European Psychiatry

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Let's focus on the insula in addiction: A refined anatomical exploration of insula in severe alcohol and cocaine use disorders

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Research Article

Cite this article: Billaux P, Segobin S, Maillard A, Bloch V, Delmaire C, Cabé N, Laniepce A, Maurage P, Poireau M, Volle E, Vorspan F, Pitel A-L (2024). Let's focus on the insula in addiction: A refined anatomical exploration of insula in severe alcohol and cocaine use disorders. *European Psychiatry*, **67**(1), e75, 1–7
https://doi.org/10.1192/j.eurpsy.2024.1784

Received: 23 April 2024
Revised: 05 August 2024
Accepted: 06 August 2024

Keywords:
addiction; brain volume; MRI; parcellation

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Abstract

Background. Theoretical and empirical contributions have identified insula as key in addiction. However, anatomical modifications of the insula in addictive states, and their variations across substance use disorders (SUDs), remain to be specifically explored. We therefore explored the specificities and commonalities of insula gray matter (GM) alterations in severe alcohol use disorder (sAUD) and severe cocaine use disorder (sCUD).

Methods. We explored insula GM volume through a refined parcellation in 12 subregions (six bilateral): anterior inferior cortex (AIC), anterior short gyrus, middle short gyrus, posterior short gyrus, anterior long gyrus (ALG), and posterior long gyrus (PLG). Using a linear mixed model analysis, we explored the insula volume profiles of 50 patients with sAUD, 61 patients with sCUD, and 36 healthy controls (HCs).

Results. In both sAUD and sCUD, we showed overall insular lower volume with a right-sided lateralization effect, and a major volume deficit in bilateral ALG. Moreover, differences emerged across groups, with higher left AIC and PLG volume deficits in sCUD compared to sAUD and HC.

Conclusions. We offered the first joint exploration of GM insular volumes in two SUD through refined parcellation, thus unveiling the similarities and dissimilarities in volume deficit profiles. Our results bring evidence complementing prior ones suggesting the core role of the right and posterior insula in craving and interoception, two crucial processes in addiction. Left AIC and PLG group differences also show that, while insula is a region of interest in SUD, sCUD and sAUD generate distinct insular profiles, which might parallel clinical differences across SUD.

Introduction

The insula is an ultra-connected cortical region [1] involved in wide array of processes, including sensory (e.g., olfaction [2]), affective [3], and cognitive (e.g., cognitive control [4]) domains. The insula also has a key functional role in interoception, the ability to build a representation of the internal self of the body, encompassing sensing, interpretation, integration, and regulation of internal signals [5].

Interoceptive signals, traditionally defined as emanating from beneath the skin, are brought to insula through the lamina I spinothalamocortical pathway (also called interoceptive pathway) [6–8]. In the insula, those signals follow a posterior-to-mid-to-anterior processing, generating a progressive refinement of interoceptive representation, notably through associations between insula and concomitant brain regions [6, 8, 9]. In the posterior insula, bodily information is processed, providing an *objective* representation of visceral bodily states, notably through connections with parietal regions [10], such as the somatosensory cortex [11]. Then, in the rostral insula, a *subjective* meta-representation of interoceptive information is hypothesized [7], capitalizing on connections with the frontal cortex [10, 12].

Such involvement in interoception through connections with somatosensory and frontal areas had led theoretical models to postulate that insula constitutes a pivotal region in addictive disorders, notably for the emergence of a key process in these disorders, namely craving. Insula would integrate visceral interoceptive information related to bodily effects of the substance consumed and refine such message with higher-level processes such as emotion and motivation [13]. In addition, through its bidirectional connection to the amygdala–striatal neural system and prefrontal cortex [14], the insula would enable an association between bodily effects of a substance and its pleasurable effects, while disabling cognitive control [15, 16]. Behavioral consequences of such neural processing would therefore be craving, the irrepressible urge to further seek the substance and its consumption, contributing to the onset and/or maintenance of substance use disorder (SUD) [16, 17].

