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Abstract

In Western societies a considerable percentage of young people expose themselves to the combination of 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') and cannabis. The aim of the present study was to assess the acute effects of co-administration of MDMA and THC (the main psychoactive compound of cannabis) on pharmacokinetics, psychomotor performance, memory and subjective experience over time. We performed a four-way, double blind, randomized, crossover, placebo-controlled study in 16 healthy volunteers (12 male, four female) between the ages of 18 and 27. MDMA (100 mg) was given orally, THC (4, 6, and 6 mg, interval of 90 min) was vaporized and inhaled. THC induced more robust cognitive impairment compared with MDMA, and co-administration did not exacerbate single drug effects on cognitive function. However, co-administration of THC with MDMA increased desired subjective drug effects and drug strength compared with the MDMA condition, which may explain the widespread use of this combination.

Keywords

MDMA, cannabis, co-administration, psychomotor, memory, subjective effects

Introduction

In Western societies, a significant proportion of young people expose themselves to 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') (Parrott, 2001). Ecstasy users are generally multidrug users, having experience with different psychoactive substances and combining them with ecstasy (Gouzoulis-Mayfrank and Daumann, 2006). Cannabis (main active compound Δ^9-tetrahydrocannabinol or THC) is frequently co-used with ecstasy (Parrott et al., 2007). While 90–98% of ecstasy users also use cannabis (Parrott et al., 2007), Winstock et al. (2001) showed that 82% of ecstasy users had used cannabis concurrently with ecstasy at least once. Boys et al. (2001) reported that out of 177 ecstasy users, 55 (31%) used cannabis concurrently in the last year to 'enhance the effects' of ecstasy and 114 (64%) used cannabis concurrently in the last year to 'ease the after effects' of ecstasy. Despite the prevalence of co-administration of MDMA and THC, the effects of combined use of these substances in humans have so far not been investigated.

MDMA releases serotonin (5-HT) from presynaptic 5-HT terminals by reversal of the reuptake transporter and thus increases 5-HT levels at the postsynaptic receptors (Liechti and Vollenweider, 2000; Mlinar and Corradetti, 2003; Pifl et al., 1995). MDMA is also a potent releaser of dopamine and (nor) adrenaline (Colado et al., 2004; Liechti and Vollenweider, 2001; Sprague et al., 2004). In a previous study by our group, MDMA was found to increase psychomotor speed without affecting psychomotor accuracy.

MDMA impaired the delayed recall of words, whereas word recognition was unaffected. MDMA increased subjective arousal and decreased subjective calmness (Dumont et al., 2008). Other studies regarding the cognitive effects of MDMA are generally in agreement with these findings (Hernandez-Lopez et al., 2002; Kuypers and Ramaekers, 2005, 2007; Dumont and Verkes, 2006). These effects generally coincided with maximal MDMA plasma concentration but declined to baseline values 5–6 h after drug administration in spite of persisting MDMA plasma concentration, which is generally consistent with the literature (Dumont and Verkes, 2006). MDMA is rapidly absorbed following oral administration, and within 30 min is detectable in the blood. MDMA plasma levels peak 1–2 h after drug intake.

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THC, the major psychoactive compound in cannabis (Ilan et al., 2005; Wachtel et al., 2002), is an agonist for the CB_1 and CB_2 receptors of the endocannabinoid system (ECS). The CB_1 receptor is abundantly expressed in the central nervous system whereas the CB_2 receptor is expressed predominantly in the periphery (Ameri, 1999). The central effects of THC have received abundant attention in the scientific literature and generally include, but are not restricted to, impairment of memory and psychomotor function and subjective relaxation (Ranganathan and D'Souza, 2006). A recent review revealed that cannabis affects most functional central nervous system domains, but because of great variations in study methodology only increases of heart rate and subjective feelings (feeling 'high') were found to be reliable biomarkers of cannabis effects (Zuurman et al., 2009). THC, a highly lipophilic compound, is rapidly distributed into fatty tissue, and after inhalation, peak plasma concentration are reached within minutes and show a rapid decline, although cognitive effects and subjective effects are maximal after 15–60 min and last for several hours (Strougo et al., 2008; Zuurman et al., 2008).

As combined use of MDMA and THC is common (Parrott et al., 2004, 2007), and these substances both affect memory as well as psychomotor function, we aimed to assess the cognitive and subjective effects of co-administration of MDMA, a potent serotonin releaser, and THC, a CB_1 agonist, over time under controlled laboratory conditions in experienced users. Previous research regarding the cognitive effects of co-administration of MDMA and THC is limited to a study in rats and showed that co-administration induced a synergistic impairment of working memory (Young et al., 2005). Thus, co-administration was expected to show additive impairment of memory, whereas effects on psychomotor performance were expected to be attenuated because of the opposing actions of the stimulant MDMA and the relaxant THC.

Materials and methods

Study design

This study utilized a four-way, double blind, randomized, crossover and placebo-controlled design, and was conducted according to the principles of the Declaration of Helsinki. Each volunteer received a capsule containing either MDMA 100 mg or placebo and inhaled a vapour containing consecutively 4, 6 and 6 mg of THC (dosing intervals of 90 min) or placebo vapour containing vehicle with a washout of 7 days between each condition. The present manuscript addresses the cognitive effects of this drug combination; this study also assessed physiological effects, which have been published elsewhere (Dumont et al., 2009).

Study outline

Subjects were admitted to each study day after a urinary drug check (opiates, cocaine, benzodiazepines, amphetamines, methamphetamines and THC, AccuSign®, Princeton BioMeditech, Princeton, NJ, USA: drug use was not allowed 14 days prior to the first study day until study

completion) and the recording of possible signs and symptoms of health problems. As THC was administered during study days, urine positive for THC led to exclusion only on study day 1. A light breakfast was offered 2 h prior to MDMA administration. MDMA administration was scheduled at 10:30 h and THC was administered at 0, 90 and 180 min after MDMA administration. It is unknown which order of recreational MDMA and THC use is most common. This administration schedule was chosen because it allows assessing the effects of the acute combinations of THC + MDMA, the addition of THC at the peak of MDMA effects or the addition of THC at the descending slope of MDMA effects. Subjects received a standardized lunch at 14:00 h and were sent home around 17:00 h.

