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MDMA, cannabis, and cocaine produce acute dissociative symptoms

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ABSTRACT

Some drugs of abuse may produce dissociative symptoms, but this aspect has been understudied. We explored the dissociative potential of three recreational drugs (3,4-methylenedioxymethamphetamine (MDMA), cannabis, and cocaine) during intoxication and compared their effects to literature reports of dissociative states in various samples. Two placebo-controlled studies were conducted. In Study 1 ($N=16$), participants received single doses of 25, 50, and 100 mg of MDMA, and placebo. In Study 2 ($N=21$), cannabis (THC 300 μg/kg), cocaine (HCl 300 mg), and placebo were administered. Dissociative symptoms as measured with the Clinician-Administered Dissociative States Scale (CADSS) significantly increased under the influence of MDMA and cannabis. To a lesser extent, this was also true for cocaine. Dissociative symptoms following MDMA and cannabis largely exceeded those observed in schizophrenia patients, were comparable with those observed in Special Forces soldiers undergoing survival training, but were lower compared with ketamine-induced dissociation. Cocaine produced dissociative symptoms that were comparable with those observed in schizophrenia patients, but markedly less than those in Special Forces soldiers and ketamine users. Thus, MDMA and cannabis can produce dissociative symptoms that resemble dissociative pathology. The study of drug induced dissociation is important, because it may shed light on the mechanisms involved in dissociative psychopathology.

1. Introduction

Dissociative symptoms form a heterogeneous class of experiences varying from absent-mindedness, excessive daydreaming, and memory problems to confusion about one's own identity. In their most radical form, such symptoms define conditions like dissociative amnesia and depersonalization/derealization disorder (American Psychiatric Association, 2013). Furthermore, dissociative symptoms may accompany a range of psychiatric disorders, such as borderline personality disorder, post-traumatic stress disorder (PTSD), obsessive compulsive disorder, and schizophrenia (Holmes et al., 2005).

Dissociative symptoms have also been shown to occur during intoxication with drugs that cover a broad range of pharmacological profiles (Medford et al., 2003; Morgan et al., 2004; Somer et al., 2010). For example, administration of subanaesthetic doses of the NMDA antagonist ketamine to healthy participants produced subjective experiences of depersonalization and derealization that closely resembled dissociative symptoms such as an altered perception of the environment (Hallak et al., 2011; Krystal et al., 1994; Pomarol-Clotet et al., 2006). Regular use of 3,4-methyldioxymethamphetamine (MDMA) has been associated with a various psychopathological symptoms (e.g., anxiety, depression; Parrott et al., 2000), including mild symptoms of depersonalization and derealization experiences (Vollenweider et al., 1998). MDMA primarily acts as a releasing agent of the monoamines (serotonin, noradrenaline and dopamine) through inhibition and reversal of the monoamine transporters (Bogen et al., 2003; Fleckenstein et al., 2007).

Cocaine also blocks the reuptake of monoamines (Rothman, 2001). It has a similar psychomotor stimulant effect to that of amphetamine and related compounds, and likewise produces euphoria, tachycardia, hypertension, and appetite suppression.

Another drug that is frequently associated with dissociative symptoms is cannabis (Martin-Santos et al., 2012), particularly in

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individuals with a predisposition to schizophrenia (Bhattacharyya et al., 2009; Bugra et al., 2012). Cannabis exerts its central effects through activation of CB1 receptors, particularly in mediotemporal and anterocingulate areas of the brain (Iversen, 2003).

It is generally assumed that the pharmacological action of drugs of abuse are the prime cause of the dissociative states during drug intoxication and that drug users may actually seek "chemical dissociation" to detach themselves from reality (Somer et al., 2010). Others have shown that dissociative symptoms increase following sleep deprivation or sleep loss, which inspired the sleep-dissociation model (Van Heugten-van der Kloet et al., 2014; van der Kloet et al., 2012). This model would predict that drugs of abuse that increase sleepiness and sedation (e.g., cannabis) are more likely to induce dissociative symptoms than stimulant drugs (e.g., MDMA, cocaine) that increase wakefulness. On the other hand, the chemical dissociation hypothesis (Somer et al., 2010) would predict that the dissociative properties of both psychostimulants and sedatives are substantial as long as they induce experiences that help people to detach themselves from reality.

