



Stress reactivity and the developmental psychopathology of adolescent substance use[☆]



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ABSTRACT

Adolescence represents a period of risk for initiation of substance use and the development of substance use disorders (SUDs). In addition, during adolescence, there is rapid development of stress reactivity systems. This paper describes a conceptual model of the role of stress reactivity in the development of substance use in adolescence. It is proposed that some children develop maladaptive patterns of emotional, physiological, and neural reactivity to stressful situations that are either too high or too low and that their patterns of reactivity interact with increased stressful life events during adolescence to lead to potential for substance use and SUDs. In one pathway, youth develop a heightened reactivity to stress, which leads to high negative emotion and using substances to cope. In a second pathway, youth develop a blunted reactivity to stress, which leads to chronic under-arousal and using substances to increase sensation/arousal. We propose that girls may be more likely to take the high-reactivity pathway to substance use and boys may be more likely to take the low-reactivity pathway. We review existing studies of stress reactivity in adolescents, which support our theory that altered stress reactivity is correlated with and, in some cases, predictive of adolescent substance use, with some studies finding high stress reactivity and some finding low stress reactivity to be correlated with increased substance use and SUD risk. Some studies find that the blunted reactivity pathway to substance use occurs particularly for youth from high-risk contexts. Further, some evidence supports the proposed sex differences in stress reactivity pathways. We discuss future directions and implications of these findings for developing and refining developmentally-sensitive stress reactivity-focused SUD prevention programs.

1. Introduction

Adolescence is a period of risk for the development of substance use and substance use disorders (SUDs). Substance use typically emerges and shows increases during adolescence (Chambers et al., 2003). In the present study, we use the term substance use to include use of alcohol, tobacco, marijuana, other illicit substances, and prescription drug misuse. Past month rates of alcohol, cigarette, and marijuana use in the United States increase from 5 to 14% in 8th grade to 9–29% in 10th grade to 16–41% in 12th grade (Johnston et al., 2016; Masten et al., 2008). For some youth, some amount of substance use experimentation during adolescence does not cause long-term problems. But, for others, particularly those who start using substances early (e.g., < age 14), those who use substances heavily (e.g., binge drinking), or those with existing risk factors such as genetic risk for addiction, using substances during adolescence is risky. Early and heavy substance use in adolescence has been shown to longitudinally predict future Substance Use

Disorders (SUDs) and associated psychological problems into adulthood (Chassin et al., 2002; Moss et al., 2014). Also, substance use during adolescence has been linked concurrently to several adolescent problems, including increased risk for unprotected sexual intercourse, unsafe driving, academic problems, physical health problems, and suicide (NIAAA, 2017; Windle et al., 2008). Finally, emerging evidence suggests that substance use during adolescence may impact the developing brain, including brain systems that underlie executive functioning (e.g., working memory), reward sensitivity, and, relevant to the present paper, stress reactivity (e.g., Squeglia et al., 2011). In addition, it is important to consider sex differences when examining adolescent substance use. Substance use rates are increasing among adolescent girls and there may be different causes and more serious consequences of substance use for girls and women versus boys and men (Amaro et al., 2001; Fox and Sinha, 2009).

Given the increases in substance use during adolescence and the negative public health consequences of substance use and SUDs, it is

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List of abbreviations		AUD	Alcohol Use Disorder
SUD	Substance Use Disorder	PCE	Prenatally cocaine exposed
ACC	Anterior Cingulate Cortex	sAA	Salivary alpha amylase
TSST	Trier Social Stress Task	ABCD	Adolescent Brain and Cognitive Development
fMRI	Functional Magnetic Resonance Imaging	ERP	Event-Related Potential
		IAPS	International Affective Picture System

critical to develop strategies that prevent, delay, or reduce adolescent substance use. In order to best develop novel interventions and strengthen existing interventions, it is necessary to develop a full understanding of the factors that contribute to the development of adolescent substance use. Developmental psychopathology models have been presented that describe several different risk factors for adolescent substance use and SUDs, including family history of substance use disorders, maladaptive parenting, environmental stressors (stressful neighborhood environments, low socioeconomic status, childhood trauma exposure), association with drug-using peers, positive alcohol and drug expectancies, and temperamental traits including impulsivity, reward sensitivity/sensation-seeking, negative affectivity, and poor emotion regulation (Chassin et al., 2014; Zucker et al., 2008).

