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► **To cite this version:**

Soumia Benbrika, Franck Doidy, Laurence Carlier, Audrey Mondou, Marie-Sonia Buhour, et al.. Alexithymia in amyotrophic lateral sclerosis and its neural correlates. *Frontiers in Neurology*, In press, 10.3389/fneur.2018.00566 . inserm-01835653

HAL Id: inserm-01835653

<https://inserm.hal.science/inserm-01835653>

Submitted on 11 Jul 2018

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1 **Alexithymia in amyotrophic lateral sclerosis and its neural**
2 **correlates.**

3
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13 **KEYWORDS:** Amyotrophic lateral sclerosis, alexithymia, emotional processing, emotional
14 awareness, cognitive function

15 **ABSTRACT**

16 **Introduction:** Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disease that
17 causes progressive and extensive motor deficits. Patients may also have cognitive
18 impairments or alteration of emotional processing. Very few studies, however, have looked at
19 deficits in how they experience their own feelings (alexithymia). **Methods:** We assessed
20 alexithymia in 28 patients with ALS using the 20-item Toronto Alexithymia Scale (TAS-20),
21 comparing them with a control group matched for sex, age and education level. We took into
22 account both the total score of the TAS-20 and its three subscores corresponding to the three
23 dimensions of alexithymia: Difficulty Identifying Feelings (DIF), Difficulty Describing
24 Feelings (DDF), and Externally Oriented Thinking (EOT). Patients also underwent a
25 neuropsychological assessment and anatomical magnetic resonance imaging (MRI) in order to
26 correlate cognitive performances and gray matter volume and level of alexithymia. **Results:**
27 On average, ALS subjects had a significantly higher total score and DIF sub-score of the

28 TAS-20 than controls indicating an increased alexithymia in patients. Total and DIF Scores
29 correlated significantly and negatively to gray matter volume of the prefrontal cortex, right
30 superior temporal pole and parahippocampal gyri. No correlations were found between scores
31 on executive functions and those on the TAS-20. **Conclusion:** the first stage of one's own
32 emotional processing seems to be affected in ALS independently of executive dysfunction.
33 This trouble seems to be underpinned by cerebral regions that are well known to be both
34 implicated in alexithymia in healthy subjects and altered in ALS.

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36 **WORD COUNT:** Abstract: 242, Main text: 4267

37

38 **MAIN TEXT**

39 1. INTRODUCTION

40 Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of upper and lower motor
41 neurons, with relentless progressive muscular paralysis causing severe functional disability
42 and leading to death. Median survival is 3 years after onset of the disease and 2 years after
43 diagnosis (Couratier et al., 2016).

44 Approximately half of all patients with ALS have some degree of cognitive impairment,
45 mainly affecting executive functions such as mental flexibility, attention and verbal fluency
46 (Phukan et al., 2012). Comorbid frontotemporal dementia (FTD) is present in 5 to 15% of
47 cases (Phukan et al., 2012; Zago, Poletti, Morelli, Doretti, & Silani, 2011). Patients also have
48 impaired emotional facial expression recognition, impaired emotional responses, impaired
49 excitability in response to emotional stimuli, and impaired judgment of emotional valence
50 (Girardi, Macpherson, & Abrahams, 2011; Palmieri et al., 2010). Affective and cognitive
51 Theory of Mind (ToM) is also affected by the disease (Beeldman et al., 2016; Bora, 2017),
52 this finding having been shown to be discrepant when comparing within ALS patients,

53 stratified by bulbar and spinal onset in some studies (Burke et al, 2016; Trojsi et al., 2016),
54 but not in others (Beeldman et al., 2016).

55 *Alexithymia* is a concept that was introduced by Sifneos and Nemiah to characterize the
56 psychological profile of patients with psychosomatic disorders. The term literally means *lack*
57 *of words for emotions*, and has been defined as “a diminution or absence of the basic human
58 ability to experience feeling” (Nemiah & Sifneos, 1970). Five salient characteristics of
59 alexithymia have been described: (a) partial or total inability to experience emotions; (b)
60 difficulty identifying feelings; (c) difficulty describing feelings; (d) externally oriented
61 thinking or inability to focus on one’s own emotions; and (e) partial or total inability to
62 fantasize. Larsen et al distinguished between two main forms of alexithymia. In Type-I
63 alexithymia, the absence of both emotional experience and cognition accompanying emotion
64 seems to be associated with psychosomatic diseases (e.g. chronic pain or gastrointestinal
65 dysfunction). Type-II alexithymia is characterized by a selective deficit in emotional
66 cognition, with a normal or high degree of conscious awareness of emotional arousal and
67 sparing of emotional experience. This type of alexithymia is thought to be associated with
68 psychiatric illness (eating disorder, anxiety, depression).

69 To our knowledge, alexithymia levels in patients with ALS have so far only been assessed in
70 two studies. When Bungener et al. assessed emotional experience and expressiveness in 27
71 patients using the Echelle d’Humeur Depressive (EHD) questionnaire, they concluded that
72 patients have no emotional blunting or anhedonia. In their study, however, there was no
73 control group, and the questionnaire they used mainly assesses emotional deficit (anhedonia,
74 sadness) and loss of emotional control (impulsivity, irritability), which are encountered in
75 depression, rather than in alexithymia. Roy-Bellina et al. (2008) evaluated the alexithymia
76 levels of 14 patients with ALS and nine healthy controls, using the 20-item Toronto

77 Alexithymia Scale (TAS-20). TAS-20 scores were significantly higher in patients than in
78 controls. The authors suggested that alexithymia is a defensive mechanism that protects
79 patients against anguish and the reality of death. In this second study, groups were small and
80 participants were not matched for sex and age. This may have biased the results, as
81 demographic characteristics and education level are known to influence the level of
82 alexithymia (Salminen, Saarijärvi, Aärelä, Toikka, & Kauhanen, 1999). Neither study
83 assessed the neural correlates of alexithymia in ALS.

84 The above findings suggest that the level of alexithymia is high in some patients with ALS.
85 As mentioned, however, alexithymia is a heterogeneous concept. We therefore set out to
86 pinpoint the difficulties patients have processing their own emotions. Furthermore, we looked
87 for the neural substrate in link with one's own emotional processing in ALS.

88 The aims of the present study were to compare patients with ALS and controls on the
89 processing of one's own emotions in ALS patients, and to determine the relationship of any
90 impairment with morphological and cognitive data yielded by an anatomical MRI scan and a
91 thorough cognitive assessment.

92 2. MATERIAL AND METHODS

93 2.1 Participants

94 We recruited 28 patients with ALS for the present study. We also included 30 healthy
95 controls. The two groups were matched for age. All participants were native French speakers,
96 were aged more than 18 years, and had more than 7 years of education. Individuals were not
97 included in the study if they had a history of alcoholism, head trauma, or neurological or
98 psychiatric illness. Finally, controls had to have good overall cognitive functioning, as

99 assessed by the Mattis Dementia Rating Scale (MDRS > 130), and no patient had a severe
100 cognitive deficit (MDRS \geq 127) (Kaszás et al., 2012).

101 All patients were examined by an experienced neurologist (F.V. or L.C.). They met the new
102 El Escorial criteria for probable or definite ALS (Ludolph et al., 2015). None of them fulfilled
103 the criteria for a diagnosis of FTD according to the core and supporting diagnostic features of
104 FTD detailed in the Lund-Manchester consensus statement (Neary et al., 1998) or Rascovsky
105 et al.'s criteria (Rascovsky et al., 2011) for a possible and/or probable behavioral variant of
106 FTD. None had primary progressive aphasia. Genetic testing was not included in the study.

107 For each patient, we noted disease duration, clinical onset topography (limb vs. bulbar), the
108 severity of ALS at the time of the study according to the ALS Functional Rating Scale revised
109 form (ALSFRRS-R), the Norris ALS Scale, which assesses the impact of bulbar involvement,
110 and the Medical Research Council Muscle Strength Scale (MRC scale). Patients were able to
111 speak and/or write intelligibly, had a forced vital capacity above 50% of the predicted value,
112 and no clinical evidence of nocturnal hypoventilation. None of the patients had any additional
113 severe or chronic illness, MRI contraindications, or communication difficulties severe enough
114 to compromise the administration of cognitive tests. They gave their written informed
115 consent, and the study was approved by the regional independent ethics committee.

