Effects of bilingualism on white matter atrophy in mild cognitive impairment: a diffusion tensor imaging study

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Keywords: bilingualism, diffusion tensor imaging, mild cognitive impairment

Background and purpose: Previous investigations show that bilinguals exhibit the first symptoms of dementia 4–5 years later than monolinguals. Therefore, bilingualism has been proposed as a cognitive reserve mechanism. Recent studies have advanced towards an understanding of the brain mechanisms underlying bilingualism’s protection against dementia, but none of them deals with white matter (WM) diffusion.

Methods: In this study, the topic was investigated by measuring WM integrity in a sample of 35 bilinguals and 53 passive bilinguals with mild cognitive impairment.

Results: No significant differences were found between the groups in cognitive level, education, age or sex. However, bilinguals showed higher mean diffusivity in the fornix, but higher fractional anisotropy, lower mean diffusivity, axial diffusivity and radial diffusivity in the parahippocampal cingulum, and lower radial diffusivity in the right uncinate fasciculus. Significant correlations were also found between WM integrity in the left parahippocampal cingulum and the Boston Naming Test in passive bilinguals.

Conclusions: These results suggest that bilingualism contributes to a differential pattern of WM disintegration due to mild cognitive impairment in fibers related to bilingualism and memory.

Introduction

Bilingualism has been proposed as one of the factors that contribute to cognitive reserve (CR) [1]. This proposal is based both on the fact that the first symptoms of dementia appear about 4–5 years later in bilinguals than in monolinguals [2–4] and on previous studies investigating brain atrophy [5,6] and hypometabolism [7]. Previous investigations showed that, in healthy young people, bilingualism increases white matter (WM) integrity in bilateral language-related pathways [8–10]. However, there is no evidence about the effects of bilingualism on WM integrity in dementia.

To date, the only evidence about the effects of bilingualism on CR in dementia using WM measures comes from studies in healthy elderly people. Regarding WM volume, Olsen et al. [11] found greater frontal lobe WM in older bilinguals compared to monolinguals. Focusing on diffusion tensor imaging (DTI) scalars, another investigation found higher fractional anisotropy (FA) (higher WM integrity) in the corpus callosum in elderly bilinguals compared to monolinguals [12]. A subsequent study with a similar sample found greater axial diffusivity (AxD) in bilinguals compared to monolinguals in the left superior longitudinal fasciculus, a fiber connecting areas relevant to the language network, which was interpreted by the authors as enhancing WM integrity in bilinguals [13]. However, opposite results have also been found. Thus, a previous study using a sample of older adults found lower FA and higher mean diffusivity (MD) (i.e. lower WM integrity) in bilinguals compared to monolinguals in a number of tracts, including the corpus callosum.
the fornix, which form part of the brain’s memory circuitry [14].

To the best of our knowledge, differences in WM between bilinguals and monolinguals with dementia have not yet been studied. Without taking bilingualism into consideration, alterations in WM in amnestic mild cognitive impairment (MCI) have been previously defined as mainly affecting the fornix, uncinate fasciculus (UF) and parahippocampal (PH) cingulum [15], i.e. brain tracts related to episodic memory. The PH cingulum and the fornix have been identified as relevant components of the hippocampal–diencephalic–cingulate networks, which are considered essential for normal episodic memory [16]. Moreover, the UF connects the lateral orbitofrontal cortex and the anterior temporal lobes bidirectionally, and it also plays a relevant role in episodic memory [17].

Thus, the objective of our study was to investigate the proposed contribution of bilingualism to CR by comparing WM atrophy in active and passive bilingual MCI patients. Based on previous studies showing that bilinguals with Alzheimer’s disease (AD) present more neuropathology than AD monolinguals in areas related to this disease [5,7], bilinguals were expected to show lower levels of WM integrity than passive bilinguals in the tracts affected in MCI, i.e. in the fornix, UF and PH cingulum [15].