The present paper focuses on stress reactivity and its role in the developmental psychopathology of adolescent substance use and SUDs. Stress reactivity, for purposes of this paper, is defined as “processes involving perception, appraisal, and response to harmful, threatening, or challenging events or stimuli” (Sinha, 2008, p. 106). In this paper, stress reactivity includes negative subjective emotional experience of, peripheral physiological responses to (including HPA axis responses, sympathetic nervous system responses), and neural responses to a stressful environmental event. Stressful environmental events encompass a range of challenging events, such as getting a low grade on a test, experiencing childhood trauma (including abuse and neglect by caregivers), being rejected by peers, or experiencing a physical illness. Although for the purposes of this paper, we focus on stress reactivity predicting substance use and SUDs, we acknowledge that other factors play a role in the development of substance use and may interact with stress reactivity to predict substance use and SUDs, including reward system functioning and executive functioning. Also, we acknowledge that adolescent substance use itself may alter adolescents’ stress reactivity, changing the way stress reactivity contributes to the further development of SUDs over time.

2. Conceptual model of the role of stress reactivity in the development of substance use

Here we present a conceptual model, based on several prior theories, that children may over time develop particular patterns of stress reactivity which might lead them to risk for adolescent substance use and SUDs (see Fig. 1). In childhood, experiencing environmental stressors activates a stress response system (environmental stressors also activate and affect reward and executive functioning systems). Environmental stressors can include several types of stressors, including stress of low-income environments, stressful life events such as getting a bad grade in school, and peer problems. In regard to stress responses, in most cases, mild stressors (e.g., studying for a test) elicit a normative stress response in children that allows them to harness mild negative emotion to adaptively respond to the stressor (e.g., they may feel slightly worried and thus may study more for the test). However, in some cases, children and adolescents may show a dysregulated stress response, including either very high reactivity to stress or very low/blunted reactivity to stress. These patterns may develop in children because they have experienced repeated chronic and uncontrollable stressors (e.g., chronic child abuse or neglect, chronic negative parenting, or chronic stressful environments such as dangerous neighborhoods) that have altered their stress reactivity systems, because they have a particular genetically-based stress reactivity pattern, and/or because of socialization by caregivers, teachers, peers, and other socialization agents that encourages either high or low stress reactivity. Childhood trauma, including physical abuse, sexual abuse, and neglect may have a particular role in affecting stress reactivity—research has found that childhood trauma predicts alterations in HPA-axis functioning and in structure and function of stress-related brain regions (Koss and Gunnar, 2018; Teicher and Sansom, 2016; Whittle et al., 2013). Some research suggests that maladaptive parenting, including low parental warmth and high negative/harsh parenting may also affect

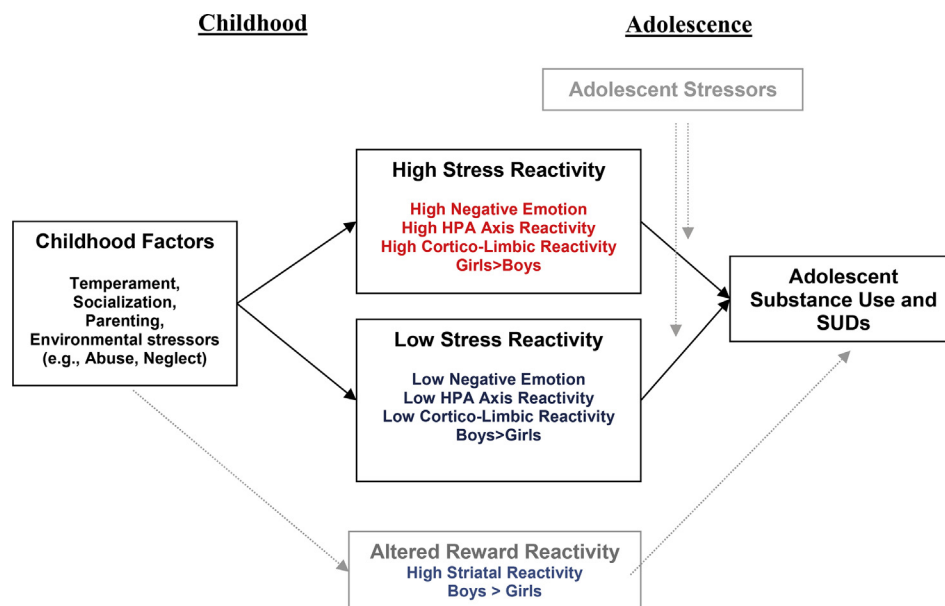


Fig. 1. Conceptual model.

stress-related brain function (e.g., Romund et al., 2016). Harsh or abusive parenting is theorized to alter levels of glucocorticoids and other neurotransmitters (e.g., dopamine, norepinephrine) which then affect structure and function in the developing brain in limbic, striatal, and prefrontal regions (Arnsten et al., 2012).

