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PROGNOSTIC FACTORS FOR LOW-RISK DRINKING AND RELAPSE IN ALCOHOL
USE DISORDER: A MULTIMODAL ANALYSIS

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ABSTRACT

Aims: To specify the determinants of low-risk alcohol drinking and relapse at different time points after detoxification in patients with severe Alcohol Use Disorder (AUD).

Methods: Fifty-four AUD patients and 36 healthy controls (HC) were evaluated early in abstinence (T1). They underwent clinical, neuropsychological and neuroimaging (structural MRI and ¹⁸FDG-PET) investigations.

AUD patients were subsequently classified as “low-risk drinkers” (LR) or “relapsers” (R) based on their alcohol drinking at 6 months (T2) and one year (T3) after discharge, using their medical record or self-reported drinking estimation at follow-up.

Results: Based on the alcohol status at T2 and compared to HC, only R had alexithymia, lower gray matter volume in the midbrain and hypermetabolism in the cerebellum and hippocampi. Based on the alcohol status at T3 and compared to HC, only R had more severe nicotinic dependence, lower episodic and working memory performance, lower gray matter volume in the amygdala, ventromedial prefrontal cortex and anterior cingulate gyrus, and hypermetabolism in cerebellum, hippocampi and anterior cingulate gyrus. Moreover, R had bilateral frontal hypometabolism, whereas LR only presented right frontal hypometabolism.

Conclusion: Nicotine dependence, memory impairments, and structural brain abnormalities in regions involved in impulsivity and decision-making might contribute to a one-year relapse. Treatment outcome at one year may also be associated with an imbalance between a hypermetabolism of the limbic system and a hypometabolism of the frontal executive system. Finally, cerebellar hypermetabolism and alexithymia may be determinants of relapse at both 6 months and one year.

Key words: Alcohol Use Disorder, cognition, low-risk drinking, neuroimaging, relapse, Treatment outcomes.

1 INTRODUCTION

2 Alcohol Use Disorder (AUD) is a highly prevalent public health problem with
3 considerable individual and societal costs. It is defined by the National Institute on Alcohol
4 Abuse and Alcoholism (NIAAA) as a chronic brain disease, characterized by a high rate of
5 relapse (1). Several psychological and biological factors seem to increase the risk of relapse.
6 Among the psychological factors, alcohol craving (2), impulsivity (3,4), altered emotion
7 processing and interpersonal relationships (5), smoking status (6) and comorbid psychiatric
8 disorders (7) have frequently been related to alcohol relapse. Regarding the impact of
9 cognitive alterations, results are less consistent. Some studies indicated that memory and
10 executive deficits do not seem to be associated with a higher risk of relapse (8–10), whereas
11 others showed that processing speed, working memory and inhibition performance early in
12 abstinence may distinguish future relapsers from abstainers (11,12). Concerning biological
13 factors, structural brain alterations are frequently suggested as reliable relapse determinants
14 (6,11,13). Despite the obvious multifactorial nature of relapse, few investigations used an
15 integrative approach to identify prognostic indicators of treatment outcome by considering
16 several clinical, neuropsychological as well as structural and functional brain measures within
17 the same study.

18 Moreover, because the attrition rate is high in longitudinal studies of AUD and relapse
19 frequently occurs within 6 months after detoxification (14,15), studies usually examine
20 determinant factors of an early relapse (9,11,16–18). Studies including a later follow-up
21 examination are scarce (1,7). Yet, relapse can be regarded as a dynamic process influenced by
22 different determinants according to the time period. Further studies investigating determinants
23 of early as well as later relapse are thus required.

24 The operational definition of relapse is difficult, changing and related to that of
25 treatment success. Until recently, total abstinence from alcohol was considered as the only
26 acceptable treatment target. However, new medications targeting a reduction of alcohol
27 consumption reached the market and resulted in a paradigm shift. Even though abstinence
28 remains often the safest treatment option, reduction of alcohol consumption is thus now
29 considered as a relevant alternative. In this perspective, the World Health Organization
30 (WHO) has defined four drinking risk levels (very high, high, medium, and low). The
31 European Medicines Agency (EMA) considers that a two-level reduction in the WHO
32 drinking risk levels can be used as a secondary endpoint for clinical trials (19). The NIAAA
33 and the United States Dietary Guidelines Advice on Alcohol recommend limiting intake to
34 two drinks in a day for men and one drink in a day for women.

35 In line with these new AUD treatment outcomes, the objective of the present study
36 was to specify the determinants of low-risk drinking and relapse at different time points. We
37 conducted a multimodal analysis by exploring several clinical, neuropsychological and
38 neuroimaging measures in early detoxified AUD patients. Two follow-up examinations were
39 conducted six months and one year after the discharge in order to specify, at each time point,
40 the risk level associated with alcohol drinking. There was no neuropsychological nor
41 neuroimaging assessment at follow-up.

42

43 **METHOD**

44 **Participants**

45 Fifty-four AUD patients and 36 healthy controls (HC) were included in this study
46 approved by the local ethics committee of Caen University Hospital (CPP Nord-Ouest III, no.
47 IDRCB: 2011-A00495-36). To be included, participants had to have French as their native

48 language, to be between 18 and 70-year-old, and to have at least 8 years of schooling.
49 Comorbid conditions such as psychiatric disorders, a history of serious chronic disease, or
50 neurological pathologies were exclusion criteria. Participants did not fulfill the criteria for
51 substance use disorder (other than alcohol for AUD patients) except tobacco. Participants
52 gave their informed written consent to the study prior to their inclusion. The study was carried
53 out in line with the declaration of Helsinki (1964).

54 AUD patients were recruited by clinicians while they were receiving withdrawal
55 treatment as inpatients at Caen University Hospital. They met both criteria for severe AUD
56 (DSM-5)(20). At inclusion, none of them presented physical symptoms of alcohol withdrawal
57 as assessed by the Cushman's scale (21) and none of them were under psychotropic
58 treatments (in particular, benzodiazepines used during the alcohol withdrawal treatment were
59 stopped at least 48h before inclusion). The three-week detoxification program usually
60 included one week of withdrawal treatment and two weeks of daily treatment sessions
61 adjusted to the patients' cognitive abilities. The daily sessions included psychoeducation,
62 motivational interview, group therapy or relapse prevention treatment based on cognitive
63 behavioral therapy.

