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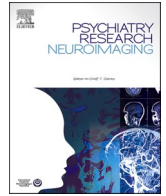
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Brain alterations in Cocaine Use Disorder: Does the route of use matter and does it relate to the treatment outcome?

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ABSTRACT

Aims: Cocaine Use Disorder (CUD) is an important health issue, associated with structural brain abnormalities. However, the impact of the route of administration and their predictive value for relapse remain unknown. **Methods:** We conducted an anatomical MRI study in 55 CUD patients (26 CUD-Crack and 29 CUD-Hydro) entering inpatient detoxification, and 38 matched healthy controls. In patients, a 3-months outpatient follow-up was carried out to specify the treatment outcome status (relapser when cocaine was consumed once or more during the past month). A Voxel-Based Morphometry approach was used.

Results: Compared with controls, CUD patients had widespread gray matter alterations, mostly in frontal and temporal cortices, but also in the cerebellum and several sub-cortical structures. We then compared CUD-Crack with CUD-Hydro patients and found that crack-cocaine use was associated with lower volume in the right inferior and middle temporal gyri, and the right fusiform gyrus. Cerebellar vermis was smaller during detoxification in subsequent relapsers compared to three-months abstainers.

Conclusions: Patients with CUD display widespread cortical and subcortical brain shrinkage. Patients with preferential crack-cocaine use and subsequent relapsers showed specific gray matter volume deficits, suggesting that different patterns of cocaine use and different clinical outcome are associated with different brain macrostructure.

1. Introduction

According to the World Drug Report 2022, 21.5 million people used cocaine in 2020, which represents 0.4 % of the global population (aged 15–64 years old). The prevalence of cocaine use is continuously rising (UNODC 2022), especially for crack-cocaine (European Monitoring Centre for Drugs and Drug Addiction 2021; Vaiano et al., 2019). Chronic

cocaine use can lead to a wide range of health issues. Many of them are somatic, including cardiovascular, neurologic or infectious (mainly related to an intravenous or smoking use) complications, but they can also be psychiatric, cognitive or social (Eiden et al., 2021). Because cocaine is a highly addictive substance, its repeated use can lead to the development of a Cocaine Use Disorder (CUD). CUD is characterized by a chronic consumption of cocaine with a loss of control, an inability to

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stop despite known harmful consequences and – especially – a chronic course due to frequent relapses (Paliwal et al., 2008). Early relapse has been associated with the use of crack-cocaine instead of cocaine hydrochloride, a shorter inpatient stay, the use of a rapid route of administration (i.e. crack or i.v. vs. snorted), and heavy consumption at treatment entrance (Poireau et al., 2024). Despite its recognition as a public health concern, there is no approved pharmacological treatment for CUD.

Chronic cocaine use affects brain structure and function. Concerning brain macrostructure examined with anatomical MRI, previous studies are mainly cross-sectional with comparisons of cocaine users and healthy controls most frequently using a whole-brain approach based on Voxel-Based Morphometry (VBM) analyses. The lateral temporal cortex is described as particularly affected, with several studies showing smaller volumes in cocaine users compared to healthy controls (Alia-Klein et al., 2011; Bartzokis, 2000; Beheshti, 2023; Franklin et al., 2002; Ide et al., 2014; Sim et al., 2007). The volumes of the frontal cortex (Ide et al., 2014; Hanlon et al., 2011; Meade et al., 2020; Rabin et al., 2022b) and more specifically the orbitofrontal cortex (Alia-Klein et al., 2011; Sim et al., 2007; Meade et al., 2020; Matuskey et al., 2014; Rabin et al., 2022a) are also lower in cocaine users. Finally, the cerebellum is consistently damaged, with many studies showing cerebellar shrinkage in cocaine users (Ide et al., 2014; Meade et al., 2020; Rabin et al., 2022b).

Results have been less consistent regarding other brain structures. For example, some studies showed volume deficits for the thalami (Sim et al., 2007; Ersche et al., 2011; Xu et al., 2014) or insula (Franklin et al., 2002; Connolly et al., 2013; Gardini and Venneri, 2012; Moreno-López et al., 2012). Regarding subcortical brain regions, the caudate nuclei (Hanlon et al., 2011; Moreno-López et al., 2012; Xu et al., 2023) and amygdala (Rabin et al., 2022b; Moreno-López et al., 2012; Barrós-Lo-scetales et al., 2011) seems especially affected by cocaine use.

The relationships between these structural brain abnormalities and treatment outcome remain unclear. A longitudinal study, including abstinent CUD patients (with different duration of abstinence maintenance) compared to healthy controls, showed that longer abstinence was positively correlated with GM volumes in the left insula, left culmen of cerebellum, right middle temporal gyrus and bilateral superior frontal gyri (Connolly et al., 2013). These observations could be interpreted as the result of recovery in abstinent CUD patients, or either as predispositions to abstinence maintenance. Another cross-sectional investigation found that the medial prefrontal and orbitofrontal cortices volumes were higher in 6-months abstinent CUD patients compared to active users (Hanlon et al., 2011). Surprisingly, one study showed opposite results, with higher hippocampal volumes associated with poorer treatment outcome (Xu et al., 2014). Another MRI study comparing 227 patients with CUD recruited in several clinical trials to large samples of around 2000 patients with various other substance use disorders (alcohol, nicotine, methamphetamine) showed intriguing results. Patients with CUD showed lower right supramarginal gyrus volumes compared to controls, but the authors could not identify specific anatomic variations in patients with CUD and rather a general "substance effect" than a specific cocaine effect (Mackey et al., 2019).

