CHAPTER

1 Neuroscience of resilience and vulnerability for addiction medicine: From genes to behavior

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Abstract

Addiction is a complex behavioral disorder arising from roughly equal contributions of genetic and environmental factors. Behavioral traits such as novelty-seeking, impulsivity, and cue-reactivity have been associated with vulnerability to addiction. These traits, at least in part, arise from individual variation in functional neural systems, such as increased striatal dopaminergic activity and decreased prefrontal cortical control over subcortical emotional and motivational responses. With a few exceptions, genetic studies have largely failed to consistently identify specific alleles that affect addiction liability. This may be due to the multifactorial nature of addiction, with different genes becoming more significant in certain environments or in certain subsets of the population. Epigenetic mechanisms may also be an important source of risk. Adolescence is a particularly critical time period in the development of addiction, and environmental factors at this stage of life can have a large influence on whether inherited risk factors are actually translated into addictive behaviors. Knowledge of how individual differences affect addiction liability at the level of genes, neural systems, behavioral traits, and sociodevelopmental trajectories can help to inform and improve clinical practice.

Keywords

Addiction, Individual differences, Cue-reactivity, Impulsivity, Dopamine, Neural circuits, Genetics

There is considerable variability in the likelihood of developing addiction upon exposure to drugs of abuse. This is evidenced by the fact that over 90% of Americans have used alcohol, but only 8–12% ever meet criteria for alcohol dependence (Anthony et al., 1994). Determining what factors render certain individuals more

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susceptible to addiction has proven difficult to discern because of the array of variables involved. Over the past few decades, we have learned that there is a complex interplay of genes and environment that govern the neurobiological and behavioral processes relevant to addiction. However, there are, unquestionably, multiple algorithms by which these factors may be combined to alter addiction liability. Below we will briefly review findings from both human and animal studies that highlight some of the behavioral, neural, and genetic variables believed to contribute to addiction liability.

1 BEHAVIORAL TRAITS

Despite the oft-repeated adage that "there is no addictive personality," there is a clear association between addiction and certain personality traits. For example, clinical studies have found that the trait known as neuroticism or negative emotionality is associated with substance use disorders as well as depressive and anxiety disorders (Kotov et al., 2010; Terracciano et al., 2008). The mechanisms underlying this association are not well-characterized, but are thought to include increased stress sensitivity (Ersche et al., 2012). Another personality trait associated with addiction is the "externalizing" phenotype, characterized by novelty- and sensation-seeking behavior, hypersensitivity to rewards, and insensitivity to punishment (Dick et al., 2013; Hicks et al., 2013; Pingault et al., 2013). Evidence from animal models suggests that the sensation-seeking trait may specifically increase the propensity to initiate and continue drug use, as opposed to predisposing toward compulsive use that would meet criteria for substance dependence (Belin et al., 2008; Deroche-Gamonet et al., 2004; Piazza et al., 1989), and some human studies have substantiated this finding (Ersche et al., 2013). Trait impulsivity, otherwise known as disinhibition or lack of constraint, has perhaps the strongest evidence for an association with addiction. In the animal literature, the transition to compulsive drug use can be predicted by measures of impulsivity (Belin et al., 2008; Dalley et al., 2007); specifically the inability to withhold a prepotent response (e.g., 5-choice serial reaction time task). Similar tasks have been used with human subjects in the laboratory to assess disinhibition or lack of constraint—and, in agreement with the rodent studies, these studies have largely shown evidence for an association between trait impulsivity and addiction (for review, see Verdejo-Garcia et al., 2008). Another addiction-related trait is "cue-reactivity"; perhaps not surprisingly, as relapse is most often triggered by cues (e.g., people, places, paraphernalia) in the environment that have been previously associated with the drug-taking experience. Indeed, both human studies and animal models suggest that individuals for whom the cue attains incentive motivational value or incentive salience are the individuals most likely to exhibit relapse (e.g., see Carter and Tiffany, 1999; Janes et al., 2010; Rohsenow et al., 1990; Saunders and Robinson, 2010, 2011). These different personality traits have not only been associated with different phases of addiction but also with different types of drugs of abuse. For example, cocaine addicts tend to be more impulsive than heroin

addicts; whereas heroin addicts are more anxious than cocaine addicts (Bornovalova et al., 2005; Lejuez et al., 2005, 2006). These data beg the question of whether certain personality traits predispose an individual to a particular phase (e.g., initiation vs. relapse) of addiction or type of drug (e.g., psychostimulants vs. opioids), or if it is the drugs themselves—via alteration of brain function—that cause the behavioral traits.

2 NEUROBIOLOGICAL FACTORS

Although it has been difficult to parse cause from consequence when it comes to elucidating the neurobiological mechanisms underlying addiction, there is general agreement as to what neurotransmitter systems and brain regions are involved. All drugs of abuse share the ability to elevate dopamine transmission, either directly or indirectly (Hyman et al., 2006). It is therefore not surprising that dopamine and the mesocorticolimbic "reward" circuitry have been a primary focus of neuroscience research related to addiction. The most consistent findings to emerge from imaging studies of addicted patients are decreased dopamine type 2/3 (D2/3) receptor binding capacity, particularly in the striatum, and decreased activity in prefrontal cortical (PFC) areas that normally provide "top-down" executive control over striatal activity (Volkow et al., 1993; Wang et al., 2012a). Decreased striatal D2/3 receptor binding has also been reliably associated with novelty-seeking and impulsivity in both human and animal studies (Buckholtz et al., 2010; Dalley et al., 2011; Leyton et al., 2002; Zald et al., 2008), as has increased dopaminergic activity in the striatum at baseline and in response to various stimuli in rats (Hooks et al., 1991; Piazza et al., 1991). Further, human studies have shown that, in addition to lower levels of functional activity in PFC areas, impulsive individuals exhibit decreased functional connectivity between the PFC and subcortical structures, including the amygdala and ventral striatum (Davis et al., 2013; Schmaal et al., 2012). Fewer studies have investigated the neurobiological basis of "cue-reactivity," though existing evidence from both humans and animals suggests increased mesolimbic dopaminergic activity in cue-reactive individuals (Flagel et al., 2011; Jasinska et al., 2014). Thus, a simplified picture has emerged that individuals predisposed toward addiction are characterized neurobiologically by relatively high dopaminergic activity, coupled with decreased "top-down" cortical control.

