



A single dose of cocaine enhances prospective memory performance

Nadia RPW Hutten¹, Kim PC Kuypers¹, Janelle HP van Wel¹, Eef L Theunissen¹, Stefan W Toennes², Robbert-Jan Verkes^{3,4} and Johannes G Ramaekers¹

Journal of Psychopharmacology
2018, Vol. 32(8) 883–892
© The Author(s) 2018



Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0269881118783299
journals.sagepub.com/home/jop



Abstract

Background: Prospective memory is the ability to recall intended actions or events at the right time or in the right context. While cannabis is known to impair prospective memory, the acute effect of cocaine is unknown. In addition, it is not clear whether changes in prospective memory represent specific alterations in memory processing or result from more general effects on cognition that spread across multiple domains such as arousal and attention.

Aims: The main objective of the study was, therefore, to determine whether drug-induced changes in prospective memory are memory specific or associated with more general drug-induced changes in attention and arousal.

Methods: A placebo-controlled, three-way, cross-over study including 15 regular poly-drug users was set up to test the influence of oral cocaine (300 mg) and vaporised cannabis (300+150 'booster' µg/kg bodyweight) on an event-based prospective memory task. Attentional performance was assessed using a divided attention task and subjective arousal was assessed with the Profile of Mood States questionnaire.

Results: Results showed that cocaine enhanced prospective memory, attention and arousal. Mean performance of prospective memory and attention, as well as levels of arousal were lowest during treatment with cannabis as compared with placebo and cocaine as evinced by a significantly increased trend across treatment conditions. Prospective memory performance was only weakly positively associated to measures of attention and arousal.

Conclusion: Together, these results indicate that cocaine enhancement of prospective memory performance cannot be fully explained by parallel changes in arousal and attention levels, and is likely to represent a direct change in the neural network underlying prospective memory.

Keywords

Cocaine, delta-9-tetrahydrocannabinol, event-based, prospective memory, attention

Introduction

The acute effects of cannabis and cocaine on cognitive functions of recreational drug users have been repeatedly assessed in placebo-controlled experimental studies. These studies have shown that a single dose of delta-9-tetrahydrocannabinol (THC), the principal psychoactive constituent of cannabis, impairs performance in laboratory tasks measuring executive function, impulse control, psychomotor performance (Ramaekers et al., 2016b; van Wel et al., 2013), attention (Ramaekers et al., 2016b; Theunissen et al., 2015) and memory (see review Hart et al., 2001; Ranganathan and D'souza, 2006; Theunissen et al., 2015). Single doses of cocaine have been shown to impair impulse control, while improving psychomotor function (Ramaekers et al., 2016b; van Wel et al., 2013) and attention (Ramaekers et al., 2016b). Acute effects of cocaine on memory, however, have not been studied extensively (Spronk et al., 2013). Studies in dependent cocaine users (Haney et al., 2005; Hopper et al., 2004) and recreational users (Higgins et al., 1990) revealed no influence of single doses of cocaine on memory.

Psychostimulants such as cocaine have been used as performance enhancers throughout history (Wood et al., 2014). At present, increasing numbers of adults, particularly college students, are misusing psychostimulants primarily for cognitive enhancement (Marraccini et al., 2016). Animal studies have demonstrated that single doses of psychostimulants such as

methylphenidate (Carmack et al., 2014a; Carmack et al., 2014b) and cocaine (Stringfield et al., 2017) enhance learning and memory. Human drug studies on memory enhancement following psychostimulant administration have mostly focused on tasks measuring retrospective memory, i.e. recalling past events or knowledge (Linssen et al., 2014; Mehta et al., 2004). Stimulant effects on prospective memory, however, have hardly been studied so far. Prospective memory involves the capacity and integrity of memory to encode, retrain and recollect future

¹Department of Neuropsychology and Psychopharmacology, Maastricht University, The Netherlands

²Department of Forensic Toxicology, Goethe University of Frankfurt, Germany

³Department of Psychiatry, Radboud University Nijmegen Medical Centre, The Netherlands

⁴Cognition and Behaviour, Donders Institute for Brain, Radboud University Nijmegen, The Netherlands

Corresponding author:

Nadia RPW Hutten, Department of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, P.O. Box 616, Maastricht 6200MD, The Netherlands.

Email: nadia.hutten@maastrichtuniversity.nl

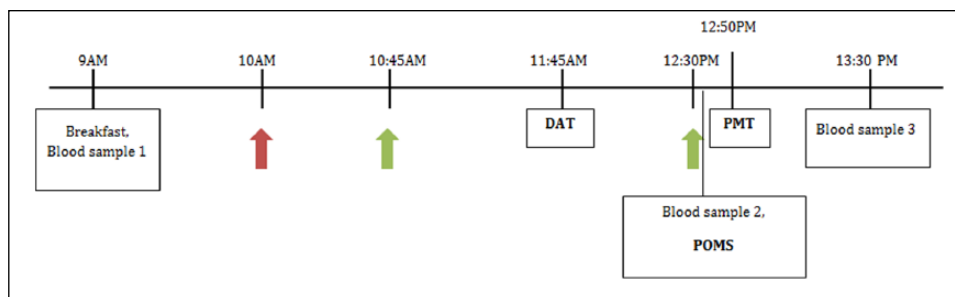


Figure 1. Timeline of the course of a testing day. The red arrow indicates the moment of cocaine (or placebo) capsule administration and the green arrows represent the delta-9-tetrahydrocannabinol (THC) (or placebo) vapour administration. DAT: divided attention task; PMT: prospective memory task; POMS: Profile of Mood States.

intentions and actions such as remembering to call a friend, take medication or go to a meeting, and differs from retrospective memory in that it involves self-initiated retrieval, sometimes cued by an event or time (Einstein et al., 2005; Ellis, 1996; Kliegel et al., 2001; McDaniel and Einstein, 1993). Chronic use of methamphetamine (Fernández-Serrano et al., 2011), cocaine and MDMA (Hadjiefthyvoulou et al., 2011a; Hadjiefthyvoulou et al., 2011b; Heffernan et al., 2001) as well as single dose administrations of MDMA (Ramaekers et al., 2009b) have been associated with impairments of prospective memory. Likewise, sedative drugs such as alcohol and cannabis have also been associated with prospective memory deficits both after acute dose administrations (Montgomery et al., 2011; Paraskevaides et al., 2010; Theunissen et al., 2015) as well as after chronic use (Cutler et al., 2012; Heffernan, 2008; Heffernan et al., 2002; Leitz et al., 2009).

