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*Published in:*  
Drug and Alcohol Dependence

*DOI:*  
[10.1016/j.drugalcdep.2014.09.016](https://doi.org/10.1016/j.drugalcdep.2014.09.016)

[Link to publication](#)

*Citation for published version (APA):*

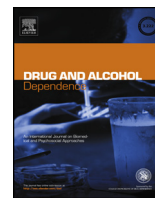
Kaag, A. M., Crunelle, C. L., van Wingen, G. A., Homberg, J., van den Brink, W., & Reneman, L. (2014). Relationship between trait impulsivity and cortical volume, thickness and surface area in male cocaine users and non-drug using controls. *Drug and Alcohol Dependence*, 144, 210-217. <https://doi.org/10.1016/j.drugalcdep.2014.09.016>

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Full length article

## Relationship between trait impulsivity and cortical volume, thickness and surface area in male cocaine users and non-drug using controls



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### ARTICLE INFO

#### Article history:

Received 25 June 2014

Received in revised form 3 September 2014

Accepted 12 September 2014

Available online 22 September 2014

#### Keywords:

Addiction

Cocaine dependence

Cortical thickness

Cortical surface area

Cortical volume

Impulsivity

### ABSTRACT

**Background:** Trait impulsivity is commonly associated with cocaine dependence. The few studies that have investigated the relation between trait impulsivity and cortical morphometry, have shown a distinct relation between impulsivity and cortical volume (CV) of temporal, frontal and insula cortex. As CV is the function of cortical surface area (SA) and cortical thickness (CT) impulsivity may be differently associated to SA than to CT.

**Method:** Fifty-three cocaine users (CU) and thirty-five controls (HC) (males aged 18–55 years) completed the Barrat impulsiveness scale and a structural scan was made on a 3T MRI scanner. CV, SA and CT were measured using Freesurfer. Multivariate analysis was used to test for group differences and group by impulsivity interaction effects in CV, SA and ST across nine regions of interest in the temporal, frontal and insular cortices. Possible confounding effects of drug- and alcohol exposure were explored.

**Results:** Compared to HC, CU had a smaller SA of the superior temporal cortex but a larger SA of the insula. There were divergent relations between trait impulsivity and SA of the superior temporal cortex and insula (positive in HC, negative in CU) and CT of the anterior cingulate cortex (negative in HC, positive in CU). Within CU, there was a negative association between monthly cocaine use and CT of the insula and superior temporal cortex.

**Discussion:** The distinct relation between trait impulsivity and cortical morphometry in CU and HC might underlie inefficient control over behavior resulting in maladaptive impulsive behaviour such as cocaine abuse.

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## 1. Introduction

High impulsivity is associated with cocaine addiction (Bolla et al., 2000; Coffey et al., 2003) and thought to be causally linked to the development of addiction (Belin et al., 2008; Crews and Boettiger, 2009; Everitt, 2014; Verdejo-García et al., 2008). Cocaine users commonly show higher scores on the Barrat impulsiveness scale (BIS-11), the most frequently used self-report instrument to assess trait impulsivity (Stanford et al., 2009). Moreover, voxel-based morphometry (VBM) studies have shown smaller volumes

of the striatum, prefrontal cortex, temporal cortex and insula, in cocaine users compared to controls (Ersche et al., 2011; Franklin et al., 2002; Moreno-López et al., 2012; Weller et al., 2011). These regions, in particular the circuit including the insula and the prefrontal cortex, play an important role in the control over impulsive behaviour in addiction (Bari and Robbins, 2013; Jentsch and Taylor, 1999; McHugh et al., 2013; Noël et al., 2013). Unfortunately, only few VBM studies directly investigated the relation between cortical morphometry and trait impulsivity in cocaine users and controls. These studies reported a positive correlation between trait impulsivity and the volume of the prefrontal cortex in cocaine users (Crunelle et al., 2014; Ersche et al., 2011; Moreno-López et al., 2012) but a negative correlation in controls (Matsuo et al., 2009; Moreno-López et al., 2012; Schilling et al., 2012). These studies also reported a negative correlation between trait impulsivity and the volume of the insula and temporal cortex in cocaine users (Ersche et al., 2011;

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Moreno-López et al., 2012) but a positive correlation in controls (Cho et al., 2013; Moreno-López et al., 2012). Together these studies suggest a distinct (opposing) relation between trait impulsivity and cortical structure of the insula, temporal and frontal cortices in cocaine users and non-drug using controls.

However, all above-mentioned studies focused on measures of cortical volume (CV) using VBM, while surface-based morphometry (SBM) allows to measure cortical thickness (CT) and cortical surface area (SA), in addition to CV. Since CV is the function of CT and SA, only assessing CV may obscure individual differences. More importantly, SA and CT carry distinct characteristics which are driven by different genetic (Eyler et al., 2012; Panizzon et al., 2009; Winkler et al., 2010) and cellular processes (Chenn and Walsh, 2002). While SA is thought to reflect the number and spacing of cortical columns, CT relates to the neuronal density (Casanova and Tillquist, 2008; La Fougère et al., 2011; Rakic, 2009). Therefore, SBM studies can provide additional information on the origin of cortical abnormalities previously shown in cocaine users and the distinct relation between impulsivity and cortical morphometry in cocaine users and controls. So far, only two SBM studies reported a thinner cortex of the dorsolateral prefrontal and insula in cocaine users compared to controls (Makris et al., 2008; Tanabe et al., 2012). These studies did not, however, include measures of SA or measures of (trait) impulsivity.

