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Cortical thickness and subcortical volume abnormalities in male crack-cocaine users

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ABSTRACT

Crack-cocaine offers a higher risk of abuse than intranasal and intravenous use of cocaine. Yet, current treatments remain disappointing and our understanding of the mechanism of crack-cocaine neurotoxicity is still incomplete. Magnetic resonance images studies on brain changes of crack-cocaine addicts show divergent data. The present study investigated gray matter (GM) abnormalities in crack-cocaine dependents ($n = 18$) compared to healthy controls ($n = 17$). MRI data was analysed using FreeSurfer and voxel-based morphometry (VBM). FreeSurfer analysis showed that CD had decreased cortical thickness (CT) in the left inferior temporal cortex (lTC), left orbitofrontal cortex (lOFC) and left rostro frontal cortex (lRFC), enlargement in left inferior lateral ventricle, and smaller GM volume in right hippocampus and right ventral diencephalon. VBM analysis showed that CD had significantly decreased GM volume in left Putamen and left nucleus accumbens. Furthermore, we found a negative correlation between duration of crack-cocaine use and lTC CT. These results provide compelling evidence for GM abnormalities in CD and also suggest that duration of crack-cocaine use may be associated with CT alterations.

1. Introduction

Brazil presents one of the highest rates of crack-cocaine use in the world, with 1.5% for lifetime use and 0.8% for last year use (Abdalla et al., 2014). Crack-cocaine offers a higher risk of abuse due to possible greater intensity of effect, easier administration, and lower costs in comparison to intranasal and intravenous use of cocaine hydrochloride (Hatsukami and Fischman, 1996). In addition to the health consequences caused by crack-cocaine addiction itself, users of this substance are exposed to several biological, physical, and social hazards that can contribute to comorbid illnesses (Butler et al., 2017). Out of all the addicting drugs, crack-cocaine addiction poses as one of the major

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threats to the public health and social security of Brazil (Dias et al., 2011; Madruga et al., 2017; Paim Kessler et al., 2012). Unfortunately, current treatments still bring disappointing results, and our understanding of the risk factors and of the neurobiological underpinning of crack-cocaine addiction still remains incomplete (Fischer et al., 2015). Thus, the mechanisms underlying crack-cocaine dependence, especially those that are clinically relevant, increase the necessity for further investigation.

MRI studies have attempted to uncover macrostructural changes in the central nervous system of cocaine-dependent individuals, although findings are inconclusive (Barrós-Loscertales et al., 2011; Ersche et al., 2012; Garza-Villarreal et al., 2017). For instance, some studies have observed lower gray matter (GM) volume in striatum (Barrós-Loscertales et al., 2011; Moreno-López et al., 2012), larger striatal and thalamic GM volumes (Ersche et al., 2011; Jacobsen et al., 2001; Sim et al., 2007), or no volumetric differences whatsoever (Garza-Villarreal et al., 2017; Narayana et al., 2010) when compared to healthy subjects. Other studies reported lower GM volumes in prefrontal cortex, temporal cortex, insula and thalamus (Ersche et al., 2012; Franklin et al., 2002; Moreno-López et al., 2012; Weller et al., 2011). In other regions including amygdala and hippocampus, findings are contradictory (Ersche et al., 2012; Mackey and Paulus, 2013; Makris et al., 2004; Mei et al., 2015). Longer cocaine use was associated with reductions in the right hippocampal region, while increases in GM were observed in the left hippocampal region (Ersche et al., 2013). Nevertheless, in addition to these regions, duration of cocaine use was also associated with GM abnormalities in the right insula, right gyrus rectus, left middle temporal gyrus, right middle temporal gyrus and right inferior frontal gyrus (Hall et al., 2015). The picture is similarly unclear regarding cortical thickness (CT), as different areas have been associated to cocaine use. There is evidence of lower CT in bilateral insula (Geng et al., 2017), lateral frontal regions (Hirsiger et al., 2019) and dorsolateral prefrontal cortex (Makris et al., 2008), and higher thickness in bilateral temporal pole (Geng et al., 2017).

In addition, most of these findings come from studies dedicated to intranasal use of cocaine hydrochloride, and only very few of them are dedicated exclusively to crack-cocaine addiction (Schuch-Goi et al., 2017). Despite that, it is possible that crack-cocaine impacts differently on brain tissue, since a growing body of evidences is displaying different consequences between these two routes of use (Kiluk et al., 2013; Paim Kessler et al., 2012; Voon et al., 2016). Crack-cocaine is associated with shorter periods of sustained abstinence within treatment, greater propensity for dependence and higher cocaine plasmatic levels. Moreover, pharmacokinetic differences between crack-cocaine and intranasal use of cocaine hydrochloride further support that GM abnormalities related to different routes of cocaine use may be different. (Kiluk et al., 2013; Strang and Edwards, 1989).

Some of these structural abnormalities have been hypothesized to play a central role in addiction-related behaviors including impulsivity and compulsivity (Ersche et al., 2011; Everitt and Robbins, 2013). Addiction-related behaviors are thought to be mediated by modifications in the mesolimbic dopamine system and by a cascade of neuroadaptations taking place from the ventral striatum to dorsal striatum and orbitofrontal cortex. Such alterations in brain chemistry and function affect neuronal circuits involved in reward, incentive motivation and inhibitory control (Koob and Volkow, 2016; G.F. 2010; Volkow et al., 2012).