Drug effects on prospective memory may represent specific alterations in memory processing or may result from more general effects on cognition that spread across multiple domains (Fernández-Serrano et al., 2011). For example, drug-induced reductions or increments in arousal and attention may indirectly lead to a decline or boost of memory performance, as high levels of arousal and attention have been associated with enhanced prospective memory performance (Marchant et al., 2008; Rich et al., 2006). Impairments in prospective memory, as observed after acute doses of cannabis (Theunissen et al., 2015) and alcohol (Montgomery et al., 2011; Paraskevaides et al., 2010), may thus result from decrements in attention and arousal, rather than from a decrement of memory processing per se. Likewise, memory enhancement, as observed for stimulants (Linssen et al., 2014; Mehta et al., 2004), may reflect an increase in concentration and arousal rather than an improvement in memory processes per se.

The current study was designed to assess the acute influence of single dose of cocaine and of cannabis on prospective memory and to assess whether drug-induced changes in prospective memory are associated with drug-induced changes in attention and arousal. In order to test these aims, a double-blind, placebo-controlled, cross-over study was designed. Drug effects on attention and arousal were assessed using a divided attention task and subjective measure of arousal. It was expected that after cannabis administration prospective memory would be impaired, while cocaine administration was expected to improve prospective memory performance.

Methods

Design

The study design was double-blind, placebo-controlled, within-subject with three treatment conditions consisting of placebo, 450 µg/kg THC and 300 mg cocaine hydrochloride (HCl). The cannabis dose was divided over two doses of 300 and 150 µg/kg THC bodyweight (booster dose) with an interval of approximately 1.5 h, in order to maintain THC concentrations throughout a three-hour time window. For a time line of the study design, see Figure 1. Cannabis was administered through a vaporiser (Volcano) obtained from Storz and Bickel GmbH and Co (Tuttlingen, Germany) and was used according to the manual provided by the producer. Cannabis vaporization is a technique by which cannabis plant material is heated to a temperature where active cannabinoid vapours form. This is considered a safe and effective way of administering cannabis (Hazekamp et al., 2006). The vapours are then collected in a detachable plastic balloon of 55 cm length. The balloon can be removed from the device and fitted with a mouthpiece for inhalation. Participants were instructed to empty the balloon in 4–5 breaths. After each inhalation, participants had to hold their breath for 10 seconds before exhaling. The vapour was prepared from batches containing 11% THC, a standard potency for cannabis sold at Dutch pharmacies for medicinal use. As placebo, a herbal plant mixture ('Knaster') was used. The density of the vapour captured in the balloon did not noticeably differ between THC and placebo. Cocaine HCl or placebo was administered in an opaque white capsule. Treatments were administered using a double dummy technique. Conditions were separated by a minimum wash-out period of seven days to avoid cross-condition contamination. The order of conditions was balanced over participants and sessions.

Participants

The present study was part of a larger trial on the association between drug use and impulse control, of which a large part of the data has been published elsewhere (Ramaekers et al., 2016a; van Wel et al., 2013; van Wel et al., 2015). Initially, 16 healthy poly-drug users from the large trial were included in this part of the study. However, due to non-compliance with the task instructions, one participant was removed from the final sample that entered the data analysis. Participants (14 males; one female)

Table 1. Mean (\pm standard deviation (SD)) drug use in the past three months and total years of use.

	Use previous three months				Years of use			
	Min	Max	Mean (SD)	n	Min	Max	Mean (SD)	n
Cannabis	10	100	50.13 (31.49)	15	3	14	6.5 (2.98)	14 ^a
Cocaine	0	10	3.80 (0.83)	15	1	6	3.62 (1.94)	13 ^a

^aMissing data.

were aged 22.8 years (standard deviation (SD)=2.6) on average and with a mean weight of 67.7 kg (SD=10.8). The details on their cannabis and cocaine use are depicted in Table 1. Cannabis use history across participants was somewhat equally divided, ranging from use on 1–24 ($n=4$); 25–49 ($n=3$); 50–74 ($n=3$) and 75–100 ($n=5$) occasions during the past three months (based on cannabis use history groups from Ramaekers et al., 2016b). Participants also reported a drug use history of ecstasy (60%), amphetamines (33%), mushrooms (47%), LSD (20%) and other drugs (20%).

Participants were recruited through advertisements in local newspapers and by word of mouth. Before inclusion, participants were examined by a medical supervisor, who checked for general health and took blood samples and a urine sample for standard chemistry and haematology. Inclusion criteria were: written informed consent; age 18–40 years; regular cannabis and cocaine use defined as two times per week or more for cannabis and at least five times in the past year for cocaine; free from psychotropic medication; good physical health as assessed by a medical doctor; normal weight as determined by body mass index (BMI) 18–28. Exclusion criteria were: addiction to cocaine according to the Diagnostic and Statistical Manual, version 5 (DSM-IV) criteria; presence or history of psychiatric or neurological disorder as assessed during a clinical interview; pregnancy or lactating; cardiovascular abnormalities; excessive drinking or smoking, and hypertension.

Procedures

Participants were familiarised with all tests and procedures during a training session, before the start of the actual test days. They were asked to refrain from all drugs of abuse (except cannabis) at least one week before the study start until the last test day. They were asked not to use any caffeinated or alcoholic beverages 24 h before testing and to get a normal night of sleep. All participants indicated that they had not smoked cannabis in the morning prior to testing. At 09:00, prior to the experimental sessions they were screened for presence of drugs of abuse in urine (THC/opiates/cocaine/amphetamines/methamphetamines) and they had to pass a breathalyser ethanol test. Women were given a pregnancy test. When tests were negative (except for cannabis), participants filled out a questionnaire to assess sleep complaints, and had a light standard breakfast. After breakfast at 10:00, participants were administered a capsule containing either 300 mg cocaine HCl or placebo orally. Forty-five minutes after capsule administration, participants inhaled 300 μ g/kg bodyweight cannabis or placebo. In between treatments, participants were allowed to read a book or watch television. After conducting laboratory tests, assessing

impulsivity, psychomotor performance (results published in van Wel et al., 2013) and divided attention (DAT at 11:45) participants received a second ‘booster dose’ of cannabis or placebo (150 μ g/kg bodyweight at 12:30) and they proceeded with the second part of the study. After the ‘booster dose’, a visual analogue scale (VAS) assessing subjective high and the Profile of Mood States (POMS) was administered, followed by the prospective memory task. Blood samples were taken three times a day, at baseline, just before the prospective memory task (12:30) and at the end of the test day (13:30). Relative to cocaine and cannabis administration, the second blood sample was collected 2.5 h post-cocaine administration and immediately after the second cannabis vapour inhalation; the third blood sample was collected 3.5 h post-cocaine administration and one hour after the second cannabis administration. A schematic representation of the time course of a testing day is represented in Figure 1.