With this in mind, we conducted two studies exploring the acute effects of MDMA (Study 1), and cocaine and cannabis (Study 2) on dissociative symptom levels. We anticipated that all drugs would promote dissociative symptoms, but to explore the clinical relevance of these effects; we compared them with dissociative symptom levels found in a variety of clinical and non-clinical samples (Ahn et al., 2011; Bremner et al., 1998; Hallak et al., 2011; Morgan et al., 2001). Bremner et al. (1998) developed the Clinician-Administered Dissociative States Scale (CADSS), and employed this instrument to discriminate patients with dissociative disorders from other patients. We compared our findings with the CADSS scores of their sample of schizophrenia patients ($N=22$) and with baseline CADSS scores of a more recent sample of patients with schizophrenia ($N=13$; Ahn et al., 2011).

Furthermore, we compared our findings with acute dissociation during Special Forces survival training in healthy soldiers ($N=50$; Morgan et al., 2001). These soldiers experienced uncontrollable stress during survival training, as they were subject to semi-starvation, sleep deprivation, lack of control over personal hygiene, and external control over movement, social contact, and communication. Finally, we related our findings to dissociation levels during ketamine intoxication in healthy men ($N=10$; Hallak et al., 2011).

2. Method

2.1. Measures

Clinician-Administered Dissociative States Scale (CADSS; Cronbach's $\alpha=0.82$; Bremner et al., 1998). The CADSS is an instrument to measure *state* symptoms of dissociation. The scale consists of 19 self-report items and 8 observation items. An illustrative self-report item is: "Do you feel as if you are watching the situation as an observer?" The intensity of each dissociative symptom can vary from 0 (not present) to 4 (extremely present). Respondents are asked to use the last 3 h as a point of reference when completing the items. We only employed the self-report items, and by summing across relevant items, we calculated the total score (range: 0–76) and the three subscores of amnesia, depersonalization, and derealization.

Dissociative Experiences Scale (DES; Cronbach's $\alpha=0.93$; Bernstein and Putnam, 1986). The DES is a self-report scale that intends to measure trait dissociation. It requires participants to indicate on 100 mm visual analog scales (anchors: 0=never; 100=always) to what extent they experience 28 dissociative experiences in daily life. Examples include feelings of depersonalization and derealization, and memory difficulties (i.e., dissociative amnesia). In study 2, we calculated total DES scores by summing across items (range: 0–100). Van IJzendoorn and Schuengel (1996) provide meta-analytic evidence for the sound psychometric properties of the DES.

2.2. Participants and procedure

Sixteen healthy participants (8 female; mean age: 22 years, S.D.=0.41) took part in Study 1. Mean lifetime use of MDMA was 27.0 (S.D.=8.4) times. A sample of 21 healthy volunteers (5 female; mean age: 23 years, S.D.=3.57) participated in Study 2. Participants for both studies were recruited via advertisements at Maastricht University, The Netherlands. Data collection of Study 1 was part of a larger sleep deprivation study. Participants were only included if they indicated to be familiar with recreational drug use. For details of the data collection in the MDMA study, we refer the reader to Bosker et al. (2010, 2012). Study 2 was part of a larger trial on the association between drug use and impulse control (Van Wel et al., 2013). Participants of both samples were medically examined by a physician, who checked for general health and took blood and urine samples for standard chemistry and hematology. For details regarding the data collection in this trial, the reader may consult Van Wel et al. (2013). Both studies were conducted according to the code of ethics on human experimentation established by the Declaration of Helsinki (1964) and amended in Seoul (2008). Approval for the study was obtained from the Medical Ethics committee of the Academic Hospital of Maastricht and Maastricht University. A permit for obtaining, storing, and administering MDMA, cannabis, and cocaine was obtained from the Dutch drug enforcement administration. After complete description of each study to the participants, written informed consent was obtained.

In Study 1, we compared three dosages of MDMA and a placebo to explore their effects on dissociative experiences. The study was conducted according to a double-blind, placebo-controlled, randomized, four-way, cross-over design. Treatments consisted of single doses of placebo, 25, 50, and 100 mg MDMA. Treatment orders were balanced over participants and treatment periods. Placebo and MDMA were administered orally in identically appearing formulations. MDMA was dissolved in 25 ml bitter orange peel sirup, and placebo consisted of only the bitter orange peel sirup. The sirup was mixed with 200 ml juice before it was given to the subjects. The wash-out period between treatments was at least 1 week.

