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Early Ontogeny of D-Amphetamine-Induced One-Trial Behavioral Sensitization

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Abstract

The early ontogeny of D-amphetamine-induced one-trial behavioral sensitization was characterized using male and female preweanling and preadolescent rats. In Experiment 1, rats were injected with saline or D-amphetamine (1, 4, or 8 mg/kg) in activity chambers or the home cage on postnatal day (PD) 12, PD 16, PD 20, or PD 24. One day later, rats were challenged with either 0.5 or 2 mg/kg D-amphetamine and distance traveled was measured in activity chambers for 120 min. In Experiment 2, saline or D-amphetamine was administered in activity chambers on PD 24, while a challenge injection of D-amphetamine (0.25–4 mg/kg) was given on PD 25. At younger ages (PD 13 and PD 17), a strong sensitized response was evident on the test day regardless of whether rats were pretreated with D-amphetamine (4 or 8 mg/kg) before being placed in the activity chamber or 30 min after being returned to the home cage. Rats did not display D-amphetamine-induced behavioral sensitization on PD 21, nor was context-dependent sensitization apparent on PD 25 even when a broad dose range of D-amphetamine was used. When low doses of D-amphetamine were administered on the pretreatment and test days (1 and 0.5 mg/kg, respectively), sensitized responding was not evident at any age. In summary, D-amphetamine-induced one-trial behavioral sensitization was only apparent within a narrow developmental window during early ontogeny. This ontogenetic pattern of sensitized responding is similar to the one produced by methamphetamine and distinct from the pattern produced by cocaine. The unique sensitization profiles resulting from repeated D-amphetamine and cocaine treatment may be a consequence of their different mechanisms of action.

Keywords

behavioral sensitization; ontogeny; D-amphetamine

1. Introduction

Dopamine (DA) acting drugs affect the developing and mature brain differently (Andersen, 2005). For example, DA agonists can produce dramatically different behavioral effects across ontogeny. Quantitative age-dependent differences are the most common, as drug

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Disclosures

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responsiveness often varies in a monotonic fashion as the animal matures (Spear, 1979). Of more interest are qualitative behavioral differences in which DA-acting drugs either leave a particular age group unaffected or induce distinctly different behavior patterns across ontogeny. Presumably, these ontogenetic behavioral differences result from age-dependent alterations in underlying neural mechanisms. Understanding the nature of these age-dependent behavior changes not only increases our knowledge of the developing organism, it provides an additional tool for determining those mechanisms or systems mediating a particular behavior.

Psychostimulant-induced behavioral sensitization is a complex phenomenon that can vary both quantitatively and qualitatively across ontogeny (for a review, see Tirelli et al., 2003). Behavioral sensitization occurs when rats pretreated with a psychostimulant drug (e.g., D-amphetamine, methamphetamine, or cocaine) exhibit an augmented behavioral response after a challenge injection of the same drug (Robinson and Becker, 1986; Kalivas and Stewart, 1991). The most pronounced ontogenetic differences are evident when sensitized responding is assessed one or two days after a single pretreatment administration of a psychostimulant. As examples, the 'one-trial' behavioral sensitization of adult rats and mice is context-specific (i.e., it is dependent on the context in which the drug was administered; Drew and Glick, 1989; Weiss et al., 1989; Battisti et al., 1999; McDougall et al., 2007), whereas the one-trial sensitized responding of young rats occurs independent of environmental context (McDougall et al., 2009, 2011b; Herbert et al., 2010). Although adult rats and mice show strong robust one-trial behavioral sensitization (Drew and Glick, 1989; Weiss et al., 1989; Fontana et al., 1993; McDougall et al., 2007; Kameda et al., 2011), young rats only exhibit one-trial sensitization during a narrow ontogenetic window that varies depending on the psychostimulant administered. More specifically, cocaine induces robust one-trial behavioral sensitization on postnatal day (PD) 21 (i.e., during the late preweanling period), but not at younger or older ages (i.e., during preadolescence) (McDougall et al., 2011a; Kozanian et al., 2012). In contrast, methamphetamine causes a strong sensitized locomotor response in younger rats (i.e., at PD 13 and PD 17), while rats tested between PD 21–PD 35 do not exhibit one-trial methamphetamine sensitization (McDougall et al., 2011a; Kozanian et al., 2012). Preliminary evidence suggests that D-amphetamine does not support one-trial locomotor sensitization during early ontogeny, however this compound was only tested on PD 21 (McDougall et al., 2011a). When these results are considered together, it appears that the characteristics of one-trial behavioral sensitization vary qualitatively across ontogeny, with sensitized responding being evident during restricted periods that differ according to the psychostimulant being administered.

It is uncertain why cocaine and methamphetamine produce distinctly different sensitization profiles in young rats, however such findings are not unique to early ontogeny. In adulthood, for example, the neural mechanisms mediating cocaine- and D-amphetamine-induced behavioral sensitization can be dissociated in terms of both the receptors systems involved and the brain areas implicated (for reviews, see Pierce and Kalivas, 1997; White et al., 1998; Vanderschuren and Kalivas, 2000). Cocaine and amphetamine-like compounds differ in terms of blood-brain barrier permeability, brain half-life, and selectivity at monoamine transporter binding sites (Howell and Kimmel, 2008). Perhaps most importantly, cocaine acts as a DA transport inhibitor, while D-amphetamine and methamphetamine enhance DA release through actions involving both the plasma membrane DA transporter and the vesicular monoamine transporter type 2 (VMAT₂) (for reviews, see McMillen, 1983; Fleckenstein and Hanson, 2003). This mechanistic distinction has a number of ramifications since cocaine increases extracellular DA from vesicular stores, whereas methamphetamine and D-amphetamine primarily rely on cytosolic pools (for a review, see Kuczenski, 1983). Because cocaine and methamphetamine vary in so many ways it is uncertain what factor, or

set of factors, is responsible for the unique sensitization profiles produced by different psychostimulants during early ontogeny.

Among amphetamine-like compounds, D-amphetamine and methamphetamine are readily dissociable in terms of pharmacokinetic factors, although they do share the same mechanism of action. Specifically, D-amphetamine and methamphetamine attach to a common binding site at the DA transporter and are carried into the cell (Wayment et al., 1998) where they increase DA release through reverse transport (Wall et al., 1995; Jones et al., 1998). If mechanism of action is the critical factor determining the occurrence of behavioral sensitization during early ontogeny, then it would be predicted that D-amphetamine should have a sensitization profile similar to methamphetamine and different from cocaine. To examine this issue, rats were pretreated and tested with D-amphetamine at various developmental stages, including the early (PD 12–13), middle (PD 16–17), and late (PD 20–21) preweanling periods and preadolescence (PD 24–25). The importance of environmental context was assessed by administering the psychostimulant in either the home cage or a novel activity chamber on the pretreatment day. In a separate experiment, a broad dose range of D-amphetamine was employed in order to ensure that the absence of sensitized responding was not the result of an inappropriate dosing regimen. It was hypothesized that D-amphetamine would only induce one-trial context-independent behavioral sensitization on PD 13 and PD 17 and not at older ages. This pattern of results would be identical to that reported for methamphetamine (and different from that reported for cocaine) and would suggest that mechanism of action is an important factor influencing the ontogeny of psychostimulant-induced behavioral sensitization.

2. Materials and methods

2.1. Animals

Subjects were 340 male and female young rats of Sprague-Dawley descent (Charles River, Hollister, CA) that were born and raised at California State University, San Bernardino (CSUSB). Litters were culled to 10 pups on PD 3. Except during testing, rats were kept with the dam and littermates. All rats were housed on racks in large polycarbonate maternity cages (56 × 34 × 22 cm) with wire lids. Food and water were freely available. The colony room was maintained at 22–23°C and kept under a 12:12 light/dark cycle. Testing was done in a separate experimental room, maintained at 24–25°C, and was conducted during the light phase of the cycle. Subjects were cared for according to the “Guide for the Care and Use of Laboratory Animals” (National Research Council, 2010) under a research protocol approved by the Institutional Animal Care and Use Committee of CSUSB.

