Title: The role of regional heterogeneity in age-related differences in functional hemispheric asymmetry: An fMRI study

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Acknowledgements

This work was supported by the JSPS-NTU research collaboration grant. It was also supported in part by a Grant-in-Aid for Scientific Research (KAKENHI) #24300186 and #15H03104 provided by the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Abstract

Neuroimaging literature has suggested that older adults show reduced hemispheric asymmetry in frontal regions as compared to young adults during cognitive task performances. However, most studies have been conducted in the context of working memory paradigms. Consequently, it is less clear if this pattern of neural reorganization would also emerge in other areas of cognition which are predominantly lateralized, or it is constrained by working memory processes. Therefore, the present study investigated age-related differences in functional hemispheric asymmetry in language and visuospatial processing, while controlling for grey matter volume. Using blocked functional magnetic resonance imaging (fMRI), 21 young and 16 older Japanese adults performed a homophone judgment task and line judgment task to elicit language and visuospatial processing respectively. Young and older adults performed both tasks with equal accuracy although older adults required a significantly longer time. Young adults showed left lateralization in inferior frontal gyrus during homophone judgment and right lateralization in angular gyrus during line judgment. Age-related functional hemispheric asymmetry reduction was found only in dorsal inferior frontal gyrus and was associated with better performance when the homophone condition was contrasted against fixation, and not line orientation condition. Our data thus highlights the importance of considering regional heterogeneity of aging effects together with general age-related cognitive processes.

Keywords: fMRI, functional hemispheric asymmetry, aging, HAROLD, region-of-interest (ROI)

The unprecedented opportunity to investigate changes within the brain afforded by neuroimaging techniques such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) reveals that the aging brain is more dynamic and adaptive than was previously thought (Reuter-Lorenz & Lustig, 2005; Greenwood, 2007). In an attempt to provide a general neurocognitive aging model to document these patterns, a very popular model that emerged is the *Hemispheric Asymmetry Reduction in Older Adults* (HAROLD) proposed by Cabeza (2002). The HAROLD model states that older adults show reduced asymmetry in prefrontal activity as compared to young adults during cognitive performances. This pattern of cognitive reorganization was reflected across a variety of cognitive tasks such as working memory (Reuter-Lorenz et al., 2000), visual perception (Grady, Bernstein, Beig, & Siegenthaler, 2002) and inhibitory control (Nielson, Langenecker, & Garavan, 2002), and hence is thought to reflect a general aging phenomenon instead of a task-specific occurrence. Moreover, recent studies suggest a link between age-related differences in asymmetric functional and structural connectivity with the HAROLD pattern in prefrontal working memory functional activations (Li, Moore, Tyner, & Hu, 2009). To account for this phenomenon, Cabeza suggested that such cognitive changes may either be by-products of aging without any specific functions (i.e., dedifferentiation), or they play a compensatory role in counteracting age-related neurocognitive decline (for reviews, see Eyler, Sherzai, Kaup, & Jeste, 2011; Morcom & Johnson, 2015).

Another prominent neurocognitive aging model that advocates the role of age-related functional compensatory processes, the *Scaffolding Theory of Aging and Cognition* (STAC; Park & Reuter-Lorenz, 2009), posits that in the face of neural challenges and functional deterioration, the aging brain engages in continuous compensatory scaffolding to maintain similar behavioral performances as young adults (Reuter-Lorenz & Park, 2014). Compensatory scaffolding entails the recruitment of additional regions or neural circuitry to provide supplementary computational support necessitated by an aging brain to maintain cognitive function in the face of localized and global neurofunctional decline. Converging evidence from structural and functional neuroimaging literature show associations between declining neural networks and the recruitment of associated compensatory circuitry in older adults to meet task demands, of which greater activation or additional recruitment of prefrontal regions in older adults are suggested to be indications of compensation (e.g., Fera et al., 2005; Gutchess et al., 2005).

Despite a plethora of studies investigating age-related differences and neural reorganization, most of the studies have been conducted in the context of memory tasks (Cabeza et al., 2004; Rossi et al., 2004; Schmitz, Dehon, & Peigneux, 2013). It is therefore less clear if the HAROLD pattern would also emerge in other areas of cognition, or if this pattern is constrained by working memory processes. Investigating cognitive processes that are instantiated in either a predominantly left- or right-lateralized neural system would thus provide an ideal platform to address these issues and to examine the extent of neural compensation due to the potential for contralateral recruitment.

Findings of left-hemispheric dominance for language processing are commonly reported. Language production is severely disturbed in patients who have injuries in the pars triangularis and pars opercularis of the left inferior frontal gyrus (IFG) (Broca, 1861), and damage to left posterior temporoparietal region, including Brodmann Areas (BAs) 39, 40, 22 and posterior 21 affected language comprehension (Wernicke, 1874). Subsequent studies found that activation in left dorsal IFG (BA 44) was more related to phonological fluency as compared to semantic fluency, and that left ventral IFG (BA 45) was more related to semantic fluency than phonological fluency. This effect has been consistently demonstrated in alphabetic languages (e.g., Costafreda et al., 2006; Katzev, Tuscher, Hennig, Weiller, & Kaller, 2013) as well as non-alphabetic languages (e.g., Matsuo et al., 2010; Wu, Ho, & Chen, 2012; Wu et al., 2014).

Research from lesion studies has shown consistent findings of right-hemispheric laterality for visuospatial processing (McFie, Piercy, & Zangwill, 1950; Vallar & Perani, 1986). An important region that is involved in visuospatial processing is the inferior parietal lobe (IPL) (Michel, Kaufman, & Williamson, 1994; Heilman, 1995; Steinmetz, 1998). Within the IPL, Göbel, Walsh, and Rushworth (2001) demonstrated that the right angular gyrus (BA 39) was more closely involved in visuospatial attention and processing as compared to the right supramarginal gyrus (BA 40). Research using fMRI and transcranial magnetic stimulation (TMS) revealed a right fronto-parietal network that underlies visuospatial processing (Kareken, Lowe, Chen, Lurito, & Mathews, 2000; Collignon et al., 2008).

Current Study

Despite extensive research on age-related differences in hemispheric asymmetry, limited neuroimaging studies have explored such neurocognitive changes in the domains of language and visuospatial processing (e.g. Springer et al., 1999; Szaflarski et al., 2002). Neurocognitive aging studies should also account for age-related structural changes that occur in the brain in order to obtain a more accurate representation of the age-related neural changes (Hayasaka et al., 2006; Takeuchi et al., 2014; Lee, Ratnarajah, Tuan, Chen, & Qiu, 2015).

Taken together, the present study aims to investigate hemispheric asymmetry for language and visuospatial processing and its accompanying age-related differences while employing a more robust statistical technique in controlling for GM volume. To best investigate age-related differences in hemispheric asymmetry, we employed a homophone judgment task to measure language processing (left-lateralization) and a line orientation judgment task (right-lateralization) to measure visuospatial processing. We hypothesized that older adults will show reduced hemispheric asymmetry in language and visuospatial processing as compared to young adults given that the HAROLD model proposed that age-related hemispheric asymmetry reductions is a general aging phenomenon. Specifically, older adults will show reduced hemispheric asymmetry in dorsal IFG (BA 44) as compared to ventral IFG (BA 45) during language processing, given the establishment of functional segregation within the left IFG. If age-related differences in hemispheric asymmetry are local and task-dependent, we would also expect older adults to exhibit hemispheric asymmetry reductions in parietal regions during visuospatial processing. In particular, the HAROLD pattern should be more prominently observed in the angular gyrus (BA 39) as compared to supramarginal gyrus (BA 40) given the functional importance of angular gyrus in visuospatial attention.

Methods

Participants

Twenty-three young and 24 older Japanese adults with no history of neurological diseases or psychiatric disorders were recruited. All participants scored greater than 26 on the Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) and greater than 20, out of 30, on the Judgment of Line Orientation (JLO; Benton, Varney, & Hamsher, 1978) task. They were right-handed as assessed by a Japanese handedness inventory (young adults: *M* = 99.33, *SD* = 3.06; older adults: *M* = 98.06, *SD* = 5.54) (Hatta, 1996, 2007). A total of ten participants (two from young and eight from older adults) were excluded on the basis of one or more of the following conditions: behavioral performances less than 70 percent accuracy on either experimental tasks, large head movements (translation exceeding 2 mm or head rotation exceeding 3.0°), or image artifacts (signal dropout in the inferior orbitofrontal cortex in the EPI sequence). Final analyses consisted of 21 young (13 males and eight females; age: $M = 22.76$, $SD = 4.43$) and 16 older adults (six males and 10 females; age: $M = 66.94$, $SD = 3.26$). Written informed consent was obtained from all participants prior to fMRI administration and the study was approved by the Institutional Review Board of the National Center for Geriatrics and Gerontology in Aichi, Japan, which adheres to the declaration of Helsinki.

