How Bilingualism Protects the Brain From Aging: Insights From Bimodal Bilinguals

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Abstract: Bilingual experience can delay cognitive decline during aging. A general hypothesis is that the executive control system of bilinguals faces an increased load due to controlling two languages, and this increased load results in a more "tuned brain" that eventually creates a neural reserve. Here we explored whether such a neuroprotective effect is independent of language modality, i.e., not limited to bilinguals who speak two languages but also occurs for bilinguals who use a spoken and a signed language. We addressed this issue by comparing bimodal bilinguals to monolinguals in order to detect age-induced structural brain changes and to determine whether we can detect the same beneficial effects on brain structure, in terms of preservation of gray matter volume (GMV), for bimodal bilinguals as has been reported for unimodal bilinguals. Our GMV analyses revealed a significant interaction effect of age × group in the bilateral anterior temporal lobes, left hippocampus/amygdala, and left insula where bimodal bilinguals showed slight GMV increases while monolinguals showed significant age-induced GMV decreases. We further found through cortical surface-based measurements that this effect was present for surface area and not for cortical thickness. Moreover, to further explore the hypothesis that overall bilingualism provides neuroprotection, we carried out a direct comparison of GMV, extracted from the brain regions reported above, between bimodal bilinguals, unimodal bilinguals, and monolinguals. Bilinguals, regardless of language modality, exhibited higher GMV compared to monolinguals. This finding highlights the general beneficial effects provided by experience handling two language systems, whether signed or spoken. *Hum Brain Mapp 38:4109–4124, 2017.* © 2017 Wiley Periodicals, Inc.

Key words: neuroprotection; bimodal bilinguals; gray matter volume; cortical surface area; neural reserve

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INTRODUCTION

People around the world now have a longer average life expectancy [Harper, 2005; Kinsella and Velkoff, 2001; Lutz et al., 2008]. As humans get older, their cognitive abilities, such as memory, executive, and word-finding functions, show signs of noticeable degradation [Bowles and Poon, 1985; Craik and Salthouse, 2011]. The cognitive decline is in turn reflected at the neural level by brain atrophy and gray matter decrease, with the anterior temporal regions being affected at an early stage [Craik and Salthouse, 2011; Dickerson et al., 2009; Fjell et al., 2009a, 2009b; Raz et al., 2005; Salat et al., 2004]. Consideration of what factors influence and eventually delay the progress of neurodegeneration is of great importance and has recently attracted the attention of a considerable amount of neuroscientific research.

Recent studies show that bilingualism is associated with delay of the onset of cognitive decline [Bialystok et al., 2007; Gold et al., 2013; Grant et al., 2014]. For example, elderly bilinguals were found to show a delay of about 4.5 years in the onset of dementia symptoms compared with age-matched monolinguals [Alladi et al., 2013; Bialystok et al., 2007], suggesting that long-term experience of speaking and managing two languages may have neuroprotective effects against cognitive decline and brain aging [Antoniou et al., 2013; Gold et al., 2013]. As Abutalebi et al. [2014] reported, bilingualism is associated with less age-induced decline of gray matter volume (GMV) in the left anterior temporal lobe (ATL) as compared to age-matched monolinguals. Researchers have tried to explain the origin of these recently observed effects. A general hypothesis that is often advocated is the "cognitive control account," which suggests that speaking more than one language recruits cognitive control processes and these processes benefit from their involvement in everyday language use [Bialystok, 2009; Costa et al., 2008]. Additionally, the nature of the bilingual lexico-semantic system could also be responsible for the neuroprotective effects [Abutalebi et al., 2014]. Following this conjecture, learning more than one set of vocabularies would result in a complex lexico-semantic system, and the high demand placed on using this system would increase the lexico-semantic processing load for bilinguals [Abutalebi and Green, 2007; Dufour and Kroll, 1995; Kroll and Stewart, 1994]. We believe that both of these mechanisms (i.e., increased cognitive control demands and the processing demands associated with a complex lexico-semantic system) are intrinsically interconnected (see below).

Bilingual language processing is based on cognitive inhibition, conflict monitoring, and attention to prevent interference from the nontarget language, thus making bilinguals experts in cognitive control [Abutalebi and Green, 2007; Bialystok, 2015; Costa et al., 2009]. However, it is important to underscore that theoretical accounts based on behavioral studies of the bilingual advantage have not yet reached consensus [Hilchey and Klein, 2011; Paap et al., 2015]. It should also be noted that inconsistencies are mostly found for studies focusing on children and young adults. Following Valian [2015], children and young adults engage in many cognitively challenging activities that may be at least equivalent to the cognitive challenges associated with bilingualism. However, elderly individuals tend to have fewer cognitively enriching experiences than younger adults, and thus, any putative advantage provided by bilingualism could be more prominent [Valian, 2015]. Studies focusing on neural differences between bilinguals and monolinguals indicate that the neural substrates underlying cognitive control can be changed by long-term bilingual experience [Green and Abutalebi, 2013; Li et al., 2014], even in the absence of behavioral advantages [see, for example, Abutalebi et al., 2012]. In general, structural neuroimaging studies with young adults have reported that bilingualism is associated with increased GMV in neural regions related to executive control, such as the prefrontal cortex, caudate nuclei, inferior parietal lobules, and the anterior cingulate cortex (ACC) [Abutalebi et al., 2013, 2012; Klein et al., 2014; Mårtensson et al., 2012; Mechelli et al., 2004; Zou et al., 2012]. For elderly bilinguals with many years of experience managing two languages, these structural changes may eventually result in a so-called neural reserve [Perani and Abutalebi, 2015]. Specifically, Luk et al. [2011] found that elderly bilinguals had better integrity of white matter in the frontal lobes as compared to age-matched monolinguals. The authors also associated the neural protection with enhanced executive control abilities [Luk et al., 2011]. Furthermore, two recent studies carried out with elderly bilinguals reported that bilinguals had increased gray matter in areas related to executive control such as in the inferior parietal lobules bilaterally [Abutalebi et al., 2015a] and over the entire extension of the ACC [Abutalebi et al., 2015b] when compared to monolinguals.

Besides the postulated different experiences related to executive control, bilingual speakers also learn more distinct words than monolinguals and thus obtain richer connections between lexical items and concepts [Kroll and Stewart, 1994]. Notably, bilinguals represent their two languages within the lexico-semantic system by building complex connections between their first language (L1), their second language (L2), and concepts [Abutalebi and Green, 2007; Dufour and Kroll, 1995; Kroll and Stewart, 1994]. For monolinguals, the structure of the lexico-semantic system is still complex but plausibly less so when compared to bilinguals. Monolinguals only need to learn one vocabulary set and competition between lexical items during language production is achieved within the single language (i.e., when a word to be produced has to compete with similar words or synonyms). In contrast, bilinguals have two sets of words for many concepts shared between the two languages, although the extent to which these lexical systems overlap or are distinct is a matter of debate [Brysbaert and Duyck, 2010; De Bot, 1992]. Some support for

the notion that the lexico-semantic system of bilinguals is more complex is the finding that that lexical access is usually slower in bilinguals than monolinguals [Gollan et al., 2005], possibly because of the need to inhibit words from the language not in use [Costa et al., 2006].

