Different patterns of gray matter atrophy in behavioral variant frontotemporal dementia with and without episodic memory impairment

Running title: Atrophy patterns in amnestic and non-amnestic frontotemporal dementia

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ABSTRACT: 244 words/250

Background: Differentiating patients with behavioral variant frontotemporal dementia (bvFTD) from Alzheimer's Disease (AD) is important as these two conditions have distinct treatment and prognosis. Using episodic impairment and medial temporal lobe atrophy as a tool to make this distinction has been debatable in the recent literature, as some patients with bvFTD can also have episodic memory impairment and medial temporal lobe atrophy early in the disease. **Objectives:** To compare brain atrophy patterns of patients with bvFTD with and without episodic memory impairment to that of patients with AD. **Methods:** We analyzed 19 patients with bvFTD, 21 with AD and 21 controls, matched by age, sex and years of education. They underwent brain MRI and the memory test from the Brief Cognitive Battery (BCB) to assess episodic memory. We then categorized the bvFTD group into amnestic (BCB delayed recall score <7) and non-amnestic. **Results:** The amnestic bvFTD group (n=8) had significant gray matter atrophy in the left parahippocamal gyrus, right cingulate and precuneus regions compared with the non-amnestic group. Compared with AD, amnestic bvFTD had more atrophy in the left fusiform cortex, left insula, left inferior temporal gyrus and right temporal pole, whereas patients with AD had more atrophy in the left hippocampus, left frontal pole and left angular gyrus. **Conclusions:** There is a group of amnestic bvFTD patients with episodic memory dysfunction and significant atrophy in medial temporal structures, which poses a challenge in considering only these features when differentiating bvFTD from AD clinically.

Keywords: episodic memory, frontotemporal dementia, gray matter, neuroimaging, Alzheimer's disease

Key points: patients with behavioral variant Frontotemporal dementia can have impairment in visual episodic memory with temporal lobe atrophy, even when compared with patients with amnestic Alzheimer's disease.

INTRODUCTION

The distinction between Alzheimer's disease (AD) and behavioral variant frontotemporal dementia (bvFTD) is often a challenge in clinical practice. Although AD biomarkers in the cerebrospinal fluid and in positron emission tomography amyloid images are increasingly helping in this distinction, they are not often available because of high costs. Furthermore, there is a considerably rate of false positives for AD biomarkers, especially at older ages[1]. The hallmark of AD dementia is a progressive episodic memory impairment underpinned mainly by hippocampal atrophy, while bvFTD is classically defined by prominent and progressive behavioral changes underpinned by frontal and anterior temporal lobe atrophy. Although episodic memory sparing is one of the criteria to define bvFTD, patients with this condition have worse episodic memory than controls [2, 3] and a subgroup of patients can have episodic memory deficits as severe as those observed in AD patients [4-8] alongside similar degree of hippocampal atrophy [9]. Therefore, episodic memory impairment and medial temporal lobe atrophy might not be helpful in clinically distinguishing these two disorders. Conversely, there is also a group of patients with AD that present with prominent behavioral changes and executive dysfunction. They are called frontal variant of AD posing a greater challenge to clinically distinguish bvFTD from AD [10,11].

Understanding the neural correlates of episodic memory impairment in AD and bvFTD might help unveil distinct brain structural-functional relationships in the context of different brain pathologies. Previous studies have found that the neural correlates of verbal episodic memory impairment in the two disorders might be distinct. In bvFTD patients, verbal episodic memory impairment correlated with hypometabolism [7] and gray matter atrophy [8] in frontal regions, while in AD patients verbal episodic memory impairment correlated with hypometabolism in mesial parietal [7] and temporal regions [3]. However, the neural correlates of visual episodic memory are poorly investigated.

Furthermore, it is unknown whether the brain atrophy patterns of patients with bvFTD with episodic memory impairment is different from those with AD. A previous study compared amnestic and non-amnestic bvFTD patients in terms of brain metabolism and found that amnestic-bvFTD patients had lower metabolism in bilateral anterior parahipocampal and inferior temporal gyri than non-amnestic-bvFTD patients [3], suggesting a medial temporal lobe involvement in amnestic bvFTD patients. Although differences in brain metabolism have been described, possible differences in brain atrophy between amnestic bvFTD patients and AD have not been explored.

