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Repeated, Intermittent Δ^9-Tetrahydrocannabinol Administration to Rats Impairs Acquisition and Performance of a Test of Visuospatial Divided Attention

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The residual neuropsychological effects of marijuana abuse in man indicate a dysfunction of the attentional/executive systems. Moreover, experimental investigations suggest that repeated, intermittent (subchronic) Δ^9-tetrahydrocannabinol (THC), the main psychoactive ingredient of marijuana, alters neurotransmission in the frontal cortex of rats and humans, a key neural site mediating attention and executive functions. In the present studies, the acquisition and performance of a test of visuospatial attention (the lateralized reaction time task) after subchronic THC administration (10.0 mg/kg twice daily for 14 days) was examined. Rats previously administered THC showed impairments in this self-paced version of the classic multiple-choice serial reaction time task, which persisted 14 days after the final drug administration. Longer time points were not examined. These attentional impairments were transiently reversible with an acute amphetamine (0.5 mg/kg) challenge. These behavioral data demonstrate that chronic THC administration to rats induces an attentional deficit, similar to that observed in humans who abuse marijuana. Finally, amphetamine's ability to reverse the attentional impairments provides indirect evidence that monoaminergic deficits may be linked to the cognitive dysfunction.
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INTRODUCTION

There is now compelling evidence that long-term intake of several drugs of abuse induces neurocognitive deficits in humans involving impairments of attention, inhibitory control, decision-making, and/or cognitive flexibility (Cosgrove and Newell, 1991; McKetin and Mattick, 1998; O'Malley *et al*, 1992; Joe *et al*, 1991; Rogers *et al*, 1999; Ornstein *et al*, 2000; Bolla *et al*, 2000; Bechara *et al*, 2001). Indeed, behavioral analysis of cannabis abusers reveals impaired performance on a battery of neuropsychological tests that assess attention, learning, and memory (Block *et al*, 1992; Block and Ghoneim, 1993). However, relatively little is known about the neurobehavioral basis of these cognitive impairments.

Recently, attentional dysfunction has been implicated in the psychopathology of cannabis-induced cognitive deficits. Well-controlled research purports behavioral evidence of frontal lobe dysfunction, detecting specific impairments of attention in users of marijuana (Pope and Yurgelun-Todd, 1996; Solowij *et al*, 1997). Additionally, the most pronounced deficits in adults after adolescent abuse are manifest as an inability to shift or sustain attention (Ehrenreich *et al*, 1999). Together, these studies strongly indicate that specific aspects of the cognitive/executive system may be impaired following repeated exposure to marijuana. It has been hypothesized that the underlying deficit in cognitive performance may be a consequence of an abuser's inability to efficiently evaluate stimuli and allocate attentional resources (Solowij *et al*, 1991). Thus, attentional dysfunction may be at the core of cannabis-induced performance deficits; however, little is known regarding the longevity of these effects in humans or animals after cessation of drug consumption. Indeed, few studies have examined attention in human subjects after a prolonged abstinence from the drug, and those that have report conflicting results as to the duration of the long-term effects of cannabis use on attention (Solowij, 1998; Pope *et al*, 2001). Therefore, it seems particularly relevant to

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assess attentional function in experimental animals after repeated exposures to Δ^9-tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis preparations, and to determine if these perturbations persist after a prolonged washout period.

Studies in rodents have reported that repeated administration of cannabinoids induces an anatomically selective reduction in prefrontal cortical dopaminergic function, which persists for at least 2 weeks (Jentsch *et al*, 1998; Verrico *et al*, 2003). In addition, animal studies into the long-term effects of cannabinoids on memory and cognition have provided evidence of their detrimental effects (Stiglick and Kalant, 1982a, b, 1983; Nakamura *et al*, 1991). However, the tasks employed in these behavioral experiments do not directly assess attentional processes, which are particularly affected in humans (MacAvoy and Marks, 1975; Marks and MacAvoy, 1989; Fletcher *et al*, 1996) and non-human primates (Golub *et al*, 1982) exposed to marijuana. Our study was designed to test the hypothesis that prior, relatively short-term, repeated exposure to THC would result in alterations in attentional performance, utilizing a task known to be dependent on intact functioning of the prefrontal cortex in rat. An elegant assay of attentional performance in rodents is the self-paced serial reaction time task (Carli *et al*, 1985; Passetti *et al*, 2000). This method allows for changes in attentional performance (accuracy) to be parceled out as direct actions on selective, sustained, and/or divided attention and/or indirect actions on other quantified measures. The accuracy of this task is dependent on the integrity of the frontal cortex, as lesions impair performance (Passetti *et al*, 2000), consistent with impaired attentional function in humans after frontal lobe damage (Robbins, 1996, 1997).

