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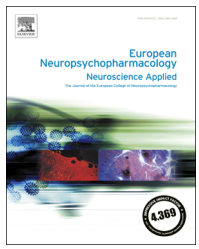

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Opposite effects of cannabis and cocaine on performance monitoring

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Abstract
Drug use is often associated with risky and unsafe behavior. However, the acute effects of cocaine and cannabis on performance monitoring processes have not been systematically investigated. The aim of the current study was to investigate how administration of these drugs alters performance monitoring processes, as reflected in the error-related negativity (ERN), the error positivity (Pe) and post-error slowing. A double-blind placebo-controlled randomized three-way crossover design was used. Sixty-one subjects completed a Flanker task while EEG measures were obtained. Subjects showed diminished ERN and Pe amplitudes after cannabis administration and increased ERN and Pe amplitudes after administration of cocaine. Neither drug affected post-error slowing. These results demonstrate diametrically opposing effects on the early and late phases of performance monitoring of the two most commonly used illicit drugs of abuse. Conversely, the behavioral adaptation phase of performance monitoring remained unaltered by the drugs.

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1. Introduction

Cannabis and cocaine are the two most commonly abused illicit drugs in Europe (EMCDDA, 2014). Cannabis contains a large number of different compounds belonging to the class of cannabinoids, of which delta-9-tetrahydrocannabinol (THC) is the most psychoactive (Mechoulam and Parker, 2013). Cocaine, by contrast, is a stimulant drug that excites the central nervous system (Rush and Baker, 2001). It increases dopaminergic activity by means of blocking the dopamine reuptake transporter (Volkow et al., 1997; Wise, 1984). The pharmacological effects of cannabis and cocaine directly affect cognition and mood (Green et al., 2003; Lukas et al., 1996). Cannabis impairs a wide range of cognitive functions including attention, memory and processing speed (Crean et al., 2011). Cocaine exerts cognitive enhancing effects on response inhibition (Fillmore et al., 2005; Garavan et al., 2008; Spronk et al., 2015) and reversal learning (Spronk et al., 2016). However, compared to cannabis, research on the acute cognitive effects of cocaine is less abundant. Cognitive changes associated with drug use might be implicated in behavior under influence and possibly contribute to unsafe and risky behavior. It is therefore surprising that performance monitoring, a collection of functions involved with safe and efficient responses to changing environmental demands, has only been scarcely investigated for cannabis (Kowal et al., 2015; Spronk et al., 2011) and not at all for cocaine. The current study sets out to investigate if and how acute administration of cannabis and cocaine affect behavioral and neurophysiological correlates of performance monitoring.

Two electrophysiological correlates of performance monitoring have been heavily investigated over the past 20 years: the error-related negativity (ERN) and error-positivity (Pe). Event-related potentials (ERPs) are particularly useful to investigate psychopharmacological effects of drugs as they provide an objective means of investigating covert cognitive processes that cannot always be investigated with behavioral measures alone. Moreover, they allow the investigation of subprocesses owing to their high temporal resolution. The error-related negativity is a negative event-related potential occurring between 50–100 ms after an erroneous response (Falkenstein et al., 1990; Gehring et al., 1993). The ERN is followed by the error positivity, which is a positive ERP component which develops between 200–400 ms after an erroneous response. The Pe reflects conscious awareness of an error (Nieuwenhuis et al., 2011; Overbeek et al., 2005) and is associated with conscious behavioral adaptations, e.g. the signaling of an error (Brazil et al., 2009; Endrass et al., 2007). Although both the ERN and Pe are indices of performance monitoring, they are functionally different and dichotomous (Brazil et al., 2009; Endrass et al., 2007; Nieuwenhuis et al., 2001). Post-error slowing (PES) is an established *behavioral* measure of performance monitoring (Debener et al., 2005; Rabbitt, 1966). It is the slowing of the reaction time to a stimulus following an erroneous response. The amplitude of the ERN has often been associated with automatic adaptive processes such as post-error slowing (Debener et al., 2005).

We and others have shown that THC administration in regular users results in a decrease of the ERN (Spronk et al., 2011; Kowal et al., 2015). This is in line with findings from other arousal-reducing drugs, such as alcohol and benzodiazepines which have also been associated with a reduced ERN (Bartholow et al., 2012; De Bruijn et al., 2004; Ridderinkhof et al., 2002; Spronk et al., 2011). The Pe was found to be reduced after THC (Kowal et al., 2015). Post-error slowing does not appear to be affected by THC (Kowal et al., 2015; Spronk et al., 2011). Performance monitoring correlates of cocaine have so far never been investigated. However, studies on the acute effects of other stimulant drugs with comparable psychopharmacological properties (e.g. caffeine, methylphenidate and *d*-amphetamine) consistently show an increase of the ERN (Barnes et al., 2014; De Bruijn et al., 2004; Tieges et al., 2004). Additionally, it has been shown that administration of methylphenidate does not affect the Pe (Barnes et al., 2014) and that *d*-amphetamine diminishes post-error slowing (Wardle et al., 2012).

Another ERP that has been associated with monitoring of behavior is the stimulus-locked N2. The N2 is associated with conflict as its amplitude is typically increased for high-conflict (incongruent) trials compared to low-conflict (congruent) trials (Kopp et al., 1996; Nieuwenhuis et al., 2003). The N2 congruency effect is reduced after administration of the benzodiazepine lorazepam, but is unaffected by a number of other substances such as THC, haloperidol, D-amphetamine and alcohol (Kenemans and Kähkönen, 2011; Kowal et al., 2015; Spronk et al., 2011). Interestingly, some of these substances do affect the ERN (e.g. THC, D-amphetamine, haloperidol and alcohol), suggesting that drugs can act independently on the separate processes reflected by the ERN and the N2 components.

Finally, the P1 and N1 ERPs reflect early visual processing and attentional processes (Luck et al., 1990), while the P300 is associated with late attentional processes and context updating (Polich and Kok, 1995). There is no evidence that cannabis and cocaine affect early attention related P1 and N1 components. In contrast, several studies have suggested that cannabis diminishes the amplitude of the P300 (Böcker et al., 2010; D'Souza et al., 2012; Spronk et al., 2015). For cocaine, the P300 findings are more mixed (Herning et al., 1985, 1987), but a recent report from our lab based on the same study sample (and thus same dosages) showed that cocaine enhances the NoGo-P300 ERP in a Go/NoGo task (Spronk et al., 2015). Taken together, these studies suggest that cannabis and cocaine might have opposite effects on the P300 ERP.

