Addiction Biology

Reappraisal of negative emotions in cocaine dependence: Dysfunctional corticolimbic activation and connectivity

Journal:	*Addiction Biology*
Manuscript ID:	AB-06-2012-0126.R2
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Albein-Urios, Natalia; Universidad de Granada, Clinical Psychology Verdejo-Román, Juan; Universidad de Granada, Clinical Psychology Asensio, Samuel; CEU Cardenal Herrera, Biomedical Sciences Soriano-Mas, Carles; Hospital de Bellvitge, Psychiatry Martínez-González, José Miguel; Diputación de Granada, Centro Provincial de Drogodependencias VERDEJO-GARCIA, ANTONIO; Universida de Granada,
Keywords:	cocaine, negative emotion, reappraisal
Abstract:	Cocaine dependence is associated with pronounced elevations of negative affect and deficient regulation of negative emotions. We aimed to investigate the neural substrates of negative emotion regulation in cocaine dependent individuals, as compared to non-drug-using controls, using functional resonance imaging (fMRI) during a reappraisal task. Seventeen cocaine dependent individuals abstinent for at least 15 days and without other psychiatric comorbidities, and 18 IQ-matched non-drug using controls participated in the study. Participants performed the reappraisal task during fMRI scanning: they were exposed to 24 blocks of negative affective or neutral pictures that they should Observe (neutral pictures), Maintain (sustain the emotion elicited by negative pictures) or Suppress (regulate the emotion elicited by negative pictures through previously trained reappraisal techniques). Task-related activations during two conditions of interest (Maintain>Observe and Suppress>Maintain) were analyzed using the general linear model in SPM8 software. We also performed psychophysiological interaction (PPI) seed-based analyses based on one region from each condition: the dorsolateral prefrontal cortex (dlPFC –Maintain>Observe) and the inferior frontal gyrus (IFG –Suppress>Maintain). Results showed that cocaine users had increased right dlPFC and bilateral temporoparietal junction activations during Maintain>Observe, whereas they showed decreased right IFG, posterior cingulate cortex, insula and fusiform gyrus activations during Suppress>Maintain. PPI analyses showed that cocaine users increased functional coupling between the dlPFC and emotion-related regions during Maintain>Observe, whereas they showed decreased functional coupling between the right IFG and the amygdala during Suppress>Maintain. These findings indicate that cocaine dependent individuals have dysfunctional corticolimbic activation and connectivity during negative emotion

	experience and reappraisal.

Reappraisal of negative emotions in cocaine dependence: Dysfunctional corticolimbic activation and connectivity.

Natalia Albein-Urios[1], Juan Verdejo-Román[1], Samuel Asensio[2], Carles Soriano-Mas[3,4], José M. Martínez-González[5], & Antonio Verdejo-García[1,6*]

[1] Department of Clinical Psychology. Universidad de Granada, Granada, Spain.

[2] Department of Biomedical Sciences. Universidad Cardenal Herrera, Valencia, Spain.

[3] Department of Psychiatry, Bellvitge University Hospital-IDIBELL, Barcelona, Spain.

[4] Carlos III Health Institute, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain.

[5] Centro Provincial de Drogodependencias. Diputación de Granada, Granada.

[6] Institute of Neurosciences F. Olóriz. Universidad de Granada, Granada.

*Corresponding author:

Antonio Verdejo-García

Facultad de Psicología, Universidad de Granada

Campus de Cartuja S/N, 18071 Granada, Spain

Phone: +34958242948, Fax: +34958243749

Email: averdejo@ugr.es

Abstract

Cocaine dependence is associated with pronounced elevations of negative affect and deficient regulation of negative emotions. We aimed to investigate the neural substrates of negative emotion regulation in cocaine dependent individuals, as compared to non-drug-using controls, using functional resonance imaging (fMRI) during a reappraisal task. Seventeen cocaine dependent individuals abstinent for at least 15 days and without other psychiatric comorbidities, and 18 IQ-matched non-drug using controls participated in the study. Participants performed the reappraisal task during fMRI scanning: they were exposed to 24 blocks of negative affective or neutral pictures that they should Observe (neutral pictures), Maintain (sustain the emotion elicited by negative pictures) or Suppress (regulate the emotion elicited by negative pictures through previously trained reappraisal techniques). Task-related activations during two conditions of interest (Maintain>Observe and Suppress>Maintain) were analyzed using the general linear model in SPM8 software. We also performed psychophysiological interaction (PPI) seed-based analyses based on one region from each condition: the dorsolateral prefrontal cortex (dlPFC –Maintain>Observe) and the inferior frontal gyrus (IFG –Suppress>Maintain). Results showed that cocaine users had increased right dlPFC and bilateral temporoparietal junction activations during Maintain>Observe, whereas they showed decreased right IFG, posterior cingulate cortex, insula and fusiform gyrus activations during Suppress>Maintain. PPI analyses showed that cocaine users increased functional coupling between the dlPFC and emotion-related regions during Maintain>Observe, whereas they showed decreased functional coupling between the right IFG and the amygdala during Suppress>Maintain. These findings indicate that cocaine dependent individuals have dysfunctional corticolimbic activation and connectivity during negative emotion experience and reappraisal.

Key words: Cocaine, Negative Emotion, Reappraisal, Dorsolateral Prefrontal Cortex, Inferior Frontal Gyrus, Amygdala, Connectivity.

Introduction

Cocaine addiction is associated with pronounced elevations of negative affect and decreased inhibitory control (Koob & Volkow 2010). These cognitive-affective deficits seem to play a major distressing role during cocaine abstinence: patients frequently experience strong negative moods (Epstein & Preston 2010), which may trigger drug-seeking responses by virtue of negative reinforcement mechanisms (Baker *et al*. 2004; Uslaner *et al*. 1999). In accordance with this notion, stress-induced cocaine craving is a robust determinant of upcoming drug relapse (Sinha *et al*. 2006).

These deficits may stem from a breakdown of the brain systems that support adequate emotion experience and regulation, namely an enhanced reactivity of the corticolimbic regions involved in the processing of negative affect, coupled with deficient regulation of this emotional input by the cognitive control network (Cheetham *et al.*, 2010). Cortical structures seem to play a key role in regulating emotions. Specifically, significant activations of the right dorsolateral prefrontal cortex have been observed during efforts to sustain negative affective responses in healthy volunteers (Phan *et al.*, 2005), and during attended vs. unexpected negative affective images in major depression patients (Grimm *et al.*, 2008). With respect to cognitive reappraisal (the cognitive control directed to reduce the negative affective experience), meta-analytic evidence highlights the role of both the ventromedial prefrontal cortex and the right inferior frontal gyrus (Diekhof *et al.*, 2011). Nonetheless, the ventromedial prefrontal cortex stands as a domain-general node for multiple forms of emotion regulation (including fear extinction or placebo effects), whereas the right inferior frontal gyrus is preferentially involved in cognitive emotion regulation in healthy subjects (Diekhof *et al.*, 2011) and in stimulant (methamphetamine) users (Tabibnia *et al.*, 2011). Both

during cognitive maintenance and during regulation of negative emotion, the activation of cortical structures is accompanied by a concordant augmentation (appraisal) or reduction (reappraisal) of activation in the amygdala (Curcic-Blake, Swart & Aleman, 2012; Phan *et al.*, 2005). Previous functional magnetic resonance imaging (fMRI) studies in cocaine users have shown that these networks may be dysfunctional; for example, cocaine users compared to controls display heightened activation of limbic regions like the amygdala and hypoactivation of cortical cognitive control regions (especially the right inferior frontal gyrus) during the induction of anger (Drexler *et al*. 2000) or the experimentation of sad emotions (Wexler *el al*. 2001). Likewise, structural imaging studies have revealed that cocaine users present volumetric abnormalities in brain regions relevant for negative emotion experimentation and regulation, such as the amygdala or the inferior frontal gyrus (Moreno-López *et al*. 2012).

