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1 **Glucometabolic changes are associated with structural gray**
2 **matter alterations in prodromal dementia**

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15 Running title: Glucometabolic changes and brain alterations

16

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23

24 **ABSTRACT**

25 **Background:** Glucometabolic changes, such as high glycemic load (GL) diet and insulin resistance (IR),
26 are potential risk factor of Alzheimer’s disease (AD). Yet, the effect of these factors on brain
27 alterations that contribute to AD pathology has not been clearly demonstrated.

28 **Objective:** We aimed to assess the relationship of GL and IR with gray matter volumes involved in
29 prodromal dementia.

30 **Methods:** GL and Triglyceride-Glucose (TyG) index, an IR surrogate marker, were calculated in 497
31 participants who underwent magnetic resonance imaging (MRI). The gray matter volumes most
32 related to prodromal dementia/mild cognitive impairment (diagnosed in 18/158 participants during
33 the 7-year follow-up) were identified using a data-driven machine learning algorithm.

34 **Results:** Higher GL diet was associated with reduced amygdala volume. The TyG index was negatively
35 associated with the hippocampus, amygdala and putamen volumes.

36 **Conclusion:** These results suggest that GL and IR are associated with lower gray matter volumes in
37 brain regions involved in AD pathology.

38

39 *Keywords:* glycemic load; insulin resistance; magnetic resonance imaging; hippocampus; amygdala;
40 putamen; dementia

41 **INTRODUCTION**

42 A large body of epidemiological evidence demonstrated the importance of insulin and glucose
43 homeostasis in the development of mild cognitive impairment (MCI) and Alzheimer’s disease (AD), to
44 the extent that AD is sometimes referred to as "type 3 diabetes" [1,2]. Cognitive impairment has
45 been associated with insulin resistance (IR) and high glycemia in several epidemiological studies [3,4].
46 Indeed, IR and high glycemia, typical features of type 2 diabetes, are promoted by high glycemic load
47 (GL) diets [5] that have been recently identified as a potential risk factor of AD and cognitive
48 impairment [4,6]. One of the underlying hypotheses is that high GL diet could promote AD
49 development through IR. However, there is no clear evidence of the impact of glucometabolic
50 changes (e.g. IR, high fasting glycemia, or high GL diet) on brain alterations that might contribute to
51 the AD pathology. For instance, lower total brain volume has been associated with IR [7] and higher
52 serum insulin concentration [8], but not with higher fasting glycemia [9]. Conversely, another study
53 found a significant association between higher fasting glycemia and lower gray matter (GM) volume
54 [10].

55 Nevertheless, the effect of glucometabolic changes on specific brain volumes remains poorly
56 described. Most studies have focused on hippocampus because within the medial temporal lobe, its
57 reduction has been consistently reported in patients with AD and predicts conversion of MCI to AD
58 [11]. Reduced hippocampal volume has been correlated with high fasting glycemia [9,12] and might
59 have a role in mediating the effects of glycemia on memory functions [13]. In two studies, IR also has
60 been associated with lower hippocampal volume [14,15], but this association was not found in a
61 large dementia-free cohort [7]. Moreover, reduced amygdala volume has been related to higher
62 fasting glycemia, but no association was found for the parahippocampal gyrus and the superior
63 temporal gyrus volumes [9]. Finally, we are not aware of studies on the association between high GL
64 diet and specific GM volumes.

65 Overall, the number of studies on the associations between glucometabolic changes and specific GM
66 volumes are rare. Moreover, sample size was often small, and the populations under study and the
67 specific GM volumes examined were heterogeneous. Therefore, we wanted to determine whether
68 high GL diet and IR are associated with changes in GM volumes involved in the prodromal phase of
69 dementia. First, we identified the GM volumes that were most related to prodromal dementia
70 (diagnosed during the 7-year follow-up) using a data-driven machine learning algorithm. Then, we
71 evaluated the association between GL diet, IR and these GM volumes.

72

73 **METHODS**

74 *Study participants*

75 The ESPRIT study is a longitudinal study of neuropsychiatric disorders in community-dwelling French
76 older adults and part of the Three-City Study (a multicenter cohort study in three French cities:
77 Bordeaux, Dijon and Montpellier) [16]. Eligible participants, aged 65 years and over and non-
78 institutionalized, were recruited from the electoral rolls between 1999 and 2001. The University
79 Hospital of Bicêtre (France) Ethics Committee approved the Three-City Study protocol, and all
80 participants signed an informed consent. Interviews were carried out by nurses, psychologists,
81 neurologists at baseline and after 2, 4, 7, 10, 12 and 15 years of follow-up. From the 1863
82 participants, only those younger than 80 years were invited for MRI; then, 760 participants were
83 randomly selected among whom 668 had complete MRI volumetric data. At the 4-year follow-up
84 visit, 549 participants completed a Food Frequency Questionnaire (FFQ) (n=119 participants were
85 lost between baseline and the 4-year follow-up visit). Moreover, participants with missing data for
86 intracranial volume (n = 10), fasting glycemia and fasting triglycerides (n = 2), GL (n = 22), and
87 apolipoprotein E ϵ 4 (*APOE- ϵ 4*) status (n = 4) also were excluded as well as participants with prevalent
88 dementia (n = 4) and who developed incident dementia after the 7-year follow-up visit (n = 10; they
89 were identified as cognitively normal during the first 7 years of follow-up). The final sample (n=497)

90 included 321 cognitively normal (CN) participants (i.e. subjects who remained cognitively normal
91 during the 7 years of follow-up) and 176 participants with prodromal dementia (MCI/dementia) (i.e.
92 subjects who developed MCI or dementia during the 7 years of follow-up).