In this study, we examined CT and GM volumes in crack-cocaine addicts compared to healthy subjects in a male population sample. The GM volume is defined as the amount of GM that lies between the gray-white interface and the pia mater. (Winkler et al., 2010). In addition, GM volume is, by geometric definition, the product of cortical surface area (CSA) and thickness. The estimation of CT represents a methodological alternative to volume measurements for the investigation of subtle cortical changes. Disentangling these two parameters is important, as different biological factors may contribute to the changes in CT and GM volume (Fischl and Dale, 2000; Makris et al., 2008, 2007; Rakic, 2007). GM volume and CSA bear a nearly linear relation (Makris et al., 2008). Furthermore, GM volume was genetically and environmentally correlated with CSA and, to a much lesser extent, with CT (Winkler et al., 2010). For this reason, CSA is not included as an outcome measure in the current study.

It is not fully understood whether GM abnormalities found in crack-cocaine dependent individuals are predisposed or cocaine-induced (or both) (Makris et al., 2008). Cross-sectional neurobiological abnormalities seen in cocaine dependents are usually interpreted as drug-induced consequences as studies reported associations between duration of cocaine intake and GM alterations (Ersche et al., 2013; Hall et al., 2015). This claim is supported by a recent longitudinal study showing that reduced or ceased cocaine intake was associated with CT recovery in lateral frontal regions whereas CT within the same regions tended to further decrease in sustained cocaine users (Hirsiger et al., 2019).

While GM abnormalities have been reported in cocaine hydrochloride addiction, evidence from cortical thinning and affected volumes in crack-cocaine addiction are yet to be fully understood. Therefore, in this study we aimed to gain more insight into the possible neuroanatomical underpinnings of crack-cocaine addiction. A secondary objective related to the exploratory investigation of differential associations between GM alterations and some core variables: Age of crack-cocaine use onset, years of crack-cocaine use, abstinence symptoms, and drug use severity. We hypothesized that CD would have GM abnormalities in striatum, hippocampus, orbitofrontal cortex, dorsolateral prefrontal cortex, inferior frontal cortices, temporal lobe, cingulate gyrus, insula, diencephalon and amygdala, which are structures associated with the development of addiction (G.F. Koob and Volkow, 2010). Moreover, cortical and subcortical variables were also expected to be negatively associated with years of crack-cocaine exposure, drug use severity and abstinence symptoms, and positively associated with age of crack-cocaine use onset.

2. Materials and methods

We conducted a case-control observational study and included 30 male crack-cocaine dependents (CD) and 20 male healthy controls (HC) for comparison. All T1 images were visually inspected for quality of the image and for absence of apparent motion artifacts. The contrast of the structures was very poor in 5 scans from CD group, so they were removed due to these motion artifacts. Images of the scans that were excluded due to motion artifacts are showed in Supplementary Data 1. Moreover, neuroimaging data from 4 subjects (2 CD and 2 HC) was discarded due to segmentation failure with FreeSurfer and another 3 scans from CD group were removed due to co-registration issues when using FSL. Furthermore, 3 participants (2 CD and 1 HC) decided to opt out of the study, finally remaining 18 subjects in CD group and 17 in HC group. All the procedures were approved and carried out according to the Ethics Committee from Pontifical Catholic University of Rio Grande do Sul (PUCRS) under protocol code 15,674,013.3.0000.5336. After complete description of the study, written informed consent was obtained from all subjects.

2.1. Participants

Eligible subjects for CD group were male crack-cocaine dependent enrolled in long-term rehab program from a non-profit organization from Porto Alegre (RS) – Brazil. Inclusion criteria for cases were: (1) should have a primary mental-disorder diagnosis of crack-cocaine use disorder (2) smoking route as preferred means of cocaine consumption, (3) 18–45 years old, (4) right handedness, (5) having between 7 and 14 days of inpatient, and (6) have an IQ $>$ 80. Handedness was checked individually using the Handedness Inventory, considering individuals with scores above nine as right-handed (Briggs and Nebes, 1975). Only crack-cocaine dependents with history of alcohol and tobacco

dependence not requiring medical detoxification were accepted. Participants were excluded if they had potential contraindications to MRI scanning (metallic implants, recent tattoos, claustrophobia), any acute or unstable clinical illness including untreated psychotic disorder and abuse of other substance during the last 14 days.

HC were matched for age, ethnicity, and education. This sample was recruited by word of mouth advertising and screened for major psychiatric disorders using the non-patient version of Structured Clinical Interview for DSM-5 (SCID) and administered by a trained member of the research staff, before the date of the MRI exam. HC subjects were required to have no history of drug and alcohol dependence/abuse and no psychiatric or neurological disorder. Additional exclusionary criteria included left-handedness, unstable medical disorder, IQ< 80 and contraindications to MRI scanning. HC should not have used any psychotropic medications in the last six months.

