Title: Experimental Evidence on Age-Related Differential Outcomes Associated with Substance Abuse

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Highlights

- Adolescent substance abuse is a growing concern worldwide
- Adolescent brain is highly vulnerable to the adverse effects of drugs
- Adolescent drug exposure persistently affects the brain responsiveness
- Drugs of abuse cause age-related differential outcomes
Abstract
A growing number of evidence indicates that adolescent substance abuse is now an alarming concern, which imposes a considerable socio-economic burden on societies. On the other hand, numerous studies have shown that due to specific neurophysiological features, the brain is more vulnerable to the adverse effects of psychoactive drugs at early ages. Unfortunately, these negative effects are not limited to the period of drug use, but, they could persistently affect the brain’s responsiveness to future exposures to the same or other types of drug. In order for researchers to develop pharmacological strategies for managing substance abuse disorders, it is important for them to gain a deep understanding of the differences in behavioral outcomes associated with each type of drug across different age groups. In the present study, we aimed to review the experimental evidence revealing the mentioned differential effects with an emphasis on common drugs of abuse, including cocaine, nicotine, cannabis and opioids. Although, the cellular mechanisms underlying age-related effects have not been exclusively addressed for each drug, the most recent findings are presented and discussed. Future studies are required to focus on these mechanisms and reveal how molecular changes during brain development could result in differential responses to drugs at the behavioral level.

Keywords: Adolescent, Adult, Cocaine, Nicotine, Cannabis, Alcohol, Opioids
1. Introduction
In humans, adolescence (from ages 10 to 19) includes a variety of physiological, psychological and social factors. Two behavioral features representing the childhood to adolescence transition are changes in the hormonal levels (characterized with partner-seeking behaviors) and increased manifestation of social, affiliative and playful behavior. However, in rodents, adolescence is defined as the period between the postnatal days 21 to 60. More specifically, this interval can be divided into three stages including early (PND= 21–34), middle (PND= 34–46) and late adolescence (PND= 46–59) (Laviola et al. 2003). In particular, the middle stage have been shown as an effective model for studying behavioral complications associated with adolescence including drug abuse. Substance abuse among adolescents is currently a growing social concern that imposes a great burden on both the individuals later in life and health care systems worldwide (Chassin et al. 2004 and Pompili et al. 2012).

normally characterized by increased locomotor activity, higher risk-taking and novelty-seeking behavior, all of which pave the way for a heightened appetitive drive for substance abuse (Doremus-Fitzwater et al. 2010 and Feldstein and Miller 2006). In this respect, drug intake may either occur as transitional periods of consumption (such as recreational/binge intake) or may continue into adulthood as an addiction or chronic consumption. Among the wide variety of drugs used by adolescents, more accessible ones including nicotine, alcohol, opioids and cannabis have extensively been studied (Barron et al. 2005 and Botvin and Botvin 1992 and Salmanzadeh et al. 2021 and Salmanzadeh et al. 2020). During the last decade, numerous studies have addressed the age-related physiological responses to drugs of abuse in adolescent vs. adult animal models. Generally, literature supports the idea that adolescents might exhibit a higher level of vulnerability to specific drugs compared to the adult subjects (Chambers et al. 2003 and Schramm-Sapyta et al. 2009 and Wong et al. 2013). Current neurophysiological evidence indicates that even short/sporadic drug exposure in adolescence could result in persistent changes in the responsiveness of specific brain circuits to future drug exposure (Moazeni et al. 2018 and Sabuee et al. 2021 and Salmanzadeh et al. 2021 and Salmanzadeh et al. 2020 and Salmanzadeh et al. 2017 and Salmanzadeh et al. 2018 and Torabi et al. 2019). Mechanistically, this results from the fact that many key brain structures undergo maturational refinements at cellular level during adolescence. Furthermore, this period of life is associated with significant changes in brain neurotransmitter balance (Murrin et al. 2007 and Pittser 2019 and Wahlstrom et al. 2010), thus any alteration of brain function at this developmental stage might be persistently maintained until adulthood.
Although long-term complications of adolescent substance abuse have been thoroughly reviewed in recent years (Salmanzadeh et al. 2021 and Salmanzadeh et al. 2020), the differential age-dependent effects of drugs on CNS function have not been duly addressed. The present study, reviews the current evidence on this concern and suggests that the researchers consider these discrepancies when investigating/interpreting the long-term complications of substance abuse in the context of early life exposure. In order to assist the readers to get acquainted with the literature, a summary of main findings is provided in table 1.

