Published in final edited form as:

Behav Brain Res. 2013 April 1; 242: 84–94. doi:10.1016/j.bbr.2012.12.044.

Age-dependent effects of repeated amphetamine exposure on working memory in rats

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Abstract

Cognitive dysfunction is a hallmark of chronic psychostimulant misuse. Adolescents may have heightened risk of developing drug-induced deficits because their brains are already undergoing widespread changes in anatomy and function as a normal part of development. To address this hypothesis, we performed two sets of experiments where adolescent and young adult rats were pre-exposed to saline or amphetamine (1 or 3 mg/kg) and subsequently tested in a prefrontal cortex (PFC)-sensitive working memory task. A total of ten injections of AMPH or saline (in control rats) were given every other day over the course of 19 days. After rats reached adulthood (> 90 days old), cognitive performance was assessed using operant-based delayed matching-to-position (DMTP) and delayed nonmatching-to-position (DNMTP) tasks. DNMTP was also assessed following challenges with amphetamine (0.1–1.25 mg/kg), and ketamine (5.0–10 mg/kg). In experiment one, we also measured the locomotor response following the first and tenth pre-exposure to amphetamine and after an amphetamine challenge given at the conclusion of operant testing. Compared to adult-exposed groups, adolescents were less sensitive to the psychomotor effects of amphetamine. However, they were more vulnerable to exposure-induced cognitive impairments. For example, adolescent-exposed rats displayed delay-dependent deficits in accuracy, increased sensitivity to proactive interference, and required more training to reach criterion. Drug challenges produced deficits in DNMTP performance, but these were not dependent on pre-exposure group. These studies demonstrate age of exposure-dependent effects of amphetamine on cognition in a PFC-sensitive task, suggesting a heightened sensitivity of adolescents to amphetamine-induced neuroplasticity.

Keywords

adolescence; amphetamine; sensitization; working memory; matching-to-position

1. Introduction

Amphetamines are among the most commonly used and abused psychoactive drugs, with more people taking them each year than heroin and cocaine combined [1]. In the United States alone, nearly 20 million people 12 years of age and older are currently using

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amphetamine (AMPH) and nearly 500,000 Americans meet criteria for dependence [2]. Clinical studies indicate a history of AMPH abuse is associated with significant deficits in attention, decision-making and information processing [3–5]. In fact, cognitive functioning of chronic abusers is often so disordered that their performance during assessments is difficult to distinguish from that of patients with frontal lobe damage [6].

Corticolimbic brain circuits, including the interconnected prefrontal cortex (PFC), dorsal striatum, nucleus accumbens, and hippocampus, are critically important for normal cognitive functioning [7] and accumulating evidence suggests that drug-induced plasticity in these regions plays an important role in psychostimulant-induced cognitive dysfunction [8–11]. For example, neuroimaging studies in recovering addicts have revealed that the deficits they exhibit in decision-making and memory are associated with functional abnormalities in the striatum and frontal cortex [12, 13]. Studies in adult laboratory animals suggest that repeated exposure to AMPH leads to enduring deficits in attention and working memory that are associated with reductions and elevations in dopamine and glutamate signaling, respectively, in the PFC [14–19].

One factor that might contribute to AMPH's potential to induce cognitive dysfunction is the age at which exposure occurs. Like most other drugs of abuse, AMPH use typically starts during adolescence [20, 21], which is the transitional period between childhood and adulthood that begins at approximately 12 years of age and extends to the early or mid-twenties [22, 23]. Notably, the frontal cortex continues to develop throughout the adolescent time period [24, 25], with alterations in cell number and morphology [26, 27] and increased synaptic pruning [28] among the most prominent changes that occur. Glutamate and dopamine systems also continue to mature during this stage of development [29–32]. For example, dopamine D₁ and D₂ receptor expression in the rodent PFC, nucleus accumbens and dorsal striatum increases significantly during early adolescence and subsequently declines by as much as 60% as animals reach young adulthood [32, 33]. Thus, the adolescent brain may be particularly susceptible to drug-induced neuroadaptations and associated cognitive changes because of the unique effects of drugs in the developing brain [34, 35].

Evidence for enhanced vulnerability to drug-induced plasticity in adolescents has come primarily from studies in rats, where adolescence has been conservatively defined as beginning around postnatal day (P) 28 and extending to P42 [36] or perhaps as late as P60 [37, 38]. For example, studies of adults exposed to AMPH, cocaine, methylphenidate, or nicotine during adolescence have reported enduring deficits in cognitive tasks that assess attention, memory, decision making, and impulse control [39–45]. Some of these cognitive dysfunctions have been associated with alterations in multiple measures of neural function and gene expression in the PFC, dorsal striatum and nucleus accumbens [39, 40, 43, 46–49]. In the majority of these studies, however, it is difficult to ascertain if adolescents are relatively more sensitive to these effects of drug exposure because comparison groups of adult-exposed subjects were rarely utilized.

The primary aim of the current study was to investigate long-lasting effects of repeated AMPH exposure on locomotor sensitization and cognition in groups of subjects exposed during adolescence or adulthood. In Experiment 1, locomotor activity was measured in an open-field arena after the first and last exposure injection and following cognitive testing. Working memory was assessed using an operant-based delayed matching-to-position (DMTP) task that is sensitive to disruptions in medial PFC function [50, 51]. After rats learned the task, we also assessed reversal learning by switching to a delayed nonmatching-to-position (DNMTP) task and then subsequently evaluated the effects of pharmacological challenges on task performance using AMPH and the NMDA antagonist ketamine. In

Experiment 2, procedural modifications were made to minimize differences in injection and rearing experiences across groups and to increase the difficulty of the working memory component of the task.

