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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.

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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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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 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,

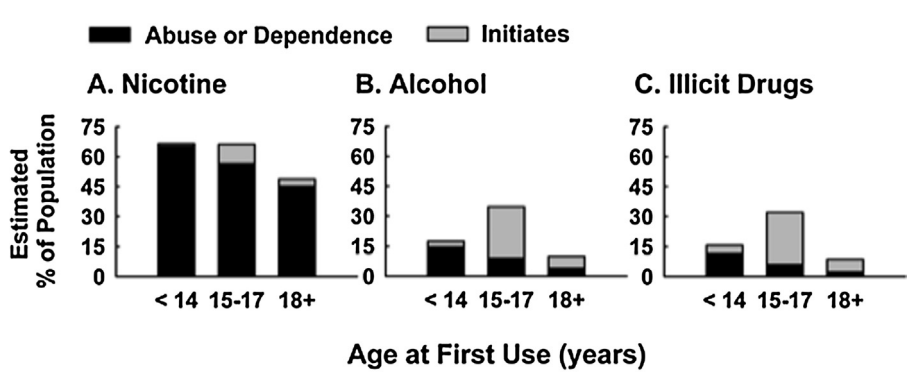

Fig. 1. Early initiation of substance use increases the risk of substance abuse or dependence. Substance abuse or dependence among persons aged 18 or older (black bars) is plotted by age at first substance use for A) nicotine, B) alcohol, and C) illicit drugs (marijuana, cocaine/crack, heroin, hallucinogens, 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.

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

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

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 pre-pubertal 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 pre-pubertal 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

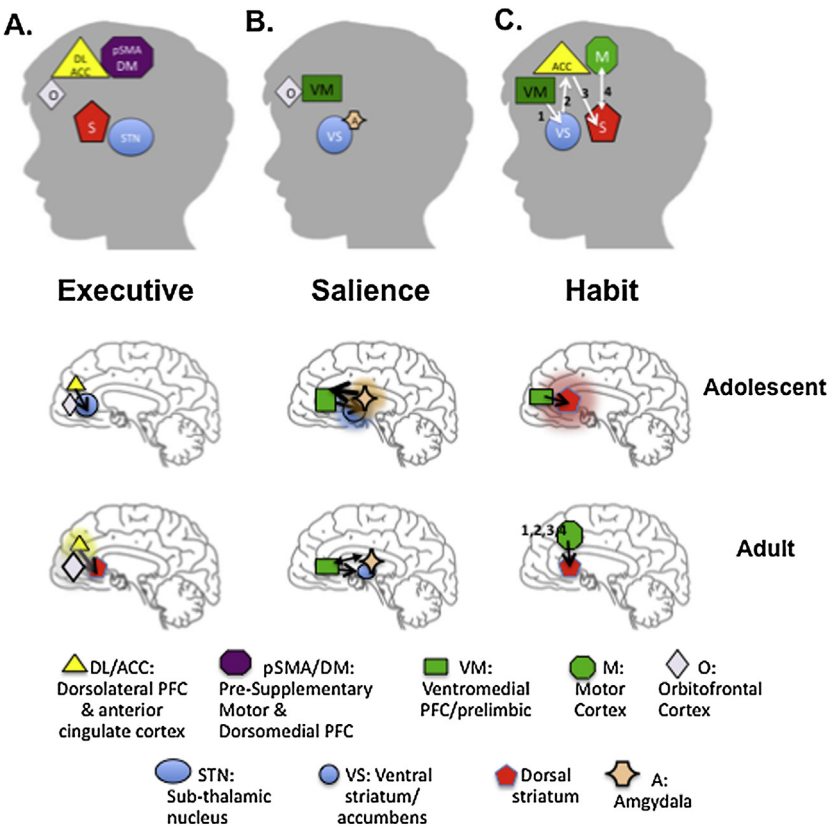

Fig. 2. Neural circuitry underlying adolescent vulnerability to substance use disorder (SUD). Current theories on the etiology of SUD indicate addiction results from an executive function deficit (A), increased incentive salience of drug-related cues (B), and the formation of compulsive drug habits (C). 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.

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, homeostatic 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 amygdalar 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 $\longleftrightarrow$ BLA and PFC $\rightarrow$ 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 $\rightarrow$ PFC (Cunningham et al., 2002, 2008) and PFC $\rightarrow$ 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 $\rightarrow$ 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 $\rightarrow$ 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 $\rightarrow$ 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 $\rightarrow$ 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 $\longleftrightarrow$ BLA and PFC $\rightarrow$ 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.

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).

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 allostatic 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 allostatic 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.

Declaration of interest

The authors do not have any competing interests with the present review.

Conflict of interest

None.