Outcome measures were assessed repeatedly, that is, before MDMA administration and at 15, 60, 105, 150, 240 and 300 min post-drug administration, with the exception of the 18 word list memory task, which was performed 120 min after drug administration. Repeated measures consisted of blood sampling for analysis of MDMA kinetics and assessments of postural stability, psychomotor function, memory and subjective effects as specified below. Pharmacokinetic data has been reported in detail elsewhere (Dumont et al., 2009). To familiarize the subjects with the tests and procedures, they performed a practice session 1 week before the actual study days.

Subjects

Sixteen healthy volunteers (12 male, four female), regular users of ecstasy (at least eight exposures in the last 2 years) and THC (on average two exposures per week in the last year), between the ages of 18 and 27, were recruited through advertisement on the Internet and at local drug testing services. Detailed demographic data are shown in Table 1.

Table 1. Demographic data of study participants, drug use is quantified as the cumulative number of lifetime drug exposures (not further specified)

	Mean	SEM	Min	Max
Age (years)	21	0.5	18	27
Education (years)	16	0.3	12	18
Height (cm)	178	1.7	165	189
Weight (kg)	71	2.1	60	86
Opiates	26	9	1	50
LSD	33	13	2	108
Ecstasy	143	53	10	702
Amphetamines	96	50	1	624
Cannabis	1716	429	364	6570
Cocaine	46	19	2	234
Alcohol	6071	1221	144	15,600
Solvents	122	70	1	834
Benzodiazepines	7	3	1	25
Psilocybin	19	6	1	60
GHB	33	19	1	208
Ketamine	211	116	1	1040

Exclusion criteria included pregnancy, (history of) psychiatric illness [assessed using the Structured Clinical Interview for DSM-IV axis I disorders, non-patient version (First et al., 1994); Axis II disorders were excluded using the Temperament and Character Inventory (Svrakic et al., 1993)], use of over-the-counter medication within 2 months prior to the study start (history of) treatment for addiction problems, excessive smoking (>10 cigarettes/day) and orthostatic dysregulation. Physical and mental health was determined by assessment of medical history, a physical and electrocardiographic examination as well as standard haematological and chemical blood examinations. The local medical ethics committee approved the study. All subjects gave their written informed consent before participating in the study, and were paid for their participation.

One subject did not refrain from drug use, after which further study participation was denied. Two subjects experienced an adverse event that was judged to be likely related to study drug administration [one subject experienced a short (lasting 55 s) heart rate increase of >180 bpm and another subject experienced mild hallucinations, the latter subsiding along with other drug effects]. These subjects were excluded from further participation; data of completed study days obtained prior to these adverse events were analysed as described.

Study drugs

THC was purified according to Good Manufacturing Practice (GMP)-compliant procedures (Farmalyse BV, Zaandam, The Netherlands) from the flowers of *Cannabis sativa* grown under Good Agricultural Practice (Bedrocan BV Medicinal Cannabis, Veendam, The Netherlands) (Choi et al., 2004; Hazekamp et al., 2004). Each dose (4, 6 and 6 mg) of THC [>98% purity by high-performance liquid chromatography (HPLC)/gas chromatography] was dissolved in 200 μl 100 vol% alcohol. THC was stored in the dark at −20°C in 1-ml amber glass vials containing a Teflon screw cap secured with Para film to minimize evaporation. The solvent was used as placebo.

On each study day, THC (4, 6 and 6 mg) or placebo were administered by inhalation at 90-min intervals using a Volcano® vaporizer (Storz-Bickel GmbH, Tüttlingen, Germany), a validated method of intrapulmonary THC administration (Abrams et al., 2007; Hazekamp et al., 2006). Concurrent with MDMA administration, THC (4 mg) was administered to ensure tolerability. Ninety and 180 min after drug administration, 6 mg of THC was administered. Within 5 min before administration, THC was vaporized at a temperature of about 225°C and the vapour was stored in a polythene bag equipped with a valved mouthpiece, preventing the loss of THC in between inhalations. The transparent bag was covered with a black plastic bag to prevent unblinding. Subjects were not allowed to speak, and were instructed to inhale deeply and hold their breath for 10 s after each inhalation. Within 2–3 min, the bag was to be fully emptied. The inhalation procedure was practised at screening using the vehicle only.

Each 6-mg THC dose was predicted to cause THC plasma concentrations and effects that roughly correspond to those of one marijuana cigarette (Zuurman et al., 2008). The decision to proceed to the next THC dose was made by a physician, based on adverse events and physical signs.

MDMA (or matched placebo) was given as a capsule in a single oral dose of 100 mg. MDMA was obtained from Lipomed AG (Arlesheim, Switzerland) and encapsulated according to GMP by the Department of Clinical Pharmacy of Radboud University Nijmegen Medical Centre.

Pharmacokinetic measurements

THC. For determination of the concentration of plasma THC and its two most important metabolites (11-OH-THC and 11-nor-9-carboxy-THC), venous blood was collected in EDTA tubes of 4.5 ml covered with aluminium foil. Blood samples were taken 5 and 20 min after each THC administration and immediately put on ice and were processed (spun at 1500 g for 10 min at 4°C) within 30 min after collection. THC blood samples were handled sheltered from light. Plasma samples were stored at a temperature of −80°C for less than 3 months before laboratory analysis. Concentrations of THC and the metabolites were shown to be stable over this period (Hazekamp et al., 2004).