116 2.2 Alexithymia level measures

117 The level of alexithymia was gauged with the validated French version of the 20-items
118 Toronto Alexithymia Scale (TAS-20) (Taylor, Bagby, & Parker, 1992), a reliable self-report
119 scale and the most widely used measure of alexithymia (Loas et al., 2001; Loas, Parker,
120 Otmani, Verrier, & Fremaux, 1997). Each of the 20 items is rated on a 5-point scale ranging
121 from 1 (*strongly disagree*) to 5 (*strongly agree*). The TAS-20 assesses three dimensions of

122 alexithymia, by means of three specific subscales : Difficulty Identifying Feelings (DIF) is
123 measured by summing responses to Items 1-3-6-11-9-13-14, Difficulty Describing Feelings
124 (DDF) by summing responses to Items 2-4-7-12-17 and Externally Oriented Thinking (EOT)
125 by summing responses to Items 5-8-10-15-16-18-19-20 (Loas et al., 2001). We thus obtained
126 a TAS-20 total score and one additional subscore for each dimension.

127 2.3 Cognitive and behavioral functioning assessment

128 Global cognitive functioning was gauged with the widely used MDRS, which provides a
129 sensitive measure of the degree of frontal-subcortical impairment (Jr, Fisher, Muñoz, &
130 Empting, 1981). Both patients and controls underwent an additional neuropsychological
131 assessment that included the second part of the French version of the Hayling Sentence
132 Completion Test (HSCT) to evaluate the ability to inhibit a dominant response (number of
133 correct responses) (Burgess & Shallice, 1997); the Letter-Number Sequencing task (LN
134 sequencing) to measure the ability to manipulate items in working memory (rearrangement
135 and transformation of representations for goal-directed behavior) (Wechsler, 2000); and the
136 Trail Making Test (TMT) and letter verbal fluency task (VF) to evaluate set-shifting abilities
137 (Godefroy, 2008). The TMT comes in two parts: the time taken to process Part A yields a
138 measurement of processing speed, while that taken to process Part B minus the processing
139 time for Part A (TMT B-A) measures the ability to flexibly shift course during an activity.
140 The verbal fluency performances of patients with a speech impairment were expressed by an
141 index based on the number of words produced in the VF task and the time it took them to read
142 out the words in a subsequent reading task (Abrahams et al., 2000). To evaluate if patients
143 were cognitively impaired, we calculated the Z-scores for each patient using means and
144 standard deviations of the control group with pathological threshold defined at $Z = \pm 2$.

145 To assess behavioral changes induced by the disease, we have proposed the French version of
146 the Neuro-Psychiatric-Inventory Questionnaire (NPI-Q) to relatives. This questionnaire is
147 composed of 12 items corresponding to 12 symptoms: apathy, delirium, hallucination, etc.
148 Caregivers had to note if each symptom is present or absent and if present they have to
149 evaluate its severity (from 1 to 3) and its impact on themselves (from 1 to 5) (Kaufer et al.,
150 2000). We thus obtained three scores for each patient: number of symptoms (/12), severity of
151 symptoms (/36) and caregiver distress (/60).

152 2.4 MRI data acquisition

153 For each patient, a high-resolution T1-weighted anatomical image was acquired on an
154 Achieva 3T scanner (Philips, Eindhoven, The Netherlands) using a three-dimensional fast
155 field echo sequence (sagittal; repetition time = 20 ms, echo time = 4.6 ms, flip angle = 20°,
156 180 slices with no gap, slice thickness = 1 mm, field of view = 256 x 256 mm², in-plane
157 resolution = 1 x 1 mm²). The MRI examination was carried out within 24 hours of the clinical
158 testing.

159 The MRI data were segmented, spatially normalized to Montreal Neurological Institute (MNI)
160 space (voxel size = 1 mm³), modulated to correct for nonlinear warping effects, and smoothed
161 with a 10-mm full width at half maximum Gaussian kernel using the VBM5 toolbox
162 implemented in SPM5 software (www.fil.ion.ucl.ac.uk). Images were masked to exclude non-
163 gray matter (GM) voxels from the analyses.

164 2.5 Statistical analysis

165 Statistical analyses of demographic characteristics, alexithymia level and cognitive data were
166 performed using STATISTICA 10.0 (StatSoft, Tulsa, OK, USA). The threshold of
167 significance was set at $p = .05$. As we expected a higher level of alexithymia as already shown

168 by Roy-Bellina et al. (2008) and lower performances to cognitive tests in patients versus
169 controls, we performed between-group comparisons using one-tailed threshold. Regarding
170 correlations, as we had no a priori hypothesis, analyses were done using two-tailed threshold.

171 As some variables were not normally distributed, non parametric tests were used. U Mann-
172 Whitney test was employed to compare the patients and healthy controls on age, years of
173 education, TAS-20 scores, MDRS score, TMT B-A reaction time difference, verbal fluency
174 score and index, HSCT score and LN sequencing score. A chi-square test allowed us to
175 compare sex ratio and proportion of non-alexithymic versus alexithymic participants across
176 the two groups. In the patient group, correlations between TAS-20 scores and cognitive
177 performances were calculated with Spearman's correlation coefficient.

178 Finally, correlations between impaired TAS-20 total and DIF scores and whole-brain GM
179 volume were calculated using the multiple regression routine of Statistical Parametric
180 Mapping (SPM 5; Wellcome Trust Center for Neurology, London, UK) across the 28 patients.
181 In line with the study's main objectives, we focused on the negative correlations (we expected
182 a higher level of alexithymia to be correlated with lower GM volume). Given the deleterious
183 effect of age on GM volume and the potential effect of educational level on alexithymia, the
184 patients' ages and educational levels were entered as confounding variables. We used a
185 statistical threshold of $p = .005$ (uncorrected for multiple tests) for the voxels and a cut-off of
186 k (corresponding to the number of voxels in a particular cluster) > 100 . Anatomical
187 localization was based on Talairach's atlas and the Anatomical Automatic Labeling atlas
188 (AAL; (Tzourio-Mazoyer et al., 2002)). We used the MNI template of SPM 5.

189 3. RESULTS

190 3.1 Demographic, clinical, behavioral and neuropsychological characteristics of the two
191 groups

192 The demographic, clinical and neuropsychological characteristics of the two groups are
193 shown in Table 1. Patients and controls were matched for sex, $\chi^2(1) = 0$, $p = 0.99$, age, =
194 .009, but not for education level, $p = .02$. Regarding global cognitive and executive
195 functioning, patients scored lower than controls on the MDRS, $p < .001$, HSCT, $p < .001$,
196 TMT B-A, $p = .01$, LN sequencing task, $p < .01$, letter verbal fluency scores, $p < .001$, and
197 index, $p < .001$). All patients were impaired in at least one cognitive test but only 57 % of
198 them were defined as "cognitively impaired", meaning that they were deficient in at least two
199 tests. Scores obtained at the NPI-Q are reported in table 1.

200 3.2 Alexithymia Level

201 Regarding alexithymia level, and as indicated in Table 2, the mean TAS-20 total and DIF
202 subscores were significantly higher in patients than controls. By contrast, even though
203 patients scored higher than controls on the other two subscores (DDF and EOT), the
204 differences were not significant. A total of 53.6% of patients were alexithymic (TAS-20 total
205 score > 51), compared with just 23.3% of controls, $\chi^2(1) = 5.62$, $p = .02$.

206 In the patient group, TAS-20 scores correlated with age ($r = .41$, $p = .03$), but not with
207 education level, clinical data (ALSFRS-R score, Norris score and MRC score), MDRS score,
208 behavioral status (scores of the NPI-Q) or executive function performances (HSCT, TMT B-
209 A, LN sequencing score and letter verbal fluency score and index).