This dysregulated stress reactivity (either too high or too low reactivity) then leads the child to react to stressful life events in a problematic way. Over time and over the experience of more environmental stressors, these patterns of stress reactivity may become ingrained and inflexible in children. Then, in adolescence, multiple stressful biological and environmental changes occur (e.g., puberty, changes in peer networks) and also brain changes in stress and emotion processing systems occur, leading to a triggering of the stress response system (Chambers et al., 2003). At this time, adolescents with a history of dysregulated stress reactivity patterns may cope with increased environmental and internal changes/stressors by using substances in order to either down-regulate overly high stress reactivity or to up-regulate low/blunted stress reactivity. Notably, there may be sex differences in childhood stress reactivity patterns that might contribute to different pathways to substance use in adolescence for girls versus boys, which we discuss below. Our two-pathway model of substance use development (high stress reactivity, low stress reactivity) is consistent with prior theories and empirical studies suggesting two pathways to substance use and SUDs. For example, Zucker and colleagues have argued that children may take either an internalizing pathway to alcohol use and alcohol use disorders (AUDs) characterized by a history of depression or anxiety symptoms or an externalizing pathway to AUDs characterized by a history of externalizing behavior problems (such as impulsivity, inattention, and aggression) (Zucker et al., 2008). In addition, one functional Magnetic Resonance Imaging (fMRI) study with young adult college students found evidence for a separate high negative emotional reactivity/low reward sensitivity pathway and a low negative emotional reactivity/high reward sensitivity pathway to problematic alcohol use (Nikolova et al., 2016).

2.1. High stress reactivity and adolescent substance use: theory and empirical research

In the high stress reactivity pathway, we propose that some youth (due to temperamental traits such as high anxious arousal/neuroticism and high emotionality and environmental emotion socialization to cope with events with high negative emotion) tend to cope with environmental stressors by showing high activation of the bio-behavioral stress system, including high negative emotional arousal, high negative emotion expression, possibly rumination on negative emotion, heightened HPA-axis activation, high sympathetic nervous system activation, and heightened reactivity in negative emotion reactivity-related brain networks to stressors. When these children experience environmental stressors, this triggers high stress reactivity, leading to high feelings of negative emotion. To cope with those feelings of negative emotion, these adolescents may use substances to down-regulate negative emotion to feel better. This is consistent with self-medication theories of addiction, stress theories of addiction (Sinha, 2008; Koob et al., 2014), and stress-coping theories of adolescent substance use (Wills and Hirky, 1996), which propose that SUDs result from and are maintained by the use of substances to manage negative emotional states. In addition, chronic stress and high activation of negative emotion reactivity-related brain regions may lead to blunted recruitment of prefrontal executive function regions and heightened activation in striatal regions, leading to increased reward-seeking and craving and lowered executive control, contributing to further substance use (Arnsten et al., 2012). This high stress reactivity pathway is consistent with an “internalizing” pathway to substance use disorders that suggests that children with high levels of depression and anxiety symptoms and high negative emotionality are at risk for later comorbid substance use and SUDs in adolescence (e.g., Conway et al., 2016).

