Remembering Molly: Immediate and delayed false memory formation after acute MDMA exposure

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Abstract
The entactogen 3,4-Methylenedioxymethamphetamine (MDMA) is increasingly being recognized for its therapeutic potential but is also widespread in nightlife settings where it may co-occur with crime. Since previous research detected impaired verbal memory during acute MDMA intoxication, understanding the drug’s ramifications in an applied legal context becomes crucial. We conducted a double-blind, placebo-controlled trial to examine acute and delayed effects of MDMA (75 mg) on false memory in 60 healthy volunteers with a history of MDMA use, using three well-established false memory methods: a basic, associative word list (Deese/Roediger-McDermott (DRM)) paradigm and two applied misinformation tasks using a virtual reality crime. Memory was tested immediately (encoding and retrieval under drug influence) and 1 week later (retrieval when sober). Small MDMA-induced impairments of true memory in the word list task were detected at both time points. MDMA increased false memory for related but non-critical lures during the immediate test, and decreased false memory for critical lures after a delay. Episodic memory assessed in the misinformation tasks was not consistently affected. Findings indicate a complex memory profile but no heightened vulnerability to external suggestion in response to MDMA intoxication. Recommendations for future applied legal psychological research include adding measures of recall on top of recognition, using study designs that separate the different memory phases, and potentially testing higher doses. Further research on false
memories and suggestibility using imagination procedures can also be relevant for the clinical context. © 2022 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA) also known under its street name “Molly” and “ecstasy” is the major psychoactive compound in ecstasy pills, a popular nightlife drug, and among the most commonly used illicit substances worldwide (EMCDDA, 2012; UNODC, 2019; Winstock et al., 2017). MDMA is a phenethylamine and a potent indirect monoaminergic agonist, producing stimulant amphetamine-like properties (Dolder et al., 2018; Holze et al., 2020). In addition, it facilitates release and reuptake inhibition of serotonin (5-HT), thus combining entactogenic effects such as increased euphoria and sociability with weak psychedelic effects (5-HT2A agonist; Nichols, 1986; Vollenweider et al., 1998). Currently, MDMA is under empirical scrutiny in clinical trials as an addition to psychotherapy to treat post-traumatic stress disorder (PTSD, Mithoefer et al., 2019). In line with its unique pharmacological profile, MDMA has been observed to affect cognition in diverse ways. While some cognitive domains are left intact or even improved (e.g., attention, psychomotor performance, Dumont and Verkes, 2006; Lamers et al., 2003; Ramaekers et al., 2006; Vollenweider et al., 1998), others tend to be prone to impairment. Specifically, acute MDMA intoxication has been found to impair true memory functioning by, for example, decreasing verbal recall (Kuypers and Ramaekers, 2005).

Evidence that MDMA affects memory functioning comes from two lines of experimentation. In retrospective studies, comparisons of current or abstinent MDMA users with polydrug-users or drug-naive subjects have revealed neurocognitive deficits particularly in prospective (Platt et al., 2019), verbal and working memory (e.g., lower recall in MDMA users, Kalezchkein et al., 2007; Nulsen et al., 2010; Rogers et al., 2009). However, two recent well-controlled studies concluded that effect sizes of memory deficits tended to be small, and that light ecstasy use was not associated with clinically deficient verbal memory performance (Kuypers et al., 2016; Rogers et al., 2009). Similarly, placebo-controlled studies have shown that a single dose of MDMA (75 mg) reduced verbal memory during acute intoxication, but this impairment was transient and could not be detected 24 h later (de Sousa Fernandes Perna et al., 2014; Kuypers et al., 2013; Kuypers and Ramaekers, 2005, 2016; van Wel et al., 2011). Recently, Doss and colleagues (Doss et al., 2018b) found that MDMA (1 mg/kg) administered before encoding or retrieval did not impair overall memory accuracy in an emotional episodic memory task. At encoding, however, MDMA attenuated the recollection of positive and negative pictures (remember) but tended to enhance familiarity (know) judgements. They also reported a trend for MDMA to increase false alarm rates at retrieval, predominantly for positive stimuli. Therefore, MDMA seems to affect memory in consistent but subtle ways.

