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Insular volumetry in severe alcohol use disorder and Korsakoff's syndrome through an anatomical parcellation: Let us go back to basics

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Abstract

Functional neuroimaging has demonstrated the key role played by the insula in severe alcohol use disorder (sAUD), notably through its involvement in craving and body signals processing. However, the anatomical counterpart of these functional modifications in sAUD patients with and without neurological complications remains largely unexplored, especially using state-of-the-art parcellation tools. We thus compared the grey matter volume of insular subregions (from anterior to posterior: anterior inferior cortex, anterior short gyrus, middle short gyrus, posterior short gyrus, anterior long gyrus, posterior long gyrus) in 50 recently detoxified patients with sAUD, 19 patients with Korsakoff's syndrome (KS) and 36 healthy controls (HC). We used a mixed linear model analysis to explore group differences in the six subregions grey matter volume and lateralization differences. Insular macrostructure was globally affected to the same extent in sAUD with and without KS, indicating that these brain abnormalities may be related to alcohol consumption per se, rather than to the presence of alcohol-related neurological complications. Insular atrophy showed a right-sided lateralization effect and was especially marked in the posterior insula, a region associated with visceral information processing and the embodiment effect of a substance, from which craving arises. Anatomical damages might thus underlie the previously reported altered insular activations and their behavioural counterparts.

KEYWORDS

addiction, craving, grey matter volume, insular parcellation, interoception, substance abuse

1 | INTRODUCTION

The insula, a cortical area located deep within the lateral sulcus of the brain, in the depths of the Sylvian fissure, has long been regarded solely as a visceral sensory region.^{1,2} However, neuroimaging

techniques showed that the insula is an ultra-connected brain region³ that shows activations during a wider range of processes (see Nieuwenhuys⁴ for a non-exhaustive review of insular functions), suggesting that insular role may go beyond simple visceral information processing. Contemporary research now considers the insula as the

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main interoception neural substrate, because it is part of the interoceptive pathway (i.e., lamina I spinothalamocortical system).^{5,6} This pathway conveys information about the physiological state of the organism to higher order processing structures (such as relay nuclei located in the thalamus), up to the insula.^{6–8} While insular functional and somatotopic organization remains relatively unclear,^{1,2,4} this interoceptive information supposedly follows a posterior-to-mid-to-anterior integration pattern within the insula.^{6–8} Firstly, the interoceptive information is processed in the posterior insula, where an objective representation of the physiological condition of the body is contained; secondly, this activity is further integrated in the middle insula with salient activity originating from sensory and sensorimotor pathways; finally, the anterior insula integrates emotionally salient activity from other forebrain regions, leading to a subjective meta-representation of the physiological body condition and giving rise to emotional awareness.^{5,9} These findings, clarifying the neural pathway of interoception, helped to better grasp how interoceptive information is processed through multiple steps and brain regions. They also provided new exploration venues for the pathology research field and, notably, the addiction field.

The insula is involved in the persistence of addictive disorders. Patients with tobacco use disorder would indeed be more likely (i.e., odds ratio higher than 136) to undergo a sudden and easy disruption of tobacco use following insular lesion, with neither craving persistence nor relapse.^{10,11} Altogether with prior conceptualizations of the insula as an interoception hub involved in the processing of bodily sensations associated to drug abuse,¹⁰ these findings led to consider the insula as a neural substrate for the conscious urge to use drug, namely craving.¹¹ Further determining the role of the insula in addiction processes has however proved challenging because discrepancies exist in the literature. On the one hand, it would seem that substance use disorders emerge from a ‘sensitized’ (as called by Naqvi et al.¹⁰) insula, because its lesion results in dependence disruption.^{12,13} On the other hand, neuroimaging studies show that substance use disorders emerge from a ‘desensitized’ insula because, overall, patients with dependency show insular atrophy, with demyelination of insula white matter tracts in severe alcohol use disorder (sAUD) for example.^{12–14}

A way to overcome such apparently contradictory findings emerging in the sAUD field is to clarify the anatomical modifications of the insula,¹² associated with chronic and excessive drinking. Such exploration has however revealed arduous due to discrepancies inherent to insular parcellation techniques used. Major differences are found in the parcellation procedure, which relies either on functional (based on functional magnetic resonance imaging [MRI], mainly in human) or anatomical (based on an atlas, mainly in animal) techniques, thus leading to discrepancies in the number, location and label of insular subregions (i.e., from 2 to 13 anatomical/functional subregions).^{12,15} This lack of homogeneity in insular parcellation methods thus impedes this field of research results comparability and exactness.¹⁵ A concrete illustration of insular heterogeneous parcellation deleterious consequences is the current state of findings in the AUD field. Although AUD investigation is scarce, the few results show major heterogeneity because findings do not concur, neither on lateralization (in right¹⁶ or

left¹⁷ versus bilateral¹⁸ insula) nor regions (in whole right¹⁶ versus bilateral anterior¹⁹ insula or aggravated in bilateral anterior and left posterior insula²⁰) atrophy in patients presenting sAUD. Moreover, all previous studies (with the exception of a previous study,¹⁷ which was not specifically exploring the insula) focused solely on sAUD, without exploring insular alterations following alcohol-related neurological complications such as Korsakoff's syndrome (KS).

