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The Architecture of Cross-Hemispheric Communication in the Aging Brain: Linking Behavior to Functional and Structural Connectivity

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Contralateral recruitment remains a controversial phenomenon in both the clinical and normative populations. To investigate the neural correlates of this phenomenon, we explored the tendency for older adults to recruit prefrontal cortex (PFC) regions contralateral to those most active in younger adults. Participants were scanned with diffusion tensor imaging and functional magnetic rresonance imaging during a lateralized word matching task (unilateral vs. bilateral). Cross-hemispheric communication was measured behaviorally as greater accuracy for bilateral than unilateral trials (bilateral processing advantage [BPA]) and at the neural level by functional and structural connectivity between contralateral PFC. Compared with the young, older adults exhibited 1) greater BPAs in the behavioral task, 2) greater compensatory activity in contralateral PFC during the bilateral condition, 3) greater functional connectivity between contralateral PFC during bilateral trials, and 4) a positive correlation between fractional anisotropy in the corpus callosum and both the BPA and the functional connectivity between contralateral PFC, indicating that older adults' ability to distribute processing across hemispheres is constrained by white matter integrity. These results clarify how older adults' ability to recruit extra regions in response to the demands of aging is mediated by existing structural architecture, and how this architecture engenders corresponding functional changes that allow subjects to meet those task demands.

Keywords: aging, cortical reorganization, diffusion tensor, fMRI, white matter

Introduction

Much of the initial work in neuropsychology focused on how the 2 cerebral hemispheres supported different cognitive processes, leading to the idea that cognition typically comprises specialized and lateralized systems (Ivry and Robertson 1998). However, a growing literature has focused on the brain's ability to augment processing in these specialized regions by recruiting contralateral regions in response to neural decline or insult. Contralateral recruitment in response to brain injury is a phenomenon that has been documented in both acute (Butefisch et al. 2005) and progressive neurodegenerative disorders (Warburton et al. 1999; Saur, Ronneberger, et al. 2010; Tyler et al. 2011). However, the neural mechanisms underlying this phenomenon remain poorly understood. We focused on the well-known phenomenon that older adults tend to over-recruit prefrontal cortex (PFC) regions contralateral to those most active in younger adults. Aging serves as an ideal model with which to explore the mechanisms of cross-hemispheric communication because contralateral PFC recruitment in older adults has been observed many times across a variety of studies using different stimuli and cognitive tasks (for reviews, see Dennis and Cabeza 2008; Park and Reuter-Lorenz 2009). For example, Reuter-Lorenz et al. (2000) found that during a verbal working memory task that engaged mainly the left PFC in younger adults, older adults over-recruited right PFC; conversely, during a spatial working memory task that activated primarily right PFC in younger adults, older adults also recruited contralateral left PFC. However, despite the prevalence of this observation within the aging literature, direct evidence linking this phenomena with straightforward relationships between behavior and brain connectivity is sparse. Given the prevalence of this finding in both the clinical and normative literatures, it is therefore an important empirical question for both normal and pathological aging as to what behavioral and neurological factors underlie this mechanism. The present study investigated the neural mechanisms mediating cross-hemispheric communication in younger and older adults by linking measures of behavior, functional activity, functional connectivity, and white matter integrity.

We therefore sought to establish both structural and functional imaging evidence that age-related contralateral over-recruitment is associated with increases in interhemispheric communication between right and left PFC. We sought to explicitly test this idea by eliciting an increase in bilateral versus unilateral processing by using a split-field matching paradigm (Banich and Belger 1990). In this task, participants match 2 stimuli projected either to the same visual field (unilateral condition) or to opposite visual fields (bilateral condition). Whereas the unilateral condition allows for the possibility that matching may be performed within a single hemisphere, the bilateral condition requires that information is transferred across hemispheres via the corpus callosum. When matching is demanding, behavioral performance tends to be better for bilateral than unilateral trials (bilateral processing advantage [BPA]), a finding that suggests cross-hemispheric interaction (Banich 1998). Reuter-Lorenz et al. (1999, 2000) found that the BPA for accuracy during a letter matching task was larger in older than younger adults, a finding that agrees with the aforementioned contralateral over-recruitment in older adults (however, see Cherry et al. 2010). In this study, we sought to replicate the age-related BPA increase in the semantic domain using a word matching task. Older adults typically perform as well as or better than young adults in semantic memory tasks, and many neuroimaging studies have shown that this lasting cognitive performance is sustained by age-related increases in brain activity (Grady and Craik 2000; Nessler et al. 2006; Burke and Shafto 2008; Shafto et al. 2010).

We took advantage of these phenomena by using a semantic task, such that differences in brain structure or activity would be less influenced by the possible confounds associated with age-related differences in overall performance. We therefore expected older adults to show observable differences in behavior between hemispheric presentation conditions, with bilateral trials eliciting greater accuracy and faster responses in older than younger adults (first prediction).

Furthermore, given the observation that older adults tend to demonstrate a less lateralized response to semantic memory tasks (Logan et al. 2002; Stebbins et al. 2002; Bergerbest et al. 2009), we expected that these differences would be reflected in an increase in bilateral functional magnetic resonance imaging (fMRI) activity during bilateral processing. We therefore measured cross-hemispheric communication by assessing fMRI activity during a semantic word matching task. Given the verbal nature of the task, we expected that both younger and older adults would show strong left hemisphere PFC activation. However, we expected that older adults would show greater activity than younger adults in contralateral PFC, particularly for bilateral trials, consistent with the idea that greater bilateral processing in older adults supports performance of a task that is distributed across hemifields. Importantly, we expected that this contralateral activity would be positively correlated with behavioral performance in the scanner (second prediction). We then expected that functional connectivity between left and right PFC regions (based on fMRI data) would be stronger in older than younger adults and would show a similar positive relationship to performance (third prediction). Thus, we predicted that aging would increase cross-hemispheric communication at both behavioral (BPA) and neural (left–right PFC connectivity) levels. Furthermore, we considered it critical that both the functional "activity" and functional "connectivity" in the PFC be positively related to accuracy on the task, furthering the idea that these increases in PFC recruitment in older adults have a positive impact on performance.

