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Reducing substance use during adolescence: a translational framework for prevention

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Abstract

Rationale—Most substance use is initiated during adolescence when substantial development of relevant brain circuitry is still rapidly maturing. Developmental differences in reward processing, behavioral flexibility, and self-regulation lead to changes in resilience or vulnerability to drugs of abuse depending on exposure to risk factors. Intervention and prevention approaches to reducing addiction in teens may be able to capitalize on malleable brain systems in a predictable manner.

Objective—To review what is known about how factors that increase vulnerability to addiction, including developmental stage, exposure to early life adversity (ranging from abuse, neglect, and bullying), drug exposure, and genetic predisposition, impact the development of relevant systems.

Results and Conclusions—Appropriate, early intervention may restore the normal course of an abnormal trajectory and reduce the likelihood of developing a substance use disorder (SUD) later in life. A considerable amount is known about the functional neuroanatomy and/or pharmacology of risky behaviors based on clinical and preclinical studies, but relatively little has been directly translated to reduce their impact on addiction in high-risk children or teenagers. An opportunity exists to effectively intervene before adolescence when substance use is likely to emerge.

Keywords

Development; substance use disorder; adolescence; delay-discounting; risk; prevention; self-regulation; behavioral flexibility; prefrontal cortex

Introduction

Adolescence is a period of life when drug use, whether for therapeutic or recreational purposes, is initiated. This period of significant structural and functional development is also when individuals are most likely to develop a substance use disorder (SUD; Wagner and Anthony 2002). The Substance Abuse and Mental Health Data Archive national sample is based on data collected from all 50 states plus the District of Columbia and includes n=70,109 respondents between five age ranges, including 12 to 17 year-olds. Based on the 2011 survey, reported alcohol use within the last 30 days rises from 1.4% of 12 year-olds, to 7.5% by 14 years, to 29.2% by 17 years of age. Marijuana use shows a similarly striking trend for use within the last 30 days: use was reported by 2.2% of teens 13 years of age and rises to 17.2% by 17 year of age. With new legislation that legalizes marijuana use for defined populations, the ensuing increased access will certainly lead to a rise in these trends.

The seriousness of teen SUD is best exemplified, however, by the fact that 64% of adult patients entering treatment for addiction started abusing drugs at age 20 or younger (Substance Abuse and Mental Health Services Administration, SAMHSA 2002). Moreover, the initiation of any drug use before age 14 leads to an approximately four-fold greater likelihood to abuse or become dependent later in life (SAMHSA 2006). Population statistics further show that specific drug class influences when teens begin to use: 50% of users started using inhalants at the age of 15 years, hallucinogens and stimulants at 17 years, and opiates at 18 years (Andersen and Teicher 2009). Consideration of the underlying mechanism of action of drug classes and their pre-pubertal development provides a window of opportunity to intervene by identifying sensitive periods of relative *invulnerability*. Sensitive periods are maturational stages when drugs have yet to attain any addictive effects – often during childhood and before adolescence (Andersen 2003). Refinement of optimal windows for intervention and identification of novel targets could be based on transient expression of neurotransmitters that occurs between early development and adolescence (Brenhouse and Andersen 2011a). The timing of this window of opportunity interacts with puberty (Waylen and Wolke 2004; Sinclair et al. this issue; Schramm-Sapota et al. this issue). An earlier than usual age of puberty onset can influence the onset of SUD to an earlier age than typical (Westling et al. 2008). Strengthening the self-regulatory and reward systems during this window may be the optimal time before drugs gain their addictive potential (Figure 1). Knowledge about the neurobiology of predisposing risk factors and sensitive periods could be used to identify those vulnerable to develop an SUD and intervene early to prevent addiction.

To this end, a number of approaches are used to prevent and intervene in teen SUD (Figure 2). This review will briefly discuss clinical approaches and then bridge the gap between discrepancies about knowledge of addiction, its risk factors, and how preclinical and clinical/human studies in immature systems may be used to better inform prevention models. A major emphasis will be placed on the neurobiological underpinnings that lead to adolescent SUD when the transition between low-to-high risk occurs.

Frameworks for prevention: universal, indicated, and selective

The initiation of substance abuse could be reduced for 1.5 million youth by simply implementing effective prevention programs (Miller and Hendrie 2008). Generally, the goal of these programs is to deter use or delay the age of initiation. Developmentally based prevention programs target specific audiences at various levels: the entire population (*universal*), those at moderate risk for substance use (*selective*), and individuals at high risk with identified vulnerabilities or currently use substances (*indicated*). Providing services to these three groups is advocated to prevent behavioral problems and substance use (Dishion et al. 2002; et al. 2007). However, the enactment of these strategies comes with a cost of time, money, and valuable resources. According to SAMHSA (2008), selective and indicated programs are twice as expensive to implement versus a universal approach. The targeted effort in selective and indicated strategy leads to greater success and ultimately more cost-effective outcomes than the universal strategy. In contrast, universal approaches cast a wide net to reduce drug use in the whole population and estimates of the effectiveness of a school-based program show an \$18 return for every \$1 invested due to reduced SUD treatment and improved quality of life (Miller and Hendrie 2008).

Universal prevention approach

Universal prevention programs are principally carried out in school systems. These programs teach children social and emotional skills to reduce peer pressure and avoid the use of alcohol, tobacco, and marijuana. For instance, the “Just say no” initiative is an

example of a universal program. More effective and validated programs that are used include the Communities Mobilizing for Change on Alcohol, the Botvin Life Skills Training Program, and the Guiding Good Choices program. The Communities Mobilizing for Change on Alcohol program provides materials for effective community-mobilizing practices that are aimed at changing policies and practices of major community institutions to reduce drug access by teenagers. The Life Skills Training Program promotes behaviors that lead to resistance of SUD: increased self-esteem, reduced anxiety, and greater resistance to peer pressure (Botvin and Kantor 2000). This commonly used training program has a cost-benefit ratio of 21:1, meaning for every dollar invested, \$21 are returned in benefits to quality of life and medical costs. The third evidence-based approach is Guiding Good Choices, a multimedia substance abuse prevention program that gives parents of children ages 9–14 the knowledge and skills needed to guide their children through early adolescence. These youth development programs build positive competence and self-esteem across social, emotional, and cognitive domains (Seidman and Pedersen 2003). Such competence is linked to reductions in drug use, anxiety, and behavioral issues often found in conduct disorder (Catalano et al. 2002; Masten et al. 2005; Masten and Obradovic 2006). While various resources are necessary from early childhood throughout the teen years, parental involvement and mentor support are critical for effective intervention (discussed below). If universal programs were implemented, it is estimated that 8–12% fewer youth would engage in drinking, using marijuana, or smoking regularly (Miller and Hendrie 2008).

