Original Paper

Psychedelic symptoms of cannabis and cocaine use as a function of trait impulsivity

Journal of Psychopharmacology
2015, Vol. 29(3) 324–334

DOI: 10.1177/0269881114563633
jop.sagepub.com

JHP van Wel[1], DB Spronk[2,3], KPC Kuypers[1], EL Theunissen[1], SW Toennes[4], RJ Verkes[2,3] and JG Ramaekers[1]

Abstract

Trait impulsivity has been linked to addiction in humans. It has been suggested that drug users with high trait impulsivity levels are more sensitive to subjective drug intoxication. This study assessed whether subjective response to drugs differs between drug users with normal or high levels of trait impulsivity. Regular drug users ($N = 122$) received doses of cocaine HCl, cannabis, and placebo in a three-way crossover study. Their mood, dissociative state, and psychedelic symptoms were measured with subjective rating scales (CADDS, Bowdle, POMS). Trait impulsivity was assessed with the Barratt Impulsiveness Scale. Cannabis increased dissociation and psychedelic state, as well as fatigue, confusion, depression and anxiety, and decreased arousal, positive mood, vigor, friendliness, and elation. Cocaine increased dissociation, psychedelic state, vigor, friendliness, elation, positive mood, anxiety and arousal, while decreasing fatigue. Only a few subjective items revealed a drug × trait impulsivity interaction, suggesting that psychedelic symptoms were most intense in high impulsivity subjects. Trait impulsiveness ratings were negatively correlated with ratings of vigor ($r = -.197$) and positively correlated with ratings of loss of thought control ($r = .237$) during cannabis intoxication. It is concluded that a broad association between trait impulsivity and psychedelic subjective drug experience appears to be absent.

Keywords

Cocaine, cannabis, subjective intoxication, addiction, impulsivity

Introduction

Impulsivity refers to actions that are poorly conceived, risky, or premature and that may result in unfavorable outcomes (Evenden, 1999; Stanford et al., 2009). Pathological forms of impulsivity may contribute to the etiology of mental disorders such as addiction (De Wit, 2008). A range of animal studies have shown that an association exists between trait impulsivity and addiction (Belin et al., 2008; Economidou et al., 2009). Rats with higher trait impulsivity were more likely to score higher on measures of addiction, e.g. self-administration rates, following drug intake than animals with lower impulsivity scores. The same has been shown in humans. Persons exhibiting high levels of trait impulsivity are more susceptible to substance abuse and display increased relapse rates after drug abstinence (Pattij and De Vries, 2013). Also, among drug addicts, comorbidity with other mental disorders associated with pathological impulsivity such as ADHD (Wilens and Morrison, 2011) and bipolar disorder (Pettinati et al., 2013) is very high.

Cannabis and cocaine are respectively the first and second most used drugs in the European Union (EMCDDA, 2012). Although mood and psychedelic effects after cannabis administration have been extensively investigated (Battistella et al., 2013; D'Souza et al., 2008; Henquet et al., 2010; Lex et al., 1984; Ramaekers et al., 2006a; Toennes et al., 2008), there is a relative paucity in psychedelic subjective data after cocaine administration. It has been shown that cocaine administration has a stimulating effect on mood (Cascella et al., 1994; Penetar et al., 2006; Rush et al., 1999; Walsh et al., 2009), but these studies mainly measured general drug effects such as "feeling good" and "wanting to take again." Also, although epidemiological evidence has associated extensive cocaine use with psychotic disorders (Morton, 1999; Roncero et al., 2012) and medication with a similar mechanism of action as cocaine, such as dexamphetamine and methylphenidate, has been shown to increase the likelihood of psychotic symptoms (Curran et al., 2004), no studies so far have investigated the acute effects of cocaine on measures of dissociation or psychedelic symptoms.

[1]Department of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands
[2]Department of Psychiatry (966), Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[3]Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, The Netherlands
[4]Department of Forensic Toxicology, Institute of Legal Medicine, Goethe University of Frankfurt, Frankfurt, Germany

Corresponding author:
JG Ramaekers, Department of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, 6229ER, The Netherlands.
Email: j.ramaekers@maastrichtuniversity.nl

Likewise, only few studies have assessed the role of trait impulsivity on the subjective experience of drug intoxication. For example, high trait impulsivity was significantly associated with greater arousal and euphoria following administration of D-amphetamine (Cascella et al., 1994; Kirkpatrick et al., 2013), but another study found no effect of trait impulsivity on mood (White et al., 2006). In the present study, we examined whether the level of trait impulsivity (normal or high) influences the subjective response to acute administration of cannabis or cocaine. We hypothesized that administration of cannabis and cocaine to high impulsive subjects would evoke more intense subjective effects as compared to normal impulsive subjects. Increased sensitivity to subjective effects of cannabis and cocaine may be particularly relevant in the realm of drug addiction and contribute to an individual's desire to seek drugs. Subjective measures of mood, dissociative state and psychedelic symptom scales were used to assess psychological states during drug intoxication.

Materials and methods

Subjects

122 healthy regular users of both cannabis and cocaine (96 male, 26 female; mean (SD) age 22.84 (3.69)) participated at two centers, Maastricht and Nijmegen. In Maastricht, subjects used cannabis on average 51.20 times in the past 3 months, while cocaine was used 4.53 times in the past 3 months. In Nijmegen, subjects used cannabis and cocaine 39.00 and 2.74 times respectively in the past 3 months. Overall, cannabis was used 44.78 times in the past 3 months and cocaine was used 3.68 times in the past 3 months. Participants also indicated having used other substances in their lives, i.e. 88% used XTC, 73% used amphetamines, 61% used mushrooms, 20% used LSD, and 59% used other drugs including but not limited to nitrous oxide, MDMA crystals, DMT, and ketamine.

Subjects were recruited through advertisements in local newspapers and by word of mouth. Before inclusion, subjects were examined by a physician. They were checked for general health and blood and urine samples were taken for standard chemistry and hematology. Inclusion criteria were: written informed consent; age 18–40 year; regular cannabis use: ≥ 2 times/week; have used cocaine at least 5 times in the past year; free from psychotropic medication; good physical health; normal weight (BMI 18–28). Exclusion criteria were: cocaine dependence according to DSM-IV criteria; presence or history of psychiatric or neurological disorder as assessed during a clinical interview; pregnancy or lactating; cardiovascular abnormalities; excessive drinking (>20 units/week) or smoking (>20 cigarettes/day); and hypertension.

This study was part of a larger trial on the association between drug use and impulse control (see Dutch Trial Register, trial number NTR2127) conducted according to the code of ethics on human experimentation established by the declaration of Helsinki (1964) and amended in Seoul (2008) and was approved by the Medical Ethics Committee of the Academic Hospital of Maastricht and Maastricht University. A permit for obtaining, storing and administering cocaine and cannabis was obtained from the Dutch drug enforcement administration. Subjects were paid for their participation in the study.

