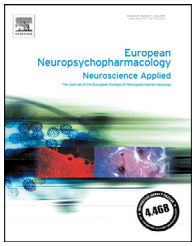
Article details

Hutten N.R.P.W., Steenbergen L., Colzato L.S., Hommel B., Theunissen E.L., Ramaekers J.G. & Kuypers K.P.C. (2019), Cocaine enhances figural, but impairs verbal 'flexible' divergent thinking, European Neuropsychopharmacology 29(7): 813-824.
Doi: 10.1016/j.euroneuro.2019.06.003

European Neuropsychopharmacology (2019) 29, 813–824

www.elsevier.com/locate/euroneuro



Cocaine enhances figural, but impairs verbal 'flexible' divergent thinking

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Received 14 December 2018; received in revised form 6 June 2019; accepted 10 June 2019

KEYWORDS
Cocaine;
Divergent creative thinking;
Convergent thinking;
Positive mood

Abstract
Anecdotal evidence suggests that cocaine use will help overcome creative 'blocks' by enhancing flexible thinking. Given that cocaine is likely to enhance dopamine (DA) levels, which in turn are positively associated with divergent thinking (DT); is a possibility that is tested in the present study. Furthermore, the impact of cocaine is tested on convergent thinking (CT), another aspect of creative thinking, which has been reported to be impaired with high DA levels. It was hypothesized that cocaine would enhance DT and impair CT. A placebo-controlled within-subjects study including 24 healthy poly-drug users was set up to test the influence of oral cocaine (300 mg) on creativity. Verbal CT was assessed with the Remote Associates Task (RAT); figural CT was assessed with the Picture Concepts Task (PCT) and the Tower of London (TOL). Verbal DT was assessed with the Alternative Uses Task (AUT); figural DT was assessed with the Pattern/Line Meanings Task (PLMT). Findings showed that, compared to placebo, cocaine impaired figural CT (TOL) and flexible DT of verbal stimuli (AUT), while it enhanced figural DT (PLMT). No significant effects of cocaine were observed regarding the PCT and RAT. It was demonstrated that cocaine-induced effects on creativity in poly-drug users are stimulus-dependent. Cocaine enhanced performance on figural DT but impaired performance on verbal (flexible) DT. Cocaine impaired CT on only one figural task and but not on the other tasks. As

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https://doi.org/10.1016/j.euroneuro.2019.06.003

creativity is an important aspect in cognitive therapies, it is important to further understand these discrepancies in creativity task performance.

1. Introduction

Cocaine is a stimulant drug with the highest lifetime prevalence in Europe as compared to other drugs of abuse (EMCDDA, 2017). While cocaine is known for its enhancing effects on mood and alertness (Farré et al., 1993; Kuypers et al., 2015; Van Wel et al., 2015), a large body of anecdotal evidence suggests that people sometimes use it to induce creative flexible thinking, helping to overcome creative 'blocks' (Douglas Fields, 2013; Greene, 2014; Hesse, 2013; Katigbak, 2014). These reports have however never been substantiated by means of objective performance measures. Of note, studies have demonstrated a discrepancy between self-rated and computer-assessed cognitive performance during intoxication with similar stimulant substances. For instance, while a mixture of amphetamines did not enhance cognition objectively, participants reported performance enhancement (Ilieva et al., 2013). Similarly, studies often fail to distinguish between enhanced performance versus increased interest in creative tasks and/or experienced creativity (Chatterjee et al., 2006).

Similar to the effect of amphetamines, the acute administration of cocaine increases synaptic dopamine (DA) levels (Volkow et al., 1999), which underlies cocaine's main effects on behaviour and mood (Han and Gu, 2006; Schweri et al., 1985), and suggested to play an important role in creativity. Although cocaine acts as a triple reuptake inhibitor, inhibiting serotonin, norepinephrine, and DA reuptake, the boost in creative performance of Parkinson patients after treatment with dopamine replacement therapy (Batir et al., 2009; Canesi et al., 2012; Inzelberg, 2013; Kulisevsky et al., 2009; Lhommée et al., 2014) and the impairment in schizophrenic patients' creativity after DA inhibition (Murry and Torrecuadrada, 1997) supports the suggestion that the dopaminergic system is a key factor in driving creativity. Interestingly, the relation between DA levels and creative performance has been suggested to be dependent on the type of creative process, potentially due to a difference in underlying neuronal mechanisms (Hommel, 2012; Jauk et al., 2012). The first stage in a typical creative act is 'flexible' *divergent thinking*, also known as brainstorming. It is the ability to come up with multiple solutions or ideas in response to a vaguely defined problem and it is usually quantified with 4 descriptors, i.e., fluency, the amount of ideas generated; originality, the novelty of the generated ideas; flexible thinking, the ability to come up with ideas from different angles (categories); and elaboration, the amount of details the idea contains (Guilford, 1967) The second stage consists in *convergent thinking;* defined as the ability to find the correct solution to a better defined problem (Guilford, 1967; Mednick, 1962). As compared to divergent thinking, convergent thinking emphasizes speed, relies on high accuracy and logic, and performance is independent of the former type (Guilford, 1967).

It has been suggested that the relationship between divergent thinking and DA levels follows an inverted u-shape, with optimal creative performance with medium DA levels (Akbari Chermahini and Hommel, 2010). Convergent thinking, in contrast, is assumed to be negatively associated with DA levels, with best performance with low and worst performance with high DA levels (Akbari Chermahini and Hommel, 2010). Importantly, however, these relations between DA levels have been reported from verbal creativity tasks, and it remains to be seen whether the observations generalize to nonverbal material. Unfortunately, the distinction between verbal and figural tasks is often not considered in creativity studies, even though different brain networks in different cortical hemispheres are involved in the processing of these stimuli (Bartolic et al., 1999; Flaherty, 2005; Foster et al., 2005; Papousek et al., 2009), which could imply different DA-creativity relations.

Personal factors like mood *state* and *trait* empathy have been shown to contribute to creative performance (Grattan and Eslinger, 1989; Shamay-Tsoory et al., 2003, 2002; Takeuchi et al., 2014), and cocaine is known to interact with mood *state*, while experienced effects of cocaine can be associated with a certain personality *trait* (Van Wel et al., 2015). According to the dopaminergic theory of positive affect, there is a positive relationship between levels of affect, DA, and creative (divergent) problem solving; with positive mood being associated with high levels of DA and enhanced verbal and figural divergent thinking, while verbal convergent thinking seems to be impaired by positive mood states (Akbari Chermahini and Hommel, 2012; Ashby and Isen, 1999; Ashby et al., 2002; Baas et al., 2008; Bartolic et al., 1999; Davis, 2009; Grawitch et al., 2003; Hirt et al., 1997, 1996; Hommel, 2012). The effect of positive mood on figural convergent thinking is unknown. In line with mood *state*, research on *trait* empathy found empathy levels to be positively associated with both, verbal and figural, divergent thinking (Grattan and Eslinger, 1989; Shamay-Tsoory et al., 2003, 2002; Takeuchi et al., 2014); higher scores on divergent thinking were associated with higher *trait* empathy, while *state* empathy does not correlate with creativity (Mason et al., 2019).

