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Use and abuse of dissociative and psychedelic drugs in adolescence

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Abstract

Adolescence is a period of profound developmental changes, which run the gamut from behavioral and neural to physiological and hormonal. It is also a time at which there is an increased propensity to engage in risk-taking and impulsive behaviors like drug use. This review examines the human and preclinical literature on adolescent drug use and its consequences, with a focus on dissociatives (PCP, ketamine, DXM), classic psychedelics (LSD, psilocybin), and MDMA. It is the case for all the substances reviewed here that very little is known about their effects in adolescent populations. An emerging aspect of the literature is that dissociatives and MDMA produce mixed reinforcing and aversive effects and that the balance between reinforcement and aversion may differ between adolescents and adults, with consequences for drug use and addiction. However, many studies have failed to directly compare adults and adolescents, which precludes definitive conclusions about these consequences. Other important areas that are largely unexplored are sex differences during adolescence and the long-term consequences of adolescent use of these substances. We provide suggestions for future work to address the gaps we identified in the literature. Given the widespread use of these drugs among adolescent users, and the potential for therapeutic use, this work will be crucial to understanding abuse potential and consequences of use in this developmental stage.

Keywords

Adolescence; Dissociatives; Psychedelics; MDMA; Reward

1. Introduction

The purpose of this paper is to review the literature on adolescent drug use and its consequences, with a particular focus on dissociatives (including ketamine, phencyclidine and related drugs), classic psychedelics (including LSD and psilocybin), and the entactogen

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MDMA. We will explore what is known in humans and what has been learned from preclinical models. It needs to be acknowledged from the outset that the literature on the effects of these drugs in adolescence is sparse. Nonetheless, there is a growing number of papers – especially in the preclinical literature – that is broadening our understanding of the acute effects of these drugs during adolescence and the longer-term consequences. This paper is a contribution to the Special Issue of *Pharmacology, Biochemistry and Behavior* on Adolescent Drug Addiction. For information on other classes of drugs of abuse, readers are encouraged to seek other papers in this Special Issue.

Adolescence is a developmental stage characterized by marked changes, ranging from physiological and anatomical, to cognitive, emotional and behavioral. There are broad changes in brain structure and circuitry, as well as significant synaptic pruning (Spear, 2000; Casey and Jones, 2010). The prefrontal cortex, which is involved in impulse control, judgment and decision-making is among the last cortical areas to mature in adolescence (Spear, 2000; Casey et al., 2011; Caballero et al., 2016; Larsen and Luna, 2018). There are also major changes in specific neurotransmitters and receptors, including dopamine, norepinephrine, serotonin, GABA, acetylcholine, endocannabinoids, opioids and glutamate, among others (Spear, 2000; Thorpe et al., 2020). Differences in brain structure, neural circuitry and neurotransmission between adolescents and adults have led to the conclusion that adolescents are not merely ‘young adults’ but distinct in many ways, as reflected in their unique cognitive, emotional and behavioral status (Spear, 2000; Casey and Jones, 2010; Doremus-Fitzwater and Spear, 2016).

Among other changes, adolescence is accompanied by increases in risk-taking and novelty-seeking and a tendency to venture away from parents and associate with peers (Spear, 2000; Casey and Jones, 2010; Casey et al., 2011). These behaviors are thought to be important to the development of autonomy, however they can also lead to sensation seeking and reckless behavior. It is well documented, for example, that experimentation with drugs typically begins during adolescence. Moreover, there is evidence that individuals who begin drug use during adolescence are more likely to develop an addiction than those who start later in life (Anthony and Petronis, 1995; Chambers et al., 2003). Because of this, it is imperative to better understand the effects of drugs in adolescence, including both acute responses and long-term consequences of drug use during this vulnerable developmental phase.

Understanding the acute effects of drugs in adolescence and elucidating the processes that lead to drug use are essential to the prevention and treatment of drug abuse and addiction. For example, do adolescents experience greater or lesser drug reward? Do they experience fewer dose-limiting side-effects (which could promote greater intake) or greater side-effects (which might be protective against drug use)? Similarly, it is essential to better understand the changes induced by repeated drug use that may contribute to addiction. Do adolescents show differences in the neuroplastic processes that contribute to addiction, such as tolerance, sensitization or physical dependence, when compared to adults? Finally, we need to understand the long-lasting or persistent effects following drug use in adolescence. Is there evidence of neurotoxicity in adolescents? Is normal developmental trajectory altered by the drugs? Are there long-lasting cognitive consequences? Is there increased desire for drugs in adults who used in adolescence? There are innumerable other questions about

adolescent drug effects that need to be answered to help us understand the motivations and consequences of use during this vulnerable life stage (see Kwan et al., 2020).

2. Dissociatives

2.1. Human research

Dissociatives produce a unique array of dose-dependent effects in users, including pleasure and excitement at lower doses and anesthesia at higher doses. The classic dissociatives are phencyclidine and ketamine, however there is a growing number of others that have appeared in recent years (Morris and Wallach, 2014; Eggleston and Stork, 2015). Phencyclidine (PCP) was first approved and marketed as an anesthetic in the 1950s but it was soon found that patients experienced an “emergence delirium” characterized by confusion and agitation (also known as an emergence reaction) when they awakened from the drug (Domino, 2010). This led to the withdrawal of PCP for clinical use in humans and its replacement by ketamine, a drug with a similar chemical structure and anesthetic properties, but shorter-acting and with a reduced incidence of emergence delirium (Domino, 2010). Ketamine was approved for use as an anesthetic by the United States Food and Drug Administration (FDA) in 1970 (Food and Drug Administration, 1970). Since then, ketamine has been widely used as an anesthetic in both humans and animals, while PCP has been reserved for veterinary use in the United States. In addition, there is a growing number of indications for clinical use of ketamine at subanesthetic doses, including pain and major depression (Domino, 2010; Trujillo et al., 2011; Zanos and Gould, 2018).

The unique effects of PCP and ketamine, including a disconnection of the individual from their surroundings, led to their identification as the first in the class of “dissociative anesthetics” (Domino et al., 1965; Domino, 2010). Early clinical work on these drugs revealed an overall profile in human subjects that was remarkably schizophrenia-like (Luby et al., 1959; Luby et al., 1962). Importantly, in contrast to other pharmacological approaches to model schizophrenia, the effects of dissociatives include a broad spectrum of schizophrenia-like symptoms, including positive symptoms, negative symptoms and cognitive disruption. Over the years, dissociatives have become a leading pharmacological model of schizophrenia and this has driven research on developing treatments (see Javitt and Zukin, 1991; Krystal et al., 1994; Jentsch and Roth, 1999; Tsai and Coyle, 2002; Krystal et al., 2003).

It was not long after their introduction that PCP and ketamine emerged as recreational drugs. The first reports of recreational PCP use appeared in the 1960s, and the first reports of recreational ketamine use appeared as early as 1970 (Lerner and Burns, 1978; Siegel, 1978; Morris and Wallach, 2014; Bertron et al., 2018). Abuse continued at relatively low levels for years but beginning in the early 2000s significant concerns were raised over abuse of these drugs, especially by young people at dance clubs and raves. Because of their popularity at dance clubs these drugs are sometimes categorized as “club drugs” (Freese et al., 2002; Krebs and Steffey, 2005; Hopfer et al., 2006; De Luca et al., 2012; Williams and Lundahl, 2019). Desired effects include a euphoric rush, sensory distortions, and mild hallucinations, which can contribute to the club experience (Lerner and Burns, 1978; Siegel, 1978; Jansen and Darracot-Cankovic, 2001; Dillon et al., 2003; Copeland and Dillon, 2005; Kalsi et al.,

2011; Morgan et al., 2012). Increased use of ketamine and PCP in recent years has resulted in dramatic increases in emergency room visits, escalating five-fold for these dissociatives between 2005 and 2011 (Center for Behavioral Health Statistics and Quality, 2014).

The United States Surgeon General Report on Alcohol, Drugs and Health notes lifetime use of PCP in 2015 at 2.4% (approximately 6.3 million people in the U.S.), with an average age of initiation of 15.3 years (Office of the Surgeon General, 2016). The same report identifies lifetime use of ketamine at 1.1% (approximately 3 million people) and an average age of initiation of 19.6 years. The Monitoring the Future Study, which surveys drug use in high schoolers in the United States (and therefore focuses on adolescents), shows past year prevalence of PCP use varying from 1.0% to 1.3% between 2016 and 2019, and past year prevalence of ketamine use varying from 0.7% to 1.2% during the same timeframe. It is important to acknowledge that there are certain subcultures where use is more prevalent. As summarized by Kalsi et al. (Kalsi et al., 2011), lifetime prevalence of ketamine use in club and dance settings approached 70% in the United Kingdom and was much higher than the general population in other countries.

A related drug that is of concern is dextromethorphan (DXM), which is a widely used cough suppressant in over-the-counter cough and cold preparations. Although DXM does not produce significant psychoactive effects at doses used to suppress cough, at higher doses it produces neurochemical, psychoactive and behavioral effects similar to ketamine and PCP. Since over-the-counter drugs are more readily available than their illicit counterparts, some users – especially teens – have turned to DXM as an alternative to PCP or ketamine (Darboe, 1996; Schwartz, 2005; Wilson et al., 2011; Morris and Wallach, 2014; Eggleston and Stork, 2015; Stanciu et al., 2016; Karami et al., 2018; Williams and Lundahl, 2019). The recreational use of DXM by teens peaked in the early 2000s and remains at high levels (Wilson et al., 2011; Karami et al., 2018).