93

94 *MRI and GM volume measurement*

95 Participants underwent MRI using the same scanner at the same examination center (Gui de Chauliac
96 Neurology Hospital, Montpellier, France). A 1.5 T GE Signa Imaging system (General Electric Medical
97 Systems, Milwaukee, WI) was used to acquire a contiguous AC-PC aligned axial IR-prepared SPGR T1-
98 weighed sequence for volumetric estimations (TR=12, TE=2.8, IT=6000, matrix, size=256 ×256, pixel
99 spacing=0.9375 ×0.9375 mm, NEX=1, slice thickness=1.0 mm). Regional reconstruction and
100 segmentation were performed with the FreeSurfer 5.3 image analysis suite

101 (<http://surfer.nmr.mgh.harvard.edu/>) as previously described [17]. For this study, 43 cortical and
102 subcortical regions of interest (ROIs) were defined using the Desikan Atlas (sum of the left and right
103 hemispheres) [18].

104 Using the segmentation tool of the SPM5 software (Wellcome Department of Cognitive Neurology,
105 London, United Kingdom), the intracranial volume (gray + white matter + cerebrospinal fluid) was
106 computed for each participant and was used as covariate in the models to minimize the effect due to
107 global brain size differences.

108

109 *Glucometabolic indexes*

110 Glycemic load

111 GL is an indicator of the cumulative exposure to postprandial glycemia and reflects insulin demand,
112 induced by the carbohydrate intake [19]. The total daily GL was calculated from the 148-item semi-
113 quantitative FFQ, as described previously [6]. In the Bordeaux Three-City study, carbohydrate intake
114 did not seem to change during the follow-up [20]. Thus, it was hypothesized that GL did not change
115 from baseline to the follow-up visit in which the FFQ was filled in.

116

117 Triglyceride-Glucose (TyG) index

118 At baseline, fasting blood samples were collected to measure classical parameters, including fasting
119 blood glucose (glycemia) and triglycerides. The TyG index has been proposed as a simple measure of
120 IR. It was calculated as the $\log(\text{fasting triglycerides} \times \text{fasting glucose}/2)$ and was expressed in mg^2/dL^2
121 [21]. This index reflects both the lipotoxicity and glucotoxicity that play a crucial role in IR
122 development [22]. It is strongly correlated with insulin sensitivity, measured with the euglycemic-
123 hyperinsulinemic clamp ($\rho = -0.68$) or the HOMA-IR ($\rho = -0.77$) [23].

124

125 *Diagnosis of dementia and MCI*

126 According to the Paquid epidemiological study, a faster global cognitive decline seems to appear 7-8
127 years before the diagnosis of AD [24]. Therefore, for this study, a narrow time window of 7 years was
128 chosen to identify with some confidence the brain structures related to prodromal dementia (MCI
129 and participants with dementia). At the 2-, 4-, and 7-year follow-up visits, a neurologist examined all
130 participants. Then, an independent committee of neurologists evaluated all potential cases of
131 dementia to reach a consensus on the diagnosis and etiology based on the Diagnostic and Statistical
132 Manual of Mental Disorders, Fourth Edition [25]. Although the dementia type was determined during
133 the clinical interview, for the present analysis, patients with AD and other dementia types were
134 grouped together due to the low number of incident cases.

135 MCI can be considered as a dementia prodrome and was diagnosed according to the revised criteria
136 for MCI (MCI-R algorithm), proposed by an international consensus group [26] and used elsewhere
137 [27]. We also previously showed that the MCI-R algorithm allows a better prediction of the cognitive
138 deficits that will progress towards dementia [28]. Briefly, MCI was diagnosed in the presence of a
139 cognitive complaint and a score within the 20th percentile for the relevant age-matched and
140 education-matched group in at least one of the neuropsychological cognitive tests used at baseline
141 and during the 7-year follow-up (Benton Visual Retention Test, Isaacs' Set Test of verbal fluency, and

142 immediate and delayed recall of the Five-Word Test by Dubois and colleagues). The dementia or MCI
143 onset date was the middle of the interval between the last follow-up without the event and the first
144 follow-up with the event. Patients with MCI or with dementia were grouped (MCI/dementia) to
145 account for slowly progressing dementia that may be diagnosed after the 7-year follow-up.

146

147 *Other variables*

148 Education level was defined as no school, primary school, high school, or graduate level. The Mini
149 Mental State Examination [29] was used as an index of global cognitive performance. APOE
150 genotyping was performed as previously described [30]. *APOE-ε4* carriers were defined as carrying at
151 least one ε4 allele. Energy intake was estimated from the FFQ as previously described [6]. Body mass
152 index was calculated as weight (kg)/height² (m). Diabetes was defined as treated diabetes, fasting
153 glycemia >7 mmol/L, and self-reported. History of stroke was established using standardized
154 questions. Information was also obtained on alcohol consumption (no drinker/drinker), and smoking
155 status (never, past, or current). Depressive symptomatology was evaluated with the Center for
156 Epidemiological Studies-Depression scale [31], using the recommended French cut-off scores of 17
157 and 23 for significant depression in older men and women, respectively [32].

158

159 *Statistical analyses*

160 Selection of GM volumes related to MCI/dementia

161 To profile the GM volumes most related to MCI/dementia, the Random Forest algorithm
162 implemented in the 'randomForest' R package was used [33]. The method is based on an ensemble
163 of decision trees from which the prediction of a categorical variable (CN *versus* MCI/dementia) is
164 obtained as the mean of the predicted values of all trees. This process, referred to as bagging,
165 prevents model overfitting and generalizes well. At each node, Random Forest randomly selects a
166 subset of variables to split. At each internal node, the best feature among a random subset of
167 features is selected to maximize the reduction of label impurity. The process is recursively repeated

168 until the tree reaches a predefined depth, the number of samples in a node falls below a threshold,
169 or all samples belong to the same class. First, the two main parameters were optimized using a grid
170 search to improve the algorithm learning step. These two parameters are: ntree (the number of trees
171 in the ensemble) and mtry (the number of variables randomly selected at each node). The following
172 ranges were implemented: ntree, from 100 to 1000, and mtry, from 5 to 40. Both parameters were
173 optimized for each tested fingerprint independently.

