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Adolescent male and female rats show enhanced latent inhibition of conditioned fear compared to adult rats

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Introduction: Latent inhibition is diminished associative memory because of pre-exposure to the conditioned stimulus without any consequences. Latent inhibition likely plays a significant role in the ontogeny of anxiety disorders, contributing to why anxiety disorders are particularly prevalent in adolescence. Therefore, the present study examined latent inhibition of conditioned fear in adolescent and adult rats of each sex. Given that adolescence is associated with deficits in fear extinction, we hypothesized that latent inhibition will be impaired in adolescents compared to adults and expected females to show age-specific estrous cycle effects.

Methods: On day 1, male (Experiment 1) and female (Experiment 2) rats were placed in fear conditioning chambers. Half of the rats received pre-exposure to the tone cue while the other half received nothing. On day 2, all rats were placed back in the same chambers and exposed to three cue-footshock pairings. Latent inhibition was tested on day 3 with 20 presentations of the cue by itself in the same chamber.

Results: We unexpectedly observed enhanced latent inhibition in adolescents compared to adults in both male and female rats, indicated by lower levels of freezing due to pre-exposure to the cue. Estrous cycle did not affect latent inhibition at any age.

Discussion: These results suggest that benign experience to a cue reduces subsequent conditioning to the cue more potently in adolescence compared to adulthood, which suggests a potential resilience mechanism naturally occurring in adolescence.

KEYWORDS

adolescence, pubertal, estrous, memory, psychology, resilience, anxiety disorders, development

1 Introduction

Latent inhibition is when prior benign experience with a cue can impede or inhibit subsequent emotional learning to the cue (Lubow, 1973; Mineka and Zinbarg, 2006). In Pavlovian conditioning, latent inhibition is observed when the pre-exposure to the conditioned stimulus (CS) interferes with acquisition (George et al., 2010; Shalev et al., 1998; Lubow and Moore, 1959) or retrieval (Leung et al., 2013; Lingawi et al., 2016) of CS association with the unconditioned stimulus, measured by decreased conditioned responding in pre-exposed compared to non-pre-exposed subjects. Latent inhibition is proposed to explain how prior benign experiences prevent the development of experience-based anxiety disorders (Mineka and Zinbarg, 2006). For example, children who did not initially experience stress with dentists are much less likely to develop dental phobias following a subsequent traumatic experience (Davey, 1989). Similarly, monkeys who have observed models playing with snakes in seemingly safe circumstances do not develop fearful behaviors when directly exposed to snakes (Mineka and Cook, 1986).

Adolescence is a period of elevated risk to anxiety disorders (Polanczyk et al., 2015), which may be associated with latent inhibition. Indeed, anxiety symptoms in humans are related to deficits in inhibitory learning and memory measured by extinction of conditioned fear (Ganella et al., 2018a; Marin et al., 2017). Like latent inhibition, extinction involves benign exposures to a cue, except that such exposure occurs after the emotional learning (Bouton, 1993). Adolescents have been shown to display extinction impairments compared to adults in rats and humans (Ganella et al., 2017a, 2018a; Ganella and Kim, 2014; Pattwell et al., 2012, 2013; Zbukvic et al., 2017). One study has shown that postnatal day 35 (P35) adolescent male rats indeed show latent inhibition, as measured by conditioned suppression of licking behavior in response to a tone CS that was paired with shocks (Zuckerman et al., 2003). However, latent inhibition has not yet been directly compared between adolescents and adults, which is the first aim of the present study. We hypothesize that the behavior of adolescents and adults will be differentially affected by latent inhibition because vulnerability towards anxiety disorders in adolescence (McGrath et al., 2023) has long been associated with the reduced function of medial prefrontal cortex (mPFC), which undergoes dramatic changes in structure and neurochemistry across adolescence (Casey et al., 2008; Kim et al., 2017; Perry et al., 2021; Gold et al., 2020). Notably, previous literature in rats gives rise to opposing predictions. On the one hand, temporary inactivation of the infralimbic cortex (IL) of mPFC led to deficits in latent inhibition (Lingawi et al., 2016, 2018), which suggests that latent inhibition would be impaired in adolescence. On the other, IL lesions facilitated latent inhibition (George et al., 2010), which suggests that latent inhibition would be facilitated in adolescents. Moreover, mPFC lesions did not affect latent inhibition in other studies (Joel et al., 1997; Lacroix et al., 1998) suggesting that latent inhibition may be comparable in adolescent and adult rats.