2. Differential drug effect in adolescent vs. adult subjects

2.1. Cocaine, nicotine and cannabis

An experimental study on rats has revealed that cocaine alters both behavioral and neurochemical indices in an age-dependent manner (Collins and Izenwasser 2002). In this study, rats received cocaine for 7 consecutive days and after 10 days drug-free period, they were challenged again with cocaine injection and locomotor activity was measured. In addition, in vitro tests were performed to determine dopamine and serotonin transporter densities in specific brain regions. Results indicated that adult rats, but not adolescents, have become sensitized to the locomotor-potentiating effects of cocaine. Furthermore, in adults treated with cocaine, dopamine transporter density was increased in caudate-putamen nuclei and serotonin transporter densities were increased in caudate-putamen nuclei, nucleus accumbens shell as well as the olfactory tubercle. In contrast, cocaine treatment did not affect the mentioned neurochemical markers in peri-adolescent rats. These findings indicate that cellular adaptations to chronic cocaine administration differentially develops in young versus adult rats. Another similar study has suggested a developmental difference between the reinforcing and locomotor activating effects of cocaine in young versus adult rats (Frantz et al. 2007). In this research, locomotor activity was recorded to reveal the occurrence of motor sensitization to repeated cocaine injections and self-administration method was applied to reveal cocaine-induced reinforcing effects. Results indicated that, although motor sensitization to chronic cocaine more significantly occurs in adults versus peri-adolescent subjects, no age-dependent disparity was found in the acquisition of cocaine self-administration or in the concentration of dopamine within the nucleus accumbens shell.

Differential behavioral responses to cocaine have also been addressed in association with nicotine pretreatment. Technically, cocaine-induced locomotor sensitization was observed in naïve adult (and not in adolescent) rats. However, when adolescent animals were pretreated with nicotine, they displayed the mentioned sensitized response similar to naïve adult subjects.
(McQuown et al. 2009). In another study, differential states of conditioned place preference (CPP) were assessed in adolescent vs. adult rats. In this regard, researchers have demonstrated that adolescents require more extinction trials than adults to extinguish cocaine place-preferences. Moreover, adolescents exhibit a higher preference for an environment which has been previously cocaine-paired representing stronger reinstatement (Brenhouse and Andersen 2008). As for the differential sensitivity to the conditioned rewarding effects of cocaine, adolescent rats, regardless of gender, were found to establish CPP at lower doses compared to their adult counterparts (Zakharova et al. 2009).

In the context of nicotine, there is evidence indicating that nicotine induces a dose-dependent CPP in peri-adolescent, but not in adult rats (Belluzzi et al. 2004 and Shram et al. 2006). On the other hand, in conditioned taste avoidance (CTA) paradigm, adult animals, and not peri-adolescents subjects, exhibited a dose-dependent avoidance to saccharin when paired with nicotine (Shram et al. 2006). These results support an age-dependent shift of balance in the rewarding and aversive effects of nicotine in rats which may explain the higher susceptibility and inclination of adolescents to continued nicotine intake. In another study on rats, it was found that a single dose of nicotine (0.125–0.5 mg/kg) does not affect the locomotor response in adolescent animals, while causing a significant suppression in adult subjects (Belluzzi et al. 2004).

