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Age differences in appetitive Pavlovian conditioning and extinction in rats

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Abstract

Mounting evidence indicates that adolescents exhibit heightened sensitivity to rewards and reward-related cues compared to adults, and that adolescents are often unable to exert behavioral control in the face of such cues. Moreover, differences in reward processing during adolescence have been linked to heightened risk taking and impulsivity. However, little is known about the processes by which adolescents learn about the appetitive properties of environmental stimuli that signal reward. To address this, Pavlovian conditioning procedures were used to test for differences in excitatory conditioning between adult and adolescent rats using various schedules of reinforcement. Specifically, separate cohorts of adult and adolescent rats were trained under conditions of consistent (continuous) or intermittent (partial) reinforcement. We found that the acquisition of anticipatory responding to a continuously-reinforced cue proceeded similarly in adolescents and adults. In contrast, responding increased at a greater rate in adolescents compared to adults during presentations of a partially-reinforced cue. We subsequently compared the ability of adolescent and adult rats to dynamically adjust the representation of a reward-predictive cue during extinction trials, in which a secondary inhibitory representation is acquired for the previously-reinforced stimulus. We observed significant age differences in the ability to flexibly update cue representations during extinction, in that the appetitive properties of cues with a history of either continuous or partial reinforcement persisted to a greater extent in adolescents relative to adults.

Keywords

Adolescence; Learning; Reinforcement; Appetitive; Pavlovian

1. Introduction

Adolescence is a dynamic period of development that is characterized by unique changes in the brain as well as behavior [1–7]. In particular, adolescent humans and other animals tend to make more impulsive decisions and engage in more risk-taking behavior compared to

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either adults or pre-adolescents [8–12]. Although this behavioral phenotype is important for gaining skills and experience necessary for becoming an independent adult, it can also lead to negative outcomes. Indeed, adolescence is marked by vulnerability to substance abuse, increased chance of injury and premature death [10, 13].

The behavioral and neurobiological factors that contribute to heightened risk-taking and impulsivity during adolescence remain unclear. However, a growing body of evidence indicates that at least one contributing factor is an inability to control behavior in the face of reward [8–10, 14]. Prior studies have demonstrated an increased sensitivity to primary rewards during adolescence compared to adulthood [2, 9, 15–22, 23]. Similarly, environmental cues that come to predict reward drive behaviors performed in service of obtaining reward to a greater extent in adolescents than in children or adults [1, 2, 18, 24–28].

For example, findings in laboratory animals suggest that motivation for many natural rewards may be enhanced during adolescence. Indeed, during a conditioned place preference paradigm adolescent rats will spend more time than adults in a chamber that has been previously paired with a rewarding stimulus, such as a novel object or social interaction, relative to an alternative chamber [8, 29]. Similarly, adolescent humans exhibit difficulties suppressing responding specifically to appetitive cues (e.g. emotionally salient faces) compared to either children or adults [2, 12, 30]. Along similar lines, substantial research suggests that adolescents are highly sensitive to the rewarding properties of alcohol and other drugs of abuse [31–40], which may contribute to the development of drug use and addiction during adolescence. Thus, an understanding of how appetitive conditioning processes develop across adolescence may be useful to mitigate health issues that present during this period [13].

Most prior studies of reward-related behavior in adolescents have focused on behavioral responding during tasks where performance has reached asymptotic levels [1, 2, 19, 20, 26, 27]. In comparison, surprisingly little is known about whether developmental differences exist in the *acquisition* of stimulus-reward associations (i.e., excitatory conditioning). Alterations in the rate or magnitude of excitatory conditioning could impact many aspects of behavior, particularly during adolescence when individuals are engaged in increased exploration and novelty-seeking, thus experiencing a range of environmental cues for the first time and actively learning the meaning of those cues. For example, more rapid acquisition of stimulus-reward contingencies could contribute to the emergence of maladaptive behaviors, such as smoking and substance abuse. Alterations in excitatory conditioning could also affect an organism's ability to inhibit behavior. Indeed, studies in both humans and laboratory animals, using a range of behavioral paradigms, indicate that adolescents often experience difficulty using environmental cues to withhold behavior [2, 5, 41–50]. This could result, for example, from stronger associations among competing excitatory cues.