Such theories of insula as key craving neural substrate received initial empirical support through a seminal study reporting insular lesions to result in addictive behaviors cessation, due to a sudden craving hiatus [18]. Moreover, insular lower volume is found across substances – being, thus, conceptualized as being part of a common addiction neural substrate [19]. However, while these empirical reports provide invaluable information regarding insular role in addiction, they remain quite imprecise as they relied on an overall exploration of insula. As previously mentioned, insula is not an anatomically and structurally unified region, as it is rather composed of multiple subregions with different functions [20, 21]. Preclinical studies have supported such argument by showing that rostral and posterior insula have differentiated involvement levels in rats' drug-seeking behaviors (i.e., inactivation of anterior insula leads to decrease in cocaine-seeking behavior, while posterior insula inactivation has no effect [22]). Recent human studies further underlined the need for refined exploration of insular subregions: in alcohol use disorder, insula has a differential volume deficit profile, with both lateralization (i.e., right-sided [23]) and subregions (i.e., lower volume in posterior insula [24]) specificities. In cocaine use disorder, similar right-sided volume deficit lateralization effect has been observed [25] but there are no refined explorations of insula subregions.

Despite these preliminary results, two major methodological limitations are impeding results generalization across addiction field and, therefore, the understanding of insula contributions in addiction onset and maintenance. First, heterogeneous parcellation techniques followed in insular studies lead to discrepancies in the localization and numbers of insular subregions [26]. While, in rodent studies, an anatomical parcellation of the insula is followed, in the human field insular parcellation relies on functional (activation results), hindering comparisons between human and animal fields but, also, within human field [26]. There are currently studies reporting parcellation ranging from 2 to 13 anatomical or functional insula subregions [20], hindering studies results comparison. Second, the lack of direct and refined comparison of insular subregions specificities across different substances. The few studies exploring gray matter (GM) volume across substances rely almost exclusively on voxel-based morphometry (VBM) technique [27], following whole-brain approaches rather than targeting specific regions of interests, generating results at the overall insular level. Therefore, these studies did not explore specifically similarities and differences in GM abnormalities in different SUD at the insular subregions level. Noteworthy, the few VBM studies exploring brain morphology across SUD report notably shared volume deficit of the insula [27, 28] – thus, again, providing first insights on insula role across addictions, while lacking in precise and refined exploration of the insula subregions profile of volume deficit for given substances.

We aimed at overcoming these limitations in addiction, by exploring GM insula subregions volume in two SUD: patients presenting a severe alcohol use disorder (sAUD) or a severe crack/cocaine use disorder (sCUD). We applied refined parcellation technique that allowed for insula bilateral parcellation in six subregions, thus ending up with a 6 × 2 insular parcellation [29]. Such atlas-based parcellation combines macro-anatomical and probabilistic technics, therefore enabling future studies comparisons, as probabilistic atlas allows for variability in shapes and volumes across subjects [29, 30].

We hypothesized a main group effect, with patient groups showing significant lower volume compared to healthy control (HC). Given the lack of prior direct comparison of insula GM volume using refined parcellation between SUD, we had no specific hypothesis regarding the shared and dissimilar GM insula subregions profiles between sAUD and sCUD. Noteworthy, having shown in a prior study [24] that sAUD had a right-sided and anteroposterior gradient of GM volume deficit compared to HC, we wanted to go further by exploring the commonalities and differences in the pattern of abnormalities of insula in addiction, by adding a sCUD group to our priorly published data.