Determination of THC, 11-OH-THC and 11-nor-9-carboxy-THC content was performed using a validated HPLC with tandem mass spectrometric detection. The calibration range was 1.00–500 ng/ml for all compounds. Over this range, the intra-assay coefficient of variation was between 4.0% and 6.5%. The inter-assay coefficient of variation was between 1.4% and 9.4%.

MDMA. An HPLC–diode array detection method was employed to assess MDMA and methylenedioxyamphetamine (MDA) plasma concentration, which has been described in detail previously (Dumont et al., 2008).

Pharmacodynamic measurements

Eye movements. Saccadic eye movements are a measure for psychomotor speed and sedation. Eye movements were quantified by recordings of field potential changes related to eye rotations. Similar to EEG patterns and the architecture of evoked potentials in rats (Meeren et al., 1998), saccadic motion is dependent on the state of alertness (van Steveninck et al., 1999). For the saccadic test, which lasted 1.5 min, the subject was instructed to look at a target that suddenly changed position at random intervals. The target consisted of an array of light-emitting diodes on a bar fixed at 50 cm in front of the head support. Each recording session consisted of 15 saccades of 15° stimulus amplitudes. The outcome measures are peak saccadic velocity and reaction time.

For smooth pursuit eye movements, a measure of psychomotor accuracy, the target moved sinusoidally at frequencies ranging from 0.3 to 1.1 Hz, by steps of 0.1 Hz during 60 s. The amplitude of target displacement corresponded to 20° of eyeball rotation to both sides. The time in which the eyes were in smooth pursuit of the target was calculated for each frequency and expressed as a percentage.

Saccadic and smooth pursuit eye movements were recorded using Nihon-Kohden® and Cambridge Electronics Design (CED®) hardware, and CED Spike2® software for

sampling and analysis of eye movements. Effects on the saccadic eye movements, the saccadic eye velocity (PV), were analysed according to published rules (Meeren et al., 1998; Sundstrom and Backstrom, 1998). Head movements were restrained using a fixed head support. Eye movements are used to locate objects and predict the path of moving objects, and as such can be expected to be relevant for driving related abilities (Orban de Xivry and Lefevre, 2007). Moreover, they are sensitive to the effects of serotonergic challenges, MDMA and cannabis (Dumont et al., 2007; Gijsman et al., 2002; Zuurman et al., 2008).

Body sway. Subjects were asked to close their eyes while in an upright position and were attached to the body sway apparatus that records cumulative horizontal body movement (in mm) for 2 min. The test is a measure for postural stability (Wright, 1971).

Pursuit task. To measure implicit procedural learning, a computerized version of the rotor pursuit task was used. This test is based on the classic rotary pursuit task (Ammons, 1951). It is a continuous motor task. Subjects had to follow the movement of a large target stimulus on the computer screen with a cursor by moving the pen over a $X–Y$-tablet. The speed of the target gradually increased when the cursor was contained within the target but decreased considerably when it was not. The target followed a spatially predictable circular path over the screen. The outcome measure for this test was the total number of rotations within 2 min.

Eighteen words list. The 18 words list is a verbal memory test based on the classic Auditory Verbal Learning Test (Vakil and Blachstein, 1993). A variant was made consisting of a list of 18 words. The classic test uses 15 words. A longer word list was chosen to prevent ceiling effects. The list was presented verbally three times 120 min after MDMA administration (30 min after the second THC administration). Under normal circumstances, subjects are supposed to remember an increasing number of words after each trial. Directly after each presentation, and after an interval of 20 min, subjects were asked to recall as many words as possible. After the delayed recall trial a list of 36 words was presented, from which they were asked to recognize the 18 words previously presented. The incorrect words were distracters and resembled the correct words in a semantic or phonological manner. Responses were either correct positive (when a word that was recognized was indeed part of the list presented during immediate recall) or false positive (when a word was recognized but was not part of the list presented during immediate recall, e.g. the word was a distracter). The outcome measure was the number of correctly recalled/recognized words for the average of the three immediate recall trials, the delayed recall trial and the delayed recognition trial (correct positive and false positive).

N-back task. The N-back task, a test of working memory, is widely used for the detection of working memory deficits (Meyer-Lindenberg et al., 2001). Subjects were presented with a starting circle and six possible target circles surrounding the starting circle on the screen, reflecting the same positions as on the paper form. In the 1-back condition, subjects had to respond to the stimulus, that is, move the pen into the target circle, which lit up in the previous trial. In the 2-back condition, subjects had to respond to the stimulus presented two trials before. In the 3-back condition, subjects had to respond to the stimulus presented three trials before. The outcome measure was the time needed until completion of 25 correct trials.

Bond and Lader (Visual Analogue) Mood Rating Scale (BLMRS). The BLMRS scale consists of 16 lines, each 10 cm in length, with opposite terms at each end of the line (Bond et al., 1974). Subjects were asked to indicate which item was more appropriate by marking the line. The outcome measure of these visual analogue scales was the distance to the marker on each scale. These scale scores were aggregated to scores for 'calmness', 'alertness' and 'contentedness', as described by Bond et al. (1974).

Subjective drug experience visual analogue scales. To assess subjective drug experience and motivation, three visual analogue scales were constructed (drug liking, drug strength and motivation, 0 being minimal and 10 maximal (i.e. 0 = no drug liking, 10 = maximal drug liking)). Similar to the BLMRS, these were each 10 cm in length, and subjects were asked to quantify these terms by marking the line. The outcome measure was the distance to the marker on each scale.

Bowdle visual analogue scales. Psychedelic effects were monitored by an adapted version of the visual analogue scales (13 items, each 10 cm in length), originally described by Bowdle et al. (1998). Individual scales were aggregated to scores for 'feeling high', 'drowsy', 'internal perception' (reflecting inner feelings not corresponding to reality) and 'external perception' (reflecting a misperception of an external stimulus or a change in the awareness of the subject's surroundings) (Zuurman et al., 2008).