Participants were asked to refrain from any drugs 1 week before the medical examination until 2 weeks after study completion. Participants were not allowed to drink alcohol and caffeine or smoke tobacco during a 24-h period prior to testing. Participants were always screened for alcohol and drugs using the Mahsan-test that specifically detects tetrahydrocannabinol, opiates, amphetamine/ecstasy, benzodiazepines, cocaine, and methamphetamine/ecstasy in breath and/or urine upon arrival (4:30 p.m.) at the laboratory on test days. At 5:00 p.m., participants received a light, standard dinner, and at 5:15 p.m., MDMA or placebo was administered. The CADSS was completed at 6.30 p.m. See Fig. 1 for the flowchart of Study 1.

In Study 2, we compared single dose administrations of cannabis, cocaine, and a placebo to explore their effects on dissociative experiences in regular cannabis and cocaine users. Screening and inclusion criteria were similar to those in Study 1, with the exception of a minimum use of cannabis of two times per week during the previous three months, and a minimum of recreational cocaine use of five times in the previous year. Participants were asked to refrain from using any drugs except cannabis one week before the medical examination until study completion. Test conditions were the same as for Study 1. Treatments were only administered when participants were negative for all drugs except cannabis. This is because high lipid-solubility of cannabinoids will be present in the body for long periods of time.

The procedure entailed three test sessions on three separate days, with a minimum of 7 days between sessions. Drugs were administered using a double-blind, placebo-controlled, double-dummy procedure. A double dummy procedure was used to control for differences in Tmax between both drugs. At T1 subjects received a cocaine or placebo capsule. At T2, 45 min after T1, subjects received either a single dose of cannabis (300 μg/kg THC) or cannabis placebo. At T3, 1 h following T2, subjects received another cannabis dose (150 μg/kg THC or cannabis placebo). Fig. 2 shows a flowchart of the drug administration procedure. Cannabis (300 μg/kg) or placebo (a herbal plant mixture (Knaster)) was administered through a vaporizer (Volcano) obtained from Storz & Bickel GmbH & Co (Tuttlingen, Germany), which was used according to the manual provided by the producer. Inhalation took place in a standardized manner (Van Hazekamp et al., 2006). Percentage of THC was 11%, a standard potency for cannabis used recreationally and sold at Dutch pharmacies for medical use. Cocaine HCl (300 mg) or placebo was administered in an opaque white capsule.

The DES was completed during a training session on a separate day before the placebo or drug sessions. The CADSS was completed three hours and 15 min after T1 (i.e., 3.5 h after cocaine and 1.25 h after the second cannabis administration).

2.3. Data analysis

Statistical analyses were performed using SPSS 18.0 software. Cronbach's α values were used to estimate internal consistency of the measures. Pearson product-moment correlations between baseline and state measures were calculated. CADSS data were analyzed using General Linear Model (GLM) repeated measures analyses, univariate analyses (ANOVA), and post-hoc pairwise comparisons. Using independent samples *t*-tests, we compared our data with findings from several previous studies (Bremner et al., 1998; Morgan et al., 2001; Ahn et al., 2011; Hallak et al., 2011) that explored the prevalence of acute dissociative symptoms in a variety of groups.

3. Results

Table 1 shows lifetime drug use of the participants enrolled in Study 1 and 2. Table 2 shows mean scores on the CADSS in Study