64 HC were recruited to match the demographics (age, sex, and education) of the AUD
65 patients. They were interviewed with the Alcohol Use Disorder Identification Test
66 (AUDIT)(22) to ensure that they did not meet the criteria for alcohol abuse (AUDIT<7 for
67 men and <6 for women). None of the controls had a score at the Beck Depression Inventory
68 (BDI) superior to 29 (23) and a Mini-Mental State Examination score inferior to 26 (24).
69 Demographical and clinical data are presented in Table 1 and in supplementary Table S1.

70 Table 1 about here

71

72 **Study Design**

73 A baseline clinical, neuropsychological and neuroimaging assessment was conducted
74 early in abstinence (11.04 ± 4.34 days after the last alcohol drink, T1). Alcohol status was
75 determined at six months (T2) and one year (T3) after discharge. Based on recommendations
76 of the NIAAA or the “Dietary guidelines for Americans 2020-2025”, patients were classified,
77 at both T2 and T3, as “low-risk drinkers” (LR) when they had consumed no more than 14
78 drinks/week for men and 7 drinks/week for women, and “relapsers” (R) when their alcohol
79 consumption exceeded these thresholds or when they reported to have lost the control of their
80 consumption (without being able to quantify it with accuracy) during the follow-up period.
81 For X patients, we also used medical records indicating hospital admission, notably in the
82 emergency department, for alcohol intoxication. We also questioned patients about potential
83 binge drinking behavior, which is characterized by the consumption of an excessive amount
84 of alcohol in a short period of time. Bingers were not included in the LR group. In this study
85 one standard drink is equivalent at 10 grams of pure ethanol. Based on their alcohol status at
86 each time point (T2 or T3), patients were classified as LR^{T2} or R^{T2}, and LR^{T3} or R^{T3}.

87

88 **Clinical evaluation**

89 At baseline (T1), all participants completed standardized questionnaires that evaluated
90 alcohol consumption (AUDIT), depression symptoms (BDI), anxiety symptoms (State-Trait
91 Anxiety Inventory; STAI)(25), nicotine dependence (Fagerstrom)(26), impulsivity (Barratt
92 Impulsiveness Scale; BIS 11)(27) and alexithymia (Toronto Alexithymia Scale; TAS-20)(28).
93 The highest Cushman score experienced during the withdrawal period (21), the number of
94 previous alcohol detoxifications, the amount of alcohol consumed the month preceding the

95 withdrawal (number of units of 10g of pure ethanol per day), and the duration of heavy
96 drinking (years) were collected by clinicians.

97

98 **Neuropsychological examination**

99 At baseline, patients performed neuropsychological tasks to evaluate episodic
100 memory, working memory, executive functions, attention and visuoconstruction.

101 *Verbal episodic memory.* The delayed free recall of a French version of the Free and Cued
102 Selective Reminding Test (FCSRT) (29) was used.

103 *Visual episodic memory.* The 30-minute delayed recall of the Rey-Osterrieth Complex Figure
104 (ROCF) (30) was used.

105 *Working memory.* The backward digit span of the WAIS-III (31) was used.

106 *Flexibility.* The number of perseverative errors of the Modified Card Sorting Test
107 (MCST)(32) was used.

108 *Inhibition.* The interference score of the Stroop test (33), corresponding to the difference
109 between the time needed to complete the interference condition (Word-Color condition) and
110 the time needed for the denomination condition (Color condition), was used.

111 *Attention.* The overall performance index (GZ-F) of the d2 test (34) was used.

112 *Visuoconstruction.* The copy score of the ROCF was used.

113

114 **Brain Imaging examination**

115 While the entire sample (N=36) of HC underwent all the neuroimaging investigations
116 at baseline (T1), MRI was conducted in only 47 AUD patients, and FDG-PET in 37 AUD

117 patients (out of the 54 AUD patients in total). Acquisitions and preprocessing of brain
118 imaging data are provided in supplementary material Method S1.

119

120 **Statistical analyses**

121 *Demographical, clinical, and neuropsychological data.*

122 Given the sample sizes and the fact that several variables were not normally
123 distributed (according to Shapiro-Wilk's tests), non-parametric tests were used.

124 First, we compared the entire group of AUD patients to HC by means of Mann-
125 Whitney's tests carried out on the data collected at T1. We then conducted between-group
126 comparisons based on alcohol status at T2 and T3 separately. Group effects (R vs. LR vs. HC)
127 were thus analyzed using Kruskal-Wallis's tests. When significant, *post-hoc* pairwise
128 comparisons were performed to compare R vs. LR, R vs. HC, and LR vs. HC using Dwass-
129 Steel-Critchlow-Fligner tests (DSCF). Given the number of comparisons carried out, we used
130 Bonferroni's corrections. Regarding the analyses of the main effects (Mann-Whitney's test
131 and Kruskal-Wallis's tests), we used $p < 0.003$ for the analyses conducted on 14 demographical
132 and clinical variables ($0.05/14 = 0.003$) and $p < 0.007$ for the 7 neuropsychological variables
133 ($0.05/7 = 0.007$). For *post-hoc* comparisons, the statistical threshold was set to $p < 0.05$.

134 *Brain imaging data.*

135 Analyses were performed in SPM 12 using a minimum cluster size of $k=60$ for MRI
136 data and $k=25$ for PET data, both corresponding to a cluster size of approximately 200 mm^3 .
137 First, voxel-based two-sample t-tests were conducted to compare gray matter (GM) and white
138 matter (WM) volumes, as well as metabolism between the entire group of AUD patients and
139 HC on the T1 data. Then, these analyses were conducted based on alcohol status at T2 and T3
140 separately. Voxel-based two-sample t-tests were carried out to compare GM and WM

141 volumes, as well as metabolism between R vs. LR, R vs. HC, and LR vs. HC. For each
142 comparison, the two contrasts were systematically analyzed. For all neuroimaging
143 comparisons, age was used as a covariate, and for volumetric comparisons, total intracranial
144 volume was also included in the analysis. Analyses were first conducted using an uncorrected
145 $p < 0.001$ threshold. Then, a more stringent threshold corrected for multiple comparisons
146 (Family-Wise Error (FWE), $p < 0.05$) was applied to highlight the most significant findings.
147 Significant clusters of gray matter volumes and metabolism were labeled using the Harvard-
148 Oxford cortical and subcortical structural, and the probabilistic cerebellar atlases implemented
149 in FSL (fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). White matter clusters were labelled using the
150 MRI Atlas of Human White Matter (35).