Design, doses, and administration

Subjects participated in a double-blind, placebo-controlled, double-dummy, three-way crossover study. Treatments were placebo, 450 µg/kg THC (cannabis plant material, divided in two doses of 300 and 150 µg/kg), as well as 300 mg cocaine HCl. In the Nijmegen center, a booster dose of 150 mg cocaine was given to a subset of subjects. Cannabis was administered using a vaporizer (Volcano) obtained from Storz & Bickel GmbH & Co (Tuttlingen, Germany) and was used according to the manual provided by the producer. Cannabis inhalation took place in a standardized manner (Hazekamp et al., 2006). The vapor was prepared from batches varying between 11–12% THC, a standard potency for cannabis sold at Dutch pharmacies. The varying potency was adjusted for in the weighing of the plant material. Cocaine HCl or placebo was administered in an opaque white capsule. Conditions were separated by a minimum wash-out period of 7 days to avoid cross-condition contamination. Order of conditions was balanced over subjects and sessions.

Procedures

Prior to experimental sessions, subjects were familiarized with procedures on a separate training day. Subjects had to refrain from all drugs of abuse (except cannabis) at least a week before the start of the experiment until study end.

A test-day started with a urine drug screen to assess the presence of benzodiazepines, opiates, cocaine, marijuana, MDMA, and (meth)amphetamine and a breath alcohol screen; female subjects underwent an additional pregnancy test. If negative for substances (except cannabis) and pregnancy, subjects could proceed with breakfast. This was followed by vital sign measurements and blood samples. Immediately hereafter, subjects received a capsule containing either 300 mg cocaine HCl or placebo orally (T0). Forty-five minutes after T0, subjects inhaled 300 µg/kg cannabis or placebo (T1). Immediately after T1, vital signs were measured, blood samples were taken, and the Profile of Mood States (POMS) questionnaire was administered. One hour after T1, a second dose THC 150 µg/kg or placebo was given (T2). In the Nijmegen center a subset (N = 47) of subjects received a second dose of cocaine 150 mg HCl just prior to administration of B-VAS. The aim of that booster dose was to prolong cocaine concentrations during task performance that were conducted after completion of the questionnaires and that will be reported elsewhere. As such the booster dose was not expected to affect B-VAS ratings because both were administered concurrently but it might have affected CADSS ratings in this subsample since these were taken 2 hours post the booster dose. At this time, blood samples were also taken. For a schematic representation of the testing day, see Figure 1.

Questionnaires

Barratt Impulsiveness Scale. The Barratt Impulsiveness Scale version 11 (BIS-11) is a 30-item self-report instrument designed to assess trait impulsiveness (Stanford et al., 2009). The BIS-11 has three subscales: (1) motor impulsivity, or acting without thinking; (2) attentional impulsiveness, inability to focus attention; and (3) non-planning, or not thinking carefully. Taken

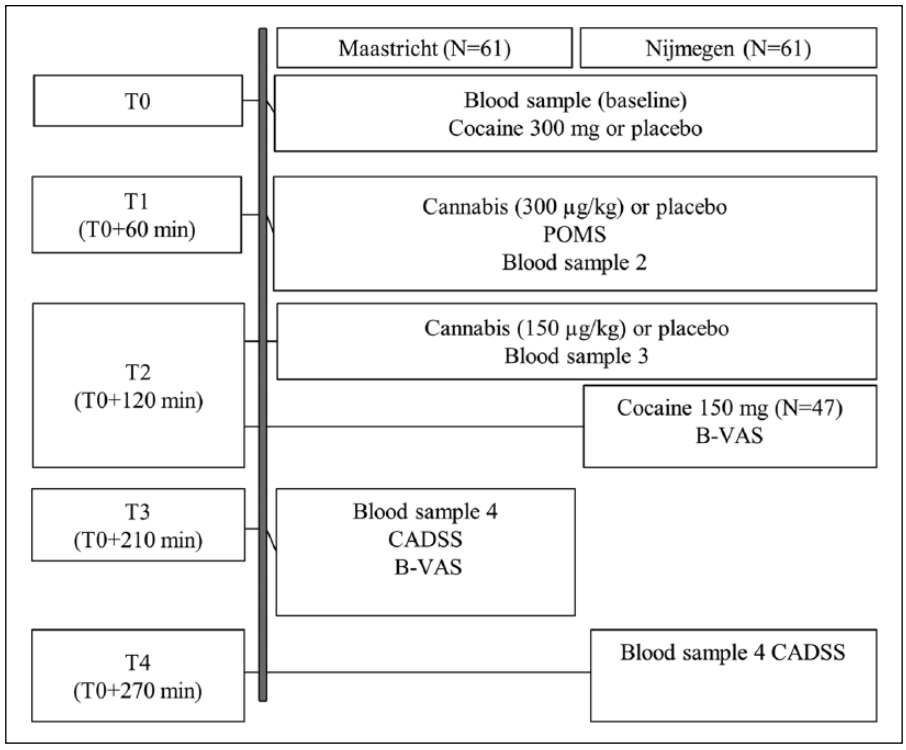

Figure 1. Schematic representation of a testing day. On the left the time is indicated from T0 to T4. On the right, the procedure per center is presented. Each study drug (cannabis, cocaine, or placebo) was administered to every participant in a randomized manner on one of three testing days.

together these subscales form a total impulsivity score. A total score of 72 or above is taken as an indication of high impulsiveness, scores between 52 and 71 are indicative of normal impulsiveness, and scores lower than 52 are representative of an individual that is unusually over-controlled or who has not honestly completed the questionnaire (Stanford et al., 2009). The BIS total score was taken as the main dependent variable to define overall trait impulsivity of study participants. The BIS-11 was administered during the training session.

Bowdle Visual Analog Scales. To assess the psychedelic effects of cannabis and cocaine, a 13-item Visual Analog Scale (B-VAS) first described in Bowdle et al. (1998) was employed. From the B-VAS, composite scores of "internal perception" (five items) and "external perception" (six items) were calculated, as described in Zuurman et al. (2008) (see Table 1). In addition, all 13 items were analyzed separately.

Profile of Mood States. The Profile of Mood States (POMS) is a self-assessment mood questionnaire with 72 items, rated on a 5-point Likert scale, with 0 being "not at all" to 4 "extremely." Subjects had to indicate to what extent these items were representative of their mood at that moment in time. Eight mood states are classified and quantified by calculating the sum score of associated items for each mood state, i.e. anxiety (9 items), depression (15 items), anger (12 items), vigor (8 items), fatigue (7 items), confusion (7 items), friendliness (8 items) and elation (6 items). Two composite scales were derived; arousal ((anxiety + vigor) − (fatigue + confusion)) and positive mood (elation − depression) (De Wit et al., 2002).

