Neurobiology of Addiction and the Adolescent Brain
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Abstract
Examining the neurobiology of addiction, the roles that comorbidity, stressors and genes play in brain reward circuitry and the changes in the adolescent brain enable us to understand why adolescence is a time of increased risk taking and, subsequently, increased risk of substance abuse. Untreated comorbid disorders, genetic predisposition, environmental stressors, personality and age of onset of use are factors which may add to both risk and a more chronic and severe form of addiction.

Introduction
Addiction can be broadly described as a large range of recurring compulsive behaviors in a specific activity in which an individual continues to engage despite harmful consequences to the individual’s social, biological and psychological health. Although the term is often associated with drug addictions, this definition can include such behaviors as compulsive gambling and overeating. Although drug dependence, as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR), is considered a disease state, the term addiction is not yet considered to be synonymous with this terminology. Also, drug dependence that involves drug withdrawal is distinct from addiction which involves compulsive use despite adverse consequences. Addiction for the purposes of this chapter will consider the DSM-IV-R definition of drug dependence.

Addiction to drugs and alcohol can occur anytime throughout the life of an individual. However, the age of onset is crucial to long, chronic and relapsing effects of substance abuse. Age is a risk factor likely to influence the onset of substance use during childhood and adolescence. Youths who begin drinking early, 11-12 years of age, had a higher percentage probability of meeting the DSM III-R criteria for substance abuse (13.5%) and substance dependence (15.9%), compared to those who began drinking at age 13 or 14 (13.7% and 9.0%, respectively). Those who initiated drinking at age 19 or 20 had rates of 2% and 1%. Schukit (1) has noted that the age when a substance abuser was most likely to have started drinking was 13, when first drunk was age 15, had their first problem associated with drinking at age 18, and first dependence was age 25-40. Death was most likely to occur at age 60. Importantly, rapid progression of alcohol and drug disorders occurred often with earlier age of onset and frequency, not duration of use (2; 3). Those individuals with earlier onset had a shorter time span from first exposure to dependence than did adult onset groups (4). Age of onset of heavy drinking also predicted alcohol-related problems (5). Early age of onset also influenced higher risks for the use of other substances, as noted in this case scenario. Adolescent onset adults had higher lifetime rates of cannabis and hallucinogen use disorders, shorter times between the development of their first and second dependence diagnosis and higher rates of disruptive behaviors and major depression (4).

Although early use may help to predict the risk of developing a substance abuse disorder (SUD), many teens who abuse substances will not develop an addiction following the maturation of the prefrontal cortex (PFC) in the early twenties (6). It is important to know the neurobiology of addiction, if and when it does occur, in order to understand the roles that comorbidity, stressors and genes play in these pathways which make the development of addiction more likely. It is also important to understand the changes that the adolescent brain undergoes in order to understand why this is a time of increased risk taking. Certain comorbid conditions may affect the brain reward circuitry leading to self medication of these conditions. However, if these comorbid conditions are detected early and treated, like Attention Deficit Hyperactivity Disorder/Attention Deficit Disorder (ADHD/ADD), the risk of developing a substance abuse disorder may be reduced. Stress or genes may be inherited that may increase the sensitivity to the reinforcing effects of the drugs on the brain reward circuitry. The goal of this article is to first discuss the neurobiology of addiction then to cite specific examples of how stressors, genes and comorbid conditions can influence the brain reward circuitry to increase the risk for substance abuse. Finally, the development of the adolescent brain will be discussed in order to understand why this stage of development is associated with the increased risk taking that can lead to substance abuse.

Changes in the Brain Reward Circuitry That Lead to Addiction
First, one must understand how one learns that a stimulus is salient so that the individual will learn to seek out the salient stimuli. When an individual uses cocaine, there is a rapid increase in dopamine in the shell of the nucleus accumbens (NAc). Since the cocaine is taken intravenously in this example, dopamine levels increase more rapidly and at higher levels, and therefore, greater magnitude is given to the pleasurable high. Now dopamine will be given off even only when one is anticipating using the drug (7). The evolution of this process will be discussed below. First, the shell of the NAc and dopamine are
involved in acute drug reinforcement but the core of the NAc; the basolateral amygdala and the OFC are involved in the chronic drug use that leads to addiction. The latter does not involve dopamine but rather the recruitment of glutamatergic efferents from the OFC to the core of the NAc (7; 8).

What causes the PFC (anterior cingulate and the orbital frontal cortex) to no longer recognize previously salient reinforcers and to recognize only drugs with chronic substance use? Chronic drug use causes changes in the intracellular level that cause changes in circuitry that lead to dysregulation of the reward circuitry involving the PFC, basolateral amygdala and the core of the NAc.