In the present study we used structural MRI to explore the neural correlates of visual-verbal episodic memory impairment in patients with bvFTD and AD using a mask targeting specific brain regions related to episodic memory. We also compared the gray matter atrophy patterns of amnestic and non-amnestic bvFTD patients with and without episodic memory impairment, and compared those groups with the atrophy patterns of patients with AD.

METHODS

Population

Three group of participants were included in this study: Patients with probable AD dementia (n=21) per the National Institute of Aging diagnostic criteria [12], patients with clinically probable bvFTD (n=19) per the 2011 bvFTD diagnostic criteria [13] and healthy controls (n=21). Patients were recruited at a tertiary memory clinic in Belo Horizonte, Brazil. The diagnosis of clinically probable AD and bvFTD was made by a consensus panel formed by neurologists, geriatricians, psychiatrists and neuropsychologists and was based on the clinical history, neuropsychological testing and neuroimaging. A subgroup of participants underwent lumbar puncture to collect cerebrospinal fluid to measure Aβ42, total tau and phosorilated tau using methods described previously [14]. The Innotest Amyloid-Tau Index (IATI)

(Aβ42/(240+1.18 x Tau)) [15] was used to determine the biomarker profile of AD. An IATI index <1 was considered positive for AD and an IATI index >=1 was considered negative.

Healthy control individuals were matched by age, sex, education and socioeconomic status with both groups of patients and they did not have any psychiatric disorder. Exclusion criteria both for patients and control groups were the presence of other neurological syndromes such as primary progressive aphasia, Parkinson's disease, vascular dementia, Lewy body dementia, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, severe traumatic brain injury, brain aneurism and brain tumors.

All patients and controls signed the written informed consent. The Ethical Committee of the Federal University of Minas Gerais approved the study, that was conducted per the Declaration of Helsinki standards.

Cognitive assessment

The Mini-Mental State Exam (MMSE) was used to assess global cognition [16].

The Brief Cognitive Battery (BCB) was used to assess episodic memory. The BCB is a visual-verbal memory test that consists of identifying and naming 10 simple figures, learning the figures in three consecutive trials and, after interference activities of clock drawing and animal's fluency for one minute, free-recalling the figures previously learned. The free recall is also called delayed recall and is assessed five minutes after learning the figures. Later on, participants need to recognize the figures amongst 10 other unrelated drawings [17]. Note that the participants do not need to draw the figures, but verbally recall them. The delayed recall is considered a proxy of episodic memory, with worse scores associated with hippocampal atrophy [18]. The BCB has similar accuracy than other tests like the CERAD list-of-words to differentiate patients with dementia from controls [19] and has been validated as a diagnostic tool to identify episodic memory impairment in dementia [17, 20, 21].

Executive functioning was tested with the frontal assessment battery (FAB) [22] that evaluates aspects such as conceptualization, attention, mental flexibility, programming, sensitivity to interference and inhibitory control. Verbal phonemic verbal fluency (F.A.S) [23] was used to assess generativity and the Stroop and the Hayling tests to assess inhibitory control [24].

The short version of the Social and Emotional Assessment (Mini-SEA) was used to assess social cognition [25]. The Mini-SEA is composed by the Theory of Mind test, in which participants need to identify socially inappropriate aspects (also called *Faux pas*) of 10 stories and the Facial Emotion Recognition Test [26]. In The Facial Emotion Recognition Test, participants need to match each of the 35 images from the Ekman database [27] to one of the seven different facial emotions (happiness, sadness, fear, disgust, surprise, anger, and neutral). The total Mini-SEA score is calculated by adding the Facial Emotion Recognition Test and *Faux Pas* scores in which lower scores mean worse social cognition [28].