3 GENETICS

Twin studies have yielded heritability estimates of 30–70% for addiction (Agrawal and Lynskey, 2008). Most of the genetic influences on substance use appear to be shared across different classes of substances (Kendler et al., 2008; Tsuang et al., 1998). However, the most robust findings from candidate gene and from genome-wide association studies (GWAS) have been specific to certain classes of drugs.

For example, polymorphisms affecting the function of the alcohol dehydrogenase and aldehyde dehydrogenase are some of the oldest and most potent known genetic risk/resilience factors for any psychiatric disorder, but these are genes that specifically affect alcohol metabolism and are therefore specifically related to alcohol use disorders (Hurley and Edenberg, 2012). To our knowledge, the only other association reliably and convincingly detected by both GWAS and candidate gene studies is that of nicotine dependence with variants of nicotinic acetylcholine receptor (nAChR) subunit genes (Bierut et al., 2008). Although genes affecting several other proteins have been associated with addiction, including gamma-amino butyric acid (GABA) receptors, opioid receptors, and cannabinoid receptors, these findings have been inconsistent across studies and generally specific to one or a few substances (Hall et al., 2013; Wang et al., 2012b). Even studies of genes involved in dopamine transmission have yielded mixed results, despite the fact that augmentation of dopamine transmission in the ventral striatum is a mechanistic pathway common to all drugs of abuse (Hyman et al., 2006). Difficulties in the replication of candidate gene findings do not necessarily mean that the associations are invalid; instead, it may indicate that individual genetic effects are limited to specific populations and endophenotypes. Indeed, transgenic animal studies of candidate genes generally show much more consistent and robust effects on drug-taking behaviors than human association studies would otherwise suggest. Thus, like most psychiatric disorders, addiction appears to be highly heritable, but the multifactorial and polygenic nature of the disorder makes specific gene associations very difficult to detect.

4 EPIGENETICS

Intriguingly, emerging evidence from the animal literature is implicating transgenerational epigenetic mechanisms as possible contributors to the heritability of addictive disorders (Vassoler and Sadri-Vakili, 2014; Yohn et al., 2015). Epigenetic changes are experience-dependent chemical alterations to chromosomes that affect gene expression. The most widely studied epigenetic markers are DNA methylation and histone methylation and acetylation. Although there have been a number of studies demonstrating epigenetic modifications in response to drugs of abuse (for review, see Renthal and Nestler, 2008), few, to our knowledge, have identified epigenetic mechanisms that contribute to addiction vulnerability. Thus, for the purpose of this chapter, we will focus on transgenerational epigenetic mechanisms, that is, those that are retained throughout embryonic development, and thereby passed on from parent to offspring. For example, exposure to alcohol causes several epigenetic changes to be passed on to offspring and successive generations of rodents, including demethylation of the imprinted gene *H19* (Ouko et al., 2009), demethylation of the promoter region of exon IV of the brain-derived neurotrophic factor (*Bdnf*) gene (Finegersh and Homanics, 2014), increased methylation of the dopamine transporter (*Dat*) promoter (Kim et al., 2014), and methylation of the pro-opioid melanocortin (*Pomc*) promoter in the arcuate nucleus (Govorko et al., 2012). Remarkably, there are a

number of common associations of these epigenetic changes, including increased *Bdnf* expression in the ventral tegmental area (VTA), decreased DAT in the cortex and striatum, decreased hypothalamic *Pomc* (Govorko et al., 2012), decreased fear behaviors, increased aggression and impulsivity (Meek et al., 2007), and attention deficits (Kim et al., 2014).

There is also evidence of transgenerational epigenetic changes induced by other substances. For example, rats exposed to opioids have progeny that exhibit altered responses to dopaminergic agents (Byrnes et al., 2013; Vyssotski, 2011). Offspring of dams exposed to nicotine are hyperactive and inattentive, and have increased methylation of the *Bdnf* promoter and decreased BDNF levels in the frontal cortex (Toledo-Rodriguez et al., 2010; Yochum et al., 2014; Zhu et al., 2014). In contrast to changes induced by other substances, the transgenerational effects of cocaine exposure may actually be protective, as the progeny of cocaine-exposed rodents have increased acetylated histone 3 associated with *Bdnf* exon IV, increased BDNF expression in the medial prefrontal cortex, and reduced cocaine self-administration (Vassoler et al., 2013). Though many mechanistic details for these effects remain to be discovered, and all of the epigenetic findings mentioned here await further confirmation from other groups, transgenerational epigenetic inheritance of risk may prove to be an important component of individual differences in vulnerability to addiction.

5 DEVELOPMENTAL FACTORS

Environmental factors and life experiences also play a large role in determining an individual's risk for developing an addictive disorder. Several studies have shown that the younger a person is upon first exposure to drugs or alcohol, the higher their risk of addiction, even after controlling for other variables (e.g., Chen et al., 2009; Dawson et al., 2008; King and Chassin, 2007). Similarly, animal studies have shown that exposure to stress, particularly in the prenatal or early childhood period, increases the risk of addiction (Deminiere et al., 1992; Henry et al., 1995; Kippin et al., 2008). Human imaging studies show that the adolescent brain is also particularly responsive to stressful stimuli (Gunnar et al., 2009; Stroud et al., 2009). Human and animal studies have shown that stress very early in life will sensitize the hypothalamic-pituitary-adrenal axis, such that later stress responses become exaggerated (Higley et al., 1991; Liu et al., 1997; Tarullo and Gunnar, 2006). In addition, dopaminergic activity increases in the striatum and decreases in cortical regions after early life stress in both humans and animals (Blanc et al., 1980; Brake et al., 2004; Pruessner et al., 2004). Importantly, animal studies indicate that many of these changes can be mitigated by increased maternal care or environmental enrichment (Barbazanges et al., 1996; Plotsky and Meaney, 1993; Solinas et al., 2010). Genetic studies in humans have shown that childhood experiences moderate the effects of several genes on addiction, including polymorphisms in the serotonin transporter, dopamine type 2 receptor, monoamine oxidase, and corticotrophin releasing hormone receptor 1 (Bau et al., 2000; Bjork et al., 2010; Blomeyer et al., 2008). Thus,

many genetic risk factors may only become relevant in the setting of known environmental stressors such as parental divorce, migration, and comorbid psychiatric illness; conversely, genetic influences may be reduced by protective environmental factors such as marriage, religiosity, and parental involvement (Dick et al., 2007a,b; Heath et al., 1989; Koopmans et al., 1999).

