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Adolescent exposure to methylphenidate impairs serial pattern learning in the serial multiple choice (SMC) task in adult rats

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ABSTRACT

The long-term effects of adolescent exposure to methylphenidate (MPD) on adult cognitive capacity are largely unknown. We utilized a serial multiple choice (SMC) task, which is a sequential learning paradigm for studying complex learning, to observe the effects of methylphenidate exposure during adolescence on later serial pattern acquisition during adulthood. Following 20.0 mg/kg/day MPD or saline exposure for 5 days/week for 5 weeks during adolescence, male rats were trained to produce a highly structured serial response pattern in an octagonal operant chamber for water reinforcement as adults. During a transfer phase, a violation to the previously-learned pattern structure was introduced as the last element of the sequential pattern. Results indicated that while rats in both groups were able to learn the training and transfer patterns, adolescent exposure to MPD impaired learning for some aspects of pattern learning in the training phase which are learned using discrimination learning or serial position learning. In contrast adolescent exposure to MPD had no effect on other aspects of pattern learning which have been shown to tap into rule learning mechanisms. Additionally, adolescent MPD exposure impaired learning for the violation element in the transfer phase. This indicates a deficit in multi-item learning previously shown to be responsible for violation element learning. Thus, these results clearly show that adolescent MPD produced multiple cognitive impairments in male rats that persisted into adulthood long after MPD exposure ended.

1. Introduction

Methylphenidate (MPD) is a psychostimulant that is related to caffeine, amphetamine, and cocaine (Urban and Gao, 2013). At the height of its use in the 1990s, more than 2 million children were prescribed MPD (Challman and Lipsky, 2000) and it continues to be the preferred pharmacotherapy for the treatment of attention-deficit–hyperactivity disorder (ADHD) (Gray et al., 2007; Teter et al., 2003; Urban and Gao, 2013). MPD has also been identified as a potential drug of abuse and its illicit use has been on the rise within the past decade (Teter et al., 2003). While acute and chronic low doses of MPD (as prescribed for licit use) have been shown to improve cognitive function in rodents (Arnsten and Dudley, 2005; Berridge et al., 2006; Mohamed et al., 2011) chronic high doses of MPD have been shown to create more deleterious effects on the brain which often persist into adulthood (Bolanos et al., 2003; Brandon et al., 2001; Carlezon et al., 2003; Gray et al., 2007; LeBlanc-Duchin and Taukulis, 2007; Mcdougall et al., 1999; Scherer et al., 2010). For example, adolescent rats chronically exposed to high doses of MPD demonstrate impaired emotional response, poor object memory, and increased cross-sensitivity to other stimulants in adulthood (Bolanos et al., 2003; Brandon et al., 2001; Carlezon et al., 2003; LeBlanc-Duchin and Taukulis, 2007). High doses of MPD in prenatal, juvenile, and adult animals have also been shown to cause cognitive deficits such as impairments in spatial memory, delayed alternation performance, and working memory (Arnsten and Dudley, 2005; Levin et al., 2011; Scherer et al., 2010).

These studies illustrate that the effects of prolonged exposure to MPD treatment on brain structure and function might vary according to the dose and pattern of drug administration, as well as the complexity of the task involved (e.g., Bethancourt et al., 2009). Given the widespread usage of MPD among humans during the developmentally sensitive periods of childhood and adolescence, understanding potential long-term effects on neuronal systems and resultant behaviors is desirable (e.g., Grund et al., 2006). However, research on the long-lasting effects of MPD during adolescence is limited, and little work has examined

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the effects of adolescent exposure to MPD on complex learning, especially effects that might persist after exposure ends. Thus the goal of the current study was to assess how exposure to MPD during adolescence affects complex learning and memory in adulthood in a rat model.

To assess potential long-lasting developmental effects of MPD, the current experiment utilized a dosing and testing schedule previously successful in studies of adolescent drug exposure effects on adult rodents (Fountain et al., 2008; Kelley and Middaugh, 1999; Kelley and Rowan, 2004; Pickens et al., 2013). Rats were exposed to either the drug or saline for a five-week period, then they were given a five-week drug-free period before behavioral assessment began. This procedure allowed the drug to clear the subject's system, enabling assessment of developmental effects as opposed to the direct effects of the drug.