Severity of apathy symptoms was assessed using the Apathy Scale [29, 30]. Caregivers from the patients with bvFTD and AD completed the Apathy Scale, while healthy controls answered the scale as a self-report questionnaire.

Definition of amnestic-bvFTD and non-amnestic-bvFTD groups

The group of amnestic-bvFTD patients scored less than seven on the BCB delayed recall score, while non-amnestic bvFTD scored seven or more. The cut-off point of seven was used for two reasons. Firstly, because seven was the score's median in the bvFTD group. The histogram and boxplot with the distribution of delayed recall scores in the bvFTD group is in the supplementary figure 1 (online only). Secondly, because a previous normative study with 240 participants showed that a score below 7 is highly predictive of an amnestic syndrome [31].

Statistical analysis

All variables had a non-parametric distribution per the Shapiro-Wilk test. Mann-Whitney or Kruskal-Wallis (when appropriate) were used to compare differences in age, years of education, years of disease duration, as well as differences on the cognitive scores. The Fisher test was used to compare differences in proportion of males.

To determine whether deficits in episodic memory measured by the delayed recall test were associated with frontal lobe dysfunction in patients with bvFTD, we correlated the delayed recall (outcome) with the FAB scores (predictor) using linear regression, after log-transforming the variables. We ran this analysis in the whole bvFTD group and then separately in the amnestic and non-amnestic-bvFTD groups.

Finally, we correlated all the cognitive tests with the delayed recall scores in the amnestic and non-amnestic-bvFTD groups calculating the Spearman correlation coefficient.

The R Studio statistical package version Version 1.1.414 – © 2009-2018 RStudio, Inc was used to conduct the statistical analyses and the level of significance was set at $p<0.05$.

Neuroimaging acquisition and preprocessing

Three dimensional T1-weighted images were acquired for all participants in a 3 Tesla Philips Achieva scanner using the same protocol (sagittal plane acquisition with spin-echo echoplanar sequences, TR/TE=16/4ms, matrix=240x240). The time between the brain scan and the cognitive tests was less than 3 months for all participants, except for one bvFTD patient, that was 6 months. Brain-extracted images were segmented into gray and white matter and cerebrospinal fluid and the gray matter images and their respective mirror images were registered to the gray matter MNI-152 template. All the registered gray matter images and the mirror images were concatenated into a 4-dimensional image and averaged to create

the study-specific template at 2x2x2 mm^3 resolution in standard space. All the gray matter images were non-linearly registered to the study-specific template and linked together into a 4-dimensional image dividing each voxel of each gray matter image by the Jacobian of the warp field. This process scales the final statistical maps for total gray matter volume, automatically correcting for differences in the head size of participants. The modulated images were then smoothed with an isotropic Gaussian kernel with a standard deviation of 3mm (full width half maximum=8 mm). All the above-described preprocessing steps were conducted in FSL version 5.0 [32, 33] using the FSL-VBM pipline [34].

Neuroimaging analysis

All analyses were carried out in specific brain regions previously associated with episodic memory functioning per functional MRI experiments. Those regions were defined by a metanalysis of 332 studies of task-based functional MRI [35]. We used these previously defined regions as a mask to restrict our statistical analyses only to voxels that are relevant to episodic memory functioning. We used a mask to a priori define our analyses instead of the standard exploratory voxel-based morphometry to increase the specificity of the findings to episodic memory-related brain regions.

First, we contrasted the disease groups with controls to explore specific patterns of atrophy in each disease (AD versus controls, bvFTD versus controls, bvFTD versus AD). Then, we correlated the delayed recall scores with the gray matter volumes to determine the correlates of episodic memory in each group (including the controls).

Finally, we contrasted the amnestic-bvFTD with the non-amnestic bvFTD to determine whether the amnestic-bvFTD had more atrophy in temporal lobe regions that could explain a worse episodic memory in this group. At last, we contrasted the amnestic-bvFTD with AD, and the non-amnestic-bvFTD

with AD to determine whether the atrophy patterns that underlie the amnestic syndrome in bvFTD are similar to AD.

