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Desperately Driven and No Brakes:

Developmental Stress Exposure and Subsequent Risk for Substance Abuse

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Abstract

ANDERSEN, S.L. and TEICHER, M.H. Desperately driven and no brakes: Developmental stress exposure and subsequent risk for substance abuse. *NEUROSCI BIOBEHAV REV* XX(X) XXX-XXX, 2008. Adverse life events are associated with a wide range of psychopathology, including an increased risk for substance abuse. In this review, we focus on the inter-relationship between exposure to adversity and brain development, and relate this to enhanced windows of vulnerability. This review encompasses clinical and preclinical data, drawing evidence from epidemiological studies, morphometric and functional imaging studies, and molecular biology and genetics. The interaction of exposure during a sensitive period and maturational events produces a cascade that leads to the initiation of substance use at younger ages, and increases the likelihood of addiction by adolescence or early adulthood. A stress-incubation/corticolimbic dysfunction model is proposed based on the interplay of stress exposure, development stage, and neuromaturational events that may explain the seeking of specific classes of drugs later in life. Three main factors contribute to this age-based progression of increased drug use: 1) a sensitized stress response system; 2) sensitive periods of vulnerability; and 3) maturational processes during adolescence. Together, these factors may explain why exposure to early adversity increases risk to abuse substances during adolescence.

Keywords

abuse; adolescence; alcohol; cocaine; sensitive period; stimulant; stress

Introduction

Childhood adversity, stemming from abuse, parental loss, witnessing of domestic violence or household dysfunction is a major cause of poor mental and physical health (Chapman et al., 2004; Dube et al., 2003; Felitti, 2002). One major consequence of early adversity is a markedly increased risk for substance use, abuse, and dependence (Dube et al., 2003). We, and others, have proposed that childhood abuse produces a cascade of physiological and neurohumoral events that alter trajectories of brain development (e.g., (Andersen, 2003; Teicher et al., 2002)), and that the neurobiological consequences of exposure to childhood abuse parallel the effects of exposure to developmental stress in preclinical studies (Teicher et al., 2006). The

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aim of this review is to summarize some of the recently reported effects of early stress on brain development in animals and man, focusing on potential associations that may help to elucidate causal links between early adversity and subsequent abuse of alcohol, nicotine, and illicit drugs. A major emphasis of this review will be on developmental/temporal factors, recognizing that drug abuse is a “developmental disorder” in which there are windows of vulnerability when exposure to drugs of abuse are more likely to lead to abuse and dependence (Chambers et al., 2003; Wagner and Anthony, 2002). To this framework we add new evidence for the existence of sensitive periods in which discrete brain regions are maximally susceptible to the effects of stress, and emphasize the substantial lag period that may intervene between time of exposure and manifestation of adverse consequences.

Developmental Stress and Substance Abuse Epidemiology

The impact of childhood adversity is shown most clearly in the Adverse Childhood Experiences (ACE) study based on retrospective surveys of 17,337 members of the Kaiser-Permanente HMO in San Diego (Chapman et al., 2004; Dube et al., 2003; Felitti, 2002). The number of different ACEs ‘dose-dependently’ increases symptoms or disease prevalence. Population attributable risk associated with early adversity was 50% for drug abuse, 54% for current depression, 65% for alcoholism, 67% for suicide attempts, and 78% for intravenous drug use (Chapman et al., 2004; Dube et al., 2003). Other studies have explored the relationship between substance abuse and childhood adversity. The severity of exposure to childhood sexual abuse (CSA) and risk of alcohol and drug abuse was evaluated based on the division of CSA into three categories (Fergusson et al., 1996). Adjusting for psychosocial factors, non-contact CSA was not associated with a significant increase in risk of alcohol or other substance abuse/dependence. Contact CSA without intercourse increased risk for alcohol abuse/dependence, but not for abuse of other substances. However, CSA involving attempted/completed intercourse increased risk of alcohol abuse/dependence 2.7-fold and increased risk of substance abuse/dependence 6.6-fold. Kendler and colleagues (Kendler et al., 2000) also showed that severity of CSA mattered, but in this study even low levels were associated with increased risk. Briefly, they found that non-genital CSA was associated with a 2.9-fold increase in risk for drug-dependence, whereas CSA involving intercourse was associated with a 5.7-fold increase (Kendler et al., 2000).

The association between early maltreatment and alcohol or drug use manifests at an alarmingly young age. As part of a large-scale public school survey of adolescent health risk behaviors, students in grades 8, 10, and 12 (N=4790) were asked about past and current substance use and were asked (yes/no) about past physical and sexual abuse (Bensley et al., 1999). Abuse was associated with more than a 3-fold increase in the odds that alcohol/cigarette experimentation had occurred, and more than a 12-fold increase in the odds that marijuana use or regular drinking occurred by 10 years of age. For eighth graders, combined sexual and physical abuse was associated with a 2-fold greater risk of light to moderate drinking and an almost 8-fold increase in risk of heavy drinking. For 10th graders, maltreatment was associated with a 2-fold increase in risk of light to moderate drinking and a more than 3-fold increase in risk of heavy drinking. However, by 12th grade, the drinking level of non-abused adolescents was essentially equal to those who reported abuse. Exposure to each category of childhood adversity is associated with a 2- to 4-fold increase in the likelihood of illicit drug use by age 14 (Dube et al., 2003). Furthermore, CSA doubled the risk of lifetime parenteral drug use, and increased by more than 12-fold the risk that parenteral drug use would begin at an early age (Holmes, 1997). Together, these studies suggest that exposure to early stress enhances psychopathology in general, and shifts initiation of drug use to younger ages. The magnitude of the effect is dependent on the degree of exposure to different forms of maltreatment or on the severity of the primary form. As a result, a substantial percentage of abuse victims become

exposed during a development window of vulnerability when use is more likely to lead to future abuse and dependence (King and Chassin, 2007; Orlando et al., 2004).

In the remaining sections of this review, we describe a model that incorporates how the timing of stress exposure interacts with normal maturational processes to enhance vulnerability to abuse substances. We have recently proposed a stress-incubation/corticolimbic development cascade that suggests early adversity may be associated with an earlier manifestation of depressive symptoms in comparison to a normal population (Andersen et al., 2008; Teicher et al., in press). Here, we apply the same model to explain how stress exposure early in life may also predispose an individual to use and abuse substances at a younger age than typically observed in the normal population.

The Neurobiology of Substance Abuse - a Very Basic Framework

Drugs that are considered rewarding produce a number of changes that are involved in the addiction process as mediated primarily by a few key brain regions (Hyman et al., 2006). First, the hedonic, pleasurable feeling that links all drugs of abuse is associated with increased dopamine in the nucleus accumbens (Dayan and Balleine, 2002; Koob and Swerdlow, 1988; Weiss, 2005). Second, the hippocampus consolidates the process of learning about this liking, and maintains the memory of the associations of the experience (Grace et al., 2007). The hippocampus can then modulate or “gate” responses of the nucleus accumbens to reflect these prior experiences. Third, the environmental cues that are linked with the drug-taking experience are assigned a value that becomes motivationally salient through conditioning processes (Berridge, 2007). The resulting motivational salience is mediated primarily by excitatory prefrontal cortex input into the accumbens (Kalivas et al., 1998; 2005; Pickens et al., 2003; Robinson and Berridge, 1993), with the drug-cue associations formed in the amygdala (See et al., 2003). Drug dependence results from a specific series of neuroadaptations that occur following repeated use (Hyman et al., 2006). These adaptations can occur at any and all of these main levels following repeated exposure to drugs. Together, the premise of “desperately drive with no brakes” incorporates three main ideas of how early adversity can differentially modulate the brain regions that underlie these addictive processes and the circuit itself (see Figure 1).

A stress-incubation/corticolimbic development cascade hypothesis of drug abuse vulnerability

Based on the literature reviewed herein, the high rates of drug addiction following childhood maltreatment may be explained partly by the stress-incubation/corticolimbic developmental cascade hypothesis (Andersen and Teicher, 2008) as applied to drugs of abuse. This hypothesis proposes that exposure to early life stress predisposes individuals to abuse drugs at an earlier age via the three following tenets:

1. Compulsive drug use increases due to a highly reactive hypothalamic-pituitary-adrenal axis (HPA) (Hyman et al., 2006).
2. Exposure to stress is associated with sensitive periods of vulnerability (Andersen and Teicher, 2008; Andersen and Teicher, 2004) that will uniquely contribute to drug abuse vulnerability. Early life stress may be more selective for the hippocampus and enhance contextual responding to drug-related cues. Early adversity may also increase dopamine activity within the nucleus accumbens, resulting in a baseline state of anhedonia that predisposes individuals to drug-seek (Matthews and Robbins, 2003). Later life stress may be more selective for the prefrontal cortex (Leussis and Andersen, 2008), and increases vulnerability to drug-associated cues (Ernst et al., 2006; Brenhouse et al., 2008a).

3. Brain regions and circuits need to mature to a certain degree for the effects of early stress exposure to manifest.

Together, these processes increase vulnerability to use drugs and shift the age of initial use earlier than typically observed in non-abused populations. We will review evidence that supports these claims and encompasses all three factors.

