FULL-LENGTH REPORT

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Brain networks alterations in cocaine use and gambling disorders during emotion regulation

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ABSTRACT

Background: Cocaine use disorder (CUD) and gambling disorder (GD) share clinical features and neural alterations, including emotion regulation deficits and dysfunctional activation in related networks. However, they also exhibit differential aspects, such as the neuroadaptive effects of long-term drug consumption in CUD as compared to GD. Neuroimaging research aimed at disentangling their shared and specific alterations can contribute to improve understanding of both disorders. *Methods:* We compared CUD ($N = 15$), GD ($N = 16$) and healthy comparison (HC; $N = 17$) groups using a network-based approach for studying temporally coherent functional networks during functional magnetic resonance imaging (fMRI) of an emotion regulation task. We focused our analysis in limbic, ventral frontostriatal, dorsal attentional (DAN) and executive networks (FPN), given their involvement in emotion regulation and their alteration in CUD and GD. Correlations with measures of emotional experience and impulsivity (UPPS-P) were also performed. *Results:* The limbic network was significantly decreased during emotional processing both for CUD and GD individuals compared to the HC group. Furthermore, GD participants compared to HC showed an increased activation in the ventral frontostriatal network during emotion regulation. Finally, networks' activation patterns were modulated by impulsivity traits. *Conclusions:* Functional network analyses revealed both overlapping and unique effects of stimulant and gambling addictions on neural networks underpinning emotion regulation.

INTRODUCTION

Cocaine use and gambling disorders share common clinical features, such as unsuccessful efforts to control use despite negative consequences, craving and withdrawal effects (Lee, Hoppenbrouwers, & Franken, 2019). Moreover, elevated impulsivity and altered reward processing, decision making and emotion regulation feature both disorders (Lee et al., 2019; Michalczuk, Bowden-Jones, Verdejo-Garcia, & Clark, 2011; Zilverstand, Parvaz, Moeller, & Goldstein, 2016). Additionally, overlapping neurobiological alterations (involving ventromedial and ventrolateral prefrontal cortices) underlie psychopathological behaviors in both disorders (Kober et al., 2016; Verdejo-Garcia et al., 2015). However, cocaine use disorder (CUD) critically differs from gambling disorder (GD) in terms of exposure to the neuroadaptive effects of long-term drug consumption (Albein-Urios, Martinez-González, Lozano, Clark, & Verdejo-García, 2012; Torres et al., 2013). Thus, comparing neural functioning in people with CUD versus GD may help disentangle the neuroadaptive effects of cocaine and its contribution to addiction neurobiology. That is, to what extent addiction is produced by predisposition, neuroadaptive or learning effects during the long-term exposure to drugs that lead to addiction.

Current research shows that alterations related to CUD may be understood in terms of large-scale brain networks dysfunction (Zilverstand, Huang, Alia-Klein, & Goldstein, 2018). Among network analysis techniques, independent component analysis (ICA) is becoming increasingly used to investigate how functional networks are modulated by experimental factors (Barrós-Loscertales et al., 2020; Costumero et al., 2015; Kim et al., 2009; Worhunsky, Potenza, & Rogers, 2017). ICA is a data-driven approach that assumes that functional magnetic resonance imaging (fMRI) data are linear mixtures of independent source signals, and it attempts to extract maximally independent signals and their mixing coefficients (Calhoun, Adali, Pearlson, & Pekar, 2001). The driving principle behind ICA is that these independent source signals represent coherent groupings of MRI activations, which implies the representation of a functionally connected network. When applied to task-fMRI data, the ICA methodology allows to first identify the intrinsic functional connectivity networks, and then to study how the estimated time courses associated with these networks are modulated during a task. The study of temporal signals estimated by ICA reveals how specific functional networks relate with experimental conditions, which may provide new insights into the functional activity hidden from conventional voxel-wise GLM analyses (Xu, Potenza, & Calhoun, 2013).

The fMRI cognitive reappraisal task can be studied using this approach. During this task, participants have to reinterpret the meaning of affective stimuli in order to modify their emotional intensity (Ochsner, Bunge, Gross, & Gabrieli, 2002). Reappraisal-evoked activation typically involves a distributed network, including the dorsolateral and ventrolateral prefrontal cortex, dorsal anterior cingulate cortex, premotor and parietal cortices (Buhle et al., 2013). These regions overlap with typical resting-state cognitive control networks such as the dorsal attentional network (DAN) and the frontoparietal networks (left and right FPN) (Buhle et al., 2013), which are also associated with addiction (Goldstein & Volkow, 2011; Zilverstand, Parvaz, & Goldstein, 2017). Zilverstand et al. (2017) highlighted that several studies in participants with substance use disorders, including CUD, have observed reduced activation in frontal and parietal regions during downregulation of negative emotions. Moreover, Buhle et al. (2013) pointed to the modulatory role of the amygdala and parahippocampus in emotion regulation, usually included within the limbic network, in non-clinical populations. However, alterations in the limbic network have not been consistently observed in addiction studies (Zilverstand et al., 2016). Instead, ventral frontostriatal circuitry alterations have been consistently reported in both CUD (Bustamante et al., 2014) and GD (Reuter et al., 2005). Therefore, emotion regulation involves several brain networks related to cognitive and emotional processes which have shown to be affected in addiction. These neural network alterations may compromise cognitive reappraisal in people with CUD or GD.