Finally, we linked behavioral and neural measures of cross-hemispheric communication to white matter integrity in the corpus callosum, as measured by diffusion tensor imaging (DTI). Studies focusing on the relationship between white matter and functional activity have shown the corpus callosum to be particularly important in mediating a range of cognitive functions in older adults (Bucur et al. 2008; Chen et al. 2009; Kennedy and Raz 2009). These findings underscore the importance of considering the role of white matter in describing consistent cortical mechanisms for interhemispheric communication. In particular, the corpus callosum may represent an important pathway for predicting the extent to which older adults engage in distributed frontal processing in the face of frontal declines (Greenwood 2007). Thus, it is conceivable that increased structural integrity of callosal pathways might support improved performance, if older adults shift to a more bilateral pattern of activity. We predicted that within the older adult group, but not the younger adult group, both accuracy on bilateral trials and left–right PFC connectivity would be correlated with white matter integrity in the anterior corpus callosum (fourth prediction). Such a finding would provide evidence for the idea that contralateral recruitment of frontal cortices is dependent on existing structural architecture. Given that a number of recent studies have demonstrated the functional relevance of the age-related myelodegenerative pattern in white matter (Sullivan et al. 2006; Vernooij et al. 2008; Davis et al. 2009), we expected these correlations to also be observed for a diffusivity measure linked to myelin health (radial diffusivity [RD], see Song et al. 2003) as well as the more general measure of white matter integrity (fractional anisotropy [FA]). Such a finding would indicate that bihemispheric processing in older adults is constrained by the integrity of cross-hemispheric callosal fibers. Together, these lines of evidence provide a cogent account of how the brains of older adults can capitalize on existing structural architecture to facilitate efficient function and performance.

Methods

Participants

Eighteen younger adults (10 males) and 16 older adults (8 males) were paid for their participation in this study. All participants were healthy, right-handed native English speakers with normal or corrected-to-normal vision and no history of neurological or psychiatric episodes (for participant characteristics, see Table 1). Older adults were screened for health problems and conditions that could affect blood flow (e.g., hypertension, medications affecting blood flow) using a questionnaire. Data were not analyzed from one younger participant because of scanner problems and from one younger and one older participant whose behavioral performance was not significantly above chance. Written informed consent was obtained from each participant, and the study met all criteria for approval from the Duke University Institutional Review Board.

Behavioral Paradigm

Crossed–Uncrossed Difference Task

Prior to the scanning session, participants completed the crossed-uncrossed difference (CUD) task (Poffenberger 1912). The CUD measure is derived from a unimanual, simple detection task, in which the left/right location of a visual stimulus either corresponds to the responding hand (uncrossed) or does not correspond (crossed). The CUD is usually positive, reflecting slower responses on crossed trials, and thus CUD magnitude has been used as a behavioral index of interhemispheric interaction (Schulte et al. 2005). We used this metric to help account for both individual and group differences in interhemispheric interaction unrelated to the task by including it as a covariate in both behavioral and functional imaging models. The CUD is typically greater for older adults than for younger adults (Jeeves and Moes 1996).

Participants viewed a fixation cross in the middle of the screen and were presented with stimuli consisting of a black circle on a white background to the left or right of the vertical meridian. The stimuli

Table 1
Demographic data and behavioral results

		YA, M (SD)	OA, M (SD)
Age		21.70 (2.6)	68.06 (4.9)
Education (years)		15.06 (1.7)	17.25 (2.2)
Edinborough handedness scale		96.5 (8.7)	98.7 (3.6)
CUD (ms)*		4.5 (0.42)	7.8 (0.62)
Word matching task (scanned)			
Accuracy (proportion correct)	Unilateral	0.89 (0.06)	0.88 (0.08)
	Bilateral	0.88 (0.10)	0.94 (0.06)
	BPA	−0.011 (0.04)	0.028 (0.03)
	d′	2.12 (0.17)	2.39 (0.16)
Reaction time (ms)	Unilateral	1369 (224)	1404 (253)
	Bilateral	1325 (210)	1312 (231)
	BPA_RT	9.69 (83.5)	−6.49 (36.1)

Note: SD, standard deviation; YA, younger adults; OA, older adults; BPA, residualized accuracy rate, bilateral condition; and BPA_RT, residualized response time, bilateral condition.
*$P < 0.05$.

subtended 1° of visual angle and were located 8° from the center of the screen. Stimuli were presented for 50 ms, with a time window of 2000 ms following stimulus onset. Subjects were instructed to respond with a key press as soon as they detected the stimulus. For 100 trials, they pressed with the key with the index finger of one hand and for 100 trials with the index finger of the other hand, with hand order counterbalanced across subjects. Consistent with other studies using this measure, the CUD was calculated by subtracting the average response time to crossed responses from the average response time to uncrossed responses for each subject and dividing this difference by 2.

Word Matching Task

During fMRI scanning, participants performed the semantic matching task illustrated in Figure 1. During each trial, 2 words were presented and participants indicated whether or not they related in meaning (i.e., semantic associates). Participants were instructed to respond as quickly and accurately as possible by pressing a key. Critically, in the unilateral condition, the 2 words were presented in the same visual field (i.e., both in the left or both in the right), whereas in the bilateral condition, the 2 words were presented in opposite visual fields (i.e., one in the left and one in the right). There were 240 trials total, 180 matching and 60 nonmatching (control) trials. All trials were divided into 120 unilateral (60 left visual field, 60 right visual field) and 120 bilateral presentation trials. Each word pair was presented for 450 ms and followed by a jittered intertrial interval that varied between 2.5 and 9.1 s. The words were projected onto a screen 1.1 m away, which participants viewed though an angled mirror. For each word pair, the distance between the 2 words, and from fixation, was between 2.1° and 4.1°, depending on variations in the visual angle of each word; presentation was the same for each pair for each participant. The words were nouns selected from the University of South Florida word association norms (Nelson et al. 2004). The pairs did not differ in their forward- or backward-association strength, and mean association strength was evenly distributed from high (1.0) to low (0.01) values. The words were matched in frequency, abstractness, and imageability.

In both the behavioral and fMRI analyses, we focused on the matching trials because on these trials all subjects reached a similar decision point, namely that the words were related semantically. On the nonmatching trials, in contrast, the response is also influenced by each subject's criterion for determining when to end the search of semantic memory (Chun and Wolfe 1996), and this criterion may vary across subjects. Consistent with this interpretation, response times for nonmatch trials was higher than for match trials ($t = 7.3$, $P < 0.005$).

Participants performed 3 runs of the word matching task and were instructed to maintain fixation on a cross displayed in the center of the screen at all times. Trials on which the subject made 2 responses were excluded from analysis, as were trials in which response times greater than 2.5 s. The number of trials excluded did not differ by age group. Eye movements were monitored with a stereoscopic eye tracker (Resonance Technologies, Inc.), and trials with lateral eye movements greater than 5° were excluded from the analyses. This exclusion criterion was established to avoid trials in which the hemifields shifted from the midline, and the total number of trials excluded on this basis was <5%. Although all 240 trials were explicitly modeled, based on accuracy and exclusion data, a mean of 205 trials were used in the contrasts depicted in Tables 2 and 3.

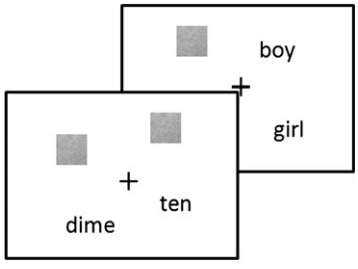

Figure 1. Illustration of experimental stimuli used in the word matching task.