**Methods**

**Participants**

Eighty-eight patients with MCI were selected for this study (43 women, mean age 73.10 ± 5.764 years), recruited from dementia units in the Valencian Community public healthcare system (see Appendix S1 for diagnosis and inclusion criteria).

All the participants were asked about their use of languages. They spoke Catalan and Spanish (n = 35) or only Spanish (n = 53) as their native languages. These groups will be referred to as bilinguals (active) and passive bilinguals, respectively. It is worth mentioning that, because Spanish speakers who permanently reside in the Valencian region do not speak Catalan but are usually able to understand it, they are referred to as passive bilinguals rather than monolinguals. All the bilinguals had learned Catalan during childhood at home. In the area of Valencia, bilinguals and passive bilinguals share the same everyday life environments, such as neighborhood, school system and workplace, with no significant differences apart from the fact that they speak only Spanish or Catalan and Spanish. None of the groups included immigrant individuals. Sample descriptive statistics are reported in Table 1.

All the participants were informed of the nature of the research and provided written informed consent prior to their participation in the study. All the study procedures were approved by the Deontological Commission of University Jaume I and conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Neuropsychological assessment**

All the participants underwent a structured clinical interview and a neuropsychological assessment (see Appendix S1 for information on the scales included). Descriptive statistics and the results of a two-sample t test for each scale are reported in Table 1.

| Table 1 | Sociodemographic and neuropsychological measures for passive bilinguals and (active) bilinguals |
|---------------------------------|---------------------------------------------------------------|
| **Sex** | **Passive bilinguals (N = 53)** | **Active bilinguals (N = 35)** | **Statistical differences** |
| | M/F = 23/30 | M/F = 22/13 | χ² = 3.195 | 0.074 |
| | M | SD | M | SD | t | P |
| --- | --- | --- | --- | --- | --- | --- |
| Age | 72.83 | 5.65 | 73.51 | 5.99 | −0.543 | 0.589 |
| Years of schooling | 8.79 | 3.64 | 8.40 | 2.37 | 0.564 | 0.575 |
| MMSE | 27.26 | 2.49 | 27.31 | 2.07 | −0.099 | 0.922 |
| FAQ | 3.26 | 2.81 | 4.29 | 3.30 | −1.558 | 0.123 |
| Boston | 9.38 | 1.46 | 9.74 | 1.31 | −1.197 | 0.235 |
| Phonetic fluency | 8.43 | 2.12 | 8.66 | 2.22 | −0.475 | 0.636 |
| Semantic fluency | 10.70 | 2.63 | 10.74 | 2.15 | −0.084 | 0.933 |
| Delayed recall | 1.06 | .86 | 1.14 | 0.94 | −0.442 | 0.660 |
| Immediate recall | 8.94 | 3.00 | 9.60 | 2.56 | −1.062 | 0.291 |
| Remote memory | 9.26 | 1.44 | 9.60 | 0.976 | −1.206 | 0.231 |
| Clock-drawing test | 7.17 | 1.85 | 7.00 | 1.45 | 0.464 | 0.644 |

Boston, Boston Naming Test; FAQ, Functional Activities Questionnaire; M, Mean; M/F, males/females; MMSE, Mini-Mental State Examination; N, sample size; P, P value regarding statistical significance; SD, Standard Deviation; t, t value for two-sample t test; χ², chi-squared test.
Diffusion tensor imaging analyses

Information about image acquisition and processing is reported in Appendix S1. For each individual, the following diffusion measures were estimated: FA, MD, AxD and radial diffusivity (RD).

Between-group comparisons, including sex, age and Mini-Mental State Examination (MMSE) scores as covariates, were conducted. The threshold-free cluster enhancement statistic was estimated, and statistical significance was determined using permutation-based nonparametric inference (5000 permutations per analysis) at a threshold of $P < 0.05$, family-wise error (FWE) corrected. The analyses were restricted to a mask that included the fornix, PH cingulum and UF as tracts of interest, based on a recent meta-analysis showing that MCI patients present microstructural WM abnormalities in these regions [15]. Whole brain analyses were also performed using the mean FA skeleton as a mask.