These neuroadaptations may actually intrude into (or stem from) more stable personality traits linked to emotional dysregulation, such as negative urgency –the tendency to act impulsively when under strong negative affects (Whiteside & Lynam 2001). In healthy individuals, negative urgency is negatively correlated with activation of cognitive control regions (e.g., anterior cingulate cortex) during emotional arousal (Joseph *et al*. 2009). Furthermore, the related construct of punishment sensitivity is positively associated with the activity of the right dorsolateral prefrontal cortex (Shackman et al., 2009). In cocaine users, negative urgency scores are increased compared to those of pathological gamblers (who share addictive mechanisms but are relatively free of neuroadaptive drug effects), and these scores correlates with volumetric measures of dorsolateral prefrontal cortex attrition (Moreno-López *et al*. 2012; Albein-Urios *et al*. 2012). Therefore, it is arguable that the cocaine-induced neuroadaptations that impact

emotion regulation systems are also associated with negative urgency traits, contributing to explain the stability of these deficits across abstinence.

The aims of this study are: (i) to investigate the neural substrates of negative emotion regulation in cocaine dependent patients, as compared to non-drug using controls, using fMRI during a reappraisal task; and (ii) to explore the link between the brain systems supporting emotion regulation and the trait of negative urgency in both groups. We hypothesized that: (i) cocaine users would display increased right dorsolateral prefrontal and amygdala activation during negative emotion experimentation, and decreased inferior frontal gyrus and other prefrontal regions activation during cognitive reappraisal; and (ii) negative urgency would positively correlate with corticolimbic activations during experimentation, and negatively correlate with prefrontal activations during reappraisal. To further explore the interaction between bottom-up and top-down systems, we also performed connectivity analyses that stemmed from empirically derived regions of interest: the right dorsolateral prefrontal cortex and the right inferior frontal gyrus.

Materials and methods

Participants

Seventeen cocaine dependent individuals and 18 non-drug using controls participated in the study. Cocaine dependent individuals were recruited as they commenced treatment in the clinic "Centro Provincial de Drogodependencias (CPD)" in Granada (Spain). This public facility provides cognitive behavioral treatment for substance use related disorders in an outpatient setting. The inclusion criteria for the cocaine dependent group were defined as follows: (i) age range between 18 and 45 years old; (ii) meeting DSM-

IV criteria for cocaine dependence –as assessed by the Structured Clinical Interview for DSM-IV Disorders – Clinician Version (SCID) (First *el al*. 1997); (iii) having IQ levels above 80 – as measured by the Kaufman Brief Intelligence Test (K-BIT) (Kaufman & Kaufman 1990); and (iv) having a minimum abstinence interval of 15 days. This abstinence period was confirmed by twice weekly urine toxicological tests plus an additional test on the scanner day. Exclusion criteria were: (i) the presence of any other Axis I or Axis II comorbid disorders –with the exceptions of alcohol abuse and nicotine dependence; (ii) the presence of history of head injury and neurological, infectious, systemic or any other diseases affecting the central nervous system; (iii) having followed other treatments within the 2 years preceding the study onset; and (iv) having entered treatment by court request. Comorbid Axis I disorders were assessed with the SCID, whereas Axis II disorders were assessed using the International Personality Disorders Examination (Loranger *et al*. 1994; López-Ibor 1999). We also used the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Conners 1999) to rule out the presence of adult ADHD symptoms (American Psychiatric Association 1994). Healthy controls were recruited from local employment agencies taking care to match them to the clinical groups in the main demographic characteristics and IQ. In addition to the former exclusion criteria, healthy controls could not meet any diagnosis of substance use disorders –with the exception of nicotine dependence. Axis I and II disorders were also assessed in this group using the SCID, the IPDE and the CAAID. The demographical data of participants is summarized in Table 1.

Insert Table 1 here

fMRI Task: Cognitive Reappraisal Task

We used a modified version of the original cognitive reappraisal task designed by (Phan *et al*. 2005). The task consists on the presentation of series of blocks showing neutral or negative picture stimuli that participants must (i) Observe (to passively observe neutral pictures), (ii) Maintain (to actively focus on the emotions elicited by negative emotional pictures, sustaining them over time), or (iii) Suppress (to reappraise the emotions induced by the negative emotional pictures by virtue of cognitive reappraisal techniques previously trained).

We used 24 stimuli that were extracted from the International Affective Picture System (Lang, Bradley & Cuthbert 2001): eight neutral pictures (e.g., household objects), which were presented in the Observe condition and 16 highly unpleasant arousing pictures (e.g., mutilations) that were presented in the Maintain and Suppress conditions. The images were selected according to IAPS Spanish normative values for valence and arousal (Moltó *et al.*, 1999); mean valence values were 2.50 (0.94), 2.50 (0.82) and 5.53 (0.82) for images included in the Maintain, Suppress and Observe conditions respectively, whereas arousal values were 6.44 (0.46), 6.40 (0.60) and 4.28 (0.73) for images included in the Maintain, Suppress and Observe conditions respectively. Pairwise comparisons showed that Maintain and Suppress values did not differ between them in valence or arousal ($p>0.9$), whereas both differed from the Observe values in valence and arousal ($p<0.001$). The task consisted of 12 blocks: four blocks for each of the three conditions. Instructions (Observe vs. Maintain vs. Suppress) were pseudo-randomized along the task to avoid the induction of sustained mood states. Each block began with the instruction prompt ("Observe" or "Maintain" or "Suppress") presented in the middle of the screen during 4 seconds. After the prompt, participants viewed two different pictures of equal valence for 10-sec each. Each block was followed by 10

seconds of baseline during which a cross fixation is presented on the screen to minimize carryover effects.

Inside scanner behavioral measures:

Immediately after the second picture of each block, the intensity of the negative emotion experienced was self-rated on a 1-5 number scale that appeared for five seconds (where 1 is "neutral" and 5 is "extremely negative").

Outside scanner behavioral measures:

The UPPS-P scale (Whiteside & Lynam 2001) is a 59-item inventory designed to measure five independent personality pathways to impulsive behavior. In this case, due to the focus on negative emotion regulation, we were specifically interested in the dimension of Negative Urgency, which refers to the tendency to experience strong impulses under conditions of negative affect.

Procedures

Participants were scheduled 60 minutes ahead of the scanner session to be debriefed about task instructions and trained to decrease the intensity of their negative emotions through cognitive reappraisal techniques (Gross 1999). Debriefing and training was conducted by a Master degree clinical psychologist (NAU). After the general training on the reappraisal techniques, all participants performed a supervised rehearsal of the maintenance and reappraisal strategies using five different trial images, and they subsequently completed a verbal yes/no questionnaire about the perceived sufficiency of the training and their perceived competency to perform the task. Only after successful rehearsal and positive responses to both questions the participants were entered into the

scanner. Stimuli were presented through magnetic resonance-compatible liquid crystal display goggles (Resonance Technology, Northridge, California, USA). Behavioral responses were recorded through a five-button box, Evoke Response Pad System (Resonance Technology Inc., Northridge, California, USA). The UPPS-P scale was administered in an independent session, along with a battery of cognitive tests that will be reported elsewhere.