To address this, the present experiments tested how Pavlovian stimuli acquire reinforcing properties in adolescent and adult rats. In Experiment 1, rats were trained on a continuous reinforcement schedule, in which they learned to discriminate between a cue that was always

followed by reinforcement (continuously reinforced cue; CRF+) and a second cue that was never reinforced (CRF–). In Experiment 2, another set of adolescent and adult rats were trained on a partial reinforcement schedule, in which they learned to respond to a cue that was reinforced on only a subset of trials (partially reinforced; PRF+/PRF–), in order to determine if there are age-related differences in associations involving partial versus continual reinforcement. After the conditioning phase, rats in both experiments underwent extinction training to test for age-related differences in the ability to learn a secondary representation of a previously-reinforced stimulus. Indeed, the ability to update the meaning of a stimulus that has previously been paired with reward is critical for adaptive behavior in a changing environment, yet few studies have examined extinction in adolescents.

2. Materials and Methods

2.1 Subjects

Naïve male Long Evans rats were obtained from Harlan Laboratories (Indianapolis, IN) at either 21 ($n = 32$) or 56 ($n = 32$) days of age. Juvenile rats were weaned from their dam on PND 21, and were shipped and received on the same day. Rats were initially group-housed and allowed at least one week to acclimate to the colony room prior to beginning food restriction and behavioral training. The colony room was maintained at 72°F. Water was available ad libitum throughout the experiment. Food (2014 Teklad Global 14% Protein Rodent Maintenance Diet, Harlan Laboratories) was available ad libitum until one week prior to behavioral training. During the week prior to behavioral training, rats were separated into individual cages, handled and weighed daily. Body weights were gradually reduced over a four day period to 85% of the daily weight of free-feeding age-matched control rats. All groups remained food restricted until completion of behavioral training, with supplemental rat chow provided after each daily session to maintain the target weight. The colony room was maintained on a 14:10 h light–dark cycle and monitored and cared for in compliance with the Association for Assessment and Accreditation of Laboratory Animal Care guidelines and the Dartmouth College Institutional Animal Care and Use Committee.

2.2 Behavioral apparatus

Behavioral procedures were carried out in standard conditioning chambers (Med Associates). The chambers ($24 \times 30.5 \times 29$ cm) consisted of aluminum front and back walls, clear acrylic sides and top, and grid floors. Each chamber was outfitted with a dimly illuminated food cup, recessed in the center of the front wall, and a speaker located 15 cm above and to the right of the food cup, used to present the auditory conditioned stimuli, a white noise (78-dB) and a clicker (Experiment 1) or a 1500-Hz, 78-dB tone (Experiment 2). Delivery of two 45-mg food pellets (Bioserv) served as the unconditioned stimulus (US). Each chamber was equipped with a pair of infrared photocells located across the entrance to the food cup to monitor entries into the cup and connected to a PC-clone computer. Each chamber was enclosed in a sound-attenuating cubicle ($62 \times 56 \times 56$ cm) with an exhaust fan to provide airflow and background noise (~68 dB) and a red house-light (mounted on the ceiling) to provide background illumination. The cubicles also contained surveillance cameras used to monitor the rats during behavioral training.

2.3 Behavioral procedure

At the start of each training session rats were moved in plastic transporters from the colony room to the conditioning chambers. Rats were first trained to eat from the food cup during a single 61-min session in which one 45-mg food pellet was delivered every minute, with the exception that no more than three food pellets could accumulate in the food cup.

2.3.1 Experiment 1: Continuous reinforcement conditioning—During the Acquisition phase of the experiment, rats underwent eight daily training sessions of Pavlovian excitatory conditioning using a continuous schedule of reinforcement. This procedure consisted of daily 61-min sessions with eight reinforced and eight non-reinforced trials. During reinforced trials the white noise or clicker (counterbalanced; CRF+) was presented for 5 sec and followed immediately by delivery of the US. On non-reinforced trials, the other cue (clicker or white noise, counterbalanced; CRF–) was presented for 5 sec, after which no US was delivered. The two trial types occurred pseudo-randomly during each session, with no more than two consecutive reinforced or non-reinforced trials. The presentation order and the inter-trial intervals (ITI) varied daily (average ITI of 3.6 min, ranging from 1.7 to 5.6 min). Rats in the adolescent group began training on postnatal day (PND) 35 and rats in the adult group started training on PND 70.