Clinical studies (in adults) have led to a better understanding of the subjective effects of dissociatives that contribute to recreational use. Low dose infusions of ketamine, for example, result in ratings of “high” by healthy volunteers (Krystal et al., 1994; Bowdle et al., 1998; Krystal et al., 1999; Krystal et al., 2003), and in ratings of “liking” the effects of the drug and “wanting” more of the drug (Morgan et al., 2004). The pleasurable effects of ketamine and PCP have also been characterized in surveys of users (Lerner and Burns, 1978; Siegel, 1978; Dillon et al., 2003; Moore and Measham, 2009). However, along with pleasurable effects, many users also report aversive effects (Lerner and Burns, 1978; Siegel, 1978; Carlson, 1979; Davis, 1982; Bowdle et al., 1998). One effect that has received considerable attention is the “k-hole,” a severe dissociative experience that is aversive to many ketamine users (Siegel, 1978; Jansen, 2000; Jansen and Darracot-Cankovic, 2001; Dillon et al., 2003; Copeland and Dillon, 2005; Muetzelfeldt et al., 2008; Stirling and McCoy, 2010; Morgan et al., 2012). A similar aversive state has been reported by PCP users (referred to by some as “too high”) (Siegel, 1978; Carlson, 1979; Davis, 1982). Therefore, ketamine and PCP (and likely other dissociatives) produce mixed effects with both pleasure and aversion. The mixed affective responses to the dissociatives differ from other classes of drugs, which may help explain the lower levels of abuse of dissociatives when compared to psychostimulants or opioids.

Anecdotal reports and case reports of compulsive use in human users raise the possibility that dissociatives are addictive. There are numerous reports of users bingeing, craving and seeking the drugs, or failing to quit – and often escalating use – despite problems (Lerner and Burns, 1978; Carlson, 1979; Davis, 1982; Jansen and Darracot-Cankovic, 2001; Dillon et al., 2003; Copeland and Dillon, 2005; Kalsi et al., 2011; Morgan et al., 2012). Although a withdrawal syndrome has not been identified, compulsive patterns of use are consistent with the development of addiction (Lerner and Burns, 1978; Kalsi et al., 2011; Morgan et al., 2012). Additionally, a large percentage of regular users express concerns over the possibility of developing an addiction and seek treatment for problematic use (Davis, 1982; Jansen and Darracot-Cankovic, 2001; Dillon et al., 2003; Copeland and Dillon, 2005; Kalsi et al., 2011; Morgan et al., 2012).

Beyond the potential for compulsive use of dissociatives, there are several other consequences that have been identified (for review see Pradhan, 1984; Dillon et al., 2003; Copeland and Dillon, 2005; Kalsi et al., 2011; Morgan et al., 2012). Because acute intoxication includes ataxia, incoordination and lack of awareness of surroundings there is the possibility of accidental injuries and death (Siegel, 1978; Jansen and Darracot-Cankovic, 2001; Morgan et al., 2012). Further, lack of awareness of surroundings and memory impairment during intoxication can leave users vulnerable. In fact, ketamine is among the drugs used to facilitate sexual assault, a so-called “date-rape drug” (Smith et al., 2002; Morgan et al., 2012). A variety of other negative consequences have been found in regular users, including urinary and gastrointestinal problems, cognitive impairment, and schizophrenia-like symptoms (Lerner and Burns, 1978; Siegel, 1978; Pradhan, 1984; Dillon et al., 2003; Copeland and Dillon, 2005; Morgan et al., 2012).

Despite recent attention given to adolescent psychopharmacology, almost nothing is known about the effects of dissociatives in young people at subanesthetic doses. This is a concern since teens appear to be disproportionately attracted to ketamine, PCP and DXM (Lerner and Burns, 1978; Siegel, 1978; Davis, 1982; Schwartz, 2005; Eggleston and Stork, 2015; Williams and Lundahl, 2019). Despite the lack of systematic research on the topic, clinical experience points to important qualitative differences between adolescents and adults in response to dissociatives. When awakening from ketamine anesthesia, adult patients often experience a distressing ‘emergence reaction’ characterized by bad dreams and psychotomimetic effects, an effect not seen (or seen at reduced levels) in children or adolescents (Dundee et al., 1970; Hollister and Burn, 1974; Mistry and Nahata, 2005). This points to the possibility that dissociatives produce fewer aversive effects in younger individuals than in adults, which could help explain the attraction of these drugs in younger users.

2.2. Animal research

Laboratory animals, including rats and mice, are critical models for better understanding the effects of drugs on the adolescent brain and the brain mechanisms that may underlie drug use during this vulnerable period. Adolescent rats and mice show behavioral changes that parallel those in humans, including increased impulsivity and risk taking. Likewise, the adolescent rodent brain undergoes developmental changes that parallel those seen in

humans. Adolescence in rats and mice ranges from approximately postnatal day (PND) 28, to around PND 60–65 (see Spear, 2000; McCutcheon and Marinelli, 2009; Brenhouse and Andersen, 2011). But there are significant changes through the adolescent period, and a laboratory rat of 30 days of age can differ significantly in drug response from a rat of 40 days of age (as illustrated below). This is important to remember as we review the preclinical literature, since differences in age (as well as other parameters) may help to explain differences in results found across studies.

2.2.1. Adults

2.2.1.1. Reward/reinforcement.: In adult animal models dissociatives can produce rewarding and reinforcing effects, but not as readily as many other drugs of abuse. Animals will work to obtain injections of PCP and ketamine by a variety of species of laboratory animals in self-administration experiments (see Marquis and Moreton, 1987; Strong and Kabbaj, 2018), although early work suggested that these drugs might not be as reinforcing as other drug classes, such as opioids and psychomotor stimulants (Collins et al., 1984). Recent research demonstrates that dissociative self-administration requires specific conditions. For example, ketamine is not readily self-administered by animals tested in a home cage environment, but instead requires a novel cage (De Luca and Badiani, 2011; De Luca et al., 2012). Additionally, ketamine ‘priming’ (pretest administration of the drug) and a conditioned stimulus paired with injections are necessary for the acquisition of ketamine self-administration (Venniro et al., 2015). One way to interpret these findings is that ‘set’ and ‘setting’, two factors important in the response to psychedelic drugs, influence dissociative self-administration. Although further work is necessary to confirm this idea, the findings suggest that self-administration of dissociatives differs from that of other drugs of abuse.

In conditioned place preference, dissociatives produce inconsistent effects. PCP, for example, has been most often reported to lead to conditioned place aversion (Barr et al., 1985; Iwamoto, 1985; Acquas et al., 1989; Acquas et al., 1990; Kitaichi et al., 1996; Kitaichi et al., 1999), however it has also been shown in at least one study to produce conditioned place preference (Marglin et al., 1989) and in others to show no effect (Barr et al., 1985). Although several studies have reported robust conditioned place preference for ketamine (Suzuki et al., 1999; Suzuki et al., 2000; Xu et al., 2006; Li et al., 2008; Botanas et al., 2015), others have shown no conditioning (Parise et al., 2013; Strong et al., 2017), have seen it only in specific situations (e.g., only in males and only at a specific dose) (Schoepfer et al., 2019), or have shown relatively weak place conditioning (van der Kam et al., 2009). In female rats, ketamine produces no conditioning (Schoepfer et al., 2019) or a conditioned place aversion (Strong et al., 2017). MK-801, a potent and selective dissociative, also produces inconsistent effects in conditioned place preference, with some showing preference, others aversion and yet others no effect (for review see Tzschentke, 1998, 2007). Taken together, the results in self-administration and conditioned place preference demonstrate that dissociatives differ from other drugs of abuse. Our current working hypothesis, based on the human and animal literature, is that these drugs produce a mix of reward and aversion, which could account for the unusual results in self-administration and conditioned place preference.

2.2.1.2. Locomotor stimulation.: Two other findings of relevance to drug abuse and addiction are that dissociatives produce a locomotor stimulant response at moderate doses and that repeated administration of these drugs leads to locomotor sensitization. Locomotor stimulation is a simple behavioral measure that can reveal differences in response induced by an experimental intervention, such as a drug. However, locomotor stimulation is also of more direct relevance to drug abuse and addiction. The stimulant effects of different classes of drugs of abuse led Wise and Bozarth to propose *A Psychomotor Stimulant Theory of Addiction* (Wise, 1988), which highlights that locomotor stimulation is a common property of different classes of addictive drugs. Dissociative drugs produce well-documented stimulant effects in rats and mice at low subanesthetic doses (McCarthy et al., 1965; Castellani and Adams, 1981; Hiramatsu et al., 1989; Tricklebank et al., 1989; Danysz et al., 1994).