In terms of pharmacological similarity, a finding of relevance here is that Ballard et al. (2012) found that the non-specific stimulant dextroamphetamine increased false memories in a word list task when administered prior to encoding, with memory tested 48 h later under sober conditions (compared to cannabis). However, stimulant properties might be less of a determinant of MDMA’s effects on memory, since these have been found to be specifically mediated by its 5-HT2A agonism (van Wel et al., 2012), i.e., blockade of 5-HT2A prevents MDMA’s usually observed impairment of verbal memory recall. Thus, MDMA might more closely resemble serotonergic psychedelics when it comes to memory. The only contemporary episodic memory study that has been conducted with psychedelics (Barrett et al., 2018) examined effects of psilocybin (psychoactive ingredient of ‘magic mushrooms/truffles’) and found that the drug decreased verbal recall (administered prior to encoding with memory tested shortly after). The study did not report how psilocybin affected false recall or recognition.

Solid and reliable memory functioning is of high relevance to the legal field, particularly in court cases where legal decision-making is largely based on testimonies from witnesses, victims, and/or offenders. However, witnesses and suspects are frequently intoxicated, and particularly so in cases of violent crime (Evans et al., 2009; Kloth et al., 2021; Palmer et al., 2013). Violence and substance use commonly co-occur in nightlife settings. For example, a Norwegian study showed that illicit drug use was more prevalent among people who reported being involved in physical violence during nightlife, 29% of whom reported being MDMA/ecstasy users (N = 103; Nordfjærn, 2017). Therefore, it is likely that a substantial number of people who are involved in or witness a crime in nightlife settings are intoxicated with MDMA.

Intoxication during a crime, during police interviewing, or both might render an individual particularly susceptible to spontaneous false memories (i.e., memories of nonexperienced events/details) or false memories due to external suggestion (Loftus, 2016; Mazzoni, 2002; Otgaar et al., 2016a). In a recent study (Kloth et al., 2020), 64 healthy participants received vaporized cannabis or placebo and completed three false memory tasks during the acute intoxication phase (immediate condition) and at a sober 1-week follow-up (delayed condition). Tasks included the Deese/Roediger-McDermott (DRM) word list paradigm, in which people spontaneously falsely remember words not presented in an associatively related list of words (Deese, 1959; Gallo, 2010; Roediger and McDermott, 1995), and two versions of the misinformation paradigm, in which exposure to misleading information following an event often leads people to report suggested details in their final memory statements (Loftus, 2005). Cannabis elevated susceptibility to false memory across all tasks: in the DRM, intoxicated participants had higher false recognition rates
of words that had low or no association to studied lists than a placebo condition, and in the misinformation tasks, they exhibited higher false memory rates for both suggestive as well as neutral questions about virtual reality eyewitness and perpetrator scenarios. False memory effects were most pronounced during acute intoxication, with only subtle impairments detected at a sober 1-week follow-up. To date, no research has investigated how MDMA implies false memory production. Given the applied relevance of examining potential false memory effects of MDMA, we conducted a randomized, placebo-controlled study examining MDMA’s effects on false memory formation using three well-established false memory tasks.

A similar design as used in a previous study (Kloft et al., 2020) to assess the effects of MDMA on false memory formation was employed. Participants received 75 mg MDMA and placebo on separate testing days 7 (±1) days apart and were subjected to the DRM (within-subjects) and one virtual reality (VR) scenario plus misinformation task (counterbalanced between-subjects) per test-day. Given that previous studies indicated MDMA-induced impairments of true memory (memory of truly presented stimuli; e.g., Kuyper and Ramaekers, 2005) but potentially also false memory (Doss et al., 2018b), we generally expected MDMA to impair memory performance, reflected in higher false memory and lower true memory rates, compared to placebo.

2. Methods

A detailed description of the materials used, procedure, study design, and administration is provided in the Supplementary Information (SI), and is briefly summarized here. All materials and data can be found on the Open Science Framework (https://osf.io/8tjkr/).

2.1. Study design

The present study employed a randomized, placebo-controlled, double-blind 2 (Group: Treatment vs. Control) by 2 (Time: Time 1 vs. Time 2) mixed design with Group as a between-subjects factor and Time as a within-subjects factor. Groups were matched for age, sex, and education level. All participants were randomly assigned to one out of 4 possible randomization sequences, counterbalancing the order of the treatment and VR scenario (see Fig. S1, Supplementary Information).