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References

Adriani, W., et al., 2002. Peculiar vulnerability to nicotine oral self-administration in mice during early adolescence. Neuropsychopharmacology 27, 212–224.
Adriani, W., et al., 2004. Behavioral and neurochemical vulnerability during adolescence in mice: studies with nicotine. Neuropsychopharmacology 29, 869–878.
Adriani, W., et al., 2006a. Methylphenidate administration to adolescent rats determines plastic changes on reward-related behavior and striatal gene expression. Neuropsychopharmacology 31, 1946–1956.
Adriani, W., et al., 2006b. Short-term effects of adolescent methylphenidate exposure on brain striatal gene expression and sexual/endocrine parameters in male rats. Ann. N. Y. Acad. Sci. 1074, 52–73.
Aguiar Jr., A.S., et al., 2008. Downhill training upregulates mice hippocampal and striatal brain-derived neurotrophic factor levels. J. Neural Transm. (Vienna) 115, 1251–1255.
Alarcon, G., et al., 2015. Developmental sex differences in resting state functional connectivity of amygdala sub-regions. Neuroimage 115, 235–244.
American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Association, Washington, DC.
Andersen, S.L., Gazzara, R.A., 1993. The ontogeny of apomorphine-induced alterations of neostriatal dopamine release: effects on spontaneous release. J. Neurochem. 61, 2247–2255.
Andersen, S.L., Navalta, C.P., 2011. Annual Research Review: new frontiers in developmental neuropharmacology: can long-term therapeutic effects of drugs be optimized through carefully timed early intervention? J. Child Psychol. Psychiatry 52, 476–503.
Andersen, S.L., Teicher, M.H., 2000. Sex differences in dopamine receptors and their relevance to ADHD. Neurosci. Biobehav. Rev. 24, 137–141.
Andersen, S.L., Teicher, M.H., 2004. Delayed effects of early stress on hippocampal development. Neuropsychopharmacology 29, 1988–1993.
Andersen, S.L., Teicher, M.H., 2008. Stress, sensitive periods and maturational events in adolescent depression. Trends Neurosci. 31, 183–191.
Andersen, S.L., Teicher, M.H., 2009. Desperately driven and no brakes: developmental stress exposure and subsequent risk for substance abuse. Neurosci. Biobehav. Rev. 33, 516–524.
Andersen, S.L., Dumont, N.L., Teicher, M.H., 1997a. Developmental differences in dopamine synthesis inhibition by (+/−)-7-OH-DPAT. Naunyn. Schmiedebergs Arch. Pharmacol. 356, 173–181.
Andersen, S.L., et al., 1997b. Sex differences in dopamine receptor overproduction and elimination. Neuroreport 8, 1495–1498.
Andersen, S.L., et al., 2002a. Altered responsiveness to cocaine in rats exposed to methylphenidate during development. Nat. Neurosci. 5, 13–14.
Andersen, S.L., et al., 2002b. Pubertal changes in gonadal hormones do not underlie adolescent dopamine receptor overproduction. Psychoneuroendocrinology 27, 683–691.
Andersen, S.L., et al., 2008a. Juvenile methylphenidate modulates reward-related behaviors and cerebral blood flow by decreasing cortical D3 receptors. Eur. J. Neurosci. 27, 2962–2972.
Andersen, S.L., et al., 2008b. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. J. Neuropsychiatry Clin. Neurosci. 20, 292–301.
Andersen, S.L., 2002. Changes in the second messenger cyclic AMP during development may underlie motoric symptoms in attention deficit/hyperactivity disorder (ADHD). Behav. Brain Res. 130, 197–201.
Andersen, S.L., 2003. Trajectories of brain development: point of vulnerability or window of opportunity? Neurosci. Biobehav. Rev. 27, 3–18.
Andersen, S.L., 2005. Stimulants and the developing brain. Trends Pharmacol. Sci. 26, 237–243.
Andersen, S.L., 2015. Exposure to early adversity: points of cross-species translation that can lead to improved understanding of depression. Dev. Psychopathol. 27, 477–491.
Andrzejewski, M.E., et al., 2011. A comparison of adult and adolescent rat behavior in operant learning extinction, and behavioral inhibition paradigms. Behav. Neurosci. 125, 93–105.
Anker, J.J., Carroll, M.E., 2010. Reinstatement of cocaine seeking induced by drugs, cues, and stress in adolescent and adult rats. Psychopharmacology (Berl.) 208, 211–222.
Arain, M., et al., 2013. Maturation of the adolescent brain. Neuropsychiatr. Dis. Treat. 9, 449–461.
Arnsten, A.F., Rubia, K., 2012. Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. J. Am. Acad. Child Adolesc. Psychiatry 51, 356–367.
Averbeck, B.B., et al., 2014. Estimates of projection overlap and zones of convergence within frontal-striatal circuits. J. Neurosci. 34, 9497–9505.
Badanich, K.A., Adler, K.J., Kirstein, C.L., 2006. Adolescents differ from adults in cocaine conditioned place preference and cocaine-induced dopamine in the nucleus accumbens septi. Eur. J. Pharmacol. 550, 95–106.
Bailey, J., Penhune, V.B., 2012. A sensitive period for musical training: contributions of age of onset and cognitive abilities. Ann. N. Y. Acad. Sci. 1252, 163–170.
Bardo, M.T., Compton, W.M., 2015. Does physical activity protect against drug abuse vulnerability? Drug Alcohol Depend. 153, 3–13.
Bardo, M.T., Donohew, R.L., Harrington, N.G., 1996. Psychobiology of novelty seeking and drug seeking behavior. Behav. Brain Res. 77, 23–43.
Barnea-Goraly, N., et al., 2005. White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. Cereb. Cortex 15, 1848–1854.
Baskin, B.M., Dwoskin, L.P., Kantak, K.M., 2015. Methylphenidate treatment beyond adolescence maintains increased cocaine self-administration in the spontaneously hypertensive rat model of attention deficit/hyperactivity disorder. Pharmacol. Biochem. Behav. 131, 51–56.
Beckmann, J.S., Bardo, M.T., 2012. Environmental enrichment reduces attribution of incentive salience to a food-associated stimulus. Behav. Brain Res. 226, 331–334.
Belin, D., Everitt, B.J., 2008. Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. Neuron 57, 432–441.
Belin, D., et al., 2008. High impulsivity predicts the switch to compulsive cocaine-taking. Science 320, 1352–1355.
Bellis, M.A., et al., 2007. Predictors of risky alcohol consumption in schoolchildren and their implications for preventing alcohol-related harm. Subst. Abuse Treat. Prev. Policy 2, 15.
Belluzzi, J.D., et al., 2004. Age-dependent effects of nicotine on locomotor activity and conditioned place preference in rats. Psychopharmacology (Berl.) 174, 389–395.
Bereczkei, T., Csanaky, A., 1996. Evolutionary pathway of child development: lifestyles of adolescents and adults from father-absent families. Hum. Nat. 7, 257–280.
Berridge, C.W., Arnsten, A.F., 2013. Psychostimulants and motivated behavior: arousal and cognition. Neurosci. Biobehav. Rev. 37, 1976–1984.
Berridge, K.C., 2007. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl.) 191, 391–431.
Berridge, K.C., 2009a. Wanting and liking: observations from the neuroscience and psychology laboratory. Inquiry (Oslo) 52, 378.
Berridge, K.C., 2009b. 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. Physiol. Behav. 97, 537–550.
Biederman, J., et al., 1999. Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. Pediatrics 104, e20.
Biegel, G.M., et al., 2009. Mindfulness-based stress reduction for the treatment of adolescent psychiatric outpatients: a randomized clinical trial. J. Consult. Clin. Psychol. 77, 855–866.
Bjork, J.M., et al., 2004. Incentive-elicited brain activation in adolescents: similarities and differences from young adults. J. Neurosci. 24, 1793–1802.
Bjorklund, D.F., Pellegrini, A.D., 2000. Child development and evolutionary psychology. Child Dev. 71, 1687–1708.
Bogin, B., Smith, B.H., 1996. Evolution of the human life cycle. Am. J. Hum. Biol. 8, 703–716.
Bolanos, C.A., et al., 2003. Methylphenidate treatment during pre- and periadolescence alters behavioral responses to emotional stimuli at adulthood. Biol. Psychiatry 54, 1317–1329.
Bowen, S., et al., 2009. Mindfulness-based relapse prevention for substance use disorders: a pilot efficacy trial. Subst. Abuse 30, 295–305.
Brandon, C.L., et al., 2001. Enhanced reactivity and vulnerability to cocaine following methylphenidate treatment in adolescent rats. Neuropsychopharmacology 25, 651–661.

