



Effects of MDMA on olfactory memory and reversal learning in rats



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ABSTRACT

The effects of acute and sub-chronic MDMA were assessed using a procedure designed to test rodent working memory capacity: the odor span task (OST). Rats were trained to select an odor that they had not previously encountered within the current session, and the number of odors to remember was incremented up to 24 during the course of each session. In order to separate drug effects on the OST from more general performance impairment, a simple olfactory discrimination was also assessed in each session. In Experiment 1, acute doses of MDMA were administered prior to select sessions. MDMA impaired memory span in a dose-dependent fashion, but impairment was seen only at doses (1.8 and 3.0 mg/kg) that also increased response omissions on both the simple discrimination and the OST. In Experiment 2, a sub-chronic regimen of MDMA (10.0 mg/kg, twice daily over four days) was administered after OST training. There was no evidence of reduced memory span following sub-chronic MDMA, but a temporary increase in omission errors on the OST was observed. In addition, rats exposed to sub-chronic MDMA showed delayed learning when the simple discrimination was reversed. Overall, the disruptive effects of both acute and sub-chronic MDMA appeared to be due to non-mnemonic processes, rather than effects on specific memory functions.

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1. Introduction

Research with recreational ecstasy users has revealed deficits on a number of cognitive tasks. A history of heavy ecstasy use is associated with impaired performance on tests of attention, learning and working memory with simple cognitive tasks (e.g., reaction time) often unaffected, and more complex tasks involving higher processing loads more severely affected (Montgomery & Fisk, 2008; Murphy, Wareing, Fisk, & Montgomery, 2009; Nulsen, Fox, & Hammond, 2010; Parrott, 2013). Of course, these studies have many limitations including the accuracy of the self-reported drug histories on which they are based and the complication that most ecstasy users are also multiple drug users. Further, pills believed by users to be ecstasy may or may not contain only MDMA (Sherlock, Wolff, Hay, & Conner, 1999). Thus, it is difficult to determine whether the differences between controls and ecstasy users are actually based on MDMA use. Indeed, when groups of ecstasy users are compared with groups of participants who do not use ecstasy, but are matched with respect to use of marijuana or other drugs, several studies have found comparable cognitive deficits (e.g., Croft, Mackay, Mills, & Gruzelier, 2001; Dafters, Hoski, & Talbot,

2004; de Sola et al., 2008), although others have found more severe deficits in ecstasy users (Daumann et al., 2005; Nulsen et al., 2010). Due to these difficulties in interpretation and given the ethical restrictions associated with administering MDMA to humans, pre-clinical studies using non-human subjects, particularly rodents, have an important role in the investigation of these cognitive disruptions.

Numerous studies have shown that acute MDMA administration can impair performance on learning and working memory tasks in rodents (e.g., Arias-Cavieres et al., 2010; Braida, Pozzi, Cavallini, & Sala, 2002; Byrne, Baker, & Poling, 2000; Galizio, McKinney, Cerutti, & Pitts, 2009; Galizio, Byrd, Robinson, Hawkey, & Rayburn-Reeves, 2014; Harper, Wisnewski, Hunt, & Schenk, 2005; Marston, Reid, Lawrence, Olverman, & Butcher, 1999). However, whether these disruptions are specific to working memory processes is not clear. For example, Harper et al. (2005) showed that MDMA effects on delayed matching-to-sample were independent of delay, that is, comparable levels of disruption were observed under conditions of no delay (which presumably do not involve working memory), as well as with delays. Similarly, Galizio et al. (2014) found that MDMA increased latency to locate the hidden platform in the Morris Swim Task, but only at doses that also impaired overall perceptual-motor ability. Finally, Kay, Harper, and Hunt (2010) found that acute doses of MDMA impaired performance on a reference memory version of the radial

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arm maze at doses that had no effect on the working memory version of the task.

There have also been a number of efforts to model the cognitive effects of sub-chronic or binge MDMA use in animals. In these studies, high doses of MDMA are generally administered twice daily for four or more days and the residual effects of the drug regimen on learning and memory are then studied. Within this literature, there are some discrepancies as to the nature of binge MDMA effects. Some studies have found impairments in working (e.g., Marston et al., 1999) or recognition memory (e.g. Camarasa, Marimon, Rodrigo, Escubedo, & Pubill, 2008) tasks, while others have found impairments in reference memory task acquisition (e.g. Skelton et al., 2008), retention (e.g. Able, Gudelsky, Vorhees, & Williams, 2006), or both (Cunningham, Raudensky, Tonkiss, & Yamamoto, 2009). Based on these and similar findings, some have questioned whether impaired performance on classic working memory tasks reflects specific working memory deficits or more general cognitive impairments (Kay, Harper, & Hunt, 2011). Additionally, results have been mixed with several studies failing to observe any cognitive deficits following binge MDMA exposure (e.g., Byrne et al., 2000; Slikker et al., 1989).

