Addiction Biology

SSA SOCIETY FOR THE STUDY OF ADDICTION

ORIGINAL ARTICLE

doi:10.1111/adb.12356

Cocaine addiction is associated with abnormal prefrontal function, increased striatal connectivity and sensitivity to monetary incentives, and decreased connectivity outside the human reward circuit

Lucía Vaquero[1,2], Estela Cámara[1], Frederic Sampedro[3], José Pérez de los Cobos[4,5,6], Francesca Batlle[4,5], Josep Maria Fabregas[7], Joan Artur Sales[8], Mercè Cervantes[8], Xavier Ferrer[9,10], Gerardo Lazcano[9], Antoni Rodríguez-Fornells[1,2,11] & Jordi Riba[6,12,13,14]*

Cognition and Brain Plasticity Group (Bellvitge Biomedical Research Institute) IDIBELL, L'Hospitalet de Llobregat, Spain[1], Department of Basic Psychology, University of Barcelona, Spain[2], School of Medicine, Universitat Autònoma de Barcelona, Spain[3], Addictive Behaviors Unit, Department of Psychiatry, Hospital de la Santa Creu i Sant Pau, Sant Pau Biomedical Research Institute (IIB Sant Pau), Spain[4], Department of Psychiatry and Legal Medicine, Autonomous University of Barcelona, Spain[5], Centro de Investigación Biomédica en Red de Salud Mental CIBERSAM, Spain[6], Center for Research and Treatment of addictions (CITA), Spain[7], Grup ATRA, Spain[8], Fundació Salut i Comunitat, Spain[9], Addiction postgraduate course, School of Psychology, University of Barcelona, Spain[10], Catalan Institution for Research and Advanced Studies, ICREA, Spain[11], Human Neuropsychopharmacology Group, Sant Pau Institute of Biomedical Research (IIB-Sant Pau), Spain[12], Centre d'Investigació de Medicaments, Servei de Farmacologia Clínica, Hospital de la Santa Creu i Sant Pau, Spain[13] and Departament de Farmacologia i Terapèutica, Universitat Autònoma de Barcelona, Spain[14]

ABSTRACT

Cocaine addiction has been associated with increased sensitivity of the human reward circuit to drug-related stimuli. However, the capacity of non-drug incentives to engage this network is poorly understood. Here, we characterized the functional sensitivity to monetary incentives and the structural integrity of the human reward circuit in abstinent cocaine-dependent (CD) patients and their matched controls. We assessed the BOLD response to monetary gains and losses in 30 CD patients and 30 healthy controls performing a lottery task in a magnetic resonance imaging scanner. We measured brain gray matter volume (GMV) using voxel-based morphometry and white matter microstructure using voxel-based fractional anisotropy (FA). Functional data showed that, after monetary incentives, CD patients exhibited higher activation in the ventral striatum than controls. Furthermore, we observed an inverted BOLD response pattern in the prefrontal cortex, with activity being highest after unexpected high gains and lowest after losses. Patients showed increased GMV in the caudate and the orbitofrontal cortex, increased white matter FA in the orbito-striatal pathway but decreased FA in antero-posterior association bundles. Abnormal activation in the prefrontal cortex correlated with GMV and FA increases in the orbitofrontal cortex. While functional abnormalities in the ventral striatum were inversely correlated with abstinence duration, structural alterations were not. In conclusion, results suggest abnormal incentive processing in CD patients with high salience for rewards and punishments in subcortical structures but diminished prefrontal control after adverse outcomes. They further suggest that hypertrophy and hyper-connectivity within the reward circuit, to the expense of connectivity outside this network, characterize cocaine addiction.

Keywords cocaine addiction, functional MRI, human, incentive-processing, structural MRI.

Correspondence to: Jordi Riba, Human Neuropsychopharmacology Group, IIB-Sant Pau. C/Sant Antoni María Claret, 167.08025, Barcelona, Spain. E-mail: jriba@santpau.cat

INTRODUCTION

A growing body of evidence suggests that chronic use of psychostimulants is associated with alterations in reward processing (Volkow *et al.* 2012). Drugs like methylphenidate and cocaine are known to acutely increase dopamine levels in the striatum (Volkow *et al.* 1999), and repeated stimulation of this system leads to neural adaptations that are believed to underlie the addicted state (Volkow *et al.* 2011). This state is characterized by compulsive

© 2016 Society for the Study of Addiction

drug-seeking, disregard for the adverse health and social consequences of illicit drug use and decreased interest in non-drug-related activities (Koob & Volkow 2010).

Cocaine-dependent individuals have shown increased responsivity of the reward circuit to drug-related cues (Volkow *et al.* 2011). However, recruitment of the reward system by non-drug incentives has yielded contradictory findings (Hommer, Bjork, & Gilman 2011). Initial evidence of decreased D_2 receptor availability in the striatum of addicted individuals (Volkow *et al.* 1993) and reduced responsiveness to dopaminergic drug challenge (Volkow *et al.* 1997) led to the postulation of the reward deficiency hypothesis of addiction (Blum *et al.* 2000). According to this theory, addicted individuals present an under-responsive meso-cortico-limbic system with a deficit in the recruitment of dopaminergic pathways by generally rewarding experiences. This under-responsive state has been proposed to be a deficit that is prior to drug use (Blum *et al.* 2000), but it has also been considered a consequence of repeated drug abuse (Koob & Le Moal 2005). In either case, this suboptimal responsiveness of the reward system may create a state of anhedonia that individuals try to compensate by further drug intake (Koob & Le Moal 2001).

However, recent data suggest that drug addiction may arise from an underlying hyperactive reward circuit (Buckholtz *et al.* 2010). This hyperactivity can lead to severe impulsivity and diminished cognitive control. Behaviorally, this would manifest as high trait impulsivity and decreased avoidance (Bechara 2005). At the neuroanatomical level, it would be caused by reduced availability of midbrain dopaminergic receptors, leading to enhanced dopamine release following rewarding stimuli (Buckholtz *et al.* 2010). Increased responsiveness to high salience rewarding stimuli could be caused by differential regulation of tonic and phasic dopamine release. The constant slow striatal release of dopamine by midbrain dopaminergic neurons (tonic activity) is inversely related with the burst firing of these neurons triggered by salient stimuli (phasic activity). Decreased tonic activity (background dopamine) facilitates phasic dopamine release (Bilder *et al.* 2004). In agreement with this hypothesis, studies assessing brain responses to notification of rewarding outcomes have found increased ventral striatum activation in CD patients (Jia *et al.* 2011). An over-reactive meso-cortico-limbic circuit coupled with decreased cognitive control would facilitate transition from an initially pleasurable experience to compulsive drug use and full addiction (Buckholtz *et al.* 2010). As a matter of fact, anomalous prefrontal cortex function is a common find in drug abusers (Goldstein *et al.* 2001).

In the present study, we wished to investigate the hyperactive reward circuit hypothesis of cocaine addiction by testing meso-cortico-limbic functional sensitivity to non-drug incentives. We postulated that CD patients would show increased neural activation following monetary gains in a lottery task. Using fMRI, we measured the BOLD response to the delivery of rewards and punishments in a sample of detoxified CD patients and their matched controls. Additionally, we studied the structural integrity of the reward circuit in the same population. We measured gray matter volume using voxel-based morphometry (VBM) and characterized white matter microstructure using a voxel-based analysis of fractional anisotropy (FA). To assess the influence of cocaine exposure on the observed imaging changes, functional and structural data were correlated with prior cocaine intake and abstinence duration.

METHODS

Study participants

Thirty detoxified CD inpatients (6 women, 24 men) and 30 drug-naive controls (6 women, 24 men) were recruited for the study. Special emphasis was placed on excluding patients with axis-I psychiatric disorders and alcohol and opiate use disorders. Also, at the time of assessment patients were free of any psychotropic medication. Detailed socio-demographic data and matching criteria are provided as supplementary information. All participants signed an informed consent prior to enrolment. The study was approved by the Ethics Committee at Hospital de Sant Pau, Barcelona, Spain.

