Effect of bilingualism on the cognitive and neuroimaging features of behavioural-variant frontotemporal dementia

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DEDICATORY

I would like to dedicate this work to my parents and sister, for their support during my whole academic path. Thank you for suffering with me.

I would also like to dedicate it to Alvaro, for standing always next to me and encouraging me to do my best. Thank you for all your love and unconditional support.
ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my supervisor Alexandre Bejanin for offering me the opportunity to participate in this project, for all the wisdom and knowledge he has shared, and for providing me with constant feedback to improve.

A special mention to Gemma Piella, for her support throughout my studies. Thank you for your constant willingness to help.

Finally, I would also like to acknowledge all the members of the Memory Unit at Hospital de la Santa Creu i Sant Pau for allowing me to collaborate and learn with them.
ABSTRACT

Current research suggests that modifiable lifestyle factors can enhance the “cognitive reserve” and protect against age related cognitive decline. Hence, bilingualism, which is thought to improve executive functions, has recently been suggested to help patients coping with large brain damage before presenting symptoms, and therefore, delay the onset of dementia. The current project aims to provide a further understanding of the effect of bilingualism on the cognitive, behavioural, and neuroimaging features of the behavioural-variant frontotemporal dementia (bvFTD). Thirty monolingual bvFTD, twenty-six bilingual bvFTD, and fifty-six age and education matched normal controls (NC) underwent neuropsychological and neurological examinations, and a high-quality Magnetic Resonance Imaging (MRI) by specialists in the Memory Unit at Hospital de la Santa Creu i Sant Pau. Linear regression models were conducted to assess the effect of bilingualism on the behavioural and cognitive measurements. Voxel-wise analyses were performed to further test differences in grey matter (GM) volumes between monolingual and bilingual patients. Our results did not evidence that bilingual bvFTD patients have a later age of onset or age at diagnosis than monolinguals patients. Moreover, bilingualism was not associated with differences in cognitive and behavioural performances, even when controlling for disease duration. Finally, neuroimaging analyses showed GM atrophy in the prefrontal cortex and medial temporal regions in bvFTD patients. However, we did not find significant differences in brain volume between bilinguals and monolinguals patients, even when controlling for the level of cognitive impairment. Overall, this study does not support that bilingualism has a positive effect in bvFTD. These results may indicate a bias of positivity in the current literature concerning bilingualism and dementia, and requires some additional study.

KEYWORDS

Bilingualism; cognition; frontotemporal dementia; grey matter; imaging; MRI; voxel-wise analyses.
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1. INTRODUCTION

Life expectancy is higher than ever before, and it is predicted to increase continuously in industrialized countries. Ageing is the highest risk factor for dementia, so an increase in the mean age of the population yields an increase in dementia’s prevalence. Epidemiological studies suggest that 35.6 million people had dementia worldwide in 2010, and this number is expected to reach 115.4 million people in 2050 [1] as each year about 9.9 million new dementia cases are diagnosed worldwide [2].

Dementia describes a group of symptoms affecting cognitive and social abilities severely enough to interfere with daily life activities. Dementias are essentially caused by neurodegenerative diseases, which are characterized by the accumulation of abnormally folded protein(s) in the intra and/or extracellular compartment of the brain. These pathological proteins disrupt cellular functioning and eventually cause the dysfunction and death of the neurons and/or glia. This neurodegeneration causes progressive defects on neuronal networks and lead to cognitive and behavioural deficits. This pathological cascade can start years before the first symptoms arise, and the clinical manifestation appears once irreversible damages within functional networks are present [3].

The deterioration in cognitive functions alter patient’s and caregivers’ daily lives. With no effective pharmacological treatment to cure neurodegenerative diseases [2], preventing and/or delaying dementia onset has become a health- and social-care priority for many high-income countries. Several recent studies [4],[5] have presented that up to a third of dementia cases may be preventable by targeting modifiable risk factors such as education, exercise, diet, social engagements, smoking, and cardiovascular disease [6]. Some of these non-pharmacological alternative approaches are aimed to stimulate the cognitive functions and therefore, delay the cognitive decline. One of these cognitive enhancement activities is bilingualism, the ability to speak more than one language [2]. In the current thesis, we will focus on the impact of bilingualism on one specific group of dementias: the Frontotemporal Dementia (FTD).

1.1 Frontotemporal dementia

FTD groups clinical syndromes characterized by progressive deficits in behaviour, executive function, or language. It is the third most common type of dementia, and one
of the most prevalent in patients younger than 65 years [7]. The age of onset of FTD commonly ranges between 45 and 65 years, even though some patients can enter into the disease in their twenties and up to their nineties. FTD can be either sporadic (none of the relatives are known to have FTD) or caused by genetic mutations. The most common genetic causes of FTD are mutations in microtubule-associated protein tau (MAPT), granulin (GRN), and hexanucleotide repeat expansions in chromosome 9 open reading frame72 (C9ORF72). These mutations account for 20–30% of the familial and 5–10% of sporadic FTD cases [8]. Epidemiological studies of FTD showed that the mean survival time from symptom onset is 8 years, and this duration decreases abruptly once the clinical diagnosis is made [7]. As previously mentioned, no approved drug is available, and the only medications prescribed aim at alleviating the behavioural symptoms.

FTD syndromes arise from frontotemporal lobar degeneration (FTLD), a pathological term denoting the progressive degeneration of the frontal and temporal cortices. FTLD is caused by intracellular aggregates of tau, TDP-43 or FUS proteins. Each of these FTLD pathological subtypes can result in different FTD syndromes: the behavioural variant FTD (bvFTD), non-fluent variant primary progressive aphasia (nvPAPPA) and semantic-variant primary progressive aphasia (svPPA). While behavioural deficits predominate in the bvFTD, the nvPAPPA and svPPA are characterized by a decline in linguistic skills: nvPAPPA presents specific deficits in speech and grammar, whereas svPPA shows disorders in semantic memory and naming. More details can be seen in Figure 1.