Imaging data acquisition and preprocessing

We used a 3.0 Tesla clinical MRI scanner, equipped with an eight-channel phased-array head coil (Intera Achieva, Philips Medical Systems, Eindhoven, The Netherlands). During acquisition, a T2*-weighted echo-planar imaging (EPI) was obtained (TR = 2000 ms, TE = 35 ms, FOV = 230 x 230 mm, 96 x 96 matrix, flip angle = 90º, 21 4 mm axial slices, 1 mm gap, 234 scans). A sagittal three-dimensional T1-weighted turbo-gradient-echo sequence (3D-TFE) (160 slices, TR = 8.3 ms, TE = 3.8 ms, flip angle = 8°, FOV = 240 x 240, 1 mm^3 voxels) was obtained in the same experimental session for anatomical reference.

The functional images were analyzed using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK), running under Matlab R2009 (MathWorks, Natick, MA, USA). Preprocessing included slice timing correction, reslicing to the first image of the time series, normalization, using affine and smoothly nonlinear transformations, to an EPI template in the Montreal Neurological Institute (MNI) space, and spatial smoothing by convolution with a 3D Gaussian kernel (full width at half maximum = 8 mm).

Statistical analyses

Behavioral Analyses: Behavioral data was analyzed with the Statistical Package for the Social Sciences version 19 (SPSS; Chicago, IL, USA). We conducted independent-sample t-tests to compare the two groups on relevant socio-demographic variables, negative urgency scores and self-reported ratings of emotional intensity inside the scanner. Prior to image analysis, the effect of task condition on self-reported emotion was calculated to assure that the participants had followed the instructions during the task (e.g, Suppress scores lower than Maintain). Intra-subject effect of the three conditions analysis was performed also with SPSS.

fMRI, main task effects: In agreement with the main aims of the study two contrasts of interest were defined at the first-level (single-subject) analysis: (1) "Maintain>Observe" and (2) "Suppress>Maintain". The first contrast indexes brain activations associated with negative emotion experimentation, whereas the second contrast indexes brain activations associated with reappraisal of negative emotions. Conditions were modeled for the 20 seconds that the images were on the screen and did not include instruction and rating periods. The BOLD response at each voxel was convolved with the SPM8 canonical hemodynamic response function (using a 128-s high-pass filter). One-sample t-tests were conducted to assess intra-group activation in each of the contrasts. In these tests the statistical threshold was set at $p<0.05$ False Discovery Rate (FDR) whole-brain corrected, with a minimum cluster size extent (KE) of 10 contiguous voxels. Between-group comparisons were conducted with two-sample t-tests on the resulting first-level contrast images. In these tests, in which we include group as an additional source of variance, the significance threshold was set at $p<0.005$

(uncorrected; KE = 10 voxels), which is optimal to achieve an appropriate balance between the risk of error Type I and II (Lieberman & Cunningham 2009).

Psychophysiological interactions analysis: To explore the effective connectivity between the brain regions activated during the task, we conducted a PsychoPhysiological Interactions (PPI) analysis using SPM8 (Friston *et al*. 1997). Here we explored the impact of the two contrasts of interest (the "psychological" factor) on the strength of time-course correlations between two empirically obtained regions of interest (ROIs) with all the other regions of the brain (the "physiological" factor). To perform the first level analysis (subject-level), the ROIs were drawn from the set of regions showing group-differences in the two contrasts performed on task activation analyses (Maintain>Observe and Suppress>Maintain). Based on the combination of our initial theoretical predictions and the results obtained in the fMRI main task effects, we selected one region from each contrast: the right dorsolateral prefrontal cortex (Maintain>Observe) and the right inferior frontal gyrus (Suppress>Maintain). These regions have previously shown to be relevant for negative emotion experimentation and reappraisal, respectively (Grimm *et al*. 2008; Curcic-Blake *et al*. 2012). Hence, we extracted the first eigenvariate time series from a 7 mm radial sphere: the dorsolateral prefrontal cortex (dlPFC) (x=54, y=12, z=42) –in the case of Maintain>Observe, and the inferior frontal gyrus (IFG) (x=56, y=24, z=16) –in the case of Suppress>Maintain. Intra-group analysis threshold (one sample t-test) was set at $p<0.001$ (uncorrected; KE = 10 voxels), and between-group differences (two sample t-test) at $p<0.005$ (uncorrected; KE = 10 voxels).

Correlation analyses: Two sets of correlation analyses were performed in SPSS using the peak activations derived from the two main fMRI contrasts (Maintain>Observe and Suppress>Maintain) and the PPI maps. For both analyses, the beta eigenvalues corresponding to each region of interest were extracted for each participant, and then correlated with inside- and outside-scanner behavioral measures; that is, with self-reported ratings of intensity of negative emotion and the Negative Urgency scores from the UPPS-P scale, respectively.

Results

Behavioral results:

Independent-sample t-tests showed no differences between the groups in the Observe, Maintain or Suppress ratings ($p>0.1$ in all cases). Related-samples t-tests showed significant differences between Maintain and Observe ($p<0.05$), and between Suppress and Maintain ($p<0.05$); as expected, the intensity of negative emotion was greater in Maintain vs. Observe, and smaller in Suppress vs. Maintain (Table 2). With respect to the UPPS-P, the scores of Negative Urgency significantly differed between the groups, with CDI subjects showing higher scores than healthy controls (Table 2).

Insert Table 2 here

Imaging results:

Maintain > Observe:

Task activations:

Similar to previous studies using the reappraisal task, both groups commonly activated bilateral posterior sensory regions, the thalamus, and the medial frontal and right inferior frontal gyrus. In addition, controls activated the midbrain, the bilateral amygdala, the left anterior cingulate cortex and the right orbitofrontal cortex, whereas cocaine users activated the right dlPFC and the supplementary motor area.

Group differences:

Compared to controls, cocaine users showed significantly increased activations in the bilateral dlPFC, the temporoparietal junction, and the left IFG. No regions showed significantly increased activation in controls vs. cocaine users.

Insert Table 3 and Figure 1 here

Suppress >Maintain:

Task activations:

Controls had significant activations in posterior sensory regions, the posterior cingulate cortex, the right medial frontal gyrus and the bilateral IFG and dlPFC (see Supplementary Table). No regions showed significant activations in the cocaine users group at the selected threshold.

Group differences:

The direct between-groups comparison showed that most of the above mentioned regions had significantly decreased activation in cocaine users relative to controls (Table 4). More specifically, these findings were located in the cerebellum, the posterior sensory regions, the right thalamus, the left insula, the posterior cingulate cortex, the left

dlPFC and the bilateral IFG (Figure 2). No regions showed significantly increased activation in cocaine users vs. controls.

Insert Table 4 and Figure 2 here

PPI Analyses on Maintain > Observe and Suppress > Maintain:

Seed selection:

Functional connectivity analyses were performed to explore whether specific regions showing significant between-group differences in the main task contrasts were abnormally connected with other regions of the emotion regulation system during the task in the group of cocaine users. Among the clusters showing significant between-group differences, we selected the right dlPFC (which showed greater activation in cocaine vs. controls during Maintain>Observe; MNI coordinates x= 54, y= 12, z= 42, see Table 3 and Figure 1), and the right IFG (hypoactivated in cocaine users during Suppress>Maintain; MNI coordinates x= 56, y= 24, z= 16, see Table 4 and Figure 2).