2. Materials and Methods

2.1. Subjects

The male subjects used in these experiments were offspring of male and female Sprague-Dawley rats that were originally obtained from Harlan (Indianapolis, IN, USA) and were bred in our animal facility. The exception to this was the adult-exposed groups used in Experiment 1; these rats were obtained from Harlan, shipped to our facility when they were postnatal day (P) 75, and housed individually upon their arrival. Rats born in our facility were housed 2–3 per cage following weaning at P24 and were housed individually after P85. All rats were maintained on a 12:12 hr light/dark cycle (lights on at 0800) with experimental sessions conducted between 0900 and 1800 hr. Rats were handled at least three times for 15 min each prior to being used in experiments. Food was available *ad libitum* before rats were housed individually, but was restricted during operant training and testing so that rats' weights were maintained at approximately 85% of their free feeding weight. Water was always available *ad libitum*. Experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Illinois, Urbana-Champaign, and were consistent with the Principles of Laboratory Animal Care (NIH Publication no. 85–23).

2.2. Apparatus

Locomotor activity was monitored in open-field arenas ($41 \times 41 \times 41$ cm) consisting of transparent acrylic walls and surrounded by photobeam frames (Coulbourn Instruments; Allentown, PA, USA) that recorded horizontal (lower frame; 2.5 cm above the arena floor) and vertical activity (15 cm above the arena floor). Whereas activity monitored with larger grid systems may be influenced by animals' body size [52], the photobeam grid used here is able to capture activity with a 1.27 cm resolution. Computer software (TruScan v 2.01, Coulbourn Instruments) was used to record photobeam breaks and to calculate distance traveled (m). Each open-field arena was housed in a sound-attenuating cubicle ($76 \times 80 \times 63$ cm) that contained a 76 mm speaker fixed to one side wall that played white noise (70 dB), two ceiling mounted white lights (4 W each), and a centrally mounted overhead camera that captured video for offline analysis of stereotyped behavior.

Operant behavior was assessed in standard operant chambers (Coulbourn Instruments). The front panel of each chamber contained a centrally located food trough flanked on either side by a retractable lever (i.e., levers A and B). White cue lights were mounted above each lever. The rear wall contained a white houselight located near the top of the chamber and a recessed nosepoke port containing a red LED light was located near the floor. Infrared photobeam detectors that were positioned in the food trough and nosepoke port were used to monitor head entries. Graphic State (v3.1; Coulbourn Instruments) was used for automated chamber control and data collection.

2.3. Drugs

D-amphetamine sulfate (Experiments 1 and 2) was purchased from Sigma-Aldrich (St. Louis, MO, USA) and dissolved in sterile saline (0.9% NaCl). Ketamine HCl (Experiment 1) was obtained in a 100 mg/ml injectable solution (Ketaset; Pfizer Animal Health; Fort Dodge, IA, USA) and diluted with sterile saline to the appropriate concentrations for injection. All dosages were calculated based on the weight of the salt and injections were given at a volume of 1 ml/kg.

2.4. Experiment 1

2.41. Pre-treatment—The male rats used in this experiment ($n = 50$) were previously used in a study of cocaine-induced locomotor activity and were therefore exposed to a single injection of 10 mg/kg cocaine at either P35 or P95. Subsequently, they were randomly assigned to one of four groups that received 0.9% saline or 3 mg/kg AMPH during late adolescence or young adulthood. Injections were given using an intermittent pattern of exposure with one injection (i.p.) occurring every other day for a total of 10 injections. We previously used this procedure to induce long-lasting behavioral sensitization (> 3 months) in rats exposed in adulthood [53]. Rats in the adolescent-exposed groups ($n = 9$ given saline; $n = 15$ given AMPH) received injections between P37 and P55, whereas those in the adult-exposed group ($n = 7$ given saline; $n = 19$ given AMPH) were injected between P98 and P116. For the first and tenth injections, activity was monitored in the open-field arena 30 min before and 60 min after injection. For injections 2–9, rats were injected in a separate test room and were then placed for 60 min in an acrylic tub ($46 \times 25 \times 22$ cm) lined with hardwood bedding.

2.42. Working memory task—When rats were P85 (adolescent exposed) or P120 (adult exposed), they were placed on food restriction (~ 15 g/day) and were trained starting 5 days later to respond on one of two levers on a continuous reinforcement schedule. Next, rats were trained in daily sessions to perform a no-delay version of a matching-to-position task. For these sessions, which consisted of 100 trials, an individual trial began with the illumination of the houselight and a 5-s ITI. Lever A or B was then presented randomly (with equal probability) and rats were required to respond on the extended lever within 10 s (i.e., sample phase). These responses were followed by retraction of this sample lever and illumination of the cue light in the trough. After the rat poked its nose into the trough, the sample lever was presented again (i.e., choice phase) and a food pellet was subsequently delivered after the rat made another response on that lever. If no response was made, the lever was retracted, the house light was extinguished, and the trial was scored as an omission. After at least two of these training sessions, the procedure was repeated except that both levers were presented during the choice phase. At this training stage, responses on the sample lever were reinforced with food pellet delivery, whereas those that were made on the non-sample lever were scored as incorrect and a 5-s ITI was initiated. Daily training sessions of 112 trials continued until rats achieved 85% correct performance on two consecutive sessions.

