

Bilingualism and healthy aging: Aging effects and neural maintenance

Virgina M. Borsa^{a,b,c}, Daniela Perani^a, Pasquale A. Della Rosa^a, Gerda Videsott^d, Lucia Guidi^a,
Brendan S. Weekes^{e,f}, Rita Franceschini^d, Jubin Abutalebi^{a,e,*}

^a Centre for Neurolinguistics and Psycholinguistics, San Raffaele University & San Raffaele Scientific Institute, Milano, Italy

^b NEtS - Center for Neurocognition, Epistemology and Theoretical Syntax, School of Advanced Studies IUSS Pavia, Pavia, Italy

^c NEUROFARBA (Department of Neuroscience, Psychology, Drug Research and Child Health), University of Florence, Florence, Italy

^d Faculty of Education and Language Study Unit, Free University of Bozen, Italy

^e Laboratory for Communication Science, Faculty of Education, University of Hong Kong, Pok Fu Lam, Hong Kong

^f School of Psychological Sciences, Faculty of Dentistry, Medicine and Health Sciences, University of Melbourne, Parkville, Australia

ARTICLE INFO

Keywords:

Bilingualism

Healthy aging

Cognitive reserve

Neural reserve

Voxel-based morphometry (VBM)

ABSTRACT

Speaking more than one language is associated with neurocognitive benefits in seniors (Alladi et al. 2013). Few studies however have tested this hypothesis directly by comparing bilingual seniors who vary in chronological age. We report a Voxel-Based Morphometry (VBM) study showing cumulative effects of age on grey matter volume (GMV) in brain structures that are involved in cognitive control in bilingual seniors and found no differences in RT or accuracy between bilingual and monolingual seniors on a behavioral test of cognitive control called the Attentional Network Task (ANT), and no differences in GMV for selected ROIs between groups. However, chronological age predicted the size of interference and conflict effects for monolingual speakers only. We also observed a more widespread pattern of bilateral aging-effects in brain regions that are classically associated with aging in monolingual speakers compared to bilingual speakers. Notably, GMV in the dorsal anterior cingulate cortex (dACC) and the level of daily exposure to a second language (L2) independently predict performance on the ANT in bilingual speakers. We conclude that regular (daily) bilingual experience mitigates the typical effects of aging on cognitive control at the behavioral and the neural level.

1. Introduction

Life expectancy is rising around the world (Harper, 2014; Lutz et al., 2008). All seniors experience a decline in cognitive abilities (memory, executive functions, word-retrieval), (Craik and Salthouse, 2011) and grey matter volume (GMV) as well as an increased risk of brain disease (Craik and Salthouse, 2011). Cognitive decline is not inevitable in typical aging. Activities such as physical exercise (Erickson et al., 2011; Kramer and Erickson, 2007), playing musical instruments (Hanna-Pladdy and MacKay, 2011; Wan and Schlaug, 2010), targeted cognitive training (Li et al., 2016) and speaking more than one language (Perani and Abutalebi, 2015; Bialystok et al., 2016) can mitigate cognitive decline in seniors. Such effects are assumed to reflect a ‘cognitive reserve’ (Stern, 2009), which is defined as a discrepancy between observed behavioral and/or cognitive functioning and the expected (reduced) levels in typical aging (Stern, 2002; Barulli and Stern, 2013). A closely related construct is called ‘neural reserve’ which is defined as a discrepancy between observed brain functioning and the expected (reduced) levels in aging particularly when accompanied by

neuropathology such as Alzheimer's disease (Luk et al., 2011; Perani et al., 2017). Cognitive reserve is typically measured using tests of controlled attention and memory whereas neural reserve can be estimated from levels of brain activity (Perani et al., 2017) and structural integrity including measures of GMV (Abutalebi et al., 2015a). There is much evidence of a correlation between cognitive and neural reserve in healthy aging. For example, the typical effect of aging on the brain is reduced for seniors who are more regularly engaged in tasks that specifically require controlled attention such as a bilingual person speaking fluently in one language only (Bialystok et al., 2016) perhaps on a daily basis. More strikingly, there is evidence of a correlation between controlled attention in individuals who speak more than one language and the onset of neuropathology - although this evidence is contested. For example, it has been reported that speaking more than one language delays the symptomatic onset of dementia by an average of 4–5 years. This evidence comes from a range of studies in different linguistic environments and populations all over the globe including India (Alladi et al., 2013), Canada (Bialystok et al., 2007; Craik et al., 2010; Schweizer et al., 2012), Belgium (Woumans et al., 2015) and Italy

* Corresponding author at: Centre for Neurolinguistics and Psycholinguistics, University San Raffaele, Via Olgettina 58, 20132 Milan, Italy.
E-mail address: abutalebi.jubin@unir.it (J. Abutalebi).

(Perani et al., 2017). These results have been attributed to the mitigating effects of cognitive reserve i.e. regular daily exercise of cognitive control in bilingual speakers recruits brain regions that are more vulnerable in healthy aging thus leading to neuroprotection for bilingual speakers when compared to monolingual speakers (see for review Bialystok et al., 2016). Cognitive control mechanisms are assumed to manage and resolve competition between distinct language networks (Abutalebi and Green, 2007). The regular engagement of cognitive control is assumed to transfer to domain general behavioral and cognitive functions, and more controversially neural function (Perani and Abutalebi, 2015; Abutalebi and Green, 2016).

Functional and structural neuroimaging studies confirm this conjecture in healthy young bilingual speakers. When compared to monolingual speakers, there is a bilingual advantage, in terms of increased neuroplasticity, in the anterior cingulate cortex (ACC) (Abutalebi et al., 2012), left prefrontal cortex (Stein et al., 2012), inferior parietal lobule (IPL) (Mechelli et al., 2004; Della Rosa et al., 2013), and left caudate nucleus (Zou et al., 2012). Of note, all of these brain regions are also assumed to be necessary in domain general cognitive control. For example, Abutalebi et al. (2012) reported more efficient use of the ACC to monitor conflict during performance on the non-verbal Flanker task (i.e. the Attentional Network task or ANT) for healthy young bilinguals compared with matched monolinguals. Structural neuroimaging studies with bilingual seniors also confirm this conjecture. For example, healthy bilingual seniors have increased GMV in the ACC (Abutalebi et al., 2015a) and the left IPL (Abutalebi et al., 2015b) and increased Fractional Anisotropy in the frontal lobes (Luk et al., 2011). Perani and Abutalebi (2015) argued that this type of evidence leads to the specific hypothesis that bilingualism increases neural reserve.

No study has directly tested this hypothesis by simultaneously examining cognitive and neural reserve in bilingual seniors. Here we test this hypothesis for the first time. Our prediction was that the typical effects of chronological age upon GMV in brain structures related specifically to cognitive control (bilateral inferior parietal lobule, bilateral inferior frontal gyrus, bilateral caudate nuclei, and dorsal ACC) and upon behavioral performance on a cognitive control task such as the Attentional Network Task (ANT) (Fan et al., 2002) would be observed in all seniors. We employed a region-of-interest (ROI) approach since our a-priori assumption is that the effects of bilingualism are most prominent on regions involved in cognitive control. Among the selected ROIs we particularly put emphasis on the ACC for further analyses because of its prominent role in domain general cognitive control during both verbal and non verbal tasks (Shenhav, Botvinick and Cohen, 2013; Abutalebi et al., 2012) as well as in populations with declining cognitive control abilities (Luks et al., 2010; Borsa et al., 2016). Of note, recent evidence highlighted greater cortical thickness in the ACC in samples of healthy elderly exhibiting and exceptional memory abilities (Harrison et al., 2012; Gefen et al., 2015; Sun et al., 2016).

Overall, we expected performance on the ANT to decline with chronological age together with GMV in selected brain regions. However, we predicted that pattern of decline would be different for bilingual and monolingual seniors. Specifically, we expected significant negative correlations between chronological age and cognitive control in monolingual speakers but for bilingual speakers, these effects may be reduced. We also expected that correlations between GMV of ACC and cognitive control performance would interact with language background variables for bilingual speakers e.g. the age of acquisition, proficiency and amount of exposure to the second language (L2). Critically, we did not necessarily expect a-priori to find evidence of a 'bilingual advantage' in cognitive control performance (see for null findings: Paap and Greenberg, 2013; Paap, 2014; Valian, 2015). Our goal instead was to test the possibility of a cumulative impact of bilingual experience on healthy aging.

2. Materials and methods

2.1. Participants and language background

Twenty bilingual seniors with relatively early age of L2 acquisition (mean age of acquisition: 6.20 years) from South Tyrol, Italy (12 females; mean age 63.70; SD \pm 7.17; age range 47–74) and twenty monolingual seniors from Milan, Italy (11 females; mean age 61.45; SD \pm 7.26; age range 49–75). Critically, the range in chronological age in the two samples was equivalent. Participants were excluded if they reported a history of neurological and/or psychiatric diseases or head injury or there was evidence of cognitive decline as tested with the MMSE i.e. total raw score below 27. Informed consent was obtained from all participants. The study was approved by the local Ethics Committees in Bolzano and Milano.

All participants completed a self-report questionnaire to assess their socio-economic status (SES). This questionnaire interrogates self-perceived social position, with respect to local community and home country, using a 10 point scale; number of years of formal education; and personal and total family income over the previous 12 months (MacArthur Foundation Network <http://www.macses.ucsf.edu/research/socialenviron/sociodemographic.php>). Participants in each group had a comparable level of age, education and socio-economic Status (SES) i.e., the results of independent samples *t*-tests found that groups did not differ in mean age [$t(38) = -0.98, p > 0.05$], level of education [$t(38) = -0.41, p > 0.05$] and socio-economic status [$t(38) = -1.22, p > 0.05$]. However for the MMSE score we found a trend $t(38) = -1.78, p = .08$ indicating that bilingual seniors exhibited a higher MMSE global score than monolingual speakers (see Table 1 for details). Although we caution against interpreting this result as strong evidence of a bilingual advantage this finding is in line with evidence indicating that, when matched for age, bilingual seniors may outperform monolinguals on cognitive testing (Perani et al., 2017).