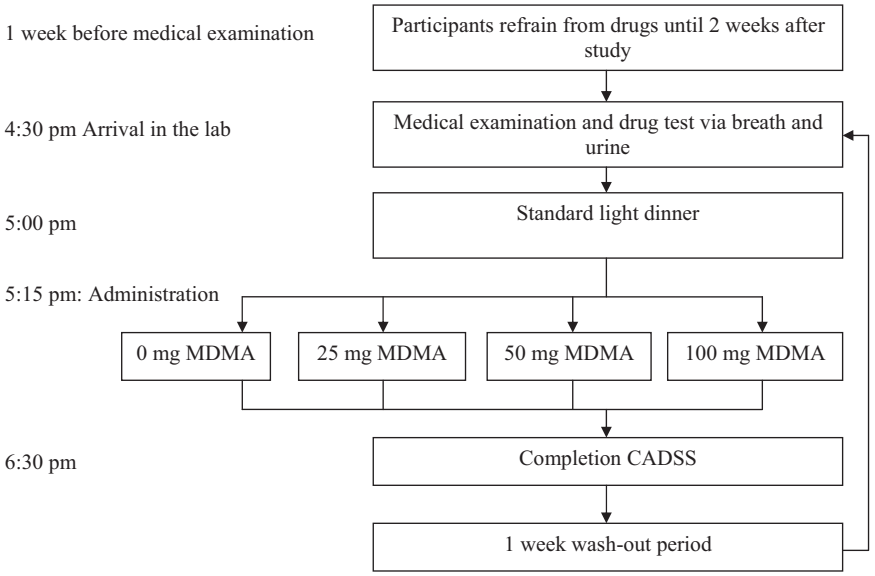

Fig. 1. Flowchart of Study 1. Participants went through the cycle four times in a randomized and counter-balanced order to ensure administration of placebo (0 mg MDMA) and three different dosages of MDMA.

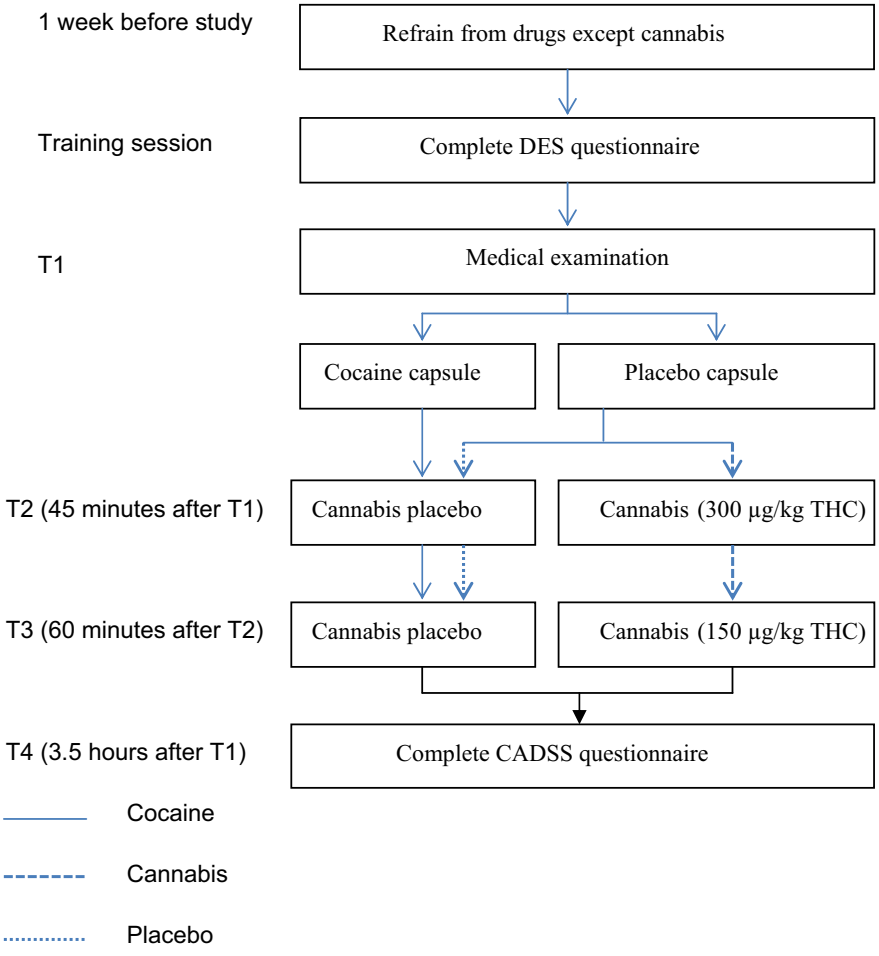

Fig. 2. Flowchart of Study 2. The participants went through the cycle three times on separate days in a randomized and counter-balanced order, with a minimum of seven days between test sessions.