2.1.1. Empirical studies

Several studies using self-report measures have found that high reported perceived stress and higher reported numbers of environmental stressors are correlated with (and predict) adolescent substance use (e.g., Siqueira et al., 2000; Wills et al., 2001). In addition, several studies have found associations between children's and adolescents' higher emotional, peripheral physiological, and neural reactivity to stressful or negative emotionally arousing tasks and adolescents' substance use behavior or substance use risk. Two studies examined adolescent reactivity to laboratory parent-adolescent conflict interaction tasks and found associations between higher adolescent negative emotional and physiological reactivity and higher levels of adolescent substance use. Parent-adolescent conflict tasks are a well-established paradigm used to induce stress among adolescents that model daily family conflict stressors that occur in real life for adolescents (e.g., Sheeber et al., 1997). In the first study, Chaplin et al. (2012) found that higher heart rate, systolic blood pressure, and salivary cortisol reactivity to the parent-adolescent conflict task was related to lifetime alcohol use (a yes/no variable) among a community sample of 10–16 year old early to middle adolescents (53% boys). The second study found that higher levels of observed negative emotion expressions (e.g., grimacing, eye rolling) during a parent-adolescent conflict task and three parent-adolescent discussions about substance use were associated with increased likelihood of lifetime alcohol, tobacco, marijuana, and other illicit drug use (yes/no variables) in a community sample of early to middle adolescents aged 11–15 years (sex not reported) that were over-sampled for parents and/or youth who were current smokers (Hops et al., 1990). Taken together, these studies suggest that higher negative emotional, sympathetic nervous system, and HPA-axis reactivity to stressful family interactions are associated with substance use in adolescents. Notably, these findings are cross-sectional. So, it is unclear if youth's high reactivity to family conflict led them to use substances or whether youth who were already using substances elicited more tense family interactions (and then showed higher stress reactivity). Future longitudinal studies could clarify this. Also, associations between stress reactivity and substance use were not examined by sex so it is unclear if girls were particularly likely to show the associations between heightened reactivity to family stress and substance use as compared to boys. The Chaplin et al. study did include slightly more boys (53% boys), but it is still possible that the girls in the study showed the higher stress reactivity to substance use pattern more strongly.

2.2. Blunted stress reactivity and adolescent substance use: theory and empirical research

In the low stress reactivity pathway to substance use, we propose that some children (due to temperamental traits and environmental history) respond to environmental stressors by showing blunted activation of the bio-behavioral stress system, including low negative emotional arousal (particularly for anxiety), blunted sympathetic nervous system activation, blunted HPA-axis activation, and blunted reactivity in brain networks involved in emotional arousal to stressful stimuli. This pattern of low stress reactivity might be due to a genetically-inherited tendency towards blunted stress reactivity, a history of socialization that discourages expression or experience of “soft” negative emotions (sadness and fear/anxiety), and/or to a history of chronic environmental stressors in childhood (such as chronic child abuse or neglect) that may “wear down” the HPA axis system, leading to an inability to appropriately mount a stress response (Gunnar and Vazquez, 2015; Koss and Gunnar, 2018). While the present paper and model focuses on stress reactivity, these children may show a combined pattern of blunted stress reactivity and also high reward sensitivity or sensation-seeking, as has been described by Nikolova et al. (2016), which may further exacerbate their tendency to use substances to up-regulate arousal. Their potential early history of heightened HPA axis

responses and release of glucocorticoids may also have affected their prefrontal functioning, leading to altered executive functioning which may contribute along with blunted stress reactivity to their substance use risk (Arnsten et al., 2012).

When these children with blunted stress reactivity experience environmental stressors in adolescence, they may show a low emotional response. To cope with under-arousal, these adolescents may seek out substances to up-regulate emotion and also induce positive emotion/sensation. This model is consistent with sensation-seeking theories of the development of substance use in adolescence (e.g. Donohew et al., 1999), which propose that some youth initiate substance use to feel high arousal/sensation. This pathway may also be consistent with an “externalizing” pathway to substance use. Zucker et al. (2008) and others have noted that childhood externalizing behavior problems, including inattention, aggression, impulsivity, and conduct problems, predict alcohol and other substance use in adolescence. Some youth with conduct problems (particularly those with callous-unemotional traits) may show blunted physiological and limbic system arousal responses to negative emotional stimuli (Jones et al., 2009; Stadler et al., 2007) and may reflect the pathway from blunted stress reactivity to substance use. Also, many youth with inattention and conduct problems have altered reward system functioning (which may be affected by a history of stressors and also by their altered stress system functioning) and high sensation-seeking traits and thus may seek out substances for reward and sensation. However, some youth with early externalizing problems do feel high emotional arousal to stress (particularly angry arousal; Chaplin and Cole, 2005) and thus may take a different path to substance use.