Immediately following Acquisition, rats underwent two Extinction Training sessions that were each 66-min in duration and consisted of 30 non-reinforced presentations of each auditory stimulus (a total of 60 trials). The two stimuli occurred pseudo-randomly during each session, with no more than three consecutive presentations of either stimulus. The presentation order and the ITIs varied daily (average ITI of 1 min, ranging from 0.3 to 1.7 min). Finally, rats underwent an Extinction Test session (30 non-reinforced presentations of each stimulus) four days following the end of extinction training. This test session occurred when rats in the adolescent group were age PND 48.

2.3.2 Experiment 2: Partial reinforcement conditioning—Previous research has established that learning is mediated by the information that one stimulus provides about another [51–54]. In particular, the temporal information that a stimulus provides about a reinforcer is critical in establishing the conditioned response patterns to that stimulus [55–58]. Experiment 1 considered how adult and adolescent rats learned about a cue that acquired excitatory and inhibitory properties in sequence. Conversely, Experiment 2 tested for age differences in acquiring similar competing properties simultaneously, i.e., a partially reinforced cue. Traditionally, the more reliably the stimulus is associated with the reinforcer, the more motivated the animal becomes to produce a conditioned response [59, 60]. To date, minimal research has considered how adolescents respond to differences in the predictive validity of a stimulus. However, recent evidence has indicated that adolescents more readily engage in behaviors for which the outcome is uncertain relative to adults [61, 62]. Furthermore, mounting evidence in adults indicates that the reinforcement history of a cue influences both initial and long-term learning about the cue's meaning, as well as the responses that occur in the presence of the cue [63–69]. Thus, Experiment 2 determined how adolescents learn about a conditioned reinforcer that does not always predict reinforcement (i.e., a partial reinforcement schedule).

During the Acquisition phase, rats underwent 10 daily training sessions in a partial reinforcement procedure consisting of daily 61-min sessions in which a 5-sec tone was presented 16 times. Four of these presentations were immediately followed by delivery of the US, while the other 12 presentations were not reinforced. The two trial types occurred pseudo-randomly during each session, with no more than three consecutive reinforced (PRF+) or non-reinforced (PRF-) trials. The presentation order and the ITIs varied daily (average ITI of 3.6 min, ranging from 1.7 to 5.6 min). Rats in the adolescent group began training on PND 35 and rats in the adult group started training on PND 70.

Immediately following Acquisition, rats underwent two Extinction Training session (68-min each) consisting of 32 presentations of the tone. The ITIs varied daily (average ITI of 1 min, ranging from 0.3 to 1.7 min). Rats underwent a final Extinction Test session (32 non-reinforced presentation of the tone) four days following the end of extinction training. The Test session occurred when rats in the adolescent group were age PND 50.

2.4 Data analysis

2.4.1 Experiment 1—The primary measure of interest was the number of snout entries into the food cup during presentation of the conditioned stimuli. For each session of the Acquisition phase, the average number of snout entries during each cue (CRF+, CRF-) was calculated and the data were subjected to a repeated measures analysis of variance (ANOVA) with Age as the between subjects factor and Session and Trial type as within subjects factors. During the two Extinction Training sessions, the number of snout entries during each cue was averaged for the first and last two trials in each session. The data were analyzed using a repeated measures ANOVA with Age as the between subjects factor and Block and Trial type as the within subjects factors. During the Extinction Test session, snout entries during each cue was averaged for the first two trials and the data were analyzed using a repeated measures ANOVA with Age as the between subjects factor and Trial type as the within subjects factor. Paired-sample t-tests were used to analyze responding during the CRF+ within each age group between the end of an extinction session and the beginning of the next session (i.e. retention of conditioning during extinction training or spontaneous recovery during the test).

To assess potential group differences in motivation to consume the food pellets, we recorded the number of snout entries into the food cup during the 5-sec period after food was delivered on CRF+ trials during the Acquisition phase. In addition, the number of snout entries into the food cup during the CRF- was used to test for age-related differences in baseline responding (since responding was expected to be very low in the absence of reinforcement). The data were collapsed across sessions and subjected to an independent measures t-test.

All analyses were conducted using SPSS statistical software and used an alpha level of 0.05. Significant ANOVAs were decomposed with appropriate pair-wise comparisons using an alpha level of 0.05.

2.4.2 Experiment 2—For the Acquisition sessions, the average number of snout entries during presentation of the tone were analyzed using a repeated measures ANOVA with Age

as the between subjects factor and Session as the within subjects factor. During Extinction Training, snout entries during the tone were averaged for the first and last two trials in each session and the data were analyzed using a repeated measures ANOVA with Age as the between subjects factor and Block as the within subjects factor. During the Extinction Test, snout entries during the tone were averaged for the first two trials and analyzed using an independent samples t-test. Paired-sample t-tests were used to analyze responding during the tone within each age group between the end of an extinction session and the beginning of the next session (i.e. retention of conditioning during extinction or spontaneous recovery during test).