The aim of the current study was to investigate the acute effects of cannabis and cocaine on the above-mentioned manifestations of performance monitoring with a Flanker task (De Bruijn et al., 2004; Spronk et al., 2014) using a placebo-controlled crossover design. A group of healthy drug-using volunteers received either placebo, a dosage of 300 μg/kg body weight of cannabis with a booster of 150 μg/kg body weight, or 300 mg of cocaine with a booster of 150 mg on three separate testing days. The Flanker task was assessed immediately after the booster dosages. We hypothesized to find decreased ERN amplitudes following cannabis and increased ERN amplitudes after cocaine administration. Given the relatively high cannabis dose, we hypothesized the Pe to be diminished after cannabis, but to be unaffected by

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cocaine. We expected no alteration in post-error slowing after cannabis, but tentatively hypothesized that post-error slowing might be diminished after cocaine. In order to investigate the specificity of the hypothesized effect on performance monitoring, we additionally investigated the stimulus-locked ERPs discussed above. Based on the aforementioned studies, we expect no drug effects on the P1, N1 or the N2 congruency effect, while we hypothesized decreased P300 ERP amplitudes after cannabis and increased P300 amplitudes after cocaine.

2. Experimental procedures

2.1. Subjects

Sixty-four healthy regular (non-addicted) polydrug users were recruited through advertisements on the internet, university campuses, and word of mouth referrals. Three subjects were excluded (one withdrew consent after the first testing day, one had a cardiovascular reaction to the blood draw and study discontinuation was decided by the investigators, and one did not adhere to the abstinence instructions as confirmed by high baseline cannabinoid levels for each testing day). All participants were between 18–40 years and reported regular use of cannabis (>2 joints per week) and cocaine (>5 times in the past year). They furthermore had to be free from psychotropic medication, be in good physical health and have a normal weight (body mass index 18–28). Exclusion criteria were drug dependence; the presence or history of psychiatric or neurological disorder as assessed during a clinical interview (Sheehan et al., 1998), pregnancy or lactation, cardiovascular abnormalities as measured by ECG; hypertension; and excessive drinking (>20 units per week) or smoking (>20 cigarettes per day). See Table 1 for subject characteristics and a summary of drug use history.

Of the remaining sixty-one subjects, eight did not complete the Flanker task in the cannabis condition due to adverse reactions (i.e. unable to do the tasks due to extreme fatigue and feeling 'stoned'; 6 subjects) or refusal by the subject (1 subject), or no-show on the final testing day (1 subject). Furthermore, for one subject there was a technical problem with the Flanker task (cannabis condition) and for one there was a problem with markers in the EEG (cocaine condition). For the latter subject, the behavioral data were included in the analyses. Thus, the final analyses were based on 61 subjects in the placebo condition, 60 in the cocaine condition (61 for behavioral analyses) and 52 subjects in the cannabis condition.

Table 1 Subject characteristics and use history in mean and standard deviation (SD) unless otherwise stated ($N=61$, unless otherwise stated).

Variable	Mean (SD)
Age, years	22.6 (4.3)
Sex (m/f)	49 / 12
Cannabis use, joints per week	6.2 (5.1)
Cocaine use, occasions past year	10.7 (10.5)
Alcohol use (drinks per week, $n=61$[a])	10.9 (5.8)
Nicotine (cigarettes per day, $n=53$[a])	9.0 (6.0)
Amphetamine (occasions past year, $n=42$[a])	9.7 (11.0)
MDMA (XTC, occasions past year, $n=55$[a])	6.4 (4.4)
Hallucinogen use (occasions past year, $n=43$[a])	8.0 (11.7)
GHB use (occasions past year, $n=19$[a])	13.8 (21.4)

[a] *n* Reflects the number of subjects who reported to use the substance. Means and SDs based on that number (history of use data was available for all subjects)

2.2. Design

This study used a double-blind double-dummy placebo-controlled three-way crossover design, in which cocaine, cannabis, or placebo were separately administered over three different testing days. The three possible conditions were (1) cocaine (placebo vapors/cocaine capsules), (2) cannabis (cannabis vapors/placebo capsules), (3) placebo (placebo vapors/placebo capsules). There were at least 7 days in between visits in which no other drug exposure was allowed, with the exception of cannabis and alcohol. All drugs were administered in a randomized order using a block design.

2.3. Procedure

On the first (screening) visit, subjects gave informed consent, received a medical examination including assessment of blood and urine samples for standard chemistry and hematology, electrocardiogram (ECG), and interview of medical history. Furthermore, subjects were familiarized with the Flanker task and received instruction on how to use the vaporizer on the testing days. All subjects were asked to abstain from caffeine and nicotine on the testing day and from cannabis and alcohol at least 24 h prior to each testing day.

A timeline of the procedures of the testing day is shown in Figure 1. Each testing day started in the morning with a light breakfast (non-caffeinated tea or water, up to four sandwiches) and a urine drug screen, pregnancy test (women only), and alcohol Breathalyzer test. This was followed by pre-drug (baseline) vital sign recordings, subjective questionnaires, and blood draws. Subjects received a capsule containing either 300 mg cocaine HCl or placebo orally (T0), and forty-five minutes later subjects inhaled 300 μg/kg body weight cannabis or placebo (T1). It takes approximately 45 min before plasma cocaine concentrations start to increase, whereas increase of THC plasma levels starts immediately after inhalation. These 45 min between T0 and T1 were used to apply the EEG cap. After T1, the first block of behavioral tasks was assessed (Testblock 1). Approximately one hour after T1 a booster dose was given: a second dose of cocaine (150 mg) or placebo followed by a second dose of cannabis 150 μg/kg or placebo (T2). Hereafter, the second block of behavioral tasks was assessed (Testblock 2). Throughout the testing day, vital sign recordings, subjective questionnaires and blood draws were obtained 5 min after drug administration (T1 and T2) and at the end of the testing day. An extra vital sign recording

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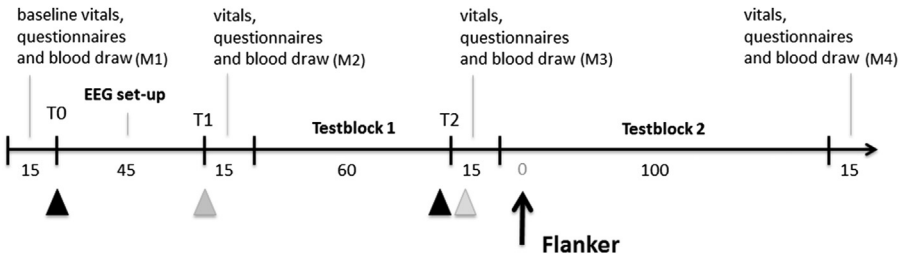

Figure 1 Timeline (in minutes) of the course of a testing day. The black triangles represent the moment of cocaine (or placebo) capsule administration and the gray triangles represent the moment of cannabis (or placebo) vapor administration. M1–M4 represent the four moments during which the visual analog scales were assessed. Note that in Testblock 1 and Testblock 2 several cognitive paradigms were performed. Those paradigms are not further discussed in the current manuscript, but will be presented elsewhere.

was performed before T2 to determine if the second dose could be safely administered.

