Sensitive periods of substance abuse: Early risk for the transition to dependence

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Abstract

Early adolescent substance use dramatically increases the risk of lifelong substance use disorder (SUD). An adolescent sensitive period evolved to allow the development of risk-taking traits that aid in survival; today these may manifest as a vulnerability to drugs of abuse. Early substance use interferes with ongoing neurodevelopment to induce neurobiological changes that further augment SUD risk. Although many individuals use drugs recreationally, only a small percentage transition to SUD. Current theories on the etiology of addiction can lend insights into the risk factors that increase vulnerability from early recreational use to addiction. Building on the work of others, we suggest individual risk for SUD emerges from an immature PFC combined with hyper-reactivity of reward salience, habit, and stress systems. Early identification of risk factors is critical to reducing the occurrence of SUD. We suggest preventative interventions for SUD that can be either tailored to individual risk profiles and/or implemented broadly, prior to the sensitive adolescent period, to maximize resilience to developing substance dependence. Recommendations for future research include a focus on the juvenile and adolescent periods as well as on sex differences to better understand early risk and identify the most efficacious preventions for SUD.

Keywords

Abuse; Adolescence; Addiction; Substance dependence; Sensitive periods; Vulnerability

1. Introduction

Adolescence is a developmental period that evolved to maximize survival and reproductive fitness. Adolescence is defined by the maturation of secondary sexual characteristics and the development of adult-like psychological and social behaviors (Bereczkei and Csanaky, 1996; Sisk et al., 2003; Surbey, 1998). Risk-taking and subsequent drug experimentation during this developmental period increases the likelihood of developing a lifelong addiction. The 2010–2011 National Survey on Substance Use and Health reports an estimated 16.6% of 25.1 million adolescents in the U.S. aged 12–17 drank alcohol or experimented with illicit

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drugs for the first time (SAMHSA, 2012). This statistic represents approximately 4 million teenagers who are at increased risk for developing substance dependence. However, the teens that initiate substance use before the age of 14 years are at greatest risk for substance dependence (Fig. 1) and have a 34% prevalence rate of lifetime substance use (Grant, 1998; SAMHSA, 2015a,b). As individuals continue to mature between 13 and 21 years, the likelihood of lifetime substance abuse and dependence drops 4–5% for each year that initiation of substance use is delayed (Grant, 1998; SAMHSA, 2015a,b), further suggesting early drug use conveys the greatest risk. While it is probable that individuals who initiate substance use early have an underlying predisposition to use (Robins, 1984), individual risk factors can interact with a specific maturational state of vulnerability, known as a sensitive period, to substantially increase the risk of addiction. Here, we integrate what is known about adolescent development with existing theories on the etiology of SUD to inform prevention efforts.

Substance use disorder is characterized by drug craving and loss of control over drug consumption, including inordinate amounts of time spent pursuing or using the drug and continued use despite negative consequences. Consequences of SUD involve a failure to fulfill work, school, and home obligations, and the development of social and interpersonal problems, physical or psychological harm, and tolerance and withdrawal symptoms (APA, 2013; NIDA, 2014). While many adolescents experiment with drugs, the transition to dependence is marked by compulsive and habitual substance use (Everitt et al., 2008; Volkow and Fowler, 2000). In the present review we use the term addiction or substance dependence in reference to more severe forms of SUD, which are characterized by chronic drug seeking and drug use (APA, 2013; NIDA, 2014).

2. An evolutionary understanding of adolescent risk behaviors

To understand how the developing brain can become vulnerable to drugs of abuse during adolescence, we first turn to evolution and the adaptive role of reward and risk-related behaviors. Our tenet is that the adaptive adolescent strategies, which evolved for survival, manifest today as risk behaviors that can be commuted to substance use disorder (SUD) in vulnerable individuals. Adolescence is maturational period unique to mammals, during which time puberty occurs before peripheral and neurological growth is complete (Bogin and Smith, 1996). Gonadal hormones released during puberty stimulate the development of adult social behaviors (Bogin and Smith, 1996). The adolescent stage allows individuals to practice more complex physical and social skills before adulthood is reached, to increase survival and reproductive fitness (Bogin and Smith, 1996; Darwin, 1871).

Behaviors that emerged during adolescence to promote survival and reproduction may no longer be adaptive, but instead can increase an individual's likelihood to experiment with, use, and become dependent on drugs (Bardo et al., 1996; de Wit, 2009; Hester and Garavan, 2004; Kreek et al., 2005; Naneix et al., 2012; Potvin et al., 2014; Vonmoos et al., 2013). For example, aggression and risk-taking in males can be a competitive strategy that increases reproductive fitness by increasing mating opportunities and genetic diversity (Gluckman and Hanson, 2006). Yet, data from the National Epidemiological Study of Alcohol and Related Conditions (a survey of n = 43,084 individuals 18 years and older) shows that violent

behavior increases risk of SUD 2.42-fold (Schwartz et al., 2015). Other traits, including hyperactivity, novelty seeking, and impulsivity were advantageous to early humans by promoting exploration of the environment and acquisition of resources (Bjorklund and Pellegrini, 2000), but are also associated with substance abuse (Belin et al., 2008; Gruber et al., 2014; Khurana et al., 2013; Mitchell et al., 2014; Sonntag et al., 2014; Volkow et al., 1999).

The early-onset of puberty may represent a unique risk factor for substance abuse due to early initiation of adolescent risk behaviors. As a risk factor early puberty is of particular concern for females, who on average mature up to two years earlier than males (Tanner, 1962). Early puberty onset is associated with earlier initiation and increased frequency of nicotine and alcohol use in adolescent males and females (Harrell et al., 1998; Patton et al., 2004; Wilson et al., 1994). Today puberty occurs at increasingly earlier ages, up to 3 years earlier than 100 years ago (Gluckman and Hanson, 2006). Earlier onset has been attributed to a number of factors, including improved nutrition, lower rates of disease in childhood, reduced early mortality, exposure to growth hormones through cow's milk, other endocrine-disrupting toxins (i.e., bisphenol A), genetic polymorphisms, and childhood obesity (Gluckman and Hanson, 2006; Parent et al., 2011; Surbey, 1998). Regardless of the cause, earlier-onset puberty has resulted in increasingly wider gaps between an individuals' cognitive and reproductive maturity (Hawley, 2011). In some cases, interventions aimed at limiting factors that accelerate puberty may therefore be protective against SUD risk (Houben et al., 2011).

3. Advantages and limitations of animal studies

Animal models, in particular rodents, represent an opportunity to investigate the contribution of behavioral and biological risk factors to substance dependence. Environment, genetics, and neurobiology can be manipulated in laboratory animals to determine mechanistic contributions to individual responses to drugs of abuse (Anker and Carroll, 2010; Brenhouse et al., 2008; Sonntag et al., 2014; Wong and Marinelli, 2016). More broadly, behaviors related to substance dependence can be studied systematically using place conditioning or self-administration paradigms.

Limitations to animal studies exist. The relatively brief adolescent period in rodents (Spear, 2000) enables rapid assessments (days/weeks in rodents vs. months/years in humans), but necessitates quick tests to study substance abuse. Place conditioning assays animals' preferences for a drug-associated environment over the course of 4–12 days (Brenhouse and Andersen, 2008; Crawford et al., 2011; Schramm-Sapyta et al., 2009; Zakharova et al., 2009b). However, in place conditioning drug delivery is non-contingent, i.e., drugs are administered by the experimenter. In contrast, self-administration paradigms allow rodents to respond voluntarily for drugs, allowing assessment of drug-seeking and drug-taking behaviors, but require weeks to months of training (Anker and Carroll, 2010; Doherty and Frantz, 2012; Levin et al., 2003, 2007; Perry et al., 2007; Wong et al., 2013; Wong and Marinelli, 2016). Drug studies in adolescent versus adult rats are reviewed further in Section 5.2.2. Another limitation to animal studies is that non-human primates, and particularly rodents, do not exhibit cortical gyriification as complex as humans (Ongur and Price, 2000).