2.2.1. Empirical studies

Some studies examining adolescents' sympathetic nervous system, HPA-axis, and neural reactivity to stressful or negative emotionally-arousing tasks have found associations between blunted stress reactivity and current or lifetime substance use. Two studies examined adolescents' emotional and physiological reactivity to standardized social stressor tasks in the laboratory. These tasks (similar to the Trier Social Stress Task (TSST)) involved standardized social interactions with unfamiliar adults, which is in contrast to the studies reviewed above that examined personalized social interactions with parents. In these standardized social stress paradigms, adolescents perform a task that includes a social-evaluative threat (giving a speech and doing mental arithmetic in front of a video-camera and an audience of unfamiliar adult judge[s]) and emotional and/or physiological reactivity is measured. These tasks are similar to life stressors that youth encounter on a daily basis in school, such as having to give a presentation in school (Gordis et al., 2006).

In the first study, adolescents' lower cortisol reactivity to the standardized social stress task (public speech, harsh feedback, and mental arithmetic task in front of an experimenter) was associated with their life-time cannabis use (yes/no) and regular cannabis use (yes/no: > = 5 occasions in last year) among early to late adolescents (aged 11–17 years, 51% boys) from a community sample (van Leeuwen et al., 2011). In the second study, adolescents' lower heart rate and cortisol reactivity to a standardized social stress task (public speech, mental arithmetic task, and computer math task in front of an experimenter) was associated with regular tobacco use (yes/no: using tobacco every day) among early to late adolescents aged 13–20 years (47% boys) in a community sample (Evans et al., 2013). In addition to these two laboratory studies, one fMRI study found that 12–16 year old adolescents' (53% boys) lower neural reactivity to negative and positive emotional faces in the parahippocampal gyrus—a region involved in responding to and regulating stress—was associated with substance use risk (family history of AUD), however the study did not examine associations with adolescents' actual substance use behavior (Cservenka et al., 2014).

In addition to these three studies finding main effects of lower stress reactivity on substance use, one study examined interactions between

adolescents' lower HPA-axis stress reactivity and adolescents' emotion regulation abilities predicting lifetime substance use (Poon et al., 2016). This study found that lower cortisol reactivity to the parent-adolescent conflict task was associated with lifetime substance use (yes/no: any substance, including alcohol, tobacco, and marijuana), but only for adolescents with high emotion regulation difficulties in community early adolescents aged 12–14 years (55% boys) (Poon et al., 2016). It is possible that blunted stress reactivity is particularly related to increased substance use risk in the context of other vulnerabilities such as emotion regulation difficulties. Consistent with this, Yip and colleagues found that blunted neural reactivity to stressful stimuli was associated with adolescents' substance use behavior in adolescents aged 14–17 years, but only in the context of prenatal cocaine exposure (2016). They found that, among prenatally cocaine exposed (PCE) middle adolescents (59% boys), but not among non-exposed adolescents, lower neural responses in stress-related regions including the amygdala, hippocampus, and the prefrontal cortex to a script of a personal stressful life event was associated with illicit substance use (yes/no on current/recent illicit substance use; Yip et al., 2016). This finding suggests that blunted neural stress reactivity was associated with greater substance use particularly with youth in the high-risk context of prenatal exposure (and likely associated compromised post-natal environments). Taken together, there is empirical evidence for blunted emotional, peripheral physiological, and neural stress reactivity to be associated with adolescents' current/lifetime substance use, perhaps particularly for high-risk adolescents. However, these studies were all correlational and cross-sectional, so it is unclear whether blunted stress reactivity led to substance use, whether youths' past substance use affected the development of stress reactivity systems, or whether a third variable (such as genetics) caused both blunted reactivity and substance use. Also, associations between blunted stress reactivity and substance use were not examined by sex, so it is unclear if boys were more likely to take this pathway. Three studies had fairly equal numbers of boys and girls (Cservenka et al., 2014; Evans et al., 2013; van Leeuwen et al., 2011) and two had somewhat more boys than girls (Poon et al., 2016: 55% boys; Yip et al., 2016: 59% boys), however sex moderation of effects was not examined. Two studies examined sex differences in stress reactivity variables, with one finding that boys showed lower cortisol (but not heart rate) reactivity than girls (Evans et al., 2013), one finding no sex differences in stress reactivity (Chaplin et al., 2012). However even without sex differences in reactivity, there may still be sex moderation of stress-reactivity-substance use links, but this was not examined.