Correlation with neuropsychological variables

For each cluster where significant differences between the groups were observed, its relationship with each of the neuropsychological variables was investigated by means of partial correlations, including age and sex as covariates, in each group separately. Statistically significant thresholds were set at $P < 0.05$, corrected using the Bonferroni method.

Results

Differences in neuropsychological variables

Our analyses showed no significant differences in the performance on any of the neuropsychological tests between bilinguals and passive bilinguals with MCI, or on age ($t = -0.543; P > 0.1$), the proportion of men and women ($\chi^2 = 3.19; P > 0.1$) or years of schooling ($t = 0.564; P > 0.1$; Table 1).

Differences in DTI

Using the mask that included the fornix, PH cingulum and UF, it was found that bilinguals exhibited higher MD in the fornix than passive bilinguals ($P < 0.05$, FWE corrected, Fig. 1). They also showed higher FA and lower MD, AxD and RD in the PH cingulum bilaterally ($P < 0.05$ FWE corrected, Fig. 2) and lower RD in the right UF ($P < 0.05$, FWE corrected, Fig. 3). Exploratory whole brain analyses did not show any significant differences.

Correlation between DTI and neuropsychological variables

In the passive bilingual group, a significant correlation was found between the performance on the Boston Naming Test (BNT) and RD levels ($R = -0.425$, $P = 0.014$ FWE corrected) in the left PH cingulum. In the bilingual group, no significant correlations with the pre-established FWE corrected threshold were found. However, taking into account uncorrected results in this group, an association was found between RD levels in the left PH cingulum and immediate recall ($R = -0.413$, $P = 0.017$ uncorrected), similar to the results reported in previous studies investigating WM integrity in MCI participants [18,19]. No other significant results were found for any of the other neuropsychological variables.

Discussion

In this study, the differences in WM diffusion between bilinguals and passive bilinguals with MCI who shared similar sociodemographic characteristics, with no significant differences in cognitive status, years of schooling, age or the proportion of men and women, were investigated. However, bilinguals showed lower WM integrity in the fornix and higher in the PH cingulum and UF. Furthermore, WM integrity in the PH cingulum was positively correlated with performance...
on the BNT in the passive bilingual group. These results suggest that the active use of two languages leads to a differential pattern of WM disintegration in MCI.

The fornix and the PH cingulum are part of the hippocampal–diencephalic–cingulate networks for memory and emotion [16], initially proposed in the work by Papez [20]. The fornix is a fiber bundle situated in the midline of the brain, originating from the hippocampus and terminating at the septal nuclei, nucleus accumbens and hypothalamus [21]. Damage to the fornix can cause memory impairment [16,22,23], its WM integrity is altered in MCI [15], and it has recently been identified as a useful target for deep brain stimulation in dementias [24,25]. Regarding the PH cingulum, it is a subdivision located in a temporal position and extending caudally, connecting the posterior cingulate cortex, visual areas from the occipital lobe and parietal areas such as the intraparietal cortex with the medial temporal lobe [26]. Its function is more related to familiarity-based memory, i.e. to the automatic feeling triggered by contextual cues that an item has been recently experienced [18]. The latter connections seem especially relevant in relation to our study because previous investigations have linked bilingualism to increased gray matter volume [27,28] and cortical thickness [6] in inferior parietal areas. Finally, the UF connects the frontal orbital cortex and the temporal lobe [17]. Due to the nature of these connections, it has also been proposed as a relevant fiber for memory, with DTI studies supporting its role in verbal and auditory memory [17].

