Tripping the Light Fantastic: Modeling the Consequences of Recreational Use of MDMA or 5-MeO-DIPT in Humans Using Weekend "Rave" Exposures in Rat

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The hallucinogenic "club drugs" 3,4-methylenedioxymethamphetamine (MDMA) and 5-methoxy-N, N-diisopropyltryptamine hydrochloride (Foxy), albeit to different degrees, remain popular as recreational drugs. Much is known about MDMA including observations that in comparison to female rodents, males appear to be more sensitive to the toxic effects associated with abuse. Less is known about the possible sex differences associated with the abuse of Foxy, especially when the consequences of its use are examined during the neuropsychological development period of adolescence. In the present study, adolescent male and female rats were given multiple doses of MDMA, Foxy, or saline across a series of 48-hr "weekends" under conditions approximating that of a rave. Behavioral testing occurred in adulthood when the rats were 131 days old and had been drug free for 66 days. Assessments included general activity, passive avoidance, and a series of Morris water maze spatial and nonspatial memory tasks. Depending on task demands, the performance of MDMA-treated rats was inferior to that of the Foxy-treated rats and saline controls. The performance of both drug groups was comparable and inferior to that of control rats on a spatial learning set task. Generally, greater impairments were observed in MDMA-treated rats than the Foxy-treated rats. Sex differences were observed on some but not all spatial tasks with MDMA-treated males performing significantly worse than similarly treated female rats. The results are in the context of putative sex-mediated differences in sensitivity to MDMA or Foxy and the disruptive effects of these drugs to central serotonergic systems that may contribute to cognitive deficits.

Keywords: Foxy, MDMA, learning, sex, development

Using animal models, there is considerable evidence suggestive of a variety of learning and memory impairments after MDMA exposure (Able, Gudelsky, Vorhees, & Williams, 2006; Arias-Cavieres et al., 2010; Compton, Selinger, Westman, & Otero, 2011; Sprague, Preston, Leifheit, & Woodside, 2003; Vorhees, Reed, Skelton, & Williams, 2004; Vorhees, Schaefer, & Williams, 2007; Vorhees et al., 2009). Similarly, MDMA appears to affect adversely prospective or working memory, as well as executive functioning in humans (Fox, Toplis, Turner, & Parrott, 2001; Heffernan, Jarvis, Rodgers, Scholey, & Ling, 2001; Heffernan, Ling, & Scholey, 2001; McCann et al., 2008; Wareing, Fisk, & Murphy, 2000). Unfortunately, declines in measures of executive function and decision-making ability persist even after abstinence from MDMA use (Zakzanis & Campbell, 2006).

Lacking the safeguards associated with legal pharmaceutical manufacturing, consumer MDMA varies widely in potency and the presence of highly undesirable impurities (Gimeno, Besacier, Bottex, Dujourdy, & Chaudron-Thozet, 2005). Further, MDMA as well as its associated analogs share biochemical similarities to that of compounds identified as stimulants as well as neurotoxins including methamphetamine, amphetamine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and paraquat (Karuppagounder et al., 2014).

As a class of drugs, indolealkylamines (IAA) are chemical derivatives of 5-hydroxytryptamine (serotonin, Jiang, Shen, & Yu, 2015), a major neurotransmitter implicated in a variety of processes ranging from attention and cognition to dreaming and pain regulation (Carlson, 2013). Although some IAAs are used for medical or religious purposes (Carod-Artal, 2015), they are also considered a major class of substances with abuse potential and classified under the Controlled Substances Act. Among these is 5-methoxy-N,N-diisopropyltryptamine (5- MeO-DIPT or Foxy; Skelton et al., 2009) placed under Schedule I of the Controlled Substances Act in 2004 (Drug Enforcement Administration, Department of Justice, 2004). The actions of the U.S. Drug Enforcement Administration were in response to the recognition that Foxy, with properties similar to other tryptaminergic hallucinogens (Shulgin & Carter, 1980), led recreational users of MDMA and other compounds to experiment with this drug.

In rodent models, Foxy-associated deficits have been reported (Compton, Dietrich, Selinger, & Testa, 2011; Compton et al., 2006; Compton, Selinger, et al., 2011; Skelton et al., 2009). These reports lend credence to the observations that the response deficits primarily implicated compromised attentional processes and response perseveration. Considered an indicator of impaired cognition and associated with a disruption in the ability to change appropriately behavior or behaviors as task demands change, response perseveration is considered distinct from motor or motivational deficits. As such, response perseveration involves a maladaptive change in executive function (Pettenuzzo et al., 2003).

Adolescent drug use is associated with higher levels of dependence in adulthood (Gilvarry & McArdle, 2007). When exposed to substances with additive properties, younger adults are more likely than older adults to develop addictions (Karuppagounder et al., 2014). Further, when compared with adult mice, adolescent mice show a greater sensitivity to the reinforcing effects associated with MDMA (Procopio-Souza et al., 2014).

In rats, the developmental phase of adolescence includes the period from the 21st postnatal day (PND) until PND 60, with mid adolescence and late adolescence spanning PNDs 34 to 46 and 46 to 59, respectively (Tirelli, Laviola, & Adriani, 2003). The two periods are considered analogous to periadolescence and late adolescence/early adulthood (Tirelli et al., 2003). Using this framework as a model of rodent development, comparative evaluation and extrapolation to humans is possible (Spear, 2000). In the present study, the use of adolescent rats allowed us to examine further the developmental consequences associated with two drugs of abuse at various points in cognitive and biological development.

Considerable evidence exists suggesting that MDMA produces degeneration of 5-hydroxytryptamine (5-HT) nerve endings in multiple areas of the brain in both experimental animals and humans (see Green, Mechan, Elliott, O'Shea, & Colado, 2003). Although the research is more limited, a similar possibility is associated with the use of Foxy (Compton, Dietrich, et al., 2011; Compton Selinger et al., 2011). The available research examining the effects MDMA monoaminergic neurotoxicity in adolescent rodents is both limited and contradictory. For example, adolescent animals appear to be less sensitive to the neurotoxic effects of MDMA than their adult counterparts (Kelly, Ritchie, Quate, McBean, & Olverman, 2002; Meyer, Grande, Johnson, & Ali, 2004; Piper, 2007) with young (PND 39) adolescent rats spared of any serotonergic neurotoxicity (Fone et al., 2002). In the Fone et al. (2002) study, MDMA did impact behavior in adulthood. Conversely, recurrent exposure of 10 mg/kg of MDMA during late adolescence adversely affected the behavior of abstinent rats with a concomitant decrease in 5-HT levels in multiple areas of the brain (Cox et al., 2014). This is consistent with other reports, some of which also examined the effects of Foxy (e.g., Compton, Selinger, et al., 2011; Skelton et al., 2009;

Skelton, Williams, & Vorhees, 2006). Where both were examined, developmental exposure of Foxy and MDMA produced long-term changes in learning and memory performance. Nonetheless, MDMA and Foxy appear to produce dissociable effects (Skelton et al., 2009). Returning to MDMA neurotoxicity, recently reported that many MDMA mediated effects associated with binge exposure comprise not only effects to 5-HT axon terminals but also to other measured hippocampal cell markers such as alterations to GABAergic activity and neurofilament proteins (García-Cabrerizo & García-Fuster, 2015).