The second aim of the present study is to assess latent inhibition in males and females. Biological sex is a significant factor for anxiety disorders, with greater prevalence reported within the female population (Kessler et al., 2005). Sex differences in inhibitory learning and memory have been observed (Milad et al., 2009), although this effect is strongly mediated by hormonal effects/estrous cycle in female rodents and humans (Lebron-Milad et al., 2012; Graham and Milad, 2013). Interestingly, these estrous cycle effects are age dependent. Stages where there are high levels of estradiol are associated with improved extinction in adult females (Lebron-Milad et al., 2012; Graham and Milad, 2013), and impaired extinction in adolescent females (Perry et al., 2020). In addition, sex effects in extinction have been associated with differences in mPFC function (Day et al., 2020). Hence, latent inhibition may also be sex-specific. To our knowledge, there have been no studies that have examined latent inhibition of conditioned fear in female rodents. We hypothesize females will show age-specific effects of estrous cycle on latent inhibition. Specifically, latent inhibition would be greater when adult rats are in proestrous (i.e., when estradiol levels are high), while the opposite may be true in adolescent rats.

2 Materials and methods

2.1 Subjects

Male (26 adults and 22 adolescents) and female (44 adults and 37 adolescents) Sprague Dawley rats were bred in-house at the Florey Institute of Neuroscience and Mental Health. All rats were weaned at P21 and housed for the remainder of experimental procedures in groups of 3–6, with same-sex littermates in individually ventilated cages under a 12/12 h cycle (lights on at 7 a.m.) with food and water available *ad libitum*. All behavioral testing occurred during the light phase. On the first day of behavioral experimentation, rats in the adolescent groups were P35 ($\pm$ 1), while rats in the adult groups were P70–P98. All rats were handled three times prior to commencement of behavioral experimentation. All procedures were approved by the Animal Care and Ethics Committee at the Florey Institute of Neuroscience and Mental Health in accordance with the guidelines for animal use set out in the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* (8th edition, 2013).

2.2 Apparatus

All behavior occurred in Contextual Near Infra-Red Fear Conditioning and Video Freeze system (Med Associates, VT, United States), which provides scrambled direct current footshocks. The dimensions of the chambers and the grid floor were as described previously (Zbukvic et al., 2017). A white house light was on during all sessions, and chambers were cleaned with 80% v/v ethanol and dried thoroughly between tests with rats being placed 5 min after drying.

2.3 Procedure

2.3.1 Pre-exposure

On day 1, all rats were placed in the novel chambers. Following a 2-min baseline period, rats in group "pre-exposure" were presented with 45 tones (5,000 Hz, 80 dB), which served as the conditioned stimulus (CS). Each CS presentation was 10 s,

with an inter-trial interval (ITI) of 10 s with 2-min post-tone period followed by the rats being returned to their home cages, which is standard in our laboratory for the first day of behavior in developing rats (Park et al., 2020; Luikinga et al., 2019). Such protocol was developed to allow some time to adjust at the end of the first behavioral session. Rats in group "No pre-exposure" were placed in the chambers for the same length of time (19 min), however, no tones were delivered.

2.3.2 Conditioning

On day 2, all rats were placed in the same chamber as the previous day. We used a fear conditioning protocol that produces robust freezing to the tone that persists to subsequent sessions in developing and adult rats (Ganella et al., 2017b, 2018b; Park et al., 2017). Following a 2 min baseline period the CS was presented for 10 s, co-terminating with a 1 s footshock (the unconditioned stimulus, US). This CS-US pairing was repeated three times with an ITI averaging 110 s, with 2-min post-shock period followed by the rats being returned to their home cages, which is standard in our laboratory to allow some time to adjust after the shock (Park et al., 2020; Luikinga et al., 2019). The intensity of the shock was different between Experiment 1 (males) and Experiment 2 (females). For males, the US was a 0.45 mA shock. Pilot data from the laboratory showed that this intensity produced robust freezing and reliable latent inhibition. However, for female rats, the US was 0.6 mA because pilot data showed that a 0.45 mA shock failed to produce robust freezing across conditioning and at test.

2.3.3 Test

On day 3, all rats were placed in the same chamber as the previous day. As for the previous sessions, there was a 2-min baseline period after which the 10 s CS was presented 20 times in the absence of any footshock. ITI was 10 s.

2.3.4 Estrous phase monitoring

For Experiment 2, vaginal lavages were taken from female rats 1 h after each behavioral session as described previously (Perry et al., 2020). Briefly, a pipette tip containing 20 μL of saline was used to flush the vagina two or three times if the vagina was opened. The fluid collected was dried on a microscope slide then stained with a 4% (v/v) methylene blue solution. Slides were then rinsed twice with distilled water, air dried, and observed under a light microscope (10 × magnification, Olympus BH-2). Slides were cross-checked by two independent researchers in a double-blind manner. They were categorized according to the proestrus, estrus, metestrus, and diestrus cycle using the morphology of cells and their relative cellular proportions (Cora et al., 2015). Rats in diestrus and metestrus were pooled together for statistical analyses as reported previously (Perry et al., 2020; Hecht et al., 1999), due to their similarities in rising levels of estrogen and the relatively short length of metestrus (Westwood, 2008).