A self-report language background questionnaire (LBQ: Li et al., 2014b) was also completed by bilingual seniors to estimate their age of acquisition (AoA) of L2, along with the duration of exposure to each language estimated in hours of daily activities i.e. working, watching TV, listening to radio, speaking with friends and family, writing, reading, other leisure activities in L2. Bilingual speakers were also tested for picture naming proficiency using 30 items presented for naming in L1 and 30 items presented for naming in L2. All stimuli were taken from the revised colored version of the Snodgrass and Vanderwart (1980) items (Rossion & Pourtois, http://spell.psychology.wustl.edu/Rossion_stimuli/) and matched for their rated familiarity and visual complexity. All measures (age of acquisition, exposure, proficiency) in L1 and L2 were transformed into z-scores for statistical analysis (see Table S1 in Supplementary Materials).

2.2. Experimental task

All participants performed the Attentional Network Task (ANT). The ANT procedure is summarized in Fig. 1. Reaction times (RTs) and

Table 1
Socio-demographic information for monolingual seniors (MONO) and bilingual seniors (BIL). P values of independent sample *t*-test are also reported.

	Group	N	Mean	SD	P value
Age	MONO	20	61.45	7.26	0.33
	BIL	20	63.70	7.17	
MMSE	MONO	20	29	0.94	0.08
	BIL	20	29.4	0.83	
Education	MONO	20	13.10	4.17	0.68
	BIL	20	13.65	4.17	
SES	MONO	20	21.85	4.90	0.23
	BIL	20	23.75	4.96	

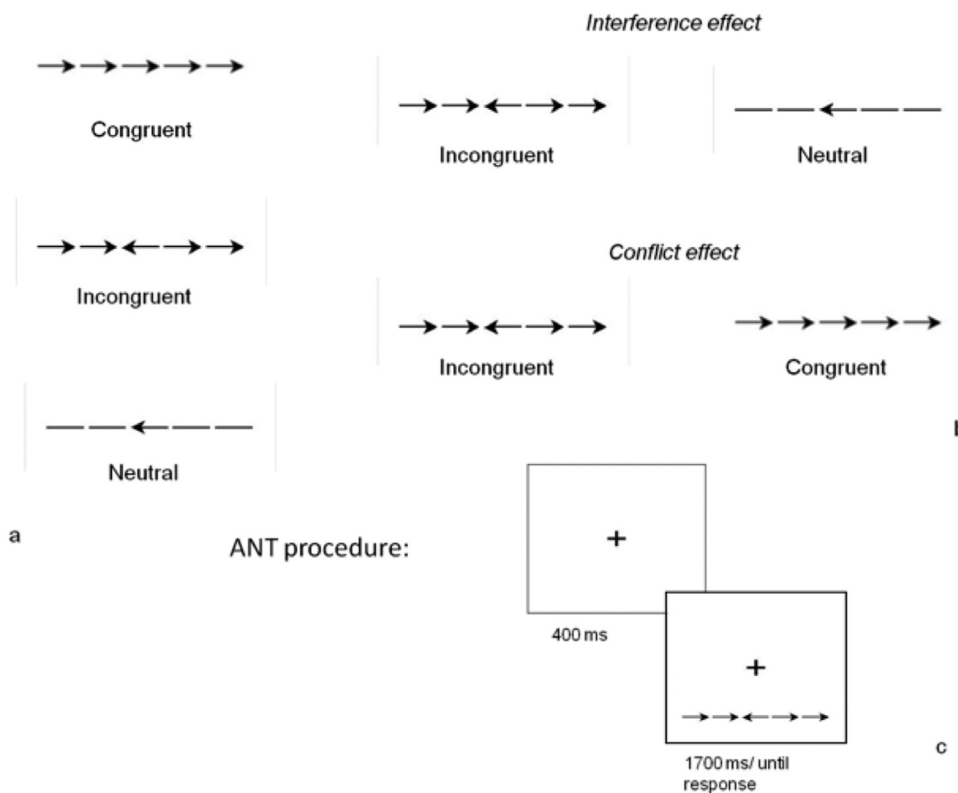


Fig. 1. Example of congruent, incongruent and neutral stimuli of the ANT (Fan et al., 2002; Abutalebi et al., 2012) (a); Graphical representation of the two ANT effect of interest (i.e. Interference and Conflict effects) (b); ANT procedure which requires subjects to respond to the direction of a central arrow (left or right) flanked on either side by two additional arrows pointing in the congruent ($\rightarrow\rightarrow\rightarrow\rightarrow\rightarrow$) or incongruent direction ($\leftarrow\leftarrow\rightarrow\leftarrow\leftarrow$) or by two straight lines ($- - - - -$) (i.e. neutral flanker). The ANT was performed using a laptop computer with a mouse. Event presentation consisted of a fixation point appearing at the center of the screen for 400 ms, followed by a row of five horizontal black lines with arrow heads pointing to left or right for 1700 ms. The task was presented with different cues (no cue, central cue, double cue and spatial cue) (Fan et al., 2005) allowing the eventual investigation of the alerting and orienting components of attentional control (Posner and Petersen, 1990). A total of 96 trials were presented across two sessions. Participants were only tested once, singularly and in a separate room, and had a training session, consisting of 24 randomized trials prior to the experiment. All participants were instructed to respond with their dominant hand.

accuracy were measured. We focused on the interference effect which is calculated as the performance on incongruent trials minus performance on neutral trials with the conflict effect calculated as performance on incongruent trials minus performance on congruent trials. These indices are widely assumed to serve as proxy measures of non-verbal i.e. domain general cognitive control.

2.3. Structural MRI data acquisition and preprocessing

All participants were scanned at the CERMAC center at the San Raffaele University in Milan, Italy. All images were acquired using a 3T Achieva Philips MR scanner (Philips Medical Systems, Best, the Netherlands). High-resolution T1-weighted structural scans were acquired for each participant enrolled in the study (magnetization prepared rapid gradient echo, 150 slice T1-weighted image, repetition time 8.03 ms, echo time = 4.1 ms; flip angle = 8° , field of view = 250×250 , matrix = 256, acquisition time (TA) = 9.35 min, mode = 3D fast-field echo (3DFFE), sense factor = 1, number of signal averages = 1, resolution = $1 \times 1 \times 1$). MRI data preprocessing was performed using SPM12 (Wellcome Department, UCL) running on MATLAB R2013a (The Mathworks, Natick, USA). Probabilistic tissue segmentation, bias correction, and spatial normalization were achieved under the unified normalization framework (Ashburner and Friston, 2005) using the New Segment tool implemented in SPM12. The New Segment procedure uses Gaussian mixture modeling to model the intensity distributions for each tissue class and incorporates spatial weighting in the form of grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) through probability maps (PPMs). The New Segment procedure differs primarily in its treatment of mixing proportions, its expansion of PPMs for modeling out of brain voxels, and its implementation of an improved registration model (SPM12 Manual, FIL Methods Group, UCL, UK). The unified normalization approach using the New Segment tool implemented in SPM12 was employed to obtain tissue probabilistic maps (TPMs) that encoded the estimated GM, WM, CSF, and non-brain tissue class probabilities for each voxel. The resulting GM modulated TPMs were then normalized to the Montreal Neurological Institute (MNI)

template space using the deformation fields provided by the New Segment tool. Maps for monolinguals and bilinguals were registered to the European brain template.

2.3.1. ROI selection and GMV data extraction

We extracted GMV from predefined regions of interest (ROIs) associated with cognitive control (Fan et al., 2005; Cieslik et al., 2015) and specifically to the language control network (Abutalebi and Green, 2007, 2016). The ROIs based on our a-priori hypothesis included in each hemisphere, the inferior frontal gyri (IFG), the insula, the inferior parietal lobules (IPL) and the caudate nuclei. An ROI was also selected for the ACC, resulting in a total of 9 ROIs. Furthermore, 4 additional ROIs not typically associated with cognitive control or the language control networks were selected as control regions. These regions included in each hemisphere the Calcarine Cortex and the Cuneus.

All ROIs were defined by the Automated Anatomical Labelling (AAL) masks (Tzourio-Mazoyer et al., 2002) implemented in the Wake Forest University (WFU)-Pickatlas (Maldjian et al., 2003). The ACC mask was created including the dorsal and pregenual ACC (BA 32 and BA 24) bilaterally and selected using the WFU-Pickatlas. GMVs for each region were subsequently extracted subject-wise from co-registered and resliced masks in MNI space superimposed on normalized modulated GM TPMs using the Easy Volume toolbox (http://www.sbirc.ed.ac.uk/LCL/LCL_M1.html).

2.4. Statistical analysis

Statistical analysis was carried out using SPSS v21. First, interference and conflict effects were estimated separately using accuracy and reaction time (RT) data. Independent sample *t*-tests were then carried out to test for group differences. Second, independent sample *t*-tests were performed on GMV in ROIs associated with cognitive control as dependent variables to compare differences in brain structure between groups. Independent sample *t*-tests were also performed on GMV in four regions of interest not typically associated with cognitive control in order to control for possible structural differences between groups.