Brandon, C.L., Marinelli, M., White, F.J., 2003. Adolescent exposure to methylphenidate alters the activity of rat midbrain dopamine neurons. Biol. Psychiatry 54, 1338–1344.
Brenhouse, H.C., Andersen, S.L., 2008. Delayed extinction and stronger reinstatement of cocaine conditioned place preference in adolescent rats compared to adults. Behav. Neurosci. 122, 460–465.
Brenhouse, H.C., Andersen, S.L., 2011. Developmental trajectories during adolescence in males and females: a cross-species understanding of underlying brain changes. Neurosci. Biobehav. Rev. 35, 1687–1703.
Brenhouse, H.C., Sonntag, K.C., Andersen, S.L., 2008. Transient D1 dopamine receptor expression on prefrontal cortex projection neurons: relationship to enhanced motivational salience of drug cues in adolescence. J. Neurosci. 28, 2375–2382.
Brenhouse, H.C., et al., 2009. Juvenile methylphenidate exposure and factors that influence incentive processing. Dev. Neurosci. 31, 95–106.
Brenhouse, H.C., Dumais, K., Andersen, S.L., 2010. Enhancing the salience of dullness: behavioral and pharmacological strategies to facilitate extinction of drug-cue associations in adolescent rats. Neuroscience 169, 628–636.
Brenhouse, H.C., Lukkes, J.L., Andersen, S.L., 2013. Early life adversity alters the developmental profiles of addiction-related prefrontal cortex circuitry. Brain Sci. 3, 143–158.
Brown, J.D., Siegel, J.M., 1988. Exercise as a buffer of life stress: a prospective study of adolescent health. Health Psychol. 7, 341–353.
Burton, A.C., Nakamura, K., Roesch, M.R., 2015. From ventral-medial to dorsal-lateral striatum: neural correlates of reward-guided decision-making. Neurobiol. Learn. Mem. 117, 51–59.
Cain, M.E., Green, T.A., Bardo, M.T., 2006. Environmental enrichment decreases responding for visual novelty. Behav. Processes 73, 360–366.
Callaghan, B.L., et al., 2014. The international society for developmental psychobiology Sackler symposium: early adversity and the maturation of emotion circuits—a cross-species analysis. Dev. Psychobiol. 56, 1635–1650.
Carlezon Jr., W.A., Mague, S.D., Andersen, S.L., 2003. Enduring behavioral effects of early exposure to methylphenidate in rats. Biol. Psychiatry 54, 1330–1337.
Casey, B.J., Jones, R.M., 2010. Neurobiology of the adolescent brain and behavior: implications for substance use disorders. J. Am. Acad. Child Adolesc. Psychiatry 49, 1189–1201.
Casey, B.J., Getz, S., Galvan, A., 2008. The adolescent brain. Dev. Rev. 28, 62–77.
Casey, B., Jones, R.M., Somerville, L.H., 2011. Braking and accelerating of the adolescent brain. J. Res. Adolesc. 21, 21–33.
Cass, D.K., et al., 2013. Developmental disruption of gamma-aminobutyric acid function in the medial prefrontal cortex by noncontingent cocaine exposure during early adolescence. Biol. Psychiatry 74, 490–501.
Chaddock, L., et al., 2010. Basal ganglia volume is associated with aerobic fitness in preadolescent children. Dev. Neurosci. 32, 249–256.
Chambers, R.A., Taylor, J.R., Potenza, M.N., 2003. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am. J. Psychiatry 160, 1041–1052.
Chang, S.E., Wheeler, D.S., Holland, P.C., 2012. Roles of nucleus accumbens and basolateral amygdala in autoshaped lever pressing. Neurobiol. Learn. Mem. 97, 441–451.
Clark, D.B., Lesnick, L., Hegedus, A.M., 1997. Traumas and other adverse life events in adolescents with alcohol abuse and dependence. J. Am. Acad. Child Adolesc. Psychiatry 36, 1744–1751.
Cobb, S., 1976. Presidential Address-1976: social support as a moderator of life stress. Psychosom. Med. 38, 300–314.
Colorado, R.A., et al., 2006. Effects of maternal separation, early handling, and standard facility rearing on orienting and impulsive behavior of adolescent rats. Behav. Processes 71, 51–58.
Congdon, E., et al., 2012. Measurement and reliability of response inhibition. Front. Psychol. 3, 37.
Connor-Smith, J.K., et al., 2000. Responses to stress in adolescence: measurement of coping and involuntary stress responses. J. Consult. Clin. Psychol. 68, 976–992.
Cook, S.C., Wellman, C.L., 2004. Chronic stress alters dendritic morphology in rat medial prefrontal cortex. J. Neurobiol. 60, 236–248.
Crawford, C.A., et al., 2011. Early methylphenidate exposure enhances cocaine self-administration but not cocaine-induced conditioned place preference in young adult rats. Psychopharmacology (Berl.) 213, 43–52.
Cressman, V.L., et al., 2010. Prefrontal cortical inputs to the basal amygdala undergo pruning during late adolescence in the rat. J. Comp. Neurol. 518, 2693–2709.
Cruz, F.C., et al., 2008. Maternal separation stress in male mice: long-term increases in alcohol intake. Psychopharmacology (Berl.) 201, 459–468.
Cui, M., et al., 2006. Enriched environment experience overcomes the memory deficits and depressive-like behavior induced by early life stress. Neurosci. Lett. 404, 208–212.
Cunningham, M.G., Bhattacharyya, S., Benes, F.M., 2002. Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence. J. Comp. Neurol. 453, 116–130.
Cunningham, M.G., Bhattacharyya, S., Benes, F.M., 2008. Increasing Interaction of amygdalar afferents with GABAergic interneurons between birth and adulthood. Cereb. Cortex 18, 1529–1535.
Curtis, C.E., D'Esposito, M., 2003. Persistent activity in the prefrontal cortex during working memory. Trends Cognit. Sci. 7, 415–423.
Darwin, C.R., 1871. The descent of man, and selection in relation to sex, 1 st Edition. John Murray, London, Vol.