Of the sixty-one subjects who completed the Flanker task in the cocaine condition, sixteen did not receive the booster capsule (five subjects did not receive a second cocaine dosage, because the decision to give a second dosage was made after start of the study; the other 11 had vital sign measurements exceeding the safety criterion). Of the 52 subjects who completed the Flanker task in the cannabis condition, seven did not receive a second administration (four subjects refused the second dosage; in three subjects vital signs were exceeded).

2.4. Study drugs

The cannabis used in the study was obtained from flowers of *Cannabis sativa*, grown according to good manufacturing practice (GMP)-compliant procedures (FarmalyseBV, Zaandam, The Netherlands). As placebo for cannabis a herbal mixture containing hemp flowers was used. Two dosages of cannabis (T1: 300 μg/kg body weight, T2: 150 μg/kg body weight) or placebo were administered. Cannabis and placebo cannabis were administered by means of a Volcano® vaporizer (Storz-Bickel GmbH, Tüttlingen, Germany). Five minutes before administration, cannabis was vaporized at a temperature of 225 °C and the vapor was stored in a polythene bag equipped with a valved mouthpiece, preventing the loss of cannabis vapor in between inhalations. Subjects were not allowed to speak, and were instructed to inhale deeply and hold their breath for ten seconds after each inhalation. Subjects were instructed to take as much time as needed in order to minimize the occurrence of adverse events. Cocaine HCl and matching placebo cocaine were encapsulated in opaque capsules. The placebo capsules contained only filling material of equivalent weight. The cocaine HCl and placebo cocaine were purchased from Mallinckrodt Pharmaceuticals, St Louis, MO, USA and encapsulated and tested by Basic Pharma Geleen according to Good Manufacturing Practices. Two dosages of cocaine (T0: 300 mg, T2: 150 mg) or placebo were administered. The capsules were taken orally with 150 ml of water. The second drug administration served as a booster dosage, because the psychoactive effects as a result of the first administration would decline in the second testing block. For cannabis, psychotropic effects of cannabis reach a maximum after 15–30 min but psychoactive effects can last up to several hours (Grotenhermen, 2003). Peak levels of psychoactive effects of oral cocaine reach a maximum after approximately 1 h (Fillmore et al., 2002; for a review Bigelow and Walsh, 1998).

2.5. Visual analog scales

Visual analog scales (VAS) were assessed on four occasions (see Figure 1) over the course of the testing day in order to assess psychoactive drug effects. The scales included the statements 'I feel high' and 'I feel active'. The scales ranged from 0 (not at all) to 10 (the most ever). Subjects were instructed to indicate how they felt 'at this moment'.

2.6. Flanker Task

A modified Flanker task (De Bruijn et al., 2004, 2006; Spronk et al., 2011) was used to assess electrophysiological correlates of performance monitoring. Subjects were asked to respond with either their left or right index finger to the central letter (H or S) of a congruent (HHHHH or SSSSS) or incongruent (HHSHH or SSHSS) letter string. First, a fixation cross was presented for 100 ms followed after 300 ms by the stimulus with a duration of 100 ms duration. During the next 900 ms the screen remained blank, after which visual feedback appeared for 1000 ms. The next trial was presented after an inter-trial interval of 100 ms. Visual feedback consisted of a yellow, a blue, or a red rectangle indicating whether the preceding response had been correct, incorrect, or too late, respectively. Participants were instructed to respond as fast as possible to avoid feedback indicating that their response was too slow according to a preset reaction time (RT) deadline. After written and verbal instructions, the participants familiarized themselves with the task in a practice block consisting of 60 trials and a liberal RT deadline of 800 ms. An individualized RT deadline was computed based on the average reaction time and standard deviation (SD) of the correct responses in the practice block (RT deadline = mean RT + 0.5 SD; De Bruijn et al., 2004, 2006). This individualized RT deadline was intended to keep error rates between the three drug conditions equal, as previous studies on the ERN have shown that the ERN may be affected by accuracy (see e.g. Gehring et al., 1993). The experiment consisted of 10 blocks of 50 trials per block with a compulsory break of a couple of minutes after 5 blocks. After each block, participants were verbally encouraged to keep accuracy around 80–90%.

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2.7. EEG recording and ERP quantification

The electroencephalogram (EEG) was recorded from thirty-two active electrodes (ActiCap, Brain Products, Munich, Germany) that were arranged according to an extension of the international 10-20 system. All electrodes were referenced to the left mastoid, but were later re-referenced offline to the average of both mastoids. The ground was placed on the nose. The vertical electro-oculogram (EOG) was recorded bipolarly from electrodes placed above and below the right eye. The horizontal EOG was also recorded bipolarly from electrodes lateral to each eye. All electrode impedances were kept below 50 kΩ at the start of the recording session and were monitored during the test session. All signals were digitized with a sampling rate of 500 Hz and no online filtering was applied. The signals were filtered offline with a filter with a pass-band between 0.01-30 Hz. Prior to running an independent component analysis-based (ICA) EOG correction; an artifact rejection procedure was performed to remove trials with large drifts in the signal and extreme low voltage. For the ERP analyses, all trials with responses faster than 150 ms were removed from the data. Response-locked ERPs were calculated for correct and incorrect trials. The EEG signals were divided into epochs of 600 ms, i.e. intervals from 100 ms before to 500 ms after response onset. The voltage in the epochs was calculated relative to the average voltage in the 100 ms pre-response baseline. Epochs associated with correct and incorrect responses were averaged separately. Epochs associated with correct responses were also averaged separately for congruent and incongruent stimuli time-locked to *stimulus* onset. Segments exceeding $\pm 75\,\mu V$ relative to a pre-stimulus or pre-response baseline were rejected.