The use of adaptive emotion regulation strategies such as cognitive reappraisal could reduce stress reactivity to negative emotional experiences in individuals with substance and behavioral addictions (Goldstein & Volkow, 2011). In this line, emotional states or cues linked to drug-related affective states are important contributors to relapse (Sinha, 2009). During emotional regulation tasks, addiction-related stimuli tend to produce upregulation of brain networks and regional activation, while non-drug related emotional stimuli tend to produce downregulation (Barrós-Loscertales, 2016; Zilverstand et al., 2018). These effects are particularly related with the reward, limbic, attentional and executive networks, although others such as the salience and default mode networks have also been implicated (Zilverstand et al., 2018). Identifying the neural underpinnings of impaired emotion regulation and their association to addiction-related traits (e.g., stress-related impulsivity) may contribute to improve understanding of both CUD and GD.

Brain regions implicated in impulsivity are largely overlapping with addiction related abnormalities in mesocorticolimbic regions (Mackey & Paulus, 2013). Thus, it has been suggested that inadequate regulation of emotion fuels addictive behaviors in impulsive individuals (Torres et al., 2013). Also, trait impulsivity has been related to poor cognitive control of emotions and inappropriate decisions (Torres et al., 2013; Verdejo-García, Alcázar-Córcoles, & Albein-Urios, 2019). The UPPS-P model has been applied to CUD (Albein-Urios, Pilatti, Lozano, Martínez-González, & Verdejo-García, 2014; Fernández-Serrano, Perales, Moreno-López, Pérez-García, & Verdejo-García, 2011) and GD (Navas et al., 2017; Torres et al., 2013). In the context of GD, impulsivity seems to play a global role (Mestre-Bach et al., 2020), but a specific role of negative urgency in the context of emotion regulation has also been shown (Navas et al.,

2017). Conversely, people with CUD compared with healthy controls (HC) score higher on several UPPS-P dimensions such as lack of premeditation, positive and negative urgency (Fernández-Serrano et al., 2011). Therefore, different dimensions of impulsivity may subserve emotion regulation effects related to CUD and GD.

In this study, we compared CUD, GD and healthy comparison groups during an fMRI negative emotion regulation paradigm. Our aim was to analyze the parallelisms and differences between these groups during regulation of negative emotions using a data-driven, network-based approach for studying temporally coherent functional networks (Kim et al., 2009). Given the scarcity of studies parsing which neural alterations result from prolonged exposure to cocaine use or as a hallmark of both substance and behavioral addictive disorders, we leveraged comparisons between CUD and GD groups to address this question. Furthermore, we sought to explore if the neural underpinnings of emotion regulation correlate with clinical and trait features related to addiction (e.g., severity, impulsivity). We focused our analysis in limbic, ventral frontostriatal, DAN and executive networks (FPN) given their involvement in emotion regulation and their alteration in CUD and GD. We hypothesized a downregulation of these networks during emotion regulation in both CUD and GD. We also explored differential patterns on CUD when compared with GD and HC, which might reflect neuroadaptive effects of prolonged cocaine use.

METHODS

Participants

We recruited 17 participants with CUD and 16 with GD from outpatient clinics, and 18 HC from the general community. Inclusion criteria were: DSM-IV-TR criteria for cocaine dependence or pathological gambling as measured by the Structured Clinical Interview for DSM-IV Disorders-Clinical Version (SCID-IV-CV) (First, Williams, Benjamin, & Spitzer, 1997) and ≥15 day abstinence tested via urine toxicological tests run twice weekly in those with cocaine dependence, or cross-validated reports from individuals with pathological gambling and their spouse/relatives. Exclusion criteria were meeting any other Axis I disorder and undergoing any addiction treatments <2 years before the study.

Controls were recruited from local employment agencies and were screened for any DSM-IV-TR criteria of substance use disorder – but nicotine dependence—or pathological gambling. All groups were required to be ≥18 years old, have an IQ score ≥80 (Kaufman & Kaufman, 1990), and no history of head injury and neurological or nervous system diseases.

Measures and procedure

fMRI cognitive reappraisal task. We used a cognitive reappraisal task described in Albein-Urios et al. (2013). The task consists of the presentation of 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); or (3) Regulate (to reappraise the emotions induced by the negative emotional pictures by virtue of cognitive reappraisal techniques previously trained). Moreover, the intensity of the negative emotion experienced in the different conditions was self-rated on a 1–5 number scale. Further information regarding the task is described in Appendix.

Outside-scanner behavioral measures. Trait Impulsivity was measured with the Spanish version of the UPPS-P impulsive behavior scale (Whiteside & Lynam, 2001), which has shown sound reliability and internal and construct validity (Verdejo-García, Lozano, Moya, & Pérez-García, 2010). The scale contains 59 items that comprehensively assess different personality pathways leading to impulsive behavior: Sensation seeking (12 items), Lack of perseverance (10 items), Lack of premeditation (11 items), Negative urgency (12 items), and Positive urgency (14 items).

Imaging data acquisition and preprocessing. We used a 3.0 T Intera Achieva Philips MRI scanner, equipped with an eight-channel phased-array head coil. Details on acquisition parameters and preprocessing are presented in Appendix.

Statistical analysis

Behavioral data. Behavioral data were analyzed with Statistical Package for the Social Sciences software version 24 (SPSS; Chicago, IL, USA). We conducted one-way Analysis of Variance (ANOVA) to compare the three groups on relevant variables (Table 1). Interactions between in-scanner negative emotion intensity ratings for each condition (Observe, Maintain and Regulate) and subject groups were evaluated using a 3×3 mixed ANOVA analysis. Moreover, participants' self-reported success in lowering their in-scanner negative emotion intensity was calculated by subtracting Regulate ratings from Maintain ratings (Success = Maintain−Regulate), while participants' reactivity during emotional processing was computed as Reactivity = Maintain−Observe.

