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

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26 **Running title:** Insula parcellation in sCUD and sAUD

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39 **Abstract**

40 Background: Theoretical and empirical contributions have identified insula as key in
41 addiction. However, anatomical modifications of the insula in addictive states, and their
42 variations across substance use disorders (SUD), remain to be specifically explored. We
43 therefore explored the specificities and commonalities of insula grey matter (GM)

44 alterations in severe alcohol use disorder (sAUD) and severe cocaine use disorders
45 (sCUD).

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

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

55 Conclusions: We offered the first joint exploration of GM insular volumes in two SUD
56 through refined parcellation, thus unveiling the similarities and dissimilarities in volume
57 deficit profiles. Our results bring evidence complementing prior ones suggesting the
58 core role of the right and posterior insula in craving and interoception, two crucial
59 processes in addiction. Left AIC and PLG group differences also show that, while insula

60 is a region of interest in SUD, sCUD and sAUD generate distinct insular profiles, which
61 might parallel clinical differences across SUD.

62 **Keywords:** Parcellation, MRI, Brain volume, Addiction

63 **Introduction**

64 The insula is an ultra-connected cortical region [1] involved in wide array of processes,
65 including sensory (e.g., olfaction [2]), affective [3] and cognitive (e.g., cognitive control
66 [4]) domains. The insula also has a key functional role in interoception, the ability to
67 build a representation of the internal self of the body, encompassing sensing,
68 interpretation, integration and regulation of internal signals [5].

69 Interoceptive signals, traditionally defined as emanating from beneath the skin, are
70 brought to insula through the lamina I spinothalamocortical pathway (also called
71 interoceptive pathway) [6-8]. In the insula, those signals follow a posterior-to-mid-to-
72 anterior processing, generating a progressive refinement of interoceptive representation,
73 notably through associations between insula and concomitant brain regions [6,8-9]. In
74 the posterior insula, bodily information is processed, providing an *objective*
75 representation of visceral bodily states, notably through connections with parietal

76 regions [10], such as the somatosensory cortex [11]. Then, in the rostral insula, a
77 *subjective* meta-representation of interoceptive information is hypothesized [7],
78 capitalizing on connections with the frontal cortex [10,12].

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

91 Such theories of insula as key craving neural substrate received initial empirical
92 support through a seminal study reporting insular lesions to result in addictive
93 behaviors cessation, due to a sudden craving hiatus [18]. Moreover, insular lower volume
94 is found across substances–being, thus, conceptualized as being part of a common
95 addiction neural substrate [19]. However, while these empirical reports provide
96 invaluable information regarding insular role in addiction, they remain quite imprecise as
97 they relied on an overall exploration of insula. As previously mentioned, insula is not an
98 anatomically and structurally unified region, as it is rather composed of multiple
99 subregions with different functions [20-21]. Preclinical studies have supported such
100 argument by showing that rostral and posterior insula have differentiated involvement
101 levels in rats' drug-seeking behaviors (i.e., inactivation of anterior insula leads to
102 decrease in cocaine-seeking behavior, while posterior insula inactivation has no effect
103 [22]). Recent human studies further underlined the need for refined exploration of
104 insular subregions: in alcohol use disorder, insula has a differential volume deficit profile,
105 with both lateralization (i.e., right-sided [23]) and subregions (i.e., lower volume in
106 posterior insula [24]) specificities. In cocaine use disorder, similar right-sided volume

107 deficit lateralization effect has been observed [25] but there are no refined explorations
108 of insula subregions.

109 Despite these preliminary results, two major methodological limitations are
110 impeding results generalization across addiction field and, therefore, the understanding
111 of insula contributions in addiction onset and maintenance. First, heterogenous
112 parcellation techniques followed in insular studies lead to discrepancies in the
113 localization and numbers of insular subregions [26]. While, in rodent studies, an
114 anatomical parcellation of the insula is followed, in the human field insular parcellation
115 relies on functional (activation results), hindering comparisons between human and
116 animal fields but, also, within human field [26]. There are currently studies reporting
117 parcellation ranging from 2 to 13 anatomical or functional insula subregions [20],
118 hindering studies results comparison. Second, the lack of direct and refined comparison
119 of insular subregions specificities across different substances. The few studies exploring
120 grey matter (GM) volume across substances rely almost exclusively on voxel-based
121 morphometry (VBM) technique [27], following whole-brain approaches rather than
122 targeting specific regions of interests, generating results at the overall insular level.
123 Therefore, these studies did not explore specifically similarities and differences in GM

124 abnormalities in different SUD at the insular subregions level. Noteworthy, the few VBM
125 studies exploring brain morphology across SUD report notably shared volume deficit of
126 the insula [27-28]—thus, again, providing first insights on insula role across addictions,
127 while lacking in precise and refined exploration of the insula subregions profile of
128 volume deficit for given substances.

