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Enhancement of posterior brain functional networks in bilingual older adults

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Abstract

Bilingualism has been said to improve cognition and even delay the onset of Alzheimer's disease (AD). This research aimed to investigate whether bilingualism leaves a neurophysiological trace even when people are highly educated. We expected bilinguals to present better preserved brain functional networks, which could be a trace of higher cognitive reserve. With this purpose, we conducted a magnetoencephalographic study with a group of healthy older adults. We estimated functional connectivity using phase-locking value and found five clusters in parieto-occipital regions in which bilinguals exhibited greater functional connectivity than monolinguals. These clusters included brain regions typically implicated in language processing. Furthermore, these functional changes correlated with caudate volumes (a key region in language shifting and control) in the bilingual sample. Interestingly, decreased Functional Connectivity between posterior brain regions had already been identified as an indicator of aging/preclinical AD but, according to our study, bilingualism seems to exert the opposite effect.

Introduction

Bilingualism could be defined as the ability to communicate in two or more languages and use them on a regular basis. It is not easy, however, to categorize people as bilinguals or monolinguals, since there are many aspects that need to be considered beyond proficiency in the first and the second acquired languages (L1 and L2 respectively). These include age of acquisition, acquisition methodology, frequency of use, etc. (Bak, Nissan, Allerhand & Deary, 2014)

Different authors have studied the potential advantages that bilingualism confers to cognitive performance and brain health. For example, bilingualism has been claimed to provide an advantage in the performance of several cognitive tasks, mainly in the domain of executive functioning (Adesope, Lavin, Thompson & Ungerleider, 2010; Costa, Hernández & Sebastián-Gallés, 2008; Stocco & Prat, 2014), although some studies have failed to identify such benefits among the bilingual population (Cox, Bak, Allerhand, Redmond, Starr, Deary & MacPherson, 2016; Hernández, Martin, Barceló & Costa, 2013; Crane, Gruhl, Erosheva, Gibbons, McCurry, Rhoads, Rhoads, Nguyen, Arani, Masaki & White, 2010; Zatorre, Belin, Crane, Gruhl, Erosheva, Gibbons, McCurry, Rhoads, Nguyen, Arani, Masaki & White, 2001), even when the specific outcomes of age of acquisition and multilingualism were taken into consideration (Paap, Johnson & Sawi, 2014). Bialystok (2017) provides an in-depth review of the influence of bilingualism on cognition in children, younger adults and older adults, and proposes executive attention as the key component that accounts for such effects. Beyond the impact of bilingualism on cognition, several authors have delved into the study of how speaking two languages shapes brain structure and function. Bilinguals have been found to present greater grey matter volumes, especially in the basal ganglia (for extensive reviews on this topic, see Grundy, Anderson & Bialystok, 2017; Wong, Yin & Brien, 2016). As for diffusion tensor imaging, there is some controversy in the literature regarding whether bilingualism truly contributes to better preserved white matter tracts in older adults in terms of higher fractional anisotropy values (Gold, Kim, Johnson, Kryscio & Smith, 2013; Luk, Bialystok, Craik & Grady, 2011), although better controlled studies point in that direction both in young (Rossi, Cheng, Kroll, Diaz & Newman, 2017) and older adults (Anderson, Grundy, De Frutos, Barker, Grady & Bialystok, 2018). Overall, bilingualism has been shown to produce an advantage in cognition and brain structure integrity, although results concerning structural connectivity are less consistent, leaving a gap about the effect of bilingualism in network organization.

Bilingualism has also been studied as a proxy of cognitive reserve (CR). CR is a construct that emerged to explain inter-individual differences in how the brain copes with underlying pathology. More specifically, bilingualism has been extensively studied as a protective factor against cognitive decline and Alzheimer's disease (AD; Abutalebi, Canini, Della Rosa, Sheung, Green & Weekes, 2014; Bialystok, Craik & Freedman, 2007; Estanga, Ecay-Torres, Ibañez, Izagirre, Villanua, Garcia-Sebastian, Iglesias Gaspar, Otaegui Arrazola, Iriondo, Clerigue & Martinez-Lage, 2017; Gold et al., 2013). Nevertheless, several studies have failed to identify such benefits among the bilingual population (Cox et al., 2016; Zahodne, Schofield, Farrell & Manly, 2014; Zatorre et al., 2001). In this regard, Klimova, Valis and Kuca (2017) concluded that, while prospective studies, in general, do not replicate the finding that bilinguals develop AD later in life, most retrospective studies come to that conclusion. Bilingualism is a complex skill, and differences in its conceptualization and measurement could be behind these discrepancies (Bialystok, 2017). For instance, immigration, educational attainment or socio-economic status have been pointed to as potential confounding factors (Calvo & Bialystok, 2014; Fuller-Thomson, 2015; Guzmán-Vélez & Tranel, 2015; Schweizer, Ware, Fischer, Craik & Bialystok, 2012). In general, despite some inconsistent results, bilingualism seems to behave as a protective factor in the aging process, delaying the onset of pathological conditions, thus making it relevant to study the potential brain mechanisms underlying such effects.

As has been shown above, most neuroimaging studies about bilingualism in the older population have focused on the potential of bilingualism to delay dementia. However, not as much is known about the neurophysiological changes that bilingual healthy older adults might exhibit. Functional connectivity (FC) is a powerful approach that provides a measure of how the activity of different regions in the brain is temporarily synchronized, which is thought to reflect communication between several key brain regions supporting cognitive functioning (Mesulam, 1990, 1998; Varela, Lachaux, Rodriguez & Martinerie, 2001). In different functional magnetic resonance imaging (fMRI) studies, FC has already been applied to the study of bilingual differences in the brain of younger adults (Berken, Chai, Chen, Gracco & Klein, 2016; Chai, Berken, Barbeau, Soles, Callahan, Chen & Klein, 2016; Hsu, Jacobs & Conrad, 2015; Perani, Farsad, Ballarini, Lubian, Malpetti, Fracchetti, Magnani, March & Abutalebi, 2017; Zou, Abutalebi, Zinszer, Yan, Shu, Peng & Ding, 2012). For example, Berken et al. (2016) found that bilinguals exhibited greater FC at rest between the inferior frontal gyrus (an area that has been demonstrated to be susceptible to structural and functional changes as a result of second language acquisition) and other brain regions. This increase in FC negatively correlated with age of acquisition. Also, Kousaie, Chai, Sander and Klein (2017) showed that simultaneous bilinguals presented stronger anti-correlation between the default mode network (DMN) and the task-positive attention network than sequential bilinguals, and that the former outperformed the latter in cognitive control as well.

The most relevant publication including healthy older adults found that bilinguals presented higher FC at rest than their monolingual counterparts in the DMN, the salience network and the frontoparietal control network, which was interpreted as a potential future advantage (Grady, Luk, Craik & Bialystok, 2015). Similarly, another study employing a slightly different metric reported that bilingual AD patients presented higher metabolic connectivity in the executive control network and the DMN (Perani et al., 2017), which was again interpreted as a sign of greater cognitive reserve, expressed as a better preserved network functioning. Interestingly, different studies have linked normal aging with a decrease in FC, particularly over posterior brain regions, an effect that was even more pronounced in AD patients and at-risk populations (Jones, Machulda, Vemuri, McDade, Zeng, Senjem, Gunter, Przybelski, Avula, Knopman, Boeve, Petersen & Jack, 2011; López-Sanz, Bruña, Garcés, Martín-Buro, Walter, Delgado, Montenegro, Lopez-Higes, Marcos & Maestú, 2017a). FC decreases have been found to correlate with a decline in cognitive performance in healthy older adults (Andrews-hanna, Snyder, Vincent, Lustig, Head, Raichle & Buckner, 2009). Moreover, healthy older adults who are carriers of the most relevant genetic risk factor for AD (namely the apolipoprotein E -*APOE*- ϵ4 allele) have been found to present altered FC patterns (Cuesta, Garcés, Castellanos, López, Aurtenetxe, Bajo, Pineda-Pardo, Bruña, Marín, Delgado, Barabash, Cabranes, Fernandez, Del Pozo, Sancho, Marcos, Nakamura & Maestú, 2015). All the above-mentioned studies highlight the relevance of FC in the context of aging and bilingualism. While FC increases have mainly been reported for bilinguals, particularly in regions related to language or task-relevant attention, normal and pathological aging have been repeatedly associated to decreases in FC, particularly over posterior brain regions. Thus, understanding how bilingualism modifies brain networks could be crucial to unravelling the mechanisms through which bilingualism may act as a protective factor during aging.

In this study, we seek to unveil whether late bilingualism results in a different organization of the brain functional networks measured by means of electrophysiological recordings. To rule out the possibility that educational attainment is driving the differences between both groups, we will exclusively focus on highly educated older adults. We will employ magnetoencephalography (MEG), a very useful non-invasive technique to study the brain functional networks. MEG measures brain activity by mapping the magnetic fields that arise perpendicularly to the tiny electrical currents that emerge in the process of neural communication. In this sense, one of the great advantages of neurophysiological techniques is that they measure neuronal activity, thus providing a more direct measure of brain activity compared to other techniques, such as fMRI that relies on BOLD signal. Moreover, it offers an excellent temporal resolution with an adequate spatial resolution. Some studies have already been carried out to address the effect of bilingualism on brain oscillations, mainly accounting for linguistic effects such as foreign language encoding (Pérez, Carreiras, Gillon Dowens & Duñabeitia, 2015), decoding (Correia, Jansma, Hausfeld, Kikkert & Bonte, 2015) or translation (Grabner, Brunner, Leeb, Neuper & Pfurtscheller, 2007). Nevertheless, to the best of our knowledge, this is the first time that MEG has been applied to the study of bilingual differences in FC among the healthy older population. In light of the previous work, we expect bilingualism to act as a protective factor, fostering brain preservation against normal aging and/or the manifestation of different potentially underlying pathological conditions. Thus, we hypothesized that healthy older bilingual adults would show more preserved functional networks, resulting in higher FC compared to their monolingual counterparts.

Materials and Methods

Participants

38 healthy older adults participated in this study. The sample was recruited from three different services: Neurology Department in "Hospital Universitario San Carlos", "Center for Prevention of Cognitive Impairment" and "Seniors Center of Chamartin District", all of them in Madrid (Spain).

Healthy status was attributed according to the participants' scores in a set of neuropsychological tests that included the Mini Mental State Examination (MMSE; Lobo, Ezquerra, Gomez Burgada, Sala & Seva Díaz, 1979), the Geriatric Depression Scale – Short Form (GDS-SF, Yesavage, Brink, Rose, Lum, Huang, Adey & Leirer, 1983), the Hachinski Ischemic Score (HIS; Rosen, Terry, Fuld, Katzman & Peck, 1980) and the Functional Assessment Questionnaire (FAQ; Pfeffer, Kurosaki, Harrah, Chance & Filos, 1982).