Response-locked averages were determined separately for erroneous and correct responses for each individual. A small negative peak is often observed in the response-locked average for correct trials: the correct-related negativity (CRN). This component was determined to account for waveform differences between error and correct responses. For the ERN/CRN, peak-to-peak amplitudes were calculated at electrode FCz/Cz, where the ERN/CRN amplitude was largest (De Bruijn et al., 2004). Peak-to-peak was defined as the difference between the negative peak in the 0 to 200 ms time window after response onset and the most positive peak in the time window starting 80 ms before and ending 80 ms after response onset. Peak-to-peak analyses were chosen as they provide a robust measure of the ERN and were also adopted in previous pharmacological studies (De Bruijn et al., 2004, 2006; Spronk et al., 2011, 2014). The peak-to-peak method, furthermore, limits the effect of a baseline on the ERN (Luck, 2005). Response-locked ERP analyses were limited to incongruent trials only (Spronk et al., 2014; De Bruijn et al., 2004, 2006). The average number of segments per drug condition was 41.9 for placebo (min: 9, max: 110), 47.4 for cocaine (min: 11, max: 105) and 43.7 for cannabis (min: 5, max: 89). The minimum criterion of 8 segments that is needed to attain adequate signal to noise ratio (Olvet and Hajcak, 2009) was met in all datasets except one (5 segments). Because an ERN could still be discerned in this subject and we followed an intention-to-treat approach, this dataset was not excluded from the analyses. Most importantly, the average number of segments that was included to compute the ERN (so for incorrect responses) did not differ between the three drug conditions ($p=0.15$). Because the Pe is a slowly varying component that might not have a clear peak, the mean amplitude at Cz/Pz between 200 and 300 ms post-response was used as outcome measure.

The stimulus-locked ERPs were computed for correct responses for all three drug conditions. In line with previous literature (e.g. Nieuwenhuis et al., 2003), the N2 component was calculated at electrode FCz (where N2 amplitudes were largest) by subtracting the most negative peak in the 200-350 ms time window after stimulus onset from the preceding positive peak. The P1 ERP was defined as the most positive peak between 70 and 130 ms poststimulus at electrode Oz. The N1 component was defined as the most negative deflection occurring in the 50-150 ms post-stimulus time-window at electrodes FCz, Cz, and Pz. The P300 was defined as the most positive peak between 300 and 500 ms at electrodes FCz, Cz, and Pz. All stimulus-locked ERPs were calculated for congruent and incongruent trials.

2.8. Statistics

The behavioral measures included the percentage of 'correct', 'error', 'too late', 'omission' and 'too early' responses, the mean reaction time (RT) to correct and error responses (only RTs > 150 ms were included) and the post-error slowing (Rabbitt, 1966). Post-error slowing was defined as the difference between the mean RT on correct trials that were preceded by errors (post-error) and mean RT on correct trials that were preceded by a correct response (post-correct). Responses that were 'too late' were included in the mean post-correct and post-error reaction times ('omission' and 'too early' trials were never included). Post-error slowing measures were only calculated for incongruent pre- and post- trials, in order to control for possible serial congruency effects (Gratton et al., 1992).

For all dependent variables, linear mixed modeling (LMM) was applied with Subject as a random factor using SPSS version 22. LMM was chosen in order to keep subjects in the analysis for whom all three drug conditions were not available on the assumption incomplete data were missing at random. For the VAS scales, Drugs (cocaine, placebo and cannabis) and Time (M1, M2, M3, M4) were entered as fixed factors. For the 'error' and 'too late' rates, Drugs (cocaine, placebo, cannabis) and Congruency (congruent, incongruent) were used as fixed factors. For reaction times, Drugs, Congruency and Correctness (correct, error) were used as fixed factors. For post-error slowing, Drugs and Post-correctness (post-correct vs. post-error) were used as fixed factors. By convention, the ERN and Pe were analyzed for incongruent trials only with Correctness and Electrode (FCz/Cz for ERN or Cz/Pz for Pe) as fixed factors (De Bruijn et al., 2004, 2006; Spronk et al., 2014). The N2 was analyzed at FCz for correct congruent and incongruent trials with Drugs and Congruency as fixed factors. The P1, N1 and P300 amplitude and P300 latency were analyzed with Congruency and Electrode site (for N1 and P300 only: FCz, Cz, Pz) as fixed factors. The analysis of ERN, Pe and PES were also performed with the subjects who had only received one cocaine administration (see Procedure) excluded.

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3. Results

3.1. VAS

The average VAS over the course of the three testing days and for the three drug conditions are presented in Table 2. There was a significant drugs × time interaction for both the 'VAS high' and 'VAS active' (p's<0.001). Follow-up analyses showed that both cannabis and cocaine were associated with significant increases in ratings of 'feeling high'. Cocaine was associated with an increase in 'feeling active', while cannabis was associated with a decrease in 'feeling active'. Importantly, there were no baseline differences on the VAS scales. The average ratings suggest that both drugs had strong psychoactive effects on subjective experiences.

3.2. Error rates and reaction times

Table 3 contains the error rates and reaction times for the congruent and incongruent trialtypes, for each drug condition. Across all three conditions, we observed the typical Flanker interference effect. Incongruent trials are associated with larger error rates (19.9% vs. 7.1%; $F_{1,\ 281.809}=549.82$, $p<0.001$) and longer reaction times compared to congruent trials (335 ms vs. 318 ms, $F_{1,624.427}=59.1$, $p<0.001$).

The main effect of Drugs on error rates was not significant ($p=0.11$), but there was a significant Drugs × Congruency interaction ($F_{2,\ 281.809}=3.84$, $p=0.023$). Pairwise comparisons showed that error rates on incongruent trials were higher in the cocaine than placebo condition ($p=0.008$). There were no differences between cannabis and placebo, and cannabis and cocaine, nor were there any drug differences on the congruent trials (all p's>0.25). With regard to the percentage of 'too late' responses, we found a similar congruency effect, i.e. there were more 'too late' responses after incongruent (13.9%) than congruent trials (5.5%; $F_{1,282.729}=316.67$, $p<0.001$). Furthermore, there was a main effect of Drugs ($F_{2,\ 287.886}=3.14$, $p=0.045$). This was caused by a higher percentage 'too late' responses in the cannabis (10.3%) compared to the cocaine condition (8.9%; $p=0.051$), while 'too late' responses after neither drug differed from placebo (9.9%, all p's >0.23). Congruency and Drugs did not interact on the 'too late' responses ($p=0.64$). 'Too early' and 'omission' responses were generally very low ($<2.7\%$, see Table 2).

For the reaction times, there was a significant Congruency × Correctness interaction ($F_{1,\ 624.427}=19.78$, $p<0.001$), indicating that that the congruency effect was stronger for correct responses (see Table 2). Furthermore, there was an overall main effect of Drugs ($F_{2,\ 627.457}=12.49$, $p<0.001$), which was caused by slower reaction times in the cannabis (335 ms) compared to the placebo (325 ms) and cocaine condition (321 ms, all p's<0.003), while the reaction times between cocaine and placebo were not different ($p=0.45$). None of the other interactions that involved Drugs were found to be significant (all p's>0.31).

In light of the interpretation of the error rates and reaction times, we additionally calculated if the individualized reaction time deadlines differed between drug conditions. Indeed, we found a main effect of Drugs ($F_{2,\ 177.891}=5.22$, $p=0.007$). Pairwise comparisons showed that more liberal deadlines were applied in the cannabis (469 ms), compared to the cocaine condition (440 ms, $p=0.005$). There were no differences between cannabis and placebo (469 ms vs. 450 ms) and between cocaine and placebo (440 ms vs. 450 ms, all p's>0.13).

