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

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Abstract

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

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

Introduction

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

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

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

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

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

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

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

Materials and methods

Participants

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

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

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

Neuropsychological assessments

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

MRI acquisition and analyses

Participants underwent whole-brain MRI on a 3T Philips scan. T_1-weighted images were acquired as follows: multi-shot 256 TFE factor (TR/TE 5.4/2.4ms, 256x256

matrix, FOV 256x256x180, flip angle 8º), slice thickness 1mm, coronal orientation, voxel size 1x1x1mm^3.

We performed VBM analyses using the Statistical Parametric Mapping 12 (SPM12; http://www.fil.ion.ucl.ac.uk/spm). The MRI data were preprocessed following a standard protocol. First, the anterior commissure of all images was set as the origin of spatial coordinates. Segmentation algorithm bias-corrected the T_1-weighted images for inhomogeneities and generated rigid-body aligned GM and white matter (WM) of the subjects. The DARTEL algorithm (Ashburner, 2007) estimated the nonlinear deformations that best aligned all images together by iteratively registering the imported images with their average, creating a mean template that was registered to the International Consortium for Brain Mapping (ICBM) template in the Montreal Neurological Institute (MNI152) space. The obtained normalized and modulated tissue probability maps of GM images were smoothed with a 3mm full width at half-maximum (FWHM) smoothing kernel. Region of interest (ROI) masks were generated using the WFU PickAtlas (http://www.nitrc.org/projects/wfu_pickatlas). Finally, we extracted the mean modulated tissue probability map of GM (in-house script in MATLAB) for the 10 ROIs defined as entorhinal cortex: Brodmann areas 28 and 34; parahippocampal gyrus: Brodmann area 36; cingulate gyrus: Brodmann areas 23. 24, 26, 29, 30, 31, 32 and 33; hippocampus and mammillary bodies (Lancaster et al., 2000). We used the Computational Anatomy Toolbox 12 (CAT12; http://www.neuro.uni-jena.de/cat) to calculate total intracranial volume (TIV).

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

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

Statistical analyses

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

Results

Demographical and clinical characteristics (Table 1)

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

Cognitive performance (Table 1)

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

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

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

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

[insert Table 1 here]

[insert Figure 1 here]

Voxel based morphometry

All VBM results were Bonferroni corrected for multiple comparisons.

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

Comparison between patient groups: bvFTD showed significant more atrophy than ALS in the left hemisphere for cingulate gyrus (mean difference= -0.04, p=0.02), hippocampus (mean difference= -0.1, p=0.05), entorhinal cortex (mean difference= -0.06, p=0.02) and mammillary body (mean difference= -0.03, p=0.04), and in the right hemisphere for parahippocampal gyrus (mean difference= -0.05, p=0.04), entorhinal cortex (mean difference= -0.07, p=0.01) and mammillary body (mean difference= -0.04, p=0.03). Figure 2 and 3 illustrate Papez circuit GM comparison between patient groups.

[Insert Figure 2 here]

[Insert Figure 3 here]

Cortical thickness and subcortical volumes

All results were Bonferroni corrected for multiple comparisons.

Comparison with controls: No significant difference in cortical thickness (given in mm) and subcortical volumes in any ROIs were found comparing ALS with HC. bvFTD patients showed reduced cortical thickness compared with HC in the left hemisphere for rostral anterior cingulate (mean difference= -0.32, p=0.01), entorhinal cortex (mean difference= -0.74, p<0.001), and in the right hemisphere for entorhinal cortex (mean difference= -0.87, p<0.001) and parahippocampal gyrus (mean difference= -0.41, p=0.003). Supplementary Table 2 shows cortical thickness measures.

Comparison between patient groups: bvFTD patients showed significant cortical thickness reduction compared with ALS, in the left hemisphere for rostral anterior cingulate (mean difference= -0.31, p=0.01), isthmus cingulate (mean difference= -0.24, p=0.01), entorhinal cortex (mean difference= -0.58, p=0.01) and in right hemisphere for entorhinal cortex (mean difference= -0.51, p=0.01). Figure 4 and 5 illustrate cortical thickness differences between patient groups.

[Insert Figure 4 here]

[Insert Figure 5 here]

Discussion

This is the first study to compare the classic Papez network between ALS and bvFTD. Our data revealed no delayed recall impairment in ALS, which was corroborated

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

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

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

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

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

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

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

Authors contributions

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

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

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Conflict of Interest

The authors report no conflict of interest.

Ethical approval

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

Informed consent

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

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