Clinician Administered Dissociative States Scale. The Clinician Administered Dissociative States Scale (CADSS) (Bremner et al., 1998) comprises 19 subjective items, ranging from 0 "not at all" to 4 "extremely." It is divided into three components: (1) depersonalization; (2) derealization; and 3) amnesia. Summed together, these subscales form a total dissociative score. The CADSS is specifically designed to be a standardized measure of present-state dissociative symptomatology.

Pharmacokinetic assessments

Blood samples to assess drug concentrations were taken directly after T2 and 2 hours after T2. Blood samples were centrifuged at 3500 rpm and serum was frozen at −20°C until analysis for pharmacokinetic assessments. For cannabinoid determinations, serum was used (Serum-Gel Vacuette system of Greiner Bio-One, Alphen a/d Rijn), whereas cocaine and metabolites were determined in plasma (Glucose FX Vacuette system containing 2.5 mg/mL sodium fluoride and 2 mg/mL potassium oxalate). The determination of Δ^9-tetrahydrocannabinol (THC), 11-hydroxy-THC (THC-OH), 11-nor-9-carboxy-THC (THC-COOH), cocaine (COC), benzoylecgonine (BZE), and ecgonine methyl ester (EME) in plasma was performed in a specialized forensic-toxicological laboratory using validated procedures (Toennes et al., 2005, 2008).

Statistics

All questionnaires were analyzed with SPSS 18.0. First general linear model (GLM) analyses were conducted using repeated

Table 1. Total mean (SE) B-VAS scores in every treatment condition and a summary of significant changes induced by cannabis, cocaine, and their interaction with impulsivity as indicated by GLM drug–placebo contrast analyses.

Barratt score	Mean (SE)						GLM *p* (F)			
	Placebo		Cannabis		Cocaine		Cannabis	Cannabis × impulsivity	Cocaine	Cocaine × impulsivity
	Normal	*High*	*Normal*	*High*	*Normal*	*High*				
Bowdle										
1: My body or body parts seemed to change shape or position	.07 (.07)	.14 (.08)	0.76 (.25)	1.36 (.28)	.20 (.19)	.70 (.21)	<.001 (30.66)	–	.001 (7.74)	–
2: My surroundings seemed to change in size, depth, or shape	.10 (.05)	.07 (.05)	1.24 (.29)	1.76 (.33)	.29 (.16)	.71 (.18)	<.001 (40.39)	–	<.001(12.40)	–
3: Passing of time was altered	.47 (.17)	.57 (.39)	3.17 (.39)	3.18 (.45)	2.23 (.33)	2.12 (.38)	<.001 (39.57)	–	<.001 (8.39)	–
4: I had feelings of unreality	.25 (.10)	.25 (.11)	1.95 (.36)	2.13 (.40)	.89 (.20)	.79 (.23)	<.001 (43.55)	–	<.001 (16.80)	–
5: It was difficult to control my thoughts	.70 (.17)	.73 (.19)	2.84 (.40)	4.21 (.45)	2.58 (.36)	2.27 (.40)	<.001 (81.77)	.03 (4.70)	<.001 (38. 40)	–
6: Color intensity change	.16 (.09)	.32 (.10)	1.86 (.32)	2.32 (.36)	.98 (.22)	.69 (.24)	<.001 (57.46)	–	<.001 (12.85)	–
7: Sound intensity change	.22 (.11)	.35 (.12)	2.62 (.35)	2.64 (.39)	1.05 (.25)	1.36 (.28)	<.001 (75.25)	–	<.001 (21.77)	–
8: I heard voices and sounds that were not real	.03 (.02)	.04 (.02)	.29 (.16)	.50 (.18)	.04 (.03)	.06 (.02)	<.001 (9.03)	–	–	–
9: I had the idea that events, objects, or other people had particular meaning that was specific for me	.10 (.07)	.00 (.08)	.39 (.23)	1.07 (.26)	.16 (.05)	.10 (.06)	<.001 (13.74)	.03 (4.65)	–	–
10: I had suspicious ideas or the belief that others were against me	.03 (.03)	.07 (.04)	.79 (.54)	.89 (.28)	.30 (.11)	.20 (.12)	<.001 (16.90)	–	.02 (6.09)	–
11: I felt high	.54 (.14)	.31 (.16)	6.29 (.38)	6.17 (.42)	3.11 (.41)	2.73 (.46)	<.001 (378.42)	–	<.001 (68.81)	–
12: I felt drowsy	1.20 (.26)	1.05 (.29)	2.71 (.40)	3.00 (.45)	1.16 (.24)	1.30 (.27)	<.001 (29.79)	–	–	–
13: I felt anxious	.10 (.04)	.12 (.05)	1.33 (.29)	1.45 (.32)	.62 (.16)	.41 (.18)	<.001 (36.09)	–	<.001 (12.16)	–
Internal perception[a]	.10 (.04)	.10 (.04)	.95 (.20)	1.21 (.22)	.40 (.09)	.31 (.09)	<.001 (44.61)	–	<.001 (18.52)	–
External perception[b]	.29 (.07)	.36 (.08)	2.06 (.24)	2.59 (.27)	1.23 (.15)	1.31 (.17)	<.001 (105.88)	–	<.01 (61.81)	–

[a]Internal perception = (VAS1 + VAS2 + VAS3 + VAS5 + VAS6 + VAS7)/6.
[b]External perception = (VAS4 + VAS8 + VAS9 + VAS10 + VAS13)/5.

measures analysis of variance (ANOVA) with drug (three levels) as within subject factor and center (Maastricht vs. Nijmegen) as between subjects factor in order to check for treatment differences between the two centers. In case of a significant difference between centers, correlation analyses between those variables and THC serum concentration and cannabis use history were conducted. Further GLM ANOVAs were done with drug (three levels) as within subject factor, trait impulsivity (two levels: high vs. normal) as between subjects factor, and drug × impulsivity as the interaction term. If the sphericity assumption was violated, the Greenhouse–Geisser correction was used. In case of significant overall effect of drug or drug × impulsivity, separate drug–placebo contrasts were conducted to establish the effects of cannabis and cocaine (cannabis vs. placebo and cocaine vs. placebo) and their interaction with impulsivity level (cannabis vs. placebo * impulsivity score, cocaine vs. placebo * impulsivity score). A sequential Bonferroni procedure was applied to correct for multiple testing. The alpha criterion level of significance was set at $p = 0.05$. Correlational analysis between subjective ratings and individual Barratt impulsiveness score were conducted to assess their association over a continuous impulsiveness scale for each treatment condition separately.

Finally, a hierarchical regression analysis was conducted to assess the effect of trait impulsivity (as a continuous variable), up and above those of drug while controlling for cannabis use history and treatment center. The analysis was conducted as a confirmation of results from GLM models and to determine the amount variance explained by each of the factors. In the hierarchical regression model cannabis use history and treatment center (model 1), drugs (model 2) and trait impulsivity (model 3) were successively entered to determine the % of variability accounted for by each of the models.