Given the integral role of dopamine in attentional processes and executive functions associated with the prefrontal cortex, we examined the cognitive consequences of repeated THC administration using a chronic but intermittent dosing regimen that induces a persistent dopaminergic deficit in the prefrontal cortex (Verrico *et al*, 2003). Specifically, we sought to determine if previous subchronic THC administration (10 mg/kg 2 × /day for 14 days, to parallel the neurochemical study of Verrico *et al*, 2003) impairs acquisition and performance of the self-paced serial reaction time task. Furthermore, we examined whether the observed impairment was transiently attenuated by an acute amphetamine challenge, a pharmacological agent known to include increased prefrontal cortical monoamine activity. Our findings show that even relatively short-term exposure to THC produces attentional deficits, and suggest that a prefrontal cortical dopaminergic mechanism might be involved.

MATERIALS AND METHODS

Animals

Male Sprague–Dawley rats (Charles River Labs, Portage, MI), with initial body weights of 200–250 g, were housed in groups of two per cage and maintained under a 12-h light, 12-h dark cycle (light on 0700 to 1900 h). The subjects were initially food-deprived to 85% of their free-feeding weights and subsequently fed 15 g of rat chow/day in their home cages within 1.5 h of test completion. Water was available on a continuous basis, except during the testing period. This feeding schedule allowed all subjects to gain between 5 and 10% of their body weight per week. The experiments in the present study were approved by the Yale University Animal Care and Use Committee, and followed the *Guide for the Care and Use of Laboratory Animals*.

Surgery

Prior to subchronic THC administration, a polyethylene catheter (Abbott Laboratories, North Chicago, IL, USA) was inserted into the intraperitoneal (i.p.) cavity, and tunneled subcutaneously to exit at the nape of the neck. Additionally, rats received an acute intramuscular injection of penicillin (200 000 units) immediately after surgery, to prevent infection. After at least a 3-day recovery period, rats were administered THC (10 mg/kg twice daily for 14 days), prior to training in the behavioral paradigm.

Drugs

THC was obtained from Sigma Chemical Co. (St Louis, MO). THC (shipped in 100% ethanol) was first evaporated under a stream of purified nitrogen, and then dissolved in saline with a drop of Tween 80 and given intraperitoneally via an indwelling intraperitoneal catheter (see above). Rats received 10 mg/kg of THC twice daily 10–14 h apart for 14 days, and were allotted a 7-day washout period. Control subjects received 1.0 ml/kg saline with a drop of Tween 80 (vehicle).

Apparatus

Standard extra-tall aluminum and Plexiglas operant chambers with a light bulb and infra-red beam-equipped pellet delivery magazine on one side and a curved panel with five nose poke apertures on the other (Med Associates, Mt Vernon, VT, USA) were used. The boxes were housed inside a sound-attenuating cubicle; background white noise was broadcasted and the environment was illuminated with a light diffuser that was located outside the operant chamber, but within the cubicle.

Procedure

Behavioral methods and analyses were as previously published (see Jentsch and Taylor (2003) for additional details).

Pretraining

All rats received free reinforcer pellets (45-mg Bioserve™ dustless precision) in their home cages for 3 days prior to commencing training. Subsequently, rats received two magazine training sessions, during which single pellets were delivered every 20 s from the illuminated magazine over a 45-min period. All nose poke apertures were occluded during magazine training.

