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BRIEF COMMUNICATIONS

Delayed Extinction and Stronger Reinstatement of Cocaine Conditioned Place Preference in Adolescent Rats, Compared to Adults

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Adolescence is a transitional period during development that is associated with a greater likelihood of addiction to drugs than any other age. One possibility for this observation is that learned associations between the rewarding experience of drugs and drug-related cues may produce greater motivational salience, and thus are more difficult to extinguish. Using an unbiased place-conditioning paradigm with two doses of cocaine (10 mg/kg or 20 mg/kg), the authors show here that adolescents require 75 ± 17% more extinction trials than adults to extinguish cocaine place-preferences. Furthermore, once extinguished, adolescents display a greater preference for a previously cocaine-paired environment upon drug-primed reinstatement compared with adults. These results suggest that adolescent vulnerability to addiction involves robust memories for drug-associated cues that are difficult to extinguish. Therefore, drug-addicted adolescents may have a higher risk of relapse than adults, leading to greater prevalence of addiction in this population.

Keywords: adolescent, extinction, reinstatement, cocaine, place-conditioning

Drug addiction is a chronic disorder characterized by compulsive drug craving, seeking, and use that persist despite severe adverse consequences. Most experimentation with drugs occurs during adolescence and early adulthood (Compton, Grant, Colliver, Glantz, & Stinson, 2004; SAMHSA, 1999; Spear, 2000b). Although increased social behavior, novelty seeking, and risk-taking may underlie experimentation (Laviola, Macri, Morley-Fletcher, & Adriani, 2003), a disproportionate number of those that experiment during adolescence become addicted relative to any other age group. O'Brien and Anthony (O'Brien & Anthony, 2005) report a fourfold higher risk for addiction if drug exposure occurs during adolescence (12–14 years of age) compared to exposure during young adulthood (21–25 years of age). The mechanisms that underlie this window of vulnerability are still unclear.

Addiction represents pathological alterations in systems that normally serve reward-related learning. Normal developmental brain changes that play a role in these behaviors contribute to a unique susceptibility to drug abuse with exposure in adolescence (Spear, 2000a), and may underlie a vulnerability to lasting perturbations in circuitry if drug abuse occurs (Crews, He, & Hodge, 2007). These key changes include increases in prefrontal cortex (PFC) dopamine (DA) fiber density (Kalsbeek, Voorn, Buijs, Pool, & Uylings, 1988) as well as overproduction of PFC DA receptors in rats (Andersen, Thompson, Rutstein, Hostetter, & Teicher, 2000). The PFC mediates the attribution of salience to learned cues as well as goal-directed behaviors (Rebec & Sun, 2005; Ventura, Morrone, & Puglisi-Allegra, 2007), and therefore these changes may place adolescents at risk for enhanced drug-cue associations and drug-seeking behaviors.

Place conditioning provides a measure of drug seeking by assessing an animal's preference for (or aversion to) environmental cues associated with drug-induced effects. Using this procedure, cocaine is exclusively paired with a previously neutral environment whereas a second environment is exclusively paired with vehicle (Carlezon, 2003). The animal is subsequently allowed to move freely between the two environments—in a drug free state—and the time spent in the drug-paired and nondrug paired environments is measured. Time spent in the drug-paired environment is interpreted as a preference, whereas time spent away from the environment is interpreted as an aversion. These Pavlovian-acquired preferences or aversions to the environmental cue are believed to reflect conditioned incentive properties (Robinson & Berridge, 2003). Several behavioral studies indicate that memory for conditioned place preference (CPP) is subject to extinction, as nonrewarded exposure to environmental contexts previously paired with rewarding drug treatments reduces subsequent CPP (Bardo, Neisewander, & Miller, 1986; Calcagnetti & Schechter, 1993; Mueller & Stewart, 2000; Schroeder & Packard, 2004). CPP memory is also subject to reconsolidation after extinction, resulting in reinstatement of drug seeking (Balda, Anderson, & Itzhak, 2006; Sanchez, Bailie, Wu, Li, & Sorg, 2003).