Results

All subjects for whom complete performance data sets were collected entered the GLM analyses. Complete datasets of the POMS were collected in 121 subjects, the CADSS was complete in 115 subjects and datasets of the B-VAS were complete in 96 subjects. Missing data were due to incomplete data (1 case in the POMS, 5 cases in the CADSS) or adverse effects (nausea) in the cannabis condition (2 cases in the CADSS). The B-VAS results were completed in a subset due to late inclusion of the questionnaire in the study protocol.

Impulsivity score (BIS-11)

Forty-nine subjects had a score of 72 or higher and scored as "high impulsive" on the BIS-11; 71 scored as "normal impulsive" with a score in the range 52–71. Two subjects did not fill out the BIS and could not be contacted to correct this. Trait impulsivity (two levels) was thus included in the statistical model as a between-subjects parameter. Trait impulsivity levels of subjects did not differ between centers ($t_{1,118}$) = .68, $p = .6$).

Bowdle VAS

Mean (SE) B-VAS-scores in every treatment condition and a summary of significant changes induced by cannabis, cocaine, and their interaction with impulsivity as indicated by GLM drug–placebo contrast analyses are given in Table 1.

Overall, all separate items of the B-VAS were affected by drug ($p < .015$). Following drug–placebo contrasts it was shown that both cannabis and cocaine increased the scores for internal and external perception significantly ($p < .001$), with subjects during cannabis intoxication scoring higher than after cocaine administration.

Drug–placebo contrasts showed that cannabis increased subjective rating on all B-VAS items, whereas cocaine increased ratings in about half of the items. Two items reached significance for the cannabis × impulsivity interaction, namely item 5 and 9. High impulsive subjects under the influence of THC had increased difficulty in controlling their thoughts, as well as having the idea that events, objects or other people had particular meaning that was specific for them. Comparison of datasets from the centers revealed that subjective feelings of high following cannabis and cocaine were generally higher in subjects recruited by the Nijmegen center as compared to the Maastricht center. There was no significant correlation between blood concentration of THC or cannabis use history and the item high. No other B-VAS scales were affected by the factor center. Hierarchical regression confirmed the overall drug effect on each of the subscales and identified a main effect of trait impulsivity on "difficulty controlling thoughts" (see Table 2).

POMS

Mean POMS scores in every treatment condition and a summary of significant changes induced by cannabis, cocaine, and their interaction with impulsivity as indicated by GLM drug–placebo contrast analyses are given in Table 3.

Overall analyses revealed an effect of drug on arousal, anxiety, positive mood, confusion, fatigue, elation, vigor, depression and friendliness ($p < .001$). Separate drug–placebo contrasts revealed that subjects under the influence of cannabis showed increased levels of fatigue, confusion, depression and anxiety, while arousal, positive mood, vigor, friendliness, and elation were significantly decreased. Under the influence of cocaine, subjects rated themselves as significantly more vigorous, friendly, elated, anxious, aroused, and as having a higher positive mood. Subjects were also significantly less fatigued after cocaine administration.

The factor Impulsivity did not affect POMS rating, but the interaction between drug × impulsivity reached significance for arousal and approached significance for vigor. However, separate drug-placebo contrasts showed no significant effects.

Comparison of datasets from the centers revealed that subjective feelings differed on almost all subscales of the POMS. Under the influence of cannabis, subjects in Nijmegen had a significantly decreased score on the subscales elation, vigor, friendliness, and arousal. Fatigue, anxiety, and confusion were significantly increased in the Nijmegen center during cannabis intoxication when compared to the Maastricht center. There were no group effects for cocaine. Correlation analyses did not show a relationship between THC concentrations and the subscales of the POMS on which a group effect was shown. However, there was a correlation between cannabis use history and almost every subscale of the POMS. Cannabis use history was inversely correlated with anxiety, depression, anger, fatigue and confusion

Table 2. Total percentage of variance explained (R^2) and R^2 change following addition of drug and trait impulsivity for B-VAS, POMS, and CADSS.

Bowdle scale	Model 1 (cannabis use past 3 months, center)		Model 2 (drug)		Model 3 (trait impulsivity)	
	R^2	R^2 change	R^2	R^2 change	R^2	R^2 change
1: My body or body parts seemed to change shape or position	0.03*	–	0.06	0.03*	0.07	0.01
2: My surroundings seemed to change in size, depth or shape	0.03*	–	0.09	0.07**	0.09	0.00
3: Passing of time was altered	0.01	–	0.03	0.03**	0.04	0.00
4: I had feelings of unreality	0.04*	–	0.11	0.07**	0.11	0.00
5: It was difficult to control my thoughts	0.01	–	0.03	0.03**	0.05	0.01*
6: Color intensity change	0.01	–	0.09	0.08**	0.09	0.00
7: Sound intensity change	0.00	–	0.08	0.08**	0.09	0.00
8: I heard voices and sounds that were not real	0.00	–	0.04	0.04**	0.05	0.00
9: I had the idea that events, objects or other people had particular meaning that was specific for me	0.02*	–	0.07	0.05**	0.08	0.00
10: I had suspicious ideas or the belief that others were against me	0.02	–	0.06	0.04**	0.06	0.00
11: I felt high	0.01	–	0.15	0.14**	0.16	0.00
12: I felt drowsy	0.02	–	0.10	0.08**	0.10	0.01
13: I felt anxious	0.03*	–	0.09	0.06**	0.09	0.00
Internal perception	0.04*	–	0.13	0.09**	0.13	0.09
External perception	0.01	–	0.10	0.09**	0.10	0.00
POMS						
Elation	0.05**	–	0.19	0.14**	0.20	0.00
Vigor	0.03**	–	0.28	0.25**	0.29	0.01*
Friendliness	0.09**	–	0.18	0.09**	0.18	0.00
Depression	0.01	–	0.06	0.05**	0.06	0.00
Fatigue	0.00	–	0.21	0.21**	0.22	0.00
Confusion	0.01	–	0.17	0.15**	0.19	0.02**
Positive mood	0.04**	–	0.17	0.14**	0.17	0.00
Anxiety	0.01	–	0.01	0.00	0.01	0.00
Anger	0.01	–	0.01	0.00	0.01	0.00
Arousal	0.01	–	0.36	0.34**	0.38	0.02**
CADSS						
Total	0.08**	–	0.14	0.06**	0.14	0.00
Depersonalization	0.06**	–	0.09	0.03**	0.09	0.00
Derealization	0.07**	–	0.13	0.06**	0.13	0.00
Amnesia	0.07**	–	0.10	0.03**	0.11	0.01

*Significant at $p < .05$ level; **Significant at $p < .01$ level.

(range $r = -.36$ to $r = -.21$, $p < .02$). There was a positive correlation between cannabis use history and friendliness, arousal and positive mood (range $r = .27$ to $r = .21$, $p < .03$). Hierarchical regression analysis confirmed the presence of treatment effects on most of the subscales and in addition identified minor contributions (R^2 change < .02) of trait impulsivity to vigor, confusion, and arousal (Table 2).

