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5-Methoxy-*N*,*N*-di(iso)propyltryptamine hydrochloride (Foxy)-induced cognitive deficits in rat after exposure in adolescence

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ABSTRACT

Foxy or Methoxy Foxy (5-methoxy-*N*,*N*-di(iso)propyltryptamine hydrochloride; 5-MeO-DIPT) is rapidly gaining popularity among recreational users as a hallucinogenic "designer drug."
Unfortunately, much remain unknown about the consequences of its use on neuropsychological development or behavior. During one of two adolescent periods, the rats were given repeated injections of 5 mg/kg or 20 mg/kg of 5-MeO-DIPT or a corresponding volume of isotonic saline. After the animals reached adulthood, they were trained and tested on a number of tasks designed to assess the impact of 5-MeO-DIPT, if any, on spatial memory, presumably involving declarative memory systems as well as a nonspatial task that is considered sensitive to disruptions in nondeclarative memory. Both the 5-MeO-DIPT- and saline-treated rats were able to master spatial navigation tests where the task included a single goal location and all groups performed comparably on these phases of training and testing. Regardless of exposure level during adolescence, the performance of the drug-treated rats was markedly inferior to that of the control animals on a task where the goal was moved to a new location and on a response learning task, suggesting a lack of flexibility in adapting their responses to changing task demands. Detected reductions in serotonin activity in the forebrain similar to the effects of extensively investigated compounds such as methylenedioxymethamphetamine (MDMA), suggest that 5-MeO-DIPT may produce its adverse effects by compromising serotonergic systems in the brain.

1. Introduction

Like other hallucinogenic drugs popular among teenagers and young adults who frequent the so-called club scene or raves, 5-methoxy-*N*,*N*-di(iso)propyltryptamine hydrochloride (5-MeO-DIPT) also known as Foxy or Methoxy Foxy is rapidly gaining popularity among recreational users. The Federal Drug Enforcement Administration, reacting to the rapid increase in use and its similarity to other tryptamine compounds that have been abused, lobbied for and received approval to permanently classify MeO-DIPT as a Schedule I drug [1]. Unfortunately, although some recent work has elucidated some of the effects of this compound [2–5], our knowledge of the consequences associated with the use of MeO-DIPT on neuropsychological development or behavior remains limited.

Adolescence in *Rattus norvegicus* is defined as a period consisting of the 21st postnatal day (PND) until the 60th postnatal day [6]. According to Tirelli et al. [6], within this period rodent adolescence can be delineated into three developmental periods consisting of early adolescence (PND 21–34), mid-adolescence (PND 34–46), and late adolescence (PND 46–59). These three periods can be thought of in terms of prepubescence, periadolescence, and late adolescence/early adulthood, respectively. Spear [7] provided support for the use of this rodent model for comparative evaluations and extrapolation to humans. Thus, the use of different adolescent age groups provides a framework for the examination of the developmental consequences associated with drugs of abuse on different stages of biological and cognitive development.

Although there are some published reports on the effects of 5-MeO-DIPT, including forensic case studies [3,5], anecdotes [8], and toxicological investigations [e.g., 9–11], attention has only recently turned to the specific central nervous system effects of 5-MeO-DIPT [2,4,12–14]. Of the published investigations, only a select few [e.g., 2,4,12–14] have explored the long-term consequences associated with exposure at different points of brain development. As the availability and popularity may increase, the possible risks on development in vulnerable adolescents may be seen as an emerging societal health problem. Thus, understanding the consequences of developmental exposure to 5-MeO-DIPT on physiology, learning, and memory may be important because as the use of 5-MeO-DIPT increases so, too, will the consequences.

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2. Materials and methods

2.1. Animals

Subjects consisted of 52 male experimentally naive Long-Evans derived rats bred in the Donnelley Behavioral Neuroscience Laboratory vivarium. Thirty-one rats were in the mid-adolescent period of development (35 days old) at the time of drug injections. The remaining 21 animals were in late adolescence period (48 days old) when injections began. Thus, animals were exposed to 5-MeO-DIPT from 35 to 46 days of age or from 48 to 59 days of age. The rats were individually housed, maintained on a 12-h light/12-h dark cycle with the lights on at 7:00 am. All animals were provided with ad lib access to food (Mazuri Rodent Chow) and water. In order to equate the number of drug-free days before behavioral testing, behavioral testing began when the animals were either 121 days old (mid-adolescence animals) or 134 days old (late adolescence animals). The research protocol was reviewed and approved by the Institutional Animal Care and Use Committee of Palm Beach Atlantic University and the animals were treated in accordance with the principles of animal care outlined in the Guide for the Care and Use of Laboratory Animals [14].