151

152 **RESULTS**

153 **Comparisons between AUD patients and HC at T1**

154 AUD patients differed significantly from HC on the BDI ($U=249$, $p < 0.001$), STAI-B
155 ($U=363$, $p < 0.001$), TAS-20 ($U=522$, $p=0.001$), Fagerstrom ($U=360$, $p < 0.001$), proportion of
156 smokers ($X^2=21.642$, $p < 0.001$), and AUDIT ($U=0$, $p < 0.001$) scores (Table 1).

157 Compared to HC, AUD patients were impaired on verbal episodic memory ($U=508$,
158 $p < 0.001$), working memory ($U=487$, $p < 0.001$), inhibition ($U=611$, $p=0.006$), and attention
159 ($U=529$, $p < 0.001$) (Table 2 and supplementary Table S2).

160 Table 2 about here.

161 Neuroimaging data are presented in Figure S1.

162

163 **Alcohol status at follow-up**

189

190 **Comparisons between HC, R^{T2}, and LR^{T2} on data acquired at T1**

191 *Demographical and clinical data*

192 A group effect was found for the BDI, STAI-B, Fagerstrom, AUDIT, and TAS-20
193 scores (all $p < 0.001$). Compared with HC, both patient groups (LR^{T2} and R^{T2}) had higher
194 scores on the BDI, STAI-B, Fagerstrom, and AUDIT, but did not differ from each other. On
195 the TAS 20, only R^{T2} significantly differed from HC (Table 1 and Table S1).

196 *Neuropsychological data*

197 A group effect was found for the verbal episodic memory, working memory ($p = 0.003$
198 in both cases), and attention ($p = 0.004$) scores only. Compared with HC, both patient groups
199 (R^{T2} and LR^{T2}) were impaired on verbal episodic memory and working memory. For
200 attention, only LR^{T2} significantly differed from HC (Table 2 and supplementary Table S2).

201 *Neuroimaging data*

202 Results are presented in Figure 2.

203 *Gray matter.* Compared to LR^{T2}, R^{T2} had lower GM volume in the right lingual gyrus
204 ($p < 0.001$ uncorrected). There were no significant results using an FWE correction ($p < 0.05$).

205 Compared to HC, R^{T2} had widespread GM alteration ($p < 0.001$ uncorrected). Using a more
206 stringent threshold (FWE, $p < 0.05$), GM shrinkage remained significant in large brain clusters
207 including parts of the frontal, parietal, temporal (including medial temporal lobes namely
208 hippocampi and parahippocampal gyri), occipital, insular, and cingulate cortices as well as in
209 the cerebellum, and in subcortical structures such as the thalami, hypothalami (including
210 mammillary bodies), amygdala, and caudate nuclei.

211 Compared to HC, LR^{T2} showed smaller volume of GM bilaterally in the frontal, cingulate
212 (anterior and middle), temporal (including medial temporal lobes namely hippocampi and

213 parahippocampal gyri), parietal, occipital, and insular cortices, as well as in the caudate
214 nuclei, thalami, and hypothalami (including mammillary bodies), and in the left amygdala,
215 lobule 6 and crus I of the cerebellum ($p < 0.001$ uncorrected). We found no significant results
216 using an FWE correction ($p < 0.05$).

217 The opposite contrasts did not reveal any significant difference.

218

219 *White matter.* Compared to LR^{T2}, R^{T2} had lower WM volume in the right cingulum,
220 body and splenium of the corpus callosum, and posterior corona radiata ($p < 0.001$
221 uncorrected). There were no significant results using an FWE correction ($p < 0.05$).

222 Compared to HC, R^{T2} had widespread WM volume reduction ($p < 0.001$ uncorrected). When a
223 more stringent threshold was applied (FWE, $p < 0.05$), WM shrinkage remained significant in
224 large clusters including parts of the midbrain, fornix, corpus callosum, corona radiata,
225 thalamic radiation, superior fronto-occipital fasciculus, superior longitudinal fasciculus,
226 internal capsule, right cerebral peduncle, left cingulum and in the WM of the middle frontal
227 gyri.

228 LR^{T2} showed smaller volume than HC in the WM of the frontal gyri, corpus callosum, corona
229 radiata, posterior thalamic radiation, superior fronto-occipital fasciculus, retrolenticular part
230 of the internal capsule, superior longitudinal fasciculus, in the left cingulum, and anterior limb
231 of internal capsule ($p < 0.001$, uncorrected). We found no significant results using an FWE
232 correction ($p < 0.05$).

233 The opposite contrasts did not reveal any significant difference.

234

235 *Metabolism.* At T1, there was no significant difference between R^{T2} and LR^{T2}
236 regarding the regional glucose metabolism ($p < 0.001$ uncorrected).

237 Compared to HC, R^{T2} had *hypometabolism* bilaterally in the medial, middle, and superior
238 frontal gyri, as well as in the left paracingulate gyrus, and in the right inferior parietal lobule
239 (p<0.001 uncorrected). The opposite contrast revealed that R^{T2} also had bilateral
240 *hypermetabolism* in lobules V-VIII, Crus I and II of the cerebellum, as well as in the temporal
241 gyri (including parahippocampal gyri and hippocampi), right precentral gyrus, and in the left
242 postcentral gyrus (p<0.001 uncorrected).

243 Compared to HC, LR^{T2} had *hypometabolism* in the bilateral inferior parietal lobule, and in the
244 superior and middle frontal gyri (p<0.001 uncorrected). The opposite contrast showed that
245 LR^{T2} also had *hypermetabolism* in the left middle temporal gyrus only (p<0.001 uncorrected).
246 None of the comparisons remained significant using an FWE correction (p<0.05).

247

248

249

Figure 2 about here.

250

251 **Comparisons between HC, R^{T3}, and LR^{T3} on data acquired at T1**

252

Demographical and clinical data

253 A group effect was found for the BDI, STAI-B, AUDIT, Fagerstrom, and TAS-20
254 scores (all p<0.001). Compared with HC, both patient groups (R^{T3} and LR^{T3}) had higher
255 scores on the BDI, STAI-B, and AUDIT, but did not differ from each other. On the
256 Fagerstrom and TAS 20, only R^{T3} differed significantly from HC (Table 1 and Table S1).

