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Trait impulsivity and prefrontal gray matter reductions in cocaine dependent individuals

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ABSTRACT

Background: Impulsivity is thought to play a key role in cocaine addiction onset and progression; therefore, we hypothesized that different facets of impulsive personality may be significantly associated with brain structural abnormalities in cocaine-dependent individuals.
Methods: Thirty-eight cocaine-dependent individuals and 38 non-drug using controls completed the UPPS-P scale (measuring five different facets of impulsivity: sensation seeking, lack of premeditation, lack of perseverance, and positive and negative urgency) and were scanned on a 3T MRI scanner. We used whole-brain voxel-based morphometry analyses (VBM) to detect differences in gray matter (GM) and white matter (WM) volumes between cocaine users and controls, and to measure differences in the way that impulsivity relates to GM and WM volumes in cocaine users vs. controls.
Results: Cocaine-dependent individuals had lower GM volumes in a number of sections of the orbitofrontal cortex, right inferior frontal gyrus, right insula, left amygdala and parahippocampal gyrus, temporal gyrus, and bilateral caudate. They also had lower WM volumes in the left inferior and medial frontal gyrus, superior temporal gyrus, right anterior cingulate cortex, insula and caudate. There was a positive correlation between trait impulsivity and GM volume in the left inferior/middle frontal gyrus of cocaine-dependent individuals, a pattern directly opposed to the association in controls. Conversely, in cocaine users lack of premeditation was negatively correlated with GM volume in the insula and the putamen.
Conclusions: Trait impulsivity may influence cocaine dependence by impacting its neurobiological underpinnings in frontostriatal systems.

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1. Introduction

Cocaine addiction is a worldwide major public health problem for which current prevention and treatment options are not fully satisfactory (EMCDDA, 2009; Substance Abuse and Mental Health Services Administration, 2010). Neuroimaging studies in cocaine-dependent individuals have revealed significant brain volume reductions, most notably in a priori selected regions of interest, such as the striatum, the amygdala or the prefrontal cortex (Barrós-Loscertales et al., 2011; Makris et al., 2004; Matochik et al., 2003; Tanabe et al., 2009). These regions are thought to contribute to critical aspects of the addictive cycle, including reinforcement learning, craving, and inhibitory control (Koob and Volkow, 2010). Nonetheless, the findings from nonbiased automated techniques, such as Voxel Based Morphometry (VBM), have yielded inconsistent results. Despite previous positive findings showing significant gray matter (GM) reductions in cocaine-dependent individuals, including the medial prefrontal cortex, superior temporal cortex, insula, thalamus and cerebellum (Franklin et al., 2002; Sim et al., 2007), a recent VBM study failed to detect any structural change (GM or white matter (WM) reductions) in cocaine users compared to non-drug using controls (Narayana et al., 2010). Perhaps more critically, most of these studies have failed to find any correlation between estimates of drug use patterns (e.g. amount, duration or age at onset) and GM and WM reductions (Franklin et al., 2002; Makris et al., 2004; Matochik et al., 2003; but see Ersche et al., 2011). This apparent lack of association between cocaine exposure and brain attrition raises the possibility that certain personality traits, such as impulsivity,

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may relate to GM and WM abnormalities in cocaine-dependent individuals.

