

1 **Papez circuit gray matter and episodic memory in amyotrophic lateral sclerosis and**
2 **behavioural variant frontotemporal dementia**

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43 **Abstract**

44 Amyotrophic lateral sclerosis and behavioural variant frontotemporal dementia are two
45 different diseases recognized to overlap at clinical, pathological and genetic
46 characteristics. Both conditions are traditionally known for relative sparing of episodic
47 memory. However, recent studies have disputed that with the report of patients presenting
48 with marked episodic memory impairment. Besides that, structural and functional
49 changes in temporal lobe regions responsible for episodic memory processing are often
50 detected in neuroimaging studies of both conditions. In this study, we investigated the
51 gray matter features associated with the Papez circuit in amyotrophic lateral sclerosis,
52 behavioural variant frontotemporal dementia and healthy controls to further explore
53 similarities and differences between the two conditions. Our non-demented amyotrophic
54 lateral sclerosis patients showed no episodic memory deficits measured by a short-term
55 delayed recall test while no changes in gray matter of the Papez circuit were found.
56 Compared with the amyotrophic lateral sclerosis group, the behavioural variant
57 frontotemporal dementia group had lower performance on the short-term delayed recall
58 test and marked atrophy in gray matter of the Papez circuit. Bilateral atrophy of entorhinal
59 cortex and mammillary bodies distinguished behavioural variant frontotemporal
60 dementia from amyotrophic lateral sclerosis patients as well as atrophy in left cingulate,
61 left hippocampus and right parahippocampal gyrus. Taken together, our results suggest
62 that sub-regions of the Papez circuit could be differently affected in amyotrophic lateral
63 sclerosis and behavioural variant frontotemporal dementia.

64 **Keywords:** amyotrophic lateral sclerosis, behavioural variant frontotemporal dementia,
65 episodic memory, Papez circuit.

66

67 **Introduction**

68 Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease
69 affecting upper and lower motor neurons, eventually leading patients to severe paralysis
70 and death (for review see Hardiman et al., 2017). In addition to motor symptoms, ALS
71 patients may display frontotemporal dysfunctions, sometimes leading to a concomitant
72 diagnose of frontotemporal dementia (FTD), typically compatible with the behavioural
73 variant FTD (bvFTD; for reviews see Goldstein & Abrahams, 2013; Salameh et al., 2015).
74 Importantly, subtle psychiatric and cognitive disturbances can precede motor impairment,
75 causing difficulties to diagnosis ALS before the onset of motor symptoms (for review see
76 Bak & Hodges, 2001).

77 bvFTD is also a neurodegenerative disease characterized by progressive
78 behavioural and cognitive deterioration, with marked structural and functional changes in
79 frontotemporal regions (for review see Piguet & Hodges, 2011). However, a large
80 proportion of bvFTD patients can also present with motor disturbances (Lillo & Hodges,
81 2009). Clinical, pathological and genetic shared characteristics between ALS and bvFTD
82 have been recognized (Lillo et al., 2016; Trojsi et al., 2015; Geser et al., 2009; Patel &
83 Sampson, 2015), but regarding episodic memory, the nature and extent of deficits remain
84 unclear in both conditions.

85 Medial temporal lobe (MTL) structures are associated with episodic memory
86 processing (for review see Aggleton, 2008) and structural/functional changes in the MTL
87 are often reported in ALS (Buhour et al, 2017; Christidi et al, 2017; Kasper et al, 2014;
88 (Bueno et al., 2018). Despite studies have reported episodic memory deficits in ALS
89 patients (Trojsi et al, 2016; Kasper et al, 2016; Machts et al., 2014; Consonni et al, 2013;
90 Consonni et al, 2015), their nature and extent are not clear yet and vary a lot among studies
91 (Trojsi et al, 2016; Kasper et al, 2016; Machts et al., 2014; Consonni et al, 2013; Consonni

92 et al, 2015), with encoding and storage/consolidation deficits previously associated with
93 MTL changes (Christidi et al, 2017; Raaphorst et al, 2015).