To assess effects of adolescent MPD exposure on adult cognitive systems, the current experiment examined the effects of adolescent MPD exposure on serial pattern learning in a SMC task in adult rats. This task was designed to be a close analog of a nonverbal method used in human studies to evaluate higher-level cognitive functions (Fountain, 2006; Fountain and Benson, 2006; Fountain and Rowan, 2000; Fountain et al., 2007; Stempowski et al., 1999). Serial pattern learning requires the subject to learn to expect and react to a prearranged patterned series of events; that is, subjects must learn to produce highly-organized patterns of behavior (Fountain, 2006; Fountain and Benson, 2006; Fountain et al., 2008). In the SMC task, rats are required to learn complex serial patterns which have been shown to recruit multiple cognitive systems concurrently, including stimulus–response (S–R) learning, multiple item memory, and abstract rule learning (for a review see, Fountain et al., 2012). Furthermore, prior research has shown that adolescent exposure to another stimulant, nicotine, causes learning impairments in adulthood in the SMC task (Fountain et al., 2008; Pickens et al., 2013). Other work with the SMC task has also demonstrated that adolescent nicotine causes both impairment and facilitation of different aspects of pattern acquisition in the same adult rats (Renaud et al., 2015). The ability to characterize drug-related effects on multiple cognitive systems concurrently in the same animals makes serial pattern learning in the SMC task ideal for assessing the effects of adolescent exposure to MPD on complex learning in adulthood.

2. Methods

2.1. Animal care and drug treatment

All procedures were approved by the institution's Animal Care and Use Committee. 14 Long Evans male rats were received on postnatal day 21 (P21) and were individually housed in stainless steel hanging cages throughout the experiment with free access to food and water. They were randomly assigned to one of two treatment groups (saline = 6; MPD = 8) on P25. For five consecutive days each week for five weeks, subjects received daily intraperitoneal injections of 20.0 mg/kg of MPD in saline solution or saline based on their body weight (1 ml/kg). As this was the first experiment performed to assess the effects of adolescent exposure to MPD in the serial pattern learning task, the current study utilized a high dose model of MPD to maximize the likelihood of detecting possible effects lasting into adulthood. Following five consecutive days of dosing each week, rats received two consecutive days free of injections, thus mimicking the common clinical practice of giving children “weekend holidays” from methylphenidate (Martins et al., 2004). Following five weeks of this dosing schedule, rats were given a 35-day drug-free period prior to the initiation of serial pattern learning training in the SMC task described below.

2.2. Apparatus

Four Plexiglas shaping chambers (30 × 30 × 30 cm) with stainless steel mesh floors and a single nosepoke receptacle 5 cm above the floor on one wall were employed. Nosepoke receptacles were constructed from 3.0-cm diameter PVC pipe end caps painted flat black with infrared emitter-detector pairs mounted on the sides and a cue light mounted in the rear of the receptacle. A solenoid (General Valve Corp., 20 psig, 24 V) was attached by tubing to a water opening at the bottom of each receptacle. A 20 ml syringe served as a water reservoir for each receptacle. Each shaping chamber was housed in a separate particleboard sound-attenuating shell.

Four clear Plexiglas training/test chambers were octagonal in shape (15 cm wide × 30 cm tall with 40 cm separating opposing walls) with a stainless steel mesh floor (Fig. 1). One nosepoke receptacle, as described above, was centered 5 cm above the floor on each of the eight chamber walls. Each test chamber was housed in a separate particleboard sound-attenuating shell.

2.3. Procedure

2.3.1. Shaping procedure

A timeline of experimental procedures is depicted in Fig. 2. Before experimental testing began, all rats underwent shaping for two days after 48 h of water deprivation. In 1-h nosepoke shaping sessions, the receptacle light was illuminated at the beginning of each trial. When the rat responded, the light was extinguished and a water droplet was delivered. A 1-s intertrial interval separated shaping trials. Rats were required to complete 240 nosepokes per day in the shaping chambers in order to continue to the training phase. All rats were successful in completing the shaping training.