1. Exposure to stress programs HPA reactivity

Exposure to stress early in life activates stress response systems, and fundamentally alters their molecular organization to modify their sensitivity and response bias (Caldji et al., 1998; Liu et al., 1997; Meaney and Szyf, 2005; Seckl, 1998; Weaver et al., 2004; Welberg and Seckl, 2001; Young, 2002). Molecular modifications identified to date include: (1) alterations in the subunit structure of the GABA-benzodiazepine supramolecular complex, resulting in the attenuated development of central benzodiazepine and high affinity GABA-A receptors in the hippocampus, amygdala and locus coeruleus (Caldji et al., 2000a; Caldji et al., 2000b; Caldji et al., 1998; Hsu et al., 2003); (2) elevations in corticotropin releasing hormone (CRH) mRNA levels in amygdala and hypothalamus and diminished CRH mRNA in hippocampus (Caldji et al., 1998; Liu et al., 1997); (3) diminished $\alpha 2$ noradrenergic receptor density in the locus coeruleus (Caldji et al., 1998); and (4) epigenetic alteration in the DNA methylation pattern of the hippocampal exon 17 glucocorticoid receptor (GR) promoter gene (Weaver et al., 2004; Weaver et al., 2006). In short, through these, or other molecular events awaiting discovery, early stress programs and primes the mammalian brain to be prone to experience enhanced stress responses, which interacts with other factors to increase drug use and dependence.

The relationship between stress and drug use—Stress has been postulated to play a significant role in the initiation and maintenance of drug abuse and has been identified as a key factor leading to relapse to drug use in humans (Kreek and Koob, 1998). In controlled experiments psychological stress was found to induce strong cravings for cocaine in addicts (Sinha et al., 1999; Sinha et al., 2000). A few studies have examined the effects of childhood abuse on stress response and HPA axis regulation. Girls (aged 7-15 years) with a history of CSA (n=13) showed significantly lower basal and net ovine CRH stimulated ACTH levels relative to controls (n=13; (De Bellis et al., 1994a)). Basal urinary and plasma cortisol levels and ovine CRH-stimulated levels, however, were similar in victims of CSA to those in controls. These results may reflect a form of HPA dysregulation with pituitary hypo-responsiveness to ovine CRH and exaggerated adrenal response to reduced levels of ACTH in children. In contrast, Heim et al., (Heim et al., 2001) reported opposite dysregulatory consequences of CSA in *adults*. Abused women without major depressive disorder exhibited greater than usual ACTH responses to ovine CRF administration, whereas abused women with major depressive disorder and depressed women without early abuse had blunted ACTH responses relative to controls. Abused women without major depressive disorder exhibited lower baseline and ACTH stimulated plasma cortisol concentrations. Similarly, men with childhood trauma histories exhibited increased ACTH and cortisol response to dexamethasone/CRF. Increased response was associated with the severity, duration, and earlier onset of the abuse (Heim et al., 2008). These findings indicate that sensitization of the anterior pituitary and counter-regulatory adaptation of the adrenal cortex occurs in abused individuals without major depressive disorder or post-traumatic stress disorder.

Animal model studies have shown that stress influences response to drugs of abuse in several ways. First repeated exposure to stressful situations increases individual reactivity to addictive drugs. A variety of stressors including repeated tail-pinch stress (Piazza et al., 1990), restraint stress (Deroche et al., 1992a), social stress (Deroche et al., 1994), and food-deprivation stress (Deroche et al., 1992a), augments the locomotor response to systemic amphetamine or morphine. Stress-induced sensitization to amphetamine and morphine depends on an intact

HPA axis, and does not occur in animals in which stress-induced corticosterone secretion is suppressed (Deroche et al., 1992a; Deroche et al., 1994; Marinelli et al., 1996). Repeated corticosterone administration alone (without exposure to stress) is sufficient to sensitize locomotor response to amphetamine, as was prenatal stress that occurred as a consequence of maternal restraint during the last week of pregnancy (Deroche et al., 1992b). Glucocorticoids themselves have direct euphoric effects in some individuals and reinforcing properties in laboratory animals, as evidenced by the development of intravenous self-administration of corticosterone, which occurs at plasma corticosterone levels comparable to those induced by stress (Piazza et al., 1993). However, there are substantial individual differences in susceptibility to corticosterone self-administration (Piazza et al., 1993).

Perhaps most importantly, exposure to a variety of stressors has been found to reinstate previously extinguished seeking of heroin (Shaham et al., 2000; Shaham and Stewart, 1995), cocaine (Ahmed and Koob, 1997; Erb et al., 1996), alcohol (Le et al., 2000; Le et al., 1998), and nicotine (Buczek et al., 1999). In some studies stress exerted an even more powerful reinstating effect than re-exposure to the drug (Shaham et al., 1996; Shaham and Stewart, 1996). Stress reinstates previously extinguished drug-induced place preferences (Wang et al., 2000). Metyrapone (which blocks stress-induced corticosterone secretion but does not modify basal corticosterone levels) attenuates stress-induced relapse of cocaine self-administration, without inducing a nonspecific disruption of motor or food-directed behaviors (Deroche et al., 1994).

In conclusion, preclinical studies have shown that stress is a prominent factor in the initiation, maintenance and reinstatement of substance use (Deroche et al., 1992a; Erb et al., 2001; Goeders, 1997; Kabbaj et al., 2001; Piazza et al., 1990; Shaham et al., 2000; Shalev et al., 2002; Shalev et al., 2001; Stewart, 2000). Enhanced or dysregulated stress responses due to childhood abuse may, at least in part, mediate the increased vulnerability of abuse survivors to drug addiction (McEwen, 2000a; Rodriguez de Fonseca and Navarro, 1998; Sinha, 2001; Stewart et al., 1997; Triffleman et al., 1995).

2. Exposure to stress is associated with sensitive periods of vulnerability that will uniquely contribute to drug abuse vulnerability

The timing of the insult may also play an under-appreciated role in substance use vulnerability. Individual neurotransmitter systems or brain regions are most vulnerable to outside influences during specific windows known as sensitive periods. Sensitive periods are associated with the maturational events of neurogenesis, differentiation, and survival (Andersen, 2003; Bottjer and Arnold, 1997; Harper et al., 2004; Heim and Nemeroff, 2001; Koehl et al., 2002; Nowakowski and Hayes, 1999; Sanchez et al., 2001). While the processes that actually define a sensitive period are unknown, plausible mechanisms of change include, but are not limited to, the modification of brain repair mechanisms, altered expression of neurotrophic factors, and the development of signaling mechanisms. Alterations in any of these factors during a sensitive period produce an enduring effect on structure and function (Adler et al., 2006; Andersen, 2003). As reviewed below, early life stress impacts a multitude of processes that shape the brain.

Increased stress reactivity alters brain development—The HPA axis changes increase stress reactivity (tenet #1), but these changes have unique effects on brain development. The dramatic and profound effects of CRH (Brunson et al., 2001) and stress hormones, work in concert with monoamine neuromodulators and excitatory amino acids (McEwen, 2000b), to modify basic neural processes. Administration of glucocorticoids during early life in laboratory animals permanently reduces brain weight and DNA content (Ardeleanu and Strescu, 1978), suppresses postnatal mitosis of granule cells in cerebellum and dentate

gyrus (Bohn, 1980), interferes with glial cell division (Lauder, 1983), and reduces the number of dendritic spines in various brain regions (Schapiro, 1971). More recent work clearly shows that early exposure to stress-induced molecular signals impacts myelination (Leussis and Andersen, 2008; Meyer, 1983; Tsuneishi et al., 1991), neuronal arborization (McEwen, 2000b), neurogenesis (Gould and Tanapat, 1999; Mirescu and Gould, 2006), and synaptogenesis (Andersen and Teicher, 2004; Garcia, 2002).

The effects of stress on the brain, however, are not universal. Specific brain regions differ in their sensitivity to stress-induced effects. Susceptibility may be influenced by genetics (Caspi et al., 2002; Caspi et al., 2003; Koenen et al., 2005), gender (Barna et al., 2003; De Bellis and Keshavan, 2003; Teicher et al., 2004), timing (Andersen, 2003; Andersen et al., 2008; Leussis and Andersen, 2008; Perlman et al., 2007), density of glucocorticoid receptors (Benesova and Pavlik, 1985; Haynes et al., 2001; McEwen et al., 1992; Pryce, 2007), and capacity of local neurons to release CRH in response to stress (Chen et al., 2004). In this review, we focus on how the timing of stress exposure may facilitate the expression of precocial drug use through regional brain changes. Brain regions that appear to show morphometric vulnerability to the effects of early stress or childhood abuse include corpus callosum, hippocampus, cerebellum and neocortex (Andersen et al., 2008). To begin, we will discuss the delayed impact of early life stress on the hippocampus, which manifests between adolescence and adulthood (Andersen and Teicher, 2004). Changes in the nucleus accumbens and the prefrontal cortex will also be discussed.