Selective/Indicated approaches

Selective and indicated approaches are more targeted to at-risk individuals due to a variety of circumstances. In selective prevention, vulnerable groups are identified based on factors associated with SUD. Risk factors include: drug exposure (prenatal, postnatal, or social modeling of drug use), stressful or negative life events (early life adversity that includes, but not limited to childhood maltreatment, abuse, and neglect, loss of a caregiver, exposure to a natural disaster), negative influence of peers (social defeat, bullying), and behavioral disorders (such as ADHD). An indicated prevention strategy focuses on children who already show symptoms of behavioral dysfunction and/or are more vulnerable to SUD due to potential genetic vulnerability. Training of local youth-serving professionals and volunteers to identify drug abuse in youth with the Screening, Brief Intervention, Referral and Treatment (SBIRT) model is recommended by our Department of Public Health Bureau of Substance Abuse Services in Massachusetts. Other screening approaches include the Substance Abuse Subtle Screening Inventory (SASSI) and the CRAFFT questionnaire, an acronym derived from six different questions assessing drug or alcohol use. Finally, law enforcement professionals should be trained to identify at-risk youth and to refer to appropriate social services in a preemptive, non-punitive manner.

On a neurobiological level, teens may also be well served by genetic screening for “risk” genes. The identification of genes related to drug metabolism, receptor expression, and reward-related behaviors may assist in determining vulnerability risk (e.g., CYP26 for nicotine metabolism; see Cicciooppo this issue) or treatment responsiveness (e.g., OPRM1 for naltrexone; Ducci and Goldman 2012; reviewed by Hall et al. 2013). However, whether treatment in the absence of illness (i.e., SUD typically does not appear until adolescence) is ethically reasonable or just is open for debate. On one hand, selected/indicated interventions that target high-risk youth would be the most cost-effective and most successful at reducing SUD. Alternatively, the initial up-front cost of genetic screening to identify those who would benefit most is expensive and opens Pandora’s box about ethical issues of genetic screening.

Based on human twin studies, the addictive potential of drugs correlates with heritability. The more addictive drugs are the most heritable: cocaine's heritability index is 0.72, whereas hallucinogens have an index of 0.39 (Goldman et al. 2005; Ducci and Goldman 2012). Genotyping could be a valuable predictor to guide prevention efforts, although the field is young. Translational research can significantly impact teen SUD by modeling negative events in animals or using genetic profiling to unveil the neural mechanisms behind the etiology of SUD. As cause can often inform cure, we will briefly discuss the prevention/intervention paradigms that are effective, followed by a discussion of appropriate animal models in which to test therapeutic approaches.

Guidelines for prevention strategies

Four key guidelines are suggested when devising prevention strategies: 1) age-related patterns of competence and disorder; 2) developmental-appropriate tasks; 3) multiple contexts to increase generalization; and 4) interactions among biological, psychological, and social factors. The following sections will integrate the three types of prevention approaches within the above-mentioned guidelines. These approaches will be further informed by investigations on the developmental readiness of the underlying neurobiology in both humans and animals with a general schematic of the most relevant systems shown in Figure 3. Unique to human prevention efforts that will not be covered in this review is the need to be culturally sensitive in the approach (Resnicow et al. 2000; Hecht et al. 2003).

1 and 2) Age-related patterns of competence and disorder and developmental appropriateness

The first and second tenets of age-related patterns of competence suggest that programs cannot be uniform across age and need to be developmentally appropriate. All universal prevention programs emphasize the importance of self-regulation as one of the most important behaviors that can prevent substance use. While broad in concept, self-regulation includes attentional control, motivation, behavioral flexibility and inhibition, and sound decision-making and executive function (Baumeister et al. 2006).

Humans—Behavioral and magnetic resonance imaging (MRI) studies show that the underlying neural substrates of self-regulatory processes emerge across the teen years and continue to mature throughout the second decade of life (reviewed by Paus 2005). Sound decision-making and impulse control improve throughout the teen years, but their immaturity constitutes risk for SUD. Similarly, cognitive processes mature in a linear manner that gradually improves good choices, while reward-related processes show the classic inverted U shape that typifies the peak of high-risk behavior during adolescence (Casey and Jones 2010). Thus, any prevention program that facilitates the maturation of skills that strengthen risk-modulating behaviors (self-regulation and cognition) during adolescence or reduces impulsivity, sensitivity to social influences, and/or reward is likely to be effective.

Age-dependent changes in self-regulation and cognition are inversely related to impulsive behavior. Impulsive behavior is greatest in younger children and gradually decreases in a mostly linear manner into adulthood (Luna et al. 2004). Using an anti-saccade task of response inhibition, the ability of children to effectively inhibit their inclination to look at the non-target reaches adult-like levels at 14 years of age. Similar findings of linear development have been shown with a go/no-go task (Somerville et al. 2011). Part of this improved regulation serves to dampen impulsive behavior as children mature.

Other forms of impulsivity, such as delayed discounting and impulse control, are predictive of initiating substance use and developing addiction (Stanger et al. 2013a). In a delayed

discounting task, a smaller reward is selected sooner more often than a larger reward is selected later. Meta analysis shows that delayed discounting is evident in individuals with clinical-level addiction (a strong effect size: Cohen's $d=0.61$); the relationship is slightly weaker in non-clinical studies ($d=0.45$; MacKillop et al. 2011). Delayed discounting is elevated during childhood and declines markedly with age beginning at ~14 years of age (Miller et al. 1978; Scheres et al. 2006). The relevance of delayed discounting to SUD at a neurobiological level is complex and is covered more in-depth by Stanger and colleagues (2013b). Briefly, patterns of brain activation in adolescent substance abusers show reduced activity in executive structures (e.g., dorsolateral prefrontal cortex, dorsomedial PFC, inferior parietal cortex, cingulate cortex, and precuneus) on a delayed discounting task, while greater activity is observed in the amygdala, hippocampus, insula, and ventromedial prefrontal cortex as devaluation increased (Stanger et al. 2013b). The lesser inhibitory/executive control in the presence of strong reward associations and their memories may drive greater discounting in teen users more than any other age. Consistent with these teen patterns of brain activity, continuous transcranial magnetic stimulation of the dorsolateral PFC impairs delay discounting in adults (Cho et al. 2010).