Changes in the intracellular level have been described as three stages (7): the acute stage, the transition stage and the end (addiction) stage.

Stage 1 - Acute Drug Effects
A review has shown that following the acute administration of cocaine, dopamine levels of the NAc are elevated with little effect on glutamatergic tone, to increase locomotor activity, and stimulate rewarding processes (9; 10; 11). However, the D1 dopamine receptor is stimulated, and the D1 dopamine receptor stimulation causes:

1. Activation of cAMP dependent protein kinase (PKA)
2. PKA induced phosphorylation of transcriptional regulator cAMP response element binding protein CREB
3. Induction of early gene products like cFOS.

CFOS causes neuroplastic changes that are short lived since the molecule cFOS is very unstable. This transcription factor activates genes that produce dynorphin, which causes dysphoria during early drug withdrawal, and genes that inhibit dopamine and locus ceruleus (ic) opioid receptors which, in turn, decrease drug reward. The transcription factor cFOS is so unstable that it dissipates in 4 to 12 hours. Therefore, limited exposure to drugs will enable the system to return to normal.

Stage 2 - Transition to Addiction
Chronic repeated administration of the drug causes stimulation of the D1 receptor to produce proteins with long half lives, such as delta FosB. Delta FosB modulates the transcription of the synthesis of certain AMPA glutamate receptor subunits and cell signaling enzymes. A GluR1 glutamate receptor in the ventral tegmental area (VTA) forms after discontinuation of substances like cocaine. Also, animals with activated Delta FosB have exaggerated sensitivity to the rewarding effects of drugs (6). In addition, Delta FosB also increases Cdk5, which, in turn, blocks the stimulating effects of cocaine or blocks the anxiolytic effect of alcohol so that, in both instances, more cocaine or alcohol is needed to get the same effect (12). Cdk5 may be one of the reasons tolerance occurs in substance abusers. Hence, if the above is true, Delta FosB may increase the rewarding effects of drugs, causing an individual to seek out these rewarding effects more often, and when the individual does, more of the drug must be used to give the same rewarding effect.

Other changes in circuitry during transition stage:

PFC to the NAc
During chronic drug use and withdrawal periods, there is an increase of G protein binding AGS3. Increased AGS3 levels inhibit D2 receptor signaling and correspondingly increase D1 receptor signaling which cause increased activity of projections from the PFC (in this case the anterior cingulate and the OFC) to the core of the nucleus accumbens which mediates behavior. What do these changes mean? The PFC determines what stimuli should be sorted out. However, these changes reduce the salience of non-drug motivational stimuli so that normal stimuli like food are no longer salient. The PFC becomes hypoactive to previously salient stimuli. However, when drug associated stimuli are available, there is a profound activation of the PFC and glutamatergic drive to the core of the NAc, and drug craving occurs.

The changes in determining what is now salient (drugs) and the activation of the PFC to the core of the NAc to produce craving move the brain from a transitional stage to the end stage of addiction. As previously mentioned, glutamate plays a more important role in drug seeking after chronic drug use as dopamine (which is involved in acute reinforcement of drugs). The NAc core increases release of glutamate in response to stimuli that induce drug seeking and intake. Such stimuli may be a cue previously associated with drug use or a mild stressor.

Stage 3 - End Stage Addiction
Changes in protein expression that mediate the transition to addiction may induce changes in protein expression that move from temporary and reversible to permanent.

What effect does glutamate produced by the NAC have on permanent adaptations that lead to continued drug use? Two things occur. First, when presynaptic glutamate is released, the GluR2/3 inhibitory autoreceptor becomes less effective. Less glutamate is released in the NAc after cocaine withdrawal; therefore, presynaptic inhibitory GluR2/3 tone is decreased, and more glutamate is released in the core of the NAc when a mild stressor or a cue associated with drug use occurs. Increase in glutamate postsynaptically causes an increase in proteins that cause rigid dendritic morphology and signaling.
The role of the amygdala is to recognize the cue-associations with drug use. In this scenario, the basolateral amygdala would recognize cue-associations with drug use (motivationally relevant events) and trigger the PFC to exert (salience) its effect on the nucleus accumbens (to mediate behavior). Thus, the PFC would not be able to restrict the compulsion to seek out stimuli which have cue-associations with drug use \( (7; 8) \). Hence, this process may correlate to addiction or the loss of control, when the addict continues to use even though there is no longer pleasure in using the drug. The changes that occur after chronic drug use are more permanent than changes that occur during acute drug use and may be the reason why relapse occurs in addicts. Since adolescents may not be able to differentiate between motivationally relevant events (see developmental effects below) when addiction occurs, the PFC may increase the seeking out of risky behaviors whether they are relevant or not, or addiction may tune the otherwise more sensitive amygdala found during adolescence into a more sensitive drug state amygdala which now seeks out only drug associated relevant events once drug use begins.