257

Neuropsychological data

258 A group effect was found for the verbal episodic memory and working memory scores
259 only (p=0.003 in both cases), with R^{T3} being impaired compared with HC (Table 2 and
260 supplementary Table S2).

261 *Neuroimaging data*

262 Results are presented in Figure 3.

263 *Gray matter.* At T1, there was no group difference in GM volume between R^{T3} and
264 LR^{T3} ($p < 0.001$ uncorrected).

265 The comparison between R^{T3} and HC revealed a similar pattern of shrinkage as the one
266 observed for the comparison between R^{T2} and HC using both statistical thresholds ($p < 0.001$
267 uncorrected and FWE correction ($p < 0.05$)).

268 LR^{T3} showed smaller GM volume than HC bilaterally in the insula, hippocampi, thalami,
269 middle frontal, precuneus, lingual, parahippocampi, and Heschl gyri, as well as in the right
270 postcentral, precentral, inferior and superior frontal gyri ($p < 0.001$ uncorrected). The analysis
271 did not reveal any significant difference after FWE correction ($p < 0.05$).

272 Opposite contrasts revealed no significant differences in any of the comparisons.

273

274 *White matter.* R^{T3} had lower WM volume than LR^{T3} in the right posterior corona
275 radiata, as well as in the body and splenium of corpus callosum, and in the WM of the
276 cingulate gyrus ($p < 0.001$ uncorrected). Using an FWE correction ($p < 0.05$), the analysis did
277 not reveal any significant difference.

278 Comparisons between R^{T3} and HC revealed a similar pattern of results to that observed for the
279 comparison between R^{T2} and HC using both statistical thresholds ($p < 0.001$ uncorrected and
280 FWE correction ($p < 0.05$)).

281 LR^{T3} showed smaller volume than HC in the WM of the frontal gyri, genu and body of the
282 corpus callosum, anterior corona radiata, right posterior thalamic radiation, left anterior limb
283 of internal capsule, posterior corona radiata, and superior fronto-occipital fasciculus ($p < 0.001$
284 uncorrected). We found no significant results using an FWE correction ($p < 0.05$).

285 Opposite contrasts revealed no significant differences in any of the comparisons.

286

287 *Metabolism.* At T1, there was no significant difference of metabolism between R^{T3} and

288 LR^{T3} (p<0.001 uncorrected).

289 Compared to HC, R^{T3} had **hypometabolism** bilaterally in the medial, middle and superior
290 frontal gyri, in the paracingulate gyri, and in the right inferior parietal lobule (p<0.001
291 uncorrected). The opposite contrast revealed similar pattern of **hypermetabolism** to that
292 observed for the comparison between R^{T2} and HC. R^{T3} had also **hypermetabolism** in the
293 anterior cingulate gyri (p<0.001 uncorrected).

294 Compared to HC, LR^{T3} had **hypometabolism** in the right middle frontal gyrus (p<0.001
295 uncorrected). The opposite contrast showed that LR^{T3} also had **hypermetabolism** in the left
296 middle temporal gyrus (p<0.001 uncorrected).

297 None of the comparisons remained significant using an FWE correction (p<0.05).

298

299 Figure 3 about here.

300 **DISCUSSION**

301 The objective of the present study was to specify the determinants of low-risk drinking
302 (no more than 14 drinks/week for men and 7 drinks/week for women) and relapse at different
303 time points after detoxification. For this purpose, clinical, neuropsychological and
304 neuroimaging data, collected in early detoxified AUD inpatients, were compared according to
305 the alcohol status of these AUD patients six months and one year after the baseline
306 assessment. Our findings indicate that future relapsers and low-risk drinkers had different
307 profiles of alexithymia, nicotine dependence, memory deficits, and volumetric and metabolic
308 brain alterations measured early in abstinence. Except for alexithymia and cerebellar
309 hypermetabolism, which can be regarded as prognostic factors for relapse at both six months
310 and one year, the determinants of relapse were different for the two time points.

311 First, results of the present study revealed that alexithymia and neuroimaging
312 alterations observed after alcohol withdrawal were the main determinants of treatment
313 outcome at six months since they made possible to distinguish patients who would relapse
314 from those who would be able to maintain low-risk alcohol consumption. In effect, only
315 patients subsequently classified as relapsers at six months presented alexithymia traits,
316 suggesting that patients who had difficulties in identifying and describing their emotions may
317 be more susceptible to relapse within the first 6 months following the detoxification. This
318 finding is consistent with previous studies reporting that negative affect and emotion
319 processing deficits increase the risk of early relapse (3,5,36). Alcohol consumption is indeed
320 sometimes used as a coping strategy to regulate emotional states and altered interpersonal
321 relationships (37,38). In addition, a recent study showed that social cognition deficits,
322 including emotion recognition and affective responsiveness, did not spontaneously recover
323 during the first months of abstinence (39). Taken together, these findings highlight the
324 relevance of developing therapeutic interventions to manage emotional deficits and ultimately
325 reduce the risk of relapse.

326 Our study also highlighted that early in abstinence, patients who subsequently relapsed
327 within the six months after alcohol withdrawal had a more severe loss of GM and WM
328 volume than those who managed to maintain a low-risk drinking. This more pronounced
329 shrinkage affected brain regions including notably the frontal, parietal, and cingulate cortices,
330 insula, as well as hippocampi and thalami, which all have already been related to relapse in
331 previous studies (6,13,40). Because these regions are cortical and subcortical nodes of the
332 executive control and salient networks (41), this finding suggests that patients who relapsed
333 may not have been able to integrate sensory, emotional and cognitive information in order to
334 control alcohol use and to maintain alcohol drinking at a low-risk level.

335 Another possible determinant of relapse at six months is the presence of a cerebellar
336 hypermetabolism. Interestingly, this pattern of glucose metabolism, which we had previously
337 interpreted as a maladaptive plasticity phenomenon within the cerebellum (42), has only been
338 found in patients who relapsed.