Early adversity affects hippocampus development—Combined clinical and preclinical research suggests that exposure to stress during early life produces delayed effects on hippocampal development. Changes in hippocampal volume seem to appear during adulthood. Clinical studies evaluating hippocampal morphometry in survivors of childhood abuse have observed significant volume loss (Andersen et al., 2008; Bremner et al., 1997; Driessen et al., 2000; Stein, 1997; Vermetten et al., 2006; Vythilingam et al., 2002). In contrast, studies in abused children with PTSD failed to find any evidence of hippocampal volume loss (Carrion et al., 2001; De Bellis et al., 1999b; De Bellis et al., 2002), and in fact, a significant increase in white matter volume was reported (Tupler and De Bellis, 2006). Thus, the effects of childhood abuse are associated with hippocampal volume loss in adulthood, but not during childhood or early adolescence (Andersen et al., 2008; Teicher et al., 2003). We recently found reductions in bilateral hippocampal volume following CSA in a young adult sample are maximally if the abuse occurred between 3-5 years of age and between 11-13 years of age (Andersen et al., 2008). These periods correspond to overproduction phases of human hippocampal gray matter (Gogtay et al., 2006). Preclinical observations seem to reconcile these seemingly disparate results between studies examining children or adults. Early isolation stress in developing rats prevents the normal peripubertal overproduction of synapses in CA1 and CA3 region of the hippocampus of rats; however, early stress does not prevent pruning, which leads to an enduring deficit in synaptic density by late adolescence/early adulthood (60 days of age in the rat) (Andersen and Teicher, 2004). Thus, it is likely that exposure to early stress alters the trajectory of hippocampal development, with the adverse impact of early stress becoming manifest during the transition from adolescence to early adulthood.

The role of the hippocampus is to provide contextual gating of information coming from the prefrontal cortex at the level of the nucleus accumbens (Grace et al., 2007), and therefore is involved in drug sensitization processes. Loss of hippocampal synaptic density, or gray matter volume, that appears to occur in early stress exposed individuals as they pass through adolescence may interfere with or alter this gating function. Currently, little is known about the effects of early stress-induced hippocampal changes on vulnerability to substance abuse. However, excitotoxic lesions of the ventromedial hippocampus during the first week of life in rats increases the amount and frequency of drug-taking behavior, but not the break point in a

progressive ratio schedule of self-administration of methamphetamine (Brady et al., 2008). These data are consistent with reduced gating of cortical inputs into the accumbens, and would render a stress-exposed pre-teen more susceptible to drug abuse at a younger age than his peers. An alternative explanation may be that stress-induced hippocampal changes reduce the negative feedback control of HPA axis (tenet #1; Goursaud et al., 2006). The findings of greater vulnerability to use drugs following hippocampal manipulations in preclinical studies are consistent with the clinical findings discussed above.

Developmental stress exposure programs the accumbens dopamine system for reduced reward and elevated anhedonia—It is well established that exposure to early life stress increases feelings of dysphoria, anhedonia, and anxiety (Ruedi-Bettschen et al., 2006). A detailed, comprehensive review presented by Matthews and Robbins in 2003 (Matthews and Robbins, 2003) suggests that early life stress dampens the reward system. Repeated maternal separation is associated with enduring reductions in behavioral responses to appetitive stimuli in the adult rat compared with handled controls (Matthews et al., 1996). As observed across multiple experimental procedures, including self-administration, intercranial self-stimulation, and sucrose preferences, the data consistently suggest that appetitive stimuli elicit less vigorous responses in separated rats (Matthews and Robbins, 2003). For example, isolated rats also show blunted positive and negative contrast effects with sucrose as the comparator solution, suggesting reduced reward processing to this natural stimulus (Matthews and Robbins, 2003). The use of drugs helps to overcome this feeling of anhedonia, and it follows that the stressed subject will be more sensitive to the effects of drugs in an attempt to normalize this basal state.

Stress exposure works, in part, by altering the dopamine (DA) system within the nucleus accumbens. Based on adult outcomes of maternal deprivation, behavioral evidence, such as increases in locomotor activity in response to novelty (Brake et al., 2004), to cocaine (Brake et al., 2004), and to tail-pinch stress support the hypothesis that maternal deprivation enhances baseline sensitivity of DA within the nucleus accumbens. We found that pre-weaning maternal deprivation increased DA content and decreases serotonin turnover (5-HT/5-HIAA ratio) in the nucleus accumbens and amygdala during adulthood (Andersen et al., 1999). Direct measurement show that isolates have elevated levels of extracellular DA in this region in response to cocaine (Kosten et al., 2003), an effect that may be mediated by lower levels of the DA transporter (Brake et al., 2004; Meaney et al., 2002). Stress effects on the nucleus accumbens, however, are not only restricted to early life events. Hall et al (Hall et al., 1998) found that post-weaning stress from isolation rearing produced an enduring decrease in 5-HIAA levels and an increase in DA levels and augmentation of stimulant-induced DA release in the nucleus accumbens. Hence, chronic early stress may increase susceptibility to substance abuse by altering the development of the mesolimbic DA system, but the effects of stress may emerge at any age.

One possible mechanism through which sustained increases in accumbens DA produces feelings of dysphoria and anhedonia is through its actions on the transcriptional regulating factor, CREB (Nestler and Carlezon, 2006). Notably, however, increased accumbens CREB levels were not observed in maternally separated animals (Lippmann et al., 2007) and suggest that the anhedonia may be driven by another mechanism or changes elsewhere in the brain. Corticosterone and/or CRH effects on the mesolimbic DA system may modulate stress-induced modulation of behavioral sensitivity to drugs of abuse (Barrot et al., 1999; Deroche et al., 1995; Koob, 1999; 2000; Marinelli and Piazza, 2002; Piazza et al., 1996; Rouge-Pont et al., 1998; Self, 1998). Chronic stress produces neural adaptations in the nucleus accumbens - ventral tegmental area that are very similar to the effects of drug exposure (Fitzgerald et al., 1996; Ortiz et al., 1996).

Exposure to childhood abuse may also increase risk for substance abuse by affecting the DA system and sensitivity to stimulants. Childhood abuse has been associated with increased peripheral levels of DA or homovanillic acid (De Bellis et al., 1999a; De Bellis et al., 1994b), and reduced plasma levels of dopamine beta-hydroxylase (Galvin et al., 1995) the enzyme responsible for the conversion of DA to norepinephrine.

Adolescent stress affects the prefrontal cortex—In contrast to the delayed effects of stress on hippocampal morphometry, stress exerts its maximal effects on the prefrontal cortex during adolescence (Andersen et al., 2008; Hall, 1998; Leussis and Andersen, 2008). Moreover, these effects are observable without a delay as observed for the hippocampus (Andersen and Teicher, 2004). The protracted development of the prefrontal cortex (Crews et al., 2007; Spear, 2000) may render it increasingly vulnerable to the effects of stress during adolescence. In addition, high levels of glucocorticoid receptors are expressed in the cortex during this stage, which may further increase the effects of stress (Pryce, 2007). Stress exposure during adolescence, including CSA in clinical studies (Andersen et al., 2008) or social isolation in preclinical studies (Hall, 1998; Leussis and Andersen, 2008), is associated with a decrease in prefrontal gray matter and synaptic density, with little to no change in other brain regions. Based on pharmacological studies, this synaptic loss reflects stress-induced increases in glutamatergic activity (Leussis et al., 2008). Enhanced glutamatergic activity in the prefrontal cortex is consistent with increased conditioning aspects of drugs of abuse (see tenet #3).

Indeed, studies that have examined the relationship between adolescent stress and drug abuse show increased vulnerability. Ibotenic lesions of the medial prefrontal cortex of rats, which presumably attenuates innervation of the accumbens, resulted in a greater behavioral response to stress and increased stress-induced dopamine release into the accumbens (Brake et al., 2000). Isolation reared, but not maternally deprived rats, showed locomotor sensitization to intermittent 1.5 mg/kg amphetamine (Weiss et al., 2001). In this regard, drugs that produce addictions with a high cue-associated drug-seeking (i.e., heroin and crack (Franken et al., 2003)) may be more likely to be affected by later stressors. As discussed in tenet #3, the prefrontal cortex is involved in the behavioral expression of drug-seeking once the drug-cue association is formed.

3. A certain level of maturation of the brain needs to occur for the effects of previous stress exposure to manifest

Adolescence represents a critical window of vulnerability for addiction to drugs, although substantial variability exists in age of onset within each drug class (see Figure 2). As Figure 2 shows, drug use is not initiated in 50% of the population until adolescence (tenet #3). This seems to hold true across all drug classes. Statistics show that earlier initiation of drug use substantially increases the relative risk for dependence and lifelong addiction (Hill et al., 2000; SAMHSA, 1999). For example, increased risk for alcoholism increases 40% for those who start drinking before 15 years (SAMHSA, 1999). Similarly, the relative risk for cocaine dependence after initial exposure is four-fold the risk if use is initiated before 12 years of age, and declines dramatically with each additional year of abstinence (O'Brien and Anthony, 2005). Enduring risk of marijuana, tobacco, and inhalants abuse also is increased if exposure occurs during adolescence (Waylen and Wolke, 2004; Westermeyer, 1999). Here, we raise the hypothesis that exposure to stress during sensitive periods of development (tenet #2) also has implications by producing a left-shift in the age of initiation curve of drug experimentation.

Tenet #3 proposes that the full effects of early stress on vulnerability to use substances lie relatively dormant until adolescence, as hypothesized for schizophrenia (Weinberger, 1987), depression (Andersen and Teicher, 2008; Teicher et al. in press), and early drug exposure (Andersen, 2005). Early life events program a trajectory of development that continues through

adolescence and young adulthood. Some effects of stress are readily observable in the short-term, including dendritic rearrangements (Leussis and Andersen, 2008; Radley et al., 2005). Others, such as an attenuation in hippocampal synaptic density, may only emerge later in life (Andersen et al., 1999; Andersen and Teicher, 2004). We propose that maturational changes in the prefrontal cortex, which plays a critical role in drug-seeking and relapse, may be key to understanding the adolescent onset of drug abuse.