The current study was designed to investigate the distinct relation between trait impulsivity, as measured by the BIS-11, and cortical morphometry in cocaine users and non-drug using controls by means of SBM. Because previous VBM studies have shown a relation between impulsivity and the cortical morphometry of the insular cortex, subregions of the temporal cortex (superior, middle and inferior) and subregions of the prefrontal cortex (superior, middle, inferior, orbitalfrontal and anterior cingulate; Cho et al., 2013; Crunelle et al., 2014; Ersche et al., 2011; Matsuo et al., 2009; Moreno-López et al., 2012; Schilling et al., 2012), all nine (sub)regions were regarded to be regions of interest (ROIs) in the current SBM study. To test for cortical differences specifically within this “impulsivity” network, a multivariate region of interest approach, instead of a univariate whole brain approach, was used. Because CT and SA of the ROIs are influenced by different (genetic and environmental) factors (Eyler et al., 2012; Panizzon et al., 2009; Winkler et al., 2010) we expected CT and SA in these ROIs to show different associations with impulsivity. As cocaine dependence and impulsivity are largely genetically determined (Crews and Boettiger, 2009; Everitt et al., 2008; Murray et al., 2014; Verdejo-García et al., 2008), while drug- and alcohol exposure among cocaine users represents an important environmental factor, we expected the relation between trait impulsivity and cortical morphometry to differ between cocaine users and controls. Finally, it should be noted that cocaine users often report extensive use of alcohol and cannabis (Brecht et al., 2008). Therefore, we also explored the relation between poly-drug use (cocaine, alcohol, cannabis, nicotine) and cortical morphometry.

## 2. Materials and methods

### 2.1. Participants

Fifty-three regular cocaine users and 35 non-drug using controls (all males aged 18–55 years) were recruited through local advertisement in the metropolitan area of Amsterdam, the Netherlands. As cocaine use is twice as high among males compared to females (EMCDDA, 2009) only males were included in the current study. Data on a subsample (30 cocaine users and 33 controls) were reported elsewhere (Crunelle et al., 2014). Cocaine users were actively using cocaine and currently non-treatment seeking.

**Table 1**

Clinical characteristics of non-drug using controls(HC) and regular cocaine users (CU).

	HC (n = 35)	CU (n = 53)	p-Value
Age <sup>a</sup>	33 ± 19	31 ± 12	0.436
IQ <sup>a</sup>	106 ± 10	104 ± 12	0.099
Trait impulsivity (BIS) <sup>b</sup>	60 ± 6.7	73 ± 9.5	<0.001
Alcohol use (units per week) <sup>a</sup>	5 ± 9	24 ± 21	<0.001
Nicotine use (amount of smokers)	5.7%	76%	
FTND score for smokers <sup>a</sup>	2.5 ± 0.7	5 ± 4	0.101
Secondary cannabis use (>once a week)		28%	<0.001
Cocaine dependence <sup>c</sup>		89%	
Years of cocaine use <sup>a</sup>		8 ± 6	
Onset age of cocaine use <sup>a</sup>		19 ± 4	
Grams of cocaine use per month <sup>a</sup>		7.6 ± 8	

<sup>a</sup> Values represent medians ± interquartile range.

<sup>b</sup> Values represent mean ± standard deviation.

<sup>c</sup> According to DSM-IV criteria.

Cocaine users were included when using cocaine regularly, i.e., at least once per week for a minimum period of 6 months. Cocaine users also reported regular use of tobacco, alcohol and cannabis (Table 1). All participants were psychiatrically evaluated using the MINI Neuropsychiatric Interview (Sheehan et al., 1998). Controls were excluded if they met criteria for drug- or alcohol dependence according to DSM-IV or were using prescribed or illicit drugs. Exclusion criteria were: major medical or neurological disease, lifetime history of psychotic or bipolar disorder or the presence of any contraindication to MRI scanning, medication use, neurological disorder and previous head trauma.

The study was approved by the Ethical review Board of the Academic Medical Center of the University of Amsterdam, the Netherlands. All subjects gave written informed consent.

### 2.2. Clinical assessment

Life-time drug use (cocaine, alcohol, cannabis, ecstasy, speed, opiates and sedatives) was documented prior to study inclusion using in-house drug use questionnaires and cocaine dependence was diagnosed according to DSM-IV criteria using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). The Fagerström Test for Nicotine Dependence (FTND) served as an indicator of nicotine dependence severity (Heatherton et al., 1991). Trait impulsivity was assessed using the BIS-11 (Patton et al., 1995).

### 2.3. MRI data collection and analyses

Images were acquired on a 3.0-T whole body MR scanner (Philips Achieva) with a 32 channel SENSE head coil. Three-dimensional T1-weighted images with the following parameters: repetition time (TR) = 8.24 ms, echo time (TE) = 3.79 ms, flip angle = 8°, slice thickness = 1 mm, scan resolution = 240 mm × 240 mm, field-of-view (anterior–posterior/feet–head/right–left) = 240/240/220 mm, and voxel size = 1 mm<sup>3</sup>.