The rats were next trained to make a sustained nose poke in the center aperture in three daily sessions. On day 1, the rats were trained to make a 10, 200, 400 or 600 ms nose

poke. The nose poke duration requirements were varied randomly from trial to trial: when the rat made a satisfactory nose poke, the center aperture light was extinguished, the head entry magazine was illuminated and a pellet was dispensed. Once the pellet was retrieved, the magazine light was extinguished and, 3 s later, the center aperture light was illuminated. The session ceased after 60 min passed or 100 pellets were earned, whichever came first. On day 2, the nose poke requirements were 10, 300, 600 or 900 ms. On day 3, the nose poke requirements were 10, 400, 800 or 1200 ms.

Acquisition and Testing

After being trained to make the sustained nose poke, rats began daily testing on a signal detection paradigm in which only one stimulus duration was presented throughout the entire session (which terminated after 60 min or 128 trials, whichever came first). Target apertures were the far right and left openings; apertures 2 and 4 remained occluded. In this task, rats were required to take a pellet from the illuminated pellet magazine to start the task. The light above the magazine was extinguished and, 3 s later, the center aperture light was illuminated. The nose poke requirements were of variable duration (10, 400, 800 or 1200 ms). The rat was required to complete the center nose poke, then either the far left or the far right aperture light was illuminated for a fixed period. The target stimulus duration varied across the 4 days of acquisition (30, 5, 2.5, and 1 s on days 1, 2, 3, and 4 respectively). After target delivery, a correct nose poke during the illumination period, or within 3 s of termination of the target, resulted in all aperture lights being extinguished and a pellet being given in the magazine. A 'correct' response was recorded. After the pellet was retrieved, the magazine light was extinguished, and 3 s later, the center aperture light was on and another trial started.

In the event, a rat responded to the wrong location (an incorrect nose poke during the illumination period), all the lights went out and a 3-s 'time out' with complete darkness ensued. An error of 'commission' (ie incorrect choice) was recorded. If the rat did not respond to the stimulus presentation within 3 s of the target, a 3-s 'time-out' in darkness was given and an 'omission' was recorded. In both cases, illuminating the house light diffuser and the center aperture light 3 s later followed the time out. In addition, a premature response was scored when the rat made a response at the target aperture prior to target delivery. A time out was given and an 'anticipatory error' was recorded.

Dependent measures for this task included: (1) choice accuracy (correct choices/total trials), (2) omissions/total trials, (3) commissions (incorrect choices/total trials), (4) total anticipatory responses, (5) total trials initiated, (6) mean initiation latency/trial (the average interval between illumination of the center nose poke aperture and the initiation of the observing response), and (7) response bias (the ratio of the total number of responses given in the preferred relative to the nonpreferred aperture).

After the 4 days of training, rats were tested in a session in which the duration of the target stimuli (4, 2, 1 or 0.5 s) was varied from trial to trial. All the other task details were identical to those described above, and the dependent measures were the same, except now, accuracy, omission, and commission frequency were analyzed with reference to stimulus duration. Anticipatory errors, response bias, trials initiated, and mean latencies were not dependent upon stimulus duration, and were analyzed independently by one-way ANOVAs.

Statistical Analysis

For acquisition testing, where sessions used single stimulus durations over successive days, the data were analyzed for group effects with factorial analysis of variance (ANOVA) coupled with Scheffe's F-test for *post hoc* comparisons. For sessions in which multiple stimulus durations were given within a single session, accuracy, omission, and commission frequency were analyzed for group effects with a repeated-measures ANOVA, with stimulus duration being the repeated measure. Other measures were analyzed by factorial ANOVAs. For these data, Tukey's and Scheffe's F-tests were used to make *post hoc* comparisons, respectively. All data are expressed as mean $\pm$ standard error of the mean (SEM).

RESULTS

Acquisition of the Signal-Detection Paradigm

All rats were treated with vehicle or THC (10 mg/kg twice/day for 14 days) prior to training. Training began after a 2-day drug-free period. Rats ($n = 7$ per group) were trained to detect 30, 5, 2.5 or 1 s target stimuli on days 1, 2, 3, and 4 of testing, respectively (these days corresponded to days 3–6 after the last drug administration). Group differences were analyzed for each of these test sessions independently. The data for all stimulus durations are shown in Figure 1. At the 30 and 5 s stimulus durations (day 1 and day 2 of training, respectively), there were no main effects of previous treatment on accuracy, omissions/total trials, commissions, anticipatory responses, total trials initiated, and mean initiation latency/trial or response bias, indicating that THC administration did not affect acquisition of the general response rules of the task. Figure 1 shows that at the 2.5-s stimulus duration (day 3; $F_{(1,12)} = 7.179$; $p = 0.02$) and 1.0-s stimulus duration (day 4; $F_{(1,12)} = 6.643$; $p = 0.02$), there were main effects of treatment on choice accuracy (ie correct choices; $p > 0.05$). No other measures were affected by previous THC administration.