Group differences in Maintain > Observe:

In cocaine users, as compared to controls, the right *dlPFC seed* showed increased functional coupling with the bilateral posterior sensory regions, the bilateral fusiform gyrus, the bilateral medial frontal gyrus, the right amygdala, the inferior temporal and orbitofrontal cortices, and the right insula/putamen region in cocaine users vs. controls (see Table 5 and Figure 3). No regions showed significantly greater right *DLPFC* connectivity in controls vs. cocaine users.

Group differences in Suppress > Maintain:

In control participants, as compared to cocaine users, the right *IFG seed* showed increased functional coupling with the bilateral amygdala, the left superior temporal and orbitofrontal cortices, the right fusiform gyrus and the bilateral anterior thalamus in controls vs. cocaine users (see Table 6 and Figure 3). No regions showed significantly greater right IFG connectivity in cocaine users vs. controls.

Insert Tables 5 and 6 and Figure 3 here

Correlations with behavioral measures:

For inside-scanner behavioral measures, the intensity of self-reported negative emotion during Maintain>Observe was negatively correlated to left insula activity in whole-sample analyses ($r=-0.53$, $p<0.05$). More specifically, this correlation was stronger in cocaine users ($r=-0.76$, $p<0.05$) than in control subjects ($r=-0.23$, $p>0.05$).

For outside-scanner measures, in the whole sample analyses negative urgency positively correlated with right dlPFC activation during Maintain>Observe ($r=0.58$, $p<0.005$). In addition, the functional connectivity between the right dlPFC and the right insula/orbitofrontal cortex during Maintain>Observe was more strongly correlated with negative urgency in cocaine users than in control subjects ($r=0.53$, $p<0.05$, and $r=0.25$, $p>0.05$, respectively) (see Figure 4A). During Suppress>Maintain, negative urgency was negatively correlated with the functional connectivity between the right IFG and the amygdala in controls ($r=-0.53$, $p<0.05$), whereas this association was non-significant in CDI subjects ($r=0.30$, $p>0.05$) (see Figure 4B).

Insert Figure 4 here

Confounders' effects: Both groups were well matched for most potentially confounding variables but in spite of recruitment efforts they significantly differed on the age distribution. Because our selection criteria only allowed age ranges between 18 and 45 years old, and age was not expected to impact on the conditions of interest, we have reported the results obtained without covariating for this variable. Nonetheless, in a conservative approach we subsequently replicated all analyses using age as a confounder and, as expected, results were unchanged.

Discussion

Our main findings show that cocaine dependent individuals have increased activations in the right dlPFC, the temporoparietal regions bilaterally, and the left IFG during experimentation of negative emotions, whereas they show decreased activation in the bilateral IFG, the posterior cingulate, the insula, the thalamus and the posterior sensory regions during cognitive reappraisal of these negative emotions. In agreement with our initial hypotheses, connectivity analyses showed that cocaine users had increased connectivity between right dlPFC and limbic (amygdala) and extra-limbic emotional regions (orbitofrontal cortex, insula) during negative emotion experimentation. On the other hand, they show reduced connectivity between the right IFG and these emotional regions (amygdala, OFC) during reappraisal. Finally, scores of negative urgency positively correlated with right dlPFC activation during negative emotion experimentation, and negatively correlated with right IFG connectivity during reappraisal. These results biologically substantiate increased sensitization towards negative emotion, coupled with abnormal regulation of these emotional states in cocaine dependent individuals without other psychiatric comorbidities.

Between-group differences in brain activations observed during negative emotion experimentation are in agreement with our initial predictions. Cocaine users showed increased activation of the right dlPFC, which has been associated with negative emotional appraisal and depression severity (Grimm *et al*. 2008; Phan *et al.*, 2005). The right dlPFC is also involved in the cognitive operations supporting drug craving (Hester & Garavan 2009), implying that cocaine users may appraise negative emotional states "as if" they were actually drug cravings (Fox *et al*. 2008). Along with the right dlPFC, the bilateral temporoparietal regions and the left inferior frontal gyrus showed significantly increased activations in cocaine users compared to controls. These regions are importantly involved in successful memory encoding, autobiographical memory, and self vs. others representations (Kim & Hamann 2012; Svoboda, McKinnon & Levine 2006), such that increased activation might represent heightened recollection of autobiographical memories during negative emotion experimentation in the cocaine group. This enhanced reactivity to negative stimuli may be associated with the patterns of task-related functional connectivity, since cocaine users showed increased connectivity between the right dlPFC and regions involved in visual-attentional processing, emotion perception and subjective appraisal (McRae *et al*. 2010), which overall indicate that cocaine users display greater reactivity of brain emotional systems during experimentation of negative emotion. Importantly, this heightened reactivity was associated with trait variations in negative urgency. This is in agreement with previous studies showing that dispositional variations in traits associated with punishment sensitivity can modulate right dlPFC tonic activity (Shackman *et al*. 2009) as well as its phasic impact on HPA-axis neuroendocrine responses (Baeken *et al*. 2011). Also in accordance with initial hypotheses, negative urgency correlated with the connectivity

between the dlPFC and the orbitofrontal cortex, supporting the association between this personality dimension and the brain dynamics involved in the processing of negative affect (Joseph *et al*. 2009). There was also a negative correlation between intensity of negative affect and insula activation, which might be explained by distorted interoceptive mechanisms leading to excessive appraisal of negative emotion (Verdejo-García, Clark & Dunn 2012). Overall, the data drawn from this contrast fit well with the notion that cocaine addiction is linked to sensitization of the brain systems involved in the processing of negative affect and stress (Koob & Volkow 2010).

Analyses of activations during reappraisal showed that cocaine users have reduced activations in a broad set of brain regions involved in cognitive control (IFG, left dlPFC) (Goldstein & Volkow 2011), down-regulation of heightened emotional states (posterior cingulate, insula and medial prefrontal cortex) (Grecucci *et al*. 2012), and attention (the thalamus and posterior visual-perceptual stream). This pattern indicates that cocaine users may be less able to engage the optimal brain circuitry to exert down-regulation of strong negative emotional states. Within this brain network, the right IFG has shown to be a critical piece to exert appropriate cognitive control of different response modalities (motor or emotional), and specifically the cognitive control of drug cravings (Tabibnia *et al*. 2011; Volkow *et al*. 2010). The analyses of right IFG connectivity showed that the activation of this region during reappraisal is temporally synchronized with activations in bilateral amygdala in controls but not in patients. Furthermore, the connectivity between the IFG and the amygdala was associated with the trait of negative urgency specifically within controls; participants with higher urgency scores showed diminished connectivity. Basic neuroimaging findings indicate that the connections between these regions are actually bidirectional, such that the

amygdala may initially update the IFG, and then the IFG may exert top-down regulation of the amygdala input (Curcic-Blake *et al*. 2012). Other regions associated with this network were the orbitofrontal cortex and the anterior thalamus, which are part of the emotional salience network (Seeley *et al*. 2007) that the right IFG purportedly works to inhibit. Cocaine users seem to have significantly impaired functioning of this emotion regulation system, which may contribute to explain a range of relevant clinical phenomena, such as persistent negative affect, emotional lability, poor anger management or intolerance to frustration. Overall, the data from this contrast fit well with the notion that cocaine addiction is associated with poor regulation of negative emotional states and high risk of negative-reinforcement based relapse episodes (Sinha *et al*. 2006). They also support the pertinence of developing and testing novel treatment interventions aimed to target emotion perception and appraisal mechanisms (Verdejo-García *et al*. 2012).