The study was conducted according to the code of ethics on human experimentation established by the Declaration of Helsinki (1964) and subsequent amendments, and it 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. Participants signed an informed consent and were paid upon completion of the testing periods for their participation.

Performance tests

Prospective memory task (PMT). The event-based PMT assessed participants’ ability to remember and execute upon the occurrence of a specific future event. Participants were engaged in a foreground task that consisted of pushing as quickly as possible one of two buttons in response to stimuli (letter A or B) presented on a screen. In total, 100 letters were presented with both letters presented equally often. Participants were also given a second prospective task, i.e. to withhold their response during trials that were part of a dynamic memory set. A trial counter that was always present in the left top corner of the screen informed the participants about the number of the trial. In addition, participants were presented at irregular times with a future trial number in the right top corner of the display. Participants were instructed to remember this future trial number and withhold from responding to the foreground task during the actual occurrence of the future trial. The memory set of subjects was dynamic and contained up to three future trial numbers. A trial number in the memory set was replaced by a novel future trial number whenever the actual trial number matched a future trial number in the set. Trials during which participants were expected to respond were classified as Go trials. Trials during which subjects were instructed to withhold a response were classified as No-Go trials (prospective memory trials). The time between the presentation of a future trial number and the actual occurrence of the trial called ‘the memory delay’; varied between one, two and three minutes, equally divided over all No-Go trials. Each trial lasted for 12 s. However, the central letters disappeared upon a button press. Presentations of future trial numbers lasted four seconds. In total, the PMT consisted of 68 Go trials and 24 No-Go trials. At the beginning and the end of the task, a total of eight trials were presented during which the memory set was empty. The

percentage of correct inhibitions in No-Go trials was the primary performance parameter. Number of correct responses and corresponding reaction time during Go trials were the secondary performance parameters. The PMT lasted for 20 min. Three parallel versions of the PMT were developed for administration during the test sessions to avoid learning effects. The PMT was proven to be sensitive to the acute effects of MDMA (Ramaekers et al., 2009b; van Wel et al., 2011).

Divided attention task (DAT). The DAT assessed participants' ability to divide attention between two tasks performed simultaneously (Moskowitz, 1973). Participants were engaged in a tracking task that measured the ability to control a displayed error signal (Jex et al., 1966), which was displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Simultaneously, participants had to monitor 24 single digits which were presented in the corners of the computer screen. Participants were instructed to react to the target number '2' by removing their foot as fast as possible from a pedal switch. Mean absolute tracking error (in mm) and percentage of correct detections (hits %) of the target number were the performance measures.

Subjective measures

Arousal. Arousal level was measured by the POMS questionnaire. Participants had to express their level of mood on a five-point Likert scale, with zero being 'not at all' to four 'extremely'. The level of arousal was determined by using a composite score of four levels of mood; anxiety (nine items), confusion (seven items), fatigue (seven items) and vigour (eight items); accordingly arousal level was calculated through combining the four levels of mood ((anxiety+vigour)-(fatigue+confusion)) (De Wit et al., 2002).

VAS. Participants had to assess their levels of subjective high via a VAS (10 cm); with zero indicating 'not high at all' and 10 indicating 'extremely high'.

Pharmacokinetic assessments

Blood samples to determine cannabis and cocaine concentrations were taken at baseline, 2.5 h and 3.5 h after cocaine or placebo capsule administration. Blood samples were centrifuged at 3500 rpm and resulting serum and plasma were frozen at -20°C until analysis for pharmacokinetic assessments. The determination of THC and its metabolites, 11-hydroxy-THC (THC-OH) and 11-nor-9-carboxy-THC (THC-COOH), was performed in serum; determination of cocaine, and its metabolites benzoylecgonine (BZE) and ecgonine methyl ester (EME) was performed in plasma. Determination took place in a specialized forensic-toxicological laboratory using validated procedures (Toennes et al., 2005; Toennes et al., 2008).

Statistical analysis

PMT and DAT data, subjective measures of arousal and subjective high, and blood concentrations were checked for normality, using Kolmogorov-Smirnov tests of normality. Normality tests

per treatment condition showed that reaction time on Go trials, percentage correct detections (hits %), VAS subjective high and baseline blood levels of THC and its metabolites were not normally distributed. In addition, normality tests across all conditions showed that percentage correct in Go trials, percentage correct in No-Go trials and percentage correct detections (hits %) were not normally distributed.

Normally distributed data were analysed by means of a general linear model (GLM) repeated measures analysis of variance (ANOVA) version SPSS 24.0 with treatment (three levels, i.e. placebo, cocaine and cannabis) as the within-subjects (WS) factor. In case of main effects, subsequent treatment contrasts were performed. In case of a main treatment effect, subsequent polynomial contrasts were added as a linear trend analysis across all treatments. Non-normal distributed data was analysed with a non-parametric Friedman test to test the main effects of treatment, with subsequent Wilcoxon signed-rank test for treatment contrasts, in case of main effects.

A series of correlation analyses was conducted to assess relationships between prospective memory and arousal levels, prospective memory and attention performance (hits % and tracking error); and between arousal levels and attention performance (hits % and tracking error) over all conditions. In addition, correlation analyses were conducted to assess relationship between cannabis and cocaine blood concentrations respectively, and drug-placebo differences of prospective memory failures. The first correlation analysis provides information about the association between prospective memory and arousal and attention, and the association between arousal and attention. The latter provides information on the drug concentration in blood and the acute effects of both drugs on prospective memory performance. Correlation analyses of normally distributed data was analysed by Pearson correlation, while non-normal data distribution was analysed using Kendall's Tau-b correlation.

The alpha criterion level of statistical significance for all analyses was set at $p=0.05$. Partial eta squared (partial η^2) is reported in case of significant effects to demonstrate the effect's magnitude, where 0.01 is defined as small, 0.06 as moderate and 0.14 as large. Partial eta squared is based on Cohen's f which defines small, medium and large as respectively 0.10, 0.25 and 0.50 which corresponds to η^2 of 0.0099, 0.0588 and 0.1379 (Richardson, 2011).

Results

Missing data

Due to technical issues, computer responses were not registered, resulting in missing data for the DAT in the placebo condition for one person and cocaine condition for another person. Some of the blood samples were missing due to inability to draw blood (see Table 2).

PMT

GLM repeated measures ANOVA revealed a main effect of treatment on percentage correct inhibitions of No-Go's ($F_{2,28}=9.47$, $p<0.01$, $\eta_p^2=0.40$). Subsequent treatment contrasts revealed that percentage of correct inhibitions was higher following cocaine as compared with placebo ($p=0.03$) and as compared with cannabis

Table 2. Mean (\pm standard deviation (SD)) concentrations of delta-9-tetrahydrocannabinol (THC) (ng/mL), cocaine (mg/L) and their main metabolites.