CADSS

Mean (SE) CADSS scores in every treatment condition and a summary of significant changes induced by cannabis, cocaine, and their interaction with impulsivity as indicated by GLM drug–placebo contrast analyses are given in Table 3.

Overall, subjective ratings of depersonalization, derealization, and amnesia were affected by the factor drug. Separate drug–placebo contrasts revealed that both cannabis and cocaine significantly increased subjective ratings of depersonalization and derealization. In addition, cannabis also significantly increased subjective ratings of amnesia. Cannabis effects on CADSS scores did not differ between both impulsivity groups. Cocaine effects on derealization however were more prominent in the group with high trait impulsivity ($F_{1,108} = 5.32$, $p < .02$).

Subjective ratings during drug treatments did not differ between the two study centers. Hierarchical regression confirmed the contribution of treatment effects to each of the CADSS sub-scores but identified no significant contributions of the factor trait impulsivity (Table 2).

Table 3. Total mean (SE) POMS and CADSS scores in every treatment condition and a summary of significant changes induced by THC, cocaine, and their interaction with impulsivity as indicated by GLM drug–placebo contrast analyses.

Barratt score	Mean (SE)						Cannabis	Cannabis × impulsivity	GLM *p* (F)	
	Placebo		Cannabis		Cocaine				Cocaine	Cocaine × impulsivity
	Normal	*High*	*Normal*	*High*	*Normal*	*High*				
POMS										
Elation	1.20 (.53)	9.85 (.64)	9.06 (.56)	8.96 (.68)	13.34 (0.57)	13.69 (0.69)	.03 (5.17)	–	<.001 (75.52)	–
Vigor	11.55 (.67)	11.16 (.81)	9.31 (.70)	7.86 (.84)	15.94 (0.73)	17.16 (0.88)	<.001 (27.23)	–	<.001 (99.87)	–
Friendliness	16.96 (.76)	16.44 (.92)	14.49 (.74)	14.52 (.90)	19.07 (0.71)	18.96 (0.86)	<.001 (15.47)	–	<.001 (22.36)	–
Depression	1.23 (.35)	.98 (.43)	3.92 (.85)	3.16 (1.02)	0.87 (0.32)	1.14 (0.39)	<.001 (14.72)	–	–	–
Fatigue	2.47 (.40)	2.35 (.49)	5.31 (.55)	5.81 (.67)	1.11 (0.21)	1.04 (0.25)	<.001 (56.24)	–	<.001 (17.46)	–
Confusion	4.37 (.29)	4.54 (.36)	8.45 (.56)	9.54(.69)	4.77 (0.36)	4.94 (0.44)	<.001 (63.06)	–	–	–
Positive mood	9.03 (.69)	9.06 (.84)	5.27 (1.13)	5.94(1.38)	12.49 (0.66)	12.92 (0.80)	<.001 (14.56)	–	<.001 (45.15)	–
Anxiety	4.07 (.31)	3.65 (.38)	7.75 (.61)	6.56(.74)	7.52 (0.57)	7.75 (0.69)	<.001 (43.69)	–	<.001 (94.02)	–
Anger	2.00 (.27)	1.92 (.32)	2.99 (.50)	2.31(.61)	2.27 (0.32)	2.98 (0.39)	–	–	<.001 (9.55)	–
Arousal	8.79 (−1.08)	7.98 (1.32)	3.30 (1.17)	−.85 (1.43)	17.58 (1.17)	19.04 (1.42)	<.001 (54.95)	–	<.001 (96.25)	–
CADSS										
Total	1.49 (.40)	1.24 (.46)	7.92 (1.20)	8.76 (1.43)	3.21 (.66)	4.48 (.78)	<.001 (54.63)	–	<.001 (26.43)	–
Depersonalization	.19 (.13)	.39 (.15)	1.76 (.44)	2.20 (.51)	.70 (.25)	1.00 (.29)	<.001 (24.96)	–	<.01 (10.00)	–
Derealization	1.10 (.26)	.61 (.31)	5.37 (.73)	5.61 (.85)	2.21 (.40)	3.09 (.47)	<.001 (65.64)	–	<.001 (35.59)	.03 (5.16)
Amnesia	.21 (.08)	.23 (.09)	.79 (.18)	.96 (.21)	.30 (.11)	.39 (.13)	<.001 (22.99)	–	–	—

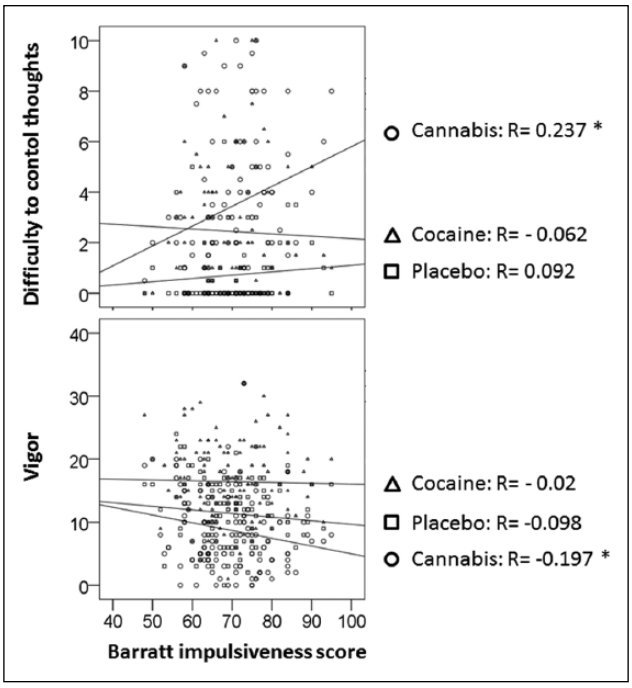

Figure 2. Scatterplots of Barratt impulsivity scores and subjective rating of vigor and difficulty controlling thoughts in every treatment condition.

Correlations between subjective ratings and trait impulsiveness

Correlational analysis between subjective ratings and Barrett impulsiveness scores revealed only 2 significant relations. Vigor ($r = -.197$) and difficulty to control thoughts ($r = .237$) respectively decreased and increased in subjects with higher impulsiveness ratings during cannabis intoxication. No significant relations were found between trait impulsiveness and subjective ratings (POMS, CADDS, and Bowdle) during cocaine or placebo. Scatterplots showing linear trends between trait impulsiveness and vigor as well as loss of though control are shown in Figure 2.

Pharmacokinetic assessments. Mean (SD) concentrations of THC, cocaine, and their metabolites per study center are given in Table 4. Mean concentrations of THC were significantly ($F_{1,91} = 18.16$, $p < .001$) higher in subjects that participated in the Nijmegen center as compared to the Maastricht center.

Discussion

The present study aimed to assess whether the level of trait impulsivity influences the subjective response to acute administration of cannabis or cocaine as determined by questionnaires measuring mood, dissociative states and psychedelic symptoms.