During the next training stage, trials were modified such that a delay phase was introduced between the sample and choice phases. Delay intervals were randomly selected from one of seven durations, with initial training utilizing “short delays” of 0, 1, 2, 3, 4, 5, and 6 s. After rats met the performance criterion (85% correct choices over two consecutive sessions), “moderate” delays of 0, 1, 2, 4, 8, 12, and 16 s were introduced. Following initial training, DMTP “long” delays of 0, 2, 4, 8, 12, 18, and 24 s were introduced. This training progression was chosen to avoid response extinction, which sometimes occurs if longer delays are introduced before task acquisition has progressed sufficiently. During these training sessions, each delay was presented on 16 trials, for a total of 112 trials/session. After rats reached criterion at the long delays on DMTP, they were given five additional training sessions (“overtraining”) before the task rule was reversed. In these delayed nonmatching-to-position (DNMTP) sessions, which utilized the long delays (0–24 s), responses during the choice phase that were made on the non-sample lever were reinforced.

2.43. Drug challenges—Following the last DNMTP training session (i.e., second consecutive session of 85% correct), the effects of challenge injections with AMPH and ketamine were assessed in two testing blocks. For the first block, rats were given injections

of vehicle (saline; 1 ml/kg, i.p.) or AMPH (0.3, 0.75, and 1.25 mg/kg, i.p.) 5 min before they were placed in the operant chambers. Injections were given over five consecutive days, with one DNMTTP test session occurring each day (i.e., SDDDS, where S = saline and D = drug). Injections were given over five consecutive sessions (i.e., SDDDS, where S = saline and D = drug). The order of drug doses was chosen based on a Latin square design, with a particular order assigned to each rat randomly. Rats were given a day off from testing before starting the second block of injections. For these tests, saline vehicle or ketamine (5, 7.5, 10 mg/kg, i.p.) was given 10 min before rats were placed in the chamber for their test session. Injection order was assigned randomly and given over five sessions (SDDDS). After their final operant session, rats were given access to food *ad libitum*. One week later, all rats were challenged with 3 mg/kg AMPH (i.p.) using the same open-field locomotor test procedures that were used during their first and tenth pre-treatment injections.

2.44. Data analysis—Data from rats pre-treated with saline during late adolescence ($n = 9$) or adulthood ($n = 7$) were combined because there were no statistically significant differences between these groups in measures of open-field behavior and working memory task performance. Locomotor activity (ambulation) was quantified as the total horizontal distance (m) during the first 60 min post-injection. This measure was calculated from consecutive photobeam breaks (i.e., coordinate changes) using computer software (TruScan; Coulbourn Instruments) that subtracted repetitive behaviors occurring in the absence of ambulation. To characterize bouts of repetitive movement (i.e., stereotypy), video recordings of open-field test sessions were scored using a semi-quantitative method we used previously [53]. Stereotyped behavior included repetitive head movements and sniffing, head bobbing, and/or side-to-side head swaying that were confined to a small area of the chamber and occurred in the absence of locomotion. Trained observers that were not given information about a rat's group membership scored 30 s segments of video taken every 5 min of the 60-min post-injection period. For each segment, behavior was rated for intensity (1-mild, 2-intense, or 3-intense) and duration (seconds spent exhibiting the scored behavior; 0–30 s); these values were then multiplied to give a single score that could range from 0–90. Ambulation and stereotypy data were analyzed using separate two-way ANOVAs, with treatment day (1, 10, and challenge) as the within-subjects factor and group (control, adolescent exposed, and adult exposed) as between-subjects factor. All main effects and interactions were further analyzed using one-way ANOVA and Student-Newman-Keuls comparison procedures.

Performance on the working memory task was measured by calculating the mean percentage of correct choices across sessions and delay blocks and the number of sessions to reach criterion. In order to assess delay-dependent changes in performance during training, rats mean accuracy across delay blocks was compared on the first two sessions a rat from any group met the performance criterion during DMTP (sessions 1 and 2) and DNMTTP (sessions 6 and 7). Separate two-way repeated measures ANOVAs (exposure group x delay) were used to assess delay-dependent changes in performance. A two-way repeated measures ANOVA with treatment group as the between-subjects factor and training phase (DMTP and DNMTTP) as the within-subjects factor was used to analyze the number of sessions to reach criteria. During working memory tasks, the stimuli and responses that occur on previous trials have a significant influence on forgetting across delay intervals on current trials. This process is referred to as proactive interference [54–56]. To assess the effects of proactive interference on rats' performance, accuracy was compared across delays on trials in which the choice response made on the previous trial differed from the correct response required on the current trial (i.e. different trials) and on trials where the correct choice and previous choice response were congruent (i.e. same trials). These data were analyzed separately for DMTP and DNMTTP using three-way repeated measures ANOVAs (exposure group x delay x trial type).

Performance following AMPH and ketamine drug challenges was assessed by calculating three measures: mean percent correct, latency to choice, and the number of trials omitted during each test session. These measures were analyzed using separate two-way repeated measures ANOVAs with exposure group as the between-subjects factor and dose as the within-subjects factor. Proactive interference during drug challenges was assessed using separate three-way ANOVAs (exposure group x trial type x dose) for AMPH and ketamine. Sessions during which an animal failed to complete > 75% of trials were not included in the analysis of percent correct. All main effects and interactions were further analyzed using one-way ANOVA and Student-Newman-Keuls comparison procedures.