The study was approved by the Medical Ethics Committee of Maastricht University and was conducted according to the Declaration of Helsinki (amended in 2013, Fortaleza) and in accordance with the Medical Research Involving Human Subjects Act (WMO). All participants were fully informed of all procedures, possible adverse reactions, legal rights and responsibilities, expected benefits, and their right for voluntary termination without consequences. All subjects gave written informed consent and received financial compensation (€150) for their participation. A permit for obtaining, storing and administering MDMA was obtained from the Dutch drug enforcement administration. The study was registered at the Netherlands National Trial Register (Nederlandse Trial Register, NL7423).

2.2. Participants

Sixty-one healthy participants with previous MDMA experience (lifetime use 3–60 occasions) were included in the study (28 female, 33 male, mean age and SD: 23.0, 3.3, age range: 18–32) of which 60 completed all procedures, i.e., underwent a pre-screening, a medical screening (assessment of medical history, physical examination including blood- and urine analyses and electrocardiogram), a VR and cognitive task training, and both treatment conditions including follow-up (for demographic and drug history information, see Table 1). Participants with prior drug experience were recruited in order to comply with local ethical regulations. All participants were light to moderate users of MDMA (i.e., < lifetime consumption of 100 MDMA pills or < 50 lifetime episode of MDMA use). Review of neuroimaging (Mueller et al., 2016) and memory performance data (Kuyper et al., 2016) indicates that there is no convincing evidence of long-term structural or functional brain alterations or memory deficits in light to moderate MDMA users, which deems this user group well fit for within-between subject designs without introducing confounding due to (excessive) MDMA use history.

2.3. Procedures

Subjects were asked to abstain from drug use 7 days before and from alcohol use 24 h before each test day, and were drug-screened (urine) and breathalyzed before each testing occasion. An additional urine pregnancy test was performed for female participants. All breath alcohol concentration readings showed 0.00 and all pregnancy tests showed a negative result. In case of a positive drug test before the start of the first test day, participants were rescheduled for a later date (n = 3, all THC). In case of a positive drug test before the start of the second test day or final follow-up session,

### Table 1: Subject demographics and drug history.

| Native language | Dutch | German | Other language |
|-----------------|-------|--------|---------------|
| English         | 26%   | 23%    | 26%           |

| Level of education | High school | Bachelor’s degree | Master’s degree |
|--------------------|-------------|-------------------|-----------------|
|                    | 52%         | 38%               | 10%             |

| Years of English education [M (SD)] | 11.0 (4.1) |
|-------------------------------------|------------|

| MDMA history [M (SD)] | Age of first use | Years since using MDMA | Times used | Frequency/past year | Regular dose (mg, n = 39) | Regular dose (pills, n = 16) | Range: 0.5–2 |
|-----------------------|------------------|------------------------|-----------|-------------------|--------------------------|-----------------------------|---------------|
|                       | 19.6 (1.9)       | 3.5 (2.2)              | 12.4 (11.4)| 3.9 (2.4)         | 230 (222.0)              |                             |               |

| Lifetime drug use (at least once) | Alcohol | Cannabis | Amphetamines | Cocaine | LSD | Truffles/psychedelic mushrooms |
|----------------------------------|---------|----------|--------------|---------|-----|--------------------------------|
|                                   | 97%     | 90%      | 28%          | 48%     | 26%| 61%                            |

Notes:

* Level of education was measured in terms of highest level of education completed.
a blood sample was taken but the test day was continued, and the samples analyzed for active drug metabolites (see SI; data exclusion section, for further information).

Participants received a single dose of MDMA (75 mg) and placebo on separate test days. This dose has previously been shown to impair verbal memory performance (Kuypers and Ramaekers, 2005), and is also relevant from a clinical point of view (Mithoefer et al., 2018). Psychoactive effects of MDMA appear between 30-60 min after ingestion lasting for 2-4 h, and plasma levels peak at 90-120 min (Dumont and Verkes, 2006). Memory tests were administered when drug effects were maximal (between 60-120 min post administration, immediate condition), and at a 1-week sober follow-up meeting (delayed condition). A venous blood sample was collected 90 min post-ingestion in order to assess concentrations of MDMA and its metabolite 3,4-methylenedioxymethamphetamine (MDA). MDMA was analyzed by gas chromatography coupled to mass spectrometry (GC/MS) following a method previously published (Pizarro et al., 2002). Subjects rated their subjective level of intoxication (subjective high) on 100 mm visual analogue scales.