Impulsivity is viewed as a multifaceted trait that varies normally across the population, but that in high levels may predispose to a range of dysfunctional behaviors, including addiction (Cyders et al., 2007; Verdejo-García et al., 2008). Animal studies have shown that increased impulsivity is associated with reduced dopamine receptors availability and cocaine use escalation and progression to dependence (Belin et al., 2008; Dalley et al., 2007). In humans, high levels of trait impulsivity (indexed with the Barratt Impulsivity Scale) are associated with lower midbrain dopamine autoreceptor binding, and greater amphetamine-induced dopamine release in the striatum (Buckholtz et al., 2010). In addition, trait impulsivity is negatively correlated with orbitofrontal cortex (OFC) GM volumes in healthy individuals (Matsuo et al., 2009). Nonetheless, in addicted individuals, continued use of stimulants is thought to further exacerbate impulsive traits (Ersche et al., 2010), and to possibly modify its neural underpinnings. In fact, the association between trait impulsivity levels and striatal dysfunction is stronger in methamphetamine-dependent individuals compared to healthy controls (Lee et al., 2009). Conversely, Ersche et al. (2011) failed to find significant correlations between particular aspects of trait impulsivity (impulsive reward-seeking) and GM reductions in cocaine-dependent subjects. Therefore, more studies are needed to specifically explore if, as expected, different facets of trait impulsivity are specifically linked to GM volumes in frontostriatal regions in cocaine-dependent individuals.

The aims of this study were (i) to use whole-brain VBM analyses to examine possible GM and WM reductions in a sample of currently abstinent (>1 month) cocaine-dependent individuals, as compared to a non-drug using control group; and (ii) to measure differences in the way impulsivity relates to GM and WM volumes in cocaine users vs. controls. Because impulsive personality in the normal population is negatively associated with GM volume in the OFC (Matsuo et al., 2009), which is also impacted by lifetime cocaine use (Alia-Klein et al., 2011), we expected cocaine-dependent individuals to have reduced GM volumes in the OFC and richly interconnected regions, such as insula, amygdala, striatum, and WM adjacent to these regions (Bechara, 2005). Because progression of cocaine use is thought to provoke neuroadaptations from the ventral striatum to the dorsal striatum, and from the OFC to more extensive prefrontal regions like the anterior cingulate and dorsolateral prefrontal cortex (Koob and Volkow, 2010), we expected impulsivity to be uniquely associated with more lateral aspects of the prefrontal cortex and more posterior aspects of the striatum in cocaine-dependent individuals.

2. Materials and methods

2.1. Participants

Thirty-eight cocaine-dependent individuals, mean age = 29.58, *SD* = 6.53, and 38 non-drug using controls, mean age = 31.08, *SD* = 5.14, participated in this study. All participants were male due to the low prevalence of women entering drug treatment during the recruitment period. Cocaine users were recruited in an inpatient therapeutic community ("Proyecto Hombre"), in the city of Granada, Spain. All of them reported cocaine as their main drug of choice and the one for which they requested treatment. Clinical interviews based on Diagnostic and Statistical Manual version IV (DSM-IV) criteria confirmed cocaine dependence diagnosis; nonetheless, they also had regular use of tobacco, alcohol, cannabis and MDMA (see Table 1). To enter the study, cocaine users had to be abstinent for at least 30 days (for any drug but tobacco), as confirmed by weekly urine tests; in this way, we could rule out acute and residual effects of previously used drugs on brain structure, with the exception of nicotine (84.2% of cocaine-dependent individuals and 44.7% of controls were current smokers). None of the cocaine patients were currently following pharmacological substitution treatments. Potential participants who had previously been diagnosed with any disorder from DSM-IV Axes I and II (other than substance dependence), or had neurological or systemic diseases affecting central nervous system (CNS) functioning were excluded.

Non-drug using controls were recruited through adverts distributed by a local employment agency, and therefore they were also matched to cocaine participants in terms of unemployment status. Selection criteria for control participants were: (i) absence of current or past substance use, excluding past or current social drinking (less than ten standard alcohol units per week); (ii) absence of documented major psychiatric disorders; (iii) absence of documented head injury or neurological disorder, and (iv) not being taking medication with effects on the CNS.

For both groups, evidence of stroke or space-occupying lesions observed on conventional clinical MR images, any contraindications to MRI scanning (including claustrophobia and implanted ferromagnetic objects), and history of loss of consciousness (LOC) for longer than 30 min or LOC with any neurological consequence were exclusionary.