174 Second, the Random Forest algorithm was run with the optimized parameters (ntree = 700, and mtry
175 = 20) and brain GM volume variables were chosen according to the mean decrease of the Gini index.

176 The mean Gini index decrease is a concept of variable importance assessed by the Gini impurity
177 metric. The Gini index is a measure of the prediction power of variables in classification, based on the
178 principle of impurity reduction. It is non-parametric and thus, it does not rely on data belonging to a
179 particular type of distribution.

180

181 Main analysis

182 Linear regression was used to assess the association between glucometabolic indexes and the GM
183 volumes identified by Random Forest. The model was adjusted for age, sex, education level,
184 intracranial volume, *APOE-ε4* status, energy intake, tobacco, alcohol, depressive symptomatology,
185 diabetes, and stroke history. As GL and energy intake are highly correlated, the residual method was
186 used [34,35]. The effect modification by cognitive status (CN *versus* MCI/dementia group) was
187 checked using interaction terms, and analyses were stratified according to the cognitive status. From
188 the fitted linear models, predicted values of the GM volumes selected were calculated according to
189 CN and MCI/dementia.

190 Secondary analysis

191 To further explore asymmetrical associations, the same analyses were done separately for left and
192 right hemisphere in the CN and MCI/dementia groups.

193 All statistical analyses were performed using R version 3.6.1.

194

195 **RESULTS**

196 The participants' mean age at baseline was 71 years, and 51% were women (Table 1). During the 7
197 years of follow-up, MCI was diagnosed in 158 participants and dementia in 18 participants.

198 Compared with the CN group (n=321), participants in the MCI/dementia group (n=176) were older
199 and more likely to have had type 2 diabetes, stroke history, and depressive symptomatology.

200

201 *GM volumes of the medial temporal region are the most related to MCI/dementia*

202 To select the GM volumes most related to MCI/dementia, a Random Forest algorithm was used to
203 predict the participants' classification in the MCI/dementia group in function of their 43 brain
204 volumes. The mean decrease of the Gini index revealed that the hippocampus (12.3), amygdala
205 (10.0), caudate nucleus (9.6), temporal pole (9.4), putamen (8.0), and caudal anterior cingulate
206 cortex (7.4) volumes contributed the most to the prediction of the MCI/dementia group (Figure 1).

207 These results allowed defining the hippocampus, amygdala, caudate nucleus, temporal pole,
208 putamen and caudal anterior cingulate cortex as the most important GM volumes related to
209 MCI/dementia in our sample.

210

211 *Glucometabolic changes are associated with reduced GM volumes in prodromal dementia*

212 To determine whether glucometabolic changes were associated with the selected GM volumes in
213 prodromal dementia, first the interactions of these volumes with GL, TyG index, glycemia, and
214 triglycerides were investigated in the two groups (CN and MCI/dementia). TyG index, glycemia, and
215 triglycerides were significantly associated with the hippocampus and amygdala volumes in the
216 MCI/dementia group (Figure 2 for the TyG index). Thus, the analysis was stratified by cognitive
217 status.

218

219 In the CN group, only an association between higher glycemia and smaller putamen volume was
220 found (Table 2, Supplementary Figure 1H).

221 In the MCI/dementia group, higher GL was significantly associated with reduced amygdala volumes
222 after adjustment for age, sex, education level, intracranial volume, *APOE-ε4*, energy intake, tobacco,
223 alcohol, depressive symptomatology, diabetes, stroke history (Table 2, Supplementary Figure 1B).

224 Conversely, no significant association was found with the hippocampus, temporal pole, caudate
225 nucleus, putamen and caudal anterior cingulate cortex volumes (Table 2). One-unit increase in the
226 TyG index was associated with a 354 mm³, 291 mm³, and 520 mm³ reduction of the hippocampus,
227 amygdala, and putamen volume, respectively (Figure 2, Supplementary Figure 1A). Conversely, the
228 TyG index was not associated with the caudate nucleus, temporal pole and caudal anterior cingulate
229 cortex volumes. Higher glycemia was significantly associated with reduced temporal pole and caudal
230 anterior cingulate cortex volumes (Supplementary Figure 1D and 1F), and tended to be associated
231 with reduced hippocampal volume (Table 2). Finally, in the MCI/dementia group, one-unit increase in
232 triglyceride concentration was associated with a 256 mm³, 217 mm³, and 393 mm³ reduction of the
233 hippocampus, amygdala, and putamen volume, respectively (Supplementary Figure 1C, 1E and 1G).

234
235 *Glucometabolic changes are associated with reduced GM volumes in both left and right hemisphere*

236 To explore asymmetrical associations, the same analyses were performed separately for the left and
237 right hemisphere. In the CN group, glycemia and putamen volume were associated only in the left
238 hemisphere (Supplementary Table 1). Moreover, high GL diet was significantly associated with lower
239 right caudate nucleus volume.

240 In the MCI/dementia group, significant associations were observed in both hemispheres, particularly
241 between TyG index and hippocampus, amygdala and putamen volumes (Supplementary Table 2).

242 However, associations were stronger in the right hemisphere, with the exception of the association
243 between GL diet and amygdala volume that was significant only in the left hemisphere.

244

245 These results showed that glucometabolic changes were associated with a decrease in the GM
246 volumes of three (hippocampus, amygdala and putamen) of the regions most related to
247 MCI/dementia.

248

249

250 **DISCUSSION**

251 This study shows that brain GM volumes related to prodromal dementia (MCI/dementia) are
252 associated with glucometabolic changes. In our sample, the hippocampus, amygdala, caudate
253 nucleus, temporal pole, putamen, and caudal anterior cingulate cortex volumes were the most
254 related to MCI/dementia diagnosed during the 7 years of follow-up. Moreover, the TyG index (a
255 surrogate marker of IR) was associated with reduced hippocampal, amygdala and putamen volumes,
256 and higher GL diet with reduced amygdala volume in the MCI/dementia group.