2.2.1.3. Sensitization.: Sensitization is an increase in a behavioral response to a drug following repeated use and is typically assessed by escalations in locomotor behavior with repeated administration of a drug. Robinson and Berridge proposed the *Incentive Sensitization Theory of Addiction*, which posits that sensitization is responsible for the increase in desire for a drug (craving) in addicted individuals following repeated use (Robinson and Berridge, 1993, 2008). Because the brain circuitry of locomotor behavior and incentive motivation overlap, locomotor sensitization can be a surrogate (albeit nonspecific and imperfect) for an increase in the motivational response to drugs of abuse following repeated use. Sensitization to dissociatives is robust and has been seen in adult animals with repeated administration of PCP, ketamine, MK-801 and other dissociatives (Uchihashi et al., 1993; Xu and Domino, 1994; Noda et al., 1996; Trujillo et al., 2008; Trujillo et al., 2011; Strong et al., 2017).

2.2.2. Adolescents compared to adults—For this section we will focus on studies that have compared the effects of dissociatives in adolescents and adults, since this helps to illustrate the distinctive nature of adolescence and how the psychoactive drug response can dramatically differ during this age range. We will also highlight sex differences in those studies that compared male and female rats. We will emphasize studies that examined ketamine, phencyclidine or dextromethorphan, since these are the dissociatives most commonly used by people. As noted earlier, there has been little work done in this area. To our knowledge there have been no studies comparing adolescents and adults for self-administration or conditioned place preference of any dissociative drug. Much of the work has instead examined locomotor response and the development of sensitization.

2.2.2.1. Reward/reinforcement.: The two primary approaches to assessing the rewarding and reinforcing effects of drugs in laboratory animals are self-administration and conditioned place preference. We found no published studies that compared self-administration or conditioned place preference to dissociatives in adolescents and adults. Only a single study examined conditioned place preference in adolescents but it did not compare adolescents to adults. Parise et al. (Parise et al., 2013) found no conditioned place preference in adolescent rats at postnatal day 35 (PND 35), suggesting that the drug is not rewarding during this developmental phase (Table 1). However, since there was no adult

comparison group in this study it cannot be determined if there were differences between the age groups. This is especially important since ketamine has produced mixed effects in studies on adult animals (see above).

2.2.2.2. Acute response: locomotor stimulation.: Examination of the locomotor stimulant effects of dissociatives at subanesthetic doses reveals striking differences between adolescents and adults (Table 1; Fig. 1A,C). Jacobs et al. (2000) showed a graded response to PCP in male rats from PND 21 to PND 90, with the youngest animals showing the greatest response and the oldest animals showing the lowest response. A similar pattern was observed by Rocha et al. (Rocha et al., 2017), who demonstrated that young adolescent male rats (PND 30) had a considerably greater stimulant response to PCP than adults (PND 60), and that older adolescents (PND 38) responded at intermediate levels between the two other age groups (Fig. 1A,C). A similar pattern was found for ketamine – PND 30 animals showed the greatest response, followed by PND 38 and then PND 60 (Rocha et al., 2017). Others have replicated these observations, with young adolescent animals showing a greater response to dissociative drugs than adults (Vasilev et al., 2003; Pesic et al., 2010; Parise et al., 2013; Bates and Trujillo, 2019; McDougall et al., 2019), The pattern was partially replicated by Wilson and coworkers (Wilson et al., 2007), who found that female PND 35 rats had a greater response to ketamine than female PND 50 animals, but male adolescent rats did not respond to the doses used in this study. In the studies by Wiley et al., low doses were used, which did not produce a stimulant effect on the first day of testing in either male (Wiley et al., 2008) or female rats (Wiley et al., 2011a) so potential differences between adolescents and adults cannot be determined. Taken together, the results point toward a greater response to dissociatives in adolescent rats than adult rats. With regard to sex, the response to ketamine in female adolescent rats is greater than in male adolescents (McDougall et al., 2017; McDougall et al., 2019; Crawford et al., 2020), replicating findings obtained in adult animals (Wilson et al., 2005; Schoepfer et al., 2019).

It’s important to note that dissociatives produce a complex locomotor response in rats, with a mix of horizontal activity, stereotypy and ataxia (McCarthy et al., 1965; Castellani and Adams, 1981; Hiramatsu et al., 1989; Tricklebank et al., 1989; Danysz et al., 1994; Trujillo et al., 2011). As my research team began work in this area we noticed qualitative differences between adolescents and adults in the locomotor response to dissociatives, with less ataxia and stereotypy, and more horizontal locomotion, in the adolescents. This was quantified by Rocha et al. (Rocha et al., 2017), who showed that PND 30 adolescents displayed more horizontal locomotion, relative to stereotypy, than PND 60 adults, with PND 38 adolescents showing an intermediate response. The pattern was found for both ketamine and phencyclidine. The greater horizontal locomotion in adolescents may reflect greater rewarding effects of the drugs, while the lower stereotypy and ataxia at this age may reflect reduced aversion (see Rocha et al., 2017). If this is confirmed, the affective response of adolescents to dissociatives resembles that of other classes of drugs with greater reward and reduced aversion than adults (see for review O’Dell, 2009; Doremus-Fitzwater et al., 2010; Spear, 2011; Doremus-Fitzwater and Spear, 2016). This pattern helps to explain why dissociatives would be more attractive to adolescents than adults, since younger individuals would be more likely to have a positive response, and less likely to have a negative response,

than adults. Although this idea is intriguing, further research is needed to clarify the balance between rewarding and aversive response to dissociatives in adolescents and adults.

2.2.2.3. Acute response: other effects.: Recent excitement over the antidepressant effects of ketamine has led to an interest in examining this phenomenon in adolescents (Parise et al., 2013; Nosyreva et al., 2014; Shepard et al., 2018; Garcia-Carachure et al., 2020a, 2020b). Although no studies to date have directly compared adolescents and adults, there is initial evidence that adolescents are less responsive than adults. For example, Nosyreva et al. (2014) found no antidepressant response to ketamine in adolescent mice (and a lack of ketamine-induced synaptic potentiation) at doses that are effective in adults. Similarly, Parise et al. (2013) found that adolescent rats require a higher dose than adults to achieve an antidepressant effect. Consistent with these findings, the first clinical trial for ketamine in treatment-resistant depression in adolescents suggests that they are less responsive than adults to the therapeutic benefits (Cullen et al., 2018). Although intriguing, given the limited number of studies, and the lack of work that directly compares adolescents and adults, further work is necessary to definitively determine if adolescents are indeed less responsive than adults (Kim et al., 2020).

In other work, dissociatives have been found to produce a neuropathological response in rats, which includes vacuolization in neurons in certain areas of cerebral cortex following a single administration of a relatively high dose (Olney et al., 1989; Olney et al., 1991). The effect is short-lived and reversible, lasting <24 h. Of relevance to the current discussion, the effect is age-dependent – young rats do not show the effect, which emerges in late adolescence around PND 45 (Farber et al., 1995; Olney and Farber, 1995). This is also the approximate age at which the locomotor stimulant response to dissociatives begins to resemble that of adults (Rocha et al., 2017), and similar to the timeframe in humans when the emergence reaction arises (Dundee et al., 1970; Hollister and Burn, 1974; Mistry and Nahata, 2005). Together, these results suggest that mid- to late-adolescence is a time when there's a shift from an "immature" response to dissociatives, to an adult pattern of responding to these drugs.

2.2.2.4. Repeated administration - locomotor sensitization.: There have been only a handful of studies to date that have compared adults and adolescents in sensitization to dissociatives (Table 2). Research from our laboratory has shown an interesting and somewhat complicated picture for sensitization to PCP and ketamine (Rocha et al., 2017; Bates and Trujillo, 2019). As discussed above, adolescent male rats show a much greater initial response to these drugs than adults. With repeated administration the response in adolescents remains high, and the response in adults grows to match the younger animals. Importantly, the developmental trajectory should result in a reduced response in the adolescents by the end of the repeated administration, however the response remains elevated (Fig. 1C,D). We therefore interpret the results as demonstrating similar sensitization in adolescents and adults (see for discussion (Rocha et al., 2017; Bates and Trujillo, 2019)). Wiley et al. (Wiley et al., 2008, 2011a) did not replicate this pattern in either male or female rats, however the doses they used did not produce a stimulant response on the first

day of testing. Clearly, more work is needed to clarify the development of sensitization in adolescents, when compared to adults.

2.2.2.5. Persisting effects - long-term consequences.: Research on other classes of drugs has revealed that adolescent use can have long-term consequences on cognition, reward and socioemotional processing, among other concerning effects (Spear, 2016). Given the potent psychoactive effects of dissociatives, there is the potential for long-term consequences following exposure during adolescence, however work is just beginning to compare persistent effects in adolescents and adults. Bates and Trujillo (2019) compared the potential for persistent sensitization and learning deficits in adolescent (PND 30) and adult (PND 60) rats treated repeatedly with ketamine. In these experiments, adults administered ketamine (25 mg/kg for 10 days), then given a washout period, showed persistent mild spatial learning and attention deficits 20 days following treatment and persistent ketamine sensitization 30 days following treatment, but adolescents did not. Similar results were found for dextromethorphan (Bates and Trujillo, in preparation). These results suggest that adolescents may be protected from some long-term consequences relative to adults.