However, working within the constraints of animal models, drug studies can be designed to study discrete stages of exposure to identify sensitive periods of risk for SUD.

4. Sensitive periods of substance abuse

Sensitive periods are stages when an individual is more responsive to particular environmental input or can more readily acquire a behavior relative to other developmental stages (Knudsen, 2004). As shown in Fig. 1, early substance use (before age 14) is associated with the highest risk of developing SUD (Grant, 1998; SAMHSA, suggesting the concept of sensitive periods applies to drug addiction (Andersen, 2003, 2005). Well-known examples of sensitive periods in development include second language acquisition and musical and athletic abilities. For example, children more readily achieve fluency in a second language and acquire musical and athletic skills than adults (Bailey and Penhune, 2012; Johnson and Newport, 1989; USAA, 2011). Early language and musical skill acquisition is associated with increased cortical grey matter density and white matter connectivity in the corpus callosum compared to later skill acquisition (Mechelli et al., 2004; Steele et al., 2013). These and other observations suggest that sensitive periods result from elevated plasticity in the brain (Knudsen, 2004). Repeated activation of a neural circuit during a sensitive period produces in long-lasting increases in the responsivity of those circuits to the stimulating environmental input (Knudsen, 2004). Drug use during a sensitive period can therefore have important long-term impact on neural development.

4.1. Evidence for sensitive periods of substance abuse in humans

Evidence indicates that drug exposure beginning in early adolescence can increase the risk of SUD long-term (Chambers et al., 2003; Grant, 1998). Predisposing risk factors, including impulsivity, exposure to early adversity, or other pre-existing conditions (such as attention deficit hyperactivity disorder [ADHD] and conduct disorder) may lead to early-onset drug use if not addressed (Enoch, 2011; Mannuzza et al., 2008; Verdejo-Garcia et al., 2008). However, individuals with ADHD who receive early treatment show the same age-related elevated rates of SUD as age-matched community controls (Mannuzza et al., 2008; Steinhausen and Bisgaard, 2014; Wilens et al., 2003). In other words, medication does not seem to increase risk of substance use when initiated early (Molina et al., 2013; Volkow and Swanson, 2008). While these former results have been shown in longitudinal studies, cross-sectional studies demonstrate a different relationship between impulsivity and marijuana use, such that early-onset use (<16 years of age) may be associated with elevated impulsivity (Gruber et al., 2014). Epidemiology studies further indicate that adolescent use of alcohol, marijuana, and cocaine adolescent increase the risk of substance dependence (Wagner and Anthony, 2002). Findings such as these raise more questions—does early drug use lead to impulsivity? Do different drugs have different long-term effects on the brain and subsequent SUD vulnerability? The prospective ABCD initiative of the NIH (abcdstudy.org) will help answer some of these issues surrounding early drug exposure.

Disentangling the cause-and-effect of SUD from individual risk factors is difficult due to shared neural substrates. Adolescent networks that underlie impulsivity risk factors are the same as those affected by illicit drugs (Nees et al., 2012; Schneider et al., 2012; Stanger et

al., 2013; Whelan et al., 2012). The prefrontal cortex (PFC) does not mature fully until late adolescence or early adulthood (Arain et al., 2013; Barnea-Goraly et al., 2005; Durston et al., 2001; Giedd et al., 1999; Sowell et al., 1999; see Section 5.1), and is pivotal for underlying SUD risk. Substance use during adolescence can induce changes in PFC activity and PFC projections to subcortical regions that persist in adulthood (Squeglia et al., 2009). Brain regions that are influenced by drug exposure depend on their state of maturation when drug exposure occurs (Andersen, 2005; Andersen and Navalta, 2011). For example, adolescent marijuana users show reduced cortical thickness in middle, superior frontal and insular cortices, but increased thickness in more posterior cortical regions such as the superior temporal and inferior parietal cortices, compared to non-users (Lopez-Larson et al., 2011). Moreover, early-onset marijuana use (<16 years) is associated with reduced white matter fiber tract integrity in the corpus callosum compared to later-onset marijuana use (>16 years; Gruber et al., 2014).

4.2. Evidence for sensitive periods of substance abuse in animals

Animal studies have demonstrated that timing of drug exposure matters. Periods of increased vulnerability to stimulant use are evident in rodent models as further evidence for a sensitive adolescent period to substance abuse (Adriani et al., 2004; Baskin et al., 2015; Brandon et al., 2001, 2003; Harvey et al., 2011; Jordan et al., 2014, 2016; Kuhn, 2015; Ruedi-Bettschen et al., 2006; Schramm-Sapyta et al., 2009; Smith, 2003; Wong et al., 2013). For example, in animal models of ADHD, which is often comorbid with SUD in humans (Mannuzza et al., 2008; Steinhausen and Bisgaard, 2014), treatment with stimulant drugs during adolescence (post-natal days [P] 28–55) enhanced the rate to acquire cocaine self-administration, and increases the efficacy and motivating influence of cocaine reinforcement (Baskin et al., 2015; Harvey et al., 2011; Jordan et al., 2014). Gulley and Juraska (2013) provide further review on the long-term effects of adolescent drug exposure.

One mechanism by which adolescent drug exposure may increase the risk of SUD is by altering the developmental trajectory of the PFC and its connections with subcortical regions. In rodents, cocaine exposure in adolescence, but not adulthood, produces a long-lasting attenuation of medial PFC (mPFC) GABAergic activity and parvalbumin cell expression that remains evident in adulthood (Cass et al., 2013). Moreover, binge-like alcohol exposure in adolescent rats reduces adult hippocampus, thalamus, dorsal striatum (STR), and cortex volumes compared to littermate controls (Gass et al., 2014; see Gulley and Juraska, 2013 for further review). Taken together, evidence from both humans and rodents indicates that substance use during the sensitive adolescent period can further exacerbate vulnerability to developing SUD, with long-term impact on cortical and subcortical development.

4.3. Prevention measures: promoting invulnerability to substance abuse

With respect to substance abuse and dependence, an individual may also experience periods of relative *invulnerability* to the long-term effects of drugs, such as during the juvenile or prepubertal periods (Andersen, 2003, 2005; Stanis and Andersen, 2014). Studies both in humans (Biederman et al., 1999; Mannuzza et al., 2008; Wilens et al., 2003) and in rodents (Adriani et al., 2006b; Andersen et al., 2002a; Bolanos et al., 2003; Carlezon et al., 2003;

Thanos et al., 2007) suggest that childhood or prepubertal exposure to stimulants reduces the rewarding properties of drugs of abuse and may protect against SUD later in life. In pre-pubertal children stimulants do not produce rewarding effects (Rapoport et al., 1978). Moreover, in pre-pubertal children exposure to methylphenidate produces an enduring increase in methylphenidate-stimulated blood flow in the STR and thalamus, with no significant change observed in adult-exposed subjects (Schrantee et al., 2016). Similar brain changes were evident in rodent males that were exposed pre-pubertally (P20-35) to methylphenidate (Andersen et al., 2008a). Under these drug exposure conditions, exposure to methylphenidate induced aversions to cocaine-associated environments in a place preference paradigm that is evident in adulthood (Andersen et al., 2002a; Carlezon et al., 2003, but see Crawford et al., 2011). In animals, pre-pubertally established 'aversions' to cocaine manifest as a deactivation of the amygdala in response to cocaine-conditioned odors (Lowen et al., 2015; discussed further in Section 5.2). Exposure to psychostimulants may also affect brain morphometry in regions relevant for SUD. In a longitudinal study of cerebral cortex thickness, psychostimulant treatment normalized the ADHD-associated excess cortical thinning during adolescence (Shaw et al., 2007, 2009; van der Marel et al., 2014). Age-dependent effects of methylphenidate treatment on brain morphometry in animals depend on the age of exposure, with a greater impact on corpus callosum white matter and striatal volume following adolescent exposure compared to adults (van der Marel et al., 2014). Together, these data suggest that there is a pre-pubertal window of *in*vulnerability to stimulants, and exposure to stimulants during this window may be protective against the rewarding effects of drugs later in life.