Pearson correlation analyses were performed between chronological age and GMV. Specific Pearson correlation analyses were carried out between interference/conflict measures and the 9 ROIs associated with cognitive control. Correlations were calculated for the whole sample and for each group separately. Multiple hierarchical regression models were then used to determine the contribution of education, chronological age and GMV of ACC as predictors in explaining the outcome variance within each model. Interference effect (RTs) was used as dependent variable in Model 1, whereas conflict effect (RTs) was the dependent variable used in Model 2. Each hierarchical regression analysis included three blocks of predictors: education as a predictor variable in the first block, age in the second block and GMV in ACC in the third block. The same multiple hierarchical regression models were then used to test the effects on the two groups of participants separately. Moreover additional hierarchical regression analyses were carried out using GMV of all other ROIs associated to cognitive control in the third block (see [Supplementary materials](#) for details).

Finally, we investigated the effects of L2 exposure and second language proficiency in two additional hierarchical regression models. As above, two separate multiple hierarchical regression models were used to test the interference effect (Model 3) and the conflict effect (Model 4) as dependent variables. For both models, the predictive variables were: level of education in Step 1, chronological age in Step 2, GMV in Step 3, L2 exposure in Step 4 and L2 proficiency in Step 5. The purpose of this analysis was to investigate the independent effect of variance explained for interference and conflict effects by differences in L2 exposure and proficiency controlling for mean levels of education, age, and GMV of extent of ACC activation.

3. Results

3.1. Independent sample *t*-tests

Independent samples *t*-tests on differential accuracy scores revealed no significant differences between groups in interference effect (bilinguals: mean = -0.15 SD = 0.13 ; $p = .15$; monolinguals: mean = -0.08 , SD = 0.17 ; $p = .15$) and conflict effect (bilinguals: mean = -0.13 SD = 0.13 ; $p = .90$; monolinguals: mean = -0.13 SD = 0.18 $p = .90$) or on RTs - no significant differences between groups in interference effect (bilinguals: mean = 141.90 ms SD = 46.66 ms, $p = .70$; monolinguals: mean = 136.35 ms SD = 46.48 ms) and conflict effect (bilinguals: mean = 135.50 ms SD = 43.10 ms, $p = .93$; monolinguals: mean = 134.14 ms SD = 61.46 ms). Similarly, independent samples *t*-tests found no significant differences between groups on mean GMV in any of the selected ROIs that are associated with cognitive control or in any of the regions of interest not associated with cognitive control (results are summarized in [Table 2](#)).

3.2. Correlation analyses

3.2.1. ROIs associated with the cognitive control network

Correlation analyses including the whole sample ($N = 40$) revealed a significant positive association between chronological age and mean conflict effect (RT) and significant negative correlations between chronological age and mean GMV for all ROIs, except for the ACC. Furthermore, significant negative correlations were observed between the mean interference and conflict effects (RT) and mean GMV in all selected ROIs that are associated with cognitive control (summarized in [Table 3](#)). We found no significant correlations between accuracy and any other variables (age and GMV of selected ROIs). Further analyses therefore focused on mean RT.

Separate correlations were calculated for each group based on our a priori predictions. We found that for monolinguals mean chronological age was positively correlated with mean conflict effects ($r = 0.59$, $p = .005$) and mean interference effects ($r = 0.57$, $p = .009$) as expected, and mean chronological age was negatively correlated with mean GMV

Table 2

Mean GMV and Standard deviation (SD) of each selected ROIs associated to cognitive control and language control network for monolingual seniors and bilingual seniors. Mean GMV and Standard deviation of additional selected ROIs not associated to cognitive control and language control network (i.e., control regions) for monolingual and bilingual seniors. P values of independent sample *t*-test are also reported.

	Group	N	Mean	SD	P value
ROIs					
L_IPL	MONO	20	0.0085	0.0010	0.62
	BIL	20	0.0083	0.0011	
L_IFG	MONO	20	0.0135	0.0014	0.45
	BIL	20	0.0131	0.0017	
L_Insula	MONO	20	0.0079	0.0008	0.26
	BIL	20	0.0076	0.0011	
L_Caudate	MONO	20	0.0036	0.0003	0.17
	BIL	20	0.0034	0.0004	
R_IPL	MONO	20	0.0087	0.0010	0.48
	BIL	20	0.0085	0.0009	
R_IFG	MONO	20	0.0140	0.0015	0.54
	BIL	20	0.0137	0.0018	
R_Insula	MONO	20	0.0076	0.0009	0.55
	BIL	20	0.0075	0.0011	
R_Caudate	MONO	20	0.0040	0.0004	0.25
	BIL	20	0.0038	0.0005	
dACC_BA24_BA32	MONO	20	0.0104	0.0011	0.53
	BIL	20	0.0102	0.0014	
Additional ROIs for Control					
L_Calcarine	MONO	20	0.0053	0.0007	0.95
	BIL	20	0.0054	0.0008	
L_Cuneus	MONO	20	0.0030	0.0005	0.67
	BIL	20	0.0029	0.0005	
R_Calcarine	MONO	20	0.0054	0.0008	0.95
	BIL	20	0.0054	0.0009	
R_Cuneus	MONO	20	0.0036	0.0005	0.71
	BIL	20	0.0037	0.0005	

in the following ROIs: bilaterally in IFG (left IFG: $r = -0.50$, $p = .02$; right IFG: $r = -0.51$, $p = .02$), insula (left insula: $r = -0.56$, $p = .005$; right insula: $r = -0.50$, $p = .023$) and IPL (left IPL: $r = -0.69$, $p = .001$; right IPL: $r = -0.78$; $p < .001$) (see [Table 4](#) and [Fig. 2](#)).

For bilinguals, there were no significant correlations between mean chronological age and the mean conflict or mean interference effects. However, there were significant negative correlations between age and mean GMV in left IFG ($r = -0.44$, $p = .051$), left insula ($r = -0.45$, $p = .03$), left IPL ($r = -0.47$, $p = .03$), and left caudate ($r = -0.44$, $p = .051$) (see [Table 5](#) and [Fig. 2](#)).

Moreover, for monolinguals we observed significant negative correlations between GMV and mean interference effects in all selected ROIs, except in the ACC where we observed only a trend: $p = .081$; and between mean GMV and conflict effects in all selected ROIs except in the ACC ($p = .254$) and the right caudate ($p = .058$) (see [Table 4](#) and [Fig. 3](#)). We also observed significant negative correlations between mean interference effects and mean GMV in all ROIs for bilingual speakers except in the left and right caudate nuclei and also between mean conflict effects and mean GMV in all ROIs (see [Table 5](#) and [Fig. 3](#)).

3.2.2. Regions of Interest not associated with cognitive control

Results from the correlation analyses including the whole sample ($N = 40$) showed significant negative correlations ($p < .05$) between mean chronological age and mean GMV in all four selected regions of interest (see [Table 6](#)). Separate correlations for each group were then computed. For monolinguals, there were significant negative correlations ($p < .05$) between mean chronological age and mean GMV in all selected ROIs, except in the right Calcarine where we found a trend ($p = .08$) (see [Table 6](#) and [Fig. S1](#) in the [Supplementary Materials](#)). For bilingual speakers, there were significant negative correlations ($p < .05$) between chronological age and GMV in all selected ROIs, except in the right Cuneus where we found a trend ($p = .06$) (see [Table 6](#) and [Fig. S1](#) in the [Supplementary Materials](#)).

Table 3
Correlation analysis between age, interference effect, conflict effect and all selected ROIs associated to cognitive control and language control network for the whole sample (N = 40).

All sample		Conflict	Interference	Left IFG	Left Insula	Left IPL	Left Caudate	Right IFG	Right Insula	Right IPL	Right Caudate	dACC,BA24,BA32
Age	Pearson correlation	0.41	0.21	-0.47	-0.53	-0.59	-0.40	-0.46	-0.47	-0.60	-0.38	-0.27
	Sign. (two tailed)	0.01	0.20	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.02	0.09
	N	40	40	40	40	40	40	40	40	40	40	40
Conflict	Pearson correlation	0.41	0.88	-0.57	-0.62	-0.64	-0.46	-0.53	-0.61	-0.68	-0.46	-0.41
	Sign. (two tailed)	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01
	N	40	40	40	40	40	40	40	40	40	40	40
Interference	Pearson correlation	0.21	0.88	-0.52	-0.59	-0.56	-0.45	-0.51	-0.58	-0.62	-0.43	-0.49
	Sign. (two tailed)	0.20	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00
	N	40	40	40	40	40	40	40	40	40	40	40

Table 4
Correlation analysis between age, interference effect, conflict effect and all selected ROIs for monolinguals (group mono).