2.3.2. Training phase: acquisition of a perfect pattern

After every second day of training, rats drank freely until satiated (about 5 min); subsequently, the water was removed to continue water deprivation. Starting on P95, rats performed 5 repetitions of the following “perfect” serial pattern: 123-234-345-456-567-678-781-812, every day for 49 days. As described above, the integers refer to the clockwise position of the 8 nosepoke receptacles while dashes indicate 3-s intertrial intervals (ITIs) that served as phrasing cues. An intertrial interval of 1 s was imposed between elements within each 3-element chunk. Additionally, a 3-s pause was also positioned between patterns to serve as an interpattern interval. The first digit of each

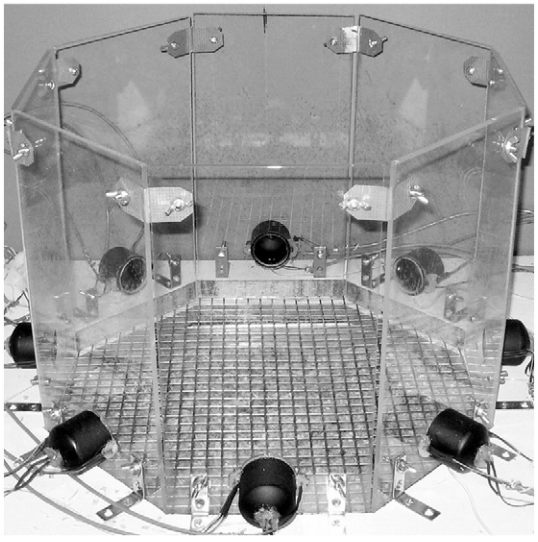

Fig. 1. Octagonal operant chamber used for serial pattern learning training. Chamber is made up of 8 walls each equipped with a nosepoke receptacle. Each receptacle contained an infra-red emitter and detector which were located on the left and right sides as well as a white LED cue light positioned on the back of the receptacle. An opening located at the bottom of each receptacle, connected to a solenoid and syringe by plastic tubing, served to deliver water to the chamber.

Fig. 2. Timeline of experimental methods and procedures. Rats were weaned on postnatal day 21 (P21). Exposure to methylphenidate of saline occurred 5 days a week between P25 and P59. Starting on P95, rats completed 49 days of serial pattern learning training of a perfect pattern (ending on P144). On the following day, P145, rats were transferred to a violation pattern and completed 28 days of transfer training (ending on P173).

chunk is called a chunk-boundary element and the two digits following the chunk boundary are called within-chunk elements.

During the training phase, at the beginning of each trial, the receptacle lights in all eight nosepoke receptacles were illuminated. If the rat's first response on a given trial was made within the correct receptacle, the response was recorded as correct, all receptacle lights were extinguished, and a droplet of water was administered. However, if the rat's first response on a trial was an incorrect response, the response was recorded as incorrect for that trial and a correction procedure was administered. In the correction procedure, all receptacle lights except for the light within the correct nosepoke receptacle were extinguished. The receptacle light within the correct receptacle remained illuminated, and water reward was administered only after the rat chose the correct receptacle. This correction procedure assured that rats received feedback regarding the correct response on each trial. Rats completed five patterns per day for 49 days.

2.3.3. Transfer phase: acquisition of an added violation element

In the next phase of the experiment (transfer phase), the rats learned a pattern that now contained a violation of the pattern structure that they had learned during their initial training. In the initial training phase, the rats had learned the pattern 123-234-345-456-567-678-781-812. In this transfer phase, a violation was inserted for the final pattern element to create the pattern 123-234-345-456-567-678-781-818. The ending 818 is a violation of the run rule governing the 'perfect' serial pattern learned in their initial training. The rats completed five transfer patterns per day for 28 days during this phase.