2.2. Drug and drug administration

All rats received a total of six injections of either 5-MeO-DIPT (Biosynth International, Naperville, IL) or a corresponding volume of isotonic saline. Purity of the 5-MeO-DIPT was determined by the manufacturer using HPLC. Within each adolescent group, the rats were randomly assigned to either a 5-mg/kg drug group ($n=16$) or 20 mg/kg drug group ($n=21$) of 5-MeO-DIPT, or injected with a comparable volume of isotonic saline ($n=15$). The animals received a total of six injections, with injections spaced at 48-h intervals. Injections were delivered IP at a rate of one injection session every 48 h. The 48-h injection period was chosen as a way of approximating the effects associated with multiple party "rave" experiences. As noted by the United States Drug Enforcement Administration, the principle effects persist for periods ranging from 3 to 6 h with peak effects occurring at least 1 h after exposure [15]. Further, while data about the half-life 5-MeO-DIPT is still somewhat limited, a 48-h exposure window seemed acceptable. In one recent report [16], analysis of 24–48 h urinary fractions suggested that 5-MeO-DIPT as well as its metabolites are rapidly eliminated, at least in rodents. The authors report that only the metabolite 5-OH-DIPT was detected, albeit as a small quantity of 0.4% [16].

2.3. Apparatus

2.3.1. Rotating rod test

In the rotating rod test, a motor rotated a wooden dowel (10 cm in circumference and 162 cm long) at a speed of five rotations per minute. The dowel was wrapped with tape to help prevent the rat from slipping and elevated 100 cm above the floor. Approximately 15 cm of foam padding was placed beneath the apparatus to prevent injury in case a rat fell.

2.3.2. Spatial training and testing–Morris water maze

With the exception of the number of trials in goal rotation testing, all spatial testing was similar to that described by Compton et al. [17] and occurred in a circular swimming pool 183 cm in diameter and composed of a white acrylic plastic. Water was filled to a depth of 30 cm and made opaque by the addition of a nontoxic paint (Sargant Art, Hazelton, PA). The pool was located in a testing room approximately 36.88 m^2 in size, with many external stimuli visible from the pool. An escape platform painted flat white and 15 cm × 15 cm in diameter was located 18 cm from the wall of the swimming pool and submerged 1 cm below the surface of the water. During constant-start training and novel-start testing, the platform was located in the northwest quadrant, and was moved to the southeast quadrant for goal rotation testing.

2.3.3. Spatial training and testing–Greek cross response testing

The circular water tank described above and fitted with galvanized partitions to form alleys, served as the apparatus for Greek cross training. Each alley measured 57.15 cm × 27.94 cm.

2.4. Procedure

As noted above, in order to equate the number of drug-free days before behavioral testing, animals exposed to 5-MeO-DIPT in mid-adolescence began testing at 121 days of age. Animals exposed to 5-MeO-DIPT and their corresponding control animals began testing at 134 days of age. All animals were tested for general motor coordination and activity levels first. Immediately following these two tests, all animals were trained or tested in the following test order – constant-start training, novel-start testing, goal rotation testing and Greek cross response learning.

2.4.1. Rotating rod test

In order to allow the rat to acclimate to the sound of the electric motor, the motor was turned on for 1 min before the beginning of the assessment. An assessment began when the rat was placed onto the rod and the experimenter verified that all four feet were securely placed on the rod. Following this, the electric motor was switch on and the experimenter counted the number of slips and falls for a 1-min period. Slips were scored whenever the rat fell off the rod but was still able to hold on to the rod through one rotation. Falls were scored whenever the rat completely fell off the rod. When a rat slipped or fell, it was immediately repositioned on the actively rotating rod.

2.4.2. Constant-start training

In this phase, training consisted of four daily trials with single start and escape loci. The platform was located in the Northwest quadrant at a distance of 15 cm from the wall of the swimming pool. All animals began each trial facing the inner wall at the North end of the pool. On a given trial, if a rat reached a behavioral ceiling of 60 s, it was placed on the platform. On all trials, the animals were permitted to remain on the platform for about 15 s. All animals were trained until they achieved a criterion of three out of four escape latencies under 10 s for two consecutive days.

