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# Emergence of Sex Differences in the Development of Substance Use and Abuse during Adolescence

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## Abstract

Substance use and abuse begins during adolescence. Male and female adolescent humans initiate use at comparable rates, but males increase use faster. In adulthood, more men than women use and abuse addictive drugs. However, some women progress more rapidly from initiation of use to entry into treatment. In animal models, adolescent males and females consume addictive drugs similarly. However, reproductively mature females acquire self-administration faster, and in some models, escalate use more. Sex/gender differences exist in neurobiologic factors mediating both reinforcement (dopamine, opioids) and aversiveness (CRF, dynorphin), as well as intrinsic factors (personality, psychiatric co-morbidities) and extrinsic factors (history of abuse, environment especially peers and family) which influence the progression from initial use to abuse., Many of these important differences emerge during adolescence, and are moderated by sexual differentiation of the brain. Estradiol effects which enhance both dopaminergic and CRF-mediated processes contribute to the female vulnerability to substance use and abuse. Testosterone enhances impulsivity and sensation seeking in both males and females. Several protective factors in females also influence initiation and progression of substance use including hormonal changes of pregnancy as well as greater capacity for self-regulation and lower peak levels of impulsivity/sensation seeking. Same sex peers represent a risk factor more for males than females during adolescence, while romantic partners increase risk for women during this developmental epoch. In summary, biologic factors, psychiatric co-morbidities as well as personality and environment present sex/gender-specific risks as adolescents begin to initiate substance use.

### Keywords

Sex; Gender; Addiction; Adolescence; Substance Abuse; Dopamine; CRF; Impulsivity; Self-regulation; Peers

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## 1. Introduction: Sex/Gender Differences in Substance Use and Abuse in Humans

The term sex/gender will be used throughout this review to indicate that both a person's biologic sex as well as her or her gender role influence the development of substance use or abuse. It will begin with an overview of sex/gender differences in drug use patterns and a description of the emergence of these patterns during development. Then there is a brief review of factors which contribute to the initiation and progression of drug use followed by the main body which describes how sex/gender influence the major factors influencing initiation of substance use. The review focuses on adolescence, as this is the developmental epoch during which substance use begins in human populations. It will emphasize commonalities driven by developmental stage across cultures and geographic location, as a complete exploration of cross-cultural differences in initiation of sex/gender differences in substance abuse is beyond the scope of the present review.

"Adolescence" throughout is considered to be the developmental epoch between childhood and adulthood (Spear, 2000). It is the development period when animals attain their adult physical potential, become reproductively competent and undergo the final stages of cognitive development. Puberty occurs during adolescence and profoundly influences the physical and cognitive changes that occur during this time (Blakemore, Burnett, & Dahl, 2010; Romeo, 2003; Romeo, Richardson, & Sisk, 2002; Sisk & Foster, 2004; Veldhuis et al., 2005), However, it is only a component of the changes that occur. For human, this occurs between 11–14 in females, and slightly later, between 13–16 in males (Parent et al., 2003). Similarly in rodents, pubertal development in female rodents occurs abruptly at about a month of age when females have their first estrus cycle, while males gradually attain adult reproductive capacity gradually over the second month of life (Ojeda, Andrews, Advis, & White, 1980). Many behavioral and neurobiologic changes that influence the initiation and progression of substance use occur during adolescence, and a primary goal of this review is to describe which of these are influenced importantly by the endocrine changes associated with puberty.

## 2. Sex Differences in Substance Use and Abuse in Humans

According to the most recently published National Household Survey on Drug Use and Health (2013), men in the United States use more of every category of psychoactive drug than women, including alcohol, tobacco, marijuana, cocaine, methamphetamine, prescription stimulants, heroin and pain relievers ("National Household Survey on Drug Use and Health," 2013). Differences are greatest at high levels of consumption: two to three times as many males as females report alcohol, marijuana, stimulant or narcotic abuse or dependence. Disparities are smallest for use of pain relievers and prescription stimulants, for which men and women report close to the same amount of use. Men consume more alcohol than women and they are disproportionately represented in the highest drinking fraction of the population (Holdcraft & Iacono, 2002; "National Household Survey on Drug Use and Health," 2013; Wilsnack et al., 2000). Men are more likely to become alcohol dependent than women, although rates of alcohol dependence are equalizing (Grant et al., 2004; Health,

2005; Kerr, Greenfield, Bond, Ye, & Rehm, 2009; Keyes, Grant, & Hasin, 2008; Simons-Morton et al., 2009; York, Welte, Hirsch, Hoffman, & Barnes, 2004).

The gender disparity in drug and alcohol use is not so obviously male dominated as it appears. These numbers are equalizing in younger age cohorts world-wide (Degenhardt et al., 2008; Geels et al., 2013; Johnson & Gerstein, 2000; Kerr et al., 2009; Keyes et al., 2008; Pitel, Geckova, van Dijk, & Reijneveld, 2010; York et al., 2004) and gender differences are somewhat exaggerated in college students, an over-sampled population, compared to non-college attending late adolescents (Bingham, Shope, & Tang, 2005; White, Kraus, & Swartzwelder, 2006). Although women on average drink fewer drinks at a time, they attain higher blood ethanol concentrations (BECs) for a given dose of alcohol even when dose is adjusted for body weight (Frezza et al., 1990; Mumenthaler, Taylor, O'Hara, & Yesavage, 1999; Whitfield & Martin, 1994). In the few studies which have evaluated BEC in people who are drinking voluntarily, women and men drank to comparable BECs (York, Welte, & Hirsch, 2003; York & Welte, 1994). Although more men than women smoke cigarettes, women on average smoke more cigarettes than men, have more trouble quitting and experience more intense withdrawal symptoms (O'Dell & Torres, 2014)

These drug use statistics parallel reports of sex/gender differences observed in laboratory studies of self-administration and subjective effects of drugs in humans. In laboratory studies, men reported more positive subjective effects of psychostimulants, cannabinoids and narcotics than women (Anker & Carroll, 2011; Becker & Hu, 2008; Carroll & Anker, 2010; Carroll, Lynch, Roth, Morgan, & Cosgrove, 2004; Evans & Foltin, 2010; Evans, Haney, Fischman, & Foltin, 1999; Fattore, Altea, & Fratta, 2008; Fattore, Fadda, & Fratta, 2009; Lynch et al., 2008; Lynch, Roth, & Carroll, 2002; Roth, Cosgrove, & Carroll, 2004; Vansickel, Stoops, & Rush, 2010). Reports of sex/gender differences in the reinforcing effects of nicotine and its self-administration in laboratory settings are mixed (O'Dell & Torres, 2014; Perkins, Donny, & Caggiula, 1999) and both men and women with family histories of alcohol dependence or current alcohol dependence report lower sensitivity to alcohol than non-users (Nolen-Hoeksema & Hilt, 2006; Schuckit, Smith, & Kalmijn, 2004). Menstrual cycle influences the subjective effects of psychostimulants (lower responses during the luteal phase) but such effects are not reported for nicotine, narcotics, marijuana or alcohol (Evans & Foltin, 2010; Fattore et al., 2008; Fattore et al., 2009; Mumenthaler, O'Hara, Taylor, Friedman, & Yesavage, 2001; Niaura, Nathan, Frankenstein, Shapiro, & Brick, 1987; Terner & de Wit, 2006).

Trajectories of drug use and alcoholism may be different in men and women. The phenomenon of “telescoping” of the time from initiation to problematic use and entrance into treatment in women has been reported for numerous drugs including alcohol, psychostimulants, narcotics and cannabis (Brady & Randall, 1999; Ehlers et al., 2010; Greenfield, Back, Lawson, & Brady, 2010; Haas & Peters, 2000; Hernandez-Avila, Rounsaville, & Kranzler, 2004; Khan et al., 2013; Lynch et al., 2002; Mann et al., 2005; Piazza, Vrbka, & Yeager, 1989; Randall et al., 1999; Schuckit, Daeppen, Tipp, Hesselbrock, & Bucholz, 1998). This phenomenon may not be present in younger age cohorts (Alvanzo et al., 2011; Johnson, Richter, Kleber, McLellan, & Carise, 2005; Keyes, Martins, Blanco, & Hasin, 2010; Zilberman, Tavares, & el-Guebaly, 2003) and may reflect early transition to

treatment seeking but not necessarily early escalation of use (Lewis & Nixon, 2014). Age of onset of drinking alcohol and perhaps other drug use has shifted earlier in recent years in women but not men (Grucza, Norberg, Bucholz, & Bierut, 2008). Even among women who started later, some studies show that they accelerate drinking more rapidly than men (Bohman, Cloninger, Sigvardsson, & von Knorring, 1987; Cloninger, Sigvardsson, & Bohman, 1988; Gilligan, Reich, & Cloninger, 1987; Lovallo, Yechiam, Sorocco, Vincent, & Collins, 2006; Piazza et al., 1989; Randall et al., 1999; Schuckit et al., 1998; Schuckit et al., 2001; Tarter et al., 1999) and may show more persistence once they are diagnosed (Edens, Glowinski, Grazier, & Bucholz, 2008).

In summary, in human populations, men use addictive drugs more than women in adulthood, and the sex difference is greatest at the highest levels of consumption. However, these differences vary by age cohort: the differences are smallest at the youngest ages, and greatest from young adulthood into old age. One question that is undergoing active study in this field is whether these age differences represent “cohort effects” with younger users reflecting changing cultural attitudes about drug use, especially in women, or stable differences across different stages of life. This will be described in more detail below.

## 3. Sex Differences in Drug Use in Animal Models

Studies in animal models can evaluate sex differences in psychoactive drug consumption in a context that is not affected by the many social and environmental factors that influence human drug and alcohol consumption. Studies in non-human primates are perhaps most relevant to humans, but not abundant and contradictory. Several studies involving multiple primate species (cynomolgous macaque, rhesus, chimpanzee, orangutan) reported males drank more ethanol than females in a free access setting (Fahlke et al., 2000; Fitzgerald, Barfield, & Warrington, 1968; Vivian et al., 2001) but in another species (vervet), greater consumption by adolescent females than adolescent males was observed (Ervin, Palmour, Young, Guzman-Flores, & Juarez, 1990). However, other studies reported only marginal sex differences in alcohol consumption by non-human primates (Fahlke et al., 2000; Lorenz et al., 2006; Pakarinen, Williams, & Woods, 1999; Vivian, Higley, Linnoila, & Woods, 1999). In most non-human primate studies, individual differences in ethanol consumption and cohort effects were substantial and the subject numbers were small, and so the ability to study endocrine and sex differences was limited. Furthermore, alcohol consumption in non-human primates is also sensitive to social influences like dominance (McKenzie-Quirk & Miczek, 2008).

There have been only a few studies of sex differences in psychostimulant self-administration in non-human primates, but these have shown that females will attain higher progressive ratios (work harder for) cocaine than males (Carroll, Batulis, Landry, & Morgan, 2005; Mello, Knudson, & Mendelson, 2007). Sex differences in cannabinoid and nicotine self-administration in non-human primates have not been studied.

Studies of sex differences in drug-self administration in rodents are more abundant and consistent in the finding that females acquire self-administration faster, escalate use more during extended access and will work harder under a progressive ratio to obtain

psychostimulants, nicotine, opioids and tetrahydrocannabinol (Anker & Carroll, 2011; Becker & Hu, 2008; Carroll & Anker, 2010; Carroll et al., 2004; Fattore et al., 2008; Fattore et al., 2009; Feltenstein, Ghee, & See, 2012; Levin et al., 2011; Lynch, 2006; Lynch et al., 2002). Most rodent studies have detected robust sex differences in alcohol consumption (females consume more, especially in mice) although the greater fluid consumption by females must be considered in evaluating reported results. Female mice consistently consume more alcohol than males under a variety of paradigms (Middaugh & Kelley, 1999; Rhodes et al., 2007; Tambour, Brown, & Crabbe, 2008) Most studies of rats report more ethanol intake in females than males, although a number of these studies were confounded by greater overall fluid intake (Blanchard & Glick, 1995; Juarez & Barrios de Tomasi, 1999; Lancaster & Spiegel, 1992; Piano, Carrigan, & Schwertz, 2005; Sluyter, Hof, Ellenbroek, Degen, & Cools, 2000). In rodents, female rats will self-administer lower doses of nicotine and respond more during progressive ratio responding, but as in humans, baseline levels of self-administration are roughly comparable in males and females (Donny et al., 2000; Feltenstein, Ghee, & See, 2012; Lynch et al., 2002; Perkins et al., 2009; Perkins et al., 1999).

In adult rats, the presence of ovarian but not testicular hormones influences self-administration. Numerous studies have shown that estradiol augments and progesterone inhibits self-administration and the reinforcing effects of psychostimulants, ethanol, nicotine and opioids (Anker & Carroll, 2011; Becker & Hu, 2008; Becker, Perry, & Westenbroek, 2012; Carroll & Anker, 2010; Carroll et al., 2004; Donny et al., 2000; Feltenstein et al., 2012; Levin et al., 2011; Lynch, 2009; O'Dell & Torres, 2014; Perkins et al., 1999). In contrast, the presence of testosterone was reported to have no effect on cocaine self-administration (Caine et al., 2004; Mello, Knudson, Kelly, Fivel, & Mendelson, 2011) self-administration of morphine (Cooper & Wood, 2014). However, testosterone could contribute to drug taking through actions on impulsive or risk-taking behavior rather than directly affecting the reinforcing properties of the drugs. There is evidence in rats that testosterone does not directly influence impulsivity in go/nogo tasks or preference for immediate vs. delayed reward, but that it does increase responding for a “risky” (large but punished) reward (Cooper, Goings, Kim, & Wood, 2014; Kritzer, Brewer, Montalmant, Davenport, & Robinson, 2007).

## 4. Emergence of Sex/Gender Differences in Drug Use during Development in Humans

The average age of initiation of tobacco use is 17.3 years, of alcohol is 17.8 years, of marijuana is 18, use of MDMA, stimulants and heroin between 20–22 ("National Household Survey on Drug Use and Health," 2013) Ages of initiation of tobacco use, cannabis and alcohol are fairly similar in males and females, with “early initiators” beginning ages 12–14, with a continuous rise in numbers of users to the early 20’s. No invariant sequence of initiation exists currently, in contrast to earlier generations in which tobacco and alcohol use typically preceded cannabis use. The rate of alcohol consumption among young adults from 18–25 is about 60%, and young adults constitute the highest proportion of heavy drinkers

(Greenfield & Rogers, 1999). Similarly, young adults constitute the highest percentage of tobacco users, with about 37% reporting some use of tobacco products.