Hence, the complex lexico-semantic system in bilinguals could also be an important factor leading to neurostructural differences. Indeed, structural alterations in the brain regions relevant to lexical-semantic processing such as the supramarginal gyrus and the ATL have been recently reported for bilinguals compared to monolinguals [Grogan et al., 2012; Stein et al., 2012]. Related to aging, researchers have observed distinct neurodevelopmental trajectories of gray matter between elderly bilinguals and age-matched monolinguals also in the left ATL [Abutalebi et al., 2014; Olsen et al., 2015], a region mostly related to lexico-semantic representations [Lambon Ralph et al., 2010] and highly vulnerable to aging [Binney et al., 2010; Fjell et al., 2009a]. Specifically, Abutalebi et al. [2014] reported that bilinguals, as opposed to monolinguals, did not display age-induced decreases of GMV in the left ATL. The authors interpreted the age-related group difference in this vulnerable-to-aging brain area as an indicator of the neural protective effect, linking this result to the higher demands of lexico-semantic processing for bilinguals. However, we are agnostic as to which mechanism (the cognitive control demands or the demands of a more complex lexico-semantic system) is mainly responsible for the protective effect because we suggest that both mechanisms are intrinsically interconnected. Specifically, the complexity of the bilingual lexico-semantic system is likely to place increased demands on cognitive control [Abutalebi and Green, 2007; Costa et al., 2006].

Our current understanding of the neurocognitive mechanism that induces a neural reserve in bilingual speakers is primarily based on findings with unimodal bilinguals, i.e., bilinguals who regularly use two spoken languages. It is unknown whether the same protective effects might be observed in bimodal bilinguals who regularly use a spoken and a signed language. Replicating the findings reported for unimodal bilinguals would indicate universal protective effects of bilingualism, independent of language modality. It is important to note that there are some similarities and differences between these two types of bilingualism. On the one hand, similar to unimodal bilinguals, bimodal bilinguals learn and represent two sets of lexical items, each for one language, within a lexico-semantic system [Williams and Newman, 2016], and thus the cognitive demands on lexico-semantic processing are also high for bimodal bilinguals [Kovelman et al., 2014]. On the other hand, since signed and spoken languages engage different sensory and motor systems for perception and articulation, bimodal bilinguals might rely on distinct executive control processes to handle their two languages [Emmorey et al., 2008b], as compared to unimodal bilinguals. Recently, Giezen et al. [2015] provided evidence that bimodal bilinguals rely on domain-general cognitive control processes to resolve cross-linguistic competition during the early stages of word comprehension. However, to the best of our knowledge, no research to date has reported cognitive control benefits for bimodal bilinguals compared to monolinguals. Previous studies with early and proficient bimodal bilinguals showed that they did not outperform monolingual speakers on cognitive control tasks [Emmorey et al., 2008b], and they also did not differ from monolinguals in GMV for brain regions related cognitive control, in contrast to unimodal bilinguals [Olulade et al., 2016].

Our main aim in the current study is to investigate whether bimodal bilingualism also induces neuroprotective effects in the brain. We addressed this issue with structural neuroimaging and compared a group of bimodal bilinguals to an age-matched monolingual group. Furthermore, to determine whether bilingualism per se, i.e., independent of language modality, provides protective effects upon neural structures during healthy aging, we further carried out a cross-group comparison of GMV in regions of interests (ROIs) between two subgroups of the participants investigated in the present study (respectively bimodal bilinguals and monolinguals) and a subgroup of the healthy aging unimodal bilinguals from the Abutalebi et al. [2014] study.

A further aim of the present investigation is to understand the morphology of the eventual differences in GMV. Gray matter within the brain can be measured by two distinct dimensions at the cortical surface-based level: cortical surface area and cortical thickness [Dale et al., 1999; Fischl et al., 1999, 2004]. As two constituent components of GMV, surface area and cortical thickness are proposed to have different neurobiological bases. Surface area is mainly determined by the number, size, and spacing of functional columns within the human cerebral cortex, while cortical thickness is related to the number of neurons and/or the amount of neuropil within a column [Chance et al., 2008; Lyttelton et al., 2009; Rakic, 2007, 2009; Sowell et al., 2004]. They are independently influenced by a variety of factors, such as aging, genes, diseases, and specific experiences [Dickerson et al., 2009; Fjell et al., 2009b; Panizzon et al., 2009; Winkler et al., 2010]. In the present study, in addition to GMV, we also measured surface area and cortical thickness in order to investigate the nature of any structural differences observed between the bimodal bilinguals and the monolinguals.

MATERIALS AND METHODS

Participants

Forty-three participants took part in the present study, including 21 high-proficient bimodal bilinguals (5 males; mean age 48.33, range from 34 to 65 years) and 22 monolinguals with comparable educational, economic, and

social backgrounds (7 males; mean age 46.05, range from 29 to 67 years). The native language of all participants was Mandarin. The bilinguals acquired their second language, Chinese Sign Language (CSL) late in life (mean age 20), and self-rated their proficiency in CSL as high (mean = 4.35 on a scale of 1–5, in which 1 denotes not proficient, and 5 denotes very proficient). They had been signing for an average of 28 years (range from 12 to 44 years). All bilinguals were teachers employed in CSL schools and used both their languages actively in daily life. In order to match their working environment and economic and social backgrounds, the age-matched monolinguals were recruited from the local university staff. The self-reported education year was not different between these two groups (mean = 15.11 years for bimodal bilinguals, mean = 15.27 years for monolinguals, $P = 0.806$). All participants were right-handed according to a five-point handedness questionnaire (10 items of daily action, e.g., write, open doors; a higher score means greater frequency of using the right hand; all scored above 40). No participants suffered from neurological diseases or head injuries. Informed consent was obtained from all participants before the experiment. The experiment was approved by the local Ethical Committee.

In order to assess the generalizability of the neuroprotective effects found for our bimodal bilinguals to bilingualism in general (i.e., the modality independence of the effects), we carried out a further analysis in which we compared two subgroups of our participants with a matched subgroup from the study of Abutalebi et al. [2014]. Eleven participants out of the 23 unimodal bilingual participants from the Abutalebi et al. [2014] study could be matched with 11 bimodal bilinguals and 11 monolinguals from the present study. The reason for choosing only 11 participants (5 males; mean age 58.2, range from 55 to 64) from the Abutalebi et al. [2014] study was due to the fact that only 11 participants could be appropriately matched for age, education, socioeconomic status, and age of second language acquisition to the two subgroups from the present study: 11 monolinguals (2 males; mean age 54.91, range from 48 to 67) and 11 bimodal bilinguals (5 males; mean age 57.64, range from 54 to 65).