Performance Under Variable Stimulus Duration Conditions

All rats were evaluated in a subsequent test session for performance on a schedule in which four different stimulus durations (4.0, 2.0, 1.0 or 0.5 s) were presented randomly across trials within the session (Figure 2). This testing took place 7 days after the final dose of THC was administered. Repeated-measures analysis of variance, considering treatment as the factor and stimulus duration as the repeated measure, revealed a main effect of treatment on choice accuracy ($F_{(1,12)} = 9.407$; $p = 0.0098$); this effect did not interact with the target stimulus duration, indicating that the impairments were not specific to the briefest target stimulus duration, as might be expected if a purely

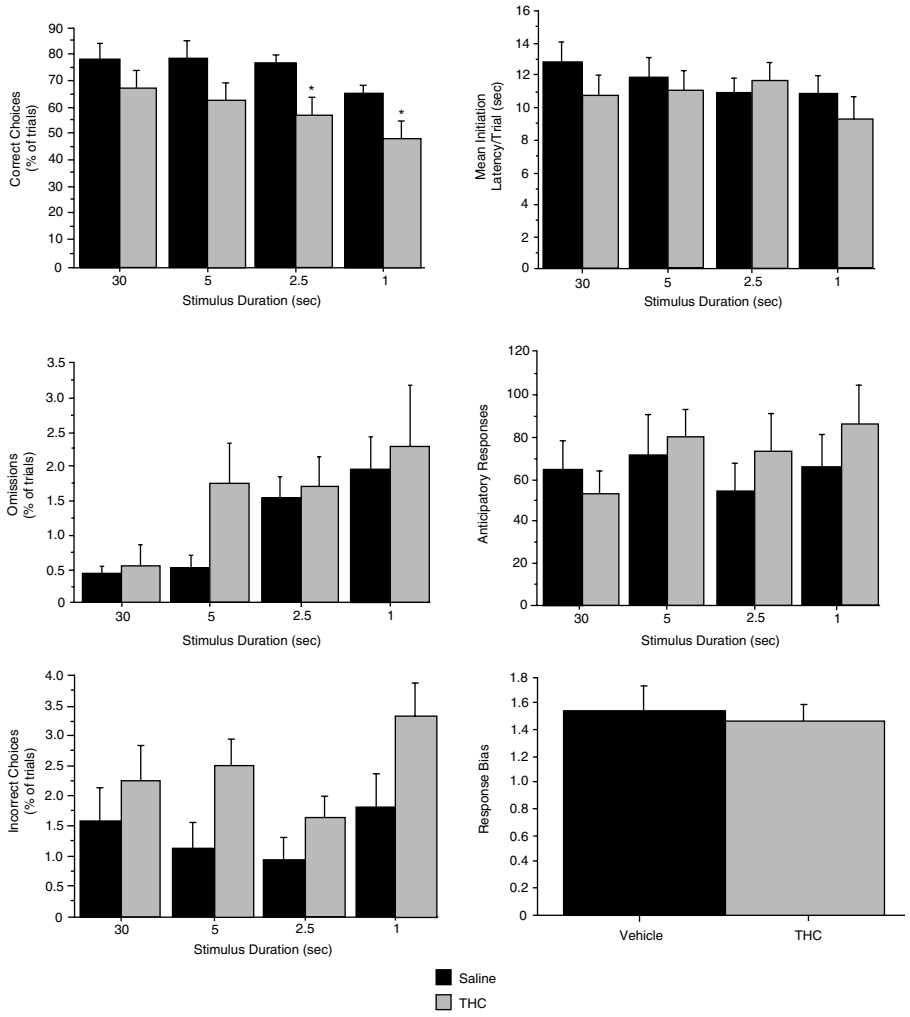

Figure 1 THC and vehicle rats differed in their acquisition of a self-paced test of spatial divided attention. Though the groups performed equivalently on the first two daily sessions (30 and 5 s target stimuli), group differences emerged on subsequent days (2.5 and 1 s target stimuli). THC rats showed choice accuracy decrements that reached statistical significance at the 2.5- and 1-s stimulus durations. There were no significant group effects for anticipatory responses, omissions, trial latencies or other measured values; no effects interacted with stimulus duration. Levels of significance: $^{*}p < 0.05$. Data represent groups means ± SEM. $N = 7$/group.

attentional deficit were the cause of the impairment. Since the accurate detection of stimuli (accuracy) did not vary with the stimulus duration (at least within the range of target durations employed here), this effect may have been due to an increased biasing of responses to one aperture in THC-exposed