GROUP MONO		Conflict	Interference	Left IFG	Left Insula	Left IPL	Left Caudate	Right IFG	Right Insula	Right IPL	Right Caudate	dACC,BA24,BA32
Age	Pearson correlation	0.60	0.57	-0.50	-0.60	-0.70	-0.31	-0.51	-0.51	-0.78	-0.28	-0.23
	Sign. (two tailed)	0.01	0.01	0.02	0.01	0.00	0.19	0.02	0.02	0.00	0.23	0.34
	N	20	20	20	20	20	20	20	20	20	20	20
Conflict	Pearson correlation	0.60	0.93	-0.53	-0.60	-0.66	-0.44	-0.45	-0.54	-0.72	-0.43	-0.27
	Sign. (two tailed)	0.01	0.00	0.02	0.00	0.00	0.05	0.05	0.01	0.00	0.06	0.25
	N	20	20	20	20	20	20	20	20	20	20	20
Interference	Pearson correlation	0.57	0.93	-0.54	-0.65	-0.60	-0.51	-0.46	-0.57	-0.67	-0.53	-0.40
	Sign. (two tailed)	0.01	0.00	0.01	0.00	0.00	0.02	0.04	0.01	0.00	0.02	0.08
	N	20	20	20	20	20	20	20	20	20	20	20

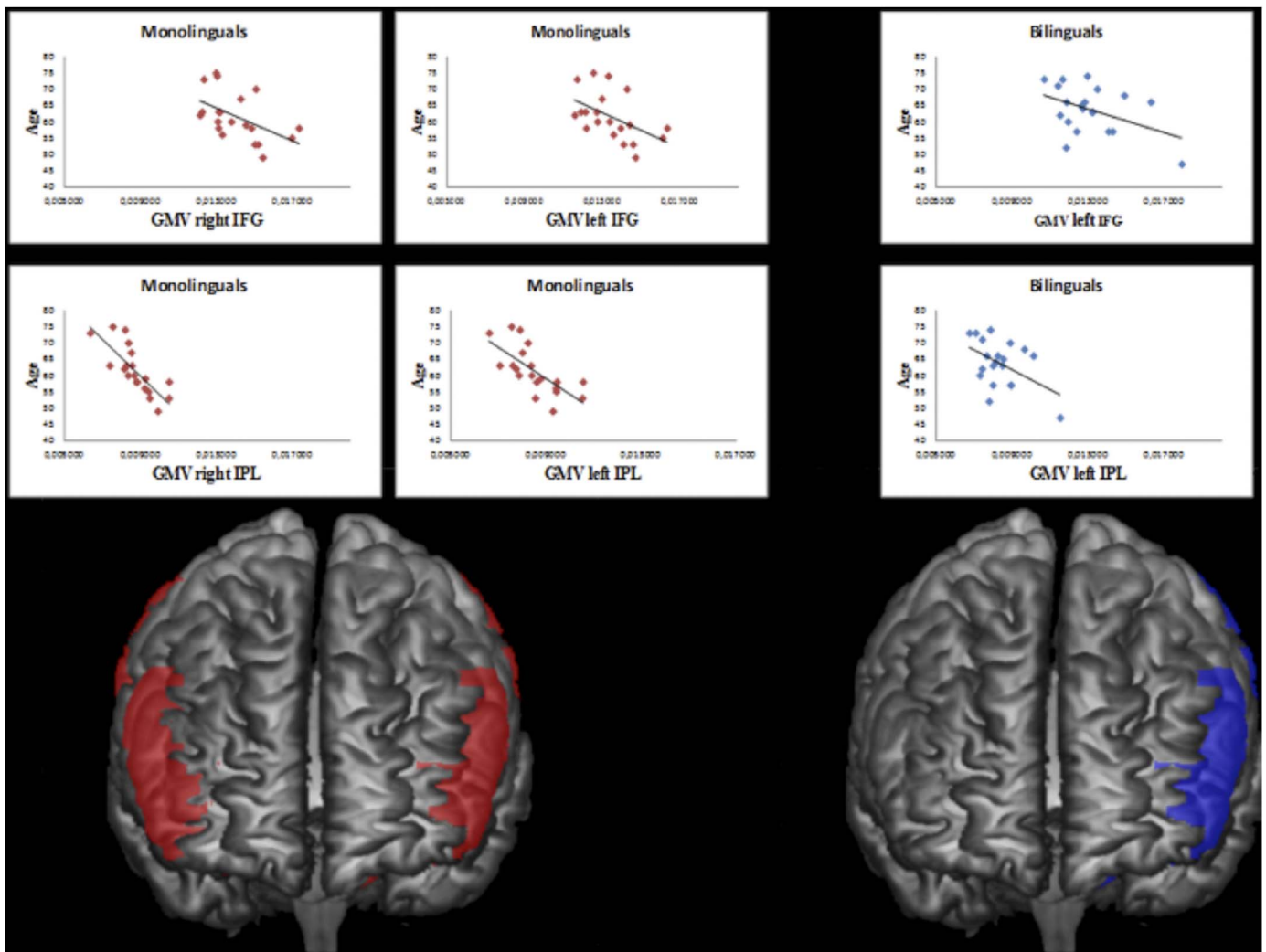


Fig. 2. Correlations between age and GMV, selecting bilateral IFG and IPL ROIs for monolinguals and the left IFG and IPL for bilinguals (i.e. MONOLINGUALS in red; BILINGUALS in blue). As illustrated in the figure, monolinguals were associated to a more extended and bilateral pattern of aging effects. Correlations between all selected ROIs and age are reported in [Table 4](#) for monolinguals and [Table 5](#) for bilinguals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.3. Hierarchical regression analysis (RTs only)

3.3.1. Whole sample

The multiple hierarchical regression model entering the interference effect for the whole sample as the dependent variable (Model 1) found that only mean GMV in the ACC was a significant predictor accounting for 19.5% of the variance after controlling for both mean education and chronological age. Indeed, the change in R^2 with the addition of mean GMV in the ACC as a predictor in the third block was significant (R^2 change = 0.195; adjusted R^2 = 0.225; F change (1,36) = 9.830, p = .003) (β = -0.460, t value = -3.135, p = .003). In Model 2, taking the mean conflict effect as the dependent variable (i) mean level of education accounted for 12.6% of the variance, (ii) mean chronological age was also significant and accounted for 9% of the variance after controlling for mean level of education and (iii) mean GMV in the ACC was also a significant predictor and accounted for an additional 9.2% of the variance after controlling for both education and chronological age i.e. R^2 change = 0.092; adjusted R^2 = 0.249; F change (1,36) = 4.77, p = .035 [beta coefficients: β (education) = -0.211, t value = -1.44, p = .170; β (age) = 0.246, t value = 1.58, p = .122; β (GMV in ACC) = -0.316, t value = -2.186, p = .035]. In sum, considering the beta coefficients of these hierarchical regression models, as mean GMV in the ACC declines with age so do the cognitive control abilities in seniors (i.e. greater mean interference and mean conflict effects) as expected.

3.3.2. Monolinguals

Splitting the multiple hierarchical regression analyses for Model 1 (the mean interference effect), in monolinguals only, mean chronological age in Block 2 was a significant predictor and accounted for 22.8% of the variance after controlling for mean level of education (R^2 change = 0.228; adjusted R^2 = 0.270; F change (1,17) = 5.942, p = .026) (β = 0.460 t value = 2.213, p = .042). Similar results were found for Model 2 (the mean conflict effect): only chronological age in Block 2 was significant and accounted for 24.9% of the variance after controlling for mean level of education (R^2 change = 0.249; adjusted R^2 = 0.318; F change (1,17) = 6.921, p = .018) (β = 0.510 t value = 2.43, p = .027). In sum, only mean chronological age but not GMV of the ACC accounted for a significant percentage of the variance in cognitive control performance for monolingual seniors.

The results from the additional regression analyses entering the other ROIs associated to cognitive control highlighted that the interference effect was predicted by chronological age and also by GMV of two ROIs (i.e. left insula and right caudate); whereas conflict effect was again predicted by chronological age and by GMV of the right IPL only (see [tables S3 and S4](#) in [Supplementary Materials](#)).

3.3.3. Bilinguals

For the bilingual speakers in Model 1 (the mean interference effect as the dependent variable), only mean GMV in the ACC was significant

Table 5
Correlation analysis between age, interference effect, conflict effect and all selected ROIs for bilinguals (group bil).

Group BIL	Conflict	Interference	Left IFG	Left Insula	Left IPL	Left Caudate	Right IFG	Right Insula	Right IPL	Right Caudate	dACC_BA24_BA32
Age	Pearson correlation	-0.18	-0.44	-0.45	-0.48	-0.44	-0.41	-0.43	-0.39	-0.42	-0.29
	Sign. (two tailed)	0.44	0.05	0.04	0.03	0.05	0.07	0.06	0.09	0.06	0.21
	N	20	20	20	20	20	20	20	20	20	20
Conflict	Age	Interference	Left IFG	Left Insula	Left IPL	Left Caudate	Right IFG	Right Insula	Right IPL	Right Caudate	dACC_BA24_BA32
	Pearson correlation	0.84	-0.68	-0.74	-0.66	-0.55	-0.70	-0.77	-0.65	-0.56	-0.64
	Sign. (two tailed)	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.01	0.00
N	20	20	20	20	20	20	20	20	20	20	20
Interference	Age	Conflict	Left IFG	Left Insula	Left IPL	Left Caudate	Right IFG	Right Insula	Right IPL	Right Caudate	dACC_BA24_BA32
	Pearson correlation	0.84	-0.52	-0.56	-0.51	-0.41	-0.56	-0.60	-0.56	-0.36	-0.57
	Sign. (two tailed)	0.00	0.02	0.01	0.02	0.07	0.01	0.01	0.01	0.12	0.01
N	20	20	20	20	20	20	20	20	20	20	20

and accounted for 41.7% of the variance after controlling for both mean level of education and mean chronological age (R^2 change = 0.417; adjusted R^2 = 0.49; F change (1,16) = 15.53, p = .001) (β = -0.675 t value = -3.94, p = .001).

In Model 2 (the mean conflict effect as the dependent variable) only mean GMV in the ACC was significant and accounted for 37.4% of the variance after controlling for both mean level of education and mean age (R^2 change = 0.37; adjusted R^2 = 0.396; F change (1,16) = 11.778, p = .003) (β = -0.640 t value = -3.432, p = .003). In sum, only mean GMV in the ACC accounted for a significant percentage of the variance in cognitive control performance for bilingual seniors.