2.4. Statistical analysis

The SPSS statistical package (version 21.0, Chicago, IL) was used for all statistical analyses. Repeated measures ANOVAs and subsequent planned comparisons using Fisher's Least Significant Difference tests based on the appropriate error term from the ANOVA were conducted to assess significant effects. Results were considered significant if $p < 0.05$.

3. Results

3.1. Training phase: acquisition of a perfect pattern

Analyses were conducted to determine whether exposure to MPD affected the various aspects of pattern acquisition. Overall, the results of this experiment show that exposure to MPD impaired acquisition of some aspects of a serial pattern.

For acquisition of within-chunk elements (Fig. 3), a 2 × 49 (drug exposure × days) repeated measures analysis of variance (ANOVA) found a significant main effect of days, $F(48,576) = 25.05$, $p < .001$. No other main effect or interactions were significant ($p > .05$). Exposure to MPD had no significant effect on acquisition of within-chunk elements.

For acquisition of chunk-boundary elements (Fig. 4), a 2 × 49 (drug exposure × days) repeated measures ANOVA found a significant main effect of days, $F(48,576) = 28.17$, $p < .001$, and drug $F(1, 12) = 4.83$, $p = .048$. No other main effect or interactions were significant ($p > .05$). Planned comparisons based on the appropriate error term from the ANOVA showed that rats exposed to MPD made significantly fewer correct responses than controls on days 13, 15–17, 20–25, 27–29, 31–39, 43, 46, 48, and 49 ($p < .05$). These results indicate that exposure to MPD significantly impaired chunk-boundary element learning.

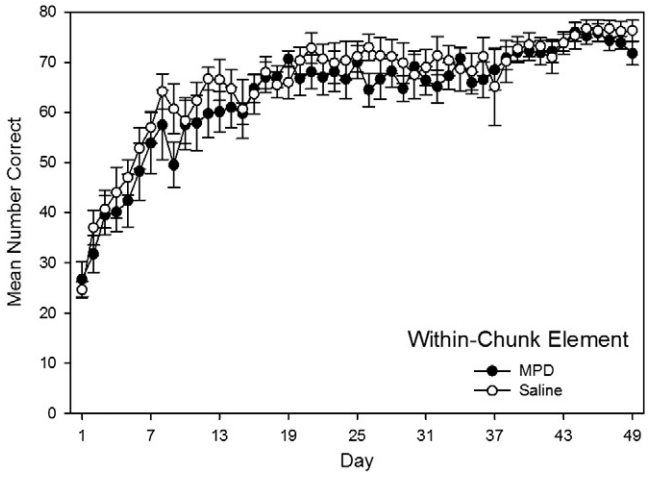

Fig. 3. Acquisition of within-chunk elements for the 49 days of the training phase beginning on P95. Rats received intraperitoneal injections of 20.0 mg/kg/day methylphenidate (MPD) or an equivalent volume of saline for 5 days/week for 5 weeks during adolescence. Mean number of correct responses were averaged for each day of training. No significant differences were observed between groups ($p > .05$). Error bars: ±SEM.

3.2. Transfer phase: introduction of a violation element

Analyses were conducted to determine whether exposure to MPD affected performance on the within-chunk and chunk-boundary element as well as acquisition of the violation element during the transfer phase.

For continued performance on within-chunk elements during the transfer phase, a 2 × 28 (exposure × days) repeated measures analysis of variance (ANOVA) found a significant main effect of days, $F(27,324) = 2.39$, $p < .001$. No other main effect or interactions were significant ($p > .05$). As shown in Fig. 5, exposure to MPD had no apparent effect on within-chunk performance.