Cortical reconstruction and volumetric segmentation were performed with the Freesurfer (v5.0) image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures are described in previous publications (Dale, 1999; Fischl and Dale, 2000; Fischl, 2004; Han et al., 2006; Jovicich et al., 2006; Reuter et al., 2012). In short, processing includes skull-stripping, automated Talairach transformation, segmentation of the (sub)cortical gray and white matter, intensity normalization, tessellation of the gray matter-white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. The segmented

images were manually checked, but no segmentation or registration inconsistencies were detected in the ROIs.

Of each participant, CV, SA, and CT of the nine predefined cortical ROIs and total intracranial volume (ICV) were calculated. ROIs were defined using the Desikan–Killiany atlas implemented in Freesurfer (Desikan et al., 2006). The ROIs included the left and right prefrontal cortex (inferior, middle, superior and medial/lateral orbital frontal cortex and the rostral/caudal anterior cingulate cortex), temporal cortex (inferior, middle and superior temporal cortex) and the insula. The mean absolute correlation between the left and right ROIs was  $r=0.68$  (range: 0.40–0.87) for CV,  $r=0.68$  (range: 0.33–0.86) for SA and  $r=0.67$  (range: 0.54–0.83) for CT. As we had not hypothesis on lateralized effects and to reduce the number of comparisons, the mean SA, CT and CV of the left and right ROIs was calculated and used in further analysis.

#### 2.4. Statistical analyses

Group differences in clinical characteristics were assessed using independent-samples *T*-tests or non-parametric tests when appropriate in SPSSv20 (Statistical Package for the Social Sciences). Correlations between clinical assessments were analyzed using partial correlations with age as a covariate. Data are presented as means  $\pm$  standard deviations (SD) or as median  $\pm$  interquartile range (IQR) where appropriate. A *p*-value  $<0.05$  was considered statistically significant.

To examine the (relative) independence between SA and CT, we have calculated the mean of the (absolute) correlations between SA and CT of all ROIs. The same was done for the correlations of CV with SA and CT.

The three subscales of the BIS-11 (attentional impulsiveness, motor impulsiveness and non-planning impulsiveness) in this current sample were highly correlated (Pearson's correlation coefficients ranging from  $r=0.71$  to  $r=0.76$ ) and, therefore, no subscale specific results were to be expected. Therefore the total score of the BIS was used in all statistical tests.

The effect of impulsivity on cortical morphometry was tested using a multivariate analyses of covariance (MANCOVA). Age and ICV were included as a covariates in accordance to previous studies (Durazzo et al., 2011). Because average total CT has also been used as a covariate in CT analyses (Makris et al., 2008), the analysis on CT was repeated using average CT instead of ICV as a covariate, to test for possible confounding effects. The main effects of group and impulsivity, as well as a group by impulsivity interaction was modelled to test if a correlation between trait impulsivity and cortical structure of the ROIs was different between cocaine users and controls. Three MANCOVAs were conducted to test for group differences: one for CV, one for SA and one for CT. Three similar MANCOVAs were conducted within cocaine users to explore the effects of impulsivity and the degree of cocaine exposure (years used, grams of cocaine used per month, onset age), alcohol use (glasses a week) and nicotine dependence (FTND), correcting for age and ICV. In an additional exploratory analysis, cocaine users were subdivided into a group that only used cocaine and a group that used both cocaine and cannabis on a regular basis ( $>$ once a week). Subsequently these groups were compared to non-drug using controls and to each other, correcting for age and ICV.

Only significant multivariate test results were followed by post-hoc ANCOVA's on all ROI (correcting for age and ICV). In case of significant group by impulsivity interactions, significant multivariate test results were also followed by partial correlation analysis (correcting for age and ICV) to test for the direction of the correlation between impulsivity and cortical structure within each group. All significant post-hoc tests were corrected for multiple comparisons using the D/AP (Dubey and Armitage–Parmar) approach in which a Bonferonni correction is adjusted for the mean

correlation between the ROIs (Sankoh et al., 1997; Zhang et al., 1997). The corrected alpha value is calculated using the following formula:  $p_{\text{adjusted}} = 1 - (1 - p(k))^{m(k)}$ , where  $m(k) = M^{1-r(k)}$ , in which  $p(k)$  is the unadjusted alpha (0.05),  $M$  = the number of outcomes being tested,  $r(k)$  = the mean correlation between the outcomes. In this study the mean correlation between CV, SA and CT is 0.650, 0.637, 0.502, respectively, the number of outcomes is 9, thus the adjusted *p*-values corrected for multiple comparison are 0.023 for CV and SA and 0.017 for CT.

To explore differences in cortical morphometry outside the ROIs, a whole brain analysis was performed using Freesurfer's QDEC, with a false-discovery rate (FDR) of  $q=0.05$  for cluster-wise correction to account for multiple comparisons.

### 3. Results

#### 3.1. Sample characteristics

The means (or medians) and standard deviations (or inter quartile ranges) of the sample characteristics are presented in Table 1. Cocaine users and controls were of similar age and IQ. Cocaine users reported higher total BIS-11 scores and weekly alcohol intake. On average, duration of cocaine use was  $8.0 \pm 5.0$  years (median  $\pm$  IQR), starting regular use at the age of  $19.0 \pm 4.0$  years, using on average  $7.6 \pm 8.0$  g of cocaine per month. 28% of the cocaine users also used cannabis on a regular basis (at least once a week). There were no differences in clinical characteristics between cocaine users with and without secondary cannabis use. There was no use of illicit drugs in the control group. Total BIS-11 score in cocaine users (corrected for age) was unrelated to monthly cocaine use, years of cocaine use, age at onset of cocaine use, alcohol use or FTND scores.