All participants were negative for cocaine, cannabis, amphetamines, opioids, and benzodiazepines in a urine screening test on the date of the MRI exam. For HIV and syphilis, the participants took a fast-track blood exam prior to MRI scan.

2.2. Assessments

Sociodemographic characteristics and drug abuse pattern were obtained by using the Addiction Severity Index – 6th version (ASI-6). This instrument is semi-structured interview that gathers information on recent and lifetime problems related to substance misuse. A validated version of ASI-6 translated into Brazilian Portuguese was used in this study (Kessler et al., 2012). The ASI-6 allows for the computation of composite scores of negative impact in nine domains: drugs, alcohol, family/children, psychiatric symptoms, medical issues, legal problems, employment, social support, and social problems. Higher scores mean more severe problems (Cacciola et al., 2011; McLellan et al., 2006).

We investigated symptoms related to crack-cocaine abstinence with the Cocaine Selective Scale Assessment (CSSA), (Kampman et al., 1998) which considers various symptoms related to abstinence of at least 24 h. It uses a 0–7 visual analogue scale, and the sum of all items returns a total score. Participants took the CSSA on the date of the MRI exam.

2.3. MRI acquisition

All magnetic resonance images (MRI) scans were acquired on a 3.0T whole body scanner (Signa, GE Healthcare, Milwaukee, USA) A three-dimensional T1-weighted images with the following parameters: repetition time (TR) = 2400 ms, echo time (TE) = 15 ms, slice thickness = 16 mm, scan matrix = 512 × 512 and voxel size = 1mm^3. All subjects were invited to experience the experiment on a fake MRI machine prior to MRI scan. The objective was to allow familiarization with the characteristics of this study.

2.4. FreeSurfer pre-processing and evaluation

In order to evaluate CT and GM cortical and subcortical volumes, cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale et al., 1999; Dale and Sereno, 1993; Fischl et al., 2004a, 2004b, 2002, 2001, 1999a, 1999b; Fischl and Dale, 2000; Han et al., 2006; Jovicich et al., 2006; Reuter et al., 2012; M. 2010; Ségonne et al., 2004). Briefly, this processing includes motion correction and averaging (M. Reuter et al., 2010) of volumetric T1 weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep subcortical structures (Fischl et al., 2004a, 2002) intensity normalization (Sled et al., 1998), tessellation of the GM white matter boundary, automated topology correction (Fischl et al., 2001; Ségonne et al., 2007), 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 (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000). Regions of interest (ROIs) were extracted by parcellating the cortex using the Desikan–Killiany Atlas32 (Desikan et al., 2006). For each of the 68 cortical parcellations, FreeSurfer calculates the average CT and the cortical GM volume. Subcortical volumes were calculated with FreeSurfer's automated procedure for volumetric measures. Each voxel in the normalized brain volume was assigned to one of 40 labels, using a probabilistic atlas obtained from a manually labelled training set (Fischl et al., 2002). Reconstructed images were visually inspected and manually corrected for segmentation or processing mistakes according to FreeSurfer's troubleshooting guidelines. The edited exams were then reprocessed, and CT and GM volumes data was extracted from the corrected images. Eventually, general Linear Model (GLM) was performed to estimate differences between HC and CD at each vertex of the surfaces, using FreeSurfer''s QDEC tool version 5.0 cross-sectional pipeline (surfer.nmr.mgh.harvard.edu/). Monte Carlo Null-Z simulation was used for multiple comparisons correction, considering a significant value of $p < 0.05$.

2.5. Voxel-based morphometry pre-processing and evaluation

Since many of the published studies on drug abuse have employed Voxel-based Morphometry (VBM) analysis for determining changes in regional brain volumes, we have also conducted Optimized VBM to investigate GM volumes differences between CD and HC. All brain images were analyzed with the FMRIB Software Library v5.0 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) using FSL-VBM (Douaud et al., 2007) to investigate changes in GM volumes. Briefly, data processing was divided into five following major steps: (1) brain extraction and manual correction if needed, (2) segmentation of images in white matter, GM and cerebrospinal fluid volume using FAST (Zhang et al., 2001), (3) creation of a GM template by registering a subset of subjects randomly chosen from both CD and HC, (4) non-linearly registration (Andersson et al., 2007) of native GM images and Jacobian modulation and, (5) image smoothing with an isotropic Gaussian kernel of 3 mm with a full-width half-maximum (FWHM) of ~ 7 mm. Eventually, voxelwise general linear model (GLM) was applied using permutation-based non-parametric testing (5000 permutations), threshold-free cluster enhancement (TFCE) was used for multiple comparison correction considering a significant p-value of < 0.05.

2.6. Statistical analyses

Descriptive analyses are presented as mean and standard deviation or absolute and relative frequencies. Differences involving continuous and categorical in sociodemographic clinical data were evaluated using independent t-test, Yate's correction chi-squared or Fisher's exact test, respectively.