A few studies particularly examined macrostructural brain damage in patients with crack-cocaine use disorder. Two studies showed shrinkage of the left accumbens nuclei compared to controls (Bittencourt et al., 2021; Schuch-Goi et al., 2017). Volume deficits were also reported for the striatum and thalamus (Garza-Villarreal et al., 2017), as well as for the prefrontal cortex (Fein et al., 2002). To the best of our knowledge, no MRI study directly compared crack-cocaine and cocaine hydrochloride users. However, given the administration mode, i.e. the fact that crack-cocaine is mostly consumed by smoking which represents a rapid route of use, we could expect more severe structural brain abnormalities in crack-cocaine users compared to cocaine hydrochloride users. From a clinical perspective, crack-cocaine use is associated with a more severe CUD, more severe cognitive impairments and an earlier

relapse (Czermaini et al., 2017; Lopes-Rosa et al., 2017) compared to cocaine hydrochloride use.

The first aim of the present study was to examine gray matter brain alterations in early-detoxified patients with severe CUD compared with healthy controls, using a VBM approach. The second aim was to conduct a direct comparison between patients with crack-cocaine and cocaine-hydrochloride use disorders. Finally, the third goal was to study, in severe CUD patients, the relationships between brain volume deficits observed early after detoxification and treatment outcome.

2. Methods and materials

2.1. Study participants

CUD inpatients ($n = 55$) were recruited in the Paris area, from specialized tertiary care (Academic Hospital Fernand-Widal) and private-based care (Château de Garches, France) clinics between 2015 and 2021. They were attending an inpatient detoxification program, with abstinence as a therapeutic goal. They all fulfilled the DSM-5 (Diagnostic and statistical manual of mental disorders: DSM-5TM 2013) diagnosis of severe CUD.

Healthy controls (HC, $n = 38$) were recruited from the ALCOBRAIN study, which took place at another University Hospital in Caen (France) between 2012 and 2016. These controls were free from current and past psychiatric disorders (including being currently under psychotropic medication) and any serious chronic disease including neurological disorders. No participants fulfilled criteria for substance use disorder except tobacco according to the DSM-5 and, regarding alcohol, according to the score at the Alcohol Use Disorders Identification Test (AUDIT), < 7 for men and < 6 for women (Gache et al., 2005). None of the controls had severe depression (evaluated by a score at the Beck Depression Inventory (BDI) superior to 29 (Beck et al., 1996)).

Both the CUD and the HC cohorts were aged ≥ 18 years. None of them were pregnant or nursing, received court-mandated care, were under guardianship, or had contraindication to MRI. All participants gave informed written consent to participate to these studies.

HC were included in this study to match the CUD patients for age and education. Main clinical and demographic data are presented in Table 1.

2.2. Study design

We leveraged data from two MRI-based prospective studies. One recruited CUD patients, the other provided data from healthy controls. Both studies were preregistered (NCT02416050 and NCT01455207, respectively), required participants to provide written informed consent and were approved by the relevant ethic committees (Comité de Protection des Personnes Ile-de France IV 15/01/2015 & Agence Nationale de Sécurité du Médicament 10/10/2014, no. IDRCB: 2014-A01169-38 ; Comité de Protection des Personnes Nord-Ouest III, no. IDRCB: 2011-A00495-36, respectively). Thus, the current prospective study compared (i) CUD patients to controls (ii) (Table 1), patients who mainly used crack-cocaine (CUD-Crack) vs. those who mainly used cocaine hydrochloride (CUD-Hydro) (Table 2) and (iii) CUD patients who relapsed vs. those who did not three months after discharge (Table 3). Main clinical and demographic data of the subgroups CUD-Hydro/Cud-Crack and abstainers/relapsers are respectively presented in Tables 2 and 3.

Within two days after admission to the hospital, an investigator informed CUD patients about the study, collected the written consent and conducted the baseline visit. Sociodemographic information (age, sex, level of education, professional and personal situation), data regarding the pattern of cocaine use (cocaine hydrochloride or crack-cocaine, route of administration, quantity consumed and days of use in the prior month), CUD characteristics (duration of CUD, Visual Analogue craving Scale, Obsessive Compulsive Cocaine craving Scale (Vorspan et al., 2012)), potential comorbid Substance Use Disorders

Table 1
Characteristics (mean and standard deviation or % and n) of the study samples.