2.2. Apparatus

Behavioral testing was done in activity monitoring chambers (25.5 × 25.5 × 41 cm, L × W × H) that consisted of acrylic walls, a plastic floor, and an open top (Coulbourn Instruments, Allentown, PA). Each chamber included an X–Y photobeam array, with 16 photocells and detectors, that was used to determine distance traveled (a measure of locomotor activity).

2.3. Drugs

D-Amphetamine hemisulfate salt (Sigma-Aldrich, St. Louis, MO) was dissolved in saline and injected intraperitoneally (IP) at 5 ml/kg.

2.4. Procedure

2.4.1. Experiment 1: Ontogeny of one-trial D-amphetamine sensitization—Four different age groups ($N = 21$ –30 per age) were tested: PD 12–13, PD 16–17, and PD 20–21 (early, middle, and late preweanling periods, respectively), as well as PD 24–25

(preadolescence). On the pretreatment day (i.e., on PD 12, PD 16, PD 20, or PD 24), rats in the AMPH-Activity Chamber groups were taken to the testing room and injected with D-amphetamine (1, 4, or 8 mg/kg, IP) before being placed in the activity chambers. Distance traveled was measured for either 60 min (1 mg/kg) or 30 min (4 or 8 mg/kg) depending upon the dose of D-amphetamine administered. Rats were then returned to the home cage and injected with saline 30 min later. Rats in the AMPH-Home Cage groups were injected with saline before being placed in the activity chambers and injected with D-amphetamine (1, 4, or 8 mg/kg, IP) 30 min after being returned to the home cage. The Acute Control groups were injected with saline in both the activity chamber and home cage. During the preweanling period, the brain half-life of D-amphetamine is approximately 150 min (Lal and Feldmüller, 1975), thus rats in the AMPH-Activity Chamber groups experienced D-amphetamine's actions in both the activity chamber and home cage.

To determine the occurrence of behavioral sensitization, rats ($n = 7$ –8 per group) pretreated with a low dose of D-amphetamine (1 mg/kg) were given a test day injection of 0.5 mg/kg D-amphetamine 24 hr after drug pretreatment; whereas, rats ($n = 8$ –10 per group) pretreated with a moderate or high dose of D-amphetamine (4 or 8 mg/kg) were injected with 2 mg/kg D-amphetamine. After D-amphetamine challenge, rats were immediately placed in activity chambers where distance traveled was measured for 120 min.

2.4.2. Experiment 2: Multi-dose testing in preadolescent (PD 24–PD 25) rats—

On PD 24 ($N = 80$), rats in the AMPH-Activity Chamber groups were injected with 4 mg/kg D-amphetamine immediately before placement in an activity chamber (this dose was based on the results of Experiment 1), whereas the Acute Control groups were injected with saline. One day later (i.e., on PD 25), rats from both pretreatment groups received a challenge injection of D-amphetamine (0.25, 0.5, 1, 2, or 4 mg/kg, IP) and distance traveled was measured for 120 min to determine the occurrence of behavioral sensitization.

2.5. Statistics

For all experiments, litter effects were controlled through both experimental design and statistical procedures. In most circumstances, no more than one subject per litter was found in a particular group. In situations where this rule was violated (e.g., analyses of the pretreatment day), a single litter mean was calculated from multiple littermates assigned to the same group (Holson and Pearce, 1992; Zorrilla, 1997). For all experiments, a nearly equal number of male and female preweanling rats were assigned to each group. Omnibus mixed factor ANOVAs, with repeated measures, were used to assess whether treatment group interacted with age and sex to affect performance. To further examine statistically significant ($p < 0.05$) higher order interactions, separate one- or two-way ANOVAs were conducted. Whenever possible, litter was used as the unit of analysis for these analyses (Zorrilla, 1997). With this statistical model each litter, rather than each rat, is treated as an independent observation (i.e., a within analysis using one value/condition/litter). When the assumption of sphericity was violated, as determined by Mauchly's test of sphericity, the Huynh-Feldt epsilon statistic was used to adjust degrees of freedom (Huynh and Feldt, 1976). Corrected degrees of freedom were rounded to the nearest whole number and are indicated by a superscripted "a". Post hoc analysis of distance traveled data was done using Tukey tests ($p < 0.05$).

3. Results

3.1. Experiment 1: Ontogeny of one-trial D-amphetamine sensitization

3.1.1. Pretreatment day—On the pretreatment day, rats injected with 1 mg/kg D-amphetamine had significantly greater distance traveled scores than saline controls (Table 1)

[Drug main effect, $F_{(1,50)}=130.56$, $p<0.001$]. Neither the Age main effect nor the Age $\times$ Drug interaction reached statistical significance, suggesting that 1 mg/kg D-amphetamine induced similar levels of locomotion in the various age groups. The only exception occurred on time block 2 (i.e., 10 to 20 min into the testing session), when D-amphetamine-treated PD 24 rats had significantly smaller distance traveled scores than similarly treated PD 16 rats (data not shown) [^aDrug $\times$ Age $\times$ Time block interaction, $F_{(10,171)}=2.91$, $p<0.01$].

In terms of the moderate- and high-dose groups (Fig. 1), D-amphetamine caused a dose-dependent increase in locomotor activity on the pretreatment day, with 8 mg/kg D-amphetamine producing significantly greater distance traveled scores than 4 mg/kg D-amphetamine or saline [Drug main effect, $F_{(2,90)}=99.49$, $p<0.001$ and Tukey tests]. The drug variable interacted with time block to affect performance, as both 4 and 8 mg/kg D-amphetamine significantly enhanced distance traveled scores relative to saline controls on time blocks 2–6 [^aDrug $\times$ Time block interaction, $F_{(7,332)}=5.85$, $p<0.001$]. At these relatively high doses (4 and 8 mg/kg), the locomotor activating effects of D-amphetamine were most apparent in PD 20 and PD 24 rats [Age main effect, $F_{(3,90)}=17.98$, $p<0.001$; Drug $\times$ Age interaction, $F_{(6,90)}=3.94$, $p<0.001$]; however, Tukey tests showed that PD 16 rats given 4 or 8 mg/kg D-amphetamine had significantly greater distance traveled scores than saline controls on time blocks 1, 2, 5, and 6 [^aDrug $\times$ Age $\times$ Time block interaction, $F_{(22,332)}=5.09$, $p<0.001$]. In PD 12 rats, 8 mg/kg D-amphetamine significantly enhanced locomotion on time blocks 1–5, while 4 mg/kg D-amphetamine increased locomotor activity on the first three time blocks (Tukey tests).

3.1.2. Test day: low-dose groups (i.e., rats pretreated with 1 mg/kg D-amphetamine)—An omnibus mixed factor ANOVA, with time block as a repeated measure, showed that distance traveled scores on the test day varied according to age (Fig. 2). More specifically, PD 12 rats given 0.5 mg/kg D-amphetamine on the test day exhibited significantly more locomotor activity than similarly-treated PD 16 rats, while PD 20 and PD 24 rats showed minimal locomotion [Age main effect, $F_{(3,63)}=144.23$, $p<0.001$ and Tukey tests]. Importantly, sensitized responding was not evident in any of the age groups on the test day, because rats pretreated with 1 mg/kg D-amphetamine in either the home cage or activity chamber did not differ from the acute control groups when challenged with 0.5 mg/kg D-amphetamine (i.e., the main effect and interactions involving the group variable were nonsignificant). Separate within-subjects ANOVAs confirmed that behavioral sensitization was not evident at any age, although the group main effect approached statistical significance in the youngest age group [Group main effect, $F_{(2,12)}=3.55$, $p=0.062$]. On PD 13, distance traveled scores increased from the first to the second time block, stabilized, and then declined at the end of the session [^aTime main effect, $F_{(5,28)}=21.32$, $p<0.001$ and Tukey tests]. Test day performance of male and female rats did not differ at any age.