Garcia-Carachure et al. (2020a, 2020b) examined the effect of repeated exposure to ketamine (20 mg/kg daily for 15 days) in adolescent (PND 35) and adult (PND 70) mice and found that male adolescents, but not female adolescents or adults of either sex showed enhanced rewarding effects of sucrose and cocaine after a 35-day washout. This suggests that adolescent ketamine use in males may result in greater vulnerability to drug use in adulthood.

In related work, Parise et al. compared the effects of repeated ketamine (20 mg/kg twice daily for 15 days) in adolescent (PND 35) and adult (PND 75) rats after a 60-day washout and found a “resilient phenotype” in both adolescent and adults, with reduced anxiety-like behavior in the elevated plus maze and antidepressant-like effects in the forced swim test. These findings suggest that some long-term consequences may be therapeutic and not differ between adolescents and adults.

There are too many differences across these studies to arrive at definitive conclusions, including the ages of the animals, the doses and treatment protocols, the washout periods, and the behavioral outcomes measured. Although there is evidence of persistent effects of dissociatives, adolescents appear more vulnerable to persisting effects for some behavioral endpoints, adults appear more vulnerable for other behavioral endpoints, and for others there is no difference between adolescents and adults.

2.2.3. Mechanisms

2.2.3.1. Neurochemical differences.: As mentioned above, adolescence is a time of significant change in multiple neurotransmitter systems and their receptors. Notably, many of the changes are seen in neurotransmitter systems known to be involved in the rewarding effects of drugs and in drug addiction, including dopamine, endogenous opioids, endocannabinoids, glutamate and others (Spear, 2000; Thorpe et al., 2020). The primary molecular target for dissociatives is *N*-methyl-D-aspartate (NMDA) receptors, which are receptors for the neurotransmitter, glutamate. Dissociatives block these receptors at

low concentrations. Of particular importance to the current discussion, NMDA receptor expression is at the highest levels during adolescence, and then decreases into adulthood (Insel et al., 1990; McDonald et al., 1990; Luo et al., 1996; Colwell et al., 1998; Henson et al., 2008). Moreover, there is a shift in electrophysiological functioning from adolescence into adulthood, especially with regard to interactions between NMDA receptors and dopamine receptors (Tseng and O'Donnell, 2005; Tseng et al., 2007; Huppe-Gourgues and O'Donnell, 2012; Flores-Barrera et al., 2014). This leads to the hypothesis that differences between adolescents and adults in behavioral responses to dissociatives result from differences in NMDA receptor expression and function. It is important to note, however, that in addition to actions on NMDA receptors, dissociatives have direct and indirect effects on several other neurotransmitter systems which could contribute to differences in response between adolescents and adults (Zanos and Gould, 2018; Kokane et al., 2020; Lavender et al., 2020; McDougall et al., 2020).

2.2.3.2. Pharmacokinetic differences.: Although differences between adolescents and adults in responses to dissociatives can be attributed to neurobiological factors, it's also possible that differences in pharmacokinetics (drug absorption, distribution, metabolism or excretion) might also contribute. In this regard, McDougall et al. (McDougall et al., 2019) examined pharmacokinetics of ketamine at an anesthetic dose (80 mg/kg) in males and females across development. In dorsal striatum and hippocampus they found reduced ketamine availability in older adolescent (PND 40) and adult (PND 80) males compared to younger males and compared to age-matched females. Although further research is necessary to confirm and extend these results, they support the idea that pharmacokinetic differences may help explain some of the behavioral differences between adolescents and adults. However, pharmacokinetics cannot easily explain all of the differences, since for some behavioral outcomes there is a reduced behavioral response to ketamine in adolescents (e.g., stereotypy, antidepressant effects, emergence phenomenon) and for others there is an enhanced behavioral response (e.g., locomotor stimulant effects).

2.2.4. Summary—Research on differences between adolescents and adults in response to dissociatives is currently emerging, so few studies have yet been published. It is especially notable that no studies have been published comparing the rewarding or reinforcing effects of these drugs in the two age groups. To better understand substance use and addiction, this should be at the forefront of future research. Despite this, there are some intriguing glimpses that warrant further study. First, it appears that adolescents show a bias toward greater positive responses and reduced aversive responses to these drugs than adults. This may help explain why adolescents are particularly attracted to dissociatives. Second, the response during adolescence changes rapidly, such that a 30-day old rat (early adolescence) responds differently than a 40-day old rat, which more closely resembles an adult. Therefore, the transition from an immature pattern to an adult pattern appears in mid- to late-adolescence. Further work is necessary to confirm (or refute) these suggestions. To help address these questions it will be important to 1) compare adolescents and adults in self-administration, conditioned place preference and other drug use paradigms; 2) examine the spectrum of adolescence, especially in the PND 30–45 timeframe; and 3) compare males and females to determine sex differences.

Considering a broader perspective it will be important for future research to address the questions raised earlier in this article: Do adolescents experience greater or lesser drug reward than adults? Do they experience greater or lesser aversive effects? Do they show differences in the neuroplastic processes that contribute to addiction, such as tolerance, sensitization or physical dependence, when compared to adults? Are there long-lasting consequences of adolescent use of these drugs?

3. Psychedelics

In this section, we will review the literature on use of psychedelics in adults and adolescents. We will cover classic psychedelics, such as LSD and psilocybin and the related entactogen, 3, 4 methylenedioxymethamphetamine (MDMA). (MDMA is often included in the category of psychedelics but is sometimes placed in the separate category of entactogens (Nichols, 1986; Nichols, 2016)). Since very little research on adolescents has addressed the classic psychedelics, MDMA will receive more attention. We will present a brief history of these substances and review the relevant human and preclinical research that addresses abuse propensity in adolescents. We will also discuss sex differences in studies that compared male and female rats. Additionally, we will highlight gaps of knowledge, as little work has been done directly comparing psychedelics in adolescents and adults.

3.1. Human research

Lysergic acid diethylamide (LSD), or acid, is a traditional psychedelic that alters sensory perception. It is typically ingested orally on absorbent (blotter) paper or tablets. When ingested, LSD's effects begin around 30 min and can last up to 12 h. LSD is derived from ergot and was discovered by Albert Hofmann in 1938. After sampling it, he noted intoxication marked by perceptual changes, including visual illusions and a dreamlike state with "extraordinary shapes with intense, kaleidoscopic play of colors" (Hofmann, 1990). His account of this experience highlights the fact that LSD can be a pleasant experience, and produce visual distortions of shapes and movement. However, it can also induce acutely dysphoric experiences, known as "bad trips." LSD use was most popular in the 1960s (Louria, 1968). During this time, several notable individuals, such as Harvard psychologists Timothy Leary and Richard Alpert, advocated the consumption of LSD. The notion that psychedelics, like LSD, may have beneficial effects has been a popular one, but it has not been fully embraced by federal agencies (Nichols, 2016). It also became a symbol of various counterculture movements and has been used to enhance creativity in music and art. Psilocybin, like LSD, also alters sensory perception in a dose-dependent manner (Carbonaro et al., 2020). It is most often ingested through psilocybe mushrooms (De Gregorio et al., 2018). Many users report brewing the mushrooms into a tea, while others report eating raw mushrooms (Peden et al., 1982). Users of classic psychedelics report similar effects, including hallucinations and concentration deficits while intoxicated (Schwartz et al., 1987). Other effects of these substances include signs of arousal, such as increased pulse and blood pressure, dilated pupils, and piloerection. Furthermore, in a controlled study, LSD dose-dependently induced subjective effects starting at a dose of 25 μg, and the subjective "good" effects of LSD peaked at 100 μg (Holze et al., 2020). Nevertheless, there is much variation in the psychedelic experience, as the mindset, environmental setting, and personality of the

individual can contribute to the experience. Unfortunately, research on LSD and psilocybin was hampered by their placement into Schedule I of the Controlled Substances Act of 1970 (Bonson, 2018).

In adolescents, both lifetime and past year use of LSD and psychedelics other than LSD (including psilocybin) have increased gradually (Johnston, 2020). Between 2007 and 2017, the rate of LSD exposure calls to poison centers showed the most precipitous increase among all illicit drugs in the U.S (Ng et al., 2019), demonstrating the renewed popularity of this substance in adolescents. Psychedelics are often used intermittently, and extended use is not common (Thompson et al., 1985). There is no evidence of addiction or compulsive use of psychedelics. Tolerance develops quickly, and serious adverse events are rare, particularly in adolescents and young adults (Johansen and Krebs, 2015; Leonard et al., 2018). Albeit infrequent, long-term LSD and psilocybin use can cause persistent psychotomimetic symptoms, and hallucinogen use disorder, which is associated with tolerance and cravings for hallucinogens (Abraham and Aldridge, 1993; Hardaway et al., 2016). Adolescent users report using psychedelics (typically LSD and psilocybin) concomitantly (Thompson et al., 1985). Other polydrug combinations with psychedelics include, marijuana, cocaine, and alcohol.