Subjects were subsequently classified as bilinguals or monolinguals after filling out a questionnaire in which they were asked if they spoke any other language besides Spanish and, if so, about their proficiency in that second language (both in the past and at present); the age of acquisition, if they had lived in a region where a language other than their mother tongue was spoken; as well as about the frequency of use of their second language in the present. More precisely, participants who qualified their L2 linguistic skills as being good or very good were considered bilinguals, while those who described them as poor or fair were not included in the final sample. Only those participants who reported not having acquired a second language or had not lived in a region where a language other than Spanish was socially or formally used were classified as monolinguals. This is important because certain regions of Spain have two official languages. However, all monolingual participants in our sample related having always resided in areas where Spanish was the only official language. In such areas of Spain, it is rare to be exposed to a second language unless the individual actively seeks out such experience. In this regard, we also collected information with respect to whether bilingual older adults still used their L2 in their everyday lives (for example to watch movies, read books or in social interactions), since most of them acquired L2 proficiency due to job requirements but are presently retired.

In Spain, it was not until 1970 that learning a second language became mandatory in the educational system (Ley 14/1970, de 4 de agosto, General de Educación y Financiamiento de la Reforma Educativa). Before that, certain schools incorporated a second language in their academic curriculum (most commonly French and/or English), usually at the age of 11-12. In our specific sample, the age of L2 acquisition ranged between 6 and 57 years. The final sample was composed of 22 bilinguals and 16 monolinguals. The age range of the participants was 65–78. More relevant information can be found in Table 1. It is important to highlight that no significant differences in cognitive status (MMSE) were observed, with all the subjects scoring high (above 27), which reflects a preserved cognitive performance. Furthermore, other relevant factors such as age, formal education and depression (as measured by the GDS) were comparable across groups, as shown in the table.

For the purpose of this study, we only included participants who held a postsecondary educational qualification. This was necessary because both in the literature and in our sample there was a close relationship between bilingualism and educational attainment, so in order to isolate the effects of the former variable we homogenised the latter across the whole sample (bilinguals and monolinguals). At the same time, in order to carefully delimit the bilingual subpopulation that was being addressed, we focused on late-bilinguals who were born and raised in Spain, and who were exposed to their L2 for the first time in a formal context. We focused on that particular bilingual subpopulation since it is the most representative of the region where the study took place. Also, it seems to make sense that if interventional studies seeking to improve cognition by means of learning a second language were to be conducted, the target population would be late-learners.

Other exclusion criteria that were applied in this study included: (1) history of psychiatric or neurological disorders or drug consumption that could affect MEG activity such as cholinesterase inhibitors; (2) evidence of infection, infarction or focal lesions in a T2-weighted scan within 2 months before MEG acquisition; (3) alcoholism or chronic use of anxiolytics, neuroleptics, narcotics, anticonvulsants or sedative hypnotics. Before they joined the study, all participants signed an informed consent. The Hospital Universitario San Carlos Ethics Committee approved this study and the procedure was performed in accordance with approved guidelines and regulations.

APOE genotyping

Genomic DNA from each participant was obtained from 10 ml blood samples in ethylenediaminetetraacetic acid (EDTA). Single nucleotide polymorphisms (SNPs) rs7412 and rs429358 genotypes were obtained using TaqMan assays in an Applied Biosystems 7900 HT Fast Real Time PCR machine (Applied Biosystems, Foster City, CA) and APOE haplotype was determined accordingly.

MEG recordings and preprocessing

Each subject underwent four minutes of eyes-closed resting state recording while comfortably sitting in dim light. MEG recordings were done with a Vectorview Elekta system including 102 magnetometers and 204 planar gradiometers inside a magnetically shielded room.

Before recording, each subject's headshape was digitalized and the position of three fiducials (left and right preauricular and nasion) was stored. Additionally, 4 head position information coils were attached and digitalized over bilateral mastoids and forehead using a Fastrak digitalizer (Polhemus, Colchester, Vermont). The recording set up also included 2 vertical electro-oculogram electrodes to detect and correct eye blinks and movements at preprocessing.

During the recording, an online anti-aliasing bandpass filter between 0.1 Hz and 330 Hz was applied and continuous information about head position was also acquired. Subsequently, an off-line filter was applied using a spatiotemporal signal space separation algorithm with movement compensation (Taulu & Simola, 2006) with a correlation window of 0.9 and a time window of 10 seconds.

For artifact detection, an automatic algorithm included in the open source Fieldtrip package (Oostenveld, Fries, Maris & Schoffelen, 2011) was used. Afterwards, artifacts were visually

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Table 1. Sample Characterization
Table 1 includes mean values ± standard deviation for age, years of education, Mini Mental State Examination (MMSE), Geriatric Depression Scale (GDS) and L2 age of acquisition (AoA) for the whole sample (N = 38), bilinguals (n = 22) and monolinguals (n = 16) where appropriate. The size of the subsamples of men (M) / women (W) and APOE4+ / APOE4- are specified. Lastly, the proportion of bilinguals currently using L2 is also reported. P-values (p) for the MannWhitney or Fisher tests (bilinguals vs monolinguals) are shown.

	Whole Sample	Bilinguals	Monolinguals	p
Sex (M : F)	14 : 24	9 : 13	5 : 11	0.49
Age	71.2 ± 3.8	70.8 ± 4.0	71.7 ± 3.8	0.485
Years of education	18.1 ± 3.2	18.4 ± 3.2	17.7 ± 3.2	0.520
APOE (ε4- : ε4+)	28 :10	15 :7	13 : 3	0.469
MMSE	29.0 ± 1.2	29.3 ± 0.9	28.6 ± 1.3	0.088
GDS	1.9 ± 2.5	1.3 ± 1.4	2.7 ± 3.4	0.099
AoA	NA	16.3 ± 11.3	NA	–
Current L2 use	NA	72.2%	NA	–

confirmed by a MEG expert. The remaining artifact-free signal was segmented into 4 second epochs and an ICA-based procedure was employed to remove the electrocardiographic component of the signal. Magnetometers data were employed for further analyses due to the redundancy of the information contained by both types of sensors after spatiotemporal filtering (Garcés, López-Sanz, Maestú & Pereda, 2017).

MRI acquisition

Each subject included in the study had a T1-weighted MRI image available, acquired in a General Electric 1.5 T system. A high-resolution antenna was employed and a homogenization PURE filter (Fast Spoiled Gradient Echo sequence, TR/TE/TI = 11.2/4.2/450 ms; flip angle 12°; 1 mm slice thickness, 256 × 256 matrix and FOV 25 cm). MRI images were processed with Freesurfer software (version 5.1.0) and its specialized tool for automated cortical and subcortical segmentation (Fischl, Salat, Busa, Albert, Dieterich, Haselgrove, van der Kouwe, Killiany, Kennedy, Klaveness, Montillo, Makris, Rosen & Dale, 2002) in order to obtain the volume of several brain areas that were included in subsequent analyses.

Source reconstruction

We employed a regular grid of 1 cm spacing in the Montreal Neurological Institute (MNI) template, ending up with a 2459 source model homogeneously distributed across the brain. These sources were linearly transformed to subjects' space between the native T1 image (whose coordinate system was previously converted to match the MEG coordinate system using in-house scripts) and a standard T1 image in the MNI stereotactic space using Fieldtrip and SPM8 (Litvak, Mattout, Kiebel, Phillips, Henson, Kilner, Barnes, Oostenveld, Daunizeau, Flandin, Penny & Friston, 2011). In order to calculate the leadfield, we used a three-shell boundary element method creating three interfaces (brain-skull, skull-scalp and scalp-air) from each subjects' T1-weighted image. We used OpenMEEG software for the leadfield calculation (Gramfort, Papadopoulo, Olivi & Clerc, 2010).

Artifact-free activity was then bandpass filtered into 4 different bands: theta (4-8 Hz), alpha (8-12 Hz), beta1 (12-20 Hz) and beta2 (20-30 Hz) with an 1800 order finite impulse response (FIR) filter using Hanning window. The analyses focused on these bands due to increased reliability, most likely linked to higher SNR in this frequency range (Deuker, Bullmore, Smith, Christensen, Nathan, Rockstroh & Bassett, 2009; Hardmeier, Hatz, Bousleiman, Schindler, Stam & Fuhr, 2014; Jin, Seol, Kim & Chung, 2011). Data was filtered in a two-pass procedure as implemented in Matlab's filtfilt function to avoid phase distortion. A padding segment of real data consisting of 2000 samples was kept at each side of clean epochs to avoid edge effects while filtering. To calculate source time-series and solve the inverse problem we employed a Linearly Constrained Minimum Variance beamformer (Van Veen, van Drongelen, Yuchtman & Suzuki, 1997).

Connectivity calculation

FC between all pairs of sources was estimated using phase-locking value (PLV) algorithm. PLV is based on the assumption that measuring the degree of non-uniformity of phase differences between two time series should be a good estimator of their coupling (Lachaux, Rodriguez, Martinerie & Varela, 1999).

$$PLV_{k,l} = \left| \frac{1}{T} \sum_{t} e^{-j(\varphi_k(t) - \varphi_l(t))} \right|$$

where $\varphi_k(t)$ and $\varphi_l(t)$ are the instantaneous phases of signal k and signal l at instant t respectively, t is the number of temporal points per segment and j is the imaginary unit. This same procedure has been previously used and described elsewhere for further details (López-Sanz et al., 2017a). As a result, we obtained a series of 2459 x 2459 FC matrices. We employed a reduced version of the Harvard-Oxford atlas, previously described in (López-Sanz et al., 2017a) consisting of 64 cortical regions of interest (ROIs). Table 2 lists the ROIs included in this atlas and their abbreviations. FC values of the links connecting sources between any given two ROIs were averaged resulting in a 64 x 64 FC matrix for each subject and frequency band.

Statistical Analyses

Functional connectivity was compared across the between-group factor bilingualism. To this aim, we conducted a procedure relying on the cluster-based permutation test (CBPT) (Maris & Oostenveld, 2007) for each frequency band using in-house scripts.