To reiterate, addiction is caused by the development of a negative emotional state involving the hypothalamic pituitary axis (HPA) that occurs when not using. The neurobiological basis of the negative emotional states, the continued use of substances to ward off these negative affective states and the increased motivation to seek out substances of abuse come from two sources which include decreased reward circuitry and increased anti-reward circuitry. As noted below in Figure 1, cues would affect the drive to seek out drugs in the VTA and the basolateral amygdala that affect changes in drug circuitry, but changes in the anti-reward system (that would affect seeking out drugs to relieve stress) would occur in the extended amygdala \( (7; 13) \).

![Figure 1](image_url)

Role of the reward circuitry and anti-reward circuitry from a developmental perspective. Adapted from Koob,G & LeMoal M, Addiction and the anti-reward system Annual Rev Psychol. 2008 59:29-53.

**Stressors**

Any compromise that would cause fetal distress or hypoxia increases the risk for the development of ADHD or learning disorders that could lead to an increased risk for substance abuse later in life. However, factors such as trauma, prenatal and postnatal stress and early life rearing experiences may alter addiction pathology later in life through changes in gene expression through chromatin remodeling without changes in DNA sequences \( (13; 14; 15) \). The interplay between stressors in the environment and genes (epigenetics) is crucial to explore when considering processes that may increase the risk for developing substance abuse. Prenatal, postnatal and abusive events that occur in childhood may cause an alteration on the expression of genes that may dysregulate the HPA which would increase the sensitivity to stress and the risk for using substances to relieve this stress. The use of substances to relieve the stress also dysregulates the HPA axis, leading to a vicious cycle of worsening sensitivity to stress each time substances are used to relieve the stress. Adolescence increases the risk of experimenting during this period. Adolescence also seems to be a time where there is increased sensitivity to stress. Therefore, there is an increased vulnerability during adolescence to abuse substances which would dysregulate the HPA and increase the likelihood of developing a substance abuse problem. However, the road to addiction that involves the interchange between stress, the environment and developmental factors during...
adolescence may only occur in individuals who inherit genes that make one more susceptible to becoming addicted under these circumstances. In the latter case, certain environmental effects can cause permanent changes in circuitry that could cause an increase in substance abuse and increase the risk for moving from substance abuse to addiction. These factors, coupled with a family history of substance abuse, may be the reason some adolescents move rapidly from one substance of abuse to another. Thus, the story of addiction and how it occurs is extremely complex. Therefore, individual pieces of the puzzle must be explored based on present knowledge. Such entities as the specific role of stress on the HPA, genes, personality, drug history, comorbidity, developmental issues and changes in the reward circuitry should be explored. First, the role of stress on the HPA will be discussed.

Effect of Stress and Substances of Abuse on the HPA-Koob's (13) Model Anti-reward System

The anti-reward system involves the hypothalamic pituitary axis (HPA) and norepinephrine NE in the brain stress/emotional system and neuropeptide Y (NPY) in the antistress system.

Role of the Reward Circuitry System and the Anti-reward System

First, all drugs have positive reinforcing effects. During acute drug use, all drugs increase dopamine in the shell of the NAc and activate the HPA. Both of these processes increase drug reward (8, 16). The role of the prefrontal cortex (PFC) on the NAc and directing the salience given to the reward will be discussed later. However, the system can still revert to normal or homeostasis if chronic drug use does not occur.

But, if chronic drug use occurs, a process known as the opponent-process theory (17) can occur that leads to motivation to use drugs. Here an affective or hedonic habituation occurs (tolerance) and a negative affective or hedonic withdrawal (abstinence) process occurs. This would increase the motivation to use drugs to ward off the negative effects of withdrawal and tolerance which would promote the substance abuse to get the same effect. However, all drugs have common effects during withdrawal, including a decrease in D2 receptors (see "changes in brain reward circuitry"), hypofunctioning of the orbital frontal cortex (OFC) and increases in adrenocorticotrophic hormone (ACTH), corticosterone and corticotrophin releasing factor (CRF) by overactivating the HPA axis. Continued use leads to increased CRF and increasing anxiety each time the individual is abstinent.

Furthermore, overactivation of the HPA axis during chronic drug use also increases Norepinephrine (NE) (in the bed nucleus of the stria terminalis of the extended amygdala) which increases sensitivity to stress. Increases in ACTH, corticosterone, CRF and NE are part of the recruitment of brain stress/emotion systems. In addition, during chronic drug use, a decrease in neuropeptide Y (NPY) in the central and medial nucleus of the extended amygdala occurs. The change in NPY is referred to as a dysregulation of the brain antistress system. All these changes in CRF, NE and NPY are referred to as the anti-reward system.