Statistical analyses

The pharmacodynamic parameters were analyzed by mixed model analyses of variance (using SAS PROC MIXED, SAS 9.1.3 for Windows, SAS Institute, Inc., Cary, NC, USA) with treatment, time and treatment by time as fixed effects, with subject, subject by time and subject by treatment as random effects, and with the baseline value as covariate, where baseline was defined as the average of the available values obtained prior to dosing. Treatment effects are reported as the contrasts between the four treatments, where the average of the measurements up to the last time point was calculated within the statistical model. Contrasts are reported along with 95% confidence intervals (CI) and analyses are two-sided with a significance level of 0.05. Statistical evaluation of the pharmacokinetics was performed with GLM Repeated Measures Analysis of Variance (ANOVA, using SPSS 11.5 for Windows).

Results

Pharmacokinetics

MDMA and MDA kinetics did not differ between MDMA alone and MDMA plus THC conditions. Mean MDMA maximal plasma concentrations (±SEM) were on average $213.3 \pm 7.9\,\mu g/l$ 105 min after drug administration and showed minimal decline during the sampling period (on average $168.3 \pm 5.4\,\mu g/l$ 300 min after drug administration).

Mean MDA plasma concentrations on average rose to $12.0 \pm 0.5 \, \mu g/l$ 300 min after drug administration.

Plasma THC concentrations and its two most important metabolites (11-OH-THC and 11-nor-9-carboxy-THC) did not differ between the THC alone and MDMA plus THC conditions (Table 2). THC and 11-OH-THC consistently showed peak concentrations directly after administration and declined thereafter, whereas 11-nor-9-carboxy-THC concentrations inclined throughout the sampling period (Dumont et al., 2009).

Pharmacodynamics

Only significant results are mentioned in this section unless noted otherwise. The main effects of treatment, time and treatment by time as well as drug condition comparisons are summarized in Table 3. For the drug condition comparisons, reported are mean change, 95% CI and corresponding *p*-values.

Body sway. Body sway was increased, that is, postural position was impaired, in all drug conditions compared with placebo. THC alone as well as co-administration of THC plus MDMA increased body sway compared with the MDMA alone condition.

Eye movements. Although smooth pursuit eye movements (psychomotor accuracy) were not significantly impaired in any drug condition compared with placebo, MDMA and THC showed opposite effects on this measure: co-administration of MDMA increased smooth pursuit eye movements compared with the THC administration.

Psychomotor speed and sedation/arousal were assessed by saccadic eye movements (respectively peak saccadic velocity (PV) and reaction time). PV was increased in the MDMA condition as well as in the MDMA plus THC condition compared with the placebo and the THC condition. THC did not affect PV. Saccadic reaction time did not show a significant main effect of drug administration.

Rotor pursuit task. The Rotor Pursuit task (Figure 1) performance was significantly impaired in the THC condition and the MDMA plus THC condition compared with the placebo and MDMA condition. MDMA alone did not affect the Rotor Pursuit task.

Eighteen word list. Immediate recall of words was impaired in all drug conditions compared with placebo. Delayed recall and delayed recognition did not show a significant main effect of drug administration (Figure 2).

N-back task. Performance on the 1-back task was impaired in the THC condition and MDMA plus THC condition compared with the placebo and MDMA condition.

Performance on the 2-back test did not show a significant main effect of drug condition, although drug condition comparisons revealed a trend for impairment of 2-back performance in the THC condition compared with the MDMA condition ($p = 0.053$).

Co-administration of MDMA plus THC impaired 3-back performance compared with placebo. THC administration showed a trend for impairment of 3-back performance compared with placebo ($p = 0.055$) (Figure 2).

Bond and Lader Mood Rating Scale. Subjective alertness was reduced in the THC condition compared with the placebo and the MDMA condition. Although co-administration of MDMA plus THC attenuated this reduction in alertness compared with the THC condition, subjective alertness was still reduced in the MDMA plus THC condition compared with placebo. Subjective contentedness was reduced in the THC condition compared with the placebo as well as the MDMA condition. Co-administration of MDMA plus THC abolished this effect: contentedness after co-administration did not differ compared with the placebo or the MDMA condition. Subjective calmness was reduced in the MDMA condition and the MDMA plus THC condition compared with the placebo and THC condition. THC did not affect calmness ratings (Figure 3).

Drug liking and Drug strength scale. 'Drug liking' ratings were increased in the MDMA condition and MDMA plus THC condition compared with the placebo and THC condition. 'Drug strength' ratings were increased after all drug conditions compared with placebo. Co-administration of THC plus MDMA further increased ratings of drug strength compared with the MDMA condition.

Motivation was decreased in the THC condition compared with the placebo, MDMA, and MDMA plus THC condition. In other words, co-administration of MDMA with THC reversed the THC-induced reduction of motivation.

Bowdle scale. All drug conditions increased ratings of internal and external perception compared with placebo. Co-administration of THC plus MDMA increased both internal and external perception compared with the placebo as well as MDMA condition, and external perception also increased compared with the THC condition. Ratings of 'feeling high' were increased in all drug conditions compared with placebo. 'Feeling high' ratings showed a more robust increase in the THC condition compared with the MDMA condition, and co-administration of THC plus MDMA further increased subjective 'feeling high' compared with the MDMA condition (but not compared with the THC condition). Feeling 'drowsy' scores were increased in the THC as well as the MDMA plus THC condition compared with placebo.