The process of addiction includes a strong, motivational component that is re-activated by cues associated with drug taking and is considered a key factor in relapse (Kalivas et al., 2005; Volkow, 2005; Robinson and Berridge, 1993; Vezina and Stewart, 1984)). Data from human imaging studies show that cues associated with drug use and craving (i.e., environmental context, paraphernalia) in humans activate motivational circuits in the frontal cortex involved in processing reward (Goldstein and Volkow, 2002; Grant et al., 1996; Maas et al., 1998; Tzschentke, 2000). This information is used to estimate the motivational value of cues based on potential reward (Elliott et al., 2003; London et al., 2000) and produces a conditioned incentive (drug craving) (Childress et al., 1999). During non-addictive conditions, GABA activity enhances behavioral flexibility by allowing multiple sources of information to modulate glutamate output (Seamans and Yang, 2004). However, under conditions that promote addiction and relapse, D1 receptors are selectively over-expressed on glutamatergic neurons that project to the accumbens. As a result, cued-induced increases in dopamine activity are more likely to stimulate this pathway and enhance drug-seeking behaviors at the expense of other behaviors (i.e., reduced behavioral flexibility; Figure 1; (Kalivas et al., 2005)).

Maturation of the adolescent brain is associated with vulnerability to drug-associated cues—Epidemiological research (Figure 2) shows that most addictions do not emerge until adolescence. The maturation of the prefrontal cortex and its connectivity to other regions may be an important factor in the timing of this process (Ernst et al., 2006). Developmental differences in reward processing have been observed in BOLD fMRI studies in children. Immature frontal cortical responsiveness to reward is more diffuse and attenuated compared with adults (Durstun, 2003). In contrast, children show greater activation in the accumbens (Ernst et al., 2005). Maturation leads to a more spatially restricted (less diffuse) cortical pattern of activation (Rubia et al., 2000), which likely reflects pruning of synaptic connections.

Building on the work of Kalivas et al, Brenhouse and colleagues {Brenhouse, 2008 #7113} recently demonstrated that D1 dopamine receptors on fibers projecting from the prefrontal cortex to the nucleus accumbens are normally over-expressed during adolescence, but D1 receptors in this region and located on these terminals are lower in younger and older animals. This observation is consistent with previous preclinical studies in rats that suggested that stimulants have diminished effects in frontal regions of the brain relative to subcortical actions before adolescence (Andersen et al., 2001; Leslie et al., 2004). Increased D1 receptors in the prefrontal cortex enhance the sensitivity to cocaine-associated environments/cues in adolescents, who require lower doses of cocaine than younger or older animals to form significant place preferences (Badanic et al., 2006; Brenhouse et al., 2008a). Once formed, these adolescent drug-context associations are more resistant to extinction than adult associations (Brenhouse and Andersen, 2008b). In summary, tenet #3 suggests that addictive-like behaviors come on-line during adolescence both in stressed and non-stressed individuals, due partly to the maturation of the prefrontal cortex.

Conclusions

Exposure to early adversity will shift drug-seeking to an earlier age within this window, but whether these shifts are due to changes in gating of the hippocampus (early stress), elevated

dopamine in the accumbens (early stress), or synaptic changes in the prefrontal cortex (adolescent stress) remains to be determined. A desperately driven model of drug use without brakes is shown in Figure 1. Together, the data reviewed in this study suggest that the reward system is revved up. A dysregulated HPA axis may predispose an individual to compulsive use, whereas increased anhedonia further enhances risk of use and dependence. The normal brakes that reduce substance use, found in the hippocampus and the prefrontal cortex, are dysfunctional and may actually drive the system to drug seek even more than expected. This review provides evidence that exposure to adverse events during the course of development predispose an individual to abuse substances earlier than non-abused individuals. Understanding the role that development plays in the expression of these risk factors is often overlooked, but needs more attention to fully understand the full impact of early life stress (CSA, maternal separation) on substance abuse. Indeed, effects of early adversity may be delayed in their expression, but manifest suddenly during early adolescence. This initial delay may provide a false sense of safety that early adversity did little to no long-term harm to the individual. However, this delay may provide a window of opportunity where early interventions may preempt the influence of developmental adversity.

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References

- Adler LA, Spencer T, Faraone SV, Kessler RC, Howes MJ, Biederman J, Secnik K. Validity of pilot Adult ADHD Self-Report Scale (ASRS) to Rate Adult ADHD symptoms. *Ann Clin Psychiatry* 2006;18:145–8. [PubMed: 16923651]
- Ahmed SH, Koob GF. Cocaine- but not food-seeking behavior is reinstated by stress after extinction. *Psychopharmacology (Berl)* 1997;132:289–95. [PubMed: 9292629]
- Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? *Neurosci Biobehav Rev* 2003;27:3–18. [PubMed: 12732219]
- Andersen SL. Stimulants and the developing brain. *Trends Pharmacol Sci* 2005;26:237–43. [PubMed: 15860370]
- Andersen SL, LeBlanc CJ, Lyss PJ. Maturation increases in c-fos expression in the ascending dopamine systems. *Synapse* 2001;41:345–50. [PubMed: 11494405]
- Andersen SL, Lyss PJ, Dumont NL, Teicher MH. Enduring neurochemical effects of early maternal separation on limbic structures. *Ann N Y Acad Sci* 1999;877:756–9. [PubMed: 10415699]
- Andersen SL, Teicher MH. Delayed effects of early stress on hippocampal development. *Neuropsychopharmacology* 2004;29:1988–93. [PubMed: 15316569]
- Andersen SL, Teicher MH. Stress, sensitive periods and maturational events in adolescent depression. *Trends Neurosci*. 2008
- Andersen SL, Tomada A, Vincow ES, Valente E, Polcari A, Teicher MH. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. *Journal of Neuropsychiatry and Clinical Neurosciences*. in press
- Ardeleanu A, Strescu N. RNA and DNA synthesis in developing rat brain: hormonal influences. *Psychoneuroendocrinology* 1978;3:93–101. [PubMed: 205895]
- Badanich KA, Adler KJ, Kirstein CL. Adolescents differ from adults in cocaine conditioned place preference and cocaine-induced dopamine in the nucleus accumbens septi. *Eur J Pharmacol* 2006;550:95–106. [PubMed: 17011546]
- Barna I, Balint E, Baranyi J, Bakos N, Makara GB, Haller J. Gender-specific effect of maternal deprivation on anxiety and corticotropin-releasing hormone mRNA expression in rats. *Brain Res Bull* 2003;62:85–91. [PubMed: 14638381]

- Barrot M, Marinelli M, Abrous DN, Rouge-Pont F, Le Moal M, Piazza PV. Functional heterogeneity in dopamine release and in the expression of Fos-like proteins within the rat striatal complex. *Eur J Neurosci* 1999;11:1155–66. [PubMed: 10103112]
- Ben-Ari Y. Excitatory actions of gaba during development: the nature of the nurture. *Nat Rev Neurosci* 2002;3:728–39. [PubMed: 12209121]
- Benesova O, Pavlik A. Brain glucocorticoid receptors and their role in behavioural teratogenicity of synthetic glucocorticoids. *Arch Toxicol Suppl* 1985;8:73–6. [PubMed: 3868384]
- Bensley LS, Spieker SJ, Van Eenwyk J, Schoder J. Self-reported abuse history and adolescent problem behaviors. II. Alcohol and drug use. *J Adolesc Health* 1999;24:173–80. [PubMed: 10195800]
- Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl)* 2007;191:391–431. [PubMed: 17072591]
- Bohn MC. Granule cell genesis in the hippocampus of rats treated neonatally with hydrocortisone. *Neuroscience* 1980;5:2003–12. [PubMed: 7432634]
- Bottjer SW, Arnold AP. Developmental plasticity in neural circuits for a learned behavior. *Annu Rev Neurosci* 1997;20:459–81. [PubMed: 9056722]
- Brady AM, McCallum SE, Glick SD, O'Donnell P. Enhanced methamphetamine self-administration in a neurodevelopmental rat model of schizophrenia. *Psychopharmacol* 2008;200:205–15.
- Brake WG, Flores G, Francis D, Meaney MJ, Srivastava LK, Gratton A. Enhanced nucleus accumbens dopamine and plasma corticosterone stress responses in adult rats with neonatal excitotoxic lesions to the medial prefrontal cortex. *Neuroscience* 2000;96:687–95. [PubMed: 10727787]
- Brake WG, Zhang TY, Diorio J, Meaney MJ, Gratton A. Influence of early postnatal rearing conditions on mesocorticolimbic dopamine and behavioural responses to psychostimulants and stressors in adult rats. *Eur J Neurosci* 2004;19:1863–74. [PubMed: 15078560]
- Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, Capelli S, McCarthy G, Innis RB, Charney DS. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse--a preliminary report. *Biol Psychiatry* 1997;41:23–32. [PubMed: 8988792]
- Brenhouse H, Sonntag KC, Andersen SL. Transient D1 dopamine receptor over-expression on prefrontal cortex projection neurons: A mechanism for enhanced motivational salience of drug cues in adolescence. *Journal of Neuroscience* 2008a;28:2375–2382. [PubMed: 18322084]
- Brenhouse HC, Andersen SL. Delayed extinction and stronger reinstatement of cocaine conditioned place preference in adolescent rats, compared to adults. *Behav Neurosci* 2008b;122:460–5. [PubMed: 18410184]
- Brunson KL, Eghbal-Ahmadi M, Bender R, Chen Y, Baram TZ. Long-term, progressive hippocampal cell loss and dysfunction induced by early-life administration of corticotropin-releasing hormone reproduce the effects of early-life stress. *Proc Natl Acad Sci U S A* 2001;98:8856–61. [PubMed: 11447269]
- Buczek Y, Le AD, Stewart J, Shaham Y. Stress reinstates nicotine seeking but not sucrose solution seeking in rats. *Psychopharmacology (Berl)* 1999;144:183–8. [PubMed: 10395000]
- Caldji C, Diorio J, Meaney MJ. Variations in maternal care in infancy regulate the development of stress reactivity. *Biol Psychiatry* 2000a;48:1164–74. [PubMed: 11137058]
- Caldji C, Francis D, Sharma S, Plotsky PM, Meaney MJ. The effects of early rearing environment on the development of GABAA and central benzodiazepine receptor levels and novelty-induced fearfulness in the rat. *Neuropsychopharmacology* 2000b;22:219–29. [PubMed: 10693149]
- Caldji C, Tannenbaum B, Sharma S, Francis D, Plotsky PM, Meaney MJ. Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. *Proc Natl Acad Sci U S A* 1998;95:5335–40. [PubMed: 9560276]
- Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, Reiss AL. Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. *Biol Psychiatry* 2001;50:943–51. [PubMed: 11750890]
- Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R. Role of genotype in the cycle of violence in maltreated children. *Science* 2002;297:851–4. [PubMed: 12161658]

- Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003;301:386–9. [PubMed: 12869766]
- Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *Am J Psychiatry* 2003;160:1041–52. [PubMed: 12777258]
- Chapman DP, Whitfield CL, Felitti VJ, Dube SR, Edwards VJ, Anda RF. Adverse childhood experiences and the risk of depressive disorders in adulthood. *J Affect Disord* 2004;82:217–25. [PubMed: 15488250]
- Chen Y, Bender RA, Brunson KL, Pomper JK, Grigoriadis DE, Wurst W, Baram TZ. Modulation of dendritic differentiation by corticotropin-releasing factor in the developing hippocampus. *Proc Natl Acad Sci U S A* 2004;101:15782–7. [PubMed: 15496472]
- Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP. Limbic activation during cue-induced cocaine craving. *Am J Psychiatry* 1999;156:11–8. [PubMed: 9892292]
- Crews F, He J, Hodge C. Adolescent cortical development: a critical period of vulnerability for addiction. *Pharmacol Biochem Behav* 2007;86:189–99. [PubMed: 17222895]
- Dayan P, Balleine BW. Reward, motivation, and reinforcement learning. *Neuron* 2002;36:285–98. [PubMed: 12383782]
- De Bellis MD, Baum AS, Birmaher B, Keshavan MS, Eccard CH, Boring AM, Jenkins FJ, Ryan ND. A.E. Bennett Research Award. Developmental traumatology. Part I: Biological stress systems. *Biol Psychiatry* 1999a;45:1259–70. [PubMed: 10349032]
- De Bellis MD, Chrousos GP, Dorn LD, Burke L, Helmers K, Kling MA, Trickett PK, Putnam FW. Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. *J Clin Endocrinol Metab* 1994a;78:249–55. [PubMed: 8106608]
- De Bellis MD, Clark DB, Beers SR, Soloff PH, Boring AM, Hall J, Kersh A, Keshavan MS. Hippocampal volume in adolescent-onset alcohol use disorders. *Am J Psychiatry* 2000;157:737–44. [PubMed: 10784466]
- De Bellis MD, Keshavan MS. Sex differences in brain maturation in maltreatment-related pediatric posttraumatic stress disorder. *Neurosci Biobehav Rev* 2003;27:103–17. [PubMed: 12732227]
- De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, Frustaci K, Ryan ND. Developmental traumatology. Part II: Brain development. *Biol Psychiatry* 1999b;45:1271–84. [PubMed: 10349033]
- De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Beers SR, Hall J, Moritz G. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. *Biol Psychiatry* 2002;52:1066–78. [PubMed: 12460690]
- De Bellis MD, Lefter L, Trickett PK, Putnam FW Jr. Urinary catecholamine excretion in sexually abused girls. *J Am Acad Child Adolesc Psychiatry* 1994b;33:320–7. [PubMed: 8169176]
- Deroche V, Marinelli M, Maccari S, Le Moal M, Simon H, Piazza PV. Stress-induced sensitization and glucocorticoids. I. Sensitization of dopamine-dependent locomotor effects of amphetamine and morphine depends on stress-induced corticosterone secretion. *J Neurosci* 1995;15:7181–8. [PubMed: 7472472]
- Deroche V, Piazza PV, Casolini P, Maccari S, Le Moal M, Simon H. Stress-induced sensitization to amphetamine and morphine psychomotor effects depend on stress-induced corticosterone secretion. *Brain Res* 1992a;598:343–8. [PubMed: 1486498]
- Deroche V, Piazza PV, Le Moal M, Simon H. Social isolation-induced enhancement of the psychomotor effects of morphine depends on corticosterone secretion. *Brain Res* 1994;640:136–9. [PubMed: 8004442]
- Deroche V, Piazza PV, Maccari S, Le Moal M, Simon H. Repeated corticosterone administration sensitizes the locomotor response to amphetamine. *Brain Res* 1992b;584:309–13. [PubMed: 1515947]
- Driessen M, Herrmann J, Stahl K, Zwaan M, Meier S, Hill A, Osterheider M, Petersen D. Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Arch Gen Psychiatry* 2000;57:1115–22. [PubMed: 11115325]

- Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WH, Anda RF. Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. *Pediatrics* 2003;111:564–72. [PubMed: 12612237]
- Durston S. A review of the biological bases of ADHD: what have we learned from imaging studies? *Ment Retard Dev Disabil Res Rev* 2003;9:184–95. [PubMed: 12953298]
- Elliott R, Newman JL, Longe OA, Deakin JF. Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. *J Neurosci* 2003;23:303–7. [PubMed: 12514228]
- Erb S, Salmaso N, Rodaros D, Stewart J. A role for the CRF-containing pathway from central nucleus of the amygdala to bed nucleus of the stria terminalis in the stress-induced reinstatement of cocaine seeking in rats. *Psychopharmacology (Berl)* 2001;158:360–5. [PubMed: 11797056]
- Erb S, Shaham Y, Stewart J. Stress reinstates cocaine-seeking behavior after prolonged extinction and a drug-free period. *Psychopharmacology (Berl)* 1996;128:408–12. [PubMed: 8986011]
- Ernst M, Nelson EE, Jazbec S, McClure EB, Monk CS, Leibenluft E, Blair J, Pine DS. Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. *Neuroimage* 2005;25:1279–91. [PubMed: 15850746]
- Ernst M, Pine DS, Hardin M. Triadic model of the neurobiology of motivated behavior in adolescence. *Psychol Med* 2006;36:299–312. [PubMed: 16472412]
- Felitti VJ. The relationship of adverse childhood experiences to adult health: Turning gold into lead. *Z Psychosom Med Psychother* 2002;48:359–69. [PubMed: 12407494]
- Fergusson DM, Horwood LJ, Lynskey MT. Childhood sexual abuse and psychiatric disorder in young adulthood: II. Psychiatric outcomes of childhood sexual abuse. *J Am Acad Child Adolesc Psychiatry* 1996;35:1365–74. [PubMed: 8885591]
- Fitzgerald LW, Ortiz J, Hamedani AG, Nestler EJ. Drugs of abuse and stress increase the expression of GluR1 and NMDAR1 glutamate receptor subunits in the rat ventral tegmental area: common adaptations among cross-sensitizing agents. *J Neurosci* 1996;16:274–82. [PubMed: 8613793]
- Francis DD, Diorio J, Plotsky PM, Meaney MJ. Environmental enrichment reverses the effects of maternal separation on stress reactivity. *J Neurosci* 2002;22:7840–3. [PubMed: 12223535]
- Franken IH, Stam CJ, Hendriks VM, van den Brink W. Neurophysiological evidence for abnormal cognitive processing of drug cues in heroin dependence. *Psychopharmacology (Berl)* 2003;170:205–12. [PubMed: 12898125]
- Galvin M, Ten Eyck R, Shekhar A, Stilwell B, Fineberg N, Laite G, Karwisch G. Serum dopamine beta hydroxylase and maltreatment in psychiatrically hospitalized boys. *Child Abuse Negl* 1995;19:821–32. [PubMed: 7583738]
- Garcia R. Stress, metaplasticity, and antidepressants. *Curr Mol Med* 2002;2:629–38. [PubMed: 12420802]
- Goeders NE. A neuroendocrine role in cocaine reinforcement. *Psychoneuroendocrinology* 1997;22:237–59. [PubMed: 9226728]
- Gogtay N, Nugent TF 3rd, Herman DH, Ordonez A, Greenstein D, Hayashi KM, Clasen L, Toga AW, Giedd JN, Rapoport JL, Thompson PM. Dynamic mapping of normal human hippocampal development. *Hippocampus* 2006;16:664–72. [PubMed: 16826559]
- Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry* 2002;159:1642–52. [PubMed: 12359667]
- Gould E, Tanapat P. Stress and hippocampal neurogenesis. *Biol Psychiatry* 1999;46:1472–9. [PubMed: 10599477]
- Goursaud AP, Mendoza SP, Capitanio JP. Do neonatal bilateral ibotenic acid lesions of the hippocampal formation or of the amygdala impair HPA axis responsiveness and regulation in infant rhesus macaques (*Macaca mulatta*)? *Brain Res* 2006;1071:97–104. [PubMed: 16412391]
- Grace AA, Floresco SB, Goto Y, Lodge DJ. Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. *Trends Neurosci* 2007;30:220–7. [PubMed: 17400299]
- Grant S, London ED, Newlin DB, Villemagne VL, Liu X, Contoreggi C, Phillips RL, Kimes AS, Margolin A. Activation of memory circuits during cue-elicited cocaine craving. *Proc Natl Acad Sci U S A* 1996;93:12040–5. [PubMed: 8876259]