The present study was set up to test the acute effects of cocaine on objective and self-rated creative performance and to test whether potential behavioural drug effects are associated with personal factors like mood *state* and *trait* empathy. Based on cocaine's biological and psychological mechanism of action, i.e. elevating dopamine levels and enhancing positive mood, it was hypothesized that cocaine would impair convergent thinking and enhance divergent thinking, as assessed by objective performance measures, and increase subjectively experienced creativity. Secondly, it was hypothesized that drug-induced divergent thinking performance would be associated with drug-induced positive mood and that higher levels of empathy would be associated with enhanced divergent thinking.

Table 1 Mean (±SD) drug use of participant in number of uses in life-time and last month.

	Life-time use			Last month use		
	Mean (SD)	Range (min-max)	N	Mean (SD)	Range (min-max)	N
Cocaine[a]	34.68 (35.1)	6-150	24	2.88 (2.6)	1-10	12
Amphetamine[a]	12.93 (16.6)	1-50	17	1.75 (1.0)	1-3	4
Cannabis[a]	163.71 (256.9)	1-1000	24	4.9 (4.3)	1-10	7
Ecstasy/MDMA[a]	23.50 (17.6)	2-70	23	1.17 (0.4)	1-2	6
LSD[a]	2.00 (2.0)	1-5	4	-	-	0
Mushrooms[a]	2.13 (1.6)	1-5	16	1 (0.0)	-	2
Other psychoactive substances[b]	2CB (3), Ketamine (30), Methoxetamine(1), 6-APB (1), GHB (30), Truffles (4), Crack cocaine (1)			Ketamine (2), GHB (4), truffles (1)		

[a] Some participants did not quantify their use in words or numbers, some only quantified it in words: Amphetamine: 'sometimes' (1x), 'regularly' (1x); Cannabis: 'yes' (2x), 'often' (1x), 'very often' (1x), 'not a lot' (1x), 'regularly (during a specific period)' (2x); Cocaine: 'yes' (1x), 'very often' (1x), 'more often' (1x), 'regularly' (1x); Ecstasy: 'yes' (1x), 'regularly' (1x), 'more often' (1x); Mushrooms: 'more often' (1x).

[b] Other psychoactive substances: the numbers between brackets indicate the number of time the participant used the substance.

2. Experimental procedures

2.1. Design

The study design was double-blind, placebo-controlled, within-subject with two treatment conditions, placebo and cocaine HCl (300 mg). Participants were randomly assigned to one of the two treatment condition orders according to a balanced block design. The dosage of cocaine was based on previous experimental studies demonstrating significant cognitive effects (Fillmore et al., 2006; Rush et al., 1999; Van Wel et al., 2013). Cocaine and placebo were encapsulated and randomized by the GMP licensed company Basic Pharma (Geleen, The Netherlands). Even though the majority of cocaine users prefer nasal as route of administration (EMCDDA, 2014), cocaine was administered orally because it allows a double-blind administration and it results in a longer intoxication hence a wider test frame. In addition, potential side-effects from nasal administration are prevented in that way (Fillmore et al., 2006). All tests were performed between 1 and 2 h post-treatment around expected peak concentrations of cocaine (Van Wel et al., 2013). Test days were separated by a minimum wash-out period of 7 days to avoid carry-over effects.

2.2. Participants

Participants were 24 healthy recreational poly-drug users (19 males; 5 females), aged 22.2 years on average (SD= 2.3). All of them were native speakers of Dutch. Participants indicated their highest level of education to be academic university (N = 12; 50%) and university of applied sciences (N = 8; 33%), two participants (8%) indicated to have finished secondary education (gymnasium etc.) but did not indicate their current level of education, and one participant indicated to be a student without reporting the level of education. Life time cocaine use was 34.7 times on average (SD= 35.1). Experience with the use of other substances such as amphetamines, cannabis, MDMA, LSD, mushrooms, and other psychoactive substances were also reported. Details of drug use history are presented in Table 1.

2.3. Procedures

Participants were recruited through advertisements in university buildings in Maastricht, via a website (digi-prik.nl), local newspaper advertisement, and by word of mouth. Before inclusion, participants underwent a medical screening by a medical supervisor. General health was checked and blood and urine samples were taken for standard blood chemistry, haematology and urinalysis. Inclusion criteria were written informed consent; age 18-40 years; good physical and mental health as determined by medical history and medical examination; BMI between 19-29 kg/m^2. Exclusion criteria were being cocaine naïve; history of drug abuse or addiction as assessed via an extensive interview by an experienced medical supervisor using the DSM-IV criteria; history of psychiatric and neurological disorders as assessed via the medical interview; cardiovascular abnormalities; hypertension; excessive alcohol use defined as drinking more than 21 alcohol consumptions per week; pregnancy or lactation.

Participants were familiarized with tests and test procedures and completed the Empathizing-Systemizing Quotient questionnaire during a training session proceeding the test days. They had to refrain from any drugs at least one week before start of the study until completion of their testing days. Participants were requested to not consume caffeinated or alcoholic beverages 24 h prior to testing and to arrive well-rested at the test facilities. Upon arrival they were screened for presence of drugs of abuse in urine (THC/opiates/cocaine/amphetamines/methamphetamines), and alcohol in breath. Women were submitted to a urine pregnancy test. When tests were negative, participants filled out a questionnaire to assess sleep quality and quantity and they had a light standardized breakfast. After breakfast participants were administered a capsule p. o. containing either 300 mg cocaine HCl or placebo. Sixty minutes post-treatment a mood questionnaire and a visual analogue scale (VAS) scale measuring subjective creativity was filled out, a blood sample was taken to determine cocaine concentration afterwards and the test battery consisting of tests of creativity and emotion recognition (results published in Kuypers et al., 2015) was presented in the following order: AUT, PLMT, PCT, RAT, TOL and emotion recognition. Between treatment administration and the tests battery participants were seated in a quiet waiting room where they could read a book or watch television.