Lottery task

The experimental paradigm was a modified version of Gehring's task (Riba *et al.* 2008) (Fig. 1). In each trial, two numbers, 25 or 5, were presented in white against a black background. Participants had to bet on one of these two numbers by pressing a button in order to increase a starting amount of 500 euro cents. One second after the selection, the numbers changed color. One of the numbers changed to red, while the other changed to green. If the selected number turned green, it indicated a win (i.e., +5 or +25), whereas if it turned red, it indicated a loss (i.e., −5 or −25). This feedback was shown for 2 s. A slow event-related design was used with a constant interstimulus interval of 12 s, during which a fixation cross was presented in the center of the screen.

The experimental session comprised 2 blocks of 94 trials each. In 80 of the 94 trials (85%), the feedback indicated a standard win or a standard loss. Additionally, in 14 of the 94 trials (15%), the so-called 'boost trials', wins were doubled, and participants won 10 cents after choosing 5 (a green '10' was shown as feedback on the screen) and 50 cents after choosing 25 (a green '50' was shown as feedback on the screen). Thus, the six possible outcomes were: win 5, win 25, lose 5, lose 25, win 10 ('boost + 10') and win 50 ('boost + 50'). Boost trials have

© 2016 Society for the Study of Addiction

13691600, 2017, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/adb.12356 by Universitat Autonoma De Barcelona, Wiley Online Library on [14/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

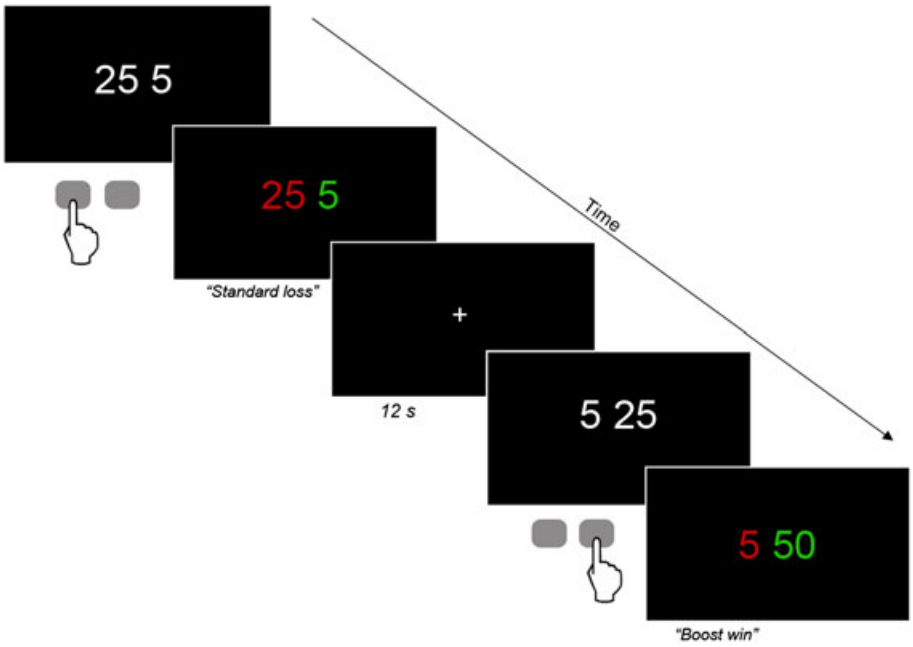

Figure 1 Schematic representation of the lottery task. Each trial of the task comprised the presentation of two numbers, 25 and 5. Participants had to choose one of two numbers by pressing the corresponding button (left button for left number). One second after selection, the numbers changed color. Green indicated a win, red a loss. A constant interstimulus interval of 12 s was used. The upper example shows a loss of 25 euro cents; the alternative choice would have yielded a win of 5 euro cents. The lower example shows an infrequent 'boost' trial in which the participant chose to bet 25 euro cents, but his gains were doubled and he won 50 euro cents

shown to robustly engage the ventral striatum in humans (Riba *et al.* 2008) in line with electrophysiological recordings in monkeys following the presentation of unexpected rewards (Hollerman & Schultz 1998).

Participants were told to adjust their choices to maximize their wins. In actual fact, the task was programmed to yield wins in 50% of the trials and losses in the other 50%. Participants were informed about the money they had won at three different times during each block. However, gains and losses were virtual, and no actual money was paid to the participants as a result of their performance.

Behavioral data analysis

The behavioral measures obtained from the gambling task included reaction times and the probability (between 0 and 1) of choosing 25 over 5. This probability was calculated using the following ratio: n25/(n25 + n5), n25 being the number of times '25' was chosen, and n5 the number of times '5' was chosen. For each participant, an overall probability was calculated for the whole experiment. These data were subjected to repeated measures ANOVAs with the within-subject factors 'choice' (25 versus 5) and the between-subjects factor 'group' (CD patients versus controls). In a second analysis, we analyzed the reaction time in a given trial as a function of choice in the immediately preceding trial. Thus, reaction time values were analyzed using repeated measures ANOVAs with the within-subject factors 'choice' in the current trial, (25 versus 5), magnitude of outcome in the preceding trial (25 versus 5) and the between-subjects factor 'group' (CD patients versus controls).

Magnetic resonance imaging acquisition

Magnetic resonance imaging data were acquired using a 3 T whole-body MRI scanner (TRIO Tim syngo MR B17, Siemens; see Supporting Information).

Functional magnetic resonance imaging data analysis

Preprocessing steps are described in the supporting information. The statistical evaluation of preprocessed functional images was based on a least-square estimation using the general linear model by modeling the different conditions with a regressor waveform convolved with a canonical hemodynamic response function as previously described (methodological references are provided in the Supporting Information). Thus, an event-related design matrix was created, including the conditions of interest: win 5, win 25, lose 5, lose 25, win 10 ('boost + 10') and win 50 ('boost + 50'). The data were high-pass filtered (to a maximum of 1/90 Hz), and serial autocorrelations were estimated using an autoregressive model [AR(1) model]. Resulting estimates were used for non-sphericity correction during the model estimation. Confounding effects in global mean were removed by proportional scaling, and signal-correlated motion effects were minimized

© 2016 Society for the Study of Addiction

13691600, 2017, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/adb.12356 by Universitat Autonoma De Barcelona, Wiley Online Library on [14/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

by including the estimated movement parameters. The individual contrast images were entered into a second level analysis using a one-sample *t*-test employing a random effects analysis within the general linear model.

Main Contrasts of Interest

We analyzed the outcome phase (reward or punishment delivery) of incentive processing. First, to reveal main brain regions involved in reward processing, we created a main contrast 'overall gain' (win5 + win25 + boost10 + boost50) versus 'overall loss' (lose5 + lose25). This main contrast was investigated in the entire sample and was thresholded at $P < 0.05$, corrected for multiple comparisons at the whole-brain level by using a family-wise error correction. Four functional main regions of interest (ROIs) were derived from the whole sample analysis by drawing a 10 mm sphere around the peak coordinate: right ventral striatum (RVstr), left ventral striatum (LVstr), medial prefrontal cortex (mPFC) including areas in the anterior cingulate and orbitofrontal cortices, and posterior cingulate cortex (PCC). To increase the number of trials in each condition, the outcomes lose5 and lose25 were collapsed into a single outcome, 'loss'; the outcomes win5 and win25 were collapsed into outcome 'win', and the outcomes boost10 and boost50 were collapsed into outcome 'boost'. The corresponding parameter estimates (β values) for each condition and participant were extracted from the ROIs and entered into a mixed-model analysis with the within-subjects factor 'outcome' (loss, win and boost) and the between-subjects factor 'group' (CD patients versus controls). Pair-wise comparisons were performed using independent-samples Student's *t*-tests. These analyses were conducted at each ROI.

Voxel-Based Morphometry of T1-weigthed images

Preprocessing steps are described in the supporting information. The individual smoothed gray matter (GM) volume images were entered into a second-level between-groups analysis to compare patients and controls. Individual values of total GM volume were extracted and included as a nuisance variable to correct for global differences in GM (methodological references are provided in the Supporting Information). This correction prevents spurious results arising from mere differences in brain size between individuals. Additionally, an absolute threshold mask of 0.2 was used, as well as an explicit mask of GM, created over the a priori SPM GM map with a threshold value of 0.2.