To ensure that the effects observed were specific to bilateral trials and not merely subject-level variance across all task conditions, we entered all subjects ($n = 31$) into a regression model using SPSS for Windows (Standard Version 16.0, SPSS Inc., Chicago, IL) with bilateral accuracy as the outcome measure and unilateral accuracy as the predictor. We then used the unstandardized residuals output directly from this model (i.e., bilateral accuracy partialed for unilateral accuracy) as the dependent variable in the subsequent correlation analyses. This "residualized" measure provides a more reliable estimate of the variance associated specifically with bilateral accuracy, as compared with a difference score (e.g., bilateral minus unilateral accuracy), which may be susceptible to spurious negative relationships and is thus unsuited for testing correlations (Cohen et al. 2003). Additionally, these residualized scores were tested for normality using a Shapiro–Wilk test and were not found to differ from a normal distribution ($W = 0.98$, $P = 0.96$).

MRI Scanning

Participants were scanned on a 3-T gradient-echo scanner. Coplanar functional images were acquired using an inverse spiral sequence (64 × 64 matrix, time repetition [TR] = 1700 ms, time echo [TE] = 31 ms, field of view [FOV] 240 mm, 37 slices, 3.8-mm slice thickness, 254 images). The DT MRI data set was based on a single-shot echo-planar imaging sequence (TR = 1700 ms, 50 contiguous slices of 2.0 mm thickness, FOV = 256 × 256 mm^2, matrix size 128 × 128, voxel size 2 × 2 × 2 mm, b value = 1000 s/mm^2, 25 diffusion-sensitizing directions, 960 total

Table 2
Neuroimaging findings from the standard GLM

Region	Lat	*x*	*y*	*z*	BA	Vox	*z* score
Younger adults							
Unilateral > bilateral trials							
Insular/temporal cortex	L	−45	−8	15	13	16	4.12
Bilateral > unilateral trials							
Superior frontal gyrus	L	−15	49	38	10	80	4.10
Inferior frontal gyrus	L	−38	49	8	47/10	19	3.86
Older adults							
Unilateral > bilateral trials							
No significant voxels							
Bilateral > unilateral trials							
Cerebellum/occipital cortex	L/R	−4	−53	−23	1	180	4.68
Hippocampus	R	19	−4	−13		15	4.34
Superior frontal gyrus	R	26	60	0	10	17	3.93
MFG	R	49	23	19	46	27	3.87
Age comparisons							
Younger > older							
Older > younger							
No significant voxels							
Age × condition interaction							
MFG[a]	L	−52	13	24	9	403	5.21
	R	49	11	34	8	92	4.57
Anterior cingulate cortex	L/R	−4	11	53	32	190	4.80
Fusiform cortex	L	−17	−30	−23	20	22	4.55

Note: Height and extent threshold: $P < 0.05$ FDR corrected, 14 voxels, respectively; BA, Brodmann area; L, right; and R, right.
[a]Seed region for PPI analysis.

Table 3
Regions showing age (young, old) × condition (unilateral, bilateral) interactions in functional connectivity with left MFG in a PPI analysis

Region	Laterality	*x*	*y*	*z*	BA	Voxels	*t*
MFG[a]	R	36	34	6	9	24	4.04
Temporal lobe	L	−41	−23	−15	21/22	151	4.17
Postcentral gyrus	L	−41	−23	56	½	57	4.26
Caudate body	L	−15	−26	23		141	4.10
Caudate head	R	19	19	15		14	4.01
Precentral gyrus	R	30	−15	54	4	17	3.92

Note: Height and extent threshold: $P < 0.05$ FDR corrected, 14 voxels, respectively; BA, Brodmann area; L, right; and R, right.
[a]Predicted interaction.

images, total scan time ~5 min). The anatomical MRI was acquired using a 3D T_1-weighted echo-planar sequence (256 × 256 matrix, TR = 12 ms, TE = 5 ms, FOV = 24 cm, 68 slices, 1.9-mm slice thickness, 248 images). Scanner noise was reduced with ear plugs, and head motion was minimized with foam pads. Behavioral responses were recorded with a 4-key fiber-optic response box (Resonance Technology, Inc.), and when necessary, vision was corrected using MRI-compatible lenses that matched the distance prescription used by the participant.

fMRI Analyses

Preprocessing and data analysis were performed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK) and custom MATLAB scripts. After discarding the 6 initial volumes to allow for scanner stabilization, images were slice-time and motion corrected using standard realignment methods in SPM, spatially normalized to the Montreal Neurological Institute template, and then smoothed using an 8 × 8 × 8 mm Gaussian kernel. Event-related blood oxygen level–dependent responses for each subject were analyzed using a modified general linear model (GLM) (Worsley and Friston 1995). Because the semantic matching task should depend primarily on left hemisphere processing, and the main goal was to examine recruitment beyond this initial task-specific activation, we excluded from the analyses trials on which the words were presented unilaterally to the right hemisphere. Nonmatch trials, incorrect trials, no-response trials, and trials with more than one response were modeled explicitly as nuisance regressors and not considered in the main analysis; consistent with standard SPM protocols, movement parameters (x, y, and z transformation, pitch, roll, yaw) were included as regressors of no interest. Intertrial fixation time was included in the model as part of the implicit baseline. We report the results of both main effects and the age group (younger, older) by condition (bilateral, unilateral) interaction; all statistical results were thresholded using a false discovery rate (FDR) correction for multiple comparisons of 0.05 (Genovese et al. 2002), with a minimum cluster size of 14 voxels. We then sought to evaluate regions that showed activation in homologous regions of cortex and thus chose regions for subsequent connectivity analysis from areas that showed corresponding left- as well as right hemisphere activity. Furthermore, in order to provide maximal similarity and volume between fMRI and functional connectivity analyses, we extracted beta values from standard regions of interest (ROIs) created from anatomical parcellation based on the Harvard–Oxford Structural Atlas provided by FSL (www.fmrib.ox.ac.uk/fsl, Kennedy et al. 1998) in order to describe the relative effects from each model (see Fig. 2).