For the impulse control task, participants are required to stop an already initiated motor response for a successful inhibition response (referred to as stop signal reaction time). In the largest single imaging study to date, Whelan and colleagues (2012) identified distinct brain networks activated during successful and failed attempts of impulse control in early adolescence (~14 years of age). During failed stop attempts, hypoactivity of the orbital frontal cortex was associated with substance use, while hypoactivity in the anterior cingulate region and basal ganglia network was associated with ADHD symptoms. Interestingly, genetic variation in the norepinephrine transporter gene was related to increased activity in the right inferior frontal gyrus and anterior cingulate region during stop successes. These findings implicate disparate pathways for the similar behavioral outcome of impulsivity that is found in several disorders. Thus, prevention measures should focus on gaining overall cognitive control, independent of specific disorders like SUD and ADHD that emerge during adolescence.

Of equal importance to drug use prevention is anticipating the consequences of one's actions and one's mistakes. Adaptive and flexible behavioral control after rewarding or punishing feedback that may be a component of insight learning (O'Doherty et al. 2003), is needed to re-evaluate the cost of a rewarding stimulus like drugs that leads to their valuation. Such learning occurs across brain networks, although the orbital frontal cortex partly determines changes in reward valence, contingency, and behavioral outcome. This region is one of the last regions in the brain to mature structurally (Gogtay et al. 2004). This protracted development, relative to the inverted-U shape of elevated reward system activity during adolescence, may drive immediacy in responding based on reward receipt rather than the final outcome (Galvan et al. 2006). The linear decline in orbital frontal cortex activation between childhood to adulthood (Galvan et al. 2006) may allow some experiential learning. However, teens have a propensity to be "sure" of their decisions no matter how incorrect they truly are (Bjork et al. 2007). Specifically, Bjork et al. found reduced activation of the posterior medial PFC in adolescents under conditions of uncertainty relative to adults, but no age difference when the outcome was predictable. How "sure" teens are of their decisions can also be targeted with an intervention by potentially focusing on future consequences and whether it will threaten their sense of self. The Above the Influence campaign takes this approach in its anti-drug advertisements and has been effective in reducing teen drug use (Slater et al. 2011).

Age-specific differences in brain responses and the effects of drugs can guide or fine-tune interventions (Geier et al. 2010). These age differences are apparent either in processing

speed or the amount of brain activity required for responding. For example, activation patterns within the superior precentral sulcus show that teens require increased preparation time to respond to a stimulus (e.g., an anti-saccade task) compared to adults (Curtis and Connolly 2008). The response latency is greater in teens with SUD (Chung et al. 2011). These data suggest that relative to adults, typical teens require more – and substance-using teens require *even more* – time to recognize the right answer and learn from it before reducing impulsive mistakes in the future. Repeated marijuana use in adolescents activates more brain regions to process information than controls, reducing the ability to multi-task (Chung et al. 2011; Gruber et al. 2012). Another example is the finding that greater “losses,” rather than small losses, lead to adult-like responses in adolescents; in other words, varying incentive-type or magnitude may improve the shaping of appropriate responding in teens (Geier et al. 2010).

Access to peers is one of the most significant risk factors for SUD and other high-risk behaviors that is also the most readily addressable. The presence of peers in a social situation further increases risky behaviors, such as driving (Chein et al. 2011) and drug use (van Ryzin et al. 2012). Curiously, peers have less of an influence on drug use during high school age itself, but have significant influence prior to and after high school ages for alcohol, tobacco, and marijuana (van Ryzin et al. 2012). Peers increase fMRI activity in the adolescent ventral striatum during a risky decision task compared with their responses when alone (Chein et al. 2011). Ventral striatum activity in response to a stoplight task (Chein et al. 2011) or an affective facial display task inversely correlates with peer influences (Pfeifer et al. 2011). Changes in ventral striatal activity may signal the emergence of greater emotional regulation and positive affect that continues to change into adulthood (Forbes et al. 2009). In addition, ventral striatal activity is negatively coupled with amygdala activity (Pfeifer et al. 2011). Peers become less influential as the task itself is rewarding. However, as amygdala activity is elevated (or ventral striatal activity is reduced), peers may have a significant impact on vulnerability to drug use. Indeed, amygdala activity is important for drug cue processing (Wilson et al. 2004). The influence of the amygdala/ventral striatum is age-dependent, and Hare et al. (2008) demonstrated peak amygdala responsiveness to affective stimuli during mid-adolescence; the peer studies were conducted in early adolescence and adulthood. Whether the amygdala is relatively more responsive to peer influences during specific stages of adolescence is not known. Amygdala responsiveness to emotional cues is already higher in teens compared with children and adults (Guyer et al. 2008; Hare et al. 2008; reviewed by Blakemore and Robbins 2012), which could significantly affect vulnerability to SUD. Risk for poor outcomes could be reduced if adolescents were provided with an opportunity to learn social control. The Life Skills Training program provides adolescents with knowledge and skills needed to resist social influences to use cigarettes, alcohol, and other drugs by increasing general personal and social competence (Luna-Adame et al. 2013).

From a prevention viewpoint, improved self-regulation can reduce the impact of risk behaviors (e.g., impulsivity and aggression) that are associated with SUDs well before children reach adolescence and are likely to start using drugs (Thompson et al. 2013). The Good Behavior Game (Barrish et al. 1969), for example, uses a classroom-based intervention approach to teach young students to interact as a member of the classroom community. Through positive reinforcement learning, these high-risk children show reduced rates of drug-and alcohol-use that may be partially mediated by internally guided rewards that have been taught. In other words, this behavioral approach offers an SUD “vaccine” through improved self-regulation and reduced impulsivity and aggression (Embry 2002).