	CUD patients (n = 55)	Healthy controls (n = 38)	Between-group comparisons (p-values)
Age (years)	42.5 (±6.2)	44.3 (±6.1)	0.072
Education (years)	12.1 (±3.9)	11.8 (±1.6)	0.592
	<i>1MD</i>		
TIV (liters)	1.4 (±0.1)	1.5 (±0.1)	0.344
Sex ratio (M/F)	44/11	34/4	0.222
Housing:		NA	NA
Stable	76 % (n = 42)		
Unstable	24 % (n = 13)		
Resources:		NA	NA
Employment	53 % (n = 29)		
Social	33 % (n = 18)		
No resources	14 % (n = 8)		
Employment:		NA	NA
Employed	47 % (n = 26)		
Unemployed	53 % (n = 29)		
Marital status:		NA	NA
Married	60 % (n = 33)		
Single	16 % (n = 9)		
Divorced	24 % (n = 13)		
Years of CUD	10.1 (±8.2)	NA	NA
	<i>17MD</i>		
Age of CUD onset	33.1 (±9.9)	NA	NA
	<i>17MD</i>		
Days of use in the prior month	18.1 (±9.1)	NA	NA
	<i>1MD</i>		
Quantity consumed (gr/week)	5.6 (±5.3)		
	<i>2MD</i>		
DSM-5 criteria for CUD	8.8 (±1.6)	NA	NA
	<i>2MD</i>		
MoCA score (n = 45)	24.7 (±4.5)	NA	NA
	<i>10MD</i>		
Craving (VAS)	3.9 (±3.2)	NA	NA
	<i>3MD</i>		
Craving (OCCS):		NA	NA
Total	27.2 (±6.4)		
Obsession	12.8 (±3.9)		
Compulsion	14.4 (±3.0)		
	<i>2MD</i>		
Other SUDs :		NA	NA
- Nicotine	93 % (n = 51)		
- Alcohol	62 % (n = 34)		
- Opiates	33 % (n = 18)		
-Cannabis	26 % (n = 14)		
Days of abstinence	32.2 (±35.2)	NA	NA
	<i>4MD</i>		
Status at 3 months follow-up:		NA	NA
Relapser (%)	81 % (n = 42)		
Abstainer (%)	19 % (n = 10)		
	<i>3MD</i>		

Mann-Whitney U test and χ^2 test for groups comparisons
CUD: Cocaine Use Disorder; DSM-5: The Diagnostic and Statistical Manual of Mental Disorders; MD : Missing Data; MoCA: Montreal Cognitive Assessment; NA: Not Applicable; OCCS: Obsessive Compulsive Craving Scale; SUD: Substance Use Disorder; TIV: Total Intracranial Volume; VAS: Visual Analogue Scale.

(SUD) and current medication were collected. Patients also completed the Montreal COgnitive Assessment (MoCA, (Nasreddine et al., 2005)) to screen for cognitive disorders. Within one week after the inclusion, an anatomical MRI was conducted at the Centre de Neuroimagerie de Recherche (CENIR, Hôpital Pitié-Salpêtrière, Paris). Follow-up interviews were conducted at two weeks, one month and three months after discharge to collect data regarding self-declared cocaine use using the timeline follow-back method (TLFB, (Robinson et al., 2014)). Those visits were conducted by phone or in person if the patient had a scheduled appointment. A patient was considered as a relapser when he/she had used cocaine once or more during the three months follow-up.

HC underwent an anatomical MRI examination performed at the

Table 2
Characteristics (mean and standard deviation or % and n) of the subgroups: CUD-Crack et CUD-Hydro.

	CUD- Hydro (n = 29)	CUD-Crack (n = 26)	Between-group comparisons (p-values)
Age (years)	41.6 (±6.5)	43.4 (±5.9)	0.205
Education (years)	13.4 (±4.1)	10.4 (±3.5)	0.003*
		<i>1MD</i>	
Housing:			
Stable	90 % (n = 26)	62 % (n = 16)	0.014*
Unstable	10 % (n = 3)	38 % (n = 10)	
Resources:			< 0.001*
Employment	79 % (n = 23)	23 % (n = 6)	
Social	17 % (n = 5)	50 % (n = 13)	
No resources	4 % (n = 1)	7 % (n = 7)	
Employment:			< 0.001*
Employed	72 % (n = 21)	19 % (n = 5)	
Unemployed	28 % (n = 8)	81 % (n = 21)	
Marital status:			< 0.001*
Married	62 % (n = 18)	58 % (n = 15)	
Single	21 % (n = 6)	11 % (n = 3)	
Divorced	17 % (n = 5)	31 % (n = 8)	
Years of CUD	8.3 (±7.1)	12.4 (±9.1)	0.227
	<i>8MD</i>	<i>9MD</i>	
Days of use in the prior month	15.0 (±8.9)	21.8 (±8.0)	0.006*
		<i>1MD</i>	
Quantity consumed (gr/week)	5.6 (±5.0)	5.8 (±5.8)	0.648
		<i>2MD</i>	
DSM-5 criteria for CUD	9 (±1.7)	8.5 (±1.6)	0.094
	<i>1MD</i>	<i>1MD</i>	
MoCA score	26.7 (±3.2)	22.4 (±4.7)	< 0.001*
	<i>5MD</i>	<i>5MD</i>	
Craving (VAS)	3.8 (±3.3)	4.0 (±3.1)	0.780
		<i>3MD</i>	
Craving (OCCS):			
Total	25.8 (±6.2)	29.0 (±6.3)	0.101
Obsession	11.9 (±3.6)	14.0 (±4.0)	0.053
Compulsion	13.9 (±3.0)	15 (±2.9)	0.239
		<i>2MD</i>	
Status at 3 months:			0.065
Relapser	71% (n = 20)	92 % (n = 22)	
Abstainer	29 % (n = 8)	8 % (n = 2)	
	<i>1MD</i>	<i>2MD</i>	
Days of abstinence	41.7 (±37.3)	21.4 (±29.8)	0.015*
	<i>2MD</i>	<i>2MD</i>	