2.4. False memory measures

2.4.1. DRM paradigm

The same false memory tasks as in Kloft et al. (Kloft et al., 2020) were used in this study. The DRM task was employed to assess spontaneous false memory. Fifteen lists each containing ten associatively related words (e.g., bed, dream, wake, rest, tired etc.) were successively presented on each test day (study phase), followed by two unrelated attention tasks (total ~10 min), and a subsequent recognition test (testing phase, immediate). The recognition test contained old, previously studied words, and new, non-studied words of differing levels of association to the studied lists: critical lures (i.e., sleep) were highly associated to the studied words, related lures were less associated (e.g., nap), whereas unrelated lures were completely unassociated (e.g., table). Old words had been previously presented, thus had the highest association.

For each DRM version (two parallel versions, counterbalanced with treatment order), there were two testing phases: one administered immediately (approximately ten minutes after end of study phase), and one administered 7 (range: ± 1) days later. These will be referred to as the immediate and the delayed tests, respectively. Thus, two test versions were created per DRM version, resulting in total in four test instances per participant. The immediate version consisted of 75 words: 45 previously presented words (words 1, 3, and 5 from each list), 10 new words critically related to the studied lists (critical lures), 10 new words related to the studied lists (related lures), partly taken from words 11-15 from the original DRM lists, and partly from https://wordassociations.net/en/ and 10 new unrelated words (unrelated words, adopted from other, non-presented DRM lists). The delayed version consisted of 100 words: 55 presented words (10 of these had been already presented at immediate test), 15 critical lures (10 from immediate test), 15 related lures (5 from immediate test), and 15 unrelated words (5 from immediate test). Before testing commenced, participants were instructed to indicate whether they recognized the words from the previous list presentation (yes or no). The words appeared on the computer screen one at a time in a random order. The study and immediate testing phases were separated by a subjective high measurement and two 5 min filler tasks (attention tasks: Psychovigilance Test and Deary-Liewald reaction time task; Deary et al., 2011; Loh et al., 2004).

2.4.2. Misinformation paradigm

Two versions of the misinformation paradigm were used to measure suggestion-based false memory. Participants were exposed to one mock crime scenario per test day (eyewitness vs. perpetrator), counterbalanced with treatment condition, and presented in a fully immersive interactive virtual reality (VR) environment, using the virtual reality headset HTC Vive. VR technology allows for high degrees of experimental control combined with high ecological validity (Kloft et al., 2021; van Gelder et al., 2014). In the eyewitness scenario (5 min total duration), participants were virtually seated on a train witnessing a fight between a man, a police officer and a security guard outside on the platform of a train station. Misinformation was introduced through a virtual co-witness recounting true and false details related to the scenario, but also through suggestive questions in the later memory test. In the perpetrator scenario (2 min duration) the participant could move around in a crowded bar and was instructed to steal a purse (grasping a physical controller). Misinformation was introduced through leading questions at the memory test. The memory test assessed recognition memory in a forced-choice interview, administered 30 min after encoding either scenario (immediate), and once during the follow-up session (7 days later, range ± 1 day i.e., delayed), and consisted of questions about truly presented details in the scenario (presented), leading questions about non-presented details (suggested), and control questions about non-presented details (non-suggested). As explained in Kloft et al. (2020) the (non)presented details varied in their strength of association to the VR scenario, with presented details strongly linked, suggested details moderately linked, and non-suggested details weakly linked to the experienced scenario.¹

Before the interview, subjects were instructed to answer with yes or no, to be as truthful as possible, and to guess if they did not know the answer. Interviews consisted of non-leading questions about truly presented details (e.g., “Were the seats on the train blue?”), leading questions about suggested details (e.g., “It was a black purse, right?”), and non-leading questions about non-presented details (e.g., “Was there a cat in the bar?”). Details of the latter category varied in their event plausibility (i.e., included questions about plausible details, such as person selling snacks on train, but also implausible details, such as clown on the platform). For the eyewitness scenario, the immediate interview consisted of 25 questions (15 presented, 5 suggested, 5 non-suggested), and the delayed of 29 questions (15 presented, 9 suggested, 5 non-suggested; 20 new and 9 old items). For the perpetrator scenario, the immediate interview contained 25 questions (15 presented, 5 suggested, 5 non-suggested), and the delayed of 27 questions (15 presented, 7 suggested, 5 non-suggested; 20 new and 7 old items²). The order of the questions remained the same for all participants.