1 and 2, as well as univariate analyses, and statistical comparisons of the state dissociation subscales for both studies. We correlated the history of drug use of the participants from both studies with drug-induced dissociation scores (CADSS), and found a significant negative correlation between duration (in years) of MDMA use and CADSS. Drug induced CADSS scores decreased with increased

exposure to MDMA ($r=-0.28$, $p=0.04$). None of the other correlations between frequency and duration of drug use and CADSS and DES scores attained significance.

3.1. MDMA Study 1

Using repeated measures analyses ANOVA, we found a significant effect of drug dosage on CADSS scores ($F(3,45)=21.27$, $p<0.001$; partial eta²=0.59). Post-hoc analyses revealed significant differences between the highest dosage MDMA (100 mg) relative to placebo for the CADSS total score and its derealization subscale. No significant differences were found between the placebo and the 25 mg and 50 mg conditions (p's=0.22–0.72).

3.2. Cannabis and cocaine Study 2

CADSS scores were skewed to the right. An approximately normal distribution was achieved using a logarithmic transformation on CADSS scores. One outlier with a CADSS score of 50 (z score=4.86) was removed from the analyses. Using repeated measures ANOVA, we found a significant main effect of drug (cannabis, cocaine, or placebo) on CADSS scores ($F(2,34)=17.00$, $p<0.001$; partial eta²=0.50). Both cannabis and cocaine treatment significantly increased acute dissociation levels as compared with placebo (both p's<0.05, See Table 2). Cannabis significantly increased all subscores of the CADSS as well as the total score. Cocaine yielded a small, but significant increase in the CADSS total score, but its effects on the separate subscores were modest.

We investigated whether participants, who scored high on trait dissociation, as measured with the DES, showed a higher sensitivity to drug-induced state dissociation. Mean DES (S.D.) for the present subject sample was 17.30 (11.05). When participants consumed cannabis or cocaine, but not when they had placebo, there was a significant correlation (cannabis: $r=0.47$, cocaine: $r=0.54$, both p's<0.05) between DES and CADSS scores, indicating that participants with higher trait dissociation are more vulnerable to experience state dissociation when under the influence of cannabis or cocaine. We performed William's test for comparing correlations with one variable in common. The CADSS–DES correlations were not significantly different for cocaine as compared with cannabis ($t=1.36$, $p=0.19$).

Table 1
Mean age, lifetime drug use (total number of times used), and drug use in years of the participants enrolled in Study 1 and 2 ($N=16$; $N=21$, respectively).

	Study 1 Frequency # times (S.D.)	Duration (years)	Study 2 Frequency # times (S.D.)	Duration (years)
MDMA	33.75 (33.71)	5.08	27.0 (8.40)	3.99
Cannabis	1367.55 (1553.17)	7.68	69.15 (76.54)	5.18
Cocaine	75.50 (104.57)	4.45	10.30 (11.63)	2.28
Alcohol	676.22 (792.14)	9.00	5248.55 (5271.17)	7.56
Amphetamines	74.88 (246.98)	3.64	4.50 (3.54)	1.29
Mushrooms	11.64 (20.23)	3.53	3.43 (2.37)	2.11
LSD	12.75 (9.14)	1.33	1 (no S.D.)	0.08
Other	7.50 (7.40)	1.53	–	–

3.3. Acute dissociation in other samples

We compared our findings with two samples of patients suffering from schizophrenia (Ahn et al., 2011; Bremner et al., 1998), a sample of healthy Special Forces soldiers who had completed the CADSS after experiencing acute, uncontrollable stress (Morgan et al., 2001), and a sample of healthy male volunteers intoxicated with ketamine (Hallak et al., 2011). Please see Fig. 3 for a display of the findings.

Our analysis showed that single doses of MDMA 100 mg and cannabis induced dissociative symptoms that significantly exceeded those of patients with schizophrenia (t's=2.61–4.00, all p's<0.01), and were comparable to dissociation levels experienced by Special Forces soldiers during their survival training course (MDMA: $t=0.52$, $p=0.60$; cannabis: $t=0.50$, $p=0.62$). However, acute dissociation levels during ketamine intoxication exceeded those produced by MDMA and cannabis (MDMA: $t=7.77$; cannabis: $t=8.31$, both p's<0.01).

Cocaine produced dissociative symptom levels that were comparable with those observed in schizophrenia patients ($t=2.03$, $p=0.05$; $t=1.21$, $p=0.23$), but were significantly lower than those in Special Forces soldiers ($t=2.30$, $p=0.02$) and ketamine users ($t=12.28$, $p<0.01$).

