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

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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 morophometry (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, orbitalfronal 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[a]	33 ± 19	31 ± 12	0.436
IQ[a]	106 ± 10	104 ± 12	0.099
Trait impulsivity (BIS)[b]	60 ± 6.7	73 ± 9.5	<0.001
Alcohol use (units per week)[a]	5 ± 9	24 ± 21	<0.001
Nicotine use (amount of smokers)	5.7%	76%	
FTND score for smokers[a]	2.5 ± 0.7	5 ± 4	0.101
Secondary cannabis use (>once a week)		28%	<0.001
Cocaine dependence[c]		89%	
Years of cocaine use[a]		8 ± 6	
Onset age of cocaine use[a]		19 ± 4	
Grams of cocaine use per month[a]		7.6 ± 8	

[a] Values represent medians ± interquartile range.
[b] Values represent mean ± standard deviation.
[c] 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 FagerströmTest 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^3.

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

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