The juvenile period may represent an opportunity to institute preventative interventions for SUD. Pharmacotherapeutic interventions, such as pre-pubertal methylphenidate exposure, can reduce the rewarding properties of drugs later in life (Adriani et al., 2006a; Andersen et al., 2002a; Brenhouse et al., 2009; Carlezon et al., 2003; Thanos et al., 2007). However, caution must be exercised as pharmacotherapies are not without side effects, and variables such as age, sex and duration of treatment can negatively impact SUD vulnerability (Baskin et al., 2015; Brandon et al., 2001, 2003; Brenhouse et al., 2009; Harvey et al., 2011; Jordan et al., 2014; Lambert and Hartsough, 1998; Steinhausen and Bisgaard, 2014). In particular, there is a greater need for research in females. Preclinical research suggests that females experience different long-term effects following pre-pubertal (Brenhouse et al., 2009), pubertal, or even adult exposure to drugs (Dow-Edwards, 2010).

In contrast to pharmacotherapies, behavioral interventions can be broadly applied to young populations with little concern for side effects, and can also be combined with medication to further increase efficacy. We propose that the prevailing theories of the etiology of SUD can inform effective interventions for at-risk individuals. Below we review four SUD theories and suggest behavioral interventions (Table 1) that can be implemented alone or in combination to address specific risk factors for the transition to substance dependence.

5. Etiology of substance abuse and relevance to adolescence

Nearly 8000 teenagers initiate substance use each day (SAMHSA, 2015a), but only 5–14% of those who try drugs develop SUD (Fig. 1; SAMHSA, 2008), suggesting early risk factors

interact with the sensitive adolescent period to mediate the transition from substance use to dependence. Currently prevailing theories on the etiology of SUD conceptualize addiction as 1) an executive function/inhibitory control deficit (e.g., Goldstein and Volkow, 2011; Hester et al., 2010), 2) increased incentive salience attributed to drug-related stimuli (Robinson and Berridge, 1993a), 3) a compulsive habit (Everitt et al., 2008), and 4) a hyperactive stress system and removal of negative reinforcement (Koob and Le Moal, 2001). Building on the work of others, we suggest that early risk for SUD emerges from an immature prefrontal control system (Casey et al., 2008; Galvan et al., 2006), combined with hyper-reactivity of reward salience (Brenhouse et al., 2008; Casey and Jones, 2010; Ernst et al., 2005; Galvan, 2010; Somerville et al., 2011), habit, and stress systems (Andersen and Teicher, 2008; Newcomb and Harlow, 1986; Sinha, 2008; Wills, 1986).

5.1. Executive immaturity in adolescence

Substance use disorder is thought to arise in part from a reduced ability to inhibit or control the desire to pursue the rewarding effects of drugs, known as an executive function deficit (Hester et al., 2010). Brain regions associated with executive function include the dorsolateral PFC, the dorsomedial PFC (Curtis and D'Esposito, 2003), the pre-supplementary motor area (Lau et al., 2006) and the ventrolateral PFC (Ridderinkhof et al., 2004; Fig. 2). In the adult brain, the PFC plays an important inhibitory role on subcortical reward and motivational systems (Arnsten and Rubia, 2012; Tekin and Cummings, 2002), including interactions with the striatum (STR) and subthalamic nucleus (STN; Diamond, 2013; Fig. 2).

5.1.1. Evidence from humans—In drug-abusing and addicted adults, subregions of the PFC are *hyper*-reactive to environmental cues associated with substance use, but *hypo*-reactive during inhibitory control tasks (Goldstein and Volkow, 2011). With executive dysfunction as a framework for SUD, adolescence represents a developmentally sensitive period of heightened reactivity to drugs of abuse and the transition to addiction (Peeters et al., 2015). The frontal cortex does not complete development until the end of adolescence or as late as the mid-twenties (Barnea-Goraly et al., 2005; Durston et al., 2001; Giedd et al., 1999; Sowell et al., 1999). Cognitive maturation results in improved integration between inhibitory networks and salience networks (Section 5.2; Marek et al., 2015) due, in large part, to increased myelination and connectivity between regions. For example, imaging studies show that white matter increases more or less linearly from childhood through early adulthood (Barnea-Goraly et al., 2005; Durston et al., 2001), whereas grey matter volume in the frontal lobe peaks in late childhood or early adolescence, and declines post-adolescence (Giedd et al., 1999; Sowell et al., 1999).

Functional MRI (fMRI) studies show that adolescents overall exhibit hypoactivity in the ventrolateral PFC, orbitofrontal cortex (OFC), and dorsal anterior cingulate cortex (ACC) compared to adults during decision-making tasks (Eshel et al., 2007; Galvan et al., 2006). These cortical regions provide top-down inhibitory control of subcortical regions, including the amygdala, NAc, and dorsal STR (Munakata et al., 2011). As a result of an immature PFC, adolescents exhibit reduced cortical inhibition and are more subject to subcortically driven, reward-based decision-making (Casey and Jones, 2010; Casey et al., 2011; Ernst et

al., 2006; Sturman and Moghaddam, 2011). The imbalance of adolescent cortical and subcortical systems, with predominance of mature subcortical reward-processing circuitry, has been conceptualized as the triadic model of motivated behavior (Ernst et al., 2006; Ernst, 2014) and is hypothesized to play a role in adolescent risk for SUD.

5.1.2. Evidence from animals—The classic study of Goldman and Alexander was among the first to show that PFC development is delayed. Specifically, early cryogenic studies in adolescent, non-human primates show that the PFC becomes functional with sexual maturity (Goldman and Alexander, 1977). The development of executive function in animals is limited due to the complexity of behavioral tasks, which often require more training time than the brief adolescent period allows (Section 3). In rodents, Newman and McGaughy (2011) found that adolescents behave less flexibly in a attentional set-shifting task than adults, but were not different in the ability to learn the initial attentional set. Structurally, the rodent brain exhibits adolescent changes mirroring observations in humans. Increases in dendritic spine density in the PFC are evident through the juvenile through early adolescent periods, and thereafter decline (prune) from mid-adolescence to adulthood (Koss et al., 2014). Conversely, in subcortical structures such as the amygdala, dendritic spine density matures before adolescence and remains relatively stable from puberty through adulthood (Koss et al., 2014). Amygdalar dendritic spines, however, are sensitive to pubertal increases in gonadal hormones (Zehr et al., 2006). Developmental sex differences are described in more detail by Brenhouse and Andersen (2011). Maturational trajectories of other subcortical structures, such as the STR, are reviewed in subsequent sections.

5.1.3. Prevention measures: promoting executive maturity in adolescence—
Promotion of executive maturity may be an effective intervention for adolescents at risk for SUD (Stanger et al., 2013). A number of PFC-mediated risk behaviors are measurable in both human and animal models, such as in stop-signal and go/no go paradigms (Congdon et al., 2012; Eagle and Baunez, 2010; Smith et al., 2014), although in rodents these paradigms require training that extends beyond adolescence. Mindfulness-based activities like meditation, yoga, or practicing martial arts improve inhibitory control, sustained attention, and emotional regulation (Diamond and Lee, 2011; Holzel et al., 2011; Lakes and Hoyt, 2004; Manjunath and Telles, 2001; Tang et al., 2012). These activities also increase activity, grey matter density, and cortical thickness in mPFC, ACC and insular cortex (Holzel et al., 2008, 2011; Lazar et al., 2005; Tang et al., 2009, 2012). Mindfulness-based interventions have some success in treating SUD (Bowen et al., 2009; Witkiewitz et al., 2005; Zgierska et al., 2009), but there is a need for research on mindfulness as a preventative intervention in at-risk youth.

