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ORIGINAL INVESTIGATION

Adolescent exposure to Δ9-tetrahydrocannabinol delays acquisition of paired-associates learning in adulthood

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Abstract

Rationale and objectives Adolescence is a sensitive period of brain development, during which there may be a heightened vulnerability to the effects of drug use. Despite this, the long-term effects of cannabis use during this developmental period on cognition are poorly understood.

Methods We exposed adolescent rats to escalating doses of Δ9-tetrahydrocannabinol (THC)—the primary psychoactive component of cannabis—or vehicle solution during postnatal days (PND) 35–45, a period of development that is analogous to human adolescence (THC doses: PND 35–37, 2.5 mg/kg; PND 38–41, 5 mg/kg; PND 42–45, 10 mg/kg). After a period of abstinence, in adulthood, rats were tested on an automated touchscreen version of a paired-associates learning (PAL) task to assess their ability to learn and recall object-location associations. Prepulse inhibition (PPI) of the startle response was also measured at three time points (5 days, 4 months, and 6 months after exposure) to assess sensorimotor gating, the ability to filter out insignificant sensory information from the environment.

Results Compared to rats exposed to vehicle alone, rats exposed to THC during adolescence took longer to learn the PAL task when tested in adulthood, even when trials contained visually identical stimuli that differed only in location. Despite this, no differences were observed later in testing, when trials contained visually distinct stimuli in different locations. Rats exposed to THC also displayed impairments in sensorimotor gating, as measured by prepulse inhibition of the startle response, though this deficit did appear to decrease over time.

Conclusion Taken together, THC exposure during adolescence produces long-term deficits in associative learning and sensorimotor gating, though the impact of these deficits seems to diminish with time. Thus, adolescence may represent a period of neurocognitive development that is vulnerable to the harms of cannabis use, though the stability of such harms is uncertain.

Keywords Adolescence · Cognition · Δ9-Tetrahydrocannabinol (THC) · Paired-associates learning · Prepulse inhibition

Introduction

Cannabis use is common among adolescents (Johnston et al. 2018), which is of particular concern given that adolescence is marked by a vulnerable period of brain maturation (Andersen 2003). During adolescence, the neural circuits that support associative learning and memory mature through processes of myelination and synaptic pruning (Rice and Barone 2000; Spear 2000; Schneider 2013). As a result, adolescents might be uniquely susceptible to the effects of cannabis on neurodevelopment and associated cognitive functions. Indeed, adolescents who regularly use cannabis tend to display performance deficits on verbal and computerized tests of memory (Harvey et al. 2007; Solowij et al. 2008; Solowij and Pesa 2011; Dougherty et al. 2013), which can persist after up to a month of abstinence (Medina et al. 2007; Schweinsburg

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et al. 2008; Hanson and Winward 2010). Despite these observations, the precise impact of cannabis use during adolescence on cognitive function later in life remains unclear. Some have linked adolescent cannabis use to neuropsychological impairment in adulthood (Ehrenreich et al. 1999; Gruber et al. 2012; Meier et al. 2012), though others have found no such direct relationship after controlling for other factors such as education and family background (Fontes et al. 2011; Meier et al. 2018). This disparity in the literature shows that the putative harms of cannabis use during adolescence are not fully understood.

Animal models, observed during developmental periods analogous to adolescence in humans, may be critical to assess the impact of cannabis use during this sensitive period. In rodents, chronic administration of the primary psychoactive component of cannabis (Δ9-tetrahydrocannabinol; THC) during adolescence produces deficits in novel object recognition and social memory (Quinn et al. 2008; Renard et al. 2016), which have been observed up to a month after exposure (Rubino et al. 2009). However, the degree to which THC exposure during adolescence causes enduring impairments in cognitive function, and whether these deficits persist into adulthood, is largely unknown.

To address this, we characterized the enduring effects of THC exposure during adolescence on paired-associates learning (PAL) in adulthood, a test of cognitive function that is sensitive to hippocampal impairment (Talpos et al. 2009, 2014). We exposed rats to escalating doses of THC for 11 days during a period of development that corresponds to human adolescence (Spear 2000). After 1 month of abstinence, we assessed their performance on an automated touchscreen version of the PAL task, analogous to the Cambridge Neuropsychological Test Automated Battery (CANTAB) version used to assess cognition in humans (Sahakian and Owen 1992). The PAL task, in which subjects must learn and recall multiple object-location associations, is sensitive to cognitive impairment resulting from a variety of etiologies, including current and previous drug use (Ersche et al. 2007), focal brain damage (Owen et al. 1995), Alzheimer's disease (Blackwell et al. 2004), and schizophrenia (Barnett et al. 2005). To assess the impact of THC exposure on sensorimotor gating, we also measured prepulse inhibition (PPI) of the startle response at three time points: 5 days, 4 months, and 6 months after THC exposure. We show that rats exposed to THC during adolescence are impaired on the PAL task when tested as adults, after 2 months of abstinence. Although THC exposure caused delayed acquisition of the PAL task, it had no effect on performance in later stages of testing. Furthermore, THC exposure impaired prepulse inhibition of the startle response, though this deficit did appear to decrease over time. These findings suggest that THC exposure during adolescence produces some impairments in associative learning that persist into adulthood.

Materials and methods

Subjects

Adolescent male Long-Evans rats ($n = 29$; Charles Rivers Laboratories, Montreal, QC, Canada) were obtained at postnatal day (PND) 30 and pair-housed in a room maintained on a 12-h light/dark cycle (lights on at 7:00 a.m.). Water and food (Purina Rat Chow) were available ad libitum. During behavioral testing, food was restricted to 20 g (Purina Rat Chow) daily, resulting in a body weight approximately 90% of the free-feeding weight, sufficient to motivate responding on the PAL task. All procedures were approved by the CAMH Animal Care Committee and were in accordance with the guidelines of the Canadian Council on Animal Care. All behavioral testing (paired-associates learning and prepulse inhibition) was conducted in the same groups of rats.