Moreover, the results from the additional regression analyses entering the other ROIs associated to cognitive control revealed, interestingly, that both interference and conflict effects were predicted by GMV of all ROIs associated to cognitive control but not by chronological age (see tables S3 and S4 in Supplementary Materials).

3.3.4. L2 exposure and proficiency

Further analysis with hierarchical regression in Model 3 revealed that mean GMV of the ACC was a significant predictor and accounted for 41.7% of the variance in the mean interference effect after controlling for both education and chronological age (R^2 change = 0.417; adjusted R^2 = 0.49; F change (1,16) = 15.53, p = .001). The amount of daily exposure to L2 (z -scores) was also a significant predictor and accounted for 10.4% of the variance in the mean interference effect after controlling for education, chronological age and mean GMV of the ACC (R^2 change = 0.104; adjusted R^2 = 0.587; F change (1,15) = 4.76, p = .045). The change in R^2 after the addition of L2 proficiency in Block 5 was not significant. Considering the standardized beta coefficients (GMV ACC: β = -0.79, t value = -4.85, p < .001 and L2 exposure: β = -0.34, t value = -2.18, p = .045) we may conclude that an increase in the mean interference effect is associated with a decrease of GMV of the ACC and lower exposure to L2 in bilingual seniors.

In Model 4, mean GMV in the ACC was significant and accounted for 37.4% of the variance for the conflict effect after controlling for the effects of age and education (R^2 change = 0.374; adjusted R^2 = 0.396; F change (1,16) = 11.78, p = .003), while L2 exposure accounted for 14.1% of the variance in the conflict effect after controlling for mean levels of education, age and GMV of the ACC (R^2 change = 0.141; adjusted R^2 = 0.534; F change (1,15) = 5.74, p = .030). Considering the significance of the standardized beta coefficients (mean GMV ACC: β = -0.77, t value = -4.48, p < .001 and mean L2 exposure: β = -0.402, t value = -2.39, p = .030) we may conclude that an increase in conflict effect is associated with a decrease in mean GMV in the ACC and less daily exposure to L2 in bilingual seniors.

4. Discussion

We have identified for the first time a significant relationship between cognitive and neural reserve in a group of healthy bilingual seniors who speak a second language on a daily basis. The results supported our prediction that the patterns of decline in cognitive control would be different for monolingual and bilingual seniors. Specifically, we observed significant negative correlations between mean chronological age and two measures of nonverbal cognitive control (mean conflict and interference effects) for monolingual speakers as expected given the course of typical aging. Furthermore, mean chronological age was found to be a significant predictor of mean interference and conflict effects in monolingual seniors but not in bilinguals. For bilingual speakers by contrast, the GMV of the ACC was found to be a significant predictor for mean interference and conflict effects. Moreover, besides the ACC, also GMV of all other selected ROIs associated to cognitive control were found to be significant predictors for mean interference and conflict effects for bilingual seniors only, while for monolinguals GMV of only three ROIs were found to be significant predictors of cognitive control performance along with, as aforementioned,

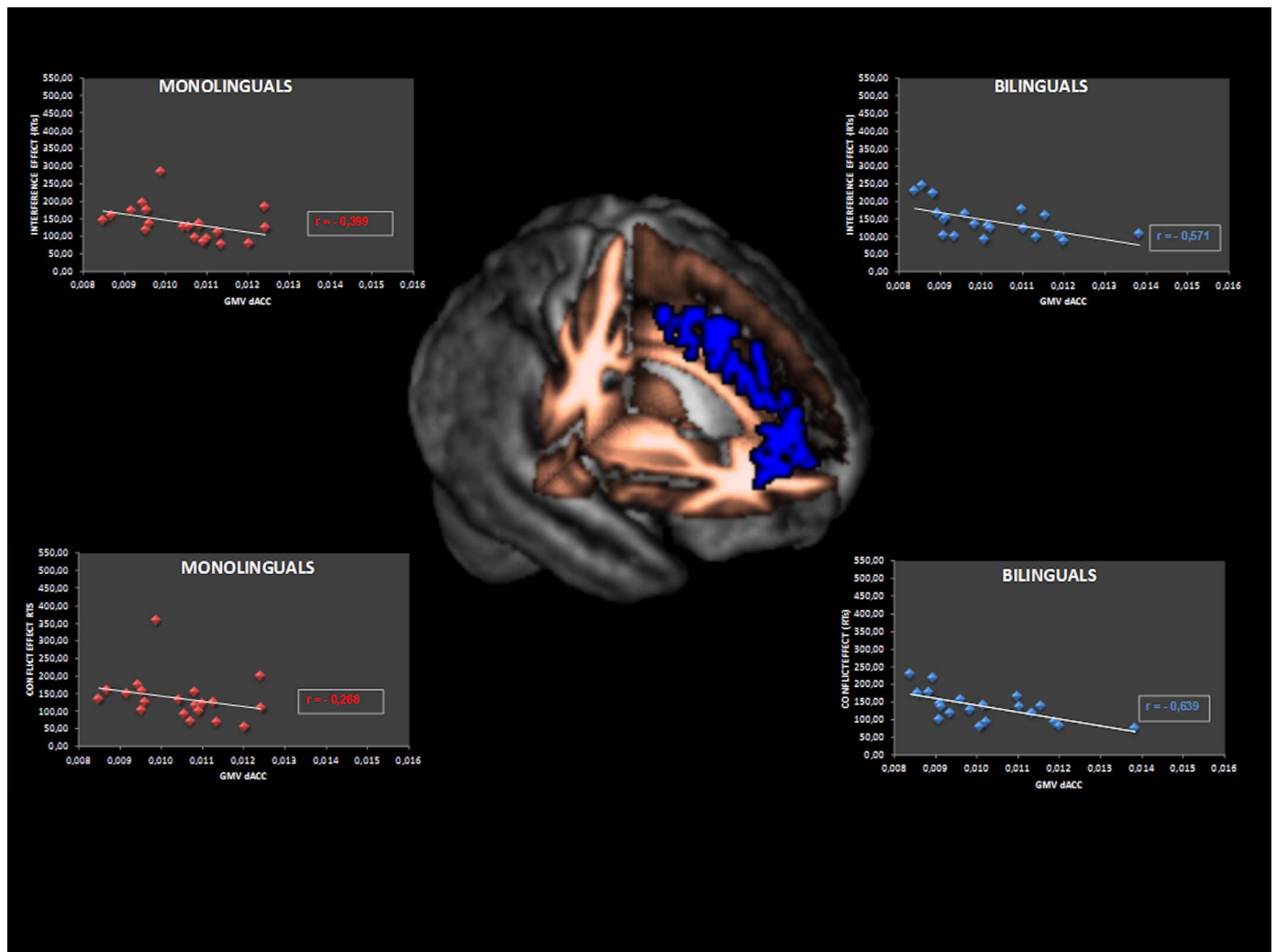


Fig. 3. GMV correlation between interference effect RTs and conflict effect RTs for the two groups separately (i.e. BILINGUALS in blue; MONOLINGUALS in red). Only for bilinguals the RTs differential score of both interference and conflict effects correlated with GMV of the ACC. For the monolingual group mean RTs for conflict effect differential score of one subject was greater than 2 SD over the group's mean. Correlation coefficients remained not significant even after the exclusion of this subject (N = 19: $r = -0.247$, $p = .267$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 6

Correlation analysis between Age and selected ROIs (i.e. Left and Right Calcarine; Left and Right Cuneus) not associated to cognitive control and language control network. Result are reported for the whole sample (N = 40) and for each group separately (i.e. monolinguals and bilinguals).

		Left Calcarine	Right Calcarine	Left Cuneus	Right Cuneus
All sample					
Age	Pearson correlation	-0.45	-0.43	-0.46	-0.43
	Sign. (two tailed)	0.00	0.01	0.00	0.01
	N	40	40	40	40
Monolinguals					
Age	Pearson correlation	-0.45	-0.40	-0.46	-0.48
	Sign. (two tailed)	0.05	0.08	0.04	0.03
	N	20	20	20	20
Bilinguals					
Age	Pearson correlation	-0.46	-0.47	-0.46	-0.42
	Sign. (two tailed)	0.04	0.04	0.04	0.06
	N	20	20	20	20

chronological age.

We also found for the first time that in addition to mean GMV of the ACC predicting the cognitive control performance of bilingual seniors,

the amount of daily exposure to L2 is a significant predictor of cognitive control performance for bilingual seniors.

Critically, bilingual seniors were no different to monolingual seniors in mean GMV, as reported in our region-of-interest analysis, or in their cognitive control performance. Although this argues against a general RT advantage for bilingual seniors, (cf. Paap and Greenberg, 2013; Paap, 2014; Valian, 2015), we contend that cumulative bilingual experience does have a moderating effect on typical aging chronological age on the cognitive and neural reserve of bilingual speakers.

The main impact of the results is the following: cumulative bilingual experience per se offers little direct neuro-protective benefit in terms of total neural reserve (mean GMV) based on our region-of-interest analysis with cognitive control brain areas. Bilingual seniors were as likely to lose total GMV as monolinguals in these regions. Similarly, cumulative bilingual experience does not necessarily improve performance on cognitive control tasks as would be expected given the bilingual advantage hypothesis. A decline in cognitive abilities and grey matter volume (GMV) is expected in typical aging. Thus we found significant effects of aging on mean GMV in nearly all the selected ROIs across the two groups except for the ACC. We did however observe that monolingual seniors have an extended and bilateral pattern of neural decline with chronological age (bilateral IFG, bilateral insula, bilateral IPL) but that bilingual seniors show a less-extended and only leftward pattern of

age related effects on specific brain regions (left insula, left IPL). One conjecture about this neural organization is that critical right hemisphere structures are better preserved in bilingual seniors as shown in Fig. 3. This is a post-hoc explanation however and awaits scrutiny with more clearly defined right hemisphere regions of interest in a follow up study.