Structural Image Acquisition

High-resolution T1-weighted structural MRI data for the bimodal bilingual and the monolingual participants were collected with a 3T Siemens Trio Scanner at the MRI Center of Beijing Normal University, using the MPRAGE sequence. The scanning parameters were as follows: TR = 2530 ms, TE = 3.39 ms, flip angle = 7°, FOV = 256 mm, matrix = 256 × 256, slice number = 128 sagittal slices, slice thickness = 1.33 mm, voxel size = 1.33 × 1.0 × 1.0 mm, and series = interleaved. The structural MRI data for the unimodal bilingual participants was collected at the 3T MRI center of the University of Hong Kong and detailed scanning parameters are described in Abutalebi et al. [2014].

Data Preprocessing

Gray matter volume

We used SPM8 to conduct the analyses on GMV [Ashburner and Friston, 2000]. For preprocessing, we first visually inspected the structural images for all participants to check for brain integrity and artifact. Second, the orientation and the origin of each image were manually modulated to match the template. Third, the "New Segment" tool was used to segment the brain into several tissue classes, rigidly align the segmented images, and then resample them in a resolution of 1.5 × 1.5 × 1.5 mm. Fourth, DARTEL was employed to create a template for warping the gray matter images for all participants such that they matched each other [Ashburner, 2007; Matsuda et al., 2012]. Fifth, the gray images in native space were normalized to the MNI space by incorporating the transformation map from the template created. Finally, the warped images were Jocobian scaled ("modulated") and then smoothed with a Gaussian kernel of 8 mm FWHM. The smoothed modulated images were entered into the group-level statistical analyses.

Cortical surface area and thickness

Cortical surface area and thickness were calculated using an automated processing pipeline, CIVET (http://wiki.bic.mni.mcgill.ca/index.php/CIVET), which has been validated by many previous studies [e.g., Lerch and Evans, 2005]. Briefly, the native structural images were registered and corrected for nonuniformity artifacts using the N3 algorithms [Sled et al., 1998]. The corrected images were segmented into gray matter, white matter, and cerebrospinal fluid [Zijdenbos et al., 2002]. Inner and outer gray matter surfaces with a total of 81,920 polygons (40,962 vertices) for each hemisphere were then extracted from each structural image using the CLASP algorithm [Kim et al., 2005; MacDonald et al., 2000]. Midsurfaces were generated by taking midpoints of the linked inner and outer surfaces. For each vertex, cortical thickness was defined as the distance between linked vertices on the inner and outer surfaces, while cortical surface area was defined as one third of the total area of all triangular facets adjoining it on the midsurface [Lyttelton et al., 2009]. Finally, individual images of cortical surface area and thickness were smoothed with a 20 and a 30 mm surface-based blurring kernel, respectively.

Statistical Analyses at Group Level

We investigated which brain regions showed a neuroprotective effect upon brain aging for bimodal bilinguals with two different types of analyses. The first type of

analysis was to explore brain regions where monolinguals exhibited a significant negative age effect on GMV but bilinguals did not (or showed a smaller effect), and these regions were considered as areas exhibiting neuroprotective effects. The same type of analysis was also conducted on surface area and cortical thickness, to clarify which dimension was responsible for the GMV effect. Second, in order to provide evidence that the neuroprotective effect may be generalized to bilingualism in general, we conducted a further analysis to compare GMV between bimodal bilinguals, monolinguals, and also unimodal bilinguals. Note that these two types of analyses reveal two facets of the protective effect of bilingualism, given that a smaller (negative) aging effect on GMV for bimodal bilinguals than monolinguals would result in relatively greater GMV for the bimodal bilinguals than the monolinguals as their age increases.

Group difference of age effects on GMV

To examine age effects, we conducted a linear regression analysis in which the modulated gray matter images across two groups were entered as a dependent variable, with the variables of age, group, and their interaction as three regressors of interest. This analysis was voxel based and conducted across the whole brain. Gender was regarded as a covariate of noninterest. We used "1" and "−1" to code the nominal variable of group, with "1" denoting the bilingual group and "−1" denoting the monolingual group. The regressor representing the interaction between age and group was generated by multiplying their values. Note that for this encoding of variables, a positive interaction effect indicates that the slope of the age effect for the bilingual group is less negative (or more positive) than that for the monolingual group. After identifying the brain regions showing significant interaction effects of age × group, we further conducted simple-effect analyses for each region, by calculating correlation between age and GMV within each group.

Under the same model of linear regression, we also implemented a conjunction analysis which combined a positive interaction effect of age × group with a negative age effect for the monolingual group. This analysis aimed to make sure that the difference in the age effect across groups was mainly caused by a negative age effect for the monolinguals.

The analyses on GMV were masked with an absolute threshold of 0.15, in order to minimize gray-white matter boundary effects [Kesler et al., 2008]. The threshold was set slightly lower than commonly used (i.e., 0.2), following the consideration that some elderly individuals may be expected to show smaller GMV [Honea et al., 2009; Lemaitre et al., 2012]. For the whole-brain voxel-based GMV analysis, multiple-comparison correction was performed at $P < 0.05$ using AlphaSim based on Monte-Carlo simulation, resulting in $P < 0.001$ (two-tailed) at voxel level together with cluster size larger than 144 voxels (486 mm^3).

It has been argued that it is necessary to exclude the effects of some variables of noninterest that may confound the results, such as total intracranial volume (TIV) [Im et al., 2008]. However, since the volume of every region in a brain adds up to the total volume of that brain, any effect or change in the brain ROI also contributes to the variation of TIV, especially for age effects that impact extensive brain areas [Fjell et al., 2009b; Lemaitre et al., 2012]. Taking TIV as a covariate may reduce or obscure the age effects of interest. Thus, TIV was not included as a covariate in our analyses.

To verify the observed differences in age effects between bimodal bilinguals and monolinguals, we further used a nonparametric permutation test to examine the significance of group differences in correlation of age and GMV [Bullmore et al., 1999; Nichols and Holmes, 2002]. The brain regions showing significant interaction effects in the above linear model were regarded as ROI in our following analyses. We conducted the permutation tests in an ROI-wise approach, in which the GMV of all voxels within a brain region was averaged and entered into the analyses. In each permutation, the division of participants into the two groups was scrambled, and meanwhile, the sample size for each group was kept unchanged. Then Pearson's correlation of age and GMV was computed and transformed to Fisher's *Z*-score for each of the two randomized groups. The *Z*-scores were subtracted between groups. This procedure was repeated 10,000 times, and we obtained a permutation distribution of group difference in the correlation *Z*-score. The null hypothesis was that there was no group difference in the correlation between age and GMV of a region. The actual group difference was placed in the permutation distribution, and significant level was defined as its percentile position. The threshold of significant level was set to 0.001, the same as that used in the above whole-brain analysis at voxel level.