Methods

Participants

We recruited 61 patients (12 females) with a DSM-5 diagnosis of sCUD (DSM-5 criteria, American Psychiatric Association, 2013). The current study comprised also 50 patients (six females) with a diagnosis of sAUD (DSM-5 criteria, American Psychiatric Association, 2013), and 36 HC (six females), priorly described in [24]. sCUD and sAUD were early abstainers recruited by clinicians from inpatient treatment units (sCUD: Fernand Widal Hospital and Garches Castle Clinic, France; sAUD: Caen University Hospital, France). Patients underwent a first assessment during which clinicians assessed SUD. When included in the study, sAUD showed no more physical symptoms of alcohol withdrawal – as assessed by Cushman's scale [31]. HC, group matched with sAUD and sCUD for education level and gender, were recruited in Caen. HC reported a low pattern of alcohol consumption (score <6 for female and <7 for male at the AUDIT [32, 33]), no symptoms of severe depression (score <29 at the Beck Depression Inventory-II; BDI [34]) and did not present signs of global cognitive alteration (score >126 at the Mattis Dementia Rating Scale; MDRS [35]). All participants spoke French fluently and presented no major medical/neurological disorders. HC and sAUD presented no polysubstance abuse except for nicotine (assessed by the DSM-5 criteria, American Psychiatric Association, 2013). sCUDs were all primarily treated for a CUD. However, due to characteristics inherent to this population, 62% of sCUD presented problematic alcohol use, 21% problematic opioid use, 18% problematic THC use, and 18% problematic benzodiazepine use. Table 1 reports sociodemographic, clinical, neuropsychological, and substances-related variables.

The study protocol was approved by ethical boards (sCUD: Comité de Protection des Personnes Ile de France IV 15/01/2015 and Agence Nationale de Sécurité du Médicament 10/10/2014, no. IDRCB: 2014-A01169-38; sAUD and HC: Caen University Hospital ethical bord, CPP Nord Ouest III, no. IDRCB: 2011-A00495-36) and complied with the Declaration of Helsinki's ethical

https://doi.org/10.1192/j.eurpsy.2024.1784 Published online by Cambridge University Press

Table 1. Sociodemographic, clinical, and substance-related variables of healthy controls (HCs), patients with severe alcohol use disorder (sAUD) and patients with severe crack/cocaine use disorder (sCUD)

	HC	sAUD	sCUD	$F/X^2/t$, p	Between-group comparisons		
Sociodemographic variables	n = 36	n = 50	n = 61		HC vs. sAUD	HC vs. sCUD	sAUD vs. sCUD
Age[a]	44.03 (6.14)	46.88 (8.93)	40.67 (7.07)	8.41, p < 0.001	p = 0.19	p = 0.04	p < 0.001
Education level[a]	11.75 (1.70)	11.78 (2.03)	12.57 (3.88)[1]	1.10, p = 0.34	/	/	/
Gender, male (%)[b]	83.33	88.00	80.33	1.19, p = 0.55	/	/	/
Neuropsychological assessment	n = 20	n = 25	n = 51				
MoCA[a]	27.60 (1.47)	25.92 (3.11)	25.12 (4.37)	7.65, p = 0.001	p = 0.06	p = 0.002	p = 0.63
Substance–related variables[c]	n = 36	n = 50	n = 61				
Abstinence duration (in days, of alcohol for sAUD and crack/cocaine for sCUD)	N/A	11.15 (4.37)[2]	7.41 (4.30)	4.47, p < 0.001	/	/	/
Duration of severe use disorder (in years, of alcohol for sAUD and crack/cocaine for sCUD)	N/A	12.87 (9.21)[3]	8.89 (7.89)[7]	2.32, p = 0.02	/	/	/
Daily consumption of alcohol (in standard units/day)	N/A	19.70 (8.85)	9.75 (10.08)[6]	5.39, p < 0.001	/	/	/
Daily consumption of crack/cocaine (in grams/day)	N/A	N/A	1.31 (0.95)[6]	/	/	/	/
AUDIT	2.61 (1.64)	28.74 (6.58)	N/A	26.95, p < 0.001	/	/	/

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; DSM, diagnostic and statistical manual of mental disorders; HCs, healthy controls; MoCA, Montreal cognitive assessment; N/A, not applicable.
[a]Welch's ANOVAs, followed by Games–Howell post hoc tests.
[b]Chi-squared tests, followed by Z-tests.
[c]Welch's t-tests.
The superscript indicates the number of missing data.

standards. All participants provided informed written consent prior to the study participation.