339 The originality of the present investigation is to enable us to specify the determinants
340 of relapse and low-risk drinking at two time-points thanks to a follow-up examination one
341 year after alcohol withdrawal. In addition to alexithymia, that also appears a determinant of
342 treatment outcome at one year, this study is in line with previous investigations showing a
343 link between the severity of nicotine dependence early in abstinence and relapse (6,43). In
344 agreement, a preclinical study showed that the use of nicotine restores alcohol-seeking
345 behaviors in rats free from this substance (44). Alcohol and tobacco are highly comorbid
346 behaviors and cross-substance craving have frequently been shown (45). The use of one of
347 these substances can indeed act as a conditioned cue for the use of the other one. The nicotinic
348 acetylcholine receptor system is assumed to play a role in the alcohol reward circuit, probably
349 through a cholinergic excitatory input in the mesolimbic system (46). This is in accordance
350 with the fact that in our study, only patients who relapsed during the year following the
351 withdrawal presented an atrophy of the midbrain and the amygdala (regions of the
352 mesolimbic system) early after detoxification. Taken together, these findings suggest the
353 relevance of conducting a combination of nicotine and alcohol withdrawal.

354 Contrary to a previous investigation conducted in our laboratory but in a different pool
355 of AUD patients (8), we showed that verbal episodic memory impairments may be a
356 determinant of a one-year relapse since only future relapsers exhibited such deficits early in
357 abstinence. Memory impairments may hamper patients to remember the negative
358 consequences of alcohol use or the situations in which they are at risk of relapse, and lead to
359 low level of motivation to change drinking behavior (47). This would result in the activation

360 of automatic drinking behaviors and would thus make patients with episodic memory deficits
361 more likely to relapse (48). Moreover, in accordance with previous studies (11,12), only
362 future relapsers had lower working memory performance than controls. On the opposite,
363 results did not show that flexibility or inhibition might influence the relapse. Previous results
364 are inconsistent (8–12) regarding the prognostic value of executive deficits. Such discrepancy
365 may be related to the different neuropsychological tasks employed in these studies. They may
366 not all be sensitive to the executive processes potentially underlying relapse. Impaired
367 response inhibition evaluated with a go/no-go task (12) or the Hayling test (11) was related to
368 a high rate of relapse. A recent investigation (4) used both a go/no-go task and the Stroop test,
369 also used in the present study. The results showed that the go/no-go task, which assesses the
370 behavioral executive component, was associated with relapse, whereas the Stroop test, which
371 assesses the cognitive executive component, was unrelated to treatment outcomes. These
372 results underly how crucial it is to use neuropsychological tests that are more appropriate to
373 identify AUD patients at risk of relapse.

374 Finally, early after detoxification, future relapsers at both 6 months and one year differ
375 from future low-risk drinkers regarding the pattern of brain alterations. It was not surprising
376 to find the same neuroimaging determinants for T2 and T3 given that the group assignments
377 differed only for 6 individuals. In effect, even though direct group comparisons between R
378 and LR did not provide any significant results after FWE corrections, potentially related to the
379 small sample sizes, the patterns of alterations compared with controls were different for each
380 patient group. Specific brain regions such as the amygdala, the ventromedial prefrontal cortex
381 and the anterior cingulate gyrus are damaged only in patients who will relapse. These brain
382 regions sustain functions such as decision-making or impulsive behaviors, which have already
383 been linked to premature treatment dropout and relapse (4). When patients act with
384 impulsiveness and tend to prefer the immediate reward of alcohol consumption ignoring the

385 negative long-term consequences, they are more likely to relapse. This finding is consistent
386 with our PET results. Future relapsers exhibited a bilateral frontal hypometabolism associated
387 with hypermetabolism in anterior cingulate gyri and hippocampi, whereas future low-risk
388 drinkers only presented frontal hypometabolism in the right hemisphere. Hypermetabolism in
389 the hippocampi and anterior cingulate gyri, two regions involved in the limbic circuit (49),
390 might reflect an overactivation of emotional responses, which may be difficult to control
391 because of frontal hypometabolism. This overactivation of limbic/emotional system
392 associated to an underactivation of the frontal/executive system would result in uncontrolled
393 alcohol consumption and relapse (50). To our knowledge, the present study is the first to
394 consider glucose metabolism early in abstinence as a potential determinant of relapse. Future
395 studies with larger sample size are needed to confirm whether this profile of glucose
396 metabolism can be considered as prognostic factors for relapse.

397 The main limitation of the present study is the sample size (especially for
398 neuroimaging data) and notably the difference regarding the sample size of the group of
399 relapsers compared with the low-risk drinkers. In effect, the small number of low-risk
400 drinkers, particularly at the one-year follow-up, decreases the statistical power. Relatively low
401 statistical power may affect the results of the structural comparisons with relapsers. However,
402 this difference in the sample size reflects the clinical reality, with only 20 to 40% of AUD
403 patients maintaining abstinence or controlled alcohol drinking over a year after detoxification
404 (1). Moreover, in this study, the small sample of women hinders considering the sex
405 difference. Another limitation relates to the multifactorial nature of relapse. Even though we
406 considered simultaneously several factors in the same sample of patients, other factors such as
407 social cognition abilities or functional connectivity measures may also be relevant prognostic
408 factors for treatment outcome. Furthermore, as indicated in the introduction, the operational
409 definition of relapse is difficult, changing and related to that of treatment success. The relapse

410 measure we chose was conservative and it was difficult to retrospectively collect alcohol
411 consumption data with accuracy. This lack of accuracy did not allow us to conduct analyses
412 using the WHO drinking risk levels. However, our findings are consistent with a recent study
413 that used the WHO drinking risk levels. This study showed that eight months after discharge,
414 GM volumes of AUD patients who had reduced alcohol consumption by two-levels were
415 comparable to those of abstainers. On the contrary, AUD patients who exhibited high-risk
416 alcohol consumption had significantly lower thalamic and frontal volumes than abstainers and
417 low-risk drinkers (51). Further studies are required to replicate our findings using other
418 definitions of relapse. Finally, there was also a great heterogeneity among patients classified
419 as relapsers, some of them being just above the NIAAA threshold while others exhibiting
420 binge drinking behaviors and/or being back to uncontrolled alcohol consumption.