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. It was registered in the Dutch Clinical Trial register (number: NTR3998 http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3998). A permit for obtaining, storing and administering cocaine was obtained from the Dutch Drug Enforcement Administration. The present study was carried out in

the context of a larger trial on emotion recognition, which for the most part (except for the present data) has been reported elsewhere (Kuypers et al., 2015).

2.4. Convergent thinking

Convergent thinking was assessed by means of three tasks, the Remote Associates Task (RAT), the Picture Concept Task (PCT), and the Tower of London (TOL). All tests had parallel versions to avoid learning effects.

The RAT is a *verbal* convergent thinking task based on Mednick (1962). The Dutch version comprised 30 validated items (Akbari Chermahini et al., 2012) divided into two versions of 15 items, of which 8 were 'easy' items and 7 'difficult'. Item difficulty categorization was based on a study by Akbari Chermahini et al. (2012). Each item consisted of three unrelated words, such as "time", "hair", and "stretch", and participants' task was to identify the common associate ("long") which would result in existing Dutch composite words. There was a time frame of 10 min for 15 items. The percentages of correct answers for 'easy' and 'difficult' items were the main dependent variables.

The PCT is a *figural* convergent thinking task consisting of 28 items per parallel version. Each stimulus contained a matrix with 4 to 12 colour pictures shown in two or three rows. Participants' task was to find an association between pictures of the different rows (one picture of each row). They were instructed to provide the correct solution, within a timeframe of 30 s per stimulus. Items consisting of 4–6 pictures were categorized as 'easy' and items with 9 - 12 pictures as 'difficult'. Percentages correct for 'easy' items and 'difficult' items were taken as dependent measures.

The TOL assesses executive function and planning (Shallice, 1982) and is not a 'typical' creativity task. However, it is used as a *figural* convergent thinking task in the present study, because the task contains the rationale of convergent thinking; finding the correct solution to one particular problem. The TOL consists of 44 computer-generated images of beginning- and end- arrangements of three coloured balls on three sticks. Participants' task was to determine as quickly as possible how many ball-movements were needed to get to the end arrangements. Items composed of 2 and 3 steps were categorized as 'easy' and items composed of 4 and 5 steps as 'difficult', two items composed of 6 steps were control items and therefore not included in the analyses. Percentages of correct answers for 'easy' items and 'difficult' items were the main performance measures. Reaction time in seconds was taken as secondary performance measure, for 'easy' and 'difficult' items separately.

2.5. Divergent thinking

Divergent thinking was assessed by means of two tasks; the Alternative Uses Task (AUT) and the Pattern/Line Meanings Task (PLMT). Both tasks had parallel versions to avoid familiarization of the stimuli presented.

The AUT is a *verbal* divergent thinking task based on Guilford (1967). Participants were presented with the names of two common household items (e.g., towel and newspaper) and were to generate as many possible alternative uses of these objects as possible within 6 min.

The PLMT (Wallach and Kogan, 1965) is a *figural* divergent thinking task consisting of eight black and white drawings, i.e. two parallel versions were created, comprising the uneven line figures and even pattern figures from the original task, or reversed. Participants had to give meaning to a configuration of patterns (4 drawings) or lines (4 drawings) and generate as many explanations for it as possible, trying to be as creative as possible and were allowed 2 min response time per item (Claridge and McDonald, 2009). Patterns and lines were analysed as two different outcome measures.

Dependent outcome variables for both tasks were fluency, originality, ratio, flexibility and elaboration. Fluency was the total number of valid responses. Originality, the uniqueness of responses which was scored with 0, 1, and 2; responses that were given by only 1% of the group counted as unique (2 points), responses given by 5% counted as unusual (1point) and answers given by more than 5% received a score of zero. Summed originality scores served as dependent variable for AUT and PLMT. Ratio (originality/fluency) was also calculated to correct the originality scores for the number of responses that were generated; somebody who gives two 'unusual' original answers and somebody who gives only one 'unique' original answer receive a score of '2' on originality in total, while the number of answers differ; the ratio will reflect this difference in quality with the first person getting a lower ratio (1) than the second one (2). Flexibility is the ability to generate a diversity of responses and was measured by combining responses into different numbers of categories. Elaboration was the amount of detail in the answers. Flexibility and elaboration are normally not used as an outcome variable for the PLMT; the present study added these variables to compare verbal and figural divergent thinking.

2.6. Subjective creativity

Participants had to assess their subjective levels of creativity via a Visual Analogue Scale (10 cm); with 0 indicating 'not creative at all' and 10 indicating 'very creative'.

2.7. Positive mood state

Positive Mood was measured by the Profile of Mood States (POMS) questionnaire. Participants were shown 72 adjectives describing a specific mood and they had to rate their current state using 5-point Likert scales, with 0 being 'not at all' to 4 'extremely'. The POMS is a validated scale, comprised of 5 positive and 5 negative affect scales. One of the positive affect scales, positive mood was determined by using composite score of 2 levels of mood (Elation – Depression) (De Wit et al., 2002).

2.8. Trait empathy

Trait empathy, the drive to identify mental states and respond to those with an appropriate emotion was assessed using the Empathizing (EQ) and Systemizing quotient (SQ) questionnaire. The EQ scale comprised of 60 statements, of which 20 filler items, in a forced-choice format (i.e., strongly agree; slightly agree; slightly disagree; strongly disagree). The maximum score, indicating very high empathy, is 80 (Baron-Cohen et al., 2003; Baron-Cohen and Wheelwright, 2004; Claridge and McDonald, 2009).

2.9. Pharmacokinetic assessments

Blood samples were centrifuged at 3500 rpm and resulting plasma was frozen at −20 °C until analysis for pharmacokinetic assessments. The determination of cocaine (COC), and its metabolites benzoylecgonine (BZE) and ecgonine methyl ester (EME) were determined in a specialized forensic-toxicological laboratory using validated procedures (Toennes et al., 2008, 2005).

2.10. Statistical analysis

Statistical analyses were performed by means of the statistical package IBM SPSS Statistics (version 24). Data of the convergent thinking tasks were analysed by means of a General Linear Model (GLM) repeated measures (RM) Multivariate Analysis of Variance (MANOVA) with Treatment (2 levels) and Item Difficulty (2 levels) as within-subjects (WS) factors, and Test Day Order (2 levels) as between-subjects (BS) factor. In case of no main effect of Test Day Order, a GLM RM Analysis of Variance (ANOVA) with Treatment (2 levels) and Item Difficulty (2 levels) as within-subjects (WS) factors was conducted. In case of interaction effects paired samples *t*-tests were conducted between treatment conditions, per item difficulty.