Each above-described analysis was carried out separately using general linear models covarying by age. We used permutation-based non-parametric testing corrected for multiple comparisons by family-wise error correction across space and an extended cluster threshold of 50 voxels. This threshold of 50 voxels or less has been previously used in the literature [36, 37]. The level of significance was considered as $p<0.05$. All the imaging processing was conducted in FSL 5.0 [32]. We used the Harvard-Oxford Structural Atlas to label the regions correspondent to the significant voxels.

RESULTS

Overall, the mean age of participants was 66.5 (±10.1), the mean years of education was 12.6 (3.3) and 31 (50.8%) were male. The clinical diagnosis of AD was confirmed by a CSF biomarker positive profile in 13/21 patients with clinically defined AD. In 5/19 patients with clinically defined bvFTD, the CSF biomarkers for AD were negative. The remaining participants did not have the CSF available.

Participants with AD, bvFTD and controls had similar age, years of education and proportion of males, as well as patients with AD and bvFTD had similar disease duration (Table 1).

Participants with AD and bvFTD performed worse than controls in all cognitive tests, except for the recognition of the emotions of happiness and fear (Table 1). Participants with AD had worse visual-verbal episodic memory than the patients with bvFTD (Table 1), while participants with bvFTD had worse performance in social cognitive tests and more severe apathy symptoms than AD patients (Table 1).

Comparing amnestic-bvFTD (n=8) and non-amnestic-bvFTD (n=11) patients, we found similar age, educational level and proportion of males (Table 2). Amnestic and non-amnestic-bvFTD patients

performed similarly at executive function and social cognition tests (Table 2) and had similar severity of apathy symptoms.

The executive functioning assessed through the FAB scores did not correlate with the delayed recall score in the whole bvFTD group (R^2= 0.06 p= 0.295), neither in the amnestic (R^2= 0.00 p= 0.999) nor the non-amnestic-bvFTD groups (R^2=0.04, p =0.542) (Supplementary figure 2, online only). Looking at the correlations between delayed recall scores and scores in all the other tests, beyond the expected significant correlation with the learning phase of the memory test, the only other significant correlation was between episodic memory and the recognition of fear in the amnestic bvFTD group (Supplementary figure 3, online only).

Atrophy patterns in bvFTD and AD

Using the mask that restricted the analyses to brain regions relevant to episodic memory processing, we found that participants with AD had significantly more atrophy in medial temporal, parietal, and posterior cingulate regions compared to controls (Supplementary figure 4, online only). Participants with bvFTD had also more medial temporal lobe atrophy and atrophy of the posterior cingulate and cerebellar regions (Supplementary figure 4, online only). We failed to find significantly more atrophy in participants with bvFTD when compared with AD, using the mask (Supplementary figure 4, online only).

Visual-verbal episodic memory dysfunction correlated with hippocampal atrophy in bvFTD and AD

In patients with AD, worse delayed recall scores correlated with bilateral hippocampal atrophy, as well as left precuneus and posterior cingulate atrophy (Supplementary figure 5, online only). In patients

with bvFTD, worse delayed recall scores also correlated with bilateral hippocampal atrophy (Supplementary figure 5, online only)

Amnestic and non-amnestic bvFTD patients had different atrophy patterns, that were different from AD

Contrasting the atrophy patterns of amnestic-bvFTD and non-amnestic-bvFTD, we found that the amnestic-bvFTD group had more atrophy on the left temporal fusiform cortex and left parahippocampal gyrus, as well as on the right cingulate and right precuneus (Figure 1, panel A). The non-amnestic-bvFTD had more atrophy on the right fornix and left angular gyrus than the amnestic-bvFTD (Figure 1, panel B).