2.4 Data analysis

All analyses were carried out using SPSS (IBM Corp., NY, United States). Percent freezing from all behavioral sessions was subjected to analysis of variance (ANOVA) or repeated-measures (RM) ANOVA. *Post hoc* analyses of simple effects using the Bonferroni correction were used to explain significant interactions wherever appropriate (Drummond et al., 2021). For analysis of CS-elicited freezing during pre-exposure, percent freezing across CS trials were averaged. For group No pre-exposure that did not receive any CS trials during the pre-exposure session, freezing was calculated for the matching periods as the group Pre-exposure. For analysis of CS-elicited freezing during conditioning, the first 9 s of each CS-US trial was used to discount the effects of shock on movement during the last second of each CS-US trial. Freezing during test was blocked into five CS presentations to result in four blocks. For all analyses in females, estrous phase at each behavioral session was included as a factor to account for potential hormonal effects. Metestrus and diestrus were pooled into a single group due to the shortness of metestrus phase as reportedly previously (Perry et al., 2020). Speed measurements of the rat center of mass were used to determine shock responsivity to the US and occurrences of darting to the CS (Carroll et al., 2025; Mitchell et al., 2024). Using DeepLabCut [version 3.0.0rc10; (Mathis et al., 2018; Nath et al., 2019)], 200 frames from ∼90% randomly selected videos from conditioning and test were assigned a tracking point to the rat center of mass. Using these annotated frames, the DeepLabCut markerless tracking model was generated using the ResNet50 neural network for 200 epochs using the PyTorch engine. All videos from conditioning and test were analyzed with this model then fed into the Simple Behavioral Analysis software [SimBA; (Goodwin et al., 2024)] to calculate speed (cm/s). Shock sensitivity was calculated as speed of movement during 1 s shock averaged across trials. Darting was defined as movement across the chamber at or exceeding 20 cm/s during the CS as previously described (Mitchell et al., 2024).

3 Results

3.1 Baseline freezing

Freezing was recorded during the 2-min baseline periods for all sessions, which was clearly low during each session (Figures 1, 2 and Table 1). However, 2-way ANOVAs (Age × Pre-exposure) revealed significant main effects of Age during the conditioning baseline period for Experiment 1 [$F(1,77) = 4.85$, $p = 0.03$] and Experiment 2 [$F(1,77) = 6.58$, $p = 0.01$], with adolescents freezing more than adults in both experiments. Neither the Pre-exposure main effect nor the Age × Pre-exposure interaction were significant in any of the three sessions in any experiment (p's > 0.05). In fact, prior to experiencing the first shock (i.e., across Pre-exposure session and Conditioning baseline), freezing in both sexes was very rarely observed (Table 1). During baseline, most rats showed 0% freezing. As such, the significant main effect of Age appears to be driven by the lack of variability and are unlikely to be meaningful.

3.2 Adolescent males show greater propensity for latent inhibition compared to adult males

Freezing during pre-exposure session was low, regardless of whether rats were presented with the CS or not (Figure 1A).

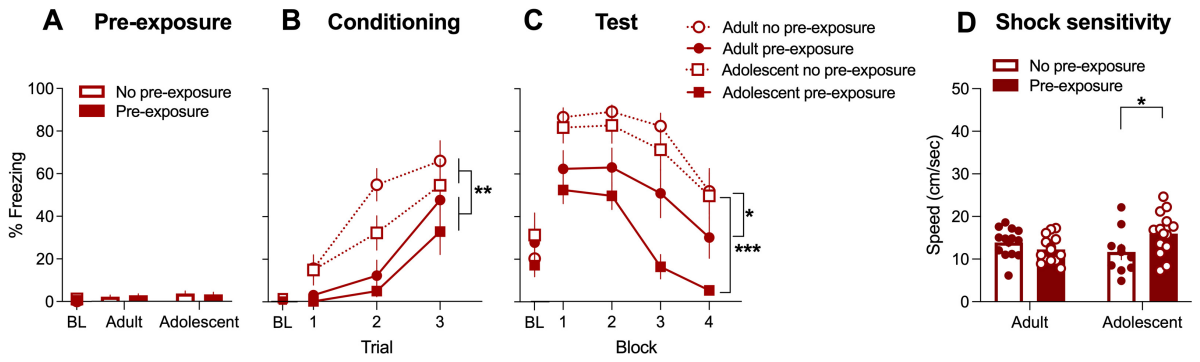

FIGURE 1
Baseline and CS-elicited freezing across **(A)** pre-exposure, **(B)** conditioning and **(C)** test sessions and **(D)** shock sensitivity in males. During conditioning, pre-exposed rats showed lower freezing compared to non-pre-exposed rats (main effect of Pre-exposure $^{**}p < 0.001$), however, there were no differences between adults and adolescents. At test, both adults and adolescents in the pre-exposed condition showed lower freezing compared to non-pre-exposed counterparts, however, this effect was greater for adolescents (significant Age × Pre-exposure interaction, post-hoc tests $^{*}p < 0.05$, $^{***}p < 0.0001$). Pre-exposed adolescent rats showed greater shock sensitivity than non-pre-exposed adolescents (significant Age × Pre-exposure interaction, post-hoc tests $^{*}p < 0.05$], whereas this effect was not evident in adult rats. BL, baseline.