Sex differences in initiation ages and use are small to negligible in the youngest adolescents in both cross sectional and longitudinal studies of drug use initiation in humans. In the rather broad 12–17 age group, NHSDUH data show that smoking, alcohol use and cannabis use are about comparable in males and females in the United States. The youngest adolescent girls (age 14–15) drink as frequently and as much as boys (McPherson, Casswell, & Pledger, 2004). Sex differences in cannabis initiation are small at the youngest ages (13–14) and become greater as youth approach the end of high school and boys begin to use more than girls (Schepis et al., 2011). In two large nationwide samples, the National Longitudinal Study of Adolescent Health (AddHealth) and the Adolescent Health Risk Study (AHRS), levels of smoking rose from the earliest age in the study (13–14) until 18, but levels of alcohol consumption increased more rapidly in males than females (Jackson, Sher, Cooper, & Wood, 2002). A community based study in Colorado showed rates of tobacco and alcohol use in males and females was similar up to age 18 (Young et al., 2002). Studies of middle- and high-school youth show that nonmedical use of prescription narcotic use is one of the few categories in which adolescent females may exceed males (Cranford, McCabe, & Boyd, 2013; McCabe, Boyd, & Teter, 2009; McCabe, West, & Boyd, 2013). By late adolescence (over 18), most studies show that men drink more frequently, and drink more in a given drinking episode than women, and male dominance in alcohol abuse is emerging (Palmer et al., 2009; White et al., 2006). Similarly, male rates of smoking, as well as use of and dependence on alcohol and marijuana use begin to exceed female rates in older age cohorts (over 17) (Hicks et al., 2007; Palmer et al., 2009).

Pubertal development represents a significant risk factor in the initiation and progression of substance use in adolescent humans, especially females. Early pubertal development is associated with early initiation of tobacco, alcohol and marijuana use (Cance, Ennett, Morgan-Lopez, Foshee, & Talley, 2013; Copeland et al., 2010; Patton et al., 2004; Windle et al., 2008) A recent study reported that early pubertal maturation predicts alcohol use in both boys and girls, and also predicts alcohol use disorders specifically in girls (Costello, 2007). Multiple factors likely contribute to this association, including biologic, social and environmental factors that will be discussed below.

## 5, Emergence of Sex/Gender Differences in Drug Use during Development in Animal Models

Animal studies can elucidate the important roles of biologic factors like pubertal hormone changes, brain maturation and pharmacokinetic and pharmacodynamic effects of drugs in the emergence of sex differences in addictive drug consumption. The vast majority of such studies address issues related to biological sex, not gender. However, there is some interesting emerging evidence about the influence of social environment on drug taking in males and females that may constitute a modest inroad in understanding drug taking and non-human “gender.” A small but growing number of animal studies address social and environmental factors like previous stress, the presence of peers and availability of alternative behaviors like the opportunity to exercise. However, such studies are limited. In

most studies, drug taking occurs in a highly structured and socially impoverished environment in comparison to human life, and such studies provide less insight about more complex human social and environmental factors that contribute to drug taking.

The vast majority of animal studies which have investigated the establishment of sex differences in addictive drug vulnerability have studied either rates of drug self-administration (the most direct analogy to the human drug taking), measures of the reinforcing or aversive effects of drugs using methods like conditioned place preference and conditioned taste or place aversion, or the sensitivity to behavioral effects of administered drug., There are numerous studies with psychostimulants and nicotine, but many fewer with ethanol, marijuana or narcotics.

Nicotine self-administration in rats during adolescence is greater than in adulthood in both sexes, but females maintain drug taking into adulthood while males decrease consumption (Levin et al., 2007; Levin, Rezvani, Montoya, Rose, & Swartzwelder, 2003; Levin et al., 2011). Adolescent but post-pubertal female rats (postnatal age 40–45) acquired nicotine self-administration at lower doses and attained higher break points than males of comparable age (Lynch, 2009). Adolescent female mice consumed more nicotine on a mg/kg basis in two bottle choice paradigms, although pharmacokinetic factors may have influenced drug consumption as plasma cotinine (the primary nicotine metabolite) levels were comparable in males and females (Klein, Stine, Vandenbergh, Whetzel, & Kamens, 2004; Nesil, Kanit, Collins, & Pogun, 2011). The emergence of sex differences in cocaine self-administration in rats showed a pattern similar to that of nicotine during adolescence: postpubertal females acquired at lower doses, exhibited higher breakpoints and escalated use more in one study, (Lynch, 2008) although another reported minimal sex differences in adolescents (Kantak, Goodrich, & Uribe, 2007). Female adolescent rats self-administered more amphetamine than adolescent males, a sex difference which persisted into adulthood (Shahbazi, Moffett, Williams, & Frantz, 2008).

While adult female rodents in most reports consume more alcohol on a mg/kg basis than males, studies in adolescents are inconsistent. The Spear group found that adolescent males drank more ethanol than adolescent females while adult females drank more than adult males (Vetter-O'Hagen, Varlinskaya, & Spear, 2009; Vetter-O'Hagen & Spear, 2011). A study from our lab using every other day drinking did not detect the emergence of a significant sex difference (Schramm-Sapyta et al., 2014). Female adolescent mice consumed more ethanol than males at the earliest age tested (PN 28) and the difference increased in age (Tambour et al., 2008). However, a similar pattern observed in adults in this study led authors to conclude that adolescence/puberty may not have been the key influence, but that females increased consumption more over time. A similar pattern of gradually exaggerating sex differences during adolescence was reported in rats (Lancaster, Brown, Coker, Elliott, & Wren, 1996), although no adult control was conducted in this study. There are virtually no studies exploring the emergence of sex differences in self-administration of cannabinoids, narcotics or sedative-hypnotics, a significant gap in the field.

Reinforcing effects of psychostimulants, nicotine and alcohol as assessed with conditioned place preference exhibit a similar development of sexual dimorphism during puberty in both

mice (Balda et al., 2006; Roger-Sanchez et al., 2012) and rats (Balda et al., 2006; Edwards et al., 2014; O'Dell & Torres, 2014; Zakharova, Wade, et al., 2009). In general, no sex differences are observed pre-pubertally, but greater CPP (or CPP at lower doses) emerge in females relative to males after puberty.

A growing literature investigating the effects of drugs of abuse on social behavior in rodents and the much smaller literature about the modulation of drug-taking by peers demonstrates that drugs influence social behavior and that peers influence drug taking, especially in adolescence. The most evidence exists for alcohol. Numerous studies by the Spear lab and others demonstrate that ethanol has developmentally specific effects on social behavior in rats: specifically that ethanol facilitates social interactions more in adolescents and cause social inhibition less in adolescents than adults (see recent review in (Varlinskaya & Spear, 2014)). These effects occur roughly comparable in males and females at the young ages at which most studies were conducted. Sex differences in these effects are not marked. Alcohol not only influences social behavior, but experience with alcohol-intoxicated peers influences alcohol consumption in a sex and developmentally specific way in rats. Experience with an alcohol-intoxicated familiar rats leads to greater alcohol consumption by both adult males and females and adolescent females, but adolescent males avoid alcohol after such experience.

Peers also affect nicotine self-administration in adolescence. In a study of nicotine self-administration in the presence of olfacto-gustatory clues, both males and females only self-administered nicotine when partnered with a peer that consumed the cue (but not the nicotine) (Chen, Sharp, Matta, & Wu, 2011). Both nicotine and cocaine also can enhance the rewarding value of peers in adolescents rats (Thiel, Okun, & Neisewander, 2008; Thiel, Sanabria, & Neisewander, 2009), although the influence of sex was not considered in these studies.

This emerging literature is at least exploring how psychoactive drugs influence adolescent rodents in social settings, and the evidence indicates that at least alcohol, nicotine and cocaine enhance social interactions or social reward, and can promote drug consumption by peers. In situations in which this has been studies, effects were comparable in males and females, but all rodent studies have employed only same-sex social partners.

In summary, the greater consumption of nicotine, cocaine, amphetamine and alcohol by female rodents has been observed most frequently after females have completed puberty, although some studies report sex differences even before puberty, during early adolescence. One critical control missing from some studies was a comparable adult control group. However, two studies with ethanol suggested that some of the acceleration in drug consumption in adolescent females represents progression of consumption that can be observed at any age, raising the possibility that sex-specific neuroadaptations play a role in the emergence of sex differences at any age. This factor could play a role in the “telescoping” effect noted above even in adult populations.

## 5. Emergence of Sex/Gender Differences in Drug Taking: Summary of epidemiologic and animal studies

In summary, both animal and human studies describe some common phenomena: a similarity of drug action and drug taking in males and females before puberty with divergence in drug taking post-pubertally for some but not all drugs. One startling contrast between human and animal studies is that adult female rodents consistently acquire drug self-administration sooner and escalate drug use more than males, while in human populations, use is about equal in males and females in early adolescence, but more males than females use addictive drugs as they progress from adolescence to adulthood. These differences are not perhaps as stark as they seem, nor do they invalidate the animal models. Some of the characteristics exhibited by mature female rodents that appear during adolescence (rapid acquisition) are mirrored in a number of human studies showing faster escalation in women users once they start Second, drug taking in animal studies is dominated by biologic factors like the rewarding effects of drugs which are likely exaggerated in the typical impoverished environment of rodent studies. As we will review below, strong social and environmental factors exert sex/gender-specific effects in human populations. Investigation of social factors influencing drug taking in animal studies are sparse, and cannot replicate human culture.

Finally, pregnancy exerts a strong influence on drug taking in human females. Alcohol, cigarette and marijuana use are dramatically lower in pregnant humans than non-pregnant humans, and after childbirth, substance use does not reach previous levels (binge alcohol and marijuana use remain less than half that of women with no children) (SAMSHA, 2009). Unfortunately, similar data are not available for men. A provocative animal study showing that cocaine self-administration diminished dramatically in pregnant rodents, only to resume after pregnancy, suggests biological factors contribute to decreased consumption by women during pregnancy (Hecht, Spear, & Spear, 1999). However, mixed data on consumption of alcohol by high-drinking rat and mouse strains during pregnancy has been published with some studies showing no change and some studies showing decreases (Brady, Allan, & Caldwell, 2012; Kleiber, Wright, & Singh, 2011; Wolfe, Means, & McMillen, 2000). As pregnancy/onset of family responsibilities occurs only after puberty, this could contribute to the emergence of sex/gender differences in drug taking that will be explored below.

## 6. Sex/Gender Differences in the Neurobiology of Addiction

In order to explain the role of neurodevelopmental events in the initiation and progression of substance use and abuse during adolescence, it is necessary to provide a brief overview of the different stages of addiction, and what is known about sex/gender differences in these factors. As the literature in this area is vast, this review has relied on a number of outstanding, recent reviews in this area for the sake of brevity. Figure 1 shows a simplified view of the sequence of substance use which progresses to compulsive use and the many intrinsic and extrinsic factors that affect this progression. An individual must first experiment and then repeat use of drug. A subset of individuals will gradually escalate use to the point that the underlying neuroadaptations induced by drug exposure will manifest as dependence and compulsive use.

**Biologic factors** which influence the progression of drug use include the extent to which an individual finds drugs reinforcing or aversive and the contribution that pharmacokinetics/pharmacodynamics influence drug effects within an individual. The neurobiology of the reward system including dopamine and opioid systems that mediate the reinforcing effects of addictive drugs, and the importance of the CRF/dynorphin systems that signal increasing drug aversiveness during escalated drug taking are prominent neurobiologic adaptations that contribute to the progression of drug use (Koob, 2010; Koob et al., 2014; Koob & Le Moal, 2001; Taber, Black, Porrino, & Hurley, 2012; Zorrilla, Logrip, & Koob, 2014).

**Genetic vulnerability** clearly plays a role in addiction, although the ideal placement of this factor in this figure would be orthogonal to the figure, as genetics certainly affects both biologic and non-biologic issues in substance abuse. This is a small but growing area. Numerous genes including cytochrome 2A6, which degrades nicotine, genes related to dopamine function (especially monoamine oxidase which is X-linked), as well as opiate GABA and glutamate receptors are involved (Ahijevych, 1999; Becker & Hu, 2008; Bobzean, DeNobrega, & Perrotti, 2014; Enoch, 2003; Enoch & Goldman, 2001; Kreek et al., 2012; Nielsen & Kreek, 2012; Reed, Butelman, Yuferov, Randesi, & Kreek, 2014; Satarug, Tassaneeyakul, Na-Bangchang, Cashman, & Moore, 2006; Seeman, 2009; Tsankova, Renthal, Kumar, & Nestler, 2007). As our understanding of how these genetic influences contribute to the emergence of sex differences in substance use and abuse is marginal, we will not consider this important topic further.

Many **intrinsic and extrinsic factors** influence whether an individual progresses along this continuum, as shown in the bottom panel. Intrinsic factors include the personality/neurobiology of the individual which influences the likelihood of initiation and progression of substance use, as well as psychiatric comorbidities. Extrinsic factors include social environment (family and peers), previous stress or abuse and engagement in “protective” activities like religious groups. Sex/gender differences in all of these factors have been identified in substance-using populations.

Figure 2 depicts the key neurobiologic components of the cycle of addiction. The cycle begins at the top with initiation of drug use, followed (in a proportion of users) by repeated use and gradual escalation of use. During this phase of escalated use, executive function (which may be deficient before initiation) becomes further biased toward immediate rather than delayed rewards and impulsive choice rather than appropriate self-regulation. As use escalates and tolerance develops, withdrawal symptoms begin to emerge. During the final and potentially most intractable stage of addition, drug use is likely driven by the desire to avoid the negative affect and symptoms of withdrawal and to satisfy the craving for drug use more than reinforcement.