Independent component analysis. Group ICA (Calhoun et al., 2001) was performed with the Gift toolbox (v3.0 b, http://icatb.sourceforge.net) using the Infomax algorithm (Bell & Sejnowski, 1995). Before ICA, voxel intensity was normalized, and data from all participants were pooled into a single dataset through a two-step data reduction approach using principal component analysis to enable the analysis of large data sets. Thirty-six independent components based on the minimum description length criteria were selected (Li, Adalı, & Calhoun, 2007). Fifty ICA iterations were performed by ICASSO (Himberg, Hyvärinen, & Esposito, 2004) to ensure stability of the estimated components. Finally, individual component maps and time courses were estimated using a group ICA 3 back-reconstruction approach.

Table 1. Sociodemographic and clinical information

	CUD (N = 15)	GD (N = 16)	HC (N = 17)	Statistic, P	Significant post-hoc test (p_{holm}, Cohen's d)
Age, Mean (SD)	37.6 (5.03)	33.13 (7.98)	32.35 (4.02)	$F(2,45) = 3.59$, **0.036**	CUD>HC: 0.047, 1.162
Sex, N males (%)	14 (93.3)	14 (87.5)	16 (94.1)	$\chi^2(2) = 0.55$, 0.759	-
Years of education, Mean (SD)	9.73 (1.83)	9.94 (1.95)	10.35 (2.03)	$F(2,45) = 0.43$, 0.655	-
Verbal IQ, Mean (SD)	101 (8.63)	101.06 (6.03)	106.06 (9.52)	$F(2,45) = 2.06$, 0.14	-
Manipulative IQ, Mean (SD)	94.6 (10.19)	96.06 (11.11)	103.12 (11.19)	$F(2,45) = 2.88$, 0.067	-
Age of onset, Mean (SD)	23.27 (8.2)	22.07 (9.18)*	-	$t(28) = 0.38$, 0.709	-
Monthly amount (CUD grams, GD hours), Mean (SD)	17.27 (26.81)	41.27 (40.92)	-	-	-
Duration of regular use (months), Mean (SD)	59.97 (61.92)	23.2 (20.66)	-	-	-
Severity, Mean (SD)	1000 (2403.37)	1174.4 (1896.24)	-	$t(28) = 0.25^{¶}$, 0.804	-
UPPS, Mean (SD)	N = 14				
Negative urgency	33.43 (7.07)	28.69 (4.38)	24.47 (4.68)	$F(2,44) = 10.54$, **<0.001**	CUD>HC: <0.001, 1.526 CUD>GD: 0.042, 0.82 GD>HC: 0.042, 0.93
Positive urgency	32.57 (10.62)	29.88 (6.7)	24.18 (6.91)	$F(2,44) = 4.39$, **0.018**	CUD>HC: 0.019, 0.957
Sensation seeking	28.36 (7.73)	30.38 (3.5)	31.24 (8.21)	$F(2,44) = 0.708$, 0.498	-
Lack of premeditation	23.43 (4.59)	26 (3.85)	22.76 (4.1)	$F(2,44) = 2.71$, 0.077	-
Lack of perseverance	21.07 (4.92)	22.25 (3.07)	19.88 (3.94)	$F(2,44) = 1.45$, 0.247	-

CUD, patients with cocaine use disorder; GD, patients with gambling disorder; HC, healthy controls; SD, standard deviation. *Missing data from one participant. ¶Between-group comparison done with a standardized severity measure.

Analysis of the component spatial maps. One-sample *t*-tests of the spatial maps generated by ICA were performed using the full sample at the second-level of analyses with SPM12 at $P < 0.05$ family-wise error (FWE)-corrected, to determine the brain regions that were significantly related to each component. Given the study hypothesis, the networks of interest were the limbic, the ventral frontostriatal, the bilateral FPNs, and the DAN, and were visually identified taking into account the presence of core regions of these networks.

Analysis of the component time courses. General Linear Model (GLM) was applied on the component time courses for each subject using a design matrix representing the task. This yielded a set of beta-weights representing the modulation of component time courses by the GLM regressors. The GLM design matrix used in these analyses included separate regressors to model each of the conditions (Observe, Maintain and Regulate), which were convolved with the hemodynamic response function. Time derivatives and parameters that modeled residual motion were also included. Then, we performed separate second-level group analyses for the contrasts Maintain > Observe and Regulate > Maintain using the estimated beta-weights.

Group comparisons were performed in SPSS by means of one-way ANOVAs with group as the between-subjects factor with three levels (CUD, GD, and HC). To study group differences during the experience of negative emotions, reactivity in the limbic network was explored for the Maintain > Observe contrast, while the modulation of the FPNs and the DAN was analyzed for the Regulate > Maintain contrast in order to study group differences during the regulation of emotions. Finally, since the ventral frontostriatal network was of clinical relevance, between-group differences in the modulation of this network were studied during both contrasts. Benjamini-Hochberg FDR correction was used to correct for the comparison of multiple networks and contrasts, while Holm's correction was used to correct for pair-wise post-hoc tests within each ANOVA.

We investigated how individual differences in the modulation of these functional networks related to clinical variables, by means of Pearson's correlation analyses with age of onset and severity. Severity of cocaine use and gambling exposure was measured via the Interview for Research on Addictive Behaviour (Verdejo-García, López-Torrecillas, Aguilar De Arcos, & Pérez-García, 2005), that provides information on monthly amounts and total duration of regular use (more information regarding this instrument can be found in Appendix). These two variables were multiplied in order to compute a composite measure of cumulative use. Additional correlation analyses were performed with the Reactivity and Success variables, and with the UPPS-P subscales. These correlation analyses were performed for each group separately. When there was a significant correlation for one group, the correlation coefficients were compared by means of the Fisher *r*-to-*z* transformation. Importantly, correlation analyses were considered exploratory secondary analyses and were not corrected for multiple comparisons. Thus, any significant results should be considered preliminary.