Image Acquisition

Head motion was minimized by using padding. All images were acquired with a 3.0 Tesla MR scanner (Siemens Tim Trio, Erlangen, Germany) using a 12-channel quadrature headcoil. A whole-brain gradient-echo echo planar imaging (EPI) sequence was used to collect blood oxygen level-dependent (BOLD) images with the following parameters: repetition time (TR) 3000 ms; echo time (TE) 30 ms; flip angle (FA) 90°; field of view (FOV) 192 mm; 64 x 64 matrix; 3.0 x 3.0 x 3.0 mm^3 voxel size; 39 axial slices with 0.75-mm gaps. A total of 128 images were acquired. T2-weighted anatomical images were obtained at the same locations as the functional images using the following parameters: TR 5920 ms; TE 95 ms; FA 150°; FOV 192 mm; 256 x 256 matrix; 0.8 x 0.8 x 3.0 mm^3 voxel size; 39 axial slices with 0.75-mm gaps. High resolution T1-weighted anatomical images covering the whole brain were obtained using a 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) imaging protocol with the following parameters: TR 2500 ms; TE 2.63 ms; FA 7°; FOV 256 mm; 256 x 256 matrix; 1.0 x 1.0 x 1.0 mm^3 voxel size.

Task Procedures

The task was presented with E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Three conditions were included: fixation (F), line judgment (L) and homophone judgment (H). In the fixation condition, participants were presented with a white crosshair at the centre of a black screen. In the line condition, participants judged if two pairs of line arrays were of similar or different orientation. Participants indicated “Yes” with the index finger on the left key if the line arrays are of exactly similar orientation or “No” with the middle finger of the dominant hand on the right key if the line arrays differed by 5, 10 or 15 degrees. For the homophone condition, participants judged if two Japanese kanji characters had similar or different pronunciations. Participants indicated “Yes” with the index finger on the left key if both homophones sounded exactly the same, or “No” with the middle finger of the dominant hand on the right key if the homophones do not sound exactly the same. The character stimuli were adopted from a previous study (Matsuo et al., 2010). Specifically, twenty-five pairs of homophonic and twenty-five pairs of non-homophonic kanji characters were included. These kanji characters only have one pronunciation; the homophonic pairs consisted of characters with the same pronunciation, while the non-homophonic pairs consisted of characters with different pronunciations. More details on character selection were reported in the previous paper by Matsuo et al. (2010).

The homophone judgment task is a substitute for rhyming tasks used in alphabetical languages (Matsuo et al., 2010). It was chosen for this study as previous studies have found that cognitive tasks which require covert rhyming of visually presented words recruited subvocal articulation and phonological processing (Démonet et al., 1992), allowing for the accurate mapping of the language cortex. Moreover, Pillai and Zaca (2011) found that covert rhyming produces the most robust lateralization results as compared to receptive language paradigms such as reading comprehension or listening comprehension. The line task was not only employed to investigate visuospatial processing, but it also served as a baseline for the visuospatial component of the homophone judgment task given that the line orientation task involves minimal verbal processes (Kareken et al., 2000).

fMRI Paradigm

Across all conditions, each trial consisted of a 2000 ms presentation of a stimulus and 400 ms inter-stimulus interval (ISI). This study employed a conventional block design, adapted from Lurito, Kareken, Lowe, Chen, and Mathews (2000). Each block consisted of ten trials, lasting a total of 24 s. One cycle consisted of three blocks in the following order: a fixation block, a line judgment block and a homophone judgment block. Each cycle lasted a total of 72 s. The task session consisted of one run, which consisted of five cycles and an additional fixation block at the end to allow the hemodynamic response function to return to baseline. This extra fixation block was not included in subsequent analysis. Hence, one run lasted for 6 minutes and 24 seconds (Fig. 1).

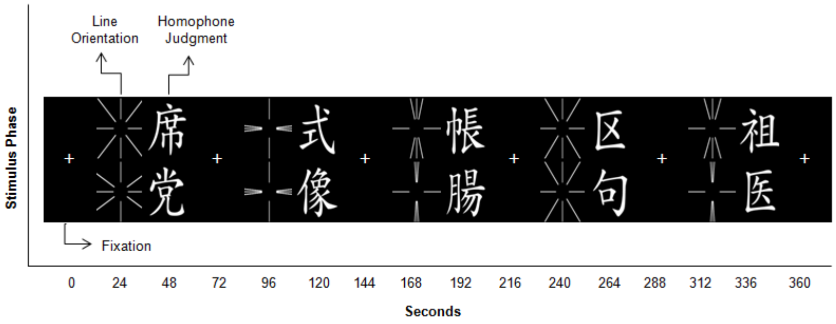

Fig. 1. fMRI paradigm consisted of five cycles of fixation, line orientation judgement and homophone judgment with an additional block of fixation.

Behavioral Data Analysis

Independent sample *t*-tests were conducted to determine group differences for MMSE and JLO scores. Behavioral responses were recorded within the scanner for each participant, and a mixed-design ANOVA was conducted independently on accuracy and reaction time to examine effects of age groups and task conditions.

Imaging Data Analysis

The Statistical Parametric Mapping software (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK) running in MATLAB (MATLAB and Statistics Toolbox Release 2009b; The MathWorks Inc., Natick, Massachusetts, US) was used to process and analyze all fMRI data. Functional images and T2-weighted images were re-oriented to the anterior commissure-posterior commissure (AC-PC) image plane from the T1-weighted image template. Slice timing correction was applied with the middle slice in the slice acquisition order as the reference slice. All data were realigned to the first volume. The T1 image was coregistered to the mean functional image. Segmentation was performed before normalization to Montreal Neurological Institute (MNI) standard brain space, which was carried out using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL). DARTEL has been reported to improve inter-subject registration (Stonnington et al., 2008; Bergouignan et al., 2009). Functional images were smoothed using an 8 mm FWHM isotropic Gaussian kernel. A modulated GM probability map obtained from segmentation was used as an imaging covariate to control for differences in GM volume for subsequent group comparisons conducted in Biological Parametric Mapping (BPM; Casanova et al., 2007). Compared to conventional SPM analyses where all voxels are assigned the same GM value, BPM allocates the appropriate voxel value for GM probability in the regression model for each voxel.

A general linear model (GLM) was conducted at first-level analysis to obtain contrast effects for task activations ("H > F", "H > L" and "L > F") for both young and older adults. Six head motion regressors were included as covariates in the individual design matrix to adjust for residual effects of head movements. To investigate language and visuospatial processing in young and older adults, a random-effects group analysis employing a one-sample *t*-test was conducted to estimate contrast effects for "H > F" and "L > F" for each group. Further analyses were conducted with "H > L" to examine regions that are critically involved during the performance of homophone judgment task. One-sample *t*-tests were all thresholded at $p < .05$, FWE corrected. Next, ANCOVAs were conducted for all contrasts using BPM to investigate age-related differences in functional hemispheric asymmetry with cluster-level threshold of $p < .05$, FWE corrected (with a cluster-defining primary threshold of uncorrected $p < .001$) (Woo, Krishnan, & Wager, 2014). GM probability maps were included in BPM ANCOVA analyses as covariates to control for GM volume. Task behavioral measures that yielded significant group differences were also included in the analysis as non-imaging covariates.