- Gustafsson L, Nylander I. Time-dependent alterations in ethanol intake in male wistar rats exposed to short and prolonged daily maternal separation in a 4-bottle free-choice paradigm. *Alcohol Clin Exp Res* 2006;30:2008–16. [PubMed: 17117966]
- Hall FS. Social deprivation of neonatal, adolescent, and adult rats has distinct neurochemical and behavioral consequences. *Crit Rev Neurobiol* 1998;12:129–62. [PubMed: 9444483]
- Hall FS, Wilkinson LS, Humby T, Inglis W, Kendall DA, Marsden CA, Robbins TW. Isolation rearing in rats: pre- and postsynaptic changes in striatal dopaminergic systems. *Pharmacol Biochem Behav* 1998;59:859–72. [PubMed: 9586842]
- Harper DG, Stopa EG, McKee AC, Satlin A, Fish D, Volicer L. Dementia severity and Lewy bodies affect circadian rhythms in Alzheimer disease. *Neurobiol Aging* 2004;25:771–81. [PubMed: 15165702]
- Haynes LE, Griffiths MR, Hyde RE, Barber DJ, Mitchell IJ. Dexamethasone induces limited apoptosis and extensive sublethal damage to specific subregions of the striatum and hippocampus: implications for mood disorders. *Neuroscience* 2001;104:57–69. [PubMed: 11311531]
- Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol Psychiatry* 2001;49:1023–39. [PubMed: 11430844]
- Heim C, Newport DJ, Bonsall R, Miller AH, Nemeroff CB. Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. *Am J Psychiatry* 2001;158:575–81. [PubMed: 11282691]
- Heim C, Mletzko T, Purselle D, Musselman DL, Nemeroff CB. The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. *Biol Psychiatry* 2008;63:398–405. [PubMed: 17825799]
- Hill SY, Shen S, Lowers L, Locke J. Factors predicting the onset of adolescent drinking in families at high risk for developing alcoholism. *Biol Psychiatry* 2000;48:265–75. [PubMed: 10960157]
- Holmes WC. Association between a history of childhood sexual abuse and subsequent, adolescent psychoactive substance use disorder in a sample of HIV seropositive men. *J Adolesc Health* 1997;20:414–9. [PubMed: 9178077]
- Hsu FC, Zhang GJ, Raol YS, Valentino RJ, Coulter DA, Brooks-Kayal AR. Repeated neonatal handling with maternal separation permanently alters hippocampal GABAA receptors and behavioral stress responses. *Proc Natl Acad Sci U S A* 2003;100:12213–8. [PubMed: 14530409]
- Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci* 2006;29:565–98. [PubMed: 16776597]
- Ito Y, Teicher MH, Glod CA, Harper D, Magnus E, Gelbard HA. Increased prevalence of electrophysiological abnormalities in children with psychological, physical, and sexual abuse. *Journal of Neuropsychiatry and Clinical Neurosciences* 1993;5:401–8. [PubMed: 8286938]
- Jaworski JN, Francis DD, Brommer CL, Morgan ET, Kuhar MJ. Effects of early maternal separation on ethanol intake, GABA receptors and metabolizing enzymes in adult rats. *Psychopharmacology (Berl)* 2005;181:8–15. [PubMed: 15830234]
- Kabbaj M, Norton CS, Kollack-Walker S, Watson SJ, Robinson TE, Akil H. Social defeat alters the acquisition of cocaine self-administration in rats: role of individual differences in cocaine-taking behavior. *Psychopharmacology (Berl)* 2001;158:382–7. [PubMed: 11797059]
- Kalivas PW, Pierce RC, Cornish J, Sorg BA. A role for sensitization in craving and relapse in cocaine addiction. *J Psychopharmacol* 1998;12:49–53. [PubMed: 9584968]
- Kalivas PW, Volkow N, Seamans J. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. *Neuron* 2005;45:647–50. [PubMed: 15748840]
- Katz LC, Shatz CJ. Synaptic activity and the construction of cortical circuits. *Science* 1996;274:1133–8. [PubMed: 8895456]
- Kendler KS, Bulik CM, Silberg J, Hettema JM, Myers J, Prescott CA. Childhood sexual abuse and adult psychiatric and substance use disorders in women: an epidemiological and cotwin control analysis. *Arch Gen Psychiatry* 2000;57:953–9. [PubMed: 11015813]
- King KM, Chassin L. A prospective study of the effects of age of initiation of alcohol and drug use on young adult substance dependence. *J Stud Alcohol Drugs* 2007;68:256–65. [PubMed: 17286344]

- Koehl M, Lemaire V, Mayo W, Abrous DN, Maccari S, Piazza PV, Le Moal M, Vallee M. Individual vulnerability to substance abuse and affective disorders: role of early environmental influences. *Neurotox Res* 2002;4:281–96. [PubMed: 12829419]
- Koenen KC, Saxe G, Purcell S, Smoller JW, Bartholomew D, Miller A, Hall E, Kaplow J, Bosquet M, Moulton S, Baldwin C. Polymorphisms in FKBP5 are associated with peritraumatic dissociation in medically injured children. *Mol Psychiatry* 2005;10:1058–9. [PubMed: 16088328]
- Koob GF. The role of the striatopallidal and extended amygdala systems in drug addiction. *Ann N Y Acad Sci* 1999;877:445–60. [PubMed: 10415664]
- Koob GF. Neurobiology of addiction. Toward the development of new therapies. *Ann N Y Acad Sci* 2000;909:170–85. [PubMed: 10911930]
- Koob GF, Swerdlow NR. The functional output of the mesolimbic dopamine system. *Ann N Y Acad Sci* 1988;537:216–27. [PubMed: 3059925]
- Koob GF, Weiss F. Neuropharmacology of cocaine and ethanol dependence. *Recent Dev Alcohol* 1992;10:201–33. [PubMed: 1350359]
- Kosten TA, Zhang XY, Kehoe P. Chronic neonatal isolation stress enhances cocaine-induced increases in ventral striatal dopamine levels in rat pups. *Brain Res Dev Brain Res* 2003;141:109–16.
- Kreek MJ, Koob GF. Drug dependence: stress and dysregulation of brain reward pathways. *Drug Alcohol Depend* 1998;51:23–47. [PubMed: 9716928]
- Kumar S, Fleming RL, Morrow AL. Ethanol regulation of gamma-aminobutyric acid A receptors: genomic and nongenomic mechanisms. *Pharmacol Ther* 2004;101:211–26. [PubMed: 15031000]
- Lauder JM. Hormonal and humoral influences on brain development. *Psychoneuroendocrinology* 1983;8:121–55. [PubMed: 6137852]
- Le AD, Harding S, Juzysch W, Watchus J, Shalev U, Shaham Y. The role of corticotrophin-releasing factor in stress-induced relapse to alcohol-seeking behavior in rats. *Psychopharmacology (Berl)* 2000;150:317–24. [PubMed: 10923760]
- Le AD, Quan B, Juzysch W, Fletcher PJ, Joharchi N, Shaham Y. Reinstatement of alcohol-seeking by priming injections of alcohol and exposure to stress in rats. *Psychopharmacology (Berl)* 1998;135:169–74. [PubMed: 9497022]
- Leslie FM, Loughlin SE, Wang R, Perez L, Lotfipour S, Belluzzia JD. Adolescent development of forebrain stimulant responsiveness: insights from animal studies. *Ann N Y Acad Sci* 2004;1021:148–59. [PubMed: 15251884]
- Leussis MP, Andersen SL. Is adolescence a sensitive period for depression? Behavioral and neuroanatomical findings from a social stress model. *Synapse* 2008;62:22–30. [PubMed: 17957735]
- Leussis MP, Lawson K, Stone K, Andersen SL. The enduring effects of an adolescent social stressor on synaptic density, part II: Poststress reversal of synaptic loss in the cortex by adinazolam and MK-801. *Synapse* 2008;62:185–192. [PubMed: 18081181]
- Lippmann M, Bress A, Nemeroff CB, Plotsky PM, Monteggia LM. Long-term behavioural and molecular alterations associated with maternal separation in rats. *Eur J Neurosci* 2007;25:3091–8. [PubMed: 17561822]
- Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, Sharma S, Pearson D, Plotsky PM, Meaney MJ. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science* 1997;277:1659–62. [PubMed: 9287218]
- London ED, Ernst M, Grant S, Bonson K, Weinstein A. Orbitofrontal cortex and human drug abuse: functional imaging. *Cereb Cortex* 2000;10:334–42. [PubMed: 10731228]
- Maas LC, Lukas SE, Kaufman MJ, Weiss RD, Daniels SL, Rogers VW, Kukes TJ, Renshaw PF. Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. *Am J Psychiatry* 1998;155:124–6. [PubMed: 9433350]
- Mackie S, Shaw P, Lenroot R, Pierson R, Greenstein DK, Nugent TF 3rd, Sharp WS, Giedd JN, Rapoport JL. Cerebellar development and clinical outcome in attention deficit hyperactivity disorder. *Am J Psychiatry* 2007;164:647–55. [PubMed: 17403979]
- Marinelli M, Le Moal M, Piazza PV. Acute pharmacological blockade of corticosterone secretion reverses food restriction-induced sensitization of the locomotor response to cocaine. *Brain Res* 1996;724:251–5. [PubMed: 8828576]