421 To conclude, the present study highlights that early in abstinence, several measures
422 could have a prognostic value regarding the six-month (mid-term) and one-year (long-term)
423 treatment outcome in terms of low-risk drinking and relapse. The nicotine dependence,
424 memory impairments, structural and metabolic brain damage (except cerebellar
425 hypermetabolism), especially in the reward circuit and limbic system, may be regarded as
426 specific determinants of a long-term relapse. Alexithymia and cerebellar hypermetabolism
427 may be prognostic factors for both mid-term and long-term relapse. This will be crucial to
428 consider in future research since most of these determinants can be therapeutic targets to
429 consider in clinical practice. From a clinical perspective, future relapse risk assessments
430 would ideally include an evaluation of the nicotine dependence, emotional disorder, episodic
431 and working memory, as well as executive abilities. Regarding treatment, it appears relevant
432 to combine alcohol detoxification program with smoking cessation, a treatment of emotional
433 deficits, as well as cognitive rehabilitation.

434

435 **Authors contribution**

436 ALP and FV were responsible for the study concept and design. AL, CB, NL, FV, and NC
437 contributed to the acquisition. AM, SS, and ALP assisted with data analysis and interpretation
438 of finding. AM draft the manuscript. AL, SS, CB, NC, and ALP provided critical revision of
439 the manuscript for important intellectual content. All authors critically reviewed content and
440 approved final version for publication.

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589

591 Table 1. Demographical and clinical data in each group and between-group comparisons

Variable	Baseline (T1)		6-month status (T2)				One-year status (T3)			
	HC N = 36	AUD N = 54	R ^{T2} N = 27	LR ^{T2} N = 15	Statistics ^a	Pairwise comparisons ^b	R ^{T3} N = 33	LR ^{T3} N = 9	Statistics ^a	Pairwise comparisons ^b
Age	45 [39-47.25]	46 [39-54]	41 [37.5-52.5]	48 [42.5-53.5]	2.87 p=0.238		41 [38-51]	53 [47-61]	6.44 p=0.04	
Education (years of schooling)	12 [11-12]	11 [10-13.5]	11 [10-12]	12 [10-14]	0.91 p=0.635		11 [10-14]	12 [10-14]	1.42 p=0.491	
Sex ratio (M/F)	30/6	45/9	21/6	13/2	p=0.744		27/6	7/2	p=0.926	
<i>BDI</i>	3 [0-5]	12 [6.25-17]	10 [5-17.5]	11 [3-17]	27.73 p<.001	1) p=0.757 2) p < .001 3) p = 0.002	10 [5-17]	11 [4-12]	27.73 p<.001	1) p=0.829 2) p < .001 3) p=0.011
<i>STAI A</i>	25.5 [22-29]	30 [24-35.25] 2MD	29 [23.5-35.5]	29.5 [24.5-33.25] 1MD	4.53 p=0.104		28 [24-34]	30 [24-34]	4.33 p=0.115	
<i>STAI B</i>	33.5 [28.75-38.25]	44 [36-56] 2MD	46 [34-56]	48.5 [36.75-52] 1MD	19.86 p<.001	1) p=0.990 2) p < .001 3) p = 0.002	45 [34-56]	52 [39-52]	20.50 p<.001	1) p=0.997 2) p < .001 3) p=0.006
<i>BIS 11</i>	66 [56.5-70.5] 1MD	71.5 [61.75-79] 2MD	72 [61.5-78]	69.5 [55.25-78] 1MD	4.82 p=0.09		71 [61-79]	71 [55-75]	4.43 p=0.109	
<i>TAS 20</i>	45 [40.5-52] 1MD	55 [49-63] 3MD	60 [53.25-65.25] 1MD	50.5 [40-60.75] 1MD	17.04 p<.001	1) p=0.09 2) p < .001 3) p=0.797	59 [49.75-66] 1MD	52 [39-60]	14.00 p<.001	1) p=0.146 2) p < .001 3) p=0.894
<i>Fagerstrom</i>	0 [0-0]	4 [2-6] 3MD	4 [2-6]	2.5 [0-6] 1MD	22.44 p<.001	1) p=0.756 2) p < .001 3) p=0.005	4 [2-6]	0 [0-3]	26.83 p<.001	1) p=0.130 2) p < .001 3) p=0.254
Proportion of smokers (%)	22.2	72.2	70.4	66.7	0.07 p=0.791		72.7	55.6	0.960 p=0.327	
<i>AUDIT</i>	3 [1-4]	29 [26-32]	29 [25.5-32]	29 [25.5-30.5]	57.76 p<.001	1) p=0.838 2) p < .001 3) p < .001	29 [26-32]	29 [19-29]	58.83 p<.001	1) p=0.341 2) p < .001 3) p < .001
Duration of dependence or use disorder (years)	N/A	9 [5-18] 3MD	8 [5-14.5]	15 [6-20.5]	N/A	1) p=0.193	8.5 [5-16.5]	15 [11-22]	N/A	1) p=0.170
Number of previous detoxifications	N/A	1 [1-2] 1MD	1 [1-2]	1 [0-1]	N/A	1) p=0.350	1 [1-2]	1 [1-1]	N/A	1) p=0.729
<i>Cushman score</i>	N/A	5 [4-6] 1MD	5 [3.5-6.5]	4 [3.5-5.5]	N/A	1) p=0.661	5 [3-6]	4 [4-4]	N/A	1) p=0.290
Alcohol consumption (units/day)	N/A	20 [14-25]	17 [13.25-25.25]	21.5 [14.25-25]	N/A	1) p=0.710	19 [14-25]	21.5 [11.5-24.25]	N/A	1) p=0.882
Follow-up intervals between T1 and T2/T3 (days)	N/A	N/A	6 [6-7]	6 [6-6.5]	147.5 p=0.111		13 [12-13.5]	12 [12-13]	110.5 p=0.237	
Duration of hospitalization (days)			18 [16.5-29]	21 [16.5-31]	195.5 p=0.864		18 [16-33]	21 [16-24]	137 p=0.735	

593

594 Median [1st – 3rd quartiles] are reported

595 Using Mann-Whitney's tests, significant difference at $p < 0.003$ between AUD and HC are in bold

596 ^a: Kruskal-Wallis ANOVA (except for the proportion of smokers: Chi² test); significant results at $p < 0.003$ are
597 in bold

598 ^b: Dwass-Steel-Critchlow-Fligner post-hoc comparisons or Mann-Whitney's tests when no data were available in
599 the HC group; 1) Comparisons between R and LR; 2) Comparisons between R and HC; 3) Comparisons between
600 LR and HC; significant results at $p < 0.05$ are in bold

601 ^c: an alcohol unit = a standard drink = 10 g of pure ethanol

602 Note: AUDIT = Alcohol Use Disorder Identification Test; BDI = Beck Depression Inventory; BIS = Barratt
603 Impulsiveness Scale; MD = Missing data; STAI = State-Trait Anxiety Scale; TAS = Toronto Alexithymia Scale;
604 AUD = Alcohol Use Disorder; HC = Healthy controls; LR = Low-risk drinkers; R = Relapsers.