In adult male rats, a cocaine place preference is effectively established for 20 mg/kg cocaine (Bardo et al., 1986). Adolescent rats have been reported to be more sensitive to the place conditioning effects of cocaine, showing preferences after conditioning with lower doses (5 mg/kg) than adults (Badanich, Adler, & Kirstein, 2006). These reports indicate a difference in sensitivity to

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the conditioning properties of cocaine as a function of age. In contrast, Campbell, Wood, and Spear (2000) reported no differences in CPP using a biased paradigm for the same moderate dose (10 mg/kg) of cocaine between adolescents and adults. However, males and females were included in their assessment. Clinical research suggests that adolescence is indeed a critical period when motivational conditioning is heightened. For example, 66% of adults who complete inpatient treatment for chemical dependence maintain total abstinence from alcohol or other drugs during the year after treatment, compared to only 42% abstinence rate reported for adolescent inpatient programs with similar treatment philosophy and geographic locations (Harrison & Hoffmann, 1989).

The current study was based on the hypothesis that adolescent vulnerability to addiction involves a developmental state, based on neurobiological changes (Brenhouse & Andersen, 2007), that is primed to assign high salience to reward-related cues, and to retain the motivational salience of these cues at the expense of competing information. Given the unique neural substrates mediating learning and motivation, as well as evidence that suggests adolescents are particularly vulnerable to addiction, we examined whether extinction of drug seeking is differentially achieved in adolescent and adult rats. We used a place-conditioning procedure to test whether adolescents have a greater latency than adults to extinguish a CPP for 10 mg/kg or 20 mg/kg cocaine. Additionally, we investigated whether reinstatement of drug seeking after extinction differs between these two age groups.

Method

Subjects

Male Sprague–Dawley rats were obtained from Charles River (Boston). Adolescents were P38 at the start of conditioning and adults were P77. Food and water were available ad libitum in constant temperature and humidity conditions on a 12-hr light:dark cycle (light period 0700–1900). All experiments were conducted in accordance with the 1996 Guide for the Care and Use of Laboratory Animals (NIH), and were approved by the Institutional Animal Care and Use Committee at McLean Hospital. Rats were given a minimum of 1 week to acclimate to our facilities before any testing began, and were handled for a minimum of 3 days before testing.

Adolescent and adult rats were conditioned to 10 or 20 mg/kg (i.p.) cocaine and tested for CPP, using an unbiased place-conditioning paradigm (Carlezon, 2003). Conditioning occurred in a three-chamber apparatus, consisting of two large (24 × 18 × 33 cm) side compartments and a small (12 × 18 × 33 cm) middle gray compartment (Med Associates, Georgia, VT). Compartments differed in floor texture, wall coloring, and lighting. Rats were screened for 30 min on Day 1, during which animals were allowed to freely explore the entire apparatus after a 5-min adaptation confined to the middle gray compartment. Two rats with an initial preference to one side (>18 of 30 min) were eliminated from further testing, and groups were organized such that average baseline preferences were further minimized (Graham, Hoppenot, Hendryx, & Self, 2006; Mueller & Stewart, 2000). Two days of conditioning (Days 2 and 3) with two sessions per day were conducted, during which rats were injected with saline (1 ml/kg, i.p.) in the morning and placed in one side for 1 hr, and 4 hrs later injected with one of two doses of cocaine (10 or 20 mg/kg, i.p.; $n = 6–8$) and placed into the opposite side for 1 hr. This order of conditioning ensured against an association with symptoms of dysphoria (e.g., acute drug withdrawal) with the nondrug environment during the afternoon session (Carlezon, 2003). On the fourth day, rats were permitted to freely explore the entire apparatus for 30 min in a drug-free state to test for CPP. Preference scores were calculated by determining the ratio of the time spent in the drug-paired side to the total time spent in both paired and unpaired sides. Twenty-four hours after this initial test, rats were again introduced to the entire apparatus in a drug-free state for 30 min, and time spent in each chamber was recorded. This test was repeated daily until each animal achieved extinction, defined as a 50% reduction of time spent in the drug-paired compartment compared to the initial CPP test for two consecutive days (Sanchez et al., 2003). Based on group averages, a 50% reduction in time spent in the drug-paired chamber implies no preference such as that observed during baseline measures. Twenty-four hours after the last extinction trial, each rat was administered 5 mg/kg cocaine (i.p.) and reintroduced to the apparatus with free access for 30 min to test for drug-primed reinstatement of CPP. There was 5 mg/kg chosen as a low priming dose that has been commonly used for reinstatement of CPP (e.g., (Mueller & Stewart, 2000; Sanchez et al., 2003; Zavala, Weber, Rice, Alleweireldt, & Neisewander, 2003) and is consistent with previous studies on reinstatement after adolescent cocaine exposure (Balda et al., 2006).