Procedure

Volumetric data acquisition

For sCUD, high-resolution T1-weighted anatomical image were acquired with a Siemens Magnetom 3 T scanner (CENIR Imaging Center in Paris), using a 3D fast-field echo sequence (176 sagittal slices, thickness = 1 mm, repetition time = 2,300 ms, echo time = 2.9 ms, flip angle = 9°, field of view, 256 × 256 mm^2, matrix, 256 × 256).

For sAUD and HC, high-resolution T1-weighted anatomical image were acquired on a Philips Achieva 3 T scanner (Philips Healthcare/Philips Medical Systems International B.V., Eindhoven, The Netherlands) using a 3D fast-field echo sequence (sagittal, repetition time = 20 ms; echo time = 4.6 ms; flip angle = 10°, 180 slices, slice thickness = 1 mm, field of view = 256 × 256 mm^2, matrix = 256 × 256).

Volumetric data preprocessing

We processed volumetric magnetic resonance imaging (MRI) data using Statistical Parametric Mapping software (SPM12; Welcome Department of Cognitive Neurology, Institute of Neurology, London, UK). We segmented MRI data into GM and normalized them spatially to Montreal Neurological Institute (MNI) template (voxel size = 1.5 mm^3, matrix = 121 × 145 × 121). We modulated these normalized GM images by Jacobian determinants to correct brain volumes for brain size. We obtained a GM mask by taking unmodulated HC's GM images in MNI space, averaging them, and thresholding resultant mean image at 0.5. We applied resulting GM mask to modulated GM maps.

While images were obtained from two different scanners, they had the same tissue properties (T1-weighted), acquired and reconstructed at the same resolutions (1 mm^3 isotropic). They were also optimally processed to produce the best tissue maps with corresponding resolutions [36]. Moreover, scanner differences are known to be minimal and statistically insignificant when compared to group differences [37].

Volumetric regions of interest (ROI) extraction

We extracted each individual insular volumes using Faillenot's GM brain atlas [29], which provides six bilateral insular GM regions of interest (ROI): six left (n° 20, 86, 88, 90, 92, and 94) and six right (n° 21, 87, 89, 91, 93, and 95). The six subregions are, from most rostral to posterior insula: anterior inferior cortex (AIC), anterior short gyrus (ASG), middle short gyrus (MSG), posterior short gyrus (PSG), anterior long gyrus (ALG), and posterior long gyrus (PLG).

Statistical analyses

We performed all statistical analyses on Jamovi 2.2.5 [38, 39] using a significance level of alpha 0.05 (bilateral).

To explore group differences in insular GM ROI volumes, we normalized each of the ROI measure by individual total intracranial volume (TIV) to correct for head-size differences. We then used the resulting ROI by TIV computed score to calculate z-scores, using HC's mean and standard deviation. We applied a linear mixed model analysis to the resulting values, where dependent variable was the computed z-scores of GM volume, factors were lateralization, subregions and group, covariates were age and gender and random factor was participants. Significant main effects were followed by Bonferroni post hoc tests.

https://doi.org/10.1192/j.eurpsy.2024.1784 Published online by Cambridge University Press

Moreover, due to the high prevalence of problematic alcohol use in sCUD patients, we conducted an exploratory analysis to examine whether sCUD patients with a concomitant problematic alcohol use had GM volumes that differed significantly from sCUD with no concomitant problematic alcohol use. We therefore conducted within sCUD group linear mixed model analysis, where the computed *z*-scores of GM volume was the dependent variable, factors were lateralization, subregions and group (i.e., sCUD with problematic alcohol use vs. no problematic alcohol use), covariates were age and gender and random factor was participants.

