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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 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.

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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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 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.

Key words: Cocaine, Borderline personality disorder, Histrionic personality disorder, Antisocial personality disorder, Negative emotion, Reappraisal, Anterior cingulate cortex, Lateral orbitofrontal cortex, Amygdala.

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; López-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., 2013a). 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., 2012). 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., 2012; Yang and Raine, 2009). Specifically, they exhibit consistent reductions in subgenual anterior cingulate cortex activation during negative emotion experience (Ruocco et al., 2012) and increased insula and decreased orbitofrontal cortex activation during reappraisal (Schulze et al., 2010). 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 vs. 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, 2001); (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 was confirmed by twice weekly urine tests plus an ad hoc test on the testing days. Inclusion criteria for cocaine dependent patients with comorbid personality disorders were restricted to diagnoses pertaining to Cluster B, which are the more prevalent among cocaine users. Axis II disorders were assessed

using the International Personality Disorders Examination (Loranger et al., 1994). The exclusion criteria were: (i) the presence of any other Axis I disorders –with the exceptions of alcohol abuse, nicotine dependence and attention deficit and hyperactivity disorder (ADHD) –as measured by the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Conners, 1999); (ii) history of head injury or neurological, infectious, systemic or any other diseases affecting the central nervous system; (iii) having followed other treatments within the two years preceding the study onset; and (iv) having entered treatment by court request. Comorbid Axis I disorders were assessed with the SCID.

Healthy controls were recruited from local employment agencies. In addition to the former exclusion criteria, healthy controls could not meet any diagnosis of substance-related 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.

All the diagnoses were conducted by a board clinical psychologist, whereas all subsequent tests were administered by an independent (blind to diagnosis) evaluator.

Insert Table 1 here

2.2. Instruments

2.2.1. fMRI task: cognitive reappraisal task:

We used a cognitive reappraisal task described in Albein-Urios et al. (2012), which adapted the original version designed by Phan et al. (2005). The task consists of the presentation of series of blocks showing neutral or negative picture stimuli that

participants must (1) Observe (to passively observe neutral pictures); (2) Maintain (to actively focus on the emotions elicited by negative emotional pictures, sustaining them over time); or (3) Suppress (to re-appraise 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 versus Maintain versus 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 seconds each. Each block was followed by 10 seconds of

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

2.2.2. 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 5 seconds (where 1 is 'neutral' and 5 is 'extremely negative').

2.2.3. Outside scanner behavioral measures:

The *UPPS-P* scale (Whiteside and 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.

The *Personality Belief Questionnaire –PBQ* (Beck and Beck, 1991) is a self-report questionnaire that consists of nine scales that measure specific beliefs and assumptions associated with the different personality disorders. Here we only used the four scales corresponding to Cluster B personality disorders: antisocial, borderline, histrionic and narcissistic. The Spanish version of the scale (Albein-Urios et al., 2011) holds appropriate psychometric characteristics and the reliability of the different scales (Cronbach's α) in this sample ranged from 0.71 (narcissistic) to 0.88 (borderline).

2.3. 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's 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 were the participants entered into the scanner. Stimuli were presented through magnetic resonance-compatible liquid crystal display goggles (Resonance Technology, Northridge, CA, USA). Behavioral responses were recorded through a five-button box, Evoke Response Pad System (Resonance Technology Inc.). The UPPS-P and PBQ scales were administered in an independent session, along with a battery of cognitive tests that will be reported elsewhere.

2.4. 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 = 90°, 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 mm3 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, re-slicing to the first image of the time series, normalization, using affine and smoothly non-linear 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).

2.5. Statistical analyses:

2.5.1. Behavioral analyses:

Behavioral data were analyzed with the Statistical Package for the Social Sciences version 19 (SPSS; Chicago, IL, USA). We conducted one-way ANOVAs followed by Tukey tests to compare the three groups on relevant socio-demographic variables. Although age showed a significant between-group difference (cocaine users with and without comorbidities older than controls), subsequent analyses showed that it was not correlated with brain activations in any of the contrasts of interest, and therefore it was not further considered. We also used ANOVAs and subsequent Tukey tests to explore potential differences on self-reported ratings of emotional intensity inside the scanner and on personality measures of impulsivity and dysfunctional beliefs. 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.