Since *trait* empathy is associated with divergent thinking (Takeuchi et al., 2014), separate GLM RM Multivariate Analysis of Covariances (MANCOVA) with empathy total score as a covariate to control for empathy levels, Treatment (2 levels) as WS factor and Test Day Order (2 levels) as BS factor were conducted on the dependent variables of the divergent thinking tasks. In case of no main effect of Test Day Order, a GLM RM Analysis of Covariance (ANCOVA) with empathy as covariate and Treatment (2 levels) WS factor was conducted. In case of interaction effects, Pearson correlation analyses were conducted to further explore the relationship between task performance and empathy levels using placebo-change performance scores (cocaine minus placebo).

The effect of Treatment on Positive Mood and subjective creativity was analysed by means of a paired samples *t*-test. In addition, a series of Pearson correlation analyses including placebo-change scores were conducted to assess the relationship between task performance and positive mood ratings on the one hand, and subjective creativity on the other hand.

Assuming an omnibus $p < 0.05$ and power = 0.8, we estimated including 24 subjects would enable detection of performance differences between cocaine and placebo with an effect size of 0.3 (i.e., a signal change of 0.3 times the standard deviation) in within subject comparisons. The alpha criterion level of statistical significance for all analyses was set at $p = 0.05$. To correct for multiple testing the alpha criterion was divided by the number of tests per construct; for convergent thinking, the alpha criterion was set at $p = 0.01$ and for divergent thinking the alpha criterions was set at $p = 0.02$. 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).

3. Results

Blood plasma concentrations (mean (SD)) 1 h after cocaine administration, at the start of cognitive testing were 0.57 mg/L (0.37) for cocaine, 0.69 mg/L (0.20) for BZE, and 0.22 mg/L (0.11) for EME.

3.1. Missing data

Due to noncompliance with task instructions, AUT data were missing for one participant in both treatment conditions. Due to technical issues, computer responses for the TOL were not registered for one participant in the placebo condition. Therefore 23 participants with complete AUT and TOL data-sets entered the analyses. For three participants, a different item of the *trait* empathy EQ scale was missing; these missing values were replaced with the mean value of the other answers on that scale for that participant.

3.2. Trait empathy and positive mood state

Participants had a mean score of 37.50 ($SD = 8.23$) on *trait* Empathy. Positive mood was significantly elevated ($t_{23} = 2.15$, $p = 0.04$) by cocaine ($M = 14.00$, $SE = 1.52$) compared to placebo ($M = 10.71$, $SE = 0.86$).

3.3. Subjective creativity

Paired samples *t*-test revealed that subjective creativity was significantly increased by cocaine compared to placebo ($t_{23} = 3.56$, $p < 0.01$); participants felt more creative after cocaine treatment ($M = 5.84$, $SE = 0.43$) compared to placebo ($M = 4.01$, $SE = 0.36$).

3.4. Convergent thinking

GLM repeated measures MANOVA showed no main effect of Test Day Order on all the outcome variables of the convergent thinking tasks.

3.4.1. Verbal convergent thinking

GLM repeated measures ANOVA revealed a main effect of Item Difficulty on verbal convergent thinking, measured by the RAT ($F_{1,23} = 40.39$, $p < 0.01$, $\eta_p^2 = 0.64$); indicating that participants had a higher percentage correct for the easy items compared to difficult items. There was no main effect of Treatment ($F_{1,23} = 0.28$, $p = 0.60$, $\eta_p^2 = 0.01$) or Treatment by Item Difficulty interaction ($F_{1,23} = 0.09$, $p = 0.76$, $\eta_p^2 < 0.01$) on percentage correct of the RAT.

3.4.2. Figural convergent thinking

GLM repeated measures ANOVA revealed a main effect of Item Difficulty on all figural convergent thinking tasks; PCT ($F_{1,23} = 239.41$, $p < 0.01$, $\eta_p^2 = 0.91$) and TOL ($F_{1,22} = 63.13$, $p < 0.01$, $\eta_p^2 = 0.74$), indicating that the easy items were answered correctly more often compared to the difficult items. In case of the TOL, a Treatment by Item Difficulty Interaction showed that this effect was dependent on the treatment condition ($F_{1,22} = 15.43$, $p < 0.01$, $\eta_p^2 = 0.41$). Performance on difficult items was impaired ($t_{22} = -3.15$, $p < 0.01$) by cocaine ($M = 76.87$, $SE = 2.67$) compared to placebo ($M = 85.43$, $SE = 1.90$), leaving performance on easy items unaffected ($t_{22} = 1.20$, $p = 0.24$).

In addition, there was a main effect of Item Difficulty on reaction time of the TOL ($F_{1,22} = 147.67$, $p < 0.01$, $\eta_p^2 = 0.87$), indicating faster responses to easy items compared to difficult items.

There were no main effects of Treatment on percentage correct of the PCT ($F_{1,23} = 0.13$, $p = 0.72$, $\eta_p^2 < 0.01$) and TOL ($F_{1,22} = 2.77$, $p = 0.11$, $\eta_p^2 = 0.11$) or reaction time of the TOL ($F_{1,22} = 2.09$, $p = 0.16$, $\eta_p^2 = 0.09$); and no Treatment by Item Difficulty interaction effects on percentage correct of the PCT ($F_{1,23} = 0.55$, $p = 0.46$, $\eta_p^2 = 0.02$) and reaction time of the TOL ($F_{1,22} = 2.39$, $p = 0.14$, $\eta_p^2 = 0.09$).

Mean (± SE) scores of the convergent thinking tasks are depicted in Table 2.

Table 2 Mean (±SE) percentage correct on the Remote Association Task (RAT), Picture Concept Task (PCT) and Tower of London (TOL); and TOL reaction time in seconds.

Creativity tests and outcome measures		Treatment (Mean ±SE)				N
		Cocaine		Placebo		
		Easy	Difficult	Easy	Difficult	
Verbal	RAT (% correct)	58.86 (5.99)	44.64 (4.73)	56.77 (4.69)	39.88 (3.43)	24
Figural	PCT (% correct)	85.69 (2.62)	45.63 (4.51)	86.11 (1.91)	43.33 (3.24)	24
	TOL (% correct)	96.09 (0.91)	76.87 (2.67)	94.13 (1.62)	85.43 (1.90)	23
	TOL (Reaction Time)	5.43 (0.36)	13.11 (1.04)	5.75 (0.38)	14.59 (1.02)	23

3.5. Divergent thinking

GLM repeated measures MANOVA showed no main effect of Test Day Order on all the outcome variables of the divergent thinking tasks.