Four neurobiologic systems are particularly important in the evolution of this cycle. Dopamine systems are integral to the reward system, and likely attach salience to reinforcement-predictive stimuli including drugs. Endogenous opioid systems also play a significant role in the reinforcing effects of drugs of abuse. While dopamine may signal “salience” of drug rewards, opioid systems in dorsal and ventral striatum as well as the ventral tegmental area contribute to the “consummatory” qualities or satisfaction provided

by drug consumption (Becker et al., 2012; Gianoulakis, 2009; Le Merrer, Becker, Befort, & Kieffer, 2009). The corticotropin releasing factor (CRF) and dynorphin systems drive the negative affect and anhedonic state which significantly control drug taking at later stages (Bari & Robbins, 2013; Bickel & Yi, 2008; George, Le Moal, & Koob, 2012; Koob, 2010; Koob et al., 2014; Koob & Volkow, 2010; Trifilieff & Martinez, 2013; Zorrilla et al., 2014). While some users successfully exit the cycle and maintain prolonged abstinence, stress or repeat drug exposure often trigger relapse and re-initiation of drug use.

Sex/gender differences exist in all four of these key substrates for the addiction cycle. The existence of sex differences in dopamine systems are the best described: both genetic sex and ovarian hormones augment dopamine function in dorsal and ventral striatum and enhance self-administration of psychomotor stimulants, narcotics and alcohol at least in rodents (Becker, 2009; Carroll & Anker, 2010; Di Paolo, 1994; Dluzen & McDermott, 2008; Dow-Edwards, 2010; Gillies & McArthur, 2010; O'Dell & Torres, 2014). Estradiol promotes while progesterone inhibits dopamine release and the reinforcing effects of most addictive drugs (Anker & Carroll, 2011; Becker & Beer, 1986; Becker & Cha, 1989; Becker et al., 2012; Becker & Ramirez, 1981; Becker & Rudick, 1999; Castner, Xiao, & Becker, 1993; Di Paolo, 1994; Walker et al., 2012; Walker, Ray, & Kuhn, 2006; Walker, Rooney, Wightman, & Kuhn, 2000). Estradiol also alters firing rate of dopamine neurons (Chiodo & Caggiula, 1983; Zhang, Yang, Yang, Jin, & Zhen, 2008). The anatomy of dopamine neurons also differs in males and females: female rats are reported to have more dopamine neurons than adults in most (but not all) studies (Johnson, Day, et al., 2010; Johnson, Ho, et al., 2010; McArthur, McHale, & Gillies, 2007). Results in mice differ, with more dopamine neurons reported in a study using quantitative stereology, and no sex differences reported in a study using somewhat less quantitative methods (Johnson, Day, et al., 2010; Johnson, Ho, et al., 2010; Levin et al., 2006; Lieb et al., 1996; McArthur et al., 2007; Sibug et al., 1996) Dopamine receptors have been studied less, and sex differences may be less robust than those observed for presynaptic functions. However, evidence suggests that sex/gender may also influence dopamine receptor number and function. D2 dopamine receptors vary over the menstrual/estrous cycle in both humans and rodents (Levesque & Di Paolo, 1990). Estradiol perhaps through ERβ, augments D2 receptor number (Morissette et al., 2008).

The existence of sex differences in dopamine function in non-human primates and humans is much less studied, contradictory data exist and interpretation of PET studies always are complicated by the ambiguity of whether results reflect higher binding to dopamine-relevant proteins because expression is higher or endogenous release of competing dopamine is lower. However, several studies conclude that basal dopamine production is greater in females than males (Evans & Foltin, 2010; Laakso et al., 2002; Laasko et al., 2002; Martin-Soelch et al., 2011; Pohjalainen, Rinne, Nagren, Syvalahti, & Hietala, 1998; Riccardi et al., 2011; Urban et al., 2010) Like rodents, non-human primates have more dopamine neurons in the ventral tegmental area, (Leranth et al., 2000). Finally, D2 receptors may vary over the menstrual cycle in humans (Munro et al., 2006; Wong et al., 1988) but see (Kaasinen, Nagren, Hietala, Farde, & Rinne, 2001). This enhanced dopamine neuron number and/or function is widely speculated to confer the protection against the development of Parkinson ’s disease in humans (Gillies, Murray, Dexter, & McArthur, 2004; Gillies, Pienaar, Vohra, & Qamhawi, 2014; Smith & Dahodwala, 2014). Similar cyclic differences

in D2 receptor occupancy also have been reported in nonhuman primates (Gould, Duke, & Nader, 2014)

Sex differences in dopaminergic function in the prefrontal cortex which is important for executive function are much less studied. The elegant work of Mary Kritzer in rats has shown that sex differences here reflect a significant role of androgen in enhancing dopaminergic innervation and working memory (Kritzer, 2003; Kritzer, 1997, 2000; Kritzer, Adler, & Bethea, 2003; Kritzer, Adler, Marotta, & Smirlis, 1999; Kritzer et al., 2007; Kritzer & Creutz, 2008; Kritzer & Kohama, 1998).

There has been considerably less investigation of underlying sex/gender differences in opioid mediation of reward, although a dominance of dynorphin expression in striatonigral neurons exist in females, and a dominance of enkephalin in striatopallidal neurons in males: how these relate to the role of opioids in drug reinforcement is not at all understood (see review in Becker (Becker et al., 2012). If dynorphin function is eventually shown to be enhanced in females, it could contribute significantly to sex differences in dynorphin-mediated anxiety during withdrawal.

Sexual dimorphism in CRF mechanisms exist across mammalian species including rodents, and humans. Marked sexual dimorphism exists in CRF regulation of HPA axis function and in CRF receptor function both in the brain and pituitary of rats, with females exhibiting greater CRF mediated responses (Bangasser et al., 2010; Bangasser et al., 2013; Bangasser & Valentino, 2012; Dalla et al., 2005; Handa, Burgess, Kerr, & O'Keefe, 1994; Ogilvie & Rivier, 1997; Rivier, 1993, 1999; Valentino, Bangasser, & Van Bockstaele, 2013; Walker, Francis, Cabassa, & Kuhn, 2001). Stress reactivity of the HPA axis is markedly greater in female mice and rats, an effect mediated both by estradiol enhancement and androgen inhibition of HPA axis function (Bale, 2006; Bangasser & Valentino, 2012; Dalla, Pitychoutis, Kokras, & Papadopoulou-Daifoti, 2010; Fernandez-Guasti, Fiedler, Herrera, & Handa, 2012; Fox & Sinha, 2009; Handa et al., 1994; Shansky, 2009; Valentino, Reyes, Van Bockstaele, & Bangasser, 2012; Veldhuis, Sharma, & Roelfsema, 2013). Such sex differences exist but they are smaller and less consistently observed in humans (Veldhuis et al., 2013; Young & Korszun, 2010; Young, 1998). In any species, sex differences at multiple levels including release of CRF, release of ACTH, adrenal sensitivity to ACTH, plasma binding of corticosteroids and corticosteroid action all must be considered (Chrousos, Torpy, & Gold, 1998; Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004; Quinn, Ramamoorthy, & Cidlowski, 2014). Sex differences in the activation of CRF systems during drug withdrawal are poorly studied although some results support an enhanced role of CRF in reinstatement in females (Buffalari, Baldwin, Feltenstein, & See, 2012).

Finally, interest in the role of norepinephrine in both rewarding effects of drugs of abuse and stress-reactivity and relapse is growing (Becker et al., 2012; Curtis, Bethea, & Valentino, 2006), and in rats at least, the noradrenergic neurons in the locus coeruleus exhibit marked sexual dimorphism with females demonstrating extensive dendritic arborization and more NE neurons than males (Bangasser & Valentino, 2012; Bangasser, Zhang, Garachh, Hanhauser, & Valentino, 2011; Curtis et al., 2006; Valentino et al., 2012). Finally, notable

sex differences exist in certain aspects of GABA and glutamate function. While differences in GABA and glutamate function may be important for the intoxicating effects of ethanol, studies relating sex differences in GABA and glutamate function to substance use and abuse are sparse. Given the special importance of glutamate adaptations to later stages of addiction, this represents an important gap in the field.

## 7. Sex Differences in Intrinsic and Extrinsic Factors Contributing to Addiction

The pharmacologic effects of drugs on specific neurotransmitter systems are not the only factors which influence the development of substances abuse. There are significant intrinsic and extrinsic risk factors that men and women share. Behavioral or personality characteristics including high sensation seeking, impulsivity and poor self-regulation are significant risk factors for substance use and abuse in men and women which precede the development of substance use (Bari & Robbins, 2013; Fineberg et al., 2014; Koob et al., 2014; Koob & Volkow, 2010; Schumann et al., 2010; Volkow, Wang, Fowler, Tomasi, & Telang, 2011). Impulsivity/novelty seeking also predict drug self-administration in animal models (Anker, Perry, Gliddon, & Carroll, 2009; Broos, Diergaarde, Schoffelmeer, Pattij, & De Vries, 2012; Carroll, Anker, & Perry, 2009; Dalley et al., 2007; Poulos, Le, & Parker, 1995). Impulsivity not only predicts the subsequent development of substance abuse, but extensive drug exposure also increases impulsivity as shown in rats and non-human primates (Carroll, Mach, La Nasa, & Newman, 2009; Winstanley et al., 2009). While high impulsivity is frequently identified in addict populations, relative normal inhibitory function in long-term abstinent addicts has been interpreted as recovery from drug-induced impulsivity (Bell, Foxe, Ross, & Garavan, 2014; Connolly, Foxe, Nierenberg, Shpaner, & Garavan, 2012; Morie et al., 2014). Although longitudinal studies of recovery would provide more rigorous evidence, these studies suggest that drug-induced impulsivity also occurs in human addict populations.

Sex/gender differences in the behavioral characteristics described above have been observed in healthy populations, even though mediating neural mechanisms are poorly understood Sensation seeking is consistently reported to be greater in males than females (Cross, Copping, & Campbell, 2011; Zuckerman & Kuhlman, 2000). However, sex differences in measures of impulsive choice or impulsive action are more subtle. Both human and rodent females typically show steeper discounting (bias toward immediate not delayed rewards) in the delayed discounting task, a widely used measured of impulsive choice, although some studies indicate human males discount more steeply for actual rewards (Cross et al., 2011; McClure, Podos, & Richardson, 2014; Perry, Nelson, Anderson, Morgan, & Carroll, 2007; Weafer & de Wit, 2014). Female mice also exhibit steeper delay discounting under conditions of mild food deprivation (Koot, van den Bos, Adriani, & Laviola, 2009), In studies of behavioral control or impulsive action, results depend upon the test (go/no vs. stop signal) but on average sex differences in adult humans are modest and task-specific (Garavan, Hester, Murphy, Fassbender, & Kelly, 2006; Weafer & de Wit, 2014). Similarly, in rat studies, females make more premature errors with long intervals in the 5 choice serial reaction time task and more errors in a go/no paradigm, but males show more motor

impulsivity in an attentional task (Anker, Gliddon, & Carroll, 2008; Burton & Fletcher, 2012; Jentsch & Taylor, 2003). Several studies document the ability of women to exhibit better inhibitory control than men in the presence of reward. In a study of "desire vs. reason" women exhibited more self-control in the presence of reward (Diekhof et al., 2012)and women show faster inhibitory responses to a rare event (Yuan, He, Qinglin, Chen, & Li, 2008). While performance in individual tasks varies, the trend in studies of inhibitory function show that men are more sensation seeking while women are more punishment sensitive (Cross et al., 2011). Hosseini-Kamkar and Morton (Hosseini-Kamkar & Morton, 2014) reviewed evidence that women are least impulsive during the follicular phase of their menstrual cycle when they are fertile, and suggested that these differences might explain inconsistent findings across studies.

The complex neural circuits encompassing cortical and subcortical regions through which humans and animals select and implement behaviors circumstances are increasingly well understood (Bari & Robbins, 2013; Fineberg et al., 2014; Pattij & De Vries, 2013; Perry et al., 2011), but studies of sex differences in these circuits are rare.

A history of physical and sexual abuse and resultant PTSD is a risk factor for substance abuse (Cottler, Compton, Mager, Spitznagel, & Janca, 1992; Greenfield et al., 2010; Lawson, Back, Hartwell, Moran-Santa Maria, & Brady, 2013). In addition, co-morbidity of substance abuse and other psychiatric disorders including depression, anxiety, conduct disorder or ADHD is common (Charach, Yeung, Climans, & Lillie, 2011; Compton, Thomas, Stinson, & Grant, 2007; Flory & Lynam, 2003; Goldstein et al., 2007; Hasin, Stinson, Ogburn, & Grant, 2007). Significant sex/gender differences in all of these factors exist. Childhood sexual abuse is reported more frequently in female than male substance-abusing populations and is associated with more drug use and higher rates of relapse (Afifi, Henriksen, Asmundson, & Sareen, 2012; Brady & Randall, 1999; Clark et al., 2012; Hyman, Garcia, & Sinha, 2006; Hyman et al., 2008). The incidence of depression, anxiety and bipolar disorder is greater among female than male substance abusers, while the incidence of conduct disorder and ADHD are higher among male than female substance abusers in most studies (although sex/gender neutral studies with ADHD also exist (Compton et al., 2000; Compton, Dawson, Conway, Brodsky, & Grant, 2013; Compton et al., 2007; Zilberman, Tavares, Blume, & el-Guebaly, 2003).

## 8. Adolescence: The Critical Period for Emergence of Drug Use

Experimentation with drugs during adolescence is virtually normative (Schramm-Sapyta, Walker, Caster, Levin, & Kuhn, 2009). Nevertheless, most individuals do not become drug-dependent. The characteristics which increase vulnerability to or protect males and females from substance abuse during this developmental transition can differ. For the purposes of understanding the latter, we will focus on events related specifically to substance abuse which exhibit sex/gender differences. The influences on adolescents which impact the initiation of substance use are shown in Figure 3. During this critical developmental epoch, genetic sex and hormones continue to sculpt the final maturation of the brain, leading to the emergence of sex differences in critical behavioral variables including function of the brain areas involved in initiation and progression of substance abuse (the reward system, threat

system and executive function), extrinsic variables including peers and family and stress intrinsic variables including the emergence of sex differences in psychiatric co-morbidities including attention deficit hyperactivity disorder (ADHD), conduct disorder and depression. These will be discussed in the following sections.

The normal neurobehavioral state of the brain which prepares the adolescent to leave the natal family predisposes vulnerable individuals to experiment with and repeat drug use. Adolescents are sensation seeking and impulsive relative to younger and older individuals (Steinberg, 2008; Steinberg et al., 2008; Steinberg et al., 2009), and are converting their social network from being family-centric to peer-centric (RJ., 2005; Smith, Steinberg, Strang, & Chein, 2014; Steinberg, 2008).