Mann-Whitney U test and χ^2 test for groups comparisons
CUD: Cocaine Use Disorder; DSM-5: The Diagnostic and Statistical Manual of Mental Disorders; MoCA: Montreal Cognitive Assessment; NA: Not Applicable; OCCS: Obsessive Compulsive Craving Scale; VAS: Visual Analogue Scale.

Cyceron neuroimaging centre in Caen (France) and sociodemographical information such as sex, age and education level were notably collected. Data using these control subjects have already been published (Laniecep et al., 2020; Ritz et al., 2016).

Table 3
Characteristics (mean and standard deviation or % and n) of the subgroups: relapsers and abstainers.

	Abstainers (n = 9)	Relapsers (n = 41)	Between-group comparisons (p-values)
Age (years)	40.6 (±7.4)	42.9 (±6.3)	0.206
Education (years)	13.1 (±4.8)	11.4 (±4.0)	0.275
		<i>1MD</i>	
Housing:			0.890
Stable	78 % (n = 7)	76 % (n = 31)	
Unstable	22 % (n = 2)	24 % (n = 10)	
Resources:			0.206
Employment	78 % (n = 7)	46 % (n = 19)	
Social	11 % (n = 1)	39 % (n = 16)	
No resources	11 % (n = 1)	15 % (n = 6)	
Employment:			0.944
Employed	56 % (n = 5)	44 % (n = 18)	
Unemployed	44 % (n = 4)	56 % (n = 23)	
Marital status:			0.378
Married	44.5 % (n = 4)	61 % (n = 25)	
Single	11 % (n = 1)	17 % (n = 7)	
Divorced	44.5 % (n = 4)	22 % (n = 9)	
Years of CUD	5.5 (±3.0)	10.5 (±8.7)	0.420
	<i>5MD</i>	<i>10MD</i>	
Days of use in the prior month	9.3 (±4.9)	20.3 (±8.3)	< 0.001*
	<i>1MD</i>	<i>1MD</i>	
Quantity consumed (gr/week)	2.5 (±1.6)	6.5 (±5.7)	0.059
	<i>1MD</i>	<i>1MD</i>	
DSM-5 criteria for CUD	8.9 (±1.2)	8.8 (±1.6)	0.854
	<i>1MD</i>	<i>1MD</i>	
MoCA score	28.0 (±2.0)	24.1 (±4.6)	0.018*
	<i>7MD</i>	<i>2MD</i>	
Craving (VAS)	3.2 (±3.0)	3.9 (±3.3)	0.636
	<i>1MD</i>	<i>1MD</i>	
Craving (OCCS):			
Total	27.4 (±5.8)	27.8 (±6.5)	0.608
Obsession	13.4 (±13.4)	13.0 (±13.0)	0.934
Compulsion	14.0 (±2.8)	14.8 (±2.9)	0.412
	<i>1MD</i>	<i>1MD</i>	

Mann-Whitney U test and χ^2 test for groups comparisons

CUD: Cocaine Use Disorder; DSM-5: The Diagnostic and Statistical Manual of Mental Disorders; MoCA: Montreal Cognitive Assessment; NA: Not Applicable; OCCS: Obsessive Compulsive Craving Scale; VAS: Visual Analogue Scale.

2.3. MRI acquisition and preprocessing

2.3.1. Images acquisition

CUD patients underwent a high-resolution T1-weighted anatomical image on a Siemens Magnetom 3T scanner (CENIR Imaging Center in Paris), using a 3D fast-field echo sequence (176 sagittal slices, thickness = 1 mm, repetition time = 2300 ms, echo time = 7.1 ms, flip angle = 9°, field of view, 256 × 256 mm², matrix, 256 × 256).

Healthy controls underwent a high-resolution T1-weighted anatomical image on a Philips Achieva 3T scanner (Cyceron Imaging Center in Caen), using a 3D fast-field echo sequence (180 sagittal slices; thickness = 1 mm; repetition time = 20 ms; echo time = 4.6 ms; flip angle = 10°; field of view, 256 × 256 mm²; matrix, 256 × 256).