In addition to the consideration of exposure during adolescence, there is evidence suggestive of sex differences associated with some of the toxic effects attributed to MDMA (Allott & Redman, 2007). Among humans, women report greater levels of dizziness, sadness and sedation, and symptoms of psychosis (de Sola et al., 2008; Kolbrich et al., 2008; Pardo-Lozano et al., 2012; Parrott et al., 2011). Although such differences could reflect a male advantage in drug disposition (Pardo-Lozano et al., 2012) such as faster 5-HT synthesis and larger reserves of 5-HT (Sakai et al., 2006), male and female users of MDMA have different patterns of consumption and it is likely that a number of factor may influence any putative sex difference (Allott & Redman, 2007).

If present, such differences have implications. Evidence of a sex difference in lifetime MDMA use among U.S. teens has been reported with higher levels of use observed among female adolescents, even after controlling for factors such as population density, race, and income (Wu et al., 2010). Although data from the Monitoring the Future study suggests a decline in use among high school students (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2014), an estimated 12.80% of adults between the age of 18 and 25 have used MDMA with a significant increase between 2012 and 2013 reported for those 26 years of age or older (National Institute on Drug Abuse, n.d.).

Additional support is found in rodent models. For example, male mice were far more susceptible to the lethal effects of a large dose of MDMA (80 mg/kg) than female mice (Cadet, Ladenheim, Baum, Carlson, & Epstein, 1994). In rats, Koenig et al. (2005) found markedly different survival rates between male and female rats, with a clear survival advantage associated with the latter sex. Similarly, MDMA LD_{50} was found to be 2.4-times lower in male rats than in female rats, with a concomitant increase in hyperthermia detected in male rats (Fonsart et al., 2008). MDMA-mediated hyperthermia, especially under the conditions of high ambient temperatures found at raves is well known to have lethal consequences (Dafters, 1994, 1995; Gordon, Watkinson, O'Callaghan, & Miller, 1991; Parrott, 2013). Conversely, Allott and Redman (2006) have noted that reports of low sodium levels in the blood resulting from the excessive consumption of water (hyponatremia; Hartung, Schofield, Short, Parr, & Henry, 2002) as a strategy to combat hyperthermia is more common among female users (see Budisavljevic, Stewart, Sahn, & Plath, 2003; Rosenson, Smollin, Sporer, Blanc, & Olson, 2007).

When compared with MDMA, less reliable information is available about the specific effects and consequences associated with the use of Foxy. However, previous reports about the consequences associated with its use (Ikeda, Sekiguchi, Fujita, Yamadera, & Kog, 2005; Wilson, McGeorge, Smolinske, & Meatherall, 2005), as well as toxicological investigations (Meatherall & Sharma, 2003; Sitaram, Lockett, Blackman, & McLeod, 1987; Smolinske, Rastogi, & Schenkel, 2005), animal models to ascertain putative central nervous system effects (Compton, Dietrich, et al., 2011; Compton et al., 2006; Compton, Selinger, et al., 2011; Jiang et al., 2015; Nagai, Nonaka, & Kamimura, 2007; Nakagawa & Kaneko, 2008; Skelton et al., 2009), and sexual dimorphic effects, if any, the conditions of exposure warrant further consideration of the effects of this drug.

The goal of the present study investigation was to examine further the effects of MDMA or Foxy on cognitive processes using a model more representative of the recreational use of MDMA or Foxy during adolescence. Thus, the protocol used in the present study included a series of "weekend" exposures under auditory and visual conditions (e.g., dance music, flashing lights) and ambient temperatures normally associated with adolescent raves. In addition, the question of sex differences was explored through inclusion of both male and female rats of comparable age as part of the experiment. Although there is evidence of persistent deficits following adolescent exposure of these two

compounds (Compton, Selinger, et al., 2011; Skelton et al., 2009), including one report of MDMA associated deficits in a rodent rave paradigm (McAleer, Schallert, & Duvauchelle, 2013), no reports are available specifically examining the consequences of MDMA or Foxy under the conditions more typical of adolescent human use at rave events.

Method

Subjects

The subjects consisted of 36 (n = 18 male,18 female) Long-Evans rats (*Rattus norvegicus*; Charles River, Wilmington, MA). All rats were individually housed in standard stainless steel cages in a climate-controlled facility and were maintained on a 12-hr light/dark cycle with food (Mazuri Rodent Chow) and water provided ad libitum. All procedures were approved by the Institutional Animal Care and Use Committee of Palm Beach Atlantic University and the animals were maintained according to the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 2011).

Drug exposure began when the rats are in the midadolescent period of development (i.e., 35 days old). All injections took place on five evenly spaced "weekends" spaced five days apart. All rats received a total of 10 injections, two per "weekend," of Foxy (5 mg/kg; Biosynth International, Naperville, IL), MDMA (5 mg/kg; Sigma-Aldrich, St. Louis, MO), or a corresponding injection volume of isotonic saline. The suppliers using high performance liquid chromatography (HPLC) verified purity of the Foxy and MDMA. During the period of all drug exposure sessions, the ambient temperature as maintained at approximately 24°c with the humidity between 45% and 50%. Prior to the commencement of the experiment male and female rats were randomly assigned to one of three drug treatment conditions: male–MDMA (n = 6), female–MDMA (n = 7), male–Foxy (n = 5), female–Foxy (n = 5), male–saline (n = 7), and female–saline (n = 6). The rats were exposed to MDMA (n = 13), Foxy (n = 10), or saline (n = 13) from 35 to 57 days of age. Behavioral testing occurred in adulthood when the rats were 131 days old and had been drug free for 66 days.

Rave Sessions

Each rave session took place in a sound deadened colony room. All rats remained in their home cages with food and water ad libitum. Each rave lasted for 6 hours. Following injections, music was from the commercial radio station Wild 95.5 of Juno Beach, FL, was streaming through iHeartRadio (iHeartRadio, Inc.) to a JBL Onbeat Venue speaker (30 W, Harmon, Stanford, CT). The station offers contemporary hit radio with a playlist dominated by pop and dance music. The music was played at an average sound level 110dB as measured by Sound Meter Pro (Android, Mobile Essentials Version 2.92). Two 5-inch strobe lights (MiniStrobe, Amscan, Elmsford, NY) flashed at 11 Hz. Last, during the rave, room temperature was raised from the normal colony temperature of 24 °C to 27 °C (± 2 °C).

Apparatus—Morris Water Maze (MWM)

All spatial testing took place in a circular white acrylic plastic swimming pool with a diameter of 183 cm. Depending on the phase of the experiment, different extramaze cues and escape parameters were used. With the exception of the cued water maze phase of the experiment (see following), the depth of the water was held constant at 30 cm and made opaque white in color using a nontoxic water-based paint (Sargant Art, Hazelton, P A). The swimming pool was located in a quiet testing room approximately 36.88 m^2 in size. White curtain panels surrounded the pool, limiting the number of external stimuli available to aid navigation when viewed from the surface of the pool. With the exception of free swim "probe" trials, a 15-cm × 15-cm flat white escape platform was used throughout all phases of training and testing. For the cued water maze task described below, the platform protruded 15 mm above the surface of the water and was located a distance of 18 cm from the wall of the swimming pool. For all other phases of the experiment, the escape platform was submerged to a depth of 15 mm below the surface of the water.