Results

In the subsequent results section, we only report group-related interaction effects and *p*-values of significant post hoc tests, for clarity's sake (Supplementary Table 1 in the Supplementary Material for all effects).

Main effects

Mixed-model conducted on insula subregions *z*-scores revealed that all main effects were significant: we found main effects of group ($F(2,144) = 39.37$, $p < 0.001$), lateralization ($F(1,1584) = 52.14$, $p < 0.001$) and subregion ($F(5,1584) = 43.95$, $p < 0.001$). Subsequent post hoc comparisons (both $p < 0.001$) showed lower insula volume in sAUD and sCUD compared to HC, while the two patient groups had, overall, similar insular volume. Post hoc comparisons on main lateralization effect revealed that right insula had lower volume than left insula ($p < 0.001$). Following subregions post hoc comparisons, we found ALG to have significantly lower GM volume than all other five subregions (from anterior to posterior insula, all *p*-values <0.001): AIC, ASG, MSG, PSG, and PLG. Moreover, PSG showed lower GM volume than AIC ($p < 0.001$), ASG ($p < 0.001$), and MSG ($p = 0.002$). PLG had lower volume than AIC ($p = 0.02$) and ASG ($p = 0.003$).

Group by lateralization interaction

We found significant lateralization by group interaction effect ($F(2,1584) = 19.83$, $p < 0.001$), with right-sided volume deficit for sAUD ($p < 0.001$) and sCUD ($p = 0.002$), which was not found in HC. Moreover, sAUD and sCUD had lower right insula volume than HC and the left insula of sAUD and sCUD had lower volume than the left insula of HC (all *p*-values <0.001). However, for both right and left insula, post hoc comparisons showed that sAUD and sCUD had similar GM volume.

Group by subregion interaction

Group by subregion interaction effect was significant ($F(10, 1584) = 14.06$, $p < 0.001$). Subsequent post hoc comparisons revealed that all of the six insular subregions of the patient groups had lower volumes than the ones of the HC (from rostral to posterior insula): AIC (sAUD: $p = 0.007$; sCUD: $p < 0.001$), ASG (sAUD and sCUD with both $p < 0.001$), MSG (both $p < 0.001$), PSG (both $p < 0.001$), ALG (both $p < 0.001$), and PLG (both $p < 0.001$). Volume differences between sAUD and sCUD were not significant.

Post hoc comparisons showed that the ALG of sCUD and sAUD had lower GM volume than all other five subregions (ant-to-post): AIC (sAUD and sCUD with both $p < 0.001$), ASG (both $p < 0.001$), MSG (both $p < 0.001$), PSG (both $p < 0.001$), and PLG (both $p < 0.001$). Moreover, the AIC of sCUD showed lower GM volume than their ASG ($p = 0.002$), the PSG was more atrophied than their ASG and MSG, and their PLG had lower volume than their ASG and MSG (all *p*-values <0.001). For sAUD patients, post hoc comparisons showed that MSG ($p = 0.04$) and PSG ($p < 0.001$) were more atrophied than AIC.

Group by lateralization and subregion triple interaction

Subregion GM volume varied significantly depending on group and lateralization ($F(10, 1584) = 4.43$, $p < 0.001$). More specifically, we found for all six right subregions that patient groups had lower volumes than HC's (ant-to-post insula): AIC (sAUD: $p = 0.03$; sCUD: $p < 0.001$), ASG (sAUD and sCUD with both $p < 0.001$), MSG (both $p < 0.001$), PSG (both $p < 0.001$), ALG (both $p < 0.001$) and PLG (both $p < 0.001$). sAUD and sCUD patients had similar subregions GM volume (Figure 1).