The contributions of genetic and environmental risk factors vary over the course of development, and multiple lines of evidence from the human and animal literature implicate adolescence as a critical period in the development of addictive disorders (Adriani and Laviola, 2004; Belsky et al., 2013; Vrieze et al., 2012). As with most psychiatric disorders, the onset of addictive disorders peaks in adolescence (SAMSHA, 2014). Brain maturation takes place unevenly throughout the brain, with basic motivational regions such as the striatum developing well before more cognitive PFC regions that are involved in exerting control over appetitive urges (Dahl, 2008; Gogtay et al., 2004; Sowell et al., 2003). Dopaminergic activity throughout the limbic system is increased during adolescence (McCutcheon et al., 2012; Rosenberg and Lewis, 1994). In addition, glutamatergic connections between the prefrontal cortex and subcortical structures, including the ventral striatum and amygdala, are reduced in adolescents (Brenhouse et al., 2008; Cunningham et al., 2002). Hence, the adolescent brain is sometimes described as a high-performance sports car with faulty brakes. As might be expected based on these neurobiological characteristics, adolescents are more impulsive and sensation-seeking than adults (Adriani and Laviola, 2003; Adriani et al., 1998; Romer et al., 2009). They are also more likely to engage in risky behaviors, including taking drugs more often and in larger quantities, than adults (Merrick et al., 2004; SAMSHA, 2014; Steinberg, 2008).

It is interesting to note that risk-taking behavior may also serve important, adaptive functions for adolescents. The transition to independence requires stepping outside of one's comfort zone in order to achieve a sense of competence in adult situations. Risky activities such as substance use may contribute to social development, as teens who experiment with drugs are more socially competent and accepted by their peers than abstainers (Spear, 2000). Social aspects of the environment are more emotionally salient for adolescents, and this sensitivity is reflected by increased limbic activity in response to social cues (Choudhury et al., 2006; Monk et al., 2003; Yang et al., 2003). Perhaps unsurprisingly, then, substance use and antisocial behavior among peers is a strong risk factor for the development of addiction in adolescence (Dick et al., 2007a,b; Harden et al., 2008). Hormonal influences are also likely to play a role in addiction during this time period, as testosterone contributes to synaptic pruning during adolescence (Nguyen et al., 2013). Women, though less likely overall to develop addictive disorders, generally have a more severe and treatment-resistant course of illness, more stress-related comorbidities, and faster transitions to compulsive drug use than men, again highlighting the influence of hormones on drug-taking behavior (Kuhn, 2015; Nguyen et al., 2013). These findings, taken together, illustrate that adolescence is an extraordinarily sensitive time window with regard to the development of addiction.

6 CONCLUSION AND FUTURE DIRECTIONS

The information garnered from research into addiction vulnerability has the potential to inform and improve treatment of addictive disorders in several ways. For instance, there is considerable interest in using biomarkers to identify individuals who are at high risk of developing addiction. Theoretically, information about a person's dopaminergic activity, functional connectivity patterns, or even BDNF expression patterns in the brain could be used to estimate risk, but currently none of these indicators are sensitive or specific enough to serve as true biomarkers. Genetic information has the potential to be very informative, as heredity can account for upward of 70% of an individual's risk for addiction. However, other than a handful of substance-specific genes, genetic studies have so far not been very successful at consistently finding particular genotypes that contribute to addiction liability. Because of the multifactorial nature of addiction, future genetic studies may need to focus on particular subpopulations, endophenotypes, or subtypes of addiction, in addition to better accounting for environmental modifiers of genetic risk, in order to identify clinically relevant risk alleles. Emerging evidence from the animal literature suggests that epigenomic association studies may also be useful for accounting for the heritable portion of addiction vulnerability.

However, despite gaps in our knowledge of the specific genes and neural circuitry involved in addiction liability, existing information is often enough to produce clinically relevant estimates of an individual's risk of developing an addictive disorder. For example, we already know that an impulsive, sensation-seeking individual, whose parents and grandparents suffered from addiction, who undergoes neglect or other trauma at an early age, and who is surrounded by peers engaging in high-risk substance use, is very likely to develop an addictive disorder. We can even predict with considerable confidence that the disorder will emerge sometime between the ages of 12 and 25. The question then becomes, how do we use this information to improve clinical outcomes? First, do no harm. In 2013, the leading cause of accidental death in the United States was drug overdose, and over 50% of the drugs involved were prescription opioids and benzodiazepines (CDC, 2014, 2015). Prescribing physicians should make a concerted effort to limit access to drugs with addictive potential for individuals *and relatives* of individuals at high risk of developing addictive disorders, because the vast majority of abused prescription drugs are prescribed either to the user themselves or to a relative of the user (SAMSHA, 2014). Patients should be educated about their own risk profile and that of their family members, so that they can make informed decisions about the way they use potentially addictive substances. Formal prevention programs aimed at adolescents have largely failed to influence substance use rates, but parental behaviors often have a profound effect on teenage substance use (SAMSHA, 2014). Thus, parents of adolescents who are at high risk of developing addiction should be encouraged to take steps that are known to reduce the risk of addiction, such as explicitly discouraging drug use, monitoring the child's peers and activities, actively involving themselves in the child's