While self-regulatory processes can be strengthened during adolescence to reduce drug use, modulation of the highly active motivational reward systems (Casey et al. 2008; Steinberg et

al. 2008) that are highly relevant for SUDs is also needed during adolescence. Functional MRI studies show greater blood flow in the nucleus accumbens (NAc) in response to a received reward in teens relative to younger and older subjects (Galvan et al. 2006; Geier et al. 2010; van Leijenhorst et al. 2010). A number of laboratory studies indicate that teens gamble with risky decisions, with the greatest proportion of risky choices made at or around age 14 (Burnett et al. 2010). The elevated activity in the NAc during adolescence positively reinforces actions relevant to SUD. Dampening the reward system, however, will have its own adverse consequences, anhedonia notwithstanding (Nestler and Carlezon 2006). Rather, prevention efforts targeting reward should include substitution-type approaches.

The reward system can be positively activated through endurance sports like running or brief aerobic exercise. Participation in school sports is associated with reduced 30-day use in tobacco, marijuana, and other illicit drugs, but not alcohol (Terry-McElrath et al. 2011). The results show that exercise delays initiation of use, rather than producing a highly significant reduction in use. As a delay in initiation is associated with reduced lifetime prevalence of addiction (SAMHSA 2006), these results are noteworthy. Exercise can also reduce craving, one of the most potent factors in relapse (Kalivas et al. 1998). In a study in adult smokers, fMRI activity in the NAc in response to smoking cues was reduced in abstinence-induced craving who were allowed 10 minutes of exercise prior to imaging (van Rensburg et al. 2012).

Animals—Substance abuse research has extensively targeted understanding reward circuitry and modifications in motivational processes (Chambers et al. 2003). The underlying neuroadaptations that occur within reward circuits during adolescent drug use are intriguing because the brain is already in a state of developmental flux (see Brenhouse and Andersen 2011a, for review). While human studies highlight brain regions involved in SUD during adolescence because most utilize functional magnetic resonance imaging (fMRI), which is an indirect measure of blood flow, they are limited in what they can tell us about the underlying neurochemistry that could facilitate pharmacological intervention. Animal studies fill this gap, although the time is approaching where practitioners might use this information to find ways to reduce SUD rather than describing its nature and risk factors.

In general, the biggest influence on teen SUD may be the inverted U peak of the reward system that occurs during adolescence. The NAc, ventral tegmental area (VTA), and PFC are principal regions of the brain reward circuitry, and the reinforcing effects of most drugs of abuse are, directly or indirectly, due to the modulatory effects of dopamine neurotransmission (Kalivas and Volkow 2005). The glutamatergic pyramidal cells in the ventral mPFC (prelimbic and infralimbic regions) predominately receive dopaminergic efferents from the VTA (Lindvall et al. 1978).

The developmental increase in dopaminergic (and serotonergic) inputs to the PFC (Kalsbeek et al. 1988; Leslie et al. 1991; Rosenberg and Lewis 1994) plays a prominent role in regulating motivational systems that are relevant to SUD. More specifically, D1 dopamine receptors on glutamate neurons influence sensitivity to drug cues, their extinction, and their reinstatement – all factors that influence drug-seeking and relapse by elevating motivational salience (Kalivas 2005; Rebec and Sun 2005; Badanich et al. 2006; Ventura et al. 2007; Andersen et al. 2008; Brenhouse et al. 2008). Dopamine receptors are overproduced in the medial PFC during adolescence (Andersen et al. 2000), with D1 receptor increases localized to glutamatergic projection neurons – including those projecting to the NAc (Brenhouse et al. 2008). The peak expression of this specific receptor population during this stage is likely to motivate adolescents to seek hedonic-related substances more than any other age group and also plays a role in novelty preferences and impulsive choice (Sonntag et al., this issue).

These preclinical data suggest that altering motivational salience in a vulnerable population with a highly targeted intervention may be a crucial step in being able to prevent SUD.

Impulsivity is another important risk factor that contributes to elevated risk for SUD. Impulsivity itself may be sub-divided into three main areas (Dalley et al. 2008; Fineberg et al. 2010): deficiencies in delaying rewards, response inhibition (i.e., stop signal reaction test), and decision-making (i.e., 5-choice serial reaction time test; Besson et al. 2010). Glutamatergic input from the PFC into the NAc is a point of convergence for impulsivity (Winstanley et al. 2004a; Fineberg et al. 2010), although each form of impulsivity seems to have one principal receptor or neurotransmitter associated with the behavior. What little is known about mechanistic changes underlying impulsivity specifically during adolescence will be presented, although a paucity of data exists due to the long training periods needed in tasks assessing operant behavior. Thus, most of what is presented is based on studies in adult animals.

Behavioral evidence in immature animals shows that delayed discounting is high during adolescence (Laviola et al. 2003). Delayed discounting is modulated by both dopamine and serotonin (5-HT). Elevated activity at the D1 receptor in the plPFC increases discounting in adult rats (reviewed by Dalley et al. 2008); D1 receptors are elevated in the plPFC during adolescence (Brenhouse et al. 2008). Excitotoxic lesions of the basolateral amygdala (BLA) increase discounting, while lesions of the OFC have the opposite effect (Winstanley et al. 2004b). If BLA activity is reduced with a GABA agonist (e.g., baclofen or muscimol) infusion, risk aversion increases while preferences for large rewards with high cost increase (Ghods-Sharif et al. 2009). The BLA encodes and maintains the representation of the reward. Developmentally, high levels of discounting in juveniles are likely to be more attributable to reduced executive control. In rats, projections from the BLA to the PFC (BLA→PFC) emerge at an earlier time point than top-down regulation brought by PFC→BLA projections, which emerge a week later (Bouwmeester et al. 2002a,b). The BLA→PFC continues to mature through adolescence (Cunningham et al. 2002) limiting the capacity of the juvenile to effectively recall a large reward with a delay. However, the PFC→BLA system prunes after adolescence (Cressman et al. 2010), as does the number of cells in both regions (Markham et al. 2007; Rubinow et al. 2009, respectively). The PFC→NAc system is also maturing until adulthood; however, sufficiently salient rewards can activate this pathway (Brenhouse et al. 2008). The emotionally activating aspects of peers elevate the rewarding nature of cocaine and nicotine in adolescent rats (Thiel et al. 2008; 2009) perhaps by this network. Responses to peers and other social stimuli are also likely to be modified by the hippocampus and its interactions with the amygdala, PFC, and the NAc (O'Donnell and Grace 1995). Both animal and human imaging studies show the involvement of the hippocampus in stress, emotional regulation, and contextual processing (O'Mara et al. 2009; Fanselow and Dong 2010). Together, modulating discounting behavior in juveniles or adolescents should capitalize on increasing the size of reward to reduce impulsivity. Pharmacological interventions that may achieve this result are discussed below under #4.