2.2. Instruments and assessment procedures

The study was approved by the Ethics Committee for Research in Humans of the University of Granada. All participants signed an informed consent form certifying their voluntary participation. Controls, but not patients, received a €40 compensation for participating in the study. Assessments were conducted across two sessions separated by less than one week. During the first session we administered the Interview for Research on Addictive Behavior, the Hamilton Rating Scales for Depression and Anxiety (HAM-D and HAM-A), and the UPPS-P Impulsive Behavior Scale, along with a battery of cognitive tests of which results will be reported separately. The second session involved the MRI scanning. The MRI scans lasted approximately 6 min.

2.2.1. Patterns of drug use. Data regarding lifetime amount and duration of use of the different drugs was self-reported by participants and collected using the Interview for Research on Addictive Behavior (Verdejo-García et al., 2005). This interview provides an estimation of monthly use of each substance during regular use (amount per month) and total duration of use of each substance (in years). The descriptive scores for these variables in the sample are presented in Table 1.

2.2.2. Trait impulsivity. We used the Spanish version of the *UPPS-P Scale* (Verdejo-García et al., 2010; Whiteside and Lynam, 2001). This is a 59-item self-report inventory designed to measure five distinct personality pathways to impulsive behavior: sensation seeking, (lack of) perseverance, (lack of) premeditation, negative urgency, and positive urgency. The first 4 dimensions were included in the original version of the UPPS scale (Whiteside and Lynam, 2001); the fifth dimension has been included based on recent work by (Cyders et al., 2007; Smith et al., 2007). Sensation seeking (12 items) incorporates two aspects: (1) a tendency to enjoy and pursue activities that are exciting, and (2) an openness to trying new experiences that may or may not be dangerous; (lack of) perseverance (10 items) refers to the individual's ability to remain focused on a task that may be boring or difficult; (lack of) premeditation (11 items) refers to the tendency to think and reflect on the consequences of an act before engaging in that act; and finally urgency (12 items) refers to the tendency to experience strong impulses under conditions of negative affect (negative urgency, 12 items) or positive affect (positive urgency, 14 items). Each item on the UPPS is rated on a 4-point scale ranging from 1 (*strongly agree*) to 4 (*strongly disagree*). We obtained the total scores of each of these five UPPS-P dimensions for analysis (Table 2).

2.3. MRI acquisition

Participants were scanned on a 3T whole body MRI scanner (Phillips Achieva) operating with 8 channels phased-array head coil for reception. For each participant, a T1-weighted 3D volume was acquired using a T1-weighted 3D-turbo-gradient-echo sequence (3D-TFE), in sagittal orientation with $0.94 \times 0.94 \times 1.0$ mm resolution (160 slides, FOV = 240×240 mm^2, matrix $256 \times 256 \times 160$) with repetition time of 8 ms, echo time 4 ms, inversion delay = 1022.6264 ms, flip angle of 8°, band with 191 Hz/pixel. The sequence was optimal for reducing motion sensitivity, susceptibility artifacts and field inhomogeneities.

2.4. Image analysis

Before automatic preprocessing, the images were checked for artifacts and manually aligned to the AC-PC line. Data were processed and analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html), for which we used the default parameters. Thus, within a unified segmentation model (Ashburner and Friston, 2005), images were corrected for bias-field inhomogeneities, registered using linear (12 parameters affine) and non-linear transformations (warped), and tissue was clustered into GM, WM, and cerebrospinal fluid (CSF). Segments were further refined by using adaptive maximum a posteriori estimations, which account for partial volume effects, and by applying a hidden Markov random field model, as implemented in VBM8. Importantly, to preserve local GM/WM values, we multiplied the segments by the Jacobian determinants of the deformation field to create modulated images. Segments were smoothed by an 8 mm full-width at half-maximum (FWHM) using an isotropic Gaussian kernel. Afterwards, we conducted analysis on modulated GM and WM segments.

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Table 1
Descriptive information about patterns of drug use in cocaine-dependent individuals.