Importantly, all follow-up memory tests for all tasks consisted of a combination of old (i.e., from immediate condition) and new test items.

2.5. Statistical analysis

2.5.1. Primary analyses

True memory (proportion of correctly recognized stimuli, or hit rate) and false memory rates (false alarm rate, proportion of incorrectly recognized stimuli, cumulative and for each level of association) were calculated for the misinformation tasks and DRM, where hit rates = p(‘old’|target) and false alarm rate = p(‘old’|critical, related, unrelated, or all types of lure). In addition, signal detection parameters were calculated to assess sensitivity as d’ = Z(hit rate) − Z(false alarm rate) with higher values signaling greater discriminating ability, and response bias as c = −1/2

¹ See https://osf.io/87jkr/ for videos of the scenarios and interview transcripts

² For analysis, 2 questions about presented details from the perpetrator scenario were excluded due to VR-related difficulties
[(Z(hit rate) + Z(false alarm rate)], where positive values indicate conservative and negative values liberal response tendencies (Macmillan and Creelman, 2004). Signal detection parameters were calculated based on all lure types. A correction was applied to true memory rates of 1 and false memory rates of 0 (1 − 1/2n and 1/2n, respectively) (Wixted, 2007).

To test MDMA effects on DRM recognition performance at immediate and delayed test respectively, two separate 2 (Drug: MDMA vs. placebo) x 4 (Level of association: old words, critical lures, unrelated lures, unreported words) repeated measures ANOVAs were conducted (within-subjects comparison). To compare between groups’ eyewitness memory performance at immediate and delayed test respectively, two separate 2 (Group: MDMA vs. placebo) x 3 (Level of association: presented, suggested, non-suggested) repeated measures ANOVAs were conducted. When a statistically significant interaction effect (i.e., between Drug/Group and Level of association) or main effect of Drug/Group was detected, simple main effects were assessed to compare MDMA and placebo at each level of association. This procedure was followed to control for excessive multiple testing (Winer, 1971). Two-tailed t-tests were used for pairwise comparisons of the signal detection parameters. Visual inspection of mean scores was also used to aid interpretation. A difference was considered statistically significant for p-values < 0.05. Cohen’s d (pairwise comparisons) and ω² (ANOVA) were calculated as effect size estimates. For ANOVA, assumptions were checked by visual inspections of boxplots for normality. No gross violations of assumptions were detected for ANOVA. When sphericity was violated, a Greenhouse-Geisser correction was applied to the degrees of freedom. Analyses were conducted using JASP, version 0.12.2 (JASP Team, 2020).

In addition, equivalence tests were carried out to further explore null findings and to determine equivalence of false memory performance during MDMA and placebo. Equivalence testing can be used to statistically reject the presence of effects large enough to be considered meaningful (Lakens, 2017; Lakens et al., 2018). When a hypothesis test is non-significant, this method can be used to improve inferences about the presence or absence of an effect.

### 3.2. DRM paradigm

Fig. 1 depicts the mean DRM true and false memory rates for the two drug conditions at immediate (1a) and delayed test (1b). Fig. 1a shows that, as would be expected, memory rates were overall highest for old (studied) words, and gradually decreasing for new (non-studied) words with decreasing levels of associations. Differences in immediate DRM performance between MDMA and placebo seemed to exist for some word categories but not others. This was reflected in a statistically significant Drug x Level of association interaction [F(2,62, 143.99) = 3.98, p = .013, ω² = 0.02], MDMA decreased true memory [F(1, 55) = 4.05, p = .049, Cohen’s d = 0.27] and increased false memory of related lures [F(1, 55) = 9.70, p = .003, Cohen’s d = 0.42]. However, MDMA did not affect false memory for critical or unrelated lures. Better memory performance during placebo as opposed to the MDMA condition was also reflected in higher discrimination ability d’ [t(55) = −2.30, p = .025, Cohen’s d = −0.31], but response bias c was unaffected.