MDMA, or ecstasy, promotes arousal and wakefulness and also produces intense sensations of well-being, euphoria, and increased sociability (Hopfer et al., 2006). It is a psychostimulant with psychedelic properties that is chemically similar to methamphetamine, and like other psychostimulants promotes blood flow, heartrate, and hyperthermia. Its popularity likely stems from its combined stimulant and psychedelic effects. Approximately 20–40 min after ingestion, users report a sense of euphoria, enhanced sociability, and heightened stimulation that lasts for about 3 h (Jerrard, 1990; Cohen, 1995). Oral methamphetamine and MDMA produce similar effects in humans, and participants sometimes report difficulty distinguishing between the two (Kirkpatrick et al., 2012). However, users also report a sense of love, peace, and connection, as well as visual illusions similar to those of classic psychedelics, which are not normally seen with methamphetamine.

MDMA was first developed and patented in 1914 by Merck (Koesters et al., 2002). It later became recognized for its prosocial, euphoric qualities, and in the 1970s and 1980s, therapists used MDMA as an adjunct to facilitate therapeutic communication. Indeed, MDMA has been shown to promote authenticity and autobiographical disclosure (Baggott et al., 2016; Gaddis et al., 2018). Given these properties, there is interest in using MDMA as a component of psychotherapy for post-traumatic stress disorder (PTSD) (Palamar et al., 2017). In the 1980s, studies using animal models hinted that MDMA may cause neurotoxicity, which spurred the United States Drug Enforcement Agency (DEA) to place it in the most restrictive category, Schedule I (Liester et al., 1992). However, these findings were seen predominantly at very high doses or following prolonged administration and there is debate concerning the relevance of neurotoxicity to occasional human use (Roberts et al., 2016; Müller et al., 2019; Aguilar et al., 2020; Costa et al., 2020). The animal literature has highlighted a lack of toxicity in adolescence, and potentially neuroprotective effects (Feio-Azevedo et al., 2018).

MDMA is one of the most commonly used illicit substances by adolescents. This substance is often used by adolescents at dance parties and raves, and is therefore sometimes labelled as a “club drug.” It is typically taken orally as a tablet or capsule. MDMA use in adolescents also occurs outside of raves, and it is common on college campuses (Wish et al., 2006). There is also evidence that it is used by some young people to self-medicate psychological distress. Adolescents who were undiagnosed with a mental health disorder were more like to use MDMA to self-medicate than those receiving treatment for a previous diagnosis (Moonzwe et al., 2011).

Polydrug combinations are popular, as use of MDMA with marijuana, cocaine, and ketamine is common (Singer et al., 2004; Wish et al., 2006; Wu et al., 2006). <1% of club drug users only use club drugs, and over 80% of them use multiple classes of drugs (Wu et al., 2006). Interestingly, despite the common use of MDMA with other substances, MDMA does not promote use of injection drugs (e.g., heroin); in fact, it has been associated with reduced injected drug use (Gaddis et al., 2018). Nonetheless, polydrug use is of concern because it is a key indicator of future drug use, a source of developing a drug habit for other substances in adolescents, and it elevates the risk of experiencing adverse consequences (Klein et al., 2009; Wu et al., 2010; Olthuis et al., 2013). Females are more likely to report using multiple club drugs than males, particularly adolescents aged 16 and 17 (Yacoubian et al., 2002). Among adolescent females, but not males, those who had engaged in vomiting weight control behaviors were more likely to use MDMA than those who had not (Cance et al., 2005). This is could be due to MDMA’s appetite suppressant properties and its ability to augment mood.

According to the Monitoring the Future study (Johnston, 2020), MDMA use by adolescents has decreased in the past year as compared to previous years. At the height of its use (1995–2002), >13% of high school seniors, and >5.2% of 8th graders, in the US reported use of MDMA (Wu et al., 2006). More recently, a nationally representative study of adolescents (aged 12–17) found that lifetime use increased in 8th graders (1.6% to 1.7%) and 10th graders (2.4% to 3.2%) but decreased in high school seniors (4.1% to 3.3%) (Johnston, 2020). It is important to note that this decrease in reported use could be related to underreporting, as MDMA is often referred to by one of its more popular street names, “Molly” (Aleksander, 2013). In a study in 2015, when “Molly” was included on a drug use survey, prevalence of use was significantly higher among high school seniors (Palamar et al., 2016). According to the Drug Abuse Warning Network, ecstasy accounted for 1.8% of hospital visits. However, the majority of emergency room visits involving illicit drugs (56.3) involved multiple drugs, and it is possible that MDMA was also involved in these visits (Findings, 2014).

Ecstasy use has also been associated with a variety of negative effects, including blood vessel constriction, insomnia, anxiety, and paranoia (Schifano, 1991). Users have also reported effects such as grinding of the teeth and vomiting. However, it is likely that these negative effects are less pronounced in adolescents (Feio-Azevedo et al., 2018). There have also been reports of residual effects including headaches, blurred vision, heighted cortisol levels, and depression, including a condition colloquially known as “Suicide Tuesdays”, which refers to a profound depression-like effect that occurs after weekend use of MDMA

(Parrott et al., 2014). Several reports in older adolescents and young adults demonstrate that MDMA users exhibit significantly higher Beck Depression Inventory scores as compared to non-users (Falck et al., 2008). However, these scores tend to fall within normal limits that suggest minimal or no psychopathology. Falck et al. (2008) found low levels of long-term (24 months) depressive symptoms among a sample of adolescents that were current and former MDMA users (Falck et al., 2008). Their data suggest that MDMA use does not result in long-term depression symptoms in adolescents. Nevertheless, these users were older adolescents (age 18), and the persisting consequences of long-term MDMA use in younger adolescents is still unknown. MDMA is also associated with memory deficits (Parrott, 2001; Montoya et al., 2002). More specifically, these memory deficits appear to occur during recollection of memories with both positive and negative emotional valence (Doss et al., 2018). More work should be done to understand the long-term ramifications of MDMA use, and attention should be paid to cognitive function and affective state.

3.2. Animal research

As previously discussed, laboratory animals are important models to understand how drugs affect the brain, including the underlying mechanisms that could potentially increase vulnerability to drug abuse, and are particularly important to understanding the effects of drugs in adolescence. Here, we review the preclinical literature that has explored the response to psychedelics in adult and adolescent rodents.

3.2.1. Adults

3.2.1.1. Reward/reinforcement.: In humans, classic psychedelics are generally considered to be mildly reinforcing, but lack the abuse potential of other substances (Degenhardt et al., 2010; Das et al., 2016; Johnson et al., 2018). However, reward and reinforcement are not normally seen in laboratory animals. LSD has been shown to produce conditioned place preference in rodent models, but only at a single dose (0.2 mg/kg), and this was prevented with a single preexposure to the conditioning apparatus (Parker, 1996; Meehan and Schechter, 1998). Moreover, LSD CPP was only exhibited in males (Meehan and Schechter, 1998). Non-human primates self-administer classic psychedelics, including LSD and mescaline, but the rates of self-administration are low, especially when compared to other widely used psychoactive drugs like cocaine and alcohol (Deneau et al., 1969; Poling and Bryceland, 1979; Goodwin, 2016). It has also been reported that, similar to dissociatives, classic psychedelics may produce mixed reinforcing and aversive effects, as LSD induced grimacing in primates (Siegel et al., 1974; Fantegrossi et al., 2004). This pattern in animals appear to reflect the observation that the effects of classic psychedelics in humans include “heightened mood,” as well as “increased psychosis-like symptoms” (Carhart-Harris et al., 2016). Therefore, classic psychedelics appear to produce mixed reinforcing and aversive effects in both humans and laboratory animals. Whether or not these drugs produce such effects in adolescence is unknown.

MDMA is self-administered in a variety of animal species, including non-human primates, mice, and rats (Beardsley et al., 1986; Lamb and Griffiths, 1987; Ratzenboeck et al., 2001; Fantegrossi et al., 2002; Schenk et al., 2003b; Trigo et al., 2006b; Orejarena et al., 2011; van de Wetering and Schenk, 2017; Frankowska et al., 2019; van de Wetering and

Schenk, 2020). Reinstatement of MDMA self-administration is also produced by exposure to both MDMA-associated cues and MDMA-priming injections (Frankowska et al., 2019). Moreover, MDMA induces CPP in rodent models across a variety of doses (0.2–20 mg/kg) (Bilsky et al., 1990; Bilsky et al., 1991; Bilsky and Reid, 1991; Schechter, 1991; Bilsky et al., 1998; Meyer et al., 2002; Braida et al., 2005). Several studies on MDMA reinforcement in animals only examined it after previous training with stimulants raising questions over its reinforcing effects in the absence of training with other drugs. For example, doses of MDMA that failed to induce CPP in rats (1.5, 3.0 mg/kg) established CPP when administered concurrently with cocaine (Panos and Baker, 2012) and MDMA pre-treatment produces a cocaine CPP (Horan et al., 2000). In other reports, while drug-naïve animals did acquire self-administration of MDMA at a variety of doses, responding for MDMA was higher in previously cocaine-trained rats than in those without a history of cocaine self-administration (Schenk et al., 2003a). Similarly, response rates and speed of responding for cocaine was higher than responding for MDMA (Ratzenboeck et al., 2001; Frankowska et al., 2019). Therefore, a takeaway from these studies is that MDMA is a low efficacy reinforcer compared to other psychostimulants. This suggests that, like LSD, MDMA may not be as reinforcing or have the same abuse propensity, as other recreationally used substances.