2.5.2. fMRI main task effects:

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). Between-group comparisons were conducted with an ANOVA on the resulting first-level contrast images.

2.5.3. 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 seed-regions of interest with all the other regions of the brain (the 'physiological' factor). To perform the first-level analysis (subject-level), the seeds were selected in accordance to two criteria: belonging to the predetermined set of regions of interest (ROIs, see below), and showing group differences in the two contrasts performed on task activation analyses (Maintain>Observe and Suppress>Maintain). Two regions met these criteria: the subgenual cingulate (for Maintain>Observe) and the orbitofrontal cortex (Suppress>Maintain). Hence, we extracted the first eigenvariate time series from a 7-mm radial sphere: the subgenual cingulate cortex (x = -14, y = 20, z = -16) –in the case of Maintain>Observe—and the

left orbitofrontal cortex (x = -30, y = 30, z = -4) and right OFC (x = 52, y = 26, z = -12) –in the case of Suppress>Maintain.

2.5.4. Imaging analyses and Threshold:

To explore main task effects and PPI, we followed a region of interest (ROI) approach using the areas previously defined in the background section: anterior cingulate cortex, insula, orbitofrontal cortex, striatum and amygdala. In these tests, the statistical threshold was set at $p<0.05$ false discovery rate (FDR) corrected across the voxels of each ROI (i.e., using Small Volume Correction, or SVC, procedures). We also performed a whole-brain voxel-wise analysis in order to explore other brain areas where could be differences between the groups. In this case the results were corrected for multiple comparisons with a combination of voxel intensity and cluster extent thresholds. The spatial extent threshold was determined by 1,000 Monte Carlo simulations using AlphaSim (Ward et al., 2000) as implemented in the SPM REST toolbox (Song et al., 2011). The input parameters included brain mask of 156.444 voxels, an individual voxel threshold probability of 0.001 (0.005 for PPI analyses) and a cluster connection radius of 5 mm, at 8 mm FWHM smoothness. A minimum cluster extent (KE) of 121 voxels (312 for PPI analyses) was estimated to satisfy a $P_{FWE} <.05$.

2.5.5. 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 ROI 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 with the negative urgency scores of the UPPS-P scale and subscales scores from the PBQ.

3. Results

3.1. Behavioral results:

Results are displayed in Table 2. ANOVAs 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 versus Observe, and smaller in Suppress versus Maintain (Table 2). With respect to the UPPS-P, the scores of negative urgency significantly differed between the groups, with cocaine users with and without comorbidities scoring higher than controls ($P<0.001$). The PBQ borderline and antisocial scales also showed differences between the groups ($P<0.05$). In the borderline scale both cocaine users with and without comorbidities scored higher than controls ($P<0.05$). In the antisocial scale the cocaine users with concurrent personality disorders scored higher than cocaine users without comorbidities and controls ($P<0.05$).

Insert Table 2 here

3.2. Imaging results:

For the sake of brevity, we only present in the main text and Figures the findings from group comparisons in the main contrasts of interest (Maintain>Observe and Suppress>Maintain), with special emphasis on the ROI results. For a detailed account of

the one-sample task activations results and the between-group whole-brain comparisons please see Supplementary Tables S1 to S7.

3.2.1. Maintain>Observe:

Cocaine users with concurrent personality disorders showed decreased activation of the subgenual anterior cingulate cortex compared to cocaine users without comorbidities and controls. In addition, according to the whole-brain analyses, cocaine users with concurrent personality disorders also showed decreased activation of the left dorsolateral prefrontal cortex, left lateral orbitofrontal cortex and left supplementary motor area with respect to cocaine users without comorbidities but not with respect to controls (Figure 1).