Condition	Concentration	<i>n</i>	Baseline	<i>n</i>	Before PMT	<i>n</i>	End test day
Placebo	THC	13 ^a	3.4 (7.6)	13 ^a	2.3 (2.3)	13 ^a	2.1 (3.0)
	THC-OH	13 ^a	1.4 (2.7)	13 ^a	0.9 (1.0)	13 ^a	0.9 (1.2)
	THC-COOH	13 ^a	42.7 (58.4)	13 ^a	33.8 (43.7)	13 ^a	36.3 (52.3)
Cannabis	THC	11 ^a	3.3 (5.9)	11 ^a	35.2 (21.3)	11 ^a	8.3 (4.5)
	THC-OH	11 ^a	1.1 (1.6)	11 ^a	5.8 (2.7)	11 ^a	3.3 (1.4)
	THC-COOH	11 ^a	40.6 (51.6)	11 ^a	50.7 (38.9)	11 ^a	41.6 (33.4)
Cocaine	THC	13 ^a	2.3 (3.3)	12 ^a	3.1 (4.3)	12 ^a	2.2 (3.1)
	THC-OH	13 ^a	1.1 (1.6)	12 ^a	1.2 (1.9)	12 ^a	1.0 (1.5)
	THC-COOH	13 ^a	31.2 (39.4)	12 ^a	34.7 (49.6)	12 ^a	30.53 (45.8)
	Cocaine	13 ^a	0.0 (0.0)	13 ^a	0.4 (0.2)	13 ^a	0.1 (0.1)
	BZE	13 ^a	0.0 (0.0)	13 ^a	1.0 (0.3)	13 ^a	1.2 (0.4)
EME	13 ^a	0.0 (0.0)	13 ^a	0.3 (0.1)	13 ^a	0.2 (0.1)	

BZE: benzoylecgonine; EME: ecgonine methyl ester; PMT: prospective memory task.
^aMissing samples.

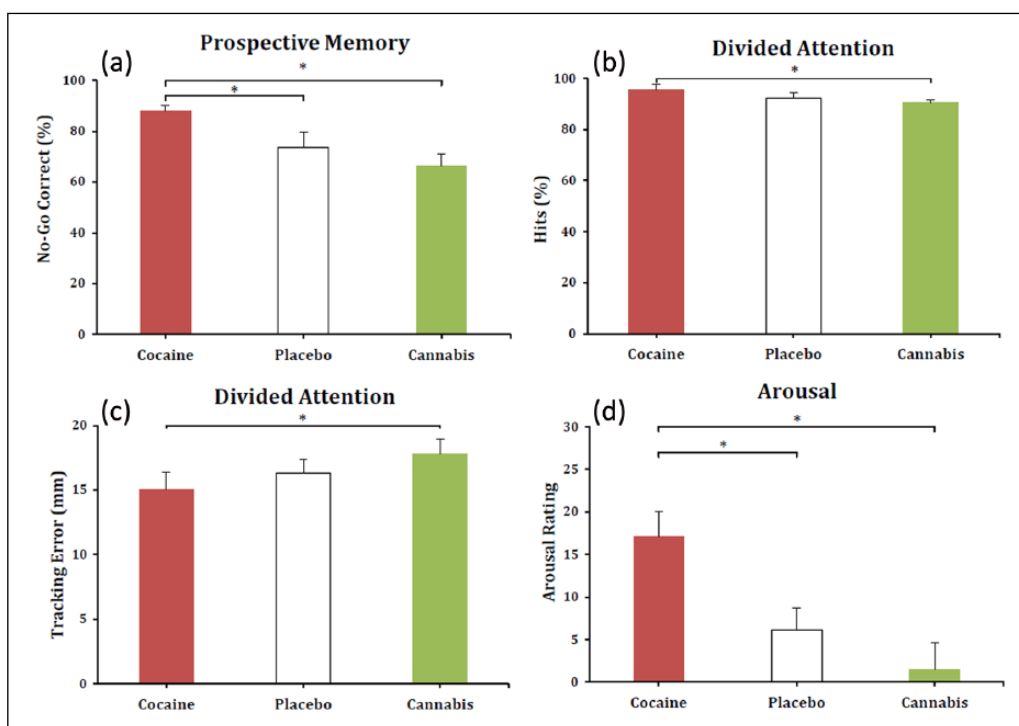


Figure 2. Mean (\pm standard error (SE)) (a) percentage correct inhibitions No-Go trials, (b) percentage correct detections, (c) tracking error and (d) arousal rating after cocaine and cannabis administration and placebo. *significant differences between conditions with $p < 0.05$.

($p < 0.01$). Treatment contrast between cannabis and placebo was not significant. However polynomial contrasts revealed a linear trend across all treatments ($F_{1,14} = 31.83, p < 0.01$), indicating that correct inhibitions during No-Go trials were highest after cocaine, intermediate after placebo and lowest following cannabis treatment. Mean (M) (\pm standard error (SE)) performance scores of the percentage correct inhibitions are shown in Figure 2(a).

Friedman test revealed treatment effects on reaction time ($\chi^2(2) = 9.73, p < 0.01$) and on percentage correct in the Go trials ($\chi^2(2) = 10.32, p = 0.01$). Subsequent treatment contrasts revealed

an impairing effect of cannabis on reaction time ($Z = -2.39, p = 0.02$) and percentage correct in the Go trials ($Z = -2.29, p = 0.02$) compared with placebo; and a significant impairing effect of cannabis as compared with cocaine on reaction time ($Z = -2.33, p = 0.02$) and percentage correct Go trials ($Z = -3.02, p < 0.01$). There was no significant difference comparing cocaine and placebo treatment on reaction time and percentage correct in Go trials. During cocaine treatment reaction time was fastest (M=1065.8, SE=106.02), placebo in between (M=1179.3, SE=72.14) and during cannabis responses were the slowest