94 In bvFTD, episodic memory is considered relatively spared as per diagnostic
95 criteria (Rascovsky et al., 2011). However, recent studies have shown encoding
96 difficulties (Irish et al, 2014; Flanagan et al, 2016), immediate/delayed recall impairments
97 (Wong et al, 2014; Frisch et al, 2013; Mansoor et al, 2015; Fernández-Matarrubia et al,
98 2017) and recognition deficits (Fernández-Matarrubia et al, 2017; St. Jacques et al, 2015).
99 Furthermore, memory findings are in accordance with imaging studies showing
100 significant MTL changes (Hornberger et al, 2012; Papma et al, 2013; Irish et al, 2014;
101 Ryan et al, 2017; Wong et al, 2016).

102 The Papez circuit originally proposed as responsible for the processing of
103 emotions (Papez, 1937) is now recognized to be critically involved in mnemonic
104 processes. Disruptions in any part of the circuit are likely to affect different aspects of
105 episodic memory depending on the structure affected (for reviews see Aggleton & Brown,
106 1999; Bubb et al., 2017). Despite its relevance, so far only one study has investigated the
107 whole Papez network in ALS (Bueno et al., 2018) and another one in bvFTD (Hornberger
108 et al., 2012). Our previous study showed significant functional changes in the memory
109 circuit of ALS patients, evidenced by decreased functional connectivity in bilateral
110 hippocampus, bilateral anterior and posterior parahippocampal gyrus and posterior
111 cingulate of ALS patients, but preserved episodic memory and minor structural changes
112 (Bueno et al., 2018). Hornberger and colleagues (2012) reported memory impairment and
113 significant atrophy in Papez circuit structures in bvFTD. To the best of our knowledge,
114 no study has compared the morphological characteristics of the Papez circuit between
115 ALS and bvFTD, conditions that have been suggested to lie on a clinical continuum (for
116 reviews see Beeldman et al., 2018; Lillo & Hodges, 2009).

117 To explore potential differences or similarities that could be helpful to
118 differentiate both diseases when cognitive information is limited and the symptoms
119 overlap, we employed voxel-based morphometry (VBM) and cortical thickness measures
120 to investigate degeneration of gray matter (GM) in Papez circuit regions of ALS and
121 bvFTD patients and healthy controls (HC). These two different magnetic resonance
122 imaging (MRI) measures can complement each other and therefore are useful tools to
123 provide higher accuracy for diagnosis and markers of disease progression. We
124 hypothesised that the Papez circuit could be differently affected in ALS and bvFTD, with
125 bvFTD showing more atrophy than ALS.

126

127 **Materials and methods**

128 *Participants*

129 We recruited participants at Hospital das Clínicas of Universidade Federal de
130 Minas Gerais, in Belo Horizonte, Brazil, following approval by the institution's human
131 research ethics committee. All participants and/or their caregivers provided written
132 consent in accordance with the Declaration of Helsinki and local regulations.

133 A group of 13 ALS patients was contrasted with 18 bvFTD patients and 13 HC.
134 ALS patients were diagnosed according to the Awaji criteria (de Carvalho et al., 2008).
135 None of the ALS patients had a concomitant diagnosis of dementia (ALS-FTD). The
136 Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R;
137 Cedarbaum et al., 1999; Guedes et al., 2010) was used to evaluate functional status with
138 a mean score of 36.36 (range 25-43). Eleven out of the 13 ALS patients were diagnosed
139 as limb onset. We did not include patients using non-invasive ventilation. bvFTD patients
140 were classified according to standard diagnostic criteria (Rascovsky et al., 2011). All
141 bvFTD patients were evaluated by an experienced neurologist for motor neuron disease

142 and none of them presented signs of motor neuron affection. Controls were recruited from
143 the community and we did not include participants with previous neurological (e.g.
144 epilepsy, dementia, multiple sclerosis, etc.) or neurosurgical diseases (e.g., brain tumors),
145 and we did not include participants with severe psychiatric disorders (e.g., schizophrenia,
146 bipolar disorder). Moreover, healthy participants had normal scores on the MMSE. None
147 of the participants had a diagnosis of depression as assessed by the Hospital Anxiety and
148 Depression scale (HADS; Botega et al., 1995).