To understand the neural substrates of these developmentally-specific behavior patterns and how they influence experimentation with drugs, Monique Ernst and colleagues have introduced the “triad of motivated behavior” as a model. As shown in Figure 4, prefrontal cortex executive function provides balance for and control over two subcortical influences on behavior: the reward system which drives motivated behavior, and the extended amygdala, which evaluates affective valence and may signal especially information about threat to the cortex (Eldreth, Hardin, Pavletic, & Ernst, 2013; Ernst & Fudge, 2009; Ernst & Korelitz, 2009; Ernst, Pine, & Hardin, 2006; Ernst, Romeo, & Andersen, 2009; Richards, Plate, & Ernst, 2012). All three points of this triangle function differently in adolescents and adults.

The bottom left point of the triangle, reward-related areas, seems to play a more dominant role in decision making in adolescents than adults. B.J Casey has shown that reward-dominated subcortical areas drive decision making during adolescence (Casey, Jones, & Somerville, 2011; Casey, Duhoux, & Malter Cohen, 2010; Casey, Getz, & Galvan, 2008; Casey, Jones, et al., 2010; Chambers, Taylor, & Potenza, 2003). This state may increase the reinforcing efficacy of drugs which activate reward systems. Similarly, the bottom right, the amygdala which responds to threat responds more powerfully to emotional content like fearful faces during adolescence than adulthood, although this response is not consistently accompanied by the behavioral inhibition/avoidance that occurs in adults (Guyer et al., 2008; Hare et al., 2008; Killgore, Oki, & Yurgelun-Todd, 2001). Finally and most importantly, cortical control, the peak of the pyramid, is weaker during adolescence. One reason for this may be that adolescents respond more to *salient* reward cues relative to adults, and may also respond more to any stimulus with strong emotional content due to weaker control over amygdala processing of environmental stimuli (Ernst, Daniele, & Frantz, 2011; Richards et al., 2012). The development of response inhibition by the cortex exhibits a gradual ontogeny in contrast to the earlier appearance of responses driven by emotional factors, which may explain this developmental trajectory that contributes to addiction risk during adolescence (Blakemore & Robbins, 2012; Brenhouse & Andersen, 2011; Ernst & Fudge, 2009).

The structural and functional changes which mediate these important neurobehavioral characteristics are poorly understood even though the structural development of the brain during adolescence is increasingly well characterized. Several excellent recent reviews

profile the most important changes that are relevant to addiction (Brenhouse & Andersen, 2011; Giedd et al., 1999; Laviola, Adriani, Terranova, & Gerra, 1999; Spear, 2000). The elegant longitudinal studies of human brain structure by Giedd and colleagues have shown that maximal brain volume is attained during childhood followed by a period of loss which proceeds caudally to rostrally (Giedd, Raznahan, Mills, & Lenroot, 2012). Gray matter in the frontal cortex falls during adolescence while myelination continues linearly, and synaptic pruning is an active process. However, two specific changes relate in an intriguing way to the triadic model described above: structural maturation of the caudate and amygdala precede that of the cortex, while cortical: amygdala connectivity is a relatively late phenomenon (Cressman et al., 2010; Cunningham, Bhattacharyya, & Benes, 2008). However each area has its own trajectory, and none are exactly linear (Mills, Goddings, Clasen, Giedd, & Blakemore, 2014). Accumbens volume falls starting early during adolescence, amygdala volume in males continues reaches an asymptote during late adolescence while cortical thinning, a marker for one aspect of cortical maturation continues into the early 20's, Finally, gray matter volume is at best an indirect measure of maturation that may reflect total neuronal volume (cell bodies and processes) but does not capture many functionally important but subtle events. Figure 5 provides a relative graphic of the structural development of accumbens, amygdala and cortex, based on the aforementioned study. By replotting the data on an increasing trajectory toward adult values, regardless of whether volume is increasing or decreasing, the later attainment of adult structure in the cortex is clear.

Functional studies using fMRI imaging during task performance have provided better insight into at least which brain areas are active when adolescents and adults are performing comparable tasks. Many of these are cited to support the triadic model. However, there are several caveats to this simple model which have been summarized in two recent reviews (Crone & Dahl, 2012; Pfeifer & Allen, 2012). First, the exact test situations vary widely in different studies, and especially the degree of motivation and use of social or non-social cues can yield quite different results. The robust activation of reward networks in adolescents by salient reinforcers can generate quite different results from a less engaging task. In addition the maturation of cortical areas involved in social-affective perceptions and behaviors (Crone & Dahl, 2012) which allows adolescents to understand and value the perspective of other people is ongoing and a key contributor to experimental results which involve social cues. Indeed, the rising importance of peers is a key characteristic of adolescent social behavior. Finally, increased activity in fMRI is often interpreted oppositely by different groups: it is interpreted by some to mean an area is "online" and functional, and by another to indicate inefficient activation of an immature network. Figure 6 provides a revised "triad" which accommodates multiple elements of executive function during adolescence (social cognition, the ability for self-reflection and self-regulation), each of which likely exhibits its gradually increasing but unique developmental trajectory across adolescence.

## 9. Factors Governing Emergence of Drug Use During Adolescence

### Neurobiologic factors influencing Drug Action during Adolescence

Neurobiologic factors influence the pharmacologic effects of addictive drugs in adolescents. In general, the rewarding effects of drugs of abuse are greater and aversive effects of drugs of abuse are less in adolescents. Both characteristics create a positive bias in drug experience.

Studies in experimental animals support the greater reinforcing effects of drugs in adolescents. Most data which directly address age differences in reinforcing effects derive from animal studies, as ethical constraints limit such studies in humans. Both self-administration and conditioned place preference studies in rodents show that nicotine, alcohol and psychomotor stimulants are more reinforcing in adolescents than adults in most (Badanich, Adler, & Kirstein, 2006; Balda et al., 2006; Edwards et al., 2014; Natarajan, Wright, & Harding, 2011; Natividad, Torres, Friedman, & O'Dell, 2013; O'Dell, 2009; Philpot, Badanich, & Kirstein, 2003; Wong, Ford, Pagels, McCutcheon, & Marinelli, 2013) but not all (Adriani & Laviola, 2003; Dickinson, Kashawny, Thiebes, & Charles, 2009; Frantz, O'Dell, & Parsons, 2007; Holtz & Carroll, 2013) studies. Narcotics provide an exception, in which self-administration in rodents has been reported to be greater in adolescent than adult rats (Doherty & Frantz, 2012) but conditioned place preference in mice less in adolescents than adults (Niikura, Ho, Kreek, & Zhang, 2013; Zhang et al., 2009)

The lower aversiveness of drugs of abuse in adolescents is an even more consistent finding than that of enhanced reward in experimental studies in rodents. Multiple laboratories have used conditioned taste aversion or conditioned place aversion to show that adolescent rodents are less likely to avoid a taste or place paired with a dose of drug than adults. This is true for every drug that has been tested including alcohol, nicotine, THC, cocaine, amphetamine, narcotics and even LiCl, the prototype GI irritant that is used as a control in these studies (Acevedo, Molina, Nizhnikov, Spear, & Pautassi, 2010; Anderson, Agoglia, Morales, Varlinskaya, & Spear, 2012; Anderson, Morales, Spear, & Varlinskaya, 2013; Anderson, Varlinskaya, & Spear, 2010; Carvalho, Reyes, Ramalhosa, Sousa, & Van Bockstaele, 2014; Drescher, Foscue, Kuhn, & Schramm-Sapyta, 2011; Hurwitz, Merluzzi, & Riley, 2013; Natarajan et al., 2011; Pandolfo, Vendruscolo, Sordi, & Takahashi, 2009; Philpot et al., 2003; Schramm-Sapyta et al., 2007; Schramm-Sapyta et al., 2010; Schramm-Sapyta et al., 2014; Schramm-Sapyta, Morris, & Kuhn, 2006; Sherrill, Berthold, Koss, Juraska, & Gulley, 2011; Shram, Siu, Li, Tyndale, & Le, 2008; Vetter-O'Hagen et al., 2009). The latter finding suggests that the lack of conditioned taste aversion reflects a fundamental aspect of how the adolescent brain processes aversive input rather than a characteristic of any particular drug. At first, these studies seem to contradict the human imaging studies showing enhanced amygdala reactivity to aversive stimuli. However, this may reflect the difference in experimental approach: rodent studies all require that animals process the aversive stimulus, remember it, recall it at a later time and behave accordingly. All that we can measure in rodents is how they behave at a later time. As pointed out in the earlier section, high amygdala reactivity is not necessarily accompanied by increased behavioral inhibition, a finding generally compatible with the “triadic” hypothesis that what is lacking

is inhibitory control facilitated by the cortex. Recent studies showing that adolescents are less likely to recall contextual fear memories than either juvenile or adult animals (Pattwell, Bath, Casey, Ninan, & Lee, 2011), but can even recall an experience in early adulthood that they did not recall earlier support this interpretation. Future research is required to understand whether memory recall, or behavioral response to the memory is different in adolescents than adults. Several studies with nicotine and one with heroin showing that adolescent animals experience fewer unconditioned negative effects of withdrawal however, support the more general hypothesis that aversive stimuli have less weight than reinforcing stimuli in adolescents (Doherty & Frantz, 2013; O'Dell, Bruijnzeel, Ghozland, Markou, & Koob, 2004; O'Dell et al., 2006; O'Dell, Torres, Natividad, & Tejeda, 2007; Shram et al., 2008).

The dopamine system which mediates reward merits particular attention as it may play a significant role in the initiation of drug use in general and the emergence of sex-specific addiction vulnerabilities. The ontogeny of dopamine systems during adolescence surprisingly does not point to the state of obvious hyperfunction that might be expected, but a situation of immature presynaptic stores and exaggerated postsynaptic reactivity. Dopaminergic innervation of dorsal, ventral striatum and prefrontal cortex reaches a peak during adolescence and then declines to adult levels in rodents and humans (Andersen & Gazzara, 1993, 1994, 1996; Haycock et al., 2003). Basal dopamine is lower in adolescent rat striatum, and studies of psychostimulant-induced changes in dopamine release are conflicting, with reports of responses both higher (for cocaine) and lower (for amphetamine) than are observed in adults (Camarini, Griffin, Yanke, Rosalina dos Santos, & Olive, 2008; Cao, Lotfipour, Loughlin, & Leslie, 2007; Kuczenski & Segal, 2002; Matthews, Bondi, Torres, & Moghaddam, 2013; Stansfield & Kirstein, 2005; Walker, Francis, Caster, & Kuhn, 2007; Walker et al., 2010). There is a hyperproduction of D1 and D2 receptors during adolescence followed by a pruning which could play a significant role in modulating dopamine function during adolescence (Andersen, Thompson, Rutstein, Hostetter, & Teicher, 2000; Meng, Ozawa, Itoh, & Takashima, 1999; Teicher, Andersen, & Hostetter, 1995). C-fos responses to dopaminergic agents in rodents which reflect the integration of pre- and postsynaptic responses reflect this pattern of lower presynaptic function but greater postsynaptic function, showing lower responses to agents that must mobilize stores but higher responses to agents like cocaine that are not limited by immature stores (Andersen, LeBlanc, & Lyss, 2001; Cao et al., 2007; Caster & Kuhn, 2009).

More dramatic discontinuities in dopamine receptor function during adolescence occur in cortex. Transient expression of D1 receptors on cortical afferents to the nucleus accumbens occurs during adolescence (Brenhouse, Sonntag, & Andersen, 2008). Furthermore, a dramatic change in cortical D2 function occurs during adolescence, with a switch from inhibitory to excitatory action (O'Donnell, 2010). The late cortical changes in D2 receptor function are particularly intriguing given the importance of D2 receptors for response inhibition, a late-appearing phenomenon (Ghahremani et al., 2012).

Behavioral effects of investigator-administered addictive drugs have been studied extensively, but their findings are contradictory across laboratories and hard to correlate with addiction risk. For example, both enhanced and decreased locomotor responses to

psychomotor stimulants, nicotine and narcotics are reported in adolescents compared to adults although reported increases outnumber decreases (Adriani & Laviola, 2000; Adriani, Macri, Pacifici, & Laviola, 2002; Cao et al., 2010; Caster, Walker, & Kuhn, 2005; Faraday, Elliott, Phillips, & Grunberg, 2003; Koek, 2014; Koek, France, & Javors, 2012; McQuown, Dao, Belluzzi, & Leslie, 2009; Zombeck, Lewicki, Patel, Gupta, & Rhodes, 2010)

Decreased sedative:hypnotic effects of ethanol, have been observed consistently in rodent models (Hefner & Holmes, 2007; Little, Kuhn, Wilson, & Swartzwelder, 1996; Silveri & Spear, 1998, 1999). Decreased sensitivity to ethanol is the variable which best predicts ethanol intake in animals (Bell, Rodd, Lumeng, Murphy, & McBride, 2006) as well as humans (Schuckit, 1992, 1994), suggesting that adolescent insensitivity could be a factor that drives high alcohol consumption during this developmental epoch.