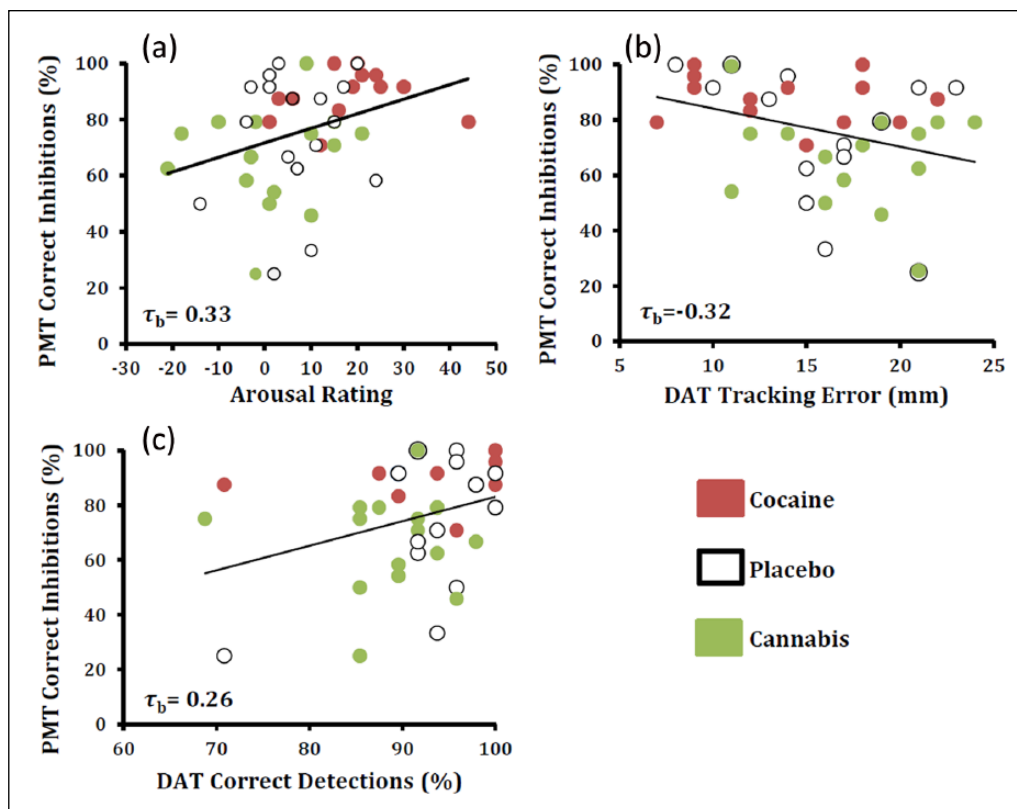


Figure 3. Scatterplots of percentage correct inhibitions No-Go trials as a function of (a) arousal, (b) tracking error and (c) correct detections. Correlations (τ_b) significant with $p < 0.05$. DAT: divided attention task; PMT: prospective memory task.

($M=1297.1$, $SE=86.61$). Percentage correct in the Go trials was highest after cocaine ($M=94.8$, $SE=1.41$), intermediate after placebo ($M=90.3$, $SE=2.87$) and lowest after cannabis administration ($M=84.2$, $SE=3.84$).

DAT

Friedman test revealed treatment effects of percentage correct detections (hits %) ($\chi^2(2)=6.68$, $p=0.04$), subsequent treatment contrasts revealed that percentage of hits was higher during cocaine as compared with cannabis ($Z=-2.04$, $p=0.04$). Treatment contrasts comparing placebo with cocaine and placebo with cannabis were not significant. GLM repeated measures ANOVA revealed a main effect of treatment on tracking error ($F_{2,24}=4.08$, $p=0.03$, $\eta_p^2=0.25$), with subsequent treatment contrasts revealing a reduction in tracking error during cocaine as compared with cannabis ($p=0.01$). Again, treatment contrasts comparing placebo with cocaine and placebo with cannabis were not significant. Polynomial contrasts revealed a linear trend across all treatments ($F_{1,12}=10.29$, $p=0.01$), indicating that tracking error was lowest after cocaine, intermediate after placebo and highest following cannabis treatment. Mean ($\pm SE$) performance scores for the divided attention task is shown in Figure 2(b) and (c).

Arousal

Mean ($\pm SE$) arousal levels in every treatment condition are shown in Figure 2(d). GLM repeated measures ANOVA revealed

a main effect of treatment on arousal levels ($F_{2,28}=9.71$, $p < 0.00$, $\eta_p^2=0.41$), subsequent treatment contrasts revealed higher arousal levels following cocaine administration as compared with placebo ($p=0.01$) and as compared with cannabis ($p < 0.01$). Treatment contrast between cannabis and placebo was not significant. Polynomial contrasts revealed a linear trend across all treatments ($F_{1,14}=13.84$, $p < 0.01$), indicating that arousal levels were highest after cocaine, intermediate after placebo and lowest following cannabis treatment.

Subjective high

Friedman test revealed treatment effects of subjective high ($\chi^2(2)=15.17$, $p < 0.01$), subsequent treatment contrasts revealed that both cocaine and cannabis increased subjective high relative to placebo ($Z=-2.20$, $p=0.03$; $Z=-3.19$, $p < 0.01$). Mean subjective high was higher during cannabis treatment as compared with cocaine ($Z=-2.35$, $p=0.02$). Mean levels of subjective high were highest after cannabis administration ($M=5.7$, $SE=0.70$), intermediate following cocaine ($M=3.3$, $SE=0.77$) and lowest after placebo ($M=1.3$, $SE=0.26$). Results show that both treatments were significantly intoxicated compared with placebo.

Blood concentrations

Blood concentrations during cocaine, cannabis and placebo treatments are shown in Table 2. The cannabinoid analyses revealed the presence of THC and its metabolites in all conditions at

baseline which are a consequence of repeated cannabis use (see Table 1, Toennes et al., 2008). Friedman test revealed no significant difference in levels of THC ($\chi^2(2)=2.25$, $p=0.33$), THC-OH ($\chi^2(2)=0.48$, $p=0.79$) and THC-COOH ($\chi^2(2)=1.11$, $p=0.58$) across all three conditions, indicating level of THC and its metabolites are similar for all three conditions at baseline.

Correlations

Kendall's Tau-b correlation analyses revealed significant but low associations between prospective memory and arousal ($\tau_b=0.33$; $p=0.01$), tracking error ($\tau_b=-0.32$; $p=0.04$), and correct detections ($\tau_b=0.26$; $p=0.02$); indicating that better prospective memory performance was somewhat associated with higher arousal levels and enhanced attention as shown in Figure 3. In the latter case, the correlation seemed to be driven by three outlying data points (see Figure 3(c)), which seemed like the results of one participant, however these data points represent three different participants. Pearson correlations between attention performance and arousal only revealed a low association between tracking error and arousal ($r_{43}=-0.34$; $p=0.03$), indicating that higher levels of arousal are only slightly associated with the primary task variable (tracking) and not associated with the secondary task variable (correct detections) of attention.

Cocaine and THC concentrations in serum were not correlated to performance in the No-Go trials of the prospective memory task, indicating a homogenous participant sample.