#### 3.2. Relationship between GM structure, trait impulsivity and substance use between and within groups

Correlations between the three structural brain parameters of the nine ROIs varied considerable: no (linear) association found between SA and CT (mean absolute  $r=0.08$ , range:  $-0.20$ – $0.12$ ), modest linear association between CT and CV (mean  $r=0.45$ , range 0.34–0.58) and a strong linear association between SA and CV (mean  $r=0.87$ , range:0.83–0.87).

**Cortical volume:** The MANCOVA on CV indicated that there was a main effect of group across all ROIs (see Table 2 for all MANCOVAs and post-hoc test-statistics). Post-hoc ANCOVAs showed that cocaine users had significantly smaller CV of the superior temporal cortex, although this finding did not remain significant after correction for multiple comparisons. There was no main effect of impulsivity and no significant group by impulsivity interaction on CV across the ROIs.

The MANCOVA within cocaine users indicated that neither impulsivity nor cocaine, alcohol or nicotine use was a significant predictor of CV (see Table 3 for all within group MANCOVA test-statistics).

**Cortical surface area:** The MANCOVA on SA indicated that there was a main effect of group and a group by impulsivity interaction across all ROIs (Table 2). Post-hoc ANCOVAs showed a main effect of group and a significant group by impulsivity interaction in the insula (Fig. 1A). Partial correlation analysis, adjusted for age and ICV, showed a positive but non-significant relation between SA of the insula and impulsivity in controls whereas it showed a trend towards a negative correlation in cocaine users, which was not influenced by cocaine exposure. In addition, cocaine users showed significant larger SA of the insula compared to controls, although the difference was very small. Post-hoc ANCOVAs further showed a main effect of group and a group by impulsivity interaction in the



**Table 2**  
Between group MANCOVA and post-hoc ANCOVA test results.

Measure and group	Size <sup>a</sup>		Main effect group			Group by impulsivity interaction				
	HC	CU	Statistic	p	$\eta^2$	Statistic	p	$\eta^2$	R(HC) <sup>b</sup>	R(CU) <sup>b</sup>
Volume (mm <sup>3</sup> )										
MANCOVA <sup>c</sup>			$F_{9,74} = 2.11$	0.04	0.20	$F_{9,74} = 1.85$	n.s.	0.18		
ANCOVA <sup>d</sup>										
Superior temporal cortex	12501 ± 279	12312 ± 167	$F_{1,82} = 4.70$	0.03*	0.05					
Middle temporal cortex	11936 ± 262	11760 ± 157	$F_{1,82} = 2.35$	n.s.	0.03					
Inferior temporal cortex	11198 ± 363	10488 ± 218	$F_{1,82} = 1.59$	n.s.	0.00					
Super frontal cortex	23588 ± 528	23519 ± 304	$F_{1,82} = 1.07$	n.s.	0.01					
Middle frontal cortex	23536 ± 515	22701 ± 309	$F_{1,82} = 0.32$	n.s.	0.00					
Inferior frontal cortex	10953 ± 274	11026 ± 164	$F_{1,82} = 1.17$	n.s.	0.01					
Orbital frontal cortex	13508 ± 241	13372 ± 145	$F_{1,82} = 2.33$	n.s.	0.03					
Anterior cingulate cortex	4824 ± 143	4826 ± 86	$F_{1,82} = 3.49$	n.s.	0.04					
Insula	7391 ± 170	7444 ± 102	$F_{1,82} = 2.51$	n.s.	0.03					
Surface area (mm <sup>2</sup> )										
MANCOVA <sup>c</sup>			$F_{9,74} = 2.87$	0.00	0.26	$F_{9,74} = 2.36$	0.02	0.22		
ANCOVA <sup>d</sup>										
Superior temporal cortex	3899 ± 84	3873 ± 50	$F_{1,82} = 6.77$	0.01**	0.08	$F_{1,82} = 6.21$	0.02**	0.07	0.10	-0.37
Middle temporal cortex	3459 ± 78	3444 ± 47	$F_{1,82} = 3.80$	n.s.	0.04	$F_{1,82} = 3.46$	n.s.	0.04		
Inferior temporal cortex	3490 ± 105	3360 ± 63	$F_{1,82} = 0.13$	n.s.	0.00	$F_{1,82} = 0.03$	n.s.	0.00		
Super frontal cortex	7490 ± 170	7585 ± 102	$F_{1,82} = 1.50$	n.s.	0.02	$F_{1,82} = 1.16$	n.s.	0.01		
Middle frontal cortex	8648 ± 195	8504 ± 117	$F_{1,82} = 0.59$	n.s.	0.00	$F_{1,82} = 0.67$	n.s.	0.01		
Inferior frontal cortex	3772 ± 89	3817 ± 53	$F_{1,82} = 2.99$	n.s.	0.04	$F_{1,82} = 2.44$	n.s.	0.03		
Orbital frontal cortex	4721 ± 85	4704 ± 51	$F_{1,82} = 0.90$	n.s.	0.01	$F_{1,82} = 0.85$	n.s.	0.01		
Anterior cingulate cortex	1637 ± 44	1591 ± 27	$F_{1,82} = 0.03$	n.s.	0.00	$F_{1,82} < 0.01$	n.s.	0.00		
Insula	2370 ± 51	2373 ± 31	$F_{1,82} = 6.06$	0.02**	0.07	$F_{1,82} = 5.34$	0.02**	0.06	0.28	-0.27
Thickness (mm)										
MANCOVA <sup>c</sup>			$F_{9,74} = 0.06$	n.s.	0.19	$F_{9,74} = 2.03$	0.05	0.20		
ANCOVA <sup>d</sup>										
Superior temporal cortex	2.78 ± 0.04	2.77 ± 0.02				$F_{1,82} = 0.01$		0.00		
Middle temporal cortex	2.79 ± 0.03	2.77 ± 0.02				$F_{1,82} = 0.77$		0.01		
Inferior temporal cortex	2.65 ± 0.03	2.62 ± 0.02				$F_{1,82} < 0.01$		0.00		
Super frontal cortex	2.71 ± 0.04	2.68 ± 0.02				$F_{1,82} = 0.08$		0.00		
Middle frontal cortex	2.41 ± 0.04	2.37 ± 0.02				$F_{1,82} = 0.01$		0.00		
Inferior frontal cortex	2.49 ± 0.04	2.48 ± 0.02				$F_{1,82} = 0.75$		0.01		
Orbital frontal cortex	2.53 ± 0.04	2.50 ± 0.02				$F_{1,82} = 0.78$		0.01		
Anterior cingulate cortex	2.67 ± 0.04	2.72 ± 0.03				$F_{1,82} = 6.81$	0.01**	0.08	-0.43	0.12
Insula	3.01 ± 0.04	3.05 ± 0.02				$F_{1,82} = 1.79$		0.02		