As in Experiment 1, potential group-differences in motivation to consume the food pellets was assessed via the amount of time each rat spent with the snout in the food cup during the 5-sec period after food was delivered during the Acquisition phase. The number of snout entries into the food cup during the 5 sec period immediately before the tone was presented serves as a measure of baseline responding. The data were collapsed across sessions and subjected to an independent measures t-test.

3. Results

3.1 Experiment 1: Continuous reinforcement

One rat in the adult group exhibited abnormally low baseline levels of responding at least one standard deviation below the group average across all three phases of the experiment. The data from this rat was excluded from the analyses, resulting in $n = 15$ for this group.

3.1.1 Acquisition—As show in Figure 1, the rates and levels of conditioned responding to either the CRF+ or CRF− during the Acquisition phase were comparable between adolescent and adult rats. This was supported by a multi-factor ANOVA, which revealed that responding was greater during CRF+ than CRF−, indicating that rats could discriminate between the reinforced cue and the non-reinforced cue [$F(1, 29) = 37.59, p < 0.001$]. In addition there was a main effect of Session [$F(7, 203) = 6.07, p < 0.001$] and a significant Trial type X Session interaction [$F(7, 203) = 10.42, p < 0.001$], which subsequent pair-wise analysis indicated was due to an increase in responding to CRF+ over the course of training. There was no main effect of age ($p > 0.9$) nor any other significant interactions (p 's > 0.6), indicating that there were no age differences in conditioning.

3.1.2 Extinction Training—Conditioned responding during the first and last two-trial blocks of Extinction Session 1 are presented in Figure 2A. A significant interaction between Block and Trial Type [$F(1, 29) = 9.94, p < 0.005$] and subsequent pair-wise analyses revealed that there was less responding to CRF+ in the second block relative to the first block, indicating that the extinction of conditioned responding was specific to the cue that had previously been paired with food. Importantly, there was also a significant Age X Trial type X Block interaction [$F(1, 29) = 8.57, p < 0.01$]. To assess the source of this three-way interaction, separate Age x Block ANOVAs were conducted within each level of Trial Type (CRF+ and CRF−). For the CRF−, this analysis revealed no differences across Blocks [$F(1, 29) = 0.05, p > 0.8$] and no interaction between Block and Age [$F(1, 29) = 1.66, > 0.2$]. However, for the previously reinforced CRF+, the analysis revealed a main effect of Block

$[F(1, 29) = 17.88, p < 0.001]$ and a significant interaction between Age and Block $[F(1, 29) = 8.79, p < 0.01]$, which was further decomposed to reveal significantly higher levels of responding by adolescents than adults specifically at the end of the extinction session $[t(29) = 2.10, p < 0.05]$. This indicates that there was a greater decrease in responding to CRF+ in adult rats than in adolescents during the first extinction session. In summary, although responding during CRF+ extinguished in both age groups, extinction was greater in adults than adolescents.

Responding during Extinction Session 2 is shown in Figure 2B. The number of snout entries into the food cup continued to be higher during CRF+ than CRF- [main effect of Trial Type, $F(1, 29) = 35.4, p < 0.001$]. In addition, the overall level of responding was higher in adolescents compared to adults [main effect of Age, $F(1, 29) = 4.6, p < 0.04$]. There was no main effect of Block and no significant interactions between any of the variables (p 's > 0.07). In addition, no differences were observed between the levels of conditioned responding during the CRF+ at the end of the first extinction session and the beginning of the second extinction session for either adolescents $[t(15) = -1.77, p > 0.09]$ or adults $[t(14) = -1.31, p > 0.2]$.

3.1.3 Extinction Test Session—Responding during both CRF+ and CRF- were relatively low during the extinction Test session carried out four days after Extinction Session 2. Overall, responding was higher during the previously-reinforced CRF+ than the CRF- $[F(1, 29) = 21.42, p < 0.01]$, but this did not differ by age $[F(1, 29) = 2.48, p > 0.1]$. There were also no differences in overall levels of responding between age groups $[F(1, 29) = 0.01, p > 0.9]$.