This study holds important strengths and also worth noting limitations. Among the first, we should number: the careful selection of cocaine dependent patients without other substance related disorders or related comorbidities, the duration of abstinence (always superior to 15 days, allowing us to rule out acute or residual drug effects), and the good match between the cocaine and control groups in terms of relevant socio-demographic variables not often controlled for (e.g., IQ). Although the groups significantly differed on age, our selection criteria stringently restricted the age range for inclusion (18-45 years old) in order to minimize the potential impact of ageing on the patterns of brain functioning. Furthermore, covariate analyses including age as a confounder did not change the results that we present here. It is also worth noting that cocaine users and controls did not differ on their subjective ratings of the images. The lack of behavioral

differences supports the validity of the reappraisal training, although we cannot fully discard subtle individual differences in the application of the reappraisal techniques. Future studies should also explore if the lack of behavioral differences are replicated in behavioral studies specifically designed for this aim. However, for the purpose of the current imaging study, the equivalence in behavioral output strengthens our specificity in investigating differences in brain activations in the absence of obvious differential performances. Other potential limitations include the relatively small sample size and the inclusion of patients with nicotine dependence and alcohol abuse. Nonetheless, in each case we should stress the difficulty of recruiting large clinical samples meeting our strict inclusion criteria, and the virtual impossibility of finding cocaine users without substantial nicotine and alcohol use.

Acknowledgements

This work has been funded by the grant COPERNICO, Plan Nacional sobre Drogas: Spanish Ministry of Health (PI: AVG). CSM is funded by a 'Miguel Servet' contract from the Carlos III Health Institute (CP10/00604).

Authors contribution

AVG designed the study. NAU and JMM conducted the recruitment and clinical characterization of participants. JVR, SA and CSM conducted neuroimaging analyses. NAU and AVG developed a first draft of the manuscript, later revised by all authors.

References

Albein-Urios N, Martínez-González JM, Lozano O, Clark L, Verdejo-García A (2012) Comparison of impulsivity and working memory in cocaine addiction and pathological gambling: Implications for cocaine-induced neurotoxicity. *Drug Alcohol Depend* [Epub ahead of print].

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Washington, DC: American Psychiatric Press.

Baeken C, Van Schuerbeek P, De Raedt R, De Mey J, Vanderhasselt MA, Bossuyt A, Luypaert R (2011) The effect of one left-sided dorsolateral prefrontal sham-controlled HF-rTMS session on approach and withdrawal related emotional neuronal processes. *Clin Neurophysiol* 122:2217-2226.

Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC (2004) Addiction motivation reformulated: an affective processing model of negative reinforcement. *Psychol Rev* 111:33-51.

Cheetham A, Allen NB, Yücel M, Lubmain DI (2010). The role of affective dysregulation in drug addiction. *Clin Psychol Rev* 30:621-634.

Conners CK (1999) Clinical use of rating scales in diagnosis and treatment of attention-deficit/hyperactivity disorder. *Pediatr Clin North Am* 46:857-870.

Curcic-Blake B, Swart M, Aleman A (2012) Bidirectional information flow in frontoamygdalar circuits in humans: a dynamic causal modeling study of emotional associative learning. *Cereb Cortex* 22:436-445.

Diekhof EK, Geier K, Falkai P, Gruber O (2011). Fear is only as deep as the mind allows: A coordinate-based meta-analysis of neuroimaging studies on the regulation of negative affect. *Neuroimage* 58:275-285.

Drexler K, Schweitzer JB, Quinn CK, Gross R, Ely TD, Muhammad F, Kilts CD (2000) Neural activity related to anger in cocaine- dependent men: a possible link to violence and relapse. *Am J Addict* 9:331-339.

Epstein DH, Preston KL (2010) Daily life hour by hour, with and without cocaine: an ecological momentary assessment study. *Psychofarmachology* 211:223-232.

First MB, Spitzer RL, Gibbon M, Williams JBW (1997) *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I)*. Washington, DC: American Psychiatric Press.

Fox HC, Hong KL, Siedlarz K, Sinha R (2008) Enhanced sensitivity to stress and drug/alcohol craving in abstinent cocaine-dependent individuals compared to social drinkers. *Neuropsychopharmacology* 33:796-805.

Friston KJ, Buchel C, Fink GR, Morris J, Rolls E, Dolan R (1997) Psychophysiological and modulatory interactions in Neuroimaging. *NeuroImage* 6:218-229.

Goldstein RZ, Volkow ND (2011) Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci* 12:652-669.

Grecucci A, Giorgetta C, Van´t Wout M, Bonini N, Sanfey AG (2012) Reappraising the Ultimatum: an fMRI Study of Emotion Regulation and Decision Making. *Cereb Cortex* [Epub ahead of print].

Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, Walter M, Ernst J, Hell D, Boeker H, Northoff G (2008) Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. *Biol Psychiatry* 63:369-376.

Gross JJ (1999) Emotion regulation: Past, present, future. *Cogn Emotion* 13:551-573.

Hester R, Garavan H (2009) Neural mechanisms underlying drug-related cue distraction in active cocaine users. *Pharmacol Biochem Behav* 93:270-277.

Joseph JE, Liu X, Jiang Y, Lynam D, Kelly TH (2009) Neural correlates of emotional reactivity in sensation seeking, *Psychol Sci* 20:215-223.

Kaufman AS, Kaufman NL (1990) *Kaufman Brief Intelligence Test.1*. American Guidance Service, Circle Pines MN.

Kim SH, Hamann S (2012) The effect of cognitive reappraisal on physiological reactivity and emotional memory. *Int Psychophysiol* 83:348-356.

Koob GF, Volkow ND (2010) Neurocircuitry of addiction. *Neuropsychofarmachology* 35:217-238.

Lang PJ, Bradley MM, Cuthbert BN (2001*) International affective picture system (IAPS)*; Instruction manual and effective ratings. Technical Report A-5, The Center for Research in Psychophysiology, University of Florida.

Lieberman MD, Cunningham WA (2009) Type I and Type II error concerns in fMRI research: re-balancing the scale. *Soc Cogn Affect Neurosci* 4:423-428.

López- Ibor JJ (1999) I.P.D.E. *Examen internacional de los trastornos de la personalidad*. Organización Mundial de la Salud, Madrid: Meditor.

Loranger AW, Sartorius N, Anfreoli A, Berger P, Buchheim P, Channabasavanna SN (1994) The International Personality Disorder Examination. The World Health Organization/Alcohol, Drug Abuse, and Mental Health Administration International pilot study of personality disorders. *Arch Gen Psychiatry* 51:215-224.

McRae K, Hughes B, Chopra S, Gabrieli JD, Gross JJ, Ochsner KN (2010) The neural bases of distraction and reappraisal. *J Cogn Neurosci* 22:248-262.

Moltó, J., Montañés, S., Poy, R., Segarra, P., Pastor, M.C., Tormo, M.P., et al., 1999. Un nuevo método para el estudio experimental de las emociones: El International Affective Picture System (IAPS) adaptación española. *Rev Psicol Gen Apl* 52:55-87.