Substance	Ever used (%)	Unit	Amount per month	Duration of use	Abstinence
Cocaine	100	# grams	18.92 ± 29.46	4.05 ± 3.07	36.76 ± 22.60
Cannabis	76.31	# joints	109.90 ± 111.40	2.35 ± 3.17	147.45 ± 203.66
MDMA	50	# tablets	9.29 ± 10.12	2.27 ± 1.90	227.68 ± 225.78
Alcohol	100	# SAU	107.58 ± 114.03	7.38 ± 5.77	33.11 ± 21.77
Tobacco	86.8	# cigarettes	488.48 ± 307.40	9.19 ± 7	7.8 ± 15.82

Note: Mean ± standard deviation of the mean. Duration of use is expressed in years. Abstinence duration is expressed in number of weeks.

Table 2
Descriptive scores – means and standard deviations (in parentheses) of cocaine users and non-drug using controls in the five UPPS-P dimensions.

UPPS-P dimensions	Cocaine-dependent individuals	Non-drug using controls	Test
Negative urgency	31.45 (6.79)	23.16 (6.99)	(t_{46} = 5.14, p = 0.000)
Positive urgency	32.91 (8.79)	21.66 (7.63)	(t_{46} = 5.86, p = 0.000)
Lack of premeditation	23.83 (5.95)	21 (3.68)	(t_{46} = 2.46, p = 0.016)
Lack of perseverance	21.26 (4.42)	18.84 (3.63)	(t_{46} = 2.56, p = 0.013)
Sensation seeking	30.63 (8.73)	29.89 (7.37)	(t_{46} = 0,34, p = 0.73)

2.4.1. Global effects of patterns of drug use. Total gray and white matter volumes (TGMV, TWMV) were computed by adding up the voxel values of GM/WM segments, including cerebellum and sub-cortical structures. Next, the total brain volume (TBV = TGMV + TWMV) was used for computing the TGMV/TBV ratios, which served to evaluate the global effects of patterns of drug use on brain tissue volumes using the backward step-wise procedure in the general linear model, including as predictors age, years of education, cocaine amount per month during regular use, duration of cocaine use, and age of onset of cocaine use. *t*-Tests were used to estimate the significance of the regression parameters. Significance threshold was set at $p < 0.05$.

2.4.2. Regional GM and WM differences between cocaine-dependent individuals and non-drug using controls. The general linear model implemented in SPM8 was used to conduct voxel-wise comparisons between cocaine-dependent individuals and controls, and to determine the relationship between consume severity factors (i.e. amount, duration and age of onset) and regional GM and WM volume variations in cocaine-dependent individuals. In both analyses the total volume of GM, or WM, was modeled as a linear confound in order to account for residual global volume variability. The significance threshold was set at $p < 0.05$ after family-wise correction for multiple comparisons (pFWE < 0.05). Significant peaks from the *t*-test maps are given in MNI space.

2.4.3. Regional relationships between GM and WM and measures of impulsivity and estimates of drug use. We performed SPM8 multiple regression analysis, in which we tested the significances of the Group (cocaine-dependent individuals vs. controls) x UPPS-P dimensions interactions across the entire brain. We only included the UPPS-P dimensions showing significant differences between the groups. The differences in the regression coefficients as a function of group were tested using a significance threshold of $p < 0.05$ after family-wise correction for multiple comparisons (pFWE < 0.05).

3. Results

3.1. Participants' characteristics

Both groups were matched on gender, ethnicity and language, and had statistically equivalent distributions for age. Controls, compared to cocaine-dependent individuals, had more years of education [(M = 17.58, SD = 4.56) vs. (M = 12.03, SD = 3.62)]; but analysis including education as a covariate did not alter the results. Cocaine-dependent individuals had greater scores for depression [(M = 5.08, SD = 3.98) vs. (M = 1.32, SD = 2.15)] and anxiety [(M = 7.05, SD = 6.40) vs. (M = 1.29, SD = 2.29)], but on average both groups were below cut-offs for clinical significance.