Studies of neuroadaptation during exposure to addictive drugs during adolescence are surprisingly sparse, but some behavioral studies provide information about the relative behavioral plasticity of adolescents and adults after repeated drug administration. Behavioral sensitization after repeated treatment with psychostimulants is widely used as a behavioral “surrogate” for neuroplasticity in the ascending dopamine system and its targets, although its relevance to addiction has been debated (Robinson & Berridge, 2008; Vanderschuren & Pierce, 2010). Studies of sensitization in adolescents and adults have yielded surprisingly contradictory results. The psychomotor stimulants amphetamine, methylphenidate and cocaine have been studied the most. Some studies report less sensitization in adolescents than adults after repeated treatment with amphetamine or cocaine (Laviola, Wood, Kuhn, Francis, & Spear, 1995; Torres-Reveron & Dow-Edwards, 2005; Zakharova, Leoni, Kichko, & Izenwasser, 2009), others report more sensitization to the challenge drug and/or cross-sensitization to another psychomotor stimulant (Adriani, Chiarotti, & Laviola, 1998; Brandon, Marinelli, Baker, & White, 2001; Caster et al., 2005; Caster, Walker, & Kuhn, 2007; Guerriero, Hayes, Dhaliwal, Ren, & Kosofsky, 2006). One factor might be that drugs which rely on dopamine release like amphetamine and methylphenidate may be less effective than drugs that inhibit uptake like cocaine due to the relative lack of stores to mobilize in adolescents compared to adults (Walker et al., 2010). However, similarly disparate findings are reported for nicotine, with one study reporting a sensitization that perseveres to adulthood (Faraday et al., 2003), another which reported sensitization in adults but not adolescents (Zago et al., 2012), and a third which reported comparable sensitization following adolescent or adult treatment (Adriani, Deroche-Gamonet, Le Moal, Laviola, & Piazza, 2006) Two studies reported increased cross-sensitization to cocaine (Santos, Marin, Cruz, Delucia, & Planeta, 2009) or amphetamine (McQuown et al., 2009) after adolescent nicotine. Similarly, one study reported comparable sensitization to heroin in adolescents and adults (Doherty & Frantz, 2013), while another reported more persevering sensitization in adolescents than adults (Koek, 2014). Overall, results of sensitization experiments are equivocal about whether sensitization is more, less or comparable in adolescents and adults. Different treatment ages, treatment paradigms, post-treatment challenge timing (immediately after treatments vs. in adulthood), different species (mice vs. rats) all could contribute to these disparate findings.

Sensitization is only a surrogate for the effects of early initiation on neuroadapation and vulnerability to escalation of drug intake during repeated intake or later vulnerability to initiation and progression in the use of other drugs. Such experiments are very difficult to accomplish because it is difficult to start self-administration studies during the brief window of rodent adolescence. While there are many studies of how investigator-administered drugs during adolescence influence subsequent self-administration, results are conflicting, drug-specific and plagued by the same differences in protocols described above for sensitization. The small number of self-administration studies in adolescents which have followed extinction, withdrawal and/or relapse point to persevering neural adaptations in adolescents. Some studies with psychomotor stimulants and ethanol indicate that self-administration is higher, escalation greater, extinction of drug-taking is slower and drug and stress-induced relapse more likely, a finding suggestive of more persevering neuroadaptations after adolescent use (Anker & Carroll, 2010; Brenhouse & Andersen, 2008; Schramm-Sapyta et al., 2008; Siegmund, Vengeliene, Singer, & Spanagel, 2005; Wong et al., 2013). The slower extinction may well reflect a general characteristic of adolescent brain function, as extinction of fear-based memories is slower in adolescent brain, a characteristic that is thought to reflect failure of neuroadaptation in specific cortical areas (prelimbic and infralimbic) of adolescent brain (Pattwell et al., 2012; Pattwell, Lee, & Casey, 2013). However, this is not a universal finding, as another study reported less cue-induced reinstatement and comparable cocaine-induced reinstatement in adolescents compared to adults (Li & Frantz, 2009).

In summary, biologic variables that influence drug taking on average promote more drug use in adolescents than adults. Human imaging and cognitive studies as well as self-administration studies in animal models suggest that enhanced behavioral control by the reinforcing properties of additive drugs plays a role in this vulnerability. The enhanced sensitivity to emotional cues combined with a relative lack of aversive input/behavioral inhibition in response to such input minimizes restraints on drug taking by aversive effects of drug taking or withdrawal.

## 10. Intrinsic and Extrinsic Factors that Influence Initiation of Addiction during Adolescence

The important intrinsic factors which enhance or protect against initiation and progression of drug use in adolescents are personality characteristics and the emergence during adolescence of psychiatric illnesses which influence the progression of substance use. “Novelty seeking” and/or sensation seeking (these are behavioral constructs with somewhat overlapping definitions) are characteristic of adolescents in general, and those who rank at extreme levels of high novelty seeking are at special risk for initiation of substance abuse (see above). Tarter’s group has developed a metric they characterize as “neurobehavioral disinhibition” which includes similar characteristics, and includes impulsivity/difficulty in response inhibition, and high ranking in this characteristic during early adolescence is strongly predictive of the later development of dependence on tobacco, marijuana, alcohol and cocaine over the next 7–9 years (Clark, Cornelius, Kirisci, & Tarter, 2005; Kirisci, Tarter, Mezzich, & Vanyukov, 2007; Tarter et al., 1999). In contrast, the personality trait of

conscientiousness, which reflects the capacity for self-regulation, is highly protective against the development of substance abuse (Whelan et al., 2014).

Anxiety, depression, bipolar disorder conduct disorder and ADHD enhance the progression of substance use (Charach et al., 2011; Deas, 2006; Matthys, Vanderschuren, & Schutter, 2013; Simkin, 2002; Zulauf, Sprich, Safren, & Wilens, 2014). While anxiety disorders tend to first appear during childhood, levels of this disorder rise during adolescence, as does depression. Bipolar disorder typically appears during late adolescence and early adulthood, and is associated with increased abuse of both alcohol (to dampen manic symptoms) and psychomotor stimulants (to relieve depressive symptoms) (Blumberg, 2007; Deas, 2006; Goldstein & Bukstein, 2010).

Extrinsic factors both contribute to and protect from initiation and progression of substance use during adolescence. A childhood history of physical or sexual abuse (Downs & Harrison, 1998; Nomura, Hurd, & Pilowsky, 2012) or profound stress (Enoch, 2011) are associated with development of substance abuse during adolescence. Peers play a dominant role in initiation of tobacco and alcohol use, and association with deviant peers is a very important predictor of the initiation and progression especially of smoking during adolescence (Haas & Schaefer, 2014; Kobus, 2003; Pollard, Tucker, Green, Kennedy, & Go, 2010). Family environment is also crucial: high levels of parental use and low parental supervision are associated with higher rates of initial use and progression (Clark et al., 2005; Kirisci et al., 2007). Overall, parental supervision and involvement is a protective factor which retards initiation and progression of tobacco and alcohol use during adolescence (Mahabee-Gittens, Xiao, Gordon, & Khoury, 2013; Morin, Rodriguez, Fallu, Maiano, & Janosz, 2012; Ryan, Jorm, & Lubman, 2010; Van Der Vorst, Engels, Dekovic, Meeus, & Vermulst, 2007; van der Zwaluw et al., 2010). However, the match between personality and parenting style has a strong impact on initiation and progression of substance use during adolescence. While effective, “authoritative” parenting is effective overall, the pairing of an impulsive, acting out adolescent and authoritarian rather than authoritative parent is a risk factor which increases the risk of substance abuse by adolescents (Armstrong et al., 2013). Finally, other activities in the life of adolescents have a protective effects, especially engagement in religious activities and sports (Agrawal & Lynskey, 2009; Metzger, Dawes, Mermelstein, & Wakschlag, 2011; Nasim, Belgrave, Jagers, Wilson, & Owens, 2007; Silins et al., 2013) Engagement is sports is especially protective against initiation of smoking (Adachi-Mejia, Gibson Chambers, Li, & Sargent, 2014).

## 11. Summary: risk and protective factors influencing the emergence of substance use and abuse in adolescence

Numerous factors contribute to the initiation and progression of substances abuse including how an individual reacts to a particular drug, the neurobiology of the adolescent brain in general, and the brain of vulnerable individuals (novelty-seeking, disinhibited). However, the interactions of the individual with his or her environment are also crucial: families, peers, individual engagement in activities all influence the initiation and progression of substance use. These factors have been outlined in such detail because a considerable body

of evidence suggests that gender/sex influences the weight of all of these key variables. The remainder of this chapter will aim to describe these interactions.

Biologic Factors that Influence the Emergence of Sex/Gender Differences in Substance Use and Abuse during Adolescence

## 12. Sexual Differentiation of the Brain: The role of genes and hormones

Many aspects of brain structure and function are sexually dimorphic. The most obvious of these are the functions and structures supporting reproduction and sexual behavior, but the reward system, executive function, aggression and stress sensitivity are different in males and females. Multiple phenomena contribute to these differences, as depicted in Figure 7. Males and females receive their complement of X and Y chromosomes at fertilization, which dictate whether a fetus will be male (XY) or female (XX). A rapidly expanding literature shows that sex-specific gene expression occurs in the brain even before ovaries and testes form (Viveros et al., 2012). XX genotype alone accelerates habit formation, a critical component in the transition from reinforced to compulsive responding (Quinn, Hitchcott, Umeda, Arnold, & Taylor, 2007), and also influences nociception, aggression and maternal behavior (Arnold & Chen, 2009) The testis-determining gene sry exerts direct effects on brain development independent of the production of testosterone (De Vries et al., 2002; Dewing et al., 2006; Gatewood et al., 2006; Quinn et al., 2007).

Once the gonads are established, hormonal factors begin to contribute to sexual differentiation of the brain. These changes take two forms which have been termed “organizational” and “activational” (Arnold, 2009). Organizational effects reflect irreversible effects on brain organization due to exposure to gonadal hormones during a critical period. Aromatization of testosterone to estradiol within the brain plays a critical role in this process in the male during fetal/early neonatal life as a fetal form of albumin prevents estradiol from entering the female brain (MacLusky, Lieberburg, & McEwen, 1979; MacLusky & Naftolin, 1981; McCall, Han, Millington, & Baum, 1981; Pardridge & Mietus, 1979). Rising testosterone and estradiol in males and females at puberty respectively causes further sexual differentiation of behaviors including aggression in males and feeding-related behaviors in females (Juraska, Sisk, & DonCarlos, 2013; Schulz, Molenda-Figueira, & Sisk, 2009; Schulz et al., 2004; Schulz & Sisk, 2006; Sisk & Foster, 2004; Sisk & Zehr, 2005). After puberty, gonadal steroid hormones exert ongoing “activational” effects that reverse when hormone is eliminated. The profound rise in gonadal hormones during puberty creates the endocrine environment of adulthood which contributes to many of these effects. Recent research also suggests a role for central production of estradiol by brain aromatase in sexual differentiation of the brain (Bakker, Honda, Harada, & Balthazart, 2002; Brock, Baum, & Bakker, 2011; Dugger, Morris, Jordan, & Breedlove, 2007; Garcia-Segura, 2008; Hill & Boon, 2009; Lephart, 1996).

All three major gonadal hormone receptors, ERα, ERβ and androgen receptor, contribute to sexual differentiation of the brain (Holterhus, 2011; Johansen, Jordan, & Breedlove, 2004; Kudwa, Michopoulos, Gatewood, & Rissman, 2006; Raskin et al., 2009; Sisk & Foster, 2004; Sisk & Zehr, 2005). Although work in this area is just beginning, epigenetic

regulation of gonadal steroid hormone gene promoters is likely a mediating mechanism in the evolving role of these different receptors in sexual differentiation of specific brain regions/behavioral functions (Matsuda, 2014; Matsuda, Mori, & Kawata, 2012). Finally, as Figure 7 depicts, adolescence, the developmental epoch when most individuals begin to experiment with drugs, overlaps with puberty and the full expression of genomic and hormonal influences which contribute to the emergence of sex/gender specific behavior.

Sexually dimorphic changes in several key brain structures relevant to the triadic model finalize during adolescence in both humans and rodents. First, structures of reward-relevant areas like the caudate nucleus change differentially in adolescent males and females. Basal ganglia volume attains peak volume and then prunes to adult size earlier in girls than boys (Giedd et al., 2012). There are conflicting data, but some studies suggest that females attain higher final volume than males (reviewed in Giedd (Giedd et al., 2012). In amygdala, changes are nucleus specific, but size of the important basolateral amygdala that is crucial for stress systems attains adult dimensions in childhood in girls, but it continues to grow during adolescence in boys to a greater final volume (Juraska et al., 2013; Viveros et al., 2012). Finally, while thinning of the cortex occurs in both boys and girls, the sex difference (thickness greater in boys than girls) diminishes in critical prefrontal areas during adolescence, and girls attain adult thickness in these areas related to executive function and behavioral inhibition before boys (Raznahan et al., 2010). Each of these anatomical changes correlates with developing sexual dimorphisms in the neurobiologic substrates of addiction including determination of reward system, executive function and neurobiologic determinants of key behaviors like sensation seeking, as well as environmental and cultural influences on gender-typical behavior/social roles. Several critical examples are described below.

The emergence of sexually dimorphic characteristics which contribute to addiction is best understood for the dopamine system involved in the initiation of addiction. Genotype, organizational and activational effects of gonadal hormones all contribute to the establishment of sex/gender differences in adulthood. The testis-determining gene, sry, affects expression of a number of genes in dopamine neurons (Czech et al., 2012; Tao et al., 2012). Greater dopamine neuron numbers occur in females even in DA cell culture, in the absence of any hormonal information, while in this context, male neurons are bigger and express higher levels of some dopamine markers (Beyer, Eusterschulte, Pilgrim, & Reisert, 1992; Beyer, Ivanova, Karolczak, & Kuppers, 2002; Beyer, Pilgrim, & Reisert, 1991; Engele, Pilgrim, & Reisert, 1989; Reisert, Engele, & Pilgrim, 1989; Reisert et al., 1987). Anatomic differences in organization of ascending dopamine systems can be detected well before the pre/postnatal “critical” period in rodents (Kolbinger, Trepel, Beyer, Pilgrim, & Reisert, 1991; Reisert, Schuster, Zienecker, & Pilgrim, 1990). Therefore, the brain structure underlying the enhanced dopamine response to females may be established early in gestation.

Events during this pre/postnatal “critical period” in rodents also contribute to the sculpting of the emerging reward system. Exposure to testosterone during this time frame “masculinizes” behavioral responses to amphetamine in females, an effect that is insensitive to hormonal manipulations later in life (Forgie & Stewart, 1993; Forgie, M. L. & J. Stewart,

1994; Forgie, M.L. & J. Stewart, 1994). Dopamine innervation of the cortex is blunted by testosterone aromatized to estradiol during the pre/postnatal critical period (Stewart & Rajabi, 1994). The final organizational events and onset of activational contributions of gonadal hormones at puberty complete the emergence of sexual dimorphisms in dopamine function. Several waves of dopamine cell loss in rats occur after birth, the final one at puberty, which occurs disproportionately for males (Kuhn et al., 2010). Adult rats, like non-human primates, exhibit greater numbers of dopamine neurons in the ventral tegmental area than males, although these findings are not universal in all rodent studies (McArthur, McHale, & Gillies, 2006; McArthur et al., 2007). The enhanced dopamine release observed consistently in females of rats and mice relative to males also emerges during puberty. The combination of an organizational effect of testicular hormones to suppress dopamine function and the onset of activational effects of estradiol to augment dopaminergic function lead to a divergence of dopaminergic function (Kuhn et al., 2010; Walker & Kuhn, 2008).