Drug preparation and administration

Rats were injected with either Δ9-tetrahydrocannabinol (THC, $n = 15$) or vehicle solution (i.p., 1 mL/kg; VEH, $n = 14$) twice daily, using an escalating dose schedule: PND 35–37, 2.5 mg/kg; PND 38–41, 5 mg/kg; PND, 42–45, 10 mg/kg (Fig. 1). During this period, rats display a number of adolescent-typical neurobehavioral characteristics including growth spurt, sexual maturation, and the timing of emergence of rats from the protected nest burrow in the wild (Spear 2000). This developmental period was therefore chosen to model the effects of cannabis exposure during early to mid-adolescence in humans. Doses of THC were increased in this manner to counteract drug tolerance (González et al. 2005). This dosing regimen was the same as that used previously elsewhere (Rubino et al. 2009; Renard et al. 2016), and has been shown to produce long-term behavioral impairments in rats. THC was dissolved in a vehicle solution consisting of ethanol, cremophor, and saline (1:1:18). Based on previous studies, it is estimated that this dosing regimen would produce blood THC levels within the range of 10–12 ng/mL at minimum 30 min after injection (Quinn et al. 2008; Klein et al. 2011). These levels of THC are typical for humans smoking cannabis (approximate THC dose 12.7–15.8 mg), which produces blood plasma levels of THC between 11 and 18 ng/mL 30 min later, depending on the THC dose and frequency of cannabis use (Lindgren et al. 1981; Huestis et al. 1992). Although the amount of cannabis that is consumed by humans varies substantially across individuals, given that we administered THC twice daily for 11 days, the doses used in the current study likely represent moderate to heavy use. Following a 28-day drug-free period, PAL testing was initiated on PND 73.

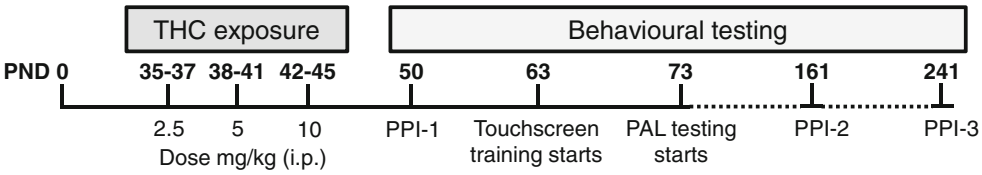

Fig. 1 Timing of mid-adolescent chronic THC treatment and behavioral testing in adult, male rats

Apparatus

Prepulse inhibition Testing was conducted in six startle chambers (SR Lab, San Diego Instruments, San Diego, CA) each mounted in a ventilated enclosure. Each chamber contained a Plexiglas cylinder (8.2 cm in diameter; 20 cm in length) mounted on a platform attached to a piezoelectric accelerometer, which detected and transduced the motion within the cylinder. The auditory stimuli were delivered by a speaker located 24 cm above the cylinder. A single computer controlled all six startle chambers and recorded the data from each.

Touchscreen testing Testing was conducted in four automated operant chambers fitted with a touchscreen monitor (Lafayette Instrument Co., Lafayette, IN) and contained within light- and sound-attenuating enclosures. The chambers were trapezoidal in shape with a clear Perspex lid on top, black Perspex walls, and a stainless-steel grid floor. A 3-W house light was located at the top of the chamber. The touchscreen monitor was located on one end of the chamber, covered by a black Perspex mask containing three response windows (10 × 6 cm) designed to restrict the rats' access to the touchscreen. The touchscreen was fixed above a spring-hinged platform (depth 6 cm; width 20.5 cm) for rats to rear onto (15 cm above the grid floor) to help orient the rats' attention to the monitor. Opposite to the touchscreen monitor was an automated pellet dispenser equipped with infrared-beams to detect entries and an LED light. The pellet dispenser delivered dustless 45-mg sucrose pellets (Bio-Serv, Flemington, NJ). The operant chambers were controlled using an IBM computer running Windows 7 using ABET II Touch software (Lafayette Instrument Co., Lafayette, IN).

Experimental procedures

Touchscreen training Rats were trained to use the touchscreens using a modified protocol adapted from Talpos et al. (2009, 2014). Touchscreen training began 18 days after the final day of THC exposure (PND 63; Fig. 1) to minimize any potential residual effects of THC. First, rats were habituated to the testing chambers for 20 min, with the fans turned on, and sucrose pellets placed throughout the chamber (typically 1 session). During reward training, rats learned to associate the delivery of a sucrose pellet with illumination of the reward tray every 30 s (one trial), with reward collection triggering the start of the next trial. Additionally, visual stimuli (white squares) were displayed in each of the three response windows of the touchscreen, with touch responses producing delivery of three sucrose pellets. Reward training continued until rats completed 50 trials within 40 min (~ 2 sessions). Next, during the touch training phase, rats were required to respond (e.g., nose poke) to a white square stimulus randomly displayed in one of three response windows of the touchscreen, which caused delivery of a sucrose pellet signaled by illumination of the reward tray. A new trial was initiated 5 s after the collection of a reward pellet. Touch responses to the other two response windows of the touchscreen had no programmed consequences. Touch training continued until 50 trials were completed within 40 min (~ 3 sessions). Finally, during the initiation training phase, rats were required to initiate each trial by making a nose poke response into the reward tray to trigger the display of the white square stimulus on the touchscreen. All other aspects of the initiation training phase were otherwise identical to the touch training phase. Initiation training continued until 50 trials were completed within 40 min (~ 1 session). At this point, rats progressed to paired-associates learning.