2.3.2. Image preprocessing

The volumetric MRI data were preprocessed and analyzed using the Statistical Parametric Mapping Software (SPM12; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). The MRI

images were segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) and normalized to the standardized Montreal Neurological Institute (MNI) space. These were then modulated by their respective Jacobian determinants to account for brain size and preserve their volumes in MNI space. Finally, the resulting images were smoothed by a Gaussian kernel of 8-mm Full Width at Half Maximum (FWHM). The resulting image resolution is 1.5mm³ isotropic, matrix size 121 × 145 × 121.

A gray matter mask was obtained taking the unmodulated gray matter images, normalized to the MNI space, averaging them, and thresholding the resultant mean image at 0.5. The resulting gray matter mask was applied to the gray matter analysis.

2.4. Statistical analysis

Brain imaging data analyses were performed with a voxel-based approach using SPM12 (Friston, 2008). As far as volumetric data is concerned, comparison of anatomical images having the same image properties and having undergone an optimized preprocessing to yield images having the same resolution do not have significant scanner-specific differences (Stonnington et al., 2008). Hence, data can be pooled together for analysis. First, we conducted two samples *t*-tests (with age, education level and total intracranial volume (TIV) as covariates) to compare brain volumes between CUD and HC. We used a significance threshold set at $p < 0.05$ (family-wise error (FWE) corrected). We set the minimum cluster size at $k = 60$ voxels (approximately 200 mm³). Also, we performed two samples *t*-tests (with age, education level and total intracranial volume (TIV) as covariates) within the CUD patients' group, categorizing them based on the presence or absence of comorbid SUD (alcohol $N = 34$ versus $N = 21$, cannabis $N = 14$ versus $N = 41$, opiates $N = 18$ versus $N = 37$). Regarding nicotine, given the high prevalence of smokers in our cohort ($N = 51$ out of 55 CUD patients), we could not examine the difference between CUD patients with and without nicotine use disorder. This analysis aimed to evaluate the potential influence of these additional SUDs on the identified brain alterations.

Secondly, we classified CUD patients into two subgroups according to whether their main cocaine use: CUD-Crack ($n = 26$) and CUD-Hydro ($n = 29$). We compared brain volumes between the two subgroups with two samples *t*-tests (with age, education levels and TIV as covariates) using a less stringent significance threshold set at $p < 0.001$ (uncorrected) since we expected more subtle differences, and a cluster size at $k = 60$ voxels.

Thirdly, we examined whether volume deficits at baseline during detoxification program was associated with three-months outcome. Relapsers ($n = 41$) and abstainers ($n = 9$) were compared with two samples *t*-tests (using age, education levels and TIV as covariates). The significance threshold was set at $p < 0.001$ (uncorrected) and the cluster size at $k = 60$ voxels.

Results were labeled using the JHU Atlas (Tzourio-Mazoyer et al., 2002).

3. Results

3.1. Gray matter volume differences CUD patients and HC ($p < 0.05$ FWE corrected)

Compared to HC, CUD patients showed widespread alterations of gray matter volume (Fig. 1). They had significantly lower GM volumes in the temporal (superior, middle and inferior temporal gyri, hippocampus, fusiform gyrus) and frontal (precentral gyrus, middle frontal gyrus (dorsal prefrontal cortex (PFC)), inferior frontal gyrus (pars opercularis), superior frontal gyrus right (PFC), lateral fronto-orbital gyrus, gyrus rectus) cortices. They also showed volume deficits in the parietal (such as the postcentral gyrus, left angular gyrus and supramarginal gyrus) and occipital (middle and superior occipital gyri, left inferior occipital