210 3.3 Correlations between alexithymia level and GM volume

211 The peaks of the significant negative correlations between the TAS-20 total or DIF scores and
212 GM volume, with age and educational level as confounding variables for 28 patients, are

213 given in Tables 3 and 4. TAS-20 total scores correlated negatively and significantly with GM
214 volume in the right and left anterior cingulate cortex (ACC), left inferior frontal gyrus
215 (triangular and opercular parts), left middle frontal gyrus, and right superior temporal gyrus
216 (see Fig. 1). TAS-20 DIF scores had significant negative correlations with GM volume in the
217 right ACC, left inferior frontal gyrus (triangular and opercular parts), and middle frontal gyrus
218 (see Fig. 1).

219 4. DISCUSSION

220 4.1 Alexithymia in ALS

221 Our results confirm that both the experience and the expression of one's own emotions are
222 altered in a high proportion of patients with ALS. These patients have significant difficulty
223 identifying their feelings compared with healthy individuals. More than half of patients are
224 alexithymic, whereas the prevalence of alexithymia in the general population ranges from 2 to
225 19%, depending on age, sex and educational level (Honkalampi, Hintikka, Tanskanen,
226 Lehtonen, & Viinamäki, 2000; Salminen et al., 1999). The prevalence of alexithymia in our
227 control group was 23%, which approximates to the highest rates in general population,
228 probably because of the predominance of men and the advanced age of the group.

229 The TAS-20 scale, which was not designed to specifically identify Type-I or Type-II
230 alexithymia, tends to emphasize its cognitive aspects (identifying, verbalizing and analyzing)
231 and to underestimate its emotional component, represented by emotionalizing and fantasizing
232 (Larsen, Brand, Bermond, & Hijman, 2003). However, if we assume that the DIF subscore
233 primarily reflects emotional experience (including first the perception of physical sensations
234 and then an awareness of their significance) whereas the other two subscores reflect emotional
235 mentalizing, then the main difficulty of patients with ALS would appear to lie in the

236 experiencing of emotion, which corresponds to Type-I alexithymia. Interestingly, Larsen et al.
237 suggested that a substantially reduced level of emotionalizing protects individuals from
238 emotional and psychiatric problems. It is a matter of fact that fewer than 10% of patients with
239 ALS experience depression (Kurt, Nijboer, Matuz, & Kübler, 2007; Rabkin et al., 2005),
240 which could partly be due to their impaired emotional experience.

241 The clinical importance of a high level of alexithymia in ALS remains to be specified. Type I
242 alexithymia could induce psychosomatic manifestations, which could in turn skew the ALS
243 patients' physical condition and make their medical management more difficult if
244 psychological care is not proposed. High levels of alexithymia have been found to be
245 correlated to less capacity of empathy (see e.g. Valdespino, Antezana, Ghane, & Richey,
246 2017). As shown by Lockwood, et al., a low capacity of empathy is associated to apathy, a
247 behavior that increases the burden of ALS caregivers (Chiò et al., 2010). Thus, a lack of
248 empathy potentially induced by the high level of alexithymia in some patients could increase
249 the burden of caregivers. Identifying and treating this psychological condition in patients is
250 crucial to prevent suffering of relatives.

251 Alexithymia has been found to impair quality of life (QoL) in the general population (Mattila
252 et al., 2009), and in several diseases as well, but not in ALS, to the best of our knowledge.
253 Further studies are needed to shed light on the clinical consequences of high level of
254 alexithymia in ALS.

255 4.2 Alexithymia and cognitive and emotional deficits in ALS

256 Our group of patients is in line with the generally accepted finding that in ALS about half of
257 the subjects have “normal cognition” and half have some sort of “cognitive impairment”
258 (Montuschi et al., 2015). Even if there are no normative data to interpret the NPI-Q, patients

259 have very little behavioral disorders compared to what is reported in pathology like
260 frontotemporal dementia (Uflacker, Edmondson, Onyike, & Appleby, 2016). Behavioral
261 impairment occurs in around 30 % of ALS patients (Bock et al., 2016; Burke et al., 2016); it
262 is usually associated to cognitive impairment but may be isolated in 6% of cases (Montuschi
263 et al, 2015). Behavioral changes mostly include disinhibition and apathy. The most
264 encountered subtype of apathy in ALS is the lack of initiation, a lack of motivation to self
265 generation of thoughts (Radakovic et al., 2017). This subtype is in link with poorer verbal
266 fluency performances, which suggests that apathy in ALS is underpinned by the medial
267 prefrontal cortex (Radakovic et al., 2017).

268 We found no correlations between our patients' set-shifting abilities, working memory and
269 ability to inhibit responses, and their alexithymia level. A high level of alexithymia has been
270 found to be associated with impairment of executive functions as assessed using the TMT and
271 verbal fluency tasks (Bogdanova, Díaz-Santos, & Cronin-Golomb, 2010; McIntosh et al.,
272 2014; Santorelli & Ready, 2015). But this association concerned mainly DDF, sometimes
273 with EOT or Total alexithymia(Bogdanova et al., 2010; McIntosh et al., 2014; Santorelli &
274 Ready, 2015). Furthermore, Paradiso et al. (2008) reported a significant association in healthy
275 volunteers between the total alexithymia score and scores on the Controlled Oral Word
276 Association test. These results suggest that alexithymia may be linked not only to impaired
277 executive functions but also possibly to poor linguistic abilities. Thus, only the cognitive
278 aspects of alexithymia (DDF and EOT dimensions) are linked to executive function or
279 language abilities. It is not surprising that we found no such association with the TAS-20 DIF
280 scores in the present study. The absence of a correlation between executive function and level
281 of affective alexithymia (DIF dimension) could be explained by the fact that the first stage of
282 emotional processing does not involve either executive functions or language abilities. The

283 impaired processing of emotions in the self could thus be *specific*, and partly independent of
284 executive dysfunction in ALS.

285 Patients with ALS are widely acknowledged to have deficits in recognition of other people's
286 emotions, and in both cognitive and affective theory of mind (ToM) (Carluer et al., 2015;
287 Girardi, MacPherson, & Abrahams, 2011). In some studies, executive functions have been
288 found to be correlated with affective and cognitive ToM (Carluer et al., 2015; Gibbons et al.,
289 2007) but alteration of ToM in ALS have also been shown to be partially independent of
290 executive function (Carluer et al., 2015; van der Hulst, Bak, & Abrahams, 2015). Van der
291 Hulst et al. (2015) showed that deficits in ToM are associated to poorer self awareness. Global
292 emotional and social dysfunctions are potentially underpinned by one's own emotional
293 processing deficit. Indeed, in order to understand the mental states of others, individuals must
294 activate representations of those states (i.e. simulate how others are feeling) within themselves
295 (Schnell, Bluschke, Konradt, & Walter, 2011). Patients' social cognition impairment may
296 therefore stem from the difficulty they have representing their own emotions (because of a
297 lack of emotional experience), insofar as this makes it harder for them to mentalize what
298 others are feeling or thinking.

299 4.3 Alexithymia and its neural correlates in ALS

300 4.3.1 Involvement of the anterior cingulate and prefrontal cortices in the processing of 301 emotions in the self.

302 This is the first study to have assessed the correlation between GM volume and alexithymia
303 level in ALS. We found significant negative relationships between the TAS-20 total score and
304 DIF subscore and the GM volume of the prefrontal cortex (inferior and middle frontal gyrus)
305 and ACC. In other words, patients with a high level of alexithymia had reduced GM volume

306 in these areas. These results are consistent with observations in healthy individuals, as several
307 neuroimaging studies have reported decreased GM volume in the ACC and medial prefrontal
308 cortex, in healthy individuals with a high level of alexithymia (Gündel et al., 2004; Ihme et
309 al., 2013; Sturm & Levenson, 2011; Grabe et al, 2014).