3.1.3. Test day: moderate-dose groups (i.e., rats pretreated with 4 mg/kg D-amphetamine)—Overall, an omnibus mixed factor ANOVA indicated that treatment group interacted with the age variable to affect performance on the test day (Fig. 3) [Age $\times$ Group interaction, $F_{(6,78)}=4.38$, $p<0.001$; ^aAge $\times$ Group $\times$ Time block interaction, $F_{(34,438)}=2.74$, $p<0.001$]. On PD 13, behavioral sensitization was evident in rats pretreated with 4 mg/kg D-amphetamine in either the home cage or activity chamber (upper left graph, Fig. 3). More specifically, PD 13 rats in the AMPH-Activity Chamber group and AMPH-Home Cage group had significantly greater distance traveled scores than rats in the Acute Control group [Group main effect, $F_{(2,18)}=8.96$, $p<0.01$ and Tukey tests]. This effect varied according to time block, with the AMPH-Activity Chamber group having greater distance traveled scores than the Acute Control group on time blocks 2–6, 8, 10, and 11, whereas the AMPH-Home Cage group differed from the Acute Controls on time blocks 1–8 [^aGroup $\times$ Time block interaction, $F_{(9,78)}=3.25$, $p<0.01$ and Tukey tests].

Similarly, PD 16 rats pretreated with 4 mg/kg D-amphetamine in either the activity chamber or home cage showed a sensitized locomotor response when challenged with D-amphetamine on the test day (i.e., PD 17) (upper right graph, Fig. 3) [Group main effect, $F_{(2,14)}=21.93$, $p<0.001$ and Tukey tests]. The AMPH-Home Cage group exhibited less locomotion than the Acute Control group on time block 1, but distance traveled scores of the AMPH-Home Cage group were significantly greater than the Acute Controls on time blocks 4–12 [^aGroup $\times$ Time block interaction, $F_{(7,50)}=11.53$, $p<0.001$ and Tukey tests]. Likewise, the AMPH-Activity Chamber group had greater distance traveled scores than the Acute Control group on time blocks 3–12 [Tukey tests].

Rats tested on PD 21 showed no evidence of a sensitized locomotor response, since the AMPH-Activity Chamber and AMPH-Home Cage groups did not differ from the Acute Control group on the test day (lower left graph, Fig. 3). Overall, locomotor activity increased across the first four time blocks and subsequently declined [^aTime block main effect, $F_{(7,47)}=24.98$, $p<0.001$ and Tukey tests]. On PD 25, behavioral sensitization was apparent but only in rats pretreated with 4 mg/kg D-amphetamine in the home cage (lower right graph, Fig. 3). In other words, rats in the AMPH-Home Cage group had significantly greater distance traveled scores on the test day than PD 25 rats in the Acute Control and AMPH-Activity Chamber groups [Group main effect, $F_{(2,14)}=7.73$, $p<0.01$ and Tukey tests]. Test day performance of male and female rats did not differ at any age.

3.1.4. Test day: high-dose groups (i.e., rats pretreated with 8 mg/kg D-amphetamine)—An omnibus mixed factor ANOVA, with time block as a repeated measure, showed that distance traveled scores did not vary according to sex, while treatment group interacted with the age variable to affect performance on the test day (Fig. 3) [Age $\times$ Group interaction, $F_{(6,78)}=7.18$, $p<0.001$; ^aAge $\times$ Group $\times$ Time block interaction, $F_{(39,503)}=3.38$, $p<0.001$]. On PD 13, rats pretreated with 8 mg/kg D-amphetamine in either the activity chamber or home cage exhibited greater test day locomotor activity than the Acute Control group (upper left graph, Fig. 4) [Group main effect, $F_{(2,18)}=11.74$, $p<0.001$]. On time block 1, both of the D-amphetamine pretreatment groups exhibited less locomotion than control rats; however, the AMPH-Activity Chamber group and AMPH-Home Cage group had significantly greater distance traveled scores than the Acute Control group on time blocks 2–10 and 2–8, respectively [^aGroup $\times$ Time block interaction, $F_{(9,85)}=4.12$, $p<0.001$ and Tukey tests].

Pretreating PD 16 rats with a high dose of D-amphetamine (8 mg/kg) also resulted in locomotor sensitization (upper right graph, Fig. 4), because the AMPH-Activity Chamber group and AMPH-Home Cage group exhibited greater locomotor activity than the Acute Control group on the test day [Group main effect, $F_{(2,14)}=25.16$, $p<0.001$ and Tukey tests]. Distance traveled scores of the AMPH-Activity Chamber group were significantly elevated relative to the Acute Control group on time blocks 4–12, while the AMPH-Home Cage group varied from control rats on time blocks 3–12 [^aGroup $\times$ Time block interaction, $F_{(7,48)}=10.20$, $p<0.001$ and Tukey tests]. On time block 1, D-amphetamine-pretreated rats exhibited less locomotor activity than the Acute Controls (Tukey tests).

Sensitized responding was not evident in rats pretreated with 8 mg/kg D-amphetamine on PD 20 or PD 24 (lower graphs, Fig. 4). The only statistically significant effect involved the time variable [^aTime block main effects, $F_{(5,51)}=19.44$, $p<0.001$; $F_{(6,44)}=23.68$, $p<0.001$, respectively], with Tukey tests indicating that distance traveled scores increased until time block 4 and then declined across the testing session.

3.1.5. Cross-age comparisons of the acute control groups—Age-dependent differences in response to the acute administration of D-amphetamine were assessed by

comparing the locomotor activity of the Acute Control groups on the test day. Rats given their initial injection of 0.5 mg/kg D-amphetamine on PD 13 had greater distance traveled scores than PD 21 or PD 25 rats (upper graph, Fig. 5), with PD 17 rats being intermediate between and significantly different from the younger and older age groups [Age main effect, $F_{(3,22)}=61.61$, $P<0.001$ and Tukey tests]. The age effect varied according to time block, as PD 13 rats injected with 0.5 mg/kg D-amphetamine exhibited significantly more locomotor activity than all other age groups on time blocks 2–12; whereas, PD 16 rats evidenced more locomotion than PD 21 and PD 35 rats on time blocks 4–9 [Age $\times$ Time block interaction, $F_{(21,152)}=3.79$, $p<0.001$ and Tukey tests].

A very different pattern of behavior was evident after an acute injection of 2 mg/kg D-amphetamine (lower graph, Fig. 5). Overall, rats injected with D-amphetamine (2 mg/kg) for the first time on PD 25 had significantly greater distance traveled scores than PD 13 or PD 17 rats [Age main effect, $F_{(3,26)}=5.69$, $P<0.01$ and Tukey tests]. More specifically, PD 21 rats exhibited more locomotor activity than PD 17 rats on time blocks 3–10 and PD 13 rats on time blocks 3–8 [Age $\times$ Time block interaction, $F_{(17,152)}=7.13$, $p<0.001$ and Tukey tests]. PD 25 rats, on the other hand, locomoted more than PD 17 rats on time blocks 5–8 and PD 13 rats on time blocks 3–6 (Tukey tests).