A Covariance Analysis (ANCOVA) was performed to estimate GM differences (Freesurfer and VBM analyses) between HC and CD adjusted by years of study. Among the CD group, Pearson's or Spearman's correlation coefficient was used to estimate the associations between crack-cocaine, alcohol and cigarettes years of use, age of crack-cocaine use onset, CSSA score, drug use severity, ASI-6 alcohol composite score and GM brain indices. The partial correlation coefficient adjusted by age was used to analyze the relationship between duration of crack-cocaine use and GM brain indices. We conducted these analyses with SPSS statistic software (IBM Corp. Released 2015. IBM SPSS Statistics for Macintosh, Version 23.0. Armonk, NY: IMB Corp.) and threshold for statistical significance was set at $p < 0.05$.

3. Results

3.1. Sample characteristics

Sociodemographic characteristics of the sample and substance use

patterns are summarized below and in Table 1.

Differences in age, marital status and ethnicity were not statistically significant between the two groups. CD had received fewer years of education ($t = 4.00$, df= 34, $p < 0.001$) and were more unemployed ($p < 0.01$) than HC. Due to these differences, we included education as covariate in all comparative analyses of brain morphometric indices. The mean time of crack-cocaine use in CD group was 9.5 ± 5.8 years and the mean age of crack-cocaine use onset was 19.6 ± 5.9 years. There was a clear concomitant use of alcohol and nicotine in all subjects of CD group whereas HC had no history of alcohol and nicotine regular use. In CD group, all subjects presented alcohol abuse and had no history of another illicit drug dependence. The mean time in life that CD group drank alcohol regularly was 7.9 ± 6.4 years and they drank at least 5 drinks in 5.7 ± 5.4 years. Furthermore, the mean time in life that CD group smoked cigarettes was 10.4 ± 7.6. In addition, among the CSSA and ASI-6 scores, CSSA score was 29.9 ± 17.9 drug use severity score was 0.49 ± 0.21, and alcohol composite score was 51.4 ± 8.1.

3.2. Gray matter volumes

FreeSurfer analyses of cortical volumes showed no significant differences between the two groups ($p>0.05$). FreeSurfer analyses of subcortical regions showed a significant lower volume in right hippocampus ($p = 0.049$) and right ventral diencephalon ($p = 0.048$) of CD when compared to HC. The ventral diencephalon in Freesurfer includes several structures: hypothalamus with mammillary body, subthalamic, lateral geniculate, medial geniculate and red nuclei, substantia nigra and surrounding white matter. In addition, CD group showed enlargement of left inferior lateral ventricle ($p = 0.012$). Nevertheless, when co-varying for years of study only the group differences in left inferior lateral ventricle remained significant ($p = 0.034$). FreeSurfer GM volumes results are summarized in table 2.

To confirm the above reported results, we conducted the same analyses with VBM. Similar to the FreeSurfer analyses, there were no cortical volumes significant differences between the two groups ($p>0.05$). VBM analyses of subcortical regions showed a significant lower volume in left Putamen and left nucleus accumbens (NAcc) of CD when compared to HC ($p = 0.015$). When co-varying for years of study the group differences remained significant ($p = 0.042$). Data from these brains and their correspondent MRI are showed in Fig. 1.

Table 1
Sample Characteristics.

Variables	CD (n = 18)	HC (n = 17)	p-value
Age (years; mean±SD)	28.3 ± 6.7	28.4 ± 7	0.98[A]
Education (years; mean±SD)	9.4 ± 1.53	11±1.56	0.04[A]
Handedness (% right)	100	100	–
Civil Status (married)	1 (5.6%)	5 (29.4%)	0.06[B]
Occupation (employed)	8 (44.4%)	14 (82.4%)	0.049[C]
Ethnicity (afrodescendant)	11 (61.1%)	6 (35.3%)	0.09[C]
Crack use (years; mean±SD)	9.5 ± 5.8	–	–
Age of crack-cocaine use onset (mean±SD)	19.6 ± 5.9	–	–
Years in life that drank alcohol regularly, 3 or more days a week (mean±SD)	7.9 ± 6.4	–	–
Years in life that drank at least 5 drinks a day, 3 or more days a week (mean±SD)	5.7 ± 5.4	–	–
Years in life that smoked cigarettes (mean±SD)	10.4 ± 7.6	–	–
CSSA score (mean±SD)	29.9 ± 17.9	–	–
ASI Drug use severity score (mean±SD)	0.49±0.21	–	–
ASI Alcohol composite score (mean±SD)	51.4 ± 8.1	–	–

A Student t-test; B Fisher's exact test; C Yates's correction chi square test; SD Standard deviation.

Table 2
Summary of FreeSurfer GM volumes results.

Region	Crack-cocaine (n = 18) Mean ±SD (mm^3)	Controls (n = 17) Mean±SD (mm^3)	p-value	Adjusted p-value*
Left inferior lateral ventricle	302±164	181±46.7	0.012	0.034
Right hippocampus	4404±425	4693±372	0.049	0.235
Right ventral diencephalon	4855±416	5185±484	0.048	0.154

GM volumes reductions in CD vs. HC.
* adjusted for years of study by Covariance Analysis.