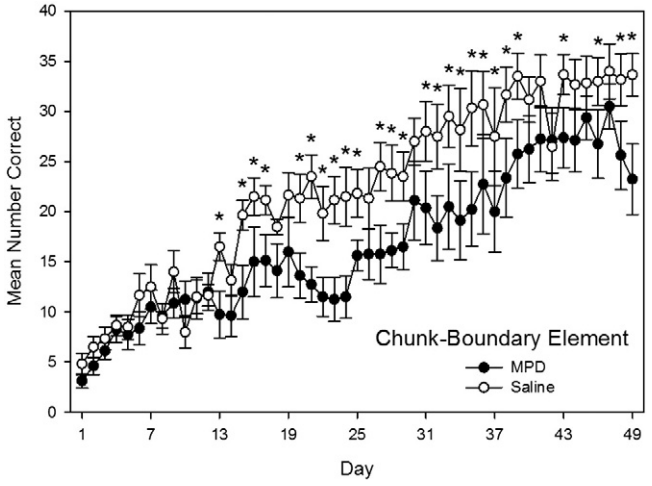

Fig. 4. Acquisition of chunk-boundary elements for the 49 days of the training phase beginning on P95. Rats received intraperitoneal injections of 20.0 mg/kg/day methylphenidate (MPD) or an equivalent volume of saline for 5 days/week for 5 weeks during adolescence. Mean number of correct responses were averaged for each day of training. Error bars: ±SEM. *$p < 0.05$.

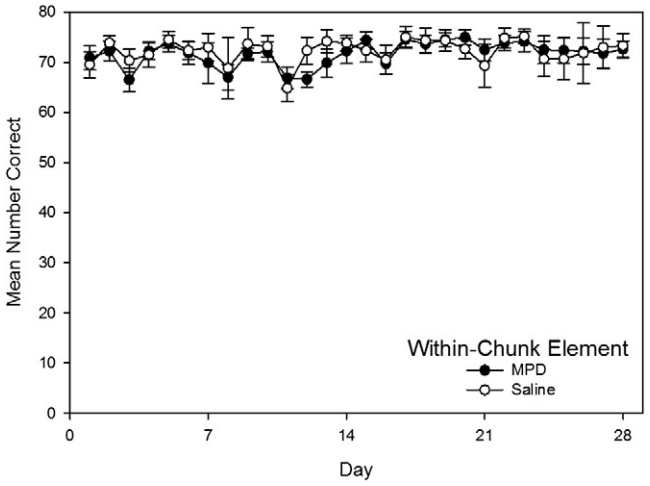

Fig. 5. Performance on within-chunk elements for the 28 days of the transfer phase. Rats received intraperitoneal injections of 20.0 mg/kg/day methylphenidate (MPD) or an equivalent volume of saline for 5 days/week for 5 weeks during adolescence. Mean number of correct responses were averaged for each day of training. No significant differences were observed between groups ($p > .05$). Error bars: ±SEM.

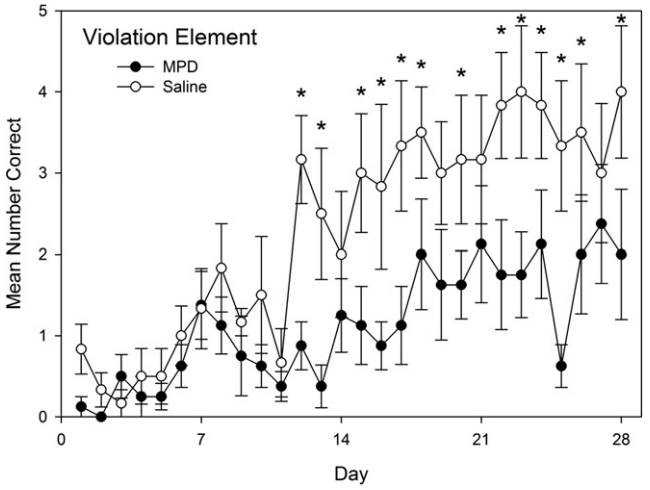

Fig. 7. Acquisition of a violation element for the 28 days of the transfer phase. Rats received intraperitoneal injections of 20.0 mg/kg/day methylphenidate (MPD) or an equivalent volume of saline for 5 days/week for 5 weeks during adolescence. Mean number of correct responses were averaged for each day of training. Error bars: ±SEM. *$p < 0.05$.