Functional Connectivity Analyses

To investigate functional connectivity, we used psychophysiological interaction (PPI) analysis as implemented in SPM5. PPI analysis captures the interaction between brain regions in relation to the experimental task by modeling an interaction term derived from the event train of a given stimulus type and the time course of a seed region chosen from a standard GLM (Friston et al. 1997). In the present context, we weighted the bilateral term positively (1) and the unilateral term negatively (–1), meaning that a significant effect for PPI means that the correlation with a seed region during a bilateral condition is significantly different from that during a unilateral condition. The seed region was a 10-mm sphere centered on the peak of left MFG region identified showing an age group (younger, older) × condition (unilateral, bilateral) interaction (x, y, z = –52, 13, 24; see Fig. 2). We extracted the first eigenvariate from this region and created an interaction term for each subject based on the time course for this region. The extracted contrast images were then taken to the second level to perform a random effects analysis using a 2-sample (younger, older adults) t-test, thus examining an age group × condition interaction for regions functionally connected to the seed region in left MFG (thresholded at $P < 0.05$ [FDR corrected], with an extent threshold of 14 voxels). To further ensure that the observed effects were in fact due to a positive relationship in the bilateral condition in older adults (and not a negative relationship in the younger adults), we masked this interaction contrast inclusively with the older adults' bilateral condition modeled against an implicit baseline.

DTI Analyses

The diffusion-weighted images were skull-stripped to remove nonbrain and ambient noise using the Brain Extraction Tool (Smith et al. 2002) and eddy-corrected to account for drifts in scanner acquisition. Diffusion tensors were calculated from the 25 diffusion-weighted images based upon a typical simple least-squares fit of the tensor model

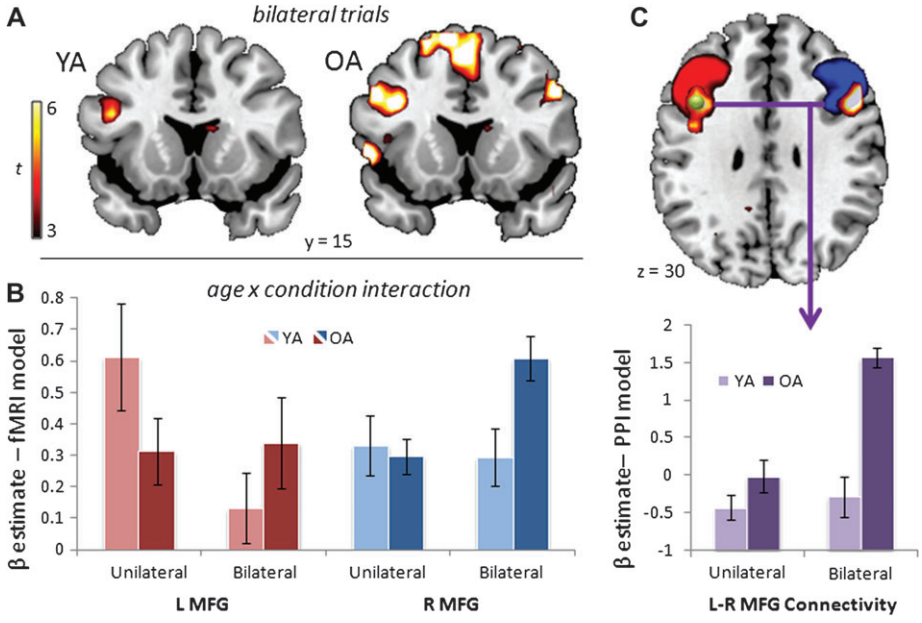

Figure 2. Neuroimaging findings. Brain figure represents both the activations observed in the age group × condition interaction (heat blobs), LMFG and RMFG ROIs (red and blue), and LMFG seed for the PPI analysis (greed dot), displayed upon a canonical brain. (*A*) Activity in younger and older adults during the bilateral condition, depicting an age-related increase in contralateral activity. (*B*) LMFG and RMFG beta estimates for the age group × condition interaction, showing greater activity in the bilateral condition in right hemisphere for older adults. This interaction contrast shows that the effects observed in (*A*) are specific to the bilateral condition. Bars represent activity summated over the entire MFG ROI. (*C*) PPI parameter estimates for the right MFG again summated over the entire ROI. YA: younger adult; OA: older adult.

to the diffusion data, using the freely available software medINRIA (http://www-sop.inria.fr/asclepios/software/MedINRIA/); fiber tracking parameters included a minimum FA of 0.2, a fiber tracking threshold of 0.125 and an angle of maximum deviation of 35°. The tractography algorithm was based on trilinear log-Euclidean interpolation and used a standard streamline algorithm (Xu et al. 2002); fiber tracking was automatic, since every voxel of the reference volume was a seeding point (Fillard et al. 2007). The resulting parameters included mean FA and RD ($[\lambda 2 + \lambda 3]/2$). Evidence from both animal models and postmortem analyses suggests that RD may be selectively sensitive to myelin damage (Song et al. 2003; Sun et al. 2007), though this suggestion is not without its caveats (Wheeler-Kingshott and Cercignani 2009). We then extracted the T_2 signal intensity, by overlaying the b0 image on tracts of interest, to address the confound that white matter hyperintensities not detected by a qualitative evaluation may influence the observation of age-related differences in the other diffusion metrics. Thus, T_2 signal intensity was treated as a quantitative measure and included as a nuisance covariate in subsequent analyses.

The present analysis focused on interhemispheric connectivity, and thus we restricted our analysis to the corpus callosum. The corpus callosum connects homologous regions of all parts of the cortex (Aboitiz, Scheibel, Fisher, et al. 1992; Aboitiz, Scheibel, and Zaidel 1992). While conventional DTI scanning currently precludes a direct elucidation of more lateral callosal connections in humans (Catani 2007), we used a restricted set of callosal pathways that can be reliably extracted 5 mm lateral (±) to the midline. We then selected sections of the corpus callosum based on canonical divisions of the midline corpus callosum (Aboitiz and Montiel 2003): genu fibers passing through the most anterior section of the corpus callosum connecting anterior frontal cortex; anterior body fibers connecting superior frontal cortices; body fibers connecting premotor and motor regions of cortex; tapetum fibers, connecting bilateral temporal cortices; and fibers passing through the splenium of the corpus callosum, connecting either parietal or occipital cortices. Reliability of user-created diffusion tractography data was assessed using methods previously described by our laboratory (Davis et al. 2009) and elsewhere (Eluvathingal et al. 2007; Wakana et al. 2007; Madden, Spaniol, et al. 2009). Briefly, all tracts were evaluated for the voxel extent of overlap within and between expert raters and were accepted when intra- and interrater reliability ratings exceeded a "high" rate of reliability (Cohen's $\kappa > 0.8$), according to criteria set forth by Landis and Koch (1977). FA and RD values were then subsequently used in both group comparisons (using pairwise *t*-tests) and correlation analyses (using Pearson's *r*). A multiple comparisons correction was applied to all age-group comparisons and correlations using these diffusion imaging data, such that all significant correlations survived a threshold of $P < 0.01$ ($P < 0.05$ with Bonferroni correction for the number of callosal regions examined herein).