Ethics

The study procedures were carried out in accordance with the Declaration of Helsinki. The Human Research Ethics Committee of the University of Granada approved the study. All subjects were informed about the study and all provided informed consent. Data collection took place between the beginning of 2010 and the summer of 2012, and neuro-imaging data from the participants included in this study using different analytical approaches have been previously reported (Albein-Urios et al., 2014; Contreras-Rodríguez et al., 2015; Irizar, Albein-Urios, Martínez-González, Verdejo-Garcia, & Lorenzetti, 2020; Navas et al., 2017). In this study, we applied ICA and compared for the first time neural activation from the three groups (CUD, GD and HC) in the cognitive reappraisal task.

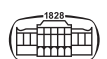## RESULTS

Behavioral results

The demographical data of participants included in the final sample are summarized in Table 1. The CUD group had significantly higher scores in the negative and positive urgency subscales of the UPPS-P compared to HC, and significantly higher scores than the GD group only for the negative urgency subscale. On the other hand, the GD group showed significantly higher scores than the HC group also in the negative urgency subscale of the UPPS-P (Table 1).

Regarding the in-scanner ratings, a main effect of condition was found ($F(2,90) = 78.85$, $P < 0.001$), and planned comparisons showed that Maintain differed from Observe, indicating successful negative emotion induction during this condition for all groups (Maintain > Observe: $F(1,45) = 137.93$, $P < 0.001$), and Regulate differed from Maintain (Maintain > Regulate: $F(1,45) = 11.04$, $P = 0.002$), indicating successful emotion regulation. No significant main effect of group ($F(2,45) = 2.28$, $P > 0.05$) nor interaction effect between condition and group ($F(4,90) = 1.39$, $P > 0.05$) were found (see Table 2 for the ratings mean and standard deviation for each group).

Table 2. In-scanner ratings during the cognitive reappraisal task

	CUD	GD	HC
Observe, Mean (*SD*)	1.78 (0.9)	1.69 (0.69)	1.73 (0.76)
Maintain, Mean (*SD*)	3.77 (0.99)	3.59 (0.88)	3.07 (1)
Regulate, Mean (*SD*)	3.29 (0.88)	3.16 (0.8)	2.59 (1)
Reactivity, Mean (*SD*)	1.99 (1.1)	1.9 (0.96)	1.35 (1.02)
Success, Mean (*SD*)	0.48 (1.24)	0.44 (0.79)	0.49 (0.86)

CUD, patients with cocaine use disorder; GD, patients with gambling disorder; HC, healthy controls; *SD*, standard deviation. Reactivity = Maintain – Observe; Success = Maintain – Regulate.

ICA results

The networks of interest were visually identified from the 36 components. The limbic network mainly included the bilateral amygdala, putamen and hippocampi; the ventral frontostriatal network included the ventral striatum and the medial prefrontal cortex (mPFC), including the rostral anterior cingulate cortex (rACC); the left and right FPN comprised either the left or the right middle frontal gyrus (MFG) and angular gyrus; and the DAN comprised, bilaterally, the inferior (IOG) and middle occipital gyri (MOG) extending to the superior parietal lobule, the fusiform gyri, the inferior frontal gyri (IFG), the lateral orbitofrontal cortex (OFC), and the midcingulate cortex (MCC) (see Fig. S1).

We found significant group differences in the limbic network ($F(2,45) = 5.83$, $P = 0.006$, $p_{FDR\text{-}corr} = 0.036$), and post-hoc tests showed that both participants with CUD ($t = -3.072$, $p_{holm} = 0.011$) and GD ($t = -2.775$, $p_{holm} = 0.016$) displayed decreased network activation in response to negative images relative to HC (Fig. 1A). Participants with CUD and GD did not differ between them ($t = -0.339$, $p_{holm} = 0.736$). Regarding the ventral frontostriatal network, groups differed only during the contrast Regulate > Maintain ($F(2,45) = 4.531$, $P = 0.016$, $p_{FDR\text{-}corr} = 0.048$), and post-hoc tests showed that participants with GD significantly differed from HC ($t = 2.804$, $p_{holm} = 0.022$) while the difference between participants with CUD and HC trended towards significance ($t = 2.3$, $p_{holm} = 0.052$). The clinical groups did not differ between them ($t = -0.45$, $p_{holm} = 0.655$). In this case, both participants with CUD and GD

showed an increased activation of this network when having to regulate negative images compared to controls (Fig. 1A). Moreover, there was a trending group effect for the DAN ($F(2,45) = 3.652$, $P = 0.034$, $p_{FDR\text{-}corr} = 0.068$), due to a decreased activation in participants with CUD compared to HC while regulating negative emotions ($t = -2.697$, $p_{holm} = 0.029$). On the other hand, participants with GD did not differ from those with CUD ($t = -1.271$, $p_{holm} = 0.318$) or HC ($t = -1.432$, $p_{holm} = 0.318$) (Fig. 1A). Finally, we found no significant effects in the FPNs (lFPN: $F(2,45) = 0.251$, $P = 0.779$, $p_{FDR\text{-}corr} = 0.779$; rFPN $F(2,45) = 0.6$, $P = 0.553$, $p_{FDR\text{-}corr} = 0.663$).

Brain-behavior correlations

There were no significant correlations with age of onset or severity measures.