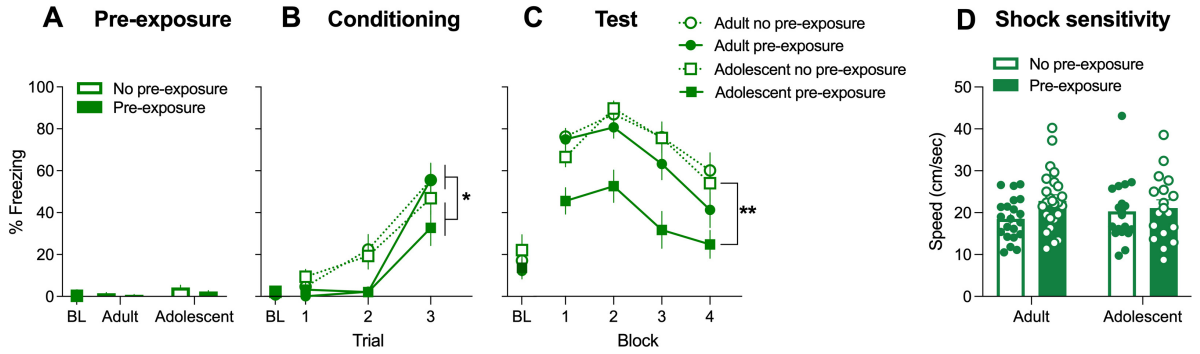

FIGURE 2
Baseline and CS-elicited freezing across **(A)** pre-exposure, **(B)** conditioning and **(C)** test sessions and **(D)** shock sensitivity in females. During conditioning, pre-exposed rats showed lower freezing compared to non-pre-exposed rats (main effect of Pre-exposure $^{*}p < 0.05$), however, there were no differences between adults and adolescents. At test, only adolescents in the pre-exposed condition showed lower freezing compared to Non pre-exposed counterparts (significant Age × Pre-exposure interaction, post-hoc tests, $^{**}p < 0.05$). There were no group differences in shock sensitivity. BL, baseline.

Two-way ANOVA (Age × Pre-exposure) of freezing during pre-exposure confirmed no main effect of Pre-exposure and no Age × Pre-exposure interaction (p's > 0.05) indicating that the pre-exposure to the CS does not trigger freezing in adolescent and adult male rats. There was also no main effect of Age ($p > 0.05$).

Conditioned stimulus-elicited freezing during conditioning (Figure 1B) was analyzed using repeated measures ANOVA (Age × Pre-exposure x Conditioning trial). Mauchley's Test of Sphericity indicated that the assumption of sphericity had been violated ($p < 0.001$), and therefore a Greenhouse-Geisser correction was applied to all repeated measures analyses. There were significant main effects of Conditioning trial [$F(2, 44) = 37.33$, $p < 0.001$] and Pre-exposure [$F(1, 44) = 16.80$, $p < 0.001$]. The main effect of Age was not significant [$F(1,44) = 3.18$, $p = 0.08$]. None of the two-way interactions, nor the three-way interactions were significant (p's > 0.05). Thus, all rats significantly increased CS-elicited freezing across the conditioning trials, with pre-exposed groups overall freezing less than no pre-exposure groups regardless of age.

Figure 1C shows freezing during the 20 CS presentations at test, binned into blocks of five CS presentations. Three-way ANOVA (Age × Pre-exposure x Block) revealed significant main effects of Age [$F(1,44) = 4.865$, $p < 0.05$], Pre-exposure [$F(1,44) = 38.983$, $p < 0.001$] and Block [$F(3,44) = 69.25$, $p < 0.001$]. There was a significant Age × Pre-exposure interaction [$F(1,44) = 11.87$, $p = 0.001$], and although Block × Pre-exposure interaction was significant [$F(3,44) = 3.23$, $p < 0.05$], Age × Block × Pre-exposure was not ($p > 0.05$). The post hoc analysis revealed that although latent inhibition was expressed for both adults and adolescents (i.e., there was a significant difference between pre-exposed and non-pre-exposed rats), this effect was greater for adolescents compared to adults [Adults: 95% CI (0.40, 30.76); Adolescents; 95% CI (37.42, 70.47)]. Furthermore, freezing for the pre-exposed rats was greater than non-pre-exposed rats at all four blocks (all p's < 0.001). Taken together, adolescent male rats showed greater latent inhibition following a protocol than adult males, and reduced freezing at test was due reduced retrieval of fear in pre-exposed rats that was apparent from the first block of CS presentations.

TABLE 1 Mean (SEM) baseline freezing expressed as a percentage of total baseline period each behavioral session.