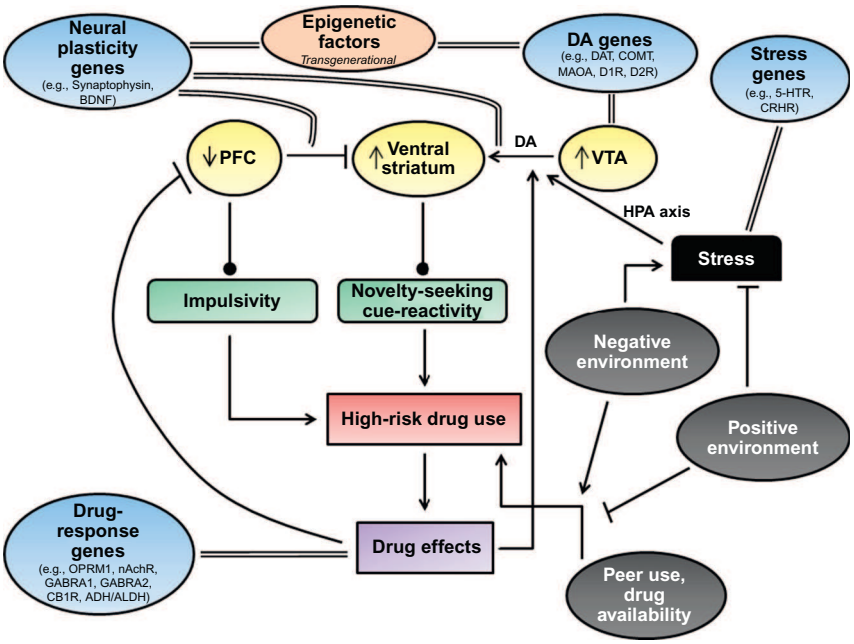

FIGURE 1

Addiction vulnerability at multiple, interacting levels. High-risk drug use (red; black in the print version) is potentiated by personality traits (green; light gray in the print version) including impulsivity, novelty-seeking, and cue-reactivity. These personality traits, in turn, reflect neurobiological traits (yellow; white in the print version) including increased dopaminergic activity and decreased prefrontal cortical control over ventral striatal impulses. Addictive drugs (purple; dark gray in the print version) directly affect this neural circuitry, which is one driver of the cycle of addiction. Stress (black), acting through the hypothalamic pituitary adrenal (HPA) axis, predisposes toward addictive behavior by enhancing dopaminergic activity. Environmental factors (gray) affect vulnerability either through their effects on stress, or via a more direct effect on the probability of drug use. Genetic polymorphisms (blue; light gray in the print version) affect this system in a variety of ways. "Drug–response genes" modulate the pharmacologic effects of drug use, while other genes modulate dopaminergic activity, stress reactivity, or corticolimbic connectivity patterns. Transgenerational epigenetic influences (orange; dark gray in the print version) may be mediated by these same gene families, with most of the evidence so far implicating dopaminergic genes and synaptic plasticity genes. Definitions of connectors: arrows indicate one variable potentiating the other; lines terminating with a hash bar indicate an inhibitory relationship; lines terminating with a circle indicate a positive association; double-hashed lines indicate a relationship that can be either positive or negative, depending on the allele. Abbreviations: 5-HTR, serotonin receptor; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; BDNF, brain-derived neurotrophic factor; CB1R, cannabinoid type 1 receptor; COMT, catechol-*O*-methyl transferase; CRHR, corticotrophin-releasing hormone receptor; D1R, dopamine type 1 receptor; D2R, dopamine type 2 receptor; DAT, dopamine transporter; GABRA1, gamma-aminobutyric acid (GABA) receptor subunit alpha-1; GABRA2, GABA receptor subunit alpha-2; HPA, hypothalamic-pituitary-adrenal; MAOA, monoamine oxidase A; nAChR, nicotinic acetylcholine receptor; OPRM1, opioid receptor mu 1; PFC, prefrontal cortex; VTA, ventral tegmental area.

homework and other activities, providing a stable family life, and involving the child in religious activities.

Treatment of patients who already have addiction may also benefit from knowledge of specific vulnerability factors. For example, personality traits associated with addiction can, in some cases, be targeted by specific clinical interventions. To date, few studies have taken this approach, but one indication of its potential utility is the finding that, for individuals with addiction and comorbid attention deficit hyperactivity disorder, treatment of their impulsivity with potentially addictive psychostimulants paradoxically reduces their risk of relapse (Levin et al., 2007). Selective serotonin reuptake inhibitors (SSRIs) have largely been disappointing as a treatment for addiction (Nunes and Levin, 2004) but because they actually reduce the neuroticism trait (Tang et al., 2009), SSRIs might be useful in treating a subset of patients for whom neuroticism is a primary driver of their addiction. Information about personality traits and other neurobiological factors might also be used to tailor specific treatment interventions; for example, emphasizing stress reduction in individuals with high neuroticism, or focusing more on identifying and avoiding cues for individuals with markers of excessive cue-reactivity. Sophisticated methods (e.g., optogenetics, designer receptors exclusively activated by designer drugs—DREADDs) are being developed in rodents to directly manipulate the neural circuitry responsible for individual differences in cue-reactivity and other behavioral traits, but because many of these approaches involve genetic modification of neurons, they are many years away from being available for clinical trials.

As research progresses, the multifactorial nature of addiction becomes even more apparent. Yet, remarkably, as outlined above, there are a number of vulnerability factors that repeatedly appear in the literature, common to both human and animal studies, and linked at multiple levels of analysis (e.g., genetic and neurobiological; see Fig. 1 for a simplified visual summary). Moving forward, the advent and accessibility of new technology (e.g., Saunders et al., 2015) will allow increasingly precise analysis of the neurobiological factors contributing to addiction liability. For example, chemogenetic approaches could be used to manipulate "top-down" cortical circuits in order to "switch" the behavioral phenotype of an animal from one that is addiction-prone, to one that is addiction-resilient. A continuing challenge for the field will be integrating this new knowledge with the other layers of genetic, epigenetic, developmental, and environmental factors that interact in multiple ways with this neural circuitry in order to determine an individual's risk for addiction.

REFERENCES

Adriani, W., Laviola, G., 2003. Elevated levels of impulsivity and reduced place conditioning with d-amphetamine: two behavioral features of adolescence in mice. Behav. Neurosci. 117 (4), 695–703.