3.2. Experiment 2: Multi-dose testing in preadolescent (PD 24–PD 25) rats

3.2.1. Pretreatment day—On PD 24, rats injected with 4 mg/kg D-amphetamine (mean = 12,149 cm, SEM = 796) had significantly greater distance traveled scores than rats given saline (mean = 2,525 cm, SEM = 302) [Drug main effect, $F_{(1,7)}=159.82$, $p<0.001$].

3.2.2. Test day—Regardless of the dose of D-amphetamine being administered (0.25–4 mg/kg), there was no evidence of behavioral sensitization on PD 25 (Fig. 6), because the various Acute Control and AMPH-Activity Chamber groups did not differ. Overall, D-amphetamine did cause a dose-related increase in test day locomotor activity [Dose main effect, $F_{(4,28)}=42.79$, $p<0.001$]. More specifically, rats injected with the two highest doses of D-amphetamine (2 or 4 mg/kg) had greater distance traveled scores than rats injected with 1 mg/kg D-amphetamine, whereas 1 mg/kg stimulated more locomotion than 0.5 mg/kg D-amphetamine (Tukey tests). Rats treated with the lowest dose of D-amphetamine (0.25 mg/kg) exhibited less locomotor activity than rats from the other dose conditions (Tukey tests). The performance of male and female rats did not differ according to sex.

4. Discussion

The expression of D-amphetamine-induced one-trial behavioral sensitization varies dramatically across early ontogeny. At younger ages (PD 13 and PD 17), a strong sensitized response was apparent on the test day regardless of whether rats were pretreated with D-amphetamine (4 or 8 mg/kg) before being placed in the activity chamber or 30 min after being returned to the home cage. A different pattern of effects was evident at slightly older ages, because rats no longer displayed D-amphetamine sensitization when tested on PD 21 (see also McDougall et al., 2011a). A weak sensitized response was apparent during preadolescence (i.e., on PD 25), but only when context-independent procedures were used and a moderate dose of D-amphetamine (4 mg/kg) was administered on the pretreatment day. The latter result may be aberrant, because locomotor sensitization was not evident if PD 25 rats were challenged with D-amphetamine (0.25–4 mg/kg) one day after receiving an injection of D-amphetamine (1–8 mg/kg) in the activity chamber. Nonetheless, the present results show that D-amphetamine is capable of supporting one-trial locomotor sensitization during early ontogeny. Sensitized responding was stronger at younger ages (PD 13–PD 17) and either weakened or disappeared as animals moved into preadolescence.

As predicted, the ontogenetic patterns of D-amphetamine- and methamphetamine-induced one-trial behavioral sensitization are nearly identical, while cocaine produces a distinctly different sensitization profile. Cocaine causes a robust sensitized response on PD 21, but not at younger or older developmental ages (Kozanian et al., 2012). In contrast, methamphetamine, in the same manner as D-amphetamine, induces strong one-trial locomotor sensitization on PD 13 and PD 17, but not on PD 21 or PD 25 (Kozanian et al., 2012). These ontogenetic differences suggest that cocaine and amphetamine-like compounds trigger their own unique pattern of neural events that have far-reaching behavioral consequences. These two classes of drugs differ in various ways, so it has been difficult to determine what factor, or set of factors, is responsible for their divergent actions. One possibility is that pharmacokinetic differences among psychostimulants are responsible for variations in sensitization profiles. Cocaine reaches peak levels in brain more quickly than methamphetamine and substantially faster than D-amphetamine (Brien et al., 1978; Benuck et al., 1987; Lau et al., 1991; Clausen and Bowyer, 1999), while the brain half-lives of cocaine and methamphetamine are shorter than D-amphetamine (Lal and Feldmüller, 1975; Brien et al., 1978; Benuck et al., 1987; Rivière et al., 2000; Carmona et al., 2005). Based on this information it is unlikely that pharmacokinetic factors are responsible for the differential ontogeny of one-trial behavioral sensitization since the permeability and half-life of methamphetamine is generally more similar to cocaine than D-amphetamine. That being said, many of the studies cited above used adult animals as subjects, and there is evidence that the pharmacokinetic properties of psychostimulants vary substantially across ontogeny (Lal and Feldmüller, 1975; Spear and Brake, 1983). The relative affinity of drugs for the various monoamine transporters is a second factor that might explain the disparate actions of D-amphetamine and cocaine. D-Amphetamine, methamphetamine, and cocaine share an approximately equal affinity for the DA and norepinephrine transporters, but only cocaine has a high affinity for the serotonin transporter (for a review, see Howell and Kimmel, 2008). Actions at the serotonin transporter are of potential importance, because serotonergic agonists and antagonists modulate the induction and expression of behavioral sensitization in adult rats and mice (King et al., 2000; Ago et al., 2006, 2007). Even so, it is unclear how differential affinity for the serotonin transporter can explain the unique sensitization profiles exhibited by cocaine- and D-amphetamine-treated preweanling rats

Instead, mechanism of action may be the critical factor responsible for the different sensitization profiles produced by and cocaine and amphetamine-like drugs. Specifically, D-amphetamine functions as a DA releaser, while cocaine is a transport inhibitor (McMillen, 1983). This difference is important, because: (a) cocaine and D-amphetamine stimulate different binding sites that reside on discrete transmembrane spanning regions of the DA transporter (Giros et al., 1994; Waymient et al., 1998; but see Beuming et al., 2008); (b) DA releasers, unlike transport inhibitors, bind at the DA substrate site and are transported into the cell, where they reverse the process of transport-mediated exchange (Carroll et al., 1992; Meiergard and Schenk, 1994; Wall et al., 1995; Jones et al., 1998); and (c) amphetamine-like compounds, unlike cocaine, act as VMAT₂ substrates that deplete vesicular neurotransmitter stores and, as a consequence, increase cytosolic DA levels (Partilla et al., 2006). Therefore, cocaine increases extracellular neurotransmitter levels by blocking re-uptake of metabolically older DA from vesicular stores, whereas amphetamine-like compounds primarily release newly synthesized DA located in cytosolic pools (Kuczenski, 1983). McNamara et al. (1993) have hypothesized that the size and turnover rate of these DA pools (unbound cytosolic vs. vesicular) are important determinants affecting the induction and ultimate expression of behavioral sensitization (see Castañeda et al., 1988, for a more detailed discussion).

On a related issue, DA release capacity increases from adolescence to adulthood, while the ratio of DA uptake to release declines (Walker and Kuhn, 2008). This set of findings has

lead Walker et al. (2010) to suggest that release capacity may account for some of the ontogenetic behavioral differences reported in adolescent and adult rats. Unfortunately, a detailed analysis of how particular DA stores change across early ontogeny has not been undertaken, although it is known that striatal and accumbal DA content increases across the preweanling period (Coyle and Campochiaro, 1976; Giorgi et al., 1987; Broaddus and Bennett, 1990). Of course, many dopaminergic elements exhibit maturational changes during early ontogeny, as striatal D₁ and D₂ receptor sites increase in number from birth through the preweanling period (Rao et al., 1991; Kuperstein et al., 2008), are dramatically overproduced during adolescence (Teicher et al., 1995; Andersen et al., 1997), and then gradually decline until adult-like levels are reached (for reviews, see Andersen and Teicher, 2000; Andersen, 2003). In addition, VMAT₂ as well as plasma membrane DA transporters increase linearly in number across the preweanling period, through adolescence, and into adulthood (Broaddus and Bennett, 1990; Truong et al., 2005; Kuperstein et al., 2008). The latter findings may be relevant to the present results, because cocaine and amphetamine-like compounds attach to different binding sites on the DA transporter (Wayment et al., 1998). If the various transporter binding sites mature at different rates, it could explain why cocaine and amphetamine-like compounds induce different sensitization profiles during the preweanling period.