We aimed to investigate insular volume in patients with sAUD and KS while overcoming the above-mentioned insular parcellation limits. To do so, we followed a refined anatomical insular parcellation, resulting in six left and six right insular subregions.²¹ The rationale for using this specific insular parcellation is that, by combining both macro-anatomical landmarks and probabilistic techniques, this parcellation based on a probabilistic atlas²¹ overcomes prior parcellation limits such as coarse subregions delimitation (i.e., ending up with a refined 6*2 parcellation) while taking account of between-subject variability. Moreover, while a recent cytoarchitecture parcellation focus has been observed in the insula field,²² the current study macro-anatomical insular parcellation allows for comparisons in future research studies (e.g., used in a previous study²³), contrarily to the cytoarchitecture technique.²¹ Indeed, due to limits inherent to the cytoarchitecture technique (i.e., developed using ex-vivo data), this parcellation technique does not allow for it to be used in neuroimaging studies.²¹

Given prior evidence for a graduation of atrophy between HC, sAUD and KS,¹⁷ we hypothesized that both patients with KS and sAUD would show insular grey matter atrophy compared to HC, but that this atrophy would be more severe in the KS group. Based on the previous reports that insular atrophy might vary with lateralization^{16,17} and subregions,²⁰ we explored the role of such variables in the patterns of grey matter atrophy observed in each clinical group.

2 | MATERIALS AND METHODS

2.1 | Participants

We enrolled 69 patients (16 females) presenting clinical forms of sAUD (DSM-5 criteria, American Psychiatric Association, 2013) and 36 HC (six females). All participants provided their written consent prior to the study participation. The study protocol followed the Declaration of Helsinki's ethical standards and was approved by the ethics committee of Caen University Hospital (CPP Nord Ouest III, no. IDRCB: 2011-A00495-36).

Out of the 69 patients, 19 (10 females) were diagnosed with KS, with reference to the DSM-5 criteria of ‘major neurocognitive disorders, confabulatory type, persistent’ (DSM-5 criteria, American Psychiatric Association, 2013). We recruited patients with KS from both an inpatient treatment centre (Caen University Hospital, France $n = 11$) and a nursing home (Maison Vauban, Roubaix, France; $n = 8$). Due to amnesia, we did not record self-reports on prior drinking habits. However, based on patients' surroundings information and medical records, patients with KS presented a long and heavy alcohol

consumption history (i.e., 15 to 42 years—for patients for whom we had access to this variable). Thorough multidisciplinary assessments of patients with KS confirmed this diagnosis since (1) patients presented memory performance (assessed by the California Verbal Learning Task and Free; CVLT²⁴ and Free and Cued Selective Reminding Test; FCSRT²⁵) disproportionately impaired compared to other cognitive functions; and (2) impairments were not due to focal brain damage, as indicated by the neuroimaging examination. Due to these major memory impairments, patients with KS were either living in sheltered housings or waiting for such possibly from the residential treatment facility.

The remaining 50 patients (six females) presented an 'uncomplicated' form of sAUD. These patients were early abstainers recruited by clinicians from an inpatient treatment unit (Caen University Hospital, France). When included to the study, patients with sAUD showed no more physical symptoms of alcohol withdrawal—as assessed by Cushman's scale.²⁶ Alcohol history was assessed using a modified version of the semi-structured lifetime drinking history²⁷ and the Alcohol Use Disorders Identification Test (AUDIT).^{28,29}

We recruited 36 HC (six females) locally, matched on age to patients with sAUD and education level to sAUD and patients with KS (Table 1). HC were eligible for the study if they: (1) reported low alcohol consumption (i.e., score <6 for female and <7 for male at the AUDIT^{28,29}); (2) reported no severe symptoms of depression (i.e., score <29 at the Beck Depression Inventory-II; BDI³⁰); and (3) showed no sign of global cognitive alterations (i.e., score >126 at the Mattis Dementia Rating Scale; MDRS³¹).

Inclusion criteria shared across groups were: (1) being 18 to 70 years of age; (2) speaking French fluently. We excluded participants if they currently presented or had an history of polysubstance use (excluding nicotine), major psychiatric or neurological diagnosis—or any disorder that might generate cognitive dysfunction (diabetes, endocrinal disorder, hepatitis, HIV) or if they were under psychotropic treatments (e.g., benzodiazepines for sAUD treatment were stopped at least 48 h before inclusion). Table 1 reports socio-demographic, clinical, neuropsychological and alcohol-related variables.