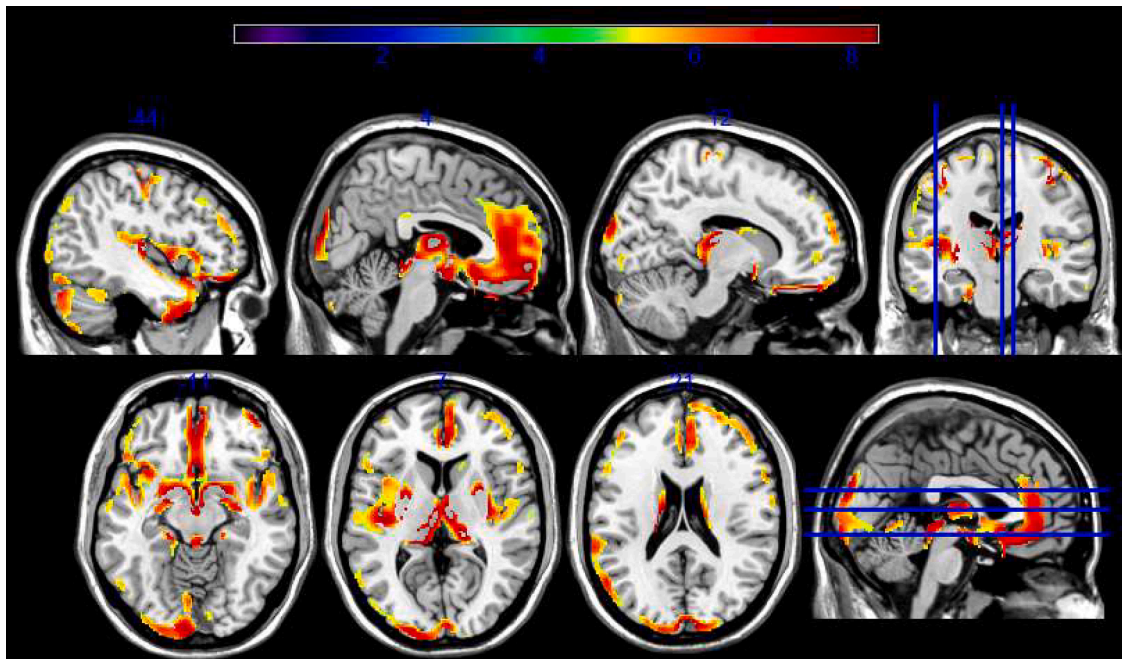


Fig. 1. Gray matter brain abnormalities in CUD patients compared to healthy controls $p < 0.05$ (FWE corrected for multiple comparisons), minimum cluster size: $k > 60$ voxels. The colored bar represents T values.

gyrus, cuneus) cortices. The insula, and more particularly the posterior insula was also affected. Lower GM volumes were observed in the amygdala, cingulate cortex (rostral, subcallosal and subgenual anterior, posterior right), thalamus, hypothalamus, and striatum (putamen, caudate and accumbens nucleus). Finally, the cerebellum was also affected, with shrinkage of the vermis 4,5, the crus 1 and 2 and the part 7b, 8 and the left part of 6, 9 and 10.

The opposite contrast (HC<CUD) did not reveal any significant difference.

Also, group comparisons of gray matter volumes conducted by dividing the CUD patients sample according to other comorbid current substance use disorders (alcohol $N = 34$ versus $N = 21$, cannabis $N = 14$ versus $N = 41$, opiates $N = 18$ versus $N = 37$) did not show significant

results.

3.2. Gray matter volume differences between CUD-Crack and CUD-Hydro patients ($p < 0.001$ uncorrected)

The CUD-Crack subgroup showed significantly lower GM volume in the right inferior and middle temporal cortex, as well as in the right fusiform gyrus compared to the CUD-Hydro subgroup (Fig. 2).

There were no significant results for the opposite contrast.

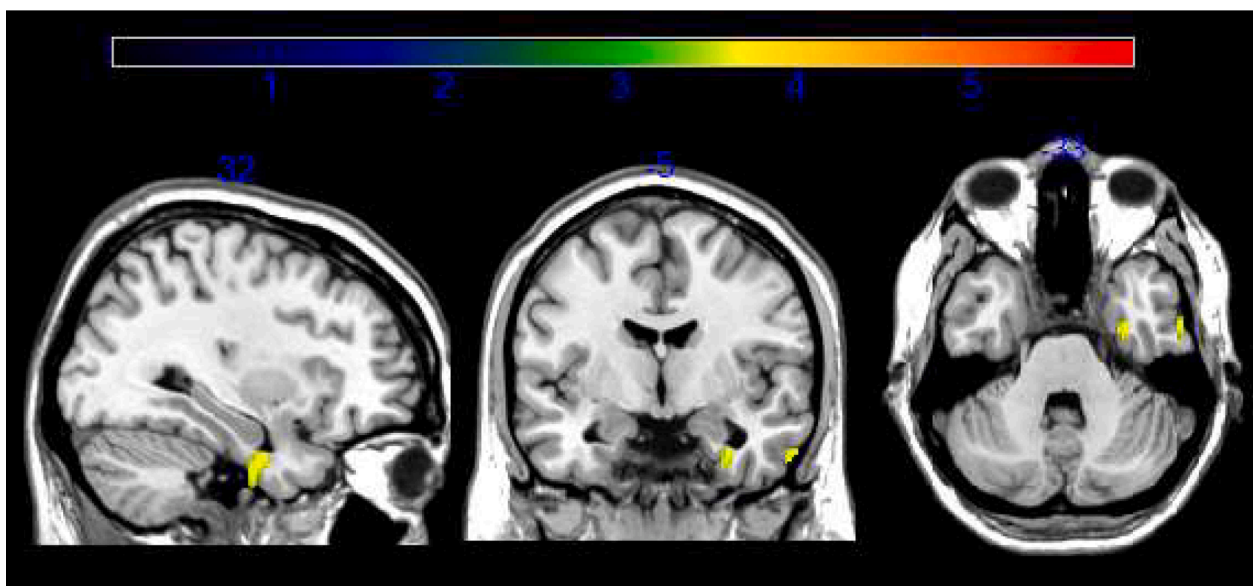


Fig. 2. Gray matter brain abnormalities in CUD-Crack compared to CUD-Hydro $p < 0.001$ uncorrected, minimum cluster size: $k > 60$ voxels. The colored bar represents T values.