3.1.4 Baseline responding—All rats exhibited similarly low levels of responding to CRF- presentations during Acquisition [mean $\pm$ SEM were 1.51 ± 0.13 s for adults and 1.59 ± 0.16 s for adolescents; $t(29) = 0.42, p > 0.6$]. Thus, differences in baseline behavior could not account for age-related differences in conditioned responding during the CRF+.

3.1.5 Post-CRF+ responding—Analysis of conditioned responding during the 5 sec period after food delivery during the Acquisition session revealed no differences between adolescents and adults $[p > 0.07]$. The means $\pm$ SEMs were 1.16 ± 0.13 s for adolescents and 1.53 ± 0.16 s for adults. Thus, motivation to consume the food pellets appeared to be similar in both age groups.

3.2 Experiment 2: Partial reinforcement

Two rats in the adult group exhibited abnormally low levels of responding at least one standard deviation below the group average across all three phases of the experiment. The data from these rats were eliminated from analyses, resulting in $n = 14$ for this group.

3.2.1 Acquisition—The average number of snout entries into the food cup during presentation of the tone in the acquisition phase is presented in Figure 4. A 2 (Age: Adolescent, Adult) $\times$ 10 (Session) ANOVA indicated that responding to the tone increased across sessions [main effect of Session, $F(9, 252) = 19.00, p < 0.001$]. Notably, between-subjects analysis revealed that adolescents exhibited higher overall levels of responding

relative to adults [main effect of Age, $F(1, 28) = 5.48, p < 0.05$]. However, the Age X Session interaction was not significant [$F(9, 252) = 1.74, p > 0.08$].

3.2.2 Extinction Training—During the first extinction session (Figure 5A), adolescent rats exhibited higher overall levels of responding relative to adults [main effect of Age, $F(1, 28) = 5.69, p < 0.05$]. In addition, there was a significant interaction between Age and Block [$F(1, 28) = 5.94, p < 0.05$]. This was decomposed by subsequent pair-wise comparisons, which revealed that adolescents exhibited significantly higher levels of responding compared to adults during the first block of trials [$t(28) = -3.18, p < 0.005$] but not the second block [$t(28) = 0.14, p > 0.8$].

Responding during Extinction Session 2 is shown in Figure 5B. A repeated measures ANOVA revealed a main effect of Block [$F(1, 28) = 5.81, p < 0.05$], indicating that responding continued to decrease over the course of the session. There were no other significant main effects or interactions. In addition, there were no significant differences in the levels of responding during the last block of Extinction Session 1 and the first block of Extinction Session 2 for either age group (p 's > 0.4).

3.2.3 Extinction Test Session—The number of times the rat poked its snout into the food cup during presentation of the tone was averaged for the first two trials of the test session (Figure 6). Responding did not differ significantly between the age groups [$t(28) = -1.90, p > 0.06$]. In addition, responding did not significantly differ from the low levels of responding reached at the end of the extinction phase for adolescents [$t(15) = -1.90, p > 0.07$] or adults [$t(13) = -0.59, p > 0.5$].

3.2.4 Baseline responding—All rats exhibited similarly low levels of baseline responding during the 5-sec period before the tone was presented during Acquisition [0.46 ± 0.07 s for adults, 0.35 ± 0.06 s for adolescents; $t(28) = 1.24, p > 0.2$], Extinction Training [0.40 ± 0.06 s for adults, 0.43 ± 0.06 s for adolescents; $t(28) = -0.27, p > 0.7$] and Extinction Test [0.36 ± 0.08 s for adults, 0.40 ± 0.07 s for adolescents; $t(28) = -0.41, p > 0.6$] sessions. Thus, differences in baseline behavior cannot account for age-related differences in conditioned responding during the PRF tone.

3.2.5 Post-PRF responding—Analysis of conditioned responding during the 5 sec period after food delivery during the Acquisition session revealed no differences between adolescents and adults [$p > 0.8$]. The means $\pm$ SEMs were 1.81 ± 0.09 s for adolescents and 1.84 ± 0.19 s for adults. Thus, as in Experiment 1, motivation to consume the food pellets appeared to be similar in both age groups.