	Pre-exposure	Conditioning	Test
Males			
Adult: no pre-exposure	0.3 (0.2)	1.6 (0.6)	20.3 (7.4)
Adult: pre-exposure	0.3 (0.1)	1.3 (0.5)	27.8 (8.8)
Adolescent: no pre-exposure	1.2 (0.5)	1.7 (0.5)	31.4 (10.9)
Adolescent: pre-exposure	0.5 (0.3)	0.6 (0.3)	17.2 (5.7)
Females			
Adult: no pre-exposure	1.5 (0.3)	1.0 (0.5)	17.1 (6.3)
Adult: pre-exposure	0.8 (0.2)	0.5 (2.7)	12.2 (3.9)
Adolescent: no pre-exposure	4.3 (1.1)	2.2 (0.7)	22.2 (7.5)
Adolescent: pre-exposure	2.4 (0.4)	1.8 (0.5)	13.7 (4.3)

Note that there was a significant difference between adolescents and adults (averaged across pre-exposure condition i.e., main effect of Age) on the Conditioning day only ($p < 0.5$). However, this constitutes a difference of 0.3% freezing for males and 1.2% freezing for females, which is negligible compared to freezing levels once shock has been experienced, and is unlikely to constitute a biologically meaningful difference.

Shock sensitivity averaged across three shock exposures (Figure 1D) was analyzed using two way ANOVA (Age × Pre-exposure). There were no main effects for Age nor Pre-exposure [$F(1,44) = 0.35$ and 1.13, respectively, p's > 0.05], however, there was a significant Age × Pre-exposure interaction [$F(1,44) = 5.38$, $p < 0.05$]. Bonferroni-corrected simple effects revealed greater sensitivity to shock in pre-exposed compared to non-pre-exposed adolescent ($p < 0.05$), but not adult ($p = 0.353$). This indicates that the interaction was driven by increased shock sensitivity in pre-exposed group for adolescents only. Darting was negligible across both conditioning and test (only a single dart of moving across the chamber in all the groups was recorded during conditioning and test). Therefore, this behavior could not be analyzed.

3.3 Adolescent females show propensity for latent inhibition compared to adult females

Three-way ANOVA of freezing during pre-exposure showed no significant main effects nor interactions of Age, Pre-exposure, and Estrous (p's > 0.05). These results suggest that the pre-exposure to the CS and different estrous phases do not elicit freezing in adolescent and adult female rats (Figure 2A).

Conditioned stimulus-elicited freezing during conditioning (Figure 2B) was analyzed using repeated measures ANOVA (Age × Pre-exposure × Estrous × Conditioning Trial). Mauchley's Test of Sphericity indicated that the assumption of sphericity had been violated ($p < 0.001$), and therefore a Greenhouse-Geisser correction was applied to all repeated measures analyses. Similarly, to males, there was a main effect of Conditioning trial [$F(2,136) = 73.23$, $p < 0.001$], indicating freezing increased across repeated trials. There also was a main effect of Pre-exposure [$F(1,68) = 8.28$, $p = 0.005$], showing that freezing across the three CS presentations was overall lower following pre-exposure to the stimulus. Main effects of Age and Estrous phase were non-significant [$F(1,68) = 1.34$, $p = 0.25$; $F(3,67) = 0.24$, $p = 0.87$, respectively]. There were no two, three nor four-way significant interactions (p's > 0.05).

Figure 3C shows freezing during the 20 CS presentations at test, binned into blocks of five CS presentations. Four-way (Age × Pre-exposure × Block × Estrous) ANOVA revealed a main effect of Pre-exposure [$F(1,68) = 12.052$, $p < 0.001$] and Pre-exposure × Age interaction [$F(1,68) = 5.00$, $p < 0.05$]. Main effects of Age and Estrous were not significant [$F(1,68) = 3.94$, $p = 0.051$; $F(3,68) = 1.15$, $p = 0.33$, respectively]. Main effect of Block was significant [$F(3,68) = 27.87$, $p < 0.001$], however, there were no significant interactions involving Block (two, three, and four-way Block interaction p's > 0.05). There were no significant interactions involving Estrous (p's > 0.05). Since there were no interactions with Estrous, we determined the simple effects averaging across Estrous phase. These showed that there was no significant effect of Pre-exposure for adults [$p = 0.86$, 95% CI (−21.55, 17.99)], where there was for adolescent female rats [$p < 0.001$, 95% CI (17.77, 59.69)]. Therefore, as with male rats, the latent inhibition effect was greater in adolescent female rats when compared with adults. Lack of interaction with Block showed that this was due to reduced retrieval of fear in Adolescent pre-exposed rats from the first CS presentation.

Shock sensitivity averaged across three shock exposures (Figure 2D) was analyzed using two-way ANOVA (Age × Pre-exposure). There were no main effects for Age nor Pre-exposure [$F(1,68) = 0.01$ and 2.55, respectively, p's > 0.05], nor was there a significant Age × Pre-exposure interaction [$F(1,68) = 1.17$, $p > 0.05$]. Darting was not observed and could not be analyzed.