Another set of commonly used psychoactive substances are cannabis derivatives among which tetrahydrocannabinol (THC) is the main constituent. Several studies have proposed that both acute and chronic doses of THC could cause a variety of changes, including reduction of locomotor activity in rats (Romero et al. 1996 and Whitlow et al. 2002). This effect has been observed in both adult and adolescent rats, however, it has been found to be less potent in adolescents (Schramm-Sapyta et al. 2007). However, there is evidence indicating that low doses of THC increase the locomotor activity during adolescence and induce no effect in adults (Wiley et al. 2008). Therefore, it seems that the differential responsiveness to THC (at locomotor response) is both age- and dose-related in rats. It should be noted that such differential effects could affect the individual’s future response to other drugs of abuse. For example, adolescent (and not adult) rats undergone THC exposure has been reported to display increased locomotor responses to cocaine challenge compared to the vehicle-treated group (Dow-Edwards and Izenwasser 2012). This may, at least in part, account for the enhanced susceptibility of transition to cocaine after early (rather than late) cannabis abuse. In the context of cognitive complications, THC has been shown to induce more potent anxiogenic and aversive effects in adult vs. adolescent rats (Schramm-Sapyta et al. 2007). From clinical aspect, this may somehow explain
why cannabis use is less frequent among adult humans compared to teenagers. Furthermore, experimental studies have shown that cannabinoid pre-exposure in adolescent rats (but not adult) results in long-lasting tolerance to future exposure in dopaminergic neurons of ventral tegmental area (VTA) (Pistis et al. 2004).

2.2. Alcohol
Similar to many other substances, alcohol drinking habit often initiates during adolescence. Previous animal studies have revealed that the degree of control over alcohol seeking depends on both age of drinking onset and level of consumption. In this regard, age-dependent differences have been suggested such that in adult rats, the level of previous alcohol exposure is negatively correlated with the future control over alcohol seeking. However, adolescent animals, even with a history of heavy alcohol consumption, could well control their craving for alcohol seeking (Labots et al. 2018). As for the blood alcohol level, experimental studies have shown that two hours after the same dose of ethanol injection (0.75 g/kg, i.p.), adolescent rats indicate lower blood alcohol levels compared to their adult counterparts (Walker and Ehlers 2009). This finding was further confirmed by the observation of higher alcohol elimination rate in adolescent animals at the dose of 1.5 g/kg. Numerous evidence support the differential cognitive outcomes of prolonged alcohol intake in adolescent vs. adult animals. For example, adolescent rats have been found to exhibit lower sensitivity to aversive effects of alcohol such as drowsiness, nausea and motor incoordination (Spear 2011). In contrast, sensitivity to the alcohol’s rewarding effects is enhanced in these animals (Spear 2011). From the clinical viewpoint, these findings may explain the biological basis for the higher inclination of adolescents for binge-like drinking compared to adults.

Animal studies have also revealed age-specific differences in response to prolonged intermittent ethanol injection (20 days, every other day, i.p.) (Acevedo et al. 2013). For example, the animals’ body weight was markedly decreased in aged and adult rats, but not in adolescent subjects (Acevedo et al. 2013). This finding might be explained by the evidence indicating that adolescent rodents do not exhibit conditioned taste aversion as much as their elder counterparts (Holstein et al. 2011). In addition, adolescent rats have been shown to be less affected by the alcohol-induced hang-over, compared to adults and therefore, they are more expected to show feeding behavior (Brasser and Spear 2002). Moreover, the results of aerial righting reflex indicated that aged rats are more vulnerable to ethanol-induced ataxia, compared to adult and adolescent animals (Acevedo et al. 2013). Mechanisms underlying this heightened vulnerability are still controversial. While some studies have proposed that the higher blood alcohol levels in aged
animals are due to more body fat and reduced hepatic metabolism (Vestal et al. 1977), some researchers have reported similar blood alcohol concentrations among various age ranges of rodents (Acevedo et al. 2013). In another study, sensitivity to the sedative effects of alcohol was tested in rats and results indicated that peri-adolescent (both 20 and 30 days-old) animals could regain their righting reflex (which was reduced by alcohol) significantly earlier than adult (80 days old) subjects (Little et al. 1996). Furthermore, locomotor activity was also decreased in adult, but not in peri-adolescent, rats following administration of 2.5 g/kg ethanol (Little et al. 1996). Another interesting finding of this study was the age-related difference in pharmacokinetics of ethanol such that adult rats display a significant delay in the time to peak serum ethanol level, compared to peri-adolescent animals (Little et al. 1996).