Discussion

The current study aimed to assess the influence of single-dose administration of cocaine and cannabis on prospective memory and to determine whether cocaine and cannabis induced changes in prospective memory depend on changes in attention and arousal. Cocaine administration enhanced prospective memory performance relative to placebo and cannabis. Prospective memory performance was lowest after cannabis, in between after placebo and highest after cocaine administration, evinced by a linear trend across treatment conditions. Cocaine also improved performance on the primary (tracking) and secondary (correct detections) task of the divided attention test, relative to cannabis. Tracking performance was lowest in the cannabis condition but increased following placebo and cocaine. After cocaine administration, subjective arousal levels were increased as compared with placebo and cannabis. Once again arousal levels were lowest in the cannabis condition and increased after placebo and cocaine. Only a small part of the enhancing effects of cocaine on prospective memory can be explained by underlying changes in arousal and attention.

The present study was the first to demonstrate that acute administrations of cocaine can enhance prospective memory. The present study however showed that prospective memory performance was only poorly associated with divided attention performance and arousal. Correlations between prospective memory performance and measures of attention and arousal ranged between $\tau_b -0.32$ and 0.33 . This indicates that these constructs only explained a very small portion of the variance observed in prospective memory performance. Memory enhancement, as observed after cocaine in the present study therefore, is more likely to have resulted from direct improvement of the

prospective memory circuits rather than from a general increase in attention. This finding seems in line with animal studies showing that exposure to cocaine may directly enhance hippocampal function and memory. For example, it has been demonstrated that cocaine induces a rapid increase in the formation and accumulation of new dendritic spines in the frontal cortex, and that such changes in structural plasticity correlate with an increased ability to learn new stimulus-related information (Muñoz-Cuevas et al., 2013). Likewise, Muriach et al. (2010) demonstrated that cocaine facilitates the learning of new tasks in rats even though retrieval of information learned prior to cocaine administration was impaired. Such improvement in memory and learning, however, does not automatically imply that cocaine should be used as a preferred cognition enhancer. Indeed, many animal studies have pointed out that the precognitive effects of cocaine may play a role in drug seeking behaviour by strengthening the formation of maladaptive associations between drug use, context and cues (Kutlu and Gould, 2016). Yet, the present data does suggest that cocaine-induced cognition, and therefore enhancement or changes in synaptic plasticity, may very well exceed the context of drug reinforcement learning.

Cocaine-induced enhancement of prospective memory might generalise to other domains of memory as well. For example, retrospective and prospective memory processes do not operate completely independent from each other which would allow transfer of procedural deficits in retrospective to prospective memory (Ferbinteanu and Shapiro, 2003; West and Kropfing, 2005). Alternatively, individuals with a deficit in prospective memory do often display normal operation of retrospective memory (van den Berg et al., 2012). This suggest that while both memory processes overlap, they are not necessarily interchangeable (Glisky, 1996; West and Kropfing, 2005). Transferability of drug effects between different memory processes, therefore, may depend on whether a drug acts on a memory mode that is being shared by memory circuits. For example, it has been pointed out that performance on prospective and retrospective memory tasks in part relies on a similar retrieval mode that is located in BA10 (Underwood et al., 2015). We do not know whether cocaine-enhanced encoding, retrieval or storage of information in our participants. Yet, in the case that a common retrieval process was positively affected by cocaine, we would expect memory enhancement to appear both in retrospective as well as PMTs. What is evident is that prospective memory performance heavily relies on working memory processes as the task is very dynamic and requires continuous updating and retrieval of novel information. Working memory and prospective memory processes are not based on the same memory system, but prospective memory is highly demanding of working memory resources (Basso et al., 2010). Several studies have shown that prospective memory is related to individual working memory capacity (Einstein et al., 2000; Smith, 2003; West and Craik, 2001). As cocaine enhanced prospective memory, it can be expected that cocaine enhances working memory as well.

Memory enhancement has also been demonstrated for stimulant drugs with similar mechanisms of action as cocaine. Adults with attention deficit hyperactivity disorder treated with methylphenidate showed improved memory functions when compared with non-medicated patients across a range of memory domains, including prospective memory (Fuermaier et al., 2017). Similar effects have been reported in healthy volunteers. A review of methylphenidate

studies in healthy volunteers (Linssen et al., 2014) showed that single doses of methylphenidate enhance working memory in 65% of the included studies and, to a lesser extent, verbal learning and memory in 31% of the studies. Cocaine and methylphenidate are also being misused by healthy college students to enhance their study performances although the effectiveness of this approach is largely unknown (Marraccini et al., 2016; Svetlov et al., 2007). Cocaine and methylphenidate share the same dopamine as well as noradrenaline enhancing effects, by blocking dopamine and noradrenaline transporters (Han and Gu, 2006; Schwenker et al., 1985). Additionally, cocaine also inhibits the serotonin transporter. Similarities in their pharmacological profiles seem to indicate that the enhancement of dopamine and noradrenaline levels during cocaine treatment may underlie the neurobiological changes in memory.

The influence of cannabis on prospective memory and attentional performance was much as expected. Previous studies already demonstrated that single doses of THC can significantly impair prospective memory (Theunissen et al., 2015) and attention (Ramaekers et al., 2016b). In the present study, performances during cannabis and placebo did not significantly differ from each other when statistically compared with cannabis-placebo contrasts. However, mean performance during cannabis was always worse as compared with placebo, and the trend showing an increase in performance from cannabis, placebo to cocaine administration was highly significant. In addition, THC blood levels after cannabis administration in the present study ($M=35.2$, $SD=21.3$) are about the same as blood levels of Theunissen et al. (2015) ($M=30.7$, $SD=27.4$), indicating adequate blood levels were reached after cannabis administration. In the present study, the cannabis condition primarily served as an active control for the placebo condition to widen the coverage of the memory, arousal and attention performance ranging from poor to normal enhancement. As such, the inclusion of cannabis treatment increased the overall reliability of correlational analyses between measures of prospective memory and measures of attention and arousal.

Repeated cannabis use leads to residual concentrations of THC and its metabolites (Toennes et al., 2008) as observed for baseline analyses in the present study. However, we do not expect that these baseline levels would interfere with test performances as these concentrations did not differ across treatment conditions. In addition, concentrations as determined here were found not to be relevant for the observed effects (Ramaekers et al., 2009a; Ramaekers et al., 2016b; Ramaekers et al., 2006). However, chronic use of cannabis can lead to memory impairments which can last for weeks, months or even years (Solowij and Battisti, 2008), so stimulants like cocaine might reverse these deficits if present.