Table 2. List of ROIs of the anatomical atlas
Table 2 shows the correspondence between abbreviations showed in Figure 1.1, Figure 1.2 and Figure 1.3 and regions depicted in the Harvard-Oxford anatomical atlas (Desikan, Ségonne, Fischl, Quinn, Dickerson, Blacker, Buckner, Dale, Maguire, Hyman, Albert & Killiany, 2006). Preceding letter l or r stands for left or right hemisphere, respectively. Abbreviations ending in -a, -p, -ap or -to stand for anterior part, posterior part, antero-posterior part or temporo-occipital part, respectively

Abbreviation	Full name
Amyg	Amygdala
Ang	Angular Gyrus
Calc	Calcarine cortex
CG	Cingulate Gyrus
Cu	Cuneal Cortex
FMC	Frontal Medial Cortex
FOC	Frontal Orbital Cortex
FP	Frontal Pole
Hip	Hippocampus
IOC	Inferior Lateral Occipital Cortex
ITG	Inferior Temporal Gyrus
ITG	Inferior Frontal Gyrus
Lin	Lingual Gyrus
M	Motor cortex
MFG	Middle Frontal Gyrus
MTG	Middle Temporal Gyrus
OP	Occipital Pole
ParaC	Paracingulate Gyrus
ParaHip	Parahippocampal Gyrus
PCu	Precuneous
PosCG	Postcentral Gyrus
PreCG	Precentral Gyrus
SFG	Superior Frontal Gyrus
SMG	Supramarginal Gyrus
SOC	Superior Lateral Occipital Cortex
SPL	Superior Parietal Lobule
STG	Superior Temporal Gyrus
TP	Temporal Pole

The methodology started by assessing the FC difference between groups for each pair of nodes using a two-tailed T-test. Then, we aimed to extract a robust, significant subnetwork, also called a cluster or motif in graph theory (Stam, 2014). These clusters consist of several connected, significant links (T-test p-value < 0.05), which systematically showed a diminished or enhanced FC in the bilingual group compared to the monolingual group. For each cluster, a cluster-statistic value was computed as the sum of all T-values obtained in the corresponding links' T-test. Then, to control for multiple comparisons, we applied the CBPT that consisted of 100000 repetitions of the analysis pipeline, creating a null distribution for each comparison. This null distribution was obtained by shuffling the original groups' configurations and performing new T-test for each pair of nodes creating new surrogate motifs. The cluster-statistics over each motif in the original dataset were compared with the same measure in the randomized data (we kept the maximum statistic at each repetition). The CBPT *p*-value represents the proportion of the permutation distribution with cluster-statistic values greater or equal than the cluster-statistic value of the original data. The Alpha level was set to 0.05 for the CBPT *p*-value. Only those clusters that survived after the CBPT were reported and used in the correlation analysis. Taking into account that we performed statistical comparisons for each frequency band separately, we Bonferroni-adjusted the p-value of each significant cluster such as $\alpha = 0.01$. Age was included as a covariate in statistical analyses.

Additionally, to explore the possible interpretation of the significant FC clusters obtained in the above-mentioned analysis, we conducted correlation analyses using Pearson correlation coefficient between the mean FC value of each significant cluster (averaging across all the corresponding links) and cortical volumes extracted from Freesurfer analyses. The regions included in the analyses were the caudate, the putamen, the globus pallidus and the anterior cingulate cortex. This subset of regions has been found to be specifically modulated by bilingualism in previous works (Grundy et al., 2017; Wong et al., 2016). Correlations were calculated for each group separately to independently observe the relationship between variables in each population. P-values were also corrected using false discovery rate (FDR) to account for multiple testing. Lastly, we conducted a set of correlations to explore whether L2 age of acquisition was significantly related to either grey matter volume or FC in the observed clusters.

Results

Functional connectivity analysis

The analyses brought significant between-group differences for five FC clusters in three frequency ranges all of them exhibiting higher FC values in bilingual older adults.

When comparing FC values in the theta band (4-8 Hz) we obtained two significant FC clusters: the theta left occipital cluster (Theta L-Occ) and the theta bilateral occipital cluster (Theta Bi-Occ). The theta L-Occ cluster was formed by 5 significant links (accumulated cluster T = 11.150; cbpt p-value = 0.002), all of them including the left inferior occipital cortex and connecting to the left lingual gyrus, the left calcarine cortex, the left cuneus, the left precuneus and the left posterior cingulate cortex (PCC) respectively (figure 1.1). These areas are either part of the DMN or the visual cortex (Hudspeth, Jessell, Kandel, Schwartz & Siegelbaum, 2013; Fransson & Marrelec, 2008). Bilinguals showed higher FC in all these links with respect to their highly educated healthy monolingual counterparts (figure 2). Additionally, the Theta Bi-Occ cluster included three significant links (accumulated cluster T = 11.490; cbpt p-value = 0.002) in which bilingual older adults exhibited higher FC values compared to monolinguals (figure 2). Two of these links connected the right lingual gyrus with the the left inferior occipital cortex and the left calcarine cortex, the third link involved the left lingual gyrus and the right calcarine cortex (figure 1.1). These are again areas involved in visual processing (Hudspeth et al., 2013).

In the alpha band (8-12 hz) there were no significant FC differences. Contrarily, we obtained a significant left parieto-occipital cluster (Beta1 L-ParOcc henceforth) in the beta1 band (12-20 Hz), comprising four links (accumulated cluster T = 13.150; cbpt p-value = 0.001). Three of these links included left

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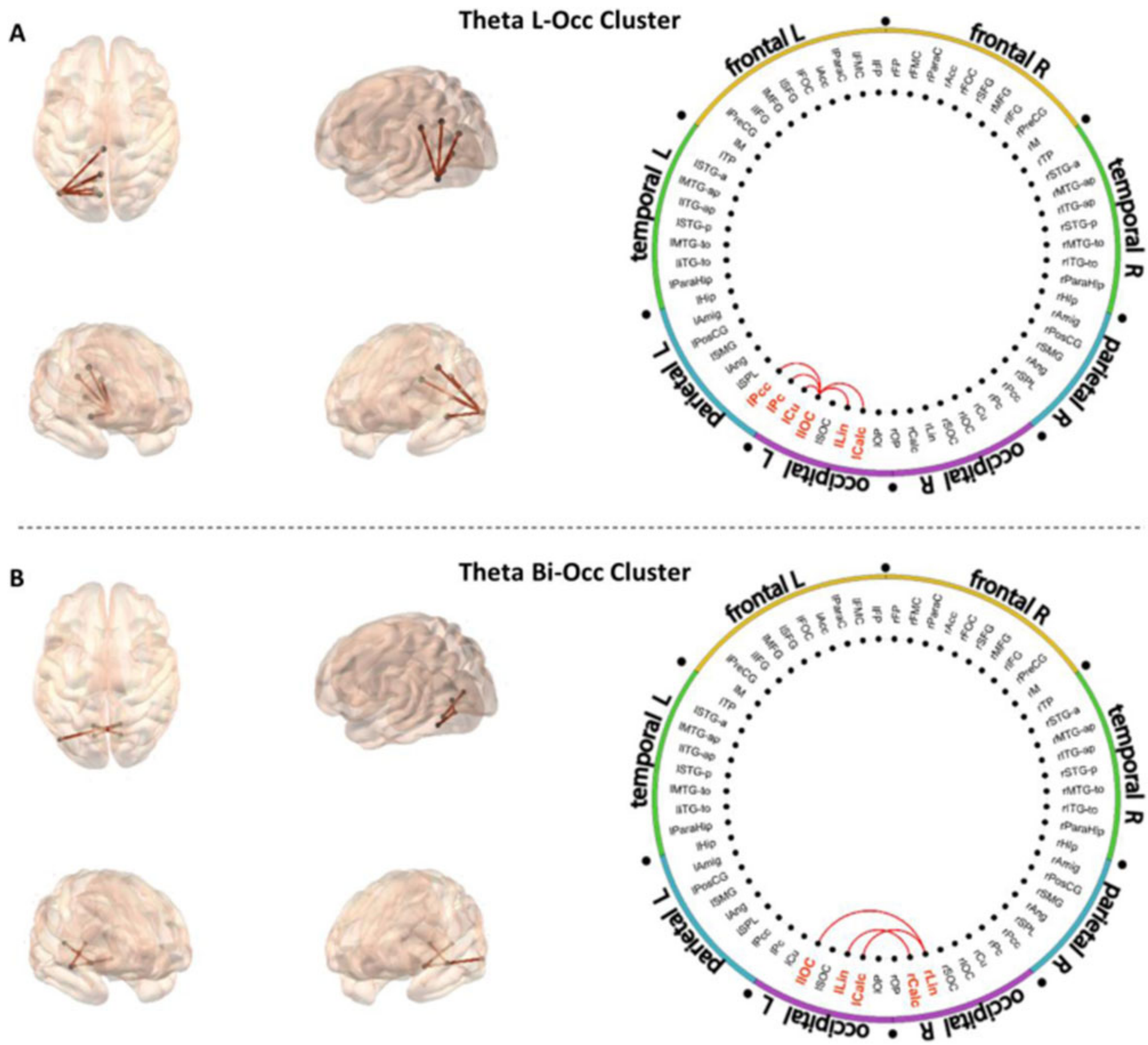

Fig. 1.1. Figure 1.1 Shows the regions included in the two clusters (A: Theta L-Occ; B: Theta Bi-Occ) in the Theta band in which bilinguals exhibit greater FC than monolinguals.

the superior occipital cortex connecting it to the left postcentral gyrus, the left supramarginal gyrus and the left superior parietal lobe respectively, while the fourth linked the left supramarginal gyrus with the left cuneus (figure 1.2). These areas are related to visual and somatosensory processing (Hudspeth et al., 2013). The FC over these regions was enhanced in the bilingual group (figure 2).

Lastly, we obtained two significant FC clusters in the beta2 range (20-30 Hz) where bilinguals also exhibited increased synchronization values when compared to monolinguals (figure 2). The first was a bilateral occipital cluster (Beta2 Bi-Occ) that comprised 5 links (accumulated cluster $T = 10.570$; cbpt p-value = 0.003). The hyper-synchronized links connected the left lingual gyrus with the left and right calcarine, the right lingual gyrus to the left calcarine and the left cuneus and, lastly, the left calcarine to the right calcarine cortex (figure 1.3). As mentioned before, these areas play a role in visual processing (Hudspeth et al., 2013). Finally, we observed a left parieto-occipital cluster showing significant FC differences (Beta2 L Par-Occ) (accumulated cluster $T = 11.640$; cbpt p-value = 0.008) included 4 links connecting the left superior occipital cortex to the left postcentral gyrus, the left supramarginal gyrus and the left superior parietal lobe, and a fourth link associating the left precuneus with the left supramarginal gyrus (figure 1.3), areas that are involved in visual and somatosensory processing among other roles (Hudspeth et al., 2013).

