are sex differences in brain structure or function, but not in fMRI task responses or substance use, findings could reflect equifinality, meaning that similar SUD outcomes have different neurodevelopmental antecedents [41]. This is consistent with emerging literature on sex differences in externalizing and internalizing vulnerability pathways in adolescent girls and boys, and with notions of compensation [42] that parallel interpretations of sex differences in brain size. Boys have larger total brain volumes than girls according to several measures beginning in childhood [43], but potential advantages of this (e.g., more or larger neurons) are offset by other features of the neural architecture in which girls are advantaged; for example, girls have greater inter-hemispheric connectivity than do boys [44]. When there are sex differences in fMRI task responses or substance use, but not in brain structure or function, findings could reflect multifinality, or that the same risk factor can lead to different SUD outcomes [i.e., the same pathway can lead to more than one endpoint; 41]. This is consistent with work reviewed above on the role of stress in the internalizing pathway for girls. Thus, accurate interpretation of the nature of sex differences in substance use relies on holistic considerations of brain structure, function, and behavior, suggesting that future work should include careful consideration of task designs and span levels of analysis.

Another methodological feature that influences the interpretation of sex differences is the way in which sex is handled in statistical analyses. The identification of sex differences is not an *a priori* aim of many developmental neuroscience or substance use studies. In fact, sex is often considered to be a confound or variable of no interest, and is included as a statistical covariate [45]. This is an especially coarse approach because it only accounts for linear relations in a dichotomous variable, and is based on the assumption that sex does not interact with other variables of interest. If the study of gender is an *a priori* research aim, however, then differences between girls and boys can simply be identified [46], interactions can be found [31,47], or sex-related processes can be examined separately in girls and boys [48]. Each approach answers different research questions. The first acknowledges individual differences, the second suggests neurodevelopment depends on sex, and the third implies that the neurodevelopment of substance use is a sex-specific process.

Regardless of how sex differences are identified, they reflect the same thing: average differences between girls and boys. Significant differences do not indicate that all boys use substances in one way for one reason, and that all girls use them in another way for a different reason; there is substantial overlap among individuals. Furthermore, individuals who are gendered in one domain may not be gendered in another. For instance, a boy can have “male-typical” amygdala volumes, but “female-typical” patterns of substance use. Thus, it will be important for future research in adolescent neuroscience to adopt methods

that account for heterogeneity in SUDs and their antecedents and outcomes within as well as between the sexes. Person-specific connectivity approaches hold promise in this regard; they can map connections between brain regions that are related to sex or unique to an individual [49].

Variation within the sexes also highlights that sex reflects biological and sociocultural influences. Sex differences, therefore, provide insight into the mechanisms underlying brain-behavior associations. One likely mechanism underlying sex differences in the neural bases of adolescent substance use is pubertal hormones. Recent research suggests that *pubertal stage at first drink* is important. Compared to those whose first drink was after puberty, adolescents who drank during puberty had more alcohol-related problems in adulthood as well as decreased frontal activation during reward anticipation and increased striatal activation to reward presentation [50]. Unfortunately, there is limited consideration of sex in this new line of research, so it is unclear what aspects of puberty (e.g., brain sensitivity to hormones or social experiences) contribute to persisting effects. Future natural experiments that disentangle biological and sociocultural experiences could be illuminating. For instance, individuals with precocious puberty begin pubertal development in late childhood [51], and thus, do not have concurrent adolescent social experiences.

Other natural experiments could be similarly leveraged– to disentangle biological and sociocultural influences on the gendered nature of substance use. For instance, girls with congenital adrenal hyperplasia (CAH) have an XX karyotype, are overwhelmingly reared and identify as female, and (if their condition is well-controlled) have female-typical puberty, but due to a genetic condition, they are exposed to sex atypical levels of prenatal androgens [reviewed in 52]. Compared to unaffected girls, those with CAH have masculinized brain structure, function, and behavior (e.g., activity interests and participation, career interests, and spatial ability). Because the gendered influences of prenatal androgen are separated from those related to genes and socialization in girls with CAH, prenatal androgen is the most likely mechanism underlying the effects. There is little conclusive evidence concerning the neural bases of substance use in girls with CAH, particularly during the adolescent transition, but preliminary evidence suggests that they are more likely than controls to misuse substances, including being nearly three times more likely to receive an alcohol disorder diagnosis [53].

Conclusions

Developmental changes occurring in the prefrontal cortex, ventral striatum and amygdala contribute to increased risk for substance use problems in adolescence through effects on risk-taking behavior and emotional lability. Sex differences in these maturational trajectories lend insight into why girls tend toward an internalizing pathway to SUD and boys tend toward an externalizing pathway. To date, however, few studies have directly probed sex differences in the function of this circuitry as it relates to SUD risk. As the use of sex as a biological (and sociocultural) variable increases in this line of research, it will be important to have a framework for interpreting sex differences. This framework should incorporate methodological considerations including careful task design, multiple levels of analysis and appropriate statistical modeling of sex in light of *a priori* study hypotheses. Furthermore,

person-specific connectivity methods that reflect heterogeneity and natural experiments that disentangle biological and sociocultural experiences hold significant potential for uncovering the gendered mechanisms that underlie sex differences in links between the brain and gendered behavior.