It is also interesting how the acute locomotor activating effects of D-amphetamine varied according to both the age of the animal being tested and the dose of drug administered. Spear and colleagues have long contended that responsiveness to acute psychostimulant administration is best represented by a U-shaped curve, with preweanling and adult rats showing robust cocaine- and D-amphetamine-induced locomotor activity, while adolescent rats exhibit a muted response to these drugs (for reviews, see Spear, 1979, 2000; Spear and Brake, 1983). In terms of preweanling and preadolescent rats, Campbell et al. (1969) showed that a low dose of D-amphetamine (i.e., 0.25 mg/kg) induced maximal locomotor responsiveness at PD 15, whereas a substantially larger dose of D-amphetamine (4 mg/kg) was required to produce peak locomotor activity in PD 25 rats (see also Lanier and Isaacson, 1977). Results from the present study are in accord with these findings, because we showed that younger rats were preferentially responsive to 0.5 mg/kg D-amphetamine (PD 13 > PD 17 > PD 21 = PD 25). PD 21 and PD 25 rats, on the other hand, exhibited relatively more locomotor activity than PD 13 and PD 17 rats when higher doses of D-amphetamine (2–8 mg/kg) were administered. For comparison, a dose of approximately 1 mg/kg D-amphetamine produces peak locomotor activity in adult rats (Campbell et al., 1969; Segal and Kuczenski, 1987). In a similar vein, we previously reported that relatively high doses of methamphetamine (2 and 4 mg/kg) induced progressively more locomotor activity as pups moved through the preweanling period and into early adolescence (Kozanian et al., 2012). It is likely that a different pattern of drug responsiveness would have been evident if lower doses of methamphetamine (e.g., 0.25 or 0.5 mg/kg) were administered.

During adulthood, DA agonists often induce pronounced sex-dependent effects, with female rats exhibiting more locomotor activity than male rats (Schindler and Carmona, 2002; Festa et al., 2004; Milesi-Hallé et al., 2007). Sex differences are also evident in behavioral sensitization, because adult females show a more robust sensitized response than males (Sircar and Kim, 1999; Chin et al., 2002; Hu and Becker, 2003). In contrast, it is frequently reported that DA agonists do not differentially affect the behavior of male and female prepubescent rats (Lal and Sourkes, 1973; Shalaby and Spear, 1980; Van Hartesveldt et al., 1994; Frantz et al., 1996), nor does the sensitized responding of preweanling rats typically differ according to sex (Bowman et al., 1997; Snyder et al., 1998; McDougall et al., 2007). Consistent with this general result, we found that none of the main effects or interactions involving sex as a variable approached statistical significance (the largest sex main effect

had an *F* value of 0.98). Of course, a lack of statistical power – there were only four males and females per group – could have contributed to the absence of significant sex effects.

In conclusion, dopaminergic drugs differentially affect behavior across development (Spear, 1979; Andersen, 2005). D-Amphetamine-induced one-trial behavioral sensitization is an excellent example of this phenomenon, because the sensitization profiles of D-amphetamine-treated rats differ in a qualitative manner during early ontogeny. Specifically, strong one-trial behavioral sensitization was only evident during a narrow developmental window that did not extend past the third postnatal week. Most authors find that one-trial psychostimulant-induced behavioral sensitization re-emerges during middle and late adolescence (Laviola et al., 1995; Kameda et al., 2011; Mathews et al., 2011; but see Collins and Izenwasser, 2002), while robust one-trial locomotor sensitization is typically, but not universally, reported during adulthood (e.g., Drew and Glick, 1989; Weiss et al., 1989; Battisti et al., 1999; McDougall et al., 2007, 2009; Kameda et al., 2011; but see Mathews et al., 2011; Caster et al., 2007). Associative factors are not important for the expression of one-trial behavioral sensitization in young rats (McDougall et al., 2009, 2011b; Herbert et al., 2010); thus, it seems likely that these ontogenetic behavioral differences result from age-dependent alterations in underlying neural mechanisms. Because D-amphetamine and cocaine cause different sensitization profiles during early ontogeny, it appears that the neural mechanisms mediating one-trial behavioral sensitization differ according to the type of psychostimulant used. Many researchers using adult rat and mouse models have come to similar conclusions since the neural mechanisms mediating cocaine- and amphetamine-induced behavioral sensitization are dissociable (Pierce and Kalivas, 1997; Vanderschuren and Kalivas, 2000). For example, D1 and D2 receptor antagonists block the induction of amphetamine-, but not cocaine-induced behavioral sensitization in adult rats and mice (Kuczenski and Leith, 1981; Stewart and Vezina, 1989; Kuribara and Uchihashi, 1993; Mattingly et al., 1994; White et al., 1998), and the prefrontal cortex is a critical component of the neural circuitry underlying cocaine sensitization, but not amphetamine sensitization (Li and Wolf, 1997; Sorg et al., 1997; Pierce et al., 1998). Therefore, data from both ontogenetic and nonontogenetic studies indicate that cocaine and amphetamine-like compounds induce behavioral sensitization through somewhat different mechanisms. We believe that the differential ontogeny of psychostimulant-induced sensitized responding can be used as an additional tool for examining the neural substrates underlying behavioral sensitization.

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Abbreviations

AMPH	amphetamine
ANOVA	analysis of variance
DA	dopamine
IP	intraperitoneal
PD	postnatal day