Moreno-López L, Catena A, Fernández-Serrano MJ, Delgado-Rico E, Stamatakis EA, Pérez-García M, Verdejo-García A (2012) Trait impulsivity and prefrontal gray matter reductions in cocaine dependent individuals. *Drug Alcohol Depend* [Epub ahead of print].

Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME (2005) Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. *Biol Psychiatry* 57:210-219.

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 27:2349-2356.

Shackman AJ, McMenamin BW, Maxwell JS, Greischar LL, Davidson RJ (2009) Right dorsolateral prefrontal cortical activity and behavioral inhibition. *Psychol Sci* 20:1500-1506.

Sinha R, García M, Paliwal P, Kreek MJ, Rounsaville BJ (2006) Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Arch Gen Psychiatry* 63:324-331.

Svoboda E, McKinnon MC, Levine B (2006) The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia* 44:2189-2208.

Tabibnia G, Monterosso JR, Baicy K, Aron AR, Poldrack RA, Chakrapani S, Lee B, London ED (2011) Different forms of self control share a neurocognitive substrate. *J Neurosci* 31:4805-4810.

Uslaner J, Kalechstein A, Richter T, Ling W, Newton T (1999) Association of depressive symptoms during abstinence with the subjective high produced by cocaine. *Am J Psychiatry* 156:1444-1446.

Verdejo-García A, Clark L, Dunn BD (2012) The role of interoception in addiction: A critical review. *Neurosci. Biobehav. Rev* [Epub ahead of print].

Volkow ND, Fowler JS, Wang GJ, Telang F, Logan J, Jayne M, Ma Y, Pradhan K, Wong C, Swanson JM (2010) Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. *Neuroimage* 49:2536-2543.

Wexler BE, Gottschalk CH, Fulbright RK, Prohovnik I, Lacadie CM, Rounsaville BJ, Gore JC (2001) Functional magnetic resonance imaging of cocaine craving. *Am J Psychiatry* 158:86-95.

Whiteside SP, Lynam DR (2001) The five factor model and impulsivity: using a structural model of personality to understand impulsivity. *Pers Individ Dif* 30:669-689.

Figure Legends:

Figure 1. Within-group activations and between-group differences in response to negative emotion experimentation (Maintain>Observe): Cocaine dependent individuals (CDI), controls, and CDI>Controls.

Figure 2. Between-group differences during reappraisal of negative emotions (Suppress>Maintain): Regions showing increased activation in cocaine dependent individuals (CDI) vs. controls.

Figure 3. Regions showing different patterns of functional connectivity in cocaine dependent individuals (CDI) vs. controls stemming from the seeds of the right dorsolateral prefrontal cortex (dlPFC) and the right inferior frontal gyrus (IFG) during negative emotion experimentation (Maintain>Observe) and reappraisal (Suppress>Maintain).

Figure 4. Correlations between regions functionally connected with the dlPFC (Maintain>Observe) (Panel A) and the IFG (Suppress>Maintain) (Panel B) seeds and outside-scanner scores of negative urgency.

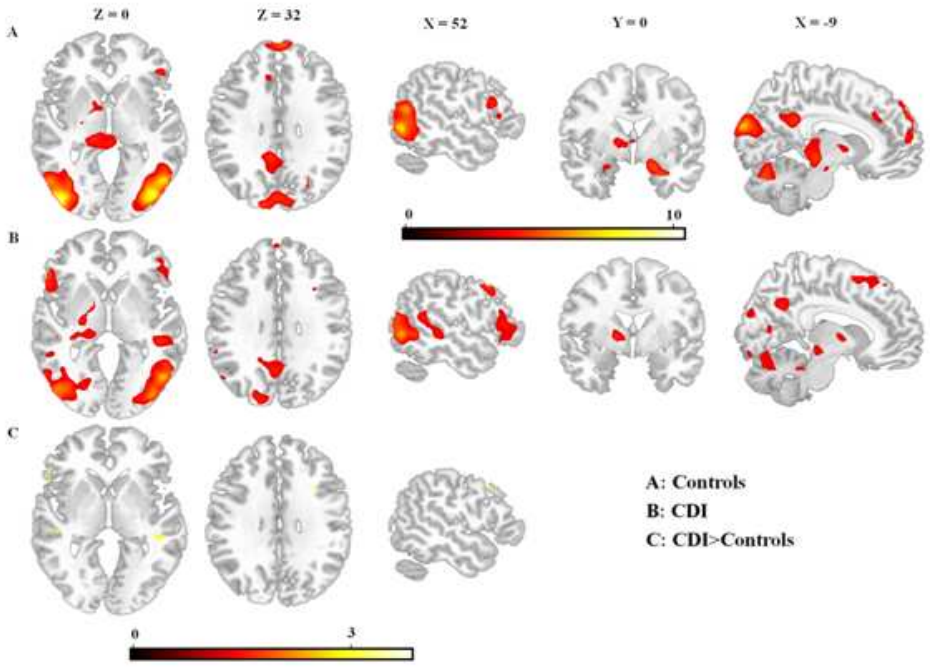

Figure 1.

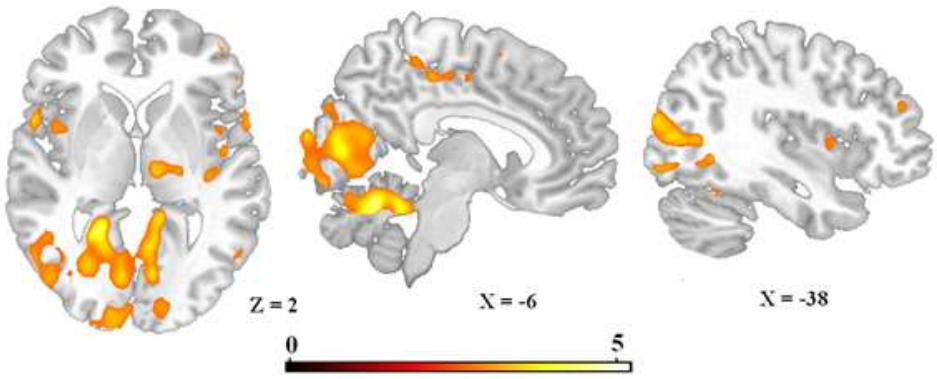

Figure 2.