Group difference of age effects on cortical surface area and thickness

These analyses aimed to explore whether the observed neuroprotective effects upon GMV for bimodal bilinguals resulted from differences in surface area, cortical thickness, or both. For this purpose, we focused the analyses on those brain regions that showed significant positive interaction effects on GMV. Subcortical brain regions (i.e., the hippocampus/amygdala) were not included because surface-based measurements are not available for them. A volume mask for each region was created and converted to a cortical mask that was used to confine the surface-based analyses. Like the GMV analyses, we built two linear regression models to explore the regions showing different age effects between groups on surface area or cortical thickness in a vertex-based approach. These two analyses were carried out with the SurfStat tool for Matlab (http://www.math.mcgill.ca/keith/surfstat). *T*-tests were conducted to examine the interaction effect of age ×

group. Multiple comparisons were corrected to $P < 0.05$ using random field theory and Monte-Carlo simulation [Hagler et al., 2006; Worsley et al., 1999]. In follow-up simple-effect analyses, we calculated the correlation between age and the measurement (surface area or cortical thickness) for each group. The models in these cortical surface-based analyses included gender as a covariate. We also conducted permutation tests to examine the significance of group differences in the correlation between age and surface area or cortical thickness for each region.

Contribution of surface-based measures to the effect on GMV

We performed a mediation approach with SPSS 16 to determine whether surface area or cortical thickness contributes to the neuroprotective effect (i.e., the interaction effect of age × group) on GMV [Ward et al., 2015]. In the mediation models, GMV is the dependent variable; age, group, and their interaction are the independent variables; and surface-based measure (surface area or cortical thickness) is the mediator variable. The mediation effect is met if (1) the mediator is significantly associated with GMV; (2) the interaction effect (of interest) on GMV is significantly reduced after controlling for the mediator. We ran a nonparametric bootstrap analysis using 10,000 iterations to test for the significance of the decrease in the interaction effect [Preacher and Hayes, 2008]. Furthermore, we calculated in advance the relative rate of GMV variation explained by each surface-based measure by building hierarchical multiple regression models with GMV as a dependent variable. Notably, the surface-based measure that showed the neuroprotective effect was entered into the models as a regressor after the other one, and hence, the common GMV variation explained by both measures was attributed to the measure that was entered first. These analyses were conducted for each of the ROIs defined from the results of VBM analyses. GMV, surface area, and cortical thickness were extracted and averaged across all voxels or vertices contained in each ROI, respectively.

GMV comparison between aging bimodal bilinguals, unimodal bilinguals, and monolinguals

As will be illustrated below in the results section, we report that bimodal bilinguals have a smaller aging effect in several brain regions in terms of gray matter decrease. Previous studies have provided strong evidence that aging unimodal bilinguals show increased GMV compared to age-matched monolinguals in the left ATL [Abutalebi et al, 2014; Olsen et al., 2015]. Given our a priori hypotheses that bilinguals independent of language modality would have increased GMV in the brain regions exhibiting a neuroprotective effect, and considering the rather small sample sizes, only an ROI-wise approach of calculating GMV differences between the three groups was employed. Each of the ROIs was defined as a sphere with a 6-mm radius of which the center was based on the results of group difference of age effects on GMV. Since the data for the unimodal bilinguals were acquired in a different location (Hong Kong), potential confounding effects due to scanner differences were corrected by adding GMV of the occipital lobes as a covariate. The occipital lobe was selected because GMV in this region is less likely to be affected by long-term bilingualism [Li et al., 2014], and thus it could provide an unbiased estimation of the scanner effect. The occipital ROI was defined from the AAL template that included the cuneus gyrus, the calcarine cortex, and the superior, middle, and inferior occipital gyrus. ANCOVAs were conducted to compare GMV between groups, with the factors of gender and occipital GMV as the covariates of noninterest. We also compared GMV of the occipital lobe to test the relationship between our analyses and the scanner effect. Information regarding acquisition of the imaging data of unimodal bilinguals was reported in Abutalebi et al. [2014].

RESULTS

Gray Matter Volume

We conducted linear regression analyses to explore the brain regions showing differential age effects between bimodal bilinguals and monolinguals. The results revealed significant positive interaction effects of age × group on GMV in several brain regions (see section 2.4.1 for details regarding the interaction effect direction), including the left insula, the left ATL, the right ATL and the left hippocampus/amygdala (Table I and Fig. 1). No significant negative interaction effects were found. As shown in Figure 1, the positive interaction effect in these regions was reflected as a negative correlation between age and GMV for monolinguals but not for bimodal bilinguals. Specifically, for the monolingual group, there was a significant negative correlation between age and GMV in the left insula ($r = -0.69$, $P = 0.001$), left ATL ($r = -0.74$, $P < 0.001$), right ATL ($r = -0.73$, $P < 0.001$), and left hippocampus ($r = -0.60$, $P = 0.004$). In the bimodal bilingual group, there was a trend for a positive correlation between age and GMV in the left insula ($r = 0.49$, $P = 0.027$), left ATL ($r = 0.47$, $P = 0.037$), right ATL ($r = 0.32$, $P = 0.174$), and left hippocampus ($r = 0.54$, $P = 0.015$). The conjunction analysis showed that both effects (a positive interaction effect of age × group, and a negative age effect for monolinguals) were present in the left insula, left ATL, right ATL, and left hippocampus/amygdala (Table I), which were largely overlapping with those reported above. This pattern of group differences related to aging strongly suggests neuroprotection for bimodal bilinguals in these brain regions.

In the permutation tests, we examined the between-group difference in the correlation of age and GMV for each ROI showing significant effects in the above regression analysis. The left insula, left ATL, right ATL, and left hippocampus showed significantly less negative

TABLE I. Interaction effect of age × group and conjunction analysis on gray matter volume

Effect	Cluster size	Brain region	Peak T value	MNI coordinates			Simple (age) effect	
				x	*y*	*z*	Bilinguals	Monolinguals
Interaction effect of age × group	548	Left insula	5.14	−40.5	7.5	12	0.49*	−0.69**
	577	Left ATL	4.96	−36	−18	−31.5	0.47*	−0.74***
		—	4.50	−42	−6	−34.5		
	267	Right ATL	4.70	51	6	−45	0.32	−0.73***
	549	Left HC/Amy	4.42	−24	−6	−15	0.54*	−0.60**
Conjunction of interaction effect and aging effect for monolinguals	616	Left insula	5.14	−40.5	7.5	12	NA	
	966	Left ATL	4.96	−36	−18	−31.5		
		—	4.39	−40.5	−4.5	−34.5		
	394	Right ATL	4.70	51	6	−45		
	202	Left Amy	3.84	−20	−3	−15		

ATL: anterior temporal lobe; HC: hippocampus; Amy: amygdala; NA: not applicable.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

correlation of age and GMV for bimodal bilinguals compared to monolinguals (Ps < 0.001). The tests further confirmed the findings of different age effects for the two groups observed in the regression analyses.

Cortical Surface Area and Thickness

These regression analyses were restricted to regions that showed protective effects on GMV and were located at the cortical surface: the left insula, left ATL, and right ATL. For surface area, a vertex-based analysis revealed that there were only significant positive interaction effects of age × group in the three regions (Fig. 2A and Table II). The interaction effect was reflected as a significant negative correlation between age and surface area for monolinguals in the left insula ($r = -0.43$, $P = 0.028$), left ATL ($r = -0.57$, $P = 0.003$), and right ATL ($r = -0.57$, $P = 0.004$; see Table II); in contrast, there were slight trends for positive correlations for bimodal bilinguals in the left insula ($r = 0.31$, $P = 0.093$), left ATL ($r = 0.16$, $P = 0.251$), and right ATL ($r = 0.28$, $P = 0.121$; see Table II). However, for the measurement of cortical thickness, there was no significant interaction effect of age × group in the mask (Fig. 2B and Table II). These findings indicate that the neural protective effect occurs with respect to cortical surface area rather than the cortical thickness.