Assessment of general activity and exploration. General activity levels were evaluated for two 5-min periods (one per day) in a 60.96-cm × 60.96-cm chamber consisting of 10.16-cm squares (i.e., a checkerboard). Activ-

ity measures included the number of squares crossed during the measurement period and the number of times the rats rose onto their hind legs. In addition, motivational and sensorimotor deficits were assessed using a cued version of the MWM task described below.

Step-down passive avoidance testing. The step-down passive avoidance testing occurred in a standard operant chamber (Lafayette Model 84022) with a stainless steel electrified grid floor. Located in the center of the 21-cm × 28-cm chamber was a 10.14-cm × 10.14-cm brick block. The rats experienced a 0.4mA current delivered to the feet whenever the animal left the block and touched the grid floor.

Water Maze Tasks

The series of water maze protocols we employed allowed us to evaluate different aspects of rat learning and memory without the provision of food deprivation associated with appetitive tests of memory. For all MWM elements, the platform was either 15 mm above the water's surface (cued memory task) or was submerged 15 mm below the surface of the water (the place & spatial learning set tasks). Across all spatial phases of the experiment, on a given trial the rat was gently released into the pool at one of four compass points, labeled north, south, east, or west, and allotted 60 s per trial to reach the escape platform. The platform location varied at one of four compass positions—northeast, northwest, southeast, or southwest. If the rat was unable find the platform within 60 s, it was gently placed on the platform. Escape times to the escape platform were recorded with a stopwatch and errors, operationally defined as crossing one of four quadrants associated with the four compass points, were tabulated by no fewer than teams of two experimenters.

Simple (cued) place learning. The cued place learning MWM navigation task was administered after the drug recovery period and assessment of general activity and exploration. This phase was used to determine whether nonassociative influences might develop over time and influence performance on subsequent place learning or learning set tasks. Thus, using a visible platform, the cued place learning phase was used to examine general swimming ability, motivational deficits, and nondeclarative memory ability that could influence performance during the spatial place and learning set tasks. The rats received 10 trials per day for two days of testing. On each trial, the escape platform was located in one of four possible locations. After successfully locating the platform, the rats were allowed to rest on the platform for about 15 s at the completion of each trial.

Spatial water maze tasks. The next two phases involved an assessment of spatial reference memory. Both were considered tests of spatial reference memory but differed in terms of difficulty. The place learning tasks involved learning the location of a submerged platform that remained constant across all trials within a given phase of the experiment. Two variations of the task were used because often only minor deficits at most are reported using the standard version of this test (Hartman, Lee, Zipfel, & Wozniak, 2005). Therefore, a more difficult version of the place-learning task was included, as the latter of the two was considered more sensitive for detecting spatial learning/memory impairments following adolescent drug exposure to MDMA or Foxy.

The simple (high-cue) version of the place-learning task consisted of training the rats for 10 trials per day for two days. At the completion of each trial, the rats were allowed to remain on the platform for 15 s. In addition, a test of retention was evaluated with a probe trial on the second day. This consisted of removing the escape platform and testing the subject for a 60-s "free swim." This assessment took place approximately two hours after the last place learning trial. Both the time spent swimming in the target quadrant and the number of crossings over the former platform location were recorded.

The next phase, a task considered more difficult, was a low-cue version of the place-learning task. Here, the task involved reducing the availability of extramaze cues to aid navigation. For this phase of place learning, the rats were trained four consecutive trials per day for five consecutive days. As in previous MWM phases, task difficulty was increased by placing a curtain around the water maze. Additional task difficulty was achieved by indirectly lighting the room with a single 60-W red light bulb located beyond the curtain, below the horizon of the pool, and approximately three meters from the water maze. As a result, few visual cues remained to aid navigation. Rats were allowed to remain on the platform

for 15 s after each trial. Daily probe trials were administered not less than two hours after the last trial of the daily four-trial series.

As a phase of testing, learning set acquisition required the animals to learn a new location for the escape platform each day for five consecutive days. All animals received four consecutive trials per day. The averaged performance on Trial 2 of each day was used as an index of working (short-term) memory because in the task the animal is required to recall its response on the immediately preceding trial. The rats were allowed to sit on the platform for 15 s at the completion of each trial.

Plus maze response learning. The final phase of the experiment involved the use of a plus maze response-learning task similar to that discussed elsewhere (Compton, Selinger, et al., 2011). In this task, the animal was faced with three response alternatives—to tum left, to tum right, or to swim straight ahead. Using a Fellows (1967) series, the ordering of placement included one of two starting points. Consistent with all earlier tests, the trials in this phase began by gently lowering the animal to the surface of the water facing the wall of the tank. As a result, the animal was required to turn 180° and swim toward the choice point located at the center of the plus maze.

This phase of assessment protocol was designed to assess nonspatial response learning as well as perseverative behavior. Thus, within a given set of trials, the configuration of the available allocentric information differed as a function of each trial. Therefore, in order to master the task, (i.e., "turn right vs. left"), the animal was required to learn a rule to turn in a specific direction regardless of the starting location (McDaniel et al., 1995). Although the goal remained fixed for each animal and a series of reversals were not considered here, we have found that the ability to adjust flexibly their behavior as a function of available allocentric cues has proven to be an effective measure of perseverative behavior.

Assessment of Brain Serotonin (5-HT) Levels

In order to assess brain serotonin (5-HT) levels, one month following the completion of the behavioral testing, the rats were euthanized. 5-HT levels were determined in the saline, MDMA, and Foxy using HPLC (Waters Model 600 with electrochemical detection). Procedures in the present experiment were based on a modified version of that described elsewhere (Chapin, Lookingland, & Moore, 1986). Briefly, the raw data were integrated and analyzed to determine 5-HT levels in three regions of the brain—the hippocampus, the prefrontal cortex, and the striatum. Concentrations in the amounts of 0.04% sodium octyl sulfate, 0.1 mM disodium-ethylenediamine-tetraacetate, 0.05 M sodium phosphate were dissolved in HPLC Grade H_2O. As part of the protocol 0.03 M citric acid acted as a buffer. The aqueous portion of the mobile phase was maintained at pH levels between 2.7 and 2.9 and the mobile phase consisted of 20% methanol and 80% aqueous phase. The HPLC column was a Waters C_{18} reverse phase analytical column (3.9 $\times$ 300 mm; 4 μm). Serotonin levels were calculated and reported as ng/g tissue.

Data Analysis

For the step-down passive avoidance task, step down latencies were assessed for each day. For all MWM tasks and the plus maze response learning task escapatencies and navigation errors were the two primary measures of performance. For the plus maze phase of the experiment, total errors was divided into working and reference memory errors (see below, nonspatial response learning section).