Discussion

This study assessed the cognitive and subjective effects of co-administration of MDMA and THC in humans, a frequent recreational drug combination. As MDMA is a

Table 2. THC, 11-OH-THC and 11-nor-9-carboxy-THC plasma concentrations, 5 min after drug administration (in ng/ml): [mean (SEM)]

Condition	Dose	THC	11-OH-THC	11-nor-9-carboxy-THC
THC	4 mg	59.7 (5.6)	2.8 (0.9)	8.4 (0.8)
MDMA + THC		53.8 (6.9)	2.9 (0.8)	9.2 (1.2)
THC	6 mg (1st)	84.5 (9.0)	3.7 (1.0)	16.0 (1.9)
MDMA + THC		84.6 (8.6)	4.7 (1.0)	18.5 (1.7)
THC	6 mg (2nd)	74.8 (6.9)	4.8 (1.2)	20.6 (1.5)
MDMA + THC		73.3 (7.1)	6.9 (1.3)	21.7 (2.6)

THC: Δ^9-tetrahydrocannabinol; MDMA: 3,4-methylenedioxymethamphetamine.

Table 3. Results, main effects, and drug comparisons (reported are mean difference, 95% CI and *p*-value)

| Test	Treatment effect	Time effect	Treatment by time interaction	THC vs Plac	MDMA vs Plac	MDMA +THC vs Plac	MDMA +THC vs MDMA	MDMA +THC vs THC	MDMA vs THC
Psychomotor									
Body sway (mm)	<0.0001	0.0468	<0.0001	70.7% (43.1–103.7%); <0.0001	27.8% (7.7–51.6%); 0.0063	58.2% (32.3–89.0%); <0.0001	23.8% (3.9–47.5%); 0.0185	ns	−25.2% (−37.1% to −11.0%); 0.0017
Smooth pursuit (%)	ns	0.0068	0.0475	ns	ns	ns	ns	3.3 (0.4, 6.3); 0.0274	3.3 (0.4, 6.2); 0.0262
Peak velocity ($°$/s)	<0.0001	0.0374	<0.0001	ns	51.3 (35.7, 66.9); <0.0001	46.3 (30.6, 62.0); <0.0001	ns	36.6 (20.6, 52.5); <0.0001	41.5 (25.6, 57.5); <0.0001
Reaction time (ms)	ns	ns	ns						
Rotor pursuit (no. of circles)	<0.0001	ns	ns	−3.2 (−4.6 to −1.8); <0.0001	ns	−2.6 (−4.0 to −1.2); 0.0007	−2.5 (−3.9 to −1.1); 0.0010	ns	3.1 (1.7, 4.5); <0.0001
Memory									
Immediate recall (no. of words)	F(3, 36.2) = 6.94; 0.0008			−2.17 (−3,4 to −0.9); 0.0011	−1.41 (−2.6 to −0.2); 0.0213	−2.48 (−3.7 to −1.3); 0.0002	ns	ns	ns
Delayed recall (no. of words)	ns								
Delayed recognition (no. of words)	ns								
1-back task (s)	0.0073	0.0212	ns	1.9 (0.6, 3.2); 0.0048	ns	1.9 (0.7, 3.2); 0.0042	1.3 (0.0, 2.6); 0.0434	ns	−1.3 (−2.5 to −0.0); 0.0488
2-back task (s)	ns	0.0041	ns	ns	ns	ns	ns	ns	ns
3-back task (s)	0.0164	ns	ns	ns	ns	5.0 (2.0, 8.0); *p* = 0.0018	ns	ns	ns

Table 3. Continued

Test	Treatment effect	Time effect	Treatment by time interaction	THC vs Plac	MDMA vs Plac	MDMA+THC vs Plac	MDMA+THC vs MDMA	MDMA+THC vs THC	MDMA vs THC
Subjective (cm)									
Bond and Lader Alertness	<0.0001	0.0016	0.0002	−2.86 (−3.75 to −1.96); <0.0001	ns	−1.38 (−2.28 to −.489); 0.0033	ns	1.473 (0.571, 2.375); 0.0020	2.346 (1.453, 3.238); <0.0001
Contentedness	<0.0001	0.0312	ns	−1.09 (−1.54 to −0.65); <0.0001	ns	ns	ns	0.91 (0.45, 1.36); 0.0003	0.99 (0.55, 1.43); <0.0001
Calmness	<0.0001	<0.0001	<0.0001	ns	−1.78 (−2.75 to −0.82); 0.0006	−2.58 (−3.53 to −1.63); <0.0001	ns	−2.02 (−2.98 to −1.07); 0.0001	−1.23 (−2.19 to −0.27); 0.0133
Bowdle Internal perception	0.0004	<0.0001	0.0016	0.4 (0.2, 0.7); $p=0.0037$	0.4 (0.1, 0.7); $p=0.0159$	0.7 (0.4, 1.0); $p=<0.0001$	0.3 (0.0, 0.6); $p=0.0365$	ns	ns
External perception	<0.0001	<0.0001	<0.0001	1.0 (0.6, 1.4); <0.0001	0.8 (0.4, 1.2); 0.0002	1.6 (1.2, 2.0); <0.0001	0.8 (0.4, 1.2); 0.0005	0.6 (0.2, 1.0); 0.0058	ns
Feeling high	<0.0001	<0.0001	<0.0001	4.6 (3.4, 5.9); <0.0001	1.7 (0.4, 2.9); 0.0092	4.8 (3.4, 6.1); <0.0001	3.1 (1.8, 4.4); <0.0001	ns	−2.9 (−4.2 to −1.7); <0.0001
Drowsy	0.0020	ns	ns	2.2 (0.9, 3.4); 0.0011	ns	2.2 (1.0, 3.5); 0.0008	ns	ns	ns
Drug experience Drug liking	<0.0001	0.0020	0.0127	ns	2.4 (1.4, 3.3); <0.0001	2.1 (1.1, 3.1); <0.0001	ns	1.7 (0.7, 2.7); 0.0016	1.9 (0.9, 2.9); 0.0003
Drug strength	<0.0001	<0.0001	<0.0001	2.0 (1.4, 2.6); <0.0001	1.5 (0.9, 2.1); <0.0001	2.4 (1.7, 3.0); <0.0001	0.9 (0.3, 1.5); 0.0049	ns	ns
Motivation	0.0038	0.0025	0.0263	−1.2 (−1.9 to −0.5); 0.0020	ns	ns	ns	1.0 (0.2, 1.7); 0.0121	1.3 (0.6, 2.0); 0.0010