310 Reductions in GM density in ALS have been observed in the frontal lobe and, more
311 specifically, in the inferior (Agosta et al., 2007; Cosottini et al., 2012), middle and superior
312 frontal gyri (Cosottini et al., 2012) and ACC (Filippini et al., 2010; Lillo et al., 2012). These
313 areas partially overlap with those thought to be involved in the processing of one's own
314 emotions, which is consistent with the emotional processing alterations found in a number of
315 patients with ALS. Lane et al. (Lane, Ahern, Schwartz, & Kaszniak, 1997) suggested that
316 alexithymia could be an "emotional equivalent" of blindsight, which is when an individual
317 claims to be blind, but responds with high accuracy in visual tracking and other selective
318 visual tasks. Extra-striate pathways allow accurate responses to some stimuli that the
319 individual denies seeing, owing to a partial lesion in area V1 of the primary visual cortex that
320 prevents conscious visual perception. Mirroring this description, alexithymia could be a
321 deficit in emotional awareness caused by an impaired connection between subcortical
322 emotion-generating mechanisms and cortical mechanisms, including the ACC, which is
323 involved in the explicit processing of emotion. Lane et al. also found increased rostral ACC
324 and ventromedial prefrontal cortex (VMPFC) activation when they asked healthy individuals
325 to selectively attend to their emotional responses to various images they were shown, and to
326 classify these emotional responses as pleasant, unpleasant or neutral (Lane, Fink, Chau, &
327 Dolan, 1997). These authors suggested that the ACC and VMPFC play a specific part in
328 generating representations of one's subjective emotional responses and regulating subcortical
329 responses. Several more recent studies in the general population have shown that the rostral
330 ACC and surrounding VMPFC regions are involved in recognizing the processing of one's

331 emotions, independently of how these emotions are expressed.

332

333 4.3.2 Dimensions of alexithymia and their neural correlates

334 In our study, the total scores of the TAS-20 were correlated with three clusters (ACC, frontal
335 inferior and middle gyri, and temporal areas), whereas for the DIF subscore, only the ACC
336 (the biggest cluster) and the frontal inferior and middle gyri were found to be correlated..

337 There have been a few studies of the neural correlates of the various dimensions of
338 alexithymia. Demers et al. (2015) found a correlation between GM thickness in the dorsal
339 ACC and DIF scores in children with posttraumatic stress disorder. On a large sample of
340 healthy subjects, Grabe et al. (2014), looked for correlations between the gray matter volume
341 and alexithymia, distinguishing the three dimensions. For the total score of the TAS-20, a
342 significant negative correlation was found with the bilateral ACC and middle right cingulate
343 cortex whereas for the DIF score, bilateral ACC, bilateral middle cingulate cortex, inferior
344 temporal and fusiform gyri were the main clusters of negative significant correlations. It is not
345 clear if each dimension of alexithymia implies a specific network, but the cingulate cortex
346 seems to have a transversal role in one's own emotional processing. Developing the initial
347 blindsight neural model of alexithymia proposed by Lane, Ahern, et al. (1997), with the aid
348 of Marr's hierarchical model of vision, Prinz et al. (Prinz, 2006, 2012) (cited in (Smith &
349 Lane, 2015)) proposed a hierarchical model of conscious and unconscious emotional self-
350 perception with a three-stage algorithm. Stage 1 (*discrete body features*) corresponds to the
351 perception of changes in the activity of discrete parts of the body (e.g., changes in heart rate,
352 breathing, temperature, muscle tension). This bodily perception is mediated by the
353 somatosensory cortex. In Stage 2 (*whole body patterns*), discrete Stage 1 representations are
354 integrated in order to detect/represent coherent whole-body patterns. The anterior and middle

355 insula and dorsal ACC may play a crucial role in this stage (Smith & Lane, 2015). Stage 3
356 (*emotion concept*) involves mentalizing the integrative whole-body perception and giving
357 meaning to what is perceived and felt. Likely candidates for Stage 3 emotion processing are
358 the rostral ACC and adjacent regions of the medial prefrontal cortex (MPFC). Different stages
359 in this emotion processing presumably correspond to different alexithymia dimensions, with
360 DIF corresponding to Stage 1 or 2 of Prinz's model insofar as this dimension reflects a
361 perceptual process of relatively low cognitive level, and DDF and EOT to Stage 3. Our results
362 support the idea that the ACC has an integrative function for perceived sensations, while the
363 inferior and middle frontal gyri are involved in mentalizing emotions.

364 4.3.3 The temporal lobe and the processing of one's own emotions

365 Cortical damage in ALS may involve both temporal and limbic areas (Agosta et al., 2007;
366 Cosottini et al., 2012). In our study, a deficit in the processing of one's emotions was
367 associated with reduced GM volume in the right superior and middle temporal pole. Healthy
368 individuals' alexithymia scores are reported in the literature to be correlated with the GM
369 volume of both the superior temporal pole and the parahippocampal region (Ihme et al., 2013;
370 Sturm & Levenson, 2011). Parts of the temporal lobe are known to be involved in facial
371 emotion recognition and social cognition (Jimura, Konishi, & Miyashita, 2009). The superior
372 part is involved in lexical and semantic retrieval, while the anterior temporal part seems to be
373 an associative structure that links representations of meaning (Vandenberghe, 2007). Cerebral
374 lesions or neurodegenerative disease affecting the temporal pole are known to cause
375 behavioral, emotional and social impairments, eg disinhibition, hypersexuality, eating
376 disorder, emotional blunting, apathy and inadequate social responses (Olson, Plotzker, &
377 Ezzyat, 2007). Neuroimaging studies have shown that the temporal pole is involved in tasks
378 requiring to think about thoughts and emotions of others (Kumfor et al., 2016; Olson et al.,

379 2007). The right temporal pole is more specifically implicated in emotional processing,
380 social behavior and personal and episodic memories whereas the left temporal pole is more
381 engaged in semantic processing (Gainotti, 2015; Olson et al., 2007). . Pehrs et al. have
382 suggested that the temporal pole integrates information from different modalities and has a
383 modulating effect on perceptual areas. This could explain its implication in alexithymia and,
384 more specifically, in the other dimensions besides DIF.

385 Our study has some limitations. The first one is that as the patients are only mildly physically
386 affected and may thus not be representative of an ALS standard population, generalization of
387 the results must be done with caution. Another limitation is that our threshold of significance
388 for neural correlates has been set at $p < 0.005$ (uncorrected for multiple tests). This threshold
389 is not very robust but our results are consistent with the few relevant data in the literature,
390 which gives credit to our study. The fact that the TAS-20 scale only captures three of the five
391 previously described dimensions of alexithymia may be a methodological limit of the present
392 study. Finally, we focused on executive functions because these are the most impaired in ALS
393 patients and thus implications of other cognitive domains in alexithymie were not studied.
394 Further studies are needed, first to validate our finding and then to better assess the clinical
395 implications of alexithymia in ALS, in terms of quality of life of both patients and caregivers
396 for example. It would also be interesting to stratify the alexithymia data along clinical and
397 genetic subtypes of the disease.

398 5. CONCLUSION

399 To our knowledge, this is the first study assessing alexithymia in patients with ALS compared
400 with a matched control group, specifically focusing on the various dimensions of alexithymia.
401 Our results add to the accumulating evidence that a number of central nervous functions are
402 impaired in ALS besides motor control, including the processing of emotions in the self.

403 These emotional disabilities could explain patients' paradoxical psychological reactions. In
404 ALS, emotional self-perception involves brain regions that are known to contribute to
405 emotion processing in healthy individuals. Even if the nature of emotional neurological
406 circuits has been well established, the precise role of specific neurological structures remains
407 to be delineated. ALS could be a good model for improving current understanding of the
408 emotional brain.

409 ETHICAL STANDARDS

410 All subjects gave their written informed consent, and the study was approved by the regional
411 independent ethics committee.

412 CONFLICT OF INTEREST

413 On behalf of all authors, the corresponding author states that there is no conflict of interest.

414 ACKNOWLEDGMENTS

415 The authors are grateful to the patients, relatives and healthy controls for their participation.
416 The authors also want to thank clinicians of the neurology department, of the University
417 Hospital Center of Caen, who permit clinical and cognitive DATA acquisition and the
418 Cycleron MRI staff members for imaging examination acquisition.