<sup>a</sup> Values represent means and standard deviations.

<sup>b</sup> Values represent Pearson's correlation between SBM measure and trait impulsivity (total score BIS-11). Are only tested when there is a significant group by impulsivity interaction effect.

<sup>c</sup> MANCOVA test results, adjusted for age and ICV.

<sup>d</sup> Follow-up ANCOVA test results, are only tested when MANCOVA is significant.

\*  $p < 0.05$  Unadjusted for multiple comparisons.

\*\*  $p < 0.05$ , Adjusted for multiple comparisons.

STC (Fig. 1B). Similar to the findings in the insula, partial correlation analysis, adjusted for age and ICV) indicated a significant positive relation between SA of the STC and impulsivity in controls, while there was an inverse trend in cocaine users. Taking into account this interaction effect, the SA of the STC was smaller in cocaine users compared to controls. There was no main effect of impulsivity.

The MANCOVA within cocaine users indicated that impulsivity was the only significant predictor of SA (Table 3). Post-hoc ANCOVAs showed that impulsivity was significantly related to the SA of the orbital frontal (OFC) and inferior frontal cortex (IFC).

**Cortical thickness:** The MANCOVA on CT indicated that there was a significant group by impulsivity interaction across all ROIs (Table 2). Post-hoc ANCOVAs showed a group by impulsivity interaction for the anterior cingulate cortex (ACC: Fig. 1C). Partial correlation analysis (adjusted for age and ICV) indicated that there was a significant inverse correlation between impulsivity and ACC thickness in controls but not in cocaine users, with or without correcting for the influence of cocaine exposure. This later correlation remained similar when correcting for the influence of cocaine exposure. There was no main effect of impulsivity or group on CT across the ROIs.

The MANCOVA within cocaine users indicated that monthly cocaine use was the only significant predictor of CT (Table 3). Post-hoc univariate tests were significant for the STC and the insula,

although the later comparison did not survive multiple comparisons correction.

Including average CT as covariate instead of ICV did not change these results, emphasizing that using ICV as a covariate did not confound these results.

### 3.3. Exploring the role of cocaine use with and without comorbid cannabis use

Three additional exploratory MANCOVAs were performed to test for the differences between controls ( $n = 35$ ), cocaine users with secondary cannabis ( $n = 15$ ) use and cocaine users without secondary cannabis use ( $n = 38$ ). Only the MANCOVA on SA showed a significant main effect of group ( $F_{9,146} = 1.98$ ,  $p = 0.014$ ,  $\eta^2 = 0.20$ ) and a significant group by impulsivity interaction ( $F_{18,146} = 1.78$ ,  $p = 0.033$ ,  $\eta^2 = 0.18$ ). Pairwise comparison showed that there was a significant group effect ( $F_{9,59} = 2.79$ ,  $p = 0.009$ ,  $\eta^2 = 0.30$ ) and a significant group by impulsivity interaction ( $F_{9,59} = 2.34$ ,  $p = 0.025$ ,  $\eta^2 = 0.26$ ) when comparing controls with cocaine users without secondary cannabis use while there were no differences between controls and cocaine users with secondary cannabis use, neither were there significant differences between cocaine users with and without secondary cannabis use. Post-hoc ANCOVAs on each individual ROI showed that the effects were significant for the SA of the