Dopamine receptor populations also exhibit marked sexually dimorphic changes in rodents during adolescence that are well described: D2 receptor numbers rise precipitously and then prune markedly in males, while changes in females are blunted in comparison (Andersen, Rutstein, Benzo, Hostetter, & Teicher, 1997; Andersen & Teicher, 2000; Andersen et al., 2000). These changes are independent of hormonal changes at puberty, but the role of earlier endocrine and genomic effects has not been explored (Andersen, Thompson, Krenzel, & Teicher, 2002).

Numerous pubertal changes both in addictive drug action and self-administration that reflect sex-specific development of dopamine systems have been reported in animal models. Enhanced self-administration of cocaine and nicotine in females relative to males emerges, although the role of gonadal hormones was not investigated in these studies (Levin et al., 2011; Lynch, 2008, 2009). However, a study of the effects of prepubertal gonadectomy on cocaine-stimulated locomotion in adulthood, a common surrogate for activation of dopamine reward systems, showed that gonadectomy lowered responses in females and elevated them in males compared to gonadally intact animals (Parylak, Caster, Walker, & Kuhn, 2008). One intriguing study comparing acquisition, intake and motivation to self-administer cocaine suggested that organizational effects of estradiol at puberty specifically organizes motivation but not the other parameters (Perry, Westenbroek, & Becker, 2013).

Studies of the emergence of behavioral sensitization tell a similar story about the importance of puberty and gonadal hormones on the appearance of elevated sensitization in females. An extensive literature shows that chronic exposure of rats to cocaine or nicotine causes enhanced behavioral responding to a test dose of cocaine (sensitization) that is greater in females than in males (Booze, Welch, et al., 1999; Booze, Wood, Welch, Berry, & Mactutus, 1999; Hu & Becker, 2003; Quinones-Jenab & Jenab, 2012; Yang, Zhao, Hu, & Becker, 2007).

A similar role for organizational/activational influences on alcohol consumption may occur during puberty. Prepubertal gonadectomy reversed sex-specific patterns of ethanol consumption in adult mice, as early gonadectomized males consumed more than early-gonadectomized females (Sherrill, Koss, Foreman, & Gulley, 2011). Sex differences in the

use-limiting effects of ethanol may emerge during puberty. Sex differences in ethanol-induced sedation exist on postnatal day 60 but not on day 30 (Cha, Li, Wilson, & Swartzwelder, 2006). Similar findings have been reported by Silveri and Spear (Silveri & Spear, 1998) who showed that adult female rats are less sensitive to the sedating effects of ethanol but that no sex difference existed during juvenile or adolescent development. While sex differences in alcohol-related impairment also develop during puberty in non-human primates, the changes are more complex. Males and females both exhibit a decrease in ataxia, but females exhibit more locomotor stimulation and impaired jumping with age compared to males (Schwandt, Barr, Suomi, & Higley, 2007).

The emergence of sex differences in stress systems during puberty may also contribute significantly to the emergence of sex-specific trajectories into drug use and abuse through effects both on the protracted stage of CRF-mediated drug craving, and on the role of stress and emergence of psychiatric disorders during puberty (see below). In both humans and rodents, HPA reactivity to stress is high in adolescence in comparison to earlier life stages and this increase interacts with the hormonal changes of puberty. In humans, cortisol responses to stress are high in adolescents compared to children (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009). Basal cortisol, stress-induced cortisol and CRH-induced rises in cortisol are higher in human females than males after puberty, reflecting a more pronounced fall in males than females (Adam, 2006; Blumenthal, Leen-Feldner, Badour, Trainor, & Babson, 2014; Gunnar et al., 2009; Kiess et al., 1995; Netherton, Goodyer, Tamplin, & Herbert, 2004; Oskis, Loveday, Hucklebridge, Thorn, & Clow, 2009; Shirtcliff et al., 2012; Stroud, Papandonatos, Williamson, & Dahl, 2011). Rodents show a similar pattern: they attain maximal HPA axis reactivity just before puberty (Jankord et al., 2011). Corticosterone responses to stress are high due in part to sluggish glucocorticoid feedback (Sapolsky & Meaney, 1986) As male rats go through puberty, HPA axis responses fall (Klein & Romeo, 2013; Romeo, 2010). Organizational effects during the perinatal period but not adolescence contribute to this fall (McCormick, Furey, Child, Sawyer, & Donohue, 1998; Patchev, Schroeder, Goetz, Rohde, & Patchev, 2004; Seale, Wood, Atkinson, Lightman, & Harbuz, 2005). However, activational effects of androgen to suppress corticosterone secretion contribute to regulation in adulthood (McCormick & Mathews, 2007; McCormick, Mathews, Thomas, & Waters, 2010). In female rats, the onset of estrous cyclicity and estradiol secretion allow them to maintain high, adolescent- like stress responses through activational effects at multiple sites including CRF production, glucocorticoid feedback and others (Evuarherhe, Leggett, Waite, Kershaw, & Lightman, 2009; Veldhuis et al., 2013).

The development of enhanced HPA axis reactivity during puberty in vulnerable human females has the potential to contribute to sex/gender specific trajectories in substance use and misuse in two ways. First, rising HPA axis reactivity is thought during puberty is thought to be related to the emergence of the higher incidence of depression in females relative to males (Young & Korszun, 2010; Young, 1998; Young & Altemus, 2004). Second, it may also be related to enhanced withdrawal from nicotine and stress-induced relapse to psychostimulant self-administration observed in animal models (Feltenstein, Henderson, & See, 2011; Hudson & Stamp, 2011; O'Dell, 2009; O'Dell et al., 2004).

Much less is known about emergence of sex differences in opioid systems of reward or dynorphin mediated stress responses: these remain gaps in the neurobiology literature.

## 13. Intrinsic Factors in Sex/Gender Differences in Emergence of Substance Use and Abuse during Adolescence

The appearance of sex differences in and hormonal influences on critical personality/ neurobehavioral domains influence substance use and abuse risk play a crucial role in the patterns of substance use and abuse in developing males and females. This is true for the risk factors of sensation seeking and impulsivity and for the protective factors of behavioral inhibition and self-regulation.

In both male and female humans, the personality constructs of neurobehavioral disinhibition/novelty seeking (Lovallo et al., 2006; Tarter et al., 1999) or high novelty seeking/low harm avoidance (Bohman et al., 1987; Cloninger et al., 1988; Gilligan et al., 1987) are highly predictive of the development of alcohol (and other substance abuse) problems. Pubertal development is a risk factor for early substance use and abuse in both males and females, and several studies suggest that sensation seeking is a behavioral mediator of this association (Castellanos-Ryan, Parent, Vitaro, Tremblay, & Seguin, 2013; Forbes & Dahl, 2010; Gunn & Smith, 2010; Kong et al., 2013; Martin et al., 2002; Steinberg et al., 2008). High testosterone predicts drug use in both sexes (Kerschbaum, Ruemer, Weisshuhn, & Klimesch, 2006; Reynolds et al., 2007). However, during adolescence, an interesting discrepancy begins to appear which differentiates drug using and non-drug using females. Levels of neurobehavioral disinhibition/sensation seeking/impulsivity are generally lower in adolescent females than males, a difference which becomes exaggerated after puberty (Shulman, Harden, Chein, & Steinberg, 2014). However, adolescent females with high scores in these domains are more likely to develop substance abuse during adolescence, like males, and they are generally correlated with pubertal development in both males and females (Castellanos-Ryan et al., 2013; Grano N, 2004; Kirisci, Mezzich, Reynolds, Tarter, & Aytaclar, 2009; Kong et al., 2013; Martin et al., 2002). Therefore, while slightly lower levels of impulsivity may protect females in general, those at the high end of the spectrum are still at significant risk.

These personality domains correlate well in brain imaging and psychophysiology studies with reward sensitivity and striatal activation, in keeping with the triadic model proposed earlier. During puberty, testosterone was correlated with striatal activation during a gambling task for both males and females, suggesting that androgen effects on reward sensitivity plays a role in both males and females (Op de Macks et al., 2011). Perhaps the most interesting study is one showing that threat cues evoked exaggerated responses in both threat-related areas (amygdala) and reward related areas (striatum) in males, and that these responses correlated with testosterone (Spielberg, Olino, Forbes, & Dahl, 2014). Startle amplitude, a measure of CNS arousal in response to emotionally arousing pictures, increased in midpuberty/late puberty in comparison to earlier ages in males and females (Quevedo, Benning, Gunnar, & Dahl, 2009). This small but intriguing literature links these “personality” constructs to neurobiologic changes which occur during adolescence, and may suggest that the emergence of exaggerated male responses in the domains of sensation/

impulsivity are driven by gonadal steroid hormone effects influencing basic neurobiologic circuits involved in threat and reward.

Emergence of sex differences in protective factors including capacity for self-regulation may also contribute to the development of male dominance in substance use and abuse in adulthood. While adult male and female humans perform similarly in tasks related to behavioral inhibition in adulthood (Garavan et al., 2006; Li, Huang, Constable, & Sinha, 2006), adolescent females perform better than boys in tasks of motor inhibition (Aarnoudse-Moens, Duivenvoorden, Weisglas-Kuperus, Van Goudoever, & Oosterlaan, 2012; Bezdjian, Baker, Lozano, & Raine, 2009) and delay of gratification (Hosseini-Kamkar & Morton, 2014). In fact, most studies show that these sex/gender differences are established well before puberty and perhaps even more prominent in children than in adolescents (Hosseini-Kamkar & Morton, 2014). The early emergence of this sexual dimorphism could reflect early sexual differentiation of these areas. Imaging studies further suggest that adolescent males and females use slightly different strategies in selecting risk vs. reward: during a gambling task, adolescent females preferentially activated left inferior, frontal and striatal areas in contrast to males, with dominant right inferior parietal activation (Rubia et al., 2013), a pattern that has been linked to “top-down,” habit-learning dominance in females compared to visuospatial “bottom up” processing in males.

Co-morbid psychiatric illness is a factor in the progression of addiction in men and women, and sex/gender differences in the most frequently observed co-morbidities emerge during adolescence. In adolescent males, the psychiatric disorders most frequently cited as increasing the risk of substance abuse are conduct disorder and attention deficit hyperactivity disorder (ADHD) (Andersen & Teicher, 2000; Dakof, 2000; Deas, 2006; Latimer, Stone, Voight, Winters, & August, 2002), while depression is the most common diagnosis in females (Latimer et al., 2002; Simkin, 2002). After puberty sex/gender differences in depression change dramatically to being female-dominated (Angold & Costello, 2006; Angold, Costello, Erkanli, & Worthman, 1999; Angold, Costello, & Worthman, 1998), and depression is more frequently a factor in substance abuse in adolescent females than adolescent males (Latimer et al., 2002). On average girls more frequently endorse coping as a rationale for drinking alcohol while males more frequently cite getting high/having fun (Kuntsche & Muller, 2012). Similarly, teenage girls more frequently cite desire to reduce anxiety as a reason to smoke cigarettes than boys (O'Dell & Torres, 2014).

The emergence of sex-differences in executive function, reward sensitivity and behavioral inhibition discussed above as well as the different pattern of association between psychiatric diagnosis and sex during adolescence all converge to generate different trajectories into substance use by adolescent males and females. While rates of initiation and use may be similar, the factors driving use diverge rapidly during adolescence for males and females. Nevertheless, individual differences in all of these domains also contribute to vulnerability: females with conduct disorder and males with depression are at increased risk of substance abuse despite not being gender-typical.

## 14. Extrinsic Factors in Sex/Gender Differences in Emergence of Substance Use and Abuse during Adolescence

The intersection of sex/gender and environment play a significant role in the emergence of gender-specific patterns of substance abuse. Early adversity, especially physical or sexual abuse or early emotional maltreatment, is a dramatic predictor of later substance abuse problems. Although early physical or sexual abuse are risk factors for the development of substance abuse in both men and women (Afifi et al., 2012; Banducci, Hoffman, Lejuez, & Koenen, 2014; Clark et al., 2012; Dube et al., 2005), some studies report that women experience more dramatic impact on substance abuse behaviors (Hyman et al., 2006; Hyman et al., 2008)

Cultural variations in gender roles contributes significantly to initiation of substance use in different countries but rates of initiation of men and women in the youngest cohorts are equalizing in developed countries (Degenhardt et al., 2008; Okoli, Greaves, & Fagyas, 2013; Piko, Wills, & Walker, 2007; Zilberman, M. et al., 2003). Environmental factors including parenting style, the impact of peers, education and socioeconomic status all influence substance use initiation in all adolescents, but also have gender specific effects in humans. Overall, the impact of deviant peers on substance use initiation may be less in girls than boys (Kirisci et al., 2009). However, consumption of alcohol, smoking and use of many drugs in females is enhanced/encouraged by romantic partners to a greater extent in females than males, a pattern that emerges during adolescence (Brady & Randall, 1999; Branstetter, Blosnich, Dino, Nolan, & Horn, 2012; Forbes & Dahl, 2010; Miller et al., 2009). Cohort studies showing that initiation of smoking, alcohol consumption and use of cannabis are occurring earlier and equalizing across gender in current adolescents compared to earlier generations suggest that lower stigmatization and changing roles for women are changing drug use patterns in adolescent females (Degenhardt et al., 2008; Geels et al., 2013; Johnson & Gerstein, 2000; Kerr et al., 2009; Keyes et al., 2008; Pitel et al., 2010).