The fornix, UF and PH cingulum are all impaired in MCI [15]. The fornix and PH cingulum have been found to play different roles in its clinical manifestation [18,19]. Thus, a study comparing healthy controls and patients with MCI found higher atrophy in the fornix and PH cingulum in patients [19]. Importantly, this study showed differential associations between performance on a free recall test and fornix and PH cingulum pathology: in controls, free recall correlated with fornix WM integrity, whereas in patients the strongest relationship was found with the PH
cingulum, a result that was replicated [29]. This was interpreted as a sequential compensatory mechanism through which, in the presence of an impairment of episodic memory functions in the fornix, the PH cingulum may later support memory performance using familiarity processing resources as an alternative route [19,29]. Based on this previous literature, a possible explanation for the similarities between the performance of our groups on neuropsychological testing might be a compensatory mechanism: due to a more compromised fornix in bilinguals, memory processes might be supported by the PH cingulum, which acquires special relevance as a compensatory route. Thus, although our initial hypothesis was to find lower WM integrity in all tracts of interest in bilinguals, our results might still be interpreted as a contribution of bilingualism to CR, considering that bilinguals use familiarity as a compensatory mechanism of episodic memory deficits that depend on the fornix. This compensatory use has been associated to a delay in the manifestation of AD [30]. Supporting this interpretation, a relationship was found between RD in the left PH cingulum and immediate recall performance only in bilinguals. However, this result did not reach significance when correcting for multiple comparisons and so it should be interpreted with caution. Alternatively, some of our findings might be explained by neuroplasticity mechanisms induced by bilingual experience. The PH cingulum connects with inferior parietal areas that are particularly relevant in bilingualism [27,28]. In young samples, bilingualism increases WM integrity in fibers related to language and adjacent to the PH cingulum, such as the inferior fronto-occipital fasciculus or the direct segment of the arcuate fasciculus [8–10]. Additionally, previous studies showed higher FA in the UF in healthy younger bilinguals [9] and greater frontal lobe WM in older bilinguals [11] compared to monolinguals. Crucially, there is also evidence that experiences during adulthood might lead to changes in the WM microstructure [31], such as cognitive training increasing WM integrity [32]. Thus, the higher WM integrity in the PH cingulum and UF might be associated with the long term active use of two languages in bilinguals and might contribute to the lack of cognitive differences between groups. Future studies should determine whether the observed differences in the PH cingulum and UF precede MCI, are a consequence of fornix pathology or are a combination of both effects.

Finally, our results may also be relevant in understanding evidence found in previous studies investigating bilingualism. First, a previous study also found lower WM integrity in the fornix in healthy older bilinguals compared to monolinguals [14]. These results were contrary to the evidence found in previous studies with elderly samples [12], and so they were interpreted by the authors as a possible higher incidence of preclinical AD in their sample of elderly bilingual participants. Our study confirms that MCI bilingual patients show lower WM integrity in the fornix than MCI monolinguals, thus validating this interpretation. Secondly, a correlation was found between performance on the BNT and WM integrity in the left PH cingulum in the monolingual group. This result might be of interest given the existing literature showing a relationship between performance on the BNT in healthy elderly individuals and gray matter volume in left temporal areas [33,34] and FA in temporal fibers [33]. Previous studies also found better performance in monolinguals compared to bilinguals on the BNT [35,36]. Therefore, our results might suggest that passive bilingual brains make use of the PH cingulum in the neural mechanisms involved in naming processes.

In conclusion, our results show that, in a sample of patients with MCI with similar sociodemographic characteristics and cognitive levels, bilinguals exhibit lower WM integrity than passive bilinguals in the fornix and higher WM integrity in the PH cingulum and UF, suggesting that bilingualism results in a differential pattern of MCI-related WM disintegration. Together, our results add knowledge about the neural mechanisms through which bilingualism may protect against dementia.

Acknowledgements

This work was supported by the project 201410-30-31 provided by Fundació Marató TV3 awarded to C.A. L.M-M. was supported by an FPU grant from the Spanish Ministry of Education (FPU17/00698) and V.C. was supported by a Juan de la Cierva postdoctoral graduate program grant from the Spanish Ministry of Economy, Industry and Competitiveness (IJC1-2016-29247).

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplementary methods.
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