rats. In other words, subjects may have simply preferred one spatial location to another and, therefore, been more likely to fail on any given trial, irrespective of target duration, because of that preference. This was not found to be the case since response bias was not differentially affected during either the acquisition or performance of the task. As in the acquisition phase, all other measures showed no main effect of treatment.

Effect of Acute Amphetamine on THC-Induced Performance Deficits

At 13 and 14 days after the final injection of THC or vehicle, rats received, in a counter-balanced design, an acute systemic saline (1 ml/kg) or amphetamine (0.5 mg/kg). injection (i.p.) 20 min prior to the test session (as described previously). Figure 3 shows the effect of an acute amphetamine/saline challenge, in rats previously administered THC or vehicle, on choice accuracy. Rats previously administered THC and challenged with saline continued to exhibit impairments in choice accuracy 2 weeks after the last exposure, consistent with the deficits observed at 1 week (see Figure 2). A repeated-measures ANOVA revealed a main group effect of the saline challenge on choice accuracy impairments induced by THC ($F_{(1,12)} = 10.2$; $p = 0.007$); however, when rats were challenged with amphetamine, there were no differences between THC- compared with saline-exposed rats on choice accuracy ($F_{(1,12)} = 0.09$; $p = 0.76$). Together, these data reveal that an acute amphetamine challenge produced a transient reversal of the THC-induced choice accuracy deficit. While it did not reach statistical significance, there was a trend for an interaction between the effect of group and stimulus duration on choice accuracy ($F_{(1,12)} = 4.2$; $p = 0.06$).