3.5.1. Verbal divergent thinking

GLM repeated measures ANCOVA revealed a main effect of Treatment on flexibility measured by the AUT ($F_{1,21}$= 6.20, p = 0.02, η_p^2 = 0.23), indicating that cocaine reduced flexible thinking when controlled for *trait* empathy. There was an interaction effect of Treatment and the covariate *trait* empathy on flexibility ($F_{1,21}$= 6.15, p = 0.02, η_p^2 = 0.23). A Pearson correlation revealed an association between *trait* empathy and the placebo-change scores of flexibility performance (r_{23}= 0.48; p = 0.02), indicating that participants with higher *trait* empathy were able to generate a higher diversity of responses while under the influence of cocaine compared with placebo (Fig. 1, panel A).

There were no Treatment effect on other outcome variables of the AUT; fluency ($F_{1,21}$= 3.32, p = 0.08, η_p^2 = 0.14), originality ($F_{1,21}$= 0.41, p = 0.53, η_p^2 = 0.02), ratio ($F_{1,21}$= 1.17, p = 0.29, η_p^2 = 0.05) and elaboration ($F_{1,21}$< 0.01, p = 0.99, η_p^2 < 0.01). There were no interaction effects of Treatment and *trait* empathy on the other outcome measures of the AUT; fluency ($F_{1,21}$= 3.48, p = 0.08, η_p^2 = 0.14), originality ($F_{1,21}$= 1.06, p = 0.31, η_p^2 = 0.05), ratio ($F_{1,21}$= 0.44, p = 0.52, η_p^2 = 0.02) and elaboration ($F_{1,21}$= 0.03, p = 0.87, η_p^2 < 0.01). Mean (± SE) of the AUT are depicted in Fig. 2.

3.5.2. Figural divergent thinking

3.5.2.1. PLMT-'Line' stimuli. GLM repeated measures ANCOVA revealed a Treatment effect on fluency ($F_{1,22}$= 6.70, p = 0.02, η_p^2= 0.23), originality ($F_{1,22}$= 6.09, p = 0.02, η_p^2= 0.22) and flexibility ($F_{1,22}$= 8.29, p< 0.01, η_p^2= 0.27) in the line category of the PLMT. When under the influence of cocaine participants were able to generate more responses, were more original and more divers compared to placebo. Furthermore, analyses revealed an interaction effect of Treatment and *trait* empathy on fluency ($F_{1,22}$= 8.15, p< 0.01, η_p^2= 0.27), originality ($F_{1,22}$= 8.29, p< 0.01, η_p^2= 0.27) and flexibility ($F_{1,22}$= 10.62, p< 0.01, η_p^2= 0.33) of the line category of the PLMT. Additional Pearson correlations revealed significant associations between the covariate *trait* empathy and placebo-change scores on fluency (r_{24}= 0.52; p< 0.01), originality (r_{24}= 0.52; p< 0.01) and flexibility (r_{24}= 0.57; p< 0.01), indicating that participants with higher *trait* empathy gave more responses and these were also more original and they were able to generate a higher diversity of responses under the influence of cocaine compared to placebo (Fig. 1, Panels B-D).

3.5.2.2. PLMT- 'Pattern' stimuli. GLM repeated measure ANCOVA revealed an interaction effect of Treatment and *trait* empathy on flexibility ($F_{1,22}$= 6.36, p = 0.02, η_p^2= 0.22) of the pattern category. Additional Pearson correlations revealed significant associations between *trait* empathy levels and placebo-change scores on flexibility (r_{24}= 0.47; p = 0.02) in the pattern category, indicating that participants with higher *trait* empathy were able to generate a higher diversity of answers under the influence of cocaine compared to placebo (Fig. 1, Panel E).

There were no Treatment effects on fluency ($F_{1,22}$= 2.71, p = 0.11, η_p^2 = 0.11), originality ($F_{1,22}$= 2.19, p = 0.15, η_p^2 = 0.09) and flexibility ($F_{1,22}$= 4.89, p = 0.04, η_p^2= 0.18) for the Patterns category, and no Treatment effects on ratio ($F_{1,22}$< 0.01, p = 0.98, η_p^2 < 0.01; $F_{1,22}$= 0.77, p = 0.39, η_p^2= 0.03) and elaboration ($F_{1,22}$= 0.32, p = 0.56, η_p^2= 0.01; $F_{1,22}$= 1.38, p = 0.25, η_p^2= 0.06) for both the Pattern and Line category respectively. There were no interaction effects of Treatment and *trait* empathy on fluency ($F_{1,22}$= 3.87, p = 0.06, η_p^2= 0.15) and originality ($F_{1,22}$= 3.42, p = 0.08, η_p^2= 0.14) for the pattern category, and no interaction effects on ratio ($F_{1,22}$= 0.01, p = 0.92, η_p^2 < 0.01; $F_{1,22}$= 1.66, p = 0.21, η_p^2= 0.07) and elaboration ($F_{1,22}$= 0.61, p = 0.44, η_p^2= 0.03; $F_{1,22}$= 0.38, p = 0.54, η_p^2= 0.02) for patterns and lines, respectively.

Mean (± SE) scores on the PLMT are shown in Fig. 2.

3.6. Correlational analyses of mood state and self-rated creativity with performance

Pearson correlation analyses revealed an association between the placebo-change scores of Positive Mood and performance measures: TOL Reaction Time for both difficulty levels (easy: r_{23}= −0.63, p< 0.01; difficult: r_{23}=−0.46, p = 0.03), and for fluency (r_{23}= 0.44, p = 0.04) and originality (r_{23}= 0.48, p = 0.02) on the AUT indicating that participants whose positive mood increased more under the influence of cocaine also became faster in responding in the TOL and were more original and gave more responses on the AUT relative to participants with smaller positive mood increments.