Figure 1. Clinicopathological representation of FTD.
1.1.1 bvFTD

The most common FTD syndrome is the bvFTD. In Europe and the USA, it encompasses 50-70% of all FTD syndromes [7]. Its main symptoms are apathy, personality changes, and disinhibition. Behavioural disinhibition can result in inappropriate social behaviour such as new criminal attitudes, impulsive actions, or embarrassing personal remarks. Loss of sympathy or empathy toward the relatives is also a very common symptom. Patients also show stereotyped behaviours, including repetitive movement, eating disorders, or neglect of hygiene [7]. Most often, bvFTD patients are not aware of their impairments and the clinical history relies on the report of the caregiver. Informants often report weight gain, disregard for others’ feelings, or increased consumption of sweets and/or alcohol in patients. Patients with bvFTD show deficits in various executive tasks very early [7], whereas memory and visuospatial deficits are unusual at the early stages of the disease [3]. Gradually, the patients develop global cognitive and motor impairments, leading to difficulties when eating or moving.

Symptoms are frequently mistaken for primary psychiatric disorders such as depression, bipolar disease, or schizophrenia. The differential diagnosis relies on the family medical history, behaviour in the clinical visits, performances on neuropsychological tests, and neuroimaging data. The neuroimaging study consists of a structural magnetic resonance imaging (MRI) that measures GM atrophy, and a fluorodeoxyglucose (FDG)-positron emission tomography (PET) to assess metabolism. The most affected brain regions in bvFTD are the frontal and anterior temporal, most often in the right hemisphere [3]. Especially, GM atrophy and reduced metabolism are typically observed in the lateral and medial prefrontal cortex, insula, anterior, middle and posterior cingulate cortex, anterior temporal regions, amygdala, hippocampus, thalamus and caudate nucleus [9],[10]. As shown in Figure 2, the pattern of atrophy and hypometabolism extends over time into adjacent structures and the parietal lobe [10].

![Figure 2. Pattern of grey matter atrophy and hypometabolism in bvFTD patients compared to normal controls. Reproduced from [10] with permission. Figures represent the cross section of the two hemispheres of the brain.](image-url)
1.2 Cognitive reserve

Current research suggests that the clinical expression of dementia is modifiable by lifelong factors, which enhance the “cognitive reserve” and protect against cognitive decline” [11]. The concept of reserve has initially been proposed to explain that some individuals had pathology in the brain (such as Alzheimer’s disease) but did not develop any cognitive symptoms [12]. According to Yaakov Stern [13], the reserve can be categorised into passive and active models. The passive model refers to the quantitative brain measures, such as the brain size or neuronal count, that may help to tolerate brain injuries including neuropathology. By contrast, the active model refers to the flexible and efficient brain mechanisms that allow to use the available brain reserve [13],[14]. One of the most famous active models is the cognitive reserve (CR), which postulates that individual differences in the cognitive processes or neural networks underlying task performance allow some people to cope better than others with brain damage [15]. Therefore, the term CR emphasizes brain function and refers to the ability to optimize performance through differential recruitment of brain networks [13]. In other words, individuals with high CR are able to maintain normal cognitive functioning for a longer time than those with low CR in the context of neurodegenerative disease. Concretely, this means that CR delays the onset of cognitive symptoms and shifts the inflexion point of cognitive decline (Figure 3). However, this inflexion means that clinical diagnosis for dementia will be later even for the same level of pathology. In other words, patients with higher CR will be diagnosed later but with a more severe pathology. Therefore, their clinical progression will be faster [15].

Lifelong factors positively influencing CR include education, occupational attainment, socioeconomic status, engagement in leisure and social activities, and the lifelong or regular use of two or more languages [14],[16]. Most studies support that these lifelong factors may act via direct neuroprotective or indirect compensatory mechanisms [14]. In addition, they are considered to be good predictors of which individuals can sustain greater brain damage before presenting clinical symptoms [13] (Figure 3B).
Figure 3. Theoretical illustration of how cognitive reserve may influence (A) the relationship between Alzheimer's Disease (AD) pathology and its clinical symptoms [15]. (B) Adaptation of Fig.3A to our study: we assume that bilingual bvFTD patients have a higher cognitive reserve than monolingual bvFTD patients. The x-axis represents the neurodegeneration (i.e., as measured with brain atrophy) and the y-axis represents the cognitive function.

1.3 Bilingualism

Recent investigations suggest that bilingualism provides advantages in executive functions, cognitive ageing and brain plasticity, and delays the onset of dementia symptoms [17]. The constant management of two languages is being studied as a training for executive functions. Bilinguals perform constant activation on executive control processes such as monitoring, selecting, and inhibiting across languages. Thus, bilinguals are shown to exhibit better general executive abilities compared to monolinguals [16]. Lifelong usage of these executive functions can induce changes in brain plasticity that make the brain more resistant against the deleterious effects of ageing [18]. This effect seems most evident when the second language is acquired early in life or used proficiently [16].

Bilingualism has been associated with increased GM and white matter (WM) volumes in brain regions involved in cognitive control, including the left inferior frontal gyrus, anterior cingulate cortex, inferior parietal lobule, and basal ganglia [2],[17],[18]. However, the specific effect of bilingualism on dementia has not been extensively studied, but evidence suggests that lifelong management attention to two languages reorganizes specific brain networks, enhances executive control, and sustains better cognitive performance throughout the lifespan [2],[19]. Therefore, these results in healthy participants suggest that bilingualism could increase the CR and therefore impact the clinical course of dementia [16].
In Alzheimer’s disease, a recent study assessing brain metabolism (a direct index of synaptic function and density), showed higher cerebral hypometabolism in bilinguals suffering from the disease than monolinguals [18]. Despite this hypometabolism, bilingual patients outperformed monolinguals on different memory tasks, suggesting that bilingual AD patients were able to compensate for the loss of brain structure and function [18].