3.3. Cortical thickness

FreeSurfer analyses revealed brain regions with significant reductions of CT in CD relative to controls, while there were no brain regions with higher CT in the CD group (Table 3). Compared to controls, the CD group showed lower CT in the left inferior temporal cortex (lTC), left orbitofrontal cortex (lOFC) and left rostro frontal cortex (lRFC) (Fig. 2). However, when co-varying for years of study only the group differences in lTC (adjusted p-value=0.018) and lOFC (adjusted p-value=0.011) remained significant.

3.4. Correlation analyses

The correlation analysis of crack-cocaine years of use with CT, showed that lTC CT was negatively correlated with crack-cocaine years of use, while there was no significant association in lRFC. Furthermore, there was no significant correlation between crack-cocaine years of use and GM volumes in VBM significant clusters (i.e. putamen and nucleus accumbens). Table 4 shows the associations between crack-cocaine years of use and GM alterations.

Additionally, there was no significant correlation between alcohol and cigarettes years of use, age of crack-cocaine use onset, CSSA score, drug use severity, ASI-6 alcohol composite score and GM alterations. Table 5 shows the associations between alcohol and cigarettes years of use, age of crack-cocaine use onset and GM brain indices. Table 6 shows the associations between CSSA score, drug use severity, alcohol use severity and GM brain indices.

4. Discussion

As far as the present state of knowledge, this is the first study using optimized VBM and FreeSurfer analyses to document GM volumes alterations and lower CT in several brain areas of crack-cocaine users. Our FreeSurfer results showed cortical thinning in lTC, lRFC and lOFC, diminished GM volume in right hippocampus and right ventral diencephalon and larger volume in left inferior lateral ventricle in CD group. Our VBM results showed lower volumes in left Putamen and left NAcc in CD compared to HC. However, when co-varying for years of study only the group differences in lTC and lOFC, left inferior lateral ventricle, putamen and NAcc remained significant. Furthermore, crack-cocaine

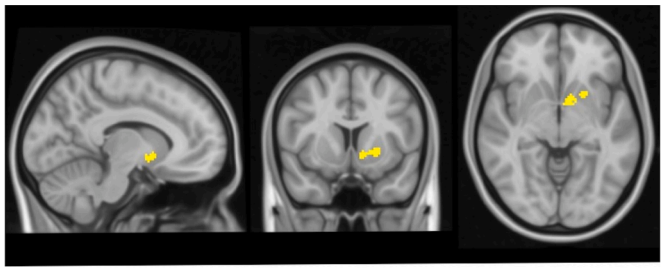

Fig. 1. Statistical parametric map o whole-brain VBM.

Table 3
Summary of FreeSurfer CT results.

Region	Talairach coordinates (X,Y,Z)	Cluster size (mm2)	*p*-value	Adjusted *p*-value*
Left inferior temporal cortex	−58.8,−43.2,−12.8	3929.23	<0.001	0.018
Left orbitofrontal Cortex	−17.1,31.2,−19.7	1884.63	<0.001	0.011
Left rostro frontal cortex	−41.5,31.8,25.3	895.63	0.014	0.053

CT reductions in CD vs. HC, as Determined from regions of interest (ROI) Analysis.
* adjusted for years of study by Covariance Analysis.

years of use was negatively correlated with lTC CT. These findings suggest close neuroanatomical pathology of fronto-striatal areas in CD.

A group of processes is supposed to explain why GM abnormalities are observed in crack-cocaine users, such as oxidative stress and neuroinflammation (Blanco-Calvo et al., 2014; López-Pedrajas et al., 2015). Although the mechanisms of crack-cocaine neurotoxicity are not fully understood, according to some studies, the current main etiological hypothesis of the addictive cycle involves a fronto-striatal circuit pathology (Garza-Villarreal et al., 2018; Jaworska et al., 2017; Volkow et al., 2016). Okita et al. suggest that the correlation between striatal D1-type (dopamine) levels and mean global CT indicates cortical adaptation due to striatum pathology (Okita et al., 2018). Our results are in agreement with these findings, bearing in mind that we observed shared morphological findings of cortical thinning and lower striatal volumes.

The findings presented here about GM abnormalities in CD individuals are consistent with previous neuroimaging studies, revealing structural modifications in brain areas concerning reward system in CD (Alia-Klein et al., 2011; Ersche et al., 2012; Garza-Villarreal et al., 2018; Schuch-Goi et al., 2017). Lower CT of lOFC and a volumetric reduction in hippocampus, ventral diencephalon, putamen and NAcc demonstrated in our study corroborates the hypothesis proposed by Koob and Volkow that the transition to addiction involves neuroplasticity in all of these structures (G.F. Koob and Volkow, 2010). The cortical thinning was observed in regions that play an important role in executive functions such as working memory, sustained attention, inhibitory control, problem solving, cognitive flexibility and decision making (Volkow and Fowler, 2000).

A pioneer report dedicated to crack-cocaine addiction observed a smaller GM volume in dorsolateral prefrontal cortex, anterior cingulate, the cerebellum, insula and superior temporal gyrus between crack-cocaine users compared to non-cocaine dependents (Weller et al., 2011). Even though this preliminary report did not analyze differences in striatal structures, a FreeSurfer study carried out by Shuch-Goi et al. found reduction of the NAcc in crack-cocaine users compared to healthy subjects (Schuch-Goi et al., 2017). Although we did not find a congruent result in our FreeSurfer analysis, our VBM analysis also presented decreased NAcc volume in CD group. Hall et al. hypothesized that the inconsistencies in the directions of reported subcortical changes could be related to methodological reasons such as the use of different image analysis methods between studies (Hall et al., 2015). Thus, our results support that hypothesis by showing distinct findings while using two different image analysis techniques in the same sample.