Analyses of variance (ANOVAs) were performed to determine the effects of age and dose on the acquisition, extinction, and reinstatement of place preference. Regression analyses were conducted to determine whether initial preference scores on test day were correlated with the number of extinction trials required to reach criterion, or with the degree of reinstatement. Because of a significant correlation, ANCOVA (with initial preference score from test day as the covariate) was used to determine the effects of age and dose on the number of days required to extinguish drug seeking. Student's *t* tests were performed for pairwise comparisons when noted. Only animals that formed a preference for the drug-paired chamber, designated by a greater preference score on test day than on screen day (8/8 adolescents at 20 mg/kg; 6/6 adolescents at 10 mg/kg); 8/8 adults at 20 mg/kg; 3/8 adults at 10 mg/kg) were included in further extinction testing and in all analyses.

Results

Both adolescents and adults formed reliable place preferences for 20 mg/kg cocaine (see Figure 1). In contrast, when a 10 mg/kg conditioning dose was given, fewer than half of the adults (3/8) formed a conditioned preference for the drug-paired chamber, whereas all of the adolescents formed a conditioned preference. Repeated testing was then performed to assay extinction of these preferences.

Collapsed across ages, the number of trials necessary to reach extinction was found to correlate with initial preference scores ($R^2 = 0.39$; $p < .01$), and therefore, ANCOVA was performed to determine whether stronger initial preferences for the drug-paired environment better predicted the latency to extinguish than age. When accounting for the variance because of initial preference scores with an ANCOVA, adolescents still required more extinc-

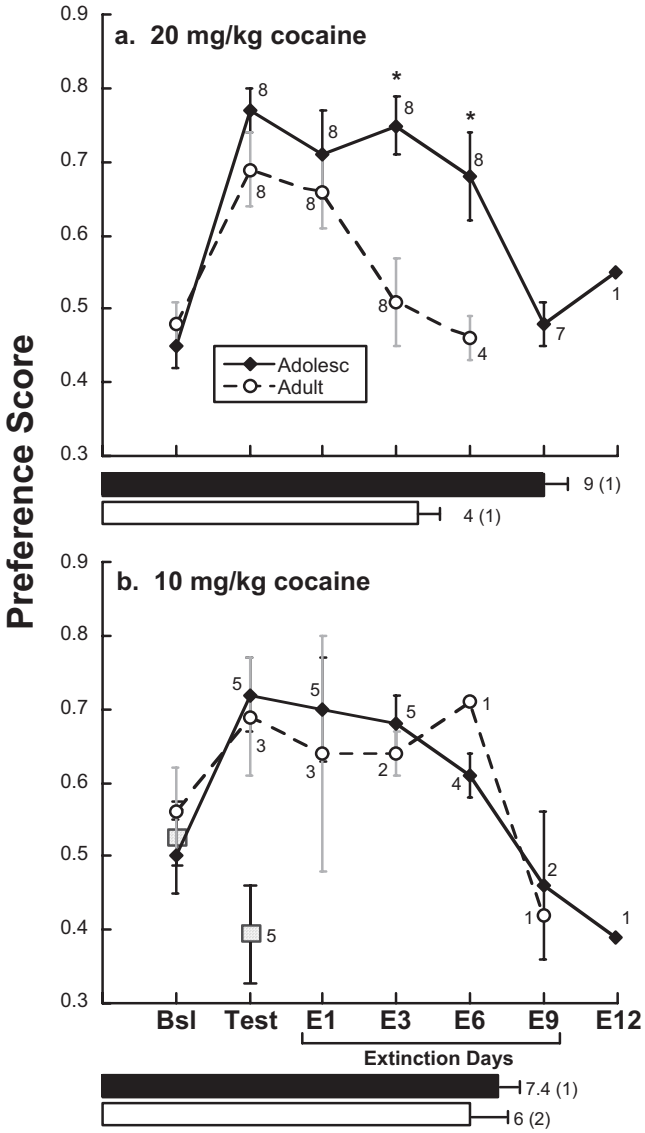


Figure 1. Adolescent rats require more extinction trials to extinguish conditioned place preferences for cocaine, compared to adults. Top and bottom graphs illustrate the acquisition and extinction of conditioned preference for an environment paired with 20 mg/kg cocaine (A) or 10 mg/kg cocaine (B). Numbers at each data point represent the number of animals that had not yet reached criterion and therefore remained in the experiment. Shaded boxes represent means ± SEM for adults that did not form preferences for the drug-paired environment, and therefore were excluded from further analyses. Preference scores represent the ratio of time spent in the drug-paired chamber to total time spent in both paired and unpaired chambers. Horizontal bars under each graph represent means ± SEM of the number of days required to reach extinction criterion for adolescent (filled) or adult (open) rats after conditioning to each dose of cocaine.

tion trials than adults to extinguish drug-seeking behavior, with a significant main effect of age ($F(1, 19) = 7.4$; $p < .05$; Figure 1). Specifically, adolescents took 8.7 ± 0.7 days to reach extinction, whereas adults reached criterion within 5 ± 0.6 days (collapsed across dose, covaried means). There was no significant interaction between age and dose on the number of days to extinguish.