In order to verify that rats were cycling, we analyzed changes in proportion of rats in each phase across behavioral days as previously reported (Perry et al., 2020). As expected, adult females showed significant [$\chi 2(4,44) = 11.07$, $p < 0.05$] changes in the proportion of estrus phases (Figure 3A) whereas adolescent females did not [$\chi 2(6,37) = 5.60$, $p = 0.47$] (Figure 3C). Examination of individual rats revealed that many adolescent rats have not begun estrus cycling (Figure 3D). Interestingly, the adolescents that have begun cycling and adults largely showed similar expected pattern of 2–3 days met/diestrus, ∼1 day of proestrus and ∼1 day of estrus (Figures 3B, D), unlike the previous study in which adolescents showed much more erratic cycling (Perry et al., 2020). Average freezing levels were graphed for each phase (Figure 3D). We could not analyze the data (even with excluding unopened groups) because there were 0–1 rats for some phases in each session. There appears to be very little impact of estrous phase within groups.

4 Discussion

The aim of this study was to examine age differences (adolescent vs. adult) in latent inhibition in male and female rats. We found that adolescents were more likely to display evidence of latent inhibition when compared to adults, with lower levels of freezing shown in adolescents compared to adults in the pre-exposed rats. These findings do not exclude that latent inhibition occurs for adults as well, since there is evidence of delayed conditioning in the pre-exposed rats on day 2 regardless of age and

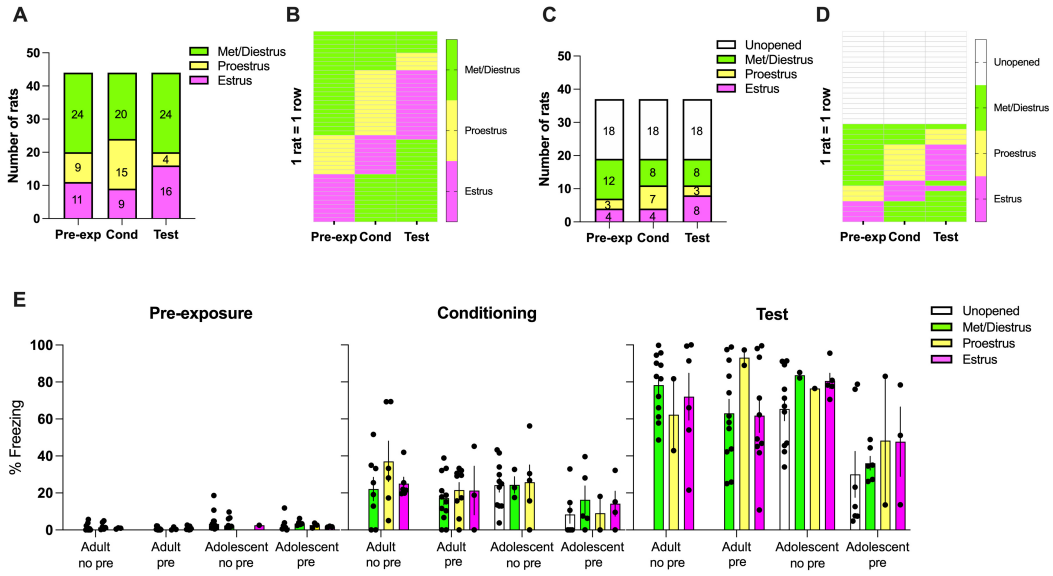

FIGURE 3
Estrous cycle information for adult and adolescent females. The number of **(A)** adult and **(C)** adolescent rats in each estrous phase on pre-exposure, conditioning and test days. Progression of individual **(B)** adult and **(D)** adolescent rats in estrous phase across experimental days. Each row represents one rat. **(E)** Average freezing on each day with respect to group and estrous phase on that day. Pre, pre-exposure, No pre, no pre-exposure.

sex (Figures 1, 3). This delayed learning was not due to decreased sensitivity to the shock as a result of pre-exposure to the CS. If anything, pre-exposed animals showed greater sensitivity, although this effect was only evident in adolescent males. Thus, during pre-exposure both adults and adolescents had learned that the CS has no aversive consequence, and this learning delays acquisition of the CS-shock association similarly across age groups. However, the effect of the initial experience is clearly more enduring for adolescents, since pre-exposure was more likely to reduce fear expression on day 3 in that age group. Surprisingly, despite previous studies that fear learning is affected by sex hormones (Graham and Milad, 2013, 2014; Perry et al., 2020), we found no effect of estrous in our female rats.