Although we used the same dataset in our FreeSurfer and VBM analyses, there was surprisingly no overlap between the results in the areas in which we found significant effects. Since our study was not designed to specifically investigate between-technique differences, we will only shortly discuss possible explanations why the VBM findings deviate from our FreeSurfer results. Whereas FreeSurfer calculates the total volume of a cortical parcellation or subcortical segmentation, VBM assesses GM volume on a voxel-by-voxel basis. VBM might, therefore, be more sensitive to detect small local effects that may be 'averaged out' when

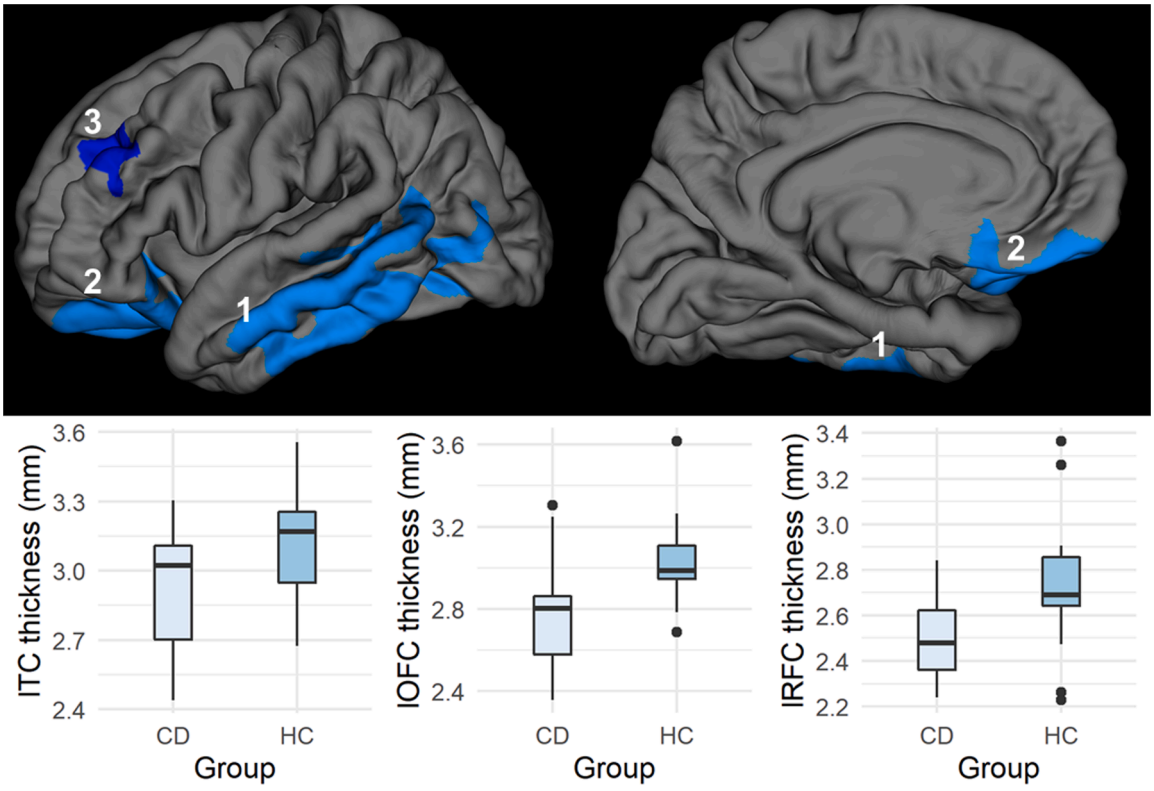

Fig. 2. CT group difference.

Table 4
Correlation between crack-cocaine years of use and CT.

Region	Correlation coefficients	*p*-value	Adjusted Correlation coefficients	*p*-value adjusted**
Left orbitofrontal cortex[a]	−0.509	0.047*	−0.460	0.098
Left inferior temporal cortex[a]	−0.488	0.036*	−0.324	0.048*
Left rostro frontal cortex[a]	−0.118	0.652	−0.204	0.485
Left inferior lateral ventricle[b]	0.579	0.038*	0.471	0.089
Right hippocampus[b]	0.345	0.249	0.108	0.712
Right ventral diencephalon[b]	0.334	0.265	0.010	0.974
VBM significant clusters[c]	0.205	0.418	0.136	0.642

Note.
[a] FreeSurfer CT results.
[b] FreeSurfer GM volumes results.
[c] VBM GM volumes results.
* $p<0.05$.
** adjusted by age.

measured over a larger area. Also minor methodological variations, such as different spatial transformations or smoothing procedures can alter results in a way similar to the biologic differences under investigation (Gerrits et al., 2016; Hall et al., 2015; Henley et al., 2010). Since FreeSurfer is a surface-based technique, and thereby differentially affected by these important preprocessing steps, this further hinders the between-technique comparison. Moreover, in our VBM evaluation, we used TFCE for multiple comparison correction considering a significant *p*-value of 0.05., whereas in the FreeSurfer evaluation we employed Monte Carlo Null-Z simulation for multiple comparisons correction, which is statistically more stringent (Gerrits et al., 2016; Lieberman and Cunningham, 2009). In addition, it is also conceivable that subcortical abnormalities in crack-cocaine users are subtler than cortical alterations. (Ersche et al., 2013; Hirsiger et al., 2019). Thus, we believe that if GM volumes differences had been more pronounced, both techniques would have detected similar findings.