It is also of interest that the integrity of the ACC (mean GMV) predicts cognitive control performance for bilingual speakers only. These aspects will be discussed in more detail below.

There is a view that bilingualism provides a cognitive and neural reserve that is beneficial in typical aging. Given that neural networks for language control and domain general cognitive control are overlapping in the brain (Abutalebi et al., 2012, 2013; Abutalebi and Green, 2008), it would hardly be surprising to find that maintenance of executive function mitigates the effect of typical aging on cognitive control performance, as it may in other domains such as music or problem solving experience. The corollary argument that the maintenance of cognitive control via cumulative bilingual *language* experience can also mitigate the effect of aging on performance is more contentious and hitherto has not been confirmed. Several authors have suggested that daily bilingual experience requires control and management of competing languages and that this could lead to beneficial effects on domain general mechanisms for cognitive control which would in turn strengthen cognitive reserve, and thus, delay typical cognitive decline (Bialystok et al., 2012; Abutalebi and Green, 2016; Perani and Abutalebi, 2015). Bilingual seniors do outperform age-matched monolinguals on various tasks requiring cognitive control such as the Simon, Stroop and ANT tasks (Bialystok et al., 2004, 2008, 2014; Abutalebi et al., 2015a). Kavé et al. (2008) using a longitudinal and cross-sectional design with a sample of 814 Israeli seniors reported that the number of languages spoken is associated with better performance on cognitive screening tests (Katzman Cognitive Screening Test and MMSE). However, it has not been certain that performance advantages are the direct result of bilingual experience only (Paap et al., 2015). The present results do so. There is however, a possibility that daily bilingual language experience is correlated with greater exposure to media, music, reading and translation as would come with a multilingual linguistic environment.

Other studies have failed to find a direct advantage for bilingual seniors on cognitive control tasks such as the Wisconsin Card Sorting task, Simon and Stroop tasks (Gathercole et al., 2014; Kirk et al., 2013; Kousaie et al., 2014; Kousaie and Phillips, 2012; Cox et al., 2016). Our results show, however, that aging to the same extent did not influence performance on the ANT for bilingual speakers as compared to monolingual speakers whereas performance was clearly influenced by chronological age for monolingual speakers. This suggests that the typically aging bilingual speaker has unique resources to mitigate age related decline on cognitive control tasks.

There are several alternative reasons why this may ensue. It may be for example that bilingual speakers compensate more actively for their perceived loss of attentional or cognitive control (e.g. word retrieval difficulties) through the wider availability of linguistic strategies (i.e. meta-linguistic awareness) or simply greater self-monitoring of behavioral performance (i.e. more conservative responding). Support for these hypotheses comes from a recent FDG PET (positron emission tomography) metabolic study with a group of bilingual seniors from the same geographical region as the present sample (Perani et al., 2017). Perani et al. (2017) reported that bilingual speakers with Alzheimer's dementia (AD) are on average 5 years older than monolingual speakers when first diagnosed and they have more extended brain hypometabolism. Moreover, yet they consistently perform as well or better on tests of cognitive functioning than monolingual speakers. In other words, bilingual speakers appear to compensate for the dramatic neuropathology of AD in terms of the functional outcomes better than monolingual speakers. We submit that the present findings offer converging evidence on the mitigating effects of bilingualism on the typical

effects of aging. Perani et al. (2017) also performed a metabolic connectivity analyses and reported an increase in the connectivity within the executive control network only in the bilingual speakers with AD, underlining the likelihood of a wider repertoire of compensatory mechanisms available for these patients. Further, as in the present study, they found that the degree of lifelong bilingualism (i.e., high, moderate, or low usage) was significantly correlated with the functional modulations in crucial neural networks, leading them to propose the hypothesis of greater neural reserve due to compensatory mechanisms in bilingual speakers.

Some studies have also failed to find direct evidence of neuro-structural advantages for bilingual seniors specifically using GMV. Indeed, it is now established that bilingual seniors can function as well as monolingual seniors with significant pathology in the brain including less GMV. For example, Schweizer et al. (2012) identified greater atrophy on CT scans of the brains of bilingual speakers with AD despite equivalent levels of cognitive function and reasoned that this was due to bilingual speakers using meta-cognitive strategies to function at a relatively high level and more than would be expected from the extent of their neuropathology. Thus, bilingual speakers may endure a greater degree of brain atrophy before the clinical onset of neuropathology is evident. Abutalebi et al. (2014) also reported that bilingual seniors show a less extended pattern of aging-induced loss of GMV. Furthermore, some studies have highlighted significant differences in grey and white matter structure between bilingual and monolingual seniors specifically in the ACC (Abutalebi et al., 2015a), in the left inferior parietal lobule (Abutalebi et al., 2015b) in the left anterior temporal lobe (Abutalebi et al., 2014; Olsen et al., 2015) and in the frontal lobes bilaterally (Luk et al., 2011). Similarly, a recent VBM study with bimodal bilinguals i.e., participants who use both a spoken and a sign language further confirms these initial findings. For example, Li et al. (2017) reported that bimodal bilingual seniors as opposed to matched monolingual seniors show reduced effects of typical aging in the brain specifically in the left insula and temporal poles bilaterally. It is apparent that these myriad patterns of neuro-structural plasticity can result in specific differences between bilingual and monolingual seniors in typical aging even with no overall differences in global GMV as reported here. This suggests a new interpretation of all extant data i.e. that dissociable cognitive and neural mechanisms can mitigate the effects of aging in bilingual seniors. On the one hand, greater neural reserve (i.e., GMV) may enhance neuro-protection in specific regions of interest such as the brain areas that are necessary for both (domain general) cognitive and (domain specific) language control. On the other hand, those studies that report no differences in overall mean GMV between groups but perhaps significant correlations between mean GMV and cognitive control together with no effects of chronological age strongly support the idea that there is a unique mechanism that is available to bilingual speakers that mitigates the typical effects of healthy aging on performance.

Some theories of typical aging have proposed that cognitive decline in the elderly is mainly related to deficiency in inhibitory mechanisms and decreased working memory capacity, which represent two of the key mechanisms assumed in models of domain-general cognitive control (Hasher and Zacks, 1988; West and Alain, 2000; Grady and Craik, 2000). This is, in turn, associated with the progressive loss of GMV in brain regions that are necessary for cognitive control, such as the pre-frontal and parietal cortices (Good et al., 2002; Jernigan et al., 2001; Raz et al., 2005; Manard et al., 2016). For example, Zimmerman et al. (2006) reported a significant effect of age on mean GMV in the lateral PFC accompanied by a decline in performance on tests of working memory and interference tasks. Also, Ruscheweyh et al. (2013) reported that chronological age significantly predicts the level of interference in the classic Stroop task. Manard et al. (2016) reported a significant relationship between the performances of seniors on executive function tests and decreased mean GMV in the anterior (i.e. frontal, insular and cingulate) cortex, as well as posterior brain areas (i.e.

temporal and parietal cortices) and in subcortical structures. Likewise, Colcombe et al. (2005) reported a group difference between healthy seniors and young adults in their performance on incongruent trials (i.e. the more demanding condition) in the ANT task as well as neuro-structural differences in the prefrontal cortex between older and younger adults. In fact, older adults exhibited decreased GMV in specific regions of the PFC as would be expected along with deterioration of frontal white matter tracts. Our results are broadly compatible with these findings.

If we accept that bilingual speakers are less susceptible to the typical effects of aging on cognitive control, then at least two possible mechanisms might induce neuroprotective effects in specific brain regions. Perani and Abutalebi (2015) propose that bilingualism produces “neural reserve” in the brain. Following this concept, lifelong bilingual experience induces neuro-structural changes, such as increased GMV (Klein et al., 2014; Li et al., 2014a; Mårtensson et al., 2012), which provide a reserve against the grey matter decrease that is invariably associated with typical aging (Barulli and Stern, 2013). On the other hand, Nyberg et al. (2012) proposed that ‘neural maintenance’ results in the preservation of neural structures but is not in itself neuroprotective. Instead, the brain is less susceptible to typical age-induced neuro-degeneration by keeping neural structures intact (Nyberg et al., 2012). The present findings support the latter account (i.e., neural maintenance) as do the findings of Abutalebi et al. (2014) and Li et al. (2017). Another important finding here was that the dACC was the only brain region that is not affected by chronological age for either monolingual or bilingual seniors. We found that GMV in the ACC was correlated with cognitive control performance, in terms of both the mean interference and conflict effects but in bilingual seniors only. On the other hand, although the conflict effect did not correlate with GMV in the ACC in monolingual seniors, a trend ($p = .080$) was found for the interference effect. This suggests first and foremost a stronger relation between cognitive control (i.e. interference and conflict effects) and the structural integrity of the ACC in bilingual seniors than in monolinguals. This possible stronger association was supported by hierarchical regression analysis which pointed out that ACC integrity predicted cognitive control for bilingual speakers while for monolingual speakers only chronological age predicted cognitive control performance.