When considering the MWM tasks, the optimal swim path distances differed depending on the start and escape loci. Therefore, the recorded escape latencies for the four start locations were normalized. Normalization involved computation of the ratio of the minimum swim distance in centimeters for each of the two longer swim paths to the escape platform (e.g., north start location and a southwest goal location) to the minimum swim of the two shorter swim paths (e.g., a north start location and a northeast goal location) trials in centimeters.

Statistical analyses involved mixed analysis of variance (ANOVAs), with drug group as the between-subjects factor and days, or blocks of trials and days as within-subjects factors. Post hoc analyses were performed using $\text{Tukey}_{\text{HSD}}$ or paired t tests with a Bonferroni correction to control for multiple comparisons. The alpha level for acceptance was set at $p < .05$ and analyses were performed using SPSS.

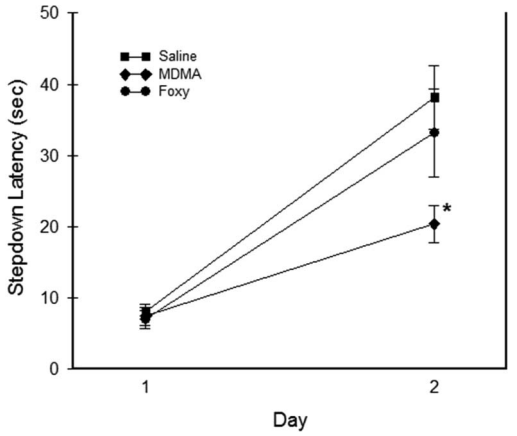

Figure 1. Stepdown passive avoidance testing for the two days of assessment. Vertical lines represent the standard error of the mean (SEM). MDMA = 3,4-methylenedioxymethamphetamine. * Significantly different from saline rats ($p < .05$).

Results

General Activity

Assessment of the activity data revealed no group differences in the number of squares traversed or in the number of rearings during the measurement period.

Stepdown Passive Avoidance

Although the main effect of sex was nonsignificant, as were the Sex × Days and Drug × Sex × Days interactions, main effects of drug group, $F(2, 30) = 4.87$, $p < .05$, $\eta_p^2 = .25$, and days, $F(2, 30) = 56.86$, $p < .001$, $\eta_p^2 = .66$, were detected. In addition, the Drug Group × Days interaction was significant, $F(2, 30) = 3.41$, $p < .05$, $\eta_p^2 = .19$, suggesting differences in stepdown latencies across the 2-day test period. As seen in Figure 1, although stepdown latencies were comparable across groups on the first trial, MDMA-treated rats left the safe platform significantly sooner than the Foxy-treated and saline animals (Tukey_{HSD}, $p < .05$). The latter two groups did not differ significantly.

Cued Place Learning

The data associated with cued place learning were collapsed into blocks of five trials and assessed for the two days of testing using a 2-between (drug, sex), 2-within (days, trials) mixed ANOVA. The ANOVA revealed the following. The main effects of days, $F(2, 30) = 66.65$, $p < .001$, $\eta_p^2 = .69$ and blocks, $F(2, 30) = 39.76$, $p < .001$, $\eta_p^2 = .57$, were significant, suggesting that escape latencies improved across both blocks of trials and the two days of testing. Although the Sex × Days × Blocks bordered on significance, $F(1, 30) = 3.96$, $p = .056$, none of the interactions were significant (all $ps > .05$). However, a main effect of sex, $F(1, 30) = 4.95$, $p < .05$, $\eta_p^2 = .14$, was found suggesting an overall difference in escape latencies between the male ($M = 5.21$, $SD = 1.80$) and female ($M = 4.06$, $SD = 0.75$) rats across the cued escape learning period.

Assessment of the errors across the cued place-learning phase revealed a similar pattern of a significant main effects of days, $F(1, 30) = 91.21$, $p < .001$, $\eta_p^2 = .75$, and blocks, $F(1, 30) = 58.60$, $p < .001$, $\eta_p^2 = .66$. Thus, all animals improved within days as well as across, although a Day × Blocks interaction generally suggests somewhat more variability among the blocks. Last, the main effect of sex was significant, $F(1, 30) = 5.78$, $p < .05$, $\eta_p^2 = .162$, with males ($M = 4.54$, $SD = 1.55$) making more errors than females ($M = 3.65$, $SD = 1.05$).

Simple Place Learning

Consideration of escape latency data from the high-cue place-learning phase revealed the following findings. Analysis of the data with 2-between (drug, sex), 2-within (days, blocks of trials) mixed ANOVA yielded significant within-subject main effects of days, $F(1, 30) = 10.51$, $p < .005$, $\eta_p^2 = .259$, and blocks of trials, $F(1, 30) = 28.14$, $p < .001$, $\eta_p^2 = .484$, suggesting that escape latencies improved as a function of training.

In addition, a significant main effect of drug group was found, $F(2, 30) = 3.91$, $p < .05$, $\eta_p^2 = .207$. Closer examination of this result using Tukey_{HSD} revealed that across this phase of the experiment, escape latencies were significantly higher for both the MDMA- and Foxy-treated animals than the saline-treated control rats. Overall, escape latencies for the two drug groups did not differ significantly. More important, although the main effect of sex was nonsignificant, a Drug × Sex interaction was found, $F(2, 30) = 4.99$, $p < .025$, $\eta_p^2 = .250$. Decom-

position of the interaction with Tukey's tests revealed that among male rats, the performance of saline-treated animals was superior to that of the MDMA and the Foxy-treated rats but that the drug groups performed comparably. When females were assessed, no effect of drug was detected, thus suggesting sex differences in the effects of the two drugs during this phase of the experiment (see Figure 2). All remaining lower-order and three-way interactions were all nonsignificant.

The effects reported above were largely consistent with the analysis of the error data. As was the case for escape latencies, main effects of days, $F(1, 30) = 20.52$, $p < .001$, $\eta_p^2 = .406$, and blocks of trials, $F(1, 30) = 66.50$, $p < .001$, $\eta_p^2 = .689$, were found. Although main effects of drug and sex were absent, a Drug × Sex interaction was found, $F(2, 30) = 3.97$, $p < .05$, $\eta_p^2 = .210$. Decomposition of the interaction revealed a similar effect of drug in the male but not female rats during this phase of training.

Difficult Place Learning

In order to analyze the data associated with a place learning task with few allocentric cues available, all trials were normalized and the four daily trials averaged. Examination of the resulting data using a 1-between (drug groups), 1-within (days) ANOVA revealed the following. A main effect of drug group, $F(2, 30) = 7.43$, $p < .01$, $\eta_p^2 = .331$, was found, suggesting differences in swim times as a function of drug condition. Post hoc examination with Tukey's tests revealed that the performance of the MDMA-treated was inferior to that of the saline-treated rats and the Foxy-treated rats. Nonetheless, the performance of Foxy-treat rats was not significantly different from that of the saline control animals. In addition, across the measurement period the performance of the female rats was superior to that of the male rats, $F(1, 30) = 11.22$, $p < .01$, $\eta_p^2 = .272$. Of related interest, the Drug × Sex interaction was significant, $F(2, 30) = 6.60$, $p < .01$, $\eta_p^2 = .305$. Closer consideration of the interaction revealed that male MDMA-treated rats were impaired relative to that of female MDMA-treated rats. Performance in the latter group was comparable to that of male and female saline-treated rats. The performance of both male and female Foxy-treated rats was comparable to saline controls as well.