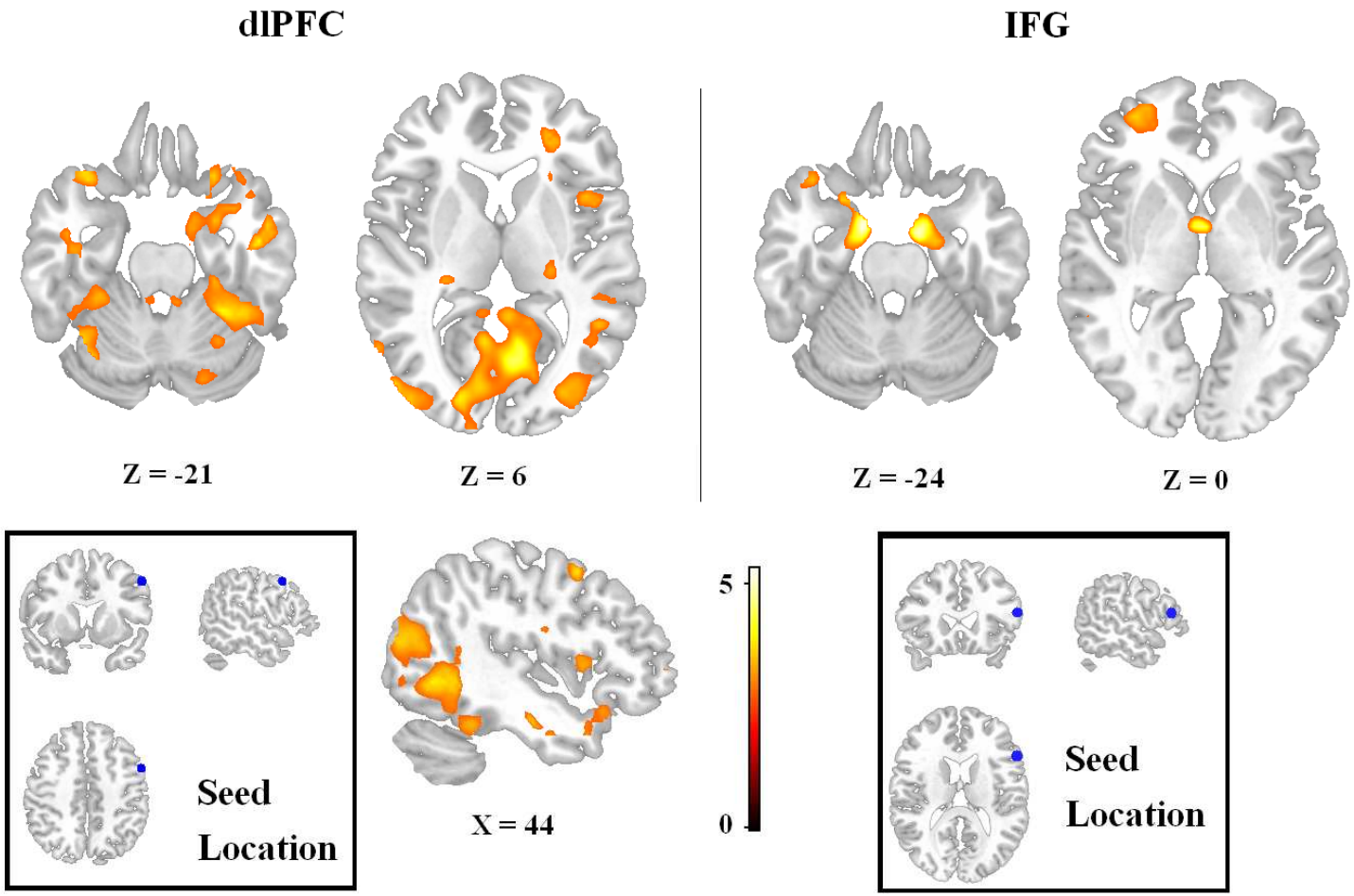

Figure 3.

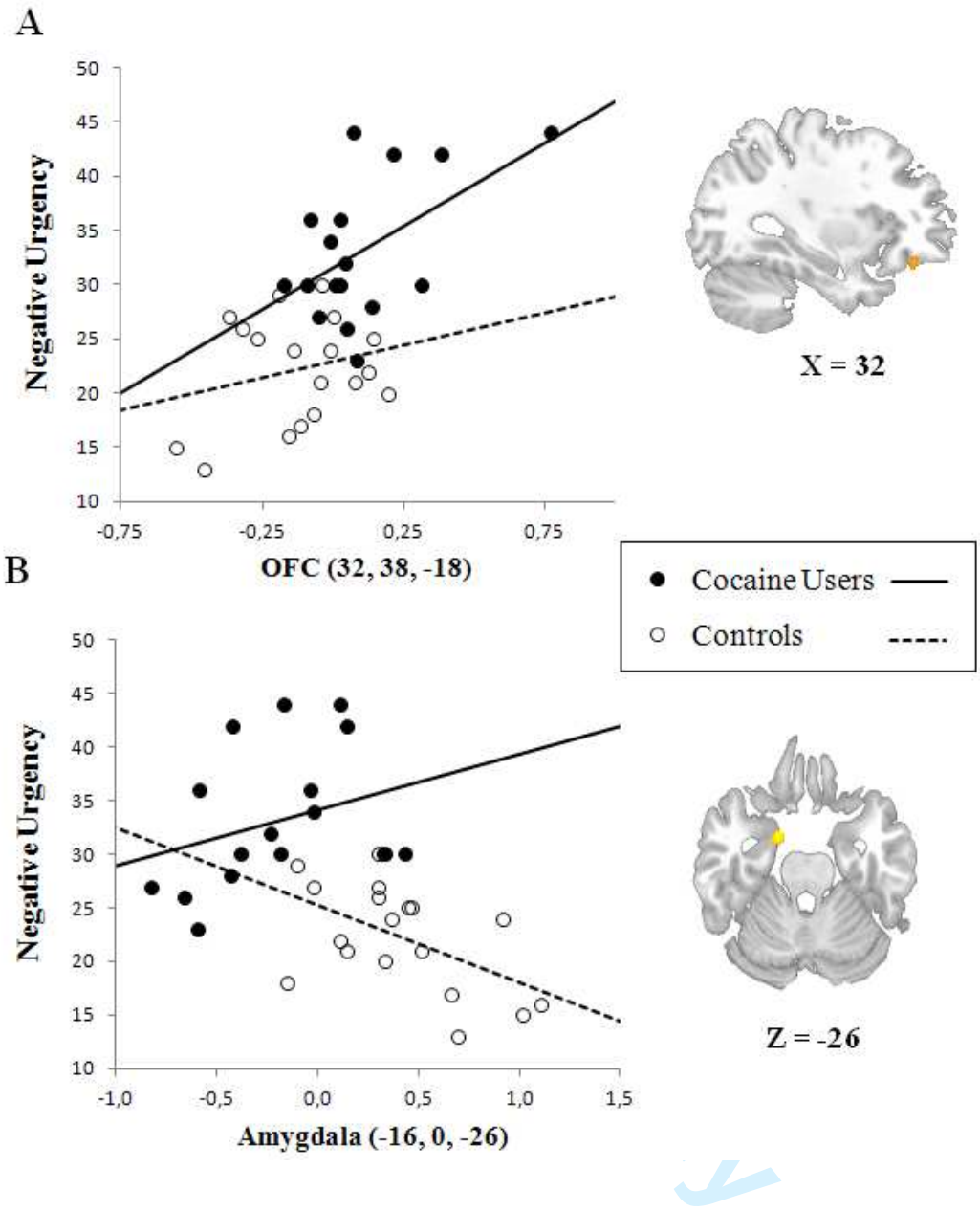
A
Negative Urgency
50
45
40
35
30
25
20
15
10
-0,75
-0,25
0,25
0,75
OFC (32, 38, -18)
X = 32
B
Cocaine Users
Controls
Negative Urgency
50
45
40
35
30
25
20
15
10
-1,0
-0,5
0,0
0,5
1,0
1,5
Amygdala (-16, 0, -26)
Z = -26

Figure 4.

Table 1. Demographic and clinical characteristics of Cocaine Dependent Individuals (CDI) and Healthy Controls (HC).