For continued acquisition of chunk-boundary elements during the transfer phase (Fig. 6), a 2 × 28 (drug exposure × days) repeated measures ANOVA found a significant main effect of days, $F(27,324) = 8.60$, $p < .001$. No other main effect or interactions were significant ($p > .05$). Planned comparisons based on the appropriate error term from the ANOVA showed that rats exposed to MPD made significantly fewer correct responses than controls on days 3, 5, 7, 8, 12, 13, 15, 16, and 23 ($p < .05$). These results indicate that exposure to MPD impaired performance on chunk-boundary elements during the transfer phase, but only on some days.

For acquisition of violation element (Fig. 7), a 2 × 28 (drug exposure × days) repeated measures ANOVA found a significant main effect of days, $F(27,324) = 7.24$, $p < .001$, and drug $F(1, 12) = 9.95$, $p = .008$. No other main effect or interactions were significant ($p > .05$). Planned comparisons based on the appropriate error term from the ANOVA showed that rats exposed to MPD made significantly fewer correct responses than controls on days 12, 13, 15–18, 20, 22–26, and 28 ($p < .05$). These results indicate that exposure to MPD significantly impaired violation element learning.

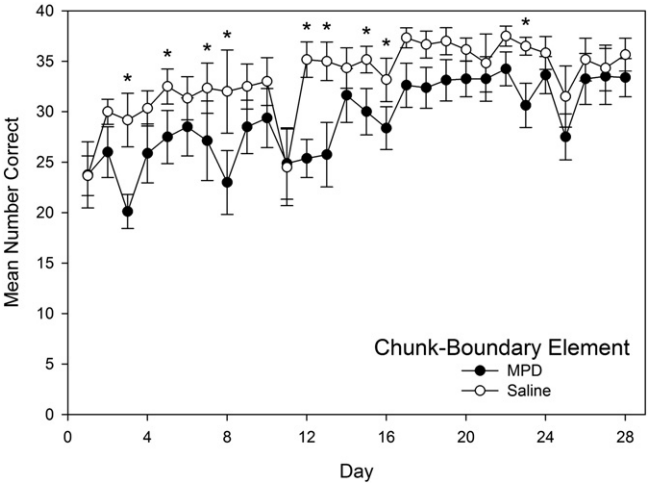

Fig. 6. Performance on chunk-boundary elements for the 28 days of the transfer phase. Rats received intraperitoneal injections of 20.0 mg/kg/day methylphenidate (MPD) or an equivalent volume of saline for 5 days/week for 5 weeks during adolescence. Mean number of correct responses were averaged for each day of training. Error bars: ±SEM. *$p < 0.05$.

4. Discussion

The results indicate that chronic adolescent exposure to high doses of MPD in rats produced persistent neurobehavioral effects that were observed as impairments of serial pattern learning during adulthood long after MPD exposure had ended. While rats receiving MPD during adolescence were able to learn their serial pattern, they showed significant impairments relative to saline controls for some aspects of the pattern, but not others. More specifically, rats in the MPD group evidenced significantly more difficulty in acquiring responses to chunk-boundary elements and the violation element relative to saline controls. MPD did not significantly impair within-chunk element learning. The results resemble the pattern of effects found for adult serial pattern learning in the SMC task after rats have been exposed to adolescent nicotine (Fountain et al., 2008; Pickens et al., 2013). Specifically, adolescent nicotine exposure impaired adult male rat learning of chunk-boundary elements while leaving within-chunk element learning unaffected, as adolescent nicotine does in adult male rats, whereas, adolescent nicotine exposure has little, if any, effect on adult male rat violation element learning (Pickens et al., 2013). Thus, even when rats are exposed to high doses of MPD for only 5 days each week during adolescence, the effect of this exposure on adult cognitive abilities appears to be somewhat more pronounced than the effects of adolescent nicotine that is given on a daily basis during adolescence.

The differential effects caused by adolescent exposure to MPD for each element type indicate that the observed impairments were not caused by general motor impairments due to drug exposure. Adolescent MPD induced impairments of adult learning were observed for both chunk-boundary and violation element acquisition. However, contrary to the notion of a general impairment, no impairment was observed for within-chunk elements; rats in the MPD group displayed acquisition equivalent to that of rats in the saline-control group for within-chunk elements.