Results

Behavior

Table 1 shows behavioral demographics, and reaction times and accuracy rates for the word matching task in younger and older adults (accuracy was defined as correct responses to both match and nonmatch trials). CUD indices were larger in older adults ($t = 2.12$, $P = 0.05$), consistent with previous studies using this measure to investigate behavioral differences between younger and older adults (Jeeves and Moes 1996). We also tested for an effect of response hand on CUD and found no significant difference between left- and right-hand responses. All participants performed significantly above chance in the scanned word matching task. We tested first for speed-accuracy trade-offs by averaging unilateral and bilateral conditions (both accuracy and response time) and testing for correlations using Pearson's *r* and Spearman's rho. We found a significant correlation between response time and accuracy in older ($r = -0.57$, $P = 0.014$; rho = 0.53, $P = 0.021$) but not the younger adults ($r = 0.019$; rho = –0.27). The age-related difference in correlations (using the Fisher transform applied multiple times in the text) was marginal ($P = 0.061$). In order to address the concern that subjects may have developed a response bias to say "match" (given the difference in the number of match/nonmatch trials), we calculated *d'* scores for each individual, using correct responses to all match trials as "hits" and incorrect responses to nonmatch trials as "false alarms." All subjects showed $d' > 1.0$, and criterion values did not differ significantly from zero in either younger ($t = 1.44$, $P = 0.19$) or older adults ($t = 1.61$, $P = 0.13$), indicating that it is unlikely that any subjects were significantly biased to respond "match." There were no group differences in *d'* ($t = 1.18$, $P = 0.2$). In the word matching task, a 2 (visual field condition: unilateral, bilateral) × 2 (age group: younger, older) analysis of variance (ANOVA) on accuracy rates yielded no main effects of age group or condition. Importantly, however, there was a significant interaction between age group and condition ($F_{1,28} = 4.11$, $P < 0.05$), reflecting a greater advantage for bilateral trials (BPA) in older than younger adults. Follow-up *t*-tests indicated that the BPA (bilateral > unilateral) was significant in older adults ($F_{1,13} = 6.73$, $P < 0.05$) but not in younger adults ($F_{1,13} = 0.42$, $P = 0.7$). Follow-up one-way ANOVA of between-groups effects revealed a significant group difference in bilateral accuracy ($F = 5.23$, $P = 0.02$). Table 1 shows reaction times for correct trials. An ANOVA on these data yielded no significant main effects or interactions, perhaps owing to the fact that older adults perform at young adult levels in tests of semantic memory and vocabulary (Park 1998). In sum, confirming our first prediction, we found the BPA in accuracy rates were greater in older than in younger adults.

fMRI Activity

Table 2 lists regions showing effects of condition (unilateral, bilateral) on younger and older adults, as well as the critical age group × condition interactions. We observed no main effects of age group (either older > younger adults or the reverse contrast) at our established threshold. Figure 2*A* depicts regions activity for bilateral trials in both younger and older adults. Younger adults showed a significant difference in activation in the insula for unilateral greater than bilateral condition, while the reverse contrast revealed greater activity in left hemisphere frontal regions, including the inferior and superior frontal gyri. Older adults showed greater activity many right hemisphere regions for the bilateral greater than unilateral conditions, including the hippocampus and middle frontal gyrus (MFG); no regions showed a significant difference for the reverse contrast. Thus, both younger and older adults engaged frontal cortices more for bilateral than unilateral trials; but whereas younger adults showed greater activity for left-lateralized regions typically associated with semantic processing, older adults showed an increase in right frontal (and hippocampal) activity, suggesting a greater flexibility in the location of regions used to successfully complete the task. Bilateral trials, which distribute stimuli across hemifields, engender a more distributed pattern of activation in older adults, while younger adults seem to employ existing neural resources.

However, a direct test of the extant theories of cross-hemispheric communication would ask to what extent these age and hemispheric factors interact. Thus, the critical fMRI data

for the present goals was the age × condition interaction, of which we observed significant activity in bilateral MFG, anterior cingulate, and left fusiform regions. We then selected the MFG as the target of functional and structural connectivity analyses, given both our PFC focus and the fact that this region was the only one to show complementary activation in both the left and right hemispheres in the interaction contrast. To ensure that the results of these analyses were not affected by the exact localization of MFG activations in different groups and conditions, we extracted mean activity from the whole left and right MFG using an anatomical mask (Wake Forest University PickAtlas software; http://www.fmri.wfubmc.edu). Mean activity in the left and right MFG ROI is displayed in Figure 2*B*. We conducted separate 2 (age group: younger, older) × 2 (condition: unilateral, bilateral) ANOVAs in left and right MFG. The analysis in left MFG yielded no significant interaction or main effects of age group or condition; the analysis in right MFG yielded a significant age group × condition interaction ($F_{1,28}$ = 4.18, $P < 0.05$), reflecting greater activity for older adults in the bilateral condition and no main effects of age group or condition. Thus, consistent with our second prediction, we found evidence that age-related contralateral over-recruitment was greater in the condition engaging cross-hemispheric communication, namely the bilateral condition.

Functional Connectivity

As noted in the Methods section, we used a 10-mm sphere centered on the left MFG activation (–52, 13, 24) as a seed region in a PPI analysis and identified regions showing age group × condition interactions in functional connectivity with left MFG (Table 3). Consistent with our third prediction, the PPI interaction indicates that older adults showed stronger functional connectivity between left and right MFG than younger adults, and that this effect was much greater in the bilateral condition than the unilateral condition (see Fig. 2*C*). This finding is consistent with our behavioral finding of an increased BPA in older adults, and it provides the first evidence that contralateral PFC over-recruitment in older adults is associated with an increase in functional connectivity between left and right PFC. To address the possibility that the right MFG activity may be due a failure to inhibit nondominant hemisphere activity representing processes unrelated to the task, we performed a post hoc analysis of both fMRI activity estimate (β value) in this right MFG region, as well as the functional connectivity with left LMFG. Residualized bilateral accuracy was significantly greater in older adults compared with younger adults (t = –2.77, $P < 0.01$). We then sought to evaluate the relationship between functional connectivity and the age-related variance in bilateral accuracy. First, we entered age and functional connectivity Beta estimates from the PPI model for each subject into a linear regression model, with residualized bilateral accuracy as the outcome variable; the significant age group by connectivity interaction (F = 2.19, $P < 0.05$) suggested that the relationship was specific to one group and justified treating age groups separately in subsequent correlation analyses. As depicted in Figure 3, both functional activity (r = 0.61, P = 0.01) and functional connectivity models (r = 0.65, P = 0.008) showed a significant relationship with the residual bilateral accuracy in older adults—but not younger adults (r = –0.05 and –0.23, respectively). In order to directly compare this relationship between age groups, we then used the Fisher r-to-z transform to test for group differences in the correlations between older and younger adults; this test revealed that the relationship between both accuracy and functional activity, and accuracy and functional connectivity represent a significant age-related difference in correlations (functional activity: z = 1.88, $P < 0.05$; functional connectivity: z = 2.52, $P < 0.01$). In other words, the relationship exists in our older but not our younger participants. These results support the notion that the age-related increases in functional activity and connectivity between regions benefit task performance; we next explored whether there is a structural basis for this increase in connectivity.