At the delayed test (Fig. 1b), the level of association effect was still visible for all three false memory rates in that there was an apparent gradual decrease in recognition from higher to lower associated lures, but this time true memory rates were overall lower than false memories for critical lures.3 The delayed test also revealed a statistically significant Drug x Level of association interaction [F(2,61, 145.88) = 3.86, p = .015, ω² = 0.01]. MDMA decreased true memory [F(1, 56) = 5.17, p = .027, Cohen’s d = 0.30] and false memory for critical lures [F(1, 56) = 5.11, p = .028, Cohen’s d = 0.30]. False memory rates of related and unrelated lures were not affected by the drug, and neither were any of the signal detection parameters at the delayed test.

### 3.3. Misinformation paradigm

#### 3.3.1. Eyewitness scenario

Fig. 2 shows the MDMA and placebo groups’ true and false memory rates for the eyewitness VR scenario at the immediate (2a) and delayed test (2b). As Fig. 2a shows, overall, true memory rates at the immediate test were high while suggestion-based and non-suggestion-based false memory rates were rather low. Moreover, judging from the figure the MDMA and placebo group seemed to have performed rather similarly. In line with this, no statistically significant Group x Level of association effect or main effect of Group were detected. Neither sensitivity nor response bias were found to statistically differ between groups.

However, at the delayed test some statistical differences between MDMA and placebo groups were detected. A statistically significant main effect of Group [F(1, 57) = 7.88, p = .007, ω² = 0.06] indicated that the placebo group had overall higher recognition rates. This effect was driven by the placebo group showing elevated suggestion-based false memories [F(1, 57) = 8.68, p = .005, Cohen’s d = 0.77].

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3 This could stem from a potential confounding effect of true memory being measured primarily with words that were not present during the immediate test, whereas false memory for critical lures was measured with ten critical lures from the immediate test and 5 new ones.
Table 2  Means from DRM and Misinformation parameters (rates in proportions): M (SE).

|                      | MDMA condition | Placebo condition |
|----------------------|----------------|------------------|
|                      | Immediate      | Delayed          | Immediate      | Delayed       |
| DRM                  |                |                  |                |               |
| True recognition (old) | .66 (0.02)     | .47 (0.02)       | .72 (0.02)     | .51 (0.02)    |
| False alarms (critical) | .53 (0.03)     | .54 (0.03)       | .51 (0.03)     | .61 (0.02)    |
| False alarms (related) | .27 (0.02)     | .41 (0.03)       | .20 (0.02)     | .40 (0.02)    |
| False alarms (unrelated) | .18 (0.02)   | .28 (0.03)       | .17 (0.02)     | .25 (0.03)    |
| Sensitivity d’        | .98 (0.09)     | .17 (0.05)       | 1.23 (0.09)    | .25 (0.05)    |
| Response bias c       | .03 (0.05)     | .18 (0.06)       | -.01 (0.04)    | .11 (0.05)    |
| Misinformation Eyewitness |        |                  |                |               |
| Presented            | .75 (0.02)     | .72 (0.02)       | .77 (0.02)     | .75 (0.02)    |
| Suggested            | .03 (0.01)     | .07 (0.02)       | .07 (0.02)     | .16 (0.02)    |
| Non-suggested        | .01 (0.01)     | .06 (0.02)       | .03 (0.02)     | .11 (0.03)    |
| Sensitivity d’        | 2.30 (0.08)    | 2.10 (0.09)      | 2.28 (0.11)    | 1.86 (0.09)   |
| Response bias c       | .42 (0.04)     | .42 (0.05)       | .34 (0.04)     | .22 (0.05)    |
| Misinformation Perpetrator |        |                  |                |               |
| Presented            | .62 (0.02)     | .68 (0.03)       | .61 (0.03)     | .61 (0.03)    |
| Suggested            | .25 (0.03)     | .27 (0.04)       | .24 (0.03)     | .23 (0.02)    |
| Non-suggested        | .01 (0.01)     | .03 (0.01)       | .03 (0.02)     | .01 (0.01)    |
| Sensitivity d’        | 1.46 (0.09)    | 1.53 (0.12)      | 1.47 (0.12)    | 1.47 (0.09)   |
| Response bias c       | .41 (0.04)     | .25 (0.06)       | .41 (0.06)     | .40 (0.07)    |

Fig. 1  DRM mean scores in proportions from immediate test (a) and delayed test (b) by drug condition (*p < .05, **p < .01, pairwise comparisons). Error bars represent 95% CIs. Note that yes responses to old words signify correct recognition, whereas yes responses to critical, related, and unrelated lures signify false recognition.