Paired-associates learning PAL testing began 28 days after the last day of THC exposure (Fig. 1). In the PAL task (Fig. 2), rats learned that each of three visual stimuli (flower, airplane, spider) is rewarded only when it is displayed in any one of three specific locations on the screen (left, middle, right). In any given trial of the PAL task, two visual stimuli are displayed on the screen; one image is displayed in its correct location, while the other is displayed in an incorrect location. In other words, responses to the flower stimulus were correct *only* when it was located on the left; responses to the airplane stimulus were correct *only* when it was located in the middle; and responses to the spider stimulus were correct *only* when it was located on the right (Fig. 2a). First, rats were tested on the same PAL (sPAL) task (Fig. 2b), in which duplicates of one of the three visual stimuli (e.g., flower) were presented in two different locations in each trial. One duplicate stimulus was displayed in its correct location (S+) and responses to this resulted in a reward, while the other was incorrect (S−) and responses to this resulted in a brief time-out. Once rats had acquired the sPAL task (accuracy criterion of 80% across 2 days), they were tested on the different PAL (dPAL) task (Fig. 2c). The dPAL task was functionally similar to the sPAL task except two different visual stimuli were presented in two

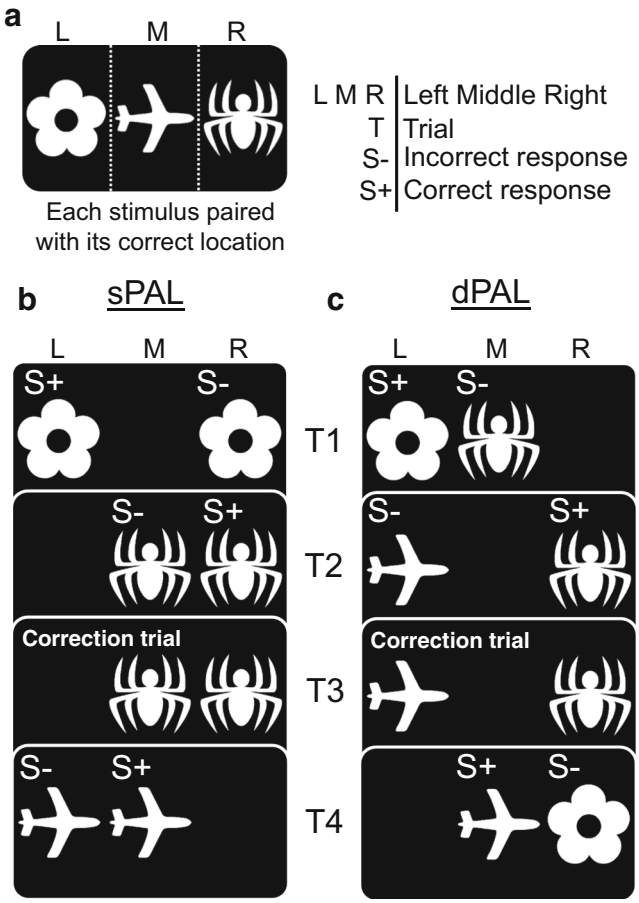

Fig. 2 A schematic depicting the paired-associates learning (PAL) task, including the stimuli used and the different types of trials that occurred. **a** Each stimulus was correct only when it is located in one of three specific locations on the screen (left, L; middle, M; right, R). For example, the flower stimulus is correct on the left side of the screen (L) but not in the middle (M) or on the right (R). **b** In the same PAL (sPAL) task, two identical stimuli were presented in each trial: one was presented in its correct location (S+) while the other was presented in an incorrect location (S−). Rats were required to respond to the S+ to receive a food reward, after which they were presented with a new trial. Responses to the S− resulted in a brief time-out period followed by a correction trial in which the same configuration of stimuli was presented again until a correct response was made. **c** In the different PAL (dPAL) task, two different stimuli were presented in each trial: one was presented in its correct location (S+) while the other was presented in an incorrect location (S−). All other aspects of the dPAL task were identical to the sPAL task

different locations in a given trial, with one in its correct location (S+) and the other in an incorrect location (S−).

Sessions of the PAL task began with the reward tray illuminated, which rats could nose poke to initiate a trial. The nose poke response extinguished the reward tray light and produced the display of visual stimuli (S+ and S−) on the touchscreen monitor. Responses made to the S+ caused delivery of a reward pellet, illumination of the reward tray, and removal of the stimuli from the screen. Collection of the reward pellet deactivated the reward tray light and initiated the 10-s intertrial interval (ITI), after which the reward tray was illuminated and a new trial could be initiated with a nose poke response. Responses made to the S− (an error) initiated a 10-s time-out period, in which the stimuli were removed from the screen and the house light was extinguished. The time-out period was followed by a 10-s ITI, during which time the house light was illuminated. Following an error, after the ITI, the reward tray was illuminated and nose poke responses to it initiated a correction trial. In a correction trial, the same S+ and S− stimuli were displayed in the same location as they were in the previous trial. Correction trials were not counted toward the total number of trials completed nor were they included in accuracy calculations. Errors committed during standard trials (errors) were counted separately from errors committed during correction trials (correction errors). The total number of correction trial errors made to criterion that a rat commits represents their tendency to respond in a perseverative fashion despite an absence of positive reinforcement. In contrast, the total errors (non-correction) to criterion reflects the number of errors rats made on trials that contain randomly selected stimuli (potentially the same or different as the previous trial), which is a more accurate measure of task performance.

Each PAL session lasted for a maximum of 40 min or completion of 50 trials (excluding correction trials). Rats were tested on the sPAL task until they reached an accuracy criterion of 80% averaged across 2 days (excluding correction trials). Then, rats were tested on the dPAL task until they achieved an accuracy criterion of 80% averaged across 2 days (excluding correction trials).

Prepulse inhibition The same groups of rats tested on the PAL task were used to assess the effects of adolescent exposure to THC on PPI. The task parameters for PPI were adapted from Tenn et al. (2005). Rats were acclimatized to the startle chambers for 10 min with a 65-dB background of white noise. First, rats were presented with a series of five startle pulse-alone (110 dB) trials. This was followed by 64 randomized trials containing eight trial types presented eight times each. These trials consisted of either no pulse (0 dB, no additional stimuli other than the background noise), startle pulse alone (110 dB; 40 ms), or three prepulse intensities (70, 75, and 80 dB; 40 ms) presented alone or 100 ms preceding a startle pulse. The session finished with another series of five startle pulse-alone trials. The intertrial interval ranged from 10 to 20 s. The startle response (mV) was measured every 1 ms for a 100-ms period following the onset of the startle stimulus. The percentage PPI was calculated as $\%PPI = 100 \times (1 - PreS/S)$ where "*PreS*" is the mean startle response for prepulse plus startle trials and "*S*" is the mean startle response for the startle pulse-alone trials. All rats were tested at three time points (Fig. 1): 5 days after THC exposure (PND 50), 4 months after THC exposure (PND 161), and 6 months after THC exposure (PND 241).