5.2. Incentive salience and sensitization

A second theory on the etiology of substance dependence describes a key process in addiction: incentive salience, or the "wanting" or motivated desire attributed by the brain to a rewarding stimulus in the environment (Berridge and Arnsten, 2013; Berridge, 2007, 2009a). During the transition from substance use to dependence, greater incentive salience is attributed to drug-related cues than to other reinforcing environmental cues or conditions (e.g., food, social cues, etc). Thus, over time, motivation to pursue the drug eclipses other

needs and drug cues increasingly drive behavior. The salience network has been identified by resting state connectivity fMRI studies, and includes dorsal ACC, OFC, and insular cortex with their strong connectivity to subcortical and limbic structures (Seeley et al., 2007). Other important nodes within the salience network include subcortical sites for emotion, home-ostatic regulation, and reward (see Fig. 2; Ongur and Price, 2000; Seeley et al., 2007). The amygdala in particular plays an integral role in encoding salience, and also maintains conditioned effects after repeated pairing of internal drug sensations with external environmental stimuli (Chang et al., 2012; Meil and See, 1997; Szalay et al., 2013). Over time, conditioned drug cues gain further salience by activating cortical sites. In turn, cortical sites impinge upon reward-associated regions of the NAc, which is associated with wanting of the drug, and the STR, which is associated with habitual drug-seeking/taking behavior.

5.2.1. Evidence from humans—Adolescence is characterized by unique patterns of neural activity and changes in innervation and myelination within brain regions that contribute to heightened incentive salience at this developmental stage (Ernst et al., 2005, 2006; Somerville et al., 2010). In fMRI studies, OFC activation patterns in adolescents (aged 13–17 years) more closely resemble those of children (aged 7–11 years) than adults (aged 23–29 years; Galvan et al., 2006). In contrast, adolescent NAc responses to anticipated reward more closely resemble those of adults than children, although the adolescent NAc may be more reactive overall compared to both other age groups (Galvan et al., 2006). Adolescents also exhibit greater amydalar activation to fearful faces (Guyer et al., 2008; Yurgelun-Todd and Killgore, 2006), a region that encodes the magnitude of cue salience (Guyer et al., 2006).

Functional connections between amygdala and mPFC do not emerge until age 10 years, and continue to mature through at least through 23 years of age (Gabard-Durnam et al., 2014). Accordingly, adolescent males and females (ages 10–16) show reduced resting state connectivity in amygdala-PFC networks, and almost no coupling between the basolateral amygdala (BLA) and PFC compared to adults, further suggesting that cortico-amygdalar pathways are not yet fully developed (Alarcon et al., 2015). Adolescents may therefore be less able to functionally recruit regions like the NAc and amygdala during reward-based tasks compared to adults (Bjork et al., 2004; Ernst et al., 2005). In contrast to the development of cortical/subcortical connectivity, positive functional connectivity between the amygdala and other subcortical regions, including the NAc and dorsal STR (caudate/putamen), is observed in childhood and remains largely stable through adulthood (Gabard-Durnam et al., 2014). Altogether, these data further indicate that subcortical systems are mature or even hyper-reactive to reward salience during adolescence, while cortical systems require more time to develop adult patterns of activity.

5.2.2. Evidence from animals—In contrast to executive function, incentive salience can be readily assessed during the brief adolescent period. Adolescents attribute greater incentive salience to rewarding stimuli, including drug-related cues, compared to juveniles or adults. Adolescent rodents form preferences for environments associated with lower doses of cocaine than juveniles or adults (Badanich et al., 2006; Brenhouse et al., 2008; Zakharova et al., 2009b) are more resistant to extinction of cocaine-associated cues, and reinstate

cocaine place preferences to a greater degree than adults (Brenhouse et al., 2010; Brenhouse and Andersen, 2011). Young adolescent rodents also form place preferences for nicotine-associated environments after a single drug-environment pairing, whereas late adolescent and adult rats may not form preferences even after repeated pairings (Adriani et al., 2002; Belluzzi et al., 2004; Vastola et al., 2002). Similarly, self-administration paradigms show that, compared to adults, adolescent rats acquire cocaine self-administration faster (Perry et al., 2007), earn more cocaine infusions, are more resistant to extinction and more readily reinstate cocaine seeking (Anker and Carroll, 2010; Wong et al., 2013; Wong and Marinelli, 2016). Furthermore, adolescent male and female rats self-administer more nicotine than adults (Levin et al., 2003, 2007), and adolescent male rats self-administer greater amounts of heroin than adults (Doherty and Frantz, 2012). Together, these findings suggest that heightened incentive or motivational salience during adolescence contributes to important characteristics of substance dependence, including augmented drug seeking, extinction resistance, and relapse behaviors.

Developing circuitry and dopaminergic markers may help to explain heightened incentive salience during adolescence (Brenhouse et al., 2008; Sonntag et al., 2014). Lesion and inactivation studies demonstrate the importance of the NAc in encoding the initial salience of the primary reward-related cue, while the BLA appears necessary for maintaining salience encoding over time (Chang et al., 2012; Szalay et al., 2013). The attribution of motivational salience to drug-related cues is mediated by elevated D1 receptor expression on excitatory input from the PFC to the NAc (Kalivas et al., 2005; Robinson and Berridge, 1993b; Sonntag et al., 2014). Over time, salient drug-related cues release dopamine in the NAc even in the absence of drug taking (Ito et al., 2002; Willuhn et al., 2010).

Altered PFC ←–→ BLA and PFC → NAc connectivity in adolescence provide additional mechanisms by which reward-related cues acquire heightened incentive salience, relative to the juvenile or adult periods. The density of axonal projections increases with age in BLA → PFC (Cunningham et al., 2002, 2008) and PFC → NAc (Brenhouse et al., 2008) pathways until late adolescence/young adulthood. Within the BLA itself, dendritic spine density, length, and complexity increase locally from the juvenile period through late adolescence, and stabilize in adulthood (Koss et al., 2014). Dendritic density also increases on long-range projections from the BLA → mPFC from the juvenile period through adulthood (Johnson et al., 2016). Inhibitory GABAergic interneurons in the mPFC are a primary target of BLA projections (Cunningham et al., 2008), suggesting growing BLA → mPFC projections closes a sensitive period of development for the PFC. Excitatory BLA projections increase cortical interneuron excitation and ultimately augment PFC inhibitory tone, which may have downstream effects on driving NAc and other subcortical activity. Axonal projections from the PFC → BLA prune after adolescence (Cressman et al., 2010), suggesting further fine-tuning of activity.

Pharmacological changes also occur during adolescence that help to explain age differences in salience attribution (Brenhouse and Andersen, 2011). For example, our work (Andersen and Teicher, 2000; Teicher et al., 1995), and others (Tarazi et al., 1998) shows that dopamine receptors are transiently overproduced and pruned over the course of adolescence in a regional- and sex-dependent manner that seems to be independent of pubertal hormone

increases (Andersen et al., 1997a,b, 2002b). More specifically, dopamine D1 and D2 receptors in the STR rise to higher levels in males than females during adolescence, and D1 remains higher in males during adulthood despite some pruning (Andersen et al., 1997b). In contrast, dopamine D1 and D2 receptors in the NAc do not show this same pattern, suggesting NAc plasticity may be more adaptive to changing needs of the reward system (Teicher et al., 1995).