THC: Δ^9-tetrahydrocannabinol; MDMA: 3,4-methylenedioxymethamphetamine; Plac: placebo; MDMA+THC: MDMA and THC co-administration.
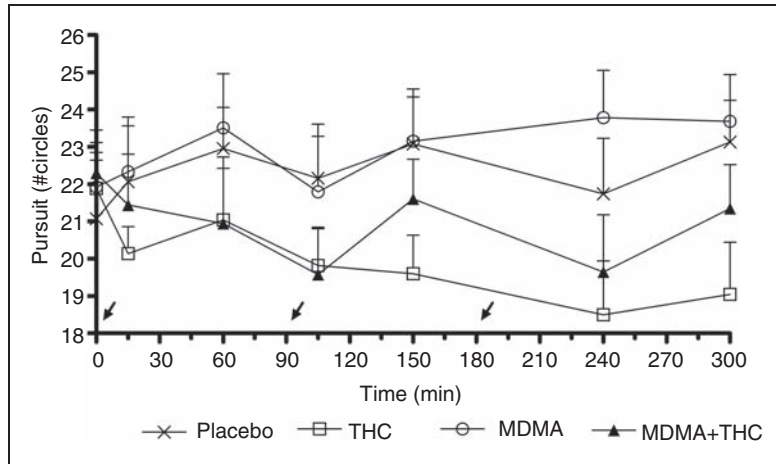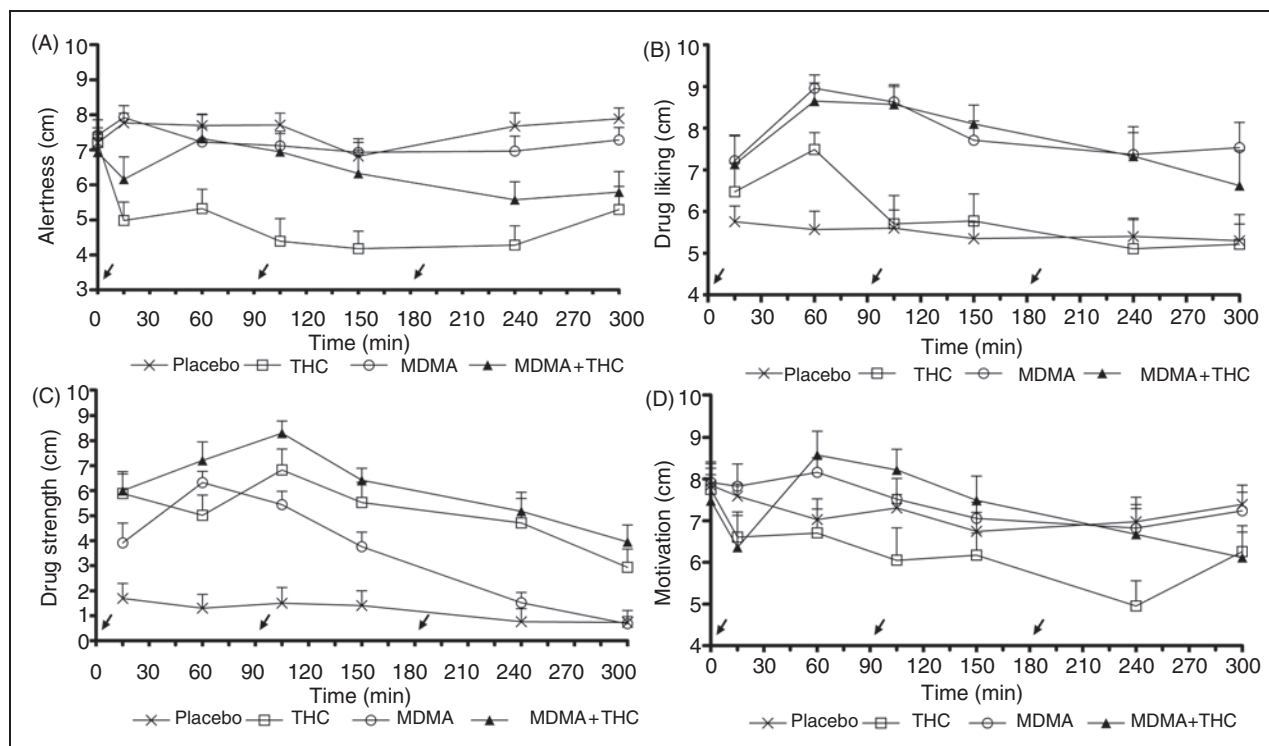
Figure 1 Rotor pursuit task scores per drug condition (mean, SEM). Arrows indicate Δ^9-tetrahydrocannabinol (THC) administration ($t=0$ (4 mg), $t=90$ (6 mg), and $t=180$ (6 mg) min).
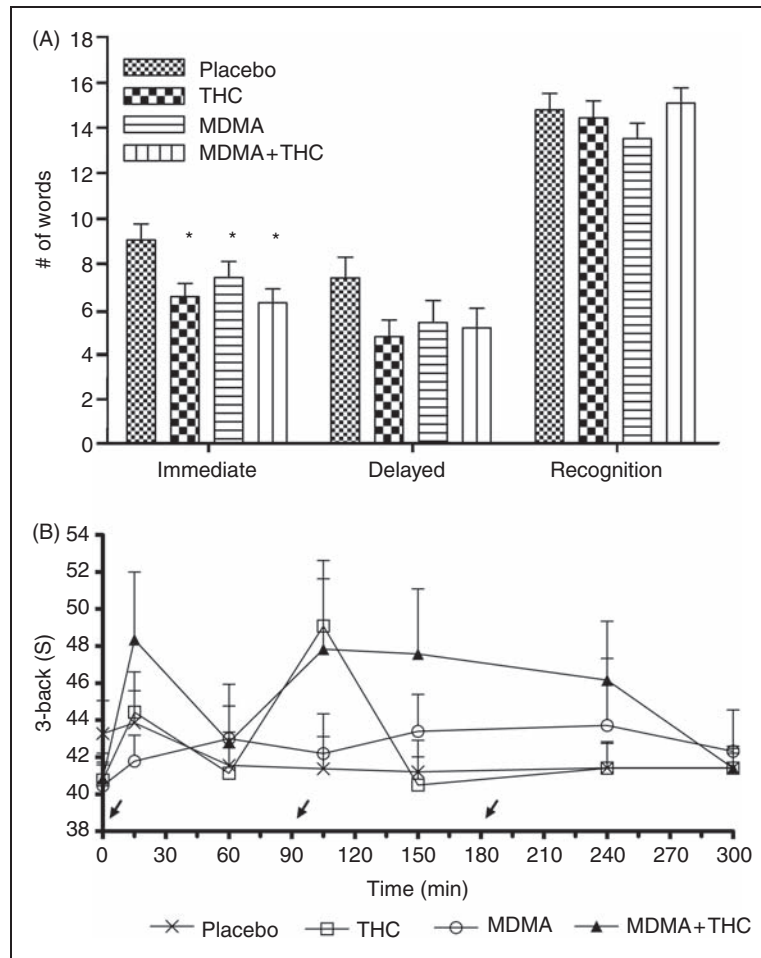
Figure 2 Memory effects. (A) 18 word list results per drug condition (mean, SEM, *$p < 0.05$). Arrows indicate Δ^9-tetrahydrocannabinol (THC) administration ($t=0$ (4 mg), $t=90$ (6 mg), and $t=180$ (6 mg) min). Immediate: average number of words immediately recalled over three consecutive immediate recall trials; Delayed: words recalled after a delay of 20 min; Recognition: number of words recognized among 18 distractor words. (B) Working memory: 3-back results per drug condition (mean, SEM). Arrows indicate THC administration ($t=0$ (4 mg), $t=90$ (6 mg), and $t=180$ (6 mg) min).