Diamond, A., Lee, K., 2011. Interventions shown to aid executive function development in children 4 to 12 years old. Science 333, 959–964.
Diamond, A., 2013. Executive functions. Annu. Rev. Psychol. 64, 135–168.
Dias-Ferreira, E., et al., 2009. Chronic stress causes frontostriatal reorganization and affects decision-making. Science 325, 621–625.
Dickinson, A., 1985. Actions and habits: the development of behavioural autonomy. Philos. Trans. R Soc. Lond. B Biol. Sci. 308, 67–78.
Doherty, J.M., Frantz, K.J., 2012. Heroin self-administration and reinstatement of heroin-seeking in adolescent vs: adult male rats. Psychopharmacology (Berl.) 219, 763–773.
Dow-Edwards, D., 2010. Sex differences in the effects of cocaine abuse across the life span. Physiol. Behav. 100, 208–215.
Duncan, D.F., 1977. Life stress as a precursor to adolescent drug dependence. Int. J. Addict. 12, 1047–1056.
Durston, S., et al., 2001. Anatomical MRI of the developing human brain: what have we learned? J. Am. Acad. Child Adolesc. Psychiatry 40, 1012–1020.
de Bruijn, G.J., van den Putte, B., 2009. Adolescent soft drink consumption, television viewing and habit strength: investigating clustering effects in the Theory of Planned Behaviour. Appetite 53, 66–75.
de Wit, H., 2009. Impulsivity as a determinant and consequence of drug use: a review of underlying processes. Addict. Biol. 14, 22–31.
Eagle, D.M., Baunez, C., 2010. Is there an inhibitory-response-control system in the rat? Evidence from anatomical and pharmacological studies of behavioral inhibition. Neurosci. Biobehav. Rev. 34, 50–72.
El Rawas, R., et al., 2009. Environmental enrichment decreases the rewarding but not the activating effects of heroin. Psychopharmacology (Berl.) 203, 561–570.
Enoch, M.A., 2011. The role of early life stress as a predictor for alcohol and drug dependence. Psychopharmacology (Berl.) 214, 17–31.
Ernst, M., et al., 2005. Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. Neuroimage 25, 1279–1291.
Ernst, M., Pine, D.S., Hardin, M., 2006. Triadic model of the neurobiology of motivated behavior in adolescence. Psychol. Med. 36, 299–312.
Ernst, M., 2014. The triadic model perspective for the study of adolescent motivated behavior. Brain Cognit. 89, 104–111.
Eshel, N., et al., 2007. Neural substrates of choice selection in adults and adolescents: development of the ventrolateral prefrontal and anterior cingulate cortices. Neuropsychologia 45, 1270–1279.
Everitt, B.J., Robbins, T.W., 2013. From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. Neurosci. Biobehav. Rev. 37, 1946–1954.
Everitt, B.J., Robbins, T.W., 2016. Drug addiction: updating actions to habits to compulsions ten years on. Annu. Rev. Psychol. 67, 23–50.
Everitt, B.J., et al., 2008. Review: neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. Philos. Trans. R Soc. Lond. B Biol. Sci. 363, 3125–3135.
Fareri, D.S., Tottenham, N., 2016. Effects of early life stress on amygdala and striatal development. Dev. Cognit. Neurosci. 19, 233–247.
Farrell, M.R., et al., 2016. Sex-specific effects of early life stress on social interaction and prefrontal cortex dendritic morphology in young rats. Behav. Brain Res. 310, 119–125.
Ferron, C., et al., 1999. Sport activity in adolescence: associations with health perceptions and experimental behaviours. Health Educ. Res. 14, 225–233.
Francis, D.D., et al., 2002. Environmental enrichment reverses the effects of maternal separation on stress reactivity. J. Neurosci. 22, 7840–7843.
Freund, N., et al., 2016. When the party is over: depressive-like states in rats following termination of cortical D1 receptor overexpression. Psychopharmacology (Berl.) 233, 1191–1201.
Fuchs, R.A., Branham, R.K., See, R.E., 2006. Different neural substrates mediate cocaine seeking after abstinence versus extinction training: a critical role for the dorsolateral caudate-putamen. J. Neurosci. 26, 3584–3588.
Gabard-Durnam, L.J., et al., 2014. The development of human amygdala functional connectivity at rest from 4 to 23 years: a cross-sectional study. Neuroimage 95, 193–207.
Galvan, A., et al., 2006. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. J. Neurosci. 26, 6885–6892.
Galvan, A., 2010. Adolescent development of the reward system. Front. Hum. Neurosci. 4, 6.
Ganella, D.E., Kim, J.H., 2014. Developmental rodent models of fear and anxiety: from neurobiology to pharmacology. Br. J. Pharmacol. 171, 4556–4574.
Garavan, H., et al., 2000. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am. J. Psychiatry 157, 1789–1798.
Gardner, B., Lally, P., Wardle, J., 2012. Making health habitual: the psychology of 'habit-formation' and general practice. Br. J. Gen. Pract. 62, 664–666.
Gass, J.T., et al., 2014. Adolescent alcohol exposure reduces behavioral flexibility, promotes disinhibition, and increases resistance to extinction of ethanol self-administration in adulthood. Neuropsychopharmacology 39, 2570–2583.
Giedd, J.N., et al., 1999. Brain development during childhood and adolescence: a longitudinal MRI study. Nat. Neurosci. 2, 861–863.
Gluckman, P.D., Hanson, M.A., 2006. Evolution, development and timing of puberty. Trends Endocrinol. Metab. 17, 7–12.
Goff, B., et al., 2013. Reduced nucleus accumbens reactivity and adolescent depression following early-life stress. Neuroscience 249, 129–138.
Goldman, P.S., Alexander, G.E., 1977. Maturation of prefrontal cortex in the monkey revealed by local reversible cryogenic depression. Nature 267, 613–615.