257 Hippocampus, amygdala, caudate nucleus, temporal pole, putamen, and caudal anterior cingulate
258 cortex volumes were the most related to MCI/dementia. Hippocampus, amygdala and temporal pole
259 are part of the medial temporal lobe area that is the first region altered in AD [11]. In our sample,
260 hippocampal and amygdala volumes were related to MCI/dementia detection during the first 7 years
261 of follow-up, in agreement with other studies [11,36]. However, to our knowledge, no study has
262 reported the association between temporal pole volume and MCI or dementia. The putamen and
263 caudate nucleus are close to the medial temporal region. Previous studies already reported that
264 putamen volume is decreased in patients with AD compared with patients with memory complaints
265 [37], and that reduced caudate nucleus is associated with higher AD risk [38]. However, data on the
266 caudate nucleus, temporal pole, putamen and caudal anterior cingulate cortex volumes are limited.
267 As previous studies on the relationships between glucometabolic changes and GM volumes were
268 mainly performed in cognitively healthy participants without dementia, cognitive impairment or
269 diabetes, it is difficult to compare previous results with our findings. For example, IR has been

270 associated with lower hippocampal volume in 50 cognitively normal women [14], but not in the
271 Framingham Offspring study [7]. However, in patients with AD, higher insulin levels after intravenous
272 glucose tolerance test have been associated with lower hippocampal volume and greater atrophy of
273 some GM regions of the putamen [8]. IR has been also associated with lower hippocampal volume
274 and significantly reduced volumes in the temporal lobe area, specifically amygdala, putamen,
275 temporal pole and caudate nucleus [15]. Overall, these studies are consistent with our results
276 showing a significant association between TyG index and GM volumes in the MCI/dementia group,
277 although we did not detect any significant association for temporal pole and caudate nucleus. We
278 also found that higher fasting glycemia was associated with lower temporal pole and caudal anterior
279 cingulate cortex volumes in the MCI/dementia group, however, we did not observe any significant
280 association with hippocampus or amygdala volumes, unlike other studies [9,12,13]. Finally, we found
281 that high GL diet was associated with lower amygdala volume in the MCI/dementia group and with
282 the right caudate nucleus volume in the CN group, but not with hippocampus. On the other hand, a
283 cross-sectional study showed that one or more servings of fruit juice per day were associated with
284 lower hippocampal volume [39,40]. The GL considers all carbohydrate-based foods, not only free
285 sugars and sugars added in beverages, and this may explain this disparity. Moreover, in children who
286 usually eat bread (higher GL) at breakfast, caudate nucleus volume also was lower compared with
287 those who eat rice (lower GL) [41]. Together, the previous and present findings suggest that both
288 high GL diet and IR alter specific brain regions.

289 The absence of common associations of GL diet and TyG index with the hippocampus and putamen
290 volumes suggests that these two glucometabolic parameters do not measure the same event.

291 Indeed, GL estimates the mean postprandial glycemetic and insulin responses, whereas the TyG index
292 is designed to assess IR. Moreover, a person showing high glycemetic and insulin responses does not
293 necessarily develop IR, which may explain why GL and TyG index are not correlated. Specifically, the
294 TyG index (measure of IR) was associated with reduced hippocampus, amygdala and putamen
295 volumes in the MCI/dementia group. These regions are characterized by high density of insulin

296 receptors and may be more prone to IR than other brain regions [2,42]. A study showed that in
297 normal conditions, insulin modulates glucose utilization in selective brain circuits. Conversely, in the
298 presence of excessive hyperinsulinemia, the functional connectivity of the default mode network
299 between the medial prefrontal cortex region and the parahippocampus and hippocampus was
300 disrupted [43]. This study suggests that hyperinsulinemia contributes to impair synaptic connectivity.
301 Moreover, IR impairs the glycolytic activity [44], and epidemiological studies demonstrated that IR is
302 associated with brain glucose hypometabolism [45,46]. Brain glucose hypometabolism could be a
303 marker of synaptic or neuronal injury. Indeed, insulin contributes to synaptogenesis and synaptic
304 remodeling [2], and is involved in neuron survival regulation [47]. IR may prevent insulin from
305 exerting its neuroprotective and neuromodulator effects in the brain. Thus, by altering the brain
306 networks and glucose metabolism, IR could contribute to neurodegeneration and to the GM volume
307 decrease of brain regions with high density of insulin receptors.

308 The main strengths of the present study include: the 1) large population-based sample for an MRI-
309 based study, 2) data-driven Random Forest selection of brain volumes, that has important
310 advantages over other techniques in terms of ability to handle non-linear data and robustness to
311 noise, and 3) adjustment for many potential confounders, including age, sex, education, intracranial
312 volume, *APOE-ε4* status, energy intake, tobacco, alcohol, depressive symptomatology, diabetes and
313 stroke history. Among the potential limitations, the cross-sectional design of our study does not
314 allow inferring about causality between glucometabolic changes and brain volumes alterations.
315 Although our data may indicate a role of glucometabolic changes in GM volume alterations related to
316 AD development, the possibility of "reverse causation" must be considered. Indeed, it has been
317 shown that amyloid- β aggregation impairs insulin signaling [48]. Moreover, brain regions that
318 regulate insulin and food intake (e.g. hypothalamus) can be altered in AD pathology [49], leading to
319 systemic insulin dysregulation. Thus, glucometabolic changes may be the result of AD effects on GM
320 volumes. Finally, it would have been important to differentiate GM alterations linked to AD and to
321 MCI by studying the dementia and MCI groups separately. However, this was not possible due to the

322 lack of statistical power. In addition, in the MCI group, some participants may develop dementia, but
323 we did not have this information.

324 Our findings suggest that targeting the glucometabolic control early in life to prevent brain
325 alterations might contribute to slow down and prevent the development of cognitive impairment
326 and dementia later in life.