Concerning FTD, little work is available. Only one study from Alladi and colleagues has been published [11]. It reports that bilingualism delays the age at onset for 6 years in the bvFTD. Surprisingly, no effect of bilingualism was observed in the aphasic variants of FTD. According to the authors, bilingualism has different effects depending on the cognitive domains involved, with strong positive effects on executive functions and a weak effect on the language [11]. Moreover, results showed that the brain regions associated with executive functions, such as the dorsolateral prefrontal cortex, remain intact at the initial stages of bvFTD, which may allow patients to compensate for more anterior and medial frontal deficits.

1.4 Objectives

To our knowledge, no study assessed specifically the effect of bilingualism on the neurodegeneration in patients with FTD. Hence, the objective of this project is to evaluate the influence of bilingualism on the cognitive and neuroimaging features of bvFTD. Specifically, we aim to assess the effect of bilingualism on i) the age of onset, ii) the cognitive and behavioural impairments and iii) the GM volume of bvFTD. Given the beneficial effects reported in the literature, including in Alzheimer’s disease [18] and bvFTD [11], we hypothesize that bilingualism will delay the age of onset in the bvFTD. We also expect that, for the same level of brain injury, bilingual patients will have a higher CR than monolinguals (see Figure 3) and thus, will perform better than them on cognitive and behavioural tests. Finally, we also expect that once we control for disease severity, the bilingual will have less GM volume than monolinguals as they are able to tolerate more brain damage for the same level of cognitive deficits.
2. METHODS

2.1 Participants

Participants were recruited at Hospital de la Santa Creu i Sant Pau by the Sant Pau Initiative on Neurodegeneration cohort (http://santpaumemoryunit.com) [20]. All subjects received detailed neurological and neuropsychological evaluations and underwent a structural 3T brain MRI scan.

The normal controls (NC) did not have memory complaints, scored between 27 and 30 at the Mini-Mental State Examination (MMSE) [21], 0 at the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) [22], and did not show significant impairment in daily living activities.

From the whole Memory Unit’s database, we selected all those patients whose diagnosis was of possible or probable bvFTD according to the frontotemporal dementia consortium criteria [23]. Moreover, patients were followed-up by specialists to evaluate if they continued presenting a progressive clinical deterioration or started to present suggestive signs of second-related FTLD syndromes as motor neuron disease. If that was the case, they were taken out of the study. In the end, our cohort was composed of 112 participants: 56 bvFTD patients and 56 NC.

Based on the information provided by the informant, the neurologist estimated the age of onset, which corresponded to the manifestation of first symptoms. Age at diagnosis was established as the one the patient had when the neuropsychological evaluation was done.

2.2 Evaluation of bilingualism

During the neuropsychological evaluation, subjects were asked for their native language. The neuropsychologists classified the participants as bilingual if they had an equal management of at least 2 languages. Additionally, we considered all native Catalan speakers as bilingual given that most of them are able to understand, speak and write in Spanish. Monolingual participants only included Spanish speakers.
2.3 Behavioural and cognitive evaluation

All participants underwent an exhaustive neuropsychological battery assessing the main cognitive domains. Specifically, the level of global cognitive impairment was assessed using the MMSE and CDR-SOB. The MMSE is a cognitive mental status examination that evaluates cognitive aspects of mental functions, excluding questions concerning mood, abnormal mental experiences, and the form of thinking [21]. The maximum MMSE score is 30 points. A score of 20 to 24 is considered mild dementia, 13 to 20 as moderate dementia, and a score below 12 is considered severe dementia. CDR-SOB is a tool to assess disease severity for dementia [22]. The CDR-SOB ranges between 0 and 18, 18 being the worst score. A score below 4 corresponds to a questionable cognitive impairment, 4.5-9 to a mild dementia, 9.5-15.5 to a moderate dementia, and 16-18 to a severe dementia.

Executive functions were evaluated with the forwards and backward digits from the Wechsler Memory Scale, design (60 seconds) fluencies, and modified Trail Making A&B tests. Episodic memory was assessed using the immediate and delayed free recall from the Free and Cued Selective Reminding Test, delayed free recall, and recognition items from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) and the delayed recall of the Benson figure. Semantic memory was assessed using the spontaneous Boston Naming Test, comprehension (for 5 and 15 items), and category fluency (60 seconds, animals). Finally, visuospatial and visuoconstructive functions were evaluated with the Poppelreuter test, clock order, copy trial of the Benson figure, and Number Location condition from the Visual Object Spatial Perception. To obtain composite scores for each cognitive domain, we used the mean and standard deviation of the NC to convert raw cognitive scores into Z-scores. Subsequently, patient Z-scores were averaged within each cognitive domain. Z-scores were harmonized so that a lower Z-score corresponded to performance a similar to NC group.

Besides this neuropsychological evaluation, data on the patient’s behaviour were collected with the informant/caregiver. Specifically, the Neuropsychiatric Inventory (NPI) was used to assess a wide range of behaviours common in dementia including delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviours, night-time behavioural disturbances and eating disturbances [24]. Informants also filled out other behavioural scales more specific to the
behavioural disturbance proper to the bvFTD including the Frontal Behavioural Inventory (FBI) [25], Cambridge Behavioural Inventory (CBI) [26] and Frontotemporal Dementia Rating Scale (FRS-FTD%). Besides, the neurologist and/or neuropsychologist used the Social Behaviours Observer Checklist (SBOC) to rate the behaviours observed during the clinical interview, such as the insensitivity, inappropriate familiarity, or stimulus bound behaviour [27]. Except for the FRS-FTD%, for which it is the opposite, a higher score at this scale reflects more behavioural difficulties.

2.4 Acquisition and preprocessing of MRI data

All subjects underwent a high-resolution T1-weighted anatomical image. Most MRI (n = 100) were acquired using a 3D field echo sequence on a 3 T Phillips Achieva scanner (time of repetition = 8.1 ms, time of echo = 3.7 ms, slice thickness = 1 mm, voxel size = 0.94 x 0.94 x 1 mm) at Hospital del Mar (Barcelona, Spain). Remaining MRI (n = 12) were acquired using a high-resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence on a 3 T Siemens TrioTrim scanner (time of repetition = 2300 ms, time of echo = 2.98 ms, slice thickness = 1 mm, voxel size = 1 x 1 x 1 mm) at Hospital Clínica de Barcelona (Barcelona, Spain).