References

- Ago Y, Nakamura S, Hayashi A, Itoh S, Baba A, Matsuda T. Effects of osetozotan, ritanserin and azasetron on cocaine-induced behavioral sensitization in mice. *Pharmacol Biochem Behav.* 2006; 85:198–205. [PubMed: 16962650]
- Ago Y, Nakamura S, Kajita N, Uda M, Hashimoto H, Baba A, et al. Ritanserin reverses repeated methamphetamine-induced behavioral and neurochemical sensitization in mice. *Synapse.* 2007; 61:757–63. [PubMed: 17568413]
- Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity. *Neurosci Biobehav Rev.* 2003; 27:3–18. [PubMed: 12732219]
- Andersen SL. Stimulants and the developing brain. *Trends Pharmacol Sci.* 2005; 26:237–43. [PubMed: 15860370]
- Andersen SL, Teicher MH. Sex differences in dopamine receptors and their relevance to ADHD. *Neurosci Biobehav Rev.* 2000; 24:137–41. [PubMed: 10654670]
- Andersen SL, Rutstein M, Benzo JM, Hostetter JC Jr, Teicher MH. Sex differences in dopamine receptor overproduction and elimination. *Neuroreport.* 1997; 8:1495–8. [PubMed: 9172161]
- Battisti JJ, Chang CH, Uretsky NJ, Wallace LJ. Sensitization of stereotyped behavior to amphetamine is context and response dependent. *Pharmacol Biochem Behav.* 1999; 63:263–9. [PubMed: 10371655]
- Benuck M, Lajtha A, Reith ME. Pharmacokinetics of systemically administered cocaine and locomotor stimulation in mice. *J Pharmacol Exp Ther.* 1987; 243:144–9. [PubMed: 3668848]
- Beuming T, Kniazeff J, Bergmann ML, Shi L, Gracia L, Raniszewska K, et al. The binding sites for cocaine and dopamine in the dopamine transporter overlap. *Nat Neurosci.* 2008; 11:780–9. [PubMed: 18568020]
- Bowman BP, Blatt B, Kuhn CM. Ontogeny of the behavioral response to dopamine agonists after chronic cocaine. *Psychopharmacology (Berl).* 1997; 129:121–7. [PubMed: 9040117]
- Brien JF, Kitney JC, Peachey JE, Rogers BJ. Methamphetamine-induced behavioural effects and brain concentrations of methamphetamine and its metabolite amphetamine in mice. *Res Commun Chem Pathol Pharmacol.* 1978; 22:313–28. [PubMed: 569889]
- Broadbudd WC, Bennett JP. Postnatal development of striatal dopamine function. I. An examination of D₁ and D₂ receptors, adenylate cyclase regulation and presynaptic dopamine markers. *Dev Brain Res.* 1990; 52:265–71. [PubMed: 2331795]
- Campbell BA, Lytell LD, Fibiger HC. Ontogeny of adrenergic arousal and cholinergic inhibitory mechanisms in the rat. *Science.* 1969; 166:635–7. [PubMed: 5823302]
- Carmona GN, Schindler CW, Greig NH, Holloway HW, Jufer RA, Cone EJ, et al. Intravenous butyrylcholinesterase administration and plasma and brain levels of cocaine and metabolites in rats. *Eur J Pharmacol.* 2005; 517:186–90. [PubMed: 15967428]
- Carroll FI, Lewin AH, Boja JW, Kuhar MJ. Cocaine receptor: biochemical characterization and structure-activity relationships of cocaine analogues at the dopamine transporter. *J Med Chem.* 1992; 35:969–81. [PubMed: 1552510]
- Castañeda E, Becker JB, Robinson TE. The long-term effects of repeated amphetamine treatment *in vivo* on amphetamine, KCl and electrical stimulation evoked striatal dopamine release *in vitro*. *Life Sci.* 1988; 42:2447–56. [PubMed: 3374264]
- Caster JM, Walker QD, Kuhn CM. A single high dose of cocaine induces differential sensitization to specific behaviors across adolescence. *Psychopharmacology (Berl).* 2007; 193:247–60. [PubMed: 17426961]
- Chin J, Sternin O, Wu HB, Burrell S, Lu D, Jenab S, et al. Endogenous gonadal hormones modulate behavioral and neurochemical responses to acute and chronic cocaine administration. *Brain Res.* 2002; 945:123–30. [PubMed: 12113959]
- Clausing P, Bowyer JF. Time course of brain temperature and caudate/putamen microdialysate levels of amphetamine and dopamine in rats after multiple doses of d-amphetamine. *Ann N Y Acad Sci.* 1999; 890:495–504. [PubMed: 10668455]
- Collins SL, Izenwasser S. Cocaine differentially alters behavior and neurochemistry in periadolescent versus adult rats. *Dev Brain Res.* 2002; 138:27–34. [PubMed: 12234655]

- Coyle JT, Campochiaro P. Ontogenesis of dopaminergic-cholinergic interactions in the rat striatum: a neurochemical study. *J Neurochem.* 1976; 27:673–8. [PubMed: 9481]
- Drew KL, Glick SD. Environment-dependent sensitization to amphetamine-induced circling behavior. *Pharmacol Biochem Behav.* 1989; 31:705–8. [PubMed: 3251253]
- Festa ED, Russo SJ, Gazi FM, Niyomchai T, Kemen LM, Lin SN, et al. Sex differences in cocaine-induced behavioral responses, pharmacokinetics, and monoamine levels. *Neuropharmacology.* 2004; 46:672–87. [PubMed: 14996545]
- Fleckenstein AE, Hanson GR. Impact of psychostimulants on vesicular monoamine transporter function. *Eur J Pharmacol.* 2003; 479:283–9. [PubMed: 14612158]
- Fontana D, Post RM, Weiss SRB, Pert A. The role of D1 and D2 dopamine receptors in the acquisition and expression of cocaine-induced conditioned increases in locomotor activity. *Behav Pharmacol.* 1993; 4:375–87. [PubMed: 11224206]
- Frantz K, Babcock D, Van Hartesveldt C. The locomotor effects of a putative dopamine D3 receptor agonist in developing rats. *Eur J Pharmacol.* 1996; 302:1–6. [PubMed: 8790984]
- Giorgi O, De Montis G, Porceddu ML, Mele S, Calderini G, Toffano G, et al. Developmental and age-related changes in D₁-dopamine receptors and dopamine content in the rat striatum. *Dev Brain Res.* 1987; 35:283–90.
- Giros B, Wang YM, Suter S, McLeskey SB, Pifl C, Caron MG. Delineation of discrete domains for substrate, cocaine, and tricyclic antidepressant interactions using chimeric dopamine-norepinephrine transporters. *J Biol Chem.* 1994; 269:15985–8. [PubMed: 8206893]
- Herbert MS, Der-Ghazarian T, Palmer AG, McDougall SA. One-trial cocaine-induced behavioral sensitization in preweanling rats: role of contextual stimuli. *Exp Clin Psychopharm.* 2010; 18:284–95.
- Holson RR, Pearce B. Principles and pitfalls in the analysis of prenatal treatment effects in multiparous species. *Neurotoxicol Teratol.* 1992; 14:221–8. [PubMed: 1635542]
- Howell LL, Kimmel HL. Monoamine transporters and psychostimulant addiction. *Biochem Pharmacol.* 2008; 75:196–217. [PubMed: 17825265]
- Hu M, Becker JB. Effects of sex and estrogen on behavioral sensitization to cocaine in rats. *J Neurosci.* 2003; 23:693–9. [PubMed: 12533629]
- Huynh H, Feldt LS. Estimation of the Box correction for degrees of freedom from sample data in randomized block and split-plot designs. *J Educ Stat.* 1976; 1:69–82.
- Jones SR, Gainetdinov RR, Wightman RM, Caron MG. Mechanisms of amphetamine action revealed in mice lacking the dopamine transporter. *J Neurosci.* 1998; 18:1979–86. [PubMed: 9482784]
- Kalivas PW, Stewart J. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. *Brain Res Rev.* 1991; 16:223–44. [PubMed: 1665095]
- Kameda SR, Fukushima DF, Trombin TF, Procópio-Souza R, Patti CL, Hollais AW, et al. Adolescent mice are more vulnerable than adults to single injection-induced behavioral sensitization to amphetamine. *Pharmacol Biochem Behav.* 2011; 98:320–4. [PubMed: 21277887]
- King GR, Xiong Z, Douglass S, Ellinwood EH. Long-term blockade of the expression of cocaine sensitization by ondansetron, a 5-HT₃ receptor antagonist. *Eur J Pharmacol.* 2000; 394:97–101. [PubMed: 10771040]
- Kozanian OO, Gutierrez A, Mohd-Yusof A, McDougall SA. Ontogeny of methamphetamine- and cocaine-induced one-trial behavioral sensitization in preweanling and adolescent rats. *Behav Pharmacol.* 2012; 23:367–379. [PubMed: 22732208]
- Kuczenski, R. Biochemical actions of amphetamine and other stimulants. In: Creese, I., editor. *Stimulants: neurochemical, behavioral and clinical perspectives.* New York: Raven Press; 1983. p. 31–61.
- Kuczenski R, Leith NJ. Chronic amphetamine: Is dopamine a link in or a mediator of the development of tolerance and reverse tolerance? *Pharmacol Biochem Behav.* 1981; 15:405–13. [PubMed: 7291244]
- Kuperstein F, Eilam R, Yavin E. Altered expression of key dopaminergic regulatory proteins in the postnatal brain following perinatal n-3 fatty acid dietary deficiency. *J Neurochem.* 2008; 106:662–71. [PubMed: 18410511]