2.4.3. Novel-start testing

The novel-start testing phase consisted of three 6-trial sessions. Each day, trials 1, 2, 4, and 5 were identical to constant-start trials. Within each daily session, trials 3 and 6 involved one of six novel-start loci presented once in the following order: southeast, west, northeast, southwest, south, and east. In order to allow for direct comparison of swim latencies across start locations with considerably different minimum swim path distances, the recorded escape latencies for each novel-start location were normalized.

Normalization was accomplished by computation of the ratio of the minimum swim distance in centimeters for each novel-start location to the minimum swim on regular (i.e., constant start) trials in centimeters. Analysis of the performance of the rats was then accomplished by collapsing the latencies for the six trials preceding the novel-start trials (i.e., the constant-start location) and collapsing the latencies for the six novel-start trials (i.e., test trials). With the exception of the novel-start loci and normalization element, the procedure was identical to that described in constant-start training.

2.4.4. Goal rotation testing

During goal rotation testing, the platform was moved to a position 180° (i.e., the Southeast quadrant) from its former or constant-start position. Testing in this phase consisted of five 4-trial sessions that

began in the north, south, east, or west quadrants, with determination of the order of the start chosen in pseudo-random manner. The remainder of the procedure was identical to that described in constant-start training.

2.4.5. Greek cross response testing

At the beginning of each trial, the rat was placed in the water facing the exterior wall of the start alley. One of two possible start locations were randomized and the order of the start or goal positions (see following) were determined through the use of a Fellows series [18]. The escape platform was located at one of two possible goal positions and the animals started at one of the two possible starting positions, depending on whether the animal was currently trained to turn right or left. Animals received 10 training trials per day, with an inter-trial interval of 15 s between trials. The criterion was defined as nine errorless responses within a given daily session consisting of 10 trials and an error was defined as entry of the head and abdomen into either of the current two incorrect alleys or premature exit from the correct alley. The animals were permitted to self-correct for errors and to explore the apparatus and locate the platform. On each trial, if an animal failed to locate the escape platform within 60 s it was placed on the platform for about 15 s. After criterion was achieved for a given turning response, either right or left, the escape platform was moved to the end of the alley 180° (i.e., the opposite alley) from the previously correct alley. If an animal failed to achieve the criterion within 100 trials, the platform was moved to the opposite goal location. Testing continued until the animals achieved criterion on 10 response position reversals.

2.5. Assessment of serotonin (5-HT) levels

Twenty-one days after the completion of data collection, all animals were euthanized for assessment of brain serotonin (5-HT) levels. The 5-HT levels were established in 5-MeO-DIPT and control animals using high performance liquid chromatography (HPLC; Waters Model 600 with electrochemical detection) with the procedure based on a modified version of that described by Chapin et al. [19]. Using Millennium32 software (Waters, Milford, MA), the raw data were integrated and analyzed to determine 5-HT levels in the target areas. Concentrations in the amounts of 0.04% sodium octyl sulfate, 0.1 mM disodiumethylenediamine-tetraacetate, 0.05 M sodium phosphate were dissolved in HPLC-grade H_2O with 0.03 M citric acid as a buffer. The aqueous portion of the mobile phase was maintained at a pH between 2.7 and 2.9. The mobile phase consisted of 20% methanol and 80% aqueous phase. The HPLC column was a Waters C_{18} reverse phase analytical column (3.9×300 mm; 4 μm).

3. Results

3.1. Assessment of spatial learning and memory

During the first phase, constant-start training, the starting position, location of the platform, and all extra-maze cues remained fixed throughout training. Under these conditions, it was expected that all animals would be capable of demonstrating the ability to learn the "place" of the platform. Here, the need for the representation of multiple positional relationships is not required [20,21].

When the animals are tested in the novel-start phase, some impairment on novel-start trials may be expected because here the requisite ability to complete the task becomes more demanding due to need for the flexible use of cues. As was concluded by Eichenbaum and colleagues [21], deficits in tasks of this type occur when there is a need for the comparison of multiple cues. Specifically, an animal must be able to understand where the new starting location is according to the way in which the cues in the environment have "moved" in relation to the subject and transpose their own understanding of where to swim based upon this change in allocentric cues [22]. Last, the goal rotation phase involved multiple starting locations and the placement of the escape platform to a new location. Successful navigation and reductions in swim times across trials require recall of multiple of the positional relationships of available extra-maze cues.