**Table 3**  
MANCOVA's and post-hoc ANCOVA's within cocaine users.

Measure and group	MANCOVA <sup>a</sup>			Follow-up ANCOVA <sup>b</sup>			
	Statistic	<i>p</i>	$\eta^2$	Statistic	<i>p</i>	$\eta^2$	<i>R</i> <sup>c</sup>
Volume (mm <sup>3</sup> )							
Impulsivity	$F_{9,23} = 1.05$	n.s.	0.29				
Years of cocaine use	$F_{9,23} = 0.22$	n.s.	0.08				
Monthly cocaine use	$F_{9,23} = 0.78$	n.s.	0.23				
Onset age cocaine use	$F_{9,23} = 0.38$	n.s.	0.13				
FTND	$F_{9,23} = 0.38$	n.s.	0.13				
Weekly alcohol intake	$F_{9,23} = 0.92$	n.s.	0.26				
Surface area (mm <sup>2</sup> )							
Impulsivity	$F_{9,23} = 2.83$	0.02*	0.53				
Superior temporal cortex				$F_{1,31} = 1.25$	n.s.	0.04	
Middle temporal cortex				$F_{1,31} = 3.98$	n.s.	0.11	
Inferior temporal cortex				$F_{1,31} = 0.70$	n.s.	0.02	
Super frontal cortex				$F_{1,31} = 1.37$	n.s.	0.04	
Middle frontal cortex				$F_{1,31} = 2.49$	n.s.	0.07	
Inferior frontal cortex				$F_{1,31} = 7.83$	0.00*	0.20	−0.45
Orbital frontal cortex				$F_{1,31} = 6.05$	0.02*	0.16	−0.40
Anterior cingulate cortex				$F_{1,31} = 0.10$	n.s.	0.00	
Insula				$F_{1,31} = 4.12$	n.s.	0.12	
Years of cocaine use	$F_{9,23} = 0.69$	n.s.	0.21				
Monthly cocaine use	$F_{9,23} = 1.60$	n.s.	0.38				
Onset age cocaine use	$F_{9,23} = 0.39$	n.s.	0.13				
FTND	$F_{9,23} = 0.45$	n.s.	0.15				
Weekly alcohol intake	$F_{9,23} = 1.17$	n.s.	0.15				
Thickness (mm)							
Impulsivity	$F_{9,23} = 0.93$	n.s.	0.27				
Years of cocaine use	$F_{9,23} = 1.12$	n.s.	0.31				
Monthly cocaine use	$F_{9,23} = 2.52$	0.04*	0.50				
Superior temporal cortex				$F_{1,31} = 6.40$	0.02*	0.17	−0.36
Middle temporal cortex				$F_{1,31} = 1.17$	0.29	0.04	
Inferior temporal cortex				$F_{1,31} = 1.93$	0.17	0.06	
Super frontal cortex				$F_{1,31} = 0.60$	0.44	0.02	
Middle frontal cortex				$F_{1,31} = 0.53$	0.47	0.02	
Inferior frontal cortex				$F_{1,31} = 0.23$	0.64	0.00	
Orbital frontal cortex				$F_{1,31} = 1.56$	0.22	0.05	
Anterior cingulate cortex				$F_{1,31} = 0.90$	0.35	0.03	
Insula				$F_{1,31} = 4.15$	0.05*	0.12	−0.34
Onset age cocaine use	$F_{9,23} = 0.99$	n.s.	0.28				
FTND	$F_{9,23} = 0.65$	n.s.	0.20				
Weekly alcohol intake	$F_{9,23} = 1.61$	n.s.	0.39				

<sup>a</sup> MANCOVA test results, adjusted for age and ICV.

<sup>b</sup> Follow-up ANCOVA's, only tested if MANCOVA is significant.

<sup>c</sup> Correlation between independent variable and SBM measure, only tested if ANCOVA is significant.

\* *p* is 0.05 bonferoni corrected.

STC (group effect:  $F_{1,67} = 6.95$   $p = 0.01$ ,  $\eta^2 = 0.09$ ; group by impulsivity interaction:  $F_{1,67} = 6.34$   $p = 0.014$ ,  $\eta^2 = 0.09$ ) and the insula (group effect:  $F_{1,67} = 5.33$ ,  $p = 0.024$ ,  $\eta^2 = 0.07$ ; group by impulsivity interaction:  $F_{1,67} = 4.80$ ,  $p = 0.032$ ,  $\eta^2 = 0.07$ ), although the latter did not survive the correction for multiple comparisons.

### 3.4. Whole brain analysis

The whole brain QDEC analysis did not reveal any significant differences or correlations with impulsivity outside the predefined regions of interest.