MDMA's reinforcing effects are likely due to interactions between DA and 5-HT systems. The D_2 antagonist, eticlopride, produced modest effects on operant responding for MDMA (Brennan et al., 2009; van de Wetering and Schenk, 2017). Furthermore, MDMA yoked rats (those receiving passive injections of MDMA) showed a decrease in D_2 binding in the NAcc, but increased binding in dorsal striatum and hippocampus (Frankowska et al., 2019). This suggests region specific alterations in D_2 expression and could underlie the modest effects of D_2 antagonism on operant responding. However, the D_1 antagonist, SCH 23390, produced a rightward shift in the dose response curve to acquire self-administration of MDMA, and highlighted that like other psychostimulants, MDMA reinforcement is dependent on the D_1 receptor system (Daniela et al., 2004). 5-HT_{2A} receptor KO mice exhibited blunted acquisition of MDMA self-administration compared to WT mice, and showed decreased DA levels in NAcc after a MDMA challenge, suggesting an interaction between 5-HT and DA in MDMA reinforcement (Orejarena et al., 2011). Overall, these data suggest that, like other drugs of abuse, MDMA reinforcement is dependent on dopaminergic mechanisms.

3.2.1.2. Locomotor activity.: LSD, and other classic psychedelics, have overwhelmingly been shown to produce a biphasic response on exploratory behavior and locomotor activity, with an initial decrease, followed by an increase in behavior, in animal models (Adams and Geyer, 1982, 1985; Mittman and Geyer, 1991; Krebs-Thomson and Geyer, 1996; Krebs-Thomson et al., 1998; Ouagazzal et al., 2001; Pálenícek et al., 2010). The LSD-induced alterations in locomotor behavior are concomitant with a flat body posture, wet dog shakes, and head twitches (Pranzatelli, 1990; Fone et al., 1991; Wettstein et al., 1999). The alteration of locomotor behavior produced by LSD is commonly used as a proxy of human psychedelic response (for a detailed review, see (Hanks and Gonzalez-Maeso, 2013)). Also, head-twitch responses in mice correlate with hallucinogenic potencies in humans (Halberstadt et al.,

2020). These behaviors may be mediated by 5-HT_{2A} receptors, as mice lacking 5-HT_{2A} receptors do not show LSD-induced alterations in locomotor behavior, and pharmacological blockade of these receptors also blocks locomotor effects after LSD-treatment (Grailhe et al., 1999; Ouagazzal et al., 2001). Females, particularly those in the estrus and proestrus phases, are less sensitive than males. to LSD's behavioral effects (Páleníček et al., 2010).

Chronic exposure (0.16 mg/kg i.p. every other day for 3 months) to LSD produces a conditioned, spontaneous hyperactivity that persists for three months after LSD treatment is ceased (Marona-Lewicka et al., 2011). This hyperactivity occurred in the absence of a challenge dose of LSD, but only after the animal was placed in the testing apparatus. The hyperactivity that persisted after chronic LSD was coupled with elevations in D_2 and 5-HT_{2C} receptors, as well as widespread alterations in gene expression in the mPFC (Marona-Lewicka et al., 2011; Martin et al., 2014).

At a variety of doses, MDMA produces hyperlocomotion that is concomitant with sniffing stereotypy in both males and females (Gold et al., 1988; Yamamoto and Spanos, 1988; Gold and Koob, 1989; Spanos and Yamamoto, 1989; Fernandez et al., 2003; Páleníček et al., 2007). This hyperlocomotion is similar to that of other psychomotor stimulants, such as methamphetamine, and is the result of increased dopamine (DA) in the NAcc and PFC, and 5-HT neurotransmission in the striatum and PFC (Yamamoto and Spanos, 1988; Matthews et al., 1989; Callaway et al., 1990; Ball et al., 2003; Ball and Rebec, 2005; Baumann et al., 2008; Rodsiri et al., 2011).

3.2.1.3. Sensitization.: There is no work that has examined locomotor sensitization to LSD or psilocybin. However, MDMA has been shown to produce locomotor sensitization after intermittent, repeated exposures, which is characteristic of other abused substances and may underlie the development of compulsive drug-seeking (Spanos and Yamamoto, 1989; Robinson and Berridge, 1993; Ramos et al., 2005; Trujillo et al., 2008). While acute locomotion to MDMA tends to occur in the periphery of an open field, animals sensitized to MDMA tend to spend more time in the center of the field (McCreary et al., 1999; Colussi-Mas and Schenk, 2008). MDMA elicits greater sensitization in females than in males pointing to sex differences in MDMA response (Walker et al., 2007). For a detailed review of sex differences in the effects of MDMA, see Allott and Redman (Allott and Redman, 2007).

Pharmacological studies of the effects of repeated exposure to MDMA have elucidated the mechanisms that underlie sensitization. McCreary et al. (1999) showed that the development of sensitization to MDMA was related to increased sensitivity to a 5-$HT_{1A/1B}$ agonist (McCreary et al., 1999). Similarly, Varela et al. (2011) found that mice that developed locomotor sensitization to MDMA demonstrated increased functionality of cortical 5-HT_{2A} receptors, revealing that MDMA broadly affects a variety of 5-HT receptors (Varela et al., 2011). It also appears that D_2 receptor activation is important for MDMA-induced locomotor sensitization, as blocking D_2 receptors during MDMA treatment blocked sensitization (van de Wetering and Schenk, 2017). Overall, these data point to serotonergic and dopaminergic systems as critical for MDMA behavioral sensitization.

3.2.2. Adolescents compared to adults

3.2.2.1. Reward/reinforcement.: No published studies were found that compared self-administration to classic psychedelics or MDMA in adolescents and adults. Furthermore, we found no studies that examined conditioned place preference to LSD or psilocybin in adolescents and adults. Because these drugs are used by both age groups, and because they may potentially have therapeutic value, it is important to explore the reward and reinforcement to these substances during adolescence.

The authors were unable to find any published studies that investigated self-administration of MDMA using adolescent animal models, either alone or to directly compare them to an adult group. This will be an important area of study to determine differences between these ages. Nevertheless, MDMA has been shown to induce conditioned place preference in adolescent mice (Ratzenboeck et al., 2001; Schenk et al., 2003a; Robledo et al., 2004; Trigo et al., 2006a; Daza-Losada et al., 2007; Daza-Losada et al., 2008; Catlow et al., 2010; Cox et al., 2014). The rewarding properties of MDMA are dependent on a variety of factors, including dose and schedule. For example, in adolescent mice, an intermittent administration schedule produces a more robust CPP acquisition and reinstatement than a binge schedule (Daza-Losada et al., 2007). This difference is likely due to the depletion of DA and 5-HT in the striatum following the binge schedule (Vidal-Infer et al., 2012).

Preclinical work demonstrates that adolescents exhibit less robust conditioned taste aversion to MDMA than adults (Cobuzzi et al., 2014), which suggests that adolescents are less sensitive to the aversive effects of MDMA than adults (Cobuzzi et al., 2014; Cox et al., 2014). Given the mixed reinforcing and aversive effects of classic psychedelics and MDMA, an open question is potential differences in these effects in adolescents compared to adults (Table 3). Further research is necessary to better understand the balance between rewarding and aversive properties of psychedelics in adolescents and adults.

3.2.2.2. Locomotor activity and sensitization.: To our knowledge, no work has been conducted examining locomotor activity or sensitization to classic psychedelics in adolescent animals. However, there is significant research on MDMA (Tables 4 & 5). Adolescent male rats are less sensitive to the locomotor-activating effects of MDMA than adult male rats. (Aberg et al., 2007; Wiley et al., 2008). In addition, adolescent male rats develop sensitization more slowly and require a higher dose than adults (Aberg et al., 2007). These data corroborate with previous studies in other psychostimulants that show that locomotor sensitization developed to cocaine and nicotine in adult, but not adolescent male rats (Collins and Izenwasser, 2002, 2004). Unlike males, female adolescent rats are more sensitive to MDMA-induced locomotor sensitization than female adult rats (Wiley et al., 2011b). Therefore, with respect to locomotor sensitization, MDMA resembles more typical psychostimulants, such as methamphetamine.

3.2.2.3. Persisting effects – long-term consequences.: Preclinical models suggest that MDMA, particularly when taken in adolescence, can enhance the rewarding effects of other drugs when taken later. Using MDMA in adolescence has also been associated with an increased likelihood of using other substances, including cocaine and morphine, in later

developmental stages (Fone et al., 2002; Aberg et al., 2007; Daza-Losada et al., 2008; Daza-Losada et al., 2009; Starosciak et al., 2012). Aberg et al. (2007) observed increased cocaine-induced CPP acquisition in MDMA-treated adolescent, but not adult rats, both 5 and 14 days after the initial MDMA treatment. Also, Fone et al. (2002) found that treatment with MDMA in adolescence enhanced cocaine CPP in adulthood. Similarly, Daza-Losada et al. (2009) demonstrated that adolescent exposure to MDMA or cocaine produced long-lasting increases in sensitivity to MDMA CPP in adulthood. However, in this report, there was not a comparison with adults. While persisting effects of MDMA exposure in adolescence have been observed, most studies have not included an adult comparison group.