3.3. Gray matter volume differences at baseline between relapsers and abstainers at 3 months ($p < 0.001$ uncorrected)

Compared to abstainers, relapsers had a significant shrinkage of the cerebellar vermis (4–5) at baseline, i.e. during detoxification (Fig. 3). Among all CUD patients, the duration of abstinence maintenance was not significantly correlated to GM volume.

4. Discussion

The present study first identified widespread cortical and subcortical GM alterations in early-detoxified patients with severe CUD compared with healthy controls. We also found that crack-cocaine use was associated with specific volume deficits compared to cocaine-hydrochloride use. Lastly, we identified that relapse at 3 months was associated with smaller cerebellar volume during early detoxification.

Our results identifying widespread brain structural alterations in patients with CUD are in line with previous investigations. We confirm that cortical shrinkage particularly affects the frontal and temporal cortices (Bartzokis, 2000; Beheshti, 2023; Ersche et al., 2011). Results concerning the limbic system (hypothalamus, amygdala, cingulate cortex) and the striatum also confirm the more limited literature regarding these brain regions (Beheshti, 2023; Xu et al., 2023; Moeller et al., 2016). For the cerebellum, smaller volumes in cocaine users have already been published in several studies (Ide et al., 2014; Sim et al., 2007; Hanlon et al., 2011; Meade et al., 2020). However, these results frequently concerned the cerebellum considered as a single brain structure, without exploring which cerebellar subregions may be especially affected. The present study enabled us to highlight more precise and localized anatomical alterations in the cerebellum.

More globally, the present study refines our knowledge of the pattern of GM brain abnormalities associated with CUD. The novelty of the present study is to explore whether there are specific structural brain alterations associated with crack-cocaine compared to cocaine-hydrochloride use. In particular, we identified that CUD-Crack patients showed smaller volumes in the right inferior and middle temporal cortex and in the right fusiform gyrus, compared to CUD-Hydro patients. We had hypothesized that CUD-Crack patients would present more severe brain damage than CUD-Hydro patients, due to the consequences of this rapid route of consumption. The use of crack-cocaine is related to a higher risk of chronic consumption, heavier cocaine use and dependence development (Martin et al., 2014) and – more importantly for our findings – shorter periods of continuous abstinence (Kiluk et al., 2013) when compared to using intranasal cocaine-hydrochloride. Some studies

had already identified alterations in the right inferior and middle temporal cortex among cocaine users, yet without comparing routes of cocaine use (Ide et al., 2014; Moreno-López et al., 2012). A meta-analysis, which reviewed original studies exploring anatomical MRI in cocaine and methamphetamine-dependent patients, reported that lower GM volumes in the right inferior and middle temporal gyri were associated with longer cocaine use in cocaine-dependent patients (Hall et al., 2015). Among studies exploring brain alterations in crack-cocaine users compared to healthy controls, one study comparing nine homeless crack-cocaine dependent users to healthy controls reported alterations in the temporal cortex, showing reduced volumes of the right superior temporal gyrus (RosallynE et al., 2011). These temporal alterations have therefore been already observed in CUD patients, but it has never been demonstrated that they could be more severe in crack-cocaine. This finding could be related to the fact that crack-cocaine patients frequently present cognitive impairments (Di Sclafani et al., 1998). Indeed, it has been reported that compared to controls, crack-cocaine patients present lower visual and verbal memory performance (Cunha et al., 2004). The relationships between altered brain structure and functions need now to be explored in CUD, taking the administration route into account.

Although the mega analysis by Mackey et al. failed to identify gray matter alterations specifically associated with CUD and rather observed a general "any-substance" effect, several points have to be kept in mind (Mackey et al., 2019). Mackey et al. included 227 patients with CUD, and around 900 patients with alcohol use disorder and 600 patients with nicotine use disorder. This study therefore could probably be underpowered to detect specific anatomic variation associated with CUD, and a more balanced design should have been chosen if this was their primary question. Furthermore, the authors did not differentiate the use of cocaine hydrochloride and crack-cocaine, which could be associated with different brain alterations as showed in our study. Indeed, in addition to the fact that crack is smoked, we showed that patients who use crack are older than those who use cocaine, and that they also present more deleterious socioeconomic backgrounds. These factors could be linked to specific brain alterations observed in crack users in our study. But we must acknowledge that we cannot rule out a general "any-substance" effect, especially since the included patients in our samples were poly-substance users. This general substance effect could be related to pre-existing brain variations related to genetic or socio-economic factors or be acquired during the patients lifespan, with the direct toxic effect of poly-substance chronic use, the toxic effect of adulterant compounds such as levamisole (Solomon and Hayes, 2017), or other nutritional or pathophysiological effects, including psychiatric