- Kuribara H, Uchihashi Y. Dopamine antagonists can inhibit methamphetamine sensitization, but not cocaine sensitization, when assessed by ambulatory activity in mice. *J Pharm Pharmacol*. 1993; 45:1042–5. [PubMed: 7908972]
- Lal S, Feldmüller F. Effect of amphetamine and apomorphine on brain monoamines and behaviour in the immature and young adult rat. *Arch Int Pharmacodyn Ther*. 1975; 218:239–51. [PubMed: 1212022]
- Lal S, Sourkes TL. Ontogeny of stereotyped behaviour induced by apomorphine and amphetamine in the rat. *Arch Int Pharmacodyn*. 1973; 202:171–82. [PubMed: 4694351]
- Lanier LP, Isaacson RL. Early developmental changes in the locomotor response to amphetamine and their relation to hippocampal function. *Brain Res*. 1977; 126:567–75. [PubMed: 861741]
- Laviola G, Wood RD, Kuhn C, Francis R, Spear LP. Cocaine sensitization in periadolescent and adult rats. *J Pharmacol Exp Ther*. 1995; 275:345–57. [PubMed: 7562570]
- Lau CE, Imam A, Ma F, Falk JL. Acute effects of cocaine on spontaneous and discriminative motor functions: relation to route of administration and pharmacokinetics. *J Pharmacol Exp Ther*. 1991; 257:444–56. [PubMed: 2020002]
- Li Y, Wolf ME. Ibotenic acid lesions of prefrontal cortex do not prevent expression of behavioral sensitization to amphetamine. *Behav Brain Res*. 1997; 84:285–9. [PubMed: 9079793]
- Mathews IZ, Kelly H, McCormick CM. Low doses of amphetamine lead to immediate and lasting locomotor sensitization in adolescent, not adult, male rats. *Pharmacol Biochem Behav*. 2011; 97:640–6. [PubMed: 21108958]
- Mattingly BA, Hart TC, Lim K, Perkins C. Selective antagonism of dopamine D₁ and D₂ receptors does not block the development of behavioral sensitization to cocaine. *Psychopharmacology (Berl)*. 1994; 114:239–42. [PubMed: 7838914]
- McDougall SA, Baella SA, Stuebner NM, Halladay LM, Crawford CA. Cocaine-induced behavioral sensitization in preweanling and adult rats: effects of a single drug-environment pairing. *Psychopharmacology (Berl)*. 2007; 193:323–32. [PubMed: 17450351]
- McDougall SA, Cortez AM, Palmer AG, Herbert MS, Martinez CE, Charntikov S, et al. Importance of environmental context for one- and three-trial cocaine-induced behavioral sensitization. *Psychopharmacology (Berl)*. 2009; 206:377–88. [PubMed: 19636537]
- McDougall SA, Kozanian OO, Greenfield VY, Horn LR, Gutierrez A, Mohd-Yusof A, et al. One-trial behavioral sensitization in preweanling rats: differential effects of cocaine, methamphetamine, methylphenidate, and D-amphetamine. *Psychopharmacology (Berl)*. 2011a; 217:559–71. [PubMed: 21537939]
- McDougall SA, Pothier AG, Der-Ghazarian T, Herbert MS, Kozanian OO, Castellanos KA, et al. Importance of associative learning processes for the one-trial behavioral sensitization of preweanling rats. *Behav Pharmacol*. 2011b; 22:693–702. [PubMed: 21897205]
- McMillen BA. CNS stimulants: two distinct mechanisms of action for amphetamine-like drugs. *Trends Pharmacol Sci*. 1983; 4:429–32.
- McNamara CG, Davidson ES, Schenk S. A comparison of the motor-activating effects of acute and chronic exposure to amphetamine and methylphenidate. *Pharmacol Biochem Behav*. 1993; 45:729–32. [PubMed: 8332631]
- Meiergerd SM, Schenk JO. Kinetic evaluation of the commonality between the site(s) of action of cocaine and some other structurally similar and dissimilar inhibitors of the striatal transporter for dopamine. *J Neurochem*. 1994; 63:1683–92. [PubMed: 7931324]
- Milesi-Hallé A, McMillan DE, Laurenzana EM, Byrnes-Blake KA, Owens SM. Sex differences in (+)-amphetamine- and (+)-methamphetamine-induced behavioral response in male and female Sprague-Dawley rats. *Pharmacol Biochem Behav*. 2007; 86:140–9. [PubMed: 17275894]
- National Research Council. Guide for the care and use of laboratory animals. 8. Washington: National Academies Press; 2010.
- Partilla JS, Dempsey AG, Nagpal AS, Blough BE, Baumann MH, Rothman RB. Interaction of amphetamines and related compounds at the vesicular monoamine transporter. *J Pharmacol Exp Ther*. 2006; 319:237–46. [PubMed: 16835371]
- Pierce RC, Kalivas PW. A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. *Brain Res Rev*. 1997; 25:192–216. [PubMed: 9403138]

- Pierce RC, Reeder DC, Hicks J, Morgan ZR, Kalivas PW. Ibotenic acid lesions of the dorsal prefrontal cortex disrupt the expression of behavioral sensitization to cocaine. *Neuroscience*. 1998; 82:1103–14. [PubMed: 9466434]
- Rao PA, Molinoff PB, Joyce JN. Ontogeny of dopamine D1 and D2 receptor subtypes in rat basal ganglia: quantitative autoradiographic study. *Dev Brain Res*. 1991; 60:161–77. [PubMed: 1832594]
- Rivière GJ, Gentry WB, Owens SM. Disposition of methamphetamine and its metabolite amphetamine in brain and other tissues in rats after intravenous administration. *J Pharmacol Exp Ther*. 2000; 292:1042–7. [PubMed: 10688621]
- Robinson TE, Becker JB. Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Res Rev*. 1986; 11:157–98.
- Schindler CW, Carmona GN. Effects of dopamine agonists and antagonists on locomotor activity in male and female rats. *Pharmacol Biochem Behav*. 2002; 72:857–63. [PubMed: 12062575]
- Segal DS, Kuczenski R. Behavioral and neurochemical characteristics of stimulant-induced augmentation. *Psychopharm Bull*. 1987; 23:417–24.
- Shalaby IA, Spear LP. Psychopharmacological effects of low and high doses of apomorphine during ontogeny. *Eur J Pharmacol*. 1980; 67:451–9. [PubMed: 7192634]
- Sircar R, Kim D. Female gonadal hormones differentially modulate cocaine-induced behavioral sensitization in Fischer, Lewis, and Sprague-Dawley rats. *J Pharmacol Exp Ther*. 1999; 289:54–65. [PubMed: 10086987]
- Snyder KJ, Katovic NM, Spear LP. Longevity of the expression of behavioral sensitization to cocaine in preweanling rats. *Pharmacol Biochem Behav*. 1998; 60:909–14. [PubMed: 9700975]
- Sorg BA, Davidson DL, Kalivas PW, Prasad BM. Repeated daily cocaine alters subsequent cocaine-induced increase of extracellular dopamine in the medial prefrontal cortex. *J Pharmacol Exp Ther*. 1997; 281:54–61. [PubMed: 9103480]
- Spear, LP. The use of psychopharmacological procedures to analyse the ontogeny of learning and retention: issues and concerns. In: Spear, NE.; Campbell, BA., editors. *Ontogeny of learning and memory*. Hillsdale: Lawrence Erlbaum Associates; 1979. p. 135–56.
- Spear LP. The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev*. 2000; 24:417–63. [PubMed: 10817843]
- Spear LP, Brake SC. Periadolescence: age-dependent behavior and psychopharmacological responsivity in rats. *Dev Psychobiol*. 1983; 16:83–109. [PubMed: 6339302]
- Stewart J, Vezina P. Microinjections of SCH-23390 into the ventral tegmental area and substantia nigra pars reticulata attenuate the development of sensitization to the locomotor activating effects of systemic amphetamine. *Brain Res*. 1989; 495:401–6. [PubMed: 2670065]
- Teicher MH, Andersen SL, Hostetter JC Jr. Evidence for dopamine receptor pruning between adolescence and adulthood in striatum but not nucleus accumbens. *Dev Brain Res*. 1995; 89:167–72. [PubMed: 8612321]
- Tirelli E, Laviola G, Adriani W. Ontogenesis of behavioral sensitization and conditioned place preference induced by psychostimulants in laboratory rodents. *Neurosci Biobehav Rev*. 2003; 27:163–78. [PubMed: 12732232]
- Truong JG, Wilkins DG, Baudys J, Crouch DJ, Johnson-Davis KL, Gibb JW, et al. Age-dependent methamphetamine-induced alterations in vesicular monoamine transporter-2 function: implications for neurotoxicity. *J Pharmacol Exp Ther*. 2005; 314:1087–92. [PubMed: 15901804]
- Van Hartesveldt C, Meyer ME, Potter TJ. Ontogeny of biphasic locomotor effects of quinpirole. *Pharmacol Biochem Behav*. 1994; 48:781–6. [PubMed: 7938135]
- Vanderschuren LJ, Kalivas PW. Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. *Psychopharmacology (Berl)*. 2000; 151:99–120. [PubMed: 10972458]
- Walker QD, Kuhn CM. Cocaine increases stimulated dopamine release more in periadolescent than adult rats. *Neurotoxicol Teratol*. 2008; 30:412–18. [PubMed: 18508233]
- Walker QD, Morris SE, Arrant AE, Nagel JM, Parylak S, Zhou G, et al. Dopamine uptake inhibitors but not dopamine releasers induce greater increases in motor behavior and extracellular dopamine