We performed the neuroimaging data processing using the Statistical Parametric Mapping Version 12 (SPM12) software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, England) implemented in MATLAB R2017 (The MathWorks, Sherborn, MA). Specifically, the preprocessing pipeline was performed using the CAT12 Toolbox and is illustrated in Figure 4. The first steps included i) the bias correction to correct the inhomogeneity of the magnetic field that depends on both the scanner and the subject, ii) segmentation into different tissue classes (GM, white matter (WM) and CSF) and iii) spatial normalization to the common space, i.e., Montreal Neurological Institute (MNI). As each step improved the quality of the others, all these 3 steps were performed iteratively to optimize the final results. GM maps were then modulated by scaling with the number of volume changes due to spatial registration so that the total amount of GM in the modulated image remained the same as in the original. Finally, GM images were smoothed in SPM using an 8 mm full-width at half-maximum Gaussian kernel. The quality of the segmentation and normalization was visually assessed, and all pre-processed images passed a standard quality control procedure.
2.5 Statistical analysis

All the demographic, cognitive, and behavioural analyses were performed using RStudio (RStudio Team, 2019), an integrated development environment for the programming language R (R CoreTeam, 2019).

First, we used the R library `matchControl` [28] to match NC to patients for demographic and bilingualism data. Specifically, we used a 1:1 ratio to select the NC that were the most similar to bvFTD patients for age, bilingualism, and years of education.

Second, to compare the demographic data across the groups, we assessed the normality of continuous variables distribution using a Shapiro normality test. For normally distributed variables, we used ANOVA and two-sample t-tests to compare the groups. Kruskal-Wallis test and Wilcoxon-Mann-Whitney were used for variables that did not follow a normal distribution. Pairwise comparisons were adjusted for multiple testing (Tukey when normal-distributed and Benjamini & Hochberg method otherwise).

In order to assess the effect of bilingualism on the behavioural and cognitive measurements, we conducted linear regression models to compare monolingual bvFTD to bilingual bvFTD. In these models, age and years of education were entered as covariates. Also, we performed these models controlling for disease duration. According to the CR model, bilingual bvFTD patients are expected to be less cognitively impaired than monolinguals for the same level of disease duration. To adjust for disease duration, we considered 2 variables: i) the disease duration per se, which was calculated as the time difference between disease onset and neuropsychological assessment; and ii) the overall
GM volume as an objective biological measurement of disease progression. The overall GM volume was extracted from the estimation of Total Intracranial Volume (TIV) performed in SPM12 for each subject.

Finally, we used SPM12 to perform voxel-wise analyses to assess differences in GM volumes across the groups of interest. Different statistical analyses were conducted: an ANOVA, which allowed us to compare all possible combinations across bvFTD and NC subgroups; and several two-sample t-tests to compare the bvFTD monolinguals to bvFTD bilinguals (see Figure 5 for more information on the VBM (Voxel-based morphology) analyses performed). To account for different brain sizes, we included the TIV in all VBM analysis. Analyses were repeated adding demographic (age and/or years of education) and cognitive measurements as covariates (MMSE, CDR-SOB, and Frontotemporal Dementia Rating Scale (FRS-FTD%)). MMSE and CDR-SOB were chosen as global measurements of disease severity. However, due to the difficulty to correctly evaluate disease severity in bvFTD, we also considered the FRS-FTD% test, which evaluates disease progression in FTD.

The voxel-wise analyses were limited to a GM mask. This mask included voxels with a GM probability higher than 0.3 in the mean GM map of the NC. For all neuroimaging analyses, a statistically significant threshold of \( p < 0.001 \) uncorrected, with a cluster extent \( k > 100 \) mm\(^3\) was used.

<table>
<thead>
<tr>
<th>VBM</th>
<th>Two-sample t-test</th>
<th>bvFTD monolingual vs bvFTD bilinguals</th>
<th>TIV and demographic CoV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>TIV and disease duration CoV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TIV and CDR-SOB CoV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TIV and MMSE CoV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TIV and FRS-FTD% CoV</td>
</tr>
<tr>
<td>ANOVA (Full factorial)</td>
<td></td>
<td>bvFTD vs NC</td>
<td>TIV and demographic CoV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bvFTD monolinguals vs NC</td>
<td>TIV and demographic CoV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bvFTD bilinguals vs NC</td>
<td>TIV and demographic CoV</td>
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<tr>
<td></td>
<td></td>
<td>bvFTD monolinguals vs NC monolinguals</td>
<td>TIV and demographic CoV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bvFTD bilinguals vs NC bilinguals</td>
<td>TIV and demographic CoV</td>
</tr>
</tbody>
</table>

**Figure 5.** Description of the statistical analyses performed. Statistical tests are summarized in the second column, groups to be compared are in the third column, and model covariates are in the last column. VBM: Voxel-Based Morphology; ANOVA: Analysis of Variance; CoV: covariates; TIV: Total Intracranial Volume.
3. RESULTS

3.1 Demographics

Our final sample included 112 participants, divided into 4 different subgroups: bilingual bvFTD (n = 26), monolingual bvFTD (n = 30), bilingual NC (n = 26), and monolingual NC (n = 30). Because of the match performed, the same proportion of bilinguals was distributed across diagnoses. All demographic information is shown in Table 1.

As expected by the 1:1 matching, the bvFTD and NC groups did not differ significantly for age and years of education. However, the bvFTD group comprised a higher proportion of males. This is consistent with previous studies showing that bvFTD is more frequent in males than in females [29],[30]. As expected, both MMSE and CDR-SOB evaluations were significantly different between bvFTD and NC subgroups.