In addition to the between-subjects effects reported above, a main effect of days was found, $F(4, 120) = 14.59$, $p < .01$, $\eta_p^2 = .607$, as was the Drug × Days interaction, $F(8, 120) = 2.46$, $p < .01$, $\eta_p^2 = .246$. Decomposition of the interaction presented in Figure 3 revealed the following. The performance of sa-

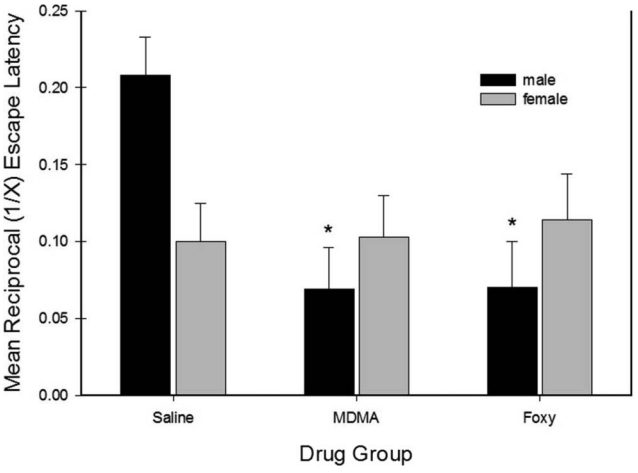

Figure 2. Simple (i.e., maximum extramaze cues) place learning task performance for male and female rats across the 2-day test period. MDMA = 3,4-methylenedioxymethamphetamine. * Significantly different from saline rats ($p < .05$). Vertical lines represent the standard error of the mean (SEM).

line-treated rats was superior to that of both drug groups on Days 3 and 4 but only the MDMA-treated rats on Day 5.

Last, consistent with earlier results, the pattern of swim error results largely mirrored that of the escape latency analyses.

Spatial Learning Set Acquisition Testing

In order to facilitate the interpretation of the data, trial one versus two performance on the first day was compared with the trial one versus two performance collapsed across Days 2 through 5. Analysis of the resulting data using a 2-between (drug, sex), 2-within (days, trials) mixed ANOVA revealed the following. The main effects of drug groups and days were nonsignificant. The main effect of trials, $F(1, 29) = 38.71$, $p < .001$, $\eta_p^2 = .572$, was significant suggesting performance difference between trials one and two of testing. In addition, Group × Days × Sex interaction, $F(2, 29) = 4.93$, $p < .05$, $\eta_p^2 = .254$, and Days × Trials, $F(1, 29) = 12.10$, $p < .05$, $\eta_p^2 = .294$, interactions were found, as well as a Group × days × trials interaction, $F(2, 19) = 3.68$, $p < .05$, $\eta_p^2 = .202$. However, all these effects must be considered in light of a significant Group × Sex × Days × Trials interaction, $F(2, 29) = 4.63$, $p < .05$, $\eta_p^2 = .242$. The resulting data are presented in Figure 4. Decomposition of the interaction by comparing the trial one versus two escape latencies for each drug group within sex revealed the following results.

Among saline-treated males, escape latencies were comparable on the first day but on subsequent days, escape latencies were superior on trial two as compared with trial one. The escape latencies of MDMA- and Foxy-treated rats were similar across trial one and trial two and did not improve across training days.

A somewhat different pattern emerged when the performance of female rats was considered. First, trial two escape latencies of saline-treated were superior to that of trial one on Day 1 and Days 2 through 5. A similar pattern was found among the MDMA-treated rats on Day 1 but not on Days 2 through 5. Last, escape latencies for the Foxy treated animals were comparable across trials regardless of day.

Plus Maze Response Learning

The final phase of testing involved an assessment of nonspatial response learning set performance using a plus maze version of the standard MWM. Daily training sessions involved 10 trials per day, continuing five days per week for two weeks or a total of 100 trials. Using an operational framework de-

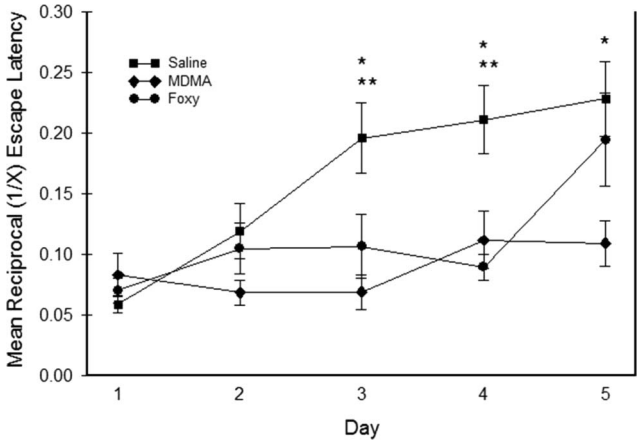

Figure 3. Difficult (i.e., minimal extramaze cues) place learning task performance for each of the five days of testing. Individual trials were collapsed for analysis. Vertical lines represent the standard error of the mean (SEM). The performance of saline-treated rats was superior to that of MDMA-treated* and Foxy-treated** rats on Days 3 and 4 but only the MDMA-treated* rats on Day 5. The * represents significant differences between MDMA and Saline rats, The ** represents significantly differences between Foxy and Saline rats.

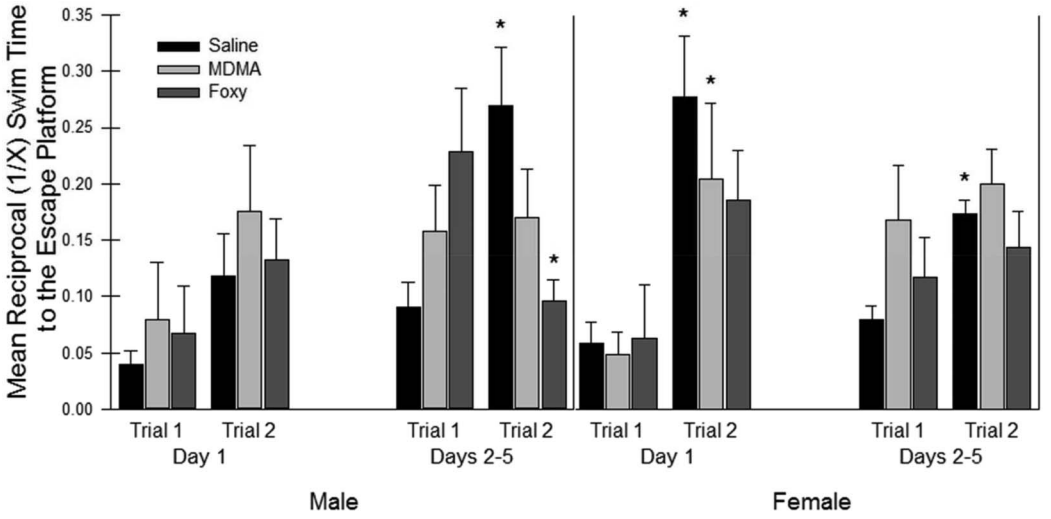

Figure 4. Graphical representation of the mean and the standard error of the mean (SEM; vertical bars) for trial one versus trial two performances on the spatial learning set task on Day 1 and Days 2 through 5 of testing. MDMA = 3,4-methylenedioxymethamphetamine. * Significant difference between trial one and trial two escape latencies ($p < .05$).

scribed elsewhere (Compton, Selinger et al., 2011), the total errors were subdivided as either reference or working memory errors. A reference memory error was assigned whenever an animal initially entered one of three incorrect alleys, whereas working memory errors were defined as reentries into incorrect alleys. Thus, working memory errors can be considered indicative of a problem in perseverative behavior. The data were analyzed using Drug × Sex × Week mixed ANOVAs, with weeks serving as a within-subjects factor and the measures of working memory, reference memory, and total errors serving as the dependent measures.