The ACC has a central role in cognitive functioning in many models of the brain. Following the conflict-monitoring hypothesis (Botvinick et al., 2001, 2004) cognitive control is monitored by the dorsal ACC (dACC) and any conflicts are resolved through the interplay between frontal, parietal and subcortical structures (Nee et al., 2007; Niendam et al., 2012; Cieslik et al., 2015). As hypothesized by Abutalebi et al. (2012, 2013) the dACC may be a common locus (domain general mechanism) used for cognitive control as well as language control. The role of the dACC for understanding the cognitive consequences of bilingual language experience is therefore crucial. Evidence to support this hypothesis comes from bilingual speakers who are more adaptive in control-demanding situations compared with monolinguals, presumably as a consequence of a more efficient use of dACC compared to monolinguals (Abutalebi et al., 2012). The additional cognitive control may reflect greater self-monitoring in bilinguals rather than better inhibitory function. The results from the regression analyses here support the hypothesis of a more efficient use of the dACC in bilingual seniors and this was specifically observed on a nonverbal task that may have recruited more efficient monitoring mechanisms. Both the ANT interference and conflict effects were explained by the mean values of GMV in the dACC for bilingual seniors only. More efficient use of the ACC may therefore have a connection with neuroprotection in typical aging. For example, studies of so-called Super Agers (seniors who have exceptional memory performance) consistently report preserved cortical thickness in the dACC when compared to typical seniors (Harrison et al., 2012; Gefen et al., 2015; Sun et al., 2016).

Finally, we verified for the first time that cognitive control

performance in bilingual speakers is predicted by the amount of daily exposure to L2. A greater amount of daily exposure to a second language will naturally lead to a more frequent requirement to control any interference from competing languages, and thus, could increase language conflicts. These results therefore confirm the cumulative impact of bilingual experience on both behavioral and cognitive performance. If bilingual seniors are more frequently exposed to potential sources of interference such as intrusions from other languages i.e. when they select a relevant language in discourse, while inhibiting the redundant language, they might also be more likely to monitor the sources of perceptual interference and adjust their behavior accordingly (see the Adaptive Control model of Green and Abutalebi, 2013). As aforementioned, if the monitoring of language conflicts (as well as non-language conflicts) both recruit the ACC, then increased and constant involvement of the ACC in language conflicts (if L2 is frequently used) may eventually result in a more efficient use of ACC and should then transfer to nonverbal conflict monitoring tasks such as the ANT. For seniors, the loss of language function (e.g. word retrieval or verbal memory lapses) might be compensated for by the availability of competitors for speech production or at least a greater repertoire of linguistic devices for discourse. In sum, our results support the view that the routine maintenance of the mechanisms used for cognitive control specifically within the linguistic domain can mitigate the typical effects of healthy aging.

Acknowledgements

The study was financed from 2013 to 2016 by the Autonomous Region of Trentino-Alto Adige (title: “Effetti del bilinguismo sull’avanzamento dell’età – iniziativa per la promozione del bilinguismo”) and the Central Research Commission of the Free University of Bozen-Bolzano (title: “NEURO-BILI-AGE: Neurobiological basis of aging in Bilinguals: the protective effect”, BW2100CRC

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.neuropsychologia.2018.01.012>.

References

- Abutalebi, J., Guidi, L., Borsa, V., Canini, M., Della Rosa, P.A., Parris, B.A., Weekes, B.S., 2015a. Bilingualism provides a neural reserve for aging populations. *Neuropsychologia* 69, 201–210.
- Abutalebi, J., Canini, M., Della Rosa, P.A., Green, D.W., Weekes, B.S., 2015b. The neuroprotective effects of bilingualism upon the inferior parietal lobule: a structural neuroimaging study in aging Chinese bilinguals. *J. Neurolinguist.* 33, 3–13.
- Abutalebi, J., Canini, M., Della Rosa, P.A., Sheung, L.P., Green, D.W., Weekes, B.S., 2014. Bilingualism protects anterior temporal lobe integrity in aging. *Neurobiol. Aging* 35 (9), 2126–2133.
- Abutalebi, J., Della Rosa, P.A., Ding, G., Weekes, B., Costa, A., Green, D.W., 2013. Language proficiency modulates the engagement of cognitive control areas in multilinguals. *Cortex* 49 (3), 905–911.
- Abutalebi, J., Della Rosa, P.A., Green, D.W., Hernandez, M., Scifo, P., Keim, R., Costa, A., 2012. Bilingualism tunes the anterior cingulate cortex for conflict monitoring. *Cereb. Cortex* 22 (9), 2076–2086.
- Abutalebi, J., Green, D.W., 2016. Neuroimaging of language control in bilinguals: neural adaptation and reserve. *bilingualism: language and cognition.* 19 (4), 689–698.
- Abutalebi, J., Green, D.W., 2008. Control mechanisms in bilingual language production: neural evidence from language switching studies. *Lang. Cogn. Process.* 23 (4), 557–582.
- Abutalebi, J., Green, D., 2007. Bilingual language production: the neurocognition of language representation and control. *J. Neurolinguist.* 20 (3), 242–275.
- Alladi, S., Bak, T.H., Duggirala, V., Surampudi, B., Shailaja, M., Shukla, A.K., Kaul, S., 2013. Bilingualism delays age at onset of dementia, independent of education and immigration status. *Neurology* 81 (22), 1938–1944.
- Ashburner, J., Friston, K.J., 2005. Unified segmentation. *Neuroimage* 26 (3), 839–851.
- Barulli, D., Stern, Y., 2013. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends Cogn. Sci.* 17 (10), 502–509.
- Bialystok, E., Abutalebi, J., Bak, T.H., Burke, D.M., Kroll, J.F., 2016. Aging in two languages: implications for public health. *Ageing Res. Rev.* 27, 56–60.
- Bialystok, E., Craik, F., Luk, G., 2008. Cognitive control and lexical access in younger and older bilinguals. *J. Exp. Psychol.: Learn. Mem. Cogn.* 34 (4), 859.