Linking Behavior and Functional Connectivity to White Matter

We first investigated the effects of aging on white matter integrity in the anterior callosal regions that were the focus of the current study. Consistent with previous research (Sullivan et al. 2006; Madden, Bennett, et al. 2009), we found that FA in the genu ($F_{1,29}$ = 4.17, $P < 0.001$), anterior body ($F_{1,29}$ = 3.39, $P < 0.005$), and body ($F_{1,29}$ = 3.21, $P < 0.05$) of the corpus callosum were significantly lower for older adults than for younger adults (see Table 4). Similarly, RD in the genu ($F_{1,29}$ =

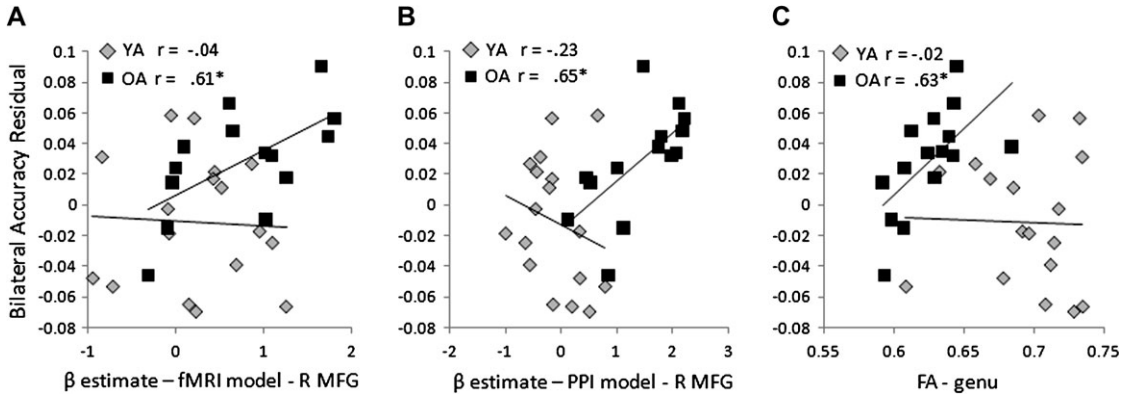

Figure 3. Relationship between residual variance in bilateral accuracy (removing the variance associated with unilateral trials) and functional imaging measures across individuals. (*A*) Residual bilateral accuracy is predicted by both (*A*) activity in the right MFG, (*B*) functional connectivity between a seed region in left MFG and right MFG, and (*C*) structural connectivity within the genu of the corpus callosum. All 3 relationships represent a significant age-related difference between correlations (P = 0.03, P = 0.006, and P = 0.03, respectively).

45.21, $P < 0.001$) and anterior body ($F_{1,29} = 13.31$, $P < 0.001$) of the corpus callosum were relatively higher for older adults, after correcting for multiple comparisons. We then performed correlation analyses linking our behavioral (residual bilateral trial accuracy) or neural (functional connectivity) measures of cross-hemispheric communication to diffusion metrics in the genu and anterior body areas of the corpus callosum. As summarized by Table 5, we found a significant correlation between residual values for bilateral trial accuracy and FA in the genu for older adults ($r = 0.62$, $P = 0.009$) but not younger adults ($r = -0.03$, $P = 0.45$). A Fisher r-to-z transform used to directly compare the correlations observed above showed a significant group difference in the correlations ($z = 2.25$, $P < 0.02$). As noted previously, the dependent measure in this analysis was selected to account for the shared variance between unilateral and bilateral trial types, indicating that the age-related increase was specific to bilateral trials. We repeated this analysis using the residual variance in response times on bilateral trials but did not obtain any significant correlations. We found a significant correlation between left-right MFG functional connectivity (PPI β estimates of left–right MFG connectivity) and FA in the genu for older adults ($r = 0.63$, $P = 0.009$) but not for younger adults ($r = -0.17$, $P = 0.26$), which amounted to a significant difference in correlations between the groups ($z = 2.28$, $P < 0.02$). Then, in order to ensure that the functional relationship between PFC regions was mediated by the genu of the corpus callosum and not regions of the callosum connecting other cortical regions, we assessed these same accuracy–FA and connectivity–FA correlations other callosal regions showing an effect of age (anterior body and body of the corpus callosum), and no correlation reached significance. Finally, we repeated the above correlations with the FA and RD in the genu while regressing out the common variance between FA and T2 signal intensity, in order to address the possibility that the observed diffusion metrics were biased by white matter hyperintensities not qualitatively observed. The pattern of correlations remained the same.

We then sought to test the extent to which the observed relationship between functional connectivity and bilateral accuracy in older adults (see Fig. 3*B*) is influenced or moderated by their mutual relationship to structural connectivity. Moderation implies a weakening of a shared association, such that a third variable affects the zero-order correlation between 2 other variables, in contrast to mediation, in which a third variable fully accounts for the relationship between predictor and outcome variables (Baron and Kenny 1986). We therefore tested whether white matter integrity acted as a moderator between the predictor (functional connectivity) and the outcome variables (residualized bilateral accuracy). As illustrated by Figure 4, white matter connectivity attenuated the Pearson correlations between functional connectivity between left and right MFG and the BPA in older adults (from 0.65 to 0.41 [37%] for FA and –0.65 to –0.50 [23%] for RD) and become nonsignificant once white matter quality was partialed out of that relationship. This result suggests that cross-hemispheric communication associated with successful performance is constrained by white matter integrity. In sum, consistent with our fourth prediction, age-related increases in cross-hemispheric communication are constrained by the integrity of callosal white matter: older adults with greater callosal integrity show greater cross-hemispheric communication both at the behavioral and neural level.

Table 4
DTI metrics in older and younger adults in the corpus callosum

	FA		RD	
CC region	YA, M (SD)	OA, M (SD)	YA, M (SD)	OA, M (SD)
Genu	0.66 (0.03)	0.62 (0.02)**	0.38 (0.05)	0.49 (0.05)**
Anterior body	0.63 (0.04)	0.58 (0.03)*	0.47 (0.03)	0.56 (0.05)**
Body	0.65 (0.04)	0.62 (0.03)	0.44 (0.03)	0.55 (0.06)*
Tapetum	0.76 (0.04)	0.75 (0.04)	0.45 (0.04)	0.52 (0.05)
Splenium—parietal	0.72 (0.03)	0.70 (0.03)	0.41 (0.04)	0.44 (0.04)
Splenium—occipital	0.74 (0.05)	0.73 (0.04)	0.40 (0.02)	0.44 (0.03)

Note: SD, standard deviation; CC, corpus callosum; YA, younger adult; and OA, older adult.
$^{**}P < 0.001$, $^{*}P < 0.005$.