Analysis of the data suggested the following. As can be seen in Figure 5 (Panel C), the animals made fewer total errors across the training period, $F(1, 29) = 17.84$, $p < .001$, $\eta_p^2 = .381$. A significant main effect of drug was found, $F(2, 29) = 4.66$, $p < .025$, $\eta_p^2 = .241$, indicating group differences in number of errors made across the assessment period (see Figure 5, inset). Post hoc comparisons using Tukey's tests indicated that the MDMA-treated animals made significantly more errors than the saline and Foxy-treated animals. Foxy-treated animals made errors that were on average intermediate between but not significantly different from the saline or MDMA-treated animals. No main effect of sex was observed and the interactions were all nonsignificant.

Similar results were found when working memory errors were considered. Once again a main effect of weeks of training was found, $F(1, 29) = 16.84$, $p < .001$, $\eta_p^2 = .367$, suggesting an improvement in performance across the measurement period (see Figure 5, Panel B). A main effect of drug was also detected, $F(2, 29) = 3.68$, $p < .05$, $\eta_p^2 = .202$. Post hoc examination of the drug effect using Tukey's tests indicated that animals exposed to MDMA made significantly more working memory errors than the saline-treated animals. Once again, the performance of the animals in the Foxy-treated group were intermediate between those of the other two groups but nonsignificant (see Figure 5, inset). Once again, no main effect of sex was observed and the interactions were all nonsignificant. Last, although consideration of the reference memory errors suggested an improvement across the 2-week period, $F(1, 29) = 9.52$, $p < .01$, $\eta_p^2 = .247$, the remaining main effects and interactions failed to reach significance.

Analysis of Brain 5-HT Levels

The mean levels of 5-HT in the hippocampus, prefrontal cortex, and striatum are pre-

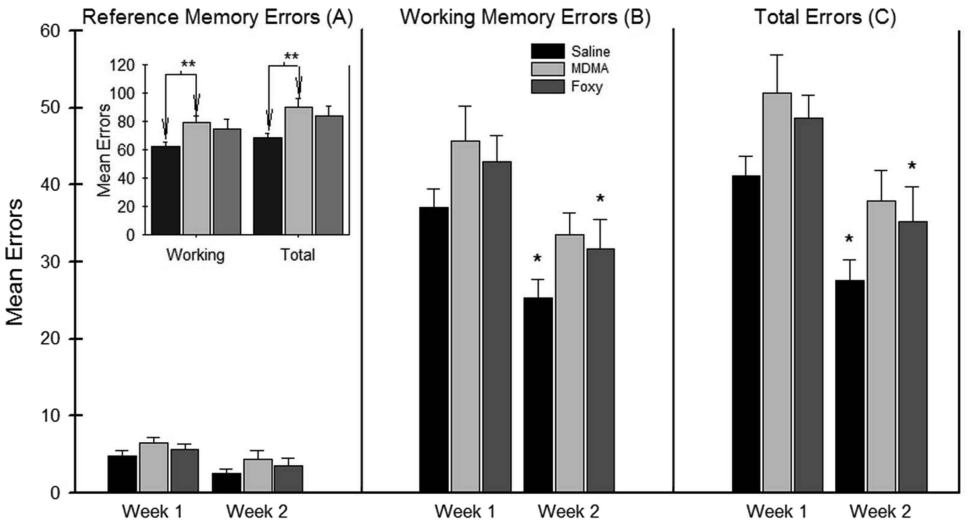

Figure 5. Graphical representation of the mean and SEM for reference memory errors, defined as reentry errors (Panel A); working memory errors, defined as initial alley entrance errors (Panel B); and total errors (Panel C). Working and total memory performance across the 2-week period is presented as an inset in the graph. MDMA = 3,4-methylenedioxymethamphetamine. * Significantly different from week one. ** Significantly different from saline rats.

sented in Table 1. Analysis of the three brain regions using a Drug × Sex multivariate analysis of variance (MANOVA) revealed the following. The overall MANOVA was significant for the main effects of drug group, Wilks's $\lambda = .108$, approximate $F(6, 54) = 18.33$, $p < .001$, $\eta_p^2 = .507$, sex, Wilks's $\lambda = .686$, approximate $F(3, 27) = 4.12$, $p < .05$, $\eta_p^2 = .314$, as well as the Drug × Sex interaction, Wilks's $\lambda = .108$, approximate $F(6, 54) = 6.86$, $p < .001$, 1lp2 = .322. Univariate analysis of 5-HT concentrations revealed an effect of drug in the hippocampus, $F(2, 29) = 33.61$, $p < .001$, $\eta_p^2 = .699$, and prefrontal cortex, $F(2, 29) = 33.61$, $p < .001$, $\eta_p^2 = .699$. Pairwise comparisons indicated a significant difference between the saline rats and rats in the two drug groups, with the latter two

Table 1
Mean Levels of 5-HT in the Hippocampus, Prefrontal Cortex, and Striatum of Saline-, MDMA-,or Foxy-Treated Rats

	Hippocampus *M* (*SD*)		Prefrontal cortex *M* (*SD*)		Striatum *M* (*SD*)	
Drug group	Male	Female	Male	Female	Male	Female
Saline	126.28 (20.04)	130.63 (12.17)	146.56 (17.99)	129.27 (16.81)	144.37 (14.31)	148.25 (13.99)
MDMA	58.11 (6.94)*†	103.57 (26.69)	63.15 (16.95)*†	94.73 (9 .03)	138.16 (23.99)	124.32 (21.47)
% difference from saline group	53.9%	20.7%	56.9%	26.7%	04.3%	16.1%
Foxy	72.85 (22.44)*	69.14 (8.81)*	82.59 (7.08)*	96.57 (9.96)	133.41 (17.67)	137.38 (9.96)
% difference from saline group	42.3%	47.1%	43.6%	25.3%	07.6%	07.3%

Note. Means and standard deviations are expressed in *ng/g* tissue. MDMA = 3,4-methylenedioxymethamphetamine; Foxy = 5-methoxy-N,N-diisopropyltryptamine hydrochloride.
† Significantly different from male rats. * Significantly different from saline rats ($p < .05$).

not significantly different. Sex differences were detected for hippocampal 5-HT levels as well, $F(1, 29) = 6.04$, $p < .001$, $\eta_p^2 = .172$.