To measure functional hemispheric lateralization quantitatively, a lateralization index, AveLI was applied. AveLI has been proposed to be a robust Lateralization Index (LI) in fMRI studies (Matsuo, Chen, & Tseng, 2012). It is based on an elegant and unbiased computational principle which uses the *t*-values of voxels that are within region-of-interests (ROIs). Subordinate LIs (sub-LIs) are first computed by using the *t*-values of each task-related positive voxel as the threshold with the following formula:

$$\text{sub-LI} = \frac{\text{Lt}-\text{Rt}}{\text{Lt}+\text{Rt}}$$

where Lt and Rt are the sums of the *t*-values that are at and above the threshold in the left and right ROIs respectively. The AveLI is simply an average of all the sub-LIs and provides an indication of the consistency in lateralization of a subject's brain activation across the full range of voxel *t*-value thresholds:

$$\text{AveLI} = \frac{\sum(\text{sub}-\text{LI})}{\text{VN}}$$

where VN is the total number of voxels with positive *t*-values within the ROIs. Using the AveLI over other LIs has several advantages, such as noise reduction (Matsuo et al., 2012). An AveLI score greater than 0.2 indicates that the activation is strongly left lateralized for all voxel *t*-value thresholds while an AveLI score smaller than -0.2 indicates that the activation is strongly right lateralized for all voxel *t*-value thresholds. Participants are categorized as showing bilateral activations if an AveLI score is between -0.2 to 0.2 (Matsuo et al., 2012).

As Chlebus et al. (2007) showed that LI had a stronger correlation with the Wada test only if language areas were used in the LI calculation, *a priori* ROIs were defined for language and visuospatial processing (Fig.2). For the homophone judgment task, three ROI masks were defined: IFG, dorsal IFG (BA 44) and ventral IFG (BA 45) (specified using SPM Anatomy toolbox; Eickhoff et al., 2005). As such, three AveLI scores were each obtained for the contrasts "H > F" and "H > L" to represent the degree of lateralization in IFG, BA 44 and BA 45 during language processing. Group differences were determined by independent sample *t*-tests with Bonferroni-corrected $p < .017$. Correlation analyses were conducted between AveLI scores of the ROIs (IFG, BA 44, BA 45) and behavioral performance (i.e., accuracy and reaction time of homophone judgment task) to investigate the relationship between age-related differences in the degree of lateralization and task performance in the older adults group with Bonferroni-corrected *p* < .017.

For the line judgment task, three ROI masks were defined: inferior parietal lobule (IPL), angular gyrus (BA 39) and supramarginal gyrus (BA 40) (specified using SPM Anatomy toolbox; Eickhoff et al., 2005). As such, three AveLI scores were obtained for the contrast "L > F" to represent the degree of lateralization in IPL, BA 39 and BA 40 during visuospatial processing. Group differences were determined by independent sample *t*-tests with Bonferroni-corrected *p* < .017. To investigate the relationship between age-related differences in the degree of lateralization in the ROIs (IPL, BA 39 and BA 40) during performance on the line judgment task, correlation analyses were conducted between AveLI scores of the ROIs and behavioral measures (i.e., accuracy and reaction time) for the older adults group with Bonferroni-corrected *p* < .017.

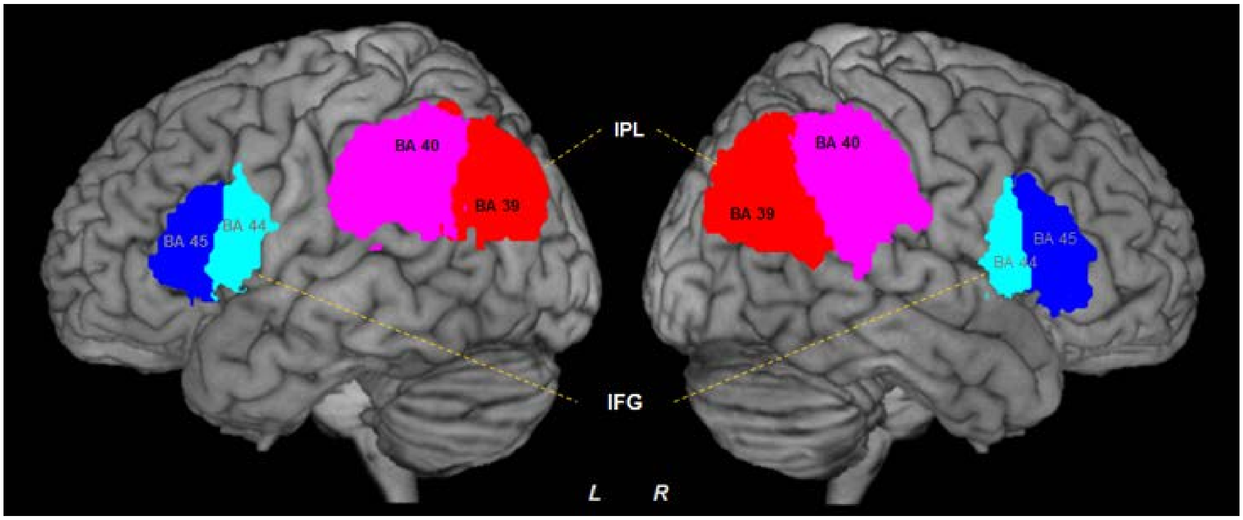

Fig. 2. An illustration of the language-related ROIs (*in blue*) and visuospatial-related ROIs (*in red*).

Finally, percent signal change was extracted for each condition for each participant using MARSeille Boîte À Région d'Intérêt (MarsBaR) in SPM8 (Brett, Anton, Valabregue, & Poline, 2002). To examine hemispheric differences in signal activity of each ROI, percent signal change was extracted separately for each ROI in its left, right or bilateral hemisphere. For ROIs related to language processing, percent signal change was extracted for (i) left IFG, BA 44, BA 45 (ii) right IFG, BA 44, BA 45. For ROIs related to visuospatial processing, percent signal change was extracted for (i) left IPL, BA 39, BA 40 (ii) right IPL, BA 39, BA 40, In sum, percent signal change was extracted for six regions for each contrast.

Independent sample *t*-tests were conducted to determine if there were significant group differences in signal activity for homophone judgment task and line judgment task with Bonferroni-corrected $p < .0083$. To investigate the relationship between age-related differences in signal activity and behavioral performance, correlation analyses were conducted between percent signal change of the aforementioned ROIs and behavioral measures (i.e., accuracy and reaction time) of homophone and line judgment tasks for the older adults group. For homophone judgment task, percent signal change of left BA 44, right BA 44, left BA 45, right BA 45, left IFG, right IFG extracted from (i) "H > F" and (ii) "H > L", were correlated with accuracy and reaction time of homophone judgment task. For line judgment task, percent signal change of left BA 39, right BA 39, left BA 40, right BA 40, left IPL, right IPL, extracted from "L > F" were correlated with accuracy and reaction time of line judgment task. In sum, six correlations for each contrast were conducted, corrected for multiple comparisons with Bonferroni-corrected $p < .0083$. All behavioral analyses were conducted using SPSS Version 23.

Results

Behavioral Data Analysis

Older adults scored lower on the MMSE (*M* = 28.88, *SD* = 1.09) as compared to young adults (*M* = 29.52, *SD* = .60) (*t*(36) = 2.34, $p < .05$) but showed no differences in JLO at $p < .05$. Young and older adults performed the homophone judgment task and line judgment task with equal accuracy (Homophone judgment task: young adults. *M* = 96.78, *SD* = 3.60; older adults. *M* = 96.35, *SD* = 4.03. Line judgment task: young adults. *M* = 87.72, *SD* = 5.03; older adults. *M* = 84.67, *SD* = 5.19). Both groups achieved higher accuracy for the homophone judgment task as compared to the line judgment task (*F*(1, 35) = 117.44, $p < .001$). Older adults required a significantly longer reaction time (*F*(1, 35) = 68.64, $p < .001$) for both tasks as compared to young adults (Homophone judgment task: young adults. *M* = 1179.96, *SD* = 163.52; older adults. *M* = 1348.33, *SD* = 163.47. Line judgment task: young adults. *M* = 1005.43, *SD* = 145.83; older adults. *M* = 1236.52, *SD* = 124.43). Moreover, both groups required a significantly longer reaction time for the homophone judgment task as compared to the line judgment task (*F*(1, 35 = 18.07, $p < .001$). Analyses did not yield any significant interaction effects between tasks and age groups for accuracy and reaction time at $p < .05$ (Fig. 3).