Dopamine receptors in the mPFC are also differentially expressed across transitions between childhood, adolescence, and adulthood (Andersen et al., 1997a,b; Lyss et al., 1999; Teicher et al., 1998). For example, D2 receptors switch from inhibitory to excitatory on parvalbumin interneurons in the mPFC during adolescence (Tseng and O'Donnell, 2007). Notably, developing signaling mechanisms are not uniform across brain regions, as initially reported in non-human primates (Lidow et al., 1991). Rather, signaling mechanisms within individual circuit develop independently. For example, we find that D1 receptors are overproduced on glutamatergic, but not GABAergic, neurons in the mPFC → NAc projections (Brenhouse et al., 2008). Elevated D1 on excitatory mPFC projection neurons is associated with increased drug seeking, taking, and drug-cue salience, as well as addiction-related behaviors such as novelty seeking, sexual activity, preferences for sweet taste, and impulsivity (Freund et al., 2016; Nair et al., 2011; Sanchez et al., 2003; Sonntag et al., 2014). As suggested by Fig. 3, we predict that subjects with elevated motivational salience at an early age may be most vulnerable to developing SUD.

Taken together, these findings suggest that increases in PFC ←–→ BLA and PFC → NAc signaling and connectivity during adolescence may underlie elevated incentive salience of drug-related cues. We propose that theory of incentive salience helps capture the early phases of adolescent drug experimentation, while vulnerability to habit development (Section 5.3) reflects underlying risk to the transition to addiction.

5.2.3. Prevention measures: promoting 'Selective' salience in adolescence—

Incentive salience can be assessed on an individual basis by quantifying hedonic pleasure, craving and preferences for rewards and associated cues (Berridge, 2009b; Pool et al., 2016). Interventions recently studied in adolescents involve text messaging during periods of high craving to reduce nicotine consumption (Mason et al., 2015), in part by re-directing behavior to other salient cues. Somewhat counter-intuitively, exposure to novel experiences and stimuli reduces reward sensitivity and the incentive salience of reward or drug-related cues, and, we propose, may represent opportunities for prevention of SUD. Novelty exposure as a SUD prevention has not been well investigated in humans. However, exposure to enriched and novel environments during the juvenile and adolescent periods in animals reduces the rewarding effects of drugs of abuse (El Rawas et al., 2009; Solinas et al., 2009; Zakharova et al., 2009a), in part by reducing incentive salience of reward-related cues (Beckmann and Bardo, 2012) and reactivity to novelty (Cain et al., 2006). From a signal-to-noise perspective, experience of novel environments and stimuli may raise the threshold of salience attribution, thereby reducing sensitivity to drug reward and the potential impact of drug-related cues in motivating behavior.

5.3. Habit formation

An alternative theory proposes that addiction reflects a shift in the neural control of behavior from a goal-directed learning mechanism to a habit-based mechanism (Everitt et al., 2008). Goal-directed learning and decision making describes choices made based upon environmental input and the affective value of the expected outcome (Hogarth and Chase, 2011; Voon et al., 2015). In contrast, habit formation maintains behaviors regardless of motivation or goals (Judah et al., 2013; Rothman et al., 2009), such that behaviors are initiated more or less "automatically" (Gardner et al., 2012). In substance users, drug seeking is driven initially by desire for the rewarding effects of the drug, a goal-directed behavior. After repeated drug pairings with the environment, drug-associated cues become behavioral triggers that ultimately lead to compulsive and habitual abuse. As use transitions to abuse, projections from limbic to associative to sensorimotor cortex gradually recruit involvement from the ventromedial striatum to progressively greater involvement of the dorsomedial to the dorsolateral striatal regions (Fig. 2; Belin and Everitt, 2008; Burton et al., 2015; Everitt and Robbins, 2013; Gremel and Cunningham, 2008; Haber et al., 2006).

5.3.1. Evidence from humans—The habit model provides a valuable framework for predicting early vulnerability to the transition from substance use to dependence. Habits such as playing music and sports are easily formed before adolescence, when the brain regions underlying these skills are still maturing. However, the same concept may also apply to drug addiction. Habits that are physically harmful, such as excessive television viewing and sugar consumption, are more persistent when established at a young age (de Bruijn and van den Putte, 2009; Kremers et al., 2007). Although substance dependence often develops after age 18, as we show in Fig. 1, early substance use (<14 years; Grant and Dawson, 1998; SAMHSA, 2014, 2015a,b; Wagner and Anthony, 2002) is associated with the highest risk of developing SUD.

Early substance use may facilitate the transition to SUD due to early activation of habit-related circuitry in the brain. The transition to SUD is mediated by a shift in neural control of behavior from the ventral STR (NAc) to the dorsal STR, considered the "habit region" of the brain (Everitt et al., 2008). In drug-dependent humans, drug cues consistently increase BOLD responses in the STR, BLA, VTA, PFC, hippocampus, and NAc (Grusser et al., 2004; Jasinska et al., 2014; Lukas et al., 2013; Maas et al., 1998). In chronic substance abusers, drug-related cues activate and increase dopamine release in the dorsal STR (Garavan et al., 2000; Volkow et al., 2006), a finding associated with greater addiction severity (Volkow et al., 2006).

5.3.2. Evidence from animals—Animal models provide evidence of a propensity to habit formation and STR reactivity during adolescence. One approach to studying habit in animals is to examine punished responding, which models the cost of addiction by training rats to take drug in the presence of a small electric shock (Jonkman et al., 2012). Only ~20% of the rats continue to respond for drug when delivery is paired with shock, which is consistent with the overall percentage of individuals who are likely to develop an addiction (Everitt and Robbins, 2016). However, this paradigm can be difficult to implement in developing rodents. Other animal studies of habit formation involve over-training to respond

for reinforcement, which is then devalued prior to a test session (Dickinson, 1985). The term "devalued" refers to the removal of motivation to pursue the reinforcer; for example, if the subject is satiated or nauseous, it will no longer be motivated to work for food. Continued responding in the absence of motivation is considered outcome insensitive, or habitual. Adolescents are less sensitive to reward devaluation than adults (Hammerslag and Gulley, 2014; Kendig et al., 2013; Naneix et al., 2012). Insensitivity to reward devaluation, in conjunction with resistance to extinction (Andrzejewski et al., 2011; Brenhouse and Andersen, 2008; Sturman et al., 2010), suggest an enhanced propensity to habit formation in adolescence. Once a habit is established, environmental cues associated with the behavior serve as triggers for the behavior. Augmented salience of environmental cues during adolescence interact with a propensity to habit formation, rendering young subjects increasingly vulnerable to SUD when substance use is initiated early.

Animal studies, like human studies, show an increasing role of the dorsal STR as habitual, compulsive substance use emerges. Tract-tracing studies reveal ascending spiral-like connections linking the ventromedial NAc shell and core to more dorsolateral STR (Averbeck et al., 2014; Burton et al., 2015; Haber et al., 2000). In the primate brain, anterior portions of the dorsal STR receive projections from multiple regions of the PFC, including the mPFC, OFC, and ACC, suggesting the dorsal STR may be a critical node for integrating cortical and subcortical processing (Averbeck et al., 2014). While acquisition of cocaine taking is associated with metabolic changes in the ventral STR, chronic, more habitual cocaine self-administration is associated with increasingly greater activity and dopamine transporter (DAT) density in the dorsal STR in adult primates (Letchworth et al., 2001; Porrino et al., 2004).