In addition to the main effects, significant Drug × Sex interactions were found for 5-HT levels in the hippocampus, $F(2, 29) = 6.20$, $p < .01$, $\eta_p^2 = .300$, and prefrontal cortex, $F(2, 29) = 9.79$, $p < .01$, $\eta_p^2 = .403$ (see Table 1). Here, the most important result was significant differences between the male and female rats on both hippocampus and prefrontal cortex measures of 5-HT.

Discussion

In the present experiment, although dependent on task demands, the performance of MDMA-treated rats was inferior to that of the Foxy-treated and saline rats. In addition, the performance of both drug groups was comparable and inferior to that of control rats on the spatial learning set task. Nonetheless, when the data are considered collectively, greater impairments were observed in MDMA-treated rats than the Foxy-treated rats.

There is considerable evidence that exposure to or recreation use of MDMA is capable of compromising cognition. Such effects lead to compromised executive control, planning deficits, perseverative behavior, and deficits in working memory (Compton, Selinger, et al., 2011; Marston, Reid, Lawrence, Olverman, & Butcher, 1999; McCardle, Luebbers, Carter, Croft, & Stough, 2004; Moyano, Frechilla, & Del Rio, 2004; Parrott, 2002; Skelton et al., 2006, 2009; Thompson et al., 2009; Wareing et al., 2000). The deficits in working memory have been reported to extend to spatial working memory processes (Fox, McLean, Turner, Parrott, Rogers, & Sahakian, 2002; Harper, Wisnewski, Hunt, & Schenk, 2005; Wareing et al., 2000). However, the effects do appear to be to some degree dependent on prior experiences, with reports of a deficit in reference memory rather working memory (Vorhees et al., 2004).

In addition, sex differences were observed on some but not all spatial tasks with MDMA-treated males performing significantly worse than similarly treated female rats. Justifying exclusion on the basis of the frequency and presence of an estrus cycle and accompanying hormonal fluctuations (Sharp & La Regina, 1998), often female animals were not included in physiological and psychopharmacological research (Wallinga, Gralhlmann, Granneman, Koolhaas, & Buwalda, 2011). More recently, recognition in support of the consideration of sex differences in the study of psychostimulants such as MDMA has increased following reports that female use of Ecstasy has increased and remains popular (Allott & Redman, 2007). Last, in humans MDMA has a more profound impact on 5-HT in females (see McCann & Ricaurte, 2014, for a review), with subjectively more potent effects reported among female users (Liechti, Gamma, & Vollenweider, 2001).

Unfortunately, when sex differences were examined in animals exposed to MDMA, the results have been equivocal (Fonsart et al., 2008; Koenig et al., 2005; Palenicek, Votava, Bubenikova, & Horacek, 2005; Walker et al., 2007; Wallinga et al., 2011; Wyeth et al., 2009). In some investigations no differences in MDMA mediated depletion of 5-HT and 5-HIAA (a metabolite of 5-HT) was detected, whereas in another study there sex differences were observed (Wallinga et al., 2011). In the Wallinga et al. investigation MDMA had a more pronounced and lasting hyperthermic effect in male rats a result that was consistent with others (e.g., Fonsart et al., 2008; Wyeth et al., 2009). Further, MDMA linked hyperthermia is associated with higher morbidity in male animals (Fonsart et al., 2008; Wallinga et al., 2011). Conversely, 5-HIAA depletion was observed only in male rats. When hyperthermic responses were equated, 5-HT depletion was higher in female animals, suggesting MDMA toxicity to 5-HT systems in female rats (Wallinga et al., 2011). Noting that the MDMA metabolite methylenedioxamphetamine was higher in male rats, Wallinga and colleagues note the normal interpretation is to postulate that the sex difference reflects higher levels of enzymatic activity associated with N-demethylation step in the pharmacokinetics of MDMA (see Fonsart et al., 2008; Meyer & Quenzer, 2013). Simply put, the higher rates of conversion to MDMA metabolites increase the vulnerability of male rats to the drug's neurotoxic effects. However, Wallinga et al. (2011) did not find a male rat disadvantage associated with 5-HT depletion following MDMA exposure. Noting a small number of studies, in the Allott and Redman (2007) review of the literature the authors offered the preliminary conclusion that adult males experience a greater impact from the acute physiological ef-

fects of MDMA and adult females are more susceptible to the both subacute and acute effects when physical and psychological indices are considered. In addition, much less is known about the effects of Foxy so any conclusion at this point would remain premature. Given the possible reasons for the reported sex differences such as hormonal differences or sex differences associated with pharmacokinetic considerations as examples (Allott & Redman, 2007), such research avenues should be explored further, especially in light of developmental considerations.

Adolescence is a developmental period marked by considerable neural change (Müller & Jacobs, 2010). For example, a number of maturational changes to 5-HT neural systems during adolescence have been described (Andrade & Beck, 2010; Sturman & Moghaddam, 2011), including differential expression of 5-HT receptors with age (Whitaker-Azmitia, 2010). More generally, because adolescence is a period of anatomical and functional transformation, adolescent exposure to drugs can be particularly problematic (Smith, 2003). When adolescent MDMA exposure has been considered, evidence emerged that such exposure produced long-term decreases in 5-HT levels, including such indices as direct neurotransmitter levels, metabolites, and binding sites (Bull, Hutson, & Fone, 2003, 2004; Compton, Selinger, et al., 2011; Piper, Fraiman, & Meyer, 2005; Piper & Meyer, 2004). After examining the effects at different time points in adolescent development, one group concluded that the neurotoxic and behavioral alterations associated with MDMA exposure are indeed dependent on age of exposure (Morley-Fletcher, Bianchi, Gerra, & Laviola, 2002). Further, Bull et al. (2004) found reductions in hippocampal, striatum, and cortical 5-HT levels 60 days following the final MDMA exposure, a result that is consistent with work in our lab (Compton, Selinger, et al., 2011). Thus, although variables such as the frequency and exposure duration are important when considering the neurochemical effects associated with MDMA use (Green et al., 2003), there is considerable evidence suggestive of the importance of the developmental age of drug exposure (Teixeira-Gomes et al., 2015).

Perhaps it is unsurprising, even when developmental exposure is considered, differences in the pattern and frequency of administration can influence the effects of MDMA exposure.

Similar to the protocol reported here, Piper and colleagues assessed the effects of MDMA in adolescent rats through multiple dose (sc) exposures occurring every 5th day from PND 35 to 60 (Piper & Meyer, 2004). The results of Piper and Meyer revealed that prior MDMA compromised cognition even though the damage to serotonergic systems was largely absent. In a subsequent study(Piper, Vu, Safain, Oliver, & Meyer, 2006), rats were periodically exposed to MDMA between PNDs 35 to 60, followed by a single MDMA binge session or testing with the 5-hydroxytryptamine$_{1A}$ receptor agonist 8-OH-DPAT at PND 67. Prior MDMA exposure lead to a predicted attenuation of the neurotoxic changes that would otherwise have been expected (Piper et al., 2006).