The continued dysregulation of the reward circuitry system associated with tolerance causes the further recruitment of the anti-reward. As this occurs, the individual becomes more sensitive to stress each time drugs are used; therefore, the individual is more likely to seek out drugs to relieve the stress. Each time drugs are used, the continued decrease in reward function in the brain reward system and the increased recruitment of the brain anti-reward system moves the brain from a reversible state where homeostasis could have been reinstated to a more dysregulated state. This dysregulation occurs through a process known as allostatics. Allostasis is the attempt of the brain to achieve stability through change. Instead of the allostatic state reaching stability, it instead causes chronic pathological states and damage. A change in baseline occurs such that environmental events that would normally elicit drug seeking behavior have more impact - hence the brain is more sensitive to stress (15) induced drug seeking and involves input into the extended amygdala (8;13). Of course, as noted above, if a person has had chronic stressful experiences such as sexual abuse in her childhood, this may cause an alteration of the expression of genes that may dysregulate the HPA axis. These alterations would increase the sensitivity to stress and increase the risk for using substances to relieve this stress. Therefore, chronic stressors that occur before drug use occurs may set the stage so that the HPA system is less likely to return to normal once drug use and experimentation begins.

Role of Genes Molecular genetics

As noted above, stressors can turn on genes that can lead to the dysregulation of the HPA axis. In fact, high alcohol preferring rats that have increased anxiety-like responses have been shown to have lower NPY activity, which is involved in the anti-reward system. However, they also have decreased dopaminergic activity. The number of dopamine receptors genetically inherited may play another role in genetic vulnerability. However, an increase in dopamine can decrease the number of postsynaptic receptors, which causes the PFC to no longer recognize normal reinforcers as salient. The role of D2 receptors may also influence compulsion, according to Volkow. When D2 receptors are decreased in the nucleus accumbens, there is a corresponding decrease in metabolism in the orbital frontal gyrus and the cingulate gyrus. The cingulate gyrus initiates the ability to restrain control, and the orbital frontal gyrus shifts attention to what is salient. If the orbital frontal gyrus is destroyed, Volkow believes the drug abuser will continue to use drugs, even if using them is no longer pleasurable. Therefore, if decreased D2 receptors decrease the metabolism in the cingulated gyrus (so it can no longer inhibit the drive to use drugs) and the orbital frontal gyrus (so that it continues to compulsively use what it sees as salient, drugs, even though it is no longer pleasurable to do so), a person who has inherited decreased D2 receptors would be at more risk for developing substance abuse (18). In fact, Volkow (19, 20) has shown on PET scans that non-alcoholic family members in alcoholic families had higher than normal D2 receptor levels in
the caudate and ventral striatum and metabolism in the anterior cingulate (Brodman area 24/25) orbitofrontal (Brodman area 11) and the prefrontal cortex (Brodman area 9/10). These individuals also had personality scores of positive emotionality on the MMPI. This suggests that higher D2 receptor levels could protect against alcoholism by regulating circuits involved in inhibiting behavioral responses and in controlling emotions. To further illustrate this, when Thanos, et al (21; 22) increased D2 receptors in mice (by using an adenovirus), alcohol consumption by the mice decreased by 70 percent. Therefore, people born with an increase in D2 receptors may be at less risk to develop substance abuse, and those who inherit a decrease in D2 receptors may be more vulnerable.

Couple the decreased D2 receptors with the changes that occur in the motivational circuitry during adolescence (see developmental vulnerability below), and it becomes clear why exposure to substances of abuse during adolescence may increase the risk for developing substance abuse.

Studies of Inheritability
Adoption studies have shown increased risk for alcoholism of adopted away children of alcoholics (23) and increased risk for substance abuse other than alcohol (24). However, alcohol use by adoptive parents did not increase risk for alcohol abuse in adoptive children (25).

Adoptive studies have shown that genetic susceptibility seemed to be a stronger predictor of risk for substance abuse than exposure to adoptive parents using substances. However, both genetic and environmental influences may be correlated to substance initiation, whereas progression to substance abuse and dependence may be more related to genetic factors alone. In adoption studies conducted by Kenneth Kendler (26), 485 monozygotic and 335 dizygotic twins demonstrated that cannabis use was influenced by genetic and familial environmental factors, whereas cannabis abuse and dependence were solely related to genetic factors. This was also true for cocaine use versus abuse and dependence (27). Marc Schukit (28) has shown greater tolerance in children of alcoholics. In his study, children of alcoholics had to use greater proportions of alcohol before the reflex response to a stimulus was delayed to the same degree found in responses of children of non-alcoholics. In children of non-alcoholics, reflex response to a stimulus was delayed to the same degree on lower proportions of alcohol. This diminished response to alcohol was also measured by subjective feelings, levels of body sway, electrophysiological functioning and change in three hormones.