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

136 We hypothesized a main group effect, with patient groups showing significant
137 lower volume compared to healthy control (HC). Given the lack of prior direct
138 comparison of insula GM volume using refined parcellation between SUD, we had no
139 specific hypothesis regarding the shared and dissimilar GM insula subregions profiles

140 between sAUD and sCUD. Noteworthy, having shown in a prior study [24] that sAUD
141 had a right-sided and antero-posterior gradient of GM volume deficit compared to HC,
142 we wanted to go further by exploring the commonalities and differences in the pattern
143 of abnormalities of insula in addiction, by adding a sCUD group to our priorly published
144 data.

145

146 **Methods**

147 *Participants*

148 We recruited 61 patients (12 females) with a DSM-5 diagnosis of sCUD (DSM-5 criteria,
149 American Psychiatric Association, 2013). The current study comprised also 50 patients (6
150 females) with a diagnosis of sAUD (DSM-5 criteria, American Psychiatric Association,
151 2013), and 36 HC (6 females), priorly described in [24]. sCUD and sAUD were early
152 abstainers recruited by clinicians from inpatient treatment units (sCUD: Fernand Widal
153 Hospital and Garches Castle Clinic, France; sAUD: Caen University Hospital, France).
154 Patients underwent a first assessment during which clinicians assessed SUD. When
155 included in the study, sAUD showed no more physical symptoms of alcohol withdrawal–

156 as assessed by Cushman's scale [31]. HC, group-matched with sAUD and sCUD for
157 education level and gender, were recruited in Caen. HC reported a low pattern of
158 alcohol consumption (score <6 for female and <7 for male at the AUDIT [32-33]), no
159 symptoms of severe depression (score <29 at the Beck Depression Inventory-II; BDI [34])
160 and did not present signs of global cognitive alteration (score >126 at the Mattis
161 Dementia Rating Scale; MDRS [35]). All participants spoke French fluently and presented
162 no major medical/neurological disorders. HC and sAUD presented no polysubstance
163 abuse except for nicotine (assessed by the DSM-5 criteria, American Psychiatric
164 Association, 2013). sCUD were all primarily treated for a CUD. However, due to
165 characteristics inherent to this population, 62% of sCUD presented problematic alcohol
166 use, 21% problematic opioid use, 18% problematic THC use and 18% problematic
167 benzodiazepine use. Table 1 reports socio-demographic, clinical, neuropsychological and
168 substances-related variables.

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

173 with the Declaration of Helsinki's ethical standards. All participants provided informed
174 written consent prior to the study participation.

175 Table 1

176 ***Procedure***

177 *Volumetric data acquisition*

178 For sCUD, high-resolution T1-weighted anatomical image were acquired with a Siemens
179 Magnetom 3T scanner (CENIR Imaging Center in Paris), using a 3D fast-field echo
180 sequence (176 sagittal slices, thickness = 1 mm, repetition time = 2300 ms, echo time =
181 2.9 ms, flip angle = 9°, field of view, 256x256 mm², matrix, 256x256).

182 For sAUD and HC, high-resolution T1-weighted anatomical image were acquired on a
183 Philips Achieva 3T scanner (Philips Healthcare/Philips Medical Systems International B.V.,
184 Eindhoven, The Netherlands) using a 3D fast-field echo sequence (sagittal, repetition
185 time = 20ms; echo time = 4,6ms; flip angle = 10°, 180 slices, slice thickness = 1mm,
186 field of view = 256x256 mm², matrix = 256x256).

187 *Volumetric data pre-processing*

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

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

201 *Volumetric Regions of Interest (ROI) extraction*

202 We extracted each individual insular volumes using Faillenot's GM brain atlas [29], which
203 provides six bilateral insular GM regions of interest (ROI): six left (n° 20, 86, 88, 90, 92

204 and 94) and six right (n° 21, 87, 89, 91, 93 and 95). The six subregions are, from most
205 rostral to posterior insula: anterior inferior cortex (AIC), anterior short gyrus (ASG),
206 middle short gyrus (MSG), posterior short gyrus (PSG), anterior long gyrus (ALG), and
207 posterior long gyrus (PLG).

208 ***Statistical analyses***

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

211 To explore group differences in insular GM ROI volumes, we normalized each of the ROI
212 measure by individual total intracranial volume (TIV) to correct for head-size differences.

213 We then used the resulting ROI by TIV computed score to calculate z-scores, using HC's
214 mean and standard deviation. We applied a linear mixed model analysis to the resulting
215 values, where dependent variable was the computed z-scores of GM volume, factors
216 were lateralization, subregions and group, covariates were age and gender and random
217 factor was participants. Significant main effects were followed by Bonferroni post-hoc
218 tests.