## 15. Conclusions

Experimentation with psychoactive drugs and the initiation of substance abuse for most humans begins during adolescence, the developmental epoch when the genetic and hormonal processes which contribute to the emergence of adult sex/gender-specific behaviors emerge. In addition, the social environment of this and earlier developmental epochs shapes social roles which further influence sex/gender-specific behaviors including drug taking. Drug experimentation and progression to substance use is enhanced in adolescent humans as well as in animal models. Peak use of addictive drugs occurs during early adulthood in humans and then tapers off dramatically into adulthood. Drug use by the youngest adolescents is similar in males and females in humans and in animal models, but differences emerge with adulthood. More men than women use and become dependent upon most drugs, and drug use falls more in females than males during the transition to adulthood. However, females may progress more rapidly from initiation of use to problematic use to treatment. In rodent models, which provide a window into the role of biologic factors in the absence of cultural and environmental risks, enhanced drug taking in females emerges at

puberty, due in large part to organizational effects of androgen and activational effects of estradiol on the dopamine system. In rodents, like humans, the enhanced stress reactivity of females which contributes to stress and cue-induced relapse also develops after puberty. The risks in the drug-using population and the protective factors in the larger population that never progresses beyond drug experimentation contribute to this developmental pattern of drug use.

Risk factors which predict the development of substance abuse are similar in adolescent males and females. These include the neurobiology of adolescence which favors selection of rewarding experiences without inhibition by aversive consequences, the novelty seeking/sensation seeking personality and psychiatric comorbidities like depression as well as environmental factors including drug-using family environment. However, sex differences in the relative importance of each of these factors emerge during puberty. These include enhanced novelty seeking/sensation seeking especially in males, depression/anxiety in females, and the emergence of stress-induced risk for relapse in females. These intrinsic factors lead to the development of a sex/gender specific trajectory from experimentation into substance abuse for males and females. These are mediated by biologic factors in part including sexual differentiation of cortical and subcortical brain areas responsible for reward, executive function and stress. The emergence of sex differences in factors which *protect* the larger population of females who do not progress or stop using drugs is rarely considered or studied. These include lower levels of impulsivity and sensation seeking, higher levels of self-regulation during adolescence specifically and greater impact of family environment which provide a window into the role of biologic factors in the absence of cultural and environmental risks. These may continue to protect a large population of females despite the gradual change in social roles which protected women historically. Many of these risk factors reflect characteristics that are difficult to model in animals, which may contribute to the apparent divergence in sex/gender specific drug taking in animal models and humans.

In summary, biologic, psychiatric co-morbidities as well as personality and environment present sex/gender-specific risks as adolescents begin to initiate substance use. In females, enhanced dopaminergic and CRF-related functions as well as psychiatric comorbidity (depression) and previous abuse represent vulnerability factors. In men, neural development during adolescence and the pubertal testosterone surge lead to a greater increase in impulsivity/sensation seeking and poorer self-regulation which represents risk factors for them.

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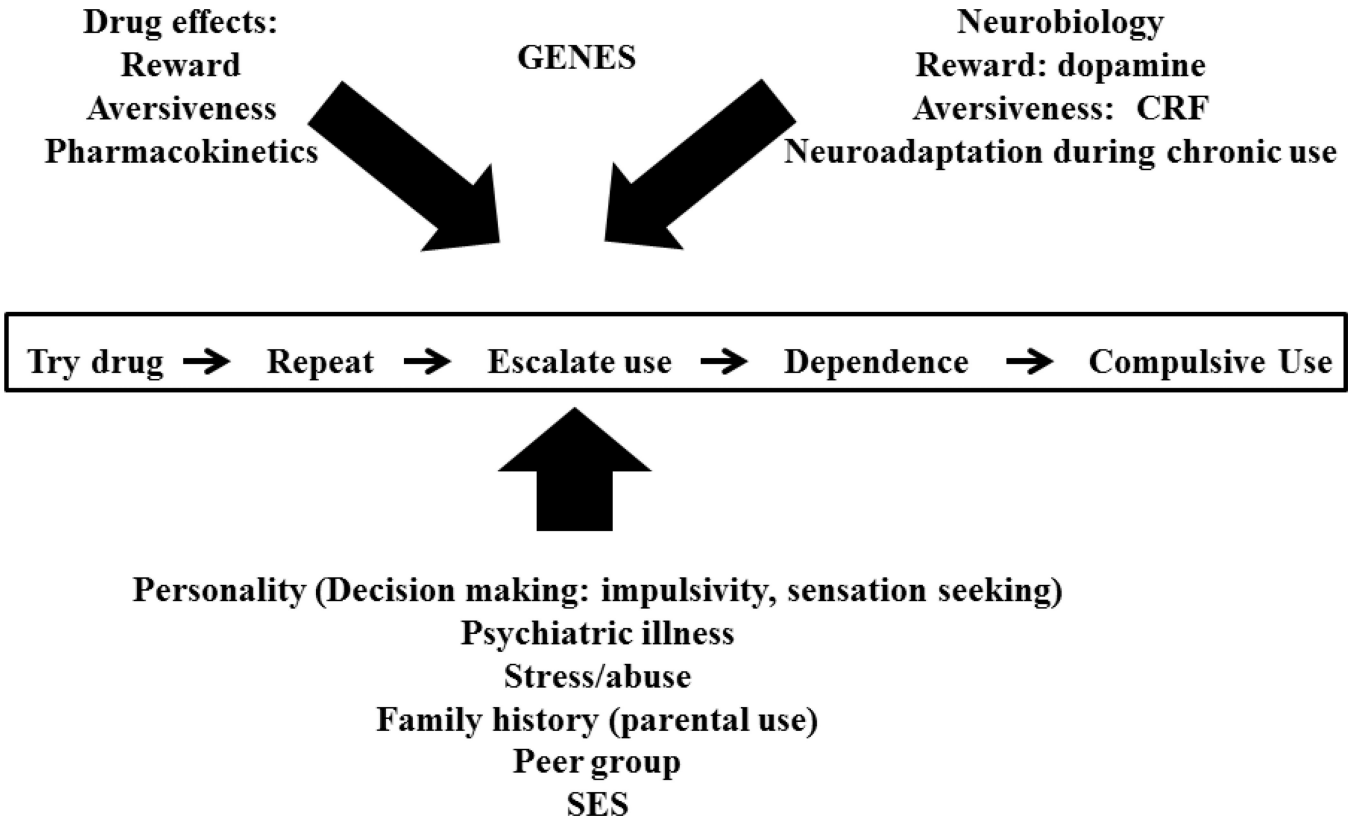