As is the case when considering the physiological consequences associated with drug use, the drug dose is a relevant variable. For example, in a recent report on the effects of daily exposure of MDMA for 4 days over PND 38 to 41, 5 mg/kg had no effect on behavioral measures such as anxiety and place conditioning while in with a 10 mg/kg dose, a number of effects were observed (Cox et al., 2014). Consistent with the behavioral results, monoaminergic parameters were only affected at the 10 mg/kg dose. It is interesting to note that no change in hippocampal 5-HT levels was found following the higher MDMA exposure but 5-HT levels were reduced in the amygdala.

Ultimately, the results of the animal studies reviewed here as well as the present results must be considered in light of their relevance to the effects of MDMA or Foxy on humans. Although tempting to perform direct mg/kg comparisons, doing so leads to underestimates in the bioavailability of a given drug (Lin, 1998), because in small animals drug elimination rates tend to be higher than in larger animals such as humans (Green et al., 2003). Using the allometric scaling formula for interspecies comparisons (Hayes & Kruger, 2014), allows for interspecies inferences concerned with drugs of abuse—$\text{Dose}_{\text{human}} = \text{Dose}_{\text{animal}} \ (\text{Weight}_{\text{human}}/\text{Weight}_{\text{animal}})^{0.25}$, with dose and weight expressed in mg/kg and kg respectively. In addition, an adjustment of the exponent to 2/3 has been suggested (White & Seymour, 2005). Thus, calculated

for a single dose of MDMA or Foxy at 5 mg/kg for a .200 kg adolescent rat would be considered equivalent to a dose in a 50 kg adolescent human of approximately 1.26 mg/kg or 63 mg of drug. Although less information concerning the pharmacodynamics of Foxy is available, research with animals (Compton, Dietrich, et al., 2011; Compton et al., 2006; Compton, Selinger et al., 2011; Skelton et al., 2009) and humans (Ikeda et al., 2005; Kiyota, 2004; Smolinske et al., 2005; Tanaka, Kamata, Katagi, Tsuchihashi, & Honda, 2006; Wilson et al., 2005) suggests that research with the dose used here has value.

Although there is support for that developmental exposure of Foxy appears to result in long-term changes that affect cognition (Compton, Dietrich, et al., 2011) the effects observed here are milder than that reported and thus dissociable from effects of MDMA (Compton, Selinger, et al., 2011; Skelton et al., 2009). Arguably, at some of the observed differences in the behavioral effects associated with each drug may simply reflect the fact that the two drugs are not equipotent and/or exerts the same level of CNS effects (Skelton et al., 2009). Indeed, it would be prudent to explore this issue further. At any rate, since the MDMA and, to a lesser extent, Foxy effects seem to persist following a relatively long abstinence period, the examination of possible permanent adverse effects in cognition is reasonable. Currently, we are examining the adolescent exposure of Foxy or MDMA by conducting a longitudinal assessment of the effects of these compounds across the rodent life span.

The developmental considerations considered here also include the specific timeframe of exposure. As an illustration of this point, consider 5-HT turnover in the rodent nucleus accumbens, part of the reinforcement system of the brain (Carlson, 2013; Teicher, 1999). Prior developmental research has shown that levels are up to four times lower in PND 30 to 40 rats than prepubescent rats or older (PND 60 to 80) rats (Teicher, 1999). 5-HT_{2A} receptors just before the onset of adolescence are at highest level of expression in the cortex and follow a decline to adult levels (Morilak & Ciaranello, 1993). Thus, the timing of MDMA or Foxy exposure could have a variety of effects, with the long-term consequences resulting from such variables as the developmental exposure period as well as the length of exposure.

Acute exposure of MDMA has been linked to a dose-dependent increase in extracellular concentration of 5-HT in a number areas of the brain including the hippocampus, cerebral cortex, and the striatum (Gough, Ali, Slikker, & Holson, 1991; Gudelsky & Nash, 1996). In addition, there is clear evidence that MDMA interferes with normal serotonergic metabolism (Leonardi & Azmitia, 1994), perhaps contributing to reported increases of serotonin efflux (Gudelsky & Yamamoto, 2008).

Unfortunately, the effects of MDMA are not limited to acute exposure (Compton, Selinger, et al., 2011; Green et al., 2003; Gudelsky & Yamamoto, 2003; Kish et al., 2010; Ricaurte, Yuan, & McCann, 2000). Considerable evidence exists across species that, as a consequence of repeated exposure to MDMA, there is a long-term reduction in both 5-HT concentration in the brain and reuptake sites (Green et al., 2003; Gudelsky & Yamamoto, 2003; Ricaurte et al., 2000). Thus, as Gudelsky and Yamamoto (2008) noted, the consensus was largely that MDMA exposure produced a number of 5-HT neurotoxic effects, stressing bioenergetic processes and stimulating oxidative stress (Darvesh & Gudelsky, 2005; Gudelsky & Yamamoto, 2003; Quinton & Yamamoto, 2006). Although dopaminergic effects have also been reported (Biezonski et al., 2013), such effects appear to be a consequence of MDMA serotonergic activation of 5-$HT_{2A/C}$ or 5-$HT_{2B/C}$ receptors (Gudelsky & Yamamoto, 2008).

A desire for greater novelty and higher levels of sensation-seeking are often associated with adolescence (Adriani & Laviola, 2004). In one recent report (Rodríguez-Arias, Vaccaro, Arenas, Aguilar, & Miñarro, 2015), adolescent mice exposed to MDMA in adolescence produced an expected increase in sensitivity to the reinforcing effects of MDMA when tested in adulthood. However, adolescent exposure produced differing monoaminergic and behavioral effects in mice classified as either high or low sensation-seeking animals.

Returning the issue of adolescent exposure of MDMA and Foxy, although there is considerable information concerned with the effects of psychostimulant exposure in adult animals, the same cannot be said for studies using adolescent animals (Teixeira-Gomes et al., 2015). This is especially true when drugs such as Foxy are considered. As such, the current literature still contains a number

of gaps about the long-term consequences to the organism, brain function, and subsequent behaviors following chronic exposure to these compounds during adolescent development. In addition, because of a number of regulatory and ethical considerations, well-designed investigations involving human adolescents are rare. Where found, they are often compromised by sampling issues and confounding variables not limited to but often including polydrug use (Teixeira-Gomes et al., 2015) and the purity of the drugs used. The results reported here provide evidence and elsewhere (Compton, Dietrich, et al., 2011; Compton et al., 2006; Compton, Selinger, et al., 2011; Skelton et al., 2009) that there are indeed consequences, albeit somewhat different in nature, associated with the use of MDMA or Foxy including long-term alterations in aspects of learning and memory performance. Higher levels of novelty and sensation seeking are often associated with adolescence (Adriani & Laviola, 2004).

Therefore, it is prudent that researchers continue to examine these drugs at different developmental time points, taking into account a number of possible sexually dimorphic effects associated with their use.

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Received July 23, 2015
Revision received January 31, 2016
Accepted February 7, 2016 ■