3.2. Trait impulsivity

Cocaine-dependent individuals had higher scores than controls across the five dimensions of the UPPS-P Scale. *t*-Tests showed these differences were significant for lack of premeditation (t = 2.46, p = 0.016, Cohen's d = 0.6), lack of perseverance (t = 2.56, p = 0.013, Cohen's d = 0.6), negative urgency (t = 5.14, p = 0.000, Cohen's d = 1.2), and positive urgency (t = 5.86, p = 0.000, Cohen's d = 1.4). We found no significant differences for sensation seeking, such that this dimension was not further used in the subsequent analysis.

3.3. Imaging analysis

3.3.1. Global effects. For cocaine-dependent individuals, the TGMV/TBV ratio variability was accounted for by monthly cocaine intake during regular use, $t(34) = 2.19$, $p = 0.035$, and age of onset, $t(34) = -2.33$, $p = 0.026$; the effect of duration of cocaine use also showed a trend to significance, $t(34) = -1.80$, $p = 0.080$. These variables explained about a 32% of the variability in TGMV/TBV ratios, $F(3,34) = 5.21$, $p = 0.005$. Noteworthy, higher amounts of cocaine ($r = 0.41$, $p = 0.01$) and younger age of onset of cocaine use ($r = -.34$, $p = 0.04$) were associated with larger TGMV/TBV. The first result is associated with a significant decrease in WM volumes (TWMV-amount of cocaine: $r = 0.43$, $p = 0.006$), but the second showed a trend in relation to reductions in GM (TGMV-age of onset of cocaine abuse: $r = -0.18$, NS).

3.3.2. Regional GM and WM differences between cocaine-dependent individuals and non-drug using controls. The cocaine group had significantly lower GM and WM volumes than controls. Cocaine-dependent individuals showed lower GM volumes in a number of sections of the OFC (left superior and medial frontal gyrus), right inferior frontal gyrus, right insula, left amygdala and parahippocampal gyrus, left inferior and middle temporal gyrus, and bilateral caudate (Table 3 and Fig. 1). Likewise, cocaine dependent-individuals showed lower WM volumes in the left inferior and medial frontal gyrus, superior temporal gyrus, right anterior cingulate cortex, insula and caudate (Table 4 and Fig. 2).

3.3.3. Regional relationships between GM and WM and measures of impulsivity and estimates of drug use. We found a number of regions in which GM volumes showed differential associations with the impulsivity dimensions of lack of premeditation and negative urgency; in all cases, there was a significant Group x Impulsivity interaction (see Table 5). The associations between impulsivity levels and GM volumes were significantly different for cocaine-dependent individuals vs. controls in the left inferior frontal gyrus, right insula and left putamen (in relation to lack of premeditation), and left middle frontal gyrus and sub-gyral (in relation to negative urgency). Left inferior frontal gyrus was positively associated with lack of premeditation in cocaine users, whereas it was negatively correlated with this dimension in controls. Conversely, right insula

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Table 3
Summary of the results obtained by the gray matter voxel-wise analysis of volume reductions in cocaine-dependent individuals and non-drug using controls.

Anatomical region	*k*	Anatomical labels for peaks	BA	*T*	*p*	*x*	*y*	*z*
Frontal Lobe	3342	L Medial Frontal Gyrus	11, 10	5.81	0.004	−9	27	−13
		Cingulate Gyrus	32, 25, 24	5.75	0.005			
Frontal Lobe	2802	R Inferior Frontal Gyrus	47, 11, 34	6.39	0.000	28	21	−15
Caudate		R Caudate Head		5.53	0.010	9	19	−15
Caudate	1118	L Caudate Head		5.52	0.010	6	−1	3
Limbic Lobe/Parahippocampal Gyrus	972	L Amygdala/Hippocampus		6.42	0.000	−33	−7	−19
Sub-Lobar	581	R Insula	13	5.81	0.004	52	−19	23
Temporal Lobe	3095	L Middle/Inferior Temporal Gyrus	21, 22, 20	5.98	0.002	−56	−14	−18

