



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



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ARTICLE INFO

Article history:

Received 28 September 2016

Accepted 10 October 2016

Available online 29 October 2016

Keywords:

Abuse

Adolescence

Addiction

Substance dependence

Sensitive periods

Vulnerability

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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<http://dx.doi.org/10.1016/j.dcn.2016.10.004>

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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,

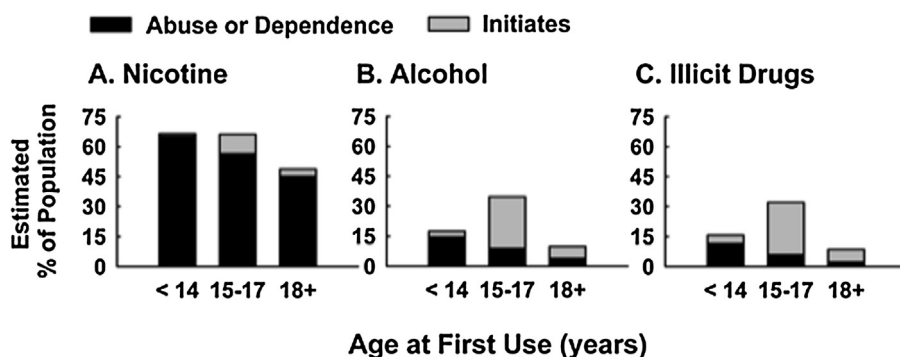


Fig. 1. Early initiation of substance use increases the risk of substance abuse or dependence. Substance abuse or dependence among persons aged 18 or older (black bars) is plotted by age at first substance use for A) nicotine, B) alcohol, and C) illicit drugs (marijuana, cocaine/crack, heroin, hallucinogens,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

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