Voxel-Based analysis of fractional anisotropy

Preprocessing steps are described in the supporting information. FA maps for each subject were calculated using the eigenvalues extracted from the diffusion tensors. To normalize the images, FA maps were eroded and registered to the FMRIB58_FA template, which is in MNI152 space, using the nonlinear registration tool FNIRT (methodological references are provided in the Supporting Information). Normalized FA maps were smoothed by using an isotropic spatial filter (FWHM = 6 mm) before including them in a second-level analysis. Both steps were carried out in SPM8. As a second-level analysis, a between-groups comparison was carried out to look for FA differences between patients and controls applying an absolute threshold mask of 0.15.

Unless indicated otherwise, all contrasts for structural data (GM and FA results) were thresholded at $P < 0.005$ uncorrected for multiple comparisons with a cluster extent of more than 50 contiguous voxels. The maxima of suprathreshold regions were localized by rendering them onto a T1 structural template-image of the Montreal Neurological Institute reference brain.

RESULTS

Lottery task functional magnetic resonance imaging

Behavior

Both patients and controls showed similar behavioral patterns. All participants systematically chose '25' more often than '5'. The global probability (mean ± SD) of choosing '25' was 0.57 ± 0.13. A two-way ANOVA with the within-subjects factor choice ('25' versus '5') and the between-subjects factor participant group showed a significant effect of choice $F[(1, 54) = 16.41, P < 0.001]$ but no group effect [$F(1, 54) = 0.00$, n.s. (not-significant)] or their interaction [$F(1, 54) = 0.38$, n.s.]. Reaction times (the time taken to choose either 25 or 5) did not differ between groups [$t(54) = 0.97$, n.s.]. Mean ±SD reaction time was 813 ± 199 ms for controls and 864 ± 198 ms for patients.

The analysis of reaction times in a given trial as a function of choice in the immediately preceding trial showed differences between groups. As shown in Fig. 2, a two-way ANOVA with magnitude in the preceding trial (5 versus 25) as within-subjects factor and group (CD patients versus controls) as between-subjects factor, showed a significant group x magnitude interaction [$F(1, 54) = 5.93$, $P = 0.018$]. Pairwise comparisons showed that in the CD group, reaction times after trials involving large incentives (+25 and −25) irrespective whether these were gains or losses were shorter than after trials involving small incentives (+5 and −5). Thus, in the CD patient group, mean ± SD reaction time was 922 ± 248 ms following a small gain or loss and 882 ± 223 following a large gain or loss [$t(29) = -3.09$, $P = 0.004$]. For the control group, values were not statistically different between small 846 ± 248 and large 857 ± 241 [$t(25) = 0.6$].

© 2016 Society for the Study of Addiction

13691600, 2017, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/adb.12356 by Universitat Autonoma De Barcelona, Wiley Online Library on [14/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

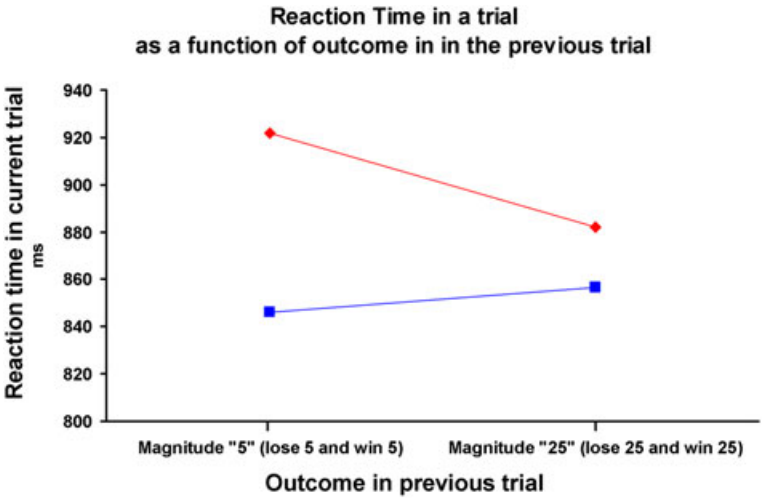

Figure 2 Behavioral results. Reaction time in a trial as a function of previous outcome. The plots show the relationship between outcome magnitude in a given trial (5 versus 25) and reaction time in the subsequent trial. Data for cocaine-dependent patients (red, diamond) and controls (blue, square). A significant interaction was found between outcome magnitude and participant group. In the cocaine-dependent patient group, reaction time was dependent on magnitude, but not valence, of the preceding trial. Thus, subsequent selections in the patient group were significantly faster following large gains and losses

Functional magnetic resonance imaging

Brain-wide statistical maps for the whole sample

Usable functional images were obtained for 30 patients and 26 controls. The images from four controls had to be removed from the analysis because of an excessive movement artifact. As shown in Fig. 3, the contrast 'overall gain' (win5 + win25 + boost10 + boost50) versus 'overall loss' (lose5 + lose25) for the entire 56-subject sample led to areas of increased BOLD response in the right and left ventral striatum (RVstr and LVstr, respectively), the medial prefrontal cortex (mPFC), including areas in the anterior cingulate and orbitofrontal cortices and the posterior cingulate cortex (PCC). Table 1 shows the spatial coordinates and maximum t values found for each of the significant clusters. The identified areas correspond to those reported in a recent meta-analysis of BOLD activations in fMRI studies of monetary outcomes (Bartra, McGuire, & Kable 2013).

Statistical comparison between patients and controls

As shown in the plots of β-values for the RVstr in Fig. 3, increased values were observed for the three possible outcomes in the patient group. The statistical analysis showed

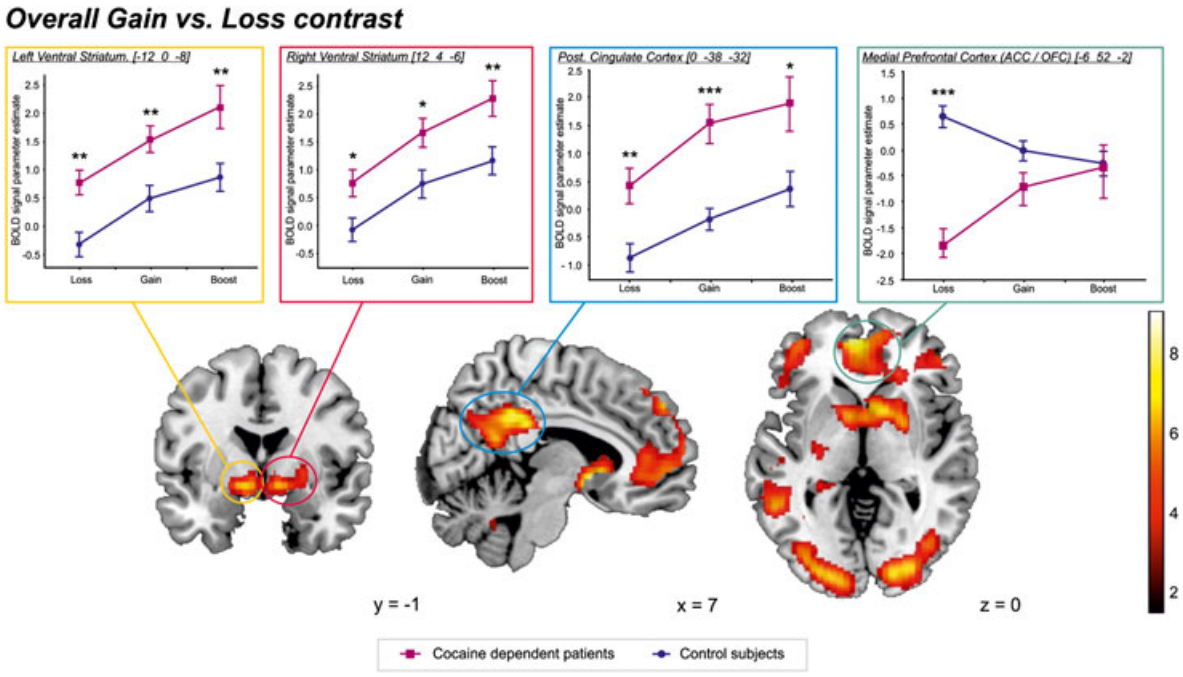

Figure 3 Functional magnetic resonance imaging results. Slices showing areas of greater activation for win trials than for loss trials for the whole sample (30 patients and 26 controls). The line graphs show the parameter estimates (β-values) for each region of interest, participant group (patients and controls) and task outcome (loss, gain and boost). Error bars in the β-value plots denote ± 1 standard error of mean. Asterisks indicate the results of pairwise comparisons between groups for each outcome. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

© 2016 Society for the Study of Addiction

13691600, 2017, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/adb.12356 by Universitat Autonoma De Barcelona, Wiley Online Library on [14/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1 Functional magnetic resonance imaging results of the monetary lottery task.