- Marinelli M, Piazza PV. Interaction between glucocorticoid hormones, stress and psychostimulant drugs. *Eur J Neurosci* 2002;16:387–94. [PubMed: 12193179]
- Matthews K, Robbins TW. Early experience as a determinant of adult behavioural responses to reward: the effects of repeated maternal separation in the rat. *Neurosci Biobehav Rev* 2003;27:45–55. [PubMed: 12732222]
- Matthews K, Wilkinson LS, Robbins TW. Repeated maternal separation of preweanling rats attenuates behavioral responses to primary and conditioned incentives in adulthood. *Physiol Behav* 1996;59:99–107. [PubMed: 8848498]
- McEwen BS. Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology* 2000a;22:108–24. [PubMed: 10649824]
- McEwen BS. Effects of adverse experiences for brain structure and function. *Biol Psychiatry* 2000b;48:721–31. [PubMed: 11063969]
- McEwen BS, Gould EA, Sakai RR. The vulnerability of the hippocampus to protective and destructive effects of glucocorticoids in relation to stress. *Br J Psychiatry Suppl* 1992;18–23. [PubMed: 1389022]
- Meaney MJ, Brake W, Gratton A. Environmental regulation of the development of mesolimbic dopamine systems: a neurobiological mechanism for vulnerability to drug abuse? *Psychoneuroendocrinology* 2002;27:127–38. [PubMed: 11750774]
- Meaney MJ, Szyf M. Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. *Dialogues Clin Neurosci* 2005;7:103–23. [PubMed: 16262207]
- Meyer JS. Early adrenalectomy stimulates subsequent growth and development of the rat brain. *Exp Neurol* 1983;82:432–46. [PubMed: 6628629]
- Mirescu C, Gould E. Stress and adult neurogenesis. *Hippocampus* 2006;16:233–8. [PubMed: 16411244]
- Nair A, Vadodaria KC, Banerjee SB, Benekareddy M, Dias BG, Duman RS, Vaidya VA. Stressor-Specific Regulation of Distinct Brain-Derived Neurotrophic Factor Transcripts and Cyclic AMP Response Element-Binding Protein Expression in the Postnatal and Adult Rat Hippocampus. *Neuropsychopharmacology*. 2006
- Navalta CP, Polcari A, Webster DM, Boghossian A, Teicher MH. Effects of childhood sexual abuse on neuropsychological and cognitive function in college women. *J Neuropsychiatry Clin Neurosci* 2006;18:45–53. [PubMed: 16525070]
- Nestler EJ, Carlezon WA Jr. The mesolimbic dopamine reward circuit in depression. *Biol Psychiatry* 2006;59:1151–9. [PubMed: 16566899]
- Nowakowski RS, Hayes NL. CNS development: an overview. *Dev Psychopathol* 1999;11:395–417. [PubMed: 10532616]
- O'Brien MS, Anthony JC. Risk of becoming cocaine dependent: epidemiological estimates for the United States, 2000–2001. *Neuropsychopharmacology* 2005;30:1006–18. [PubMed: 15785780]
- Orlando M, Tucker JS, Ellickson PL, Klein DJ. Developmental trajectories of cigarette smoking and their correlates from early adolescence to young adulthood. *J Consult Clin Psychol* 2004;72:400–10. [PubMed: 15279524]
- Ortiz J, Fitzgerald LW, Lane S, Terwilliger R, Nestler EJ. Biochemical adaptations in the mesolimbic dopamine system in response to repeated stress. *Neuropsychopharmacology* 1996;14:443–52. [PubMed: 8726755]
- Perlman WR, Webster MJ, Herman MM, Kleinman JE, Weickert CS. Age-related differences in glucocorticoid receptor mRNA levels in the human brain. *Neurobiol Aging* 2007;28:447–58. [PubMed: 16540204]
- Peterson BS, Staib L, Scahill L, Zhang H, Anderson C, Leckman JF, Cohen DJ, Gore JC, Albert J, Webster R. Regional brain and ventricular volumes in Tourette syndrome. *Arch Gen Psychiatry* 2001;58:427–40. [PubMed: 11343521]
- Piazza PV, Deminiere JM, le Moal M, Simon H. Stress- and pharmacologically-induced behavioral sensitization increases vulnerability to acquisition of amphetamine self- administration. *Brain Res* 1990;514:22–6. [PubMed: 2357527]

- Piazza PV, Deroche V, Deminiere JM, Maccari S, Le Moal M, Simon H. Corticosterone in the range of stress-induced levels possesses reinforcing properties: implications for sensation-seeking behaviors. *Proc Natl Acad Sci U S A* 1993;90:11738–42. [PubMed: 8265619]
- Piazza PV, Rouge-Pont F, Deroche V, Maccari S, Simon H, Le Moal M. Glucocorticoids have state-dependent stimulant effects on the mesencephalic dopaminergic transmission. *Proc Natl Acad Sci U S A* 1996;93:8716–20. [PubMed: 8710937]
- Pickens CL, Saddoris MP, Setlow B, Gallagher M, Holland PC, Schoenbaum G. Different roles for orbitofrontal cortex and basolateral amygdala in a reinforcer devaluation task. *J Neurosci* 2003;23:11078–84. [PubMed: 14657165]
- Pryce CR. Postnatal ontogeny of expression of the corticosteroid receptor genes in mammalian brains: Inter-species and intra-species differences. *Brain Res Rev*. 2007
- Radley JJ, Rocher AB, Janssen WG, Hof PR, McEwen BS, Morrison JH. Reversibility of apical dendritic retraction in the rat medial prefrontal cortex following repeated stress. *Exp Neurol* 2005;196:199–203. [PubMed: 16095592]
- Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev* 1993;18:247–91. [PubMed: 8401595]
- Rodriguez de Fonseca F, Navarro M. Role of the limbic system in dependence on drugs. *Ann Med* 1998;30:397–405. [PubMed: 9783839]
- Roman E, Nylander I. The impact of emotional stress early in life on adult voluntary ethanol intake—results of maternal separation in rats. *Stress* 2005;8:157–74. [PubMed: 16323264]
- Rouge-Pont F, Deroche V, Le Moal M, Piazza PV. Individual differences in stress-induced dopamine release in the nucleus accumbens are influenced by corticosterone. *Eur J Neurosci* 1998;10:3903–7. [PubMed: 9875367]
- Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, Andrew C, Bullmore ET. Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI. *Neurosci Biobehav Rev* 2000;24:13–9. [PubMed: 10654655]
- Ruedi-Bettschen D, Zhang W, Russig H, Ferger B, Weston A, Pedersen EM, Feldon J, Pryce CR. Early deprivation leads to altered behavioural, autonomic and endocrine responses to environmental challenge in adult Fischer rats. *Eur J Neurosci* 2006;24:2879–93. [PubMed: 17156212]
- SAMHSA. Summary of findings from the 1998 national household survey on drug abuse. U.S. Department of Health and Human Services; Rockville, MD: 1999. p. 128
- Sanchez MM, Ladd CO, Plotsky PM. Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. *Dev Psychopathol* 2001;13:419–49. [PubMed: 11523842]
- Sapolsky RM. A mechanism for glucocorticoid toxicity in the hippocampus: increased neuronal vulnerability to metabolic insults. *J Neurosci* 1985;5:1228–32. [PubMed: 3998819]
- Schapiro, S. Hormonal and environmental influences on rat brain and behavior. In: Serman, MB.; McGinty, DJ., editors. *Brain Development and Behavior*. Academic Press; NY: 1971. p. 307-34.
- Schiffer F, Teicher MH, Anderson C, Tomoda A, Polcari A, Navalta CP, Andersen SL. Determination of hemispheric emotional valence in individual subjects: A new approach with research and therapeutic implications. *Behav Brain Funct* 2007;3:1–22. [PubMed: 17214890]
- Schiffer F, Teicher MH, Papanicolaou AC. Evoked potential evidence for right brain activity during the recall of traumatic memories. *Journal of Neuropsychiatry and Clinical Neurosciences* 1995;7:169–75. [PubMed: 7626959]
- Seamans JK, Yang CR. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Prog Neurobiol* 2004;74:1–58. [PubMed: 15381316]
- Seckl JR. Physiologic programming of the fetus. *Clin Perinatol* 1998;25:939–62. vii. [PubMed: 9891623]
- See RE, Fuchs RA, Ledford CC, McLaughlin J. Drug addiction, relapse, and the amygdala. *Ann N Y Acad Sci* 2003;985:294–307. [PubMed: 12724166]
- Self DW. Neural substrates of drug craving and relapse in drug addiction. *Ann Med* 1998;30:379–89. [PubMed: 9783837]
- Shaham Y, Erb S, Stewart J. Stress-induced relapse to heroin and cocaine seeking in rats: a review. *Brain Res Brain Res Rev* 2000;33:13–33. [PubMed: 10967352]