Regarding the in-scanner ratings, correlations with the Reactivity variable were tested for those networks showing significant differences in the ANOVA for Maintain > Observe, and with the Success variable for Regulate > Maintain results. There was a significant positive correlation for the CUD group between Reactivity and the limbic network ($r(13) = 0.602$, $P = 0.018$, Fig. 1B). This correlation was significantly higher for the CUD group when compared with the HC group (Fisher $Z = 2.36$, one-tailed $P = 0.009$). Moreover, there was a significant positive correlation for the HC group between Success and the DAN ($r(15) = 0.569$, $P = 0.017$, Fig. 1B).

Finally, correlations were also performed with the UPPS-P subscales. There was a negative correlation in the CUD
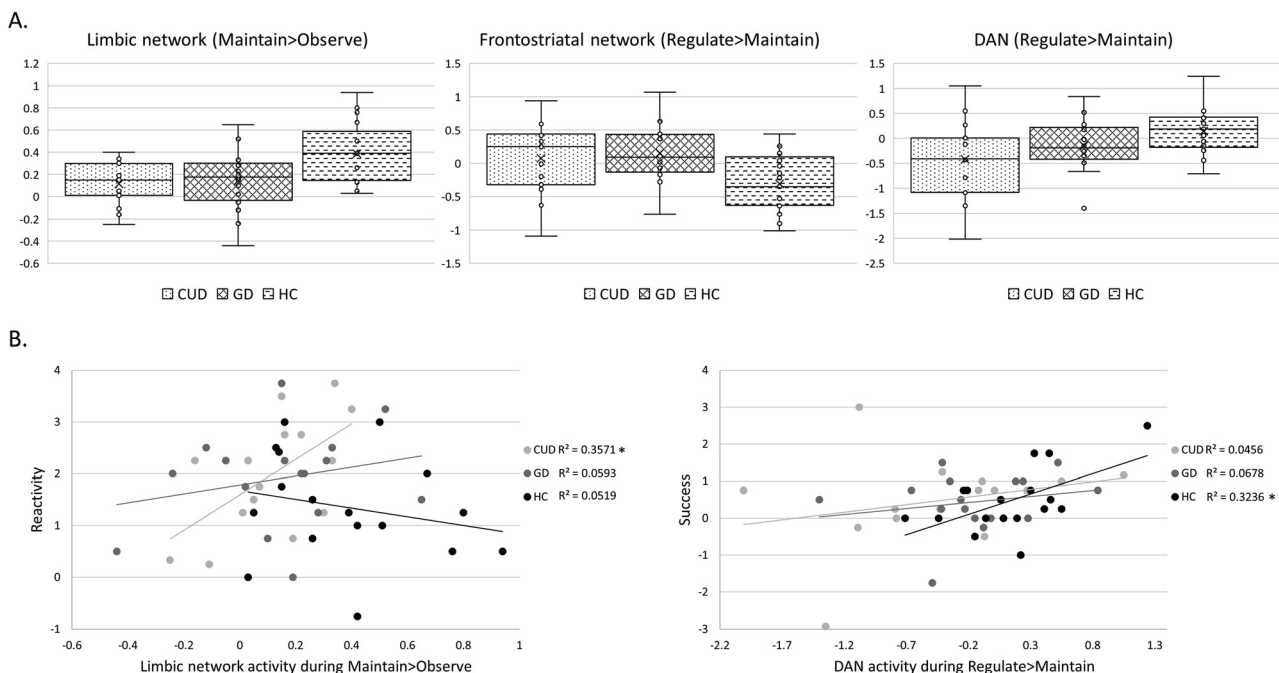

Fig. 1. A) Boxplots representing the activation in each group (CUD, GD and HC) for each component and contrast with significant results. B) Scatterplots showing the correlation between activity in those networks showing significant between-group differences and the corresponding ratings reported for that contrast, separately for each group. CUD, patients with cocaine use disorder; GD, patients with gambling disorder; HC, healthy controls; DAN, dorsal attention network

group between the limbic network and the sensation seeking ($r(12) = -0.557$, $P = 0.039$) and positive urgency ($r(12) = -0.574$, $P = 0.032$) subscales of the UPPS-P (Fig. 2). For sensation seeking, the correlation coefficient of the CUD group was significantly lower than that of HC (Fisher $Z = -2.28$, one-tailed $P = 0.011$). For positive urgency, the correlation coefficient of the CUD group was significantly lower than that of GD (Fisher $Z = -1.95$, one-tailed $P = 0.026$). Regarding the regulation of negative images, the DAN was significantly correlated with negative urgency in the CUD group ($r(12) = 0.614$, $P = 0.019$). This correlation was significantly higher than that of HC (Fisher $Z = 2.6$, one-tailed $P = 0.005$) (Fig. 2).

DISCUSSION

Emotion regulation elicited differential modulation of limbic and ventral frontostriatal networks in people with CUD and GD relative to healthy controls. Both clinical groups showed downregulation of the limbic network during emotional experience, and upregulation of the ventral frontostriatal network during emotion regulation. These results suggest that altered emotional reactivity in the limbic and ventral

frontostriatal networks may be considered a general effect of addiction.

The downregulation of the limbic network agrees with the pivotal role suggested for limbic regions in emotion regulation in neuropsychiatric disorders (Zilverstand et al., 2017). In healthy participants, exposure to negative affective stimuli is associated with increased activation in limbic network structures such as the amygdala, the hippocampus or the striatum (García-García et al., 2016). In our sample, this limbic response seems to be blunted, in line with previous reports of attenuated neural response to emotional cues in individuals with CUD (Canterberry, Peltier, Brady, & Hanlon, 2016). Moreover, in our exploratory correlations, we found an association between the downregulation of the limbic network and the Sensation Seeking and Positive Urgency scores in the CUD group. This suggests a potential link to impulsivity variables related to exploration and reward-related traits in addiction (Meade, Bell, Towe, & Hall, 2020; Moreno-López et al., 2012; Yip, Worhunsky, et al., 2018), although these results were not corrected for multiple comparisons and should be considered preliminary.