149

150 *Neuropsychological assessments*

151 All participants underwent cognitive screening with the Mini-Mental State
152 Examination (MMSE; Brucki et al., 2003). Cognitive assessment was performed with the
153 Frontal Assessment Battery (FAB; Beato et al., 2007), phonemic fluency test (FAS;
154 Machado & Fichman, 2009), animal fluency (Brucki et al., 1997) and digit span
155 (Zimmermann et al., 2015). Episodic memory was specifically measured by the visual
156 memory sub-test of the Brief Cognitive Screening Battery (BCSB; Nitrini et al., 1994;
157 Yassuda et al., 2017). The BCSB is a multidimensional brief test used to discriminate
158 dementia in populations with heterogeneous educational background and includes the
159 following categories: memory, visual perception, clock drawing and category fluency
160 (animals/min.). The memory sub-test consists of the presentation of 10 items followed by
161 a naming phase, incidental memory, immediate recall, a five-minute delayed recall of the
162 10 items previously shown and a recognition test.

163

164 *MRI acquisition and analyses*

165 Participants underwent whole-brain MRI on a 3T Philips scan. T₁-weighted
166 images were acquired as follows: multi-shot 256 TFE factor (TR/TE 5.4/2.4ms, 256x256

167 matrix, FOV 256x256x180, flip angle 8°), slice thickness 1mm, coronal orientation, voxel
168 size 1x1x1mm³.

169 We performed VBM analyses using the Statistical Parametric Mapping 12
170 (SPM12; <http://www.fil.ion.ucl.ac.uk/spm>). The MRI data were preprocessed following
171 a standard protocol. First, the anterior commissure of all images was set as the origin of
172 spatial coordinates. Segmentation algorithm bias-corrected the T₁-weighted images for
173 inhomogeneities and generated rigid-body aligned GM and white matter (WM) of the
174 subjects. The DARTEL algorithm (Ashburner, 2007) estimated the nonlinear
175 deformations that best aligned all images together by iteratively registering the imported
176 images with their average, creating a mean template that was registered to the
177 International Consortium for Brain Mapping (ICBM) template in the Montreal
178 Neurological Institute (MNI152) space. The obtained normalized and modulated tissue
179 probability maps of GM images were smoothed with a 3mm full width at half-maximum
180 (FWHM) smoothing kernel. Region of interest (ROI) masks were generated using the
181 WFU PickAtlas (http://www.nitrc.org/projects/wfu_pickatlas). Finally, we extracted the
182 mean modulated tissue probability map of GM (in-house script in MATLAB) for the 10
183 ROIs defined as entorhinal cortex: Brodmann areas 28 and 34; parahippocampal gyrus:
184 Brodmann area 36; cingulate gyrus: Brodmann areas 23, 24, 26, 29, 30, 31, 32 and 33;
185 hippocampus and mammillary bodies (Lancaster et al., 2000). We used the
186 Computational Anatomy Toolbox 12 (CAT12; <http://www.neuro.uni-jena.de/cat>) to
187 calculate total intracranial volume (TIV).

188 Cortical thickness and subcortical volumes estimations were obtained with
189 Freesurfer v6 (<http://surfer.nmr.mgh.harvard.edu>). Preprocessing pipeline used the fully-
190 automated “recon-all” command and included: normalization, removal of non-brain
191 tissues, Talairach transforms, segmentation and tessellation of GM and WM boundaries

192 (Fischl et al., 2004). The cortical surface of each hemisphere was parcellated according
193 to the atlas proposed by Desikan and colleagues (2006) with 34 cortical regions per
194 hemisphere; “aparc” segmentation). Cortical thickness was estimated as described
195 elsewhere (Han et al., 2006; Dale et al., 1999a; Dale et al., 1999b). Subcortical volumes
196 were obtained via whole-brain automatic “aseg” segmentation procedure (Fischl et al.,
197 2004). Mean cortical thickness was extracted (in-house script in MATLAB) for 16 ROIs
198 defined as: caudal anterior cingulate, rostral anterior cingulate, isthmus cingulate,
199 posterior cingulate, entorhinal, parahippocampal, thalamus and hippocampus.