Table 2 Mean percentages and standard deviations for the behavioral measures for each drug condition.

	VAS high				VAS active			
	M1	M2	M3	M4	M1	M2	M3	M4
Cocaine	0.2±0.6	3.9±2.9	3.9±2.9	1.8±1.9	5.6±2.3	7.5±1.5	6.9±1.7	4.3±2.0
Placebo	0.1±0.4	0.8±1.2	0.6±1.0	0.2±0.5	5.6±2.1	5.7±2.0	5.1±2.2	4.9±2.2
Cannabis	0.3±1.1	7.3±2.2	6.8±2.1	3.2±2.0	5.5±2.2	4.0±2.0	4.1±2.0	4.1±2.0

Table 3 Means percentages and standard deviations for the behavioral measures for each drug condition

	Congruent			Incongruent		
	Cocaine	Placebo	Cannabis	Cocaine	Placebo	Cannabis
% Correct	87.9±8.6	85.4±13.4	81.5±12.4	64.5±11.1	64.5±13.6	61.6±13.5
% Error	6.5±5.2	6.8±4.9	8.0±4.6	21.4±9.6	18.6±8.3	19.8±7.6
% Too late	4.7±2.8	5.4±4.9	6.3±3.4	13.1±5.5	14.3±6.6	14.1±.7
% Omission	0.2±0.5	0.4±0.9	1.4±2.7	0.4±0.6	0.7±1.1	1.8±3.3
% Too early	0.7±2.6	2.0±7.6	2.7±7.4	0.7±2.3	1.9±7.7	2.8±7.8
RT correct	322±29	329±34	342±38	350±37	356±43	367±48
RT error	304±42	302±61	314±54	309±35	312±36	320±40

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3.3. Error-related negativity

As evident in Figure 2, there was a larger negative deflection after errors (8.11 μV) compared with correct responses (2.86 μV; main effect of Correctness ($F_{1,620.125}=516.29$, $p<0.001$)). The Correctness × Electrode interaction ($F_{1,620.125}=8.18$ $p=0.004$) was significant. These results demonstrated a fronto-central distribution, which was present after errors ($p<0.001$), but not after correct responses ($p=0.19$). There was a significant main effect of Drugs ($F_{2,624.552}=21.71$, $p<0.001$). Most importantly, the analyses revealed a significant Drug × Correctness interaction ($F_{2,620.125}=9.66$, $p<0.001$). Pairwise comparisons indicated that this interaction was caused by significant differences between the three drug conditions in the ERN, not the CRN. The ERN was larger in the cocaine (9.63 μV) compared with the placebo (8.21 μV, $p=0.001$) and cannabis condition (6.51 μV, $p<0.001$). The ERN after cannabis was significantly smaller compared with placebo ($p<0.001$). No drug differences were found on the CRN (all p's>0.083). The three-way Correctness × Electrode × Drugs interaction was not significant ($F_{2,620.125}=0.12$, $p=0.89$), indicating that

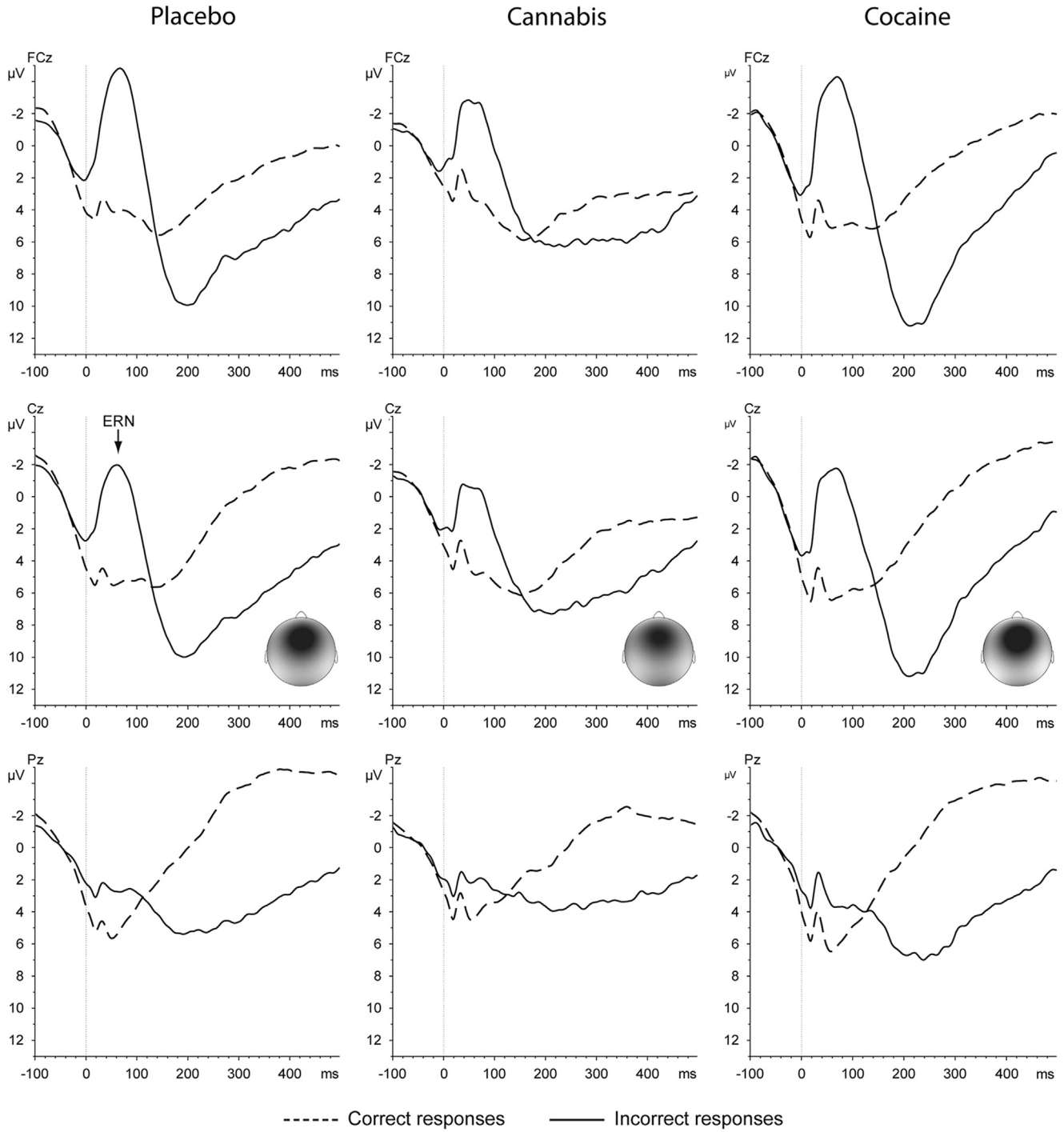

Figure 2 Response-locked grand average waveform for placebo, cocaine and cannabis.