When animals were conditioned to 20 mg/kg cocaine, preference scores across extinction trials were significantly different between ages ($F(1, 14) = 31.8$; $p < .01$; see Figure 1). However, when animals were conditioned to 10 mg/kg cocaine, the three (of eight) adults that formed an initial preference for the cocaine-paired environment did not differ from adolescents in their preference scores throughout extinction.

Figure 2 illustrates that drug-primed reinstatement of CPP was significantly affected by age ($F(1, 14) = 5.1$; $p < .05$). After extinction was achieved, a priming injection with 5 mg/kg of cocaine caused adolescents to spend more time in the previously cocaine-paired chamber, compared to adults, regardless of the conditioning dose. Both adolescents ($p < .01$) and adults ($p < .05$) displayed significant increases in preference scores between the last extinction trial and the reinstatement trial after being conditioned to 20 mg/kg of cocaine. However, only adolescents conditioned to 10 mg/kg displayed significant reinstatement ($p < .05$) whereas adults did not. No significant correlations were found between either initial preferences or days to extinguish with degree of reinstatement.

Discussion

Following acquisition of CPP for cocaine-paired environments, adolescents took significantly (75% ± 17) longer than adults to extinguish these learned preferences. Adolescents were also more vulnerable to drug-primed reinstatement of CPP after extinction, displaying significant reinstatement for a lower conditioning dose of cocaine than adults and spending more time than adults in a previously drug-paired environment. These results suggest that, in

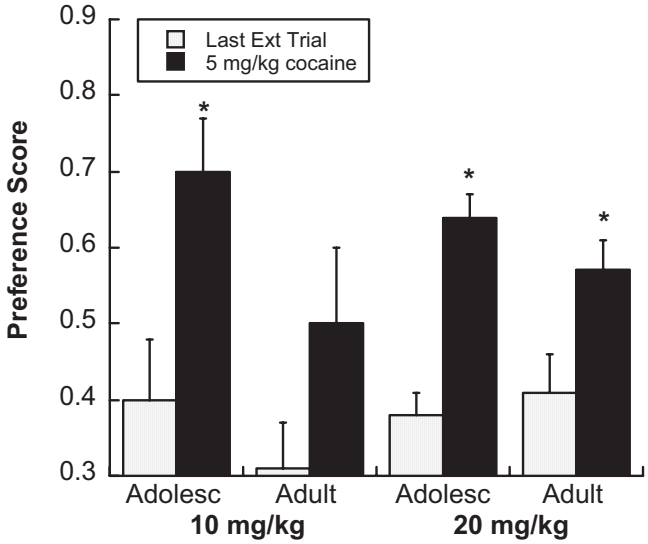


Figure 2. Reinstatement of conditioned place preference is achieved in adolescents conditioned to either 10 or 20 mg/kg cocaine, while reinstatement is achieved in adults only to environments paired with 20, but not 10 mg/kg cocaine. Bars represent means ± SEM of preference scores on the last extinction trial for each animal and after challenge with 5 mg/kg cocaine (24 hr after last extinction trial).

an unbiased place-conditioning paradigm, adolescent rats form preferences for a cocaine-paired environment that take longer to extinguish than preferences formed by older adults.

The one other study we know of examining extinction and reinstatement of cocaine CPP during development (Balda et al., 2006) was conducted using mice and yielded similar propensities for relapse after prepubertal exposure as reported here. However, reinstatement was assessed later in adulthood, while the present data is related to extinction and reinstatement within the adolescent period. Additionally, adult mice failed to extinguish after 28 days of intermittent, nonrewarded exposure to the context (Balda et al., 2006), which is in contrast to other reports (Sanchez et al., 2003) and ours that used daily extinction trials. Taken together, we report that when adolescents and adults are directly compared, adolescents show delayed extinction of cocaine-seeking behavior, and may maintain stronger and more resilient preferences for drug-paired cues during this stage. Differences in memory and reconsolidation processes between these two age groups should be examined more directly in future studies, and may reflect important developmental changes in cue-processing brain regions such as the amygdala and PFC (Andersen et al., 2000; Kerstetter & Kantak, 2007; Quirk & Mueller, 2007)