Insert Figure 1 here

3.2.2. Suppress>Maintain:

In comparison to cocaine users without comorbidities, cocaine users with concurrent personality disorders showed increased activation of the amygdala and the lateral orbitofrontal cortex (bilaterally), as well as the inferior frontal and subcallosal gyri of the left hemisphere. The behavioral scores of negative urgency and antisocial beliefs positively correlated with amygdala activation in the cocaine comorbid group, but not in cocaine users without comorbidities or controls (Figure 2).

Insert Figure 2 here

3.2.3. PPI Analyses:

3.2.3.1. Group differences in Maintain>Observe:

Cocaine users with concurrent personality disorders, in comparison to cocaine users without comorbidities, showed *decreased* functional coupling between the subgenual cingulate cortex and left amygdala and bilateral fusiform gyri in comparison to cocaine users without comorbidities (see Figure 3, left top panel). In addition, they showed *increased* functional coupling between the subgenual cingulate cortex and the right anterior insula in comparison to cocaine users without comorbidities and controls (see Figure 3, left bottom panel).

3.2.3.2. Group differences in Suppress>Maintain:

In comparison with cocaine users without comorbidities, cocaine users with concurrent personality disorders showed *increased* functional coupling between the left orbitofrontal cortex and the left amygdala, thalamus, and tempo-occipital cortex (see Figure 3, right top panel). Conversely, also in comparison to cocaine users without comorbidities, cocaine users with concurrent personality disorders showed *decreased* functional coupling between the right orbitofrontal cortex and the left lenticular nucleus (putamen and globus pallidus), extending to the adjacent posterior insular cortex (see Figure 3, right bottom panel). We found no significant differences in connectivity between the cocaine groups and controls.

Insert Figure 3 here

4. Discussion

In agreement with initial hypotheses, cocaine users with concurrent Cluster B personality disorders showed reduced subgenual anterior cingulate cortex activation during negative emotion maintenance, and increased lateral orbitofrontal cortex (BA 47) and amygdala activations during cognitive reappraisal. The personality scores of negative urgency and antisocial beliefs were significantly elevated in the cocaine comorbid group, and both scores positively correlated with the reappraisal-related amygdala activation exclusively within this group. Connectivity analyses further showed that within the cocaine comorbid group the subgenual cingulate was less efficiently connected with the left amygdala and fusiform gyri and more efficiently connected with the right anterior insula during maintenance, whilst during reappraisal the left orbitofrontal cortex was more efficiently connected with the left amygdala and the right orbitofrontal cortex was less efficiently connected with the dorsal striatum.

According to these findings, cocaine users with concurrent Cluster B personality disorders are specifically characterized by reduced subgenual anterior cingulate cortex activation during active maintenance of negative emotions. The subgenual anterior cingulate cortex is normally engaged during recall of aversive states, and its activation correlates with the appraisal of negative emotions (Kross et al., 2009). Conversely, brain lesions encompassing the subgenual anterior cingulate cortex result in insensitivity to punishment (relative to reward) in the guidance of decision-making (Bechara et al., 1994), which is a hallmark of the social behavior of individuals with personality disorders (Dadds and Salmon, 2003). Our connectivity results further showed that in the cocaine comorbid patients the subgenual anterior cingulate cortex was less efficiently connected with a broader network of regions (amygdala and

fusiform gyri) which are also importantly involved in moderating responses to aversive stimuli (Pujol et al., 2009). On the other hand, also in comorbid patients, the subgenual cingulate cortex was more efficiently connected with the anterior insula, which is part of a large-scale brain network associated with emotional salience (Taylor et al., 2009). All in all, the results from this contrast suggest that cocaine users with concurrent personality disorders have deficient functioning of the brain regions supporting experiential and appraisal aspects of negative emotion with respect to non-comorbid cocaine users and controls. There were also a number of regions in which non-comorbid cocaine users showed increased activation than comorbid users (left lateral orbitofrontal, dorsolateral prefrontal cortex and supplementary motor regions). Because these areas are involved in cognitive control (Cole and Schneider, 2007) and they did not significantly differ between cocaine users and controls, we interpret that this finding reflects higher cognitive effort to sustain negative emotion in the non-comorbid vs. the comorbid patients.