Figure 3 Subjective effects. Arrows indicate Δ^9-tetrahydrocannabinol (THC) administration ($t = 0$ (4 mg), $t = 90$ (6 mg), and $t = 180$ (6 mg) min).
(A) Subjective alertness (mean, SEM). (B) Subjective drug liking (mean, SEM). (C) Subjective drug strength (mean, SEM). (D) Subjective motivation (mean, SEM).

psychostimulant, while THC generally impairs psychomotor function, psychomotor effects of these substances separately were expected to be attenuated after co-administration. However, results show that MDMA generally could not attenuate THC's impairment of psychomotor function.

Rotor pursuit performance was impaired by THC administration. This is in agreement with previous findings, where THC moderately impaired driving-related performance (Weinstein et al., 2008), and actual driving behaviour (Ramaekers et al., 2000). THC also robustly impaired postural stability, an effect that has been reported previously (Zuurman et al., 2008). MDMA had no effect on rotor pursuit performance, but it increased body sway, albeit to a lesser extent than THC. Co-administration of MDMA and THC further impaired rotor pursuit performance and postural stability compared with MDMA, but not compared with THC, indicating that the detrimental effects of THC prevailed. Direct comparison of the MDMA condition with the THC condition also showed that the effect of THC on rotor pursuit performance and postural stability was more robust.

Although psychomotor performance was impaired by THC, THC did not affect eye movements, which confirms previous reports (Ploner et al., 2002; Zuurman et al., 2008), and is congruent with cannabinoid receptor distribution patterns: eye movements are primarily driven by brain stem areas, which show little CB_1 receptor expression (Zuurman et al., 2008). MDMA on the other hand increased saccadic peak velocity but not accuracy, which is also in line with a previous study (Dumont et al., 2007). Effects of co-administration of MDMA

and THC were similar to those observed in the MDMA only condition.

The effects of THC and MDMA on memory were complex. Both THC and MDMA impaired word recall: immediate recall of words was significantly reduced in both single drug conditions. Delayed recall and recognition were unaffected by drug administration. Previous results regarding THC effects on memory generally are congruent with our results, where THC impaired immediate (Curran et al., 2002; D'Souza et al., 2004; Hart et al., 2001; Heishman et al., 1997; Morrison et al., 2009) but also delayed recall (Curran et al., 2002; D'Souza et al., 2004) of a word list. MDMA's impairment of word list performance in the current study was comparable in size to the effects reported earlier. However, in a previous study the reduction of immediate recall failed to reach significance, whereas impaired delayed recall did (Dumont et al., 2008). Reports by Kuypers and Ramaekers (2005, 2007) showed acute impairment of both immediate and delayed recall of words as well as spatial memory by MDMA. Co-administration of MDMA and THC did not exacerbate impairment of word list recall compared with either drug alone.