Anatomical region	*Cluster size (voxels)*	*t* value	*MNI coordinates (x, y, z)*
Right ventral striatum	98	10.4	12, 4, −6
Posterior cingulate cortex	184	8.47	0, −38, 32
Medial prefrontal cortex	130	8.22	−6, 52, −2
Left ventral striatum	108	7.25	−12, 0, −8

Clusters of significantly greater activation after wins than after losses for the whole sample (30 patients and 26 controls). Results corrected for multiple comparisons at the whole-brain level using a family-wise error correction at $P < 0.05$. MNI = Montreal Neurological Institute stereotactic space.

significant effects of outcome [$F(2, 108) = 30.36$, $P < 0.001$] and group [$F(1, 54) = 9.75$, $P = 0.003$] but did not show the interaction between the two factors [$F(2, 108) = 0.32$, n.s.]. To assess the potential involvement of impulsivity in the differences between groups, we conducted a reanalysis using the global score on the Dickmann impulsivity inventory (DII) as a covariate. This analysis showed no significant effects of outcome or the interaction outcome by group, but it did show a significant overall effect of group [$F(1, 53) = 5.06$, $P = 0.029$]. Thus, when controlling for impulsivity as a confound, overall responsiveness in the RVstr was greater in CD patients than in the control group. Pairwise comparisons showed higher β-values in the patient group after losses [$t(54) = 2.58$, $P = 0.013$], wins [$t(54) = 2.52$, $P = 0.015$] and boost trials [$t(54) = 2.70$, $P = 0.009$].

In the LVstr, the plots of β-values also showed increased values for the three possible outcomes in the patient group. Again, the statistical analysis showed significant effects of outcome [$F(2, 108) = 21.12$, $P < 0.001$] and group [$F(1, 54) = 14.88$, $P < 0.001$] but did not show the interaction between the two factors [$F(2, 108) = 0.17$, n.s.]. The reanalysis including the DII global score as a covariate again showed a significant overall effect of group [$F(1, 53) = 7.05$, $P = 0.010$]. Pairwise comparisons showed higher β-values in the patient group after losses [$t(54) = 3.61$, $P = 0.001$], wins [$t(54) = 3.20$, $P = 0.002$] and boost trials [$t(54) = 2.76$, $P = 0.008$].

In the mPFC, the β-value plots showed a pattern for the patient group that was the mirror image of that observed for the controls. Statistically, this was reflected as a main effect of group [$F(1, 54) = 8.15$, $P = 0.006$] and as an interaction between group and outcome [$F(2, 108) = 17.69$, $P < 0.001$]. In the reanalysis including the DII global score as a covariate, both effects of group [$F(1, 53) = 6.17$, $P = 0.016$] and the interaction outcome x group were maintained. [$F(2, 106) = 13.30$, $P < 0.001$]. The pairwise comparisons showed a significant difference between the groups for the outcome 'loss' only [$t(54) = -7.34$, $P < 0.001$]. A trend was observed for outcome 'gain' [$t(54) = -1.93$, $P = 0.059$] and no effect for outcome 'boost' [$t(54) = -0.11$, n.s.]. Thus, whereas losses led to higher activation than gains and boost trials in the mPFC in the control group, the reverse was observed in the patient group. In the latter, boost trials led to the higher activations, which decreased for gains and were minimal for losses.

In the PCC, patients showed higher mean activation values. ROI analysis showed significant effects of outcome [$F(1, 54) = 18.73$, $P < 0.001$] and group [$F(1, 54) = 13.45$, $P = 0.001$], but did not show the interaction outcome by group [$F(2, 108) = 0.44$, n.s.]. In the reanalysis including the DII global score as a covariate, only a trend to an effect of group was observed [$F(1, 53) = 3.25$, $P = 0.077$]. Pairwise comparisons showed higher β-values in the patient group after losses [$t(54) = 3.10$, $P = 0.003$], wins [$t(54) = 4.26$, $P < 0.001$] and boost trials [$t(54) = 2.63$, $P = 0.012$].

Voxel-based morphometry

Usable scans were obtained for the 60 participants and were all included in the VBM analysis. The between-subject analysis showed that patients had greater gray matter volume in the right caudate nucleus and in the right inferior and middle orbitofrontal gyri than controls. No decreases in gray matter volume were found in the patient group. Results are shown in Fig. 4 and Table 2.

Fractional anisotropy

Usable data were obtained from all 60 participants and were all included in the FA analysis. Results are shown in Fig. 5 and Table 3. The statistical analysis showed higher FA in the patient group in the white matter surrounding the putamen bilaterally, the insula bilaterally, a small region between the left putamen and the left caudate nucleus, the left thalamus, the anterior cingulate cortex (ACC) bilaterally, the middle OFC bilaterally, a small region neighboring the right hippocampus and the left inferior OFC. On the contrary, FA decreases in the patient group were found in the white matter of the anterior and middle parts of the middle cingulate gyrus bilaterally (including also some parts of the corpus callosum and the caudate body), and around the right caudate nucleus, the right inferior OFC, the right putamen, the right insula and the right hippocampus.

Correlation analysis

Correlations between functional and structural data

In the CD patient sample, the correlation analysis between functional and GMV data showed that BOLD activity (β-value) in the mPFC cluster (ACC/OFC) following

© 2016 Society for the Study of Addiction

13691600, 2017, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/adb.12356 by Universitat Autonoma De Barcelona, Wiley Online Library on [14/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

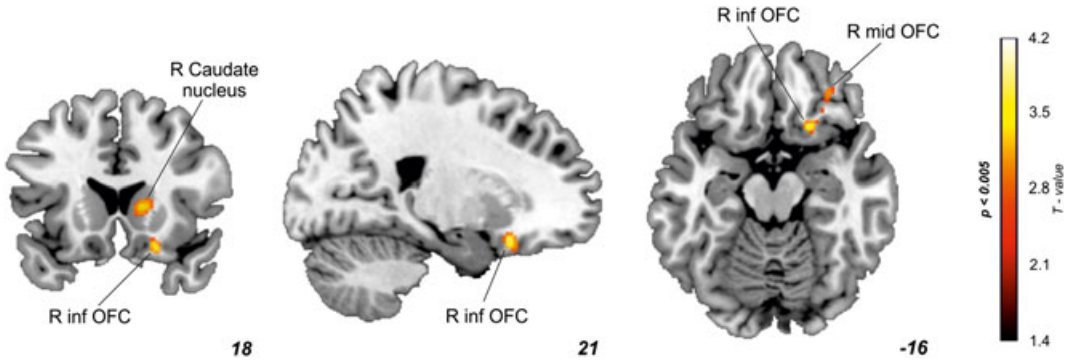

Figure 4 Results of the voxel-based morphometry analysis of the structural T1-weighted images. The slices show regions of greater gray matter volume in the patient sample: ofc: orbitofrontal cortex, inf: inferior, mid: middle, R: right. The numbers indicate the coordinate of the slice in Montreal Neurological Institute space

Table 2 Results of the voxel-based morphometry analysis of gray matter at $P < 0.005$ (minimum cluster extension of 50 contiguous voxels).

Larger gray matter volume in patients versus controls			
Anatomical region	*Cluster size (voxels)*	*t* value	*MNI coordinates (x, y, z)*
Inferior orbitofrontal cortex	162	3.80	24, 21, −20
Caudate nucleus	342	3.53	14, 17, 4
Middle orbitofrontal cortex	66	3.02	33, 39, −17

MNI = Montreal Neurological Institute stereotactic space.

the delivery of unexpectedly high monetary rewards (boost trials) correlated positively with increased GMV in the left OFC ($r = 0.411$, $r^2 = 0.169$, $P = 0.024$). No significant association was observed between functional and GMV in the control group ($r = 0.254$, $r^2 = 0.065$, $P = 0.211$).