On the other hand, we observed a higher upregulation of the ventral frontostriatal network in individuals with CUD and GD compared to controls. This result may be interpreted
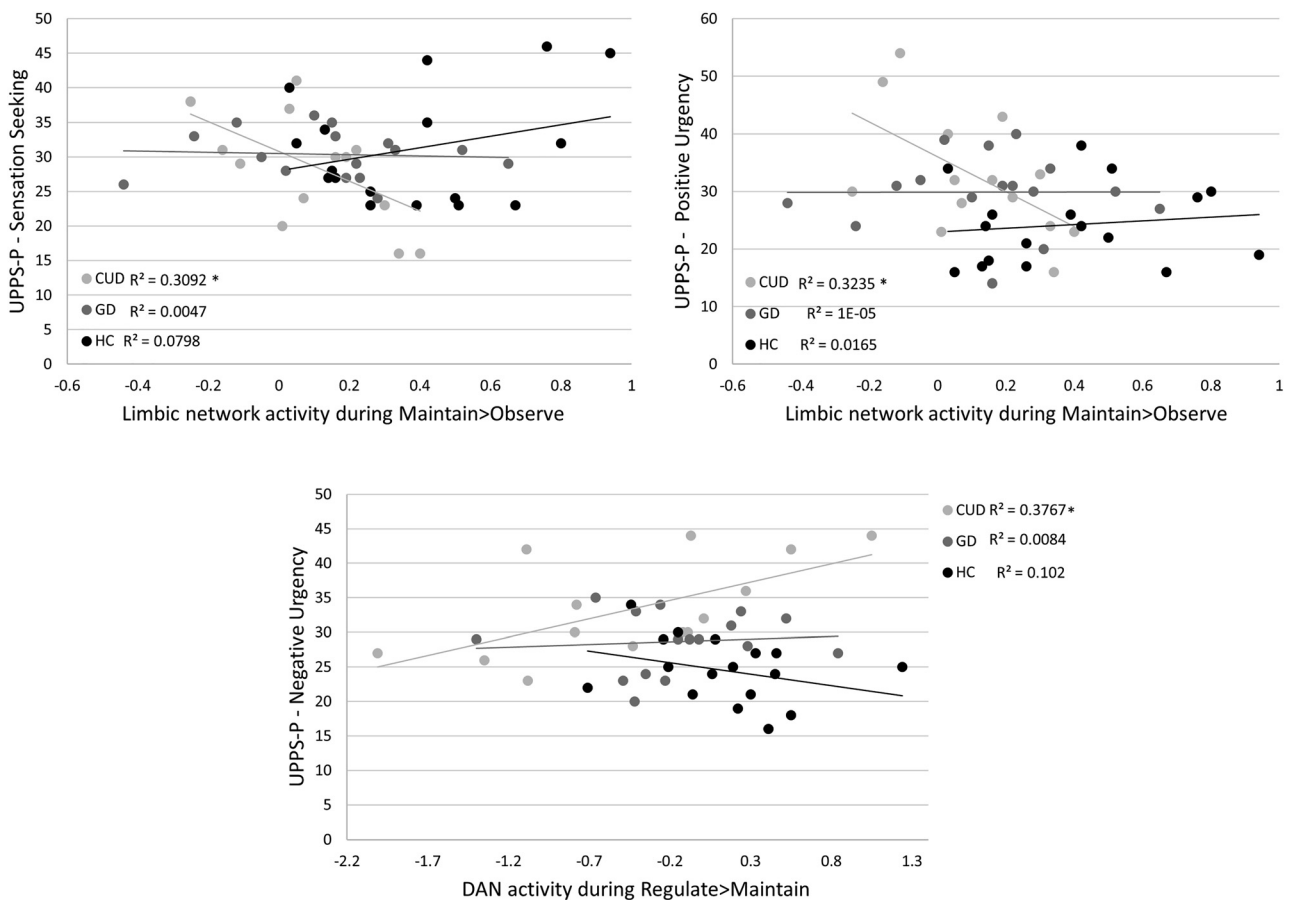

Fig. 2. Scatterplots showing the correlation between activity in those networks showing significant between-group differences and the UPPS-P subscales, separately for each group. CUD, patients with cocaine use disorder; GD, patients with gambling disorder; HC, healthy controls; DAN, dorsal attention network

as a general signature of addiction, and suggests that the neuroadaptive effects of cocaine may target the same regions that contribute to general addiction vulnerability. Regions of the ventral frontostriatal network (medial OFC and rACC) have previously shown increased activation to highly arousing stimuli in participants with elevated sensation seeking traits (Joseph, Liu, Jiang, Lynam, & Kelly, 2009). In this regard, compromised regulation of drug wanting has been suggested to explain the loss of control over drug intake in addiction (Goldstein & Volkow, 2011), and an increased frontostriatal activation when participants are expected to exert regulation might underlie this deficit.