Adriani, W., Laviola, G., 2004. Windows of vulnerability to psychopathology and therapeutic strategy in the adolescent rodent model. Behav. Pharmacol. 15 (5-6), 341–352.

Adriani, W., Chiarotti, F., Laviola, G., 1998. Elevated novelty seeking and peculiar d-amphetamine sensitization in periadolescent mice compared with adult mice. Behav. Neurosci. 112 (5), 1152–1166.

Agrawal, A., Lynskey, M.T., 2008. Are there genetic influences on addiction: evidence from family, adoption and twin studies. Addiction 103 (7), 1069–1081.

Anthony, J.C., Warner, S.A., Kessler, R.C., 1994. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. Exp. Clin. Psychopharmacol. 2 (3), 244–268.

Barbazanges, A., Vallee, M., Mayo, W., Day, J., Simon, H., Le Moal, M., Maccari, S., 1996. Early and later adoptions have different long-term effects on male rat offspring. J. Neurosci. 16 (23), 7783–7790.

Bau, C.H., Almeida, S., Hutz, M.H., 2000. The TaqI A1 allele of the dopamine D2 receptor gene and alcoholism in Brazil: association and interaction with stress and harm avoidance on severity prediction. Am. J. Med. Genet. 96 (3), 302–306.

Belin, D., Mar, A.C., Dalley, J.W., Robbins, T.W., Everitt, B.J., 2008. High impulsivity predicts the switch to compulsive cocaine-taking. Science 320 (5881), 1352–1355.

Belsky, D.W., Moffitt, T.E., Baker, T.B., Biddle, A.K., Evans, J.P., Harrington, H., et al., 2013. Polygenic risk and the developmental progression to heavy, persistent smoking and nicotine dependence: evidence from a 4-decade longitudinal study. JAMA Psychiatry 70 (5), 534–542.

Bierut, L.J., Stitzel, J.A., Wang, J.C., Hinrichs, A.L., Grucza, R.A., Xuei, X., et al., 2008. Variants in nicotinic receptors and risk for nicotine dependence. Am. J. Psychiatry 165 (9), 1163–1171.

Bjork, K., Hansson, A.C., Sommer, W.H., 2010. Genetic variation and brain gene expression in rodent models of alcoholism implications for medication development. Int. Rev. Neurobiol. 91, 129–171.

Blanc, G., Herve, D., Simon, H., Lisoprawski, A., Glowinski, J., Tassin, J.P., 1980. Response to stress of mesocortico-frontal dopaminergic neurones in rats after long-term isolation. Nature 284 (5753), 265–267.

Blomeyer, D., Treutlein, J., Esser, G., Schmidt, M.H., Schumann, G., Laucht, M., 2008. Interaction between CRHR1 gene and stressful life events predicts adolescent heavy alcohol use. Biol. Psychiatry 63 (2), 146–151.

Bornovalova, M.A., Daughters, S.B., Hernandez, G.D., Richards, J.B., Lejuez, C.W., 2005. Differences in impulsivity and risk-taking propensity between primary users of crack cocaine and primary users of heroin in a residential substance-use program. Exp. Clin. Psychopharmacol. 13 (4), 311–318.

Brake, W.G., Zhang, T.Y., Diorio, J., Meaney, M.J., Gratton, A., 2004. Influence of early postnatal rearing conditions on mesocorticolimbic dopamine and behavioural responses to psychostimulants and stressors in adult rats. Eur. J. Neurosci. 19 (7), 1863–1874.

Brenhouse, H.C., Sonntag, K.C., Andersen, S.L., 2008. Transient D1 dopamine receptor expression on prefrontal cortex projection neurons: relationship to enhanced motivational salience of drug cues in adolescence. J. Neurosci. 28 (10), 2375–2382.

Buckholtz, J.W., Treadway, M.T., Cowan, R.L., Woodward, N.D., Li, R., Ansari, M.S., et al., 2010. Dopaminergic network differences in human impulsivity. Science 329 (5991), 532.

Byrnes, J.J., Johnson, N.L., Carini, L.M., Byrnes, E.M., 2013. Multigenerational effects of adolescent morphine exposure on dopamine D2 receptor function. Psychopharmacology (Berl) 227 (2), 263–272.