4. Discussion

Learning and updating the meaning of informative environmental cues is critical to adaptive behavior. The present experiments were designed to determine whether learning about the appetitive properties of Pavlovian cues differs between adolescents and adults. In Experiment 1, both adolescents and adults similarly acquired Pavlovian excitatory conditioning to a continuously reinforced auditory cue (CRF+). In addition, both ages

exhibited low levels of responding during the CRF–, indicating that adolescents were able to discriminate between the stimuli and differentiate behavioral response patterns directed towards these stimuli like adults. Conversely, in Experiment 2, adolescents acquired excitatory responding to a partially-reinforced cue faster than adults. Thus, age-related differences in excitatory conditioning may be specifically related to the reinforcement schedule of an appetitive cue.

A general feature of learning about a partially reinforced cue is that conditioned responding is initially slow to develop [63–70], because each PRF– trial causes a decrement in associative strength (or an increment in inhibition) that offsets the associative increments that occur on PRF+ trials. However, the occurrence of a reinforcer, even intermittently, may increase the salience of the stimulus in adolescents. Thus, the associative strength may not decrease in the same way as for adults during PRF– trials. In this manner, the increased responding during the acquisition phase by adolescents relative to adults in Experiment 2 may reflect an adolescent proclivity towards the excitatory properties of the partially reinforced cue. An additional factor may be that PRF– trials are less aversive for adolescents. Indeed, adults, but not adolescents favor choices that attach certainty to an outcome over alternatives with identical expected values [71]. Furthermore, adolescents exhibit a higher tolerance for aversive outcomes in general [33, 72–74].

Another major finding of these experiments was that conditioned responding differed between adolescents and adults during extinction training. During the first extinction training session in Experiment 1, both groups reduced responding to the previously reinforced cue once the reinforcer was no longer present. However, extinction learning was much more robust in adults. Indeed, adult rats initially exhibited higher levels of responding than adolescents, but responding decreased to baseline levels by the end of the session. Conversely, adolescents exhibited a much smaller difference in responding across the session and made significantly more snout entries into the food cup at the end of the session than adults. These findings indicate that adolescents exhibit difficulties extinguishing responding to a previously continuously-reinforced cue compared to adults.

One possible explanation is that adolescents experience difficulties encoding the new meaning of the previously-reinforced (now non-reinforced cue). Indeed, medial prefrontal regions known to be involved in extinction are not fully mature during this time [75–81], whereas subcortical regions such as nucleus accumbens that are involved in the initial reward contingency learning have reached maturity [1]. As a result, enhanced salience of the appetitive properties of a cue could strengthen the initial excitatory representation and subsequently take precedence over the inhibitory representation of the same cue formed during extinction training. The results of Experiment 1 indicate that age-related differences in sensitivity to rewards do not manifest in differences in the acquisition of conditioned responding to a reward-predictive cue. However, the neurobiological processes involved in encoding the meaning of the CRF may have differed. Previously, differences in neuronal activity indicative of reward processing have been shown to differ despite similar learning and performance of operant excitatory conditioning [6, 22]. Thus, heightened activity in brain regions associated with representing the value of a potential reward (e.g. nucleus accumbens [82–85]) during adolescence may have increased the salience of the CRF+.

Notably, the experiments described here were carried out using *Pavlovian* excitatory conditioning procedures. Although an animal learns to associate a stimulus with a reinforcer, delivery of the reinforcer is not contingent upon a response. Thus, behavior exhibited during the stimulus period (conditioned responding) reflects anticipation of reinforcer delivery. In this way, the experiments tested for age-related differences in how appetitive cues are represented and thus extends previous research that considered differences between adolescents and adults in *instrumental* responding in the face of reward [86, 87]. For example, the present data are consistent with the performance of adolescents during an operant excitatory conditioning paradigm [87]. Indeed, the authors did not observe age differences in the acquisition a nose poke behavior required to obtain a reinforcer, but did observe perseverative responding by adolescents but not adults when the poke no longer produced a reward. Additional research has also shown that adolescents are slower to extinguish an operant response that previously triggered delivery of a reward [43]. The present results extend these findings to Pavlovian excitatory learning and anticipatory food cup behavior. Moreover, these findings indicate notable similarities between how adolescents represent expectancies about stimuli in the environment and how responding is directed towards predictive stimuli. Moreover, our data are also in line with evidence that adolescents exhibit delayed extinction of a learned fear response to a cue previously paired with a footshock [4, 88].