## 4. Discussion

### 4.1. Summary

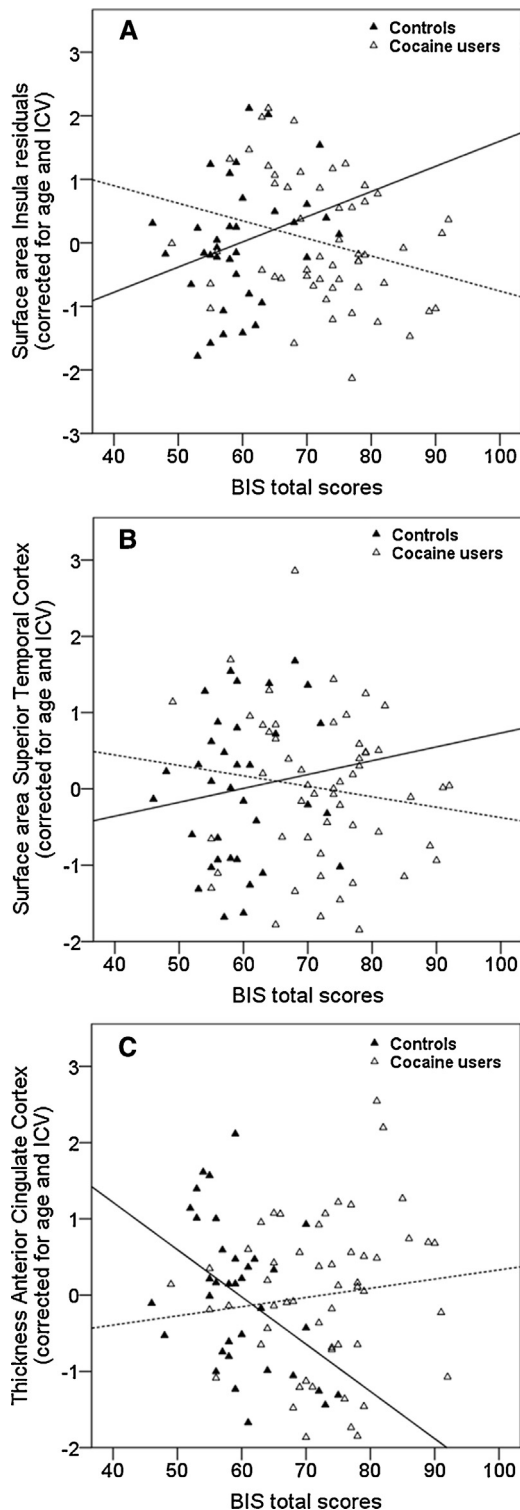
To our knowledge, this is the first study that investigated the relation between impulsivity and cortical morphometry in cocaine users and non-drug using controls. There was no correlation between SA and CT, demonstrating the linear independence of these structural parameters.

While there was no main effect of impulsivity on cortical morphometry, we found a distinct relation between impulsivity and cortical morphometry in cocaine users and controls. In addition,

groups differed significantly in SA of the insula and STC. Monthly cocaine use correlated negatively with CT of the STC, but not with CV or SA. An exploratory analysis revealed that the group by impulsivity interactions on SA of the insula and STC where only present in cocaine users without secondary cannabis use, although cocaine users with and without secondary cannabis use did not differ significantly from each other.

### 4.2. The relation between impulsivity and cortical morphometry

High impulsivity is suggested to be a predisposing factor to (cocaine) dependence (Belin et al., 2008; Verdejo-García et al., 2008; De Wit, 2009). We found a negative correlation between impulsivity and SA of the insula and STC in cocaine users but a positive correlation in controls, which is in line with previous studies showing similar correlations with CV of these regions (Churchwell and Yurgelun-Todd, 2013; Ersche et al., 2011; Moreno-López et al., 2012; Schilling et al., 2012). In addition, a positive correlation was shown between CT of the ACC in cocaine users, but a negative correlation in controls, similar to what has been found for CV of other prefrontal regions (Crunelle et al., 2014; Matsuo et al., 2009; Moreno-López et al., 2012; Schilling et al., 2012, 2013). Our study expands on previous studies by showing that the relation between cortical morphometry and impulsivity is different for SA and CT.



**Fig. 1. Correlation between BIS-11 scores and cortical surface area/thickness measures.** There was a significant interaction between the total score of the Barrat Impulsiveness Scale (BIS-11) and group in cortical surface area of the superior temporal cortex (panel A)  $r=0.38$ ,  $p=0.03$  for controls,  $r=-0.26$ ,  $p=0.07$  for cocaine users; surface area of the insula (panel B)  $r=0.27$ ,  $p=0.13$  for controls,  $r=-0.27$ ,  $p=0.06$  in cocaine users) and cortical thickness of the anterior cingulate cortex (panel C)  $r=-0.43$ ,  $p=0.012$  for controls,  $r=0.09$ ,  $p=0.54$  for cocaine users).

The insula, STC and ACC are involved in the control of (impulsive) behaviour (Bechara, 2005; Koob and Volkow, 2010; Paulus et al., 2005). Abnormal functioning of the insula and ACC is associated with impaired decision making in controls (Carroll et al., 2013;

Goldstein et al., 2009; Naqvi and Bechara, 2009) and drug dependent individuals (Gowin et al., 2014; Verdejo-García et al., 2006). Also, the functional connectivity between these regions is weaker in highly impulsive, compared to low impulsive individuals (Jung et al., 2013). Overall these studies suggest that a functional balance between the insula, ACC and STC is necessary to control impulsive behaviour. The distinct relation between cortical morphometry and impulsivity in cocaine users compared to controls might underlie a functional imbalance resulting in disrupted decision making and maladaptive impulsive behaviour such as continued drug use. While these morphological abnormalities might recover with abstinence, improving the functional imbalance between these brain regions may be an important treatment strategy. This could be achieved for instance by the use of cognitive enhancers such as modafinil (Canavan et al., 2014), cognitive behavioural therapy (Dutra et al., 2008) or cognitive remediation (Vocci, 2008).