Analogously, the correlation analysis between functional and FA data showed that BOLD activity (β-value) in the mPFC cluster (ACC/OFC) following the delivery of an adverse outcome (loss trials) correlated negatively with increased FA in the right OFC ($r = -0.685$, $r^2 = 0.469$, $P < 0.001$). Again, no significant association was observed between these variables in the control group ($r = 0.045$, $r^2 = 0.002$, $P = 0.826$).

Figure 6 presents the brain areas showing the aforementioned correlations and the associated scatter plots.

Correlations between neuroimaging data and history of cocaine use

To assess potential relationships between the intensity of cocaine use, the abstinence period and the functional and structural differences found, we conducted additional correlation analyses. Regarding cocaine use, a significant positive correlation was found between the weekly cocaine consumption in grams in the month prior to admission and GM volume in the OFC ($r = 0.462$, $r^2 = 0.213$, $P = 0.010$). Additionally, a significant negative correlation was found between the aforementioned weekly cocaine consumption and the parameter estimate (β-value) of the loss condition in the mPFC ($r = -0.394$, $r^2 = 0.155$, $P = 0.031$).

Duration of the abstinence period was inversely correlated with the parameter estimates of the boost condition in the clusters of the left ($r = -0.453$, $r^2 = 0.205$, $P = 0.012$) and right ($r = -0.387$, $r^2 = 0.150$, $P = 0.035$) ventral striata. Figure 7 shows the corresponding scatter plots.

DISCUSSION

In the present study, we assessed the functional and structural integrity of the human reward circuit in CD patients. Using a comprehensive approach involving three neuroimaging techniques, we showed a deviant pattern of activation in the patient group and structural modifications that were evidenced in both gray matter volume and white matter microstructure.

The gambling task involving three possible outcomes showed a monotonical increment in the BOLD response from losses through standard gains to unexpected high gains (boost trials) in the ventral striatum and the PCC for the whole participant sample. Compared with controls, CD patients also showed a monotonical increase in BOLD response as a function of outcome, but the whole curve was displaced upwards. This overall increase reveals an enhanced general sensitivity to non-drug incentives in the striatum and paralimbic areas in detoxified chronic cocaine users. The outcome-response curve observed in the mPFC in the patient group was the reverse of that obtained for the controls. Thus, whereas the control group showed the highest response for monetary losses and the lowest for unexpectedly high gains,

© 2016 Society for the Study of Addiction

13691600, 2017, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/adb.12356 by Universitat Autonoma De Barcelona, Wiley Online Library on [14/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

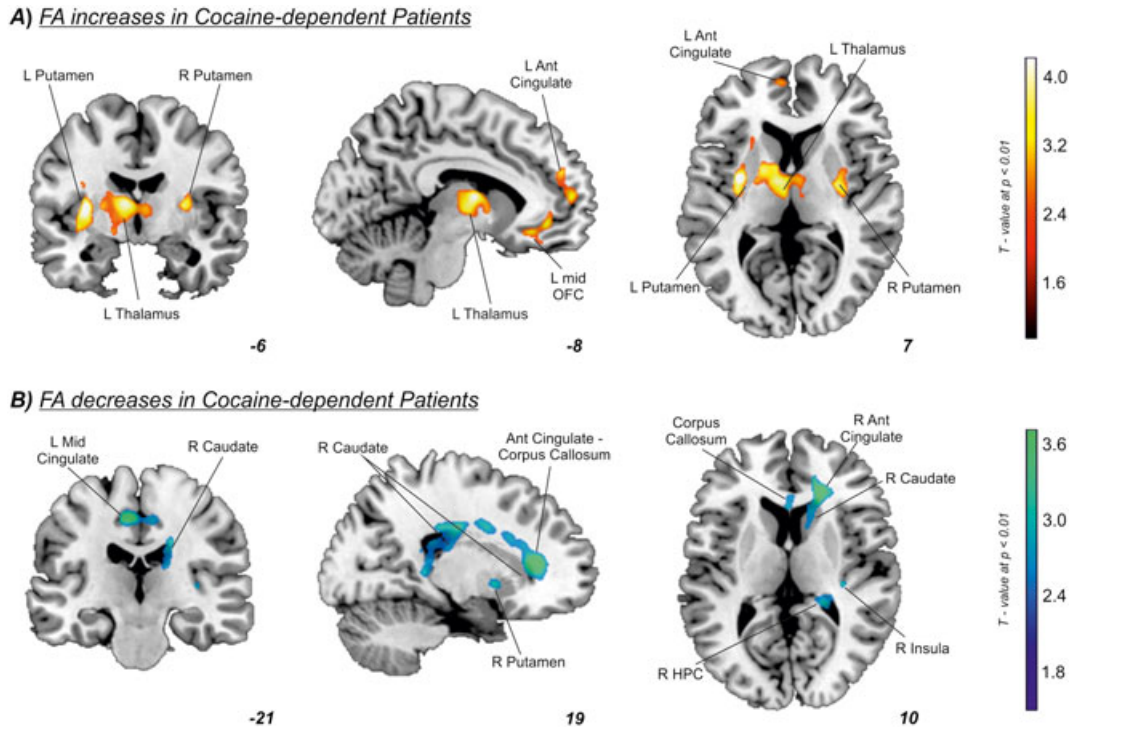

Figure 5 Results of the voxel-based analysis of fractional anisotropy (FA) maps. (a) Significant areas in which cocaine-dependent patients showed higher fractional anisotropy than controls. (b) Areas in which cocaine-dependent patients showed lower FA than controls. Significant clusters at $P < 0.005$ are listed in Table 3. The image shows results at $P < 0.01$ for depiction purposes. Ant: anterior, Mid: middle, OFC: orbitofrontal cortex, HPC: hippocampus, L: left, R: right

Table 3 Results for the fractional anisotropy analysis at $P < 0.005$ (minimum cluster extension of 50 contiguous voxels).

Anatomical region	*Cluster size*	*t* value	*MNI coordinates (x, y, z)*
Fractional anisotropy higher in patients versus controls			
Putamen + insula	2443	4.84	−32, −4, 7
Anterior ventral thalamus + putamen	3504	4.32	−9, −4, 10
Anterior cingulate gyrus	459	4.28	12, 45, 22
Putamen + insula	806	3.88	29, −7, 8
Middle orbitofrontal gyrus	259	3.87	−6, 42, −7
Inferior orbitofrontal gyrus	224	3.87	−40, 25, −7
Middle orbitofrontal gyrus	279	3.72	28, 47, −13
Anterior cingulate gyrus	207	3.40	−8, 56, 10
Insula	497	3.38	−33, −12, 22
WM surrounding hippocampus	71	3.27	39, −33, −10
Anterior cingulate gyrus	132	3.27	−7, 50, 25
Fractional anisotropy lower in patients versus controls			
ACC + caudate + corpus callosum	1714	4.38	19, 33, 11
Middle cingulate gyrus	1083	4.20	−7, −22, 48
Inferior orbitofrontal gyrus	207	3.89	23, 11, −21
Putamen	386	3.80	22, 6, −2
Insula	80	3.59	36, −23, 7
Hippocampus	661	3.44	26, −40, 2
Middle cingulate gyrus	541	3.37	20, −17, 34
Corpus callosum	156	3.03	0, 22, 12

ACC = anterior cingulate cortex; MNI = Montreal Neurological Institute stereotactic space; WM = white matter.

CD patients showed a greatly diminished activity following losses, which increased after gain trials and was maximal following the boost trials.