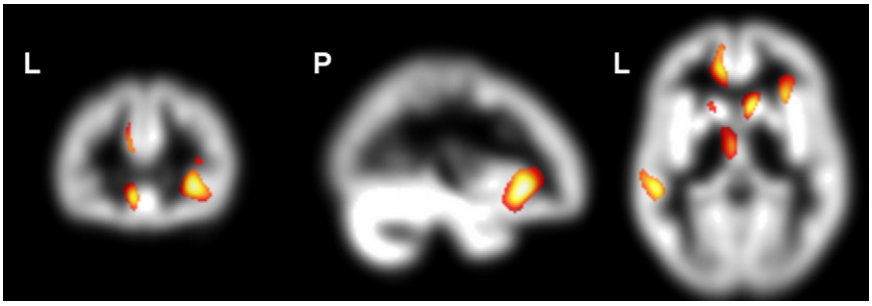

Fig. 1. Brain regions showing significant gray matter decreases in cocaine-dependent individuals with respect to non-drug using controls.

Table 4
Summary of the results obtained by the white matter voxel-wise analysis of volume reductions in cocaine-dependent individuals and non-drug using controls.

Anatomical Region	*k*	Anatomical Labels for peaks	*T*	*p*	*x*	*y*	*z*
Frontal Lobe	1181	L Inferior Frontal Gyrus Sub-Gyral	6.07	0.001	−26	18	−17
Frontal Lobe	623	L Medial Frontal Gyrus	5.46	0.003	−20	57	−3
Temporal Lobe	389	L Superior Temporal Gyrus	5.24	0.007	−48	−25	−3
Frontal Lobe	1651	R Anterior Cingulate R Medial Frontal Gyrus Caudate	6.81	0.001	7	33	−15
Sub-Lobar	1531	Extra-Nuclear Lentiform Nucleus Insula	5.86	0.001	12	12	−3
Temporal Lobe	674	R Superior Temporal Gyrus R Transverse Temporal Gyrus	5.82	0.001	46	−26	12

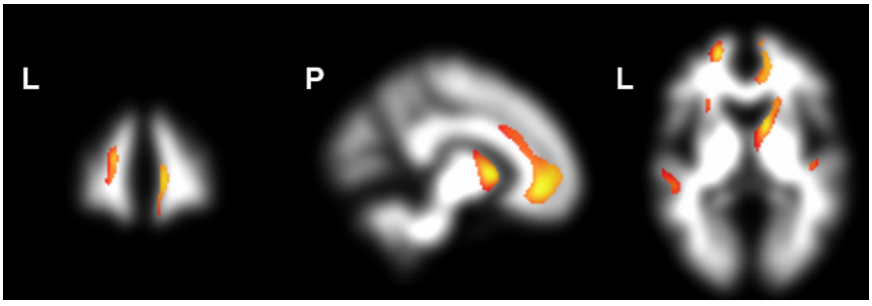

Fig. 2. Brain regions showing significant white matter decreases in cocaine-dependent individuals with respect to non-drug using controls.

Table 5
Regression slopes showing different associations between impulsivity and gray matter volumes between cocaine-dependent individuals (CDI) and non-drug-using controls (NDC) (pFWE = 0.05).