- Shaham Y, Rajabi H, Stewart J. Relapse to heroin-seeking in rats under opioid maintenance: the effects of stress, heroin priming, and withdrawal. *J Neurosci* 1996;16:1957–63. [PubMed: 8774462]
- Shaham Y, Stewart J. Stress reinstates heroin-seeking in drug-free animals: an effect mimicking heroin, not withdrawal. *Psychopharmacology (Berl)* 1995;119:334–41. [PubMed: 7675970]
- Shaham Y, Stewart J. Effects of opioid and dopamine receptor antagonists on relapse induced by stress and re-exposure to heroin in rats. *Psychopharmacology (Berl)* 1996;125:385–91. [PubMed: 8826544]
- Shalev U, Grimm JW, Shaham Y. Neurobiology of relapse to heroin and cocaine seeking: a review. *Pharmacol Rev* 2002;54:1–42. [PubMed: 11870259]
- Shalev U, Morales M, Hope B, Yap J, Shaham Y. Time-dependent changes in extinction behavior and stress-induced reinstatement of drug seeking following withdrawal from heroin in rats. *Psychopharmacology (Berl)* 2001;156:98–107. [PubMed: 11465640]
- Sinha R. How does stress increase risk of drug abuse and relapse? *Psychopharmacology (Berl)* 2001;158:343–59. [PubMed: 11797055]
- Sinha R, Catapano D, O'Malley S. Stress-induced craving and stress response in cocaine dependent individuals. *Psychopharmacology (Berl)* 1999;142:343–51. [PubMed: 10229058]
- Sinha R, Fuse T, Aubin LR, O'Malley SS. Psychological stress, drug-related cues and cocaine craving. *Psychopharmacology (Berl)* 2000;152:140–8. [PubMed: 11057517]
- Sowell ER, Thompson PM, Toga AW. Mapping changes in the human cortex throughout the span of life. *Neuroscientist* 2004;10:372–92. [PubMed: 15271264]
- Spear L. The adolescent brain and age-related behavioral manifestations. *Neuroscience and Bio-behavioral Reviews* 2000;24:417–463.
- Stein MB. Hippocampal volume in women victimized by childhood sexual abuse. *Psychol Med* 1997;27:951–9. [PubMed: 9234472]
- Stewart J. Pathways to relapse: the neurobiology of drug- and stress-induced relapse to drug-taking. *J Psychiatry Neurosci* 2000;25:125–36. [PubMed: 10740986]
- Stewart SH, Karp J, Pihl RO, Peterson RA. Anxiety sensitivity and self-reported reasons for drug use. *J Subst Abuse* 1997;9:223–40. [PubMed: 9494951]
- Teicher MH. Early abuse, limbic system dysfunction, and borderline personality disorder. In: Silk, K., editor. *Biological and Neurobehavioral Studies of Borderline Personality Disorder*. American Psychiatric Assoc. Press; Washington DC: 1994. p. 177–207.
- Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP. Developmental neurobiology of childhood stress and trauma. *Psychiatr Clin North Am* 2002;25:397–426. [PubMed: 12136507]
- Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. *Neurosci Biobehav Rev* 2003;27:33–44. [PubMed: 12732221]
- Teicher MH, Dumont NL, Ito Y, Vaituzis C, Giedd JN, Andersen SL. Childhood neglect is associated with reduced corpus callosum area. *Biol Psychiatry* 2004;56:80–5. [PubMed: 15231439]
- Teicher MH, Tomoda A, Andersen SL. Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? *Ann N Y Acad Sci* 2006;1071:313–23. [PubMed: 16891580]
- Teicher M, Samson J, Polcari A, Andersen S. Length of time between onset of childhood sexual abuse and emergence of depression in a young adult sample. *Journal of Clinical Psychiatry*. in press
- Triffleman EG, Marmar CR, Delucchi KL, Ronfeldt H. Childhood trauma and posttraumatic stress disorder in substance abuse inpatients. *J Nerv Ment Dis* 1995;183:172–6. [PubMed: 7891064]
- Tsuneishi S, Takada S, Motoike T, Ohashi T, Sano K, Nakamura H. Effects of dexamethasone on the expression of myelin basic protein, proteolipid protein, and glial fibrillary acidic protein genes in developing rat brain. *Brain Res Dev Brain Res* 1991;61:117–23.
- Tupler LA, De Bellis MD. Segmented hippocampal volume in children and adolescents with posttraumatic stress disorder. *Biol Psychiatry* 2006;59:523–9. [PubMed: 16199014]
- Tzschentke TM. The medial prefrontal cortex as a part of the brain reward system. *Amino Acids* 2000;19:211–9. [PubMed: 11026491]

- Vermetten E, Schmahl C, Lindner S, Loewenstein RJ, Bremner JD. Hippocampal and amygdalar volumes in dissociative identity disorder. *Am J Psychiatry* 2006;163:630–6. [PubMed: 16585437]
- Vezina P, Stewart J. Conditioning and place-specific sensitization of increases in activity induced by morphine in the VTA. *Pharmacol Biochem Behav* 1984;20:925–34. [PubMed: 6463076]
- Vincent SL, Pabreza L, Benes FM. Postnatal maturation of GABA-immunoreactive neurons of rat medial prefrontal cortex. *J Comp Neurol* 1995;355:81–92. [PubMed: 7636016]
- Volkow ND. What do we know about drug addiction? *Am J Psychiatry* 2005;162:1401–2. [PubMed: 16055760]
- Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, Brummer M, Staib L, Vermetten E, Charney DS, Nemeroff CB, Bremner JD. Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry* 2002;159:2072–80. [PubMed: 12450959]
- Wagner FA, Anthony JC. From first drug use to drug dependence; developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. *Neuropsychopharmacology* 2002;26:479–88. [PubMed: 11927172]
- Wang B, Luo F, Zhang WT, Han JS. Stress or drug priming induces reinstatement of extinguished conditioned place preference. *Neuroreport* 2000;11:2781–4. [PubMed: 10976962]
- Waylen A, Wolke D. Sex 'n' drugs 'n' rock 'n' roll: the meaning and social consequences of pubertal timing. *Eur J Endocrinol* 2004;151(Suppl 3):U151–9. [PubMed: 15554900]
- Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. Epigenetic programming by maternal behavior. *Nat Neurosci* 2004;7:847–54. [PubMed: 15220929]
- Weaver IC, Meaney MJ, Szyf M. Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. *Proc Natl Acad Sci U S A* 2006;103:3480–5. [PubMed: 16484373]
- Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 1987;44:660–9. [PubMed: 3606332]
- Weiss F. Neurobiology of craving, conditioned reward and relapse. *Curr Opin Pharmacol* 2005;5:9–19. [PubMed: 15661620]
- Weiss F, Ciccocioppo R, Parsons LH, Katner S, Liu X, Zorrilla EP, Valdez GR, Ben-Shahar O, Angeletti S, Richter RR. Compulsive drug-seeking behavior and relapse. Neuroadaptation, stress, and conditioning factors. *Ann N Y Acad Sci* 2001;937:1–26. [PubMed: 11458532]
- Welberg LA, Seckl JR. Prenatal stress, glucocorticoids and the programming of the brain. *J Neuroendocrinol* 2001;13:113–28. [PubMed: 11168837]
- Westermeyer J. The role of cultural and social factors in the cause of addictive disorders. *Psychiatr Clin North Am* 1999;22:253–73. [PubMed: 10385932]
- Young JB. Programming of sympathoadrenal function. *Trends Endocrinol Metab* 2002;13:381–5. [PubMed: 12367819]

Figure 1.

“Desperately driven with no brakes” is illustrated by this circuit of the stress-exposed brain. Under non-addictive states, the nucleus accumbens receives input from a number of brain regions, including the hippocampus and the prefrontal cortex. These inputs serve to modulate the response of the nucleus accumbens in a manner that is controlled, flexible, and contextually relevant. Following stress exposure, this system is less well modulated. Hippocampal gating of cortical inputs is reduced. Moreover, the prefrontal cortex inputs respond more selectively to drug-conditioned cues, which is vital is a critical factor leading to for relapse.

Percent of Actual Users

Figure 2.

Age of first use of various types of abusable substances. Data are plotted as the cumulative percentage of total users for a given type of abusable substance by age of first use. Data were collected by the National Survey on Drug Use and Health, 2002 (www.samhsa.gov/oas/p0000016.htm) and were extracted for this graph using the data-base search engine provided by the Inter-university Consortium for Political and Social Research (www.icpsr.umich.edu).