Personality, Drug History and Comorbidity
Although Koob and LeMoal (13) state that personality, drug history and comorbidity are more likely to influence drug use later, they all have some root in early childhood and adolescent behavior. Seldom does any substance abuser develop substance dependence without some significant precursors in their developmental history. Certainly, comorbid conditions can get worse under the influence of drugs and alcohol, but few individuals develop new comorbid conditions without some relevant family history. Therefore, one could argue that personality, drug history and comorbidity which originates in childhood and adolescence may together increase the likelihood of moving from substance abuse to a more severe form of dependence or addiction as the individual moves into and through adulthood. ADHD/ADD will be used as an example to illustrate how early detection and treatment can decrease the risk of substance use.

ADHD
It is well recognized that ADHD with conduct disorder has a much greater risk for developing substance abuse than ADHD alone. In fact, in a twin study done by Elizabeth Disney (13) of 626 pairs of 17-year-old twins, ADHD did not increase the risk for substance abuse unless it was associated with a co-occurring conduct disorder. Biederman, et al (86) have shown that untreated ADHD has more risk for future substance abuse than ADHD that is treated. If an adolescent has ADHD and is not treated, the risk of developing substance use disorder is two times higher than those who have ADHD and were treated with stimulants. The role of stimulants in the treatment of ADHD and possible explanations for the decreased risk for substance abuse will be discussed below. However, untreated ADHD seems to involve an underactive anterior cingulate and PFC (31;32). The role of the anterior cingulate and PFC in inhibiting impulsivity found with ADHD patients could increase the risk of using substances of abuse and lead to substance abuse and addiction.

Exposure to stimulants for treatment of ADHD/ADD
Since there is so much controversy over the use of stimulants in the treatment of attention deficit hyperactivity disorder/attention deficit disorder (ADHD/ADD), a common pediatric disease, some point of clarification between the uses of stimulants for medicinal versus recreational purposes should be noted.

First and foremost, one must consider the speed with which substances of abuse move through the blood brain barrier. Swanson and Volkow (33) have pointed out that the liability of a drug to cause reinforcing acute euphoric feelings is associated with the instant high achieved by using drugs of abuse either by smoking, snorting or using intravenously. There is a rapid dopamine blockade of dopamine transporters in the ventral striatum (containing the shell of the nucleus accumbens), causing a euphoric high. However, methylphenidate taken orally does not produce this rapid high because it enters the brain barrier more slowly and is less associated with a high that causes a reinforcing effect of the drug. In fact, oral methylphenidate may not induce craving even if it is taken by a cocaine addict. Volkow, et al (34) have shown that 20 mg of oral methylphenidate will not elicit drug craving unless it is associated with a cocaine
the effects of stimulants, whereas the effects of stimulants are not reinforcing in ADHD patients who did
not smoke cigarettes.

Although early use and abuse of alcohol increased the risk of later substance abuse, new studies on the
use of stimulants for the treatment of ADHD/ADD may actually decrease the risk of developing substance
abuse. Reasons for this may be explained by research done by Castellanos (35). Castellanos reviewed
total cerebral volume of treated and untreated adolescents with ADHD. Total white matter in the
unmedicated ADHD adolescents was lower than medicated and normals. It is hypothesized that perhaps
the trophic effect on myelination, dendritic branching and length of spines in the treated ADHD youth was
somewhat protective. How might this occur? Luna (36) has shown that a normal process that occurs during
adolescence is an increase in myelination. The effect is an increase in processing speed. Therefore, the
lack of myelination may decrease processing speed, and these effects may increase the risk for
substance abuse related to poor academic success.

Research by Thanos et al (37) may give further explanation for the role between early use of stimulants
for medicinal reasons and decreased risk for development of substance abuse. As noted before,
overexpression of D2 receptors reduces alcohol and cocaine self administration in mice (20,21, 38),
decreases drug liking and may be protective against substance abuse in humans (19,22). Thanos found
significantly reduced rates of cocaine self stimulation during adulthood in periadolescent rats treated with
2mg/kg oral methylphenidate for eight months as compared to periadolescent rats treated with 1mg/kg or
rats receiving water. The availability of D2 receptors was significantly lower after two months of treatment
in rats given 1 or 2 mg/kg of methylphenidate compared with control rats, but after 8 months of treatment it
was significantly higher. The rats given 2mg/kg of methylphenidate at eight months had greater D2
receptor binding availability than rats given 1mg/kg. Therefore, consistent methylphenidate treatment
(started in adolescence) attenuated cocaine self-administration during adulthood.