Correlation analyses

We first conducted Pearson correlations between mean FC of each significant cluster and age, to discard any possible contribution of this variable to the results, and confirmed that none of the clusters demonstrated a significant relationship with age in any of the groups ($\alpha = 0.050$). Furthermore, we ensured that there were no

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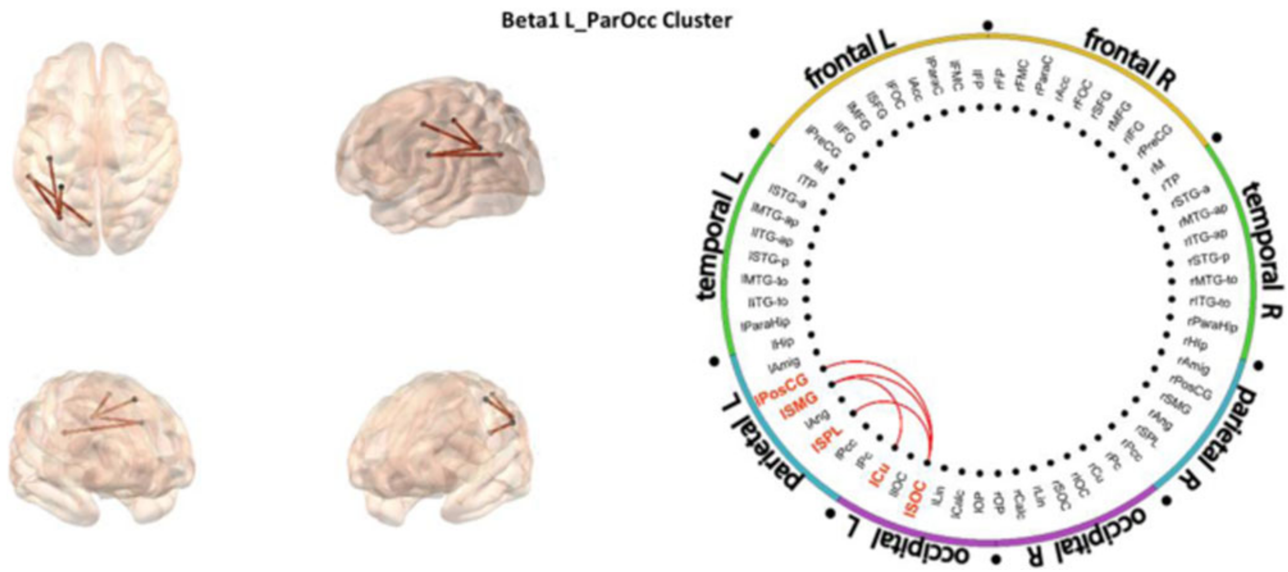

Fig. 1.2. Figure 1.2 Shows the regions included in the cluster in the Beta1 band (Beta1 L-ParOcc) in which bilinguals exhibit greater FC than monolinguals.

significant differences in grey matter volume between bilinguals and monolinguals in any of the structures included in the analyses that could potentially bias the results ($\alpha = 0.050$).

In order to study the possible functional meaning of these FC changes observed in bilingual older adults, we decided to conduct a set of correlations between FC values and the volume of certain structures linked to bilingualism (i.e., anterior cingulate cortex; ACC), caudate, putamen and pallidum. The complete set of results for bilinguals is shown in table 3. Two significant correlations remained significant after FDR correction only in the bilingual group. We observed a strong positive association between mean Theta Bi-Occ connectivity with the left caudate volume (rho = 0.600; $p = 0.004$) and the right caudate volume (rho = 0.640; $p = 0.002$). It is remarkable, however, that the left and the right caudate volumes were also significantly associated with the mean FC of other clusters such as Theta L-Occ and Beta2 Bi-Occ at a less conservative threshold (uncorrected $\alpha < 0.050$). These correlations highlighted a remarkable positive association ($0.470 < \text{rho} < 0.530$) between the FC among these subsets of regions and caudate nuclei volumes bilaterally. Figure 3 presents scatter plots of the above-mentioned associations for both groups.

None of the correlations calculated in the monolingual group of older adults reached significance, not even employing the uncorrected threshold. Furthermore, the age of acquisition of the second language in the bilingual group was not significantly associated with grey matter volumes nor with FC ($\alpha < 0.050$).

Discussion

Approximately half of the world's population is bilingual (European Commission Special Eurobarometer, 2012). Bilingualism has been suggested to modify brain structure and function, to enhance cognition and even to delay the onset of dementia (Adesope et al., 2010; Craik, Bialystok & Freedman, 2010; Grundy et al., 2017). Nevertheless, such claims have given rise to controversy among the scientific community, since other research groups failed to replicate those findings (Cox et al., 2016; Zahodne et al., 2014; Zatorre et al., 2001). The aim of the present research work was to unravel the influence of bilingualism on the functional network organization in healthy highly-educated older adults using MEG. Our presumption was that a better understanding of how bilingualism shapes the brain could shed light on this debate. This would enable the emergence of a plausible explanation with regards to how this skill results in the beneficial effects that certain studies have reported.

With this purpose, we compared the brain connectivity at rest of a group of monolingual and a group of bilingual healthy older adults. The performed analyses exposed five significant FC clusters in three different frequency ranges in which bilinguals exhibited greater FC than monolinguals (figures 1.1, 1.2 and 1.3). Interestingly, most of the areas within the clusters in which bilinguals exhibited greater FC than monolinguals are involved in language processing, which seems to support the relevance of our results. One of the regions showing increased FC in bilinguals, the supramarginal gyrus, has been reported to play a role in the network involved in word processing (Oberhuber, Hope, Seghier, Parker Jones, Prejawa, Green & Price, 2016; Zou, Abutalebi et al., 2012) and language switching (Luk, Green, Abutalebi & Grady, 2012; Moritz-Gasser & Duffau, 2009; Olsen, Pangelinan, Bogulski, Chakravarty, Luk, Grady & Bialystok, 2015; Price, Green & Von Studnitz, 1999). Similarly, the superior parietal lobe is well-known for its role in the circuit of phonological processing (Wong et al., 2016; Zatorre et al., 2001). Suh, Yoon, Lee, Chung, Cho and Park (2007) report that sentence processing in bilinguals (both in L1 and L2) involves a network composed of the inferior frontal gyrus, the inferior parietal lobe and several occipital areas, such as the cuneus and the lingual gyrus. Also, the superior parietal cortex, as well as the superior occipital cortex (together with other temporal and frontal structures), are part of the network described by García-Pentón, Pérez Fernández, Iturria-Medina, Gillon-Dowens and Carreiras (2014) involved in visual word recognition, reading and semantic processing. Therefore, our results (i.e., increased FC between most of these areas) could represent the neurophysiological substrate of improved language abilities in the bilingual senior population. This hypothesis could be supported by previous findings reporting that FC at rest between several regions involved in the FC changes that we described (including the supramarginal gyrus,

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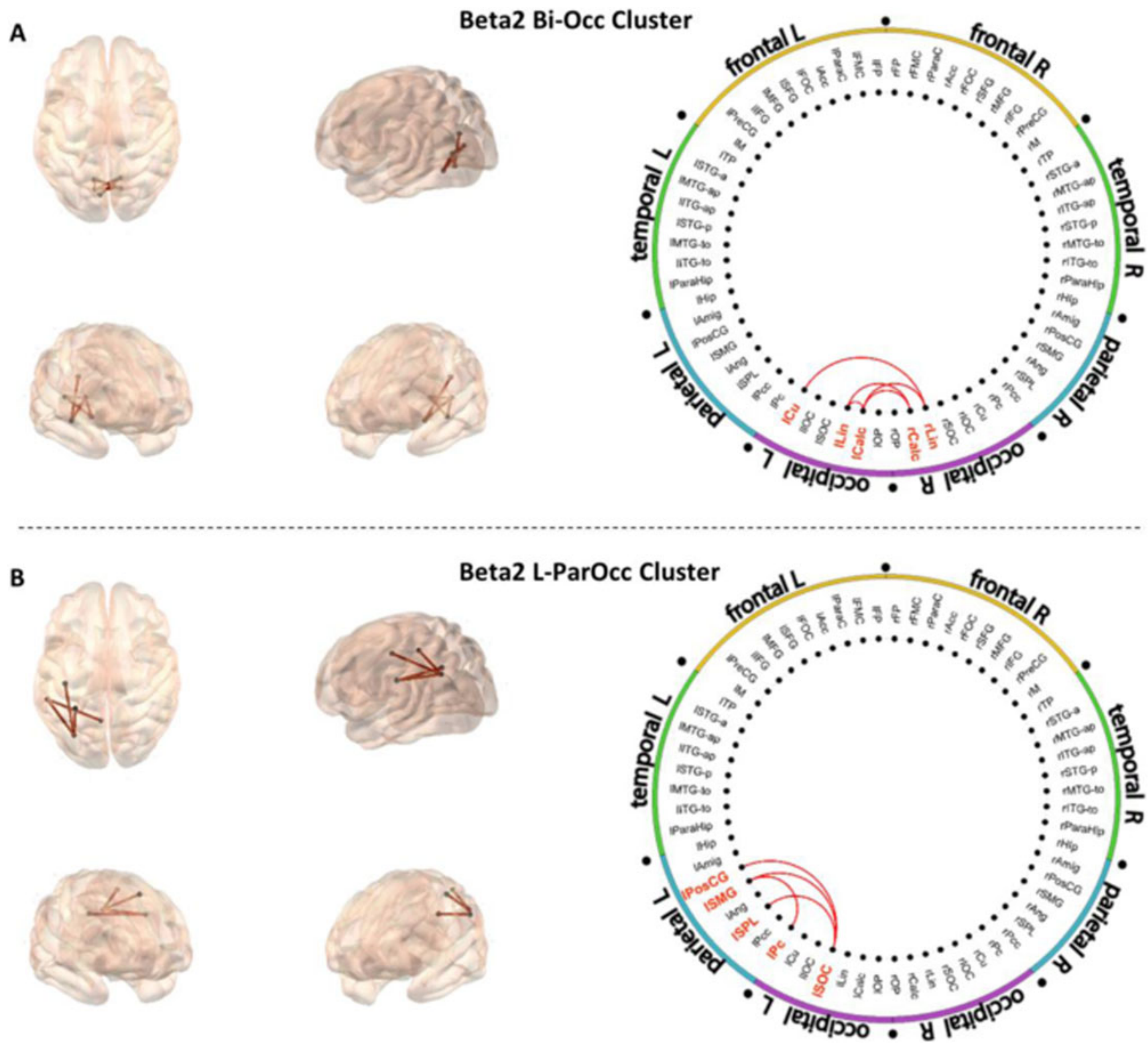

Fig. 1.3. Figure 1.3 Shows the regions included in the two clusters in the Beta2 band (A: Beta2 Bi-Occ; B: Beta2 L-ParOcc) in which bilinguals exhibit greater FC than monolinguals.

the postcentral gyrus, the superior parietal cortex, the lingual gyrus and several areas within the occipital lobe) correlated with reading abilities in bilingual younger adults (Zhang, Li, Chen, Xue, Lu, Mei, Xue, Xue, He, Chen, Wei & Dong, 2014). Thus, our results strongly suggest that bilingualism directly affects FC within networks involved in language processing.