Prior studies on the responsivity of the human reward circuit in drug dependence have found mixed results. While increased activation has repeatedly been demonstrated for

© 2016 Society for the Study of Addiction

13691600, 2017, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/adb.12356 by Universitat Autonoma De Barcelona, Wiley Online Library on [14/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

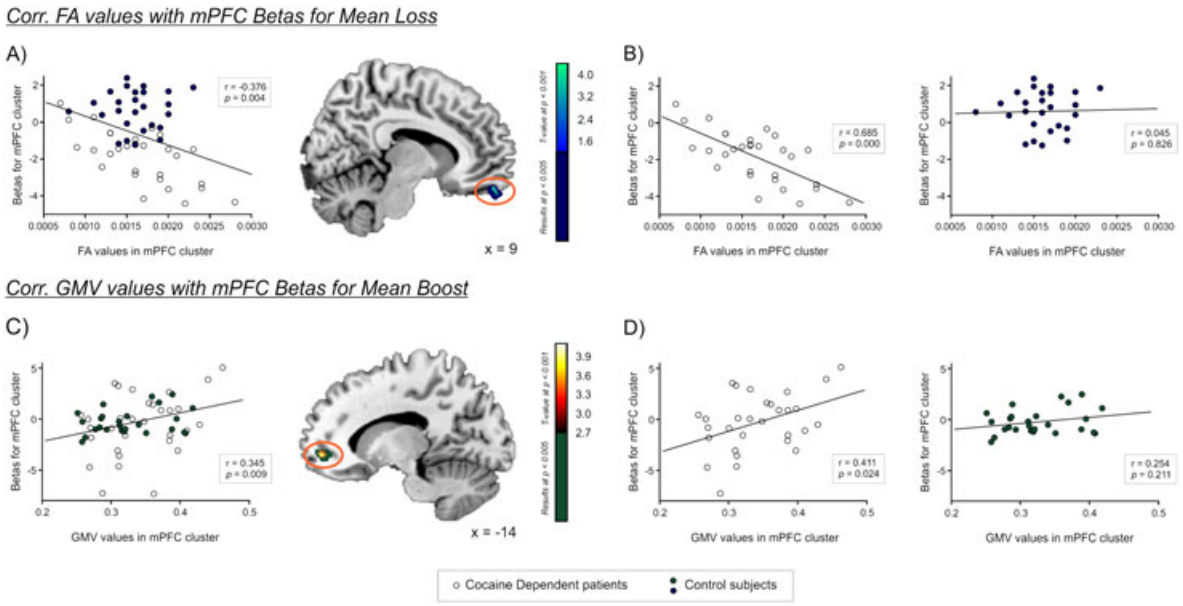

Figure 6 Brain maps and scatter plots showing the correlations between functional and structural data. (a) Correlations between the parameter estimates in the loss condition (betas) and fractional anisotropy (FA) values in the mPFC cluster for the whole sample. (b) Scatter plots separated for each participant group. (c) Correlations between the parameter estimates in the boost condition (betas) and GMV values in the mPFC cluster for the whole sample. (d) Scatter plots separated for each participant group

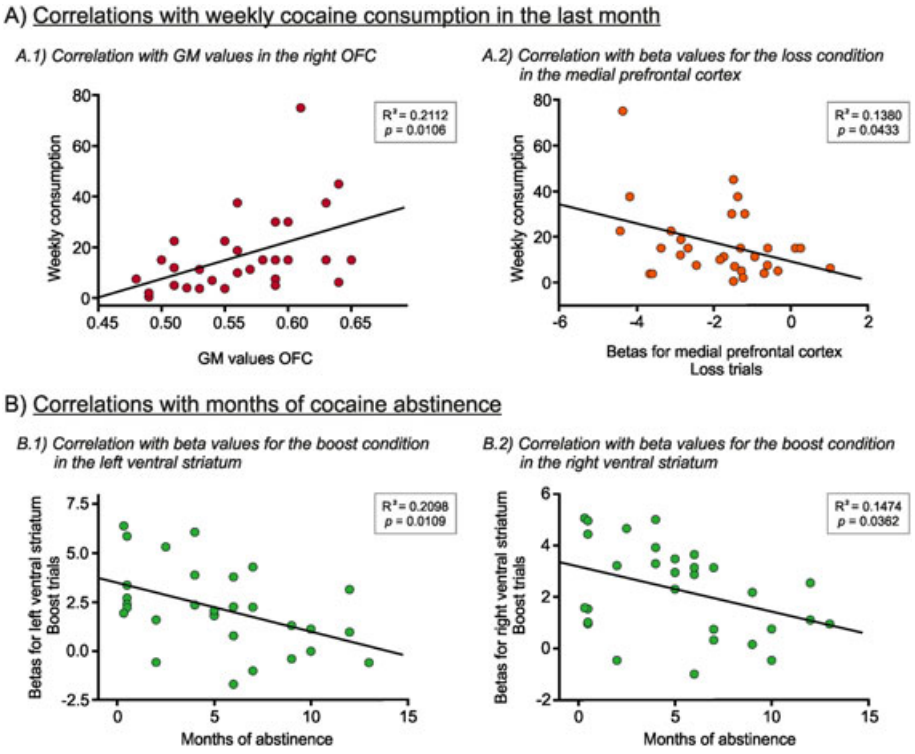

Figure 7 Scatter plots showing the correlations with pre-detoxification cocaine consumption and abstinence duration. (a) Correlations between the weekly amount of cocaine (in grams) used in the month prior to detoxification and: (a.1) gray matter volume in the right orbitofrontal cortex (OFC); and (a.2) the parameter estimate of the loss condition in the OFC. (b) Correlations between the months of cocaine abstinence and: (b.1) the parameter estimate of the boost condition in the left ventral striatum; and (b.2) the same parameter estimate in the right ventral striatum

drug-related cues (Volkow *et al.* 2011), initial PET studies showed reduced general dopaminergic tone in the striatum of addicted individuals (Volkow *et al.* 1993, 1997). More recently, it has been postulated that an underlying hyperactive reward circuit may lead to increased impulsivity and maladaptive behaviors such as drug abuse (Buckholtz

© 2016 Society for the Study of Addiction

13691600, 2017, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/adb.12356 by Universitat Autonoma De Barcelona, Wiley Online Library on [14/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

et al. 2010). Our results are in line with this latter view. Indeed, activation in the patient group was higher than that observed in the control group. The increased BOLD response in the ventral striatum was evidenced through the whole range of possible results, from adverse outcomes (losses) to highly favorable outcomes (boost gains). Increased sensitivity in this brain area has been reported for CD patients by other researchers (Jia *et al.* 2011).

Our results are in line with prior studies showing exaggerated responses to gains and losses in gambling tasks in alcohol-dependent subjects (Bjork, Hommer, & Smith 2008). A potential confound of our present findings is the high trait impulsivity measured in the CD patients. Gilman and coworkers recently found that increased striatal sensitivity to cumulative gains and losses correlates with impulsivity scores in alcohol-dependent patients (Gilman *et al.* 2015). However, when impulsivity was introduced as a covariate in the analysis in the present study, higher overall activation in CD patients in the ventral striatum remained significant.

Interestingly, opposite patterns of activation were observed between patients and controls in the mPFC, in an area encompassing regions of the ACC and the OFC. These brain structures play prominent roles in performance monitoring, reinforcement-learning and encoding of reward and punishment signals (Ridderinkhof *et al.* 2004). The ACC is robustly engaged by conflict, behavioral errors and negative outcomes (van Veen & Carter 2002). Reductions in dopamine receptor density in the ACC and its decreased engagement have been associated with poor behavioral monitoring and loss of control over drug intake (Volkow *et al.* 2012). Analogous receptor modifications in the OFC are believed to alter salience attribution (Goldstein & Volkow 2011; Volkow *et al.* 2012). Also, a recent study in animals has shown that whereas ventral striatal activity signals reward prior to decision making, the OFC shows post-decision activation. The authors proposed that the OFC is involved in the comparison between the predicted and actual consequences of behavior (Stott & Redish 2014). In line with these findings, damage to the OFC in neurologic patients is associated with insensitivity to punishment (Anderson *et al.* 1999), impulsivity and bias toward more immediate rewards (Berlin, Kischka, & Rolls 2004). Camara and coworkers also found high prefrontal activation to unexpected high gains in individuals with the val/val COMT genotype. These subjects have decreased tonic dopamine release because of increased COMT activity (Camara *et al.* 2010). Analogously to our current findings, previous studies by Goldstein and coworkers found a reversal of the role of OFC in addiction (Goldstein *et al.* 2001), and Garavan and coworkers described reduced ACC responses to punishment in cocaine users (Hester *et al.* 2013). Our results can be tentatively interpreted as CD patients showing a bias toward highly rewarding signals or prediction error violations (Hollerman & Schultz 1998) and a diminished activation of cognitive control mechanisms over negative outcomes. In other words, while monetary losses appear to lead to deactivations in the mPFC of patients, they are very effective in engaging this region in healthy subjects. This anomalous pattern of response in the mPFC of CD patients was also maintained when impulsivity was included in the analysis as a nuisance variable.