327

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341

342 **Disclosure statement**

343 The authors have no conflict of interest to report

344

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Table 1. Characteristics of the study population

Characteristics Mean (SD) or n (%)	Whole sample n = 497	CN n = 321	MCI/dementia n = 176	P value
Age (years)	71.0 (3.9)	70.4 (3.8)	72.1 (4.0)	<.0001
Women	255 (51.3)	177 (55.1)	78 (44.3)	0.0268
Education level				0.8162
No school	123 (24.7)	77 (24.0)	46 (26.1)	
Primary school	134 (27.0)	90 (28.0)	44 (25.0)	
High school	92 (18.5)	57 (17.8)	35 (19.9)	
Graduated	148 (29.8)	97 (30.2)	51 (29.0)	
MMSE (IQR)	27.7 (1.8)	27.8 (1.6)	27.4 (1.9)	0.0045
<i>APOE-ε4</i> carriers	99 (19.9)	58 (18.1)	41 (23.3)	0.2013
BMI (kg/m ²)	25.0 (3.3)	25.1 (3.3)	24.8 (3.3)	0.4666
Alcohol use	419 (84.3)	269 (83.8)	150 (85.2)	0.5646
Tobacco use	226 (45.5)	146 (45.5)	80 (45.5)	1
Type 2 diabetes	52 (10.5)	25 (7.8)	27 (15.3)	0.0132
Stroke history	21 (4.2)	8 (2.5)	13 (7.4)	0.0186
Depressive symptomatology	52 (10.5)	22 (6.9)	30 (17.0)	0.0006
Energy intake (kcal/day)	1267 (432)	1244 (394)	1309 (492)	0.1084
Glycemic load (/day)	116 (39.2)	114 (35.9)	118 (44.5)	0.2746
Glycemic load residuals (/day)	0 (15.0)	0.5 (14.6)	-0.9 (15.6)	0.3066
Glycemia (mol/L)	5.07 (1.05)	4.98 (0.82)	5.23 (1.36)	0.011
Triglycerides (mol/L)	1.26 (0.61)	1.26 (0.63)	1.26 (0.58)	0.9665
TyG index (mg ² /dL ²)	8.42 (0.48)	8.41 (0.47)	8.45 (0.50)	0.7059

Abbreviations: *APOE-ε4*, apolipoprotein E ε4 allele; BMI, body mass index; CN, cognitively normal;

IQR, interquartile range; MCI, Mild Cognitive Impairment; MMSE, Mini Mental State Examination; SD, standard deviation; TyG, Triglycerides-Glucose.

Table 2. Association between GL, TyG index, glycemia, triglycerides and Random Forest-selected GM volumes stratified in function of the cognitive status.

Exposures	Hippocampus		Amygdala		Caudate nucleus		Temporal pole		Putamen		Caudal anterior cingulate	
	β (SE)	<i>P</i> value	β (SE)	<i>P</i> value	β (SE)	<i>P</i> value	β (SE)	<i>P</i> value	β (SE)	<i>P</i> value	β (SE)	<i>P</i> value
<u>Cognitively normal during the follow-up (n = 321)</u>												
GL	-7.63(29.9)	0.7988	-17.8(13.2)	0.1794	-58.5(33.9)	0.0856	12.5(29.3)	0.6698	-8.81(45.2)	0.8458	13.7(22.9)	0.55
TyG index	-41.4(93.1)	0.6567	31.1(41.3)	0.4517	-9.0(106)	0.9321	91.5(91.1)	0.3159	-142(141)	0.3119	-40.7(71.3)	0.5689
Glycemia	-32.6(63.2)	0.6061	-12.2(28.0)	0.6633	-44.1(71.9)	0.54	-31.0(61.8)	0.6162	-195(95.1)	0.0414	-4.70(48.4)	0.9222
Triglycerides	-20.4(67.0)	0.761	24.1(29.7)	0.418	15.6(76.3)	0.8381	118(65.3)	0.0707	2.80(102)	0.9783	-53.4(51.2)	0.2979
<u>MCI/dementia during the follow-up (n = 176)</u>												
GL	-54.0(44.1)	0.2222	-46.4(22.2)	0.0381	-85.6(55.2)	0.123	-53.3(43.4)	0.2205	-39.1(63.1)	0.5366	-22.5(28.8)	0.4356
TyG index	-354(146)	0.0168	-291(72.0)	0.0001	-130(187)	0.4895	-208(146)	0.156	-520(209)	0.0137	-163(96.2)	0.0921
Glycemia	-129(69.3)	0.0637	-56.9(35.3)	0.1088	-105(87.7)	0.2316	-154(67.9)	0.0245	-106(99.6)	0.2887	-105(44.9)	0.0203
Triglycerides	-256(116.5)	0.0297	-217(57.5)	0.0002	-62.5(149)	0.6747	-59.2(116)	0.6116	-393(166)	0.019	-118(76.5)	0.1257

Linear model adjusted for age, sex, education, intracranial volume, *APOE- ϵ 4*, energy intake, tobacco, alcohol, depressive symptomatology, diabetes, stroke history.