We also observed a trend towards a significant down-regulation of the DAN in the CUD group compared to HC, which was in agreement with previous studies reporting the alteration of this network in addiction (Zilverstand et al., 2016, 2018). DAN downregulation in GD was observed but to a lower extent, which might suggest a neuroadaptive effect of cocaine in brain function rather than a general addiction effect. Nonetheless, the pattern of activation in GD seems to overlap to a greater extent with CUD than HC participants, so this interpretation should be taken with caution. More-over, other factors may also influence differences between clinical groups, such as differential predispositions (impulsivity traits) or comorbid disorders (although this was controlled by including only participants with no current DSM-IV-TR Axis I comorbidities). Yip, Gross, et al. (2018) also observed a downregulation of the cingulo-parietal network during emotion regulation using ICA in a negative emotion regulation task. However, there were no significant effects in the other IC identified in their study, such as the dorsolateral and dorsomedial inhibitory networks. These IC partially overlap with ours and suggest a pattern of down-regulation in posterior portions of the DAN. Interestingly, our study shows that HC's upregulation of the DAN was associated with reduced affective scores to negative stimuli during emotion regulation, suggesting that subjective experience during regulation aligns with appropriate DAN activation. On the other hand, in participants with CUD, Negative Urgency was related to increased DAN upregulation, which suggests an opposite effect of cocaine in DAN-impulsivity related effects. Nonetheless, these interpretations should be taken with caution and require further replication.

These results contrast with a lack of between-group differences in the subjective scoring of stimulus. This is similar to previous reports (Albein-Urios et al., 2013; Yip, Gross, et al., 2018). Zilverstand et al. (2017) suggest in their review that it may be attributed to sensitivity of the procedure employed for subjective ratings during fMRI. This may be affecting our results, but the fMRI paradigm was the same in every group, which guarantees that the effects are comparable across groups. On the other hand, it might reflect limited introspection and self-awareness in individuals with addiction as was suggested by Goldstein and Volkow (2011) and Moeller et al. (2010). Nonetheless, the interpretation of functional alterations of brain networks during emotion regulation in the absence of between-group differences in subjective experience aligns with those provided across studies involving healthy controls (Buhle et al., 2013) and clinical samples (Picó-Pérez, Radua, Steward, Menchón, & Soriano-Mas, 2017; Zilverstand et al., 2017).

Our study has some limitations that need to be addressed in future studies. First, as in most studies with human clinical groups, it was not possible to address the etiology of these activity pattern differences. We suggest that the DAN is the only network that seems to be specifically impacted by cocaine use instead of a general addiction trait. Nonetheless, this result is only trending towards significance after multiple comparison correction, and is limited by the absence of significant differences with the GD group. Similarly, the sample size was modest, due to the difficulty of recruiting homogeneous groups fulfilling inclusion and exclusion criteria in clinical groups within the time of the project. Thus, the results of this study should be considered preliminary and replication is needed before drawing firm conclusions. Also, we did not acquire objective psychophysiological measures such as electroencephalography (EEG) or heart-rate variability, which would allow for a more robust verification of reappraisal success, complementing the in-scanner reported scores. Future studies should consider including this type of measures in their project design to overcome the self-report issues abovementioned. Finally, the cross-sectional design precludes a causal interpretation of substance effects given that other variables associated with substance use behavior and contextual factors, as compared to gaming associated ones, may be affecting cocaine effects beyond substance intake. The lack of effects in the FPNs in CUD contrast with previous reports (Barrós-Loscertales et al., 2020; Costumero et al., 2015, 2018). However, these previous studies had shown FPN alterations in CUD related to reactivity to external emotional stimuli involving drug and reward related effects, but not general negative stimuli. Future studies may clarify the role of different frontoparietal networks (DAN vs FPN) in addiction regarding emotion reactivity and regulation.

CONCLUSIONS

Cocaine use and gambling disorders have overlapping patterns of brain network's activation during negative emotion processing and regulation involving downregulation of limbic and upregulation of ventral frontostriatal networks compared to HC. Moreover, DAN activation during emotion regulation was reduced in participants with CUD compared to HC. Finally, the patterns of activation in these networks were further modulated by impulsivity traits. These findings illustrate both overlapping and unique effects of substance versus behavioral addictions on neural networks underpinning emotion regulation.

Authors' contribution: JVR, NAU, JMMG, and AVG were responsible for the study concept and design. JVR and NAU contributed to the data acquisition. MPP and VC performed the statistical analysis. CSM and ABL assisted with data analysis and interpretation of findings. MPP and ABL drafted the manuscript. CSM, VC and AVG provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

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

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APPENDIX

METHODS

fMRI cognitive reappraisal task

Stimuli were presented through magnetic resonance-compatible liquid crystal display goggles (Resonance Technology, Northridge, CA, USA). We used 24 stimuli that were extracted from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2005): 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 Regulate conditions. The images were selected according to IAPS Spanish normative values for valence and arousal (Moltó et al., 1999), and their mean values can be found in Albein-Urios et al. (2013).

The task consisted of 12 blocks: four blocks for each of the three conditions. Conditions 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 'Regulate') presented in the middle of the screen during 4s. After the prompt, participants viewed two different pictures of equal valence for 10s each. Immediately after the second picture, the intensity of the negative emotion experienced was self-rated on a 1–5 number scale that appeared for 5s (where 1 is 'neutral' and 5 is 'extremely negative'), recorded through a five-button box, Evoke Response Pad System (Resonance Technology Inc.). Each block was followed by 10s of a cross-fixation baseline to minimize carryover effects.

Imaging data acquisition and preprocessing

During acquisition, a T2*-weighted echo-planar imaging (EPI) was obtained [repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, field of view (FOV) = 230×230 mm, 96×96 matrix, flip angle = 90°, 21 4-mm axial slices, 1-mm gap, 234 scans]. A sagittal three-dimensional T1-weighted turbo-gradient-echo sequence (160 slices, TR = 8.3 ms, TE = 3.8 ms, flip angle = 8°, FOV = 240×240, 1 mm³ voxels) was obtained in the same experimental session for anatomical reference.