2.3. Differential stress reactivity pathways to substance use by sex: theory and empirical research

In understanding the role of stress reactivity in the development of SUDs in adolescence, sex differences are critical to consider. First, substance use is increasing among adolescent girls, with girls now showing equal or greater rates as boys of alcohol, nicotine, and illicit drug use in middle adolescence (Johnston et al., 2016). However, the causes and consequences of substance use may be different for girls versus boys (Kuhn, 2015). For example, girls who use substances are particularly susceptible to dating violence, sexual assault, and teen pregnancy (Kuhn, 2015; Nolen-Hoeksema, 2004). Females may also show greater negative physiological effects of substance use and a faster progression from initial substance use to addiction than males (Fox and Sinha, 2009; Stewart et al., 2009), and some work finds that SUD treatments are less effective for women than men (Stewart et al., 2009). Thus, understanding potentially different developmental pathways to substance use and SUD risk for girls versus boys is important.

Second, the literature on stress reactivity has shown sex differences, with females showing higher negative emotion experience and expression in response to stress in childhood, adolescence, and adulthood than males (particularly for sadness and fear/anxiety) (Chaplin and

Aldao, 2013; Fox and Sinha, 2009), and with adult women showing greater neural reactivity to negative emotional stimuli in emotion processing brain networks than men (Stevens and Hamann, 2012). Third, there are sex differences in childhood disorders that are related to the two stress reactivity pathways, with girls showing higher rates of depression than boys starting in adolescence, girls showing higher levels of anxiety symptoms than boys in childhood and boys showing higher levels of externalizing symptoms than girls in childhood (Hankin et al., 1998; Kimonis et al., 2014; Lewinsohn et al., 1998). Finally, some research has found that externalizing symptoms are more predictive of problem substance use (e.g., binge drinking) for boys than girls (Chassin et al., 2002), supporting sex differences in pathways to substance use. We propose that, due to a combination of biologically-based sex-differentiated reactivity patterns and environmental socialization into gender roles (which encourage high emotionality in girls and discourage it in boys), girls will be more likely to show high stress reactivity and take that pathway to substance use and that boys may be more likely to show low stress reactivity and take that pathway to substance use (see Fig. 1). Other scholars have suggested similar hypotheses of sex differences in stress-addiction associations (Fox and Sinha, 2009; Hammerslag and Gulley, 2016).

2.3.1. Empirical studies

While not all studies examined stress-reactivity to substance use associations by adolescent sex, a few studies of adolescent emotional, physiological, and neural stress reactivity have found evidence for sex-differentiated pathways. First, Chaplin et al. (2015) showed that higher sadness expressions (facial, vocal, and postural) in response to a standardized social stressor task (the TSST) among low-income prenatally cocaine exposed and non-exposed middle adolescents aged 14–16 years predicted longitudinal increases in substance use one year later for girls, but not for boys. These findings are consistent with our hypothesis that girls are more likely to follow a high stress reactivity pathway to substance use. Additional findings from Chaplin et al. (2015) showed that lower salivary Alpha Amylase (sAA) reactivity to the TSST predicted increased substance use one year later for boys, but not for girls. sAA levels are a marker of sympathetic nervous system reactivity, thus lower sAA responses to stress in boys is consistent with our conceptual model that boys would show an association between blunted physiological stress reactivity and substance use. Second, a study of sons of fathers with SUDs found that lower cortisol reactivity during anticipation of an event-related potential (ERP) in the boys at age 10 to 12 longitudinally predicted the boys' regular monthly cigarette and marijuana use (yes/no) 4 years later at age 14–16 (Moss et al., 1999). This finding with boys may support the hypothesis that boys take a blunted stress reactivity pathway to substance use, although the study did not include girls as a comparison. In addition, several studies with adults have found sex differences in emotional and physiological responses to stress in adults with SUDs. For example, women with cocaine dependence show higher reported stress and anxiety responses to stress (Back et al., 2005) and higher pre-stress heart rate and prolactin levels (Fox et al., 2006) than men with cocaine dependence, suggesting a stronger association between heightened stress reactivity and substance use for females than males (but some research finds higher HPA axis reactivity in men with SUDs than women with SUDs; Fox et al., 2006).