Abbreviations: GL, glycemic load; MCI, Mild Cognitive Impairment; SE, standard error; TyG, Triglycerides-Glucose; GM, Gray Matter

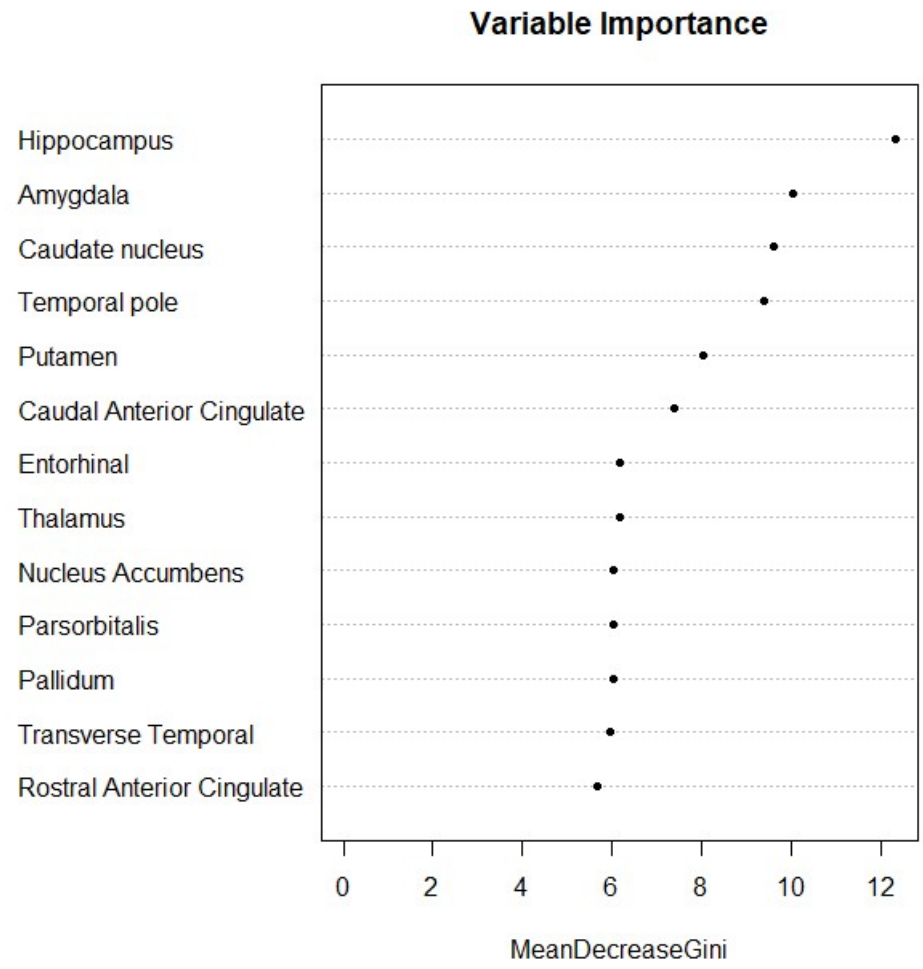


Figure 1. Gray matter (GM) volume importance for predicting MCI/dementia. The figure shows the most relevant brain regions for MCI/dementia detection based on the mean decrease of the Gini index.

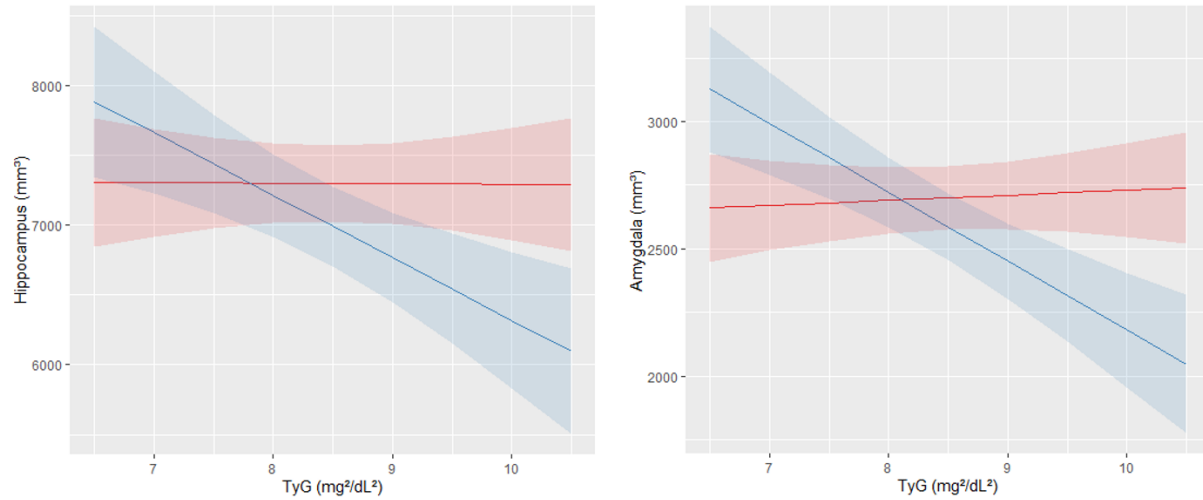


Figure 2. Predicted values of hippocampal volume and amygdala volume in function of the TyG index according to the cognitive status. Predicted values of hippocampal volume are on the left and those of amygdala volume on the right. Red line represented cognitively normal group and blue line MCI/dementia group.

Supplementary Table 1. Association between GL, TyG index, glycemia, triglycerides and Random Forest-selected GM volumes in the left and right hemisphere in the **cognitively normal** group (n = 321).

Exposures	Hippocampus		Amygdala		Caudate nucleus		Temporal pole		Putamen		Caudal anterior cingulate	
	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value
<u>Left Hemisphere</u>												
GL	-6.2(16.8)	0.7118	-3.49(7.51)	0.642	-17.9(17.0)	0.2934	-5.09(18.4)	0.7823	3.08(25.1)	0.9025	5.03(14.6)	0.7312
TyG index	8.6(52.2)	0.8688	21.6(23.3)	0.3558	10.1(53.2)	0.8499	49.2(57.2)	0.3908	-69.1(78.0)	0.3761	23.7(45.5)	0.6038
Glycemia	-18.2(35.4)	0.6072	-10.1(15.8)	0.5232	-9.20(36.0)	0.7991	-1.80(38.8)	0.9623	-108(52.6)	0.0414	0.70(30.9)	0.9824
Triglycerides	6.1(37.5)	0.8718	21.2(16.8)	0.2079	15.4(38.2)	0.6873	66.7(41)	0.1047	1.80(56.1)	0.9745	6.40(32.7)	0.845
<u>Right Hemisphere</u>												
GL	-1.43(15.5)	0.9266	-14.3(7.68)	0.0634	-40.6(18.0)	0.0248	17.6(17.4)	0.3122	-11.9(23.4)	0.6114	8.68(15.9)	0.5852
TyG index	-50.0(48.3)	0.301	9.50(24.0)	0.6928	-19.1(56.5)	0.7351	42.3(54.2)	0.435	-73.3(72.6)	0.3137	-64.3(49.4)	0.1935
Glycemia	-10.6(32.8)	0.7473	-1.40(16.3)	0.934	-35.4(38.2)	0.3558	-30.0(36.7)	0.4148	-82.3(49.1)	0.0949	-5.4(33.6)	0.8724
Triglycerides	-28.9(34.7)	0.4057	2.40(17.3)	0.8896	0.50(40.6)	0.9904	51.8(38.9)	0.1833	-1.50(52.3)	0.9766	-59.8(35.4)	0.0924