Discussion

The results support our 4 predictions and converge on the idea that older adults benefit from the ability to flexibly shift the regions functionally activated for a task in the face of increasing demands in order to facilitate performance. First, the behavioral advantage of bilateral over unilateral trials (BPA) was larger in older than younger adults (Table 1), consistent with the idea that older adults benefit more from distributing processing across hemispheres. Second, compared with younger adults, older adults showed greater activity in contralateral (right) PFC

Table 5
Correlations between DTI metrics and functional imaging measures

		FA	RD
Bi AccR	OA	0.63*,[a]	–0.63*,[a]
	YA	–0.02	0.08
fMRI β	OA	0.35	–0.29
	YA	0.17	–0.09
fCON β	OA	0.62*,[a]	–0.48
	YA	–0.16	0.18

Note: Bi AccR, bilateral accuracy residual; fMRI, fMRI model beta estimate; fCON, functional connectivity model estimate; OA, older adult; and YA, younger adult.
[a]Significant age-related difference in correlations ($P < 0.05$).
$^{*}P < 0.01$.

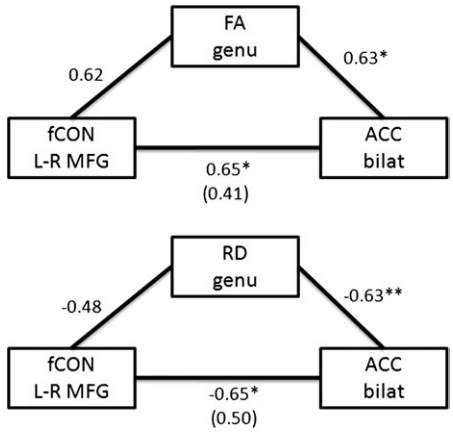

Figure 4. The correlation between functional connectivity (β estimates from PPI model for RMFG, based on a LMFG seed) and the BPA (residualized bilateral accuracy) is reduced by partialing out the variance associated with FA (*A*) and RD (*B*) in the genu. Parentheses indicate correlations after partialing out the variance associated with the corresponding white matter measure. This result suggests that white matter acts as a moderator by weakening the effect of functional connectivity on bilateral accuracy.

regions in the bilateral condition (Fig. 2*B*), activity that was related positively to performance on bilateral trials (Fig. 3). Third, older adults showed greater functional connectivity between left and right PFC, again, particularly in the bilateral condition (Fig. 2*C*). This finding provides evidence that contralateral PFC over-recruitment in older adults is associated with increased left-right PFC connectivity, and furthermore, that this connectivity is beneficial for performance (Fig. 3*A*,*B*) given specific behavioral conditions. Finally, both behavioral (BPA) and neural (functional connectivity) measures of cross-hemispheric communication were significantly correlated with DTI measures of callosal integrity in older—but not younger—adults (Table 5, Fig. 4). This finding provides the first evidence that task-related functional connectivity between the hemispheres is constrained by white matter integrity in older adults. Each of the 4 findings is discussed below.

Our first finding was that older adults, but not younger adults, showed a significant advantage in the accuracy of a semantic decision for a bilateral over a unilateral presentation. This finding is consistent with the notion that older adults benefit by distributing processing demands across hemispheres (Cabeza 2002; Reuter-Lorenz and Stanczak 2000) and extends Reuter-Lorenz et al. (1999) finding of an increased BPA in older adults during a simple letter matching task to a more complex semantic word matching task. Although the BPA is typically observed in perceptual matching tasks, such as matching colors (Dimond and Beaumont 1972), faces (Mohr et al. 2002), or rotated stimuli (Yoshizaki et al. 2007), a few studies have observed BPA for semantic matching tasks, such as word pairs (Berger 1988; Zhang and Feng 1999; Koivisto and Revonsuo 2003). Implicit in these results is the notion that the semantic processing benefits associated with bilateral presentation are engendered by an increase in bilateral hemispheric processing. Though semantic processing is typically more strongly represented in the left hemisphere (Binder et al. 2009), a number of studies have demonstrated bilateral cortical activity in response to semantic tasks (Thompson-Schill et al. 1997; Putnam et al. 2008; Hartwigsen et al. 2010; Vigneau et al. 2011). In our study, both young adults and older adults showed a main effect of condition on response times, suggesting an overall benefit for bilateral presentation. Our study, however, is the first to show that BPA in accuracy rates for a complex semantic matching task is enhanced by aging, providing more direct evidence that bilateral processing provides a benefit to performance. Taken together with previous findings, this result suggests that older adults show better performance when distributing processing across the hemispheres.

Our second finding was that older adults showed greater activity in contralateral (right) PFC regions, but only in the bilateral condition (Fig. 2*B*). Contralateral PFC over-recruitment in older adults has been observed for many types of stimuli and cognitive domains, including perception, attention, memory, and executive functions (for reviews, see Dennis and Cabeza 2008; Reuter-Lorenz and Park 2010). Although the phenomenon is well established, the mechanisms underlying this phenomenon are uncertain. Our second finding has significant implications for the compensation–dedifferentiation debate concerning interpretation of age-related increases in bilaterality (Daselaar and Cabeza 2005). Briefly, the"compensation view" asserts that contralateral over-recruitment reflects a reorganization of cognitive functions in the aging brain that is beneficial for cognitive performance, whereas the"dedifferentiation view" portrays contralateral over-recruitment as a failure to inhibit irrelevant activity in the nondominant hemisphere. Our second finding is more consistent with the compensation account because contralateral PFC over-recruitment occurred in the condition associated with better (more accurate) bilateral matching performance in older adults (Fig. 3*A*). This result is in contrast to other aging studies which have found that right contralateral activity is associated with decreases in episodic memory performance and is negatively correlated with callosal FA (Persson et al. 2006). This earlier finding is in agreement with the view that the corpus callosum serves to inhibit the nondominant hemisphere, particularly during motor tasks (e.g., Langan et al. 2010) and is also in agreement with more perceptually based theories such as the"competition hypothesis" (Volberg and Hubner 2004), which states that the hemispheres compete for the processing of stimuli, especially when both hemispheres have access to the same amount of information. However, while these hypotheses would suggest that bilateral stimulation engenders slower processing than unilateral stimulation, we found that sharing processing across the hemispheres benefits performance. The discrepancy between the findings from our study and Persson et al. (2006) may be due to a number of factors, including differences in the task design (inclusion of lateralized trials) or differences in the location of contralateral activity (right MFG vs. right IFG activations). Furthermore, we demonstrate that the well-known phenomenon of over-recruitment in older adults was present only during the bilaterally presented condition. Nonetheless, both studies demonstrate that activity in right PFC is functionally relevant to cognitive performance. Thus, our second finding has implications for the underlying mechanisms of contralateral PFC over-recruitment in older adults (Colcombe et al. 2005). The finding that contralateral recruitment occurred in the bilateral condition—but not in the unilateral condition—therefore suggests a selective mechanism involving the distribution of processing demands across hemispheres and provides a greater specificity to the oft-observed effect that older adults show more bilateral patterns of PFC activity than younger adults. While much work remains in order to determine what behavioral factors modulate the lateralization of specific cognitive functions in both normative younger as well as older adult populations (though, for review, see Gazzaniga 2000; Schulte and Muller-Oehring 2010), the present findings suggest that some bilateral patterns may be sensitive to the degree to which the task demands can be distributed across hemispheres.