Functional MRI responses to drug-associated cues in adult rodents after chronic cocaine exposure show remarkable faithfulness to human and other primate fMRI changes, including elevated responses in the dorsal STR, NAc, mPFC, and insular cortex (Johnson et al., 2013; Liu et al., 2013). Similar changes in blood flow in response to cocaine-associated cues are found when a mechanism underlying salience (PFC D1 receptors; Sonntag et al., 2014) is increased in the PFC in young rats (Lowen et al., 2015). Like primates, repeated drug taking in rodents increases dopamine release in the dorsal STR in response to drug-related cues (Ito et al., 2002). Inhibition of the dorsolateral STR, but not the NAc, impairs cue-induced cocaine seeking and prevents the reinstatement of seeking after prolonged abstinence (Fuchs et al., 2006; See et al., 2007; Vanderschuren et al., 2005). Similarly, disrupting functional connectivity between the NAc and dorsolateral STR decreases cocaine-seeking maintained by a second-order schedule, but does not affect acquisition of self-administration (Belin and Everitt, 2008). Taken together, converging evidence across species implicates the dorsal STR as critical for the transition to habitual, compulsive substance abuse.

More studies are needed to determine the role of the dorsal STR in adolescent drug seeking. However, as with the other brain regions, the dorsal STR undergoes unique developmental changes during adolescence. Male rats exhibit a more prominent rise and decline in striatal dopamine D1 and D2 receptors from adolescence to adulthood than female rats, although adult levels of each receptor subtype are comparable in both sexes (Andersen et al., 1997b; Naneix et al., 2012; Teicher et al., 1995). Functional reactivity to stimulation of dopamine

receptors, at the cyclic AMP level, is also elevated during adolescence compared to adulthood (Andersen, 2002). DAT density increases in the STR from early adolescence until peaking in late adolescence (Moll et al., 2000), and thereafter declines through adulthood (Moll et al., 2000; but see Matthews et al., 2013). In parallel with DAT, dopamine concentrations in the dorsal STR increase through late adolescence, although they transiently dip at P35 in rats (Andersen and Gazzara, 1993), and then rise into adulthood (Naneix et al., 2012). The dorsal STR also shows increased firing during reward anticipation in adolescents, an effect not observed in adults (Sturman and Moghaddam, 2012). Together, these data suggest that ongoing development in the dorsal STR may underlie an vulnerability to habit formation in adolescence and the development of addiction in adulthood, if drugs are sampled early.

5.3.3. Prevention measures: promoting healthy habits in adolescence—An individual propensity to form automatic habit-guided behaviors may represent an additional risk factor of SUD, and can be assessed in both humans and animal models using paradigms such as reward devaluation, as described earlier (Dickinson, 1985; Schwabe and Wolf, 2009; Seger and Spiering, 2011). The risk of drug-related habits can be combated by the earlier formation of physically beneficial habits, particularly exercise. In individuals with SUD, exercise is effective in promoting abstinence and reducing relapse (Bardo and Compton, 2015; Weinstock et al., 2008). High-school aged male and female athletes are less likely to use illicit drugs such as marijuana and cocaine (Ferron et al., 1999; Taliaferro et al., 2010). Moreover, eighth grade to high school-aged students participating in fitness consultations are less likely to abuse alcohol or cigarettes, even at 12-month follow-up (Werch et al., 2003, 2005). Aerobically fit children have enhanced cognitive control and greater dorsal STR volumes (Chaddock et al., 2010), suggesting physical exercise has important effects on the "habit" region of the brain.

Similar to humans, in male and female rodents access to running wheels reduces cocaine and heroin seeking (Lacy et al., 2014; Ogbonmwan et al., 2015; Peterson et al., 2014; Zlebnik et al., 2014; Zlebnik and Carroll, 2015). Wheel running during adolescence also reduces concurrent nicotine consumption in male rats (females were not examined; Sanchez et al., 2015), and concurrent cocaine consumption in female rats (males were not examined; Zlebnik et al., 2012). In adult rodents, aerobic exercise increases brain-derived neurotrophic factor (BDNF) levels in the STR (Aguiar et al., 2008; Marais et al., 2009), as well as phosphorylated TrkB (the BDNF receptor) and D2 receptor mRNA (Thompson et al., 2015). However, the protective effects of pre-pubertal exercise (prior to the sensitive adolescent window) in the brain require further study.

5.4. Stress reactivity and negative reinforcement

Recent evidence suggests that stress facilitates the attribution of incentive salience and the recruitment of habit-related circuitry during learning, which further augment vulnerability to addiction (Dias-Ferreira et al., 2009; Sadowski et al., 2009; Schwabe et al., 2008, 2011; Taylor et al., 2014). A fourth theory on the etiology SUD proposes that compulsive substance use critically involves negative reinforcement, or the removal of an aversive (physically or psychologically uncomfortable) affective state, such as stress. Over time, the

hedonic effects caused by drug activation of the brain's reward system are increasingly countered by an up-regulation of an anti-reward system (opponent-process counter-adaptation; Koob and Le Moal, 2001). The process drives formation of a new allo-static state in the reward set point (i.e., an increase in what is perceived as rewarding) such that increasingly greater amounts of reinforcement are needed to maintain functioning, leading to further substance abuse and the development of SUD. Higher allo-static reward set points can additionally be driven by prenatal or early life stress (Hanson et al., 2016). Exposure to stressors may therefore represent important risk factors for the transition from early substance use to dependence in young individuals.

5.4.1. Evidence from humans—Stress is one of the most commonly recognized triggers for early substance use and dependence (Sinha, 2008; Wills, 1986; Wills et al., 1992, 2001). Poverty, low socioeconomic status (SES), and a family history of SUD and other psychiatric disorders are associated with addiction (Hawkins et al., 1992; Patrick et al., 2012; Uhl, 2004). While the stress associated with a low SES household predicts neuropathology in adolescence and adulthood (McEwen and Gianaros, 2010), high SES is also linked to SUD. For example, low childhood SES is associated with smoking in late adolescence and young adulthood, but high childhood SES is associated with alcohol use, binge drinking, and marijuana use (Patrick et al., 2012). Adolescents and young adults from high SES may even be more likely to binge drink and to use marijuana or cocaine (Humensky, 2010), due in part to more expendable income (spending money; Bellis et al., 2007).

One contributing factor to SUD that is independent of SES is early life stress, often in the form of abuse, loss of a caregiver, or exposure to a natural disaster. Early life stress is associated with early onset substance use as well as SUD in young adulthood (Enoch, 2011). Adolescents with alcohol abuse or dependence are up to 21 times more likely to have a history of physical or sexual abuse (Clark et al., 1997; Kilpatrick et al., 2000), and drug-dependent adolescents report significantly higher life stress than non-dependent teens (Duncan, 1977). Exposure to early life stress also accelerates the onset of puberty (Mendle et al., 2011), which may in itself be a risk factor for the transition to substance dependence (see Section 2).

Functional MRI studies in human adolescents show that early life stress alters activity in the PFC and STR, resulting in impaired cognitive control (Mueller et al., 2010). Correspondingly, individuals experiencing severe early deprivation show blunted ventral STR (NAc) activity during a reward anticipation task (Mehta et al., 2010). In addition to PFC → STR changes, the amygdala shows increased activity in human fMRI studies and in animals exposed to early life stress (recently reviewed by Callaghan et al., 2014). Pharmacologically, positron emission tomography (PET) studies suggest acute stress induces dopamine release in the ventral STR, particularly in individuals reporting low parental care (Pruessner et al., 2004). Early life stress thus impacts cognitive and reward-processing circuitry, and by extension may alter an individual's response to drugs of abuse and risk for addiction.