200

201 ***Statistical analyses***

202 Kolmogorov–Smirnov and Levene’s tests were used to test normality and
203 homogeneity of demographic, clinical, neuropsychological and neuroimaging data,
204 respectively. Since Kolmogorov-Smirnov and Levene’s tests did not return any
205 significant result, we verified the differences regarding disease duration and age via one-
206 way analyses of variance (ANOVA) and Tukey’s HSD *post hoc* tests. Chi-square test was
207 used to check differences in sex. The processed imaging measures were fit to a general
208 linear model (GLM) considering ROIs as dependent variables, age (and TIV, for the VBM
209 data; Barnes et al., 2010) as a covariate, and sex as a fixed factor. Pairwise comparisons
210 for cognitive scores were obtained using the GLM, considering age as a covariate and sex
211 as a fixed factor. All tests were two-tailed, and the statistical significance threshold was
212 set at $p < 0.05$, Bonferroni’s correction where applicable.

213

214 **Results**

215 ***Demographical and clinical characteristics (Table 1)***

216 Chi-square test showed that ALS, bvFTD and HC groups were matched for sex
217 ($\chi^2 = 1.51, p=0.46$). One-way ANOVA indicated ALS and bvFTD demonstrated no
218 significant differences for disease duration [$F(1,29)=0.32, p=0.57$]. There was a
219 statistically significant difference in age between ALS and bvFTD patients (mean
220 difference = -10.63, $p=0.02$), with the latter group being older, although neither of the
221 groups differed from HC.

222

223 *Cognitive performance (Table 1)*

224 **Comparison with controls:** ALS and bvFTD patients showed significant difference in the
225 MMSE scores compared with HC (mean difference= -2.7, $p=0.02$; mean difference= -
226 3.1, $p=0.004$, respectively). In naming, incidental memory and recognition tasks, ALS
227 and bvFTD groups did not differ from HC. In immediate recall, ALS score was not
228 statistically significant from HC, but bvFTD showed lower performance compared with
229 HC (mean difference= -2.09, $p=0.001$). In delayed recall, the pairwise comparison
230 showed no significant differences between ALS and HC, but bvFTD showed lower
231 performance compared with HC, with 7 patients scoring below the cut off score (mean
232 difference= -2.3, $p=0.007$). Figure 1 illustrates performances on the delayed recall task.

233 Patient groups did not differ from HC in FAB or digit span. In animal fluency, no
234 significant difference was found between ALS and HC, but bvFTD showed lower scores
235 compared with HC (mean difference= -7.67, $p<0.001$). In the FAS test, ALS did not differ
236 from HC, but bvFTD performed worse compared with HC (mean difference= -18.93,
237 $p<0.001$).

238 **Comparison between patient groups:** No difference was found in the MMSE total scores,
239 between ALS and bvFTD. Naming, incidental memory and recognition performances of
240 ALS compared with bvFTD were not statistically different, but there was a difference in

241 immediate recall, with bvFTD performing worse (mean difference= -1.7, p=0.01). In the
242 delayed recall task, bvFTD showed significantly worse performance as well (mean
243 difference= -1.9, p=0.03). ALS and bvFTD showed no statistically significant difference
244 in FAB and digit span. In animal fluency, there was significant difference between ALS
245 and bvFTD (mean difference= -6.25, p=0.004), with the latter group presenting lower
246 scores. In the FAS test, there was a significant difference comparing ALS with bvFTD
247 (mean difference= -13.08, p=0.02), with bvFTD underperforming ALS.

248

249 [insert Table 1 here]

250 [insert Figure 1 here]

251

252 ***Voxel based morphometry***

253 All VBM results were Bonferroni corrected for multiple comparisons.

254 ***Comparison with controls:*** We did not find significant differences in GM between ALS
255 and HC in any ROI. When contrasting bvFTD and HC, the former group showed
256 significantly more atrophy in all Papez circuit structures of both hemispheres (all mean
257 difference \leq -0.02, all p \leq 0.05). Supplementary Table 1 shows VBM results.

258 ***Comparison between patient groups:*** bvFTD showed significant more atrophy than ALS
259 in the left hemisphere for cingulate gyrus (mean difference= -0.04, p=0.02), hippocampus
260 (mean difference= -0.1, p=0.05), entorhinal cortex (mean difference= -0.06, p=0.02) and
261 mammillary body (mean difference= -0.03, p=0.04), and in the right hemisphere for
262 parahippocampal gyrus (mean difference= -0.05, p=0.04), entorhinal cortex (mean
263 difference= -0.07, p=0.01) and mammillary body (mean difference= -0.04, p=0.03).