Data analysis

The primary variables measured in the sPAL and dPAL tasks were the number of sessions to criterion, total errors committed during trials (errors) to criterion, total errors committed during correction trials (correction errors) to criterion, mean response latency (time from display of the stimuli on the screen to a response at the screen), and mean reward latency (time from delivery of a reward to its collection). Latencies were averaged for each rat across individual sessions as well as across all sessions completed to criterion. Mixed repeated measures ANOVAs or independent samples *t* tests were used to assess the significance of effects related to THC exposure during adolescence. A two-way ANOVA was used to assess the effect of THC exposure during adolescence on PPI using three different prepulse intensities (70, 75, and 80 dB) at three time points relative to the THC exposure period (5 days, 4 months, and 6 months). The startle response magnitude recorded during the 110-dB pulse-alone trials was analyzed at each time point using an independent samples *t* test. To compare the proportion of rats that acquired the sPAL and dPAL task criteria across sessions, a log-rank Mantel-Cox test was applied to each. In all cases, assumptions of the ANOVA procedure or *t* test including sphericity and equality of variances were assessed with Mauchly's test or Levene's test, respectively. Wherever these assumptions were violated, the *F* or *t* scores were tested against more restrictive degrees of freedom. Post hoc analyses were performed with Fisher's LSD test.

Results

Touchscreen training Relative to rats exposed to vehicle (VEH) alone, adult male rats exposed to THC during adolescence did not take significantly longer to learn any phase of the touchscreen training protocols (data not shown). Sample sizes for the PAL data were as follows: THC, $n = 15$; VEH, $n = 14$.

Same paired-associates learning Using the criterion of 80% accuracy across 2 days, the number of sessions required by rats to acquire the sPAL task was compared. Analysis of the percentage of rats that had reached criterion across sessions (Fig. 3a) revealed a significant difference between the rate at which rats exposed to THC or VEH alone during adolescence acquired the sPAL task ($\chi^2 = 3.919$, $p < 0.05$). To investigate this further, a one-tailed *t* test was applied to examine if THC exposure during adolescence increased the number of sessions rats required to reach criterion. Relative to rats exposed to VEH alone during adolescence, rats exposed to THC required significantly more sessions of the sPAL task to reach criterion (Fig. 3b; $t_{(19.2)} = 1.794$; $p < 0.05$; $d = 0.658$).

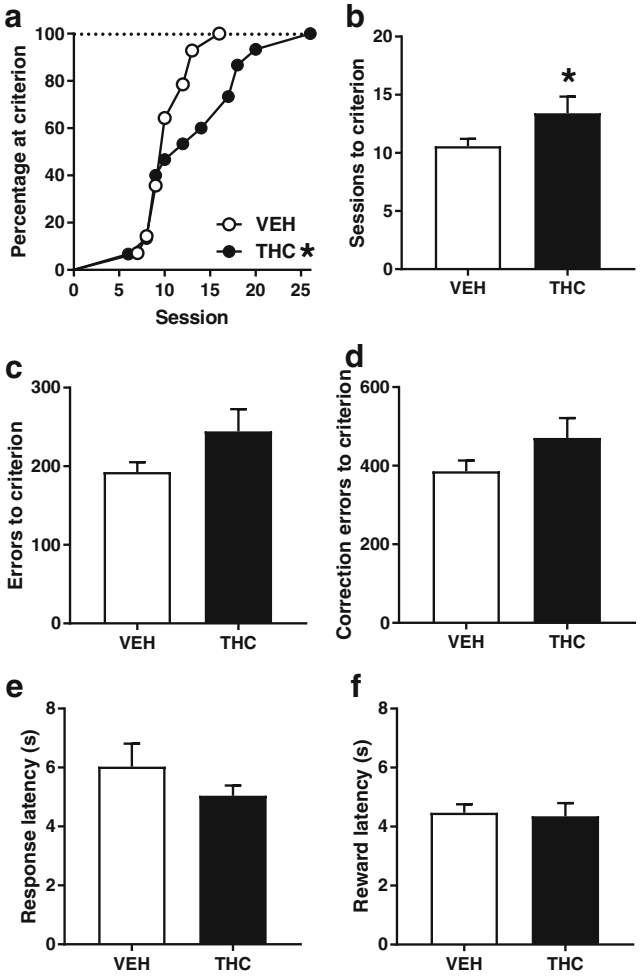

Fig. 3 THC exposure during adolescence delays acquisition of paired-associates learning (PAL) in adulthood when rats are tested on the same PAL (sPAL) phase of the task. Performance of adult, male rats exposed to Δ9-tetrahydrocannabinol (THC; $n = 15$) or vehicle (VEH; $n = 14$) during adolescence on the sPAL. **a** Acquisition of the task depicted as percentage of THC and VEH rats that have reached criterion (80% accuracy for 2 days) across sessions. **b** Number of sessions required to reach criterion. **c** Number of errors made to criterion. **d** Number of correction trial errors made to criterion. **e** Latency (s) to make a response to a stimulus. **f** Latency (s) to collect food reward. All data is presented as mean ± S.E.M. $*p < 0.05$ relative to rats exposed to vehicle during adolescence

Rats exposed to THC during adolescence did not commit more errors in standard trials (Fig. 3c; $t_{(27)} = 1.630$; $p = 0.115$; $d = 0.613$) and correction trials (Fig. 3d; $t_{(27)} = 1.436$; $p = 0.162$; $d = 0.539$) on the sPAL task. No differences were observed in the latency to make a response (Fig. 3e; $t_{(18.1)} = 1.158$; $p > 0.05$; $d = 0.435$) or the latency to collect reward (Fig. 3f; $t_{(27)} = 0.225$; $p > 0.05$; $d = 0.084$).