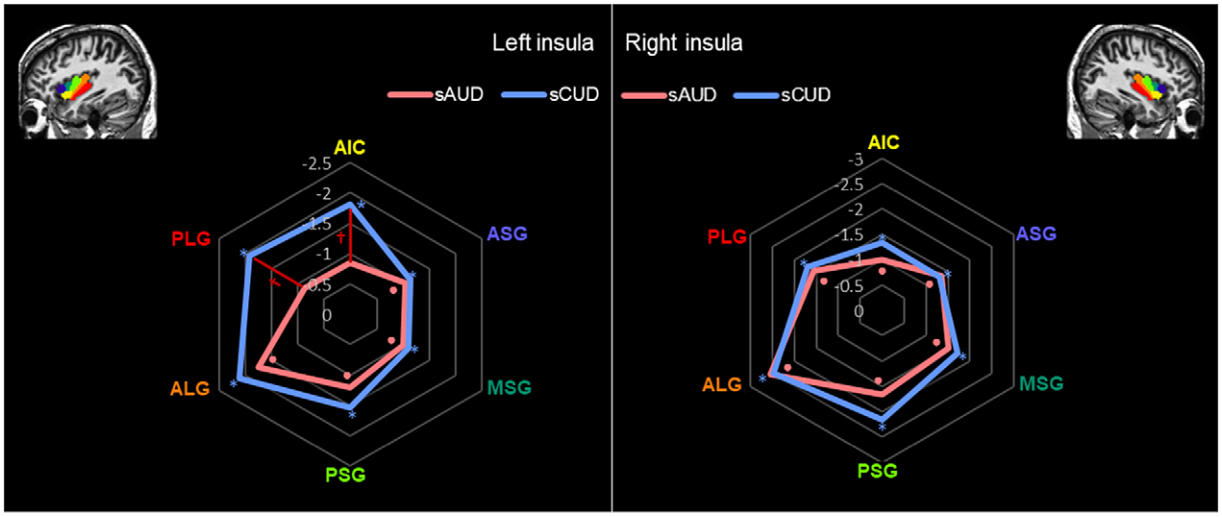

Figure 1. Gray matter volume deficits (*z*-scores) of insula subregions in sAUD and sCUD patients. AIC, anterior inferior cortex; ALG, anterior long gyrus; ASG, anterior short gyrus; MSG, middle short gyrus; PLG, posterior long gyrus; PSG, posterior short gyrus; sAUD, severe alcohol use disorder; sCUD, severe crack/cocaine use disorder. † = significant difference between the clinical groups, within a subregion; • = significant difference between sAUD and healthy controls, within a subregion; * = significant difference between sCUD and healthy controls, within a subregion For healthy controls, $mean_{z\text{-score}} = 0$, standard deviation $_{z\text{-score}} = 1$.

https://doi.org/10.1192/j.eurpsy.2024.1784 Published online by Cambridge University Press

However, for the left insula, the most rostral (AIC) and posterior (PLG) subregion of the insula of sCUD had lower volume than the ones of both sAUD (AIC: $p = 0.006$; PLG: $p < 0.001$) and HC (AIC: $p < 0.001$; PLG: $p < 0.001$), while sAUD and HC had similar AIC and PLG volume. For the four other insular subregions, post hoc comparisons showed significant lower insula volumes for the two patient groups compared to HC, but no difference between sAUD and sCUD (ant-to-post): ASG (sAUD: $p = 0.015$; sCUD: $p < 0.001$), MSG (sAUD: $p = 0.002$; sCUD: $p = 0.026$), PSG (sAUD and sCUD with both $p < 0.001$), and ALG (both $p < 0.001$).

Exploratory sCUD (problematic alcohol use vs. not) analysis

This linear mixed model analysis found that sCUD patients who had problematic alcohol use ($n = 38$) did not show a different pattern of GM abnormalities of the insula than sCUD with no problematic alcohol use ($n = 23$, $F(1,59) = 0.71$, $p = 0.40$; Supplementary Figure 1 in the Supplementary Material).