264 Figure 2 and 3 illustrate Papez circuit GM comparison between patient groups.

265

266 [Insert Figure 2 here]

267

268 [Insert Figure 3 here]

269

270

271

272 ***Cortical thickness and subcortical volumes***

273 All results were Bonferroni corrected for multiple comparisons.

274 ***Comparison with controls:*** No significant difference in cortical thickness (given in mm)

275 and subcortical volumes in any ROIs were found comparing ALS with HC. bvFTD

276 patients showed reduced cortical thickness compared with HC in the left hemisphere for

277 rostral anterior cingulate (mean difference= -0.32, $p=0.01$), entorhinal cortex (mean

278 difference= -0.74, $p<0.001$), and in the right hemisphere for entorhinal cortex (mean

279 difference= -0.87, $p<0.001$) and parahippocampal gyrus (mean difference= -0.41,

280 $p=0.003$). Supplementary Table 2 shows cortical thickness measures.

281 ***Comparison between patient groups:*** bvFTD patients showed significant cortical

282 thickness reduction compared with ALS, in the left hemisphere for rostral anterior

283 cingulate (mean difference= -0.31, $p=0.01$), isthmus cingulate (mean difference= -0.24,

284 $p=0.01$), entorhinal cortex (mean difference= -0.58, $p=0.01$) and in right hemisphere for

285 entorhinal cortex (mean difference= -0.51, $p=0.01$). Figure 4 and 5 illustrate cortical

286 thickness differences between patient groups.

287

288 [Insert Figure 4 here]

289

290 [Insert Figure 5 here]

291

292 **Discussion**

293

294 This is the first study to compare the classic Papez network between ALS and

295 bvFTD. Our data revealed no delayed recall impairment in ALS, which was corroborated

296 by preserved GM of the Papez circuit. At the group level, bvFTD patients performed
297 slightly above the limits of normality, but a subgroup of patients showed very poor
298 performance characterizing an amnesic profile. Marked atrophy of the Papez circuit
299 structures was evidenced in both amnesic and non-amnesic subgroups of bvFTD. We
300 showed distinct memory profiles in our cohort of ALS and bvFTD supported by different
301 characteristics of structures composing the Papez circuit.

302 Memory profile in ALS varies widely among studies from no deficits (Hsieh et
303 al., 2016) to deficits even in short-term delays (Massman et al., 1996). This large variation
304 suggests that some ALS patients might present marked EM impairment. Beeldman and
305 colleagues (2018) showed in their meta-analysis that verbal memory impairment is
306 consistently found in ALS. However, the identification of patients with memory
307 impairment may be hampered by the relatively low number of subjects included in the
308 studies or even the different tests employed. MRI findings also differ and show memory-
309 related structures either preserved or with distinct changes (Bueno et al., 2018); Machts
310 et al., 2018; Buhour et al., 2017; Raaphorst et al., 2015) and this may be related to the
311 inclusion of patients predominantly in early disease stages.

312 Likewise, bvFTD patients with marked episodic memory deficits are described in
313 the literature (Hornberger et al., 2010; Pennington et al., 2011; Bertoux et al., 2014;
314 Ramanan et al., 2017). Accordingly, MRI studies also show changes in the Papez circuit
315 or components of this system in bvFTD (Hornberger et al., 2012; de Souza et al., 2013;
316 Wong et al., 2016). Marked GM atrophy of the Papez circuit is present in bvFTD patients,
317 but interestingly, our cohort of bvFTD patients had very high performances in the
318 recognition task and this could suggest that the memory difficulties present could be
319 related to an executive dysfunction problem instead of a genuine episodic memory deficit.