Carter, B.L., Tiffany, S.T., 1999. Cue-reactivity and the future of addiction research. Addiction 94 (3), 349–351.
CDC, 2014. Centers for Disease Control and Prevention. Web-based Injury Statistics Query and Reporting System (WISQARS). http://www.cdc.gov/injury/wisqars/fatal.html.
CDC, 2015. Centers for Disease Control and Prevention. National Vital Statistics System Mortality Data. http://www.cdc.gov/nchs/deaths.htm.
Chen, C.Y., Storr, C.L., Anthony, J.C., 2009. Early-onset drug use and risk for drug dependence problems. Addict. Behav. 34 (3), 319–322.
Choudhury, S., Blakemore, S.J., Charman, T., 2006. Social cognitive development during adolescence. Soc. Cogn. Affect. Neurosci. 1 (3), 165–174.
Cunningham, M.G., Bhattacharyya, S., Benes, F.M., 2002. Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence. J. Comp. Neurol. 453 (2), 116–130.
Dahl, R.E., 2008. Biological, developmental, and neurobehavioral factors relevant to adolescent driving risks. Am. J. Prev. Med. 35 (3 Suppl.), S278–S284.
Dalley, J.W., Fryer, T.D., Brichard, L., Robinson, E.S., Theobald, D.E., Laane, K., et al., 2007. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 315 (5816), 1267–1270.
Dalley, J.W., Everitt, B.J., Robbins, T.W., 2011. Impulsivity, compulsivity, and top-down cognitive control. Neuron 69 (4), 680–694.
Davis, F.C., Knodt, A.R., Sporns, O., Lahey, B.B., Zald, D.H., Brigidi, B.D., Hariri, A.R., 2013. Impulsivity and the modular organization of resting-state neural networks. Cereb. Cortex 23 (6), 1444–1452.
Dawson, D.A., Goldstein, R.B., Chou, S.P., Ruan, W.J., Grant, B.F., 2008. Age at first drink and the first incidence of adult-onset DSM-IV alcohol use disorders. Alcohol. Clin. Exp. Res. 32 (12), 2149–2160.
Deminiere, J.M., Piazza, P.V., Guegan, G., Abrous, N., Maccari, S., Le Moal, M., Simon, H., 1992. Increased locomotor response to novelty and propensity to intravenous amphetamine self-administration in adult offspring of stressed mothers. Brain Res. 586 (1), 135–139.
Deroche-Gamonet, V., Belin, D., Piazza, P.V., 2004. Evidence for addiction-like behavior in the rat. Science 305 (5686), 1014–1017.
Dick, D.M., Pagan, J.L., Holliday, C., Viken, R., Pulkkinen, L., Kaprio, J., Rose, R.J., 2007a. Gender differences in friends' influences on adolescent drinking: a genetic epidemiological study. Alcohol. Clin. Exp. Res. 31 (12), 2012–2019.
Dick, D.M., Viken, R., Purcell, S., Kaprio, J., Pulkkinen, L., Rose, R.J., 2007b. Parental monitoring moderates the importance of genetic and environmental influences on adolescent smoking. J. Abnorm. Psychol. 116 (1), 213–218.
Dick, D.M., Aliev, F., Latendresse, S.J., Hickman, M., Heron, J., Macleod, J., et al., 2013. Adolescent alcohol use is predicted by childhood temperament factors before age 5, with mediation through personality and peers. Alcohol. Clin. Exp. Res. 37 (12), 2108–2117.
Ersche, K.D., Turton, A.J., Chamberlain, S.R., Muller, U., Bullmore, E.T., Robbins, T.W., 2012. Cognitive dysfunction and anxious-impulsive personality traits are endophenotypes for drug dependence. Am. J. Psychiatry 169 (9), 926–936.
Ersche, K.D., Jones, P.S., Williams, G.B., Smith, D.G., Bullmore, E.T., Robbins, T.W., 2013. Distinctive personality traits and neural correlates associated with stimulant drug use versus familial risk of stimulant dependence. Biol. Psychiatry 74 (2), 137–144.

Finegersh, A., Homanics, G.E., 2014. Paternal alcohol exposure reduces alcohol drinking and increases behavioral sensitivity to alcohol selectively in male offspring. PLoS One 9 (6), e99078.

Flagel, S.B., Clark, J.J., Robinson, T.E., Mayo, L., Czuj, A., Willuhn, I., et al., 2011. A selective role for dopamine in stimulus-reward learning. Nature 469 (7328), 53–57.

Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., et al., 2004. Dynamic mapping of human cortical development during childhood through early adulthood. Proc. Natl. Acad. Sci. U. S. A. 101 (21), 8174–8179.

Govorko, D., Bekdash, R.A., Zhang, C., Sarkar, D.K., 2012. Male germline transmits fetal alcohol adverse effect on hypothalamic proopiomelanocortin gene across generations. Biol. Psychiatry 72 (5), 378–388.

Gunnar, M.R., Wewerka, S., Frenn, K., Long, J.D., Griggs, C., 2009. Developmental changes in hypothalamus-pituitary-adrenal activity over the transition to adolescence: normative changes and associations with puberty. Dev. Psychopathol. 21 (1), 69–85.

Hall, F.S., Drgonova, J., Jain, S., Uhl, G.R., 2013. Implications of genome wide association studies for addiction: are our a priori assumptions all wrong? Pharmacol. Ther. 140 (3), 267–279.

Harden, K.P., Hill, J.E., Turkheimer, E., Emery, R.E., 2008. Gene-environment correlation and interaction in peer effects on adolescent alcohol and tobacco use. Behav. Genet. 38 (4), 339–347.

Heath, A.C., Jardine, R., Martin, N.G., 1989. Interactive effects of genotype and social environment on alcohol consumption in female twins. J. Stud. Alcohol 50 (1), 38–48.

Henry, C., Guegant, G., Cador, M., Arnauld, E., Arsaut, J., Le Moal, M., Demotes-Mainard, J., 1995. Prenatal stress in rats facilitates amphetamine-induced sensitization and induces long-lasting changes in dopamine receptors in the nucleus accumbens. Brain Res. 685 (1–2), 179–186.

Hicks, B.M., Foster, K.T., Iacono, W.G., McGue, M., 2013. Genetic and environmental influences on the familial transmission of externalizing disorders in adoptive and twin offspring. JAMA Psychiatry 70 (10), 1076–1083.

Higley, J.D., Hasert, M.F., Suomi, S.J., Linnoila, M., 1991. Nonhuman primate model of alcohol abuse: effects of early experience, personality, and stress on alcohol consumption. Proc. Natl. Acad. Sci. U. S. A. 88 (16), 7261–7265.

Hooks, M.S., Jones, G.H., Smith, A.D., Neill, D.B., Justice Jr., J.B., 1991. Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. Synapse 9 (2), 121–128.

Hurley, T.D., Edenberg, H.J., 2012. Genes encoding enzymes involved in ethanol metabolism. Alcohol Res. 34 (3), 339–344.

Hyman, S.E., Malenka, R.C., Nestler, E.J., 2006. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu. Rev. Neurosci. 29, 565–598.

Janes, A.C., Pizzagalli, D.A., Richardt, S., deB Frederick, B., Chuzi, S., Pachas, G., et al., 2010. Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. Biol. Psychiatry 67 (8), 722–729.

Jasinska, A.J., Stein, E.A., Kaiser, J., Naumer, M.J., Yalachkov, Y., 2014. Factors modulating neural reactivity to drug cues in addiction: a survey of human neuroimaging studies. Neurosci. Biobehav. Rev. 38, 1–16.

Kendler, K.S., Schmitt, E., Aggen, S.H., Prescott, C.A., 2008. Genetic and environmental influences on alcohol, caffeine, cannabis, and nicotine use from early adolescence to middle adulthood. Arch. Gen. Psychiatry 65 (6), 674–682.