During extinction of the partially reinforced cue in Experiment 2, the greater reduction in responding across the first extinction training session by adolescents compared to adults suggests that adolescents may be able to extinguish responding to a partially reinforced cue more rapidly than adults. However, conditioned responding was very similar between the groups during the second extinction training session. This pattern of results differs from the delayed extinction of conditioned responding exhibited by adolescents in Experiment 1. This result may be particularly noticeable relative to the slow rate of extinction in adult rats. This is common in operant conditioning, where behavior that is reinforced intermittently is more resistant to extinction than behavior that is always reinforced [89–91]. This occurs because the discrepancy, or error, between actual and predicted reward contributes extensively to the extent to which learning occurs [82]. Thus, extinguishing the response to a partially reinforced stimulus may be slow to develop because non-reinforced presentations of the stimulus are expected and thus less prediction error occurs. The present results indicate that adolescents are more able to overcome the low prediction error in order to flexibly update the meaning of the cue. An important avenue for future research will be to determine whether the extinction of a partially reinforced aversive cue during adolescence is also facilitated relative to adulthood. This would provide important insight about the extent to which extinction learning is influenced by reinforcement schedule as well as whether this influence is generalizable to the appetitive or aversive history of a cue.

Developmental differences in associative learning prior to adolescence have also been shown previously. For example, in preweanling rodents, the presence of additional cues, even those unpaired with the outcome, (e.g. CS–) can strengthen learning about a paired cue (CS+) as well as a CS-US relationship [92, 93]. Furthermore, the extent to which a CS– influences learning about a CS+ depends on the amount of information that the CS– provides about the CS-US pairing [94]. Finally, there is evidence that extinction processes in pre-weanlings

involves unlearning of the CS-US association, in contrast to the secondary inhibitory association that is believed to be formed during extinction trials in adulthood [95, 96]. Considering these and other developmental findings along with established adult learning and behavioral patterns will aid the interpretation of future research directed at elucidating age-related differences in associative learning.

Taken together, our data suggest that extinction of a Pavlovian excitatory association is subject to age differences. Importantly, the history of reinforcement (i.e., continuous or partial reinforcement) determines whether the rate of extinction is delayed or enhanced in adolescents, respectively. Here, adolescents were delayed relative to adults when extinguishing responding to a cue that had previously been continuously paired with reinforcement, consistent with previous research [4, 43, 87, 88]. Conversely, we show evidence that exposure to non-reinforced presentations of a cue (partial reinforcement) may subsequently facilitate extinction in adolescents. This parallels previous research suggesting that adolescents are more readily able than adults to adjust behavioral patterns directed towards a stimulus that has previously acquired inhibitory properties [86]. Importantly, our findings in this regard may provide insight to unify previous research that has considered age-related differences in flexibly updating cue representations. Indeed, these seemingly disparate results may be attributed to differences in the ratio of reinforced and non-reinforced presentations of a given cue. Moreover, difficulties learning a secondary meaning of a cue during adolescence may be particularly robust when the initially encoded representation of that cue is exclusively excitatory.

The present experiments also extend the current literature by including test sessions following extinction to address the longevity of learning about a Pavlovian appetitive cue. The passage of time after the acquisition and extinction phases can serve as a temporal context shift that increases retrieval interference [97] and may result in spontaneous recovery of the initially conditioned response [98]. In Experiment 1 neither age group exhibited spontaneous recovery of anticipatory responding to the cues previously followed by reinforcement during the test session. In contrast, during the test session in Experiment 2, although responding between the age groups was statistically similar, we observed a trend towards spontaneous recovery of responding by adolescents but not adults, as well as overall higher levels of responding by adolescents than adults. This suggests somewhat less retention of the inhibitory representation of the tone encoded during extinction by adolescent rats. These test sessions were conducted four days after completion of the extinction phase in order to remain within the developmental window of adolescence. However, the interval between extinction and testing is a critical determinant of the magnitude of spontaneous recovery of conditioned responding [98, 99]. Thus, greater differences may be observed with test sessions conducted after longer delays.

In both Experiments 1 and 2, conditioned responding during Extinction Training and Extinction test was consistently higher than baseline responding (CRF– in Experiment 1, Pre-PRF in Experiment 2). This indicates that both groups maintain a representation of the excitatory properties of a cue. This is consistent with the well-established notion that extinction learning does not erase the initial memory, but rather results in a new inhibitory association between the now neutral stimulus and its previously reinforcing outcome [98].

Notably, differential levels of conditioned and baseline responding were observed even after the non-reinforced presentations of the stimulus outnumbered the reinforced presentations. This suggests robust persistence of the initial discrimination learning, consistent with evidence that when time passes from the end of acquisition and extinction training, the representation that was learned first will contribute more to performance [97, 100].