605

606 **Table 2. Neuropsychological performance (raw data) in each group and between-group**

Variable	Neuropsychological tests	Participants		6-month status (T2)				One-year status (T3)			
		HC N = 36	AUD N = 54	R ^{T2} N = 27	LR ^{T2} N = 15	Statistics ^a (df=2)	Pairwise comparisons ^b	R ^{T3} N = 33	LR ^{T3} N = 9	Statistics ^a (df=2)	Pairwise comparisons ^b
Verbal episodic memory	FCSRT: delayed recall	13	11	11	12	11.33	1) p = 0.995	11	12	11.37	1) p = 0.774
		[12-14]	[9-13]	[10-13]	[8-13]	p=0.003	2) p = 0.008 3) p = 0.035	[10-13]	[7-13]	p=0.003	2) p = 0.007 3) p = 0.056
Visual episodic memory	ROCF: delayed recall	19.25	17	17	19.5	3.94		17	20	2.78	
		[16-25.25]	[11.5-22.63]	[8.75-21.75]	[13.63-23.38]	p=0.139		[13.5-23]	[12-23.5]	p=0.249	
Working memory	Backward digit span	5	4	4	4	11.94	1) p = 0.924	4	4	11.50	1) p = 0.997
		[4.75-6]	[3-5]	[3-5]	[3-5]	p=0.003	2) p = 0.011 3) p = 0.014	[3-5]	[3-5]	p=0.003	2) p = 0.005 3) p = 0.077

607 **comparisons**

Flexibility	MCST:	1	1	1	2	5.03		1	2	3.53
	perseverative errors	[0-1]	[0-4]	[0-3.5]	[1-3]	p=0.081		[0-3]	[0-7]	p=0.171
Inhibition	Stroop: interference	47	58	50	63	7.80		50.5	65	8.44
	score (sec.)	[33-58.5]	[46-81]	[37.25-65]	[51.5-80]	p=0.02		[37.75-65]	[54-84]	p=0.015
Attention	D2: overall	415.5	343	378	340.5	11.10	1) p = 0.532	378	316	9.52
	performance index (GZ - F)	[378.5-447.25]	[277-409.75]	[291-427]	[265.25-388.75]	p=0.004	2) p = 0.058 3) p = 0.006	[284-421]	[261-389]	p=0.009
Visuoconstruction	ROCF: copy score	36	35	35	35.5	3.05		35	36	3.87
		[34-36]	[33-36]	[33-36]	[34.25-36]	p=0.217		[33-36]	[35-36]	p=0.145

608

609 Median [1st – 3rd quartiles] are reported

610 ^a: Kruskal-Wallis ANOVA; significant results at p < 0.007 are in bold

611 ^b: Dwass-Steel-Critchlow-Fligner pairwise comparisons 1) Comparisons between R and LR; 2) Comparisons
612 between R and HC; 3) Comparisons between LR and HC; significant results at p < 0.05 are in bold

613 Using Mann-Whitney's tests, significant difference at p < 0.003 between AUD and HC are in bold

614 Note: FCSRT = Free and Cued Selective Reminding Test; MCST = Modified Card Sorting Test; ROCF = Rey-
615 Osterrieth complex figure; AUD = Alcohol Use Disorder; HC = Healthy controls; LR = Low-risk drinkers; R =
616 Relapsers.

617

618 **FIGURES LEGENDS**

619 **Figure 1: Study design and sample size at each time point and for each measure**

620 LR = Low-risk drinkers; R = Relapsers; T1 = early in abstinence.

621

622 **Figure 2: Structural and metabolic abnormalities in relapsers (R) and low-risk drinkers**
623 **(LR) compared with healthy controls (HC) based on alcohol status at 6 months (T2)**