2.3. Opioid drugs
Age-related differential effects have also been noticed by researchers working on opioid drugs. For example, adolescent male rats have been found to exhibit higher locomotor activity and sensitization following chronic and acute morphine injections compared to adult animals (Koek et al. 2012 and White and Holtzman 2005 and White et al. 2008). Also, adolescent male rats self-administer less morphine than adult animals during sessions on a schedule of reinforcement test (Doherty et al. 2009). Similarly, in another research, adolescent male mice were found to self-administer less oxycodone than adults (Zhang et al. 2009). These findings have raised the hypothesis that opioid drugs might act more potently in the adolescent brain. Consistent to this notion, it is evident that adolescent animals have higher levels of oxycodone-induced dopamine release within the striatum than adults. As measured by the locomotor activity test, the forced swim test and the weight loss records, adolescent mice displayed less severe morphine withdrawal signs compared to adults (Hodgson et al. 2009 and Koek 2014). Thus, the lower intensity of negative consequences related to drug abstinence during adolescence may contribute to the development of a compulsive drug abuse behavior in teenagers (O’Dell et al. 2006). Some studies have addressed the effects of heroin in different age ranges of rodents. In this regard, heroin withdrawal signs have not been observed in adolescent rats as occur in adults. These mainly include physical signs of withdrawal as well as attenuation of locomotion, food intake and body mass. However, locomotor sensitization induced by heroin is not significantly affected by age (Doherty and Frantz 2013). Consistent to this finding, adolescent rats have been observed to self-administer more heroin than adults and show less heroin-seeking behavior than adults following drug abstinence (Doherty and Frantz 2012). As for the opioids analgesic effects, age-related differences are still the matter of controversy and depending on the method of analgesia
assessment, inconsistent/opposing results have been reported. For example, in one study, researchers found that morphine analgesic effect is greater in adult (12-weeks-old) than adolescent (4- or 7-weeks-old) rats (Nozaki et al. 1975). However, another study showed that older mice experience less morphine analgesic effect than their older counterparts in tail-flick test (Webster et al. 1976). In addition, this study has reported slower rate of absorption and longer half-life of morphine following i.p. injection in older animals. However, there seems to be a consensus on the point that opioid analgesic tolerance develops more rapidly in adolescent, rather than adult, animals following repeated drug exposure (Nozaki et al. 1975 and Wang et al. 2005). In the context of pain perception, formalin test results have revealed that adolescent rats received morphine pre-treatment exhibit higher pain-related signs compared to control (saline-treated) group, however, this finding was not observed in morphine-treated adult rats compared to their control counterparts (Ghasemi et al. 2019).

Researchers have also addressed the cellular and molecular mechanisms underlying age-dependent differential responsiveness to opioid drugs. For example, the protein expression and distribution of endogenous opioids (such as preproenkephalin, preproendorphin, preprodynorphin, and prepronociceptin) have been found to be age-related (De Vries et al. 1994 and Tseng et al. 1995) and expression of opioid receptors also vary among different developmental stages (Hoskins et al. 1998 and Volterra et al. 1986). Moreover, expression of arrestin-2 (Gurevich et al. 2004), protein kinase C (Pascale et al. 1998), inhibitory G proteins (Ihnatovych et al. 2002), and RGS proteins (Ingi and Aoki 2002 and Wilson et al. 2005), all of which are key molecules mediating opioid receptor activation and desensitization, are affected by age. Finally, another less addressed issue is to reveal whether developmental changes in pharmacokinetics of opioid drugs may cause differential responsiveness to these drugs when tested at different ages.