Taken together, the age-related differences in conditioned responding during extinction training (Experiment 1) and test (Experiment 2) phases suggest that adolescents perseverate on the excitatory properties of Pavlovian appetitive cues to a greater extent than adults. Importantly, this appears to be the case for cues with a history of either continuous or partial reinforcement. One explanation for these findings is that the salience of a Pavlovian appetitive cue is increased as a result of the predisposition of adolescents towards positive rewards compared to adults [9, 15–18, 21, 24–28, 41, 101–103]. Indeed, a key theme emerging from research regarding adolescence is that the neurobiological environment during this time provides a basis for behaviors that are biased toward risk, reward, and emotional reactivity [9, 16, 17]. It has been postulated that the differential development of top-down control systems and subcortical areas results in a functional imbalance during adolescence [9, 14, 16, 17, 104]. Ultimately, activity in subcortical regions (e.g. ventral striatum and amygdala) is disproportionately higher than PFC during adolescence [1, 17, 105–109]. As a result subcortical regions exert a stronger influence on behavior, effectively signaling enhanced approach motivation [2].

5. Conclusions

The findings described here indicate that differences in excitatory conditioning processes during adolescence may underlie behavioral tendencies that are apparent during this developmental time period. In particular, a bias towards the excitatory properties of cues may outweigh alternative meanings of the same cue and underlie a variety of reward-biased behaviors. These behaviors could in turn contribute to a number of negative outcomes including interpersonal conflicts, increased chance of injury, vulnerability to substance abuse, and even premature death [10, 13, 16, 110–112]. Moreover, we have presented evidence of the robust influence that the reinforcement history of a cue can have on learning, maintaining and updating cue representations during adolescence. The exact conditions that mediate differences in how the schedule of reinforcement contributes to age-related differences in associative learning processes will be an important avenue for further study.

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Highlights

- Adolescent and adult rats condition similarly to continuously reinforced stimuli
- Adolescents exhibit heightened responding to partially-reinforced cues compared to adults
- The appetitive properties of cues persist longer in adolescents relative to adults
- Flexibly mediating competing cue representations depends on reinforcement history

Figure 1. Acquisition of conditioned responding as measured by snout entries into the food cup during presentation of the CRF+ (solid lines) or CRF- (dashed lines) by adult (black) and adolescent (grey) rats. Both adolescents and adults increased responding during the CRF+ compared to low levels of responding during the CRF-. Data are means $\pm$ SEM.

Figure 2A

Figure 2B

Figure 2.

Extinction of conditioned responding as measured by snout entries into the food cup during presentation of the previously reinforced cue (CRF+; solid lines) or CRF- (dashed lines) by adult (black) and adolescent (grey) rats during session 1 (**panel A**) and session 2 (**panel B**). Adolescents exhibit difficulties extinguishing responding to a previously reinforced cue compared to adults. Data are means $\pm$ SEM. * $p < 0.05$.

Figure 3.

Test of conditioned responding after a four day interval as measured by snout entries into the food cup during presentation of the previously reinforced cue (CRF+) or CRF- by adult (black) and adolescent (grey) rats. Both adolescents and adults exhibited higher responding during the previously reinforced CRF+ compared to lower levels of responding during the CRF-. Within each trial type, adolescents responded similarly to adults. Data are means $\pm$ SEM from the first two-trial block of the session.

Figure 4. Acquisition of conditioned responding as measured by snout pokes into the food cup during presentation of the PRF tone by adult (black) and adolescent (grey) rats. Adolescents increased responding during the CS+ faster than adults and exhibited higher overall levels of responding. Data are means $\pm$ SEM. * $p < 0.05$.

Figure 5A

Figure 5B

Figure 5.

Extinction of conditioned responding as measured by snout pokes into the food cup during presentation of the previously reinforced tone by adult (black) and adolescent (grey) rats during session 1 (**panel A**) and session 2 (**panel B**). Adolescents exhibit initially higher levels of responding than adults and subsequently extinguish at a faster rate than adults. However, responding at the end of the session was similar between age groups. Data are means $\pm$ SEM. * $p < 0.05$, ** $p < 0.005$.

Figure 6.

Test of conditioned responding after a four day interval as measured by snout pokes into the food cup during presentation of the previously reinforced tone by adult (black) and adolescent (grey) rats. Responding did not differ significantly between adolescents and adults. Data are means $\pm$ SEM from the first two-trial block of the session.