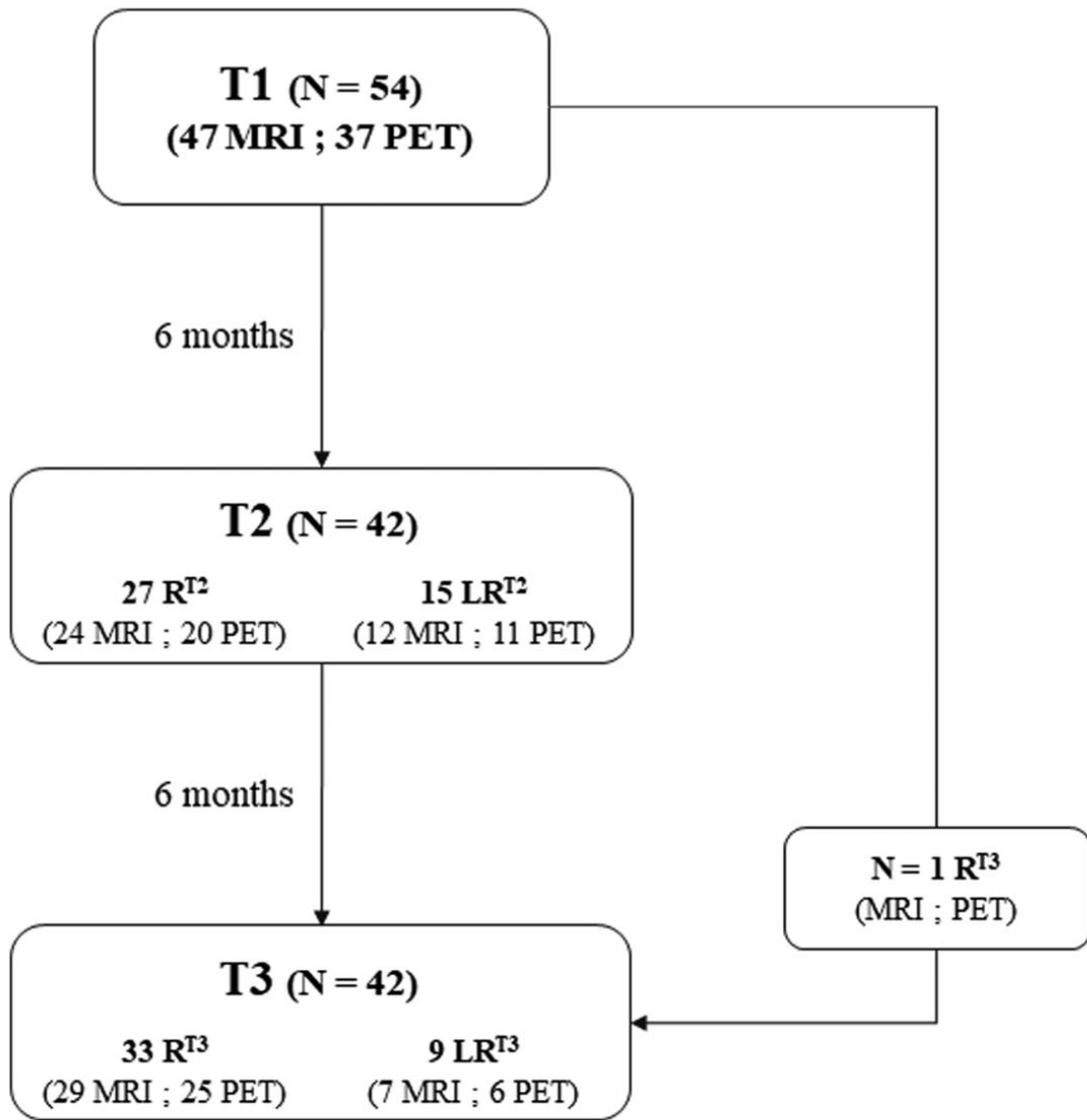
624 Results are presented using a threshold of $p < 0.001$, uncorrected for multiple comparisons
625 (k=60 for MRI data and k=25 for PET data). Ø: no significant results. Color bars represent T-
626 values. Abbreviations: HC = Healthy controls; LR = Low-risk drinkers; R = Relapsers.

627

628 **Figure 3: Structural and metabolic abnormalities in relapsers (R) and low-risk drinkers**
629 **(LR) compared with healthy controls (HC) based on alcohol status at one year (T3)**

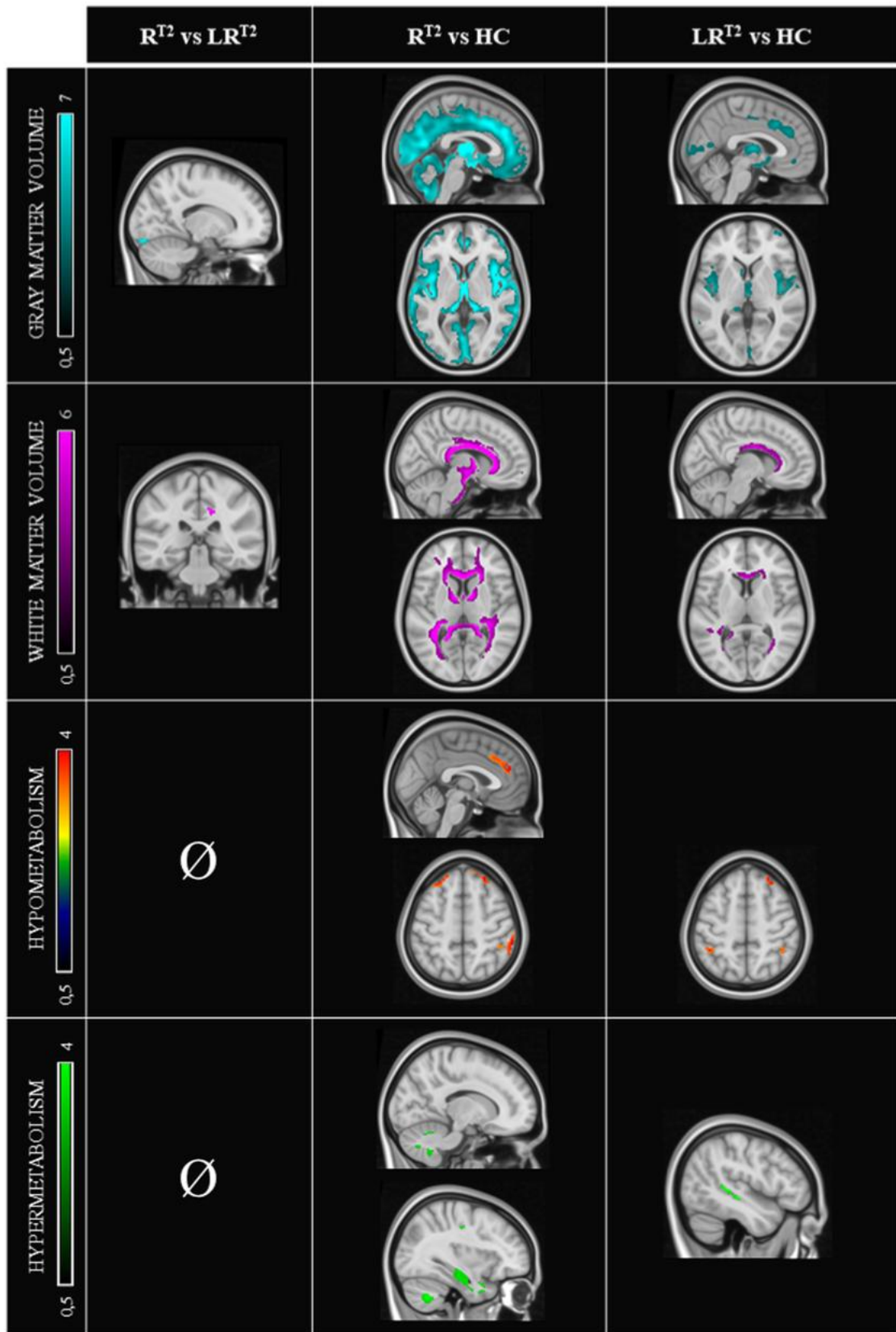
630 See legend of Figure 2.

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