Results indicate that administration of cannabis and cocaine significantly altered subjective ratings on nearly all subscales of all questionnaires. Cocaine significantly increased ratings of dissociation, psychedelic state, and feelings of vigor, friendliness, elation, positive mood, anxiety, and arousal, while decreasing fatigue. The effects on mood are in accordance with other studies also showing mood improvement following cocaine (Penetar et al., 2006; Rush et al., 1999; Walsh et al., 2009). Increased ratings of dissociation and psychedelic state following cocaine appear in line with studies reporting similar findings after administration of other stimulant drugs such as dexamphetamine and methylphenidate (Curran et al., 2004). Cocaine use has been implied in the occurrence of psychotic disorders, albeit mostly with long-term cocaine "crack" users (Morton, 1999; Roncero et al., 2012). Although none of the present subjects developed a psychosis, the present results do suggest that cocaine can cause dissociative symptoms (e.g. depersonalization, derealization, psychedelic effects) even in non-addicted cocaine users.

Cannabis intoxication increased ratings of dissociation and psychedelic state, as well as feelings of fatigue, confusion, depression and anxiety, and decreased feelings of arousal, positive mood, vigor, friendliness and elation. Previous studies have also reported that cannabis increased subjective feelings of high, fatigue (Ballard et al., 2012, 2013; Battistella et al., 2013; D'Souza et al., 2008, 2012; Henquet et al., 2010; Kaufmann et al., 2009; Kirk et al., 1998; Lex et al., 1984; Ramaekers et al., 2006a, 2006b; Toennes et al., 2008; Zuurman et al., 2008), confusion, and anxiety (Battistella et al., 2013; D'Souza et al., 2008; Lex et al., 1984). Likewise, previous research has shown that cannabis can induce psychedelic or dissociative states as assessed with a CADDS questionnaire, Hallucinogen Rating Scale, or a Psychotomimetic States Inventory (Ballard et al., 2012; D'Souza et al., 2008, 2012; Stokes et al., 2009; Zuurman et al., 2008). The latter scale particularly identified perceptual distortion, cognitive disorganization, and mania as major psychotomimetic symptoms following acute THC intoxication (Stokes et al., 2009). In general, the scope of subjective experiences reported by the subjects in the present study appears in line with previous reports on the use of cannabis.

Trait impulsivity of subjects was classified using the Barratt Impulsiveness Scale. Impulsivity levels of about 60% of the

Table 4. Mean (SD) values of THC, cocaine, and their metabolites separately and averaged over study center.

Study center	Time point	THC (µg/L)	THC-OH (µg/L)	THC-COOH (µg/L)	Cocaine (mg/L)	Benzoyl-ecgonine (mg/L)	Ecgonine methyl ester (mg/L)
Maastricht	*T0*	1.62 (3.38)	0.75 (1.64)	23.72 (38.90)	0.00 (0.00)	0.00 (0.02)	0.00 (0.00)
	T1	55.34 (29.20)	6.90 (4.76)	41.31 (33.89)	0.27 (0.20)	0.50 (0.24)	0.16 (0.12)
	T2	37.62 (19.63)	5.90 (3.50)	43.41 (32.38)	0.32 (0.19)	1.02 (0.37)	0.25 (0.11)
	T3	8.41 (5.02)	3.22 (1.89)	36.36 (30.90)	0.16 (0.10)	1.27 (0.53)	0.24 (0.10)
Nijmegen	*T0*	1.52 (4.75)	0.51 (1.78)	18.38 (36.66)	0.00 (0.02)	0.01 (0.04)	0.00 (0.01)
	T1	90.49 (79.19)	6.81 (3.92)	36.31 (33.01)	0.23 (0.19)	0.48 (0.30)	0.12 (0.08)
	T2	54.07 (42.54)	5.70 (3.54)	41.17 (39.49)	0.31 (0.17)	1.21 (0.34)	0.26 (0.09)
	T4	4.55 (2.95)	2.04 (1.23)	30.21 (27.65)	0.18 (0.09)	1.80 (0.44)	0.33 (0.12)
Average	*T0*	1.57 (4.14)	0.62 (1.72)	20.91 (37.68)	0.00 (0.02)	0.00 (0.03)	0.00 (0.01)
	T1	73.81 (63.09)	6.86 (4.32)	38.69 (33.38)	0.25 (0.19)	0.49 (0.27)	0.14 (0.11)
	T2	46.00 (34.19)	5.79 (3.51)	42.27 (36.03)	0.31 (0.18)	1.12 (0.37)	0.26 (0.10)
	T3/T4	6.46 (4.52)	2.63 (1.69)	33.25 (29.33)	0.17 (0.09)	1.54 (0.55)	0.29 (0.12)

subjects were classified as normal whereas the remaining 40% displayed high levels of impulsivity. GLM analyses revealed that the subgroup of high impulsive subjects were more sensitive to some of the psychedelic and dissociative effects produced by cocaine and cannabis. Feelings of derealization following cocaine administration were more prominent in high impulsive subjects as compared to subjects with normal levels of impulsiveness. During THC intoxication, high impulsive subjects displayed stronger psychedelic effects than subjects will normal impulsivity levels. They reported more difficulties controlling thoughts and were more likely to attribute personal meaning to events, objects and other people. Drug-induced states of mood, as assessed with the POMS rating scale, were not affected by the level of trait impulsivity. Correlational analyses between impulsiveness (as a continuous variable) and subjective experiences only partly supported the interaction effects observed in the GLM model. Trait impulsiveness ratings were negatively correlated with ratings of vigor ($r = -.197$) and positively correlated with ratings of difficulty controlling thought ($r = .237$) during cannabis intoxication. No significant correlations between trait impulsiveness and subjective experience were observed during placebo and cocaine treatment. These data suggest that the influence of trait impulsivity level on subjective drug experience is very limited and restricted to a few selective experiences only such as loss of thought control during cannabis intoxication. In general, an association between psychedelic effect, mood and trait impulsively seems absent.

It has been suggested that personality traits may in part determine risk of developing substance use problems (Koob et al., 1998; Kreek et al., 2005). For example, preclinical work in rats has demonstrated that impulsivity predicts susceptibility to drug seeking and relapse (Everitt et al., 2008). Furthermore, MR-imaging of high impulsive subjects revealed increased dopamine release in response to pharmacological reinforcers (e.g. amphetamine) whereas this effect was not seen in low impulsive persons (Buckholtz et al., 2010). This suggests that a pattern of exaggerated dopamine response to reinforcers such as amphetamines could develop into drug abuse (Buckholtz et al., 2010).