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Highlights

- Sex differences exist in underlying risk factors for substance use disorder
- Sex differences in brain development may underlie these divergent risk pathways
- Interpretation of sex differences depends on study methods
- Future research on mechanisms underlying sex differences is needed

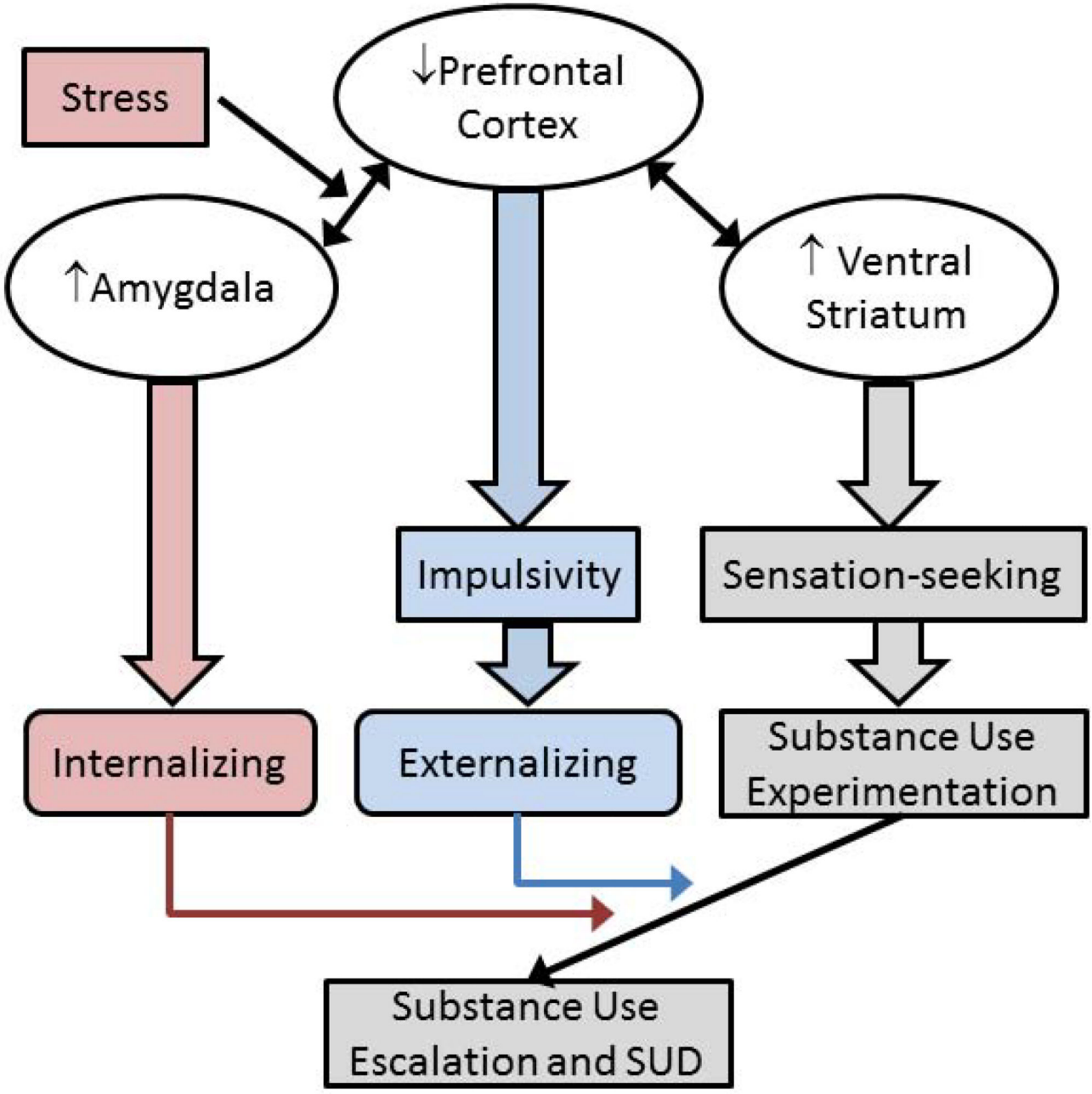

Figure 1.

Theoretical schematic of the influence of sex differences in adolescent brain development on vulnerability pathways to substance use disorder (SUD). Gray indicates pathways proposed to influence girls and boys similarly. This illustrates the suggestion that normative increases in ventral striatal responsivity during adolescence may account for comparable levels of substance use in girls and boys. Blue indicates pathways proposed to be more influential in boys than girls. Weaker inhibitory control due to individual differences in prefrontal cortex development may underlie greater externalizing problems, which in turn influences progression of substance use and development of SUD. Red indicates pathways believed to

be more influential in girls than boys. Developmental imbalances between amygdala and prefrontal cortex increase emotional lability, enhancing vulnerability to internalizing problems, which in turn influences progression of substance use and development of SUD. Stress impacts this pathway.