The enhanced latent inhibition observed here in adolescents is similar to effects seen following experimental lesion of the IL (George et al., 2010). Compared to other brain regions, the mPFC is last to reach maturity in rodents and humans (Casey et al., 2008; Kim et al., 2017; Gogtay et al., 2004; Giedd, 2004; Bjerke et al., 2025). It is therefore possible that the enhanced latent inhibition effect observed here in adolescents may be due to reduced functionality in the IL mPFC, which led to stronger effects of pre-exposure. When IL lesions facilitated latent inhibition, George et al. (2010) argued that the role of IL is to allow the learning of a second, conflicting information about a cue. As such, IL hypofunction during adolescence results in enhanced latent inhibition because the second association (cue-shock) is not encoded properly. Such a role for IL is also consistent with previous studies showing impaired extinction and reduced IL function in adolescents (Ganella et al., 2018a; Kim et al., 2011). In contrast, others have shown that temporary inactivation of the IL inhibited retrieval of latent inhibition (Lingawi et al., 2016, 2018). The differences in findings may be explained by specific methodology. In George et al. (2010), IL lesions occurred prior to any behavioral training. Thus, function was impaired across pre-exposure and at test. When IL inactivation only occurred immediately prior to retrieval test (Lingawi et al., 2016, 2018), IL function would have been intact during pre- exposure. From this, IL may be critical for remembering the latent inhibition memory once pre-exposure and conditioning have already occurred. In our study, assumed IL hypofrontality was due to developmental stage rather than experimental manipulation, hence would have been present during pre-exposure and conditioning as with George et al. (2010).

Importantly, brain maturation is not restricted to the IL and the present results may be due to dopamine signaling in the nucleus accumbens (NAc). A recent study showed that cue-elicited dopamine release in the NAc core was directly linked to latent inhibition (Kutlu et al., 2022). Specifically, exposure to the cue evokes dopamine release, which declines with repeated exposures across the pre-exposure session. Therefore, during conditioning, the pre-exposed cue evokes a smaller dopamine release than the non-pre-exposed cue, meaning that it is less able to form an association with the US (Kutlu et al., 2022). At conditioning, intra-nucleus accumbens (NAc) injections of amphetamine attenuated, while a dopamine receptor 2 (D2) antagonist (haloperidol) enhanced latent inhibition (Joseph et al., 2000). However, intra-mPFC injection of amphetamine or apomorphine had no effects (Lacroix et al., 2000; Broersen et al., 1999). Furthermore, deficits in latent inhibition of conditioned fear due to adolescent social isolation were associated with increased D2 expression in the mPFC and NAc (Han et al., 2012). Conversely, a dopamine receptor 1 (D1) agonist administered systemically prior to pre-exposure and conditioning sessions mildly inhibited latent inhibition of fear conditioning (Feldon et al., 1991). A D1 antagonist (SCH23390) administered alone had no effect, but did block amphetamine-induced disruption of latent inhibition (Nelson et al., 2012). In summary, attenuated D1 or D2 signaling appears to promote latent inhibition, which can explain the present age differences observed with D1 reduced in the ventral striatum but not mPFC

in adolescence compared to adulthood (Bjerke et al., 2025; Cullity et al., 2019). Future studies should look at differential effects of D1 and D2 receptor modulators in adults and adolescents in order to better understand these effects.

Latent inhibition involves targeted redirection of attention following pre-exposure to the stimulus (Colagiuri et al., 2021; Lubow, 2005). In other words, there is decreased attention directed towards to the target stimulus following pre-exposure, making it less available for association to the US in subsequent conditioning sessions. Children with attention deficit hyperactivity disorder showed reduced latent inhibition compared to controls in a discrimination task (Lubow and Josman, 1993) and a visual search task (Lubow, 2005). Within this context, the current findings suggest that adolescents were more able to attend to non-predictive stimuli than adults. However, we also observed that both adults and adolescents acquired conditioned fear to the non-pre-exposed stimulus, meaning that both ages are equally able to attend to a stimulus when it is novel. Further, the age difference in latent inhibition only emerged at test, which suggests a retrieval rather than an encoding effect. Nevertheless, this does not rule out that a weaker association was formed between the pre-exposed CS and the US due to increased attention in the adolescent group.

We did not find any effects for estrous cycle during conditioning or at test. In contrast, extinction is impacted by the estrous phase (Milad et al., 2009; Perry et al., 2020), and by the experimental manipulation of gonadal hormones (Perry et al., 2020; Zeidan et al., 2011; Maeng et al., 2017). Interestingly, this effect on extinction is also apparently age-dependent, because in adults high levels of estrogen facilitate extinction (Milad et al., 2009; Maeng and Milad, 2015; Velasco et al., 2019), while in adolescents extinction is facilitated where estrogen is not present/present at low levels (Perry et al., 2020). In the current study there were no differences in latent inhibition reported where rats were at different stages of estrous cycle, regardless of age. This suggests that interference between a benign memory and a traumatic experience is not dependent on cycling gonadal hormones and implies that there are distinct neural mechanisms underlying extinction and latent inhibition. Notably, the present study observed overall reduced variation in estrous cycling in adolescents due to many animals staying unopened throughout the behavioral days, which is different from the previous study in which the adolescent female rats of the same age were much more variable in their estrus phases (Perry et al., 2020). It is possible that testing adults and adolescents together as in the present study affected estrous cycling, as previous studies have shown female rats in proximity can affect their estrous phase (Alekhina et al., 2015). Different outcomes may be observed if the adolescent and adult females are not concurrently tested.