Goldstein, R.Z., Volkow, N.D., 2011. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat. Rev. Neurosci. 12, 652–669.
Grace, A.A., et al., 2007. Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. Trends Neurosci. 30, 220–227.
Grant, B.F., Dawson, D.A., 1998. Age of onset of drug use and its association with DSM-IV drug abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. J. Subst. Abuse 10, 163–173.
Grant, B.F., 1998. Age at smoking onset and its association with alcohol consumption and DSM-IV alcohol abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. J. Subst. Abuse 10, 59–73.
Gremel, C.M., Cunningham, C.L., 2008. Roles of the nucleus accumbens and amygdala in the acquisition and expression of ethanol-conditioned behavior in mice. J. Neurosci. 28, 1076–1084.
Gruber, S.A., et al., 2014. Worth the wait: effects of age of onset of marijuana use on white matter and impulsivity. Psychopharmacology (Berl.) 231, 1455–1465.
Grusser, S.M., et al., 2004. Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. Psychopharmacology (Berl.) 175, 296–302.
Gulley, J.M., Juraska, J.M., 2013. The effects of abused drugs on adolescent development of corticolimbic circuitry and behavior. Neuroscience 249, 3–20.
Gustafsson, L., Ploj, K., Nylander, I., 2005. Effects of maternal separation on voluntary ethanol intake and brain peptide systems in female Wistar rats. Pharmacol. Biochem. Behav. 81, 506–516.
Guyer, A.E., et al., 2006. Striatal functional alteration in adolescents characterized by early childhood behavioral inhibition. J. Neurosci. 26, 6399–6405.
Guyer, A.E., et al., 2008. A developmental examination of amygdala response to facial expressions. J. Cognit. Neurosci. 20, 1565–1582.
Haber, S.N., Fudge, J.L., McFarland, N.R., 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J. Neurosci. 20, 2369–2382.
Haber, S.N., et al., 2006. Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning. J. Neurosci. 26, 8368–8376.
Hammerslag, L.R., Gulley, J.M., 2014. Age and sex differences in reward behavior in adolescent and adult rats. Dev. Psychobiol. 56, 611–621.
Hanson, J.L., et al., 2016. Cumulative stress in childhood is associated with blunted reward-related brain activity in adulthood. Soc. Cognit. Affect. Neurosci. 11, 405–412.
Harrell, J.S., et al., 1998. Smoking initiation in youth: the roles of gender, race, socioeconomics, and developmental status. J. Adolesc. Health 23, 271–279.
Harvey, R.C., et al., 2011. Methylphenidate treatment in adolescent rats with an attention deficit/hyperactivity disorder phenotype: cocaine addiction vulnerability and dopamine transporter function. Neuropsychopharmacology 36, 837–847.
Hawkins, J.D., Catalano, R.F., Miller, J.Y., 1992. Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: implications for substance abuse prevention. Psychol. Bull. 112, 64–105.
Hawley, P., 2011. The evolution of adolescence and the adolescence of evolution: the coming of age of humans and the theory about the forces that made them. J. Res. Adolesc. 21, 307–316.
Hester, R., Garavan, H., 2004. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. J. Neurosci. 24, 11017–11022.
Hester, R., Lubman, D.I., Yucel, M., 2010. The role of executive control in human drug addiction. Curr. Top. Behav. Neurosci. 3, 301–318.
Hogarth, L., Chase, H.W., 2011. Parallel goal-directed and habitual control of human drug-seeking: implications for dependence vulnerability. J. Exp. Psychol. Anim. Behav. Process. 37, 261–276.
Holzel, B.K., et al., 2008. Investigation of mindfulness meditation practitioners with voxel-based morphometry. Soc. Cognit. Affect. Neurosci. 3, 55–61.
Holzel, B.K., et al., 2011. Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Res. 191, 36–43.
Hostinar, C.E., 2013. The Impacts of Social Support and Early Life Stress on Stress Reactivity in Children and Adolescents. University of Minnesota Digital Conservancy.
Houben, K., Wiers, R.W., Jansen, A., 2011. Getting a grip on drinking behavior: training working memory to reduce alcohol abuse. Psychol. Sci. 22, 968–975.
Humensky, J.L., 2010. Are adolescents with high socioeconomic status more likely to engage in alcohol and illicit drug use in early adulthood? Subst. Abuse Treat. Prev. Policy 5, 19.
Huot, R.L., et al., 2001. Development of adult ethanol preference and anxiety as a consequence of neonatal maternal separation in Long Evans rats and reversal with antidepressant treatment. Psychopharmacology (Berl.) 158, 366–373.
Ito, R., et al., 2002. Dopamine release in the dorsal striatum during cocaine-seeking behavior under the control of a drug-associated cue. J. Neurosci. 22, 6247–6253.
Jasinska, A.J., et al., 2014. Factors modulating neural reactivity to drug cues in addiction: a survey of human neuroimaging studies. Neurosci. Biobehav. Rev. 38, 1–16.
Johnson, J.S., Newport, E.L., 1989. Critical period effects in second language learning: the influence of maturational state on the acquisition of English as a second language. Cognit. Psychol. 21, 60–99.
Johnson, T.R., et al., 2013. Neural processing of a cocaine-associated odor cue revealed by functional MRI in awake rats. Neurosci. Lett. 534, 160–165.
Johnson, C.M., et al., 2016. Long-range orbitofrontal and amygdala axons show divergent patterns of maturation in the frontal cortex across adolescence. Dev. Cognit. Neurosci. 18, 113–120.
Jonkman, S., Pelloux, Y., Everitt, B.J., 2012. Differential roles of the dorsolateral and midlateral striatum in punished cocaine seeking. J. Neurosci. 32, 4645–4650.
Jordan, C.J., et al., 2014. Cocaine-seeking behavior in a genetic model of attention-deficit/hyperactivity disorder following adolescent methylphenidate or atomoxetine treatments. Drug Alcohol Depend. 140, 25–32.
Jordan, C.J., et al., 2016. Adolescent D-amphetamine treatment in a rodent model of ADHD: Pro-cognitive effects in adolescence without an impact on cocaine cue reactivity in adulthood. Behav. Brain Res. 297, 165–179.
Judah, G., Gardner, B., Aunger, R., 2013. Forming a flossing habit: an exploratory study of the psychological determinants of habit formation. Br. J. Health Psychol. 18, 338–353.
Kalinichev, M., et al., 2002. Long-lasting changes in stress-induced corticosterone response and anxiety-like behaviors as a consequence of neonatal maternal separation in Long-Evans rats. Pharmacol. Biochem. Behav. 73, 131–140.
Kalivas, P.W., Volkow, N., Seamans, J., 2005. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. Neuron 45, 647–650.
Kendig, M.D., et al., 2013. Chronic restricted access to 10% sucrose solution in adolescent and young adult rats impairs spatial memory and alters sensitivity to outcome devaluation. Physiol. Behav. 120, 164–172.
Khurana, A., et al., 2013. Working memory ability predicts trajectories of early alcohol use in adolescents: the mediational role of impulsivity. Addiction 108, 506–515.
Kilpatrick, D.G., et al., 2000. Risk factors for adolescent substance abuse and dependence: data from a national sample. J. Consult. Clin. Psychol. 68, 19–30.
Kilpatrick, D.G., et al., 2003. Violence and risk of PTSD, major depression, substance abuse/dependence, and comorbidity: results from the National Survey of Adolescents. J. Consult. Clin. Psychol. 71, 692–700.
Knudsen, E.I., 2004. Sensitive periods in the development of the brain and behavior. J. Cognit. Neurosci. 16, 1412–1425.
Koob, G.F., Le Moal, M., 2001. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24, 97–129.
Koss, W.A., et al., 2014. Dendritic remodeling in the adolescent medial prefrontal cortex and the basolateral amygdala of male and female rats. Synapse 68, 61–72.
Kosten, T.A., Miserendino, M.J., Kehoe, P., 2000. Enhanced acquisition of cocaine self-administration in adult rats with neonatal isolation stress experience. Brain Res. 875, 44–50.
Kosten, T.A., et al., 2004. Neonatal isolation enhances acquisition of cocaine self-administration and food responding in female rats. Behav. Brain Res. 151, 137–149.
Kosten, T.A., Zhang, X.Y., Kehoe, P., 2006. Heightened cocaine and food self-administration in female rats with neonatal isolation experience. Neuropsychopharmacology 31, 70–76.
Kreek, M.J., et al., 2005. Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. Nat. Neurosci. 8, 1450–1457.
Kremers, S.P., van der Horst, K., Brug, J., 2007. Adolescent screen-viewing behaviour is associated with consumption of sugar-sweetened beverages: the role of habit strength and perceived parental norms. Appetite 48, 345–350.
Kuhn, C., 2015. Emergence of sex differences in the development of substance use and abuse during adolescence. Pharmacol. Ther. 153, 55–78.
Lacy, R.T., et al., 2014. Exercise decreases speedball self-administration. Life Sci. 114, 86–92.
Lakes, K.D., Hoyt, W.T., 2004. Promoting self-regulation through school-based martial arts training. Appl. Dev. Psychol. 25, 283–302.
Lambert, N.M., Hartsough, C.S., 1998. Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. J. Learn. Disabil. 31, 533–544.
Lau, H., Rogers, R.D., Passingham, R.E., 2006. Dissociating response selection and conflict in the medial frontal surface. Neuroimage 29, 446–451.
Laviola, G., et al., 2004. Beneficial effects of enriched environment on adolescent rats from stressed pregnancies. Eur. J. Neurosci. 20, 1655–1664.
Lazar, S.W., et al., 2005. Meditation experience is associated with increased cortical thickness. Neuroreport 16, 1893–1897.
Letchworth, S.R., et al., 2001. Progression of changes in dopamine transporter binding site density as a result of cocaine self-administration in rhesus monkeys. J. Neurosci. 21, 2799–2807.
Levin, E.D., et al., 2003. Adolescent-onset nicotine self-administration modeled in female rats. Psychopharmacology (Berl.) 169, 141–149.
Levin, E.D., et al., 2007. Adolescent vs: adult-onset nicotine self-administration in male rats: duration of effect and differential nicotinic receptor correlates. Neurotoxicol. Teratol. 29, 458–465.
Lidow, M.S., Goldman-Rakic, P.S., Rakic, P., 1991. Synchronized overproduction of neurotransmitter receptors in diverse regions of the primate cerebral cortex. Proc. Natl. Acad. Sci. U. S. A. 88, 10218–10221.
Liston, C., et al., 2006. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J. Neurosci. 26, 7870–7874.
Liu, H.S., et al., 2013. Dorsolateral caudate nucleus differentiates cocaine from natural reward-associated contextual cues. Proc. Natl. Acad. Sci. U. S. A. 110, 4093–4098.