3.1.1. Constant-start training

In order to assess the learning ability of the rats in this phase of training, the first eight training trials and the last four training trials associated with the criterion (see Section 2.4.2) were examined. The swim time data were analyzed using a 2-Between (3-Drug Groups and 2-Adolescent Periods), 1-Within (12 trials) analysis of variance (ANOVA). Across groups, all animals improved as a function of training, $F(15,690) = 47.58$, $p < .001$. When considered across the training period, the overall performances between the 5-MeO-DIPT-treated and saline-treated rats did not differ and the drug group × trials interaction was nonsignificant as well. Last, no effects associated with the period of adolescent exposure were found. Thus, at the end of constant-start training, swim times for all three drug conditions were comparable. The number of trials through the criterion three out of four trials under 10 s for two consecutive days was comparable across all drug conditions.

3.1.2. Novel-start testing

As noted in Section 2, the recorded escape latencies for each novel-start location were normalized. To assess the performance of the animals when starting from a new location, the swim times for the trials preceding the novel-start trials were averaged as were the all of the novel-start test trials. Analysis of these data with a 2-Between (3-Drug Groups and 2-Adolescent Periods), 1-Within (Constant-Start vs. Novel-Start locations) ANOVA produced only a main effect of Constant-Start versus Novel-Start test trial performance, $F(1,46) = 91.19$, $p < .001$. This result shown in Fig. 1 suggests that all the animals were impacted by the switch from the Constant-Start location to a new starting location. However, no effects associated with the 5-MeO-DIPT treatments were detected in this phase of testing. In addition, the effect of the period of adolescent exposure during development was nonsignificant.

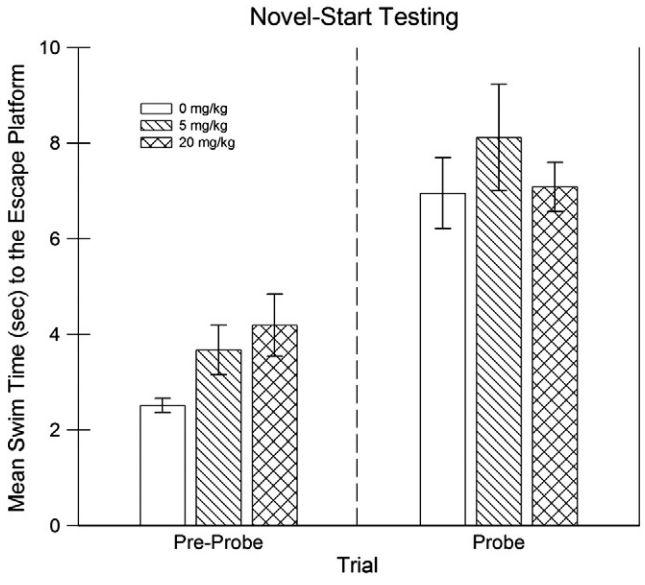

Fig. 1. Mean escape latencies across novel-start (test) trials. The mean escape latencies on regular (i.e., constant-start) trials that preceded the test trials were collapsed and compared to the mean escape latencies collapsed across the six novel-start loci. Vertical lines represent the standard error of the mean (SEM).

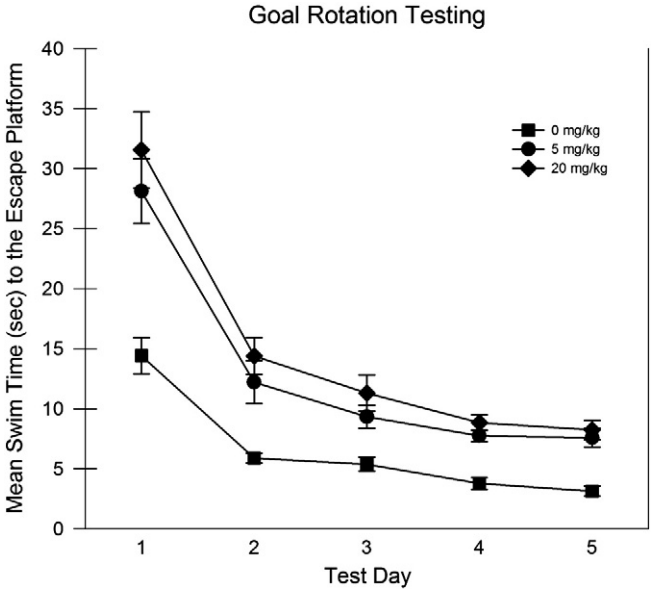

Fig. 2. Daily mean escape latencies across the 20 goal rotation test trials. Vertical lines represent SEM.