TABLE 1 Sociodemographic, clinical and alcohol-related variables of healthy controls (HC), patient with severe alcohol use disorder (sAUD) and patients with Korsakoff's syndrome (KS).

	HC (n = 36)	sAUD (n = 50)	KS (n = 19)	Between-group comparisons
Sociodemographics variables				
Age ^a	44.03 (6.14)	46.88 (8.93)	55.47 (5.44)	HC = sAUD; HC < KS ^{†††} ; sAUD < KS ^{†††}
Education level ^b	11.75 (1.70)	11.78 (2.03)	10.32 (2.47)	HC = sAUD; HC = KS; sAUD = KS
Gender, male (%) ^c	83	88	47	HC = sAUD; HC < KS; sAUD < KS
Depressive symptoms				
BDI ^c	3.19 (3.21)	12.41 (8.78)	8.32 (7.81)	HC < sAUD ^{†††} ; HC < KS [†] ; sAUD = KS
Neuropsychological assessment				
MDRS: Total score ^c	142.03 (2.02)	136.76 (6.10)	103.06 (38.80)	HC = sAUD; HC > KS ^{†††} ; sAUD > KS ^{†††}
CVLT: Sum of the five free recalls (in z-scores) ^{b*}	0.00 (1.00)	-0.59 (1.74)	-6.35 (0.61)	HC = sAUD; HC > KS ^{†††} ; sAUD > KS ^{†††}
CVLT: Delayed recall (in z-scores) ^{b*}	0.00 (1.00)	-0.89 (1.70)	-6.94 (0.66)	HC = sAUD; HC > KS ^{†††} ; sAUD > KS ^{†††}
FCSRT: Sum of the three free recalls (in z-scores) ^{b**}	0.00 (1.00)	-1.11 (1.30)	-4.17 (1.61)	HC > sAUD ^{†††} ; HC > KS ^{†††} ; sAUD > KS ^{†††}
FCSRT: Delayed recall (in z-scores) ^{b**}	0.00 (1.00)	-1.07 (1.50)	-4.99 (1.47)	HC > sAUD ^{††} ; HC > KS ^{†††} ; sAUD > KS ^{†††}
Alcohol-related variables				
Abstinence duration (in days)	N/Ap	11.15 (4.37)	N/A	
Alcohol consumption per day (over the last month, in standard units)	N/Ap	19.70 (8.85)	N/A	
Duration of severe alcohol use disorder (in years)	N/Ap	22.21 (10.20)	N/A	
AUDIT ^c	2.61 (1.64)	28.74 (6.58)	15.60 (11.59)	HC < sAUD ^{†††} ; HC < KS [†] ; sAUD > KS [†]

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; BDI, Beck depression inventory; CVLT, California verbal learning task; FCSRT, free and cued selective reminding test; HC, healthy controls; KS, Korsakoff's syndrome; MDRS, Mattis dementia rating scale; N/A, not available; N/Ap, not appropriate; sAUD, severe alcohol use disorder.

^aWelch's ANOVAs, followed by Games-Howell post-hoc tests.

^bFisher's ANOVAs, followed by Tukey post-hoc tests.

^cChi-squared tests, followed by Z-tests.

*In z-scores, only part of the sample underwent the CVLT (n = 49; 20 HC, 25 sAUD and 4 KS), z-scores were therefore computed using solely mean and standard deviation of HC who underwent this test (n = 20).

*In z-scores, computed based on HC's (n = 36) mean and standard deviation.

[†]p < 0.05.

^{††}p < 0.01.

^{†††}p < 0.001.

Noteworthy, participants were seen in the context of a large protocol, from which prior results have been published.^{32–38}

2.2 | Procedure

2.2.1 | Volumetric data acquisition

We acquired a high-resolution T1-weighted anatomical image for each participant on a Philips Achieva 3T 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 mm², matrix = 256 × 256; Figure 1A,B).

2.2.2 | Volumetric data pre-processing

We processed the volumetric MRI data using the Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). We

segmented MRI data into grey matter and normalized them spatially to the Montreal Neurological Institute (MNI) template (voxel size = 1.5 mm³, matrix = 121 × 145 × 121). We modulated these normalized grey matter images by the Jacobian determinants to correct the brain volumes for brain size. We obtained a grey matter mask by taking the unmodulated grey matter images of HC in MNI space, averaging them and thresholding the resultant mean image at 0.5. We applied the resulting grey matter mask to the modulated grey matter maps.