Our third finding was that older adults showed greater functional connectivity between left and right PFC than younger adults in the bilateral but not the unilateral condition (Fig. 2*B*), and furthermore that this increase in functional connectivity was associated with an increase in bilateral accuracy (Fig. 3*B*). This finding provides the first evidence that contralateral PFC over-recruitment in older adults is associated with increased left–right PFC connectivity. Although many studies have reported contralateral PFC over-recruitment in older adults (for reviews, see Cabeza 2002; Park and Reuter-Lorenz 2009), none have investigated whether this effect was associated with a parallel increase in cross-hemispheric connectivity. The fact that the age-related increase in left–right PFC connectivity occurred only in the bilateral condition is consistent with our interpretation in terms of an increase in cross-hemispheric communication. Although other tasks have yielded evidence of age-related decline in functional connectivity (Dennis et al. 2008; Madden et al.

2010), our third finding fits well with recent evidence that selective increases in large scale networks change in aging that may support cognitive performance (Daselaar et al. 2006; Chen et al. 2009; Gong et al. 2009; Meunier et al. 2009; Wang et al. 2010). However, there is also evidence that changes in functional connectivity between regions do not support cognitive performance (Andrews-Hanna et al. 2007) or may even be detrimental to cognitive performance (Rajah and McIntosh 2008). Further work would therefore benefit from a focus on either 1) specific localization of over- or under-recruited regions to establish the regional basis for compensatory effects or 2) subpopulations of older adults that do or do not demonstrate positive relationships between network changes and cognitive performance.

Our fourth finding was that both behavioral (BPA) and neural (functional connectivity) measures of cross-hemispheric communication were significantly correlated with DTI measures of callosal integrity in older adults. These 2 correlations represent direct evidence that bihemispheric processing in older adults is constrained by white matter integrity. First, we found the correlation between BPA and FA differed significantly across age groups and was significant only in the older group (Fig. 3*C* and Table 5); this finding contributes both to the behavioral literature seeking to explain the role of the interhemispheric connectivity in the successful completion of tasks requiring bihemispheric integration (Banich and Belger 1990; Reuter-Lorenz and Stanczak 2000; Santhouse et al. 2002), as well as the growing literature linking age-related changes in white matter tractography to cognitive performance (Sullivan et al. 2006; Zahr et al. 2009; Voineskos et al. in press). Notably, the same pattern of results was present when using RD as a measure of white matter health, indicating that the observed structure–function relationships may be mediated by age-related differences in myelin (Bartzokis 2004). Furthermore, for older adults, both callosal FA and RD in the genu attenuated the significant relationship between functional connectivity and accuracy associated with bilateral trials (Fig. 4). This finding supports the idea that white matter connectivity mediates task-relevant functional connectivity and is more broadly consistent with the observation that the networks recruited for cognitive tasks differs in aging populations (Ward and Frackowiak 2003; Colcombe et al. 2005). For example, the finding that functional connectivity in older adults correlated with callosal FA (Table 5) is consistent with other studies linking white matter measures to both to fMRI activity (Olesen et al. 2003; Persson et al. 2006; Putnam et al. 2008; Mazerolle et al. 2010) as well as resting state and task-related functional connectivity (Andrews-Hanna et al. 2007; Chen et al. 2009; Greicius et al. 2009; Saur, Schelter, et al. 2010). Furthermore, the observation that this correlation was significantly greater in older than younger adults provides evidence that older adults rely on this interhemispheric pathway to a greater extent than younger adults in order to coordinate activity between complementary prefrontal regions.

Limitations of the Current Study

Before concluding, it is important to note that the present study had several limitations. Broadly, cross-sectional studies such as ours cannot easily differentiate between whether the age-related increase in bilateral processing is evidence of an adaptive compensatory mechanism acquired over time in response to the deleterious effects of aging on brain health (Reuter-Lorenz and Cappell 2008) or instead reflects a cognitive reserve of previously underutilized cognitive resources revealed by progressive changes in brain morphology (Stern 2002; Reed et al. 2010). Longitudinal studies tracking both behavioral and structural changes over time may help to address this uncertainty. More specifically, our task was based on a domain of cognitive functions largely preserved in older adults; thus, the use of one type of cognitive task may limit the interpretation of these results, and further work should address whether the distribution of task demands across hemispheres in other behavioral tasks engender a similar increase in interhemispheric connectivity in older adults. Another limitation is that we investigated inter- but not intrahemispheric communication. As a result, this study does not completely address the issue of information transfer at early versus late stages of processing, or how lateralized input to the visual cortex affects later processing in contralateral or ipsilateral PFC. Finally, although we were able to link behavioral and neural measures of cross-hemispheric communication to white matter integrity using correlations, correlational data cannot identify the causal mechanisms that bring about contralateral PFC recruitment at a neural level. In order to identify these neural mechanisms, it is important to complement imaging methods with evidence from brain-damaged patients or paradigms linking the inhibition of contralateral cortex using transcranial magnetic stimulation (TMS). For example, a recent study by Manenti et al. (2010) found evidence that high-performing (but not low-performing) older adults show performance decrements after selective TMS pulses to right PFC during semantic retrieval, suggesting that older adults show less asymmetry as an efficient strategy to counteract age-related cognitive decline.

In conclusion, we found 4 pieces of evidence in support of the theory that older adults benefit from a bilateral neural representation. Behaviorally, older adults showed greater benefits from a bilateral than unilateral display than younger adults. Our second and third findings from functional neuroimaging support this behavioral result, in that we found that older adults showed a greater fMRI response than younger adults in right hemisphere regions for bilateral trials and greater functional connectivity between complementary PFC regions. Finally, white matter integrity in the genu of the corpus callosum predicted both the functional connectivity between these complementary regions of PFC, as well as the accuracy advantage associated with bilateral trials. Taken together, these findings clarify the mechanisms and limits of contralateral over-recruitment in older adults and demonstrate an means of combining data from difference sources in order to clarify the mechanisms underlying interhemispheric communication.

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