Working memory tasks in rodents are typically characterized by remembering a stimulus or place within a single trial or session, but not over longer durations or between sessions (Dudchenko, 2004). However, human models of working memory also emphasize its limited capacity (Baddeley, 1986; Cowan, Chen, & Rouder, 2004), meaning that the number of items to be remembered is a key determinant of memory accuracy, and as noted, the deficits observed in human MDMA users seemed linked to those tasks which involve high memory demands (Parrott, 2013). Relevant to this point, the rodent odor span task (OST) can be used to study memory of varying numbers of stimuli (Dudchenko, Wood, & Eichenbaum, 2000). The OST is an adaptation of the delayed non-match to sample task in which the rats are presented with a series of odors and only responses to new odors are rewarded. Unlike the standard delayed non-match-to-sample task, once a sample has been presented, it serves as a sample for all subsequent trials. This allows the number of samples to accumulate over the course of the session, meaning that accurate responding is based on a steadily increasing number of remembered items. This feature is unique to the OST and for this reason it was nominated as the task to model memory capacity by the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) group (Dudchenko, Talpos, Young, & Baxter, 2013).

At this point though, there are only a few studies on the behavioral pharmacology of the OST. Several studies have found that NMDA antagonists such as MK-801 and ketamine can impair accuracy in the OST and that nicotine can enhance it (Galizio, Deal, Hawkey, & April, 2013; MacQueen, Bullard, & Galizio, 2011; Rushforth, Steckler, & Shoab, 2011), but no research with stimulant drugs other than nicotine has been published using this procedure. The present study used the OST to test the effects of acute and binge MDMA under conditions in which the number of stimuli to remember varied. In Experiment 1, performances were assessed under a range of acute doses of MDMA. In Experiment 2, rats were exposed to binge doses of MDMA or saline. Then any residual impairment on task performance was assessed. In both experiments, an olfactory simple discrimination task was included to measure generalized forms of performance impairment which are unrelated to working memory, but might reduce accuracy on the OST. In Experiment 2, after the initial assessment, a contingency reversal of the simple discrimination was performed to test for effects of binge MDMA on behavioral flexibility. This was done in an attempt to replicate the findings of Kay et al. (2011) who found residual deficits in reversal learning in the radial arm maze following binge exposure to MDMA.

2. Experiment 1: effects of acute MDMA on OST performance

2.1. Method

2.1.1. Subjects

Subjects were six male Sprague-Dawley (Harlan) rats. All subjects were between 90 and 150 days old at the beginning of testing. Rats were individually housed in a temperature and humidity controlled vivarium on a 12/12 h light–dark cycle. Water was continuously accessible in the home cage and food access was restricted to maintain each rat at approximately 85% of its free-feeding weight.

2.1.2. Apparatus/stimuli

Olfactory span training and testing took place in a circular open-field apparatus. This apparatus consisted of a circular table 94 cm in diameter bordered by a wall of sheet metal baffling. The surface of the table contained eighteen holes positioned in two concentric circles. Plastic cups (2 oz) were placed in each hole during session trials. Speakers adjacent to the span arena provided white noise (70 dB) during all sessions. A web cam (Logitech, Inc.) was used to digitally record each session.

All stimuli consisted of plastic cups half filled with fine grained, white, play sand and covered by scented plastic lids. The lids were scented by storing them in airtight plastic containers containing household spices and flavorings (e.g. oregano, nutmeg, etc.—see Galizio et al., 2013 for a complete list of odorants). These scented lids were placed lightly on the stimulus cups for each trial and were exchanged for unused lids prior to each presentation of a given scent.

2.1.3. Initial training

Subjects were tested five sessions per week (daily, Monday–Friday) throughout training and testing. At first exposure to the arena, cups containing sugar pellets (45 mg Bio-Serv) were presented. Once pellets were readily consumed from these cups, trials were conducted where the baited cups were presented with an unscented plastic lid partially covering the opening. The position of the lid was gradually shifted to cover the opening of the cup completely. Once the rat was reliably removing the unscented lid to retrieve the sucrose pellet, odor training began.

2.1.4. Odor span training

The current study used an OST procedure adapted for behavioral pharmacology (Galizio et al., 2013) illustrated in the top row of Fig. 1. On trial 1, a single olfactory stimulus (A) was presented and marked the location of a reinforcer (+). Removal of this lid allowed access to the pellet inside the cup. On trial 2, the previous odor (A–) and a novel odor (B) were presented and the novel odor marked the location of the reinforcer (B+). On trial 3, the two previously presented stimuli were presented (A–, B–), as was a new odor (C). Again, the novel stimulus indicated the location of the reinforcer (C+). This pattern continued for subsequent trials, but for all trials after the fifth, the novel scent was presented with four comparison scents pseudo-randomly selected from the pool of previously presented scents (see Trial N of Fig. 1). This was designed to eliminate the confound between the number of comparison stimuli in the arena and the number of stimuli to remember which is present in some previous OST studies (e.g., Dudchenko et al., 2000).

OST trials were presented on a multiple schedule in each testing session with trials of an olfactory simple discrimination (SD) task (see Fig. 1, bottom row). The SD procedure used five odors which were not included in the pool of odors for span trials, one of which was designated as S+(ex. bubblegum) and four were designated as

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