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

227

228 **Results**

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

232 *Main effects*

233 Mixed-model conducted on insula subregions z-scores revealed that all main effects
234 were significant: we found main effects of group ($F(2, 144) = 39.37, p < 0.001$),

235 lateralization ($F(1, 1584) = 52.14, p < 0.001$) and subregion ($F(5, 1584) = 43.95, p < 0.001$).
236 Subsequent post-hoc comparisons (both $p < 0.001$) showed lower insula volume in sAUD
237 and sCUD compared to HC, while the two patient groups had, overall, similar insular
238 volume. Post-hoc comparisons on main lateralization effect revealed that right insula
239 had lower volume than left insula ($p < 0.001$). Following subregions post-hoc
240 comparisons, we found ALG to have significantly lower GM volume than all other five
241 subregions (from anterior to posterior insula, all p-values < 0.001): AIC, ASG, MSG, PSG
242 and PLG. Moreover, PSG showed lower GM volume than AIC ($p < 0.001$), ASG ($p < 0.001$)
243 and MSG ($p = 0.002$). PLG had lower volume than AIC ($p = 0.02$) and ASG ($p = 0.003$).

244 *Group by lateralization interaction*

245 We found significant lateralization by group interaction effect ($F(2, 1584) = 19.83,$
246 $p < 0.001$), with right-sided volume deficit for sAUD ($p < 0.001$) and sCUD ($p = 0.002$), which
247 was not found in HC. Moreover, sAUD and sCUD had lower right insula volume than HC
248 and the left insula of sAUD and sCUD had lower volume than the left insula of HC (all
249 p-values < 0.001). However, for both right and left insula, post-hoc comparisons showed
250 that sAUD and sCUD had similar GM volume.

251 *Group by subregion interaction*

252 Group by subregion interaction effect was significant ($F(10, 1584) = 14.06, p < 0.001$).

253 Subsequent post-hoc comparisons revealed that all of the six insular subregions of the

254 patient groups had lower volumes than the ones of the HC (from rostral to posterior

255 insula): AIC (sAUD: $p = 0.007$; sCUD: $p < 0.001$), ASG (sAUD & sCUD with both $p < 0.001$),

256 MSG (both $p < 0.001$), PSG (both $p < 0.001$), ALG (both $p < 0.001$) and PLG (both $p < 0.001$).

257 Volume differences between sAUD and sCUD were not significant.

258 Post-hoc comparisons showed that the ALG of sCUD and sAUD had lower GM volume

259 than all other five subregions (ant-to-post): AIC (sAUD & sCUD with both $p < 0.001$), ASG

260 (both $p < 0.001$), MSG (both $p < 0.001$), PSG (both $p < 0.001$) and PLG (both $p < 0.001$).

261 Moreover, the AIC of sCUD showed lower GM volume than their ASG ($p = 0.002$), the PSG

262 was more atrophied than their ASG and MSG, and their PLG had lower volume than

263 their ASG and MSG (all p-values < 0.001). For sAUD patients, post-hoc comparisons

264 showed that MSG ($p = 0.04$) and PSG ($p < 0.001$) were more atrophied than AIC.

265 *Group by lateralization and subregion triple interaction (Figure 1)*

266 Subregion GM volume varied significantly depending on group and lateralization ($F(10,$
267 $1584) = 4.43, p < 0.001$). More specifically, we found for all six right subregions that
268 patient groups had lower volumes than HC's (ant-to-post insula): AIC (sAUD: $p = 0.03$;
269 sCUD: $p < 0.001$), ASG (sAUD & sCUD with both $p < 0.001$), MSG (both $p < 0.001$), PSG
270 (both $p < 0.001$), ALG (both $p < 0.001$) and PLG (both $p < 0.001$). sAUD and sCUD patients
271 had similar subregions GM volume.

272 However, for the left insula, the most rostral (AIC) and posterior (PLG) subregion of the
273 insula of sCUD had lower volume than the ones of both sAUD (AIC: $p = 0.006$; PLG:
274 $p < 0.001$) and HC (AIC: $p < 0.001$; PLG: $p < 0.001$), while sAUD and HC had similar AIC and
275 PLG volume. For the four other insular subregions, post-hoc comparisons showed
276 significant lower insula volumes for the two patient groups compared to HC, but no
277 difference between sAUD and sCUD (ant-to-post): ASG (sAUD: $p = 0.015$; sCUD: $p < 0.001$),
278 MSG (sAUD: $p = 0.002$; sCUD: $p = 0.026$), PSG (sAUD & sCUD with both $p < 0.001$) and ALG
279 (both $p < 0.001$).