It is worth mentioning that the abnormal pattern of incentive processing found was seen in detoxified patients who had abstained from cocaine for an average of 6 months. This suggests that deficits are long-lasting and gives rise to the possibility that they involve enduring adaptations in neural networks. This possibility is supported by the structural differences found. VBM showed an enlargement in gray matter of the dorsal striatum and the OFC, and FA measures showed their increased interconnection at the expense of pathways outside the reward circuit. Other studies have found significant changes in gray matter in the prefrontal and striatal brain regions of cocaine addicts (Jacobsen *et al.* 2001; Di Sclafani, Fein, & Meyerhoff 2002), and Ersche and colleagues found increased gray matter volume in the basal ganglia (Ersche *et al.* 2011). The potential to induce these modifications may not be exclusive to cocaine, as analogous changes have been observed following use of other psychostimulants (Nyberg 2014). D-Amphetamine is able to alter the morphology of the striatum (Kolb & Robinson 1997), and methamphetamine is known to activate astrocytes (Narita *et al.* 2008), cause microgliosis (Sekine *et al.* 2008) and to increase striatal volume in addicts (Chang *et al.* 2005). At the sub-cellular level, psychostimulants can increase dendrite spines and the complexity of axon and dendrites in the nucleus accumbens and the prefrontal cortex (Dietz *et al.* 2009). These modifications could underlie the gray matter increases observed in our study.

Our finding of alterations in white matter microstructure is in line with data describing neuroadaptive changes induced by drugs of abuse in the fronto-striatal networks of animals (Everitt & Robbins 2005). Diffusion tensor imaging studies in humans have also reported changes in white matter microstructure in psychostimulant users. Furthermore, most studies on CD patients have described lower FA in areas such as the corpus callosum (Moeller *et al.* 2007; Ma *et al.* 2009) and in fibers within the frontal and parietal brain regions (Romero *et al.* 2010; Ersche *et al.* 2011). In still another study, it has been found that lower white matter integrity in cocaine dependence is inversely related with performance in neuropsychological tasks, demonstrating an association between these structural abnormalities and behavioral deficits (Lane *et al.* 2010).

© 2016 Society for the Study of Addiction

13691600, 2017, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/adb.12356 by Universitat Autonoma De Barcelona, Wiley Online Library on [14/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

The region-specific nature of the differences in FA found in our study is of particular note. Although decreases in FA were seen in antero-posterior association bundles, increases were observed within the reward circuit, in white matter around the ACC, OFC, the thalamus and the putamen. While studies have shown that cocaine induces persistent white matter lesions following chronic use (Lane *et al.* 2010) and acute overdose (Arlien-Soeborg, Danielsen & Kondziella 2009), it can also disrupt the balance of stimulatory and inhibitory growth factors, leading to increased axon sprouting (Narayana *et al.* 2014). Narayana and colleagues found that chronic cocaine administration reduces the expression of Nogo-A, a protein that inhibits axonal growth (Chen *et al.* 2000), while it stimulates the expression of GAP-43, which stimulates axon growth and nerve sprouting (Aigner *et al.* 1995). The combined effect of these two factors could lead to the aberrant hyperconnectivity found and may be associated with compulsive drug use (Fowler & Volkow 2000).

The link between cocaine exposure and neural adaptations is supported by the correlation between the pretreatment intensity of drug use and functional and structural anomalies in the mPFC. Also, the hyperactivation pattern observed for the unexpected and highly rewarding boost trials in the ventral striatum appeared to normalize as the abstinence period increased. Alternatively, lower reward responsiveness may have facilitated an increase in the duration of abstinence. The converging evidence of deviant activation, hypertrophy of the OFC and basal ganglia, and increased fronto-striatal connectivity suggests that abnormalities in incentive processing in patients have a structural basis. Considering that the prefrontal cortex and the striatum interact dynamically in salience attribution, inhibitory control and decision making, the neural differences observed in our patient sample very likely have an impact on goal-directed behavior. Disruption of fronto-striatal interactions in cocaine-dependent individuals may be at the core of the behavioral manifestations of addiction, such as compulsive drug seeking and impaired self-control. Indeed, studies in animals have shown that cocaine exposure causes an inability of the OFC to signal adverse outcomes (Stalnaker *et al.* 2006), which in association with enhanced dorso-striatal activity leads to rigid patterns of behavior (Caprioli, Lucantonio & Schoenbaum 2014). Thus, the 'hard wired' nature of the observed neural changes could explain the notorious difficulties experienced by addicts to abandon drug use even in the face of serious health and social consequences and the high relapse rate observed in this population.

As potential limitations of the present investigation we would like to mention that some studies have found that cocaine abusers may behave differently when tasks involve abstract points as compared with real rewards (Vadhan *et al.* 2009). This should be taken into account when generalizing from experimental reward tasks such as the one used here. Also, the behavioral differences observed in our experiment were modest, with faster reaction times following trials with large gains or losses. Finally, the ROIs studied were derived from an initial analysis using the whole sample and implementing a stringent correction for multiple comparisons using a family-wise error correction. However, no correction for multiple comparisons was performed later on the selected ROIs themselves.

To conclude, CD patients show an enhanced general responsivity to non-drug incentives in the ventral striatum but decreased engagement of the prefrontal cortex following negative behavioral outcomes. This deviant activation pattern correlated with the intensity of drug use and was observed together with volume increases in the dorsal striatum and enhanced fronto-striatal connectivity. In contrast, connectivity outside the reward circuit was found to be abnormally reduced. While functional hypersensitivity to highly rewarding stimuli in the Vstr decreased as the abstinence period increased, structural alterations did not. These findings reveal long-lasting prefrontal functional and structural abnormalities in cocaine addiction.

Acknowledgements

This work was supported by a grant from the 'Fondo de Investigación Sanitaria' of the Spanish Government. Marta Valle is supported by the 'Fondo de Investigación Sanitaria' through grant CP04/00121 from the Spanish Ministry of Health in collaboration with Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau, Barcelona. Frederic Sampedro is supported by an FPU grant from the Spanish government. The authors wish to thank Jaime Kulisevsky for his critical reading of the manuscript, and Cesar Garrido and Núria Bargalló for technical assistance. The authors declare no financial interests or potential conflicts of interest.

Authors Contributions

J. R., A. R. F., J. P. C. and F. B. were responsible for the study concept and design. J. P. C., F. B., J. M. F., J. A. S., M. C., X. F. and G. L. were responsible for patient recruitment. J. R. assessed participants, L. V., E. C. and F. S. analyzed the data. All authors participated in result interpretation and manuscript drafting. All authors critically reviewed content and approved final version for publication.

References

Aigner L, Arber S, Kapfhammer JP, Laux T, Schneider C, Botteri F, Brenner HR, Caroni P (1995) Overexpression of the neural

© 2016 Society for the Study of Addiction

13691600, 2017, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/adb.12356 by Universitat Autonoma De Barcelona, Wiley Online Library on [14/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

growth-associated protein GAP-43 induces nerve sprouting in the adult nervous system of transgenic mice. Cell 83:269–278.

Anderson SW, Bechara A, Damasio H, Tranel D, Damasio AR (1999) Impairment of social and moral behavior related to early damage in human prefrontal cortex. Nat Neurosci 2:1032–1037.

Bartra O, McGuire JT, Kable JW (2013) The valuation system: a coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. Neuroimage 76:412–427.

Bechara A (2005) Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nat Neurosci 8:1458–1463.

Berlin HA, Rolls ET, Kischka U (2004) Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. Brain 127:1108–1126.

Bilder RM, Volavka J, Lachman HM, Grace AA (2004) The catechol-O-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacol 29:1943–1961.

Bjork JM, Smith AR, Hommer DW (2008) Striatal sensitivity to reward deliveries and omissions in substance dependent patients. Neuroimage 42:1609–1621.

Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, Lubar JO, Chen TJ, Comings DE (2000) Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J Psychoactive Drugs 32:1–112.

Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Kessler RM, Zald DH (2010) Dopaminergic network differences in human impulsivity. Science 329:532.