The fronto-striatal circuit is linked to addiction-related behaviors concerning a series of transitions from initial voluntary drug use to drug seeking and taking behaviors. The current hypothesis is that voluntary goal-directed behaviors mediated by the ventral striatum dynamically shift towards habitual and compulsive behaviors by dorsal striatum as drug addiction progress (Everitt and Robbins, 2013). NAcc has an important function to integrate associative information and reward from limbic circuits (Corbit and Balleine, 2011). Functional MRI (fMRI) studies also show a correlation with the brain areas affected by crack-cocaine in our study. Early studies of fMRI in humans (Volkow et al., 2006) found an association between cocaine craving and dopamine increases in dorsal striatum, but failed to show association between craving and dopamine changes in ventral striatum. Some findings in laboratory animals have shown that NAcc presents an impairment to acquire new associations after cocaine exposure (Saddoris and Carelli,

Table 6
Correlation between CSSA score, drug use severity, alcohol composite score and GM brain indices (correlation coefficients are presented*).

Region	CSSA score	Drug use severity	Alcohol composite score
Left orbitofrontal cortex[a]	−0.174	−0.133	0.032
Left inferior temporal cortex[a]	−0.081	−0.144	−0.192
Left rostro frontal cortex[a]	−0.095	−0.370	−0.006
Left inferior lateral ventricle[b]	0.452	0.111	−0.108
Right hippocampus[b]	−0.418	−0.174	0.069
Right ventral diencephalon[b]	0.038	0.177	−0.004
VBM significant clusters[c]	0.399	−0.176	−0.133

Note.
[a] FreeSurfer CT results.
[b] FreeSurfer GM volumes results.
[c] VBM GM volumes results.
* all $p>0.05$.

Table 5
Correlation between alcohol and cigarettes years of use, age of crack-cocaine use onset and GM brain indices (correlation coefficients are presented*).

Region	Years in life that drank alcohol regularly, 3 or more days a week	Years in life that drank at least 5 drinks a day, 3 or more days a week	Years in life that smoked cigarettes	Age of onset of crack-cocaine use
Left orbitofrontal Cortex[a]	−0.263	−0.006	−0.313	0.150
Left inferior temporal cortex[a]	−0.028	0.164	−0.239	−0.469
Left rostro frontal cortex[a]	−0.109	0.433	0.083	0.114
Left inferior lateral ventricle[b]	−0.114	−0.410	−0.022	−0.036
Right hippocampus[b]	0.083	0.244	−0.066	0.033
Right ventral diencephalon[b]	0.076	0.032	0.288	0.453
VBM significant clusters[c]	0.479	0.171	0.481	−0.194

Note.
[a] FreeSurfer CT results.
[b] FreeSurfer GM volumes results.
[c] VBM GM volumes results.
* all $p>0.05$.

2014). Dorsal striatum (caudate and putamen) are implicated in stimulus-response learning, including habit formation in drug addiction (White and McDonald, 2002). A recent research performed by Wang et al. (Wang et al., 2018) demonstrated an abnormal function of fronto-striatal-thalamic during response inhibition in cocaine users compared to HC. Taken together, results from structural and fMRI suggest that structural damage in fronto-striatal circuit plays a key role in drug addiction.

Our study revealed lower CT in lTC, lOFC and lRFC in CD group compared to HC. These findings are not surprising as cortical thinning have been found in studies of cocaine addiction (Garza-Villarreal et al., 2018, p.; Hirsiger et al., 2019; Kaag et al., 2014; Makris et al., 2008). These CT alterations may be associated with loss of inhibitory and emotional control, as well as difficulties for functioning in a social context (Beer et al., 2003; Szczepanski and Knight, 2014). Thus, alterations in thickness would be an important indicator of functional brain illness (Makris et al., 2008). Furthermore, we found a negative correlation between crack-cocaine years of use and ITC and lOFC CT. However, the partial correlation adjusted by age between lOFC CT and crack-cocaine years of use did not remain significant. Two meta-analyses also reported an association between duration of cocaine use and GM abnormalities (Ersche et al., 2013; Hall et al., 2015). Moreover, our findings of lower lOFC CT are consistent with findings reported by Hirsiger et al. (Hirsiger et al., 2019). The authors also found longitudinal CT changes in the middle frontal gyrus, which includes the lRFC region shown to have cortical thinning in this study (Hirsiger et al., 2019). These findings suggest that the CT abnormalities of crack-cocaine users are, at least in part, drug-induced.