The results also fit well with previous studies showing that different cognitive processes, involving different neural and behavioral systems, are recruited in rat serial pattern learning in the SMC task (Fountain et al., 2000, 2008; Kelley and Middaugh, 1999). Briefly, our research indicates that serial pattern learning in the SMC task involves associative stimulus response (S–R) learning, multiple cue learning, and rule abstraction (Fountain and Benson, 2006; Fountain et al., 2008, 2012;

Kundey and Fountain, 2010; Muller and Fountain, 2010). Learning to anticipate chunk-boundary elements, for example, depends on concurrently using associative S–R learning and serial-position learning (Muller and Fountain, 2010; Stempowski et al., 1999). Learning to anticipate the violation element requires multiple-item associative learning about cues from preceding trials in the context of apparatus cues (Kundey and Fountain, 2010; Muller and Fountain, 2010). Learning to perform within-chunk elements requires learning a motor program or abstract rules, a 'turn right' rule, that are independent of external stimuli (Muller and Fountain, 2010). Thus, results from this experiment indicates that adolescent exposure to high doses of MPD impairs S–R learning and multiple cue learning but spares abstract rule learning in adult rats.

These findings parallel a number of prior experiments which suggest that chronic exposure to high doses of MPD in adolescence negatively affect adult learning and behavior (Bolanos et al., 2003; Carlezon et al., 2003; LeBlanc-Duchin and Taukulis, 2007). Future experiments should determine if this effect is dose-dependent by conducting a dose–response study. It should be also be acknowledged that the chosen dose of MPD was outside the therapeutic range for treating ADHD and that any group differences in food intake and/or weight gain could have contributed to the observed learning deficits. Furthermore, the current experiment did not expose adult rats to MPD. Therefore, we cannot claim that the effects found are specific to adolescent exposure. Additionally, it is not known whether MPD has sex-specific effects on adult acquisition of this task that would parallel the sex-specific effects of adolescent nicotine on adult pattern learning in the SMC task (Pickens et al., 2013). Given the extent of the literature describing sex differences on the behavioral and pharmacokinetic effects of MPD (Dafny and Yang, 2006; Hughes and Syme, 1972; Wooters et al., 2006), there are good reasons to expect differential effects in male and female rats.

In conclusion, the current study revealed that high doses of MPD experienced during adolescence can produce learning deficits in adult rats long after exposure to MPD ended. These deficits appear to parallel deficits found after adolescent nicotine exposure in adult male rats (Fountain et al., 2008; Pickens et al., 2013) in that adolescent exposure to both drugs causes impairment of learning chunk-boundary elements, which is attributed to impairment of associative S–R learning and serial-position learning. However, methylphenidate, but not nicotine, causes impairment of learning the violation element, which is attributed to impairment of multiple-item associative learning and memory. Thus, high doses of MPD produced larger effects than nicotine on adult violation element learning even when MPD adolescent exposure was not experienced on a daily basis. However, it is possible that MPD rats' exaggerated impairment for violation element acquisition may have resulted from the fact that the violation element was added to an already-learned pattern. That is, learning to anticipate the newly added violation element that replaced an already-learned pattern element may have been a reversal learning problem that was more difficult than the problem faced by adolescent-nicotine-exposed rats in Pickens et al. (2013) where the violation element was present in the pattern from the beginning of training. Thus, it is not clear whether or not MPD caused a more severe impairment than that observed for nicotine, and it is yet to be determined whether adolescent methylphenidate and adolescent nicotine exposure negatively affect the development of the same cognitive systems. Such a determination awaits careful studies directly comparing the effects of methylphenidate and nicotine under identical conditions across a range of doses with both sexes of rats. Nonetheless, these results clearly show that high doses of MPD during adolescence produced multiple cognitive impairments in male rats that persisted into adulthood long after MPD exposure ended. Although we are loath to extrapolate our results of experiments with rats to humans, the fact that adolescent exposure to both methylphenidate and nicotine produce learning deficits in rats raises public health concerns that emphasize the importance of additional work in this area to increase our understanding of the neurobehavioral teratology of these common drugs.

Transparency document

The Transparency document associated with this article can be found, in online version.

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