Different paired-associates learning Using the criterion of an average accuracy of 80% across 2 days, the effect of THC exposure during adolescence on the rate at which rats acquired the dPAL task was examined. Analysis of the survival curves

of the percentage of rats that had reached criterion across sessions (Fig. 4a) indicates that the rate of acquisition for rats exposed to THC or VEH was not significantly different (χ^2 = 0.0404, $p > 0.05$). THC exposure during adolescence did not affect the number of sessions required to reach criterion on the dPAL task (Fig. 4b; $t_{(27)} = 0.229$; $p > 0.05$; $d = 0.085$).

Rats exposed to THC during adolescence did not differ from rats exposed to VEH alone on the number of errors committed to criterion during standard trials (Fig. 4c; $t_{(27)} = 0.143$; $p > 0.05$; $d = 0.053$) and correction trials (Fig. 4d; $t_{(27)} = 0.057$; $p > 0.05$; $d = 0.021$). No differences were observed in the latency to make a response (Fig. 4e; $t_{(20.4)} = 0.770$; $p > 0.05$; $d = 0.289$) or the latency to collect reward (Fig. 4f; $t_{(27)} = 0.903$; $p > 0.05$; $d = 0.337$).

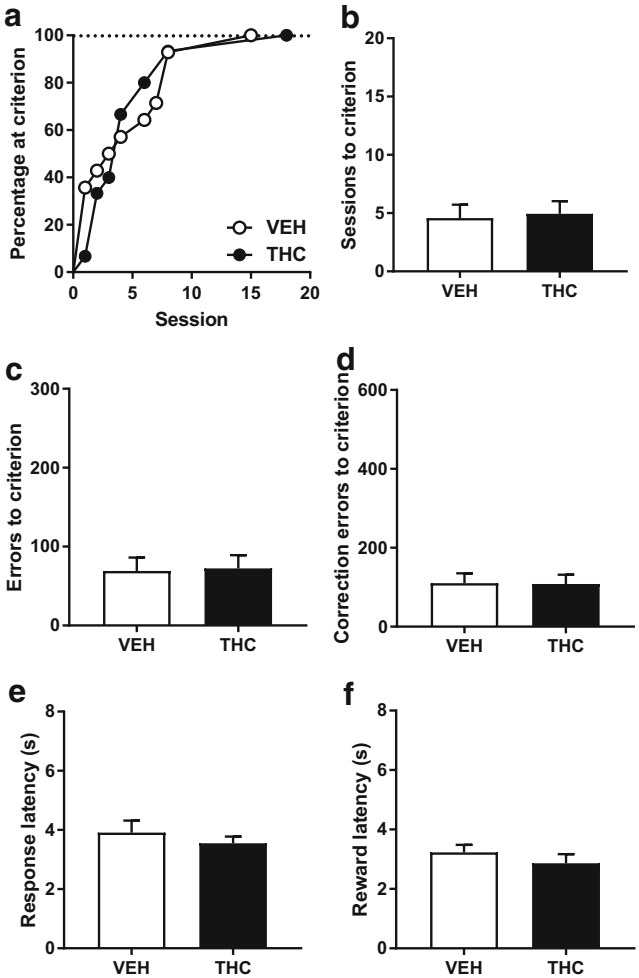

Fig. 4 THC exposure during adolescence has no effect on paired-associates learning (PAL) in adulthood when rats are tested on the different PAL (dPAL) phase of the task. Performance of adult, male rats exposed to Δ9-tetrahydrocannabinol (THC; $n = 15$) or vehicle (VEH; $n = 14$) during adolescence on the dPAL. **a** Acquisition of the task depicted as percentage of THC and VEH rats that have reached criterion (80% accuracy for 2 days) across sessions. **b** Number of sessions required to reach criterion. **c** Number of errors made to criterion. **d** Number of correction trial errors made to criterion. **e** Latency (s) to make a response to a stimulus. **f** Latency (s) to collect food reward. All data is presented as mean ± S.E.M.

Prepulse inhibition Using the same adult, male rats that were tested on the PAL task (THC: $n = 15$; VEH: $n = 14$), PPI was measured at three different prepulse intensities (70, 75, and 80 dB) at three time points relative to THC exposure: 5 days later, 4 months later, and 6 months later. In all instances, there was a main effect of prepulse intensity (all $p < 0.05$) on prepulse inhibition of the startle response. Five days after the exposure period, the PPI of rats exposed to THC during adolescence did not differ from that of rats exposed to VEH alone (Fig. 5a; $F_{(1,27)} = 0.144$; $p > 0.05$; $\eta^2 = 0.005$) nor was there an interaction between THC exposure and prepulse intensity ($F_{(2,54)} = 1.232$; $p > 0.05$; $\eta^2 = 0.044$). Four months after the exposure period, there was a main effect of THC treatment on PPI (Fig. 5b; $F_{(1,27)} = 7.115$; $p < 0.05$; $\eta^2 = 0.209$) and no interaction between THC exposure and prepulse intensity ($F_{(2,54)} = 0.476$; $p > 0.05$; $\eta^2 = 0.017$). Based on a priori evidence of reduced PPI in rats exposed to THC during adolescence (Renard et al. 2016), one-tailed t tests were applied to examine the effect of THC treatment on PPI at each prepulse intensity. These tests revealed that THC exposure during adolescence significantly reduced PPI at all prepulse intensities ($p < 0.05$). Six months after the exposure period, there was no main effect of THC treatment on PPI (Fig. 5c; $F_{(1,27)} = 0.515$; $p > 0.05$; $\eta^2 = 0.019$) and no interaction between THC exposure and prepulse intensity ($F_{(2,54)} = 1.431$; $p > 0.05$; $\eta^2 = 0.050$). Startle response magnitude in pulse-alone trials were significantly lower for rats exposed to THC after 5 days of abstinence (Fig. 5d; $t_{(27)} = 2.086$; $p < 0.05$; $d = 0.772$) but were unaffected after 4 ($t_{(27)} = 0.516$; $p > 0.05$; $d = 0.192$) and 6 ($t_{(27)} = 0.519$; $p > 0.05$; $d = 0.193$) months of abstinence.