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there was no difference in the Correctness × Drugs interaction between the two electrodes.

When in the cocaine condition, a total of 16 subjects had not received the second cocaine administration, and a total of 7 of the 52 subjects in the cannabis condition have not received the second cannabis administration. To investigate if the number of dosages had an impact on the outcomes, two supplementary analyses were performed excluding those subjects who had received 1 drug administration across all three conditions. These analyses showed that the results remained similar for both analyses. Of most relevance, there was a significant Drug × Correctness interaction ($p<0.001$). The follow-up analyses again showed that this effect was driven by amplitude differences between placebo and cannabis (p's<0.001) and placebo and cocaine condition to the incorrect responses (p's<0.024).

3.4. Error positivity

For the Pe, there was a main effect for Correctness ($F_{1,619.952}=423.0$, $p<0.001$), indicating increased amplitudes following incorrect (6.78 μV) compared to correct responses (0.57 μV). There was a significant for Electrode ($F_{1,619.952}=126.4$, $p<0.001$) as indicated by larger Pe amplitudes at Cz compared to Pz (5.37 μV vs. 1.98 μV). Furthermore, there was a significant main effect for Drugs ($F_{2,626.659}=3.30$, $p=0.038$), which was further qualified by a significant Drugs × Correctness interaction ($F_{2,619.952}=19.0$, $p<0.001$). Pairwise comparisons showed that the Pe after incorrect responses was larger in the cocaine compared to placebo (8.32 μV vs. 6.68 μV, $p=0.004$), and smaller in the cannabis compared to placebo condition (5.34 μV vs. 6.68 μV, $p<0.001$). Furthermore, the Pe after correct responses was larger after cannabis than after placebo (1.67 vs. −0.050, $p=0.004$), while there were no differences between cocaine and placebo ($p=1.0$). None of the other possible two-way or three-way interactions reached significance (p's>0.57). Moreover, the supplementary analyses excluding the participants who had only received 1 cocaine administration did not show a change in the pattern of results. There was a significant Drug × Correctness interaction ($p<0.001$), that was caused by larger Pe amplitudes after incorrect responses in the cocaine compared to the placebo condition ($p=0.019$).

3.5. Performance adjustments

Analyses of post-response reaction times demonstrated a main effect for Post-correctness ($F_{1,282.669}=23.55$, $p<0.001$). As expected, subjects slowed down after committing an error compared with after correct responses (394 ms vs. 377 ms). There was a main effect of Drugs ($F_{2,285.561}=12.83$, $p<0.001$), caused by general slowing in the cannabis condition compared to placebo and cocaine (all p's<0.001). Most importantly, drugs did not differentially affect post-error slowing, as evidenced by a lack of Drug × Post-correctness interaction effect ($F_{2,282.669}=0.11$, $p=0.90$). The supplementary analyses on the subset of subjects who have received 2 drug administrations showed a similar pattern of results for all tests, including an absence of Drug × Post-correctness interaction (p's>0.82).

3.6. Stimulus-locked ERPs

Grand average *stimulus*-locked ERP waveforms for congruent and incongruent trials in the different conditions are shown in Figure 3. The P1 amplitude was not different for the three drug conditions as indicated by an absence of a main effect for Drugs and an absence of a Drugs × Congruency interaction effect (p's>0.34). There was a main effect for Congruency ($F_{1,279.456}=10.7$, $p<0.001$), with larger P1 amplitudes for incongruent compared to congruent trials. For the N1 amplitude, the analyses revealed a main effect for Electrode ($F_{2,949.021}=37.12$, $p<0.001$). Pairwise comparisons showed that the N1 amplitude was larger at FCz (−3.12 μV) and Cz (−2.72 μV) compared with the Pz electrode (−2.14 μV, p's <0.001). There was neither a main effect of Drugs nor Congruency, nor were any of the interactions significant (all p's >0.094). The analyses on the P300 amplitude demonstrated a significant main effect for Electrode ($F_{2,948.924}=38.7$, $p<0.001$) and for Drugs ($F_{2,952.313}=83.7$, $p<0.001$). The P3 amplitude was significantly larger at electrode Cz (12.9 μV) compared to FCz and Pz (10.7 μV and 11.1 μV, p's<0.001). The main effect of Drugs was caused by larger P3 amplitudes after cocaine (13.2 μV) compared to placebo (11.8 μV, $p=0.002$), and smaller P3 amplitudes after cannabis (9.7 μV) compared to placebo ($p<0.001$). None of the other main and interaction effects reached significance (p's>0.22).

For the latency of the P300 ERP, there was a significant main effect of Drugs ($F_{2,965.456}=32.3$, $p<0.001$, see Figure 2), a main effect of Electrode ($F_{2,960.144}=39.0$, $p<0.001$) and a main effect of Congruency ($F_{2,960.144}=87.3$, $p<0.001$). The effect of Drugs is due to a longer P300 latency in the cannabis (442 ms) compared with the placebo and cocaine condition (399 ms and 391 ms, $p<0.001$); the P300 latency for placebo and cocaine did not differ ($p=0.2$). The main effect of Electrode was due to a longer P300 latencies at the anterior electrode compared to posterior electrode positions. The main effect of Congruency was due to longer latencies after the incongruent (427 ms) compared to the congruent trials (404 ms). None of the interaction effects reached significance (p's>0.098).

3.7. Stimulus-locked N2

As expected, there was a significant main effect of Congruency, indicating larger N2 amplitudes for incongruent (4.49 μV) than for congruent trials (3.22 μV, $F_{1,280.342}=49.05$, $p<0.001$). Furthermore, there was a significant main effect of Drugs ($F_{2,282.944}=8.98$, $p<0.001$). The pairwise comparisons indicated that the overall N2 amplitudes were *larger* in the cannabis (4.42 μV) compared to the placebo (3.50 μV, $p<0.001$) and the cocaine condition (3.65 μV, $p=0.003$). There was no difference between cocaine and placebo (idem $p=1.00$). The Congruency × Drugs interaction was not significant ($F_{2,280.342}=2.256$, $p=0.079$).