5.4.2. Evidence from animals—Consistent with the allostasis model, early life stress increases feelings of dysphoria, anhedonia, and anxiety by dampening the reward system

(Matthews et al., 1999; Ruedi-Bettschen et al., 2006), suggesting an increase in the reward set point. In rodent models, stress in the form of maternal separation reduces responding for reward in an intracranial self-stimulation (ICSS) procedure (Michaels et al., 2007), and decreases sensitivity to the reinforcing value of cocaine (Matthews et al., 1999; Moffett et al., 2007; Phillips et al., 1994). As a consequence, maternally separated or neonatally isolated rats show enhanced cocaine and ethanol intake in adulthood (Cruz et al., 2008; Huot et al., 2001; Kosten et al., 2000, 2004, 2006; Moffett et al., 2006, 2007; Ploj et al., 2003), although these effects of separation are dependent upon the duration and precise ages at which pups are separated, as well as sex. For example, females show greater enhancement of cocaine self-administration, but no change in ethanol consumption, than males following early separation (Gustafsson et al., 2005; Kosten et al., 2004, 2006; Matthews et al., 1999; Roman et al., 2004).

In addition to increasing reward set point, early life stress may facilitate the transition from experimental substance use to SUD by increasing the salience of reward-related stimuli. Early life stress (deprivation of maternal care) enhances the salience of a rewarding food cues in adulthood (Lomanowska et al., 2011), which may be mediated by increased PFC D1 receptors on projections to the NAc (Brenhouse et al., 2013). Early life stress may also induce a propensity towards habit formation (Schwabe and Wolf, 2011; Sinha, 2008). Both humans and rodents exposed to chronic stress have increased habit-guided, stimulus-response learning over goal-directed responding (Dias-Ferreira et al., 2009; Sadowski et al., 2009; Schwabe et al., 2008; Schwabe and Wolf, 2011), which may increase the risk of SUD (see Section 5.3).

Adolescence itself may be a sensitive period to the effects of stress. Stress sensitivity and the reactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which initiates and terminates the body's stress response via a negative feedback loop (Koob and Le Moal, 2001; Myers et al., 2014), ramps up during adolescence (Romeo et al., 2016). Adolescent rats, especially females, are hyper-responsive to stressors and take longer to return to baseline after provocation (Lupien et al., 2009; Romeo and McEwen, 2006; Romeo, 2013). Behaviorally, rats with a maternal separation history show increased impulsive behavior and hyperactivity in a novel environment (Colorado et al., 2006; Marin and Planeta, 2004). Andersen and Teicher (2008) provide a more detailed review of the effects of early childhood stress and abuse as it relates to the sensitive adolescent period.

The long-term impact of stress during development may be different from that of stress in adults (Andersen, 2015; Fareri and Tottenham, 2016). The effects of stress depend upon the brain's maturational state at different developmental periods and often do not fully manifest until adolescence or later (Andersen and Teicher, 2004, 2008; Andersen et al., 2008b). Subcortical structures, with their earlier maturation, are often dysfunctional before later-developing cortical structures (Andersen and Teicher, 2009). Neither the NAc nor the hippocampus, which consolidate the process of reward "liking" (Grace et al., 2007), develop normally following exposure to early life stress (Andersen and Teicher, 2004; Goff et al., 2013; Teicher et al., 2006). Furthermore, a reduction in D1 receptor expression on mPFC → NAc projections in adolescence is observed following maternal separation (Brenhouse et al., 2008, 2013), and may represent a depressive affect state (Freund et al., 2016). Chronic stress

also reduces dendritic branching and/or spine density in mPFC and dorsomedial STR (including the NAc; Cook and Wellman, 2004; Dias-Ferreira et al., 2009; Liston et al., 2006; Radley et al., 2004; Taylor et al., 2014; but see Farrell et al., 2016). In contrast, chronic stress increases dendritic branching in OFC and dorsolateral STR, the latter of which is involved in habit-driven behaviors (Dias-Ferreira et al., 2009; Taylor et al., 2014).

Taken together, these above findings indicate that chronic or early life stress alter the trajectory of neural development and can increase the risk of SUD (Fig. 3), potentially by increasing reward set points, the incentive salience of drug-related cues, and the propensity to form drug abuse habits. The combination of these elevated risk factors with an immature PFC during the sensitive adolescent period may dramatically increase an individual's vulnerability to the transition to substance dependence, once drugs are sampled.

5.4.3. Prevention measures: promoting emotional regulation in adolescence—
Exposure to early life stress augments the risk of initiating drug use in early adolescence and later transitioning to substance dependence. The National Child Traumatic Stress Network (2008) notes that one in four children and adolescents experience a traumatic event before age 16 years (Kilpatrick et al., 2003), making it imperative to identify and intervene in at-risk subjects. Individual stress reactivity can be quantified as a risk factor for SUD by assessing emotional dysregulation, startle and other physiological responses, and in open-field and elevated plus maze tests (Connor-Smith et al., 2000; Ganella and Kim, 2014; Kalinichev et al., 2002; Quas et al., 2014). Practices that reduce arousal and promote emotional regulation, such as yoga, meditation, exercise and social support can help counteract the effects of early life stress in pre-teens and adolescents (Biegel et al., 2009; Brown and Siegel, 1988; Cobb, 1976; Hostinar, 2013; White, 2012). In rodents, environmental enrichment during the pre-pubertal or adolescent periods (in the form of toys, elaborate habitats, and social housing) reverses the effects of pre-natal and post-natal early life stress on HPA axis function, spatial memory, social play and fear responses (Cui et al., 2006; Francis et al., 2002; Laviola et al., 2004). Most importantly, it is critical that preventative interventions are implemented early in life, before the sensitive adolescent manifests, in order to be maximally effective.

6. Conclusions

Substance use is a substantial public health issue that is estimated to cost the U.S. over $600 billion each year (NIDA, 2015). Given that early substance use increases the risk of SUD four-fold, it is imperative to identify and intervene with high-risk individuals before dependence develops. Adolescence represents an evolved sensitive period when the circuitry underlying incentive salience, habit formation and stress are uniquely vulnerable to hijacking by drugs of abuse, in part due to reduced cortical control and elevated drive of subcortical systems. Current theories on the etiology of substance dependence lend insight into the risk factors that render a young person vulnerable to transitioning from experimental substance use to substance dependence. By identifying at-risk individuals early, preventative interventions can be used to promote resilience to substance dependence. Additional research that focuses on the juvenile and adolescent period is needed to understand sex

differences in the risk for substance dependence and to determine the most efficacious early preventative interventions for SUD.

Acknowledgements

Abbreviations

ACC	Anterior Cingulate Cortex
ACTH	Adrenocorticotropic Hormone
ADHD	Attention-Deficit/Hyperactivity Disorder
BLA	Basolateral Amygdala
BNST	Bed Nucleus of the Stria Terminalis
cAMP	Cyclic AMP
CK	Cam-Kinase II
CRF	Corticotropin Releasing Factor
DAT	Dopamine Transporter
fMRI	Functional Magnetic Resonance Imaging
HPA	Hypothalamic-Pituitary-Adrenal
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
NAc	Nucleus Accumbens
OFC	Orbitofrontal Cortex
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
P(#)	Post-Natal Day
SERT	Serotonin Transporter
SES	Socioeconomic Status
STN	Subthalamic Nucleus
STR	Striatum
SUD	Substance Use Disorder