Personality
Temperament may explain why some adults continue to demonstrate characteristics of dependence. Both
Robert Cloninger (25) and Thomas Babor (39) identified personality traits consistent with those who have
poorer prognoses. Cloninger’s type 2 and Babor’s type B alcoholics share common characteristics: early
onset of spontaneous alcohol-seeking behavior; diagnosis during adolescence; rapid course of onset;
genetic precursors that put them at risk to develop substance abuse; severe symptoms of deviant
behavior, including fighting and arrests when drinking; and greater psychological vulnerability. Cloninger’s
type 2 and Babor’s type B alcoholics may be related to youth who are thought to have conduct disorder.
The conduct disorder is thought to be related to genetic vulnerability, negative environmental factors
(poverty, parental neglect, marital discord, parental illness and/or parental alcoholism) and are thought to
have an impairment in frontal lobe activity which affects their ability to plan, to avoid harm and to learn
from negative consequences - traits often found in the type 2 or type B alcoholics. The same type of
personality characteristics were found in kindergartners who had an increased risk for development of
SUD in adolescence (40).

More recent research has tried to describe the relationship between personality and risk taking behaviors
in six areas including smoking, drinking, drugs, sex, driving and gambling (41). Risk taking across all six
areas was related to impulsivity, sensation seeking, aggression and sociability but not to neuroticism-
anxiety and activity.

Development of the Adolescent Brain
Obviously, if psychiatric disorders and learning disorders are detected early and treated, there is less risk
for developing substance abuse. However, adolescence is a time of experimentation. Why do adolescents
experiment with risky behaviors? Much of this may be due to the dramatic changes that occur during
adolescence. The following is an explanation of these changes.

The literature suggests that adolescent cognitive development is progressively increasing during
adolescence and that this cognitive control capacity is positively associated with maturation or increased
activity within the prefrontal cortex (41,42,43). Therefore, one would assume that there would be a linear
increase in changes in behavior with better control during adolescence as compared to childhood.
However, adolescence has shown to be a developmental stage associated with suboptimal choices or a
nonlinear change in behavior from childhood to adulthood. If cognitive control and an immature PFC were
the basis for suboptimal choice behavior, then children should behave remarkably similar or even worse
than adolescents, given their less developed prefrontal cortex and cognitive abilities. Thus, immature
prefrontal function alone cannot account for adolescent behavior.
It has been suggested that perhaps researchers should consider adolescence as a period where two separate entities are independently working, lack of cognitive control (immature prefrontal cortex) and risk taking (due to earlier maturation of the nucleus accumbens (44; 45; 46, 47, 48, 49)). According to this model, the individual is biased more by functionally mature limbic regions during adolescence (i.e., imbalance of limbic relative to prefrontal control) compared to children for whom these systems (i.e., limbic and prefrontal) are both still developing and to adults for whom these systems are fully mature. Further, the model reconciles the contradiction of health statistics of risky behavior during adolescence with the astute observation by Reyna & Farley (50) that adolescents are able to reason and understand risks of behaviors in which they engage. However, during emotionally salient situations, the limbic system will win over control systems, given its maturity relative to the prefrontal control system.

Casey and colleagues’ (unpublished) neurobiological model proposes that the combination of heightened responsiveness to rewards and immaturity in behavioral control areas may bias adolescents to seek immediate rather than long-term gains, perhaps explaining their increase in risky decision-making and impulsive behaviors. They hypothesized that relative to children and adults, adolescents would show exaggerated activation of the accumbens in concert with less mature recruitment of top down prefrontal control regions. Recent work showing delayed functional connectivity between these prefrontal and limbic subcortical regions in adolescence relative to adults provides a mechanism for the lack of top down control of these regions (Hare et al, in press Bio Psychiatry).

**Development of Goal-Directed Behavior**

Specifically, a review of the literature suggests that impulsivity diminishes with age across childhood and adolescence (46; 47; 48) and is associated with protracted development of the prefrontal cortex (49).

In contrast to impulse/cognitive control, risk taking appears to increase during adolescence relative to childhood and adulthood and is associated with subcortical systems known to be involved in evaluation of rewards. Human imaging studies that will be reviewed suggest an increase in subcortical activation (e.g., accumbens) when making risky choices (51;52;53) that is exaggerated in adolescents, relative to children and adults (44; 45). These findings suggest different trajectories for reward- or incentive-based behavior, with earlier development of these systems relative to control systems that show a protracted and linear developmental course in terms of overriding inappropriate choices and actions in favor of goal-directed ones.