Linear model adjusted for age, sex, education level, intracranial volume, *APOE- ϵ 4*, energy intake, tobacco, alcohol, depressive symptomatology, diabetes, stroke history.

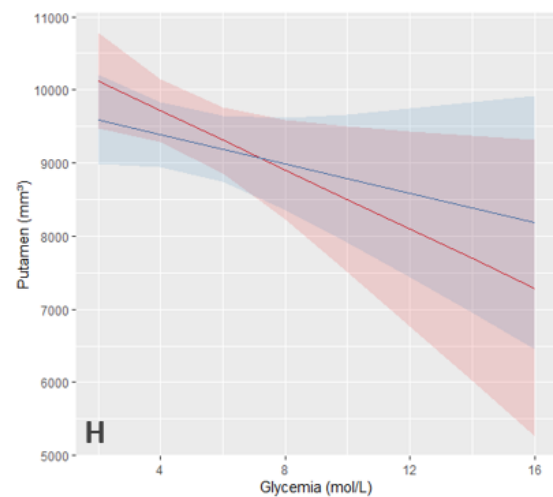
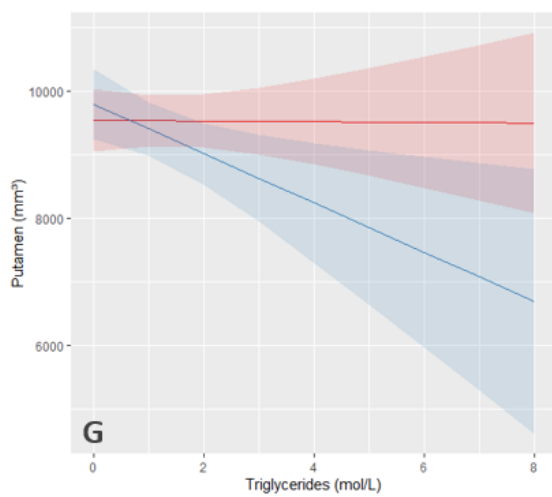
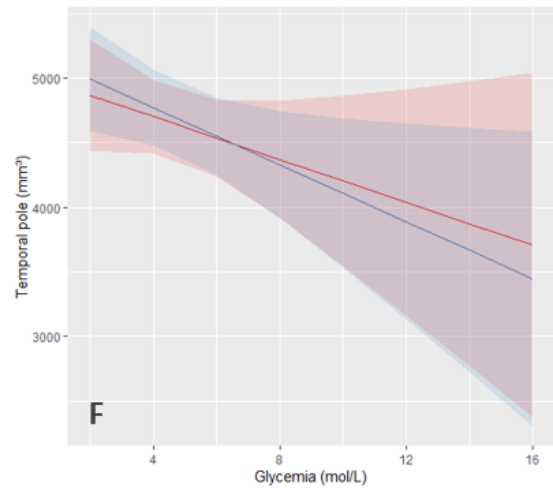
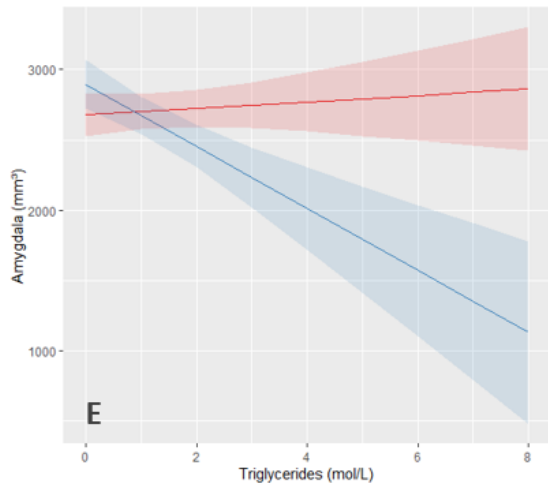
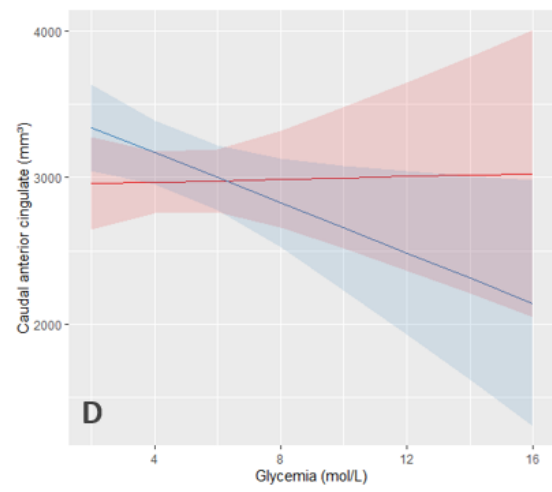
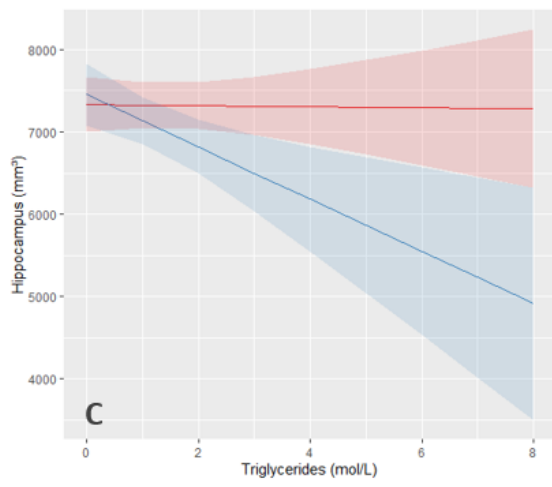
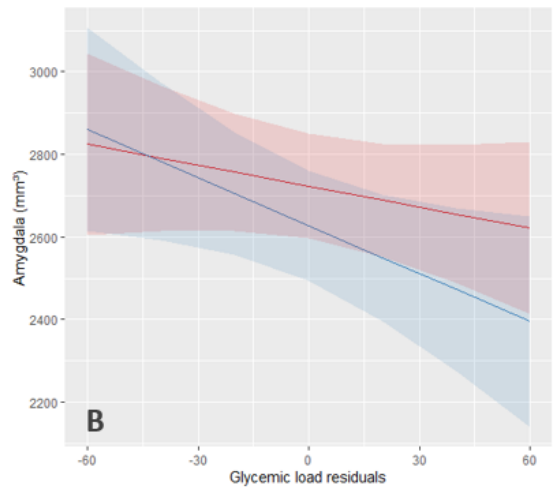
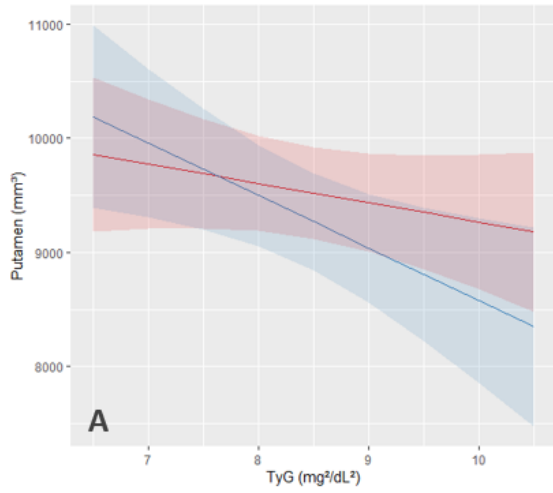
Key: GL, glycemic load; SE, standard error; TyG, Triglycerides-Glucose; GM, Gray Matter.