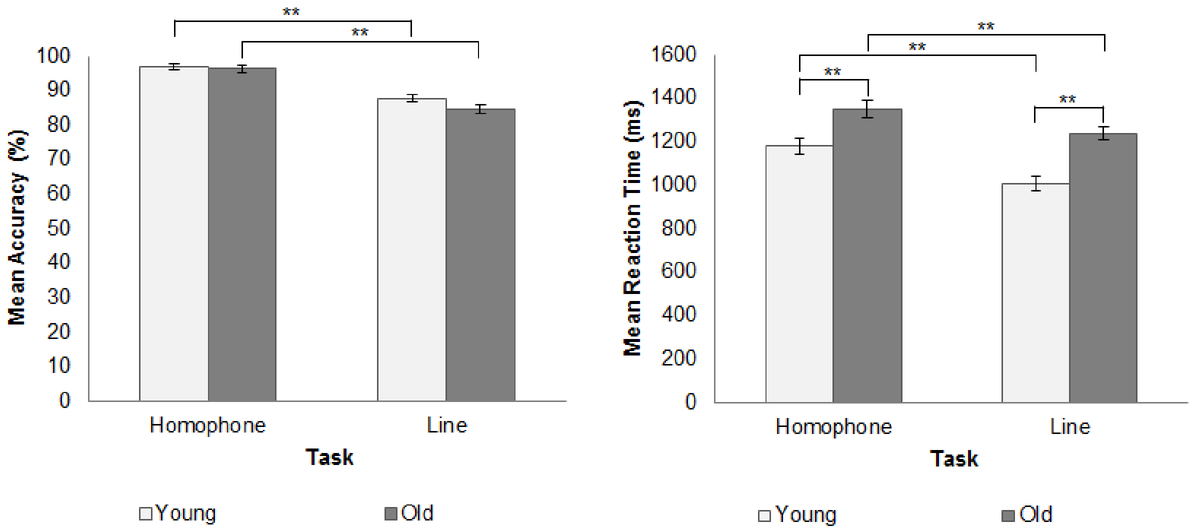

Fig. 3. Behavioral results. Mean accuracy (ACC) and reaction time (RT) of homophone and line judgment tasks with error bars of standard error. $**p < .001$.

Imaging data analysis

Homophone judgment task. A whole brain analysis of the contrast “H > F” revealed peak coordinates in left medial/middle frontal gyrus (BA 6/46) and bilateral precentral gyrus (BA 6/9) for young adults. Activations in left IPL (BA 40), bilateral superior parietal lobule (SPL) and lingual gyrus (BA 17) were also observed. Older adults showed peak activations in left inferior (BA 44/45) and middle frontal gyri (BA 9/46), and bilateral medial frontal gyrus (BA 6). Activations in left middle occipital gyrus (BA 18), cerebellar lobule VI and right cerebellar lobule VIIIB were also observed (Table 1; Supplementary material Fig. S1 left). ANCOVA analysis with RT of homophone judgment task and GM probability maps as covariates revealed significant temporal and parietal activations only in the “H > F : old > young” contrast and not the “H > F : young > old” contrast. Specifically, older adults showed greater activations in left middle temporal gyrus (BA 39), middle occipital gyrus (BA 37) and bilateral precuneus (BA 7) as compared to young adults. Significantly greater cerebellar activations in left lobule VIIB and right Crus I were also observed in older adults as compared to young adults (Table 1; Fig. 4A).

Given that contrasting the homophone condition with fixation produced additional activations beside the expected frontal regions, a random-effects group analysis employing a one-sample *t*-test was then carried out with contrast “H > L” as subtracting the line condition from the homophone condition controls for attentional demands and simple visuospatial processing. With this contrast, young adults showed activations in bilateral lingual gyri (BA 17) and left cerebellar lobule VI. Distinct activations observed in older adults were centered at left middle frontal gyrus (BA 46), IFG (BA 45/47), lingual gyrus (BA 17) and right cerebellar lobule VIIB (Table 1; Fig. 4B). ANCOVA analysis with RT of homophone judgment and line judgment tasks, and GM probability maps as covariates revealed significant cerebellar activations only in the “H > L : old > young” contrast and not the “H > L : young > old” contrast. Specifically, older adults showed greater activations in right Crus I and Crus II as compared to young adults.

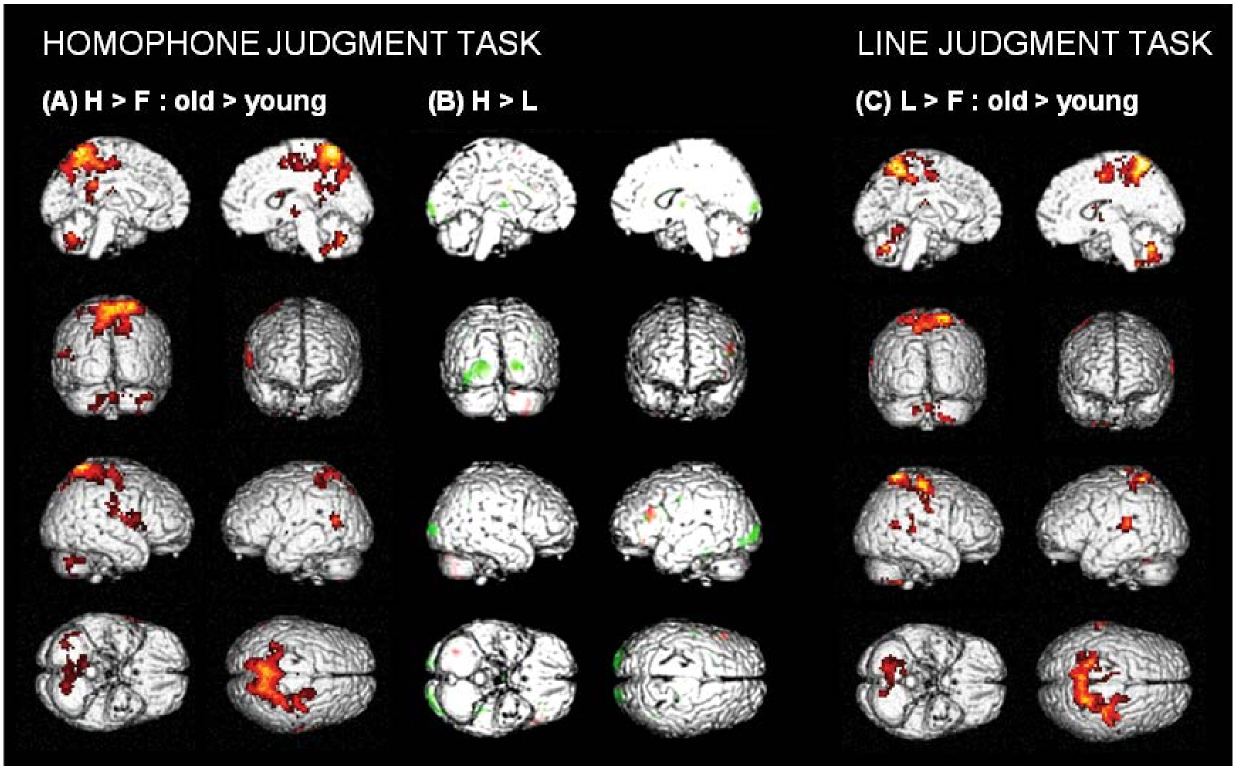

Fig. 4. Task-related activations. (A) age-related differences during the performance of homophone judgment task for “H > F : old > young”. “H > F : young > old” did not produce any significant activations at cluster-level threshold of $p < .05$, FWE corrected (with a cluster-defining primary threshold of uncorrected $p < .001$). (B) whole brain activation maps for young (in red) and older (in green) adults when homophone condition is contrasted against line condition at $p < .05$ (FWE corrected). (C) age-related differences during the performance of line judgment task for “L > F : old > young”. “L > F : young > old” did not produce any significant activations at cluster-level threshold of $p < .05$, FWE corrected (with a cluster-defining primary threshold of uncorrected $p < .001$).