There was a significant correlation between the placebo-change scores (cocaine minus placebo) of self-rated

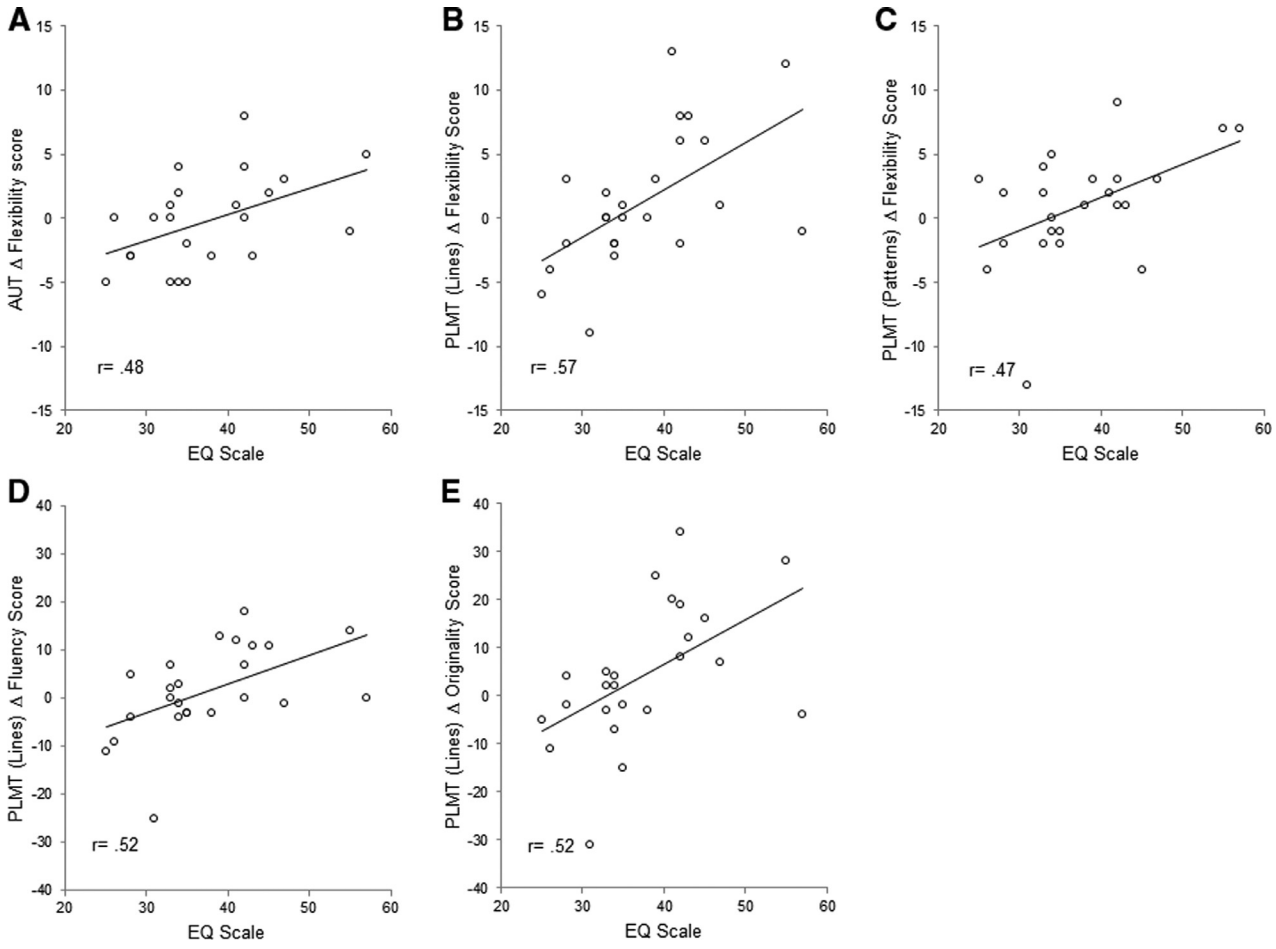

Fig. 1 Scatterplots of different scores on divergent thinking tasks (cocaine minus placebo) as a function of Empathy Quotient. Pearson correlations (r) statistically significant at $p<0.05$. EQ: empathy quotient; AUT: alternative uses task; PLMT: pattern/line meanings task.

creativity and correct responses on the TOL for the difficult items ($r_{23}= -0.50$, $p=0.02$), indicating that participants who had larger increases in self-rated creativity when under the influence of cocaine showed the largest decrease in performance for the difficult items of the TOL compared to participants who had smaller increases in figural convergent thinking when under the influence of cocaine.

There were no statistically significant correlations between other outcome measures of the creativity tasks and positive mood or subjective creativity (see Tables 3 and 4 respectively).

4. Discussion

The present study aimed to assess the acute effects of cocaine on self-rated creativity and creative task performance and the association between potential behavioural drug effects and personal factors like mood *state* and *trait* empathy in poly-drug users. Based on cocaine's mechanism of action it was expected that creative performance would be impaired during cocaine intoxication. Findings showed a dissociation of cocaine effects on DT with impairment of verbal flexible DT and enhancement of figural DT. CT was in general unaffected by cocaine, only one task (TOL) showed drug-induced impairment for difficult figural stimuli compared to easy stimuli. Cocaine increased self-rated creativity and these ratings were negatively associated with CT, only on difficult figural items. With regard to personal factors it was found that cocaine significantly increased positive mood compared to placebo and this was positively associated with figural CT (TOL) response time and verbal DT (AUT). Higher levels of *trait* empathy were associated with enhanced verbal and figural DT when under the influence of cocaine.

Interestingly, the anecdotal relationship between creative performance and cocaine intake reported by users was confirmed in the present study: when under the influence of cocaine, self-rated creativity levels were higher. However, this pattern was not reflected in the objective behavioural data, since cocaine enhanced figural DT only but it impaired verbal flexible DT and figural CT for difficult items, while performance on two other CT tasks was unaffected. These findings highlight the mismatch between subjective experiences and objective performance also demonstrated by other research with psychoactive substances (Ilieva et al., 2013; Lang et al., 1984).