3. Conclusion and future directions

Nowadays, a growing number of evidence indicate that the human brain undergoes progressive maturational changes critical for survival and promotion of cognitive functions. These include both structural and functional changes at the level of neural circuits, neurotransmitter systems and signaling molecules. As mentioned earlier, such neurobiological changes would finally define how the brain responds to the wide variety of stimuli such as hormones and drugs. During the last decade, numerous studies have demonstrated the growing rate of adolescent substance abuse as an alarming concern in societies. It is now well established that the adolescents’ brains are more vulnerable than adults to the adverse effects of most drugs and recent evidence indicate
that many of drug-induced changes in the function of CNS are rather persistent and in some cases they could affect the brain responsiveness to other drugs of abuse even when taken later in life. Therefore, researchers seeking therapeutic strategies for the management of substance abuse disorder, need to first get well acquainted with the age-related disparities associated with the effect of each specific drug. In other words, the brain of an adolescent subject may respond quite differently to the effects of a drug compared to that of an adult individual, even when drug dose and administration route is the same. Therefore, adopting a similar approach for the management of subjects belonging to different age ranges may lead to ineffective or in some cases detrimental outcomes. In the present study, we aimed to review the most recent experimental evidence demonstrating age-related differences in responsiveness to common drugs of abuse, including cocaine, nicotine, alcohol, and opioid drugs. It should be noted that the current literature lacks in depth research on the cellular mechanisms underlying the age-related effects of drugs. However, in case of opioid drugs, the upcoming horizon is more promising, since there are strong evidence supporting age-related changes at the level of receptors and signaling molecules, as discussed earlier. Indeed, future research need to focus on these mechanistic gaps in CNS and reveal how developmental changes at molecular levels could result in differential behavioral responses to drugs.

Table 1. A summary of age-related differential effects associated with common drugs of abuse