Strikingly, bilingual older adults did not show changes in frontal structures, in contrast to previous studies (García-Pentón et al., 2014; Olsen et al., 2015; Perani et al., 2017). However, our functional results are in line with Grundy et al.'s (2017) proposition, stating that during the first stages of L2 acquisition bilinguals rely more on frontal structures but over time they devote more resources to posterior and subcortical circuits. According to this hypothesis, FC changes over posterior areas could be interpreted as a reorganization of functional networks driven by speaking two languages. This goes in line with the suggestion by Grant, Dennis and Li (2014) to study FC patterns of the bilingual brain focusing not only on the frontal lobe but also considering temporal, parietal, occipital and subcortical regions. As an example, Berroir, Ghazi-Saidi, Dash, Adrover-Roig, Benali and Ansaldo (2017) report that, during a Simon task in an fMRI scanner, monolinguals recruited motor, visual and executive function areas, while bilinguals relied solely on visuospatial processing. Similar results had been previously found by Ansaldo, Ghazi-Saidi and Adrover-Roig (2015), who concluded that bilinguals do not activate a circuit that is particularly vulnerable to the aging process. Gold et al. (2013) also proposes that bilingualism protects against age-related changes in fMRI measurements, such as the over-recruitment of frontal areas (during a perceptual switching task). Furthermore, it is important to mention that some key structures in the field of bilingualism such as the caudate or putamen nuclei among others are not present in our FC results. Beyond the above-mentioned reasons explaining the absence of frontal regions involvement, it is crucial to bear in mind that such deep structures cannot be detected with MEG, which is mainly sensitive to tangential sources located in the

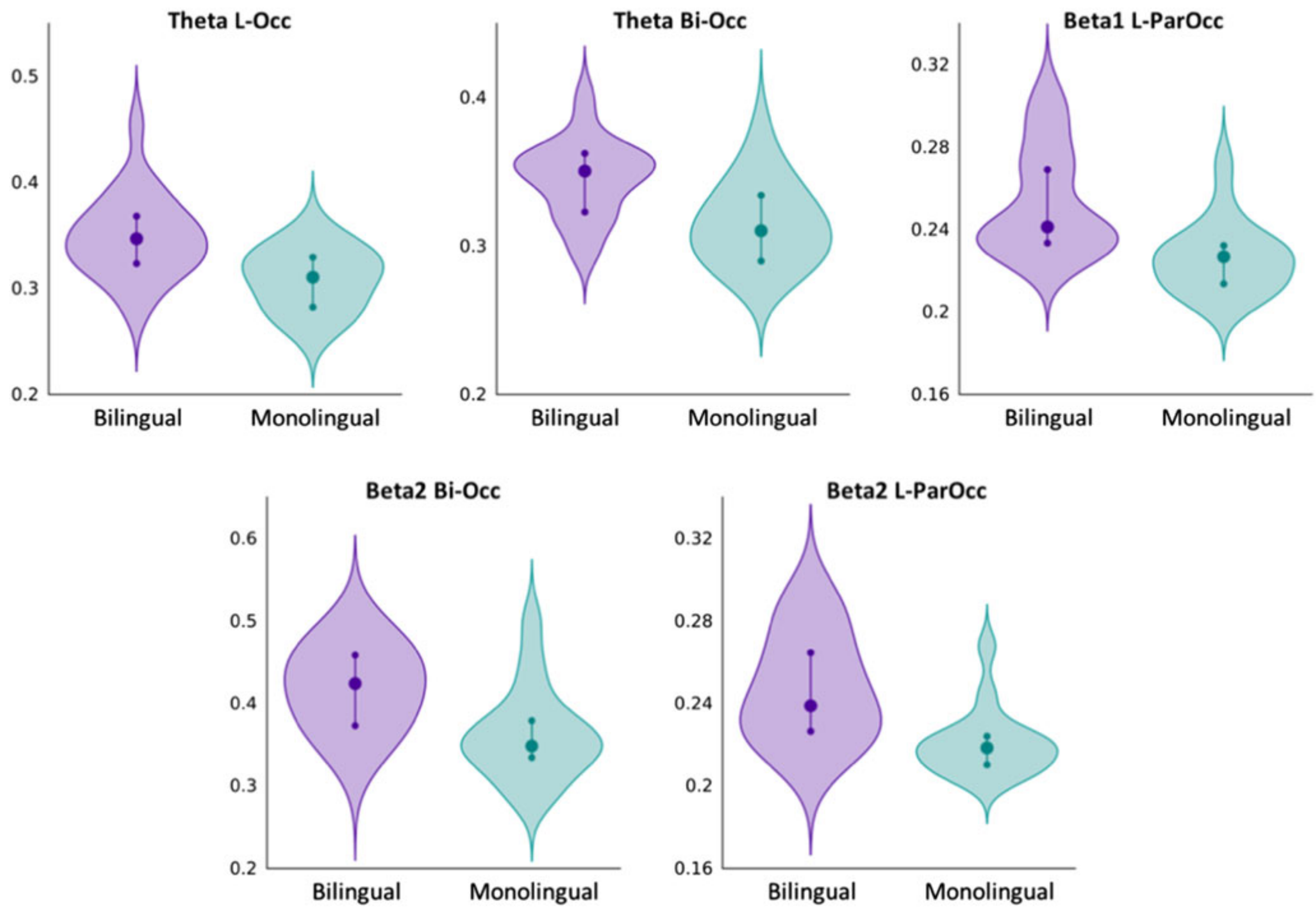

Fig. 2. Figure 2 presents violin plots displaying the distribution of individual FC values in each cluster.

cortex. Therefore, we cannot rule out that such deep structures could also be involved in network reorganization in healthy highly educated older adults, in addition to the regions described in our results.

Additionally, bilingualism has been related to later onset of Alzheimer's disease (Alladi, Bak, Duggirala, Surampudi, Shailaja, Shukla, Chaudhuri & Kaul, 2013). AD is commonly regarded as a disconnection syndrome (Delbeuck, Linden & Collette, 2003), and it is known to particularly impair FC over posterior brain regions such as occipital and parietal regions, reducing the strength of hub regions over these brain areas (Jones, Knopman, Gunter, Graff-Radford, Vemuri, Boeve, Petersen, Weiner & Jack, 2015; Nakamura, Cuesta, Kato, Arahata, Iwata, Yamagishi, Kuratsubo, Kato, Bundo, Diers, Fernández, Maestú & Ito, 2017; Yu, Engels, Hillebrand, van Straaten, Gouw, Teunissen, van der Flier, Scheltens & Stam, 2017). These brain regions suffer alterations very early in the course of the disease, even in the preclinical stages (López-Sanz et al., 2017a; López-Sanz, Garcés, Álvarez, Delgado-Losada, López-Higes & Maestú, 2017b). Interestingly, our results could bridge the gap between the above-mentioned findings, providing a plausible neurophysiological substrate for this protective effect. According to this hypothesis, it could be argued that bilingualism enhances FC within posterior brain regions in healthy older adults. Later on, should neurodegeneration initiate, such stronger FC would be hypothesized to delay 2-4 functional changes associated with AD symptomatology, (i.e., posterior disconnection) which could in turn result in later disease onset. In this vein, the enhanced FC values over posterior brain regions observed in healthy bilingual older adults could be interpreted as an increased brain reserve capacity (Satz, 1993) or a sign of network flexibility due to increased cognitive reserve (Stern, 2002). However, this hypothesis should be confirmed by future work using longitudinal designs. Although changes in posterior regions were not easily foreseeable in the specific context of bilingualism, the fact that aging is also typically accompanied by FC decreases over these same regions (Damoiseaux, Beckmann, Arigita, Barkhof, Scheltens, Stam, Smith, & Rombouts, 2008) supports the interpretation of the observed network reorganization as a potential brain protective mechanism against healthy and pathological aging.

Beyond that, in the present study, FC values in Theta Bi-Occ cluster were strongly correlated with caudate volumes bilaterally. Remarkably, these correlations were only significant for the bilingual subsample. A significant uncorrected correlation was also evident for Beta2 Bi-Occ cluster with bilateral caudate and Theta L-Occ cluster with right caudate (and a tendency was observed with left caudate). The caudate nucleus is a key structure in the field of bilingualism, and has been widely studied, mainly for its involvement in executive function (Pliatsikas & Luk, 2016). Allegedly, this region plays an important role when switching between two languages (Abutalebi, Annoni, Zimine, Pegna, Seghier, Lee-Jahnke, Lazeyras, Cappa & Khateb, 2008; Luk et al., 2012; Moritz-Gasser & Duffau, 2009), also in bimodal bilinguals (Zou, Ding, Abutalebi, Shu & Peng, 2012). More specifically, the head of the left caudate is part of a language control network

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Table 3. Correlations between Grey Matter Structures Volumes and Functional Connectivity Values in Bilinguals

Table 3 presents Pearson correlation coefficients (rho) and p-values (p) for the correlations between selected grey matter structures (where Caud, Put and Pal stand for caudate, putamen and pallidus respectively and ACC stands for anterior cingulate cortex; laterality is indicated by an r -right- or -l- left) and average functional connectivity (FC) values for each cluster (*alpha < 0.05; **FDR corrected)

	ACC		r-Caud		r-Put		r-Pal		l-Caud		l-Put		l-Pal	
	rho	p	rho	p	rho	p	Rho	p	Rho	p	rho	p	Rho	p
Theta L-Occ	0.137	.553	0.471	.031*	0.293	.197	0.258	.259	0.414	.062	0.184	.426	−0.01	.966
Theta Bi-Occ	0.245	.285	0.641	.002**	0.406	.067	0.418	.060	0.599	.004**	0.272	.233	0.168	.467
Beta1 L-ParOcc	0.138	.550	0.179	.436	−0.067	.773	0.1	.665	0.047	.841	−0.068	.768	0.111	.631
Beta2 Bi-Occ	0.263	.250	0.533	.013*	0.359	.110	0.36	.109	0.499	.021*	0.265	.246	0.029	.900
Beta2 L-ParOcc	0.206	.371	0.195	.396	0.028	.906	0.255	.266	0.066	.776	−0.067	.772	0.271	.234

(Abutalebi & Green, 2016; Friederici, 2006), and it is particularly involved when a cognitive process cannot be automatically carried out. Furthermore, caudate activation has been found to be higher when switching to a less dominant language (Abutalebi, Brambati, Annoni, Moro, Cappa & Perani, 2007). In our study, only late bilinguals were included, and Spanish was the dominant language for all of them (most of them reported having acquired proficiency in their L2 for professional reasons). Thus, we propose that this lack of codominance between L1 and L2 in our sample could be enhancing the role of the caudate nucleus in language processing. The fact that we observed strong correlations between FC values and caudate volumes only in the bilingual group supports the relationship between FC changes and network reorganization in bilinguals. Along with our results, previous studies have shown increased FC between the left caudate and language processing regions in bilinguals (Li, Abutalebi, Zou, Yan, Liu, Feng, Wang, Guo & Ding, 2015). This is a very relevant finding, since the development of a gating system in the striatum to the prefrontal cortex has been hypothesized to underpin the improved executive function that bilinguals show (Stocco & Prat, 2014).