Our findings are consistent with research in both humans and animals demonstrating that adolescence is characterized by a particular vulnerability to drug abuse and addiction (Badanich et al., 2006; Laviola, Wood, Kuhn, Francis, & Spear, 1995; O'Brien & Anthony, 2005; Spear, 2000a). Addiction often occurs when drug-paired cues are processed as salient events that motivate procurement of more drug, while simultaneously solidifying memories linked to the experience (Baler & Volkow, 2006). Increased salience attribution facilitates memory consolidation of drug-related events (Baler & Volkow, 2006). Therefore, it is possible that adolescents assign higher salience to drug-associated contexts, making nonrewarded exposure to the drug-associated environment less able to compete as a new memory. The paradigm of place conditioning allows assessment of these incentive motivational properties that endure in the absence of the direct, rewarding effects of cocaine.

Adolescents have previously been reported to be more sensitive to the conditioning effects of cocaine, forming preferences for contexts associated with a lower dose (5 mg/kg) than those required for adults (Badanich et al., 2006). Our results support these reports given that only three of eight 80-day-old male adults conditioned with 10 mg/kg of cocaine formed a preference for the drug-paired context. Therefore, this reveals an important caveat in the comparison of P80 adults to adolescents at the 10 mg/kg dose because the adults that formed conditioned place preferences may represent an atypical sample compared to the majority of P80 rats that did not form preferences. This small sample size of adults resembled adolescents in the time required for extinction, yet did not display significant reinstatement upon cocaine challenge. More research on these apparent individual differences is needed, possibly involving early life experiences given the genetic homogeneity within strains.

Important differences exist between the paradigms used to assess extinction, which perhaps depend more on the methodology used to produce drug-seeking behaviors. This is highlighted in the difference between the hypersensitivity to cocaine place conditioning and the *hypo*sensitivity to the locomotor effects of cocaine (Frantz, O'Dell, & Parsons, 2007), or the lack of age effects on cocaine self-administration (Frantz, O'Dell, & Parsons, 2007; Kerstetter & Kantak, 2007). As described by Calcagnetti and Schechter (1992), place conditioning pairs a drug with a cue-specific environment, independent of the animal's emitted operant behavior. The resulting change in affective state, measured by preference or aversion, is related to the reinforcing properties of the drug. In contrast, self-administration depends on the reinforcing effects of the drug itself and its ability to maintain responding. Here, we measured the ability of animals to form drug-cue associations, rather than examining the direct reinforcing effects of cocaine in these animals. A recent study highlights this difference between these two behavioral assays (Kerstetter & Kantak, 2007). Although adolescents and adults self-administered comparable levels of cocaine, conditioned-cue preferences to cocaine differed as a function of age later in life.

A number of studies have shown that adolescents are more sensitive to drug-associated environments than adults, although sex, age of the subjects, and prior handling are important variables to consider. For example, nicotine and alcohol elicit greater place preferences in adolescents relative to adult rats (Belluzzi, Lee, Oliff, & Leslie, 2004; Philpot, Badanich, & Kirstein, 2003; Vastola, Douglas, Varlinskaya, & Spear, 2002). However, other place conditioning studies using cocaine (Aberg, Wade, Wall, & Izenwasser, 2007; Campbell, Wood, & Spear, 2000) did not report greater preferences in adolescents. Experimental differences may account for these disparities. First, the sex of the animals is an important factor to consider. Age differences in place conditioning to 10 mg/kg cocaine are diminished if female rats are included in the assessment, as females demonstrate a greater choice ratio for the cocaine-associated side (Campbell et al., 2000). Similar results are found in adult female mice, which also demonstrated greater place preferences to cocaine-associated environments, in an unbiased paradigm (Balda et al., 2006). Second, the age of the adult used for comparison is important because of differences in cortical maturation (e.g., Andersen et al., 2000; Brenhouse & Andersen, 2007), which is important for cue processing (Kalivas, Volkow, & Seamans, 2005). Adults used in earlier studies were as young as 65 days old (Campbell et al., 2000), compared to the current study, which used rats that were 80 days old. Third, prior handling seems to influence the degree of place conditioning. For example, adolescents at ages similar to those used in the present study *failed to show preferences for environments associated with 10 mg/kg of cocaine* (Aberg et al., 2007). However, methodological differences may explain these disparities, because the animals had all been previously handled and injected repeatedly with either MDMA or saline for 7 days. Taken together, it should be noted that a wide variety of place conditioning protocols have been used in the existing literature and results may differ for several methodological reasons such as sex, age, and prior handling.