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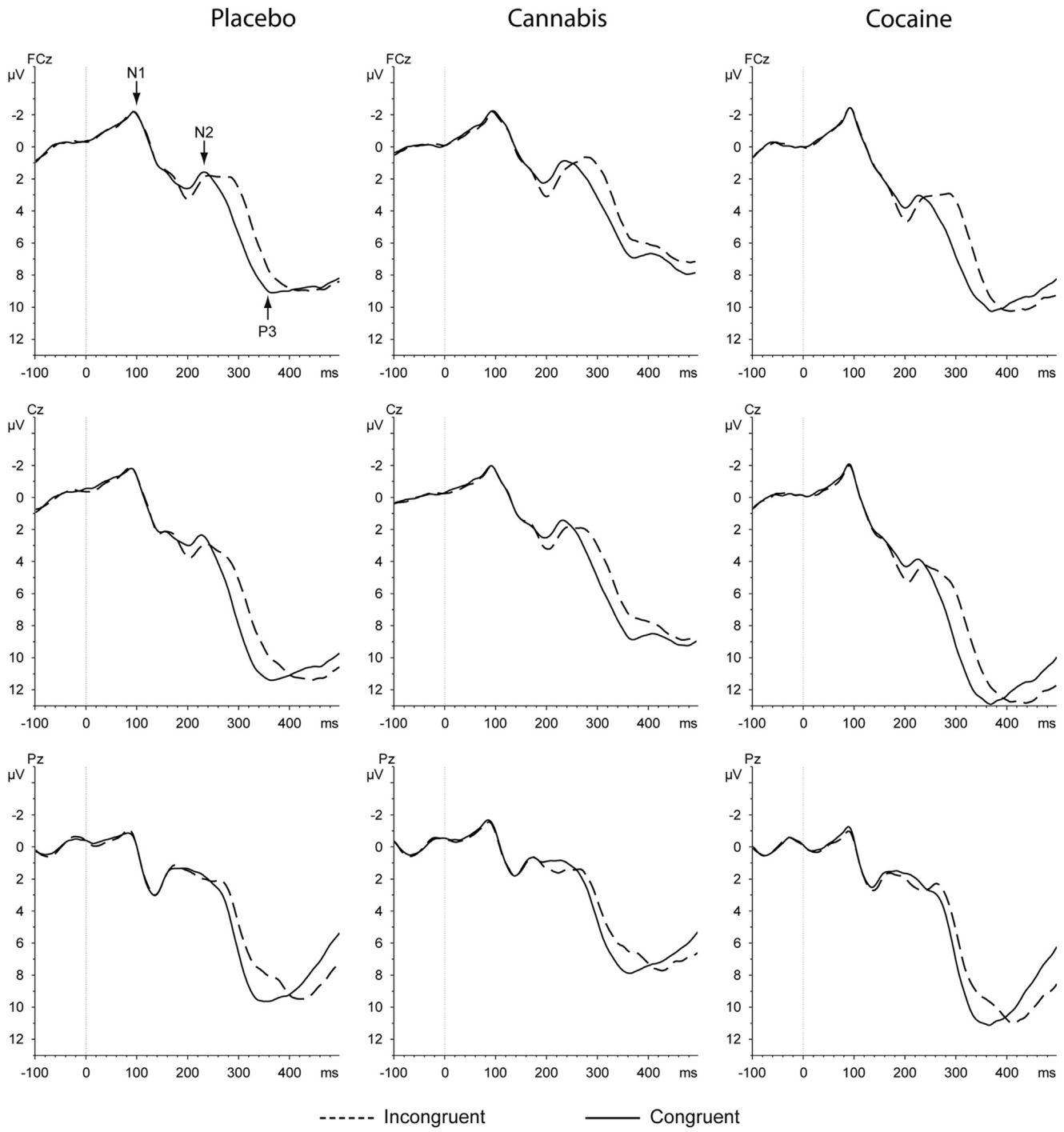

Figure 3 Stimulus-locked grand average waveform for placebo, cocaine and cannabis.

4. Discussion

The current study revealed opposite effects of acute administration of cocaine and cannabis on performance monitoring. For cocaine, the results showed an increased ERN, whereas cannabis decreased the ERN. For the Pe, there was an enhancing effect of cocaine and a diminishing effect of cannabis. Neither drug affected post-error slowing.

The decreased ERN and Pe after cannabis suggests reduced performance monitoring of both the early and late performance monitoring stages (see also Spronk et al., 2011; Kowal et al., 2015). The results suggest that cannabis not only leads to impaired detection of errors, but also to decreased awareness that an error has been made. The ERN has previously been shown to be reduced in a range of situations promoting high impulsivity. For example, the ERN is reduced after alcohol intake (Spronk et al., 2014; Ridderinkhof et al., 2002) as well as in psychiatric populations characterized by increased impulsivity, such as borderline personality disorder (De Bruijn et al., 2006). Notably, impulsivity is a known risk factor for continued drug use

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(Verdejo-García et al., 2008). The current findings might therefore imply that suboptimal processing of erroneous behavior could promote continued drug use. Similar processes might happen when people are under the influence of alcohol (Spronk et al., 2014; Ridderinkhof et al., 2002).

The enhanced ERN and Pe after cocaine, in contrast, suggests improved performance monitoring. This implies that people become better in the early automatic detection of an error, but they might also be more aware that they have made an error. Previous studies have shown that cocaine acts as a cognitive enhancer and leads to improved response inhibition (for a review see Spronk et al., 2013). It is also consistent with other psychopharmacological studies that indicate that arousal-enhancing substances promote enhancement of the ERN. In agreement, the subjective 'feel active' VAS showed that cocaine successfully induced arousal. The current finding thus further supports that dopamine- and arousal-enhancing substances contribute to an enhanced ERN.

Like cocaine, caffeine also enhanced the Pe (Tieges et al., 2004). The administration of the dopamine agonist methylphenidate previously did not affect the Pe (see e.g. Barnes et al., 2014). It has been argued that the lack of a clear operationalization of the Pe (e.g. in terms of time window, measured location, etc.) is a major factor contributing to inconsistency in findings (Overbeek et al., 2005). Furthermore, psychopharmacological studies on the Pe are scarce. We argue that more systematic studies are needed in other to understand the pharmacological moderators of this later component.

Whereas the ERN is thought to be related to an internal error monitoring system, the Pe is associated with an external monitoring system related to the conscious perception and awareness of errors (Hewig et al., 2011). As such, both are hypothesized to reflect separate performance monitoring systems and the dissociable findings thus suggest that cannabis and cocaine impacts the internal and external monitoring system in an opposite manner.

Although both the ERN and Pe are theoretically linked to behavioral adaptation, we found equal levels of post-error slowing across the three drug conditions. The intact behavioral adaptation appears, at first, to contrast with our electrophysiological results. However, the use of the strict reaction-time deadline allowed for less variability in reaction times which could conceal drug effects on alterations in post-error adaptations. In addition, post-error slowing is only one operationalization of behavioral adaptation. We cannot exclude the possibility that other measures are more sensitive to drug-induced alterations.