Focusing on the role of education, bilingual participants have been said to potentially have higher educational levels. Although this is not necessarily the case of older simultaneous bilinguals in Spain (mainly those who were born in bilingual regions), in general, sequential bilinguals within our age range are those who had access to a better education (bear in mind that L2 acquisition was not mandatory at the time) and those who held highly qualified job positions. For that reason, educational attainment has been suggested as a relevant confounding factor in bilingual research. Evidence so far has not been able to solve this question. For example, while Liu, Liu, Yip, Meguro and Meguro (2017) and Gollan, Salmon, Montoya and Galasko (2011) describe a protective effect of speaking several languages only among low educated older adults, Alladi et al. (2013) claim that bilingualism delays the onset of dementia independently of other cofounding factors. In this regard, it is important to highlight that in this study we constrained the sample to healthy highly educated older adults with the intention to reveal the effect that bilingualism exerts on the brain FC beyond the already widely studied effect of educational attainment (Arenaza-Urquijo, Landeau, La Joie, Mevel, Mézenge, Perrotin, Desgranges, Bartrés-Faz, Eustache & Chételat, 2013; Bastin, Yakushev, Bahri, Fellgiebel, Eustache, Landeau, Scheurich, Feyers, Collette, Chételat & Salmon, 2012; Lopez, Aurtenetxe, Pereda, Cuesta, Castellanos, Bruña, Niso & Maestu, 2014). In other words, we were interested in unveiling the potential contribution of bilingualism given an already high educational level. At this respect, we have been able to describe a neurophysiological signature specific to bilingualism. However, we cannot dismiss the possibility that there was an actual causal relationship between being bilingual and acquiring a higher educational level.

Finally, L2 age of acquisition did not correlate either with FC values or grey matter volumes. However, it is relevant to emphasize that only sequential bilinguals were included in this work. Thus, individuals who acquired an L2 very early in life were not considered in this study. Additionally, most bilinguals in this sample were firstly exposed to their L2 in school, but they only developed L2 proficiency and began to actively and or/socially use their L2 later in life, when their professional or personal context required so. Beyond AoA, bilingual experience is a relevant factor (Luk & Bialystok, 2013) and therefore we consider that "degree of L2 social usage" or "age of L2 immersion" could

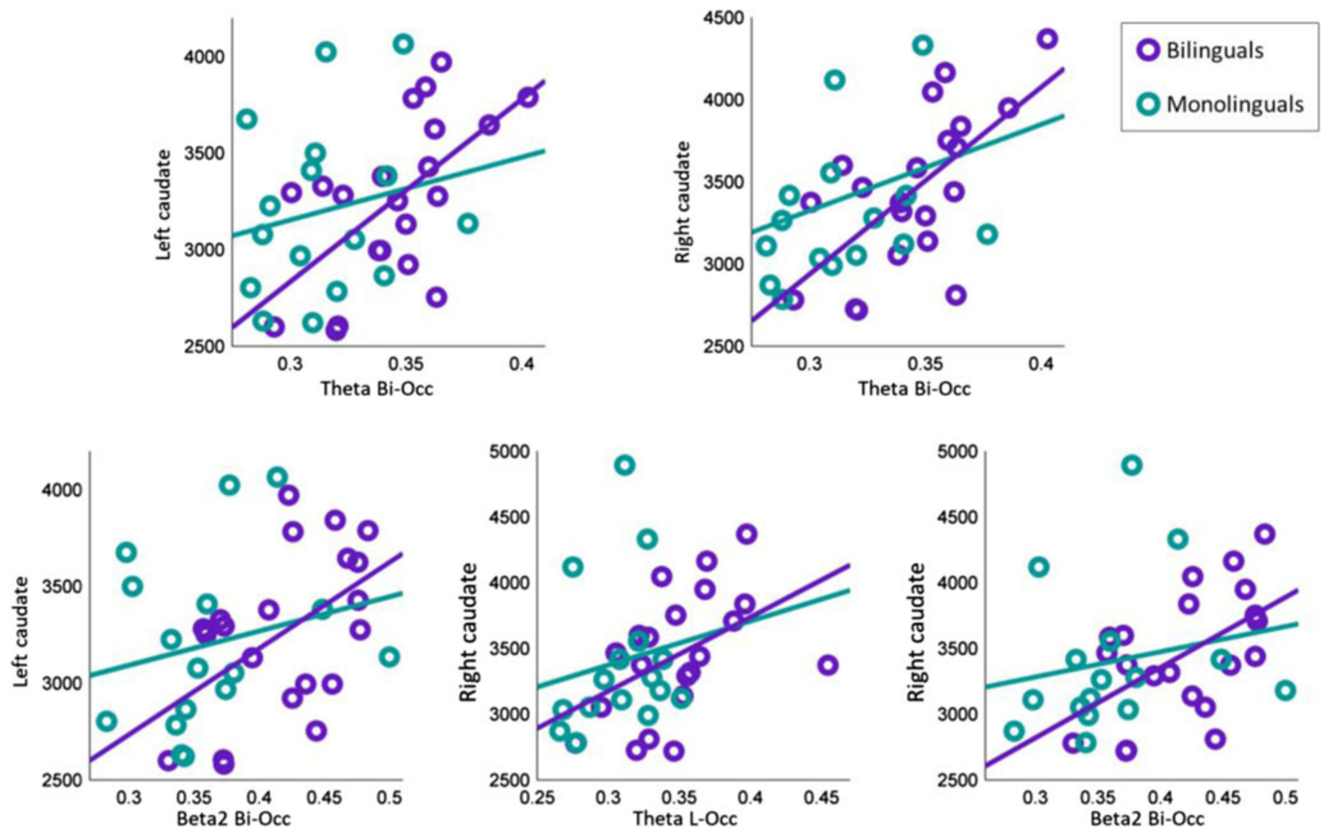

Fig. 3. Figure 3 presents the scatter plots of the significant correlations (p <0.05) between caudate volume and FC values in each cluster.

be more closely related to the functional and structural changes that we reveal in this study. More accurate information regarding these two variables should be collected in future studies in order to perform such analyses.

Also, as has already been said in this article, bilingualism is a complex skill that encompasses several aspects. In this regard, a potential limitation of our study was not to incorporate a specific test for L1 and L2 proficiency. This would enable the analysis of how proficiency in L2 relates to the functional differences that we have reported in highly educated bilingual older adults.

To the best of our knowledge, this is the first MEG study addressing the effect of bilingualism at the neurophysiological level. Also, the fact that we focused on a specific subpopulation of bilinguals (late bilinguals having been introduced to L2 in a formal setting) allows us to more accurately compare our results with those from other studies and unravel presumed discrepancies. Rigorous inclusion criteria are critical for more accurate interpretations in the field of bilingualism, although at the cost of sample representativeness. Yet, our results are promising and support the relevance of bilingualism as it enhances posterior functional circuits typically impaired in aging (Jones et al., 2011). Based on these results, policies promoting the use of a second language in typically monolingual populations could be beneficial to promote healthy aging.

Disclosure statement. The authors have no conflicts of interest to disclose.

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References

Abutalebi J, Annoni JM, Zimine I, Pegna AJ, Seghier ML, Lee-Jahnke H, Lazeyras F, Cappa SF and Khateb A (2008) Language control and lexical competition in bilinguals: An event-related fMRI study. *Cerebral Cortex* **18**(7), 1496–1505. https://doi.org/10.1093/cercor/bhm182

Abutalebi J, Brambati SM, Annoni J-M, Moro A, Cappa SF and Perani D (2007) The Neural Cost of the Auditory Perception of Language Switches: An Event-Related Functional Magnetic Resonance Imaging Study in Bilinguals. *Journal of Neuroscience* **27**(50), 13762–13769. https://doi.org/10.1523/JNEUROSCI.3294-07.2007

Abutalebi J, Canini M, Della Rosa PA, Sheung LP, Green DW and Weekes BS (2014) Bilingualism protects anterior temporal lobe integrity in aging. *Neurobiology of Aging* **35**(9), 2126–2133. https://doi.org/10.1016/j.neurobiolaging.2014.03.010

Abutalebi J and Green DW (2016) Neuroimaging of language control in bilinguals: Neural adaptation and reserve. *Bilingualism* **19**(4), 689–698. https://doi.org/10.1017/S1366728916000225

Adesope OO, Lavin T, Thompson T and Ungerleider C (2010) A Systematic Review and Meta-Analysis of the Cognitive Correlates of Bilingualism. *Review of Educational Research* **80**(2), 207–245. https://doi.org/10.3102/0034654310368803

Alladi S, Bak TH, Duggirala V, Surampudi B, Shailaja M, Shukla AK, Chaudhuri JR and Kaul S (2013) Bilingualism delays age at onset of dementia, independent of education and immigration status. *Neurology* **81**(22), 1938–1944. https://doi.org/10.1212/01.wnl.0000436609.20587.65

Anderson JAE, Grundy JG, De Frutos J, Barker RM, Grady C and Bialystok E (2018) Effects of bilingualism on white matter integrity in older adults. *NeuroImage* **167** (November 2017), 143–150. https://doi.org/10.1016/j.neuroimage.2017.11.038

Andrews-hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME and Buckner RL (2009) Disruption of Large-Scale Brain Systems in Advanced Aging. *Neuron* **56**(5), 924–935. https://doi.org/10.1016/j.neuron.2007.10.038.Disruption

Ansaldo AI, Ghazi-Saidi L and Adrover-Roig D (2015) Interference control in elderly bilinguals: Appearances can be misleading. *Journal of Clinical and Experimental Neuropsychology* **37**(5), 455–470. https://doi.org/10.1080/13803395.2014.990359

Arenaza-Urquijo EM, Landeau B, La Joie R, Mevel K, Mézenge F, Perrotin A, Desgranges B, Bartrés-Faz D and Chételat G (2013) Relationships between years of education and gray matter volume, metabolism and functional connectivity in healthy elders. *NeuroImage* **83**, 450–457. https://doi.org/10.1016/j.neuroimage.2013.06.053

Bak TH, Nissan JJ, Allerhand MM and Deary IJ (2014) Does bilingualism influence cognitive aging? *Annals of Neurology* **75**(6), 959–963. https://doi.org/10.1002/ana.24158

Bastin C, Yakushev I, Bahri MA, Fellgiebel A, Eustache F, Landeau B, Scheurich A, Feyers D, Collette F, Chételat G and Salmon E (2012) Cognitive reserve impacts on inter-individual variability in resting-state cerebral metabolism in normal aging. *NeuroImage* **63**(2), 713–722. https://doi.org/10.1016/j.neuroimage.2012.06.074

Berken JA, Chai X, Chen J-K, Gracco VL and Klein D (2016) Effects of Early and Late Bilingualism on Resting-State Functional Connectivity. *Journal of Neuroscience* **36**(4), 1165–1172. https://doi.org/10.1523/JNEUROSCI.1960-15.2016

Berroir P, Ghazi-Saidi L, Dash T, Adrover-Roig D, Benali H and Ansaldo AI (2017) Interference control at the response level: Functional networks reveal higher efficiency in the bilingual brain. *Journal of Neurolinguistics* **43**, 4–16. https://doi.org/10.1016/j.jneuroling.2016.09.007