2.5. Experiment 2

2.51. Pre-treatment—The experimentally naïve, male rats ($n = 46$) used in this experiment were administered saline or AMPH using similar methods as those used in Experiment 1, but with several changes to the experimental design. First, all rats were offspring of breeders maintained in our facility and they were assigned to exposure groups so that rats from each litter were represented within each group. Second, rats were given injections (i.p.) every other day during both adolescence (P27–45) and young adulthood (P85–103). Those assigned to the control group were given saline (1 ml/kg) at both time points, those in the adolescent-exposed groups were given AMPH (1 or 3 mg/kg) during adolescence and saline during adulthood, and those in the adult-exposed groups were given saline during adolescence and AMPH (1 or 3 mg/kg) during adulthood. A lower dose was included in this experiment in order to further test animals' sensitivity to age-dependent effects of AMPH; a higher dose was not used due to the potential for drug-induced neurotoxicity [57]. Following each injection, rats were placed individually into the same type of enclosures that were used during injections 2–9 in Experiment 1, where they remained undisturbed for 60 min post-injection.

2.52. Working memory task—Rats began operant training after reaching P120. The animals were food deprived (~85%) over a period of 5 days then began lever press training on a continuous reinforcement schedule. Training on the working memory task was similar to that described in Experiment 1, with the following changes. During each trial, a cue light was illuminated above the corresponding sample lever and three lever presses (FR 3) were required during the sample phase to initiate the delay interval. In addition, during the delay interval, rats were required to nosepoke into the nosepoke port located on the rear wall of the chamber. These modifications were implemented to increase the salience of the sample and to discourage further the development of non-mnemonic (e.g., positional) strategies [54]. A final procedural difference from Experiment 1 involved the introduction of longer delay intervals. Rats were trained on DMTP until delay blocks ranged from 0–30 s [delay blocks: 0, 2, 4, 8, 12, 18, 24, 30 s]. Rats progressed to DNMT (0–30 s delays) once they achieved 85% correct on two consecutive sessions.

2.53. Data analysis—Performance during training on DMTP and DNMT was assessed as described for Experiment 1, with individual rats' mean performance across sessions 1 and 2 (DMTP) and 4 and 5 (DNMT) used in the analysis. Separate two-way ANOVAs for DMTP and DNMT were conducted to investigate within session delay-dependent changes in accuracy. A two-way repeated measures ANOVA was used to analyze the number of sessions to criterion during DMTP and DNMT training. Proactive interference during DMTP and DNMT training was assessed using two- and three-way repeated measures ANOVAs. Sessions during which an animal failed to complete > 75% of trials were not included in the analysis of percent correct. All main effects and interactions were further analyzed using one-way ANOVA and Student-Newman-Keuls comparison procedures. All data are presented as group mean $\pm$ SEM.

3. Results

3.1. Experiment 1

3.11. Pre-treatment—AMPH produced significant changes in ambulation and stereotyped behavior following the first (T1) and tenth (T10) injections (Fig. 1). These changes in activity were also evident when an AMPH challenge was given at the conclusion of operant testing, which occurred approximately 4 months after pre-treatment for rats in the adolescent-exposure group and approximately 3 months for those in the adult-exposed group. Separate two-way ANOVAs revealed significant interactions between group and treatment day for ambulation [$F(4,92) = 54.7, p < 0.001$] and stereotypy [$F(4,92) = 14.1, p < 0.001$]. Compared to saline-treated controls, rats in both the adolescent- and adult-exposed groups exhibited significant increases in ambulation and stereotypy the first and tenth injections with 3 mg/kg AMPH. For adolescent-exposed rats, ambulation was elevated to a similar magnitude following the first and tenth injections. In adult-exposed rats, however, there was a significant reduction in ambulation following injection 10 compared to injection 1. All animals received 3 mg/kg AMPH during the challenge session. Compared to saline pre-treated controls, adolescent- and adult-exposed rats displayed significantly less ambulation, but greater stereotyped behavior. The AMPH-exposed groups also showed enhanced stereotypy relative to controls following the injection 10. Stereotypy in both pre-exposed groups reached a maximal level following the AMPH challenge injection. Yet, the overall magnitude of the stereotypy response was lower in adolescent-exposed rats compared to the adult-exposed group after the tenth and challenge injections. Thus, sensitization to AMPH-induced stereotypy was still evident in both pre-exposure groups at the time of AMPH challenge, and these high levels of stereotypy were associated with a concomitant decrease in ambulatory activity these rats.

3.12. Working memory task—Significant impairments in performance during the working memory task were observed in adolescent-exposed rats (Fig. 2). Two-way repeated measures ANOVA (group $\times$ delay) of DMTP accuracy revealed significant main effects of exposure group [$F(2,47) = 5.30, p < 0.01$] and delay [$F(6,282) = 172, p < 0.001$], and a significant group $\times$ delay interaction [$F(12,282) = 1.88, p < 0.05$]. Post-hoc analysis indicated that the accuracy of adolescent-exposed rats was significantly impaired relative to controls and the adult-exposed group when the delay interval exceeded 12 s (Fig. 2A). With repeated training, all rats reached the performance criterion. However, those exposed to AMPH during adolescence required more sessions than rats in the other groups (Fig. 2C). When the task was then reversed to DNMT, performance decreased in all groups and there were no apparent delay-dependent differences (Fig. 2B). Adolescent exposed rats did require more trials to reach the performance criterion, however (Fig. 2C). Two-way repeated measures ANOVA of the sessions to criterion data revealed significant main effects of group [$F(2,47) = 4.20, p < 0.05$] and training phase [$F(1,47) = 177, p < 0.001$]. The interaction between group and training phase was not significant ($p > 0.05$).