Cocaine yielded an increase in error rate on incongruent trials in the absence of differences in reaction times. This contrasts with previous findings where cocaine resulted in a decrease in errors as well as reaction times in a Go/NoGo task (Spronk et al., 2015, 2016). In the current paradigm, we aimed to manipulate task performance (by coaching and setting an individualized reaction time deadline) such that the drug conditions would have equal error rates. Therefore, interferences about drug differences on behavioral performance should be made with caution. Furthermore, the strict reaction time deadline and the repeated instruction for speedy responses might have resulted in a floor-effect, i.e. participants could not have responded any faster under cocaine. This probably explains the absence of a reaction time difference in the presence of a difference in error rates.

While supporting our hypothesis that drugs affect performance monitoring, the selectivity of this finding could only be partly demonstrated. The P300 ERP was decreased and increased for cannabis and cocaine, respectively. The P300 ERP was affected in a similar manner as the Pe, which is agreement with suggestions that the P300 and Pe reflect similar components (Overbeek et al., 2005). Of particular interest is the enhanced P300 latency after cannabis, which suggests that cannabis does not only lead to slower motor responses, but also to a prolonging of stimulus evaluation (Kutas et al., 1977). The results suggest that cannabis impacts performance at both the response level (as indicated by the ERN) as well as the stimulus-evaluation level (as indicated by the P300). This argues for an aspecific effect of cannabis on a variety of cognitive stages. The unaffected P1 and N1 suggest that cocaine and cannabis leave early attention intact.

The N2-congruency effect (i.e. the larger N2 in incongruent vs. congruent trials) was not differentially affected by any of the drugs, suggesting that there were no differences in conflict monitoring. However, the overall N2 amplitude (across trials) was larger in the cannabis condition. At first, this might seem surprising, given that many studies have reported cognitive impairment and reduced ERP amplitudes after cannabis (e.g. Böcker et al., 2010; D'Souza et al., 2012). However, studies that specifically addressed the determinants of the N2 amplitude have shown that the N2 is increased when the 'flanking' letters are in closer proximity (Danielmeier et al., 2009) as well as when subjects show enhanced processing of the (irrelevant) 'flanking' information (Larson et al., 2013). Solowij et al. (1991) observed that chronic cannabis users showed an enhanced N2 component, which was indicative of unnecessary pitch processing in an auditory selection task. Possibly, the observed enlarged N2 in the current study suggests that people had more difficulty to reject the irrelevant flanking information. This interpretation is in line with the increased reaction times under influence of cannabis.

Comparisons of the current results, with studies investigating performance monitoring in chronic users highlight that acute and chronic effects of drugs on cognitive performance do not necessarily correspond. For example, the finding of enhanced performance monitoring after cocaine contrasts with a wealth of studies indicating impaired performance in addicted cocaine users who are not tested under acute influence (Spronk et al., 2013). In relation to cannabis, both acute and chronic effects are often in the direction of impairment, rather than improvement (for reviews see Crane et al., 2013; Crean et al., 2011). Notably, a recent study in chronic cannabis users investigating the exact same performance monitoring parameters as in the current study, i.e. ERN and Pe (Fridberg et al., 2013) reported that the Pe was affected, but the ERN was intact. This finding suggests that different performance monitoring subfunctions might be affected depending on the stage (acute or chronic) of drug taking behavior.

Our study has several limitations. Most importantly, it cannot be determined to what extent the observations may be ascribed to non-specific alternative explanations that

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could not be controlled for in the current experiment. For example, on most testing days it was rather obvious for both the participant and the experimenter which drug they had been given (although we have no written statements regarding the success of blinding of the drug conditions). The participants' familiarity with the drugs, the relatively high dosages and the behavior that is typically associated with drugs are a number of factors that have contributed to this. It cannot be excluded that expectancy effects or enhanced motivation to do well under influence of cocaine has influenced the results. Additionally, a relatively high number of subjects experienced side-effects in the cannabis condition (e.g. not feeling well or extreme fatigue). Factors such as fatigue, sedation, and motivation are known to affect the ERN (e.g. Boksem et al., 2006; de Bruijn et al., 2004, 2006). We cannot exclude the possibility that those side-effects have contributed to the impaired performance monitoring under the influence of cannabis.

Another potential limitation that concerns the generalizability of the results is the route of administration of cocaine. The oral intake in the form of capsule is different from the most frequently used route of administration in recreational use (intranasal or snorting). Because the route of administration can have profound effects on experienced subjective and cognitive effects, we cannot exclude the possibility that the current data would not have been observed after intranasal administration of cocaine. However, the subjective reported feelings of 'high' and 'active' are comparable to those reported after the intranasal route of administration, which at least suggests that the performance monitoring findings might generalize to the recreational route of administration. In addition, all our subjects were regular users of both cannabis and cocaine (and in most cases also of other drugs). Hence, the results can only be interpreted in relation to this particular population, as it is unknown if the result would be the same in drug-naive individuals. Furthermore, almost all subjects were smokers (see Table 1). Participants were instructed not to smoke during the testing day and this might have led to nicotine-withdrawal symptoms. Nicotine withdrawal symptoms can impair performance monitoring in itself (Luijten et al., 2011) although this nicotine-withdrawal is likely to have been the same across all three testing days.

Other limitations are that not all subjects received the second administration of cannabis or cocaine. As the Flanker task was assessed after the second administration, this could have affected the results. Follow-up analyses show, however, that the results are in the same direction, irrespective of the number of administrations. Moreover, even if subjects had only received one administration the drug, results were still within limits of the psychoactive effects, because the Flanker task was assessed no longer than 80 min after the first cannabis administration and 125 min after the first cocaine administration.

To conclude, our data highlight the impact of cocaine and cannabis on performance monitoring. Cannabis decreases the ERN and the Pe, whereas cocaine increases the ERN and Pe. Both drugs do not affect post-error slowing. These results demonstrate opposing effects on the early and late phases of performance monitoring of the two common drugs of abuse. Conversely, the behavioral adaptation phase of performance monitoring remained unaltered by the drugs. The current results suggest a cognitive mechanism by which acute drug effects can contribute to risky behavior.

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Contributors

RJV, RC, BF, JvW, JR and EdB designed the study and wrote the protocol. DBS and EdB performed analyses. DBS carried out the experiments, performed statistical analyses and wrote the first draft of the manuscript. RJV performed medical examinations and supervised the experiments. All authors contributed to and approved the final manuscript.

Conflict of interest

Barbara Franke has received a speaker fee from Merz, but she is not an employee or a stock shareholder. All other authors report no potential conflicts of interest.

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