Conclusions

This study provides a novel and refined exploration of insula GM profile in two substances use disorders, thus disentangling general insular macrostructural abnormalities across substances from substance-specific volume deficit profiles. More specifically, our results have four main implications, respectively related to overall shared GM insula lower volume, volume deficits lateralization effect, similarities and specificities of the subregions GM abnormalities across substances, and specific volume deficits of left AIC and PLG in sCUD.

First, we showed shared alteration of overall insula GM volume in SUD. Theoretical models and empirical findings concur on insula key role in addiction [26] but a fundamental contradiction remains across previous work. On the one hand, major models [17] and seminal studies [18] theorize that addictive states are related to increased insula activation (leading to intense and irrepressible craving [40]), as notably, insular damage would lead to cessation of addictive states [18]. However, on the other hand, other studies report insula to be desensitized in addiction, as it undergoes major structural (e.g., insula GM volume deficit in SUD [27]) modifications in addiction. At the anatomical level, we found the insula to be structurally altered in addiction, since in both sAUD and sCUD we found insula to have lower volume than in HC. While anatomical findings warrant any conclusion at the functional level, we could however hypothesize that, as soon as in the subclinical binge/intoxication stage [17], an hypersensitized insula to substance-related cues would already be present [13]. Then, due to mechanisms including notably neurotoxic effect of substances, a damaged insula would thus be observed in the preoccupation/anticipation stage [17], when the addiction is already set – which, due to its impediment, would maintain the addiction. This suggests that insula would contribute to all stages of the addiction framework, albeit differently. Noteworthy, while longitudinal studies are needed to explore such hypothesis, there are already reports in binge-drinkers of insula hyperactivation (e.g., while undergoing the Iowa gambling task [41]) and of higher volumes of insula white matter, that is notably associated to alcohol craving [42].

Second, our results identify lateralization effect as we observed right-sided volume deficit in both sAUD and sCUD. This lateralization trend, already reported in sCUD [43] and sAUD [23], might constitute predisposing risk factor for sAUD emergence [44]. While the current study design, focusing on insula GM at the anatomical level, prevent any conclusion at the functional level, one possible explanation for this right-sided lateralization effect could be found in insular role as neural substrate of craving and interoception, which are both related to preferential activation of the right insula [45–47]. In fact, according to interoception models, as interoceptive information is being processed through insula, it is in right anterior insula that interoceptive information operates its final and highest-level processing, enabling a sense of the self [7, 48]. Thus, one implication of this stronger reduction of GM volume in right insula could be associated to disruption of sentient-self that is observed in SUD, which takes multiple forms such as interoceptive impairments [49], abnormal emotions experiencing and impeded decision making [50].

Thirdly, sCUD and sAUD patients have differential pattern of volume deficits of insular subregions. These results, which further highlight the need to follow refined parcellation of insula, provides first insights on the patterns of commonalities and specificities in substance profiles of macrostructural abnormalities. Regarding shared insular GM lower volume between SUD, there is major GM volume deficits of the ALG (localized in the posterior insula) compared to other insula subregions. Current study results concur with prior ones regarding volume deficit of posterior insula in sCUD [51] and sAUD [52]. As abovementioned, interoceptive information follows posterior-to-mid-to-anterior processing, corresponding to a refinement pathway [6, 8, 9]. In posterior insula, visceral-related information (e.g., effect of substance on body) is processed [7]. While the current study design provides information solely at the anatomical level, such results could be related, at the functional level, with impairments of the first steps of interoceptive information processing, which provides objective representation of internal states [7]. This could explain impairments of body-related perception in SUD, with reports of, for example, heightened interoceptive sensibility [53] and hyperalgesia [54]. Regarding specific patterns of lower insular GM volume for sCUD and sAUD, volume deficits observed in ALG expand to surrounding subregions (i.e., PSG and PLG) in sCUD while, for sAUD, AIC seems more preserved than its concomitant subregions (i.e., MSG and PSG). However, to further explore this hypothesized parallel between interoception, craving and insula volume deficits, further studies going deeper than basic volumetric exploration and including measures of these processes are needed.