3.1.3. Goal rotation testing

The data from the four daily trials were normalized and averaged resulting in comparisons of performance across a 5-day period. The resulting data associated with the swim time to the escape platform, presented in Fig. 2, were analyzed using a 2-Between (3-Drug Groups and 2-Adolescent Periods), 1-Within (5 Days) ANOVA. Analysis of the data produced main effects of the drug treatment, $F(2,46) = 25.16$, $p < .001$, and test days, $F(4,164) = 88.56$, $p < .001$, suggesting that group swim times differed and that the swim times decreased significantly across the test period. Once again, the effect of the period of adolescent exposure during development was nonsignificant.

Of greater importance, a significant drug group × test days interaction was detected, $F(8,184) = 4.31$, $p < .01$, suggesting that, while all three groups improved across test days, such changes occurred at a different rate. When the means were compared ($Tukey_{HSD}$; $p < .05$), the saline control animals found the platform significantly faster than both groups of the 5-MeO-DIPT-treated rats on all 5 days of goal rotation testing. Performances of the two 5-MeO-DIPT-treated groups were comparable.

3.2. Assessment of nonspatial learning and memory

3.2.1. Greek cross response training

In the Greek cross response learning task used in the present study, the animal is faced with three spatial alternatives. The configuration of available allocentric information changes depending on the start location both within individual trials and across reversals [23]. The correct behavioral response (i.e., "turn left" vs. "turn right") depends on first learning a rule to turn in a specific direction regardless of starting point and then, when the goal position is changed, to turn in the opposite direction after a nonrewarded trial. Thus, the Greek cross task may be considered especially sensitive to the behavioral flexibility of the animal [23]. As such, the inability to alter behavior as environmental and behavioral demands change should be reflected in perseverative behavior in tasks with a reversal requirement [24].

Fig. 3 is a presentation of the mean proportion of correct responses across reversal training for the first 10 trials per reversal. Analysis of the data with a 2-Between (3-Drug Groups and 2-Adolescent Periods), 1-Within (10 Reversals) ANOVA revealed the following. A robust main effect of drug condition was detected, $F(2,46) = 46.43$, $p < .001$, suggesting an overall effect of 5-MeO-DIPT on the proportion of errorless trials following a response reversal. A main effect of reversal was also found, $F(9,414) = 47.67$, $p < .001$, a result indicating that the performance of the animals improved as a function of experience with the task.

However, as can be seen in Fig. 3, a drug group × reversal interaction, $F(18,414) = 2.84$, $p < .001$, was present suggesting that the performances of the Saline- and 5-MeO-DIPT-treated animals differed across training. Consideration of this interaction using $Tukey_{HSD}$ ($p < .05$) revealed that by the second reversal the performance of the saline-treated rats was superior to that of the 5-MeO-DIPT-treated animals. The performance of animals treated with 5 mg/kg of 5-MeO-DIPT was reliably superior to that of the animals treated with 20 mg/kg of 5-MeO-DIPT on the 4th, 5th, and 9th reversals. Consistent with these observations, both 5-MeO-DIPT groups required significantly more trials to achieve the criterion than the saline-treated animals, a result that is evident in a review of the inset in Fig. 3.

In addition to these results, the period of adolescent exposure appeared to have some impact on the overall performance of the animals. Specifically, a drug group × adolescent period interaction was found, $F(2,46) = 4.40$, $p < .05$, suggesting that the time of exposure during development was capable of impacting the adult performance on the nonspatial but not spatial tasks employed here. Closer examination of this result and presented in Fig. 4 indicated that the two adolescent control groups were comparable. Conversely, unlike

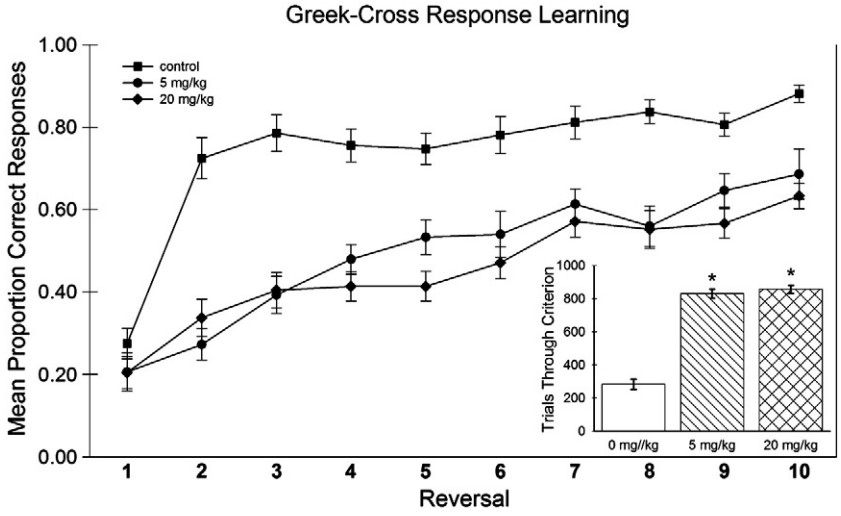

Fig. 3. Response accuracy on the first 10 trials following a reversal across the 10 response learning reversals. Vertical lines represent SEM.