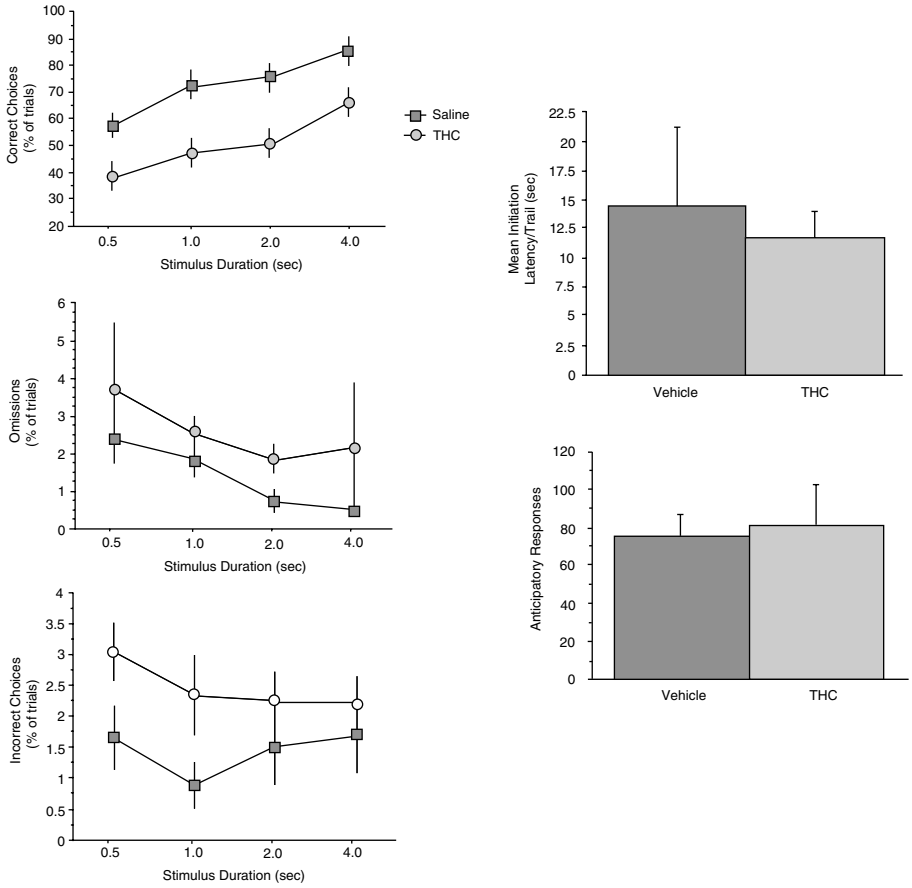

Figure 2 At 7 days after the final administration of THC or vehicle, rats differed in their performance during a single session in which four target stimulus durations (0.5, 1.0, 2.0 or 4.0 s) were presented randomly. THC rats exhibited decreased choice accuracy, with no differences for anticipatory responses, omissions, trial latencies or other measured values; no effects interacted with stimulus duration. Data represent groups means ± SEM. $N = 7$/group.

DISCUSSION

Prior subchronic THC exposure produced clear and definitive deficits on the acquisition and performance of a self-paced lateralized reaction time task. THC-exposed rats exhibited enduring impairments in choice accuracy that persisted for 14 days after the final drug injection. This dose regimen would predictably induce dependence (Aceto *et al*, 1996), and we have found that it produces an anatomically selective reduction in dopamine metabolism in the prefrontal cortex that persists for at least 2 weeks (Jentsch *et al*, 1998; Verrico *et al*, 2003). The finding that subchronic THC exposure produces analogous impairments in visual-spatial divided attention to those produced by prefrontal cortical lesions utilizing this specific task (Passetti *et al*, 2000) supports the hypothesis that THC induces dysfunction of the prefrontal cortex. Moreover, amphetamine's ability to transiently reverse the THC-induced attentional impairment indicates that the THC-exposed animals have acquired and are able to perform the task, as well as vehicle-exposed animals, but are unable to perform the task optimally without stimulant treatment. While the performance deficit appears not to exclusively involve attentional dysfunction (due to the failure of the deficit to interact directly with stimulus durations), the lack of altered trial initiation latencies indicates that a general motor suppression cannot explain the deficit. These data indicate that a failure of executive aspects of response preparation or selection may underlie these deficits.

Impairments in choice accuracy (correct responses/total trials) were largely due to combined increases in omissions and commissions, because analysis of omission and commission error rates per total trials, individually, failed to reach statistical significance. Clearly, THC-exposed rats were able to initiate trials, but were unable to optimally process the information and/or formulate effective responses. Importantly, prior repeated THC exposure did not induce perseverative behavior (response bias), affect the total trials initiated, the mean initiation latency/trial or motor impulsivity (anticipatory responses). These data indicate that although general motivational and motor functions appear to be preserved in THC-exposed subjects, attentional and/or executive processes are negatively affected. This is consistent with a recent report in humans that suggests that acute THC-induced impairments in memory-guided saccades are due to deficits in spatial attentional shifts (Ploner *et al*, 2002). The enrichment of CB_1 receptors in the prefrontal cortex (Glass *et al*, 1997), the anatomically selective and persistent dopaminergic deficit in prefrontal cortex following subchronic THC administration (Verrico *et al*, 2003), and the above data, which indicates a persistent THC-induced attentional deficit in