In addition to DA, serotonin receptors (5-HTRs) are also involved in impulsivity. 5-HTRs have both inhibitory and excitatory influences and play a role in controlling impulsive choice (Zhang 2003; Beique et al. 2004; Kirby et al. 2011). Both the 5-HT1A and the 5-HT2C receptors are implicated in choice behavior, but with opposing actions (reviewed more completely by Cunningham and Anastasio 2013). For example, the 5-HT1A agonist 8-hydroxy-2-dipropylaminotetralin increases delay discounting (Winstanley et al. 2005; Stanis et al. 2008), whereas antagonism of the 5-HT2C is needed to increase impulsivity (Winstanley et al. 2004c). 5-HTRs mature earlier than DA receptors (Lambe et al. 2000) and have distinct subtypes, localization (pyramidal neurons versus interneurons), and differ in

expression levels across development (reviewed by Andersen and Navalta 2011). Studies on changes in adolescent rodent 5-HTRs have yet to be conducted; however, a recent study by Lambe and colleagues (2011) examined mRNA expression of 5-HTRs in human postmortem brains from infancy to adulthood. Within the PFC, 5-HT2A shows an inverted U pattern of expression that peaks during childhood and adolescence; 5-HT2C demonstrates a more linear course than 5-HT2A, with a slight down-regulation from adolescence to adulthood. 5-HT1A shows linear development; however, pre- and post-synaptic distribution of this receptor subtype may change differentially across age. Because impulsive choice is directly related to 5-HT2A manipulations (Winstanley et al. 2004c), this receptor may provide a unique target for adolescent treatment.

Impulsive action, or impairment in the ability to inhibit a pre-potent motor response, is measured by the stop signal reaction time test (Robinson et al. 2008; Eagle et al. 2008; Fineberg et al. 2010). No developmental data are available on this task in animal models due to the extensive training; however, human data show increased speeding in responses during childhood, followed by a gradual slowing into adulthood (Bedard et al. 2002). This task is mediated by norepinephrine (α 2A receptor) within the OFC through projections to the NAc (Chamberlain et al. 2006; Chamberlain et al. 2007a,b; Bari et al. 2009). Lesions of the orbital frontal cortex slow stop signal reaction times (Eagle et al. 2008). Work by Arnsten (Arnsten, 2009; Arnsten and Pliszka 2011) suggests that α 2A receptors are co-localized on the dendrites with D1 receptors. Neurons that respond to similar stimuli can be further activated by α 2A receptor agonism, aiding in attentional control and focus; neuronal firing to dissimilar features is modulated by D1 receptor agonism and increases distractibility and impulsivity. Given that D1 receptors peak during adolescence and α 2A receptors are still maturing through adulthood (Happé et al. 2004), performance is likely to be biased towards distractibility. Together, the development of dopamine, serotonin, and norepinephrine systems during adolescence contributes to elevated impulsivity that increases risk for SUD.

Norepinephrine dysfunction is also directly linked to SUD (Weinshenker and Schroeder 2007). Specifically, noradrenergic receptors play a role in drug reward and reinstatement of drug-seeking behavior (Drouin et al. 2002; Ventura et al. 2003; Lee et al. 2004; Shepard et al. 2004; Zhang and Kosten 2005) and impulsivity (reviewed by Chamberlain and Robbins 2013; Bari and Robbins 2013). In adult animals, reinstatement can be blocked by antagonizing α 1 with prazosin (Zhang and Kosten 2005) or induced by antagonizing 2 receptors with yohimbine (Lee et al. 2004; Shepard et al. 2004). Given that SUD risk changes in an age-dependent manner, we can speculate on the importance of α 1 and α 2a receptors driving actions during adolescence. The PFC continues to receive noradrenergic input through late adolescence (measured by noradrenergic transporter binding; Moll et al. 2000; Sanders et al. 2005) and indirectly affects dopamine transmission in the NAc. Nontraditional interactions also exist between norepinephrine and dopamine, as noradrenergic fibers via the noradrenergic transporter can take up, package, and release both dopamine and norepinephrine in the PFC (Morrison et al. 1981; DeVoto et al. 2001). This is presumably one mechanism of action of atomoxetine, a drug used to treat ADHD (Bymaster et al. 2002). In stark contrast to dopamine and 5-HT receptors, the developmental expression of noradrenergic receptors has not been fully examined in rats. A linear increase occurs in α 2a receptors across development in both the PFC and amygdala, although adolescence was not assessed (Happé et al. 2004; also see review by Murrin et al. 2007). In the non-human primate, α 2a receptors increase monotonically in the cortex with age-related changes in laminar distribution (Lidow and Rakic 1992). The α 2A receptor is the prevailing noradrenergic mechanism in impulsivity and cognitive flexibility (Lapiz and Morilak 2006; Caetano et al. 2012; Kim et al. 2012; Chamberlain and Robbins 2013).

Importantly, multiple aspects of self-regulation are linked to these aforementioned underlying neurobiological processes. Self-regulation can be behaviorally characterized in animals, although more studies have focused in adults rather than in adolescents due to the timing and complexity of operant training necessary to measure behavior (e.g., Chudasama and Muir 1997; Birrell and Brown 2000; Dalley et al. 2004; Floresco 2013). For the sake of this review, we will focus on several aspects of self-regulation that have been studied in adolescent animals. First, behavioral flexibility, defined as the ability to change behavior in response to different environmental task conditions, gradually improves during the transition to adulthood (Weed et al. 2008). Second, self-regulatory skills can also be measured with decision-making tasks.