Analysis of the signal detection parameters showed that response bias but not sensitivity differed statistically significantly between groups [t (57) = −2.70, p = .009, Cohen’s d = 0.70, t (57) = −1.90, p = .063, respectively] with the MDMA group showing more conservative responding compared to the placebo group at follow-up (see Table 1).

3.3.2. Perpetrator scenario

Fig. 3 depicts the two groups’ true and false memory rates for the perpetrator VR scenario in the immediate (3a) and delayed conditions (3b). A clear level of association effect in the expected direction is visible in both figures. At the immediate test, again no visible differences in memory performance emerged (Fig. 3a), and statistically no interaction or main effect of Group was detected, meaning that MDMA-intoxicated individuals showed similar memory performance as their sober counterparts at immediate test. Analysis of the signal detection parameters did not show significant differences between groups.

At the delayed test (Fig. 3a), no statistically significant interaction effect or Group main effect emerged (however note that p = .052 for Group main effect). No statistically significant group differences were detected on the signal detection parameters.

3.3.3. Equivalence testing

Given the null findings in some of the misinformation analyses, equivalence tests were conducted for those conditions where no statistically significant effects were detected (i.e., eyewitness immediate, perpetrator immediate
3.3.4. Additional analyses

In short (see SI for details), the subjective sense of presence in the VR simulation was elevated in MDMA-intoxicated subjects, but was not a statistically significant covariate. Isolating effects of MDMA at encoding by differentiating between novel and repeated test items indicated that in the DRM paradigm, the most robust effects were for true memory, but did not affect findings in the misinformation paradigms.

4. Discussion

This is the first study examining effects of the entactogen MDMA on the susceptibility to form false memories, using a basic (DRM) and two applied (misinformation) paradigms. Small memory impairments in response to MDMA were detected in the DRM at both time points, particularly pertaining to true recognition. However, MDMA did not consistently affect recognition performance in the two misinformation tasks, and we did not find any evidence that MDMA increased the tendency to go along with suggestive questions.

In the DRM paradigm, true recognition was impaired during acute MDMA intoxication but also one week later when sober. Although verbal recognition memory was not affected in previous research (Kuypers and Ramaekers, 2005), this generally conforms with findings of impaired verbal memory. Moreover, the fact that impairments were
detected at both time points fits with the findings by Doss et al. (2018b) that MDMA impairs both the encoding and the retrieval stage. MDMA also elevated DRM false memories (i.e., increased false alarms) of related lures during acute intoxication, which is in line with the trend of MDMA-induced increase in false alarms during retrieval as reported by Doss and colleagues. In our study however this seemed to be an isolated finding, and no other false memory measure was increased by MDMA. In terms of signal detection parameters, intoxicated participants were less able to correctly discriminate between presented and nonpresented words (i.e., sensitivity) compared to their unintoxicated state, but their response bias was not affected by MDMA intoxication at any point.

At the delayed test, false memory for critical, thus highly associated lures was reduced following MDMA. This finding as well as the detected true memory impairments might result from encoding deficits of the studied word lists, preventing adequate processing and storing of words, and their underlying meaning or overarching associated theme. False memory theories such as Fuzzy-Trace-Theory (Brainerd and Reyna, 2019) and Associative-Activation Theory (Otgaar et al., 2019) postulate that gist processing and associative activation, respectively, support false memory. Drugs that impair encoding and true memory performance might reduce these mechanisms, resulting in reduced associative or gist-based false memory (Ballard et al., 2012; Kloft et al., 2021). The current findings provide some support for this explanation. Furthermore, the finding that associative false memory is differentially affected depending on whether a drug is present mostly at encoding versus retrieval is reminiscent of research on THC (main psychoactive cannabis compound; Ballard et al., 2012; Doss et al., 2018a; Kloft et al., 2021, 2019, 2020). Although the current study design does not permit full disentanglement of these memory stages, we see tendencies that MDMA, similarly to THC, increases DRM false memory at retrieval but reduces it when encoding effects are isolated.