3.2.2.4. Persisting effects - anxiety.: Exposure to a neurotoxic regimen of MDMA in adolescence (PND 45) increased anxiety-like behavior in the elevated plus maze (EPM) and decreased 5-HT content in the amygdala 10 days after exposure (Faria et al., 2006). Similarly, an intermittent schedule (10 consecutive days of exposure, 1× daily) in late adolescence (PND 45) increased anxiety in adulthood (PND 90) in male and female adult rats (Kolyaduke and Hughes, 2013). In contrast, another report using an intermittent dosing schedule showed that MDMA exposure spanning from mid adolescence to early adulthood lead to reduced anxiety in the EPM (Piper and Meyer, 2004). The observation that chronically, MDMA acts as an anxiogenic, is in line with reports in humans (Parrott, 2000; MacInnes et al., 2001; Verkes et al., 2001). Differences in age of MDMA exposure and dosing schedule produce discrepant effects on anxiety. Additional work should be done to understand precise qualities that contribute to an anxious versus an anxiolytic phenotype following MDMA experience.

3.2.2.5. Other effects - neurotoxicity.: In laboratory animals MDMA is able to induce neurotoxicity following repeated dosing regimens (Battaglia et al., 1987). This neurotoxicity is evident in a reduction of 5HT terminals and 5-HT transporters. This work has largely been conducted in adult animals, with some exploration in utero or during the early postnatal period (Broening et al., 1994; Aguirre et al., 1998; Kelly et al., 2002). In adolescents, MDMA has been shown to alter biomarkers of 5-HT, including loss of 5-HT terminals, and depletion of levels of 5-HT (Battaglia et al., 1987; Kelly et al., 2002; Capela et al., 2009). However, several reports suggest that in younger animals MDMA neurotoxicity is reduced or absent. A regimen of MDMA treatment (20 mg/kg subcutaneously, twice daily for four consecutive days) has been shown to be neurotoxic, measured by [^{3}H]-mazindol binding, in the adult rat (>PND 90) brain (Battaglia et al., 1987). This same regimen produced no effect on [^{3}H]-paroxetine binding in frontal cortex, a marker of 5-HT nerve terminals, in rats treated in the early juvenile period (PND 15, 20) (Kelly et al., 2002). Moreover, in rats treated in periadolescence (PND 25, 30), neurotoxicity occurred, but to a lesser extent than in adult (PND 90) animals (Kelly et al., 2002). A similar effect was observed by Aguirre et al. (1998), who found that rat pups become susceptible to MDMA-induced neurotoxicity, measured as a reduction in 5-HT and 5-HIAA levels, in early adolescence (after PND 35). Klomp et al. (2012) and others have observed that MDMA produced reductions in 5-HT transporter binding in various brain regions, including frontal cortex, hippocampus, and striatum in both adolescents and adults, but these reductions were less robust in adolescent rats than in adults (Bull et al., 2004; Klomp et al., 2012). These results demonstrate that

adolescents are less susceptible to MDMA-induced neurotoxicity than adults. However, the reduced toxicity in adolescents is not universal, as Chitre et al. observed that adolescent Swiss Webster mice had increased acute lethality and hyperthermia after MDMA than adults (Chitre et al., 2020). It is also important to note that the doses/regimens used to induce neurotoxicity are high and are generally not reflective of doses that would be used by humans (Feio-Azevedo et al., 2018). For a detailed review of psychostimulant-induced neurotoxicity in adolescents, see (Teixeira-Gomes et al., 2015).

3.2.3. Mechanisms—LSD and psilocybin are potent serotonergic agonists and bind to most serotonin receptors. Their psychedelic effects are most likely due to actions at 5-HT_{2A} receptors, as 5-HT_{2A} antagonists block these effects (Willins et al., 1997; Preller et al., 2017; Preller et al., 2018). Also, unlike most other drugs in its class, LSD enhances dopamine D2 receptor activity, which might contribute to its psychotomimetic effects (Nichols, 2004). LSD alters functional connectivity among a variety of regions, effectively altering the ability of the thalamus to regulate information sent to the cortex (Preller et al., 2019). MDMA accomplishes its psychological and physiological effects through actions on dopamine, norepinephrine, and serotonin (5-HT) sites (Gudelsky and Nash, 1996; White et al., 1996; Green et al., 2003; Gouzoulis-Mayfrank and Daumann, 2006). As discussed above, much of the evidence suggests that adolescents are less susceptible to MDMA-induced neurotoxicity than adults, which may be due to developmental differences in 5-HT systems. Indeed, serotonergic innervation of basal forebrain reaches adult levels by PND 14, but then declines below adult levels before puberty (PND 21) (Dinopoulos et al., 1997). Also, 5-HT turnover in cingulate cortex was lower in adolescent rats, as compared to adults (Teicher and Andersen, 1999). Lastly, it appears that 5-HT1A receptor binding decreases markedly during adolescence (Dillon et al., 1991).

The dopamine system also undergoes significant changes during adolescence. In primates, cortical and subcortical concentrations of dopamine are increased in adolescence, as compared to adults (Goldman-Rakic and Brown, 1982; Irwin et al., 1994). Also, in rodents, dopamine and its receptors (D_1 and D_2) peak in the caudate putamen between PND 28–42, and decline thereafter (Teicher et al., 1995; Andersen et al., 1997; Tarazi et al., 1998, 1999). For a more detailed review of developmental differences in dopamine neurotransmission, see (Wahlstrom et al., 2010). These data suggest that developmental differences between adolescents and adults in response to MDMA could be due to differences in serotonergic and dopaminergic function. Given the increase in activity of dopaminergic systems in adolescents as compared to adults, studies examining the role of dopamine in MDMA reinforcement are necessary and important. Furthermore, there is a dearth of data on developmental differences in serotonergic systems, but the evidence presented here leads to the hypothesis that serotonergic systems are less active in adolescents than adults, and should be a point of investigation.

3.2.4. Summary—The data reviewed here demonstrates that classic psychedelics are less reinforcing than other drugs of abuse, such as psychostimulants or opioids. Although MDMA reliably produces reward and reinforcement in animal models it too appears to produce less-robust effects than other drugs of abuse. There are some interesting parallels

to the effects described above for dissociatives, in that the psychedelics produce a mix of rewarding and aversive effects and that adolescents show reduced aversion compared to adults. In addition, like the dissociatives, neurotoxic effects of MDMA are reduced in adolescents when compared to adults.

Overall, very few studies have compared the effects of psychedelics in adolescents and adults. These drugs are used by adolescents, so it is important that more work is done to understand their effects in this age group. It will also be important for future research to explore the questions posed earlier for dissociatives in the context of psychedelics; specifically, whether or not the drug experience differs between the two groups, or if there are long-lasting consequences of adolescent psychedelic use. Similarly, it is important that more studies be done that focus on doses that are more likely to be used by humans, as well as exposure regimens that resemble human use.

4. Conclusions

The present review surveyed the existing literature on adolescent drug use of dissociatives, psychedelics, and MDMA, including what is known in both human and preclinical models. As adolescence is a period with myriad neural and behavioral differences in comparison to adults, one would expect differences in drug responses between adolescents and adults.

An interesting aspect of the literature is that these drugs fail to produce the same level of reinforcement in animal models as other drug classes, like stimulants and opioids, but rather produce mixed reinforcing and aversive effects. An essential unanswered question is whether reinforcement and aversion differ in adolescents and adults. There is suggestive evidence that this is the case, however further work is necessary to develop definitive conclusions. Therefore, a direct comparison of the mixed reinforcing and aversive effects of these substances in adolescents and adults will be an important step to determining how age affects the abuse potential of these substances. Another important area that is largely unexplored with regard to these drugs is that of sex differences. Understanding sex differences in the consequences of adolescent drug use will be critical to the prevention and treatment of problematic drug use.

An additional area that needs attention is the long-term consequences of adolescent use. This is particularly important since there is growing interest in the psychotherapeutic use of these compounds. Will adolescent use lead to positive outcomes, such as the “resilient phenotype” identified by Parise et al., (Parise et al., 2013) or problematic outcomes, such as increased potential for abuse and addiction later in life. Of course, these outcomes are not mutually exclusive and there may be a myriad of long-term changes induced by adolescent exposure to dissociatives or psychedelics.

A methodological suggestion for future work is that researchers move toward more consistency in approaches. Differences in ages of animals, doses and regimens of exposure, behavioral outcomes and many other variables makes it difficult to find patterns in the literature. Although some patterns are beginning to emerge, much more work is necessary before we have confidence in the trends.

In closing, the differences between adolescents and adults in response to dissociatives, classic psychedelics, and MDMA are largely unexplored. This should serve as an invitation to anyone interested in making an impact on the field. Given the widespread use of these drugs among adolescents, and the potential for therapeutic use, this work will be crucial to understanding abuse potential and consequences of use in this developmental stage.