Lomanowska, A.M., et al., 2011. Inadequate early social experience increases the incentive salience of reward-related cues in adulthood. Behav. Brain Res. 220, 91–99.
Lopez-Larson, M.P., et al., 2011. Altered prefrontal and insular cortical thickness in adolescent marijuana users. Behav. Brain Res. 220, 164–172.
Lowen, S.B., et al., 2015. Cocaine-conditioned odor cues without chronic exposure: implications for the development of addiction vulnerability. Neuroimage Clin. 8, 652–659.
Lukas, S.E., et al., 2013. Extended-release naltrexone (XR-NTX) attenuates brain responses to alcohol cues in alcohol-dependent volunteers: a bold FMRI study. Neuroimage 78, 176–185.
Lupien, S.J., et al., 2009. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat. Rev. Neurosci. 10, 434–445.
Lyss, P.J., et al., 1999. Degree of neuronal activation following FG-7142 changes across regions during development. Brain Res. Dev. Brain Res. 116, 201–203.
Maas, L.C., et al., 1998. Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. Am. J. Psychiatry 155, 124–126.
Manjunath, N.K., Telles, S., 2001. Improved performance in the Tower of London test following yoga. Indian J. Physiol. Pharmacol. 45, 351–354.
Mannuzza, S., et al., 2008. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. Am. J. Psychiatry 165, 604–609.
Marais, L., Stein, D.J., Daniels, W.M., 2009. Exercise increases BDNF levels in the striatum and decreases depressive-like behavior in chronically stressed rats. Metab. Brain Dis. 24, 587–597.
Marek, S., et al., 2015. The contribution of network organization and integration to the development of cognitive control. PLoS Biol. 13, e1002328.
Marin, M.T., Planeta, C.S., 2004. Maternal separation affects cocaine-induced locomotion and response to novelty in adolescent but not in adult rats. Brain Res. 1013, 83–90.
Mason, M., et al., 2015. Time-varying effects of a text-based smoking cessation intervention for urban adolescents. Drug Alcohol Depend. 157, 99–105.
Matthews, K., et al., 1999. Repeated neonatal maternal separation alters intravenous cocaine self-administration in adult rats. Psychopharmacology (Berl.) 141, 123–134.
Matthews, M., et al., 2013. Reduced presynaptic dopamine activity in adolescent dorsal striatum. Neuropsychopharmacology 38, 1344–1351.
McEwen, B.S., Gianaros, P.J., 2010. Central role of the brain in stress and adaptation: links to socioeconomic status health, and disease. Ann. N. Y. Acad. Sci. 1186, 190–222.
Mechelli, A., et al., 2004. Neurolinguistics: structural plasticity in the bilingual brain. Nature 431, 757.
Mehta, M.A., et al., 2010. Hyporesponsive reward anticipation in the basal ganglia following severe institutional deprivation early in life. J. Cognit. Neurosci. 22, 2316–2325.
Meil, W.M., See, R.E., 1997. Lesions of the basolateral amygdala abolish the ability of drug associated cues to reinstate responding during withdrawal from self-administered cocaine. Behav. Brain Res. 87, 139–148.
Mendle, J., et al., 2011. Associations between early life stress, child maltreatment, and pubertal development among girls in foster care. J. Res. Adolesc. 21, 871–880.
Michaels, C.C., Easterling, K.W., Holtzman, S.G., 2007. Maternal separation alters lCSS responding in adult male and female rats: but morphine and naltrexone have little affect on that behavior. Brain Res. Bull. 73, 310–318.
Mitchell, M.R., et al., 2014. Adolescent risk taking, cocaine self-administration, and striatal dopamine signaling. Neuropsychopharmacology 39, 955–962.
Moffett, M.C., et al., 2006. Maternal separation and handling affects cocaine self-administration in both the treated pups as adults and the dams. J. Pharmacol. Exp. Ther. 317, 1210–1218.
Moffett, M.C., et al., 2007. Maternal separation alters drug intake patterns in adulthood in rats. Biochem. Pharmacol. 73, 321–330.
Molina, B.S., et al., 2013. Adolescent substance use in the multimodal treatment study of attention-deficit/hyperactivity disorder (ADHD) (MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. J. Am. Acad. Child Adolesc. Psychiatry 52, 250–263.
Moll, G.H., et al., 2000. Age-associated changes in the densities of presynaptic monoamine transporters in different regions of the rat brain from early juvenile life to late adulthood. Brain Res. Dev. Brain Res. 119, 251–257.
Mueller, S.C., et al., 2010. Early-life stress is associated with impairment in cognitive control in adolescence: an fMRI study. Neuropsychologia 48, 3037–3044.
Munakata, Y., et al., 2011. A unified framework for inhibitory control. Trends Cognit. Sci. 15, 453–459.
Myers, B., et al., 2014. Central stress-integrative circuits: forebrain glutamatergic and GABAergic projections to the dorsomedial hypothalamus medial preoptic area, and bed nucleus of the stria terminalis. Brain Struct. Funct. 219, 1287–1303.
Nair, S.G., et al., 2011. Role of dorsal medial prefrontal cortex dopamine D1-family receptors in relapse to high-fat food seeking induced by the anxiogenic drug yohimbine. Neuropsychopharmacology 36, 497–510.
Naneix, F., et al., 2012. Parallel maturation of goal-directed behavior and dopaminergic systems during adolescence. J. Neurosci. 32, 16223–16232.
National, Institute of Drug Abuse, (2014). Principles of Adolescent Substance Use Disorder Treatment: A Research-Based Guide. Retrieved 18 Sept. 2016. Available at. https://www.drugabuse.gov/publications/principles-adolescent-substance-use-disorder-treatment-research-based-guide/introduction.
National Institute of Drug Abuse, (2015). Trends and Statistics. Retrieved 9 Nov. 2016. Available at. https://www.drugabuse.gov/related-topics/trends-statistics.
Nees, F., et al., 2012. Determinants of early alcohol use in healthy adolescents: the differential contribution of neuroimaging and psychological factors. Neuropsychopharmacology 37, 986–995.
Newcomb, M.D., Harlow, L.L., 1986. Life events and substance use among adolescents: mediating effects of perceived loss of control and meaninglessness in life. J. Pers. Soc. Psychol. 51, 564–577.
Newman, L.A., McGaughy, J., 2011. Adolescent rats show cognitive rigidity in a test of attentional set shifting. Dev. Psychobiol. 53, 391–401.
Ogbonmwan, Y.E., et al., 2015. The effects of post-extinction exercise on cocaine-primed and stress-induced reinstatement of cocaine seeking in rats. Psychopharmacology (Berl.) 232, 1395–1403.
Ongur, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats monkeys and humans. Cereb. Cortex 10, 206–219.
Parent, A.S., et al., 2011. Early developmental actions of endocrine disruptors on the hypothalamus, hippocampus, and cerebral cortex. J. Toxicol. Environ. Health B Crit. Rev. 14, 328–345.
Patrick, M.E., et al., 2012. Socioeconomic status and substance use among young adults: a comparison across constructs and drugs. J. Stud. Alcohol Drugs 73, 772–782.
Patton, G.C., et al., 2004. Puberty and the onset of substance use and abuse. Pediatrics 114, e300–6.
Peeters, M., et al., 2015. Weaknesses in executive functioning predict the initiating of adolescents' alcohol use. Dev. Cognit. Neurosci. 16, 139–146.
Perry, J.L., et al., 2007. Acquisition of i: v. cocaine self-administration in adolescent and adult male rats selectively bred for high and low saccharin intake. Physiol. Behav. 91, 126–133.
Peterson, A.B., Abel, J.M., Lynch, W.J., 2014. Dose-dependent effects of wheel running on cocaine-seeking and prefrontal cortex Bdnf exon IV expression in rats. Psychopharmacology (Berl.) 231, 1305–1314.
Phillips, G.D., et al., 1994. Isolation rearing enhances the locomotor response to cocaine and a novel environment: but impairs the intravenous self-administration of cocaine. Psychopharmacology (Berl.) 115, 407–418.
Ploj, K., Roman, E., Nylander, I., 2003. Long-term effects of maternal separation on ethanol intake and brain opioid and dopamine receptors in male Wistar rats. Neuroscience 121, 787–799.
Pool, E., et al., 2016. Measuring wanting and liking from animals to humans: a systematic review. Neurosci. Biobehav. Rev. 63, 124–142.
Porrino, L.J., et al., 2004. Cocaine self-administration produces a progressive involvement of limbic, association, and sensorimotor striatal domains. J. Neurosci. 24, 3554–3562.
Potvin, S., et al., 2014. Cocaine and cognition: a systematic quantitative review. J. Addict. Med. 8, 368–376.
Pruessner, J.C., et al., 2004. Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [11C]raclopride. J. Neurosci. 24, 2825–2831.
Quas, J.A., et al., 2014. The symphonic structure of childhood stress reactivity: patterns of sympathetic, parasympathetic, and adrenocortical responses to psychological challenge. Dev. Psychopathol. 26, 963–982.
Radley, J.J., et al., 2004. Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. Neuroscience 125, 1–6.
Rapoport, J.L., et al., 1978. Dextroamphetamine: cognitive and behavioral effects in normal prepubertal boys. Science 199, 560–563.
Ridderinkhof, K.R., et al., 2004. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. Brain Cognit. 56, 129–140.
Robins, L.N., 1984. The natural history of adolescent drug use. Am. J. Public Health 74, 656–657.
Robinson, T.E., Berridge, K.C., 1993a. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Brain Res. Rev. 18, 247–291.
Robinson, T.E., Berridge, K.C., 1993b. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Brain Res. Rev. 18, 247–291.
Roman, E., Ploj, K., Nylander, I., 2004. Maternal separation has no effect on voluntary ethanol intake in female Wistar rats. Alcohol 33, 31–39.
Romeo, R.D., McEwen, B.S., 2006. Stress and the adolescent brain. Ann. N. Y. Acad. Sci. 1094, 202–214.
Romeo, R.D., 2013. The teenage brain: the stress response and the adolescent brain. Curr. Dir. Psychol. Sci. 22, 140–145.
Rothman, A.J., Sheeran, P., Wood, W., 2009. Reflective and automatic processes in the initiation and maintenance of dietary change. Ann. Behav. Med. 1 (38 Suppl), S4–17.
Romeo, R.D., et al., 2016. Adolescence and the ontogeny of the hormonal stress response in male and female rats and mice. Neurosci. Biobehav. Rev. 70, 206–216.
Ruedi-Bettschen, D., et al., 2006. Early deprivation leads to altered behavioural, autonomic and endocrine responses to environmental challenge in adult Fischer rats. Eur. J. Neurosci. 24, 2879–2893.