A limitation of this study is that male and female cohorts were run in separate experiments, meaning that direct statements regarding sex differences cannot be made. We chose to treat the two cohorts as separate experiments due to differences in shock sensitivity. Specifically, male rats showed robust freezing and latent inhibition effect (at least for adolescents) using a 0.45 mA shock, while for females freezing was unreliable using these parameters, and the shock needed to be increased to 0.6 mA in order to obtain reliable conditioning. Sex differences in sensitivity to footshock and consequent conditioning have been observed previously (Stock et al., 2001; Gupta et al., 2001; Wiltgen et al., 2001; Baran et al., 2009), although this is not always the case (Orsini et al., 2016). Sex differences in latent inhibition have been reported for a conditioned taste aversion whereby adult female rats showed weaker latent inhibition than males (Angulo et al., 2020; Angulo and Arévalo-Romero, 2021). Interestingly, the same study saw delayed extinction in males compared with females (Angulo and Arévalo-Romero, 2021), which is different from what we (Perry et al., 2020) and others (Velasco et al., 2019) have observed. Furthermore, human participants did not show sex differences in latent inhibition for a discrimination task (Lubow and Josman, 1993). Indeed, it is possible that sex specificity of latent inhibition is task-dependent.

Notably, all sessions occurred in the same context in the present study, which means that latent inhibition of context conditioning may have occurred (Killcross et al., 1998; Westbrook et al., 1994; Kiernan and Westbrook, 1993). That is, prolonged pre-exposure to a context can reduce subsequent conditioning in that context. However, typical latent inhibition of contextual conditioned fear involves extensive pre-exposure to the context, such as 20 min twice a day for 11 days (Killcross et al., 1998). Interestingly, shorter exposure to the context can lead to "context pre-exposure facilitation effect" (Heroux et al., 2018; Fanselow, 1986; Robinson-Drummer and Stanton, 2015), which is increased context conditioned fear when there is a presentation of the footshock as soon as the rodent is placed into the context. Without context pre-exposure, such immediate shock in a context leads to a failure in context conditioning ("immediate shock deficit") (Fanselow, 1986; Robinson-Drummer and Stanton, 2015). Such deficit is not so apparent with discrete cues, highlighting how forming a contextual representation requires longer time than forming a discrete cue representation (Rudy, 1993; Kim and Richardson, 2009). This may be due to the necessity of the different elements in the context to come together to form a spatial representation in contextual learning (Rudy and Sutherland, 1995). In any case, with the inclusion of "No pre-exposure" group that received an identical amount of context exposure as the pre-exposed group, it is unlikely that the present age effects are due to differences in latent inhibition of contextual conditioned fear.

In summary, the current findings show that adolescents show stronger latent inhibition than adults. Latent inhibition serves an adaptive purpose (Lubow, 2005). For example, it helps to focus attention away from stimuli less likely to be relevant in a new situation, thereby preserving cognitive load. It may also prevent too much predictive value being attributed to stimuli that are only salient in passing/in certain contexts. Thus, this facilitated latent inhibition in adolescents reflects experience-dependent resilience as they are able to form robust CS-no-event association that is more readily retrieved following conditioning when the rats are tested in extinction (i.e., safe) conditions (Mineka and Zinbarg, 2006). The fact that age-differences in expression of latent inhibition did not emerge until test (under extinction conditions) provides weight to this interpretation. However, future studies should explore this possibility among others, such as reduced behavioral flexibility and changes in attention, in order to provide a more comprehensive understanding on how learning styles change across development. Anxiety disorders often emerge in adolescence, and this has led to the perspective that adolescents are more vulnerable (Polanczyk et al., 2015; Ganella et al., 2018a; Kim and Ganella, 2015). The current findings show that this story is more complex,

because facilitated latent inhibition may provide resilience against development of anxiety. Notably, this resilience is dependent on experiential factors, since latent inhibition is dependent on prior exposure to the stimuli. In other words, timing of traumatic experiences relative to other experiences across adolescence is critical for determining how much of an impact the trauma will have on subsequent behavior.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was approved by Florey Animal Ethics Committee. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

CJP: Investigation, Supervision, Writing – review & editing, Project administration, Formal analysis, Methodology, Writing – original draft, Data curation, Visualization, Validation. RJ: Investigation, Project administration, Writing – review & editing, Writing – original draft. HT: Methodology, Project administration, Investigation, Writing – original draft. BKR: Formal analysis, software, Writing – review & editing. KD: Methodology, Writing – review & editing. CHP: Supervision, Validation, Writing – review & editing, Methodology. JK: Funding acquisition, Writing – review & editing, Conceptualization, Supervision, Writing – original draft, Resources, Validation, Project administration, Software, Formal analysis, Data curation, Visualization, Methodology.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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