Kim, P., Choi, C.S., Park, J.H., Joo, S.H., Kim, S.Y., Ko, H.M., et al., 2014. Chronic exposure to ethanol of male mice before mating produces attention deficit hyperactivity disorder-like phenotype along with epigenetic dysregulation of dopamine transporter expression in mouse offspring. J. Neurosci. Res. 92 (5), 658–670.

King, K.M., Chassin, L., 2007. A prospective study of the effects of age of initiation of alcohol and drug use on young adult substance dependence. J. Stud. Alcohol Drugs 68 (2), 256–265.

Kippin, T.E., Szumlinski, K.K., Kapasova, Z., Rezner, B., See, R.E., 2008. Prenatal stress enhances responsiveness to cocaine. Neuropsychopharmacology 33 (4), 769–782.

Koopmans, J.R., Slutske, W.S., van Baal, G.C., Boomsma, D.I., 1999. The influence of religion on alcohol use initiation: evidence for genotype X environment interaction. Behav. Genet. 29 (6), 445–453.

Kotov, R., Gamez, W., Schmidt, F., Watson, D., 2010. Linking "big" personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. Psychol. Bull. 136 (5), 768–821.

Kuhn, C., 2015. Emergence of sex differences in the development of substance use and abuse during adolescence. Pharmacol. Ther. 153, 55–78.

Lejuez, C.W., Bornovalova, M.A., Daughters, S.B., Curtin, J.J., 2005. Differences in impulsivity and sexual risk behavior among inner-city crack/cocaine users and heroin users. Drug Alcohol Depend. 77 (2), 169–175.

Lejuez, C.W., Paulson, A., Daughters, S.B., Bornovalova, M.A., Zvolensky, M.J., 2006. The association between heroin use and anxiety sensitivity among inner-city individuals in residential drug use treatment. Behav. Res. Ther. 44 (5), 667–677.

Levin, F.R., Evans, S.M., Brooks, D.J., Garawi, F., 2007. Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo. Drug Alcohol Depend. 87 (1), 20–29.

Leyton, M., Boileau, I., Benkelfat, C., Diksic, M., Baker, G., Dagher, A., 2002. Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C]raclopride study in healthy men. Neuropsychopharmacology 27 (6), 1027–1035.

Liu, D., Diorio, J., Tannenbaum, B., Caldji, C., Francis, D., Freedman, A., et al., 1997. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. Science 277 (5332), 1659–1662.

McCutcheon, J.E., Conrad, K.L., Carr, S.B., Ford, K.A., McGehee, D.S., Marinelli, M., 2012. Dopamine neurons in the ventral tegmental area fire faster in adolescent rats than in adults. J. Neurophysiol. 108 (6), 1620–1630.

Meek, L.R., Myren, K., Sturm, J., Burau, D., 2007. Acute paternal alcohol use affects offspring development and adult behavior. Physiol. Behav. 91 (1), 154–160.

Merrick, J., Kandel, I., Birnbaum, L., Hyam, E., Press, J., Morad, M., 2004. Adolescent injury risk behavior. Int. J. Adolesc. Med. Health 16 (3), 207–213.

Monk, C.S., McClure, E.B., Nelson, E.E., Zarahn, E., Bilder, R.M., Leibenluft, E., et al., 2003. Adolescent immaturity in attention-related brain engagement to emotional facial expressions. Neuroimage 20 (1), 420–428.

Nguyen, T.V., McCracken, J., Ducharme, S., Botteron, K.N., Mahabir, M., Johnson, W., et al., 2013. Testosterone-related cortical maturation across childhood and adolescence. Cereb. Cortex 23 (6), 1424–1432.

Nunes, E.V., Levin, F.R., 2004. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. JAMA 291 (15), 1887–1896.

Ouko, L.A., Shantikumar, K., Knezovich, J., Haycock, P., Schnugh, D.J., Ramsay, M., 2009. Effect of alcohol consumption on CpG methylation in the differentially methylated regions

of H19 and IG-DMR in male gametes: implications for fetal alcohol spectrum disorders. Alcohol. Clin. Exp. Res. 33 (9), 1615–1627.
Piazza, P.V., Deminiere, J.M., Le Moal, M., Simon, H., 1989. Factors that predict individual vulnerability to amphetamine self-administration. Science 245 (4925), 1511–1513.
Piazza, P.V., Rouge-Pont, F., Deminiere, J.M., Kharoubi, M., Le Moal, M., Simon, H., 1991. Dopaminergic activity is reduced in the prefrontal cortex and increased in the nucleus accumbens of rats predisposed to develop amphetamine self-administration. Brain Res. 567 (1), 169–174.
Pingault, J.B., Cote, S.M., Galera, C., Genolini, C., Falissard, B., Vitaro, F., Tremblay, R.E., 2013. Childhood trajectories of inattention, hyperactivity and oppositional behaviors and prediction of substance abuse/dependence: a 15-year longitudinal population-based study. Mol. Psychiatry 18 (7), 806–812.
Plotsky, P.M., Meaney, M.J., 1993. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. Brain Res. Mol. Brain Res. 18 (3), 195–200.
Pruessner, J.C., Champagne, F., Meaney, M.J., Dagher, A., 2004. Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [11C]raclopride. J. Neurosci. 24 (11), 2825–2831.
Renthal, W., Nestler, E.J., 2008. Epigenetic mechanisms in drug addiction. Trends Mol. Med. 14 (8), 341–350.
Rohsenow, D.J., Niaura, R.S., Childress, A.R., Abrams, D.B., Monti, P.M., 1990. Cue reactivity in addictive behaviors: theoretical and treatment implications. Int. J. Addict. 25 (7A–8A), 957–993.
Romer, D., Betancourt, L., Giannetta, J.M., Brodsky, N.L., Farah, M., Hurt, H., 2009. Executive cognitive functions and impulsivity as correlates of risk taking and problem behavior in preadolescents. Neuropsychologia 47 (13), 2916–2926.
Rosenberg, D.R., Lewis, D.A., 1994. Changes in the dopaminergic innervation of monkey prefrontal cortex during late postnatal development: a tyrosine hydroxylase immunohistochemical study. Biol. Psychiatry 36 (4), 272–277.
SAMSHA, 2014. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. Substance Abuse and Mental Health Services Administration, Rockville, MD.
Saunders, B.T., Robinson, T.E., 2010. A cocaine cue acts as an incentive stimulus in some but not others: implications for addiction. Biol. Psychiatry 67 (8), 730–736.
Saunders, B.T., Robinson, T.E., 2011. Individual variation in the motivational properties of cocaine. Neuropsychopharmacology 36 (8), 1668–1676.
Saunders, B.T., Richard, J.M., Janak, P.H., 2015. Contemporary approaches to neural circuit manipulation and mapping: focus on reward and addiction. Philos. Trans. R. Soc. Lond. B Biol. Sci. 370 (1677).
Schmaal, L., Goudriaan, A.E., van der Meer, J., van den Brink, W., Veltman, D.J., 2012. The association between cingulate cortex glutamate concentration and delay discounting is mediated by resting state functional connectivity. Brain Behav. 2 (5), 553–562.
Solinas, M., Thiriet, N., Chauvet, C., Jaber, M., 2010. Prevention and treatment of drug addiction by environmental enrichment. Prog. Neurobiol. 92 (4), 572–592.
Sowell, E.R., Peterson, B.S., Thompson, P.M., Welcome, S.E., Henkenius, A.L., Toga, A.W., 2003. Mapping cortical change across the human life span. Nat. Neurosci. 6 (3), 309–315.