There is one fMRI study with adolescents supporting a differential stress reactivity-substance use association by sex. In that study, 12–14 year old community early adolescents' responses to negative emotion-eliciting images (negatively-valenced images from the IAPs database) found that heightened activation in regions involved in negative emotion and stress reactivity including left anterior insula and left anterior cingulate cortex (ACC) were associated with lifetime substance use (yes/no) for girls, but not for boys (Chaplin et al., 2017, 2018). This study also found, notably, that negative parenting experienced by the adolescents was associated with this heightened neural activation to negative emotional stimuli in right ACC for girls but blunted neural

activation to negative emotional stimuli in left ACC, and left and right anterior insula for boys. This supports our theory that girls take a heightened stress reactivity pathway to substance use and also gives some explanation for environmental triggers that may contribute to this stress reactivity pathway (i.e., negative parenting). In addition to the adolescent study, studies with adults have shown sex differences between neural stress reactivity and substance use. For example, Potenza and colleagues (2012) found that heightened cortico-limbic brain activation to stress was associated with cocaine dependence in women, but not men.

Much more research is needed examining sex differences in neural responses to stressful stimuli and the development of substance use. In general, there are a lack of studies of neural functional activation to stress and adolescent substance use behavior with only two studies to our knowledge examining this (Yip et al., 2016; Chaplin et al., 2018). There are a few studies of adolescent brain structure in stress and negative emotion processing regions and adolescent substance use behavior, with some suggesting differential brain structure pathways to substance use by sex. These structural studies have found that smaller volumes in stress processing brain regions are associated with adolescent SUDs. For example, adolescents aged 13–21 with AUDs (compared to youth without AUDs) had smaller hippocampus and anterior ventral PFC (prefrontal cortex) volumes (De Bellis et al., 2000; Medina et al., 2008). Additionally, sex may also impact these structural phenotypes associated with adolescent SUDs. For example, in one sample of 15–17 year-olds with and without an alcohol use disorder (AUD), there was a group by sex interaction such that, compared to controls, girls with AUD had smaller PFC volumes and boys with AUD had larger PFC volumes (Medina et al., 2008). Thus, girls with AUD showed the maladaptive brain structure profile (smaller PFC volume), whereas boys with AUD showed a different pathway characterized by larger PFC volume. Notably, these results could reflect that altered PFC and hippocampus structure predict adolescent alcohol use or it could reflect that heavy alcohol use in adolescence lead to alterations of brain structure and more longitudinal research is needed to examine these possibilities.

3. Summary, limits and future directions, and implications

3.1. Summary

In sum, a small but growing body of research on adolescents' negative emotional, sympathetic nervous system, HPA-axis, and neural reactivity to stressful stimuli suggests that, indeed, altered stress reactivity is an important factor in the development of adolescent substance use behavior and SUD risk. Several studies found associations between high levels of stress reactivity or blunted levels of stress reactivity and adolescents' current/lifetime substance use. Furthermore, a few studies found differential associations by risk-status, with higher-risk youth (due to prenatal cocaine exposure or emotion regulation difficulties) showing stronger associations between blunted stress reactivity and current substance use. And, finally, consistent with our theoretical model, a few studies found support for differential associations depending on adolescent sex. These showed heightened negative emotional and neural reactivity to stress associated with current (and, in one study, future) substance use for girls, blunted sympathetic nervous system reactivity predicting future substance use for boys, and blunted HPA axis reactivity predicting future substance use in a sample of high-risk boys. Adult studies also supported sex differences in stress reactivity-substance use associations (Fox and Sinha, 2009). This may suggest, as we theorized, that there may be two stress reactivity pathways to substance use, which may depend on child sex.