SAMHSA, 2008. Results from the 2008 National Survey on Drug Use and Health: National Findings. Office of Applied Studies, Rockville, MD.
SAMHSA, 2012. Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings. Substance Abuse and Mental Health Services Administration, Rockville, MD.
SAMHSA, 2014. Results from the 2013 National Survey on Drug Use and Health: Detailed Tables. Center for Behavioral Health Statistics and Quality, Rockville, MD.
SAMHSA, 2015. Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15–4927, NSDUHSeries H-50).
SAMHSA, 2015b. 2014 National Survey on Drug Use and Health: Detailed Tables. Center for Behavioral Health Statistics and Quality, Rockville, MD.
Sadowski, R.N., et al., 2009. Effects of stress, corticosterone, and epinephrine administration on learning in place and response tasks. Behav. Brain Res. 205, 19–25.
Sanchez, C.J., et al., 2003. Manipulation of dopamine d1-like receptor activation in the rat medial prefrontal cortex alters stress- and cocaine-induced reinstatement of conditioned place preference behavior. Neuroscience 119, 497–505.
Sanchez, V., et al., 2015. Wheel running exercise attenuates vulnerability to self-administer nicotine in rats. Drug Alcohol Depend. 156, 193–198.
Schneider, S., et al., 2012. Risk taking and the adolescent reward system: a potential common link to substance abuse. Am. J. Psychiatry 169, 39–46.
Schramm-Sapyta, N.L., et al., 2009. Are adolescents more vulnerable to drug addiction than adults?: Evidence from animal models. Psychopharmacology (Berl.) 206, 1–21.
Schrantee, A., et al., 2016. Age-dependent effects of methylphenidate on the human dopaminergic system in young vs adult patients with attention-deficit/hyperactivity disorder: a randomized clinical trial. JAMA Psychiatry 73, 955–962.
Schwabe, L., Wolf, O.T., 2009. Stress prompts habit behavior in humans. J. Neurosci. 29, 7191–7198.
Schwabe, L., Wolf, O.T., 2011. Stress-induced modulation of instrumental behavior: from goal-directed to habitual control of action. Behav. Brain Res. 219, 321–328.
Schwabe, L., et al., 2008. Chronic stress modulates the use of spatial and stimulus-response learning strategies in mice and man. Neurobiol. Learn. Mem. 90, 495–503.
Schwabe, L., Dickinson, A., Wolf, O.T., 2011. Stress, habits, and drug addiction: a psychoneuroendocrinological perspective. Exp. Clin. Psychopharmacol. 19, 53–63.
Schwartz, J.A., Beaver, K.M., Barnes, J.C., 2015. The association between mental health and violence among a nationally representative sample of college students from the United States. PLoS One 10, e0138914.
See, R.E., Elliott, J.C., Feltenstein, M.W., 2007. The role of dorsal vs ventral striatal pathways in cocaine-seeking behavior after prolonged abstinence in rats. Psychopharmacology (Berl.) 194, 321–331.
Seeley, W.W., et al., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349–2356.
Seger, C.A., Spiering, B.J., 2011. A critical review of habit learning and the Basal Ganglia. Front. Syst. Neurosci. 5, 66.
Shaw, P., et al., 2007. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc. Natl. Acad. Sci. U. S. A. 104, 19649–19654.
Shaw, P., et al., 2009. Psychostimulant treatment and the developing cortex in attention deficit hyperactivity disorder. Am. J. Psychiatry 166, 58–63.
Sinha, R., 2008. Chronic stress, drug use, and vulnerability to addiction. Ann. N. Y. Acad. Sci. 1141, 105–130.
Sisk, C.L., Schulz, K.M., Zehr, J.L., 2003. Puberty: a finishing school for male social behavior. Ann. N. Y. Acad. Sci. 1007, 189–198.
Smith, J.L., et al., 2014. Deficits in behavioural inhibition in substance abuse and addiction: a meta-analysis. Drug Alcohol Depend. 145, 1–33.
Smith, R.F., 2003. Animal models of periadolescent substance abuse. Neurotoxicol. Teratol. 25, 291–301.
Solinas, M., et al., 2009. Environmental enrichment during early stages of life reduces the behavioral, neurochemical, and molecular effects of cocaine. Neuropsychopharmacology 34, 1102–1111.
Somerville, L.H., Jones, R.M., Casey, B.J., 2010. A time of change: behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. Brain Cognit. 72, 124–133.
Somerville, L.H., Hare, T., Casey, B.J., 2011. Frontostriatal maturation predicts cognitive control failure to appetitive cues in adolescents. J. Cognit. Neurosci. 23, 2123–2134.
Sonntag, K.C., et al., 2014. Viral over-expression of D1 dopamine receptors in the prefrontal cortex increase high-risk behaviors in adults: comparison with adolescents. Psychopharmacology (Berl.) 231, 1615–1626.
Sowell, E.R., et al., 1999. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. Nat. Neurosci. 2, 859–861.
Spear, L.P., 2000. The adolescent brain and age-related behavioral manifestations. Neurosci. Biobehav. Rev. 24, 417–463.
Squeglia, L.M., Jacobus, J., Tapert, S.F., 2009. The influence of substance use on adolescent brain development. Clin. EEG Neurosci. 40, 31–38.
Stanger, C., et al., 2013. Neuroeconomics and adolescent substance abuse: individual differences in neural networks and delay discounting. J. Am. Acad. Child Adolesc. Psychiatry 52, 747–755 (e6).
Stanis, J.J., Andersen, S.L., 2014. Reducing substance use during adolescence: a translational framework for prevention. Psychopharmacology (Berl.) 231, 1437–1453.
Steele, C.J., et al., 2013. Early musical training and white-matter plasticity in the corpus callosum: evidence for a sensitive period. J. Neurosci. 33, 1282–1290.
Steinhausen, H.C., Bisgaard, C., 2014. Substance use disorders in association with attention-deficit/hyperactivity disorder, co-morbid mental disorders, and medication in a nationwide sample. Eur. Neuropsychopharmacol. 24, 232–241.
Sturman, D.A., Moghaddam, B., 2011. Reduced neuronal inhibition and coordination of adolescent prefrontal cortex during motivated behavior. J. Neurosci. 31, 1471–1478.
Sturman, D.A., Moghaddam, B., 2012. Striatum processes reward differently in adolescents versus adults. Proc. Natl. Acad. Sci. U. S. A. 109, 1719–1724.
Sturman, D.A., Mandell, D.R., Moghaddam, B., 2010. Adolescents exhibit behavioral differences from adults during instrumental learning and extinction. Behav. Neurosci. 124, 16–25.
Surbey, M.K., 1998. Parent and offspring strategies in the transition at adolescence. Hum. Nat. 9, 67–94.
Szalay, J.J., Jordan, C.J., Kantak, K.M., 2013. Neural regulation of the time course for cocaine-cue extinction consolidation in rats. Eur. J. Neurosci. 37, 269–277.
Taliaferro, L.A., Rienzo, B.A., Donovan, K.A., 2010. Relationships between youth sport participation and selected health risk behaviors from 1999 to 2007. J. Sch. Health 80, 399–410.
Tang, Y.Y., et al., 2009. Central and autonomic nervous system interaction is altered by short-term meditation. Proc. Natl. Acad. Sci. U. S. A. 106, 8865–8870.
Tang, Y.Y., et al., 2012. Improving executive function and its neurobiological mechanisms through a mindfulness-based intervention: advances within the field of developmental neuroscience. Child Dev. Perspect. 6, 361–366.
Tanner, J.M., 1962. Growth at Adolescence. With a General Consideration of the Effects of Hereditary and Environmental Factors upon Growth and Maturation from Birth to Maturity. Blackwell Scientific Oxford (Vol.).
Tarazi, F.I., Tomasini, E.C., Baldessarini, R.J., 1998. Postnatal development of dopamine D4-like receptors in rat forebrain regions: comparison with D2-like receptors. Brain Res. Dev. Brain Res. 110, 227–233.
Taylor, S.B., et al., 2014. Chronic stress may facilitate the recruitment of habit- and addiction-related neurocircuitries through neuronal restructuring of the striatum. Neuroscience 280, 231–242.
Teicher, M.H., Andersen, S.L., Hostetter Jr., J.C., 1995. Evidence for dopamine receptor pruning between adolescence and adulthood in striatum but not nucleus accumbens. Brain Res. Dev. Brain Res. 89, 167–172.
Teicher, M.H., Dumont, N.L., Andersen, S.L., 1998. The developing prefrontal cortex: is there a transient interneuron that stimulates catecholamine terminals? Synapse 29, 89–91.
Teicher, M.H., Tomoda, A., Andersen, S.L., 2006. Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? Ann. N. Y. Acad. Sci. 1071, 313–323.
Tekin, S., Cummings, J.L., 2002. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. J. Psychosom. Res. 53, 647–654.
Thanos, P.K., et al., 2007. Effects of chronic oral methylphenidate on cocaine self-administration and striatal dopamine D2 receptors in rodents. Pharmacol. Biochem. Behav. 87, 426–433.
Thompson, A.B., et al., 2015. Methamphetamine blocks exercise effects on Bdnf and Drd2 gene expression in frontal cortex and striatum. Neuropharmacology 99, 658–664.
Tseng, K.Y., O'Donnell, P., 2007. Dopamine modulation of prefrontal cortical interneurons changes during adolescence. Cereb. Cortex 17, 1235–1240.
USAA, 2011. USAA Training Systems: Critical Periods for Optimal Development.
Uhl, G.R., 2004. Molecular genetics of substance abuse vulnerability: remarkable recent convergence of genome scan results. Ann. N. Y. Acad. Sci. 1025, 1–13.
van der Marel, K., et al., 2014. Long-term oral methylphenidate treatment in adolescent and adult rats: differential effects on brain morphology and function. Neuropsychopharmacology 39, 263–273.
Vanderschuren, L.J., Di Ciano, P., Everitt, B.J., 2005. Involvement of the dorsal striatum in cue-controlled cocaine seeking. J. Neurosci. 25, 8665–8670.
Vastola, B.J., et al., 2002. Nicotine-induced conditioned place preference in adolescent and adult rats. Physiol. Behav. 77, 107–114.
Verdejo-Garcia, A., Lawrence, A.J., Clark, L., 2008. Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. Neurosci. Biobehav. Rev. 32, 777–810.
Volkow, N.D., Fowler, J.S., 2000. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. Cereb. Cortex 10, 318–325.
Volkow, N.D., Swanson, J.M., 2008. Does childhood treatment of ADHD with stimulant medication affect substance abuse in adulthood? Am. J. Psychiatry 165, 553–555.
Volkow, N.D., et al., 1999. Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels. Am. J. Psychiatry 156, 1440–1443.
Volkow, N.D., et al., 2006. Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. J. Neurosci. 26, 6583–6588.
Vonmoos, M., et al., 2013. Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving and early age at onset. Br. J. Psychiatry 203, 35–43.
Voon, V., et al., 2015. Disorders of compulsivity: a common bias towards learning habits. Mol. Psychiatry 20, 345–352.