419 AUTHOR CONTRIBUTIONS STATEMENT

420 SB was actively involved in this study from design to drafting. She conducted all the statistical
421 analyses and played a central role in interpreting the results and writing the article. FD and
422 MSB greatly contributed to the neuroimaging part of the study. AM and LC participated in
423 the acquisition of clinical and cognitive data, especially in the careful screening of our cohort.
424 FD, LC and FE provided their critical revision of the manuscript. BD and FV supervised and
425 coordinated the teamwork from start to finish. Their Knowledge and expertise in
426 neuropsychology and ALS pathology were crucial for the design, analyses and interpretation

427 of the result of the project. They were also particularly involved in the revising of the
428 manuscript. All authors read and improved the final manuscript. .

429 FUNDING

430 This work was supported by the French Minister of Health (PHRC, 2008, n°ID-RCB A01150-
431 55) and Fondation pour la Recherche Medicale (FRM).

432 DATA AVAILABILITY STATEMENTS

433 The raw data supporting the conclusions of this manuscript will be made available by the
434 authors, without undue reservation, to any qualified researcher.

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	Patients	Range	Controls	Range
Sex (M/F)	15/13		16/14	
Age (years)	61.28 (\pm 11.17)	43-81	57.30 (\pm 9.72)	45-75
Education (years)*	9.68 (\pm 2.59)	7-17	11.03 (\pm 2.57)	7-16
Onset (bulbar/limb)	5/23			
Disease duration (months since clinical onset)	17.89 (\pm 6.37)	5-44	\	\
ALSFRS-R score/48	37.57 (\pm 5.89)	27-48	\	\
Norris score/39	35.10 (\pm 5.65)	16-39	\	\
MRC score/120	99.78 (\pm 15.29)	63-120	\	\
MDRS**	136.39 (\pm 5.34)	127-144	142.40 (\pm 2.13)	130-144
HSCT correct responses**	5.89 (\pm 3.02)	0-12	9.00 (\pm 3.14)	4-14
TMT B-A (s)*	73.25 (\pm 86.59)	8-371	34.55 (\pm 30.90)	3-121
Letter verbal fluency scores**	15.11 (\pm 4.43)	8-25	24.59 (\pm 5.75)	13-38
Letter verbal fluency index **	6.89 (\pm 2.27)	5-13	4.35 (\pm 1.24)	3-8
LN sequencing score **	8.46 (\pm 3.63)	3-17	10.48 (\pm 2.06)	8-16
NPI-Q number of symptoms	2.08 (\pm 1.55)	0-4	\	\
NPI-Q severity of symptoms	3.91 (\pm 3.22)	0-12	\	\
NPI-Q caregivers distress	5.20 (\pm 4.25)	0-15	\	\

Note. Values are means (\pm *SD*). ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-revised form; MRC = Muscle Strength Scale; MDRS = Mattis Dementia Rating Scale; HSCT = Hayling Sentence Completion Test; TMT = Trail Making Test. NPI-R: Neuro-Psychiatric Inventory Questionnaire. * $p < 0.05$. ** $p < 0.001$. Disease duration was the period between clinical onset and the date of patient inclusion in the study

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Table 2. Scores on the 20-item Toronto Alexithymia Scale and proportion of

alexithymic versus nonalexithymic participants				457
	Patients	Controls	<i>P</i>	458
TAS-20 Total	49.36 (±13.38)	42.80 (± 10.06)	0.03*	459
TAS-20 DIF (/35)	15.78 (± 6.05)	12.43 (± 5.03)	0.01*	460
TAS-20 DDF (/25)	15.21 (± 4.93)	13.73 (± 5.07)	0.12	461
TAS-20 EOT (/40)	18.32 (± 4.86)	16.63 (± 3.46)	0.08	462
A/NA	15/13	7/23	0.02*	463
TAS-20 = Toronto Alexithymia Scale; DIF = Difficulty Identifying Feelings; DDF = Difficulty Describing Feelings; EOT = Externally Oriented Thinking; A = alexithymic; NA = non alexithymic. * <i>p</i> < 0.05.				464
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Table 3: Mean peaks and regions of significant negative correlation between TAS-20 total score and gray-matter volume ($p \leq 0.005$)

MNI coordinates			Labels	K	Z (voxel label)
x	y	z			
-33	15	30	Frontal_Inf_Oper_L	203	3.83
			Frontal_Inf_Tri_L		3.68
			Frontal_Mid_L		
6	29	19	Cingulum_Ant_R	435	3.68
-36	45	4	Frontal_Mid_L	232	3.60
			Frontal_Inf_Tri_L		
			Frontal_Mid_Orb_L		
-4	18	24	Cingulum_Ant_L	143	3.24
22	13	-33	Temporal_Pole_Sup_R	111	3.23
			ParaHippocampal_R		
			Temporal_Pole_Mid_R		

Labels were obtained using the AAL toolbox (see Materials and methods). K = cluster size; L = left; R = right; Oper = opercular; Tri = triangular; Orb = orbital; Inf = inferior; Ant = anterior; Sup = superior; Mid = middle.

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Table 4: Mean peaks and regions of significant negative correlation between TAS-20 DIF score and gray-matter volume ($p \leq 0.005$)

MNI coordinates			Labels	K	Z (voxel label)
x	Y	z			
8	37	10	Cingulum_Ant_R	375	4.04
-32	14	30	Frontal_Inf_Oper_L	147	3.67
			Frontal_Mid_L		
			Frontal_Inf_Tri_L		

Labels were obtained using the AAL toolbox (see Materials and methods). K = cluster size, L = left, R = right, Oper = opercular, Tri = triangular, Orb = orbital, Inf = inferior, Ant = anterior, Sup = superior, Mid = middle.

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500 Fig 1: Sagittal views of regions in which gray-matter volume correlated significantly and
501 negatively with TAS-20 total and DIF scores in 28 patients with ALS.

502 TAS-20 = 20-item Toronto Alexithymia Scale; DIF = Difficulty Identifying Feelings. Results
503 are displayed at $p < 0.005$ uncorrected and $k > 100$ mm³. Numbers in the figure indicate x
504 coordinate in MNI space.

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509 REFERENCES

510 Abrahams, S., Leigh, P. N., Harvey, A., Vythelingum, G. N., Gris , D., & Goldstein, L. H.
511 (2000). Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis
512 (ALS). *Neuropsychologia*, 38(6), 734-747.

- 513 Agosta, F., Pagani, E., Rocca, M. A., Caputo, D., Perini, M., Salvi, F., ... Filippi, M. (2007).
514 Voxel-based morphometry study of brain volumetry and diffusivity in amyotrophic
515 lateral sclerosis patients with mild disability. *Human Brain Mapping*, 28(12),
516 1430-1438. <https://doi.org/10.1002/hbm.20364>
- 517 Beeldman, E., Raaphorst, J., Klein Twennaar, M., de Visser, M., Schmand, B. A., & de Haan,
518 R. J. (2016). The cognitive profile of ALS: a systematic review and meta-analysis
519 update. *Journal of Neurology, Neurosurgery, and Psychiatry*, 87(6), 611-619.
520 <https://doi.org/10.1136/jnnp-2015-310734>
- 521 Bock, M., Duong, Y.-N., Kim, A., Allen, I., Murphy, J., & Lomen-Hoerth, C. (2016).
522 Cognitive-behavioral changes in amyotrophic lateral sclerosis: Screening prevalence
523 and impact on patients and caregivers. *Amyotrophic Lateral Sclerosis &*
524 *Frontotemporal Degeneration*, 17(5-6), 366-373.
525 <https://doi.org/10.3109/21678421.2016.1165257>
- 526 Bogdanova, Y., Díaz-Santos, M., & Cronin-Golomb, A. (2010). Neurocognitive correlates of
527 alexithymia in asymptomatic individuals with HIV. *Neuropsychologia*, 48(5),
528 1295-1304. <https://doi.org/10.1016/j.neuropsychologia.2009.12.033>
- 529 Bora, E. (2017). Meta-analysis of social cognition in amyotrophic lateral sclerosis. *Cortex; a*
530 *Journal Devoted to the Study of the Nervous System and Behavior*, 88, 1-7.
531 <https://doi.org/10.1016/j.cortex.2016.11.012>
- 532 Bungener, C., Piquard, A., Pradat, P.-F., Salachas, F., Meininger, V., & Lacomblez, L.
533 (2005). Psychopathology in amyotrophic lateral sclerosis: a preliminary study with 27
534 ALS patients. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders:*
535 *Official Publication of the World Federation of Neurology, Research Group on M*