2.2.3 | Volumetric regions of interest (ROI) extraction

For each participant, we extracted insular volumes using the Faillenot's grey matter brain atlas.²¹ It provides six left (n° 20, 86, 88, 90, 92 and 94) and six right (n° 21, 87, 89, 91, 93 and 95) ROI. These six bilateral insular grey matter ROI were, namely (from the anterior to posterior insula): (i) anterior inferior cortex (AIC); (ii) anterior short gyrus (ASG), (iii) middle short gyrus (MSG), (iv) posterior short gyrus (PSG), (v) anterior long gyrus (ALG), (vi) posterior long gyrus (PLG).

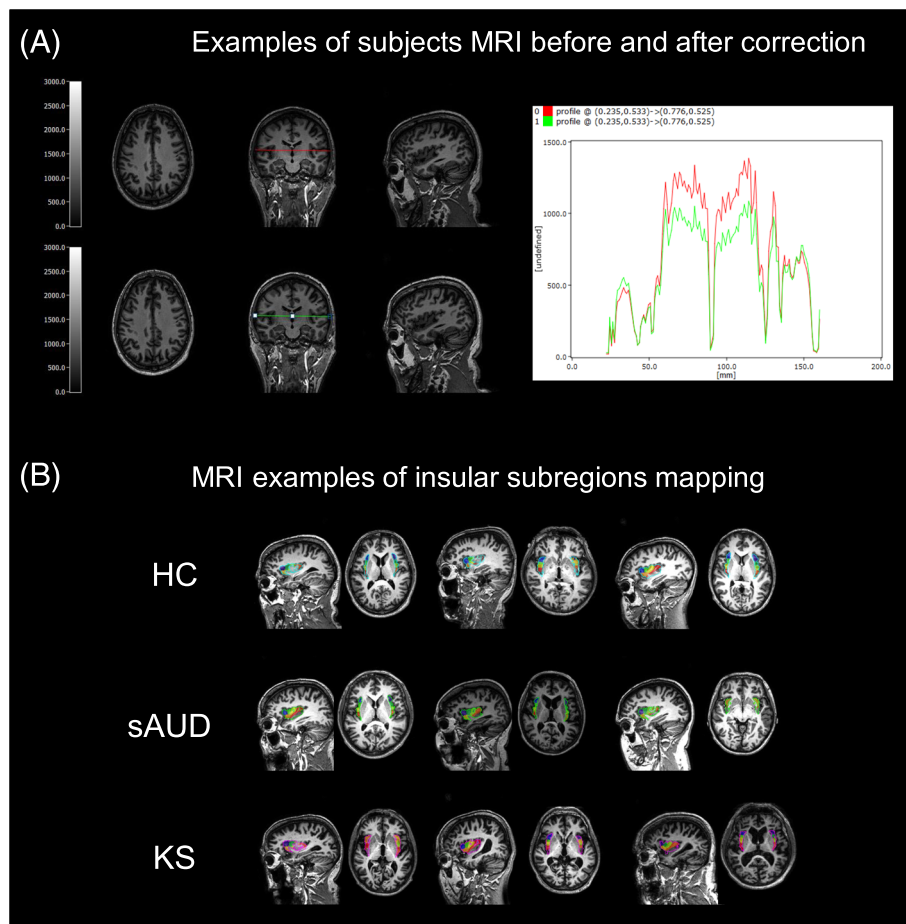


FIGURE 1 (A) Examples of subjects MRI before and after correction. Note: MRI of healthy controls (HC) before (top) and after (bottom) correction for magnetic field inhomogeneity. Correction for field inhomogeneity is particularly significant at the centre of the image as can be quantitatively observed through profiles across coronal slice passing through the insula (red profile before correction and green profile after correction). (B) MRI examples of insular subregions mapping. Note: Example MRIs of subjects in their native space with the atlas of the insula superimposed on them (i.e., three subjects per group). Top row shows examples from the HC group; middle row from the severe alcohol use disorder (sAUD) group and bottom row from the Korsakoff's syndrome (KS) group. The boundaries of the insular region is shown in cyan for the HC group, green for the sAUD group and magenta for the KS group. The colours represent the different parcellations of the insula as per described in the manuscript. One region is in black so appears as 'transparent' when superimposed.

2.3 | Statistical analyses

We performed all statistical analyses via Jamovi 2.2^{39,40} using a significance level of alpha 0.05 (unilateral).

We explored group differences in insular grey matter ROI volumes. Beforehand, we normalized each of the ROI measure by the individual total intracranial volume to correct for head-size differences. Then, for each of these measures, we calculated z-scores using HC's mean and standard deviation. We then used the resulting values to conduct a linear mixed model analysis with the computed z-scores as dependent variable, lateralization, subregions and group as factors, age and gender as covariates and participants as random factor. When significant main effects emerged, we performed Bonferroni post-hoc tests.