in adolescent rats than in adult male rats. *J Pharmacol Exp Ther.* 2010; 335:124–32. [PubMed: 20605908]

Wall SC, Gu H, Rudnick G. Biogenic amine flux mediated by cloned transporters stably expressed in cultured cell lines: amphetamine specificity for inhibition and efflux. *Mol Pharmacol.* 1995; 47:544–50. [PubMed: 7700252]

Wayment H, Meiergerd SM, Schenk JO. Relationships between the catechol substrate binding site and amphetamine, cocaine, and mazindol binding sites in a kinetic model of the striatal transporter of dopamine in vitro. *J Neurochem.* 1998; 70:1941–9. [PubMed: 9572278]

Weiss SRB, Post RM, Pert A, Woodward R, Murman D. Context-dependent cocaine sensitization: differential effect of haloperidol on development versus expression. *Pharmacol Biochem Behav.* 1989; 34:655–61. [PubMed: 2623021]

White FJ, Joshi A, Koeltzow TE, Hu X-T. Dopamine receptor antagonists fail to prevent induction of cocaine sensitization. *Neuropsychopharmacology.* 1998; 18:26–40. [PubMed: 9408916]

Zorrilla EP. Multiparous species present problems (and possibilities) to developmentalists. *Dev Psychobiol.* 1997; 30:141–50. [PubMed: 9068968]

Research Highlights

- Early ontogeny of amphetamine-induced one-trial behavioral sensitization was assessed
- One-trial sensitized responding was evident on PD 13 and PD 17, but not at older ages
- Neural mechanisms mediating sensitization differ according to psychostimulant used

Fig. 1.

Mean distance traveled scores ($\pm$ SEM) of rats injected with saline or D-amphetamine (4 or 8 mg/kg, IP) immediately before a 30-min placement in the activity chambers on the pretreatment day (i.e., PD 12, PD 16, PD 20, or PD 24). * Significantly different from PD 12 rats when collapsed across the session. † Significantly different from PD 16 rats when collapsed across the session. ‡ Significantly different from saline-treated rats (collapsed across age group, Drug $\times$ Time block interaction).

Fig. 2. Mean distance traveled scores ($\pm$ SEM) of rats ($n = 7-8$ per group) given a challenge injection of D-amphetamine (0.5 mg/kg, IP) before the 120-min testing session on PD 13, PD 17, PD 21, or PD 25. On the pretreatment day (i.e., 24 h earlier), rats had been injected with 1 mg/kg D-amphetamine either prior to placement in the activity chamber (AMPH-Activity Chamber group) or 30 min after being returned to the home cage (AMPH-Home Cage group). The Acute Control group received saline injections at both time points. The insets show mean distance traveled collapsed across the testing sessions.

Fig. 3. Mean distance traveled scores ($\pm$ SEM) of rats ($n = 8-10$ per group) given a challenge injection of D-amphetamine (2 mg/kg, IP) before the 120-min testing session on PD 13, PD 17, PD 21, or PD 25. On the pretreatment day (i.e., 24 h earlier), rats had been injected with 4 mg/kg D-amphetamine either prior to placement in the activity chamber (AMPH-Activity Chamber group) or 30 min after being returned to the home cage (AMPH-Home Cage group). The Acute Control group received saline injections at both time points. The insets show mean distance traveled collapsed across the testing sessions. * Significant difference between the AMPH-Activity Chamber group and the Acute Control group. † Significant difference between the AMPH-Home Cage group and the Acute Control group.

Fig. 4. Mean distance traveled scores ($\pm$ SEM) of rats ($n = 8-10$ per group) given a challenge injection of D-amphetamine (2 mg/kg, IP) before the 120-min testing session on PD 13, PD 17, PD 21, or PD 25. On the pretreatment day (i.e., 24 h earlier), rats had been injected with 8 mg/kg D-amphetamine either prior to placement in the activity chamber (AMPH-Activity Chamber group) or 30 min after being returned to the home cage (AMPH-Home Cage group). The Acute Control group received saline injections at both time points. The insets show mean distance traveled collapsed across the testing sessions. * Significant difference between the AMPH-Activity Chamber group and the Acute Control group. † Significant difference between the AMPH-Home Cage group and the Acute Control group.

Fig. 5.

Mean distance traveled scores ($\pm$ SEM) of rats given an acute injection of 0.5 or 2 mg/kg D-amphetamine before the 120-min testing session on PD 13, PD 17, PD 21, or PD 25 (these rats are the Acute Control groups from Fig. 2–4). * Significantly different from all other age groups. † Significantly different from PD 21 and PD 25 rats ($P < 0.05$). ‡ Significantly different from PD 13 and PD 17 rats. § Significantly different from PD 13 rats. ¶ Significantly different from PD 17 rats.

Fig. 6.

Mean distance traveled scores ($\pm$ SEM) of rats ($n = 8$ per group) given a challenge injection of D-amphetamine (0.25, 0.50, 1, 2, or 4 mg/kg, IP) before the 120-min testing session on PD 25. On the pretreatment day (i.e., PD 24), rats had been injected with saline (Acute Control group) or 4 mg/kg D-amphetamine prior to placement in the activity chamber (AMPH-Activity Chamber group). * Significantly different from rats challenged with 0.25, 0.5, or 1 mg/kg D-amphetamine. † Significantly different from rats challenged with 0.25 or 0.5 mg/kg D-amphetamine. ‡ Significantly different from rats challenged with 0.25 mg/kg D-amphetamine.

Table 1

Mean (+SEM) distance traveled scores of rats injected with saline or 1 mg/kg D-amphetamine immediately before a 60-min placement in the activity chambers on the pretreatment day.

Postnatal Day (PD)	Treatment	
	Saline	D-Amphetamine (1 mg/kg)
PD 12	4,509 (+950)	15,391 (+2,071)
PD 16	5,465 (+1,248)	16,201 (+1,493)
PD 20	3,509 (+480)	15,329 (+1,761)
PD 24	3,645 (+212)	13,732 (+1,409)
$\bar{x}_{(PD\ 12 - PD\ 24)}$	4,322 (+437)	15,200 (+817) *

* Significantly different from saline-pretreated rats ($P < 0.05$).