In order to assess the extent to which proactive interference contributed to group differences in DMTP performance, accuracy was analyzed on a trial-by-trial basis (Fig. 3). Analysis of these data indicated that rats were less accurate on ‘different’ trials compared to ‘same’ trials when the delay interval exceeded 8 s [significant trial type $\times$ delay interaction: $F(6,282) = 5.90, p < 0.001$]. Furthermore, on different trials, adolescent-exposed rats were significantly less accurate than control and adult-exposed groups at delay intervals 8 s and longer [significant group $\times$ delay interaction: $F(12,282) = 2.53, p < 0.01$]. During DNMT training (data not shown), rats were also less accurate on different compared to same trials [main effect of trial type: $F(1,46) = 35.3, p < 0.001$], but there were no group differences in susceptibility to proactive interference.

3.13. Drug challenges—After rats met the performance criterion on DNMT, they were tested for their response to pre-session challenge injections of AMPH or ketamine (Fig. 4). Separate two-way repeated measures ANOVAs (exposure group x dose) for AMPH and ketamine revealed a main effect of dose for AMPH [$F(3,6) = 51.9, p < 0.001$]. Accuracy was significantly impaired following each challenge dose of AMPH. However, there were no significant effects of ketamine on accuracy [NS main effect of dose, $p > 0.05$], and neither drug was found to influence any one particular group more than others [NS main effects of group, $ps > 0.05$]. Separate three-way repeated measures ANOVAs were used to analyze proactive interference during sessions following drug challenges (Fig. 5). AMPH reduced accuracy on both same and different trials, while ketamine impaired performance only on different trials [significant trial type x dose interactions: $F_s(3,6) = 21.8, ps < 0.001$]. Changes in accuracy following AMPH and ketamine were accompanied by significant increases in the mean number of trials omitted and choice latency (Table 1). Following challenge with 0.75 and 1.25 mg/kg AMPH, and all test doses of ketamine, rats showed a significant increase in omissions [main effects of dose: $F_s(3,6) = 28.6$ and 18.0 , respectively, $ps < 0.001$]. There were no significant effects of AMPH on choice latency; however, ketamine increased choice latency at all doses tested relative to saline [main effect of dose: $F(3,6) = 11.7, p < 0.001$].

3.2. Experiment 2

3.21. Working memory task—In order to extend the findings from Experiment 1, we modified the pre-treatment and working memory task protocols to include a second AMPH dose, control procedures for injection experience, and additional task demands for DMTP and DNMT. As shown in Fig. 6, accuracy during DMTP decreased as a function of the delay interval. Two-way repeated measures ANOVA (exposure group x delay) revealed a main effect of group [$F(4,41) = 3.20, p < 0.05$] and delay [$F(6,246) = 65.7, p < 0.001$]. Rats exposed to 3 mg/kg AMPH during adolescence were significantly impaired relative to rats exposed to the same dose during adulthood. While there were no significant group differences in DNMT performance, all rats showed a significant reduction in accuracy across delays [main effect of delay: $F(6,246) = 39.2, p < 0.001$]. In addition, rats exposed to 1 mg/kg AMPH during adolescence and both adult-exposed groups required significantly more trials to reach criterion on DNMT compared to DMTP [group x training phase interaction: $F(4,246) = 3.00, p < 0.05$]. Follow-up analyses of proactive interference effects revealed that during DMTP training, rats were significantly more accurate on same compared to different trials, with rats exposed to 3 mg/kg AMPH during adolescence particularly susceptible to proactive interference (Fig. 7). The adolescent-exposed group was found to perform significantly worse than all other groups. These effects were confirmed with a three-way repeated measures ANOVA with significant main effects of group [$F(4,41) = 3.30, p < 0.05$], trial type [$F(1,41) = 88.4, p < 0.001$], and delay [$F(6,246) = 64.4, p < 0.001$]. Separate analysis on different trials alone, revealed a significant group x delay interaction, with adolescents exposed to 3 mg/kg performing worse than control and adult-exposed groups [$F(24,246) = 1.59, p < 0.05$]. Analysis of proactive interference during DNMT (data not shown) indicated that rats were less accurate on ‘different’ compared to ‘same’ trials [main effect of trial type: $F(1,41) = 59.9, p < 0.001$], but there were no statistically significant group differences in susceptibility to proactive interference.

4. Discussion

The findings of the present study demonstrate long-lasting effects of AMPH on cognitive performance that are dependent on the developmental time period during which drug exposure occurs. Adult rats that were exposed to AMPH during adolescence displayed delay-dependent deficits in choice accuracy, they required more sessions to optimize

performance and learn task rules, and they were more susceptible to proactive interference, compared to control and adult-exposed groups. AMPH-induced locomotor sensitization, however, was enhanced in adult- compared to adolescent-exposed rats. Thus, AMPH-induced changes in cognition were dissociable from the drug's lasting effects on sensitivity to its motor activating effects. Moreover, the enhanced vulnerability of adolescents to the disruptive effects of repeated AMPH exposure in a medial PFC-sensitive cognitive task suggests that these age-dependent effects may be due to AMPH-induced disruptions in the normal development of the PFC.