- 536 Burgess, P. W., & Shallice, T. (1997). *The Hayling and Brixton Tests* (Thurston, Suffolk).
537 Thames Valley compagny.
- 538 Burke, T., Pinto-Grau, M., Lonergan, K., Elamin, M., Bede, P., Costello, E., ... Pender, N.
539 (2016). Measurement of Social Cognition in Amyotrophic Lateral Sclerosis: A
540 Population Based Study. *PloS One*, *11*(8), e0160850.
541 <https://doi.org/10.1371/journal.pone.0160850>
- 542 Carlier, L., Mondou, A., Buhour, M.-S., Laisney, M., Pélerin, A., Eustache, F., ...
543 Desgranges, B. (2015). Neural substrate of cognitive theory of mind impairment in
544 amyotrophic lateral sclerosis. *Cortex; a Journal Devoted to the Study of the Nervous*
545 *System and Behavior*, *65*, 19-30. <https://doi.org/10.1016/j.cortex.2014.12.010>
- 546 Chiò, A., Vignola, A., Mastro, E., Giudici, A. D., Iazzolino, B., Calvo, A., ... Montuschi, A.
547 (2010). Neurobehavioral symptoms in ALS are negatively related to caregivers'
548 burden and quality of life. *European Journal of Neurology*, *17*(10), 1298-1303.
549 <https://doi.org/10.1111/j.1468-1331.2010.03016.x>
- 550 Cosottini, M., Pesaresi, I., Piazza, S., Diciotti, S., Cecchi, P., Fabbri, S., ... Siciliano, G.
551 (2012). Structural and functional evaluation of cortical motor areas in Amyotrophic
552 Lateral Sclerosis. *Experimental Neurology*, *234*(1), 169-180.
553 <https://doi.org/10.1016/j.expneurol.2011.12.024>
- 554 Couratier, P., Corcia, P., Lautrette, G., Nicol, M., Preux, P.-M., & Marin, B. (2016).
555 Epidemiology of amyotrophic lateral sclerosis: A review of literature. *Revue*
556 *Neurologique*, *172*(1), 37-45. <https://doi.org/10.1016/j.neurol.2015.11.002>
- 557 Demers, L. A., Olson, E. A., Crowley, D. J., Rauch, S. L., & Rosso, I. M. (2015). Dorsal
558 Anterior Cingulate Thickness Is Related to Alexithymia in Childhood Trauma-Related
559 PTSD. *PloS One*, *10*(10), e0139807. <https://doi.org/10.1371/journal.pone.0139807>

- 560 Filippini, N., Douaud, G., Mackay, C. E., Knight, S., Talbot, K., & Turner, M. R. (2010).
561 Corpus callosum involvement is a consistent feature of amyotrophic lateral sclerosis.
562 *Neurology*, 75(18), 1645-1652. <https://doi.org/10.1212/WNL.0b013e3181fb84d1>
- 563 Gainotti, G. (2015). Is the difference between right and left ATLs due to the distinction
564 between general and social cognition or between verbal and non-verbal
565 representations? *Neuroscience and Biobehavioral Reviews*, 51, 296-312.
566 <https://doi.org/10.1016/j.neubiorev.2015.02.004>
- 567 Gibbons, Z. C., Snowden, J. S., Thompson, J. C., Happé, F., Richardson, A., & Neary, D.
568 (2007). Inferring thought and action in motor neurone disease. *Neuropsychologia*,
569 45(6), 1196-1207. <https://doi.org/10.1016/j.neuropsychologia.2006.10.008>
- 570 Girardi, A., Macpherson, S. E., & Abrahams, S. (2011). Deficits in emotional and social
571 cognition in amyotrophic lateral sclerosis. *Neuropsychology*, 25(1), 53-65.
572 <https://doi.org/10.1037/a0020357>
- 573 Godefroy, O. (2008). *Fonctions exécutives et pathologies neurologiques et psychiatriques:*
574 *Évaluation en pratique clinique*. Louvain-la-Neuve (Belgique): De Boeck Supérieur.
- 575 Grabe, H. J., Wittfeld, K., Hegenscheid, K., Hosten, N., Lotze, M., Janowitz, D., ...
576 Freyberger, H. J. (2014). Alexithymia and brain gray matter volumes in a general
577 population sample. *Human Brain Mapping*, 35(12), 5932-5945.
578 <https://doi.org/10.1002/hbm.22595>
- 579 Gündel, H., López-Sala, A., Ceballos-Baumann, A. O., Deus, J., Cardoner, N., Marten-
580 Mittag, B., ... Pujol, J. (2004). Alexithymia correlates with the size of the right
581 anterior cingulate. *Psychosomatic Medicine*, 66(1), 132-140.

- 582 Honkalampi, K., Hintikka, J., Tanskanen, A., Lehtonen, J., & Viinamäki, H. (2000).
583 Depression is strongly associated with alexithymia in the general population. *Journal*
584 *of Psychosomatic Research*, 48(1), 99-104.
- 585 Ihme, K., Dannlowski, U., Lichev, V., Stuhmann, A., Grotegerd, D., Rosenberg, N., ...
586 Suslow, T. (2013). Alexithymia is related to differences in gray matter volume: a
587 voxel-based morphometry study. *Brain Research*, 1491, 60-67.
588 <https://doi.org/10.1016/j.brainres.2012.10.044>
- 589 Jimura, K., Konishi, S., & Miyashita, Y. (2009). Temporal pole activity during perception of
590 sad faces, but not happy faces, correlates with neuroticism trait. *Neuroscience Letters*,
591 453(1), 45-48. <https://doi.org/10.1016/j.neulet.2009.02.012>
- 592 Jr, R. G., Fisher, L., Muñoz, S. O., & Empting, L. (1981). Mattis dementia rating scale:
593 Internal reliability study using a diffusely impaired population. *Journal of Clinical*
594 *Neuropsychology*, 3(3), 271-275. <https://doi.org/10.1080/01688638108403130>
- 595 Kaszás, B., Kovács, N., Balás, I., Kállai, J., Aschermann, Z., Kerekes, Z., ... Karádi, K.
596 (2012). Sensitivity and specificity of Addenbrooke's Cognitive Examination, Mattis
597 Dementia Rating Scale, Frontal Assessment Battery and Mini Mental State
598 Examination for diagnosing dementia in Parkinson's disease. *Parkinsonism & Related*
599 *Disorders*, 18(5), 553-556. <https://doi.org/10.1016/j.parkreldis.2012.02.010>
- 600 Kaufer, D. I., Cummings, J. L., Ketchel, P., Smith, V., MacMillan, A., Shelley, T., ...
601 DeKosky, S. T. (2000). Validation of the NPI-Q, a brief clinical form of the
602 Neuropsychiatric Inventory. *The Journal of Neuropsychiatry and Clinical*
603 *Neurosciences*, 12(2), 233-239. <https://doi.org/10.1176/jnp.12.2.233>
- 604 Kumfor, F., Landin-Romero, R., Devenney, E., Hutchings, R., Grasso, R., Hodges, J. R., &
605 Piguet, O. (2016). On the right side? A longitudinal study of left- versus right-