Supplementary Table 2. Association between GL, TyG index, glycemia, triglycerides and Random Forest-selected GM volumes in the left and right hemisphere in the **MCI/dementia** group (n = 176).

Exposures	Hippocampus		Amygdala		Caudate nucleus		Temporal pole		Putamen		Caudal anterior cingulate	
	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value
<u>Left Hemisphere</u>												
GL	-25.7(25.49)	0.3149	-23.4(11.5)	0.0428	-39.7(27.6)	0.1524	-43.5(25.1)	0.0856	-6.60(31.8)	0.8359	-9.89(20.3)	0.627
TyG index	-166.4(85.1)	0.0522	-138.5(37.5)	0.0004	-89.1(93.3)	0.3409	-78.5(85.2)	0.3583	-254(105)	0.0171	-58.2(68.3)	0.3954
Glycemia	-69.4(40.1)	0.0856	-29.1(18.3)	0.1131	-59.9(43.7)	0.1723	-67.1(39.8)	0.0938	-54.7(50.2)	0.2774	-54.8(31.9)	0.0876
Triglycerides	-115.9(67.7)	0.0891	-99.2(30.1)	0.0012	-38.7(74.2)	0.6027	-27.0(67.8)	0.6905	-185(83.8)	0.0285	-46.8(54.2)	0.3892
<u>Right Hemisphere</u>												
GL	-28.3(21.3)	0.1854	-22.9(12.4)	0.0674	-45.9(29.0)	0.1155	-9.83(25.1)	0.6956	-32.5(34.5)	0.3489	-12.6(19.4)	0.5165
TyG index	-187(70.4)	0.0086	-152.1(40.5)	0.0002	-40.5(98.4)	0.6814	-129(83.9)	0.1254	-266(115)	0.0217	-105(64.7)	0.1076
Glycemia	-60.0(33.5)	0.0753	-27.8(19.8)	0.1618	-45.3(46.2)	0.3275	-87(39.1)	0.0276	-51.3(54.7)	0.3495	-50.3(30.4)	0.1003
Triglycerides	-139.7(56.1)	0.0137	-118.2(32.2)	0.0003	-23.8(78.2)	0.7611	-32.2(67)	0.6322	-208(91.1)	0.0239	-70.9(51.5)	0.1706

Linear model adjusted for age, sex, education level, intracranial volume, *APOE- ϵ 4*, energy intake, tobacco, alcohol, depressive symptomatology, diabetes, stroke history.

Key: GL, glycaemic load; SE, standard error; TyG, Triglycerides-Glucose, GM, Gray matter.



2 Supplementary Figure 1. Predicted values of GM volume in function of the GL, TyG index, glycemia or
3 triglycerides according to the cognitive status. Red line represented cognitively normal group and
4 blue line MCI/dementia group. (A) Predicted values of putamen volume in function of the TyG index.
5 (B) Predicted values of amygdala volume in function of the GL. (C) Predicted values of hippocampal
6 volume in function of the triglycerides. (D) Predicted values of caudal anterior cingulate cortex
7 volume in function of the glycemia. (E) Predicted values of amygdala volume in function of the
8 triglycerides. (F) Predicted values of temporal pole volume in function of the glycemia (G) Predicted
9 values of putamen volume in function of the triglycerides. (H) Predicted values of putamen volume in
10 function of the glycemia.

11