During reappraisal of negative emotions the cocaine users with concurrent Cluster B personality disorders showed increased lateral orbitofrontal cortex (BA 47) and amygdala activations compared to the non-comorbid cocaine users. Connectivity analyses further showed that comorbid patients exhibited increased functional coupling between the left lateral orbitofrontal cortex and the left amygdala, the thalamus and temporal-occipital regions. Noteworthy, the neural pathway connecting the lateral orbitofrontal cortex with the amygdala has been associated with reduced reappraisal success (Wager et al., 2008) and with predominantly distracting vs. reappraisal strategies of emotion regulation (McRae et al., 2010). In agreement with these notions, our correlation analyses showed that specifically within the comorbid group there was a

positive association between the reappraisal-related amygdala activation and the intensity of negative urgency (the tendency to act impulsively when under strong negative affect). We also found a significant correlation between reappraisal-related amygdala activation and the scores of antisocial-related cognitive beliefs, which is in fitting with evidence showing that amygdala activation during reappraisal is associated with the tendency to ruminate and focus on negative aspects of one's self (Ray et al., 2005). Therefore, these findings indicate that cocaine patients with comorbid personality disorders display enhanced engagement of neural networks conveying low efficiency to perform adequate emotion regulation strategies, and that this brain patterns are associated with negative beliefs and negative-emotion driven impulsive behavior. Conversely, the cocaine comorbid patients showed decreased functional connectivity between the right lateral orbitofrontal cortex and the dorsal striatum, a pathway purported to support successful cognitive reappraisal and behavioral restraint (Holmann et al., 2012).

In summary, cocaine dependent individuals with comorbid Cluster B personality disorders differ from cocaine dependent individuals without comorbidities and healthy controls in terms of decreased activation and connectivity of the brain networks involved in moderating responses to aversive stimuli during negative emotion maintenance. In addition, cocaine dependent individuals with comorbid Cluster B personality disorders differ from cocaine dependent individuals without comorbidities in terms of less efficient connectivity of the emotion regulation network during negative emotion reappraisal, being these abnormalities correlated with the impulsive trait of negative urgency, and with the intensity of Cluster-specific dysfunctional beliefs. Since both cocaine using groups were matched in terms of cocaine exposure, and the brain

activation patterns of Cluster B comorbid users specifically correlated with trait measures of impulsivity and personality dysfunction, it is reasonable to assume that the differences between Cluster B and non-comorbid cocaine users may be pre-existing. This notion is in agreement with recent data that we obtained through retrospective assessments in this same sample, which showed that the behavioral symptoms associated with frontal-striatal dysfunction (e.g., disinhibition) were elevated in comorbid users before onset of drug use (Albein-Urios et al., 2013b). Nonetheless, it is important to acknowledge that the brain activation differences reported here occurred in absence of significant behavioral differences in emotion experience or regulation. Neuroimaging tasks are typically less suited to detect behavioral differences because their repeated multiple blocks design may favor utilization of compensation strategies, therefore allowing participants to adjust their behavioral performance. Hence, future studies are warranted to explore whether these distinct patterns impact on emotion regulation using more sensitive behavioral tests. All in all, this study holds important strengths and also worth noting limitations. Among the first, we should number the careful selection of cocaine dependent patients with and without Cluster B disorders but not other comorbidities, the duration of supervised 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) and age was not significantly correlated with the patterns of brain functioning in any of the contrasts of interest. A potentially relevant limitation is that whereas males and females were evenly distributed within the borderline diagnostic subgroup, males were predominant in the other diagnostic categories (antisocial and histrionic).

Although the sample sizes of the different diagnostic subsets are too small to formally test sex by diagnosis interactions, we conducted post-hoc exploratory analyses within the Cluster B cocaine group to test possible differences between males and females. We only found that the pattern of subgenual cingulate deactivation during emotion maintenance was more prominent in males than in females. We did not find any differences in the reappraisal contrast. Future studies should further explore whether sex differences play a key role on the brain substrates of cocaine use and personality disorder comorbidities. 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.

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Figure Captions:

Figure 1: Brain regions showing significantly reduced activation during Maintain>Observe in cocaine users with comorbid personality disorders compared to cocaine users without comorbidities (in yellow) and controls (in blue).