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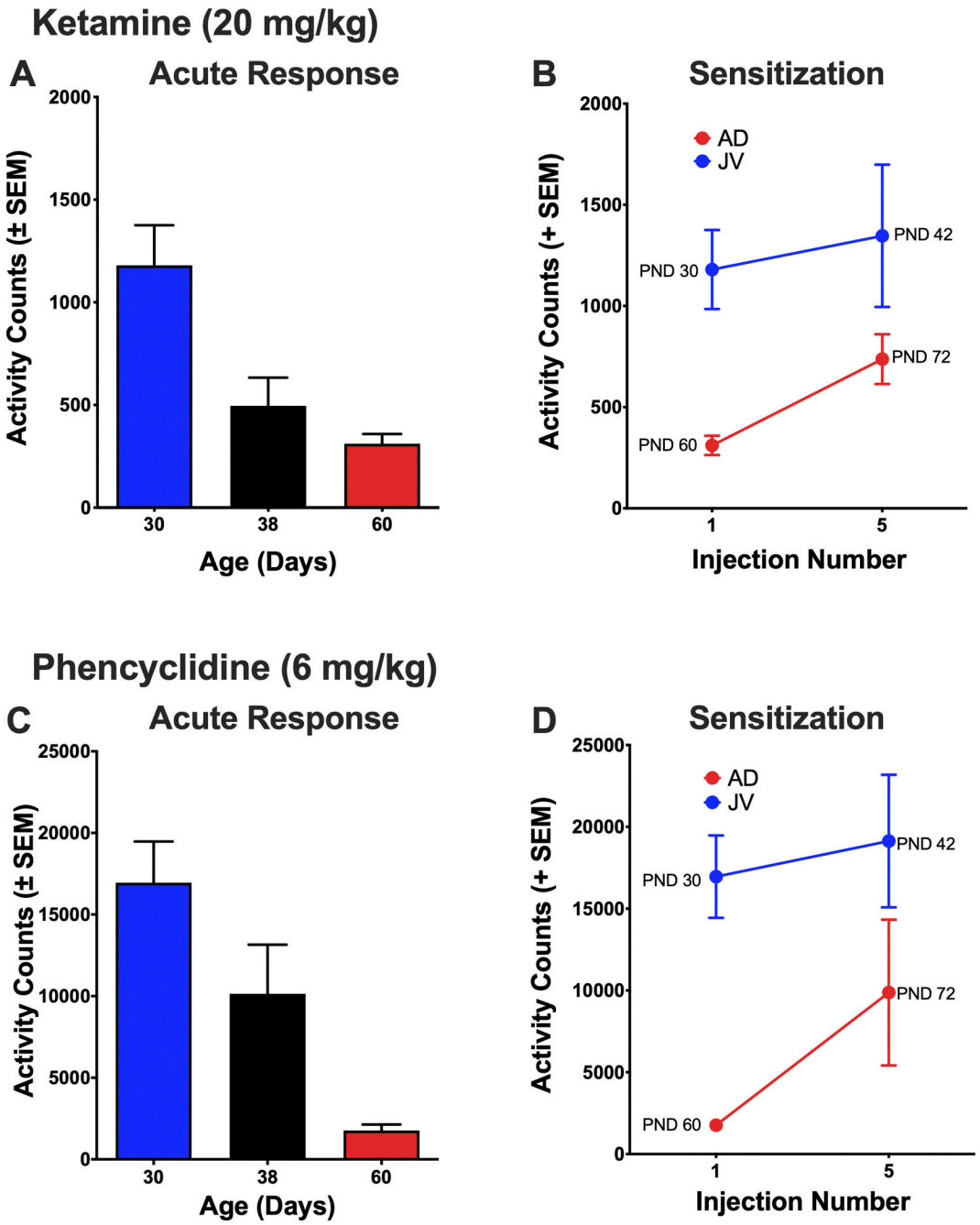

Fig. 1.

Responses to subanesthetic doses of ketamine and phencyclidine in adolescent and adult male rats. A,C) Locomotor response to the first injection of ketamine (20 mg/kg) or phencyclidine (6 mg/kg) in PND 30, PND 38 or PND 60 animals. There is a descending response as animals age from early adolescence to adulthood. B, D) Sensitization to ketamine (20 mg/kg) or phencyclidine (6 mg/kg) in adolescent (JV) and adult (AD) male rats. Drug was injected once every three days for five total injections starting at PND 30 in adolescents or PND 60 in adults. An increase in response is seen in adults following repeated injection, while adolescents remain high (despite the influence of age, which

should lead to a reduced response). Responses shown as horizontal locomotor counts. Redrawn from Rocha, Hart and Trujillo, 2017.

Table 1

List of studies that compared the locomotor stimulant effects of phencyclidine (PCP) or ketamine at subanesthetic doses in adolescents and adults.

Drug	Dose	Species	Age	Behavior	Effects	Reference
PCP		Rat, Male	PA: 37 Adult: 60, 90	Locomotor activity	Younger > older	Jacobs et al., 2000
PCP	6.0 mg/kg i.p.	Rat, Male	PA: 30, 38 Adult: 60	Locomotor activity	PND 30 > PND 38 > PND 60	Rocha et al., 2017
Ketamine	10 mg/kg i.p.	Rat, Female, Male	PA: 35 Adult: 50	Locomotor activity	Female: PND 35 > PND 50 Male: no response Female > Male	Wilson et al., 2007
Ketamine	3.0, 10 mg/kg i.p.	Rat, Male	PA: 27 Adult: >65	Locomotor activity	No acute effect at either age	Wiley et al., 2008
Ketamine	3.0, 10 mg/kg i.p.	Rat, Female	PA: 27 Adult: > 65	Locomotor activity	No acute effect at either age	Wiley et al., 2011a, b
Ketamine	20 mg/kg i.p.	Rat, Male	PA: 35–39 Adult: 75	Locomotor activity	PND 30 > PND 75	Parise et al., 2013
Ketamine	20 mg/kg i.p.	Rat, Male	PA: 30, 38 Adult: 60	Locomotor activity	PND 30 > PND 38 > PND 60	Rocha et al., 2017
Ketamine	25 mg/kg i.p.	Rat, Male	PA: 30 Adult: 60	Locomotor activity	PND 30 > PND 60	Bates and Trujillo, 2019
Ketamine	20, 40 mg/kg i.p.	Rat, Female, Male	PA: 41 Adult: 81	Locomotor activity	Female > Male	Crawford et al., 2020
Ketamine	20, 40 mg/kg i.p.	Rat, Female, Male	PA: 38–41 Adult: 78–81	Locomotor activity	Female > Male	Crawford et al., 2020

Table 2

List of studies that compared sensitization to the locomotor stimulant effects of phencyclidine (PCP) or ketamine, following repeated administration of subanesthetic doses, in adolescents and adults.

Drug	Dose	Species	Age	Behavior	Effects	Reference
PCP	6.0 mg/kg i. p.	Rat, Male	PA: 30 Adult: 60	Locomotor Sensitization (5 days)	PND 30 yes = PND 60 yes	Rocha et al., 2017
Ketamine	3.0, 10 mg/kg i. p.	Rat, Male	PA: 27 Adult: >65	Locomotor Sensitization (10 days)	PND 27 no PND 65 yes	Wiley et al., 2008
Ketamine	3.0, 10 mg/kg i. p.	Rat, Female	PA: 27 Adult: >65	Locomotor Sensitization (10 days)	PND 27 yes slower onset than PND 65	Wiley et al., 2011a, b
Ketamine	20 mg/kg i. p.	Rat, Male	PA: 30 Adult: 60	Locomotor Sensitization (5 days)	PND 30 yes = PND 60 yes	Rocha et al., 2017
Ketamine	25 mg/kg i. p.	Rat, Male	PA: 30 Adult: 60	Locomotor Sensitization (10 days)	PND 30 yes = PND 60 yes	Bates and Trujillo, 2019

Table 3

List of studies that examined the rewarding/aversive effects of MDMA in adolescents.

Drug	Dose	Species	Age	Behavior	Effects	Reference
MDMA	1.0, 1.8, 3.2 mg/kg, i. p.	Rats, male	PA: 26–27 Adult: 78–88	Conditioned Taste Aversion	PA < Adult	Cobuzzi et al., 2014

Table 4

List of studies that compared the locomotor stimulant effects of MDMA in adolescents and adults.

Drug	Dose	Species	Age	Behavior	Effects	Reference
MDMA	2, 5 mg/kg, i.p.	Rats, male	PA: 33 Adult: 60	Locomotor stimulation	Adult > PA	Aberg et al., 2007
MDMA	3, 10, 30 (PA only) mg/kg, i.p.	Rats, male	PA: 27–38 Adult: 70–83	Locomotor stimulation	Adult > PA	Wiley et al., 2008
MDMA	3, 10, 30 (PA only) mg/kg, i.p.	Rats, female	PA: 27–38 Adult: 72–83	Locomotor stimulation	PA > Adult	Wiley et al., 2011a, b

Table 5

List of studies that compared sensitization to the locomotor stimulant effects of MDMA, following repeated administration, in adolescents and adults.

Drug	Dose	Species	Age	Behavior	Effects	Reference
MDMA	2, 5 mg/kg, i.p.	Rats, male	PA: 33 Adult: 60	Locomotor Sensitization	Adult > PA	Aberg et al., 2007
MDMA	3, 10, 30 (PA only) mg/kg, i.p.	Rats, male	PA: 27–38 Adult: 70–83	Locomotor sensitization	Did not occur at either age	Wiley et al., 2008