Although a significant emphasis has been placed on the acquisition of drug seeking, less attention has been paid to the extinction of this process during adolescence. Extinction of nicotine self-administration was found to be shorter in adolescents (Shram, Funk, Li, & Le, 2007), which points again to distinctions in what different behavioral assays measure. It appears from the present data that the association between cocaine and cocaine-paired environments is retained longer in adolescents, compared to adults. We propose that the delayed extinction observed in adolescence is

because of greater salience attribution to drug-paired cues, rather than a greater "liking" of the drug. Indeed, when accounting for individual correlations between higher initial preferences and time to extinction, adolescents required more extinction trials than adults.

As an active learning process, extinction is largely mediated by the formation of a new memory that is in competition with existing drug-paired associations (Quirk, 2006). Adolescent latency to extinguish suggests that nonrewarded new memories may not be strong enough to drive motivation in adolescence. Interestingly, anatomical differences in the PFC of adolescents are consistent with this line of thinking. We have recently discovered that the D1 dopamine receptor is overexpressed on glutamatergic output neurons in the PFC during adolescence, whereas the D1 receptor is preferentially expressed on GABAergic interneurons before and after the adolescent period (Brenhouse & Andersen, 2007). In the PFC, D1 receptors on pyramidal projection neurons regulate the "perceived" significance of stimuli by gating nucleus accumbens (NAc) activation (Seamans & Yang, 2004). Greater D1 activation on these projections is coupled with a heightened inhibition by interneurons in adolescence (Tseng, Amin, Lewis, & O'Donnell, 2006). D1-mediated activation increases stimulus-driven PFC output to the NAc only when stimuli are of sufficient potency to overcome this hypofrontality (Kalivas et al., 2003). Adolescent resistance to extinction may therefore involve the heightened D1 tone on PFC output neurons, allowing only potent stimuli (such as cocaine-related cues) to overcome a high threshold for PFC output and acquisition of motivational salience. Consequentially, during this window of receptor distribution and overexpression (Andersen et al., 2000), stimuli strongly associated with DA release (such as cocaine exposure) may lock in a memory for associated contexts. This impact of cortical DA on drug-cue associations is separable from the amount of DA in downstream structures such as the nucleus accumbens, which influences the direct reinforcing and motor effects of cocaine and does not differ after cocaine exposure between adolescents and adults (Frantz et al., 2007).

A priming injection of a drug after extinction renews the significance or salience of the drug-related environmental stimuli, driving the animal to seek the drug (Mueller & Stewart, 2000). Reinstatement of extinguished drug-seeking with the learning paradigm of CPP (Mueller & Stewart, 2000) was used here to show that adolescents display more robust drug-primed reinstatement of CPP than adults. Magnitude of reinstatement, however, was not found to correlate directly with either initial place preferences or with the number of days required for extinction. This further suggests that stronger initial associations are not sufficient to explain the adolescent vulnerability to relapse after a drug challenge. The preferential salience attribution to potent stimuli discussed above may cause a cocaine exposure to reinstate adolescent drug seeking to a greater extent than adults. It is also important to note that stress-induced reinstatement is mediated through a different circuitry than drug-primed reinstatement (Kreibich & Blendy, 2004; Sanchez et al., 2003), and therefore, developmental differences in the vulnerability to stress-primed reinstatement still needs to be investigated.

The present results suggest that adolescents may establish more resilient associations between rewarding drug exposure and drug-paired cues, and therefore show delayed extinction of drug seeking compared to adults. Once extinguished, adolescents also displayed reinstatement of memory for a lower dose of cocaine than adults and showed a greater preference for a previously drug-paired environment upon reinstatement. These findings suggest that, in the behavioral paradigm examined here, memories for cocaine-associated cues are particularly strong during this stage, likely because of enhanced motivational salience for drug-paired events at the expense of other information. This heightened salience attribution during adolescence may require atypical strategies for drug abuse intervention during the adolescent period, such as extended treatment that involves substitution with different rewards, for example, exercise or music. The coincidence of cortical remodeling (Brenhouse & Andersen, 2007), its role in associating reward-related cues to consequences (Kalivas et al., 2005), and drug exposure during adolescence may produce drug-linked associations that are extremely difficult to change, reduce, or extinguish.

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