Figure 2: Brain regions showing significantly increased activation during Suppress>Maintain in cocaine users with comorbid personality disorders compared to cocaine users without comorbidities and correlations between these regions and personality scores of negative urgency and antisocial dysfunctional beliefs.

Figure 3: Left panel displays the regions showing significantly reduced (top) and increased (bottom) functional connectivity with the subgenual anterior cingulate cortex seed in cocaine users with comorbid personality disorders compared to cocaine users without comorbidities during Maintain>Observe. Right panel displays the regions showing significantly increased (top) and decreased (bottom) functional connectivity with the lateral orbitofrontal cortex seed in cocaine users with comorbid personality disorders compared to cocaine users without comorbidities during Suppress>Maintain.

Table(s)

Table 1: Demographic and clinical characteristic of the three study groups: Cocaine users without comorbidities (Cocaine), Cocaine users with comorbid Personality Disorder (Cocaine+PD) and non-drug using Controls.

	Cocaine n=17 Mean (SD)	Cocaine+PD n=18 Mean (SD)	Controls n=21 Mean (SD)	P-value
Demographic variables				
Age	36.41 (5.99)	35.83 (7.88)	31.00 (4.60)	0.016
Gender	16 (M) / 1 (F)	12 (M) / 6 (F)	20 (M) / 1 (F)	
Laterality	14 (R) / 3 (L)	16 (R) / 2 (L)	20 (R) / 1 (L)	
Years of education	9.76 (1.71)	11.11 (2.08)	10.38 (1.96)	0.128
Verbal IQ	100.82 (8.62)	102.33 (10.64)	105.76 (8.75)	0.253
Clinical variables				
Monthly cocaine use (g)	18.79 (27.53)	21.33 (26.71)		0.784
Duration cocaine (months)	56.55 (59.02)	54.33 (47.96)		0.903
Abstinence cocaine (months)	2.50 (5.59)	6.38 (9.68)		0.158
Age of onset cocaine use (years)	23.00 (7.70)	22.77 (7.10)		0.930
Monthly alcohol use (SDU)	30.18 (30.64)	42.60 (51.30)	10.07 (9.74)	0.054
Duration alcohol (months)	91.15 (94.79)	93.00 (85.04)	83.75 (56.20)	0.950
Age of onset alcohol use (years)	18.33 (4.46)	19.71 (4.10)	19.14 (5.53)	0.733
Monthly tobacco use (cig.)	608.33 (415.88)	458.69 (314.39)	286.25 (458.69)	0.125
Duration tobacco (months)	141.50 (132.13)	151.87 (112.64)	76.37 (104.25)	0.327
Age of onset tobacco use (years)	16.16 (2.88)	17.93 (6.46)	17.75 (5.23)	0.663

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

Table(s)

Table 2. Self- reports of the intensity of the negative emotions induced by each of the task conditions (inside-scanner) and scores of the UPPS-P negative urgency subscale and of the Personality Belief Questionnaire Cluster B subscales (outside-scanner).

	Cocaine Mean (SD)	Cocaine+PD Mean (SD)	Controls Mean (SD)	P- value
Inside scanner ratings				
Maintain	3.68 (0.93)	3.54 (0.70)	3.12 (0.97)	0.101
Suppress	3.24 (0.82)	2.70 (0.63)	2.69 (1.00)	0.130
Observe	1.86 (0.86)	2.03 (1.08)	1.68 (0.71)	0.483
UPPS-P scale				
Negative Urgency	33.17 (6.51)	36.59 (4.76)	23.48 (5.71)	0.000
Personality Belief Questionnaire				
Borderline	13.36 (10.04)	18.44 (10.31)	7.62 (7.54)	0.008
Antisocial	23.71 (11.63)	29.56(9.92)	19.44 (7.51)	0.019
Narcissistic	14.79 (8.84)	16.81 (7.54)	14.43 (7.39)	0.663
Histrionic	15.36 (8.11)	16.81 (10.92)	12.94 (9.44)	0.521

SD = standard deviation; UPPS = impulsive behavior scale; PBQ = Personality Belief Questionnaire.