Table 1. Demographic data for each clinical subgroup

<table>
<thead>
<tr>
<th></th>
<th>B.bvFTD N=26</th>
<th>M.bvFTD N=30</th>
<th>B.NC N=26</th>
<th>M.NC N=30</th>
<th>B.bvFTD vs. M.bvFTD</th>
<th>M.bvFTD vs. M.NC</th>
<th>B.bvFTD vs. B.NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.5 [67.0;76.8]</td>
<td>75.0 [70.0;83.8]</td>
<td>68.5 [65.0;72.0]</td>
<td>71.0 [66.0;75.8]</td>
<td>0.214</td>
<td>0.121</td>
<td>0.272</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>19/7</td>
<td>22/8</td>
<td>11/15</td>
<td>11/19</td>
<td>1.000</td>
<td>0.042*</td>
<td>0.074</td>
</tr>
<tr>
<td>MMSE (/30)</td>
<td>27 [26;28]</td>
<td>25 [22;27]</td>
<td>29 [29;30]</td>
<td>29 [28.3;30]</td>
<td>0.026*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Years of schooling (years)</td>
<td>12.0 [8.2;17.5]</td>
<td>12.0 [8.2;15.0]</td>
<td>12.0 [10.0;17.5]</td>
<td>12.5 [8.2;16.0]</td>
<td>0.744</td>
<td>0.744</td>
<td>0.744</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>67.4 ±7.8</td>
<td>70.6 ± 6.9</td>
<td>N.A</td>
<td>N.A</td>
<td>0.101</td>
<td>N.A</td>
<td>N.A</td>
</tr>
<tr>
<td>Disease onset (years)</td>
<td>64.2 ± 7.2</td>
<td>66.1 ± 9.1</td>
<td>N.A</td>
<td>N.A</td>
<td>0.39</td>
<td>N.A</td>
<td>N.A</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>4.68 [2.37;5.81]</td>
<td>5.13 [3.04;7.8]</td>
<td>N.A</td>
<td>N.A</td>
<td>0.22</td>
<td>N.A</td>
<td>N.A</td>
</tr>
</tbody>
</table>

Values are median [1st quartile;3rd quartile] or mean ± standard deviation according to the normality of the distribution. p values refer to the Wilcoxon-Mann-Whitney test for continuous variables not normally distributed, and a two-sample t-test for normal continuous variables.

B.bvFTD: bilingual bvFTD; M.bvFTD: monolingual bvFTD; B.NC: bilingual normal controls; M.NC: monolingual normal controls. * Significant p-value at 0.05.
Comparisons between bilingual and monolingual patients with bvFTD showed no significant differences for any of the demographic variables (Table 1, Figure 6), including the educational level. The mean age at diagnosis was not significantly different (p = 0.1) between the bilingual (67.4 ± 7.8 years) and the monolingual bvFTD (70.6 ± 6.9). Similarly, the mean age at disease onset showed no significant difference (p = 0.39) between bilingual (64.2 ± 7.2) and monolingual (66.1 ± 9.1) bvFTD patients. Following the same trend as the other demographic values, disease duration median value was not significantly different (p = 0.22) between bilinguals (4.68) and monolinguals (5.13). Regarding the global measurements, both CDR-SOB and MMSE scores presented significant results (p = 0.03 each) between subgroups. According to the median obtained scores, the bilingual bvFTD subgroup was very mildly impaired, and the monolingual bvFTD subgroup was mildly impaired.

Figure 6. Clinical measurement in bvFTD patient. Boxplots show the age at disease onset, age at diagnosis, and disease duration in monolingual (orange) and bilingual (blue) bvFTD patients. The box represents the interquartile range, the band inside of it represents the median value, dots represent patients’ values. Value above each boxplot refers to the P-value for the two-sample t-test between monolingual and bilingual bvFTD.

3.2 Cognitive and behavioural performances

To assess the effect of bilingualism on cognitive and behavioural performances, we conducted linear regression models to compare bilingual bvFTD and monolingual bvFTD. Models were performed i) without covariates, and controlling for ii) demographic and iii) disease duration or iv) overall GM volume.
As shown in Table 2 and Figure 7, we did not observe any significant difference between bilingual and monolingual for any cognitive domain. However, there was a trend toward statistical significance (p < 0.1) between groups for the Executive and Visuospatial Functions, with better performances for bilingual bvFTD than monolingual bvFTD. Results remained highly similar when we controlled for demographic and disease progression covariates. The estimates and confidence interval further suggest no relationship between bilingualism and performance on cognitive and behavioural tests. Indeed, for all the statistical models, the 95% confidence interval included 0. Overall, as shown in Figure 7, there is a non-significant tendency for bilinguals to perform better in all tests and evaluations than monolingual bvFTD.

Table 2. Effect of bilingualism on neuropsychological and behavioural measurements