Bialystok E (2017) The bilingual adaptation: How minds accommodate experience. *Psychological Bulletin* **143**(3), 233–262. https://doi.org/10.1037/bul0000099

Bialystok E, Craik FIM and Freedman M (2007) Bilingualism as a protection against the onset of symptoms of dementia. *Neuropsychologia* **45**(2), 459–464. https://doi.org/10.1016/j.neuropsychologia.2006.10.009

Calvo A and Bialystok E (2014) Independent effects of bilingualism and socioeconomic status on language ability and executive functioning. *Cognition* **130**(3), 278–288. https://doi.org/10.1016/j.cognition.2013.11.015

Chai XJ, Berken JA, Barbeau EB, Soles J, Callahan M, Chen J-K and Klein D (2016) Intrinsic Functional Connectivity in the Adult Brain and Success in Second-Language Learning. *Journal of Neuroscience* **36**(3), 755–761. https://doi.org/10.1523/JNEUROSCI.2234-15.2016

Correia JM, Jansma B, Hausfeld L, Kikkert S and Bonte M (2015) EEG decoding of spoken words in bilingual listeners: From words to language invariant semantic-conceptual representations. *Frontiers in Psychology* **6** (FEB), 1–10. https://doi.org/10.3389/fpsyg.2015.00071

Costa A, Hernández M and Sebastián-Gallés N (2008) Bilingualism aids conflict resolution: Evidence from the ANT task. *Cognition* **106**(1), 59–86. https://doi.org/10.1016/j.cognition.2006.12.013

Cox SR, Bak TH, Allerhand M, Redmond P, Starr JM, Deary IJ and MacPherson SE (2016) Bilingualism, social cognition and executive functions: A tale of chickens and eggs. *Neuropsychologia* **91**, 299–306. https://doi.org/10.1016/j.neuropsychologia.2016.08.029

Craik FIM, Bialystok E and Freedman M (2010) Delaying the onset of Alzheimer disease: Bilingualism as a form of cognitive reserve. *Neurology* **75**(19), 1726–1729. https://doi.org/10.1212/WNL.0b013e3181fc2a1c

Crane PK, Gruhl JC, Erosheva EA, Gibbons LE, McCurry SM, Rhoads K, Rhoads K, Nguyen V, Arani K, Masaki K and White L (2010) Use of spoken and written Japanese did not protect Japanese-American men from cognitive decline in late life. *Journals of Gerontology - Series B Psychological Sciences and Social Sciences* **65 B**(6), 654–666. https://doi.org/10.1093/geronb/gbq046

Cuesta P, Garcés P, Castellanos NP, López ME, Aurtenetxe S, Bajo R, Pineda-Pardo JA, Bruña R, Marín AG, Delgado M, Barabash A, I, Cabranes JA, Fernandez A, Del Pozo F, Sancho M, Marcos A, Nakamura A and Maestú F (2015) Influence of the APOE ϵ4 allele and mild cognitive impairment diagnosis in the disruption of the MEG resting state functional connectivity in sources space. *Journal of Alzheimer's Disease* **44**(2), 493–505. https://doi.org/10.3233/JAD-141872

Damoiseaux JS, Beckmann CF, Arigita EJS, Barkhof F, Scheltens P, Stam CJ, Smith SM and Rombouts SARB (2008) Reduced resting-state brain activity in the default network in normal aging. *Cerebral Cortex* **18** (8), 1856–1864. https://doi.org/10.1093/cercor/bhm207

Delbeuck X, Linden M Van der and Collette F (2003) Alzheimer' Disease as a Disconnection Syndrome? *Neuropsychology Review* **13**(2), 79–92. https://doi.org/10.1023/A:1023832305702

Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman B, Albert MS and Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage* **31**(3), 968–980.

Deuker L, Bullmore ET, Smith M, Christensen S, Nathan PJ, Rockstroh B and Bassett DS (2009) Reproducibility of graph metrics of human brain functional networks. *NeuroImage* **47**(4), 1460–1468. https://doi.org/10.1016/j.neuroimage.2009.05.035

Estanga A, Ecay-Torres M, Ibañez A, Izagirre A, Villanua J, Garcia-Sebastian M, Iglesias Gaspar MT, Otaegui Arrazola A, Iriondo A, Clerigue M and Martinez-Lage P (2017) Beneficial effect of bilingualism on Alzheimer's disease CSF biomarkers and cognition. *Neurobiology of Aging* **50**, 144–151. https://doi.org/10.1016/j.neurobiolaging.2016.10.013

Fransson P and Marrelec G (2008) The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *Neuroimage* **42**(3), 1178-1184.

Friederici AD (2006) What's in control of language? *Nature Neuroscience* **9** (8), 991–992. https://doi.org/10.1038/nn0806-991

European Commission Special Eurobarometer (2012) Europeans and their languages (386). Available at: http://ec.europa.eu/publicopinion/archives/ebs/ebs243

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B and Dale AM (2002) Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* **33** 341–355. Available at http://www.ncbi.nlm.nih.gov/pubmed/11832223

Fuller-Thomson E (2015) Emerging evidence contradicts the hypothesis that-bilingualism delays dementia onset. A Commentary on "Age of dementia diagnosis incommunity dwelling bilingual and monolingual Hispanic Americans" by Lawton et al., 2015. *Cortex* **66**, 170–172. https://doi.org/10.1016/j.cortex.2015.01.024

Garcés P, López-Sanz D, Maestú F and Pereda E (2017) Choice of magnetometers and gradiometers after signal space separation. *Sensors (Switzerland)* **17**(12), 1–13. https://doi.org/10.3390/s17122926

García-Pentón L, Pérez Fernández A, Iturria-Medina Y, Gillon-Dowens M and Carreiras M (2014) Anatomical connectivity changes in the bilingual brain. *NeuroImage* **84**, 495–504. https://doi.org/10.1016/j.neuroimage.2013.08.064

Gold BT, Kim C, Johnson NF, Kryscio RJ and Smith CD (2013) Lifelong Bilingualism Maintains Neural Efficiency for Cognitive Control in Aging. *Journal of Neuroscience* **33**(2), 387–396. https://doi.org/10.1523/JNEUROSCI.3837-12.2013

Gollan TH, Salmon DP, Montoya RI and Galasko DR (2011) Degree of bilingualism predicts age of diagnosis of Alzheimer's disease in low-education but not in highly educated Hispanics. *Neuropsychologia* **49**(14), 3826–3830. https://doi.org/10.1016/j.neuropsychologia.2011.09.041

Grabner RH, Brunner C, Leeb R, Neuper C and Pfurtscheller G (2007) Event-related EEG theta and alpha band oscillatory responses during language translation. *Brain Research Bulletin* **72**(1), 57–65. https://doi.org/10.1016/j.brainresbull.2007.01.001

Grady CL, Luk G, Craik FIM and Bialystok E (2015) Brain network activity in monolingual and bilingual older adults. *Neuropsychologia* **66**, 170–181. https://doi.org/10.1016/j.neuropsychologia.2014.10.042

Gramfort A, Papadopoulo T, Olivi E and Clerc M (2010) OpenMEEG: open-source software for quasistatic bioelectromagnetics. *Biomedical Engineering Online* **9**, 45. https://doi.org/10.1186/1475-925X-9-45

Grant A, Dennis NA and Li P (2014) Cognitive control, cognitive reserve, and memory in the aging bilingual brain. *Frontiers in Psychology* **5**(DEC), 1–10. https://doi.org/10.3389/fpsyg.2014.01401

Grundy JG, Anderson JAE and Bialystok E (2017) Neural correlates of cognitive processing in monolinguals and bilinguals. *Annals of the New York Academy of Sciences* 183–201. https://doi.org/10.1111/nyas.13333

Guzmán-Vélez E and Tranel D (2015) Does bilingualism contribute to cognitive reserve? Cognitive and neural perspectives. *Neuropsychology* **29**(1), 139.

Hardmeier M, Hatz F, Bousleiman H, Schindler C, Stam CJ and Fuhr P (2014) Reproducibility of functional connectivity and graph measures based on the phase lag index (PLI) and weighted phase lag index (wPLI) derived from high resolution EEG. *PloS One* **9**(10), e108648. https://doi.org/10.1371/journal.pone.0108648

Hernández M, Martin CD, Barceló F and Costa A (2013) Where is the bilingual advantage in task-switching? *Journal of Memory and Language* **69**(3), 257–276. https://doi.org/10.1016/j.jml.2013.06.004

Hsu CT, Jacobs AM and Conrad M (2015) Can Harry Potter still put a spell on us in a second language? An fMRI study on reading emotion-laden literature in late bilinguals. *Cortex* **63**, 282–295. https://doi.org/10.1016/j.cortex.2014.09.002

Hudspeth AJ, Jessell TM, Kandel ER, Schwartz JH and Siegelbaum SA (Eds) (2013) *Principles of neural science*. McGraw-Hill, Health Professions Division.

Jin S-H, Seol J, Kim JS and Chung CK (2011) How reliable are the functional connectivity networks of MEG in resting states? *Journal of Neurophysiology* **106**(6), 2888–2895. https://doi.org/10.1152/jn.00335.2011

Jones D, Knopman DS, Gunter JL, Graff-Radford J, Vemuri P, Boeve BF, Petersen RC,Weiner MW and Jack CR (2015) Cascading network failure across the Alzheimer's disease spectrum. *Brain* **139**(2), 547–562. https://doi.org/10.1093/brain/awv338

Jones DT, Machulda MM, Vemuri P, McDade EM, Zeng G, Senjem ML, Gunter SA, Przybelski RT, Avula DS, Knopman BF, Boeve RC, Petersen and Jack CR (2011) Age-related changes in the default mode network are more advanced in Alzheimer disease. *Neurology* **77**, 1524–1531. https://doi.org/10.1212/WNL.0b013e318233b33d

Klimova B, Valis M and Kuca K (2017) Bilingualism as a strategy to delay the onset of Alzheimer's disease. *Clinical Interventions in Aging* **12**, 1731–1737. https://doi.org/10.2147/CIA.S145397

Kousaie S, Chai XJ, Sander KM and Klein D (2017) Simultaneous learning of two languages from birth positively impacts intrinsic functional connectivity and cognitive control. *Brain and Cognition* **117**(March), 49–56. https://doi.org/10.1016/j.bandc.2017.06.003

Lachaux J-P, Rodriguez E, Martinerie J and Varela FJ (1999) Measuring Phase Synchrony in Brain Signals. *Human Brain Mapping* **8**, 194–208.