Interestingly, we did not find a significant correlation between striatal subnuclei volume and years of crack-cocaine consumption. Studies with a similar design as presented here also failed to demonstrate an association between years consuming crack-cocaine and striatum volume (Barrós-Loscertales et al., 2011; Garza-Villarreal et al., 2017; Hirsiger et al., 2019). Although we found lower volume in right hippocampus in CD, we did not find the same negative correlation reported by hall et al. between right hippocampus volume and duration of crack-cocaine use (Hall et al., 2015). Additionally, when co-varying for years of study the group differences in ventral diencephalon and right hippocampus did not remain significant. We also found enlargement in the left inferior lateral ventricle in CD, but the positive correlation between duration of crack-cocaine use and left inferior lateral ventricle did not remain significant after adjusting for age. It is not surprising as ventricular enlargement has been found in normal aging (Lg et al., 2012). Taken together, these findings may imply that cocaine has either no chronic effect on the volume of subcortical structures or even it could be a neural indicator linked to a higher vulnerability for crack-cocaine addiction.

Future steps in neuroimaging are moving toward the use of this knowledge to improve patient care to crack-cocaine addicted individuals. The integration of neuromarkers into the diagnosis and prognosis of addictions may help psychiatrists to select the most beneficial treatment for each patient. Interestingly, a recent longitudinal study showed that decreasing cocaine consumption was associated with increasing CT in the follow-up. In addition, the same study showed a tendency of decreased frontal CT in subjects with sustained or increased cocaine intake (Hirsiger et al., 2019). The corroboration of our results in longitudinal studies provides information that support the importance of prolonged abstinence periods, since GM fronto-striatal dysfunction recovery may be associated with more effective treatments. Surprisingly, we found no associations between drug use severity, abstinence symptoms, age of crack-cocaine use onset and GM measures. Outcome studies investigating differential treatment modalities may help elucidate the clinical implications of these GM abnormalities.

Strengths of this study include the investigation of contradictory MRI imaging aspects of crack-cocaine addiction, a suitable matched control sample and the use of recognized methods of image analysis. Nevertheless, we recognize some limitations in this report. The small sample size reduces the power of the study, and as such the results should be interpreted with caution. Furthermore, neuroimaging data from 12 participants were excluded from the analyses. We argue that crack-cocaine addicts are a difficult population to study, especially in the context of neuroimaging research, due to its social vulnerability, impulsive behaviors, unfamiliarity about medical procedures such as MRI scans, and possible weak motivation to complete this study. In addition, other authors have reported similar difficulties (Kiluk et al., 2013; Paim Kessler et al., 2012; Schuch-Goi et al., 2017; Weller et al., 2011). Even though we demonstrated significant results with a relatively small sample size, studies enrolling more subjects may provide more substantial differences in other brain areas in crack-cocaine users. Our sample consisted exclusively of men, so collected results could not be generalized to a larger population.

Bearing in mind that CD subjects presented concomitant regular use of alcohol and tobacco, it is not clear how specific our findings might be for crack-cocaine use. Co-occurring substance use is a general issue for all studies of human substance dependence. The mega-analysis of Mackey et al. reported that alcohol had the greatest effects on GM structures (Mackey et al., 2019). Alcohol use disorder is very prevalent in the population of crack-cocaine addicts, so exposure to alcohol is nearly inevitable in this population (Gossop et al., 2006). However, we found no association between alcohol consumption patterns and GM abnormalities. In order to maintain the generalization of our findings, we chose not to exclude alcohol use disorder in the sample. Furthermore, years in life that smoked cigarettes was not significantly correlated with GM alterations, supporting previous findings that showed that GM alterations found in CD were not associated with tobacco use severity (Crunelle et al., 2014; Hirsiger et al., 2019). Moreover, the mixture of cocaine with levamisole is linked to neurotoxic effects in addicts with regular use of levamisole-contaminated cocaine (Vonmoos et al., 2018). Therefore, it is another potential source of variance in our analyses, bearing in mind that levamisole is currently one of the most common crack-cocaine adulterants in Brazil (Ribeiro et al., 2019).

Finally, the cross-sectional design of our studies cannot let us define cause-and-effect in crack-cocaine addiction. We acknowledge that this question can only be tested using longitudinal studies in populations at risk of crack-cocaine use. Despite these shortcomings, our findings can stimulate new studies aiming to deepen the knowledge about neuroanatomical underpinnings of different ways of cocaine consumption and the role that fronto-striatal pathology plays in crack-cocaine addiction.

Contributors

Pedro Eugenio Mazzucchi Santana Ferreira, Mario Francisco Pereira Juruena and Rodrigo Grassi de Oliveira directed the experiment's overall thinking and design. Augusto Martins Lucas Bittencourt, Vinicius Faccin Bampi, Rafael Canani Sommer and Vanessa Schaker conceived of the design' details and analytic plan and performed statistical analyses, then drafted the manuscript together. Ricardo Bernardi Soder, Alexandre Franco da Rosa and Breno Sanvicente Vieira led data collection. All authors contributed to and approved the final manuscript.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Supplementary materials

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