Drugs administered in the present study are known to affect dopamine release in the brain. Cocaine has been shown to increase tonic dopamine (Di Chiara and Imperato, 1988), while the effects of cannabis on dopamine release are indirect and more complex. Preclinical evidence shows that cannabis increases dopamine in the mesolimbic circuit during occasional, infrequent use but decreases dopamine levels following repeated, chronic use (Pistis et al., 2002; Verrico et al., 2003). Subjects participating in the present study were all very experienced and regular cannabis users. Therefore, it was expected that subjective experiences after cannabis or cocaine administration would be more prominent in subjects displaying either very low or very high levels of tonic dopamine, since it has been suggested that the relation between impulse control and dopamine follows a U-shaped curve (Kreek et al., 2005; Weinshenker and Schroeder, 2007). This means that individuals with relatively low or high levels of tonic dopamine may be more impulsive whereas individuals with intermediate levels of tonic dopamine may exert optimal control over their impulses. Since tonic dopamine levels can influence mood, psychotic symptoms, and reality monitoring (Artigas, 2013; Nieoullon, 2002; Schnider, 2001), it was expected that high impulsive subjects would be more susceptible to the subjective effects of cocaine (increase of dopamine release) and less to the subjective effects of cannabis (decrease in dopamine release). So far, it is unclear whether differences in trait impulsivity caused by low and high levels of tonic dopamine underlie Barratt's classification of normal and high trait impulsivity. The present data seems to suggest this is not the case because such a scenario would predict a generalized, exacerbated subjective drug experience in high impulsive subjects which was not seen in the current study. These results support a study by White et al. (2006), in which subjective response to amphetamine administration was also shown not to be affected by trait impulsivity.

The present study was conducted in two study centers that followed comparable study protocols. We conducted GLM analyses to evaluate whether drug effects recorded in both centers were comparable. These analyses revealed that changes in subjective mood following cannabis administration were generally more intense in subjects that participated in the Nijmegen study center as compared to the Maastricht center. We speculate that THC influence was larger in the Nijmegen sample due to differences in cannabis use history and mean THC concentrations that were observed between both centers. Subjects in the Nijmegen sample were (somewhat) less experienced while their mean THC concentration during cannabis treatment was higher as compared to the Maastricht sample. Correlation analyses

indicated that positive feelings (i.e. friendliness, arousal, positive mood) during THC intoxication were positively correlated with cannabis use history, while negative feelings (i.e. anxiety, depression, anger, fatigue, and confusion) were inversely related to history of use. This finding partly fits with previous research showing that negative, impairing effects of acute THC intoxication decrease with increasing cannabis experience, while positive experience (i.e. subjective high) remains unaltered (Ramaekers et al., 2009). Analyses of pharmacokinetic data furthermore revealed that mean THC concentrations in subjects from the Nijmegen center were about twice as high relative to the Maastricht center. Explanations for the observed difference in THC concentrations are all speculative but might include variations in titration of THC vapor, number of inhalations, and duration of inhalation. Though THC administration protocols were identical in both centers, adherence may have differed. However, no significant correlations between THC concentration and magnitude of psychedelic effect were found. It has been shown previously (Ramaekers et al., 2006b) that correlations between THC concentration and magnitude of THC impairments are relatively low due to large inter-individual variations. Yet, in general it is also clear that the number of subjects that respond to THC intoxication increase with dose and concentration (Ramaekers et al., 2006b). The present finding that the mean THC concentration in the Nijmegen sample was twice as high as compared to the Maastricht sample may therefore in part explain why the former appeared more sensitive to the effects of THC.

Subjects were asked not to use illicit drugs the week before a testing day, but were allowed to use cannabis throughout the study. All subjects were regular cannabis users and as consequence they would be expected to test positive for cannabis use in urine screens since cannabis use can be detected in blood and urine after at least one month of abstinence (Bergamaschi et al., 2013; Ellis et al., 1985; Karschner et al., 2009). This introduces the potential risk that subjects were high on cannabis even before they received study treatments in our laboratory. We did however collect blood samples at baseline prior to treatments to check for baseline THC concentrations in the study participant. These samples indicated that mean baseline THC levels on average were very low (i.e. <2 μg/L) . Previous research (Ramaekers et al., 2006b) has established that THC concentrations <2 μg/L do not produce noticeable changes in performance. We therefore expect that baseline THC levels in the current study did not significantly affect treatment results.

In conclusion, the present study demonstrated that drug users with high trait levels of impulsivity were somewhat more sensitive to the psychedelic effects of drugs. However, these associations were limited to a few subjective items and very low in correlational strengths. It is therefore concluded that the influence of trait impulsivity on subjective experiences of drug use is mild and restricted.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by a research grant from ZonMW (grant number 31160206), The Netherlands, awarded to JGR and RJV.

References

Artigas F (2013) Developments in the field of antidepressants, where do we go now? *Eur Neuropsychopharmacol* Epub ahead of print. doi:10.1016/j.euroneuro.2013.04.013.

Ballard ME, Bedi G and De Wit H (2012) Effects of delta-9-tetrahydrocannabinol on evaluation of emotional images. *J Psychopharmacol* 26: 1289–1298.

Ballard ME, Gallo D and De Wit H (2013) Pre-encoding administration of amphetamine or THC preferentially modulates emotional memory in humans. *Psychopharmacology* 226: 515–529.

Battistella G, Fornari E, Thomas A, et al. (2013) Weed or wheel! fMRI, behavioural, and toxicological investigations of how cannabis smoking affects skills necessary for driving. *PLoS One* 8: e52545.

Belin D, Mar AC, Dalley JW, et al. (2008) High impulsivity predicts the switch to compulsive cocaine-taking. *Science* 320: 1352–1355.

Bergamaschi MM, Karschner EL, Goodwin RS, et al. (2013) Impact of prolonged cannabinoid excretion in chronic daily cannabis smokers' blood on per se drugged driving laws. *Clin Chem* 59: 519–526.

Bowdle T, Radant A, Cowley D, et al. (1998) Psychedelic effects of ketamine in healthy volunteers. *Anesthesiology* 8: 82–88.

Bremner JD, Krystal JH, Putnam FW, et al. (1998) Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress* 11: 125–136.

Buckholtz JW, Treadway MT, Cowan RL, et al. (2010) Mesolimbic dopamine reward system hypersensitivity in individuals with psychopathic traits. *Nat Neurosci* 13: 419–421.

Cascella NG, Nagoshi CT, Muntaner C, et al. (1994) Impulsiveness and subjective effects of intravenous cocaine administration in the laboratory. *J Subst Abuse* 6: 355–366.

Curran C, Byrappa N and McBride A (2004) Stimulant psychosis: systematic review. *Br J Psychiatry* 185: 196–204.

De Wit H (2008) Impulsivity as a determinant and a consequence of drug use: a review of underlying processes. *Addict Biol* 14: 22–31.

De Wit H, Enggasser JL and Richards JB (2002) Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. *Neuropsychopharmacology* 27: 813–25.

Di Chiara G and Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci U S A* 85:5274–5278.