Contrary to expectation, no acute MDMA effects on memory were detected in the two misinformation tasks. That is, when answering leading and non-leading questions about presented and non-presented details of a mock eyewitness and perpetrator crime experienced in virtual reality, intoxicated participants performed similarly to sober individuals. At the delayed test, participants who had experienced the crime under MDMA influence even showed reduced false memories in response to suggestive questions, exhibiting a more conservative responding pattern compared to the placebo group, but these effects were found only in the eyewitness condition. This leads us to conclude that any effects of MDMA on episodic recognition memory using the misinformation paradigm, at least in the procedure that we used, were weak to perhaps nonexistent. In any case, our results suggest that MDMA does not seem to heighten suggestibility or response bias. However, equivalence analyses could not entirely reject the presence of a small effect.

In sum, MDMA-intoxicated people recognized fewer correct stimuli both when questioned immediately and a week later, but these were small effects and were not found in the misinformation paradigms, where true memory was not affected. False memory rates increased after MDMA at immediate retrieval on one DRM measure, but decreased on some measures at 1-week follow-up. Importantly, MDMA did not induce a more liberal response bias (as e.g. with cannabis, Kloft et al., 2020); rather, the response bias did not change overall, or was more conservative at one occasion. Possibly, the DRM paradigm was more sensitive in detecting memory effects due to the higher statistical power that is inherent to a within-subjects comparison, as opposed to the between-groups analyses of the misinformation tasks. Also, recognition memory tends to be less consistently affected by drugs, compared to measures of recall (Flowe et al., 2020; Söderlund et al., 2005).

The small and at times inconsistent memory impairments detected in this study seem to mirror the generally small effect sizes in the MDMA memory literature and may in part reflect its psychostimulant effects. For example, participants viewed the VR scenarios 60 min post-administration, a time when MDMA’s stimulant effects are pronounced (de la Torre et al., 2000). This might have potentially helped the encoding (e.g., sharpening attention) of this fully immersive complex autobiographical event, which is arguably more attention-grabbing compared to a rather monotonous word list task, and might have protected against misinformation.

The present study reconfirms that MDMA impairs true memory, which is potentially problematic in the applied legal context where intoxicated individuals might remember fewer details. However, small effect sizes and inconsistent results preclude making strong claims about practical relevance, and whether lower true memory performance is also evident in more applied settings first has to be examined in more depth. Therefore, future studies should assess whether MDMA affects recall (instead of recognition) of a forensically relevant event, using study designs that separate different memory phases, and potentially testing higher doses. Intoxicated participants reported being less under influence, on average, compared to their usual experiences with the drug (Fig. S3) and regular self-reported mean doses were around 230 mg, divided over 0.5-2 pills per occasion (Table 1). However, observed MDMA blood concentrations (Table S3) were very much comparable to those observed in recreational users (cf. Morefield et al., 2011), confirming that the given dose was forensically and clinically relevant. Additionally, future research could test memory when stimulant versus entactogenic effects are dominant, similar to alcohol research where cognition is differentially affected during the ascending versus descending limbs of the blood alcohol concentration curve (Schweizer et al., 2006; Söderlund et al., 2005).

With respect to future research applications, it is further important to evaluate false memories in the context of MDMA-assisted cognitive therapy to treat PTSD. Such therapies strongly rely on trust and openness between counselors and patients when evaluating, destabilizing, and reprocessing traumatic events, and memory reconsolidation has been suggested a key mechanism to symptom improvement (Feduccia and Mithoefer, 2018). If MDMA were to cause false memories in patients due to suggestive pressure of a counselor, this might potentially result in false diagnoses and other adverse consequences. Our data from the misinformation tasks suggest that vulnerability to suggestive pressure and misinformation might not be increased during or after MDMA intoxication in recognition tasks. Further research could explore this more thoroughly, using imagi-
nation inflation or primary suggestibility measures (Carhart-Harris et al., 2015; Otgaar et al., 2016b) to assess whether MDMA’s entactogenic effects translate into people misremembering things they merely imagined.

To summarize, MDMA seems to have a complex memory profile, with much more subtle memory impairments compared to, for example, cannabis (Kloft et al., 2020). An associative word list task indicated small but robust effects on true memory, and differential effects on associative false memory that varied with immediate (intoxicated) and delayed (sober) retrieval. True and false recognition in two applied false memory tasks was not consistently affected. Studies that consider the complexity of how drug effects interact with memory phases are needed to elucidate the boundary conditions of MDMA-induced memory distortion.

Author contributions

HO, AB, JR, and LK designed the research; LK collected data; LK, ST, HO, AB, and JR analyzed data; and LK, HO, AB, and JR wrote the paper.

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Supplementary materials

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