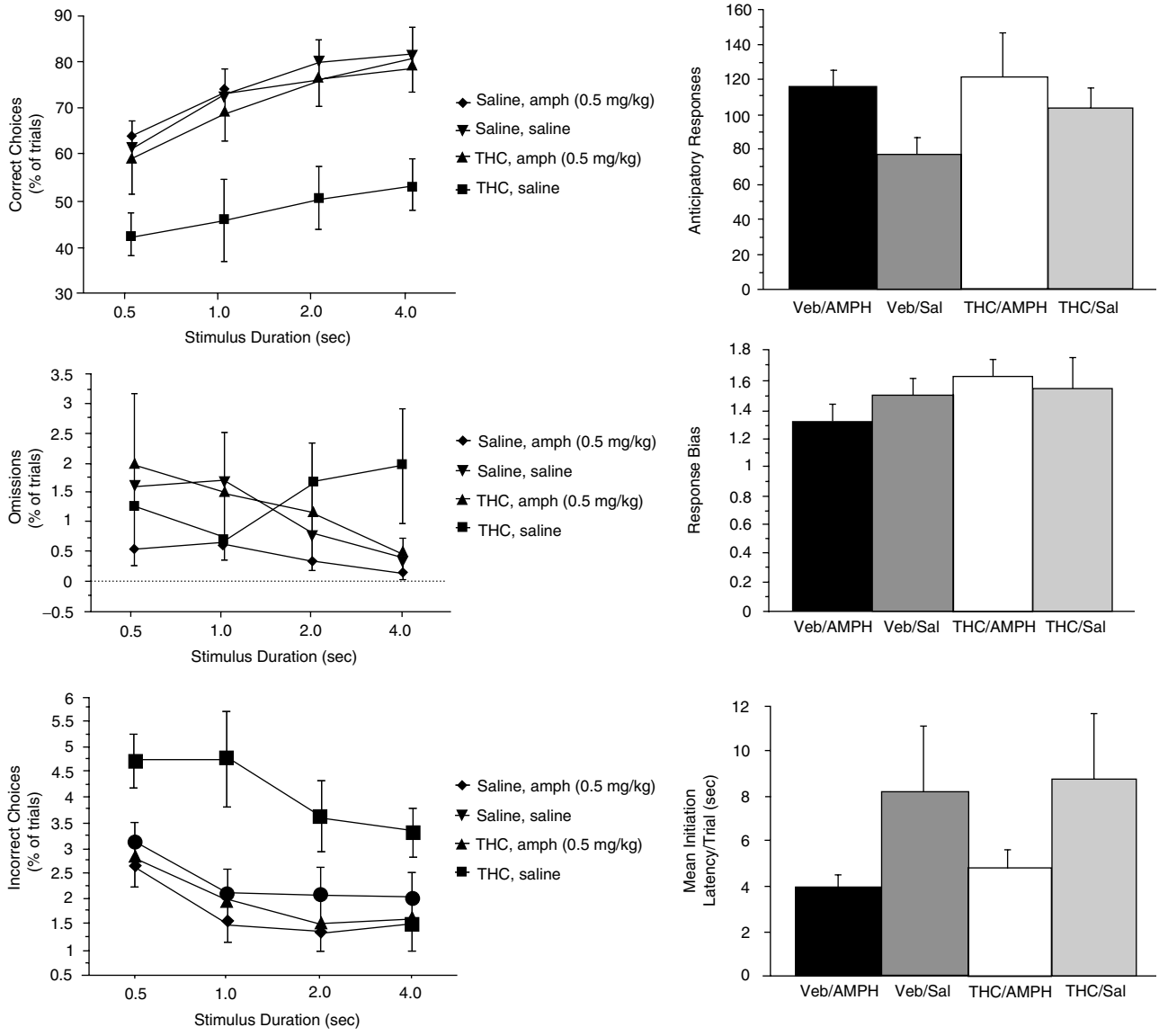

Figure 3 At 13 or 14 days after the final administration of THC or vehicle, following a single amphetamine (AMPH) injection, given in a counter-balanced design, rats differed in their performance during a single session in which four target stimulus durations (0.5, 1.0, 2.0 or 4.0 s) were presented randomly. THC/AMPH rats exhibited increased choice accuracy, with no differences for anticipatory responses, omissions, trial latencies or other measured values; no effects interacted with stimulus duration. THC/VEH rats continued to exhibit attentional impairments, as previously noted. Data represent groups means ± SEM. $N = 7$/group.

rats, suggest that both intake of cannabinoids or prior exposure to cannabinoids can disrupt proper prefrontal cortical functions.