**Evidence from Neuroimaging Studies of Human Development**

Studies have begun to focus primarily on the region of the accumbens, a portion of the basal ganglia involved in predicting reward, rather than characterization of the development of this region in conjunction with top down control regions (PFC). A recent report of less ventral prefrontal activity in adolescents relative to adults during a monetary decision-making task on risk-taking behavior has been shown, however (54).

Given evidence of prefrontal regions in guiding appropriate actions in different contexts (55), immature prefrontal activity might hinder appropriate estimation of future outcomes and appraisal of risky choices and might thus be less influential on reward valuation than the accumbens. During adolescence, relative to childhood or adulthood, the immature ventral prefrontal cortex may not provide sufficient top down control of robustly activated reward processing regions (e.g., accumbens), resulting in less influence of prefrontal systems (orbitofrontal cortex) relative to the accumbens in reward valuation.

**Why Would the Brain Be Programmed To Develop This Way?**

Evolutionarily speaking, adolescence is the period in which independence skills are acquired to increase success upon separation from the protection of the family. Seeking out same-age peers and fighting with parents, which all help get the adolescent away from the home territory for mating, are seen in other species including rodents, nonhuman primates and some birds (56). Humans had to engage in high-risk behavior to leave their family and village to find a mate at the same time when hormones drive adolescents to seek out sexual partners. In fact, Luna, et al (26) have suggested that these risk taking behaviors may be necessary to sculpt the brain in order to reach the adult pattern necessary for efficient processing. Hence, adolescence is a crucial period of plasticity when brain circuitry and behavior are beginning to be established. Risk taking and novelty seeking may provide a mechanism for increasing exposure to the environment necessary for successful sculpting of the brain. However, in today’s society when adolescence may extend indefinitely, with children living with parents and having financial independence and choosing mates later in life, this evolution may be deemed inappropriate. Secondary to extended adolescence, many high risk behaviors may be engaged in that could increase chances for harmful circumstances (e.g., injury, depression, anxiety, drug use and addiction (57).

**Biological Predispositions, Development and Risk**

Impulsivity plays a major role in risk for developing an SUD. Mischel showed that children typically behave in one of two ways: 1) either they ring the bell almost immediately in order to have the cookie, which means they only get one; or 2) they wait and optimize their gains, and receive both cookies. This observation suggests that some individuals are better than others in their ability to control impulses in the face of highly salient incentives, and this bias can be detected in early childhood (58) and remain throughout adolescence and young adulthood (59). Some theorists have postulated that dopaminergic mesolimbic circuitry, implicated in reward processing, underlies risky behavior (50). Individual differences
in this circuitry, such as allelic variants in dopamine-related genes resulting in too little or too much dopamine in subcortical regions, might relate to the propensity to engage in risky behavior (61). The NAc has been shown to increase in activity immediately prior to making risky choices on monetary-risk paradigms (51;52;53), and as described previously, adolescents show exaggerated accumbens activity to anticipated or rewarding outcomes relative to children or adults (44,45). However, some adolescents may be more prone than others to engage in risky behaviors. Therefore, it is important to consider individual variability when examining complex brain-behavior relationships related to risk taking and reward processing in developmental populations.

To explore individual differences in risk-taking behavior, Galvan and colleagues (46) recently examined the association between activity in reward-related neural circuitry in anticipation of a large monetary reward with personality trait measures of risk taking and impulsivity in adolescence. Functional magnetic resonance imaging and anonymous self-report rating scales of risky behavior, risk perception and impulsivity were acquired in individuals between the ages of 7 and 29 years. There was a positive association between accumbens activity and the likelihood of engaging in risky behavior across development. This activity varied as a function of individuals’ ratings of anticipated positive or negative consequences of such behavior. Those individuals who perceived risky behaviors as leading to dire consequences activated the accumbens less to reward. This association was driven largely by the children, with the adults rating the consequences of such behavior as possible. These findings suggest that during adolescence, some individuals may be more prone to engage in risky behaviors due to developmental changes in concert with variability in a given individual’s predisposition to engage in risky behavior (46). Cloninger’s Type 2 personality may be one explanation for this variability since negative consequences do not have much bearing on choices made by these individuals.

The question as to whether changes in impulsivity could also be a variability was also studied by Galvan (46). Impulsivity is associated with immature ventral prefrontal development and gradually diminishes from childhood to adulthood (49). The negative correlation between impulsivity ratings and age in the study by Galvan and colleagues (46) further supports this notion. In contrast, risk taking is associated with an increase in accumbens activity (51;52;53) that is exaggerated in adolescents, relative to children and adults (44;45). Thus, adolescent choices and behavior cannot be explained by impulsivity or protracted development of the prefrontal cortex alone, as children would then be predicted to be greater risk takers. The findings not only provide a neural basis for why some adolescents are at greater risk than others, but also a basis for how adolescent behavior is different from children and adults in risk taking.