VTA   Ventral Tegmental Area

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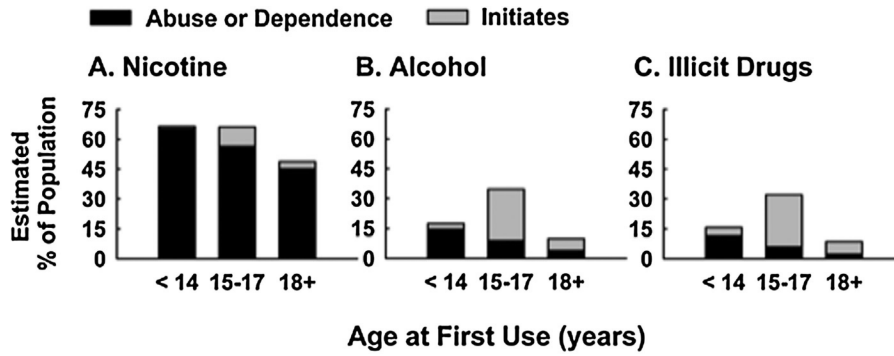
Fig. 1.
Early initiation of substance use increases the risk of substance abuse or dependence.
Substance abuse or dependence among persons aged 18 or older (black bars) is plotted by
age at first substance use for A) nicotine, B) alcohol, and C) illicit drugs (marijuana,
cocaine/crack, heroin, hallucinogens, inhalants, non-medial prescription use, and
methamphetamine), based on results of the 2014 National Survey on Substance use and
Health (SAMHSA, 2015a,b). Past year initiation of each drug (gray bars) is also shown for
each age group for comparison; this data is based on the 2013 National Survey on Substance
use and Health (SAMHSA, 2014). Although adolescents aged 15–17 are most likely to
experiment with drugs of abuse, initiation before age 14 is associated with the highest risk of
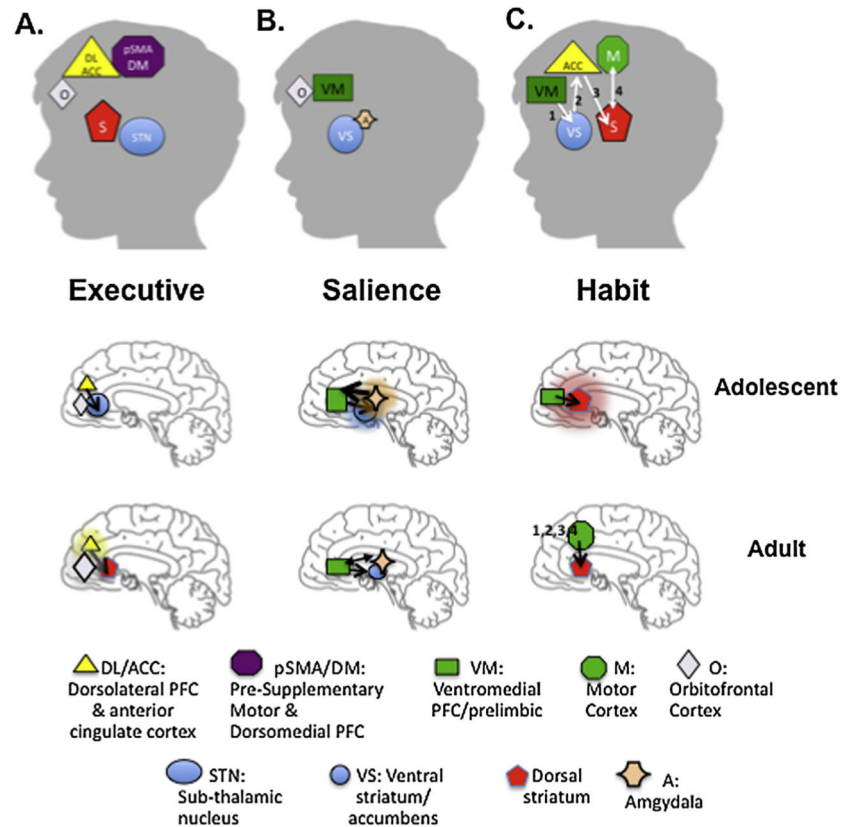developing abuse or dependence later in life.

Fig. 2.
Neural circuitry underlying adolescent vulnerability to substance use disorder (SUD).
Current theories on the etiology of SUD indicate addiction results from an executive
function deficit (A), increased incentive salience of drug-related cues (B), and the formation
of compulsive drug habits (C). Adolescence is a sensitive period of ongoing
neurodevelopment in which these traits are expressed even in the absence of drug taking.
Specifically, adolescents exhibit A) poor executive control, resulting from reduced inhibitory
control of the orbitofrontal cortex (OFC), dorsolateral PFC (DL), and anterior cingulate
cortex (ACC), over more developed subcortical regions such as the striatum (S) and
subthalamic nucleus (STN). Adolescents also attribute B) increased incentive salience to
reward-related cues, due to elevated excitation in projections between the ventromedial PFC
(VM), the ventral striatum (including the nucleus accumbens) and amygdala (A). Finally,
adolescents are more prone to C) formation of habitual over goal-directed behaviors. Habit
formation in adults involves a progressive recruitment (increased activation) of the VMPFC
to the ventral striatum (pathway 1) followed by increased activity in the ACC (pathway 2),
to the striatum (pathway 3), and motor cortex (pathway 4). In contrast, adolescents show
evidence of direct excitatory projections between the VMPFC and dorsal striatum (S),
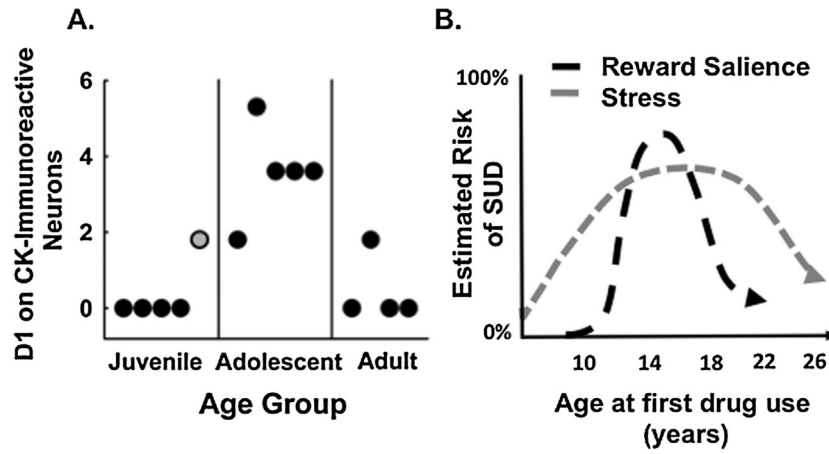providing a shortcut to the formation of habits.

Fig. 3.
Risk for the transition to substance use disorder (SUD). Substance use before age 14 is associated with the greatest risk of developing substance abuse or dependence later in life. However, while many individuals try drugs, only a small percentage transition to SUD. Individual risk factors for SUD may include heightened motivational salience of reward cues. Heightened incentive salience in adolescence is due to elevated dopamine D1 receptors on glutamatergic projections (CK-immunoreactive) from the medial prefrontal cortex (mPFC) to the nucleus accumbens (NAc). Subjects expressing high motivational salience/D1 receptor levels early may be the most vulnerable to developing SUD (e.g., the grey-dotted juvenile in panel A). Additional risk factors include exposure to stress chronically (e.g., neglect, abuse, loss of a caregiver, natural disaster) or acutely during the sensitive adolescent period, which can interact with reward salience to further augment SUD risk in young subjects (panel B).

Table 1

Summary of substance dependence etiology and relevance to adolescents.

Substance Dependence Theory	Associated Risk Behaviors	Predictions for Vulnerable Adolescents	Affected Neural Substrate(s)	Preventative Interventions
Executive Dysfunction	Inhibitory control, Sustained attention	Decreased	PFC	Meditation/Yoga, Martial Arts, Mindfulness Training
Incentive Salience	Reward cue reactivity, Sensitivity to Reward	Increased	NAc → mPFC, BLA ←–→ mPFC	Novelty, Enrichment
Habit Formation	Automatic behaviors, Insensitive to devaluation	Increased	Dorsal STR	Exercise
Stress Reactivity	Emotional dysregulation, Heightened startle/arousal	Increased	Hypothalamus, Amygdala, Hippocampus, NAc, STR, mPFC	Yoga, Mindfulness, Social Support