Our measures of AMPH-induced activity in an open-field arena (Experiment 1) revealed similar psychomotor activation in adolescents and adults following an acute injection of 3 mg/kg AMPH. In addition, after ten intermittent injections of AMPH, sensitization to the stereotypy-inducing effects of AMPH were evident in both age groups, but this effect was greater in adult-exposed rats, who also displayed a concomitant reduction in ambulation. A similar pattern of ambulation was observed in both age groups following AMPH challenge, although adult-exposed rats again showed more robust stereotypy than animals exposed to AMPH during adolescence. While it is possible that the additional injections of AMPH (0.3, 0.75 and 1.25 mg/kg) and ketamine (5, 7.5, and 10 mg/kg) rats received during DNMTF testing may have influenced the expression of their sensitized behavior following AMPH challenge, all groups (including controls) had this same experience. Inspection of the data shown in Fig. 1 reveals that the magnitude of AMPH-induced activity in rats pre-exposed to saline (i.e., controls) was similar to that seen in adult-exposed rats during their first treatment. Thus, it's unlikely that the drug challenges during the working memory task had differential effects among the groups.

Age-dependent differences in AMPH-induced activity in rats and mice have been documented previously, with some studies showing that adults are more sensitive to acute AMPH compared to adolescents [58–60]. Others, however, report no age-dependent differences [58, 61–63]. There are also inconsistent findings for AMPH-induced sensitization. Some studies report greater AMPH-induced sensitization in adolescent-exposed rodents [61, 64–66], whereas others indicate greater effects in adults [44, 67, 68] or no difference between age groups [62, 68]. Methodological differences contribute to some of these discrepant findings, with key factors being AMPH dose and the aspect of drug-induced behavior that is measured (e.g., locomotion or stereotypy). At lower doses (< 1.5 mg/kg), adolescents tend to show an attenuated response to the first injection but enhanced locomotor sensitization relative to adults [58, 59, 67, 69]. With higher doses (> 2 mg/kg), however, age-dependent differences in initial responsiveness diminish and repeated exposure produces robust stereotypy and reduced locomotor activity, particularly in adults, as shown here and elsewhere [61, 70]. Thus, adolescents appear to have a higher threshold for the psychomotor-activating effects of AMPH, but once activated their response is similar to that seen in adults. In addition, their qualitatively different pattern of sensitization following repeated exposure suggests the neuroadaptations induced by repeated AMPH exposure may be unique in adolescents relative to adults. Interestingly, age-dependent differences in AMPH-induced behavior are often not observed unless subjects experience a period of withdrawal. For example, sensitization is expressed following repeated AMPH exposure during adolescence only when animals are challenged weeks later [71, 72]. Two potential explanations for this phenomenon are that AMPH-induced neuroadaptations in adolescent-exposed animals are not evident until adulthood, or alternatively, that plasticity in younger animals is enhanced following an extended drug withdrawal period. Dissociating these two hypotheses in rodents may prove difficult given the relative brevity of the adolescent time period. Nevertheless, future studies are needed to elucidate the potential role that drug withdrawal plays in the age-dependent effects of AMPH on plasticity and behavior.

In both Experiments 1 and 2, we observed age-dependent differences in the effects of AMPH on working memory. Rats exposed to 3 mg/kg AMPH during adolescence, but not those exposed during adulthood, showed delay-dependent deficits in choice accuracy during DMTP training. Analyses of proactive interference indicated the impaired performance of adolescent-exposed rats was largely due to decreased accuracy on different trials. On these trials, their accuracy dropped to near chance at longer delays. This floor effect may have contributed to the lack of group differences in overall accuracy at longer delays observed in Experiment 2. Nevertheless, rats exposed to AMPH during adolescence in both experiments were more susceptible to proactive interference compared to control and adult-exposed animals. Previous have shown that acute exposure to psychostimulants impairs performance on DMTP tasks via proactive interference [55, 73]. Enhanced susceptibility to proactive interference is suggested to reflect difficulties with encoding and organizing stimulus events and behavioral responses across trials. Thus, accuracy is often worse on trials with incongruent stimuli and/or choices compared to previous trials [54–56, 74]. The results reported here extend these earlier findings to suggest that repeated exposure to AMPH during adolescence has a lasting impact on proactive interference and DMTP performance. In addition to the deficits in choice accuracy found within sessions, adolescent-exposed rats also required a greater number of sessions to reach performance criterion on both DMTP and DNMT. Age-dependent differences in the rate of acquisition were only observed in Experiment 1. In order to further explore the specificity of AMPH exposure during adolescence and the degree of cognitive impairment from that exposure, Experiment 2 was performed with a few procedural changes.

First, in order to better control for group differences in rearing environment and injection experience, rats in Experiment 2 were offspring of dams bred in our facility and all animals received injections during both adolescence and adulthood. The pre-treatment injections in Experiment 2 also began earlier in adolescence (P27) and young adulthood (P85) compared to those in Experiment 1 (P37 and P98). Rearing environment and early-life stress can have significant effects on PFC development and cognitive processes mediated by this brain region [75–79]. There are also numerous reports demonstrating the long-lasting effects of rearing conditions on drug-induced behavior [80–82]. Second, the working memory task was altered such that a wider range of delay intervals was used and rats were required to perform a response at the nosepoke port on the chamber wall opposite to the sample before the choice phase began. The former change was made because delay-dependent deficits in Experiment 1 were found at the longest delay interval tested (i.e. 24 s). The requirement for a nosepoke response at the back wall of the chamber was implemented to better control for the development of mediating behavior and non-mnemonic performance strategies that may arise with increased task difficulty or following psychostimulant exposure [54]. Notably, we and others have shown that repeated AMPH exposure alters the development of conditioned approach and attention/perseverative behaviors [18, 42, 83, 84]. The fact that the results of Experiments 1 and 2 are largely consistent provides strong support for the interpretation that intermittent exposure to a moderately high dose of AMPH induces cognitive dysfunction that is long-lasting and dependent on the age of exposure.