As previous (animal) research showed that co-administration of MDMA and THC induced a synergistic impairment of working memory (Young et al., 2005), co-administration was expected to show additive impairment on tests of working memory compared with single drug effects. However, the effects of these substances on the N-back task, a test of working memory, were subtle and

did not appear to be additive, although the complexity of THC-induced impairment warrants further research regarding this topic. The effects of THC on the N-back working memory task were time and dose dependent, where THC generally induced a robust but short-lived impairment of working memory. The 2-back condition did not show an effect of drug administration. THC impaired performance in the 1-back condition and showed a trend of impairment ($p = 0.055$) in the 3-back condition, congruent with previous reports where THC impaired working memory (D'Souza et al., 2004; Ilan et al., 2004), although Curran et al. (2002) found no effect of THC on working memory using the serial sevens task. The discrepancy of THC effects on 2- and 3-back performance versus the 1-back performance may be explained by the fact that the 1-back condition may assess psychomotor function rather than working memory as subjects only have to locate the dot that lit-up, that is, performance will primarily be determined by the time the subject needs to reach the target, rather than correctly memorizing which dot lit up n times before. In this sense, these results may reflect THC-induced impairment of psychomotor function rather than working memory. A recent systematic literature review also showed complex effects of THC/cannabis on working memory, with possible indications for an inverse dose–response relationship (Zuurman et al., 2009).

N-back performance was unaffected in the MDMA condition. Co-administration of MDMA and THC impaired 1-back and 3-back performance. Although THC alone did not significantly impair 3-back performance, the observed trend suggests that the impairment of n-back performance after co-administration was driven primarily by THC, and co-administration of MDMA and THC did not, contrary to our hypothesis, exacerbate single drug-induced memory impairment.

These results suggest that THC may exert much of its cognitive impairment via a common mechanism of reduced alertness. This is in line with its classification as a relaxant/sedative drug, and with reports that show that subjects are able to compensate for these impairments at the cost of greater effort (Curran et al., 2002). The stimulant effects of MDMA may attenuate this effect, but could not overcome THC-induced impairments in the current study. Subjective ratings show that the subjects were aware of these impairments: THC increased subjective ratings of feeling 'drowsy', and reduced ratings of 'motivation' and 'alertness'. Co-administration of MDMA reversed the THC-induced reduction of subjective motivation, and attenuated the reduction of alertness by THC, although the latter was still significantly decreased after co-administration compared with placebo. The fact that subjects reported that THC reduced subjective alertness may be of significance when driving while intoxicated. Subjects who report reduced alertness are likely to adapt their behaviour, thus reducing the risk of traffic accidents (Ronen et al., 2008; Sewell et al., 2009).

Subjective effects further suggest that the combination may be popular because it enhances the pleasurable subjective effects of each drug alone. Both THC and MDMA-induced robust subjective drug effects and increased subjective ratings of 'feeling high', internal perception (reflecting inner feelings not corresponding to reality) and external perception (reflecting a misperception of an external stimulus or a change in the awareness of the subject's surroundings), and both were comparable in 'drug strength'. MDMA increased subjective 'drug liking', whereas in the THC condition 'drug liking' ratings appeared inversely dose-related: 'drug liking' was robustly decreased after the high THC dose (6 mg) compared with the lower dose (4 mg). Congruent with drug liking ratings, subjective contentedness was dose-dependently reduced in the THC condition. This apparent inverse dose–response relationship is in line with an overall assessment of the literature on the effects of cannabis/THC (Zuurman et al., 2009). Co-administration of THC and MDMA enhanced subjective drug effects: ratings of 'drug strength', 'internal and external perception' and 'feeling high' were increased compared with the MDMA condition, whereas ratings of 'contendedness', 'external perception' and 'drug liking' were increased compared with the THC condition. The perceived increase of drug strength, combined with enhanced sensory drug effects, without an unacceptable decrease of cognitive function, offers a plausible incentive for combining cannabis with ecstasy in recreational settings. Some caution should be taken into account, as the 'drug liking' ratings after co-administration were comparable to MDMA alone. However, MDMA alone increased drug liking rating to near maximal values, which may point to ceiling effects explaining this discrepancy.

Some limitations should be addressed. In the current study, some effects of THC on memory failed to reach significance (although trends were observed). It is likely this may be related to the short-lived effects of THC on memory. As can be seen in Figure 2, the effects of THC on memory were robust around 15 min but were diminished 60 min after drug administration, a pattern that could be observed after all three doses, although memory was assessed 60 min after the third dose only. This suggestion is congruent with previous studies showing that THC impaired N-back task performance 20 but not 60 min after THC administration (Ilan et al., 2004), and that THC-induced impairment of immediate recall was the strongest in the period immediately after drug administration (Heishman et al., 1997). Future studies with more frequent test intervals relative to drug administration are recommended to elucidate the time profile and possible dose dependency of THC-induced memory impairment. Alternatively, as we recruited volunteers with considerable cannabis use (on average two or more exposures per week), subjects may have developed tolerance to some of the cognitive effects of cannabis (D'Souza et al., 2008).

This also points to another limitation of our study. To maintain a stable effect level of THC during co-administration of MDMA, we assessed the effects of a single dose of MDMA and three consecutive vaporized THC doses. Effects may differ depending on the dose assessed, the timing of drug administration, the order in which drugs are used and the method of drug delivery (i.e. vaporized THC vs smoked cannabis). Our approach cannot be considered fully representative of all modes of combined drug use in practice. In general, the circumstances in which these substances are normally used cannot be fully recreated in the laboratory, although they may influence the effects of MDMA (Sumnall et al., 2006). However, the doses of each drug used in this study

were similar to normal recreational use. In this sense, the current study sets a relevant benchmark for future evaluations of other dose combinations.

In conclusion, our study shows that co-administration of MDMA and THC did not exacerbate single drug-induced cognitive impairment. Compared with MDMA (100 mg), THC (4, 6 and 6 mg) induced more robust impairment of cognitive function. Subjective effects show that subjects were aware of these impairments, and that the combination of THC with MDMA enhanced the perceived drug strength and desired drug effects compared with the MDMA condition. These results suggest that cannabis increases the desired effects of ecstasy without an unpredictable increase in cognitive impairment, which may explain the widespread recreational use of this combination.

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