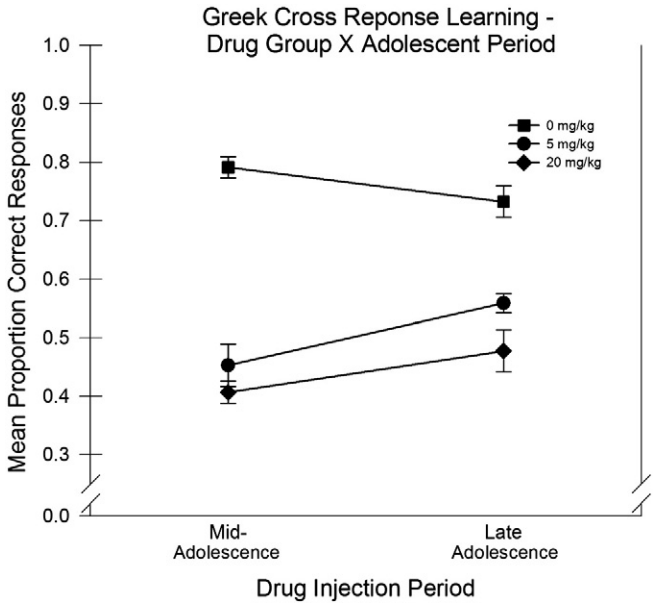

Fig. 4. Mean proportion of correct responses on trial 2 of Greek cross response learning as a function of drug group and adolescent exposure period. Vertical lines represent SEM.

the spatial assessments, the performance of the animals exposed to 5-MeO-DIPT during mid-adolescence was inferior to that of animals exposed during late adolescence. As expected, the drug-treated animals differed from the controls.

3.3. Locomotor assessment

An ANOVA was used to explore the possible effect of the drug on motor performance.

Although the groups did better across assessments, no differential effects associated with 5-MeO-DIPT treatments were found suggesting that the drug did not impair gross motor function.

3.4. Neurochemical analysis of 5-HT levels

One-way ANOVAs suggested differences in 5-HT levels as a function of drug group in both the frontal lobe, $F(2,49) = 344.46$, $p < .001$, and hippocampus, $F(2,49) = 62.30$, $p < .001$.

Post hoc examination of these results revealed the following. Compared to control animals, there were 43.6% and 48.6% reductions in cortical 5-HT levels of the 5 mg/kg and 20 mg/kg 5-MeO-DIPT-treated rats. The 5-HT levels in both groups differed significantly. In an examination of 5-HT levels in the hippocampus, there were significant reductions (25.8% & 28.8%) in both the 5 mg/kg and 20 mg/kg drug groups. However, when the two drug groups were compared, 5-HT levels were comparable (i.e., $p > .05$).

Bivariate analysis of the correlations between the amount of drug exposure and 5-HT levels revealed significant correlations in the frontal lobe ($r = -.89$, $p < .01$) and the hippocampus ($r = -.765$, $p < .01$). On the basis of this result as well as the results described above, two stepwise regression analyses were performed, with 5-HT levels in the prefrontal cortex and the hippocampus serving as predictor variables. Each predictor variable was entered separately with order of each variable determined on the basis of bivariate correlations. The drug related deficits were observed in two tasks, goal rotation testing and Greek cross response learning. Therefore, day 5 performance on the goal rotation task and the trials through criterion measure of the Greek cross task were chosen as the dependent measures. The results of the regression analyses are presented in Table 1. The accompanying scatterplots are presented in Fig. 5. For

Table 1
Stepwise multiple regression analyses of the trials through criterion measure of Greek cross response learning and swim times of day 5 of goal rotation testing with the predictor variables of 5-HT levels in the prefrontal cortex and hippocampus.