3 | RESULTS

For the sake of clarity, this section only reports group-related interaction effects and the post-hoc tests for the significant main effects. Moreover, for post-hoc results, only *p*-values are reported, all significant statistics related to the linear mixed model analysis being detailed in Table 2.

3.1 | Main effects

We found an overall effect of group on the insula volume ($F[2, 102] = 26.61, p < 0.001$), with grey matter atrophy in patients with sAUD ($p < 0.001$) and KS ($p < 0.001$) compared to HC, while the two clinical forms of AUD did not differ ($p = 0.12$).

Regarding the main lateralization effect ($F[1, 1122] = 56.40, p < 0.001$), the right insula was overall smaller than the left insula ($p < 0.001$).

For the main subregion effect ($F[5, 1122] = 32.52, p < 0.001$), the AIC subregion was significantly larger than the five other subregions (from anterior to posterior insula): ASG ($p < 0.01$), MSG ($p < 0.01$), PSG ($p < 0.001$), ALG ($p < 0.001$) and PLG ($p < 0.01$). The ALG was significantly smaller than the other subregions (from anterior to posterior insula): ASG ($p < 0.001$), MSG ($p < 0.001$), PSG ($p < 0.001$) and PLG ($p < 0.01$).

3.2 | Lateralization by group interaction

We found a significant lateralization by group interaction ($F[2, 1122] = 17.58, p < 0.001$), explained by the fact the right insula volume was significantly smaller than the left one in both sAUD ($p < 0.001$) and KS ($p < 0.001$) groups, but not in HC ($p = 1.00$). The main group effect (i.e., similar pattern of insular atrophy in sAUD and KS compared to HC) was found in both sides of the insula.

3.3 | Subregion by group interaction

There was a significant insular subregion by group interaction ($F[10, 1122] = 9.53, p < 0.001$). While HC did not show significant volume differences across subregions, both sAUD and KS groups presented more severe atrophy of the ALG than (from anterior to posterior insula): AIC (sAUD: $p < 0.001$; KS: $p < 0.001$), ASG (sAUD: $p < 0.001$; KS: $p < 0.001$), MSG (sAUD: $p < 0.001$; KS: $p < 0.001$), PSG (sAUD: $p < 0.001$; KS: $p < 0.001$) and PLG (sAUD: $p < 0.001$; KS: $p < 0.001$). In addition, PSG was more severely affected than AIC in both groups (sAUD: $p < 0.001$; KS: $p < 0.001$). A main group effect (i.e., similar pattern of insular atrophy in sAUD and KS compared to HC) was found for each of the six subregions (see Figure 2A,B).

3.4 | Subregion by lateralization and group (triple interaction)

The subregion by lateralization and group interaction was not significant ($F[10, 1122] = 1.49, p = 0.14$). See the Figure S1 for a representation of insula grey matter volume for each lateralized subregion, per group.

4 | DISCUSSION

We explored insular grey matter volume in AUD, with two major novelties: (1) the direct comparison between recently detoxified patients with sAUD and patients with KS and; (2) the use of a refined and anatomically based human insular parcellation methodology.²¹ Capitalizing on scarce previous work,¹⁷ we hypothesized a gradation in atrophy across population (i.e., KS > sAUD > HC) and we explored the role of lateralization and subregion, since these variables appear to influence insula grey matter atrophy.^{16,21,41}

We showed that both sAUD and KS are associated with insular shrinkage compared to HC, without differing from each other. A first implication of these results is that grey matter volume deficits do not appear to be specifically associated with KS, nor to be more severe in KS than sAUD, contrary to previous results found with a VBM approach.¹⁷ Insular shrinkage in sAUD and KS might thus result from common mechanisms, like excessive and chronic alcohol consumption, and would not, contrary to previous evidence,⁴² recover following drinking cessation (as patients with sAUD were early in abstinence whereas patients with KS were long-term abstainers, from 1 month up to 10 years). Further studies comparing insular volumes among early versus late abstinent patients with AUD or using a longitudinal design are necessary to explore such a hypothesis. An alternative interpretation is that the similar grey matter volume deficits in both patient groups could imply that insular shrinkage represents a risk factor for the onset and maintenance of substance use disorder. Such shrinkage could thus be premorbid to the substances consumption and, as a consequence, would thus not recover with its cessation.

TABLE 2 Values of the significant post-hoc tests of the linear mixed model analysis.