Figure(s)

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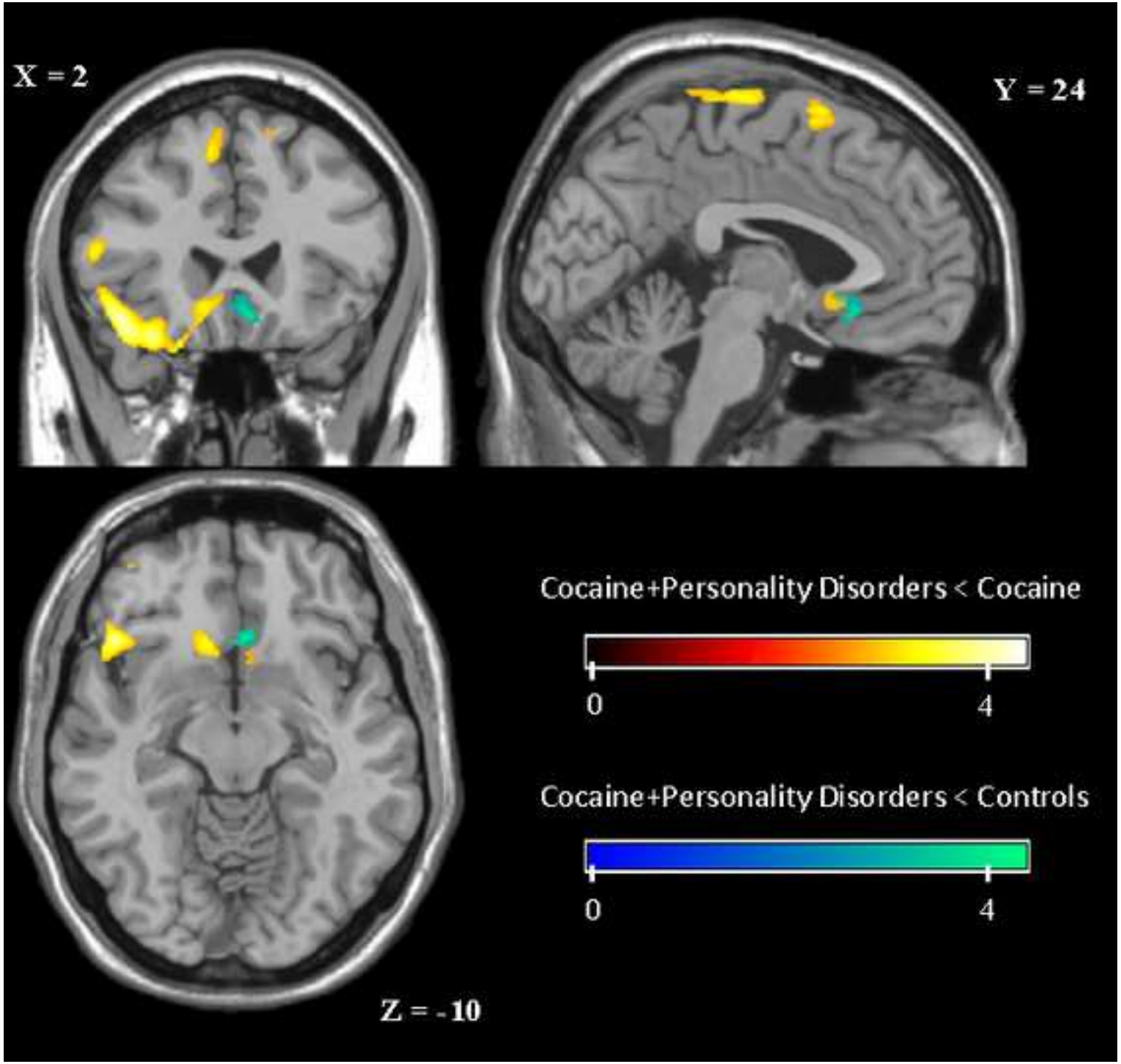