- 606 lateralized semantic dementia. *Brain: A Journal of Neurology*, 139(Pt 3), 986-998.
607 <https://doi.org/10.1093/brain/awv387>
- 608 Kurt, A., Nijboer, F., Matuz, T., & Kübler, A. (2007). Depression and anxiety in individuals
609 with amyotrophic lateral sclerosis: epidemiology and management. *CNS Drugs*, 21(4),
610 279-291.
- 611 Lane, R. D., Ahern, G. L., Schwartz, G. E., & Kaszniak, A. W. (1997). Is alexithymia the
612 emotional equivalent of blindsight? *Biological Psychiatry*, 42(9), 834-844.
- 613 Lane, R. D., Fink, G. R., Chau, P. M., & Dolan, R. J. (1997). Neural activation during
614 selective attention to subjective emotional responses. *Neuroreport*, 8(18), 3969-3972.
- 615 Larsen, J. K., Brand, N., Bermond, B., & Hijman, R. (2003). Cognitive and emotional
616 characteristics of alexithymia: a review of neurobiological studies. *Journal of*
617 *Psychosomatic Research*, 54(6), 533-541.
- 618 Lillo, P., Mioshi, E., Burrell, J. R., Kiernan, M. C., Hodges, J. R., & Hornberger, M. (2012).
619 Grey and white matter changes across the amyotrophic lateral sclerosis-frontotemporal
620 dementia continuum. *PloS One*, 7(8), e43993.
621 <https://doi.org/10.1371/journal.pone.0043993>
- 622 Loas, G., Corcos, M., Stephan, P., Pellet, J., Bizouard, P., Venisse, J. L., ... Réseau INSERM
623 no. 494013. (2001). Factorial structure of the 20-item Toronto Alexithymia Scale:
624 confirmatory factorial analyses in nonclinical and clinical samples. *Journal of*
625 *Psychosomatic Research*, 50(5), 255-261.
- 626 Loas, G., Parker, J. D., Otmani, O., Verrier, A., & Fremaux, D. (1997). Confirmatory factor
627 analysis of the French translation of the 20-item Toronto Alexithymia Scale.
628 *Perceptual and Motor Skills*, 85(3 Pt 1), 1018.
629 <https://doi.org/10.2466/pms.1997.85.3.1018>

- 630 Lockwood, P. L., Ang, Y.-S., Husain, M., & Crockett, M. J. (2017). Individual differences in
631 empathy are associated with apathy-motivation. *Scientific Reports*, 7(1), 17293.
632 <https://doi.org/10.1038/s41598-017-17415-w>
- 633 Ludolph, A., Drory, V., Hardiman, O., Nakano, I., Ravits, J., Robberecht, W., ... WFN
634 Research Group On ALS/MND. (2015). A revision of the El Escorial criteria - 2015.
635 *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration*, 16(5-6), 291-292.
636 <https://doi.org/10.3109/21678421.2015.1049183>
- 637 Mattila, A. K., Saarni, S. I., Salminen, J. K., Huhtala, H., Sintonen, H., & Joukamaa, M.
638 (2009). Alexithymia and health-related quality of life in a general population.
639 *Psychosomatics*, 50(1), 59-68. <https://doi.org/10.1176/appi.psy.50.1.59>
- 640 McIntosh, R. C., Ironson, G., Antoni, M., Kumar, M., Fletcher, M. A., & Schneiderman, N.
641 (2014). Alexithymia is linked to neurocognitive, psychological, neuroendocrine, and
642 immune dysfunction in persons living with HIV. *Brain, Behavior, and Immunity*, 36,
643 165-175. <https://doi.org/10.1016/j.bbi.2013.10.024>
- 644 Montuschi, A., Iazzolino, B., Calvo, A., Moglia, C., Lopiano, L., Restagno, G., ... Chiò, A.
645 (2015). Cognitive correlates in amyotrophic lateral sclerosis: a population-based study
646 in Italy. *Journal of Neurology, Neurosurgery, and Psychiatry*, 86(2), 168-173.
647 <https://doi.org/10.1136/jnnp-2013-307223>
- 648 Neary, D., Snowden, J. S., Gustafson, L., Passant, U., Stuss, D., Black, S., ... Benson, D. F.
649 (1998). Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria.
650 *Neurology*, 51(6), 1546-1554.
- 651 Nemiah, J. C., & Sifneos, P. E. (1970). Psychosomatic illness: a problem in communication.
652 *Psychotherapy and Psychosomatics*, 18(1), 154-160.

- 653 Olson, I. R., Plotzker, A., & Ezzyat, Y. (2007). The Enigmatic temporal pole: a review of
654 findings on social and emotional processing. *Brain: A Journal of Neurology*, *130*(Pt
655 7), 1718-1731. <https://doi.org/10.1093/brain/awm052>
- 656 Palmieri, A., Naccarato, M., Abrahams, S., Bonato, M., D'Ascenzo, C., Balestreri, S., ...
657 Sorarù, G. (2010). Right hemisphere dysfunction and emotional processing in ALS: an
658 fMRI study. *Journal of Neurology*, *257*(12), 1970-1978.
659 <https://doi.org/10.1007/s00415-010-5640-2>
- 660 Paradiso, S., Vaidya, J. G., McCormick, L. M., Jones, A., & Robinson, R. G. (2008). Aging
661 and alexithymia: association with reduced right rostral cingulate volume. *The*
662 *American Journal of Geriatric Psychiatry: Official Journal of the American*
663 *Association for Geriatric Psychiatry*, *16*(9), 760-769.
664 <https://doi.org/10.1097/JGP.0b013e31817e73b0>
- 665 Pehrs, C., Zaki, J., Schlochtermeyer, L. H., Jacobs, A. M., Kuchinke, L., & Koelsch, S. (2015).
666 The Temporal Pole Top-Down Modulates the Ventral Visual Stream During Social
667 Cognition. *Cerebral Cortex (New York, N.Y.: 1991)*.
668 <https://doi.org/10.1093/cercor/bhv226>
- 669 Phukan, J., Elamin, M., Bede, P., Jordan, N., Gallagher, L., Byrne, S., ... Hardiman, O.
670 (2012). The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a
671 population-based study. *Journal of Neurology, Neurosurgery, and Psychiatry*, *83*(1),
672 102-108. <https://doi.org/10.1136/jnnp-2011-300188>
- 673 Prinz, J. J. (2006). *Gut Reactions: A Perceptual Theory of Emotion*. Oxford, New York:
674 Oxford University Press.
- 675 Prinz, J. J. (2012). *The Conscious Brain: How Attention Engenders Experience (Philosophy of*
676 *Mind)*. Oxford, New York: Oxford University Press.

- 677 Rabkin, J. G., Albert, S. M., Del Bene, M. L., O'Sullivan, I., Tider, T., Rowland, L. P., &
678 Mitsumoto, H. (2005). Prevalence of depressive disorders and change over time in
679 late-stage ALS. *Neurology*, 65(1), 62-67.
680 <https://doi.org/10.1212/01.wnl.0000167187.14501.0c>
- 681 Radakovic, R., Stephenson, L., Newton, J., Crockford, C., Swingler, R., Chandran, S., &
682 Abrahams, S. (2017). Multidimensional apathy and executive dysfunction in
683 amyotrophic lateral sclerosis. *Cortex; a Journal Devoted to the Study of the Nervous*
684 *System and Behavior*, 94, 142-151. <https://doi.org/10.1016/j.cortex.2017.06.023>
- 685 Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., ...
686 Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural
687 variant of frontotemporal dementia. *Brain: A Journal of Neurology*, 134(Pt 9),
688 2456-2477. <https://doi.org/10.1093/brain/awr179>
- 689 Roy-Bellina, S., Brunel, H., Almohsen, C., Gely-Nargeot, M. C., Carton, S., & Camu, W.
690 (2008). Alexithymia in amyotrophic lateral sclerosis. A neuropsychological approach.
691 *Journal of Neurology*, 255(2), 51-51.
- 692 Salminen, J. K., Saarijärvi, S., Aärelä, E., Toikka, T., & Kauhanen, J. (1999). Prevalence of
693 alexithymia and its association with sociodemographic variables in the general
694 population of Finland. *Journal of Psychosomatic Research*, 46(1), 75-82.
- 695 Santorelli, G. D., & Ready, R. E. (2015). Alexithymia and Executive Function in Younger
696 and Older Adults. *The Clinical Neuropsychologist*, 29(7), 938-955.
697 <https://doi.org/10.1080/13854046.2015.1123296>
- 698 Schnell, K., Bluschke, S., Konradt, B., & Walter, H. (2011). Functional relations of empathy
699 and mentalizing: an fMRI study on the neural basis of cognitive empathy.
700 *NeuroImage*, 54(2), 1743-1754. <https://doi.org/10.1016/j.neuroimage.2010.08.024>