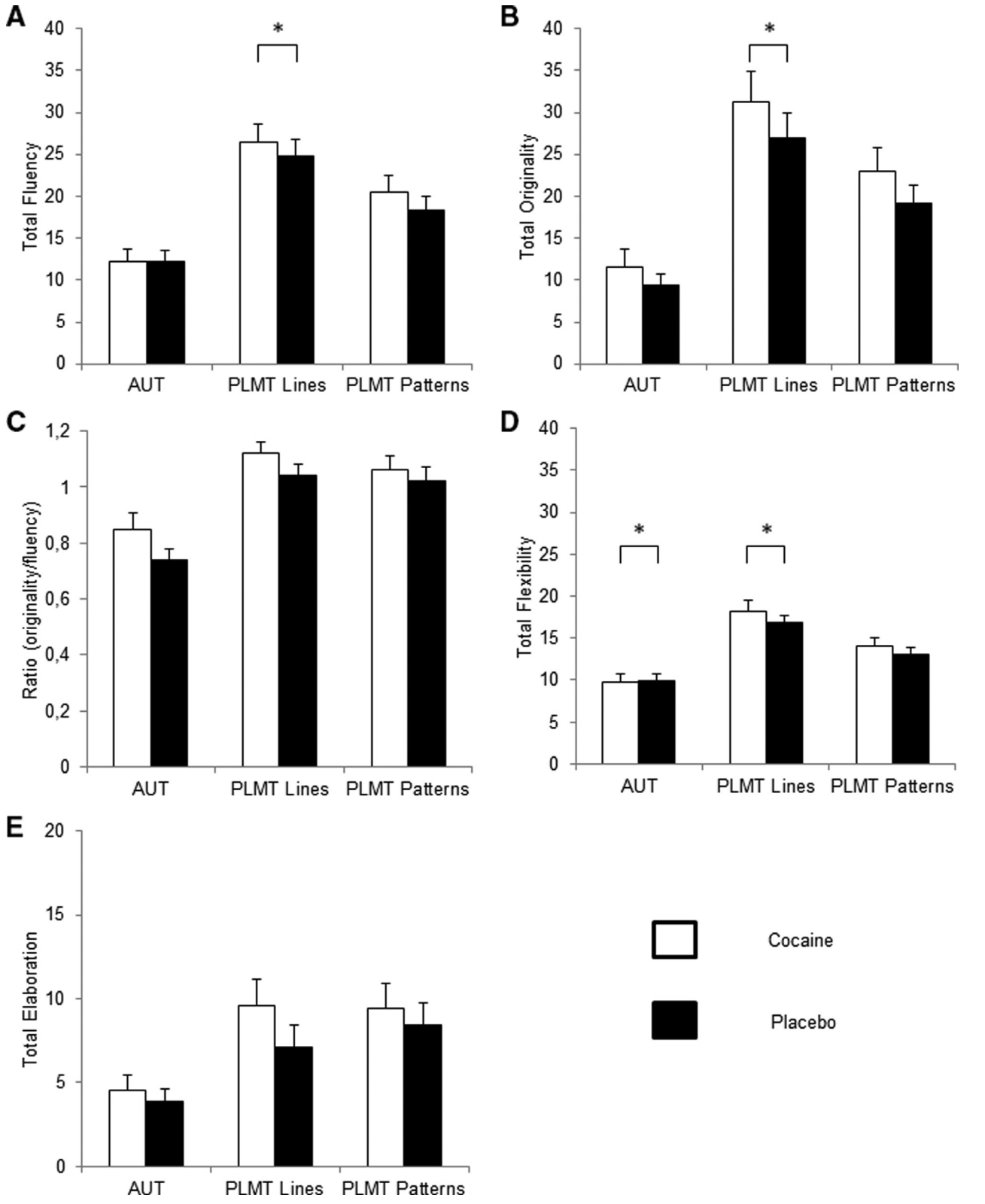

Fig. 2 Mean (±SE) scores of fluency (A), originality (B), ratio (C), flexibility (D) and elaboration (E) after cocaine and placebo administration of the AUT and over all items (patterns and lines) of the PLMT. * signifies statistically significant main Treatment at $p < 0.02$. AUT: alternative uses task; PLMT: pattern/line meanings task.

Table 3 Pearson correlations (r) between cocaine-induced positive mood ratings and the outcome measures of creativity tasks and corresponding significance levels (p).

Creativity tasks		Positive Mood			
Convergent		Easy Items		Difficult Items	
Verbal	RAT (% correct)	$r_{24}= 0.21$	$p=0.34$	$r_{24}= 0.23$	$p=0.29$
Figural	PCT (% correct)	$r_{24}= 0.07$	$p=0.75$	$r_{24}= -0.06$	$p=0.76$
	TOL (% correct)	$r_{23}= -0.09$	$p=0.70$	$r_{23}= -0.15$	$p=0.51$
	TOL (Reaction Time)	$r_{23}= -0.63$	$p< 0.01$	$r_{23}= -0.46$	$p=0.03$*
Divergent					
Verbal	AUT				
	Fluency	$r_{23}= 0.44$		$p=0.04$	
	Originality	$r_{23}= 0.48$		$p=0.02$	
	Ratio	$r_{23}= 0.11$		$p=0.63$	
	Flexibility	$r_{23}= 0.10$		$p=0.65$	
	Elaboration	$r_{23}= 0.10$		$p=0.66$	
Figural	PLMT	Patterns		Lines	
	Fluency	$r_{24}= 0.13$	$p=0.55$	$r_{24}= 0.25$	$p=0.24$
	Originality	$r_{24}= 0.23$	$p=0.29$	$r_{24}= 0.31$	$p=0.15$
	Ratio	$r_{24}= 0.19$	$p=0.39$	$r_{24}= 0.30$	$p=0.15$
	Flexibility	$r_{24}= 0.23$	$p=0.27$	$r_{24}= 0.19$	$p=0.38$
	Elaboration	$r_{24}< 0.01$	$p=0.97$	$r_{24}= 0.07$	$p=0.76$

* Statistically significant at $p<0.05$.

Table 4 Pearson correlations between cocaine-induced subjective creativity ratings and the outcome measures of creativity tasks and corresponding significance levels.

		Subjective creativity			
Convergent		Easy		Difficult	
Verbal	RAT (% correct)	$r_{24}= 0.19$	$p=0.35$	$r_{24}= -0.09$	$p=0.67$
Figural	PCT (% correct)	$r_{24}= -0.06$	$p=0.79$	$r_{24}= -0.29$	$p=0.17$
	TOL (% correct)	$r_{23}= -0.11$	$p=0.60$	$r_{23}= -0.50$	$p=0.02$*
	TOL (Reaction Time)	$r_{23}= -0.29$	$p=0.19$	$r_{23}= -0.20$	$p=0.36$
Divergent					
Verbal	AUT				
	Fluency	$r_{23}= 0.04$		$p=0.87$	
	Originality	$r_{23}= 0.11$		$p=0.61$	
	Ratio	$r_{23}= 0.07$		$p=0.76$	
	Flexibility	$r_{23}= 0.10$		$p=0.65$	
	Elaboration	$r_{23}= 0.03$		$p=0.90$	
Figural	PLMT	Patterns		Lines	
	Fluency	$r_{24}= -0.08$	$p=0.70$	$r_{24}= 0.08$	$p=0.71$
	Originality	$r_{24}= -0.16$	$p=0.46$	$r_{24}= 0.03$	$p=0.88$
	Ratio	$r_{24}= -0.22$	$p=0.30$	$r_{24}= 0.04$	$p=0.86$
	Flexibility	$r_{24}= -0.23$	$p=0.29$	$r_{24}= 0.03$	$p=0.88$
	Elaboration	$r_{24}= -0.06$	$p=0.77$	$r_{24}= 0.01$	$p=0.95$

* Statistically significant at $p<0.05$.