Anatomical region	*k*	Anatomical Label	BA	*p* (*β*)	Slopes	Volume	*x*	*y*	*z*
Lack of premeditation									
Sub-lobar	179	R Insula	BA 47/BA	0.02	CDI−/NDC+	CDI < NDC	30	10	−3
	358	L Putamen	13	0.05	CDI−/NDC+	CDI < NDC	−21	10	−4
Fontal Lobe	249	L Inferior Frontal Gyrus	BA 10	0.005	CDI+/NDC−	CDI < NDC	−37	41	1
Negative urgency									
Frontal	228	L Middle Frontal Gyrus	BA10/46	0.038	CDI+/NDC−	CDI < NDC	−39	37	19
Lobe	381	R Sub-Gyral	BA 8	0.024	CDI+/NDC−	CDI < NDC	25	24	36

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and left putamen were negatively correlated with lack of premeditation in cocaine users, but did not correlate with this dimension in controls. With regard to negative urgency, the sub-gyral showed significant positive correlations in the cocaine group, whereas the association was negative in controls. Finally, in the case of the left middle frontal gyrus, none of the slopes significantly differed from zero, but the trend was positive in cocaine-dependent individuals, and negative in controls.

We did not find significant associations between WM volumes and the different dimensions of impulsivity in the cocaine or control groups.

Finally, we did not find significant associations between the main patterns of drug use (amount, duration and age of onset of cocaine abuse) and GM and WM volumes.

4. Discussion

Our results showed that cocaine-dependent individuals, compared to controls, have lower GM volumes in the OFC cortex, anterior cingulate, inferior frontal gyrus, insula, amygdala, temporal gyrus, and caudate. We also found WM reductions in adjacent regions of the anterior cingulate, inferior/middle frontal gyrus, insula and putamen. As expected, we found significant differences in the way that impulsivity dimensions correlates with GM volumes in cocaine users vs. controls: cocaine patients had elevated levels of trait impulsivity, and these scores were differentially associated with GM volumes in the left inferior frontal gyrus, insula and putamen (lack of premeditation), and left middle frontal gyrus (negative urgency). Inferior and medial superior frontal clusters positively correlated with impulsivity in cocaine users, and negatively in controls; conversely, insula and putamen correlated negatively with impulsivity in cocaine patients and showed no correlations in controls. These results point to a distinctive link between trait impulsivity and regional GM among cocaine-dependent individuals, which specifically relates to frontostriatal systems regions. The measures of patterns of cocaine use correlated with general indices of GM/TBV ratios but had no significant influence on GM volumes at the stricter voxel level. Overall, our findings are in agreement with the notion that GM reductions in cocaine-dependent individuals are at least partly mediated by trait impulsivity.

Our findings of GM reductions in cocaine-dependent individuals are largely consistent with previous neuroimaging studies in revealing structural abnormalities in brain regions relevant to reinforcement learning (amygdala, OFC) and inhibitory control (anterior cingulate, inferior frontal gyrus, insula and caudate) (Ersche et al., 2011; Franklin et al., 2002; Makris et al., 2004; Matochik et al., 2003). Recent findings from fMRI connectivity analyses also provide support to the notion that neural networks connecting the medial frontal cortex with paralimbic and temporal regions are significantly less functional in cocaine users (Gu et al., 2010). Biological abnormalities in these regions are thought to underlie psychological alterations leading to overestimation of the motivational relevance of drug-related reinforcement (the impulsive system) and to breakdown of inhibitory processes necessary to achieve long-term abstinence (the reflective system) (Bechara, 2005; Goldstein and Volkow, 2002; Redish et al., 2008; Verdejo-García and Bechara, 2009). These alterations are proposed to anchor pervasive drug taking in the face of increasing aversive consequences, one of the key features of addiction (DSM-IV).

A key unresolved issue is that if these structural abnormalities are reflective of cocaine induced brain attrition, or are related to personality traits, or reflect a combination of both factors. Our findings, in agreement with growing neuroscience evidence, are supportive of the impact of personality traits. However, these traits may interact with cocaine use in producing GM alterations, as suggested by the global TGMV analysis. Recent studies indicate that, in healthy individuals, impulsivity is negatively correlated with midbrain and striatal D2/D3 receptors availability (Buckholtz et al., 2010; Lee et al., 2009), but this association is stronger in methamphetamine dependent individuals (Lee et al., 2009) and correlates with amphetamine-induced dopamine release in the striatum (Buckholtz et al., 2010). Striatal D2 availability is associated with metabolic rate in the prefrontal cortex of psychostimulant users (Volkow et al., 2001). Therefore, different strands of evidence indicate that frontostriatal systems mediate impulsive behavior and thereby promote psychostimulant addiction. Nonetheless, we acknowledge that these issues can only be tested by longitudinal imaging studies in individuals at high risk of developing psychostimulant dependence, or by gene association imaging studies (Kreek et al., 2005; Verdejo-García et al., 2008).