The present data revealed that the prospective-memory-enhancing effects of cocaine can only be explained partly by enhanced attention and arousal levels. It might be argued that a low association between prospective memory and attention might have resulted from a lack of a very strong drug effect on attentional performance. Indeed, performance on the DAT primarily differed between drug conditions and not between drug and placebo treatment. Perhaps drug effects on attention would have appeared more prominent if the sample size had been bigger. However, the cocaine effect on prospective memory and arousal were very robust and significantly different from placebo. However, levels of arousal were only weakly associated with prospective memory performance despite the presence of a strong drug effect on both parameters. The latter therefore seems to indicate the validity of current observations. It would be advisable to replicate the

current findings in a larger sample and, perhaps, with the inclusion of a broader range of memory and attention tests (Rich et al., 2006), to further elucidate and differentiate the effects of cocaine.

In summary, the current findings suggest that cocaine administration enhances prospective memory performance, while cannabis tends to impair prospective memory. Prospective memory performance was only weakly associated with measures of attention and arousal, suggesting that cocaine exerts a direct influence on memory processing. Replication studies are needed to examine whether the enhancing effects of cocaine are generalisable to other memory domains, and whether other aspects of attention play a role in these effects.

Acknowledgements

The authors would like to thank Cees van Leeuwen for the medical supervision, and all the interns who have worked on these projects and helped out with data collection.



Declaration of conflicting interest

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

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by a research grant from ZonMw (grant number 31160206), The Netherlands, awarded to JG Ramaekers and R-J Verkes.

ORCID iD

Nadia RPW Hutten  <https://orcid.org/0000-0003-0033-8119>
Kim PC Kuypers  <https://orcid.org/0000-0001-7634-3809>

References

- Basso D, Ferrari M and Palladino P (2010) Prospective memory and working memory: Asymmetrical effects during frontal lobe TMS stimulation. *Neuropsychologia* 48: 3282–3290.
- Carmack SA, Block CL, Howell KK, et al. (2014a) Methylphenidate enhances acquisition and retention of spatial memory. *Neurosci Lett* 567: 45–50.
- Carmack SA, Howell KK, Rasaei K, et al. (2014b) Animal model of methylphenidate's long-term memory-enhancing effects. *Learn Mem* 21: 82–89.
- Cuttler C, McLaughlin RJ and Graf P (2012) Mechanisms underlying the link between cannabis use and prospective memory. *PLoS One* 7: e36820.
- De Wit H, Enggasser JL and Richards JB (2002) Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. *Neuropsychopharmacology* 27: 813–825.
- Einstein GO, McDaniel MA, Manzi M, et al. (2000) Prospective memory and aging: Forgetting intentions over short delays. *Psychol Aging* 15: 671.
- Einstein GO, McDaniel MA, Thomas R, et al. (2005) Multiple processes in prospective memory retrieval: Factors determining monitoring versus spontaneous retrieval. *J Exp Psychol Gen* 134: 327.
- Ellis J (1996) Prospective memory or the realization of delayed intentions: A conceptual framework for research. In: Brandimonte M, Einstein GO and mcdaniel MA (eds) *Prospective Memory: Theory and Applications*. Mahwah, NJ: Lawrence Erlbaum, pp. 1–22.
- Ferbinteanu J and Shapiro ML (2003) Prospective and retrospective memory coding in the hippocampus. *Neuron* 40: 1227–1239.