Discussion

We show that THC exposure during adolescence, which is marked by a sensitive period of brain development, produces impairments in cognition that persist into adulthood. Specifically, rats exposed to THC during PND 35–45 display impairments in PAL after a drug-free period of 2 months after exposure. This impairment in associative learning was not limited to an individual test conducted on a single day, but rather was expressed across several days on the simplified version of the PAL task. On the PAL task, rats learned to associate each of three distinct visual stimuli with one of three specific locations on the touchscreen (see Fig. 2). In the first phase of the PAL task (sPAL), duplicates of one of the three stimuli were displayed in two different locations (one correct, one incorrect); rats were required to respond to the stimulus presented in its correct location to receive a palatable reward. Under these conditions, rats previously exposed to THC

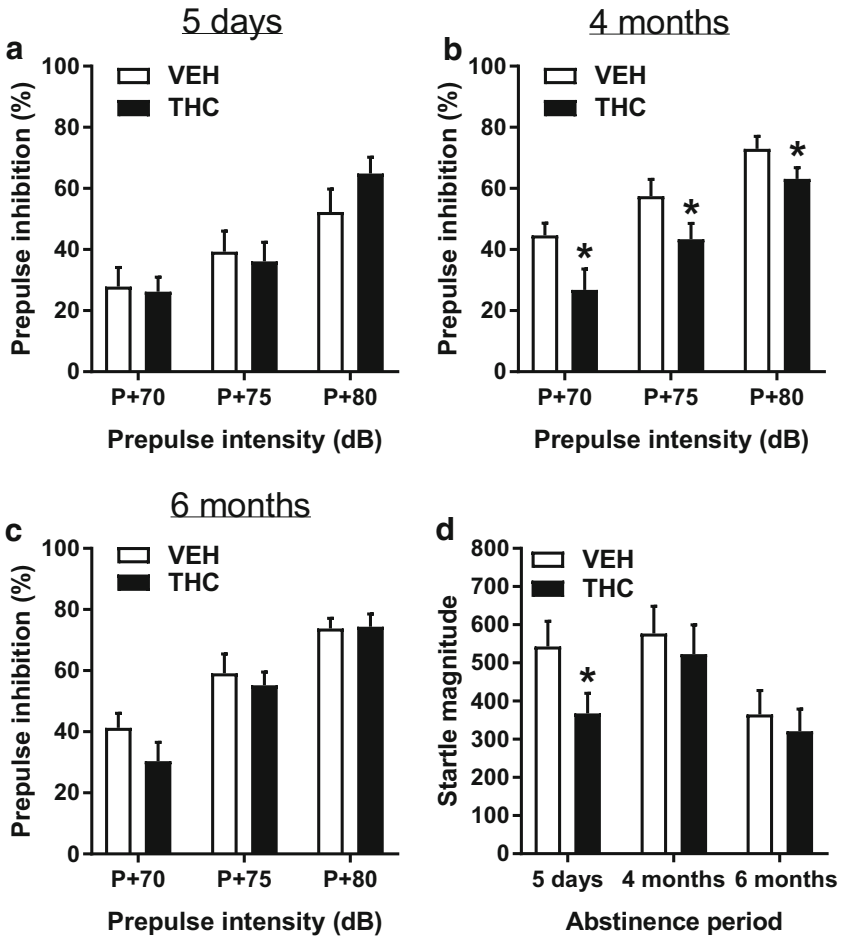

Fig. 5 THC exposure during adolescence impaired prepulse inhibition (PPI) of the startle response 4 months after exposure. **a**–**c** Prepulse inhibition of the startle response at three different prepulse intensities (70, 75, and 80 dB) for adult, male rats exposed to Δ9-tetrahydrocannabinol (THC; $n = 15$) or vehicle (VEH; $n = 14$) during adolescence. Rats were tested at three time points: after **a** 5 days, **b** 4 months, and **c** 6 months of abstinence following THC exposure. **d** Startle magnitude response (110-dB pulse-alone trials) after 5 days, 4 months, and 6 months of abstinence. All data is presented as mean ± S.E.M. $*p < 0.05$ relative to rats exposed to vehicle during adolescence

committed more errors and thus required more training sessions to reach the 80% accuracy acquisition criterion. When rats progressed to the next phase of the PAL task (dPAL), in which two different stimuli were presented concurrently in different locations (one correct, one incorrect), THC exposure during adolescence had no discernible effect on performance. Given that the PAL task is repeatable, it can be used to show how rats exposed to THC during adolescence learn across time and how their performance changes as they age across different levels of task difficulty. Using this paradigm, we show for the first time that the cognitive impairments produced by adolescent THC exposure may be transient in nature and are most evident when rats first learned the task (sPAL) but were seemingly absent in a more challenging version of the task (dPAL). Furthermore, rats given THC during adolescence exhibited impaired sensorimotor gating, but only 4 months after the period of exposure. Taken together, these findings show that exposure to THC during adolescence impairs associative learning and information processing in adulthood, though the overall impact of these deficits may diminish over time.

