

## Alexithymia in amyotrophic lateral sclerosis and its neural correlates

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

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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

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## 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 mm<sup>2</sup>, in-plane  
157 resolution = 1 x 1 mm<sup>2</sup>). 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 mm<sup>3</sup>), 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](http://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.

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#### 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. .

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#### 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  $k > 100$  mm<sup>3</sup>. Numbers in the figure indicate x  
504 coordinate in MNI space.

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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  
740 reviewer 1

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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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