- Bialystok, E., Craik, F.I., Freedman, M., 2007. Bilingualism as a protection against the onset of symptoms of dementia. *Neuropsychologia* 45 (2), 459–464.
- Bialystok, E., Craik, F.I., Klein, R., Viswanathan, M., 2004. Bilingualism, aging, and cognitive control: evidence from the Simon task. *Psychol. Aging* 19 (2), 290.
- Bialystok, E., Craik, F.I., Luk, G., 2012. Bilingualism: consequences for mind and brain. *Trends Cogn. Sci.* 16 (4), 240–250.
- Bialystok, E., Poarch, G., Luo, L., Craik, F.I., 2014. Effects of bilingualism and aging on executive function and working memory. *Psychol. Aging* 29 (3), 696.
- Borsa, V.M., Della Rosa, P.A., Catricalà, E., Canini, M., Iadanza, A., Falini, A., Abutalebi, J., Iannaccone, S., 2016. Interference and conflict monitoring in individuals with amnesic mild cognitive impairment: a structural study of the anterior cingulate cortex. *J. Neuropsychol.* <http://dx.doi.org/10.1111/jnp.12105>.
- Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., Cohen, J.D., 2001. Conflict monitoring and cognitive control. *Psychol. Rev.* 108 (3), 624.
- Botvinick, M.M., Cohen, J.D., Carter, C.S., 2004. Conflict monitoring and anterior cingulate cortex: an update. *Trends Cogn. Sci.* 8 (12), 539–546.
- Cieslik, E.C., Mueller, V.I., Eickhoff, C.R., Langner, R., Eickhoff, S.B., 2015. Three key regions for supervisory attentional control: evidence from neuroimaging meta-analyses. *Neurosci. Biobehav. Rev.* 48, 22–34.
- Colcombe, S.J., Kramer, A.F., Erickson, K.I., Scalf, P., 2005. The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. *Psychol. Aging* 20 (3), 363.
- Cox, S.R., Bak, T.H., Allerhand, M., Redmond, P., Starr, J.M., Deary, I.J., MacPherson, S.E., 2016. Bilingualism, social cognition and executive functions: a tale of chickens and eggs. *Neuropsychologia* 91, 299–306.
- Craik, F.I., Salthouse, T.A., 2011. *The handbook of aging and cognition*. Psychology Press.
- Craik, F.I., Bialystok, E., Freedman, M., 2010. Delaying the onset of Alzheimer disease: Bilingualism as a form of cognitive reserve. *Neurology* 75 (19), 1726–1729.
- Della Rosa, P.A., Videsott, G., Borsa, V.M., Canini, M., Weekes, B.S., Franceschini, R., Abutalebi, J., 2013. A neural interactive location for multilingual talent. *Cortex* 49 (2), 605–608.
- Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., White, S.M., et al., 2011. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci* 108 (7), 3017–3022.
- Fan, J., McCandliss, B.D., Sommer, T., Raz, A., Posner, M.I., 2002. Testing the efficiency and independence of attentional networks. *J. Cogn. Neurosci.* 14 (3), 340–347.
- Fan, J., McCandliss, B.D., Fossella, J., Flombaum, J.I., Posner, M.I., 2005. The activation of attentional networks. *Neuroimage* 26 (2), 471–479.
- Gathercole, V.C.M., Thomas, E.M., Kennedy, I., Prys, C., Young, N., Guasch, N.V., Jones, L., 2014. Does language dominance affect cognitive performance in bilinguals? Lifespan evidence from preschoolers through older adults on card sorting, Simon, and metalinguistic tasks. *Front. Psychol.* 5.
- Gefen, T., Peterson, M., Papastefan, S.T., Martersteck, A., Whitney, K., Rademaker, A., Mesulam, M.-M., 2015. Morphometric and histologic substrates of cingulate integrity in elders with exceptional memory capacity. *J. Neurosci.* 35 (4), 1781–1791.
- Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N., Fristen, K., Frackowiak, R.S., 2002. A voxel-based morphometric study of ageing in 465 normal adult human brains. Paper presented at the Biomedical Imaging, 2002. 5th IEEE EMBS International Summer School on.
- Grady, C.L., Craik, F.I., 2000. Changes in memory processing with age. *Curr. Opin. Neurobiol.* 10 (2), 224–231.
- Green, D.W., Abutalebi, J., 2013. Language control in bilinguals: the adaptive control hypothesis. *J. Cogn. Psychol.* 25 (5), 515–530.
- Hanna-Pladdy, B., MacKay, A., 2011. The Relation Between Instrumental Musical Activity and Cognitive Aging. *Neuropsychology* 25 (3), 378.
- Harper, S., 2014. *Ageing Societies*. Routledge.
- Harrison, T.M., Weintraub, S., Mesulam, M.-M., Rogalski, E., 2012. Superior memory and higher cortical volumes in unusually successful cognitive aging. *J. Int. Neuropsychol. Soc.* 18 (6), 1081–1085.
- Hasher, L., Zacks, R.T., 1988. Working memory, comprehension, and aging: a review and a new view. *Psychol. Learn. Motiv.* 22, 193–225.
- Jernigan, T.L., Archibald, S.L., Fennema-Notestine, C., Gamst, A.C., Stout, J.C., Bonner, J., Hesselink, J.R., 2001. Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiol. Aging* 22 (4), 581–594.
- Kavé, G., Eyal, N., Shorek, A., Cohen-Mansfield, J., 2008. Multilingualism and cognitive state in the oldest old. *Psychol. Aging* 23 (1), 70.
- Kirk, N., Scott-Brown, K.C., Kempe, V., 2013. Do older Gaelic-English bilinguals show an advantage in inhibitory control? Paper presented at the CogSci.
- Klein, D., Mok, K., Chen, J.-K., Watkins, K.E., 2014. Age of language learning shapes brain structure: a cortical thickness study of bilingual and monolingual individuals. *Brain Lang.* 131, 20–24.
- Kousaie, S., Phillips, N.A., 2012. Ageing and bilingualism: absence of a “bilingual advantage” in Stroop interference in a nonimmigrant sample. *Q. J. Exp. Psychol.* 65 (2), 356–369.
- Kousaie, S., Sheppard, C., Lemieux, M., Monetta, L., Taler, V., 2014. Executive function and bilingualism in young and older adults. *Front. Behav. Neurosci.* 8.
- Kramer, A.F., Erickson, K.I., 2007. Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. *Trends Cogn. Sci.* 11 (8), 342–348.
- Li, L., Abutalebi, J., Emmorey, K., Gong, G., Yan, X., Feng, X., Ding, G., 2017. How bilingualism protects the brain from aging: insights from bimodal bilinguals. *Hum. Brain Mapp.* 38 (8), 4109–4124.
- Li, P., Legault, J., Litcofsky, K.A., 2014a. Neuroplasticity as a function of second language learning: anatomical changes in the human brain. *Cortex* 58, 301–324.
- Li, P., Zhang, F., Tsai, E., Puls, B., 2014b. Language history questionnaire (LHQ 2.0): a new dynamic web-based research tool. *Biling.: Lang. Cogn.* 17 (3), 673–680.
- Li, T., Yao, Y., Cheng, Y., Xu, B., Cao, X., Waxman, D., Wang, J., 2016. Cognitive training can reduce the rate of cognitive aging: a neuroimaging cohort study. *BMC Geriatr.* 16 (1), 12.
- Luk, G., Bialystok, E., Craik, F.I., Grady, C.L., 2011. Lifelong bilingualism maintains white matter integrity in older adults. *J. Neurosci.* 31 (46), 16808–16813.
- Luks, T.L., Oliveira, M., Possin, K.L., Bird, A., Miller, B.L., Weiner, M.W., Kramer, J.H., 2010. Atrophy in two attention networks is associated with performance on a Flanker task in neurodegenerative disease. *Neuropsychologia* 48 (1), 165–170.
- Lutz, W., Sanderson, W., Scherbov, S., 2008. The coming acceleration of global population ageing. *Nature* 451 (7179), 716–719.
- Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 19 (3), 1233–1239.
- Manard, M., Bahri, M.A., Salmon, E., Collette, F., 2016. Relationship between grey matter integrity and executive abilities in aging. *Brain Res.* 1642, 562–580.
- Mårtensson, J., Eriksson, J., Bodammer, N.C., Lindgren, M., Johansson, M., Nyberg, L., Lövdén, M., 2012. Growth of language-related brain areas after foreign language learning. *Neuroimage* 63 (1), 240–244.
- Mechelli, A., Crinlin, J.T., Noppeney, U., O’Doherty, J., Ashburner, J., Frackowiak, R.S., Price, C.J., 2004. Neurolinguistics: structural plasticity in the bilingual brain. *Nature* 431 (7010), 757 (–757).
- Nee, D.E., Wager, T.D., Jonides, J., 2007. Interference resolution: insights from a meta-analysis of neuroimaging tasks. *Cogn. Affect. Behav. Neurosci.* 7 (1), 1–17.
- Niendam, T.A., Laird, A.R., Ray, K.L., Dean, Y.M., Glahn, D.C., Carter, C.S., 2012. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cogn. Affect. Behav. Neurosci.* 12 (2), 241–268.
- Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., Bäckman, L., 2012. Memory aging and brain maintenance. *Trends Cogn. Sci.* 16 (5), 292–305.
- Olsen, R.K., Pangelinan, M.M., Bogulski, C., Chakravarty, M.M., Luk, G., Grady, C.L., Bialystok, E., 2015. The effect of lifelong bilingualism on regional grey and white matter volume. *Brain Res.* 1612, 128–139.
- Paap, K.R., 2014. The role of componential analysis, categorical hypothesising, replicability and confirmation bias in testing for bilingual advantages in executive functioning. *J. Cogn. Psychol.* 26 (3), 242–255.
- Paap, K.R., Greenberg, Z.I., 2013. There is no coherent evidence for a bilingual advantage in executive processing. *Cogn. Psychol.* 66 (2), 232–258.
- Paap, K.R., Johnson, H.A., Sawi, O., 2015. Bilingual advantages in executive functioning either do not exist or are restricted to very specific and undetermined circumstances. *Cortex* 69, 265–278.
- Perani, D., Abutalebi, J., 2015. Bilingualism, dementia, cognitive and neural reserve. *Curr. Opin. Neurol.* 28 (6), 618–625.
- Perani, D., Farsad, M., Ballarini, T., Lubian, F., Malpetti, M., Fracchetti, A., Magnani, G., March, A., Abutalebi, J., 2017. The impact of bilingualism on brain reserve and metabolic connectivity in Alzheimer’s dementia. *Proc Natl. Acad. Sci.* 114 (7), 1690–1695.
- Posner, M.I., Petersen, S.E., 1990. The attention system of the human brain. *Ann. Rev. Neurosci.* 13 (1), 25–42.
- Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb. Cortex* 15 (11), 1676–1689.
- Ruscheweyh, R., Deppe, M., Lohmann, H., Wersching, H., Korsukewitz, C., Duning, T., Knecht, S., 2013. Executive performance is related to regional gray matter volume in healthy older individuals. *Hum. Brain Mapp.* 34 (12), 3333–3346.
- Schweizer, T.A., Ware, J., Fischer, C.E., Craik, F.I., Bialystok, E., 2012. Bilingualism as a contributor to cognitive reserve: evidence from brain atrophy in Alzheimer’s disease. *Cortex* 48 (8), 991–996.
- Shenhav, A., Botvinick, M.M., Cohen, J.D., 2013. The expected value of control: an integrative theory of anterior cingulate cortex function. *Neuron* 79 (2), 217–240.
- Snodgrass, J.G., Vanderwart, M., 1980. A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *J. Exp. Psychol.: Human Learn. Mem.* 6 (2), 174.
- Stein, M., Federspiel, A., Koenig, T., Wirth, M., Strik, W., Wiest, R., Dierks, T., 2012. Structural plasticity in the language system related to increased second language proficiency. *Cortex* 48 (4), 458–465.
- Stern, Y., 2002. What is cognitive reserve? Theory and research application of the reserve concept. *J. Int. Neuropsychol. Soc.* 8 (3), 448–460.
- Stern, Y., 2009. Cognitive reserve. *Neuropsychologia* 47 (10), 2015–2028.
- Sun, F.W., Stepanovic, M.R., Andreano, J., Barrett, L.F., Touroutoglou, A., Dickerson, B.C., 2016. Youthful brains in older adults: preserved neuroanatomy in the default mode and salience networks contributes to youthful memory in superaging. *J. Neurosci.* 36 (37), 9659–9668.
- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15 (1), 273–289.
- Valian, V., 2015. Bilingualism and cognition. *Biling.: Lang. Cogn.* 18 (1), 3–24.
- Wan, C.Y., Schlaug, G., 2010. Music making as a tool for promoting brain plasticity across the life span. *Neuroscientist* 16 (5), 566–577.
- West, R., Alain, C., 2000. Age-related decline in inhibitory control contributes to the increased Stroop effect observed in older adults. *Psychophysiology* 37 (2), 179–189.
- Woumans, E., Santens, P., Sieben, A., Versijpt, J., Stevens, M., Duyck, W., 2015. Bilingualism delays clinical manifestation of Alzheimer’s disease. *Biling.: Lang. Cogn.* 18 (3), 568–574.
- Zimmerman, M.E., Brickman, A.M., Paul, R.H., Grieve, S.M., Tate, D.F., Gunstad, J., Clark, C.R., 2006. The relationship between frontal gray matter volume and cognition varies across the healthy adult lifespan. *Am. J. Geriatr. Psychiatry* 14 (10), 823–833.
- Zou, L., Ding, G., Abutalebi, J., Shu, H., Peng, D., 2012. Structural plasticity of the left caudate in bimodal bilinguals. *Cortex* 48 (9), 1197–1206.