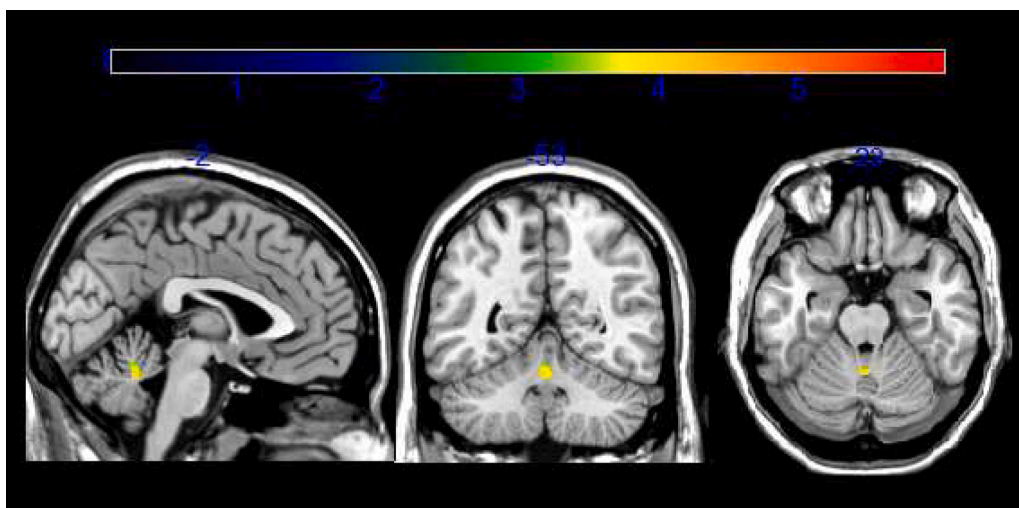


Fig. 3. Gray matter brain abnormalities in relapsers compared to abstainers $p < 0.001$ uncorrected, minimum cluster size: $k > 60$ voxels. The colored bar represents T values.

or neurological conditions, or treatments.

Finally, our results suggest that CUD patients who will relapse 3 months after detoxification have significantly smaller cerebellar vermis volumes than patients who achieve to maintain abstinence. In the few studies that investigated associations between brain volume and abstinence, patients already abstinent for several weeks were typically compared to active users. The observed volume differences may thus reflect the cerebral recovery that is thought to accompany abstinence. Interestingly, one clinical study focused on abstinent CUD patients examined at different time-points. Longer abstinence maintenance was positively correlated with the volume of the upper part of the superior vermis (Connolly et al., 2013). In our study, all patients were scanned one week after treatment entry and had used cocaine the month before. We can thus hypothesize that they stand at similar stages of the detoxification process. Our results might thus truly reflect a predisposition to relapse after discharge. Several studies have explored the role of cerebellum in CUD. A preclinical study has especially investigated the association between cerebellar vermis and drug-induced Pavlovian memories, suggesting that the cerebellum could be involved in the inhibition of cocaine-related memories (Gil-Miravet et al., 2019). Furthermore, an increased activity of the cerebellum has been related to cocaine craving in PET-imaging studies (Bonson et al., 2002; Grant et al., 1996). One functional imaging study also demonstrated that the vermis was activated in cocaine abusers during cocaine-related cues exposition (Anderson et al., 2006). As craving has already been associated with relapse in cocaine dependent patients (Bell et al., 2014; Bordnick and Schmitz, 1998; Weiss et al., 2003), it would be interesting to further explore the role of cerebellum in craving and the association with relapse.

Our study also has limitations. The group of CUD patients was homogeneous in terms of main substance use disorder and detoxification stage, but suffered from a variety of comorbid conditions and used medications that were not controlled for. This could have slightly biased the comparison with HC and may have influenced our findings regarding relapse. Additionally, the group of abstainers was small (nine patients), which could have affected the statistical power of our third analysis. Nevertheless, this group size difference is clinically representative of treatment outcome in CUD patients, with more than 72 % of relapse within three months after detoxification (Paliwal et al., 2008).

The present study confirmed the widespread brain structural damage observed in CUD patients. The temporal and frontal cortices, the cerebellum, several regions of the limbic system and the striatum are significantly affected by chronic cocaine use. We also demonstrated for the first time that the administration route of cocaine use matters, since CUD-Crack patients showed lower volumes in the right inferior and middle temporal gyrus, as well as in the fusiform gyrus, compared to CUD-Hydro patients. Finally, the use of structural MRI data can be useful to predict cocaine relapse. Indeed, CUD patients relapsing within three months after cocaine inpatient detoxification showed lower volumes in the cerebellar vermis compared to those maintaining abstinence after discharge. While the literature exploring structural abnormalities associated with CUD is already documented, our results on their association with the administration route and treatment outcome could notably pave the way for further specific research about crack-cocaine use disorder, as well as provide new possible directions for cocaine treatment improvement.

CRedit authorship contribution statement

Margaux Poireau: Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Shailendra Segobin:** Writing – review & editing, Resources, Methodology. **Angéline Maillard:** Writing – review & editing, Methodology, Formal analysis. **Virgile Clergue-Duval:** Writing – review & editing, Investigation. **Romain Icick:** Writing – review & editing, Investigation. **Julien Azuar:** Investigation. **Emmanuelle Volle:** Conceptualization. **Christine Delmaire:**

Conceptualization. **Vanessa Bloch:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Anne-Lise Pitel:** Writing – review & editing, Supervision, Resources, Methodology. **Florence Vorspan:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

All authors declared no financial disclosures or conflict of interest.

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