Behavioral flexibility tasks in rats have focused primarily on attentional set-shifting (i.e., Wisconsin Card Sorting Task) and reversal learning. Adolescent rats show a lack of attentional and cognitive flexibility. Rats show impairment when they have to attend to a once irrelevant dimension for a predicted reward (Newman and McGaughy 2011) and respond after inhibiting a previous response (Simon et al. 2013). However, the positive cognitive consequences of a juvenile developmental state suggest that juveniles might be suited to changing environments (i.e., reversal learning; Johnson and Wilbrecht 2011). While adolescent rats eventually learn, previous findings suggest that the amount of distractibility should be monitored and minimized, and the pressure of multi-tasking should be reduced. Promisingly, deficits could be remediated with the administration of the noradrenergic reuptake inhibitor, atomoxetine (Cain et al. 2011), suggesting a critical role for noradrenergic, or as discussed above, dopaminergic, function.

Likewise, decision-making, including working memory and impulsive choice, improves during the transition from adolescence to adulthood (Koss et al. 2011). Adolescent rats generally commit more errors and are less accurate than adults on delay-dependent tasks that are highly sensitive to changes in PFC function (such as delayed alternation or matching to sample; Koss et al. 2011). Work in adult animals has focused on glutamatergic (Wang et al. 2013) and dopaminergic function (Vijayraghavan et al. 2007; reviewed in depth by Arnsten and Pliska 2011; Floresco 2013).

Similar to exercise in humans, animal studies (e.g., rats) have shown that exercise reduces drug-reinforced behaviors in adolescents compared to adults. Chronic exercise (treadmill running for six weeks, up to one hour/day) reduces the rewarding properties of cocaine compared to sedentary rats (Thanos et al. 2010). Wheel running also reduces drug-taking behaviors in rats that were concurrently trained to self-administer cocaine during long access sessions (Zlebnik et al. 2012). Some of these exercise effects in adolescent rats may modulate the potency of cues. Adolescent rats that self-administered nicotine showed a reduction in drug-seeking during abstinence if they had the opportunity to exercise, although exercise did not have a clear effect on reinstatement (Sanchez et al. 2013).

3) Multiple contexts to increase generalization of intervention

Exposure to drug-associated cues elicits strong drug-seeking behavior even after a long period of abstinence (Shaham and Stewart 1995; Kalivas and McFarland 2003; Taylor et al. 2009). For this reason, interventions need to be long lasting and flexible. One goal of prevention research is to reduce drug-seeking behavior by strengthening extinction learning (i.e., when the drug-paired stimuli no longer result in the delivery of reward). Extinction can influence reinstatement or relapse (Kelamangalath et al. 2007).

Humans—Multiple contexts of learning prevention are more effective in reducing drug use versus merely trying to avoid drug-related cues altogether. Cue exposure therapy is one such clinical method, although the effects of this therapy as a stand-alone treatment strategy have

been relatively weak ($d=0.08$; Conklin and Tiffany 2002). Combining cue exposure therapy with cognitive-enhancing drugs holds promise for adolescents, and a number of agents are available (Sofuoglu et al. 2013). The partial NMDA agonist d-cycloserine enhances extinction and reduces reinstatement of drug conditioning and taking (reviewed by Myers and Carlezon 2012). Rather than targeting extinction processes, a recent study in both humans and rats demonstrated that altering the reconsolidation process may be an effective strategy (Xue et al. 2012). In this study, exposure to drug cues (a “reactivation”) followed by a second exposure to drug cues in the absence of drugs 10 min later, but not 6 hours later, produced enduring decreases in craving. A third methodology aimed at reducing the potency of drug-associated cues is to pre-expose the individual to reward-based cues that s/he may encounter during the course of the day (Peters and Buchel 2010). Finally, devaluing future rewards as “nothing now, but something later” also reduces impulsive choice with the potential to reduce relapse (Magen et al. 2008).

Animals—Adolescent rats are up to 75% more resistant to extinction of cocaine-conditioned associations than adults in a place conditioning procedure (Brenhouse and Andersen 2008). Although once the drug cues were extinguished, adult rats showed greater cue-based reinstatement than adolescents, while adolescents are more sensitive to stress and drug primes (Li and Frantz 2009; Anker and Carroll 2010). Orexin A antagonists block stress- and cue-induced, but not drug-primed, reinstatement of both cocaine and alcohol self-administration in adult rats (Boulter et al. 2013; Mahler et al. 2013). Their effectiveness in addictive processes in developing animals has yet to be determined.

Distinct behavioral and pharmacological strategies in the adolescent population have been proven effective, suggesting that the competition between strong memories of potent rewards and new memories can be overcome (Brenhouse et al. 2010). Extinction can be greatly facilitated in adolescent rats by explicitly pairing the drug-associated cues with the absence of the reinforcer (Brenhouse et al. 2010). If the context is more vague (e.g., unexplicit pairing of no drug and cues), adolescent rats require significantly more time than adults to extinguish (Brenhouse and Andersen 2008). The non-explicit contextual pairing might be more “real-world” where treatment needs to generalize to multiple contexts to be effective. Pharmacological manipulations with a D1 agonist SKF38393 or a noradrenergic reuptake inhibitor atomoxetine facilitate extinction in the unpaired condition. Moreover, these treatments blocked drug-primed reinstatement of cocaine conditioning.

4) Interactions among biological, psychological, and social factors

Humans—Prevention/intervention programs have to address the special needs of children and teens that are biologically vulnerable to develop an SUD. This group includes those who are exposed to adversity early in life where SUD is reported in up to 26% (Molnar et al. 2001); drug-exposed (which will not be reviewed here; but see the following papers in this issue: Leslie et al.; Izenwasser et al.; Ciccocioppo); or children with a disorder, such as ADHD or conduct disorder/oppositional defiant disorder where SUD occurs in nearly 10% of these populations (Polanczyk et al. 2007). A number of clinical studies recognize neurobiological differences between teens that initiate drug use earlier than their non-using peers (Stanger et al. 2013a), suggesting that a biological predisposition exists.

a) Exposure to early adversity—For the majority of these at-risk children, the importance of greater structure and positive stimulation as an intervention cannot be underestimated. Because environments can widely differ between children or teens in the same peer groups, selective or indicated approaches may be more appropriate and effective to address specific environmental deficits or liabilities. One of the most relevant outcomes of early life stress relevant to SUD is the recent observation of reduced and slower incentive

processing in exposed teens compared with typical controls (Mueller et al. 2012). Home visits to more-at-risk, low-income families not only prevent the likelihood of child abuse, but visitation that continues into the teen years also reduces SUD (Karoly et al. 1998). Similarly, more structured programs, such as the Strengthening Families Program, work towards increasing family support, parental monitoring, and stable friends and also mitigate effects on teen substance use. High parental monitoring reduces use by nearly 4-fold in 14–16 year-olds relative to low parental monitoring (Fallu et al. 2010). Based on Sher's model (Sher 1991), greater parental monitoring can further guide friend choice from affiliation with more deviant peers to more conventional peers with a more positive influence.