4. Discussion

The present study demonstrates that MDMA and cannabis can induce dissociative symptoms. Cannabis significantly increased subjective ratings of depersonalization, derealization, and amnesia during intoxication. MDMA primarily increased feelings of derealization. The magnitude of total dissociation following cannabis and MDMA, however, was comparable. On the other hand, cocaine only mildly increased the total CADSS score when compared with placebo. CADDS ratings were negatively correlated to MDMA use history, indicating that MDMA induced dissociative symptoms were less in more experienced users. The effects of MDMA on dissociative symptoms were also shown to be dose dependent. MDMA 100 mg significantly increased dissociative symptoms, whereas MDMA 25 and 50 mg did not.

We compared our results with the data of schizophrenia patients, Special Forces soldiers, and ketamine users (Ahn et al., 2011; Bremner et al., 1998; Hallak et al., 2011; Morgan, et al., 2001). Total CADSS

Table 2
Mean scores (S.D.), repeated measures analyses, and statistical comparisons of state dissociation subscales (CADSS) between the MDMA groups (Study 1; $N=16$), and cocaine, cannabis, and placebo group (Study 2; $N=21$).

	Study 1				Study 2		
	MDMA			Placebo	Cannabis	Cocaine	Placebo
	25 mg	50 mg	100 mg				
CADSS							
Amnesia	0.00 (0.00)	0.12 (0.34)	0.56 (0.73)	0.06 (0.25)	0.95 (1.27)[a]	0.80 (1.64)	0.05 (0.21)
Deperson.	0.25 (0.68)	0.44 (0.89)	2.63 (3.76)	0.06 (0.25)	3.42 (4.63)[a]	1.90 (3.14)	0.10 (0.30)
Derealiz.	1.25 (1.39)	1.94 (2.52)	9.88 (7.02)[a]	0.56 (0.96)	5.95 (5.50)[a]	3.45 (3.78)	0.86 (1.56)
Total	1.50 (1.41)	2.50 (3.16)	13.06 (10.06)[a]	0.69 (1.25)	10.32 (10.61)[a]	6.15 (7.86)[a]	1.00 (2.00)

Note: CADSS=Clinician-Administered Dissociative States Scale.

[a] Drug treatment differs from placebo (Pairwise comparisons significant at the 0.05 level (2-tailed, Bonferroni corrected).

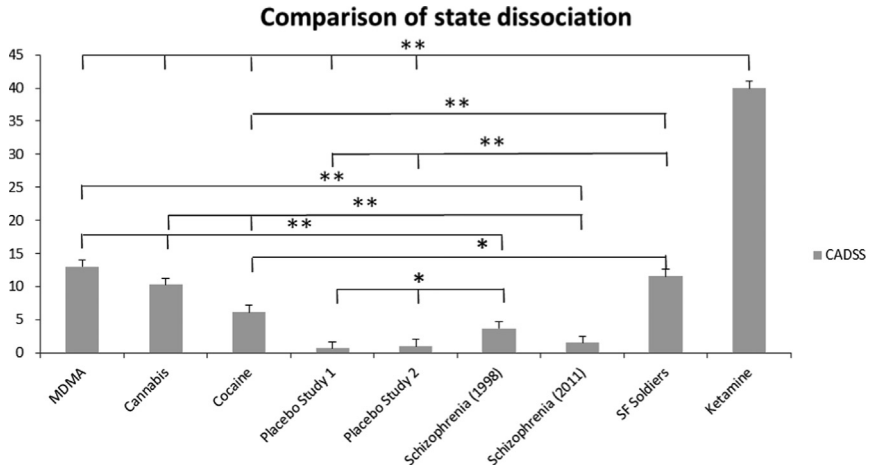

Fig. 3. Comparison of state dissociation levels (CADSS) between drug- and placebo treatments from Study 1 and 2 and state dissociation (CADSS) in schizophrenia samples (Ahn et al., 2011; Bremner et al., 1998), Special Forces soldiers during survival training (Morgan et al., 2001), and healthy men during ketamine intoxication (Hallak et al., 2011). Displayed are SEM bars and significant differences between the groups ($^{*}p < 0.05$, $^{**}p < 0.001$).

scores of schizophrenia patients were generally low and ranged from 1.5–3.7. Their scores were similar to those observed in our participants during placebo treatments, with only the highest mean CADSS score (i.e., 3.7) in Bremner et al.'s study being significantly raised. However, in our study, all values obtained under placebo conditions stayed within 1–2 times the standard deviation.