Comparison						
Group (I)	Group (J)	Mean difference (I-J)	Standard error	t	p-Value	
Main group effect						
HC	sAUD	1.36	0.23	5.88	<0.001	
	KS	1.95	0.30	6.50	<0.001	
Main lateralization effect						
Left	Right	0.31	0.04	7.52	<0.001	
Main subregion effect						
AIC	ASG	0.25	0.07	3.53	0.01	
	MSG	0.26	0.07	3.68	0.01	
	PSG	0.40	0.07	5.63	<0.001	
	ALG	0.87	0.07	12.13	<0.001	
	PLG	0.27	0.07	3.85	<0.001	
	ALG	ASG	−0.61	0.07	−8.60	<0.001
		MSG	−0.60	0.07	−8.45	<0.001
		PSG	−0.46	0.07	−6.50	<0.001
		PLG	−0.59	0.07	−8.28	<0.001
Lateralization by group interaction—within sAUD						
Left	Right	0.49	0.06	8.82	<0.001	
Lateralization by group interaction—within KS						
Left	Right	0.44	0.09	4.95	<0.001	
Lateralization by group interaction—within left insula						
HC	sAUD	1.12	0.24	4.75	<0.001	
	KS	1.73	0.31	5.67	<0.001	
Lateralization by group interaction—within right insula						
HC	sAUD	1.61	0.24	6.81	<0.001	
	KS	2.18	0.31	7.11	<0.001	
Subregion by group interaction—within sAUD						
ALG	AIC	−1.21	0.10	−12.70	<0.001	
	ASG	−0.94	0.10	9.82	<0.001	
	MSG	−0.88	0.10	9.25	<0.001	
	PSG	−0.70	0.10	−7.28	<0.001	
	PLG	−0.93	0.10	−9.71	<0.001	
PSG	AIC	−0.52	0.10	−5.42	<0.001	
Subregion by group interaction—within KS						
ALG	AIC	−1.38	0.15	−8.93	<0.001	
	ASG	−0.90	0.15	−5.83	<0.001	
	MSG	−0.93	0.15	−5.97	<0.001	
	PSG	−0.70	0.15	−4.49	<0.001	
	PLG	−0.85	0.15	−5.46	<0.001	
PSG	AIC	−0.69	0.15	−4.44	<0.001	
Subregion by group interaction—within AIC						
HC	sAUD	0.93	0.25	3.69	0.048	
	KS	1.36	0.33	4.19	0.01	
Subregion by group interaction—within ASG						
HC	sAUD	1.20	0.25	4.79	<0.001	
	KS	1.84	0.33	5.67	<0.001	

TABLE 2 (Continued)

Comparison		Mean difference (I-J)	Standard error	t	p-Value
Group (I)	Group (J)				
Subregion by group interaction—within MSG					
HC	sAUD	1.26	0.25	5.01	<0.001
	KS	1.82	0.33	5.60	<0.001
Subregion by group interaction—within PSG					
HC	sAUD	1.44	0.25	5.76	<0.001
	KS	2.05	0.33	6.31	<0.001
Subregion by group interaction—within ALG					
HC	sAUD	2.14	0.25	8.53	<0.001
	KS	2.75	0.33	8.44	<0.001
Subregion by group interaction—within PLG					
HC	sAUD	1.21	0.25	4.83	<0.001
	KS	1.90	0.33	5.84	<0.001

Note: AIC, anterior inferior cortex; ALG: anterior long gyrus; ASG: anterior short gyrus; HC: healthy controls; KS: Korsakoff's syndrome; MSG: middle short gyrus; PLG: posterior long gyrus; PSG: posterior short gyrus; sAUD: severe alcohol use disorder.

Comparison of insular volume in groups of patients with different substance use disorder would be relevant in that context.

When exploring grey matter insular shrinkage lateralization effect, we found differences between the right and left insula for the patient groups only, with a right-sided atrophy predominance. While anatomical and functional reasoning for such lateralization differences is still to be investigated, this more marked atrophy in the right insula is however largely found in the addiction literature.⁴³ To illustrate, similarly to the current results, patients with sAUD,^{16,44} cocaine⁴⁵ and heroin⁴⁶ use disorder all showed such a right-sided posterior atrophy (noteworthy, described as a postero-right sided shrinkage tendency in heroin⁴⁶). The specificities of the right insular lobe and its central involvement in multiple processes such as interoception have been largely reported in the literature.^{6,47} Interestingly, a previous study found that right insula grey matter shrinkage may represent a genetic risk factor for the emergence of alcohol abuse.⁴⁸

The volumetric exploration of insular subregions highlights the need to go beyond a simple exploration of the total insula volume, as ALG presents a major grey matter shrinkage compared to other subregions. We priorly discussed how insula follows a 'posterior-to-mid-to-anterior' type of interoceptive signals processing pattern,⁶⁻⁸ meaning that posterior parts process initial interoceptive signals, while anterior parts (i.e., AIC and ASG) accomplish the highest levels of such signals processing.^{5,9} Altogether with the PLG, the ALG constitutes the posterior insula: where information from the viscera is processed, providing an objective representation of the physiological condition of the body.^{5,9} One main possible implication related to this severe ALG shrinkage could be that interoceptive processes impairments (e.g., reduced interoceptive accuracy) observed in AUD⁴⁹ might be caused by failure of the first and more basic processing steps in the posterior insula, impeding the efficient processing of raw interoceptive signals. Such failure could happen directly through ALG damage

and/or because the ALG receives already impaired interoceptive signals. Indeed, according to Craig's interoceptive pathway, before arriving to the posterior insula, interoceptive signals go through two thalamic nuclei (i.e., posterior and basal ventral medial nuclei).^{6,7} There is major empirical evidence for thalamic alterations in both patients with KS and sAUD.^{37,50}