Animal: Less is known about the effects of prevention/intervention in a number of high-risk animal models during development (Andersen and Navalta 2011). One important exception is the role of early environmental enrichment in animal models of early adversity. While exposure to stress can occur at any age, exposure during development has unique and enduring effects on neurobiology depending on the age of exposure (Andersen and Teicher 2008; Teicher et al. 2006; Leussis et al. 2008; Novick et al. 2011; Kolb et al. 2012; Muhammad et al. 2012). The effects of exposure to post-weaning (e.g., Gipson et al. 2011) and adolescent stress are reviewed by Burke and Miczek (this issue) and will not be discussed here. Animal models and the human condition show that both the risk and protective factors are familial for younger children, whereas teens are more vulnerable or supportive by their peers.

One approach to model early life adversity in rats is to separate neonatal pups from their mothers before weaning (Smotherman et al. 1977; Lehmann and Feldon 2000). Early maternal separation stress (MS) has been studied with a variety of paradigms, ranging from MS between postnatal day (P) 2–9, P2–20, P9–16 and for time periods ranging from short (5–15 min; Stanton and Levine 1985) to long (180–360 min; Andersen and Teicher 2004; Plotsky et al. 2005). While differences do exist in their enduring effects, the increased drug use that has been observed may be more predictable – and preventable – based on the underlying neurobiological effects. For example, the long MS rats preferred and consumed more alcohol in adulthood than the normally reared or short MS subjects (Huot et al. 2001; Ploj et al. 2003).

Alterations in dopamine and serotonin systems are widely implicated in the neurobiological consequences of MS (see Miczek et al. 2008). For example, studies show down-regulation of striatal DAT (Meaney et al. 2002), decreased D3 binding in the striatum (Brake et al. 2004), and decreased levels of serotonin in the amygdala in both rats (Vicentic et al. 2006; Orelund et al. 2009) and non-human primates (Ichise et al. 2006). These data suggest that the striatal dopamine system is over-active, although the behavioral data show that MS blunts reward processing of stimulants and sucrose in adulthood producing anhedonia (Matthews and Robbins 2003; Stoker et al. 2012). Within this framework, the MS paradigm where pups are individually isolated (i.e., removed from the dam and littermates) increases cocaine self-administration in adulthood (Kosten et al. 2000, 2004; Moffett et al. 2006; Vazquez et al. 2006).

In the case of MS, we have recently shown a selective decline in DA D1 receptors on the pIPFC → NAc (core, specifically; Brenhouse et al. 2013). Given the predominant role of this receptor in motivated behavior, its loss may partially play a role in the reduced motivation for rewarding substances. One possibility for an intervention approach is to increase motivation by increasing pIPFC activity by social stimulation in animals with a deprivation history. Consistent with MS attenuation in the pIPFC→NAc pathway, reduced pIPFC activity by pharmacological inactivation decreased the duration of social play in adolescent rats (Van Kerkhof et al. 2013). Similar to the effectiveness of home visits to

reduce SUD in the clinical setting discussed above (e.g., exposure to early adversity), developing rats also respond positively to improved living conditions and show less drug use. Environmental enrichment beginning post-weaning in rats reduced intake of cocaine in a low unit dose of amphetamine (1 hour/day escalation procedure) in adulthood that may be more attributable to the presence of social cohorts than novel objects (Gipson et al. 2011). While these studies were conducted in normal animals, a social intervention is likely to restore some of the motivational deficits in animals with a deprivation history.

While improved living conditions for children exposed to early adversity would be ideal, pharmacological approaches may be a more realistic intervention. MS rats show more depressive-like effects that are associated with GABA cell loss in the adolescent, but not the juvenile, PFC (Leussis et al. 2012). As alcohol acts as positive allosteric modulator, MS subjects may be more likely to consume alcohol to compensate. Moreover, MS reduces social behaviors (reviewed by Bardo et al. 2013), which maybe the result of elevated N-methyl-D-aspartate receptor (NMDA) 2A (NR2A) receptors in MS rats (Wieck et al. 2013). Pharmacological intervention with a NR2A antagonist, such as PEAQX, increases social interactions (Morales et al. 2013; Morales et al. this issue). Therefore, NR2A antagonism may serve as a potential intervention to reduce the likelihood of alcohol consumption in this population.

A third novel intervention approach to reducing SUD in this population capitalizes on the link between neuroinflammatory processes, aberrant glutamatergic drive, and MS (Brenhouse and Andersen 2011b; Wieck et al. 2013). The proactive administration of an anti-inflammatory cytokine (IL-10) during the juvenile period prevents the loss of parvalbumin-positive GABAergic interneurons in adolescents that were exposed to MS. This same treatment also modulates MS-induced upregulation of NMDA receptors. Pascual et al. (2007) showed that the non-steroidal anti-inflammatory compound, indomethacin (an inhibitor of cyclooxygenase-2 activity; Shibata et al. 2003), reduced ethanol-associated effects on behavior. As MS adolescents have elevated cyclooxygenase-2 level in the pIPFC (Brenhouse and Andersen 2011b), these data suggest a potential intervention to reduce SUD. While human studies are limited, evidence that relates neuroinflammatory processes to childhood adversity and psychiatric disorders is emerging (Dennison et al. 2012).

b) Defined clinical populations that are at-risk for SUD

Human: Medication plays an important role in prevention paradigm for children that have been clearly identified as high-risk. For example, children with ADHD, especially with comorbid Conduct Disorder, were almost 3 times more likely to develop a SUD compared with the typical adolescent (Wilens et al. 2011). Onset of SUD is also earlier in these teens, which is associated with an exacerbation of severity and duration of ADHD (Wilens and Biederman 2006). Medication may significantly reduce SUD in a subset of high-risk children when given before puberty (Wilens et al. 2008; Mannuzza et al. 2008).