Contrasting the atrophy patterns of the amnestic-bvFTD group with the AD group, the amnestic-bvFTD had more atrophy in temporal areas adjacent to the hippocampi bilaterally, as well as the left insular cortex and the right cerebellum (Figure 2, panel A). Contrasting AD patients with amnestic bvFTD, we found that patients with AD had more atrophy in the left hippocampus, frontal pole and angular gyrus (Figure 2, panel B). Finally, contrasting the non-amnestic-bvFTD group with the AD group, the non-amnestic-bvFTD had more atrophy in the middle temporal gyrus (Figure 3, panel A). Conversely, the AD group had more atrophy in the bilateral hippocampi, left parahippocampal gyrus, left cingulate gyrus and left frontal pole (Figure 3, panel B).

DISCUSSION

Patients with bvFTD with visual-verbal episodic memory impairment had different patterns of brain atrophy than bvFTD patients without episodic memory impairment. Those atrophy patterns were also different than those of AD patients. Amnestic-bvFTD patients had more atrophy on peri-hippocampal and parietal regions than non-amnestic-bvFTD, similar to the pattern of hypometabolism previously

described [3], as well as more atrophy on peri-hippocampal, insular and cerebellar regions than patients with AD. These results support the emerging concept that clinically differentiating bvFTD from AD based only on episodic memory dysfunction and mesial temporal lobe atrophy can be challenging. Identifying other atrophy patterns beyond mesial temporal lobe may be more helpful. For instance, using a grading system to visually rate parietal and orbitofrontal atrophy worked better to differentiate AD from frontotemporal lobe degeneration [38].

In our study, visual-verbal episodic memory impairment correlated with bilateral hippocampal atrophy, both in bvFTD and AD patients suggesting that the visual component of episodic memory might be more hippocampal dependent in these patients, especially because we did not find any association between memory and executive dysfunction. Although a previous study found bilateral hippocampal atrophy in bvFTD and AD patients with prospective memory dysfunction [39], most studies correlated memory dysfunction with lateral-temporal and frontal atrophy in bvFTD [5-8, 40]. The visual component of the BCB test and its hippocampal "dependency" might explain the discrepancy.

Amnestic bvFTD patients had more cerebellar and insular atrophy than patients with AD, calling attention for the possible role of the cerebellum and insula in episodic memory dysfunction in bvFTD. Previous research suggested that cerebellar atrophy in bvFTD patients correlated with attention and working memory performance [41], important steps for episodic memory processing. Interestingly, a recent study found that changes in cerebellar white matter correlate with episodic memory in bvFTD [42]. The role of the insula in episodic memory could be explained by its possible modulation of the default mode network [43, 44] a set of brain regions believed to be activated at rest and deactivated when focused on external cognitive activities, like episodic memory tasks [45]. Furthermore, a study reported left insular activation during episodic memory tests in patients with right hippocampal sclerosis [46]. The intensity of activation correlated with better episodic memory function, suggesting that the insula might play a

(compensatory) role when there is hippocampal dysfunction. Further exploring the role of cerebellar and insular atrophy in episodic memory dysfunction in amnestic bvFTD patients may unveil novel mechanisms of episodic memory dysfunction in bvFTD.

This study has strengths and limitations. The patients were well characterized clinically and a subset of them had the diagnosis supported by AD biomarkers. It was also the first time that the neural correlates of a visual memory test were directly compared between AD and bvFTD.

Limitations include the small number of participants, especially when splitting bvFTD patients into amnestic and non-amnestic. Another limitation is that we did not have a specific measurement of disease severity other than disease duration. Because we did not have AD biomarkers available for all the participants it was challenging to rule out with certainty the possibility that some patients had the frontal variant of AD. However, the deep neuropsychological profiling that the participants underwent, including socioemotional cognition assessment, increase the confidence on the clinical diagnosis. Although we recognize that disease severity is highly heterogenous in bvFTD, the median of disease duration was 3 years for non-amnestic bvFTD and 4 years for amnestic bvFTD. Therefore, because most participants were relatively early in the disease course, we do not believe that more advanced disease staging is driving episodic memory impairment in the amnestic group. Also, one can argue that the amnestic bvFTD group has a worse MMSE than the non-amnestic, but the MMSE not always reflect disease staging [47] and is highly dependent upon preserved episodic memory and medial temporal lobe structures [48, 49]. Thus, patients with worse memory tend to perform worse on the MMSE, regardless of disease severity.