In the current study, THC exposure during adolescence delayed the rate at which rats acquired object-location associations in the sPAL task when tested in adulthood. Compared to rats exposed to vehicle alone, rats exposed to THC during adolescence committed more errors while acquiring the accuracy criterion of 80%, overall requiring ~25% longer to learn the task. Since the PAL task requires a subject to be driven to respond for reward in the form of sucrose pellets, it requires a certain level of motivation. Therefore, it is possible that the learning impairment in the sPAL task reported here was due to a motivational deficit. Indeed, adolescent exposure to the synthetic CB_1 receptor agonist WIN 55,212-2 has been shown to reduce breakpoints when responding for palatable casein pellets on a PR schedule (Schneider and Koch 2003). It is therefore possible that the learning deficit we observed may be a reflection of low levels of motivation in the animals exposed to THC. If rats exposed to THC experienced lower motivation for food reward, their latencies to respond to the touchscreen or collect a reward should be longer than latencies for rats exposed to vehicle. Rats exposed to THC did not take longer to make a response in a given trial nor did they take longer to collect reward after making a correct response. Furthermore, performance on the dPAL task was not affected by THC exposure, which would be expected to have comparable motivational demands as the

simpler sPAL task. Indeed, non-human primates exposed to cannabis smoke in young adulthood earn fewer reinforcements on a progressive ratio task; however, such deficits do not persist and disappear within 2–3 months of cessation of treatment (Paule et al. 1992). Based on these observations, the learning impairment on the sPAL task is not likely to be due to a persistent motivational deficit, but instead reflects a deficit in encoding and retrieving object-location associations.

Several factors seem to influence the degree to which THC exposure impacts cognitive performance. The first factor relates to the age of exposure of the subjects. It is known that animals are more sensitive to the effects of THC exposure during adolescence than they are during adulthood. Rats exposed to THC or analogous cannabinoids during adolescence (PND 35–45) are impaired in behavioral tests that require the encoding and recall of spatial information, such as in radial-arm maze (Stiglick and Kalant 1983; Nakamura et al. 1991), object recognition (Renard et al. 2013), and water maze tasks (Cha et al. 2006). In the current study, we have added to these findings by showing that rats exposed to THC during adolescence display learning impairments in the PAL task using visual stimuli displayed on a screen, a behavioral test that requires learning both visual object and spatial information. In contrast, adult rats (PND 60+) exposed to THC or analogous cannabinoids tend to not be impaired when subsequently tested under similar conditions (Stiglick and Kalant 1985; Schneider et al. 2003; Renard et al. 2013), unless higher doses of THC and longer treatment periods are employed (Fehr et al. 1976; Nakamura et al. 1991). Therefore, in addition to the age of exposure, the dose or concentration of THC that is used, and the duration of the exposure period, also influences the impact of THC exposure on cognition.

Yet another factor that seems to impact the effect of THC exposure on cognitive performance relates to the precise aspects of cognition being examined. Specifically, the effects of THC exposure during adolescence are more pronounced in tasks that require the maintenance of information, such as the location of a platform or the novelty of an object, across a delay period. For example, after over a month of abstinence, rats exposed to THC during adolescence (or adulthood) do not display any significant impairment in the Morris water maze when tested with short delays between acquisition and recall (Cha et al. 2006, 2007). In the current study, we show that rats exposed to THC during adolescence (compared to vehicle only) require ~25% more trials to acquire the first phase of PAL (sPAL), when the object-location associations are first learned. When later tested in the next phase of PAL when two distinct visual stimuli are displayed simultaneously in different locations, adolescent exposure to THC had no effect on performance. Based on these observations, THC exposure during adolescence may delay the initial acquisition or encoding of information in adulthood. However, once learned, adolescent THC exposure does not seem to impact the later retrieval of this information, even when faced with competing, incorrect response alternatives as is the case in the dPAL task. In fact, all animals acquired the dPAL task at a faster rate compared to the sPAL task, irrespective of adolescent THC exposure. Thus, it is expected that a THC-induced deficit would have been detected if rats had been tested on the dPAL task without prior sPAL training. Taken together, the precise, long-term impact of adolescent exposure to THC on cognition seems to depend on several factors, including the age of exposure, the dose of THC, the duration of the exposure, and the aspects of cognition being tested.

The factors that determine the impact of THC exposure on cognition in animal models are analogous to those that determine the long-term effects of adolescent cannabis use in humans. Adolescence is marked by a crucial period of brain development in which repeated use of drugs like cannabis may disrupt the healthy maturation of cognitive functioning. As a result, the degree of impairment that is observed in adolescent cannabis users can vary depending on a variety of factors, including the age of initiation, the amount of cannabis used, the frequency of cannabis use, and the duration of time spent abstaining from cannabis use (for reviews, see Pope et al. 1995; Solowij and Pesa 2011). For example, in one sample of adolescent cannabis users (moderate exposure, 2–3 years), the degree of impairment in verbal learning and memory relative to age-matched controls correlates with the duration, quantity, frequency, and age of onset of cannabis use (Solowij et al. 2011). Furthermore, the mnemonic deficits displayed by this sample of adolescent cannabis users were comparable to those displayed by long-term adult cannabis users with over 10 years of use (Solowij et al. 2002). Regular adolescent cannabis users (e.g., more than once per week) display a range of deficits in attention, impulsivity, and spatial working memory on the Cambridge Neuropsychological Test Automated Battery (CANTAB) and other cognitive tests after at least 12 h of abstinence (Harvey et al. 2007; Dougherty et al. 2013). Taken together, these observations suggest that adolescent cannabis users are more vulnerable than adult users to the harmful effects of cannabis on cognition. This idea is further supported when adolescents who began using cannabis at different ages (e.g., before or after age 16) are compared in terms of neuropsychological functioning later in life. Given that adolescent development is a period of constant change, younger and older adolescents can differ substantially in terms of brain development and cognitive capacity (Spear 2000), which may differentially affect how younger and older adolescents are affected by cannabis use. Cannabis use that is initiated in early adolescence (e.g., before age 16) is an especially strong predictor of attentional deficits during adulthood (Ehrenreich et al. 1999) as compared to late-onset cannabis use (after age 16). Furthermore, early-onset cannabis users display more deficits in verbal memory and executive function, including impulse

control and decision-making (Pope et al. 2003; Fontes et al. 2011; Gruber et al. 2012), though they also tend to use cannabis more frequently and in greater amounts compared to late-onset cannabis users. In the current study, we exposed rats to THC during a period designed to model the effects of early to mid-adolescent cannabis use. We demonstrate that THC exposure during this developmental phase has a long-term impact on associative learning in adulthood.