Collectively, these data suggest that although adolescents as a group are considered risk-takers (62), some adolescents will be more prone than others to engage in risky behaviors, putting them at potentially greater risk for negative outcomes. Further, these individual and developmental differences may help explain vulnerability in some individuals to risk-taking associated with substance use and, ultimately, addiction.

In conclusion, human imaging studies show structural and functional changes in frontostriatal regions (49;63;64;65;66) that seem to parallel increases in cognitive control and self-regulation (42;68;69;70). These changes appear to show a shift in activation of prefrontal regions from diffuse to more focal recruitment over time (68;70;71;72;73) and elevated recruitment of subcortical regions during adolescence (47;68;73). Although neuroimaging studies cannot definitively characterize the mechanism of such developmental changes, these changes in volume and structure may reflect development within, and refinement of, projections to and from these brain regions during maturation suggestive of a fine-tuning of the system with development.

Taken together, the findings synthesized here indicate that increased risk-taking behavior in adolescence is associated with different developmental trajectories of subcortical pleasure and cortical control regions. These developmental changes can be exacerbated by individual differences in activity of reward systems. Although adolescence has been distinguished as a period characterized by reward seeking and risk taking behaviors (56;62), individual differences in neural responses to reward predispose some adolescents to take more risks than others, putting them at greater risk for negative outcomes. These results provide crucial groundwork by synthesizing the various findings related to risk-taking behavior in adolescence and in understanding individual differences and developmental markers for propensities to engage in negative behavior.

**Role of Family and Peers During Key Developmental Stages**

Modeling the use of alcohol or drugs by parents when children are young increases the notion that drugs and alcohol are not harmful substances, and this risk factor increases the risk for using as a teen (75). Peers have a stronger influence on adolescents than their parents and not only influence initiation of use but relapse (76;77). Neurobiological reasons for this can be found in a study by Steinberg, et al (78). Examination of fMRI data indicated that the presence of peers activated certain regions that were not activated when peers were not present during a risky driving game. These regions included increased activity in the medial frontal cortex, left ventral striatum (primarily the accumbens), left superior temporal sulcus and the left medial temporal structures. This increased activity in the presence of peers was associated with a significant increase in oxytocin which heightened adolescents' attentiveness to memory for social information. Therefore, after puberty adolescents are more likely to seek out risky behaviors, especially in the presence of their peers. This oxytocin may also explain the role of sex hormones during puberty and the increase in risk taking behavior. Although sex hormones may not influence the amygdala and the accumbens directly, the influence of sex hormones on oxytocin and the corresponding effect of
oxytocin in regulating social bonding and recognition and memory of social stimuli in combination with the reasons for increased risk taking behavior may more correctly explain the increase in risk taking, especially in the presence of peers.

Conclusion
As noted by Iacono, et al (79) at the neurobiologic level, behavioral disinhibition can occur via bottom up mechanisms whereby stimuli acquire excessive salience or motivational drive is high or via failure of top down control mechanisms. During adolescence, the bottom up mechanisms become more important and may explain why adolescents experiment more with risky behaviors during this developmental stage. Special care should be given to the access to substances of abuse during adolescence. For instance, unused medications for pain in the home should be properly monitored so as to avoid the use of these substances by adolescents. Underage drinking is still an important factor, and adolescents should be monitored by parents during this risky period. Obviously, if an adolescent is using or experimenting with substances of abuse and the patient is being treated with a stimulant for ADHD/ADD, careful monitoring should be used by the physician involved. If a patient is abusing substances, it is critical to determine whether a stimulant is appropriate to use under these circumstances in order to ensure that the stimulant will also not be abused, diverted or contribute to a worsening of the substance abuse. During these situations, other medications like atomoxetine should be considered for the treatment of ADHD/ADD. However, one cannot discuss onset of substance abuse without addressing risk factors which may lead to abuse. No one risk factor leads to substance abuse. In fact, the more risk factors an individual has, the greater the risk of developing the disorder. Untreated comorbid disorders, genetic predisposition, environmental stressors, personality and age of onset of use are factors which may add to the increased risk for using substances of abuse during adolescence and may contribute to a more chronic and severe form of addiction. Therefore, one must understand risk factors and never underestimate the importance of early intervention. No one can understand addiction without understanding when, where and why risk factors began from a developmental perspective. For these reasons, addiction may be thought of as having pediatric origins. Early intervention can obviously decrease the risk of developing substance abuse. However, missed opportunities to intervene may increase the probability of using during adolescence.

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