Interestingly, the deficits displayed by adolescent-exposed animals in the present study are similar to those observed in PFC-lesioned animals performing DMTP [51]. There are numerous reports showing that damage to the medial PFC produces selective deficits in working memory performance, increased sensitivity to proactive interference, and impaired attention [50, 51, 85–87]. Adolescent-exposed rats in the present study showed decreased accuracy and greater susceptibility to proactive interference that was most pronounced at delay intervals between 12 to 24 s. Rats were not impaired at short delays, suggesting the deficits found here are due primarily to mnemonic dysfunction, rather than delay-independent disruptions in mediating behavior or attention. However, attention deficits

cannot be ruled out entirely because rats' accuracy was susceptible to proactive interference, which requires attention allocated to the sample stimulus within each trial [73, 88]. Given that adolescent-exposed rats were impaired on different trials at longer, and not shorter delays, suggests that if non-mnemonic deficits were induced by repeated AMPH exposure, they were not significant enough to impair performance when task demands were relatively easier at short delays [50, 89].

A candidate mechanism for these effects of AMPH is altered signaling in the mesocorticolimbic system. The PFC and interconnected subcortical areas, such as the hippocampus and striatum, undergo significant structural and functional plasticity with repeated exposure to AMPH during adolescence [90–94]. Notably, AMPH [65], MDMA [95], and binge-like exposure to methamphetamine [96] have been shown to produce unique, age-dependent effects on glutamate and dopamine activity in the PFC. In addition, AMPH has a significant effect on neuronal excitability and dopamine release in animals exposed to the drug during adolescence [72, 92, 97]. Electrophysiological studies from our lab and others indicate that repeated exposure to AMPH modulates the single-unit spike and bursting activity of pyramidal neurons in the mPFC of awake behaving adult rats [98, 99]. Interestingly, changes in single-unit activity tend to emerge along the same timeline as behavioral sensitization. To our knowledge, there have not been similar studies performed with adolescent animals, though they are necessary given the differences in plasticity and sensitization reported here and elsewhere [38]. The mesocorticolimbic network undergoes significant changes as individuals progress from adolescence to adulthood, with the PFC 'maturing' more slowly than other structures. These differences may contribute to less coordinated signaling between cortical and subcortical regions during adolescence [100]. Given the importance of the PFC in AMPH-induced sensitization and working memory performance, future studies are needed to elucidate the role age-dependent plasticity in the PFC plays in the differences observed here.

In the present study, pharmacological manipulation of glutamate and dopamine systems with challenge injections of AMPH or ketamine had differential effects on DNMT performance. AMPH dose-dependently reduced accuracy overall, while both drugs enhanced rats' sensitivity to proactive interference. The importance of glutamate and dopamine systems in working memory tasks has been well documented [101, 102], and, consistent with previous reports, rats' performance was impaired on different trials following challenge with drugs that target these systems [73, 89]. Additionally, the number of trial omissions and choice latencies were increased following drug challenge. These findings suggest that rats may have become disoriented while performing the task and as a result they were more susceptible to proactive interference [50, 89]. This hypothesis is further supported by studies showing that the organization of delay mediating behaviors and instrumental actions are disrupted by manipulations of dopamine and glutamate activity in the PFC [86, 103, 104]. Despite differences in working memory performance during task acquisition, all groups were eventually performing with similar accuracy, and continued to do so during AMPH and ketamine challenge sessions. Given that drug challenge occurred following extensive training, the lack of group differences could be due to "overtraining" on the task. Previous studies indicate that impairments in working memory and proactive interference following PFC lesions dissipate with training [105, 106]. What's more, numerous studies in laboratory animals suggest that working memory training and increased performance on working memory tasks are associated with plasticity in dopamine and glutamate systems [107–110]. Our findings are consistent with this notion. Interestingly, there is growing evidence that cognitive enhancement mitigates the effects of long-term psychostimulant misuse and may be a valuable treatment technique for individuals who suffer from substance use disorders [111–113].

In conclusion, the results presented here suggest that repeated, intermittent exposure to AMPH during adolescence has long-lasting consequences on drug sensitivity and cognitive function. While previous studies from our lab and others have demonstrated the negative consequences of psychostimulant exposure during adolescence [39, 42, 43], the present findings indicate that repeated exposure to AMPH at this age produces long-lasting mnemonic dysfunction. Thus, it is likely that age-dependent differences in cognitive dysfunction following repeated exposure to AMPH are the result of unique and persistent neuroadaptations in animals still undergoing neural development. AMPH-induced dysfunction in the PFC may be an important mediating factor in the observed cognitive impairments. This hypothesis will require further investigation, but it is noteworthy that adolescent development is marked by periods of altered receptor expression and signaling, increased synaptic pruning, and myelination in multiple brain regions, including the PFC [32, 36, 114–117]. Future studies employing neurophysiological and neuroanatomical methods are warranted to elucidate the specific neuroadaptations that accompany long-term cognitive dysfunction in animals exposed to AMPH during adolescence.

Acknowledgments

This study was supported by a grant from the National Institute on Drug Abuse (R01 DA029815). We thank Avishkar Sharma and Alex McClory for technical assistance.

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- Amphetamine-induced sensitization is greater in adults than adolescents.
- Exposure to amphetamine in adolescence leads to cognitive deficits later in life.
- Amphetamine exposure during young adulthood did not impair working memory.
- The effects of amphetamine on activity and cognition vary with age.

Figure 1.