- 701 Smith, R., & Lane, R. D. (2015). The neural basis of one's own conscious and unconscious
702 emotional states. *Neuroscience and Biobehavioral Reviews*, *57*, 1-29.
703 <https://doi.org/10.1016/j.neubiorev.2015.08.003>
- 704 Sturm, V. E., & Levenson, R. W. (2011). Alexithymia in neurodegenerative disease.
705 *Neurocase*, *17*(3), 242-250. <https://doi.org/10.1080/13554794.2010.532503>
- 706 Taylor, G. J., Bagby, R. M., & Parker, J. D. (1992). The Revised Toronto Alexithymia Scale:
707 some reliability, validity, and normative data. *Psychotherapy and Psychosomatics*,
708 *57*(1-2), 34-41.
- 709 Trojsi, F., Siciliano, M., Russo, A., Passaniti, C., Femiano, C., Ferrantino, T., ... Santangelo,
710 G. (2016). Theory of Mind and Its Neuropsychological and Quality of Life Correlates
711 in the Early Stages of Amyotrophic Lateral Sclerosis. *Frontiers in Psychology*, *7*,
712 1934. <https://doi.org/10.3389/fpsyg.2016.01934>
- 713 Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N.,
714 ... Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a
715 macroscopic anatomical parcellation of the MNI MRI single-subject brain.
716 *NeuroImage*, *15*(1), 273-289. <https://doi.org/10.1006/nimg.2001.0978>
- 717 Uflacker, A., Edmondson, M. C., Onyike, C. U., & Appleby, B. S. (2016). Caregiver burden
718 in atypical dementias: comparing frontotemporal dementia, Creutzfeldt-Jakob disease,
719 and Alzheimer's disease. *International Psychogeriatrics*, *28*(2), 269-273.
720 <https://doi.org/10.1017/S1041610215001647>
- 721 Valdespino, A., Antezana, L., Ghane, M., & Richey, J. A. (2017). Alexithymia as a
722 Transdiagnostic Precursor to Empathy Abnormalities: The Functional Role of the
723 Insula. *Frontiers in Psychology*, *8*, 2234. <https://doi.org/10.3389/fpsyg.2017.02234>

- 724 van der Hulst, E.-J., Bak, T. H., & Abrahams, S. (2015). Impaired affective and cognitive
725 theory of mind and behavioural change in amyotrophic lateral sclerosis. *Journal of*
726 *Neurology, Neurosurgery, and Psychiatry*, 86(11), 1208-1215.
727 <https://doi.org/10.1136/jnnp-2014-309290>
- 728 Vandenberghe, R. (2007). Functional specialisation within the cortical language network:
729 effects of cortical dysfunction. *Verhandelingen - Koninklijke Academie Voor*
730 *Geneeskunde Van Belgie*, 69(1), 5-22.
- 731 Wechsler, D. (2000). *Echelle d'Intelligence de Wechsler pour adultes: manuel : WAIS-III*. (J.
732 Grégoire, Trad.). Paris, France: Les Editions du Centre de Psychologie Appliquée.
- 733 Zago, S., Poletti, B., Morelli, C., Doretti, A., & Silani, V. (2011). Amyotrophic lateral
734 sclerosis and frontotemporal dementia (ALS-FTD). *Archives Italiennes De Biologie*,
735 149(1), 39-56.

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737 ANNEX FOR REVIEWER 1 :

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739 Here, you will find the tables corresponding to the supplementary analyses asked by the
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Table 1 : Mean peaks and regions of significant negative correlation between TAS-20 total score and gray-matter volume using SPM 5 and the Total Intracranial Volume as a confounding variable ($p \leq 0.005$;)

MNI coordinates			Labels	K	Z (voxel label)
x	y	z			
9	38	9	Cingulum Ant R	664	6.32
-11	45	1	Cingulum Ant L	410	2.93
			Frontal Sup Medial L		
			Frontal Med Orb L		
-33	43	5	Frontal Mid L	170	0.25
			Front Inf Tri L		
			Frontal Mid Orb L		
-33	15	29	Frontal Inf Oper L	177	0.86
		-	Frontal Inf Tri L		
			Frontal Mid L		
18	-51	58	Postcentral R	257	0.48
			Parietal Sup R		
-4	17	23	Cingulum Ant L	221	
20	11	-34	Temporal Pole Sup R	217	0.22
			ParaHippocampal R		
			Temporal Pole Mid L		
-16	-74	-10	Lingual L	144	0.86
-37	-8	49	Precentral L	144	0.52

Labels were obtained using the AAL toolbox (see Materials and methods). K = cluster size; L = left; R = right; Oper = opercular; Tri = triangular; Orb = orbital; Inf = inferior; Ant = anterior; Sup = superior; Mid = middle.

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Table 2: Mean peaks and regions of significant negative correlation between TAS-20 DIF score and gray-matter volume using SPM 5 and the Total Intracranial Volume as a confounding variable ($p \leq 0.005$)

MNI coordinates			Labels	K	Z (voxel label)
x	Y	z			
9	38	9	Cingulum_Ant_R	420	4.00
-3	18	31	Frontal_Inf_Oper_L Frontal_Mid_L Frontal_Inf_Tri_L	139	0.87
-7	39	-6	Cingulum Ant L Frontal Med Orb L	154	1.1

Labels were obtained using the AAL toolbox (see Materials and methods). K = cluster size, L = left, R = right, Oper = opercular, Tri = triangular, Orb = orbital, Inf = inferior, Ant = anterior, Sup = superior, Mid = middle.

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Table 3: Mean peaks and regions of significant negative correlation between TAS-20 total score and gray-matter volume using SPM 8 and the Total Intracranial Volume as a confounding variable ($p \leq 0.005$;)

MNI coordinates			Labels	K	Z (voxel label)
x	y	z			
-36	44	4	Frontal Mid Orb L Frontal Mid L Frontal Inf Tri L Frontal inf Orb L	564	3.9
4	32	12	Frontal Mid Orb R Cingulum ant R Cingulum Ant L Frontal Mid Orb L	834	7.69
8	38	7	Cingulum Ant R	372	
-12	44	42	Frontal sup L Frontal sup Medial L	219	0.77
-18	-75	49	Parietal Sup L	138	0.94
38	2	-18	Temporal Pole Sup R	100	0.09
16	40	26	Frontal Sup Orb R	141	1.52
21	12	-35	Temporal Pole Sup R Temporal Pole Mid R Parahippocampal R	156	0.54

Labels were obtained using the AAL toolbox (see Materials and methods). K = cluster size; L = left; R = right; Tri = triangular; Orb = orbital; Inf = inferior; Ant = anterior; Sup = superior; Mid = middle.

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table 4: Mean peaks and regions of significant negative correlation between TAS-20 DIF score and gray-matter volume using SPM 8 and the Total Intracranial Volume as a confounding variable ($p \leq 0.005$)

MNI coordinates			Labels	K	Z (voxel label)
X	Y	z			
8	38	7	Cingulum_Ant_R	114	1.22
-3	18	31	Frontal_Mid_Orb L Frontal_Mid_L Frontal Inf Orb L	228	3.42
11	42	45	Frontal Sup L	117	0.46

Labels were obtained using the AAL toolbox (see Materials and methods). K = cluster size, L = left, R = right, Orb = orbital, Inf = inferior, Ant = anterior, Sup = superior, Mid = middle.

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