Another limitation was the lack of genetic analysis, which prevented us from determining whether the differences we found in atrophy patterns of amnestic and non-amnestic-bvFTD could be associated to a particular genetic profile such as the *C9orf72* expansion. A previous study found that in bvFTD patients with the *C9orf72* expansion, the neural correlates of episodic memory dysfunction was related to frontal,

temporal and parietal lobes, as opposed to sporadic bvFTD in which episodic memory deficits were related to medial prefrontal, medial and lateral temporal cortices [50].

Often times clinicians rely only on the absence of episodic memory impairment and on the absence of medial temporal lobe atrophy to differentiate bvFTD from AD. Our findings suggest that this strategy may be tricky, exposing the need to develop new ways to clinically distinguish these two conditions, especially considering that the treatment is different and that AD biomarkers are expensive and not ubiquitously available. Our results corroborate the need to develop specific biomarkers for bvFTD, mainly not exclusively based on episodic memory impairment and absence of mesial temporal lobe atrophy.

DATA AVAILABILITY STATEMENT

The raw data is available for researchers under reasonable request.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest related to the present study.

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TABLES

Table 1: Demographics and neuropsychological performance across controls and patients with AD and bvFTD

	Controls n=21	**AD n=21**	**bvFTD n=19**	**p value**
Male n (%)	8 (38.1)	11 (52.4)	12 (63.2)	0.281
Age	67.0 [56.0, 70.0]	74.0 [64.0, 77.0]	66.0 [57.0, 71.0]	0.106
Years of education	11.0 [11.0, 15.0]	14.0 [11.0, 16.0]	11.0 [11.0, 14.0]	0.651
Disease duration (years)	-	2.50 [2.0, 3.0]	3.0 [2.0, 4.5]	0.140
BCB Naming	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	10.0 [9.0, 10.0]	0.035 *
BCB Learning	10.0 [9.0, 10.0]	6.0 [6.0, 8.0]	8.0 [6.0, 10.0]	<0.001*, **
BCB Delayed Recall	9.0 [9.0, 10.0]	4.0 [3.0, 5.0]	7.0 [5.5, 9.0]	<0.001*, **, ***
BCB Recognition	10.0 [10.0, 10.0]	10.0 [9.0, 10.0]	10.0 [10.0, 10.0]	0.020 *, **
MMSE	29.0 [29.0, 30.0]	24.0 [24.0, 26.0]	26.0 [23.5, 27.5]	<0.001 *, **
FAB	15.0 [14.7, 17.0]	13.0 [11.0, 15.0]	12.0 [9.0, 14.0]	0.001 *, **
Animals/min	19.0 [17.0, 21.0]	12.0 [9.0, 14.0]	10.0 [7.0, 13.0]	<0.001 *, **
Phonemic fluency total	31.5 [28.5, 37.2]	25.0 [18.0, 36.0]	14.0 [10.0, 22.0]	0.001*, **, ***
Stroop inhibition (time)	31.5 [26.5, 38.7]	42.0 [35.0, 57.0]	36.0 [32.0, 43.0]	0.01 *, **
Faux Pas total	36.5 [34.2, 38.7]	31.0 [30.0, 34.0]	24.0 [14.0, 27.0]	<0.001 *, **, ***
Hayling part B (Errors/15)	6.5 [4.0, 9.7]	9.0 [7.0, 11.0]	12.5 [9.2, 15.0]	0.004 *, **, ***
Ekman emotion recognition (total)	27.0 [27.0, 30.0]	26.0 [25.0, 28.0]	23.0 [15.5, 25.0]	<0.001 *, **, ***
Happiness	5.0 [5.0, 5.0]	5.0 [5.0, 5.0]	5.0 [5.0, 5.0]	0.212
Surprise	5.0 [4.0, 5.0]	4.0 [4.0, 5.0]	3.0 [2.0, 5.0]	0.028 *, **
Disgusting	5.0 [4.2, 5.0]	4.0 [3.0, 5.0]	3.5 [1.2, 4.0]	0.003 *, **
Fear	1.5 [1.0, 3.0]	2.0 [1.0, 3.0]	1.5 [0.2, 2.0]	0.702
Angry	4.0 [3.0, 4.0]	4.0 [3.0, 4.0]	2.0 [2.0, 3.0]	0.011 *, ***
Sadness	4.0 [4.0, 5.0]	3.0 [2.0, 4.0]	2.0 [1.0, 3.0]	0.001 *, **
Neutral	5.0 [4.2, 5.0]	5.0 [5.0, 5.0]	4.5 [2.0, 5.0]	0.021 *, **, ***
Apathy scale	7.0 [3.2, 9.0]	16.5 [11.5, 21.7]	27.5 [19.5, 31.5]	<0.001 *, **, ***
Mini-SEA	26.6 [24.3, 27.5]	23.2 [20.3, 25.6]	19.04 [12.4, 20.3]	<0.001 *, **, ***

