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# Cocaine users with comorbid Cluster B personality disorders show dysfunctional brain activation and connectivity in the emotional regulation networks during negative emotion maintenance and reappraisal

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Anterior cingulate cortex;

## Abstract

Cocaine dependence often co-occurs with Cluster B personality disorders. Since both disorders are characterized by emotion regulation deficits, we predicted that cocaine comorbid patients would exhibit dysfunctional patterns of brain activation and connectivity during reappraisal of negative emotions. We recruited 18 cocaine users with comorbid Cluster B personality disorders, 17 cocaine users without comorbidities and 21 controls to be scanned using functional magnetic resonance imaging (fMRI) during performance on a reappraisal task in which they had to maintain or suppress the emotions induced by negative affective stimuli. We followed region of interest (ROI) and whole-brain approaches to investigate brain activations and connectivity associated with negative emotion experience and reappraisal. Results showed that cocaine users with comorbid personality disorders had reduced activation of the subgenual anterior cingulate cortex during negative emotion maintenance and increased activation of the lateral orbitofrontal cortex and the amygdala during

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Lateral orbitofrontal cortex;  
Amygdala

reappraisal. Amygdala activation correlated with impulsivity and antisocial beliefs in the comorbid group. Connectivity analyses showed that in the cocaine comorbid group the subgenual cingulate was less efficiently connected with the amygdala and the fusiform gyri and more efficiently connected with the anterior insula during maintenance, whereas during reappraisal the left orbitofrontal cortex was more efficiently connected with the amygdala and the right orbitofrontal cortex was less efficiently connected with the dorsal striatum. We conclude that cocaine users with comorbid Cluster B personality disorders have distinctive patterns of brain activation and connectivity during maintenance and reappraisal of negative emotions, which correlate with impulsivity and dysfunctional beliefs.

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## 1. Introduction

Cocaine dependence is frequently associated with comorbid psychiatric disorders, being the highest rates for mood, anxiety and personality disorders—especially Cluster B diagnoses (Chen et al., 2011). The co-occurrence of personality disorders is particularly influential for cocaine addiction severity and treatment outcomes; for example, the presence of comorbid personality disorders is associated with heavier cocaine intake, lower rates of treatment request, and decreased likelihood of cocaine dependence remission (Ford et al., 2009; Lopez-Quintero et al., 2011). In terms of cognitive-affective functioning cocaine dependent patients with comorbid personality disorders, compared to non-comorbid cocaine users, exhibit higher levels of negative emotion-driven impulsivity (negative urgency), more intense dysfunctional beliefs associated with personality pathology, poorer cognitive control skills, and reduced gray matter in brain regions relevant for social-emotional cognition (Albein-Urios et al., in press-a). This profile, together with previous evidence (Fox et al., 2007), is indicative of greater difficulties in cognitive-emotion regulation skills among cocaine users with comorbid personality disorders. However, little is known about the functioning of the brain systems involved in cognitive-emotion regulation among comorbid patients.

We recently demonstrated that cocaine dependent individuals without comorbid psychopathologies have dysfunctional activation of the frontal-limbic networks involved in negative emotion experience and reappraisal: they showed increased right dorsolateral prefrontal activation during negative emotion maintenance and decreased right inferior frontal gyrus-limbic connectivity during cognitive reappraisal (Albein-Urios et al., in press-c). Although no studies up to now have investigated the brain functioning of cocaine users with concurrent Axis II disorders, the neuroimaging findings in non-substance dependent individuals with Cluster B personality disorders demonstrate that they also show significant deficits in the emotion regulation networks (Ruocco et al., 2013; Yang and Raine, 2009). Specifically, they exhibit consistent reductions in subgenual anterior cingulate cortex activation during negative emotion experience (Ruocco et al., 2013) and increased insula and decreased orbitofrontal cortex activation during reappraisal (Schulze et al., 2011). The subgenual cingulate cortex and the anterior insula are primarily involved in the emotional salience network (Taylor et al., 2009), whereas the lateral orbitofrontal cortex connects with two different pathways involved in negative emotion regulation: the striatum

pathway, associated with better reappraisal success, and the amygdala pathway, associated with poorer reappraisal success (Wager et al., 2008). Since both cocaine dependence and Cluster B personality disorders are associated with dysfunctions in the brain regions and networks supporting emotion regulation, the co-occurrence of both diagnoses may presumably convey more profound deficits in these regions and networks.

Here we used the cognitive reappraisal paradigm (Phan et al., 2005) to investigate potential differences in the patterns of functional activation and connectivity of these regions of interest (anterior cingulate cortex, insula, orbitofrontal cortex, striatum and amygdala) between cocaine users with versus without comorbid personality disorders compared to normal controls. In agreement with previous evidence, we hypothesized that the cocaine dependent patients with comorbid personality disorders—compared to non-comorbid users and controls—would show differential patterns of brain activation in the subgenual anterior cingulate cortex during negative emotion maintenance and in the lateral orbitofrontal cortex-amygdala pathway during negative emotion reappraisal. We also predicted that the personality traits and beliefs that characterize cocaine comorbid patients (negative urgency and dysfunctional beliefs) would correlate with the brain substrates of negative emotion maintenance and regulation.

## 2. Experimental procedures

### 2.1. Participants

Thirty-five cocaine users and 21 non-drug-using controls statistically matched for education and IQ distributions were recruited for study purposes (see Table 1). Cocaine users were classified in two groups based on personality disorders diagnosis: 18 participants met criteria for cocaine dependence and Cluster B personality disorders (9 with borderline diagnosis—four males, 7 with histrionic diagnosis—six males, and 2 with antisocial diagnosis—both males) and 17 participants met criteria for cocaine dependence without comorbidities (12 males).

Cocaine users were recruited as they started treatment in the clinic “Centro Provincial de Drogodependencias (CPD)” in Granada (Spain), which provides behavioral treatment for substance-related disorders in an outpatient setting. The inclusion criteria for the cocaine groups were defined as follows: (i) age range between 18 and 45 years old; (ii) IQ levels above 80—as measured by the Kaufman Brief Intelligence Test (K-BIT) (Kaufman and Kaufman, 1990); (iii) meeting DSM-IV criteria for cocaine dependence—as assessed by the Structured Clinical Interview for DSM-IV Disorders—Clinician Version (SCID) (First et al., 1997); (iv) being treatment commencers; and (v) abstinence duration >15 days. Abstinence

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