Table 1. Peak coordinates of brain regions activated in homophone judgment task in MNI space

Classification	Brain regions	BA	Left hemisphere			*T*	Cluster Size	Right hemisphere			*T*	Cluster Size
			x	*y*	*z*			*x*	*y*	*z*		
Homophone > Fixation												
Young Adults												
Frontal lobe	Precentral gyrus	6, 9	-39	3	30	13.75	305	48	12	30	7.99	46
	Medial frontal gyrus	6	-6	6	56	10.14	194					
	Middle frontal gyrus	6, 46	-30	-3	49	7.17	305					
Parietal lobe	Inferior parietal lobule	40	-42	-36	45	10.27	473					
	Superior parietal lobule	7	-30	-57	53	9.41	473	33	-57	49	9.50	69
Occipital lobe	Lingual gyrus	17	-9	-99	8	18.28	3810	18	-87	8	17.81	3810
Older Adults												
Frontal lobe	Medial frontal gyrus	6	-6	3	53	13.85	433	9	12	49	13.58	433
	Middle frontal gyrus	9, 46	-51	30	23	10.63	405					
	Inferior frontal gyrus	44, 45	-33	30	0	13.10	116					
Occipital lobe	Middle occipital gyrus	18	-33	-84	8	25.88	4118					
Cerebellum	Lobule VI		-33	-78	-15	23.68	4118					
	Lobule VIIIB							27	-57	-49	9.41	21
Young > Old												
-	-	-	-	-	-	-	-	-	-	-	-	-
Old > Young												
Temporal lobe	Middle temporal gyrus	39	-51	-60	15	4.58	68					
Parietal lobe	Precuneus	7	0	-54	64	7.60	2138	12	-57	68	7.46	2138
Occipital lobe	Middle occipital gyrus	37	-42	-66	8	3.73	68					
Cerebellum	Lobule VIIB		-12	-69	-38	5.21	218					
	Crus I							45	-54	-34	4.53	60
Homophone > Line												
Young Adults												
Occipital lobe	Lingual gyrus	17	-15	-99	0	12.34	118	24	-96	4	11.44	58
Cerebellum	Lobule VI		-33	-39	-23	8.93	33					
Older Adults												
Frontal lobe	Middle frontal gyrus	46	-45	27	23	9.83	39					
	Inferior frontal gyrus	45, 47	-48	24	15	9.44	39					
Occipital lobe	Lingual gyrus	17	-21	-96	0	12.05	25					

Cerebellum	Lobule VIIB	33	-66	-45	8.40	12
Old > Young						
Cerebellum	Crus I	30	-72	-34	4.68	94
	Crus II	36	-75	-41	4.13	94

Notes. Peak coordinates are summarized for young and older adults with $p < .05$ (FWE corrected) while peak coordinates for “old > young” and “young > old” are presented at cluster-level threshold of $p < .05$, FWE corrected (with a cluster-defining primary threshold of uncorrected $p < .001$).

Line judgment task. A whole brain analysis of the contrast “L > F” revealed a bilateral network of frontal and occipital activations for young adults. Specifically, peak coordinates in the frontal region include bilateral precentral gyrus (BA 6) and left medial frontal gyrus (BA 6). Activations were also observed in left lingual gyrus (BA 17), middle occipital gyrus (BA 19) and cerebellar lobule VIIIA. Similar to young adults, older adults also showed a bilateral fronto-occipital network when performing the line judgment task. Peak coordinates include right inferior and middle frontal gyri (BA 6/9), left middle occipital gyrus (BA 18), cerebellar lobule V and bilateral cerebellar lobule VIIIB (Table 1; Supplementary material Fig. S1 right.). ANCOVA analysis with RT of line judgment task and GM probability maps as covariates revealed greater fronto-parietal activation only in the “L > F : old > young” contrast and not the “L > F : young > old” contrast. Specifically, older adults activated the left precentral gyrus, right medial frontal gyrus and superior parietal lobule (BA 7), and bilateral STG (BA 22/42) significantly more than young adults. Older adults also showed significantly greater cerebellar activations in left cerebellar lobule V and VIIB, and right lobule VIIIB as compared to young adults (Table 2; Fig. 4C).

Table 2. Peak coordinates of brain regions that are activated during line orientation judgment task in MNI space

Classification	Brain regions	BA	Left hemisphere			*T*	Cluster Size	Right hemisphere			*T*	Cluster Size
			x	*y*	*z*			*x*	*y*	*z*		
Line > Fixation												
Young Adults												
Frontal lobe	Precentral gyrus	6	-42	3	34	9.86	60	48	9	30	9.75	82
	Medial frontal gyrus	6	-6	6	56	10.12	61					
Occipital lobe	Lingual gyrus	17	-3	-96	8	22.13	4991					
	Middle occipital gyrus	19	-27	-87	23	20.47	4991					
Cerebellum	Lobule VIIIA		-30	-66	-49	7.53	8					
Older Adults												
Frontal lobe	Inferior frontal gyrus	9						42	12	26	12.13	153
	Middle frontal gyrus	6, 9						39	39	15	13.05	85
Occipital lobe	Middle occipital gyrus	18	-33	-84	8	26.34	6158					
Cerebellum	Lobule V		-21	-54	-15	28.40	6158					
	Lobule VIIIB		-27	-42	-53	12.16	29	27	-57	-53	10.76	39
Young > Old												
-	-	-	-	-	-	-	-	-	-	-	-	-
Old > Young												
Frontal lobe	Precentral gyrus	6	-9	-12	68	3.85	92					
	Medial frontal gyrus	6						6	-9	53	4.47	92
Temporal lobe	Superior temporal gyrus	22, 42	-66	-30	15	5.17	65	45	-54	15	5.26	43
Parietal lobe	Superior parietal lobule	7						21	-42	68	5.55	1153
Cerebellum	Lobule V		-21	-54	-19	6.50	85					
	Lobule VIIB		-12	-72	-38	4.92	213					
	Lobule VIIIB							9	-63	-38	5.24	213

Notes. Peak coordinates are summarized for young and older adults with $p < .05$ (FWE corrected) while peak coordinates for “old > young” and “young > old” are presented at cluster-level threshold of $p < .05$, FWE corrected (with a cluster-defining primary threshold of uncorrected $p < .001$).

AveLI scores. Activations in the IFG were predominantly lateralized to the left in both young (*M* = .48, SD = .26) and older adults (*M* = .36, SD = .29) during homophone judgment (H > F) as measured by AveLI. When homophone condition was contrasted against line condition, AveLI score was significantly closer to 1 for older adults (*M* = .66, SD = .31) (*t*(15) = -4.62, *p* < .001), and not for young adults (*M* = .62, SD = .40) (*t*(20) = -1.59, *p* = .13) as compared to AveLI scores obtained from "H > F" contrast. However, a one-sample *t*-test did not yield any significant differences between the AveLI scores of young and older adults for both "H > F" and "H > L" at Bonferroni-corrected *p* < .017 with IFG as ROI. Upon further investigations with BA 44 and BA 45 as separate ROIs using the "H > F" contrast, one-sample *t*-tests revealed a significant age-related reduction in hemispheric asymmetry only in BA 44 (young adults: *M* = .76, SD = .20, older adults: *M* = .49, SD = .29; *t*(35) = 3.38, *p* = .002) but not BA 45 (Fig. 5). However, in the "H > L" contrast, this effect in BA 44 did not remain significant (young adults: *M* = .66, SD = .42, older adults: *M* = .76, SD = .29; *t*(35) = -.82, *p* = .42). Spearman's rho revealed that AveLI scores obtained with BA 44 was negatively associated with accuracy on the homophone judgment task (*r*(16) = -.62, *p* = .011) while no significant correlation was observed between AveLI scores obtained with BA 45 and accuracy at Bonferroni-corrected *p* < .017. However, these effects were not observed in the H > L contrast.

When line condition was contrasted against fixation (L > F), IPL activations were bilateral in both young (*M* = -.062, SD = .26) and older adults (*M* = -.042, SD = .25) rather than right lateralized as measured by AveLI. Similar to the homophone judgment task, one-sample *t*-test did not yield any significant differences between the AveLI scores of young and older adults for "L > F" with IPL as ROI at Bonferroni-corrected *p* < .017. Further investigations with BA 39 and BA 40 as separate ROIs using the "L > F" contrast showed right lateralization only in BA 39 in young (*M* = -.26, SD = .50) and older adults (*M* = -.22, SD = .31) but not BA 40 (young adults: *M* = -.010, SD = .36; older adults: *M* = .0045, SD = .30). However, one sample *t*-test did not reveal any significant age-related reduction in hemispheric asymmetry for BA 39 and BA 40 at *p* < .017. No significant correlation between AveLI scores and behavioral performance was obtained in the older adults group with Bonferroni-corrected *p* < .017.