In the permutation analyses, we found that with regard to surface area, all three regions revealed distinct age effects between groups ($P = 0.003$ for left insula; $P = 0.021$ for left ATL; $P = 0.019$ for right ATL), with bimodal bilinguals showing significantly less negative correlation between age and surface area than monolinguals. In contrast, for cortical thickness, the age effect was not different between groups ($P = 0.929$ for left insula; $P = 0.595$ for left ATL; $P = 0.420$ for right ATL). These results are consistent with the findings reported in the regression analyses.

Contribution of Surface-Based Measures to the Neuroprotective Effect on GMV

We further determined whether surface area or rather cortical thickness directly contributed to the neuroprotective effect on GMV by examining which measurement mediated the interaction effect of age × group on GMV. The results first showed that the GMV variance explained by cortical thickness was not significant in the ROIs of the left insula ($R^2 = 0.06$, $P = 0.121$), left ATL ($R^2 = 0.02$, $P = 0.337$), or right ATL ($R^2 = 0.04$, $P = 0.187$), even when cortical thickness was entered first in the hierarchical regression models (see Fig. 3). In contrast, the GMV variance explained by surface area was significant in the ROIs of the left insula ($R^2 = 0.53$, $P = 0.001$), left ATL ($R^2 = 0.14$, $P = 0.012$), and right ATL ($R^2 = 0.24$, $P = 0.001$; all FDR corrected; see Fig. 3), suggesting an association between GMV and surface area. For the mediation analyses, the bootstrap tests showed that the mediation effect of surface area was significant for the ROIs of the left insula ($P < 0.001$) and right ATL ($P = 0.014$); the surface area of the left ATL showed a trend for a medication effect ($P = 0.067$), indicating that the neuroprotective effect on GMV is partially due to surface area. There is no need to test for the mediation effect of cortical thickness because its association with GMV was not significant. The findings suggest that the preservation of cortical surface area, rather than cortical thickness, underlies the neuroprotective effects of bilingualism.

GMV Comparison Between Aging Bimodal Bilinguals, Unimodal Bilinguals, and Monolinguals

The comparison of GMV between the three groups revealed a significant effect of group for the left insula ($F = 6.8$, $P = 0.004$), left ATL ($F = 13.0$, $P < 0.001$) and right

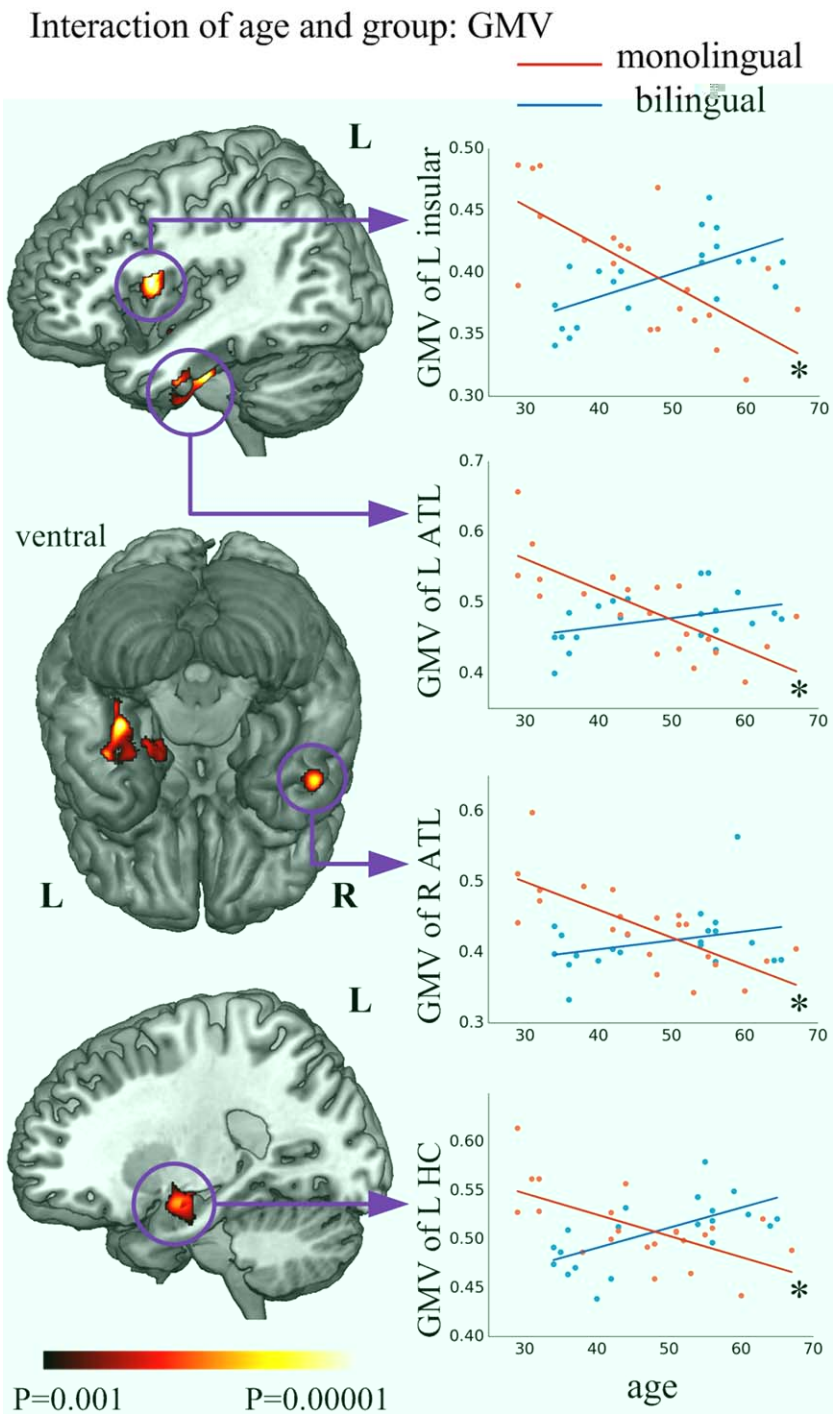

Figure 1.