The functional images were analyzed using Statistical Parametric Mapping (SPM12) software (https://www.fil.ion.ucl.ac.uk/spm/), running under Matlab R2009 (MathWorks, Natick, MA, USA). Preprocessing included slice timing correction, head motion correction, normalization to the EPI template in the Montreal Neurological Institute (MNI) space (voxel size of 2×2×2 mm), and spatial smoothing by convolution with a 3D Gaussian kernel (full width at half maximum = 8 mm). The realignment parameters were inspected, and participants were excluded when they had more than 2 mm or degrees of movement in any of the six directions, leaving a final sample of 15 CUD patients, 16 GD patients and 17 HC (Table 1).
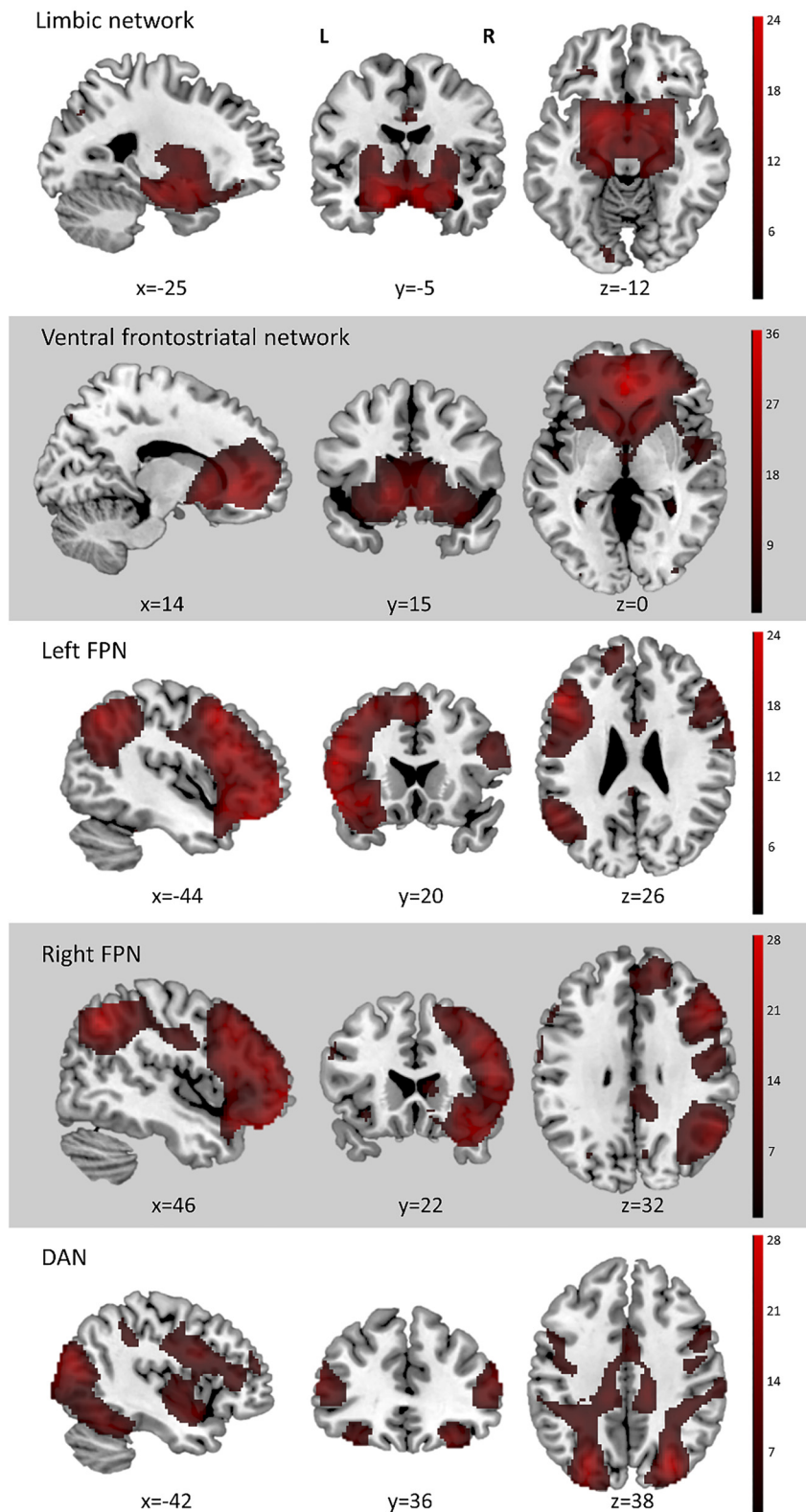
Fig. A1. Networks of interest identified through group ICA. FPN = frontoparietal network; DAN = dorsal attention network. Coordinates are x, y, z MNI coordinates

Interview for Research on Addictive Behavior

This instrument evaluates, by means of a brief interview, the quantity (dosing), frequency (consumption episodes by month), and chronicity (years of duration) of the use of a series of substances (such as cocaine) that can produce physical or psychological dependence, as well as of the exposure to gambling. For each of this, the following information is requested: (1) the average amount of each target drug ingested/gambling in each episode of use (number of grams for cocaine; and number of hours for gambling); (2) the frequency of these consumption episodes per month: daily, between one and three times upon a week, once a week, between one and three times upon a month, or once a month; and (3) the number of years that elapsed since the onset of the use. Then, composite severity scores can be calculated from these variables.