<table>
<thead>
<tr>
<th>Drug</th>
<th>Subject</th>
<th>Differential age-dependent manifestations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>rat</td>
<td>Locomotor sensitization to cocaine occurs more significantly in adults vs. adolescent animals.</td>
<td>(Collins and Izenwasser 2002 and Frantz et al. 2007)</td>
</tr>
<tr>
<td></td>
<td>rat</td>
<td>Adolescent animals require more extinction trials than adults to extinguish cocaine place-preferences (CPP).</td>
<td>(Brenhouse and Andersen 2008)</td>
</tr>
<tr>
<td></td>
<td>rat</td>
<td>Adolescent animals establish CPP at lower doses of cocaine compared to their adult counterparts.</td>
<td>(Zakharova et al. 2009)</td>
</tr>
<tr>
<td>Nicotine</td>
<td>rat</td>
<td>Nicotine induces CPP in peri-adolescent, but not in adult animals.</td>
<td>(Belluzzi et al. 2004 and Shram et al. 2006)</td>
</tr>
<tr>
<td><strong>THC/ Cannabinoids</strong></td>
<td><strong>Animal</strong></td>
<td><strong>Observation</strong></td>
<td><strong>Reference</strong></td>
</tr>
<tr>
<td>------------------------</td>
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</tr>
<tr>
<td>rat</td>
<td>Adult, and not peri-adolescent, animals exhibit avoidance to saccharin when paired with nicotine.</td>
<td>(Shram et al. 2006)</td>
<td></td>
</tr>
<tr>
<td>rat</td>
<td>Nicotine does not affect the locomotor response in adolescent animals, while causes significant suppression in adult subjects.</td>
<td>(Belluzzi et al. 2004)</td>
<td></td>
</tr>
<tr>
<td>rat</td>
<td>THC reduces locomotor activity in rats, however, this effect is less potent in adolescent vs. adult subjects. Anxiogenic and aversive effects of THC are more potent in adult vs. adolescent rats.</td>
<td>(Schramm-Sapyta et al. 2007)</td>
<td></td>
</tr>
<tr>
<td>rat</td>
<td>Low doses of THC increases the locomotor activity in adolescence and not in adult subjects.</td>
<td>(Wiley et al. 2008)</td>
<td></td>
</tr>
<tr>
<td>rat</td>
<td>Adolescent, but not adult, rats received THC, display higher locomotor responses to cocaine.</td>
<td>(Dow-Edwards and Izenwasser 2012)</td>
<td></td>
</tr>
<tr>
<td>rat</td>
<td>Cannabinoid exposure in adolescent rats (but not adult) results in long-lasting tolerance to future exposure in dopaminergic neurons of the VTA.</td>
<td>(32)</td>
<td></td>
</tr>
<tr>
<td>rat</td>
<td>Animals with adolescent onset of alcohol exposure exhibit better control over alcohol seeking, compared to those with an adult onset profile.</td>
<td>(Labots et al. 2018)</td>
<td></td>
</tr>
<tr>
<td>rat</td>
<td>Adolescent rats indicate higher elimination rates and lower blood levels compared to their adult counterparts.</td>
<td>(Walker and Ehlers 2009)</td>
<td></td>
</tr>
<tr>
<td>rat</td>
<td>There is lower and higher sensitivity to aversive and rewarding effects of alcohol in adolescent vs. adult animals, respectively.</td>
<td>(Spear 2011)</td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>Body weight decreases in aged and adult rats, but not in adolescents following chronic alcohol intake. Rats are more vulnerable to ethanol-induced ataxia, compared to adult and adolescent animals.</td>
<td>(Acevedo et al. 2013)</td>
<td></td>
</tr>
<tr>
<td>rat</td>
<td>Adolescent mice do not show conditioned taste aversion as much as their elder counterparts.</td>
<td>(Holstein et al. 2011)</td>
<td></td>
</tr>
<tr>
<td>mouse</td>
<td>Adolescent rats are less affected by alcohol-induced hangover, than adults.</td>
<td>(38)</td>
<td></td>
</tr>
<tr>
<td>rat</td>
<td>Peri-adolescent rats are less sensitive to the sedative effects of ethanol, than adults.</td>
<td>(40)</td>
<td></td>
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<tr>
<td>Drug</td>
<td>Species</td>
<td>Effect</td>
<td>Reference(s)</td>
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<tr>
<td>Morphine</td>
<td>mouse,</td>
<td>Adolescent male rats self-administer less morphine and oxycodone than adults.</td>
<td>(Doherty et al. 2005 and Zhang et al. 2009)</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>rat</td>
<td>Adolescent rats have higher oxycodone-induced dopamine release within the striatum than adults.</td>
<td>(Koek et al. 2012 and White and Holtzman 2005 and White et al. 2008)</td>
</tr>
<tr>
<td>Morphine</td>
<td>mouse,</td>
<td>Adolescent rats exhibit higher morphine-induced locomotor activity and sensitization than adults.</td>
<td>(Doherty and Frantz 2013 and Hodgson et al. 2009 and Koek 2014)</td>
</tr>
<tr>
<td></td>
<td>rat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>rat</td>
<td>Adolescent rats self-administer more heroin and show less heroin-seeking behavior than adults.</td>
<td>(Doherty and Frantz 2012)</td>
</tr>
<tr>
<td></td>
<td>mouse</td>
<td>Opioid analgesic tolerance develops more rapidly in adolescent rats than adult.</td>
<td>(Nozaki et al. 1975 and Wang et al. 2005)</td>
</tr>
<tr>
<td></td>
<td>rat</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rat</td>
<td>Adolescent, but not adult, morphine-treated rats display higher pain perception, compared to control subjects.</td>
<td>(54)</td>
</tr>
</tbody>
</table>

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**Authors’ contribution**

Conceptualization, Methodology, Writing – Original Draft Preparation [S.M.A, H.S.]; Conceptualization, Writing – Review & Editing, Supervision [H.A.].

**Conflict of interest statement**

The authors report no conflict of interest related to this study.

**Table legend:**

**Table 1.** A summary of age-related differential effects associated with common drugs of abuse.
References