Interaction effect of age × group on gray matter volume. On the left are brain images from lateral and ventral views showing the regions with positive interaction effect. No negative interaction effect was found. Four scatter diagrams of age vs. GMV are presented on the right for each region. *Significance of negative correlation between age and GMV only for the monolingual group in the simple-effect analyses. GMV: gray matter volume; L: left; R: right; ATL: anterior temporal lobe; HC: hippocampus. [Color figure can be viewed at wileyonlinelibrary.com]

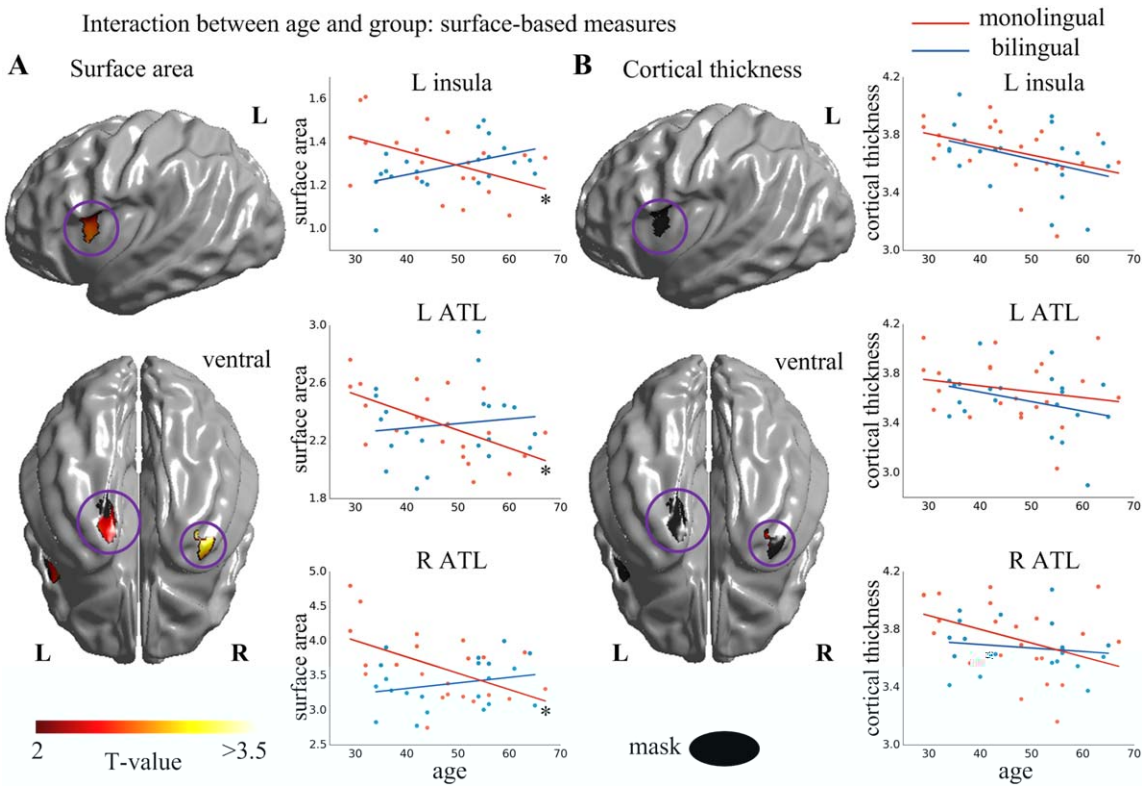

Figure 2.

Interaction effect of age × group on surface area (A) and cortical thickness (B) within the mask (black area). Within the two subplots (A) and (B), on the left are brain images from lateral and ventral views showing the regions with positive interaction effect, while the scatter diagrams of age vs. surface area or cortical thickness are displayed on the right. No negative interaction effect was found. *Significance of negative correlation between age and surface area only for the monolingual group in the simple-effect analyses. L: left; R: right; ATL: anterior temporal lobe. [Color figure can be viewed at wileyonlinelibrary.com]

ATL ($F = 4.5$, $P = 0.020$; all FDR corrected; see Fig. 4). Post hoc analyses showed greater GMV for the bimodal bilinguals than the monolinguals in the left insula ($F = 7.7$, $P = 0.013$) and left ATL ($F = 15.4$, $P = 0.001$), but not in the right ATL ($F = 2.6$, $P = 0.124$). The post hoc analyses also showed greater GMV for the unimodal bilinguals than the monolinguals in the left insula ($F = 12.1$, $P = 0.003$), left ATL ($F = 18.7$, $P < 0.001$), and right ATL ($F = 11.0$, $P = 0.004$). In addition, the two bilinguals groups did not differ from each other in the GMV of the three brain regions (all $P > 0.05$). We further tested whether the three groups showed GMV difference in the bilateral occipital lobe as a control region, and no significant group differences were found ($F = 0.023$, $P = 0.977$; see Fig.4), indicating that the above group difference was not affected by potential confounding effects, such as scanner differences.

TABLE II. Interaction effect of age × group on surface area and cortical thickness within the regions of interest

				MNI coordinates			Simple (age) effect	
Surface-based measure	Cluster size	Brain region	Peak T value	*x*	*y*	*z*	Bilinguals	Monolinguals
Surface area	170	Left insula	2.67	−36.8	3.5	4.5	0.31	−0.43*
	142	Left ATL	2.40	−26.7	−9.6	−34.7	0.16	−0.57**
	50	Right ATL	3.33	42.9	3.1	−43.4	0.28	−0.57**
Cortical thickness	No significant interaction effect of age × group							NA

ATL: anterior temporal lobe; NA: not applicable.
*$P < 0.05$.
**$P < 0.01$.

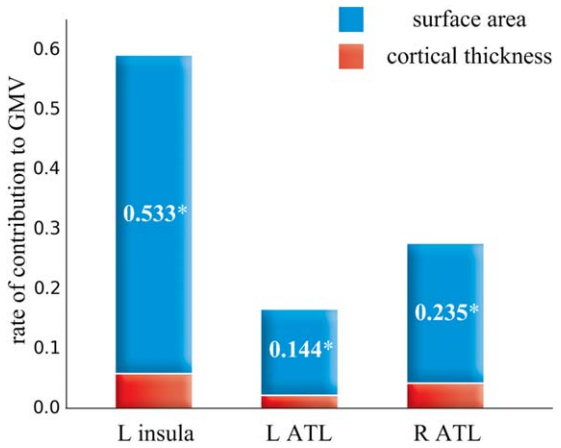

Figure 3.

Proportion of GMV variation explained by cortical thickness and surface area in the multiple regression models for three ROIs. * and the affiliated value indicate significance and the proportion of additive contribution of the variables entered the models. GMV: gray matter volume; L: left; R: right; ATL: anterior temporal lobe. [Color figure can be viewed at wileyonlinelibrary.com]

These results emphasize that overall bilinguals, independently of modality (bimodal or unimodal) exhibit increased GMV within the left insula and left ATL.

DISCUSSION

In the present study, we investigated the neuroprotective effects of bimodal bilingualism upon brain structure during aging. Healthy bimodal bilinguals with a wide age range were compared to age-matched monolinguals, and gray matter changes associated with aging were examined.