Domain and predictor variable	β	t	ΔR^2	Total R^{2b}
Trials through criterion				.791**
(Step 1) PFC 5-HT levels	−.688	−5.99**	.773**	
(Step 2) HIP 5-HT levels	−.233	−2.04**	.018**	
$R = .889$, $F(2,49) = 92.80$				
Goal Rotation – Day 5				.406**
(Step 1) HIP 5-HT levels	−.587	−3.04**	.405**	
(Step 2) PFC 5-HT levels	−.059	−0.31**	.001**	
$R = .637$, $F(2,49) = 16.72$				

Each predictor variable was entered separately with the order of entry determined by examination of the bivariate correlations. *$p < .05$; **$p < .01$.
[b] Total R^2 with both predictors entered into the regression model.

goal rotation testing, 5-HT levels were predictive of performance accounting for 40.6% of the variance in swim times. However, only the standardized regression coefficient (β) associated with hippocampal 5-HT levels was significant. Examination of the trials through criterion measure indicated that collectively 5-HT levels in the prefrontal cortex and the hippocampus accounted for 79.1% of the variance associated with performance on this task. Both regions appeared to play a role in performance with a greater impact associated with prefrontal cortex 5-HT levels ($\beta = -.688$) than 5-HT hippocampus levels ($\beta = -.233$).

4. Discussion

A number of studies have demonstrated that the use of MDMA can produce long-term impairments to cognition, including executive

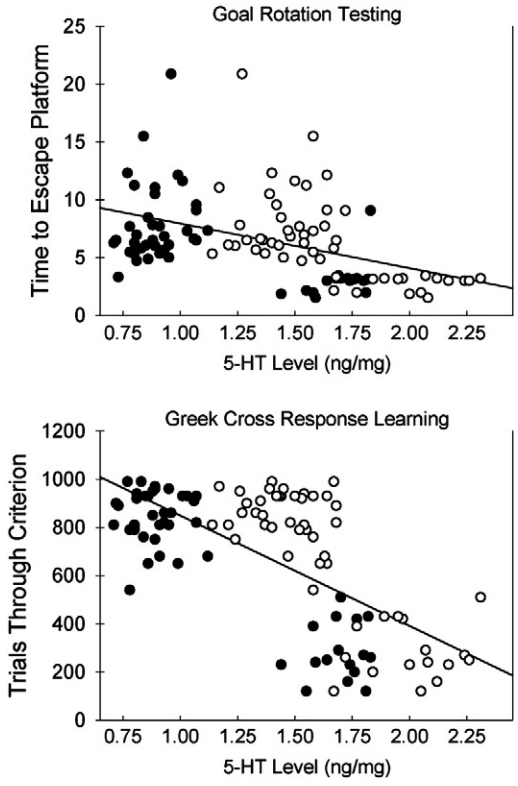

Fig. 5. Scatterplots for goal rotation (top) and trials through criterion (bottom) with 5-HT levels in the prefrontal cortex and hippocampus as predictor variables. The linear combination of predictor variables accounted 40.6% and 79.1% of the variance in goal rotation and trials through criterion performance, respectively.

control, cognitive impulsivity, the ability to plan effectively, and working memory [4,25–31]. Further, marked reductions in 5-HT have been reported months after exposure [14,32–34]. Among the documented impairments is a dysfunction of working memory processes, including spatial working memory [34–36] although, depending upon prior experiences, there have been reports of a deficit in reference memory but not in working memory [e.g., 37].

While additional research is required to definitively answer questions about the physiological nature of the 5-MeO-DIPT-associated deficits reported here, the response patterns observed are consistent with both deficits in attention and perseveration. Perseveration is considered a cognitive deficiency associated with the ability to switch behavior as a function of changing demands. Such deficits are considered distinct from motor or motivational deficits and involve a maladaptive alteration in executive function [38]. Specifically, the effects of 5-MeO-DIPT observed in the present study do not appear to produce some of the adverse effects on spatial navigation observed in MDMA-treated organisms. Nonetheless, navigational deficits were observed in the goal rotation phase and marked deficits were found in a response learning version of the Greek cross. This evidence suggests the possibility of compromised impulse control, warranting additional examination of the effects of 5-MeO-DIPT on the prefrontal cortices and such subcortical structures as the dorsal hippocampus.

While further examination of the physiological effects of 5-MeO-DIPT are warranted, past research has demonstrated that this compound binds with the monoaminergic transporter protein SERT blocking 5-HT reuptake [39]. Conversely, 5-MeO-DIPT does not stimulate release of 5-HT [4,12,13]. Transport of 5-HT by the SERT protein terminates the action of serotonin and recycling 5-HT in a sodium-dependent manner [40].