D'Souza DC, Fridberg DJ, Skosnik PD, et al. (2012) Dose-related modulation of event-related potentials to novel and target stimuli by intravenous Δ^9-THC in humans. *Neuropsychopharmacology* 37: 1632–46.

D'Souza DC, Ranganathan M, Braley G, et al. (2008) Blunted psychotomimetic and amnestic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacology* 33: 2505–2516.

Economidou D, Pelloux Y, Robbins TW, et al. (2009) High impulsivity predicts relapse to cocaine-seeking after punishment-induced abstinence. *Biol Psychiatry* 65: 851–856.

Ellis GM, Mann MA, Judson BA, et al. (1985) Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. *Clin Pharmacol Ther* 38: 572–8.

EMCDDA (2012) *Annual Report 2012: The State of the Drugs Problem in Europe*. Luxembourg: European Union, p.101.

Evenden JL (1999) Varieties of impulsivity. *Psychopharmacology* 146: 348–361.

Everitt BJ, Belin D, Economidou D, et al. (2008) Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philos Trans R Soc Lond B Biol Sci* 363: 3125–3135.

Hazekamp A, Ruhaak R, Zuurman L, et al. (2006) Evaluation of a vaporizing device (Volcano 1) for the pulmonary administration of tetrahydrocannabinol. *J Pharm Sci* 95: 1308–1317.

Henquet C, Van Os J, Kuepper R, et al. (2010) Psychosis reactivity to cannabis use in daily life: an experience sampling study. *Br J Psychiatry* 196: 447–453.

Karschner EL, Schwilke EW, Lowe RH, et al. (2009). Implications of plasma Δ9-tetrahydrocannabinol, 11-hydroxy-THC, and 11-nor-9-carboxy-THC concentrations in chronic cannabis smokers. *J Anal Toxicol* 33: 469–477.

Kaufmann RM, Kraft B, Frey R, et al. (2010). Acute psychotropic effects of oral cannabis extract with a defined content of Δ9-tetrahydrocannabinol (THC) in healthy volunteers. *Pharmacopsychiatry* 43: 24–32.

Kirk JM, Doty P and De Wit H (1998) Effects of expectancies on subjective responses to oral Δ9-tetrahydrocannabinol. *Pharmacol Biochem Behav* 59: 287–293.

Kirkpatrick MG, Johanson C-E and De Wit H (2013) Personality and the acute subjective effects of D-amphetamine in humans. *J Psychopharmacol* 27: 256–264.

Koob GF, Sanna PP and Bloom FE (1998) Neuroscience of addiction. *Neuron* 21: 467–476.

Kreek MJ, Nielsen DA, Butelman ER, et al. (2005) Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nat Neurosci* 8: 1450–1457.

Lex BW, Mendelson JH, Bavli S, et al. (1984) Effects of acute marijuana smoking on pulse rate and mood states in women. *Psychopharmacology* 84: 178–187.

Morton WA (1999) Cocaine and psychiatric symptoms. *Prim Care Companion J Clin Psychiatry* 1: 109–113.

Nieoullon A (2002) Dopamine and the regulation of cognition and attention. *Prog Neurobiol* 67: 53–83.

Pattij T and De Vries TJ (2013) The role of impulsivity in relapse vulnerability. *Curr Opin Neurobiol* 23: 1–6.

Penetar DM, Looby AR, Su Z, et al. (2006) Benztropine pretreatment does not affect responses to acute cocaine administration in human volunteers. *Hum Psychopharmacol* 21: 549–559.

Pettinati HM, Brien CPO and Dundon WD (2013) Current status of co-occurring mood and substance use disorders: a new therapeutic target. *Am J Psychiatry* 170: 23–30.

Pistis M, Ferraro L, Pira L, et al. (2002). Δ9-Tetrahydrocannabinol decreases extracellular GABA and increases extracellular glutamate and dopamine levels in the rat prefrontal cortex : an in vivo microdialysis study. *Brain Res* 948: 155–158.

Ramaekers JG, Kauert G, Theunissen EL, et al. (2006a) High-potency marijuana impairs executive function and inhibitory motor control. *Neuropsychopharmacology* 31: 2296–2303.

Ramaekers JG, Kauert G, Theunissen EL, et al. (2009). Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. *J Psychopharmacol* 23: 266–277.

Ramaekers JG, Moeller MR, Van Ruitenbeek P, et al. (2006b) Cognition and motor control as a function of Δ9-THC concentration in serum and oral fluid: limits of impairment. *Drug Alcohol Depend* 85: 114–122.

Roncero C, Ros-Cucurull E, Daigre C, et al. (2012) Prevalence and risk factors of psychotic symptoms in cocaine-dependent patients. *Actas Españolas Psiquiatr* 40: 187–197.

Rush CR, Baker RW and Wright K (1999) Acute physiological and behavioral effects of oral cocaine in humans: a dose-response analysis. *Drug Alcohol Depend* 55: 1–12.

Schnider A (2001) Spontaneous confabulation, reality monitoring, and the limbic system – a review. *Brain Res Rev* 36: 150–160.

Stanford MS, Mathias CW, Dougherty DM, et al. (2009) Fifty years of the Barratt Impulsiveness Scale: an update and review. *Pers Individ Dif* 47: 385–395.

Stokes PR, Mehta M, Curran HV, et al. (2009) Can recreational doses of THC produce significant dopamine release in the human striatum? *Neuroimage* 48: 186–190.

Toennes SW, Ramaekers JG, Theunissen EL, et al. (2008) Comparison of cannabinoid pharmacokinetic properties in occasional and heavy users smoking a marijuana or placebo joint. *J Anal Toxicol* 32: 470–477.

Toennes SW, Steinmeyer S, Maurer H-J, et al. (2005) Screening for drugs of abuse in oral fluid—correlation of analysis results with serum in forensic cases. *J Anal Toxicol* 29: 22–27.

Verrico CD, Jentsch JD and Roth RH (2003) Persistent and anatomically selective reduction in prefrontal cortical dopamine metabolism after repeated, intermittent cannabinoid administration to rats. *Synapse* 49: 61–66.

Walsh SL, Stoops WW, Moody DE, et al. (2009). Repeated dosing with oral cocaine in humans: Assessment of direct effects, withdrawal and pharmacokinetics. *Exp Clin Psychopharmacol* 17: 205–216.

Weinshenker D and Schroeder JP (2007) There and back again: a tale of norepinephrine and drug addiction. *Neuropsychopharmacology* 32: 1433–1451.

White TL, Lott DC and De Wit H (2006) Personality and the subjective effects of acute amphetamine in healthy volunteers. *Neuropsychopharmacology* 31: 1064–1074.

Wilens TE and Morrison NR (2011) The intersection of attention-deficit/hyperactivity disorder and substance abuse. *Curr Opin Psychiatry* 24: 280–285.

Zuurman L, Roy C, Schoemaker RC, et al. (2008) Effect of intrapulmonary tetrahydrocannabinol administration in humans. *J Psychopharmacol* 22: 707–16.