The findings on objective measures were not completely in line with the hypotheses, which were based on the biological effects of cocaine and previous creativity research suggesting that high levels of dopamine are in general negatively related to creativity (Akbari Chermahini and Hommel, 2010; Hommel, 2012). Important here might be the role of personal factors which also played a role in the present study. Participants whose mood increased the most compared to placebo showed more beneficial effects of cocaine on figural CT and verbal DT performance. Participants who scored higher on *trait* empathy also showed greater positive effects of cocaine on verbal and figural DT. Although this is a highly interesting finding, some caution is needed here. Research has shown that females, score in general higher on *trait* empathy than males (Baron-Cohen et al., 2003), which might indicate that cocaine-induced effects on DT are stronger in females than in to males. However, the current sample was too small to further explore the association between gender differences and *trait* empathy on creativity. In addition, while we only studied empathy as a

personality trait, future studies might also include creativity as a personality trait since it has previously been shown that participants low in trait creativity benefited the most from stimulant-induced creativity enhancement (Mohamed, 2016).

A strength of the present study is that creativity was tested with a broad range of tasks addressing verbal and figural, convergent and divergent thinking. In this light, the fact that cocaine only impaired performance on one CT task is interesting and is probably be due to task differences between the PCT and TOL and can perhaps be attributed to the basic cognitive processes that differ between tasks; the PCT asks for semantic associations while the TOL involves a strong spatial component. In addition, the direction of the cocaine effect on divergent thinking was dependent on the presented stimuli; i.e., whereas flexible thinking for figural stimuli was increased, flexibility was decreased when verbal stimuli were presented. A possible explanation for these findings might be sought in the underlying brain networks that are different for verbal and figural stimuli (Bartolic et al., 1999; Flaherty, 2005; Foster et al., 2005; Papousek et al., 2009). Furthermore, cocaine primarily affected flexibility in DT and while it was previously shown that a DA marker (eye-blink rate) selectively predicted flexible thinking (Akbari Chermahini and Hommel, 2010), it might be speculated that only this particular process is affected by DA changes while other outcome measures of DT are not. These findings underline the importance of using a large variety of tasks and stimuli in order to get a complete picture of the effects of a substance on a complex concept such as creativity.

Besides DA levels and personal factors, cocaine affects other neurotransmitters (Han and Gu, 2006; Schweri et al., 1985) which might have played a role as well (Wang et al., 2018). For instance, creativity was reportedly influenced by dexamphetamine (Farah et al., 2009), a stimulant drug targeting not only dopamine, but norepinephrine as well (Sallee and Smirnoff, 2004). Furthermore, in the study by Farah et al. (2009), effects of dexamphetamine on creativity performance were different when taking baseline performance into account; dexamphetamine was beneficial when participants scored low on baseline creativity, while the drug had detrimental effects when baseline creativity was high. Such baseline differences may be explained by baseline DA differences, as reflected in genetic polymorphisms. For example, an interaction between the catechol-O-methyltransferase (COMT) val/met and DA transporter (DAT) polymorphisms was found to predict individual differences in creativity performance (Zabelina et al., 2016). Regarding effects of cocaine, it is previously shown that cocaine effects on impulsivity are different depending on DBH genotype (Ramaekers et al., 2016). Hence, future studies might also include genetics to assess baseline differences in DA levels.

Although this study addressed an important question, only people with prior cocaine experience were included. This could limit the generalizability of the findings towards a drug-naïve population due to premorbid differences between these populations or changes caused in neural networks because of the recreational use of illicit substances (Colzato et al., 2008; Spronk et al., 2013). On the other hand, the level of education of the current sample was high which suggests the integrity of cognitive functions. Of interest here would be to include participants who differ in baseline cognitive functioning in future research, since it was previously shown that the cognition-enhancing effects of stimulant drugs is dependent on baseline performance with the highest gain for the low performers (Farah et al., 2009). Another interesting point for further research relates to the question which role personal factors that are directly affected by cocaine play in the cocaine-induced effect on creativity. Since previous studies have shown that mood influences creative thinking (Akbari Chermahini and Hommel, 2012; Ashby and Isen, 1999; Ashby et al., 2002; Baas et al., 2008; Bartolic et al., 1999; Davis, 2009; Grawitch et al., 2003; Hirt et al., 1997, 1996; Hommel, 2012) and the present study demonstrates that cocaine enhances positive mood; the possibility of positive mood being e.g. a mediator or moderator in the demonstrated effects on creativity cannot be substantiated. Future studies could include an extra condition in which mood is manipulated by a mood inducing technique and compare with positive mood induced by cocaine on behaviour. Furthermore, in order to understand the neurobiological underpinnings of the cocaine-induced creativity effects on neurotransmitter level, mechanistic studies can combine additional conditions in which cocaine is for instance combined with a dopamine and a serotonin receptor blocker. Previous studies have shown that besides dopamine, serotonin is also involved in creative thinking, with e.g. action of the 5-HT2A receptor leading to enhanced creativity (Kuypers et al., 2016; Mason et al., 2019).

To conclude, the present study demonstrated that a single dose of cocaine has different effects on creativity in poly-drug users, depending on a distinction between CT and DT as well as a difference in verbal and figural creativity tasks. Personal factors like positive mood *state* and *trait* empathy play an important role in the effects of cocaine on creativity, both showing to be positively associated with enhanced divergent thinking. As creativity is shown as an important aspect in cognitive therapies (Forgeard and Elstein, 2014), it is important to further understand the influence of personal factors on creativity and understand the underlying role of neurotransmitters.

Conflict of interest

The authors declare no conflict of interest.

Role of funding source

There was no funding.

CRediT authorship contribution statement

Nadia R.P.W. Hutten: Formal analysis, Writing - original draft, Writing - review & editing. **Laura Steenbergen:** Writing - review & editing, Project administration, Conceptualization. **Lorenza S. Colzato:** Writing - review & editing, Conceptualization. **Bernhard Hommel:** Writing - review & editing, Conceptualization. **Eef L. Theunissen:** Writing - review & editing, Conceptualization. **Johannes G. Ramaekers:** Writing - review & editing, Conceptualization. **Kim P.C. Kuypers:** Writing - review & editing, Conceptualization.

Acknowledgements

The authors would like to thank Cees van Leeuwen for the medical supervision and all the interns who have worked on this project.

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