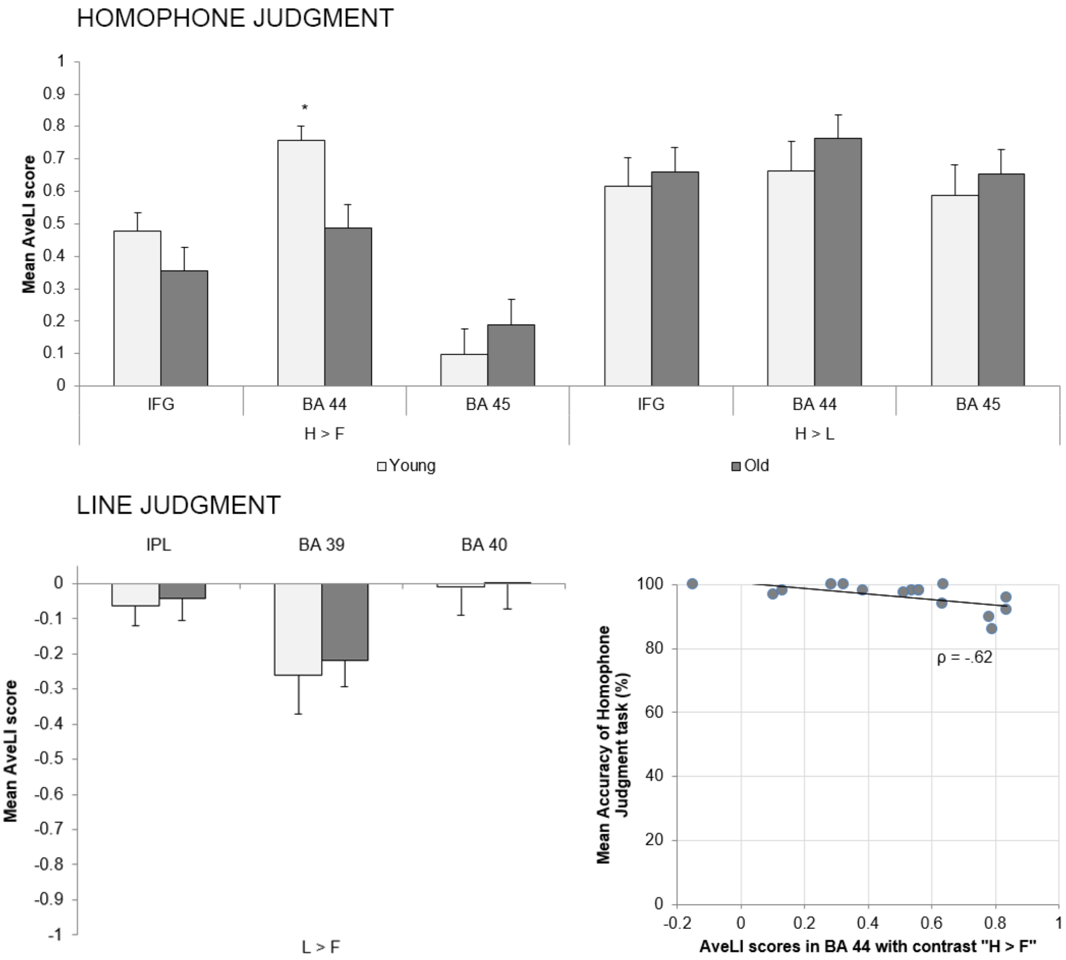

Fig. 5. Summary of AveLI scores. *Top.* AveLI scores for H > F and H > L, by age group with IFG, BA 44 and BA 45 as ROIs. *Bottom left.* AveLI scores for L > F with IPL, BA 39 and BA 40 as ROIs. *Bottom right.* Significant negative correlation between AveLI scores in BA 44 and accuracy of homophone judgment task in older adults group. **p* < .017.

Percent signal change. Significant between-group differences were observed in left and right IFG ($t(35) = -3.64$, $p = .001$; $t(35) = -4.89$, $p < .001$), left and right BA 44 ($t(35) = -3.21$, $p = .003$; $t(35) = -4.97$, $p < .001$), left and right BA 45 ($t(35) = -3.44$, $p = .002$; $t(35) = -3.46$, $p = .001$) with older adults eliciting greater activity in these regions for the contrast “H > F” as compared to young adults (Fig. 6). No significant between-group differences were observed in right BA 44 or left BA 45 for the contrast “H > L” at Bonferroni-corrected $p < .0083$. Spearman’s rho did not yield any significant correlations of percent signal change in aforementioned language-related ROIs with behavioral performance on the homophone judgment task within the older adults group at Bonferroni-corrected $p < .0083$.

Significant between-group differences were observed in the left and right IPL ($t(35) = -5.40$, $p < .001$; $t(36) = -5.87$, $p < .001$), right BA 39 ($t(35) = -4.87$, $p < .001$), and left and right BA 40 ($t(35) = -5.31$, $p < .001$; $t(35) = -5.51$, $p < .001$) with older adults eliciting greater activity in these regions for the contrast “L > F” as compared to young adults (Fig. 5). Response magnitude did not differ between the groups for left BA 39 ($t(35) = -1.91$, $p = .065$). Next, Pearson’s correlations with behavioral performance on the line judgment task were calculated for these regions in the older adults group. Significant correlations were observed between brain responses in left BA 39 and accuracy only at uncorrected $p < .05$ ($r(15) = .60$, $p = .014$).

