European Neuropsychopharmacology (2016) **26**, 1127–1139

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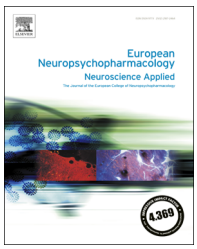

Opposite effects of cannabis and cocaine on performance monitoring

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Received 4 March 2015; received in revised form 16 December 2015; accepted 24 March 2016

KEYWORDS
Cannabis;
Cocaine;
Performance monitoring;
Error-related negativity;
Error positivity

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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http://dx.doi.org/10.1016/j.euroneuro.2016.03.015
0924-977X/

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