It has been reported that lesions of 5-HT neurons in rats produce increased impulsivity in rodents [41]. Consistent with this observation are studies that found that reductions in 5-HT activity are associated with impulsivity [42,43]. Further, using SERT knockout (_/_) gene models, multiple reports of maladaptive perseverative have been published [see 44,45] and deficits in the Morris water maze have been described [46].

Serotonin plays an important role in cognition including in the development of associative learning experiences [44] and long-term memory [47], with an inverse relationship between 5-HT levels and impulsivity also reported [48]. Thus, it can be argued that 5-HT directly impacts ability of the organism to respond effectively [49,50] on the basis of stimulus–response demands and to learn to adjust behavior accordingly in response to changes in these contingencies [44].

Among other areas of the brain, the prefrontal cortex plays a central role in responding effectively to changing contingencies between a stimulus and response [51,52]. In the present investigation, the Greek cross task served as an effective assessment of the flexibility in stimulus–response contingencies. In fact, similar to previous reports involving depletion of prefrontal/orbitofrontal 5-HT depletion [e.g., 49,50], 5-HT levels were highly correlated with the perseverative impairments on the present reversal learning task (see Section 3.4). Experimentally induced reductions in the cerebral cortex and striatum are associated with an enduring increase in response impulsivity [53]. Unfortunately, determination of whether the observed deficits were a result of cognitive flexibility and the development of new habit contingencies or another process cannot be answered here. Nonetheless, Borg et al. [54] have shown that genetic variations in SERT can influence cognitive flexibility.

Following exposure to MDMA during development, long-term deficits in learning and memory have been observed [4,25]. Similarly, developmental exposure of 5-MeO-DIPT appears to result in long-term changes in learning and memory performance, although the MDMA and 5-MeO-DIPT appear to produce dissociable effects [4]. Skelton et al. have proposed that some of the observed differences in the behavioral effects of the two compounds may be due to questions about whether the drugs are equipotent and whether 5-MeO-DIPT exerts the same degree of CNS effects as MDMA. Certainly, this proposition is worthy of addition exploration.

One goal of the present investigation was to determine if the period of exposure during adolescence had an impact on performance in adulthood. As noted, no effects of adolescent exposure period were observed on the spatial assessment phases of the experiment. However, the performance of the animals exposed to 5-MeO-DIPT during mid-adolescence was inferior to that of animals exposed during late adolescence and both drug groups were inferior to saline-treated animals. The results reported differ from those reported elsewhere. [4]. In a battery of neuropsychological assessments, Skelton et al. [4] found that rats treated with 5-MeO-DIPT during PND 11–20 were impaired relative to control animals in spatial learning but not tests of spatial memory or path integration. Interestingly, in related work with adult rats [55], a path integration deficit was observed. The authors suggest that the difference is possibly due to the hippocampal development [see 56] that occurs during the exposure period used in their study.

As is the case with exposure to a variety of environmental events and agents, the timing of exposure during the development of the organism is an important consideration. For example, in a consideration of 5-HT turnover in the nucleus accumbens of rats [57], levels were four times lower in adolescent rats measured during PND 30–40 than either older rats (PND 60–80) or prepubescent rats (PND 10–15). Research has also been reported indicating that just before the onset of adolescence, 5-HT_{2A} receptors achieve their highest level of expression in the cortex and then decline to adult levels [58]. Thus, the timing of 5-MeO-DIPT exposure could have a variety of effects that differ markedly depending on the period of exposure.

At any rate, in the present study, the 5-MeO-DIPT appeared to produce an effect that, although not as severe as reports about MDMA [4,25], does not appear to diminish with age. In future research, we plan to compare adolescent exposure of 5-MeO-DIPT with MDMA and periodically test the animals across the lifespan.

Because of the reported long-term consequences of its use, it has been suggested that MDMA is one of a number of induced risk factors for early onset or perhaps more severe declines associated with age-related memory and nonmemory (e.g., Parkinson's disease) [59] deficits. The results reported here provide convincing evidence that the consequences of the use of 5-MeO-DIPT include but are not necessarily limited to, long-term deleterious effects on learning and memory. As noted earlier, during adolescence, a number of areas of the brain are undergoing developmental changes. Higher levels of novelty and sensation-seeking are considered common in adolescence [60]. Because of the serotoninergic and possible dopaminergic properties of 5-MeO-DIPT, these designer drugs should be examined in greater detail, especially among a teenage population at risk for the possible consequences associated with the use of 5-MeO-DIPT.

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