Animal: Early pharmacological intervention for children that have clearly identifiable clinical disorders should target relevant neurobiological risk mechanisms during a sensitive period of *invulnerability* (Andersen and Navalta 2011). Clinical observations of reduced drug use have been recapitulated in animal models (Andersen et al. 2002; Bolanos et al. 2003). The importance of these animal studies lies in their ability to dissociate psychosocial factors in the clinical domain (e.g., concerned parents or treatment) from the underlying neurobiology that can be manipulated as to reduce SUD risk. As children transition to adulthood, the use and abuse of different substances rises (Andersen and Teicher 2009). As many of the papers in this Special Edition show (Bolanos et al.; Sinclair et al.), the progressive development of neurotransmitter systems implies that they are still

programmable (Andersen 2003). Intervention during this stage may prevent problems later in life by selectively locking-in this invulnerable state.

Sensitive periods of invulnerability to SUD can be manipulated to protect at-risk children from developing an addiction (Andersen 2005). However, such an approach requires certainty in diagnosis before treatment with the sole purpose of protection (versus other, more immediate reduction in symptoms) is initiated. Pre-pubertal treatment with methylphenidate, cocaine, or amphetamines reduces preferences for cocaine-associated cues in late adolescence (Andersen et al. 2002; Mague et al. 2003). While such an intervention seems paradoxical (e.g., to administer an addictive substance to reduce addiction), the brain is still being programmed to respond to its environment. If a drug is given for a period of time and then withdrawn, a deficit state is produced that requires more drug to achieve a normal state. In normal animals, this deficit state appears as anhedonia (Bolanos et al. 2003), but in children with ADHD this could normalize function (Andersen 2005).

Drugs such as atomoxetine and guanfacine are widely prescribed in children for the treatment of ADHD disorders (Biederman et al. 2008; Sallee et al. 2009). Unfortunately, very little is known about their effects in animals. Atomoxetine (Strattera) blocks the norepinephrine transporter and reduces impulsive choice, but not impulsive action, in rats treated during adolescence and tested in adulthood (Sun et al. 2012). Atomoxetine also reduces set-shifting, but not initial discrimination learning, in adolescent normal rats (Cain et al. 2011) and Spontaneously Hypertensive rats (SHR; a model for ADHD; Harvey et al. 2013). For atomoxetine, the single juvenile study suggests 1 mg/kg reduces hyperactivity, with similar effects in non-impulsive adults (Robinson et al. 2008). Like atomoxetine, a paucity of preclinical information exists about the effectiveness of guanfacine, an α_2 agonist, to reduce impulsivity. To our knowledge, no studies exist in developing animals. Doses of 0.1–0.7 mg/kg that improved cognition in normal mice (Franowicz et al. 2002; Bari et al. 2009) found 0.3 mg/kg effective in the stop signal reaction time task. A reduction in impulsivity is similar to the effects of guanfacine in the treatment of children and adolescents with ADHD (Garnock-Jones and Keating 2009). Unlike methylphenidate exposure (e.g., Andersen et al. 2002), juvenile exposure to guanfacine does not have sustained effects on reducing SUD (e.g., preferences for cocaine-associated cues) in adulthood (Lukkes et al. 2013).

c) General prevention approaches—More promising pharmacotherapy on prevention involves vaccination against stimulant, nicotine, and opiate use (Orson et al. 2008; Kosten and Domingo 2013). Vaccines stimulate the production of antibodies that bind to the drug, preventing it from entering into the brain. While vaccination would be convenient to administer during the window of sensitivity, research is in the early stages. A number of critical questions exist: 1) are the amount of circulating antibodies sufficient for blocking substance use later in life; 2) will vaccines be more effective after initial drug use rather than prophylactically; and 3) how many or what kinds of substances should be targeted? The use of vaccines warrants concern in regard to the potential “slippery slope” of escalation intake, and for the most part, does not differ from a number of medications that are readily available to directly stop substance abuse in adults. Most of the current medications are aimed at treating withdrawal, cravings, and blocking metabolism: naltrexone, acamprosate, and disulfiram (for alcohol), replacement (for nicotine), and methadone and buprenorphine (for opiates).

Conclusion

Prevention of the initiation of substance use is ultimately the best way to reduce addiction. Efforts to reduce risk need to be multifaceted and occur across the course of development.

Neuroscience research can play a key role in informing other fields involved in addiction prevention and treatment (e.g., clinicians, social workers, preventionists, education specialists, and parents) through education about optimal windows to intervene and which neural systems to target at a given stage in development. Similarly, neuroscientists can benefit from learning more about what works in the real world and find ways for improvement. In this review, we discussed what is known clinically and preclinically about windows of invulnerability and windows of vulnerability when the developmental risk factors for addiction, including impulsivity, poor self-regulation and decision-making, peak during adolescence.

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Fig. 1. Adolescent substance abuse and its prevention through the course of developmental risk Normal developmental trajectory (solid line) for risk of cocaine dependence is depicted based on the work of O'Brien and Anthony (2005). Risk for developing a lifelong-dependence declines with age. A child's immature reward system prevents positive drug experiences, resulting in window of SUD prevention. By managing risk factors, facilitating better judgment in teens, and recognizing co-occurring disorders and mental health issues, a preventative trajectory may be achievable (dotted line).

Fig. 2. Balancing risk with protective factors

A number of social, behavioral, and environmental factors can cause the balance to tip to a teetering point towards either adolescent SUD or its prevention. Protective factors can outweigh risks, but the timing of the intervention needs to be developmentally appropriate.

Self-regulation

Fig. 3. Self-regulation: a brain-based hypothesis that encompasses multiple parts

In this model, the hippocampal-amygdala-PFC pathway is susceptible in self-regulation and emotional control. Projections from the amygdala→PFC emerge prior to PFC→amygdala projections (Bouwmeester et al. 2002a,b), which are pruned in adulthood (Cressman et al. 2010). Thus, a window exists for strengthening the connections in this glutamatergic-driven system leading to increased self-regulation (i.e., better decision-making and greater cognitive flexibility). The PFC→NAc system is also maturing until adulthood (Brenhouse et al. 2008). During this developmental time, increased cortical drive leads to SUD, whereas reduced excitatory output to the NAc can reduce SUD but may produce anhedonia.