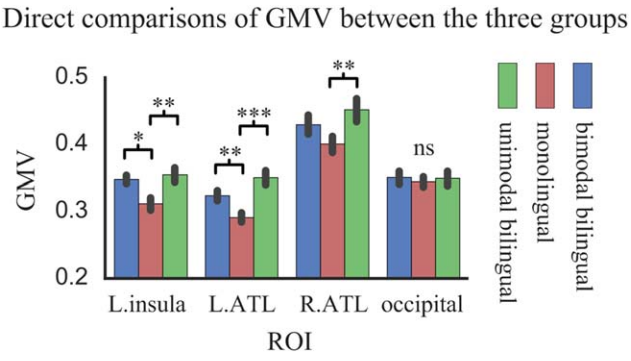

Figure 4.

Cross-group comparisons of GMV between bimodal bilinguals, monolinguals, and unimodal bilinguals in the three brain regions exhibiting significant interaction effect of age × group on GMV, and in the occipital lobe which was regarded as a control region. GMV: gray matter volume; L: left; R: right; ATL: anterior temporal lobe. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ns: no significance. [Color figure can be viewed at wileyonlinelibrary.com]

Our results highlight that in several brain regions, the left ATL, right ATL, left hippocampus/amygdala, and left insula, bimodal bilinguals displayed different age effects on GMV than monolinguals. Follow-up analyses revealed a negative relationship between age and GMV in monolinguals, but a trend for a positive relationship in bimodal bilinguals. As to the surface-based measures, the same pattern of different age effects between groups was found for cortical surface area but not for cortical thickness. The permutation tests further verified the observed group differences in age effects on GMV and surface area. Interestingly, we again found that surface area rather than cortical thickness contributed significantly to the protective effects on GMV. These findings deepen our understanding of the neuroprotective effects of bilingualism in several ways.

First of all, we show that similarly to unimodal bilinguals in previous studies [e.g., Abutalebi et al., 2014; Olsen et al., 2015], bimodal bilinguals, i.e., individuals who use a spoken and a signed language, may also benefit from the neuroprotective effects of using two languages. In other words, the neuroprotective effects of speaking two languages are not confined to the spoken modality but extend to signed languages as well. These results further add to the growing literature showing that bilingualism is beneficial to healthy aging. Indeed, there is ongoing research that consistently reports from different populations around the world that bilingualism delays the symptomatic onset of dementia by an average of 4–5 years [Alladi et al., 2013; Bialystok et al., 2007; Perani et al., 2017; Woumans et al., 2015]. The reason for this delay of onset of cognitive decline is usually attributed to more tuned executive control functioning in bilinguals which would render their brain more resistant to cognitive decline. In turn, the enhanced executive control functioning in bilinguals is generally traced to the need to control two jointly activated language systems [Green and Abutalebi, 2013]. At the neural level, bilingualism has been found to induce beneficial neural changes (i.e., increased GMV) in the neural areas subserving executive control which may protect the brain from age-induced atrophy [Perani and Abutalebi, 2015].

As mentioned above, extensive experience with the control of two languages is often found to benefit the executive control system for bilinguals (but see Valian [2015] for evidence that this effect is confined only to aging populations and does not extend to younger populations). In the present study, we investigated a special type of bilingualism (i.e., bimodal bilingualism) that has been argued to rely less upon executive control for managing the language systems because the two languages are in different modalities [Emmorey et al., 2008a; Zou et al., 2012]. For example, high demands may not be placed on executive control processes (e.g., conflict monitoring, inhibition) in bimodal bilinguals since the competing nontarget language is in a different modality from the target language. Indeed, research in this field does not report any evidence that bimodal bilinguals have superior conflict resolution

abilities compared to their monolingual peers. Only one published study by Emmorey et al. [2008b] with early bimodal bilinguals addressed this issue and found a null effect, and this null effect contrasted with the results from unimodal bilinguals (but see Paap et al. [2015] for null findings from unimodal bilinguals). How may we then explain our findings that bimodal bilingualism may entail similar neuroprotective effects upon aging? Indeed, we observed clear neuroprotective effects in our bimodal bilingual group, specifically in the temporal lobes including the bilateral ATL and the left hippocampus/amygdala. The same pattern of findings was also obtained from the measure of surface area of the bilateral ATL, hence, reinforcing the findings with GMV. Further, similar effects on the left ATL were observed in two previous studies carried out with unimodal bilinguals [Abutalebi et al., 2014; Olsen et al., 2015].

Based on the findings of both the present study with bimodal bilinguals and previous studies with unimodal bilinguals, we suggest that the neuroprotective effects may be related to some common features to these two types of bilingualism. Bimodal bilinguals and unimodal bilinguals must both learn and represent two sets of vocabulary within a complex lexico-semantic system [Kroll and Stewart, 1994]. Learning lexical items and linking semantic concepts consistently to lexical items in two different languages may increase the load of lexico-semantic processing for bilinguals. We thus hypothesize that extensive experience in handling a complex lexico-semantic system could be one of the critical contributing factors to the neuroprotection from brain aging.

The ATL is, indeed, believed to be critical for amodal lexico-semantic representation [Binney et al., 2010; Lambon Ralph et al., 2010; Lambon Ralph and Patterson, 2008] and acts as a semantic convergence zone across different categories [Patterson et al., 2007; Visser et al., 2012]. The ATL is also found to be involved in lexical retrieval [Tranel, 2009], and to encode semantic inputs from the different languages of bilinguals [Correia et al., 2014; Crinion et al., 2006]. Notably, the ATL is also one of the brain regions most vulnerable to physiological aging [Fjell et al., 2009a; Lemaitre et al., 2012; Raz et al., 1997]. Its atrophy is usually linked to word-finding difficulties and semantic dementia [Lambon Ralph and Patterson, 2008; Pobric et al., 2007]. Therefore, we suggest that the neuroprotective effects on the bilateral ATL for bilinguals could derive from their experience handling a complex lexico-semantic system that encompasses the lexicons of two distinct languages.

Besides the ATL, we further found neuroprotective effects in the left insula in our bimodal bilinguals. The comparison of GMV between the three groups revealed that both groups of bilinguals showed greater GMV of the left insula than the group of monolinguals. These results thus suggest that the neuroprotective effect in the left insula is also independent of language modality, and can be generalized to different types of bilingualism. It is known that sign language experience from birth induces GMV changes of the insula [Allen et al., 2008]. Sign language production also activates the left insula, as reported in functional imaging studies [Braun et al., 2001; Hu et al., 2011; San Jose-Robertson et al., 2004]. Notably, the left insula is not only involved in sign language processing, but also in spoken language processing such as in coordinating articulation [Ackermann and Riecker, 2004; Dronkers, 1996; Eickhoff et al., 2009; Riecker et al., 2000].