320 Although much attention has been traditionally given to hippocampal atrophy,
321 changes in anterior cingulate are suggested to be a better candidate to distinguish bvFTD
322 from Alzheimer’s disease (AD; Hornberger et al., 2012). In ALS, studies have also
323 focused on the hippocampal region (Abdulla et al., 2014; Raaphorst et al., 2015). Here
324 we show left anterior cingulate and left hippocampal changes in bvFTD while these
325 regions are spared in ALS. Hornberger and colleagues did not report mammillary bodies
326 atrophy in their bvFTD cohort despite significant fornix damage. Importantly, marked
327 bilateral entorhinal and bilateral mammillary bodies atrophy distinguished bvFTD from
328 ALS in our study.

329 Our study has important limitations that must be acknowledged. First, the small
330 sample size in each group limits the generalizability of our findings, hence our analyses
331 must be replicated in larger cohorts. Importantly, patients in late stages were not included
332 in the ALS group. This could influence the results as memory problems and brain changes
333 in the memory circuit could be marked in more advanced stages as suggested by *post-*
334 *mortem* neuropathological studies showing TDP-43 depositions in memory related
335 structures in ALS (e.g., hippocampus; Brettschneider et al., 2013), as well as TDP-43 is
336 shown to reflect in characteristic damage of WM in bvFTD patients (Kassubek et al.,
337 2018). Additionally, our ALS population consisted on patients who could be classified as
338 “pure ALS” as they did not show frontal/executive changes to qualify for ALS with
339 cognitive impairment (Strong et al., 2017) and though this was not purposely done, we
340 recognize that the inclusion of an ALS group with cognitive changes would enrich the
341 study. Another important limitation is that our study is based on clinical diagnosis with
342 no pathological confirmation. Furthermore, genetic information is not available. It is well
343 established that ALS patients with C9orf72 mutations are suggested to be more prone to
344 cognitive impairment (Strong, 2017), as well as bvFTD patients carrying this mutation

345 may show different cognitive profiles. Moreover, we acknowledge that not only GM
346 atrophy influences episodic memory performance, therefore the analyses of other
347 parameters (e.g., WM of fornix, cingulum bundle among others) should be carried out.
348 WM analyses have proven to be useful in the study of TDP-43 spread (Gorges et al., 2018
349 Kassubek et al., 2018); and therefore, investigations of WM memory related structures
350 could bring new insights into the study of episodic memory deficits in ALS and bvFTD.
351 We also suggest more exhaustive cognitive assessment to better characterise the nature
352 and extension of the memory deficits. And finally, we recognize that educational levels
353 should be included as an important covariate in studies of the MTL.

354 Pennington and colleagues (2011) have shown that bvFTD and AD patients can
355 present similar performances on episodic memory tests, but the deficits have different
356 neural correlates, with AD presenting prominent temporal lobe atrophy while bvFTD
357 presents more frontal lobe changes. In our study, bilateral atrophy of entorhinal cortex
358 and mammillary bodies distinguished bvFTD from ALS patients as well as atrophy in left
359 cingulate, left hippocampus and right parahippocampal gyrus, however in other studies
360 these regions are shown to be affected in ALS. Further studies are still warranted to clarify
361 memory impairments in ALS and if they differ from bvFTD, as well as how the Papez
362 circuit is affected in both conditions.

363

364 **Authors contributions**

365 APAB preprocessed MRI images, performed statistical analyses, drafted and edited the
366 manuscript; LCS diagnosed the patients and performed cognitive assessments, drafted
367 and revised the manuscript; WHLP supervised MRI preprocessing, prepared MRI figures
368 and revised the manuscript; ALT diagnosed the patients, worked on financial support for
369 MRI acquisition and revised the manuscript; LGRP has worked on patient selection, on

370 financial support for MRI and revised the manuscript; PC diagnosed the patients and
371 revised the manuscript; MH conceived the study and revised the manuscript; JRS
372 supervised MRI preprocessing and statistical analyses, and revised the manuscript. All
373 authors approved the final version of the manuscript.

374

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384

385 **Conflict of Interest**

386 The authors report no conflict of interest.

387

388 **Ethical approval**

389 All procedures performed in this study were in accordance with the ethical standards of
390 national research committee, the institutional ethics committee of Universidade Federal
391 de Minas Gerais and with the 1964 Helsinki declaration and its later amendments or
392 comparable ethical standards.

393 **Informed consent**

394 Written informed consent was obtained from all individual participants included in the
395 study or from a close relative.

396

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