**Figure 1.**
Factors In Addiction

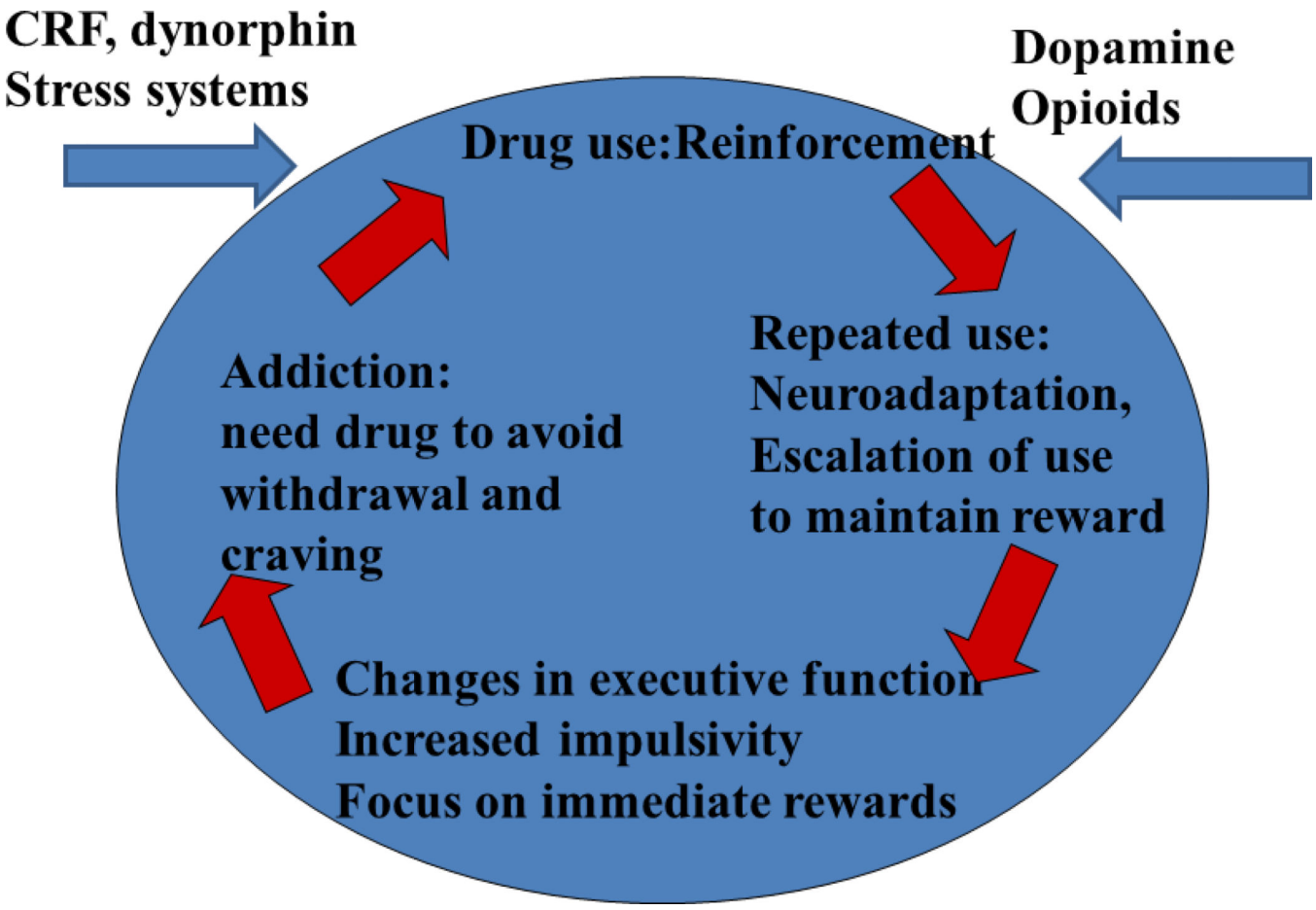


**Figure 2.**
Neurobiology Factors in Addiction

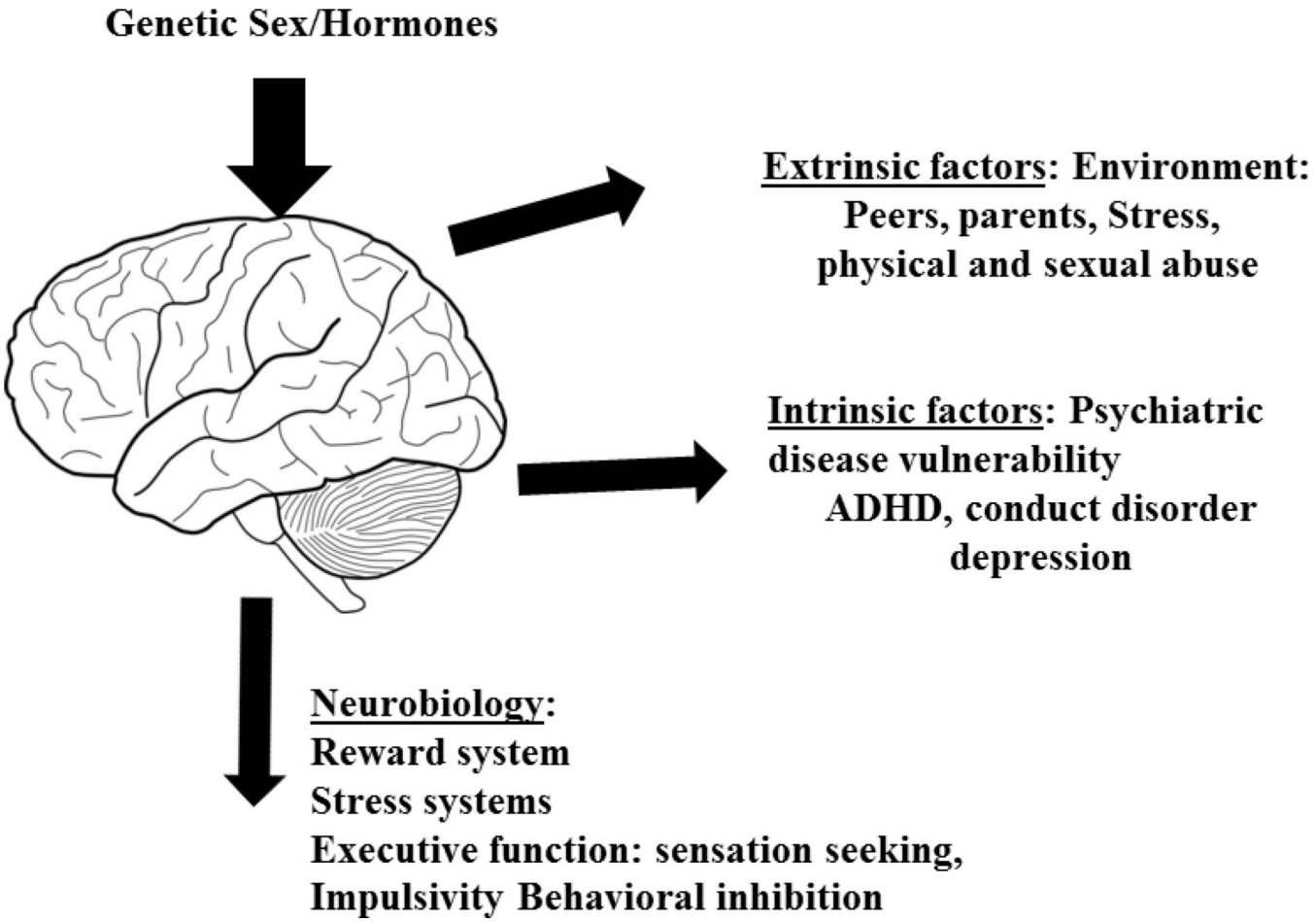


**Figure 3.**
Factors Influencing Initiation of Substance Use during Adolescence

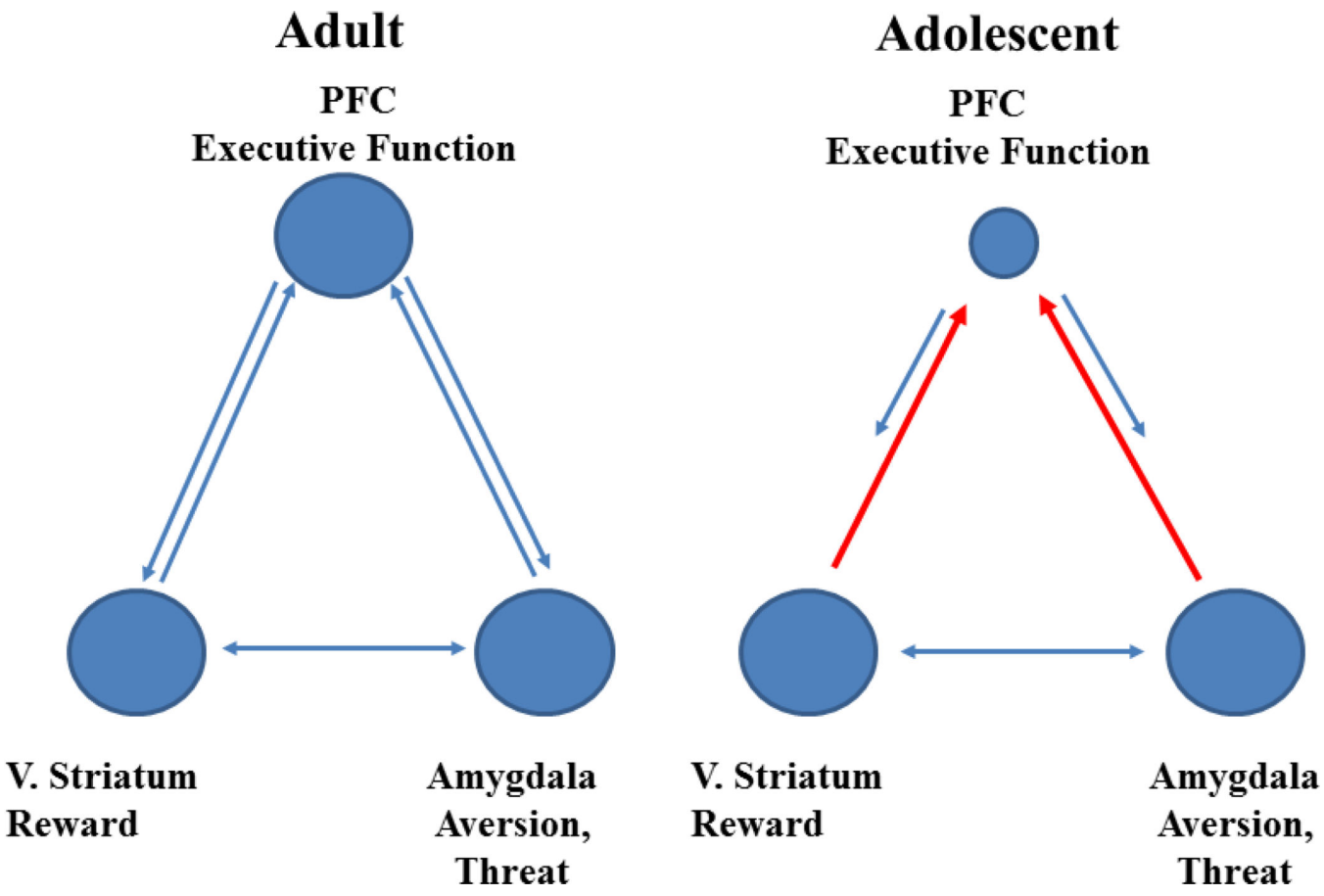


**Figure 4.**
The triadic model of executive function (adapted from (Richards et al., 2012)

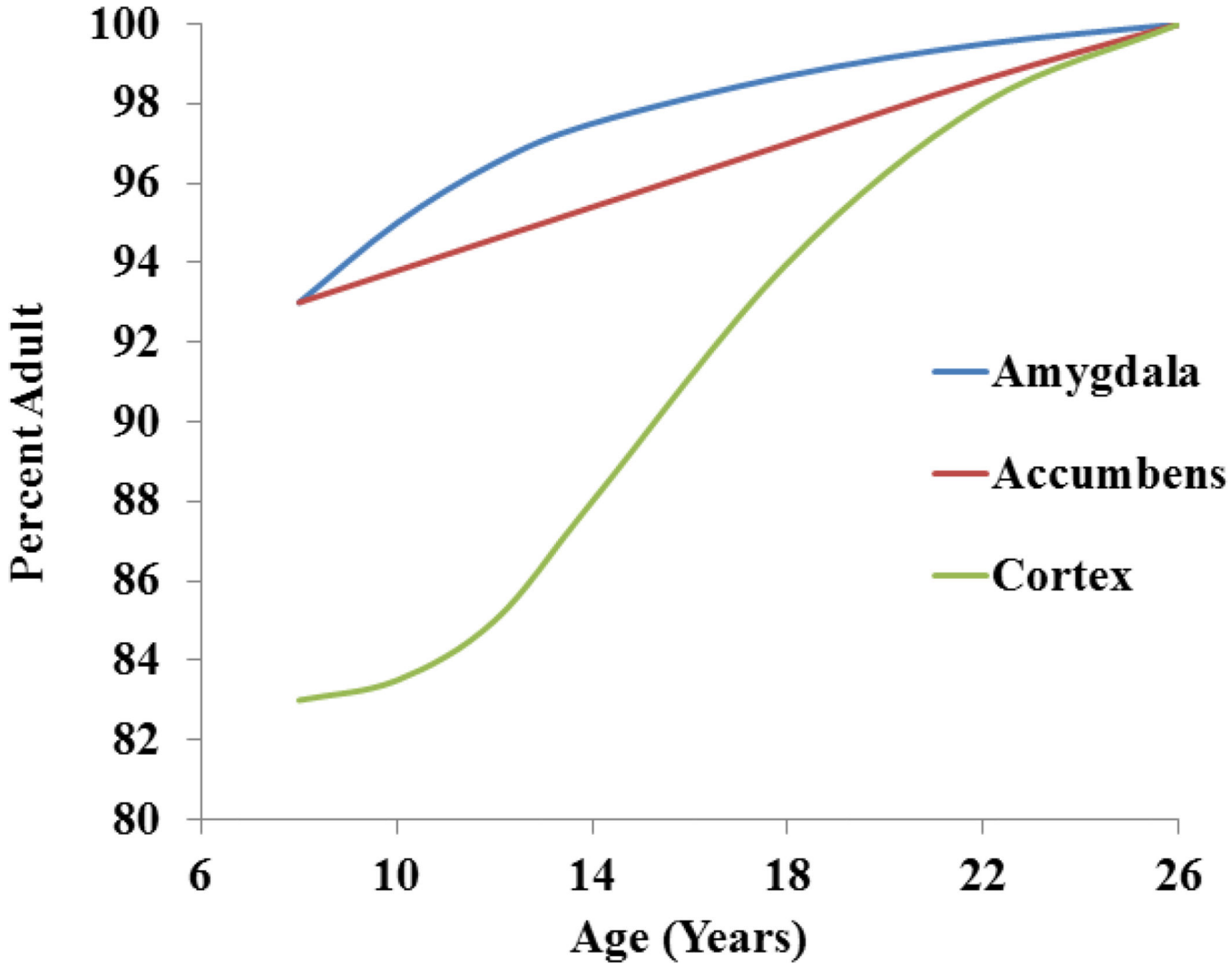


**Figure 5.**
Trajectory of accumbens, amygdala and cortical development (modified from (Mills et al., 2014)

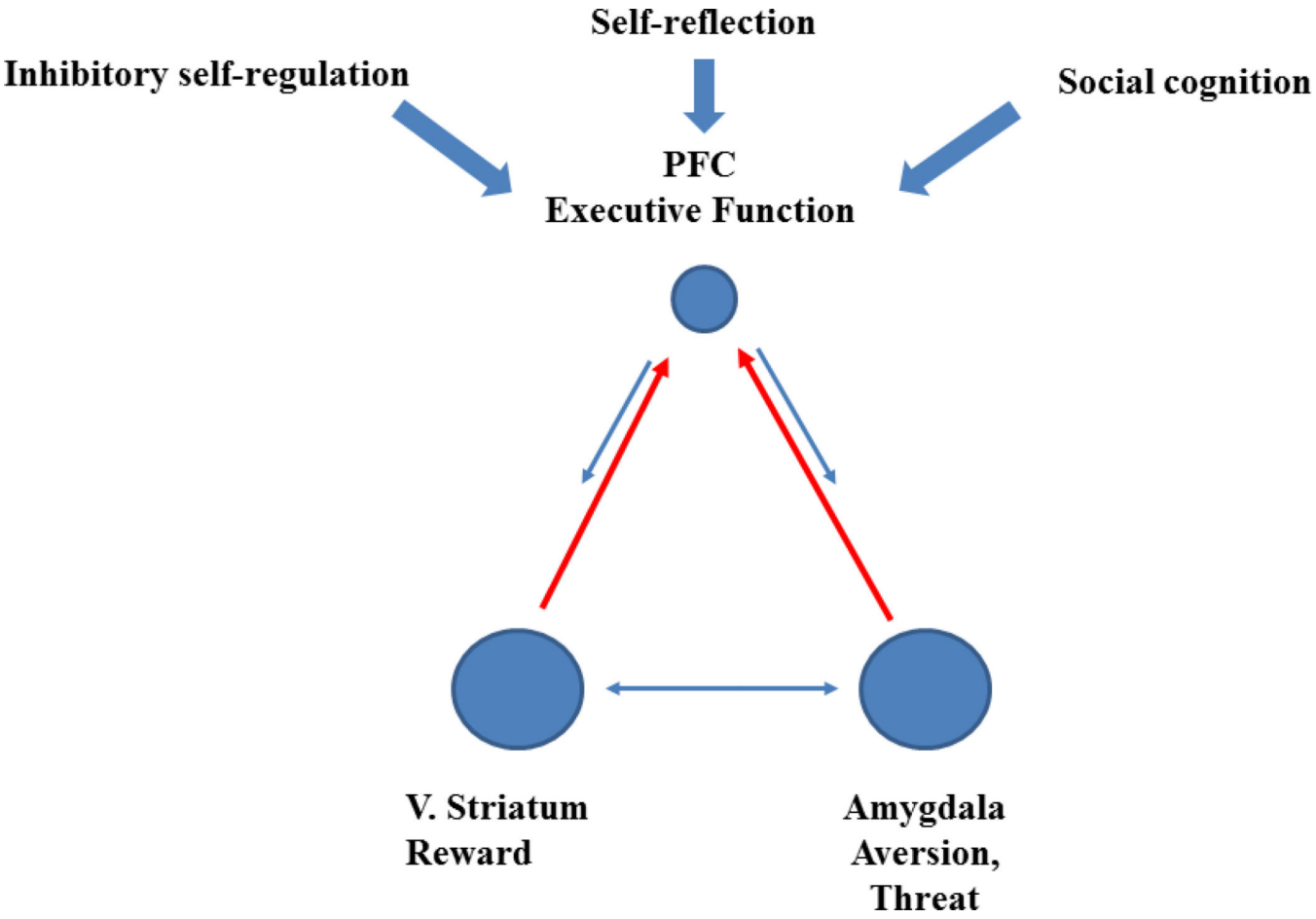


**Figure 6.**
The modified triadic model of executive function

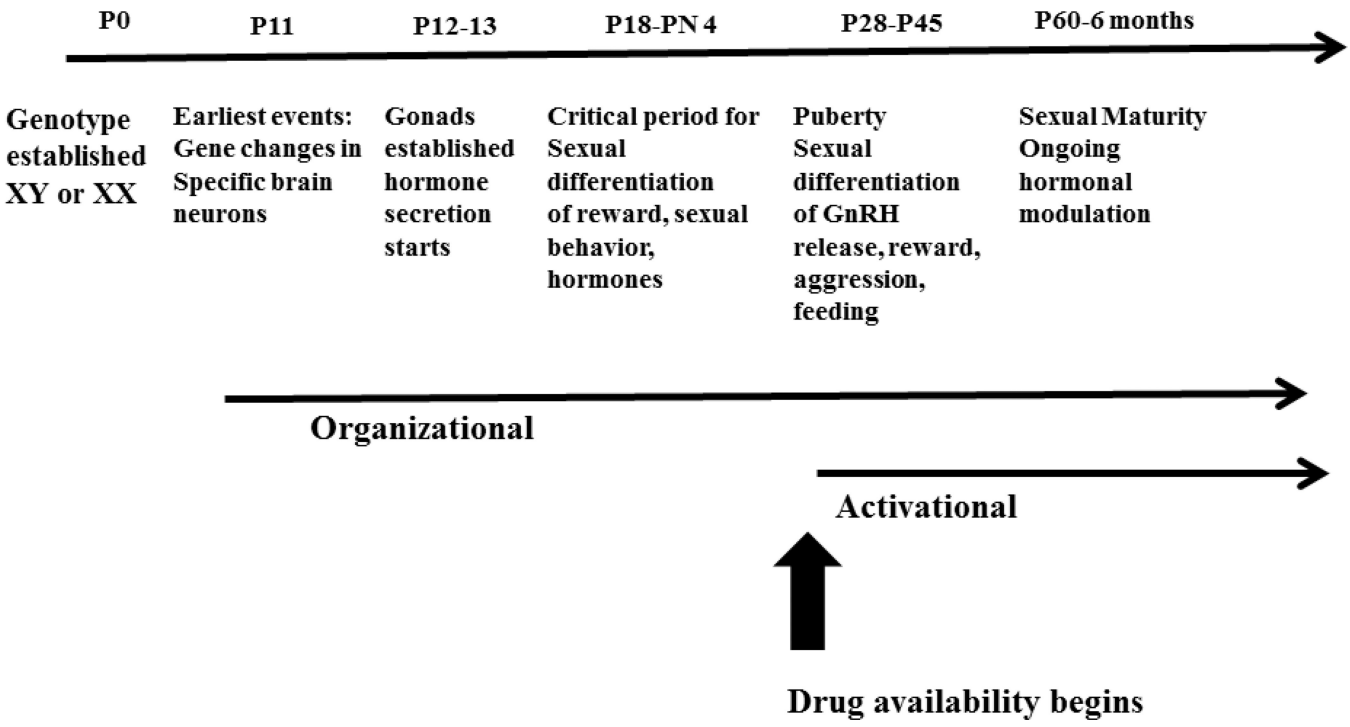


**Figure 7.**
Sexual differentiation of brain and behaviour.