<table>
<thead>
<tr>
<th>Covariates</th>
<th>No covariate</th>
<th>Demographic</th>
<th>Demographic + disease duration</th>
<th>Demographic + overall grey matter volume</th>
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</thead>
<tbody>
<tr>
<td><strong>Cognitive domains</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive Functions</td>
<td>-1.33 [-2.89/0.23], p=.09</td>
<td>-1.02 [-2.58/0.54], p=.19</td>
<td>-1.02 [-2.61/0.57], p=.20</td>
<td>-0.66 [-2.17/0.85], p=.38</td>
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<td>Episodic Memory</td>
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<td>0 [-0.81/0.81], p=1.00</td>
<td>-0.01 [-0.84/0.82], p=.98</td>
<td>0.19 [0.6/0.97], p=.64</td>
</tr>
<tr>
<td>Semantic Memory</td>
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<td>-0.63 [-1.47/0.21], p=.14</td>
<td>-0.64 [-1.5/0.22], p=.14</td>
<td>-0.51 [-1.35/0.34], p=.23</td>
</tr>
<tr>
<td>Visuospatial Functions</td>
<td>-0.84 [-1.74/0.07], p=.07</td>
<td>-0.72 [-1.65/0.21], p=.13</td>
<td>-0.59 [-1.51/0.33], p=.20</td>
<td>-0.62 [-1.56/0.32], p=.19</td>
</tr>
<tr>
<td><strong>Behavioural scales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI total (n=50)</td>
<td>2.56 [8.04/13.16], p=.63</td>
<td>0.81 [-10.31/11.94], p=.88</td>
<td>-0.43 [-11.67/10.8], p=.94</td>
<td>2.33 [-8.99/13.66], p=.68</td>
</tr>
<tr>
<td>SBOC (n=39)</td>
<td>2.36 [0.82/5.54], p=.14</td>
<td>2.59 [-0.94/6.11], p=.14</td>
<td>2.22 [-1.39/5.84], p=.22</td>
<td>2.58 [-1/6.16], p=.15</td>
</tr>
<tr>
<td>FRS FTD % (n=39)</td>
<td>-6.92 [-18.74/4.9], p=.24</td>
<td>-4.15 [-16.08/7.77], p=.48</td>
<td>-4.14 [-16.2/7.92], p=.49</td>
<td>-2.73 [-14.84/9.38], p=.65</td>
</tr>
<tr>
<td>FBI (n=49)</td>
<td>4.58 [-1.55/10.71], p=.14</td>
<td>3.63 [-2.64/9.9], p=.25</td>
<td>4.6 [-1.46/10.65], p=.13</td>
<td>2.22 [-3.81/8.25], p=.46</td>
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<tr>
<td>CBI (n=29)</td>
<td>8.2 [-11.29/27.69], p=.40</td>
<td>2.59 [-16.5/21.68], p=.78</td>
<td>4.79 [-14.41/24], p=.61</td>
<td>-0.38 [-18.53/17.76], p=.97</td>
</tr>
</tbody>
</table>

Results of the linear regression models assessing the effect of bilingualism on cognitive and behavioural measurements. Results are presented as the estimated coefficient [low confidence interval/high confidence interval], p-value for the estimate. The confidence interval signifies the range in which the true population parameter lies at a 95% level of confidence. The statistical models were performed without covariate, and controlling for different covariates: demographic, and disease duration or overall grey matter volume. Demographic covariate includes age and years of education.

Notes: Behavioural tests are FBI: Frontal Behavioural Inventory; SBOC: Social Behaviour Observer Checklist. Data were not complete for each test. The number of participants that undertook each one is placed next to each name’s test.
Figure 7. Cognitive and behavioural data in monolingual and bilingual bvFTD patients. Boxplots show the composite Z-scores for (A) Executive functions, (B) Episodic Memory, (C) Semantic Memory, (D) Visuospatial Memory, and the global scores for (E) Neuropsychologic inventory, (F) SBOC, (G) FBI, (H) CBI, and (I) FRS-FTD%. The box represents the interquartile range, the band inside of it represents the median value, dots represent patients’ values. Value above each boxplot refers to the p-value for the model without covariates between monolingual and bilingual bvFTD. More behavioural or cognitive deficits are associated with lower Z-score and FRS-FTD% scores, and higher scores at the SBOC, FBI, and CBI.
3.3 Neuroimaging features

3.3.1 The pattern of GM atrophy in bvFTD

The whole-brain analysis revealed a characteristic pattern of GM atrophy in patients with bvFTD (Figure 8). As compared with NC, bvFTD patients showed less GM volume in lateral and medial prefrontal and temporal cortices. Specifically, the atrophy includes the middle and inferior temporal gyrus, insula, hippocampi, superior and inferior frontal gyrus, and middle cingulate gyri.

The comparison between the monolingual or bilingual bvFTD subgroups to the NC revealed very similar patterns of GM atrophy. The volume loss tended to be slightly more extended in the monolingual group, especially in the hippocampi, left middle temporal gyrus, middle cingulate, and right gyrus rectus.

Finally, results were essentially similar when each patient group was compared to its particular matched group of NC. Here again, the pattern of volume loss was slightly more extensive in the monolingual group than in the bilingual. Monolinguals presented larger atrophy in the hippocampi and middle cingulate than bilinguals.

3.3.2 GM volume reduction for the same level of cognition

To test if bilingual bvFTD patients are able to tolerate more brain damage for a similar level of cognitive impairment, we used two-sample t-tests to compare monolingual and bilingual bvFTD patients for brain volume while controlling for the severity of the symptoms using different covariates: disease duration, CDR-SOB, MMSE, and FRS-FTD%. We additionally performed the group comparisons with no covariates and the demographic data as covariate (age and years of education) for reference. The results of these analyses are illustrated in Figure 9.

Taking into account the literature, we expected that the bilingual bvFTD would have less GM volume than monolinguals for the same degree of disease severity. However, our analyses did not reveal any statistically significant results. Indeed, no brain region showed significantly less volume in bilinguals than monolinguals.

On the contrary, our results revealed less volume in monolinguals than bilinguals for some of the statistical models. These differences in volumes were found in hippocampi, left supplementary motor area, and left medial prefrontal cortex for the model without
covariates. Similar differences in left supplementary motor area and left medial prefrontal cortex were obtained for the models with the demographic and disease duration as covariates. However, these differences did not reach significance in the models controlling for the CDR-SOB, MMSE, or FRS-FTD% scores.