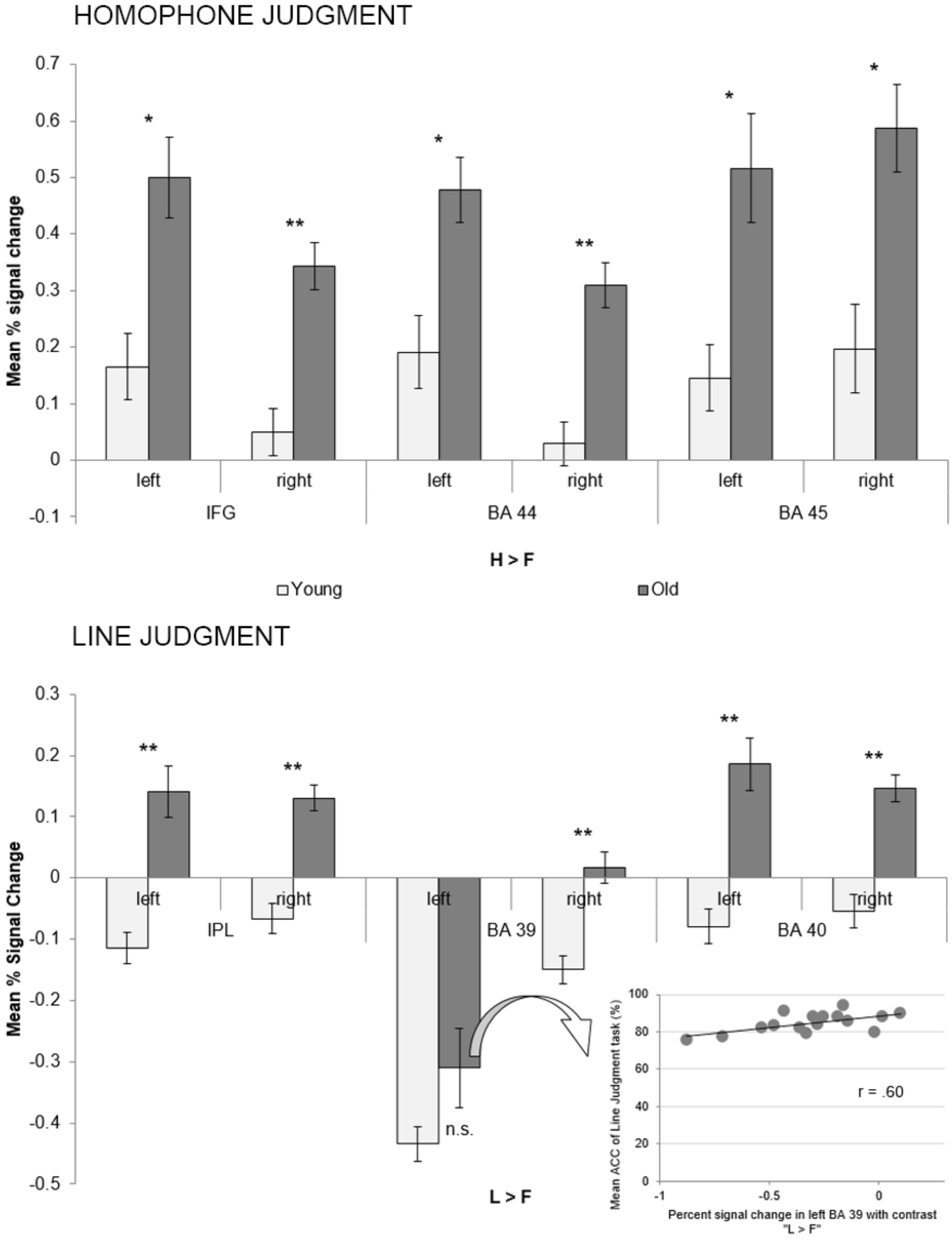

Fig. 6. Summary of percent signal change analyses. *Top.* Mean percent signal change in IFG, BA 44 and BA 45 during homophone condition relative to fixation (H > F : old > young). *Bottom.* Mean percent signal change in IPL, BA 39 and BA 40 during line condition relative to fixation (L > F : old > young). **$p < .001$, *$p < .0083$.

Discussion

Homophone Judgment Task for Evaluating Language Processing

In our whole-brain fMRI study, the homophone judgment task elicited left prefrontal laterality in young and older adults with foci localized to left inferior, middle and medial frontal gyri. Left prefrontal laterality was stronger and more focal when homophone condition was contrasted against line condition as compared to fixation. In addition, both groups showed bilateral parietal activations only when homophone condition was contrasted against fixation and not line condition. As the homophone judgment task in this study employed kanji characters, it is plausible that the parietal activations shown by participants might be a result of simple visuospatial processing given the possibility of a closer relationship between shape and meaning in reading kanji than alphabetic languages (Matsuo et al., 2010). Indeed, when visual frequency, focused attention and the need for response selection was matched by using line condition as a baseline (Kareken et al., 2000), stronger left laterality in Broca's area was observed in older adults, and there was no significant activation in parietal regions.

In addition, cerebellar activations were elicited in young and older adults during the performance of the homophone judgment task. The involvement of the cerebellum during homophone judgment is consistent with previous studies that documented a cerebro-cerebellar network in language processing (Chen & Desmond, 2005a, 2005b) and phonological processing (e.g. Wu et al., 2012).

Age-related Neural Differences in Language Processing

Age-related differences in language processing were documented as increased activations in older adults as compared to young adults (old > young) in the current study; greater activations in young adults as compared to older adults during the performance of the homophone judgment task was not seen (young > old). This corroborates with previous studies that reported only an *old > young* effect (e.g., Wierenga et al., 2008; Meinzer et al., 2009). After controlling for GM volume, we did not find a significant reduction in hemispheric asymmetry in IFG when older adults were performing the homophone judgment task relative to fixation. Considering the functional differentiation within the IFG – pars opercularis (BA 44) for phonological fluency and pars triangularis (BA 45) for semantic fluency (Kareken et al., 2000), we further examined age-related differences in laterality within these regions and found that older adults showed significant hemispheric asymmetry reductions only in BA 44, and not BA 45, as compared to young adults during the performance of the homophone judgment task relative to fixation. However, this effect did not remain significant when homophone judgment was contrasted against line condition. Contrary to this finding, Springer et al. (1999) and Szaflarski et al. (2002) reported a negative association between LI and age in a semantic decision task relative to a tone decision task, demonstrating a decline in laterality during lexical-semantic processing and phonetic processing with increasing age. This effect was observed when LI was calculated for each hemisphere (Springer et al., 1999), and frontal, temporal, medial and lateral ROIs (Szaflarski et al., 2002). Given that the current study employed a homophone task which involves phonological processing – a different aspect of language processing, it is plausible that different components of language processing could show different degrees of age-related reduction in hemispheric asymmetry.

An interesting finding was the observation of only greater cerebellar activations in older adults, specifically right Crus I and Crus II, as compared to young adults during the homophone judgment task relative to the line judgment task. Existing literature has documented a crossed cerebro-cerebellar network in language processing (Stoodley & Schmahmann, 2009; E, Chen, Ho, & Desmond, 2014), of which strongest activation peaks for language tasks were lateralized to right Crus I and Crus II. Moreover, the increased right cerebellar laterality is consistent with previous studies (Luo et al., 2016), suggesting a pattern of intra-hemispheric changes in the cerebellum as contrast to the increased inter-hemispheric changes (HAROLD) in cerebral regions.

It is of interest to note that the same experimental paradigm was used in a previous study (Wu et al., 2014) to examine age-related differences in the effective connectivity of brain regions involved in homophone judgment. While the dynamic causal modeling analysis revealed that young and older adults preferred differential reading pathways in the left prefrontal cortex, no age-related differences were found in regional brain activation. In contrast, greater frontal activation was found for the older adults compared to the young adults in the current study. The discrepant results of group differences between the two studies might be attributed to the several aspects in which the current study differs from Wu et al. (2014), including participant exclusion criteria, data preprocessing procedures, measures to control for GM density, and applied statistical thresholds. Most important of all, it is worth considering that the resulting discrepancy could plausibly be due to a qualitatively more sophisticated iterative process employed in DARTEL preprocessing (Peelle, Cusack, & Henson, 2012) and the use of BPM to adjust for GM density at the voxel level. Compared to the conventional preprocessing and analysis in SPM8, the combination of both DARTEL preprocessing and BPM analysis may provide a more sensitive approach to accounting for age-related brain atrophy in aging studies (e.g. Pudas et al., 2013).

Line Judgment Task for Evaluating Visuospatial Processing

Both young and older adults showed bilateral activations in frontal, parietal and occipital regions when line condition was contrasted against fixation. As the strongest peak activations are located in the occipital regions instead of the expected parietal regions, we postulate that this pattern of activation could reflect a stronger reliance on early visual sensory processes, or it could also reflect a use of other strategies when performing the task. Nonetheless, there is abundant neuroscience research to support that the right parietal region is critical for cognitive tasks involving visuospatial processing (Goebel, Khorram-Sefat, Muckli, Hacker, & Singer, 1998a; Ng et al., 2000). Further investigations examining brain activations separately in BA 39 (angular gyrus) and BA 40 (supramarginal gyrus), right lateralization, as indicated by an AveLI score lesser than -0.2, was observed only in BA 39 for both young and older adults, showing differential involvements of sub-regions in the IPL.

In addition, the observed cerebellar activations in young and older adults during the line judgment task corroborates with existing literature, suggesting that task categories can indeed be topographically represented within the cerebellum (Lee et al., 2005).

Age-related Neural Differences in Visuospatial Processing

As compared to young adults, older adults showed reduced bilateral frontoparieto-occipital specificity for line condition relative to fixation. Increased frontal activations, including the precentral gyrus and medial frontal gyrus, were observed in older adults as compared to young adults as well. However, older adults did not show significant age-related hemispheric reductions in IPL. Further investigations of specific regions in IPL (i.e., BA 39 and BA 40) also did not yield any significant group differences, suggesting a lack of HAROLD-effect in the inferior parietal region during visuospatial processing. While the lateralization scores were not correlated with the behavioral performance, older adults exhibited greater signal activity in task-specific regions (i.e. right IPL, BA 39, BA 40) and contralateral regions including left IPL and left BA 40 as compared to young adults when performing the line orientation task. It is interesting to note that no group differences were found in signal intensity in left BA 39, and that greater signal activity in left BA 39 was associated with higher accuracy on the line judgment task only in older adults.

Therefore, the increased activation and recruitment of other regions not specific to visuospatial processing, as evident from significantly greater activity in right IPL, BA 39 and BA 40, as well as their contralateral regions in older adults as compared to young adults putatively help to compensate for the reduced neural efficiency in right IPL, albeit at the cost of increased reaction time. Indeed, this is consistent with existing literature that noted a preponderance of increased frontal and decreased sensory activation in older adults as compared to young adults across attentional, working memory and long-term memory tasks (Cabeza et al., 2004; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008). The increased frontal activation in older adults has been suggested to compensate for reduced efficiency in information processing that accompanies normal aging, such as speed of processing, working memory capacity, inhibitory function and long-term memory (Park & Reuter-Lorenz, 2009). Moreover, older adults showed greater activations in left cerebellar lobules IV and VIIB as well as right cerebellar lobule VIIIB when line condition is contrasted against fixation, of which these over-activations could help support processes related to visuospatial processing (MacLullich et al., 2004).