Camara E, Krämer UM, Cunillera T, Marco-Pallarés J, Cucurell D, Nager W, Mestres-Missé A, Bauer P, Schüle R, Schöls L, Tempelmann C, Rodriguez-Fornells A, Münte TF (2010) The effects of COMT (Val108/158Met) and DRD4 (SNP −521) dopamine genotypes on brain activations related to valence and magnitude of rewards. Cereb Cortex 20:1985–1996.

Chang L, Cloak C, Patterson K, Grob C, Miller EN, Ernst T (2005) Enlarged striatum in abstinent methamphetamine abusers: a possible compensatory response. Biol Psychiatry 57:967–974.

Chen MS, Huber AB, van der Haar ME, Frank M, Schnell L, Spillmann AA, Christ F, Schwab ME (2000) Nogo-A is a myelin-associated neurite outgrowth inhibitor and an antigen for monoclonal antibody IN-1. Nature 403:434–439.

Dietz DM, Dietz KC, Nestler EJ, Russo SJ (2009) Molecular mechanisms of psychostimulant-induced structural plasticity. Pharmacopsychiatry 42:S69–S78.

Ersche KD, Barnes A, Jones PS, Morein-Zamir S, Robbins TW, Bullmore ET (2011) Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. Brain 134:2013–2024.

Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci 8:1481–1489.

Fein G, Di Sclafani V, Meyerhoff DJ (2002) Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. Drug Alcohol Depend 68:87–93.

Gilman JM, Smith AR, Bjork JM, Ramchandani VA, Momenan R, Hommer DW (2015) Cumulative gains enhance striatal response to reward opportunities in alcohol-dependent patients. Addict Biol 20:580–593.

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

Goldstein RZ, Volkow ND, Wang GJ, Fowler JS, Rajaram S (2001) Addiction changes orbitofrontal gyrus function: involvement in response inhibition. Neuroreport 12:2595–2599.

Hester R, Bell RP, Foxe JJ, Garavan H (2013) The influence of monetary punishment on cognitive control in abstinent cocaine-users. Drug Alcohol Depend 133:86–93.

Hollerman JR, Schultz W (1998) Dopamine neurons report an error in the temporal prediction of reward during learning. Nat Neurosci 1:304–309.

Hommer DW, Bjork JM, Gilman JM (2011) Imaging brain response to reward in addictive disorders. Ann N Y Acad Sci 1216:50–61.

Jacobsen LK, Giedd JN, Gottschalk C, Kosten TR, Krystal JH (2001) Quantitative morphology of the caudate and putamen in patients with cocaine dependence. Am J Psychiatry 158:486–489.

Jia Z, Worhunsky PD, Carroll KM, Rounsaville BJ, Stevens MC, Pearlson GD, Potenza MN (2011) An initial study of neural responses to monetary incentives as related to treatment outcome in cocaine dependence. Biol Psychiatry 70: 553–560.

Kondziella D, Danielsen ER, Arlien-Soeborg P (2009) Fatal encephalopathy after an isolated overdose of cocaine. BMJ Case Rep 2009; doi: 10.1136/bcr.06.2009.2003

Koob GF, Le Moal M (2001) Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24:97–129.

Koob GF, Le Moal M (2005) Plasticity of reward neurocircuitry and the "dark side" of drug addiction. Nat Neurosci 8: 1442–1444.

Koob GF, Volkow ND (2010) Neurocircuitry of addiction. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol 35:217–238.

Lane SD, Steinberg JL, Ma L, Hasan KM, Kramer LA, Zuniga EA, Narayana PA, Moeller FG (2010) Diffusion tensor imaging and decision making in cocaine dependence. PLoS One 5(7): e11591.

Lucantonio F, Caprioli D, Schoenbaum G (2014) Transition from "model-based" to "model-free" behavioral control in addiction: Involvement of the orbitofrontal cortex and dorsolateral striatum. Neuropharmacology 76:407–415.

Ma L, Hasan KM, Steinberg JL, Narayana PA, Lane SD, Zuniga EA, Kramer LA, Moeller FG (2009) Diffusion tensor imaging in cocaine dependence: regional effects of cocaine on corpus callosum and effect of cocaine administration route. Drug Alcohol Depend 104:262–267.

Moeller FG, Hasan KM, Steinberg JL, Kramer LA, Valdes I, Lai LY, Swann AC, Narayana PA (2007) Diffusion tensor imaging eigenvalues: preliminary evidence for altered myelin in cocaine dependence. Psychiatry Res 154:253–258.

Narayana PA, Herrera JJ, Bockhorst KH, Esparza-Coss E, Xia Y, Steinberg JL, Moeller FG (2014) Chronic cocaine administration causes extensive white matter damage in brain: diffusion tensor imaging and immunohistochemistry studies. Psychiatry Res 221:220–230.

Narita M, Suzuki M, Kuzumaki N, Miyatake M, Suzuki T (2008) Implication of activated astrocytes in the development of drug dependence: differences between methamphetamine and morphine. Ann N Y Acad Sci 1141:96–104.

Nyberg F (2014) Structural plasticity of the brain to psychostimulant use. Neuropharmacology 87:115–124.

© 2016 Society for the Study of Addiction

13691600, 2017, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/adb.12356 by Universitat Autonoma De Barcelona, Wiley Online Library on [14/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Riba J, Krämer UM, Heldmann M, Richter S, Münte TF (2008) Dopamine agonist increases risk taking but blunts reward-related brain activity. PLoS One 3(6):e2479.

Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S (2004) The role of the medial frontal cortex in cognitive control. Science 306:443–447.

Robinson TE, Kolb B (1997) Persistent structural modifications in nucleus accumbens and prefrontal cortex neurons produced by previous experience with amphetamine. J Neurosci Off J Soc Neurosci 17:8491–8497.

Romero MJ, Asensio S, Palau C, Sanchez A, Romero FJ (2010) Cocaine addiction: diffusion tensor imaging study of the inferior frontal and anterior cingulate white matter. Psychiatry Res 181:57–63.

Sekine Y, Ouchi Y, Sugihara G, Takei N, Yoshikawa E, Nakamura K, Iwata Y, Tsuchiya KJ, Suda S, Suzuki K, Kawai M, Takebayashi K, Yamamoto S, Matsuzaki H, Ueki T, Mori N, Gold MS, Cadet JL (2008) Methamphetamine causes microglial activation in the brains of human abusers. J Neurosci 28:5756–5761.

Stalnaker TA, Roesch MR, Franz TM, Burke KA, Schoenbaum G (2006) Abnormal associative encoding in orbitofrontal neurons in cocaine-experienced rats during decision-making. Eur J Neurosci 24:2643–2653.

Stott JJ, Redish AD (2014) A functional difference in information processing between orbitofrontal cortex and ventral striatum during decision-making behaviour. Philos Trans R Soc Lond B Biol Sci 369:1655.

Vadhan NP, Hart CL, Haney M, van Gorp WG, Foltin RW (2009) Decision-making in long-term cocaine users: effects of a cash monetary contingency on gambling task performance. Drug Alcohol Depend 102:95–101.

van Veen V, Carter CS (2002) The anterior cingulate as a conflict monitor: fMRI and ERP studies. Physiol Behav 77:477–482.

Volkow ND, Fowler JS (2000) Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. Cereb Cortex 10:318–325.

Volkow ND, Fowler JS, Gatley SJ, Dewey SL, Wang GJ, Logan J, Ding YS, Franceschi D, Gifford A, Morgan A, Pappas N, King P (1999) Comparable changes in synaptic dopamine induced by methylphenidate and by cocaine in the baboon brain. Synapse 31:59–66.

Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ, Dewey SL, Wolf AP (1993) Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. Synapse 14:169–177.

Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Hitzemann R, Chen AD, Dewey SL, Pappas N (1997) Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. Nature 386:830–833.

Volkow ND, Wang G-J, Fowler JS, Tomasi D (2012) Addiction circuitry in the human brain. Annu Rev Pharmacol Toxicol 52:321–336.

Volkow ND, Wang G-J, Fowler JS, Tomasi D, Telang F (2011) Addiction: beyond dopamine reward circuitry. Proc Natl Acad Sci U S A 108:15037–15042.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Sociodemographic data and personality scores expressed as means (standard deviation). The between-group comparisons (CD patients vs. controls) were conducted using independent-samples Student's t tests.

© 2016 Society for the Study of Addiction

13691600, 2017, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/adb.12356 by Universitat Autonoma De Barcelona, Wiley Online Library on [14/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License