3.2. Limits and future directions

There are a few limits to the research reviewed. First, the empirical

findings above were found with correlational studies that were mostly cross-sectional. Thus, they cannot determine if stress reactivity patterns that develop in childhood cause youth to seek out substance use in adolescence, if early substance use in adolescence alters stress reactivity systems, or if a third variable, such as genetics, causes both altered stress reactivity and risk for substance use/SUDs. Animal work that has experimentally manipulated stress levels has found that high stress levels increase drug self-administration (Holly et al., 2012), with some work finding sex differences with stress increasing behavioral and neural sensitivity to substances for females more than males (Holly et al., 2012; Kawakami et al., 2007). Also, two of the human adolescent studies reviewed here found that, among youth with a family history of cocaine abuse or AUDs, altered stress reactivity in childhood and middle adolescence predicted *future* substance use behavior 1 and 4 years later (Chaplin et al., 2015; Moss et al., 1999). These findings suggest that patterns of stress reactivity are developed earlier on prior to substance use initiation. The temporal order found in these studies suggest that interventions can identify youth with altered stress reactivity in late childhood/early adolescence and provide them with stress regulation interventions in order to prevent or delay the onset of substance use. Further longitudinal studies are needed that start with youth in late childhood before onset of substance use to determine effects of neural stress reactivity systems on substance use and effects of substance use on the development of neural stress reactivity systems, such as the NIH-funded Adolescent Brain and Cognitive Development (ABCD) study (Volkow et al., 2018). In addition, experimental studies should be conducted *with humans* to examine if experimentally altering stress reactivity in childhood affects substance use in adolescence. For example, researchers could conduct a study randomly assigning children to either a behavioral intervention to decrease stress-reactivity or a control group. If the intervention normalizes stress reactivity and then subsequently prevents substance use, that would be evidence that stress reactivity *causes* substance use.

A second limit to the literature is that there are very few fMRI studies of adolescents' brain reactivity to stressful or negative emotional stimuli and substance use behavior. This is unusual given that there are a number of fMRI studies of substance use and adolescent neural reactivity to executive function/working memory tasks and to reward tasks. Stress reactivity systems are changing rapidly in adolescence, are vulnerable to environmental impact, and are found in the adult literature to be critically important for addiction processes (e.g., Sinha and Li, 2007), so it is important that future research examine adolescent neural stress reactivity and substance use. A third limit is that many of the studies reviewed above did not examine findings by adolescent sex. Given that there are known sex differences in the correlates and consequences of substance use and sex differences in efficacy of current treatments, it would be important for future studies to consider sex/gender as a key variable in analyses. In addition, studies did not typically consider effects of pubertal developmental level or gonadal hormone levels on sex differences in stress reactivity and substance use in adolescents, despite the known intersections between Hypothalamic Pituitary Gonadal (HPG) axis and HPA axis function (Fox and Sinha, 2009). It would be of interest to understand the role of sex hormones in the development of stress reactivity patterns and in susceptibility to substance use in adolescence to better target interventions.

3.3. Implications

If future longitudinal and experimental studies continue to find that stress reactivity is important in the development of substance use and SUDs in adolescence, there are several implications. The first implication is that it will then be important to understand how stress reactivity develops in childhood so that we can be able to target the genetic, epigenetic, and environmental factors that lead to altered/maladaptive stress reactivity and sensitive developmental periods. We propose that children develop patterns of responding to stress early in childhood,

based on genetics, prenatal factors, and post-natal environmental factors including caregiving and neighborhood environments. This could be tested with studies examining early developmental precursors of altered stress reactivity, by sex. Some developmental scientists have studied early caregiving and emotion socialization behaviors of caregivers that influence later emotion regulation capacities in children and these could be useful paradigms to help understand the development of stress reactivity (e.g., Calkins and Hill, 2007; Chaplin et al., 2005).

Second, if it is true that stress reactivity *leads to* the development of substance use and SUD risk in adolescence (perhaps differently by sex or by high-risk context), there are several implications for SUD prevention programs. First, these programs should have a strong focus on stress and stress reactivity. Perhaps it may be less critical to focus programs on skills such as problem-solving and more important to focus on bottom-up methods of regulating stress reactivity, such as relaxation or meditation. Second, stress reactivity-focused prevention programs should be gender-sensitive. Interventions may select girls with high reactivity and then may focus on reducing high stress reactivity and high negative emotion, such as through teaching meditation skills, through medications that affect high stress reactivity, and/or through cognitive restructuring approaches that encourage active coping with stress rather than passive rumination strategies that amplify negative emotional arousal. For boys, a different approach may be needed. Traditionally, many therapeutic approaches aim to reduce negative emotionality, however for boys (and possibly also for youth in high-risk contexts), it may be important to practice allowing the experience of anxiety or stress rather than dampening it. This may help normalize stress reactivity systems to adaptively mount a stress response when it is appropriate. In sum, work on stress reactivity and the development of substance use may help us to better understand and intervene on important risk factors to delay and prevent increases in substance use and substance use problems in youth.

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.yjnstr.2018.09.002>.

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