Ambulatory activity and stereotypy ($n = 15\text{--}19$ rats/group) during the first (T1) and tenth (T10) saline or 3 mg/kg AMPH treatment and after a challenge with 3 mg/kg AMPH, which was given after training and testing in the working memory task. For ambulation (A), data are presented as the mean cumulative activity during the 60 min after injection. For stereotypy, scores obtained every 5 min after injection were averaged to yield a single rating for the post-injection period. *** $p < 0.001$, compared to AMPH-exposed groups within treatment day; matching letters indicate significant differences (ambulation: $p < 0.01$; stereotypy: $p < 0.01$, for a,b,c,d,e and $p < 0.05$, for f,g).

Figure 2.

Performance on the working memory task in rats from Experiment 1 ($n = 15\text{--}19/\text{group}$). Shown in (A) and (B) is mean choice accuracy (% correct) within each delay block averaged across the first two training sessions that any rat achieved the performance criterion. These were sessions 1–2 for DMTP and sessions 6–7 for DNMT. Shown in (C) is the mean number of sessions to reach a performance criterion (STC) of 85% correct choices for two consecutive sessions. Matching letters indicate $p < 0.001$; *** $p < 0.001$ vs control and adult-exposed groups within delay; ### $p < 0.001$ vs DNMT, collapsed across exposure group.

Figure 3. Proactive interference during DMTP training in rats from Experiment 1 ($n = 15-19/\text{group}$). Delay-dependent performance was assessed across delay blocks in trials that required either the same correct response (A) or a different correct response (B) compared to the choice made on the immediately preceding trial. Shown are the group means within each delay block averaged across the first two training sessions on DMTP. ** $p < 0.01$ vs control; # $p < 0.05$ vs adult, within delay.

Figure 4. Effects of challenge injections with AMPH (A) or ketamine (B) on task performance in Experiment 1 (n = 15–19 rats/group). Drugs were administered i.p. 5–10 min prior to the start of DNMT sessions. *** $p < 0.001$ vs 0 (saline), collapsed across exposure group.

Figure 5.

Proactive interference during sessions following drug challenges in Experiment 1 ($n = 15-19$ rats/group). Performance was assessed in trials that required either the same correct response or a different correct response compared to the choice made on the immediately preceding trial following AMPH (A and C) and ketamine (B and D). Shown are the group means for each dose tested. $**p < 0.01$ vs 0 (saline), collapsed across exposure group.

Figure 6.

Performance on the working memory task in rats from Experiment 2 ($n = 8-10/\text{group}$). Data in (A) and (B) are presented as in Fig. 2. Because there were no significant effects of treatment on sessions to criterion (STC), data in (C) are plotted to emphasize differences in STC on DMTP compared to DNMTP. Criterion performance was 85% correct for two consecutive sessions. Matched letters indicated significant difference ($p < 0.05$); * $p < 0.05$ vs adult-exposed (3.0 mg/kg) group.

Figure 7. Proactive interference during DMTP training in rats from Experiment 2 ($n = 8-10/\text{group}$). Data were analyzed and presented as in Fig. 2. $\#p < 0.05$ vs adult (3.0) within delay; $+p < 0.05$ vs adult (1.0) within delay; $*p < 0.05$ vs control within delay.

Effects of AMPH and ketamine challenges on choice latencies and the number of trials omitted during the working memory task in Experiment 1. Rats had a maximum of 10 s to respond on a lever during the choice phase before the trial was scored as an omission. The omission data also include trials wherein rats failed to respond in 10 s during the sample phase. Numbers in parentheses indicate the number of rats/group.

Table 1

Latency (s)	AMPH (mg/kg)				Ketamine (mg/kg)			
	Saline	0.3	0.75 ^{^^}	1.25 ^{^^}	Saline	5.0 ^{***}	7.5 ^{***}	10 ^{***}
Control (n=16)	0.67 ± 0.04	0.63 ± 0.05	0.57 ± 0.04	0.66 ± 0.04	0.62 ± 0.03	0.65 ± 0.04	0.61 ± 0.04	0.71 ± 0.04
Adolescent exposed (n = 15)	0.58 ± 0.04	0.55 ± 0.04	0.64 ± 0.05	0.56 ± 0.04	0.58 ± 0.04	0.69 ± 0.04	0.76 ± 0.04	0.67 ± 0.04
Adult exposed (n = 19)	0.46 ± 0.04	0.44 ± 0.04	0.51 ± 0.04	0.51 ± 0.04	0.46 ± 0.03	0.57 ± 0.04	0.61 ± 0.04	0.71 ± 0.04
Omissions (number/session)								
Control (n=16)	3.56 ± 5.91	11.4 ± 5.91	15.1 ± 5.91	41.8 ± 5.91	4.63 ± 9.06	21.3 ± 9.06	35.9 ± 9.06	58.7 ± 9.06
Adolescent exposed (n = 15)	0.27 ± 6.10	7.98 ± 6.52	30.8 ± 6.52	45.8 ± 6.52	0.53 ± 9.36	24.5 ± 10.0	39.2 ± 10.0	41.6 ± 10.0
Adult exposed (n = 19)	2.05 ± 5.42	0.90 ± 5.42	14.1 ± 5.42	40.3 ± 5.42	1.58 ± 8.31	38.0 ± 8.31	50.8 ± 8.31	60.5 ± 8.31

^{^^} $p < 0.001$, compared to saline (omissions only, collapsed across exposure group);

^{***} $p < 0.01$, compared to saline (latency and omissions, collapsed across exposure group).