Wagner, F.A., Anthony, J.C., 2002. From first drug use to drug dependence; developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. Neuropsychopharmacology 26, 479–488.
Weinstock, J., Barry, D., Petry, N.M., 2008. Exercise-related activities are associated with positive outcome in contingency management treatment for substance use disorders. Addict. Behav. 33, 1072–1075.
Werch, C., et al., 2003. A sport-based intervention for preventing alcohol use and promoting physical activity among adolescents. J. Sch. Health 73, 380–388.
Werch, C.C., et al., 2005. A multihealth behavior intervention integrating physical activity and substance use prevention for adolescents. Prev. Sci. 6, 213–226.
Whelan, R., et al., 2012. Adolescent impulsivity phenotypes characterized by distinct brain networks. Nat. Neurosci. 15, 920–925.
White, L.S., 2012. Reducing stress in school-age girls through mindful yoga. J. Pediatr. Health Care 26, 45–56.
Wilens, T.E., et al., 2003. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics 111, 179–185.
Wills, T.A., Vaccaro, D., McNamara, G., 1992. The role of life events, family support, and competence in adolescent substance use: a test of vulnerability and protective factors. Am. J. Community Psychol. 20, 349–374.
Wills, T.A., et al., 2001. Coping dimensions, life stress, and adolescent substance use: a latent growth analysis. J. Abnorm. Psychol. 110, 309–323.
Wills, T.A., 1986. Stress and coping in early adolescence: relationships to substance use in urban school samples. Health Psychol. 5, 503–529.
Willuhn, I., et al., 2010. Dopamine signaling in the nucleus accumbens of animals self-administering drugs of abuse. Curr. Top. Behav. Neurosci. 3, 29–71.
Wilson, D.M., et al., 1994. Timing and rate of sexual maturation and the onset of cigarette and alcohol use among teenage girls. Arch. Pediatr. Adolesc. Med. 148, 789–795.
Witkiewitz, K., Marlatt, G.A., Walker, D., 2005. Mindfulness-based relapse prevention for alcohol and substance use disorders. journal of cognitive psychotherapy. Int. Q. 19, 212–228.
Wong, W.C., Marinelli, M., 2016. Adolescent-onset of cocaine use is associated with heightened stress-induced reinstatement of cocaine seeking. Addict. Biol. 21, 634–645.
Wong, W.C., et al., 2013. Adolescents are more vulnerable to cocaine addiction: behavioral and electrophysiological evidence. J. Neurosci. 33, 4913–4922.
Yurgelun-Todd, D.A., Killgore, W.D., 2006. Fear-related activity in the prefrontal cortex increases with age during adolescence: a preliminary fMRI study. Neurosci. Lett. 406, 194–199.
Zakharova, E., et al., 2009a. Social and physical environment alter cocaine conditioned place preference and dopaminergic markers in adolescent male rats. Neuroscience 163, 890–897.
Zakharova, E., Wade, D., Izenwasser, S., 2009b. Sensitivity to cocaine conditioned reward depends on sex and age. Pharmacol. Biochem. Behav. 92, 131–134.
Zehr, J.L., et al., 2006. Dendritic pruning of the medial amygdala during pubertal development of the male Syrian hamster. J. Neurobiol. 66, 578–590.
Zgierska, A., et al., 2009. Mindfulness meditation for substance use disorders: a systematic review. Subst. Abus. 30, 266–294.
Zlebnik, N.E., Carroll, M.E., 2015. Prevention of the incubation of cocaine seeking by aerobic exercise in female rats. Psychopharmacology (Berl.) 232, 3507–3513.
Zlebnik, N.E., Anker, J.J., Carroll, M.E., 2012. Exercise to reduce the escalation of cocaine self-administration in adolescent and adult rats. Psychopharmacology (Berl.) 224, 387–400.
Zlebnik, N.E., Saykao, A.T., Carroll, M.E., 2014. Effects of combined exercise and progesterone treatments on cocaine seeking in male and female rats. Psychopharmacology (Berl.) 231, 3787–3798.