Values are depicted in median and interquartile intervals

AD: Alzheimer's disease; BCB: Brief Cognitive Battery, bvFTD: behavioral variant frontotemporal dementia; FAB: Frontal Assessment Battery, MMSE: Mini Mental-State Exam, Mini-SEA: Short version of the Social and Emotional Assessment

* Controls x bvFTD ** Controls x AD *** bvFTD x AD

Table 2: Demographics and neuropsychological comparisons between the amnestic-bvFTD and non-amnestic-bvFTD patients.

	Amnestic-bvFTD n=8	Non-amnestic-bvFTD n=11	Controls n=21	p value
Male n (%)	4 (50.0)	8 (72.7)	8 (38.1)	0.177
Age (years)	61.0 [54.7, 71.2]	67.0 [58.0, 71.0]	67.0 [56.0, 70.0]	0.800
Years of education	12.5 [11.7, 15.2]	11.0 [11.0, 11.0]	11.0 [11.0, 15.0]	0.204
Disease duration (years)	4.0 [3.0, 4.2]	3.0 [2.0, 5.0]	NA	0.426
MMSE	23.5 [22.2, 26.0]	27.0 [24.5, 28.0]	29.0 [29.0, 30.0]	<0.001*,**,***
BCB naming	10.0 [9.7, 10.0]	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	0.085 *,**
BCB Learning	5.5 [5.0, 6.5]	10.0 [8.5, 10.0]	10.0 [9.0, 10.0]	<0.001 *,**,***
BCB Delayed Recall	4.5 [2.7, 6.0]	9.0 [7.5, 9.0]	9.0 [9.0, 10.0]	<0.001 *,**,***
BCB recognition	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	0.368
FAB	10.5 [7.5, 13.0]	13.0 [11.0, 15.0]	15.0 [15.0, 17.0]	0.001 *,**
Animals/min	8.5 [7.0, 11.5]	13.0 [8.5, 15.0]	19.0 [17.0, 21.0]	<0.001 *,**
Phonemic fluency total	12.0 [9.5, 19.5]	16.0 [10.5, 26.0]	31.5 [28.5, 37.2]	0.001 *,**,
Stroop inhibition (time)	36.0 [29.2, 43.7]	36.5 [32.0, 42.2]	40.5 [34.0, 52.5]	0.566
Faux Pas total	21.5 [11.5, 26.0]	27.0 [15.8, 29.0]	31.0 [28.5, 34.0]	0.644
Hayling part B (Errors/15)	12.5 [6.7, 15.0]	12.5 [10.2, 15.0]	9.0 [6.0, 11.0]	0.445
Ekman emotion recognition (total)	24.5 [15.0, 25.2]	21.5 [17.7, 24.7]	26.0 [21.5, 27.5]	0.427
Happiness	5.0 [5.0, 5.0]	5.0 [5.0, 5.0]	5.0 [5.0, 5.0]	0.241
Surprise	3.0 [1.7, 4.2]	3.5 [2.2, 5.0]	5.0 [4.0, 5.0]	0.847
Disgusting	3.0 [2.5, 4.2]	4.00[1.2, 4.0]	4.0 [3.0, 4.0]	0.579
Fear	2.0 [0.7, 2.2]	1.0 [0.2, 2.0]	1.0 [0.0, 2.5]	0.154
Angry	2.0 [1.7, 4.0]	2.5 [2.0, 3.0]	4.0 [2.0, 4.0]	0.138
Sadness	1.5 [1.0, 4.0]	2.5 [1.2, 3.0]	3.0 [1.0, 4.0]	0.522
Neutral	4.5 [3.5, 5.0]	4.5 [2.0, 5.0]	5.0 [4.0, 5.0]	0.024
Apathy scale	27.5 [24.0, 30.5]	26.5 [18.2, 31.5]	18.0 [11.0, 29.0]	0.511
Mini-SEA	19.4 [10.7, 20.1]	18.6 [17.2, 20.5]	23.33 [19.5, 25.7]	0.463