Ley 14/1970, de 4 de agosto, General de Educación y Financiamiento de la Reforma Educativa. Boletín Oficial del Estado, núm. 187, de 6 de agosto de 1970, páginas 12525 a 12546 https://www.boe.es/buscar/doc.php?id=BOE-A-1970-852

Li L, Abutalebi J, Zou L, Yan X, Liu L, Feng X, Wang R, Guo T and Ding G (2015) Bilingualism alters brain functional connectivity between "control" regions and "language" regions: Evidence from bimodal bilinguals. *Neuropsychologia* **71**, 236–247. https://doi.org/10.1016/j.neuropsychologia.2015.04.007

Litvak V, Mattout J, Kiebel S, Phillips C, Henson R, Kilner J, Barnes G, Oostenveld R, Daunizeau J, Flandin G, Penny W and Friston K (2011) EEG and MEG data analysis in SPM8. *Computational Intelligence and Neuroscience* 852961. https://doi.org/10.1155/2011/852961

Liu YC, Liu YY, Yip PK, Meguro M and Meguro K (2017) Speaking one more language in early life has only minor effects on cognition in Taiwanese with low education level: the Taishan Project. *Psychogeriatrics* **17**, 256–261. https://doi.org/10.1111/psyg.12230

Lobo A, Ezquerra J, Gomez Burgada F, Sala JM and Seva Dıaz A (1979) Cognocitive mini-test (a simple practical test to detect intellectual changes in medical patients). *Actas luso españolas Neurol. Psiquiatr. y ciencias afines.* **7** 189–202. Available at: http://europepmc.org/abstract/med/474231

López-Sanz D, Bruña R, Garcés P, Martín-Buro MC, Walter S, Delgado ML, Montenegro M, Lopez-Higes R, Marcos A and Maestú F (2017a) Functional Connectivity Disruption in Subjective Cognitive Decline and Mild Cognitive Impairment: A Common Pattern of Alterations. *Frontiers in Aging Neuroscience* **9**, 109. https://doi.org/10.3389/fnagi.2017.00109

López-Sanz D, Garcés P, Álvarez B, Delgado-Losada ML, López-Higes R and Maestú F (2017b) Network Disruption in the Preclinical Stages of Alzheimer's Disease: From Subjective Cognitive Decline to Mild Cognitive Impairment. *International Journal of Neural Systems* **27**(8), 1750041. https://doi.org/10.1142/S0129065717500411

Lopez ME, Aurtenetxe S, Pereda E, Cuesta P, Castellanos NP, Bruña R, Niso G, Maestu F and Bajo R (2014) Cognitive reserve is associated with the functional organization of the brain in healthy aging: A MEG study. *Frontiers in Aging Neuroscience* **6**(JUN), 1–9. https://doi.org/10.3389/fnagi.2014.00125

Luk G, Bialystok E, Craik FI and Grady CL (2011) Lifelong bilingualism maintains white matter integrity in older adults. *Journal of Neuroscience* **31**(46), 16808-16813.

Luk G, Green DW, Abutalebi J and Grady C (2012) Cognitive control for language switching in bilinguals: A quantitative meta-analysis of functional neuroimaging studies. *Language and cognitive processes* **27**(10), 1479-1488.

Luk G and Bialystok E (2013) Bilingualism is not a categorical variable: Interaction between language proficiency and usage. *Journal of Cognitive Psychology* **25**(5), 605-621.

Maris E and Oostenveld R (2007) Nonparametric statistical testing of EEG- and MEG-data. *Journal of Neuroscience Methods* **164**(1), 177–190. https://doi.org/10.1016/j.jneumeth.2007.03.024

Mesulam MM (1990) Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Annals of Neurology: Official* Journal of the American Neurological Association and the Child Neurology Society **28**(5), 597-613.

Mesulam M (1998) From sensation to perception. *Brain* **121**, 1013–1052. https://doi.org/10.1093/brain/121.6.1013

Moritz-Gasser S and Duffau H (2009) Cognitive processes and neural basis of language switching: Proposal of a new model. *NeuroReport* **20**(18), 1577–1580. https://doi.org/10.1097/WNR.0b013e328333907e

Nakamura A, Cuesta P, Kato T, Arahata Y, Iwata K, Yamagishi M, Kuratsubo I, Kato K, Bundo M, Diers K, Fernández A, Maestú F and Ito K (2017) Early functional network alterations in asymptomatic elders at risk for Alzheimer's disease. *Scientific Reports* **7**(1), 1–11. https://doi.org/10.1038/s41598-017-06876-8

Oberhuber M, Hope TMH, Seghier ML, Parker Jones O, Prejawa S, Green DW and Price CJ (2016) Four Functionally Distinct Regions in the Left Supramarginal Gyrus Support Word Processing. *Cerebral Cortex* **26**(11), 4212–4226. https://doi.org/10.1093/cercor/bhw251

Olsen RK, Pangelinan MM, Bogulski C, Chakravarty MM, Luk G, Grady CL and Bialystok E (2015) The effect of lifelong bilingualism on regional grey and white matter volume. *Brain Research* **1612**, 128–139. https://doi.org/10.1016/j.brainres.2015.02.034

Oostenveld R, Fries P, Maris E and Schoffelen JM (2011) FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational Intelligence and Neuroscience* **2011**, 156869. https://doi.org/10.1155/2011/156869

Paap KR, Johnson HA and Sawi O (2014) Are bilingual advantages dependent upon specific tasks or specific bilingual experiences? *Journal of Cognitive Psychology* **26**(6), 615–639. https://doi.org/10.1080/20445911.2014.944914

Perani D, Farsad M, Ballarini T, Lubian F, Malpetti M, Fracchetti A, Magnani G, March A and Abutalebi J (2017) The impact of bilingualism on brain reserve and metabolic connectivity in Alzheimer's dementia. *Proceedings of the National Academy of Sciences* **114**(7), 1690–1695. https://doi.org/10.1073/pnas.1610909114

Pérez A, Carreiras M, Gillon Dowens M and Duñabeitia JA (2015) Differential oscillatory encoding of foreign speech. *Brain and Language* **147**, 51–57. https://doi.org/10.1016/j.bandl.2015.05.008

Pfeffer RI, Kurosaki TT, Harrah CH, Chance JM and Filos S (1982) Measurement of Functional Activities in Older Adults in the Community. *J. Gerontol.* **37**, 323–329. Available at: 0.1093/geronj/37.3.323.

Pliatsikas C and Luk G (2016) Executive control in bilinguals: A concise review on fMRI studies. *Bilingualism* **19**(4), 699–705. https://doi.org/10.1017/S1366728916000249

Price CJ, Green DW and Von Studnitz R (1999) A functional imaging study of translation and language switching. *Brain* **122**(12), 2221–2235. https://doi.org/10.1093/brain/122.12.2221

Rosen WG, Terry RD, Fuld PA, Katzman R and Peck A (1980) Pathological verification of ischemic score in differentiation of dementias. *Ann. Neurol.* **7**, 486–488. Available at: 10.1002/ana.410070516.

Rossi E, Cheng H, Kroll JF, Diaz MT and Newman SD (2017) Changes in white-matter connectivity in late second language learners: Evidence from diffusion tensor imaging. *Frontiers in Psychology* **8**(NOV), 1–15. https://doi.org/10.3389/fpsyg.2017.02040

Satz P (1993) Brain Reserve Capacity on Symptom Onset After Brain Injury: A Formulation and Review of Evidence for Threshold Theory. *Neuropsychology* **7**(3), 273–295. https://doi.org/10.1037/0894-4105.7.3.273

Schweizer TA, Ware J, Fischer CE, Craik FIM and Bialystok E (2012) Bilingualism as a contributor to cognitive reserve: Evidence from brain atrophy in Alzheimer's disease. *Cortex* **48**(8), 991–996. https://doi.org/10.1016/j.cortex.2011.04.009

Stam CJ (2014) Modern network science of neurological disorders. *Nature Reviews Neuroscience* **15**(10), 683–95. https://doi.org/10.1038/nrn3801

Stern Y (2002) What is cognitive reservce? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society* 448–460.

Stocco A and Prat CS (2014) Bilingualism trains specific brain circuits involved in flexible rule selection and application. *Brain and Language* **137**, 50–61. https://doi.org/10.1016/j.bandl.2014.07.005

Suh S, Yoon HW, Lee S, Chung JY, Cho ZH and Park HW (2007) Effects of syntactic complexity in L1 and L2; An fMRI study of Korean-English bilinguals. *Brain Research* **1136**(1), 178–189. https://doi.org/10.1016/j.brainres.2006.12.043

Taulu S and Simola J (2006) Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. *Physics in Medicine and Biology* **51**(7), 1759–68. https://doi.org/10.1088/0031-9155/51/7/008

Van Veen BD, van Drongelen W, Yuchtman M and Suzuki A (1997) Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Transactions on Bio-Medical Engineering* **44**(9), 867–80. https://doi.org/10.1109/10.623056

Varela F, Lachaux JP, Rodriguez E and Martinerie J (2001) The brainweb: Phase synchronization and large-scale integration. *Nature Reviews Neuroscience* **2**(4), 229–239. https://doi.org/10.1038/35067550

Wong B, Yin B and O'Brien B (2016) Neurolinguistics: Structure, function, and connectivity in the bilingual brain. *BioMed research international* **2016**.

Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M and Leirer VO (1983) Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research* **17**, 37–49. Available at: 10.1016/0022- 3956(82)90033-4.

Yu M, Engels MMA, Hillebrand A, van Straaten ECW, Gouw AA, Teunissen C, van der Flier WM, Scheltens P and Stam CJ (2017) Selective impairment of hippocampus and posterior hub areas in Alzheimer's disease: an MEG-based multiplex network study. *Brain* **140** (5), 1466–1485. https://doi.org/10.1093/brain/awx050

Zahodne LB, Schofield PW, Farrell MT, Stern Y and Manly JJ (2014) Bilingualism does not alter cognitive decline or dementia risk among spanish-speaking immigrants. *Neuropsychology* **28**(2), 238–246. https://doi.org/10.1037/neu0000014

Zatorre RJ, Belin P, Crane PK, Gruhl JC, Erosheva EA, Gibbons LE, McCurry SM, Rhoads K, Nguyen V, Arani K, Masaki M and White L (2001) Use of spoken and written Japanese did not protect Japanese-American men from cognitive decline in late life. *Cerebral Cortex* (New York, N.Y.: 1991), **65 B**(6), 654–666. https://doi.org/10.1093/geronb/gbq046

Zhang M, Li J, Chen C, Xue G, Lu Z, Mei L, Xue H, Xue F, He Q, Chen C, Wei M and Dong Q (2014) Resting-state functional connectivity and reading abilities in first and second languages. *NeuroImage* **84**, 546–553. https://doi.org/10.1016/j.neuroimage.2013.09.006

Zou L, Abutalebi J, Zinszer B, Yan X, Shu H, Peng D and Ding G (2012) Second language experience modulates functional brain network for the native language production in bimodal bilinguals. *NeuroImage* **62**(3), 1367–1375. https://doi.org/10.1016/j.neuroimage.2012.05.062

Zou L, Ding G, Abutalebi J, Shu H and Peng D (2012) Structural plasticity of the left caudate in bimodal bilinguals. *Cortex* **48**(9), 1197–1206. https://doi.org/10.1016/j.cortex.2011.05.022i