While the current study offered no direct analysis of the relationships between craving and anatomical measures, putting altogether prior findings on insular interoceptive processing path with the hypothesized role of insula as the craving neural substrate^{10,11,43} would imply that the patient groups show an atrophy of the insular part (subregion and laterality) responsible for the substance consumed embodiment effects.²⁰ When going further in such hypothesized implication, this could possibly mean that the postero-anterior gradient of atrophy could in fact also be interpreted in the framework of addiction models, which posit the insula as being involved in both bottom-up and top-down processes,^{11,43,49} depending on the stage of substance use disorder development.⁵¹ At the early stages, the urge for substance use follows a bottom-up process: craving emerges from environmental cues.^{11,52} Therefore, an individual sees a substance-related environmental cue, consumes such substance and has the embodiment effect of the substance that is processed in the insula following a posterior-to-mid-to anterior type of processing.^{6-8,11,43,52} It is in the most anterior part of the insula that lower level information (i.e., visceral information regarding the substance effect) will be associated to higher order level information⁵¹ (i.e., association between the pleasurable effect of a substance that is concomitant to its embodiment effect). At later stages, the switch from substance use to abuse is associated to a switch from bottom-up to top-down processes, where an individual will crave for a substance regardless of the presence of environmental cues related to it. It is by *remembering* an effect of a substance (and the association between its pleasurable and