Figure 8. Clusters of significant grey matter atrophy in bvFTD patients when controlling for the Total Intracranial Volume, age, and years of education. Results show the cross-sections of the two hemispheres of the brain. Overall, bvFTD showed less grey matter volume in prefrontal and temporal cortices. Comparison between monolingual bvFTD or bilingual bvFTD to NC showed that monolinguals had larger volume loss in hippocampi, left middle temporal gyrus, middle cingulate, and right gyrus rectus than bilingual bvFTD. Results between same level of bilingualism showed that monolinguals had more brain loss in the hippocampi and middle cingulate than bilinguals. Results are displayed at the same statistical threshold of $p = 0.001$ (uncorrected) and cluster level threshold $k > 100 \text{ mm}^3$. The $t$-value measures the size of the difference relative to the variation in our sample data. L: left, R: right.
Figure 9. Grey matter regions showing differences in volume between bilingual and monolingual bvFTD. Results show the cross-sections of the two hemispheres of the brain. No brain region shows less volume in bilinguals than monolinguals. Models are controlled for different covariates. Demographic covariate includes age and years of education. Results are displayed at the same statistical threshold of $p = 0.001$ (uncorrected) together with a cluster size of $k > 100$ mm$^3$. L: left, R: right.
4. DISCUSSION

Existing literature suggests that bilingualism may protect the brain from the age-related cognitive decline and delay the symptoms of dementia onset [18],[19],[30]. However, the mechanisms underlying these effects are not well understood. In the present study, we aimed at providing a better understanding of the effect of bilingualism in bvFTD. Our results showed that bilingual patients with bvFTD did not have a later disease onset or any cognitive advantage as compared to the monolinguals. Similarly, neuroimaging results did not show any differences in brain volumes between bilingual and monolingual bvFTD patients. Altogether, these results question the real influence of bilingualism on the clinical trajectory of bvFTD.

Previous studies in AD have shown that the first symptoms can be delayed approximately 5 years in bilinguals [18],[31]. Alladi and colleagues [11] recently reported that bilingualism can also delay the age at onset in bvFTD 5.7 years. In the present study, we could not evidence that bilingualism delayed the onset of symptoms in bvFTD. In fact, our results showed that the bilinguals were, on average, diagnosed with bvFTD 2-3 years before the monolinguals. Results were similar when considering the age at diagnosis, with bilingual patients diagnosed 3 years before than monolinguals patients. Existing literature claims that the effect of bilingualism depends critically on the exact diagnosis and presentation [32], therefore we also wanted to compare whether the time between the appearance of first symptoms and neuropsychiatric evaluation was similar across patients. However, the results were practically identical. Hence, our results do not support that bilinguals have a later onset than monolinguals in bvFTD.

One may suggest that even though there was no difference in the age of onset, bilingual patients might be at a more advanced stage of the disease than monolingual when their symptoms started, as they should be able to tolerate more brain damage. We, therefore, assessed the cognitive and behavioural differences while controlling for disease duration. According to the CR models [16], we expected bilingual bvFTD patients to be less cognitively impaired than monolinguals. However, our results did not show significant differences in cognitive impairment across the groups and results were similar when we controlled for demographic covariates. Additionally, the confidence intervals in the linear regression models systematically included 0, suggesting that our results were dependent on the sample size.
Following the reserve theory and its compensation pattern, we also expected that, for the same degree of atrophy, bilingual bvFTD patients would show worse performances on behavioural and cognitive measurements. However, here again, we were unable to evidence significant results. Finally, we were also expecting that once we adjust for cognition, bilinguals would show less brain volume than monolinguals due to the compensation pattern. Once again, our results were the opposite and showed that bilinguals performed equally as monolinguals and did have more GM than them.

Altogether, our results are discrepant with the literature and do not argue in favour of a beneficial effect of bilingualism in bvFTD. Several explanations can be proposed to explain this discrepancy.

First, the effect of bilingualism might depend on the proximity of the language. In the previous study from Alladi [11], the languages assessed included English and various Indian languages, which are very different and do not share a lot of words. It has been suggested that the closer are the languages, the stronger are the effects of bilingualism as more attentional control is required to maintain separation between them [33]. In the present study, the languages studied were Catalan and Spanish, which are both derived from Latin and share a high percentage of words. Hence, taking into account the similarity of these languages, we would have expected stronger effects than those previously reported in the literature.

Second, the effect of bilingualism might be disease-specific. Most results were previously found in AD and not in bvFTD. Despite being both dementias, their neuropathology and symptoms are different. In addition, it is possible that the beneficial effect of bilingualism would be more constraint to the parietal cortex [34], which is sensible for AD and not for bvFTD.

Some limitations intrinsic to our study may also explain that we did not find significant associations with bilingualism. Ideally, bilingualism should be defined by objective measurements. However, in our study, we used the classification made by the neuropsychologists and/or neurologists, which was based on a single question about the patient’s native language. The evaluation did not include details on i) the number of languages, ii) the level of the communicative language skills or iii) the age of acquisition, which made overall a subjective assessment. Moreover, we decided to classify all Catalan individuals as bilingual as the vast majority of Catalan people speak and understand
Spanish [35]. Yet, we are aware that the degree of bilingualism might be very different among various Catalans, and that a deeper evaluation of communicative abilities (reading, writing, speaking, and understanding) is necessary. However, individuals can never be perfectly monolingual or bilingual, and all bilinguals have preferred languages [19] depending on the situations or the people they are addressing, which makes the assessment not 100% objective. In summary, bilingualism assessment is a complex task, but asking it objectively can provide us with very powerful information.

Finally, the discrepancy between our results and the literature might also be explained by a bias of publication in the literature. Our study presents what is known as negative results: findings suggesting no effect or opposite effect than what is already published [36]. It is known that negative results are more difficult to be accepted or published than positive results, which may distort the perception of available scientific evidence [37]. As an illustration, the proportion of positive results in scientific literature has increased in the last decades [38], and this trend has not gone unnoticed among scientists, who are continuously reproducing already published works. Several reasons may explain this bias of positivity. First, significant positive results might help the journals to increase their sales and impact factors [36]. Hence, positive findings tend to be more published in journals with higher impact factors, and this trend is specifically observed in the medical fields [37]. Second, interested parties, such as sponsors and pharmaceutical companies, do not have an interest in negative results as far as they do not obtain any benefit from them. Finally, another reason is the authors themselves, who may also lead to a citation bias by only recalling significant articles when reading the literature. Hence, disseminating negative results is currently complicated. This leaves negative findings unreported and induces useless expenditure of time and resources, as well as questioning whether the obtained results are the correct ones or not. Given that we were unable to reproduce some previously published results, especially concerning the beneficial effects of bilingualism, we wonder if the literature on it may also suffer from this bias of positivity. We reckon that upcoming studies including patients classified more objectively should be able to demonstrate and replicate our suspicion.