There is some evidence that neuropsychological impairments recover in adolescent cannabis users after a period of abstinence, though the evidence is quite limited. We show that rats exposed to THC during adolescents are initially impaired on associative learning in adulthood, though this deficit recovered given enough time and training. In human adolescents, some have reported improvements in mnemonic functioning after a period of abstinence of 6 weeks (Schwartz et al. 1989), though some impairments were still evident at this stage. Others have observed persistent impairments in adolescent cannabis users in attention and spatial working memory after 21–28 days of abstinence (Medina et al. 2007; Schweinsburg et al. 2008; Hanson and Winward 2010). Based on these findings, the impact of cannabis use during adolescence on cognitive function seems to be greatest for younger users (e.g., 16 years or younger) who consume large amounts of cannabis on a regular basis, suggesting that mid-adolescent users at-risk of developing cannabis use disorder are most vulnerable to the long-term effects of cannabis use. In a large prospective study of over 1000 people, adolescents who regularly used cannabis displayed greater neuropsychological decline from childhood to midlife (Meier et al. 2012). However, in a well-controlled follow-up study with a cohort of twins, these authors found that the neuropsychological decline observed in some participants is not related to cannabis use and is better explained by other factors such as education and family background (Meier et al. 2018). In spite of the impact of these external factors, the cognitive deficits produced by early-onset cannabis use in particular do not appear to recover fully in adulthood (Fontes et al. 2011), and it is unclear if any recovery is observed after extended periods of abstinence (e.g., several months to years). Future research should examine the putative relationship between adolescent age and amount of THC exposure (e.g., varying doses and exposure periods), and their corresponding effects on cognition in animal models following multiple intervals of abstinence.

Rats exposed to THC during adolescence also displayed impaired prepulse inhibition (PPI) of the acoustic startle response 4 months after exposure. Although the magnitude of the startle response was attenuated shortly after THC exposure, no differences were observed after 4 and 6 months of abstinence, suggesting that the initial reduction in startle response was due to a residual effect of the recent THC exposure. This replicates previous reports showing similar disruptions in sensorimotor gating following exposure to THC (Nagai et al. 2006; Renard et al. 2016), including nearly 3 months after exposure (Schneider and Koch 2003). Disruptions of PPI are widely accepted as an endophenotype of psychotic disorders with high translational validity between humans and rodents (Braff et al. 2001; Perry et al. 2001; Van Den Buuse 2010). It is therefore possible that a deficit in PPI as a result of THC exposure might suggest that cannabis use may confer a vulnerability to develop psychotic symptoms, given that sensorimotor gating deficits are a core feature of schizophrenia (Braff and Geyer 1990). Indeed, using cannabis in adolescence increases the likelihood of experiencing psychotic symptoms in adulthood (Andréasson et al. 1987; Arseneault et al. 2004), though the mechanism underlying this relationship is poorly understood. When PPI was measured immediately after the THC exposure period, or 6 months after the exposure period, no significant deficit in PPI was observed. This suggests the possibility of an incubation period following THC exposure before deficits in PPI emerge. Despite the potential existence of such an incubation period, it is unclear why the deficits observed 4 months after exposure disappear later on 6 months after exposure. On close inspection of the PPI data collected from vehicle-treated rats, it seems as if PPI is attenuated at 5 days in comparison to 4 months and 6 months, as others have previously shown in control animals (Schneider and Koch 2003). It is possible that this may have prevented detection of an effect of THC treatment on PPI 5 days after treatment. Given the apparently transient nature of this deficit in sensorimotor gating, if THC exposure does indeed produce long-term deficits in sensorimotor gating, there may be a specific time window during which time the vulnerability to develop psychotic symptoms is greatest. Indeed, it has been reported that the risk of developing psychosis in moderate cannabis users declines over time (Manrique-Garcia et al. 2012), though it is unclear if this reduced risk coincides with a similar reduction in sensorimotor gating deficits. Given that sensorimotor gating reflects the ability to direct attention to salient features in the environment and filter out irrelevant information (Braff and Geyer 1990), a deficit in PPI reflects impairment in information processing. This deficit could have implications for the way in which visual information is processed, encoded, and recalled, as is required in PAL, where correct stimuli must be selected alongside competing, incorrect alternatives. The temporal coincidence of deficits in the early phases of PAL testing (~ 3 months after THC exposure) and in PPI (~ 4 months after THC exposure) may reflect different measures of a common deficit in information processing. Indeed, when patients with schizophrenia are examined across a 6-month period, an improvement in positive symptoms (e.g., hallucination, delusion) correlates with an improvement in cognitive functioning (Addington et al. 1991). Taken together, exposure to THC during adolescence seems to impair sensorimotor gating, which could relate to the expression of long-term impairments

in cognitive function, as well as the incidence of psychotic symptoms experienced by some cannabis users.

In summary, in accordance with a growing body of evidence in humans, we have demonstrated that adolescence is marked by a period of vulnerability to the effects of THC on brain development and cognition. We have shown that adolescent exposure to THC impairs the initial acquisition of PAL and sensorimotor gating after an extended period of abstinence (e.g., 3–4 months); however, these deficits did not seem to persist beyond this timeframe. Although rats exposed to THC during adolescence initially displayed impaired learning of the PAL task, this deficiency was less evident as time passed, and their performance was seemingly unaffected in the more challenging version of the task. Although cognitive development during adolescence seems to be vulnerable to THC exposure, the impairments that arise may represent an interval of cognitive deficiency and vulnerability in young adulthood that recovers over time, as opposed to one that persists indefinitely. These findings also lend further support for the utility of using touchscreen testing to assess cognition in animals, using tests that are analogous to those used in humans (e.g., the CANTAB) to facilitate cross-species comparisons and translational discoveries. In conclusion, the long-term effects of adolescent THC exposure reported here will help inform the impact of cannabis use on associative learning and information processing later in life, which may also relate to the incidence of psychosis in some cannabis users.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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