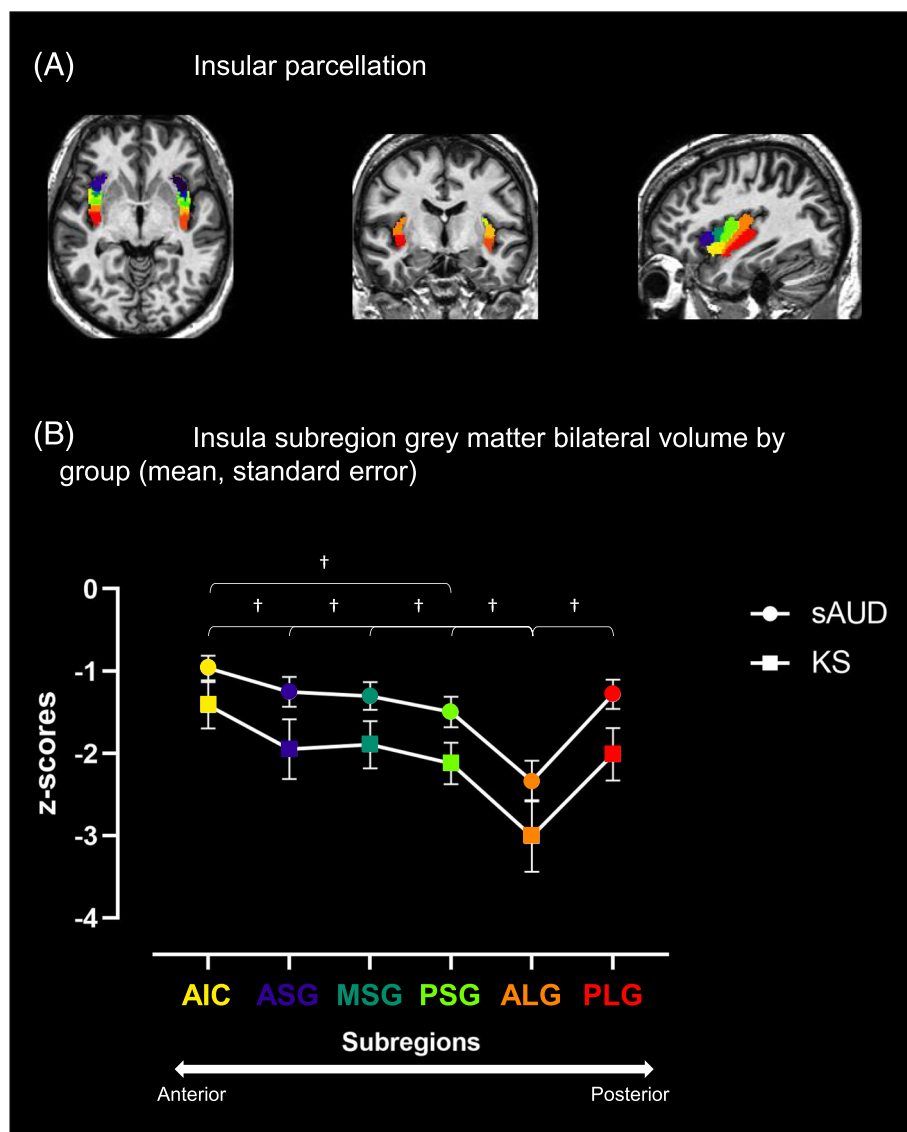


FIGURE 2 (A) Insular parcellation. (B) Insula subregion grey matter bilateral volume by group (mean, standard error). *Note:* AIC, anterior inferior cortex; ALG, anterior long gyrus; ASG, anterior short gyrus; KS, Korsakoff's syndrome; MSG, middle short gyrus; PLG, posterior long gyrus; PSG, posterior short gyrus; sAUD, severe alcohol use disorder. $\dagger$ = significant difference between two subregions ($p < 0.001$), for both KS and sAUD. Each patient groups subregion was significantly smaller than the corresponding subregion among healthy controls (mean_{z-score} = 0, standard deviation_{z-score} = 1).

embodied effects) that the individual will crave for it.¹¹ There could be two explanations for this effect: (i) the switch from bottom-up to top-down processes could be considered as a consequence of major damage of the posterior insula, which would force the insula to rely on information brought by the anterior insula (i.e., top-down); (ii) top-down processing (and therefore anterior insula) is favoured at the detriment of the posterior-to-mid-to-anterior/bottom-up processing, leading to an atrophy of the posterior insula.

Although being hypothetical, this bottom-up/top-down switch would reconcile the priorly mentioned literature discrepancy in literature, with insula being reported as both desensitized (demyelination of insula in sAUD¹²⁻¹⁴) and sensitized (insular lesion leads to tobacco use disorder cessation^{10,11}) in use disorders. Indeed, it could be that insular desensitization (e.g., interoception deficiencies) emerges from the top-down switch, which would result in an erroneous processing resulting from the favouring of memory rather than actual processing of bodily information. Therefore, insular lesions would lead to use disorders disruption not due to the disruption of bodily sensations

processing (bottom-up), but because one cannot remember anymore the pleasurable effect of a substance (top-down). However, further studies are needed to explore such hypothesized switch.

Although the current study provides novel evidence regarding insular shrinkage in two clinical forms of AUD using an anatomical insular parcellation,²¹ it shows a set of limits. First, we had no measure of craving and interoception, thus rendering inference on GM volume shrinkage deficits to insula-dependent processes (i.e., craving and interoception) only hypothetical. Second, we focus solely on an exploration of insula volume, capitalizing on prior evidence that this brain region is the *main* neural substrate of craving. However, as underlined notably by authors⁵³ hypothesizing insular role in addiction emergence and maintenance, one should keep in mind that the insula, like any other brain region, does not function in isolation, with bidirectional links being observed between insula and concomitant brain regions. Thus, craving experience is not solely dependent upon the insula and, although the insula has been reported as modulating the surrounding brain regions through its craving role, these brain

regions might, in return, modulate the craving experience.⁵⁴ Third, although the current paper focuses solely on the insula role as the main interoceptive hub, insular activations have been reported to multiple processes that are not only interoception-related.³ Finally, although providing insula GM volume evidence in both KS and sAUD patients, this study was limited to solely one imaging modality. Future venues would therefore be to also investigate insular metabolic activity as well as functional and structural connectivity.²⁰ Moreover, it would also be of interest to compare GM insular volume in different substance use disorders.

To conclude, using an anatomical insular parcellation,²¹ we found that both patients with sAUD and KS had overall smaller insular volumes. When exploring subregions more specifically, the posterior insula (i.e., responsible for the visceral interoceptive processing) shrinkage was more severely affected for both patient groups with a right-sided lateralization effect. Taken altogether, the current results provide an empirical background for sAUD and KS insula subregions alterations, enabling future studies to develop more complex exploration, such as insular activation and connectivity, in the addiction field.

AUTHOR CONTRIBUTIONS

Nicolas Cabé contributed to patients' recruitment. Alice Laniepece contributed to the HC's recruitment and data acquisition. Shailendra Segobin performed the pre-processing of the brain imaging data. Pauline Billaux performed the statistical analysis and drafted the manuscript. Anne-Lise Pitel, Shailendra Segobin and Pierre Maurage assisted with data analysis and interpretation of findings. Anne-Lise Pitel and Pierre Maurage provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

CONFLICT OF INTEREST STATEMENT

Pierre Maurage (Senior Research Associate) and Pauline Billaux (Junior Research Associate) are funded by the Belgian Fund for Scientific Research (FRS-FNRS, Belgium). No other conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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