Besides the analyses focused on bilingualism, our results showed a pattern of frontotemporal atrophy in bvFTD patients. This is consistent with a previous study [9] that shows that the brain areas most affected in bvFTD include the frontal lobe (anterior medial frontal, gyrus rectus, and superior frontal) as well as the anterior cingulate, and
anterior insula. The frontal lobe is known to be particularly sensitive to the pathological process involved in bvFTD. Results showed the prefrontal cortex and temporal lobe as the most affected brain areas. Moreover, a notorious hippocampi atrophy was also found for bvFTD patients compared to NC.

Our study has some limitations. First, the sample size of our cohort was relatively small. However, it is important to remember that bvFTD is a rare dementia which is difficult to diagnose. Furthermore, if we compare our cohort to the one in Alladi and colleagues’ study [11], they had a bigger number of participants, however, our bilingual sample size was proportionally higher than theirs. Second, as previously commented, we used a subjective assessment of bilingualism. Therefore, a perspective of this work is to collect more accurate and detailed data concerning bilingualism to confirm our results. In this regard, we developed a new questionnaire in collaboration with the neuropsychologists of the Memory Unit (see in Appendices the Proposed questionnaire to assess bilingualism), which measures objectively all the communicative abilities and considers age at language acquisition and lifelong usage as well. To design it, we got inspired from different validated tests, such as the Language Experience and Proficiency Questionnaire [39], the Language History Questionnaire [40], and the Language and Social Background Questionnaire [41]. Our proposed questionnaire was built taking into account the trade-off between the most relevant communicative aspects and the constraint of the clinical interview, which needs to fit in the established interview time and to be written in a clearly and concisely enough way that demented patients can understand it unequivocally.

In conclusion, our study reveals negative results concerning the beneficial effect of bilingualism on bvFTD. Indeed, we were not able to find a significant association between bilingualism and the age of the first symptoms in bvFTD patients. Moreover, we could not demonstrate in our cohort that bilingualism increased the CR and allowed patients to tolerate more brain damage for the same level of cognitive impairment. Given these results, we suspect the existence of a bias of positive results in the literature concerning the positive effect of bilingualism on dementia, and we encourage to reproduce studies to verify that the observed results are not an isolated case.
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**Figure 8.** Clusters of significant grey matter atrophy in bvFTD patients when controlling for the Total Intracranial Volume, age, and years of education. Results show the cross-sections of the two hemispheres of the brain. Overall, bvFTD showed less grey matter volume in prefrontal and temporal cortices. Comparison between monolingual bvFTD or bilingual bvFTD to NC showed that monolinguals had larger volume loss in hippocampi, left middle temporal gyrus, middle cingulate, and right gyrus rectus than bilingual bvFTD. Results between same level of bilingualism showed that monolinguals had more brain loss in the hippocampi and middle cingulate than bilinguals. Results are displayed at the same statistical threshold of \( p = 0.001 \) (uncorrected) and cluster level threshold \( k > 100 \) mm\(^3\). The t-value measures the size of the difference relative to the variation in our sample data. L: left, R: right................................................................. 17

**Figure 9.** Grey matter regions showing differences in volume between bilingual and monolingual bvFTD. Results show the cross-sections of the two hemispheres of the brain. No brain region shows less volume in bilinguals than monolinguals. Models are controlled for different covariates. Demographic covariate includes age and years of education. Results are displayed at the same statistical threshold of \( p = 0.001 \) (uncorrected) together with a cluster size of \( k > 100 \) mm\(^3\). L: left, R: right. .......................... 18
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**BIBLIOGRAPHY**


D. Alcolea et al., “The Sant Pau Initiative on Neurodegeneration (SPIN) cohort: A data set for biomarker discovery and validation in neurodegenerative...


### ALPHABETICAL INDEX

**AD** - Alzheimer’s Disease  
**bvFTD** - behavioural-variant Frontotemporal Dementia  
**CBI** - Cambridge Behavioural Inventory  
**CR** - Cognitive Reserve  
**FBI** - Frontal Behavioural Inventory  
**FDG-PET** - Fluorodeoxyglucose Positron Emission Tomography  
**FTD** - Frontotemporal Dementia  
**FTD-FRS** - Frontotemporal Dementia Rating Scale  
**FTLD** - Frontotemporal Lobar Degeneration  
**GM** - Grey Matter  
**MMSE** - Mini-Mental State Examination  
**MRI** - Magnetic Resonance Imaging  
**NC** - Normal Controls  
**NPI** - Neuropsychiatric Inventory  
**nfvPPA** - non-fluent variant Primary Progressive Aphasia  
**SBOC** - Social Behaviour Observer Checklist  
**SPM** - Statistical Parametric Maps  
**svPPA** - semantic-variant Primary Progressive Aphasia  
**TIV** - Total Intracranial Volume  
**VBM** - Voxel-Based Morphometry  
**WM** - White Matter
APPENDICES

Proposed questionnaire to assess bilingualism

The following questionnaire was designed to assess bilingualism more objectively at the Memory Unit at Hospital de la Santa Creu i Sant Pau.

Neuropsychologists agreed on incorporating it in their clinical evaluation. However, once firsts results were obtained, the COVID-19 impacted on our society, postponing the questionnaire implementation and assessment of validity.
Enumere todos los idiomas y dialectos que puede hablar y entender en orden de fluidez: Valore su capacidad para leer, escribir, hablar y entender el idioma según la siguiente escala:

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<th>Idioma</th>
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<td>o Escuela</td>
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Enumeri tots els idiomes i dialectes que pot parlar i entendre en ordre de fluidesa: Valori la seva capacitat per llegir, escriure, parlar i entendre l'idioma segons la següent escala:

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<td>2._____</td>
<td>o Casa o Escola o Societat o Altres: __________</td>
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| 5.___________ | o Casa  
o Escola  
o Societat  
o Altres:  
___________ |   |   |   |   |