In contrast, total CADSS scores reported in Special Forces soldiers (i.e., 11.6) and in ketamine users (i.e., 40) have been found to be elevated and much more indicative of a dissociative state. A comparison between their CADSS data and the current data revealed that dissociative symptoms following cannabis and MDMA largely exceeded those observed in schizophrenia patients and were comparable with those observed in Special Forces soldiers, yet lower relative to ketamine induced dissociation. Cocaine produced dissociative symptoms that were similar to those observed in schizophrenia patients, but they were well below the dissociative levels found in Special Forces soldiers and ketamine users. Thus, MDMA and cannabis, but not cocaine, can produce severe dissociative symptoms that resemble dissociative pathology.

We measured trait dissociation in participants of Study 2 with the DES. Mean DES scores were relatively low (i.e., 17.3) and well below the cut-off score > 30 that is thought to be indicative of a dissociative disorder (Bernstein and Putnam, 1986). These data suggest that our participants had not developed dissociative pathology despite their regular drug use history. A correlational analysis between DES and CADSS scores revealed a moderate but significant association between cannabis and cocaine induced CADSS scores and DES. The absolute increments in CADSS following cocaine, however, were generally small, and the association between DES and CADSS scores did not exist for MDMA, even though this drug did produce severe dissociative symptoms. Our results, then, fail to provide strong evidence for any direct causality between drug-induced state dissociation and trait dissociation. This was to be expected because the current sample did not include any participants with a psychiatric background.

All in all, our findings demonstrate that stimulant drugs such as MDMA and, to a lesser extent, cocaine may produce dissociative effects, a finding that is at odds with the idea that only sleep producing manipulations may increase dissociation levels (Van der Kloet et al., 2012). Clearly, the psychostimulant MDMA produced acute dissociative symptoms that were similar to those obtained with cannabis, a sedative and sleep promoting drug. Therefore, our data are much more in line with the chemical model of dissociation that poses that drug- induced dissociation occurs due to detachment from reality and not necessarily because of the sleep-promoting properties of the drugs involved.

Research showing that dissociative disorders and substance abuse disorders are often co-occurring is consistent with the current finding that dissociative states can be drug-induced (Medford et al., 2003; Somer et al., 2010). Relatedly, in clinical practice, dual diagnoses patients are known to pose serious treatment challenges due to drug abuse, increased risk of suicidal and violent behaviors, and overall poorer functioning (Schwartz et al., 1998). According to the chemical dissociation hypothesis (Somer et al., 2010), individuals suffering from a traumatic past may use illicit drugs to blunt traumatic feelings, when dissociative pathology is not effective any longer to defend against intrusions of traumatic memories. Alternatively, the use of drugs like cannabis may elicit dissociative symptoms such as depersonalization (Kessler et al., 1995; Medford et al., 2003).

Our studies were subject to a number of limitations that restrict the generalizability of the current findings to clinical groups. First, our data set as well the historical datasets consisted of relatively small samples, which due to chance fluctuations may limit the reliability of our findings. Second, participants in our studies had a history of drug use, which may have mitigated their response to acute drug challenges. The present results may therefore underestimate drug-induced dissociative responses in novice drug users. Third, Bremner et al. (1998) used the full version of the CADSS (including observer-rated items), whereas we only used the 19 self-report items. This hampers a fine grained comparison and given our reliance on a relatively small sample, the differences with the Bremner et al.'s (1998) study should not be over interpreted.

In sum, our findings show that MDMA, cannabis, and cocaine all induce acute dissociative symptoms. Dissociative symptoms were most prominent after MDMA and cannabis and similar to pathological symptomatology. Future studies might want to include mechanistic designs to further distinguish the neuropharmacology of drug-induced dissociative states that might clarify why some substances have stronger dissociative properties than others. Thus, studies that compare drugs with regard to their dissociative potential might clarify the physiological drivers of these symptoms, especially when the drugs differ in a systematic way in terms of their hypnotic, psychotomimetic, and stimulant properties.

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