In accordance with the notion that impulsivity is a multifaceted construct (Smith et al., 2007; Whiteside and Lynam, 2001), our results showed differential links between impulsivity dimensions and GM volumes. Lack of premeditation was positively associated with left inferior frontal gyrus GM in cocaine users but not controls. This region is importantly involved in the representation of expected values (Bermpohl et al., 2010); such that persistent stimulation by drug-expected rewards could have induced GM enlargements linked to an increased tendency to rapidly engage in non-adequately forethought behavior. On the other hand, both insula and putamen have been involved in drug-related neuroadaptations related to attentional bias and craving (Childress et al., 2008; Luijten et al., 2011; Volkow et al., 2006), such that reduced volumes may predict increased prepotency of drug-related action tendencies. On the other hand, negative urgency was positively associated with GM in subgyral BA 8 in cocaine users, negatively in controls. This region has been previously associated with the experience of uncertainty (Volz et al., 2003), which is a key aspect of the associative learning processes mediating expected drug effects (D'Souza and Duvauchelle, 2008). In fact, adjacent regions of the medial frontal gyrus (BA 10) display increased activation during uncertain outcome selection in psychostimulant users (Leland et al., 2006). Therefore, in this case the rationale could be similar to that posited for inferior frontal gyrus; repeated exposure to uncertainty-loaded scenarios may be associated with increased subgyral volumes and higher risk to trigger impulsive acts when under emotionally uneasy conditions. Remarkably, in both dimensions (lack of premeditation and urgency) there was a positive correlation between trait impulsivity and GM volume in the inferior/middle frontal gyrus of cocaine-dependent individuals, a pattern directly opposed to the association in controls. Given that GM in these regions is reduced in cocaine users, one may speculatively argue that high impulsivity may render some cocaine users more similar to controls. Nonetheless, given the role of these regions in emotional valuation, greater GM in these areas may hold specific emotional motives in cocaine users: high impulsive individuals, with greater GM in inferior/middle frontal gyrus, might be – for example – highly sensitive to craving (Garavan et al., 2000). More research is warranted to resolve this issue.

Strengths of this study include the adequate sample size, the sound clinical characterization and the agreement between results from the different analytical approaches (between-group differences and regressions testing the link between impulsivity and GM). On the other hand, we should also acknowledge a number of limitations. The cross-sectional design precludes us from drawing conclusions about the causality of GM deficits; one way out of addressing this issue would be by using longitudinal designs, but these studies are costly and convey important ethical concerns and methodological complexities. Furthermore, we cannot completely rule out the influence of depression and anxiety levels, although they were on average below the cut-off for clinical

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significance and they had very low impact on regression models when included. Finally, although we discuss our results as pertaining to cocaine dependence, polysubstance abuse is almost ubiquitous among cocaine-dependent individuals. However, the current sample was carefully selected for relative specificity of cocaine related problems and low use of other drugs. The illegal drugs more frequently and intensely co-abused in the sample were cannabis and MDMA, but estimates of the use of these drugs failed to predict regional GM.

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Contributors

Laura Moreno-López and Antonio Verdejo-García have worked in the conception and design of the manuscript. Andrés Catena has carried out the analysis and interpretation of the data as well as the revision of the manuscript. María José Fernández-Serrano, Elena Delgado-Rico and Miguel Pérez-García have contributed to the revision of the manuscript.

Conflict of interest

The authors declare that, except for income received from their primary employer, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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