Finally, exploring sAUD and sCUD patterns of insular volume deficit following 12 subregions (six bilateral) parcellation further set lights not only to the similarities but also to the differences in patterns of insula volume deficits. While the integrity of rostral and posterior subregions of left insula (i.e., AIC and PLG) of sAUD patients is maintained, this is not the case of sCUD patients. While the current study design using anatomical data prevents any conclusion at the functional level, possible explanations for such differences could be inherent to each SUD specificities. For example, a study exploring the similarities and differences between the two disorders at the clinical level found sCUD patients to be characterized by heightened impulsivity [55]. As previously mentioned, anterior insula might highjack cognitive control [14] through its bidirectional connections with the frontal cortex [10, 12]. One explanation of the study results could be that impulsivity, which is core to sCUD, is related to this specific GM lower volume of AIC. Another specificity of sCUD has also been underlined through insula maker-gene exploration and profiling, revealing that insula expresses cocaine-related genes [56]. The differentiated pattern of GM lower volume in sCUD could be related to this differentiated gene expression

https://doi.org/10.1192/j.eurpsy.2024.1784 Published online by Cambridge University Press

[1, 56]. This differentiated pattern of volume deficit could also be related to specific neurotoxic mechanisms and effects of these substances [57], which could thus lead to differentiated impairments of insular GM. Thus, to further comprehend these differences and their association to differentiated volume deficit profiles, further studies are needed that could, for example, look at insula activation in sCUD and sAUD but also explore the association between macro- and microanatomy specificities of sCUD's insula and their association to clinical profiles of sCUD patients. Moreover, it would be of interest for future studies to acquire such data on the same scanner, as our current study data were acquired on two scanners. However, given the fact that our mixed model has a R-squared conditional value of 0.78, meaning that our fixed and random model effects explain 78% of the overall variance, it is unlikely that the group effect is solely explained by the scanner effect.

To conclude, the current study offers the first direct comparison of GM insular volume in two SUD, using refined parcellation. We found sCUD and sAUD to share similarities in their overall profile of insula volume deficits, notably regarding right-sided volume deficit effect but, also, in major alteration of ALG, a region related to the processing of bodily information. However, specificities emerged when looking more precisely at insula subregions, with most anterior (AIC) and posterior (PLG) subregions of left insula being atrophied in sCUD, while preserved in sAUD. Nevertheless, the current study results lack prior literature to identify intrinsic differences of these two subregions, as studies rarely compare directly insula GM volume across substances and, to our knowledge, never using such a refined parcellation. Our results thus constitute a first step in the exploration of insula profile of volume deficit specificities in addiction more generally.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1192/j.eurpsy.2024.1784.

Data availability statement. Data from the current study can be made available upon request to the corresponding author.

Acknowledgments. We are grateful to the URC (Unité de Recherche Clinique) professionals Eric Vicaut, Véronique Jouis, and Samira Djababali.

Financial support. P.M. and P.B. are funded by the Belgian Fund for Scientific Research (FRS-FNRS, Belgium). This study was funded by ANR-Retour postdoctorant 2010, Conseil Regional de Normandie, MILDECA, and Institut Universitaire de France. This study was also funded by the Ministère de la Santé et de la Prévention (France), Programme Hospitalier de Recherche Clinique, AOM12390 (Quit-Coc) to F.V. The study was sponsored by the DRCI (Direction de la Recherche Clinique et de l'Innovation) from the APHP (Assistance Publique – Hôpitaux de Paris).

Competing interest. The authors declare no competing interests.

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https://doi.org/10.1192/j.eurpsy.2024.1784 Published online by Cambridge University Press