280 Figure 1

281 *Exploratory sCUD (problematic alcohol use Vs. not) analysis (Supplementary Figure 1)*

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

285

286 **Conclusions**

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

294 Firstly, we showed shared alteration of overall insula GM volume in SUD. Theoretical
295 models and empirical findings concur on insula key role in addiction [26] but a
296 fundamental contradiction remains across previous work. On the one hand, major
297 models [17] and seminal studies [18] theorize that addictive states are related to

298 increased insula activation (leading to intense and irrepressible craving [40]), as notably,
299 insular damage would lead to cessation of addictive states [18]. However, on the other
300 hand, other studies report insula to be desensitized in addiction, as it undergoes major
301 structural (e.g., insula GM volume deficit in SUD [27]) modifications in addiction. At the
302 anatomical level, we found the insula to be structurally altered in addiction, since in
303 both sAUD and sCUD we found insula to have lower volume than in HC. While
304 anatomical findings warrant any conclusion at the functional level, we could however
305 hypothesize that, as soon as in the subclinical binge/intoxication stage [17], an
306 hypersensitized insula to substance-related cues would already be present [13]. Then,
307 due to mechanisms including notably neurotoxic effect of substances, a damaged insula
308 would thus be observed in the preoccupation/anticipation stage [17], when the
309 addiction is already set—which, due to its impediment, would maintain the addiction.
310 This suggests that insula would contribute to all stages of the addiction framework,
311 albeit differently. Noteworthy, while longitudinal studies are needed to explore such
312 hypothesis, there are already reports in binge-drinkers of insula hyperactivation (e.g.,
313 while undergoing the Iowa gambling task [41]) and of higher volumes of insula white
314 matter, that is notably associated to alcohol craving [42].

315 Secondly, our results identify lateralization effect as we observed right-sided volume
316 deficit in both sAUD and sCUD. This lateralization trend, already reported in sCUD [43]
317 and sAUD [23], might constitute predisposing risk factor for sAUD emergence [44].
318 While the current study design, focusing on insula GM at the anatomical level, prevent
319 any conclusion at the functional level, one possible explanation for this right-sided
320 lateralization effect could be found in insular role as neural substrate of craving and
321 interoception, which are both related to preferential activation of the right insula [45-
322 47]. In fact, according to interoception models, as interoceptive information is being
323 processed through insula, it is in right anterior insula that interoceptive information
324 operates its final and highest-level processing, enabling a sense of the self [7;48]. Thus,
325 one implication of this stronger reduction of GM volume in right insula could be
326 associated to disruption of sentient-self that is observed in SUD, which takes multiple
327 forms such as interoceptive impairments [49], abnormal emotions experiencing and
328 impeded decision making [50].

329 Thirdly, sCUD and sAUD patients have differential pattern of volume deficits of insular
330 subregions. These results, which further highlight the need to follow refined parcellation
331 of insula, provides first insights on the patterns of commonalities and specificities in

332 substance profiles of macrostructural abnormalities. Regarding shared insular GM lower
333 volume between SUD, there is major GM volume deficits of the ALG (localized in the
334 posterior insula) compared to other insula subregions. Current study results concur with
335 prior ones regarding volume deficit of posterior insula in sCUD [51] and sAUD [52]. As
336 above-mentioned, interoceptive information follows posterior-to-mid-to-anterior
337 processing, corresponding to a refinement pathway [6,8-9]. In posterior insula, visceral-
338 related information (e.g., effect of substance on body) is processed [7]. While the current
339 study design provides information solely at the anatomical level, such results could be
340 related, at the functional level, with impairments of the first steps of interoceptive
341 information processing, which provides objective representation of internal states [7].
342 This could explain impairments of body-related perception in SUD, with reports of, for
343 example, heightened interoceptive sensibility [53] and hyperalgesia [54]. Regarding
344 specific patterns of lower insular GM volume for sCUD and sAUD, volume deficits
345 observed in ALG expand to surrounding subregions (i.e., PSG & PLG) in sCUD while, for
346 sAUD, AIC seems more preserved than its concomitant subregions (i.e., MSG & PSG).
347 However, to further explore this hypothesized parallel between interoception, craving

348 and insula volume deficits, further studies going deeper than basic volumetric
349 exploration and including measures of these processes are needed.

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

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

377 To conclude, the current study offers the first direct comparison of GM insular
378 volume in two SUD, using refined parcellation. We found sCUD and sAUD to share
379 similarities in their overall profile of insula volume deficits, notably regarding right-sided
380 volume deficit effect but, also, in major alteration of ALG, a region related to the
381 processing of bodily-information. However, specificities emerged when looking more

382 precisely at insula subregions, with most anterior (AIC) and posterior (PLG) subregions of
383 left insula being atrophied in sCUD, while preserved in sAUD. Nevertheless, the current
384 study results lack prior literature to identify intrinsic differences of these two subregions,
385 as studies rarely compare directly insula GM volume across substances and, to our
386 knowledge, never using such a refined parcellation. Our results thus constitute a first
387 step in the exploration of insula profile of volume deficit specificities in addiction more
388 generally.

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