Values are depicted in median and interquartile intervals

AD: Alzheimer's disease; BCB: Brief Cognitive Battery, bvFTD: behavioral variant frontotemporal dementia; FAB: Frontal Assessment Battery, Mini-SEA: Short version of the Social and Emotional Assessment; MMSE: Mini Mental-State Exam, *Controls x Non-amnestic **Controls x Amnestic ***Amnestic x non-amnestic

FIGURES CAPTIONS

Figure 1: Contrasting the atrophy patterns of the amnestic-bvFTD and non-amnestic bvFTD groups.

Panel A shows the significant clusters of less gray matter volume in amnestic- behavioral frontotemporal dementia (bvFTD) compared with non-amnestic. Panel B shows the significant clusters of less gray matter volume in non-amnestic-bvFTD compared with amnestic. Both analyses used Family Wise Error correction for multiple comparison analyses and a p value of 0.05, adding age as a covariate. A mask was used to restrict the analyses only to brain regions previously associated with episodic memory tasks from fMRI studies [35] . The brain regions were labeled using the Harvard-Oxford Structural Atlas. The color bar represent the p value. The coordinates (X,Y, Z) were placed per the Montreal Institute Neuroimaging (MNI) template and the images are displayed in radiological convention.

Figure 2: Contrasting the amnestic-bvFTD and the AD groups.

Panel A shows the significant clusters of less gray matter volume in patients with amnestic-behavioral frontotemporal dementia (bvFTD) compared with those with Alzheimer's dementia (AD). Panel B shows the significant clusters of less gray matter volume in AD patients compared with those with amnestic-bvFTD. Both analyses used Family Wise Error correction for multiple comparison analyses and a p value of 0.05, adding age as a covariate. A mask was used to restrict the analyses only to brain regions previously associated with episodic memory tasks from fMRI studies [35] . The brain regions were labeled using the Harvard-Oxford Structural Atlas. The color bars represent the p value (red for the amnestic-bvFTD – AD

contrast and blue for the AD – amnestic-bvFTD contrast). The coordinates (X,Y, Z) were placed per the Montreal Institute Neuroimaging (MNI) template and the images are displayed in radiological convention.

Figure 3: Contrasting the non-amnestic-bvFTD and the AD groups.

Panel A shows the significant clusters of less gray matter volume in patients with non-amnestic-behavioral frontotemporal dementia (bvFTD) compared with those with Alzheimer's dementia (AD). Panel B shows the significant clusters of less gray matter volume in AD patients compared with those with non-amnestic-bvFTD. Both analyses used Family Wise Error correction for multiple comparison analyses and a p value of 0.05, adding age as a covariate. A mask was used to restrict the analyses only to brain regions previously associated with episodic memory tasks from fMRI studies [35] . The brain regions were labeled using the Harvard-Oxford Structural Atlas. The color bars represent the p value (red for the non-amnestic-bvFTD – AD contrast and blue for the AD – non-amnestic-bvFTD contrast). The coordinates (X,Y, Z) were placed per the Montreal Institute Neuroimaging (MNI) template and the images are displayed in radiological convention.