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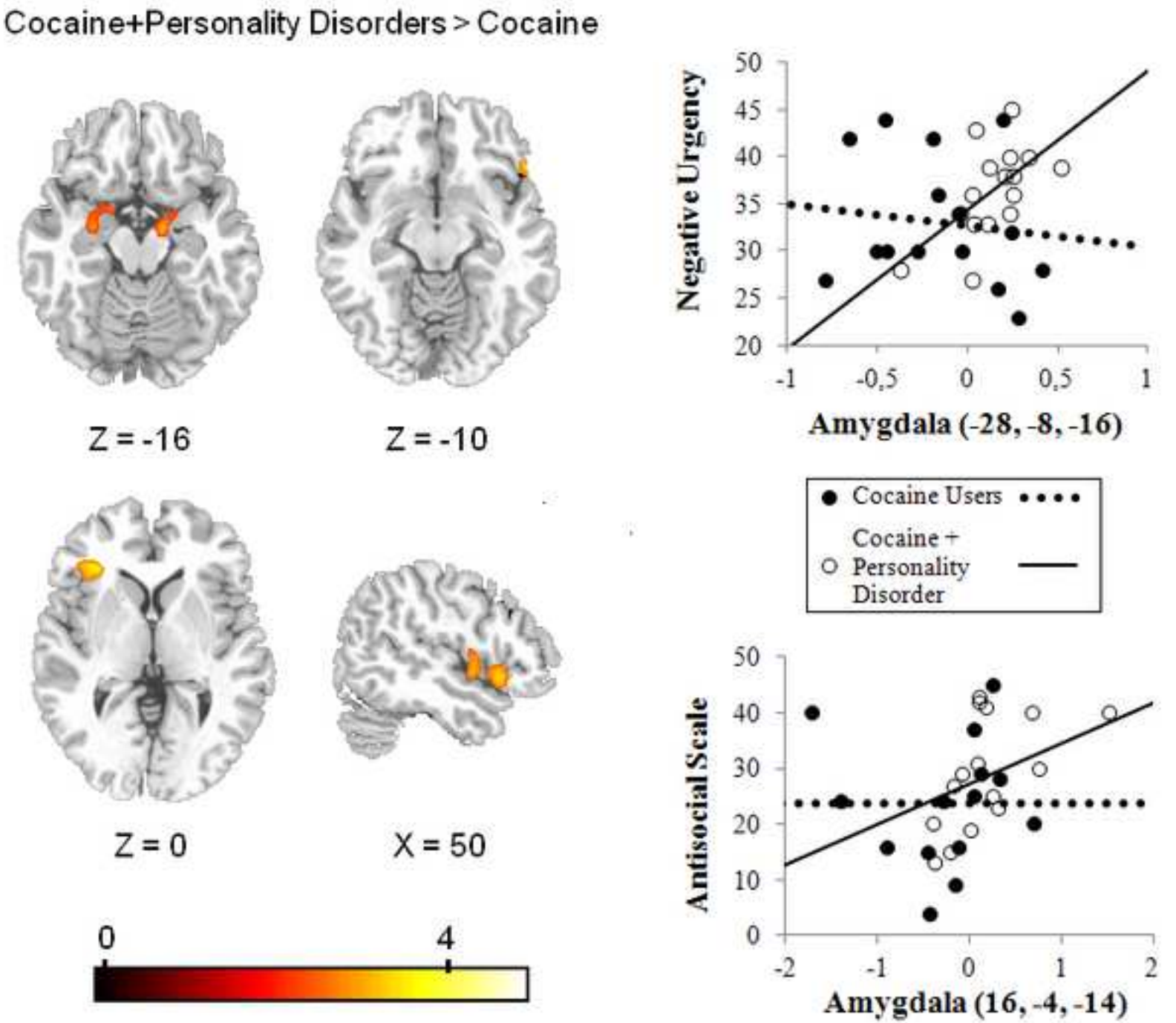