	CDI n=17 Mean (SD)	HC n=18 Mean (SD)	*p* value
Demographic variables			
Age	36.41 (5.99)	30.50 (4.64)	*p*=0.002
Gender	16 (M)/1 (F)	17 (M)/1 (F)	
Laterality	14 (R)/3 (L)	17 (R)/1 (L)	
Years of education	9.76 (1.71)	10.56 (1.91)	*p*=0.208
Verbal IQ	100.82 (8.62)	105.77 (7.94)	*p*=0.090
Clinical variables			
Monthly cocaine use (gr.)	18.79 (27.53)		
Duration cocaine (months)	56.55 (59.02)		
Abstinence cocaine (months)	2.50 (5.59)		
Monthly alcohol use (SDU)	30.18 (30.64)	8.91 (8.44)	*p*=0.016
Duration alcohol (months)	91.15 (94.79)	91.70 (56.77)	*p*=0.986

SD, standard deviation; (M), male; (F), female; (R), right; (L), left; IQ, intelligence quotient; gr., grams; SDU, standard drinking units.

Table 2. Self- reports of the intensity of negative emotions induced on each task condition and negative urgency scores in cocaine dependent individuals (CDI) and healthy controls (HC).

Inside scanner ratings	CDI n=17 Mean (SD)	HC n=18 Mean (SD)	*p* value
Maintain	3.68 (0.93)	3.13 (0.97)	*p*=0.103
Suppress	3.24 (0.82)	2.76 (1.04)	*p*=0.154
Observe	1.86 (0.86)	1.64 (0.67)	*p*=0.439
Outside scanner UPPS scale			
Negative Urgency	33.17 (6.51)	22.22 (5.01)	*p*=0.000

Note. SD, standard deviation; UPPS, impulsive behavior scale.

Table 3. Regions showing significant activations during Maintain>Observe: One-sample t-tests for Controls and Cocaine Dependent Individuals (CDI), and independent-sample t-tests showing significant differences between the groups (CDI>Controls).

	BA	Side	MNI Coordinates			Volume (mm^3)	*t*
			X	Y	Z		
Controls							
Occipitotemporal Cortex	18/19/37	L	-44	-88	0	31.552	10.31
Occipitotemporal Cortex	18/19/37	R	42	-80	0	39.416	8.53
Cerebellum		L/R	-18	-74	-26	23.480	5.71
Medial Frontal Gyrus	9/10	L/R	6	60	26	5.264	5.60
Amygdala	34	R	20	-4	-22	1.888	5.37
Amygdala / Hippocampus	34	L	-22	0	-20	1.360	3.54
IFG	44/45	R	50	14	20	1.248	5.07
IFG	47	R	48	34	-2	224	4.35
Post. Thalamus / Tectum		L/R	-8	-28	-8	5.872	4.97
Ant. Thalamus		L/R	-12	0	0	1.112	4.45
Precuneus	31	L/R	-6	-48	28	3.056	4.74
OFC	47	R	34	32	-22	368	4.26
Midbrain		L/R	-4	-18	-18	240	4.14
ACC	32	L	-8	28	32	312	4.03
CDI							
Occipitotemporal Cortex	18/19/37	R	40	-52	-24	19.120	7.10
Occipitotemporal Cortex	18/19/37	L	-46	-78	2	20.920	6.86
IFG	45/47	R	58	28	8	2.992	5.38
IFG	45/47	L	-52	28	-2	4.880	4.99
Cerebellum		L/R	-18	-72	-26	12.184	4.70
Post. Thalamus / Tectum		L	-12	-24	-8	2.960	4.70
Precuneus	7/31	L/R	-4	-62	34	3.384	4.43
Ant. Thalamus		L	-14	-2	2	1.152	4.41
Supplementary Motor Area	6/8	L/R	-6	8	60	2.192	4.34
dlPFC	10	R	36	56	20	400	4.11
Medial Frontal Gyrus	9	L/R	0	56	34	784	3.89
CDI > Controls							
dlPFC		R	32	14	30	160	3.82
dlPFC	9	R	54	12	42	176	3.54
Temporoparietal	21	R	46	-32	-6	592	3.65
Temporoparietal	22	L	-46	-30	-2	200	3.14
IFG	47	L	-52	30	-2	160	3.04

Note. CDI, cocaine dependent individuals; IFG, inferior frontal gyrus; ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex.

Table 4. Brain regions showing significantly increased activation in Controls vs. Cocaine Dependent Individuals (CDI) during reappraisal (Suppress>Maintain).

	BA	Side	MNI Coordinates			Volume (mm^3)	*t*
			X	Y	Z		
Controls > CDI							
Fusiform Gyrus	30	L	-18	-50	-2	79.008	5.18
Fusiform Gyrus	19	R	16	-58	-12		4.41
Cerebellum		L/R	-12	-66	-28		5.13
Occipitotemporal Cortex	37/39	L	-42	-66	8		4.49
Occipitotemporal Cortex	18	R	38	-86	-12		4.23
Parieto-Occipital	7/19	L	-14	-86	34		4.43
Cuneus	17/31	L	-6	-80	6		4.14
Cuneus	18	R	10	-76	-2		3.86
Posterior Cingulate Cortex	31	L/R	-6	-30	46	2.040	3.45
Thalamus		R	14	-18	-2	2.312	3.67
IFG	44	L	-56	8	6	1.176	4.04
IFG	6	R	64	2	8	1.016	3.76
IFG		R	60	26	14	320	3.36
OFC	10	R	50	44	-4	232	3.40
dlPFC		L	-36	44	22	152	3.18
Insula	13	L	-40	6	0	472	3.16

Note. CDI, cocaine dependent individuals; IFG, inferior frontal gyrus; OFC, orbitofrontal cortex; dlPFC, dorsolateral prefrontal cortex.

Table 5. Brain regions showing increased functional connectivity with the right dorsolateral prefrontal cortex seed in Cocaine Dependent Individuals (CDI) vs. Controls during experimentation of negative emotions (Maintain>Observe).

	BA	Side	MNI Coordinates			Volume (mm^3)	*t*
			X	Y	Z		
CDI > Controls							
Cuneus/Fusiform	18/19/30/37	L/R	10	-68	2	82.824	4.78
Inferior Temporal Gyrus	20/21	R	48	-14	-22	1.104	4.30
OFC	47	L	-34	24	-24	848	3.81
dlPFC	8	R	46	8	50	488	3.75
Medial Frontal Gyrus	10	R	12	54	10	360	3.55
Medial Frontal Gyrus	10	L	-8	56	4	1.072	3.49
Temporal/Amygdala/OFC	28/38/47	R	28	22	-26	3.664	3.54
Insula	13	R	44	12	6	544	3.41
Putamen		R	30	14	0	456	3.35
Precuneus	7	L/R	6	-56	46	408	3.18

Note. CDI, cocaine dependent individuals; OFC, orbitofrontal cortex; dlPFC, dorsolateral prefrontal cortex.

Table 6. Brain regions showing increased functional connectivity with the right inferior frontal gyrus seed in Controls vs. Cocaine Dependent Individuals (CDI) during reappraisal (Suppress>Maintain).

	BA	Side	MNI Coordinates			Volume (mm^3)	*t*
			X	Y	Z		
Controls> CDI							
Amygdala	28/34	R	14	-6	-26	1.760	5.03
Amygdala	28/34	L	-14	-4	-26	1.248	5.19
Ant. Thalamus		L/R	0	-2	0	576	4.50
OFC	10	L	-30	52	-2	1.208	3.71
Superior Temporal Gyrus	38	L	-38	20	-26	416	3.47
Fusiform Gyrus	20	R	56	-4	-30	336	3.36

Note. CDI, cocaine dependent individuals; OFC, orbitofrontal cortex.