It has previously been reported, using this identical subchronic dosing regimen, that prior THC exposure induces an anatomically selective hypodopaminergic state in the prefrontal cortex of rats, which also persists for at least 2 weeks (Jentsch *et al*, 1998; Verrico *et al*, 2003). Reductions in dopamine turnover in the frontal cortex underlie poor attention in a task with similar constructs, the 5-choice serial reaction time task (Puumala and Sirvio 1998), and stimulation of cortical dopamine levels improves performance under some circumstances (Puumala *et al*, 1996; Puumala and Sirvio, 1998; Granon *et al*, 2000). As such, the attentional impairment induced by subchronic THC administration could be related to a hypodopaminergic state induced by the same treatment paradigm. This hypothesis is strengthened by the observation that an acute amphetamine challenge led to a transient reversal of the choice accuracy performance impairments in rats exposed to subchronic THC: effects consistent with increased levels of dopamine in the prefrontal cortex following systemic amphetamine treatment (Brown *et al*, 2000). More specific pharmacological agents and manipulations following long-term THC administration will be required to elucidate the relative contributions of dopamine to the observed deficits, since increases in cortical acetylcholine, norepinephrine and serotonin, and subcortical monoamines are also a product of an acute amphetamine challenge in the rat (Hedou *et al*, 2000). Furthermore, it is unclear why the effects of amphetamine are specifically observed in THC-treated animals, as opposed to control subjects. However,

this is most likely explained by the fact that improvements in performance are always difficult to observe in control subjects, especially under task conditions that support high levels of successful performance (Granon *et al*, 2000).

To appreciate how cannabinoids persistently impair attentional performance, it is critical to understand how the effect of an initial exposure progressively leads to stable molecular and cellular changes after repeated exposures. Alterations in gene expression are known to lead to relatively stable neuroadaptations (Nestler *et al*, 1993; Berke and Hyman, 2000). As such, repeated exposure to THC could lead to changes in intracellular signal transduction pathways, resulting in alterations of gene expression, plasticity, and ultimately cognitive impairment. Cannabinoids act neuronally on CB_1 receptor proteins, which are G-protein-coupled receptors, to inhibit cAMP formation and long-term exposure to cannabinoids results in adaptations in cannabinoid receptor density and alterations in the cAMP/PKA signaling pathway (Rubino *et al*, 1997). These adaptations include reductions in $G\alpha_i$ and $G\alpha_o$ mRNA expression in the mesencephalon (Rubino *et al*, 1997). With this information, one might speculate that subchronic THC administration leads to a downregulation of cannabinoid receptors in the mesencephalon, which regulates prefrontal cortical dopaminergic transmission, leading to decreased dopamine turnover and ultimately impaired attentional performance, effects possibly reversed by amphetamine-induced activation of dopamine receptors. A future challenge then is to elucidate how repeated THC exposures induce molecular changes that result in behavioral impairments.

The current study is the first to demonstrate that prior repeated THC exposure persistently and profoundly impairs attentional performance in the rat. In addition, these data show that the THC-induced behavioral impairments are persistent (at least 14 days). These impairments are consistent with the cortical dopaminergic dysfunction observed in rats (Jentsch *et al*, 1998; Verrico *et al*, 2003), neurocognitive deficits in humans, as assessed by neuropsychological tasks (Solowij, 1998; Pope *et al*, 2001), and cortical alterations observed using brain imaging techniques (Tunving *et al*, 1986; Mathew *et al*, 1989; Volkow *et al*, 1996). Thus, the THC-induced attentional impairments reported here could provide a useful animal model to investigate the mechanism(s) involved in the pathophysiology of THC-induced cognitive dysfunction, and possibly result in the development of improved and/or novel therapeutic strategies for putative THC-induced neurocognitive deficits. Finally, the ability of a stimulant to reverse these attentional impairments suggests that prior exposure to THC or cannabinoid agonists might be a useful pharmacological method to model the aspects of attentional deficit hyperactivity disorder (ADHD), which is also thought to be associated with dysfunction of prefrontal cortical systems (Biederman and Faraone, 2002; Bush *et al*, 1999; Ernst *et al*, 1998, 2003; Rubia *et al*, 1999).

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