Spear, L.P., 2000. The adolescent brain and age-related behavioral manifestations. Neurosci. Biobehav. Rev. 24 (4), 417–463.
Steinberg, L., 2008. A social neuroscience perspective on adolescent risk-taking. Dev. Rev. 28 (1), 78–106.
Stroud, L.R., Foster, E., Papandonatos, G.D., Handwerger, K., Granger, D.A., Kivlighan, K.T., Niaura, R., 2009. Stress response and the adolescent transition: performance versus peer rejection stressors. Dev. Psychopathol. 21 (1), 47–68.
Tang, T.Z., DeRubeis, R.J., Hollon, S.D., Amsterdam, J., Shelton, R., Schalet, B., 2009. Personality change during depression treatment: a placebo-controlled trial. Arch. Gen. Psychiatry 66 (12), 1322–1330.
Tarullo, A.R., Gunnar, M.R., 2006. Child maltreatment and the developing HPA axis. Horm. Behav. 50 (4), 632–639.
Terracciano, A., Lockenhoff, C.E., Crum, R.M., Bienvenu, O.J., Costa Jr., P.T., 2008. Five-Factor Model personality profiles of drug users. BMC Psychiatry 8, 22.
Toledo-Rodriguez, M., Lotfipour, S., Leonard, G., Perron, M., Richer, L., Veillette, S., et al., 2010. Maternal smoking during pregnancy is associated with epigenetic modifications of the brain-derived neurotrophic factor-6 exon in adolescent offspring. Am. J. Med. Genet. B Neuropsychiatr. Genet. 153B (7), 1350–1354.
Tsuang, M.T., Lyons, M.J., Meyer, J.M., Doyle, T., Eisen, S.A., Goldberg, J., et al., 1998. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. Arch. Gen. Psychiatry 55 (11), 967–972.
Vassoler, F.M., Sadri-Vakili, G., 2014. Mechanisms of transgenerational inheritance of addictive-like behaviors. Neuroscience 264, 198–206.
Vassoler, F.M., White, S.L., Schmidt, H.D., Sadri-Vakili, G., Pierce, R.C., 2013. Epigenetic inheritance of a cocaine-resistance phenotype. Nat. Neurosci. 16 (1), 42–47.
Verdejo-Garcia, A., Lawrence, A.J., Clark, L., 2008. Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. Neurosci. Biobehav. Rev. 32 (4), 777–810.
Volkow, N.D., Fowler, J.S., Wang, G.J., Hitzemann, R., Logan, J., Schlyer, D.J., et al., 1993. Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. Synapse 14 (2), 169–177.
Vrieze, S.I., McGue, M., Iacono, W.G., 2012. The interplay of genes and adolescent development in substance use disorders: leveraging findings from GWAS meta-analyses to test developmental hypotheses about nicotine consumption. Hum. Genet. 131 (6), 791–801.
Vyssotski, D.L., 2011. Transgenerational epigenetic compensation. Evolocus 1, 1–6.
Wang, G.J., Smith, L., Volkow, N.D., Telang, F., Logan, J., Tomasi, D., et al., 2012a. Decreased dopamine activity predicts relapse in methamphetamine abusers. Mol. Psychiatry 17 (9), 918–925.
Wang, J.C., Kapoor, M., Goate, A.M., 2012b. The genetics of substance dependence. Annu. Rev. Genomics Hum. Genet. 13, 241–261.
Yang, T.T., Menon, V., Reid, A.J., Gotlib, I.H., Reiss, A.L., 2003. Amygdalar activation associated with happy facial expressions in adolescents: a 3-T functional MRI study. J. Am. Acad. Child Adolesc. Psychiatry 42 (8), 979–985.
Yochum, C., Doherty-Lyon, S., Hoffman, C., Hossain, M.M., Zelikoff, J.T., Richardson, J.R., 2014. Prenatal cigarette smoke exposure causes hyperactivity and aggressive behavior: role of altered catecholamines and BDNF. Exp. Neurol. 254, 145–152.

Yohn, N.L., Bartolomei, M.S., Blendy, J.A., 2015. Multigenerational and transgenerational inheritance of drug exposure: The effects of alcohol, opiates, cocaine, marijuana, and nicotine. Prog. Biophys. Mol. Biol. 118 (1-2), 21–33.

Zald, D.H., Cowan, R.L., Riccardi, P., Baldwin, R.M., Ansari, M.S., Li, R., et al., 2008. Midbrain dopamine receptor availability is inversely associated with novelty-seeking traits in humans. J. Neurosci. 28 (53), 14372–14378.

Zhu, J., Lee, K.P., Spencer, T.J., Biederman, J., Bhide, P.G., 2014. Transgenerational transmission of hyperactivity in a mouse model of ADHD. J. Neurosci. 34 (8), 2768–2773.