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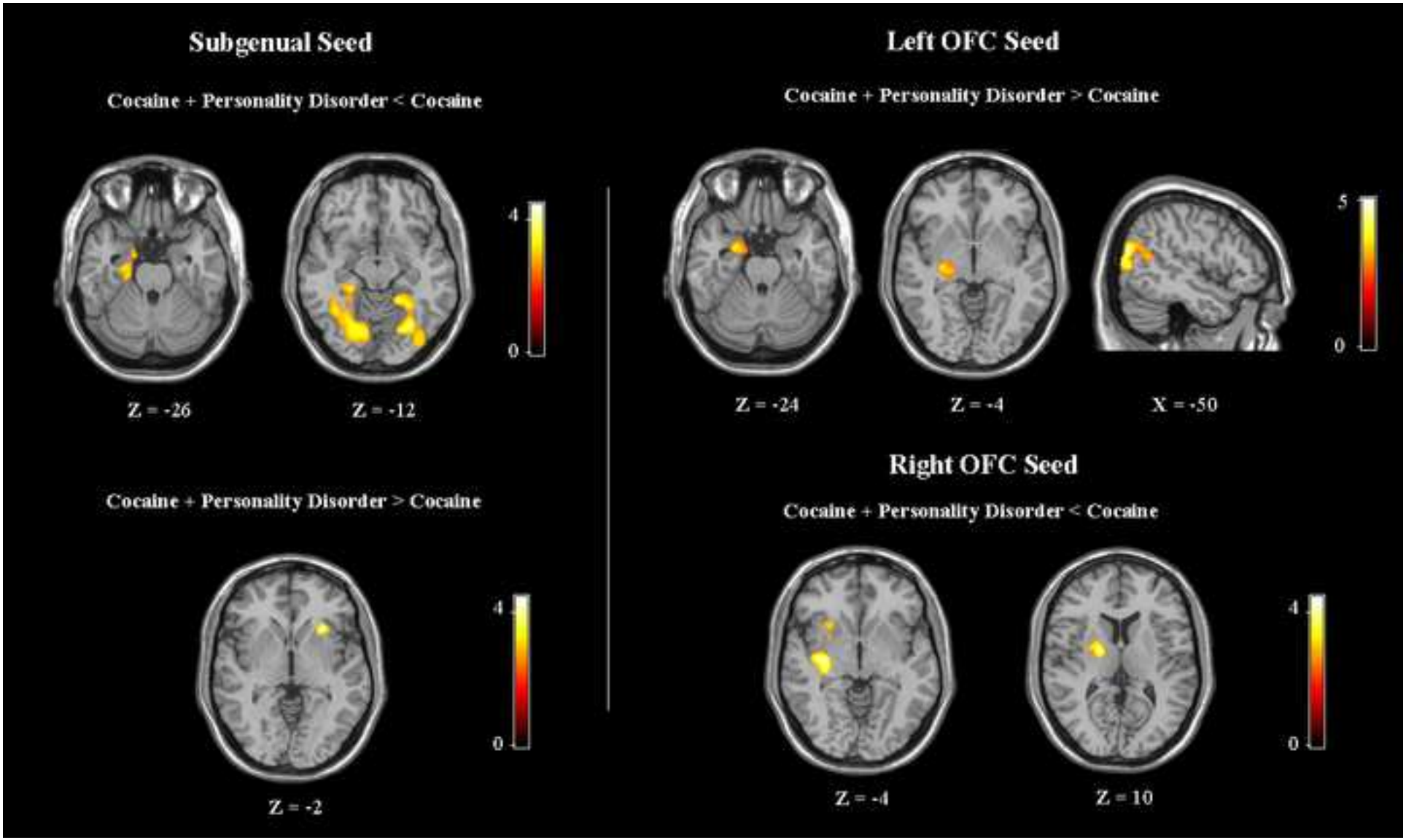

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***Contributors**

Contributors: N. Albein-Urios collected the data and wrote the initial draft of the manuscript. A. Verdejo-García and J.M. Martínez-González designed the study. J. Verdejo-Román, C. Soriano-Mas and S. Asensio designed and performed the imaging analyses. All authors contributed to the final version of the manuscript.

***Conflict of Interest**

Conflict of interest: The authors declare no conflicts of interest.

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