An Integrated View of Age-related Differences in Language and Visuospatial Processing

It is evident in the current study that older adults are able to achieve similar task performance accuracy as young adults albeit requiring longer processing time. This finding of slower processing speed converges with theories on age-related differences in speed of information processing (Salthouse, 1996; Verhaeghen & Cerella, 2008), which may reflect an underlying decline in task-specific neural network efficiency. According to the compensatory view, the aging brain engages in various scaffolding mechanisms to maintain similar behavioral performance, of which one robust finding is increased frontal bilterality (Cabeza, 2002; Persson et al., 2006; Park & Reuter-Lorenz, 2009). Further specifying this pattern of age-related neural reorganization, the current study demonstrated the importance of considering regional heterogeneity of aging effects when examining HAROLD patterns in the prefrontal region. In particular, we showed that less lateralization in BA 44 only is related to higher accuracy on the homophone judgment task in older adults. This converges with prior studies that reported BA 44 to be related with phonological processing (Wu et al., 2012; Katzev et al., 2013) and that older adults preferred a direct phonological pathway during homophone judgment task (Wu et al., 2014).. It should be noted that this effect was only observed in the *homophone > fixation* contrast – a contrast which would necessarily include other cognitive processes not directly related to phonological processing. Nonetheless, the specificity of this effect suggests that it could be worthwhile to consider that the recruitment of contralateral activation in older adults in part reflect phonological factors, rather than general age-related cognitive resource limitations. This notion has previously been discussed in the context of age-related changes in syntactic processing (Tyler et al., 2010; Davis, Zhuang, Wright, & Tyler, 2014).

While the current study did not find significant quantitative age-related hemispheric asymmetry reduction in the inferior parietal regions during visuospatial processing, other studies have reported age-related reduction in hemispheric asymmetry in regions outside the prefrontal cortex, such as the temporal regions during syntactic task (Tyler et al., 2010), sentence judgment and sentence recognition tasks (Berlingeri, Danelli, Bottini, Sberna, & Paulesu, 2013); parieto-occipital regions during face processing (Grady et al., 2002) and picture recognition task (Berlingeri et al., 2013). The inconsistent finding of increased bilaterality across task domains in older adults is also demonstrated in a recent meta-analytic investigation of task-fMRI studies (Li et al., 2015). Instead, Li and colleagues (2015) showed that age-related differences in activation could be presented by different network patterns across cognitive domains (Li et al., 2015). More specifically, they found different hypo- and hyper-activation in different networks in memory encoding tasks, memory retrieval tasks and executive function tasks. Hence, it is plausible that a similar trend would emerge in the cognitive domains of language and visuospatial processing. Despite the lack of significant findings of age-related reductions in inferior parietal region during visuospatial processing, we showed a trend for signal activity in contralateral region homologous to task-specific region (i.e. BA 39) to be correlated with accuracy in older adults. This provides preliminary support for a pattern of compensatory scaffolding in visuospatial processing although a clear HAROLD-pattern was not observed. In addition, qualitative observations of age-related differences in visuospatial processing show greater activations of the superior parietal regions in older adults. Therefore, it is plausible that additional sites for scaffolding may be in the penumbra of primary activation sites as well as a spread of over-activation in the contralateral region (Goh & Park, 2009).

Taken together, results of age-related functional differences in language and visuospatial processing are in agreement with the perspective of compensatory scaffolding in older adults, although the HAROLD pattern may be more prominently observed in the frontal regions as compared to other sites. Greater effort should be taken to link age-related differences in cerebral hemispheres and cerebellum in aging, which is relatively less addressed in current neurocognitive aging models.

Limitations of This Study

One of the limitations of this study is the small and unequal sample size between young (N = 21) and older adults (N = 16) with unbalanced gender ratio. In addition, the fMRI task reliability may have been hampered as there was only one run of few trials at six minutes total task. Participants in this study also showed little variance in task accuracy, with near ceiling performance for the homophone judgment task. One should also note that the ROI analyses were only significant for *task > fixation* contrast, which would certainly involve general cognitive processes unrelated to specific language or visuospatial processing, despite specifying the selection of ROI. In a similar vein, discretion should be exercised in considering how the current results fit with different neurocognitive aging models.

While the current study provides a platform for a more comprehensive understanding of the aging brain in the domains of language and visuospatial processing through investigations of functional activations, future studies with larger and equal samples are necessary to verify the consistency of age-related neural differences in the domains of language and visuospatial processing. More specifically, future studies investigating visuospatial processing should include a baseline condition of simple visual images as a control. In addition, recent studies have started to highlight the importance of extending task-fMRI studies to examining functional and structural connectivity. For instance, Li et al. (2009) extended the discussion on HAROLD to resting connectivity as well as structural connectivity, and showed that they were related to age-related differences in functional lateralization. As such, future studies could consider multimodal approaches in studying the aging brain.

Summary

The present study investigated age-related differences in functional hemispheric asymmetry in cognitive domains which are well-established to be lateralized (i.e., language and visuospatial processing), yet less often investigated as compared to working memory paradigms. Using a homophone judgment task and line judgment task, we showed the presence of HAROLD-effect only in prefrontal regions critically involved in the type of processing elicited by the language task, but not in parietal regions which are functionally important to visuospatial processing, after controlling for GM volume. While the parietal regions did not reach statistical significance in age-related hemispheric asymmetry reduction, the overactivation of the contralateral region was correlated with accuracy, suggesting a compensatory mechanism.

Supplementary material

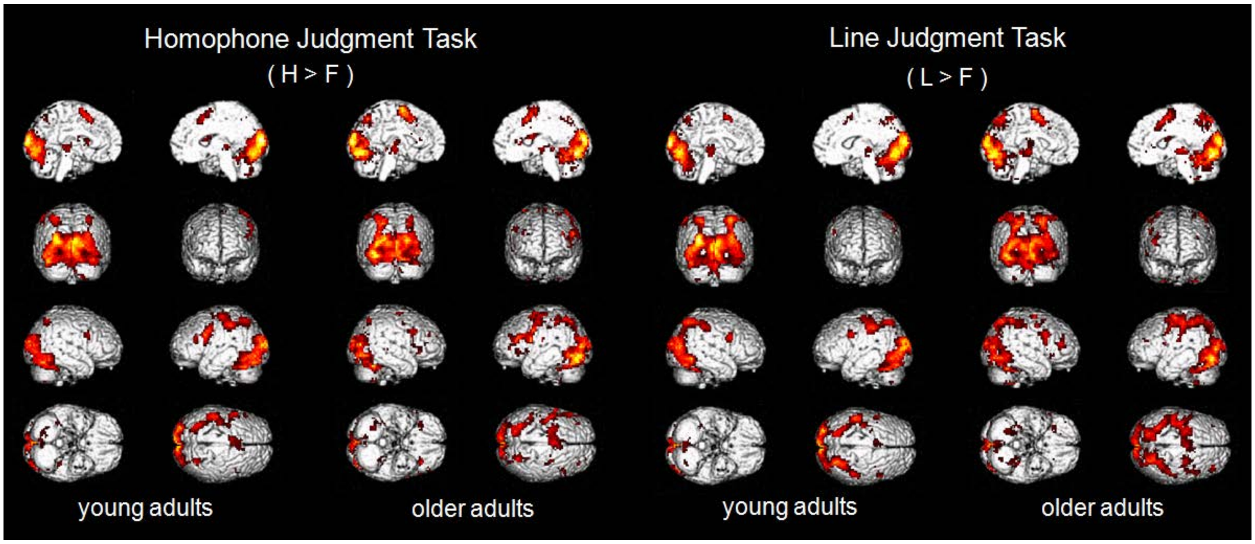

Fig. S1. Activation maps of young and older adults during the homophone judgment task (left) and line judgment task (right). $p < .05$, FWE corrected.

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