It should be noted that the distinct relation between impulsivity and SA was not found in cocaine users with secondary cannabis use, which may reflect a neuroprotective effect of cannabis or opposing mechanisms of cocaine and cannabis on macromorphometry (Medina et al., 2007).

#### 4.3. Abnormal brain morphometry in cocaine users: A predisposition or a consequence of cocaine use?

The distinct relation between cortical morphometry and impulsivity in cocaine users compared to controls could be a predisposition, a consequence of cocaine use or a combination of both. Although we acknowledge that these issues can only be proven with longitudinal studies, SBM analysis allows to explore the origin of cortical abnormalities in more detail than VBM: A group by impulsivity interaction was found within the SA of the STC and insula, regions of which 64% and 74% of the variance, respectively, can be explained by genetic factors (Eyler et al., 2012; Winkler et al., 2010). In addition, around 45% of the variance in trait impulsivity can be explained by genetic factors as well (Congdon and Canli, 2008; Varga et al., 2012), suggesting that the distinct association between impulsivity and SA of the insula and STC might, for a large part, be pre-existing.

However, impulsivity is not solely determined by genetic factors, as acute and chronic drug use has shown to increase impulsivity (De Wit, 2009). Furthermore, only 36% of the variance in ACC thickness can be explained by genetic factors (Winkler et al., 2010), suggesting that ACC thickness is mainly influenced by environmental factors. Also, the negative correlation between the amount of cocaine use and CT of the STC and insula suggests cocaine induced reduction in neuronal density (Casanova and Tillquist, 2008; La Fougère et al., 2011; Rakic, 2009). In summary, cortical pathology in cocaine users can be characterised by specific differences in CT and SA, which may reflect a combination of both a pre-existing disposition to drug abuse as well as a consequence of cocaine use (Makris et al., 2008).

#### 4.4. The added value of surface-based morphometry

In contrast to previous studies we did not find differences in CV between cocaine users and controls (Ersche et al., 2011; Franklin et al., 2002; Moreno-López et al., 2012; Weller et al., 2011). Although groups differed significantly in SA, the differences were very small. Two previous studies have shown thinner insular cortex in cocaine users (Makris et al., 2008) and in substance dependent patients (Tanabe et al., 2012); another result that was not replicated in the current study. A possible explanation for this discrepancy in results is that these previous studies included cocaine addicted patients that were in treatment, while we included non-treatment seeking cocaine users. Another possible explanation is the large

portion of secondary cannabis users in the current study, however cortical thinning of the insula has also been reported in cannabis users (Lopez-Larson et al., 2011). A more likely explanation for the absence of large scale cortical morphometric differences between cocaine users and controls could be the method used in the current study (SBM versus VBM): while SBM (using Freesurfer) defines regions in subject space, VBM (using SPM or FSL) defines regions in standard space, making this latter technique more sensitive for differences in smoothing, registration and normalization templates (Frye et al., 2010; Jones et al., 2005; Park et al., 2004; Voets et al., 2008). As a consequence, Freesurfer is suggested to be more reliable and suitable for gray matter measurements. Therefore results of VBM studies may differ from results of SBM studies and direct comparisons between these different types of morphological studies should be made with great caution (Eggert et al., 2012; Klauschen et al., 2009; Palaniyappan and Liddle, 2012).

#### 4.5. Limitations and future directions

Limitations of this study include the reliance on self-reported cocaine use and impulsivity. Despite its limitation, self-reported cocaine use is the only method for assessing cocaine exposure. In addition, the BIS-11 is a widely used and validated measure for trait impulsivity, although we acknowledge that including measures of behavioural impulsivity in addition to trait impulsivity may better captures all facets of impulsivity (Broos et al., 2012). Moreover, there was a high level of secondary cannabis use among the cocaine users (28%), a number that is in line with what is generally reported among cocaine users in Europe (European Monitoring Centre for Drugs and Drug Addiction, 2009). An exploratory analysis of our data suggested that secondary cannabis use might be a neuroprotective factor. However, as the study was not designed to investigate the effects of secondary cannabis use, we cannot draw firm conclusions from this finding. Neither can we draw conclusions on causality of abnormal cortical morphometry because of the cross-sectional design. Larger and longitudinal studies are required to address both issues. Lastly, it also needs to be pointed out that only male participants were included in the study. While this is a strength of the study as it increases the homogeneity within the sample, care should be taken when generalizing these results to female cocaine users.

Despite these shortcomings, the current study provides additional evidence for the distinct relation between impulsivity and cortical morphometry in cocaine users compared to controls. These structural differences would have been missed if we had only focused on measures of CV, emphasizing the importance of including measures of CT and SA in addition to CV for detecting and understanding the origin of cortical abnormalities in cocaine abuse and cocaine dependence.

#### Author disclosures

#### Role of funding source

This study was made possible by two grants from a ZonMW-NWO (grant number 91211002 and 31160305). Sponsors had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

#### Contributors

Data were obtained by AMK and CLC, who prepared the first draft. AMK and GvW analyzed the data. JRH, LR and WvdB actively participated in writing and revising the manuscript for publication.

#### Conflict of interest

All authors declare that there are no conflicts of interest.

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