In addition, we also found neuroprotective effects in the left hippocampus extending to the amygdala. The left hippocampus is traditionally considered to be critical for the formation and retrieval of episodic memory [Di Paola et al., 2007; Squire and Zola, 1998; Squire and Zola-Morgan, 1991], and shows atrophy and volume loss during aging [Du et al., 2006; Raz et al., 2004]. On the basis of the present findings, we suggest that it is likely that memory functions in bilinguals may also be more resistant to age-induced decline. This is in line with a previous study with amnestic mild cognitive impairment which showed that bilinguals developed amnesia 4.5 years later than monolinguals [Ossher et al., 2013]. Moreover, several behavioral studies show that bilingual children outperform their monolingual peers in episodic and semantic memory tasks [Kormi-Nouri et al., 2003, 2008]. The authors argue that this memory benefit for bilingual children occurs because the enriched lexico-semantic representations of their two languages offer more cues for memory encoding and retrieval [Kormi-Nouri et al., 2008]. Thus, it is very likely that the protective effect observed in the left hippocampus, a core brain region of the memory system, may also be ascribed to the bilingual experience of managing and controlling a complex and enriched lexico-semantic system. During aging, many regions in the brain are associated with gray matter decrease, which is usually paralleled by cognitive decline [Craik and Salthouse, 2011; Karas et al., 2004; Raz and Rodrigue, 2006]. For bilinguals, being associated with less (or even reversed) gray matter decrease during aging, such as in the ATL, the insula, and the hippocampus, might imply that they could suffer less cognitive decline, resulting in a delay of dementia onset [see, for example, Alladi et al., 2013].

The direct comparisons of GMV among the three groups of participants in the three ROIs provide evidence of consistency between the two types of bilinguals. We report increased GMV for both unimodal and bimodal bilingual groups compared to the monolingual group except for the right ATL, where only unimodal bilinguals showed significantly increased GMV compared to monolinguals. Although the right ATL showed a strong neuroprotective effect of bimodal bilingualism on GMV during aging, the direct group comparison of GMV between bimodal bilinguals and monolinguals did not show a significant group difference. The sample size may have been too small and/or the age of the bimodal bilinguals was not high enough to show a significant group effect. This result may also suggest that the

effect of bimodal bilingualism is not as strong as that of unimodal bilingualism. In the left ATL and insula, we found that both unimodal and bimodal bilingual groups showed increased GMV compared to the monolingual group. This finding is consistent with previous studies that found increased GMV for unimodal bilinguals in areas related to cognitive control and to language processing in general [see Abutalebi and Green, 2016, for review]. Thus, bimodal bilingualism and unimodal bilingualism appear to share common features in term of the structurally beneficial changes within these brain regions.

Two possible mechanisms may induce neuroprotective effects in these specific brain regions. On the one hand, Perani and Abutalebi [2015] propose that bilingualism induces a "neural reserve" in the human brain. Following this concept, life-long bilingual experience induces structural neural changes, such as an increase of GMV [Klein et al., 2014; Li et al., 2014; Mårtensson et al., 2012], which eventually could provide a reserve against the gray matter decrease caused by physiological aging [Barulli and Stern, 2013]. On the other hand, Nyberg et al. [2012] proposed a mechanism referred to as "brain maintenance." According to this proposal the neuroprotective effect comes from reduced susceptibility to age-induced neural degeneration that helps to keep neural structures relatively intact, rather than from changes in neural structures (e.g., increase in GMV) which then offset neural degeneration [Nyberg, et al., 2012]. The findings of our study favor the former proposal since GMV of the left ATL and left hippocampus for the bimodal bilinguals showed a trend for a positive correlation with age. The positive correlation, we argue, reflects the combined effect of beneficial changes derived from bilingual experience (specific to bilinguals) and neural degeneration induced by natural aging (applied to both bilinguals and monolinguals). GMV of these regions increased as the bilinguals became older and gained more experience handling two distinct language systems, and the speed of the GMV increase slightly exceeded the speed of natural aging-induced GMV decrease. This argument is supported by a previous study showing that the GMV of the ATL increased after participants learned and used a foreign language for 5 months [Stein et al., 2012].

Our findings also reveal that the neuroprotective effect mainly occurs for cortical surface area rather than cortical thickness. We observed an interaction effect of age × group only for the surface area measurement, which was similar to that of the GMV analysis. The subsequent analysis further confirmed that surface area, but not cortical thickness, significantly contributed to the neuroprotective effects on GMV. These results are consistent with previous studies highlighting that GMV and its association with the verbal ability are more related to surface area than to cortical thickness [Vuoksimaa et al., 2015; Winkler et al., 2010]. Although the neurobiological implication of changes in surface area versus cortical thickness is still unknown, a consideration of the radial unit hypothesis of cortical development could be helpful for understanding the present results [Rakic, 2009]. This hypothesis proposes that neurons in the cortex are organized into columns (structural units) that run perpendicular to the cortical surface, and that surface area is mainly determined by the number and spacing of cortical columns [Chance et al., 2006, 2008; Lyttelton et al., 2009]. Since the column number cannot increase after birth [Rakic, 1988], and the neural reserve mechanism may play a major role in neuroprotection [Perani and Abutalebi, 2015], it is likely that bilingualism affects columnar spacing. Specifically, long-term bilingual experience may eventually increase columnar spacing which in turn offsets age-induced decrease in cortical surface area. In contrast, based on evidence from postmortem studies, the "balloon model" suggests that larger surface area (and thinner cortical thickness) of a cortical region is related to richer afferent connectivity in that region and to its greater capacity of differentiating incoming signals [Harasty et al., 2003; Seldon, 2005]. This idea is consistent with our suggestion that the more complex processing demands of bilingual language processing in bimodal bilinguals (as opposed to monolinguals) are a critical contributing factor to neuroprotection. Notably, bimodal bilinguals did show a trend for larger surface area and thinner cortical thickness (see Fig. 2) as their age and bilingual experience increased. More studies using surface-based measurements are needed to address the underlying mechanism of the bilingual neuroprotective effect. It should be noted that some previous studies have observed a bilingualism effect using cortical thickness measures [Klein et al., 2014; Olsen et al., 2015]. For example, Olsen et al. [2015] reported neuroprotective effects for unimodal bilinguals on cortical thickness of the left ATL, but the authors did not measure surface area. The absence of such effects in the present study (in the measure of cortical thickness) may be due to the age of participants (mean age = 47.16), which is younger than the age of participants in the Olsen et al. study (mean age = 70.26). Future studies are needed to clarify this possibility.

Some limitations should be noted in the present study. First, this study is based on cross-sectional data so that the age effect is derived across individuals. Indeed, longitudinal research is needed to provide more persuasive evidence for aging trajectories on gray matter and specifically for the bilingual effect on these aging trajectories. Second, the sample size in this study is limited so that only linear relationships between age and gray matter can be examined.

In conclusion, learning and long-term use of two languages may protect against age-induced neural degeneration in the human brain. Specifically, we report that this effect is universal to all types of bilingualism since, unlike previous work where only unimodal bilinguals were investigated, our study examined bimodal bilinguals. Our cross-group comparisons of bimodal bilinguals, unimodal bilinguals from the Abutalebi et al. [2014] study, and monolinguals further highlight that these protective effects

are universally linked to processing, managing and controlling two languages, independently of language modality. Moreover, we have highlighted that the reserve of cortical surface area rather than cortical thickness is the main neuroanatomical substrata where the neuroprotective effect of bilingualism is manifest. These findings deepen our understanding of how long-term bilingualism acts as a beneficial experience which may protect the aging human brain.

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