- Fernández-Serrano MJ, Pérez-García M and Verdejo-García A (2011) What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance? *Neurosci Biobehav Rev* 35: 377–406.
- Fuermaier AB, Tucha L, Koerts J, et al. (2017) Effects of methylphenidate on memory functions of adults with ADHD. *Appl Neuropsychol Adult* 24: 199–211.
- Glisky EL (1996) Prospective memory and the frontal lobes. In: Brandimonte MA, Einstein GO and McDaniel MA (eds) *Prospective Memory: Theory and Applications*. Mahwah, NJ: Lawrence Erlbaum, pp. 249–266
- Hadjiefthymiou F, Fisk JE, Montgomery C, et al. (2011a) Everyday and prospective memory deficits in ecstasy/polydrug users. *J Psychopharmacol* 25: 453–464.
- Hadjiefthymiou F, Fisk JE, Montgomery C, et al. (2011b) Prospective memory functioning among ecstasy/polydrug users: Evidence from the Cambridge Prospective Memory Test (CAMPROMPT). *Psychopharmacology* 215: 761–774.
- Han DD and Gu HH (2006) Comparison of the monoamine transporters from human and mouse in their sensitivities to psychostimulant drugs. *BMC Pharmacol* 6: 6.
- Haney M, Hart C, Collins ED, et al. (2005) Smoked cocaine discrimination in humans: Effects of gabapentin. *Drug Alcohol Depend* 80: 53–61.
- Hart CL, Van Gorp W, Haney M, et al. (2001) Effects of acute smoked marijuana on complex cognitive performance. *Neuropsychopharmacology* 25: 757–765.
- Hazekamp A, Ruhaak R, Zuurman L, et al. (2006) Evaluation of a vaporizing device (Volcano®) for the pulmonary administration of tetrahydrocannabinol. *J Pharm Sci* 95: 1308–1317.
- Heffernan TM (2008) The impact of excessive alcohol use on prospective memory: A brief review. *Curr Drug Abuse Rev* 1: 36–41.
- Heffernan TM, Jarvis H, Rodgers J, et al. (2001) Prospective memory, everyday cognitive failure and central executive function in recreational users of Ecstasy. *Hum Psychopharm Clin* 16: 607–612.
- Heffernan TM, Moss M and Ling J (2002) Subjective ratings of prospective memory deficits in chronic heavy alcohol users. *Alcohol Alcohol* 37: 269–271.
- Higgins ST, Bickel WK, Hughes JR, et al. (1990) Effects of intranasal cocaine on human learning, performance and physiology. *Psychopharmacology* 102: 451–458.
- Hopper J, Karlsgodt K, Adler C, et al. (2004) Effects of acute cortisol and cocaine administration on attention, recall and recognition task performance in individuals with cocaine dependence. *Hum Psychopharm Clin Exp* 19: 511–516.
- Jex H, Mc Donnell J and Phatak A (1966) A “critical” tracking task for man-machine research related to the operator’s effective delay time. Part I-Theory and experiments with a first-order divergent controlled element. NASA CR-616. *NASA Contract Rep NASA CR*: 1–105.
- Kliegel M, Martin M, McDaniel MA, et al. (2001) Varying the importance of a prospective memory task: Differential effects across time- and event-based prospective memory. *Memory* 9: 1–11.
- Kutlu MG and Gould TJ (2016) Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: Contributions to development and maintenance of addiction. *Learn Mem* 23: 515–533.
- Leitz JR, Morgan CJ, Bisby JA, et al. (2009) Global impairment of prospective memory following acute alcohol. *Psychopharmacology* 205: 379–387.
- Linssen A, Sambeth A, Vuurman E, et al. (2014) Cognitive effects of methylphenidate in healthy volunteers: A review of single dose studies. *Int J Neuropsychopharmacol* 17: 961–977.
- Marchant NL, Trawley S and Rusted JM (2008) Prospective memory or prospective attention: Physiological and pharmacological support for an attentional model. *Int J Neuropsychopharmacol* 11: 401–411.
- Marracini ME, Weyandt LL, Rossi JS, et al. (2016) Neurocognitive enhancement or impairment? A systematic meta-analysis of prescription stimulant effects on processing speed, decision-making, planning, and cognitive perseveration. *Exp Clin Psychopharmacol* 24: 269–284.
- McDaniel MA and Einstein GO (1993) The importance of cue familiarity and cue distinctiveness in prospective memory. *Memory* 1: 23–41.
- Mehta MA, Goodyer IM and Sahakian BJ (2004) Methylphenidate improves working memory and set-shifting in AD/HD: Relationships to baseline memory capacity. *J Child Psychol Psychiatry* 45: 293–305.
- Montgomery C, Ashmore KV and Jansari A (2011) The effects of a modest dose of alcohol on executive functioning and prospective memory. *Hum Psychopharmacol* 26: 208–215.
- Moskowitz H (1973) Laboratory studies of the effects of alcohol on some variables related to driving. *J Safety Res* 5: 185–199.
- Muñoz-Cuevas FJ, Athilingam J, Piscopo D, et al. (2013) Cocaine-induced structural plasticity in frontal cortex correlates with conditioned place preference. *Nat Neurosci* 16: 1367–1369.
- Muriach M, López-Pedrajas R, Barcia JM, et al. (2010) Cocaine causes memory and learning impairments in rats: Involvement of nuclear factor kappa B and oxidative stress, and prevention by topiramate. *J Neurochem* 114: 675–684.
- Paraskevaides T, Morgan CJ, Leitz JR, et al. (2010) Drinking and future thinking: Acute effects of alcohol on prospective memory and future simulation. *Psychopharmacology* 208: 301.
- Ramaekers JG, Kauert G, Theunissen EL, et al. (2009a) Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. *J Psychopharmacol* 23: 266–277.
- Ramaekers JG, Kuypers KPC, Wingen M, et al. (2009b) Involvement of inferior parietal lobules in prospective memory impairment during acute MDMA (ecstasy) intoxication: An event-related fMRI study. *Neuropsychopharmacology* 34: 1641.
- Ramaekers JG, Moeller M, van Ruitenbeek P, et al. (2006) Cognition and motor control as a function of $\Delta 9$ -THC concentration in serum and oral fluid: Limits of impairment. *Drug Alcohol Depend* 85: 114–122.
- Ramaekers JG, van Wel J, Spronk D, et al. (2016a) Cannabis and cocaine decrease cognitive impulse control and functional corticostriatal connectivity in drug users with low activity DBH genotypes. *Brain Imaging Behav* 10: 1254–1263.
- Ramaekers JG, van Wel JH, Spronk DB, et al. (2016b) Cannabis and tolerance: Acute drug impairment as a function of cannabis use history. *Sci Rep* 6: 26843.
- Ranganathan M and D’souza DC (2006) The acute effects of cannabinoids on memory in humans: A review. *Psychopharmacology* 188: 425–444.
- Rich JB, Svoboda E and Brown GG (2006) Diazepam-induced prospective memory impairment and its relation to retrospective memory, attention, and arousal. *Hum Psychopharmacol Clin Exp* 21: 101–108.
- Richardson JTE (2011) Eta squared and partial eta squared as measures of effect size in educational research. *Educ Res Rev* 6: 135–147.
- Schweri MM, Skolnick P, Rafferty MF, et al. (1985) [3H] Threo-(±)-Methylphenidate binding to 3, 4-Dihydroxyphenylethylamine uptake sites in corpus striatum: Correlation with the stimulant properties of ritalinic acid esters. *Journal of neurochemistry* 45: 1062–1070.
- Smith RE (2003) The cost of remembering to remember in event-based prospective memory: Investigating the capacity demands of delayed intention performance. *J Exp Psychol Learn Mem Cogn* 29: 347.
- Solowij N and Battisti R (2008) The chronic effects of cannabis on memory in humans: a review. *Current drug abuse reviews* 1: 81–98.
- Spronk DB, van Wel JH, Ramaekers JG, et al. (2013) Characterizing the cognitive effects of cocaine: A comprehensive review. *Neurosci Biobehav Rev* 37: 1838–1859.
- Stringfield S, Higginbotham J, Wang R, et al. (2017) Role of glucocorticoid receptor-mediated mechanisms in cocaine memory enhancement. *Neuropharmacology* 123: 349–358.

- Svetlov SI, Kobeissy FH and Gold MS (2007) Performance enhancing, non-prescription use of Ritalin: A comparison with amphetamines and cocaine. *J Addict Dis* 26: 1–6.
- Theunissen EL, Heckman P, de Sousa Fernandes Perna EB, et al. (2015) Rivastigmine but not vardenafil reverses cannabis-induced impairment of verbal memory in healthy humans. *Psychopharmacology* 232: 343–353.
- 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.
- Underwood AG, Guynn MJ and Cohen A-L (2015) The future orientation of past memory: The role of BA 10 in prospective and retrospective retrieval modes. *Front Hum Neurosci* 9: 668.
- van den Berg E, Kant N and Postma A (2012) Remember to buy milk on the way home! A meta-analytic review of prospective memory in mild cognitive impairment and dementia. *J Int Neuropsychol Soc* 18: 706–716.
- van Wel J, Spronk D, Kuypers K, et al. (2015) Psychedelic symptoms of cannabis and cocaine use as a function of trait impulsivity. *J Psychopharmacol* 29: 324–334.
- van Wel JHP, Kuypers KPC, Theunissen EL, et al. (2011) Blockade of 5-HT₂ receptor selectively prevents MDMA-induced verbal memory impairment. *Neuropsychopharmacology* 36: 1932–1939.
- van Wel JHP, Kuypers KPC, Theunissen EL, et al. (2013) Single doses of THC and cocaine decrease proficiency of impulse control in heavy cannabis users. *Br J Pharmacol* 170: 1410–1420.
- West R and Craik FI (2001) Influences on the efficiency of prospective memory in younger and older adults. *Psychol Aging* 16: 682–696.
- West R and Kropfing J (2005) Neural correlates of prospective and retrospective memory. *Neuropsychologia* 43: 418–433.
- Wood S, Sage JR, Shuman T, et al. (2014) Psychostimulants and cognition: A continuum of behavioral and cognitive activation. *Pharmacol Rev* 66: 193–221.