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Aging, cognition, and the brain: effects of age-related variation in white matter integrity on neuropsychological function

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ABSTRACT

Alterations in brain structure are viewed as neurobiological indicators which are closely tied to cognitive changes in healthy human aging. The current study used diffusion tensor imaging (DTI) tractography to investigate the relationship between age, brain variation in white matter (WM) integrity, and cognitive function. Sixteen younger adults (aged 20–28 years) and 18 healthy older adults (aged 60–75 years) underwent DTI scanning and a standardized battery of neuropsychological measures. Behaviorally, older adults exhibited poorer performance on multiple cognitive measures compared to younger adults. At the neural level, the effects of aging on theWM integrity were evident within interhemispheric (the anterior portion of corpus callosum) and transverse (the right uncinate fasciculus) fibers of the frontal regions, and the cingulum-angular fibers. Our correlation results showed that age-related WM differentially influenced cognitive function, with increased fractional anisotropy values in both the anterior corpus callosum and the right cingulum/angular fibers positively correlated with performance on the visuospatial task in older adults. Moreover, mediation analysis further revealed that the WM tract integrity of the frontal interhemspheric fibers was a significant mediator of age–visuospatial performance relation in older adults, but not in younger adults. These findings support the vulnerability of the frontal WM fibers to normal aging and push forward our understanding of cognitive aging by providing a more integrative view of the neural basis of linkages among aging, cognition, and brain.

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Brain aging; cognition; diffusion tensor imaging; frontal interhemispheric fibers; visuospatial ability

Introduction

Age-related cognitive decline is one of the most common causes of disability among older adults (Aguero-Torres, Thomas, Winblad, & Fratiglioni, 2002; Courtney-Long et al., 2015). Evidence from behavioral research has long identified age-related differences in cognitive performance between young and older adults, especially in the domains of speed of processing, visuospatial skills, executive function, and memory (Park & Gutchess, 2002; Park & Schwarz, 2000; Park et al., 2002). Brain studies show that these age-related cognitive differences are frequently accompanied by changes in brain structure and function (Goh & Huang, 2012; Grady, 2012; Hedden & Gabrieli, 2004; Park & Reuter-Lorenz, 2009) and reveal that alterations in cognitive performance and mental ability may stem from structural and functional brain changes with advanced age (Cabeza, Nyberg, & Park, 2016; Goh & Huang, 2012; Grady, 2012; Huang, Meyer, & Federmeier, 2012).

Diffusion tensor imaging (DTI) is a non-invasive brain imaging technique that measures the structural integrity of white matter (WM) tracts by visualizing water diffusion characteristics in the brain (Cox et al., 2016; Lanyon, 2012; Yang, Tsai, Liu, Huang, & Lin, 2016). The advantage of DTI is that it can better identify early signs of degeneration that precede gross changes in brain anatomy and is therefore particularly useful for investigating the microstructural changes associated with advanced aging and neurodegenerative conditions (Bosch et al., 2012; Cox et al., 2016; Jahng et al., 2011; Madden, Bennett, & Song, 2009; Wang et al., 2012). Several studies using DTI suggest that age-related WM change involves reduced integrity of white matter fibers that may be related to de-myelination along the axonal fibers resulting in less efficient conduction of neural signals and impaired transmission of information across the brain (Cox et al., 2016; Madden et al., 2009; Sullivan & Pfefferbaum, 2006).

Fractional anisotropy (FA) is a widely used DTI-based measure that reflects the degree of anisotropic diffusion of water molecules along the axis of the axonal pathway and degradation of structural barriers to water diffusion (Basser & Pierpaoli, 1996; Wang et al., 2012; Yang et al., 2016). Decreasing FA is typically thought to reflect reduced WM integrity. Several DTI-based aging studies have converged on the major finding that age-related decline in the FA was typically greater in magnitude for anterior brain regions (e.g. the genu, pericallosal frontal WM tracts) (Bennett, Madden, Vaidya, Howard, & Howard, 2010; Madden et al., 2004; Salat et al., 2005; Sullivan & Pfefferbaum, 2006; Sullivan, Rohlfing, & Pfefferbaum, 2010). For example, both the cross-sectional and longitudinal studies noted that the frontal corpus callosum (CC) areas (the genu or the forceps minor) had a significant negative relationship with advanced age, whereas the FA in the splenium is

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relatively stable (Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Sullivan et al., 2010).There is also increasing evidence that reduced WM integrity is associated with age-related cognitive decline, with older adults who have greater WM integrity showing better cognitive performance compared to those with WM reductions (Bennett & Madden, 2014; Madden et al., 2009; Madden et al., 2004; Kennedy & Raz, 2009; Gratton, Wee, Rykhlevskaia, Leaver, & Fabiani, 2009). These findings suggest that changes in the WM integrity may be linked with cognitive decline in normal aging, however, the possibility that these neurological and behavioral variables may be interrelated, especially effects of the WM in age-related differences in cognitive performance has not been fully understood (Bennett & Madden, 2014).

In the present study, we performed diffusion MRI scans on younger and older adults to assess age-related differences in brain structural integrity. Both age groups were compared on the diffusivity parameter, as measured by the FA. In addition to the neuropsychological testing for cognitive function, relations between WM integrity and cognitive performance were also examined. Recent neuroimaging studies have suggested that regional WM integrity (i.e. the genu) may mediate cognitive performance in older adults (Bennett & Madden, 2014; Gazes et al., 2016; Kievit et al., 2014; Salami, Eriksson, Nilsson, & Nyberg, 2012). Given that mediation analysis provides a descent way to investigate the role of intermediate variables in relation between two variables, we applied this approach to identify the brain mediators of behavioral changes on neuroimaging data (Atlas, Bolger, Lindquist, & Wager, 2010; Lindquist, 2012). We hypothesized that older adults compared to younger adults would exhibit poorer cognitive performance and greater FA reductions within the frontal WM tracts (e.g. the genu and fibers traversing frontal regions), and that age-related WM reductions would correlate with declines in cognitive performance. Further, we also conducted mediation analyses to test whether age-related differences in WM integrity is a significant mediator between advanced age and age-related differences in cognitive functioning.

Methods

Participants

A total of 16 younger adults (13 female) aged 20–26 years (M = 22.88, SD = 2.16) and 18 healthy community-dwelling older adults (9 female) aged 60–74 years (M = 64.72, SD = 4.10) participated in the study. All participants were screened using a detailed self-report health questionnaire and had no prior history of neurological (e.g. epilepsy, traumatic head injury, or other neurological diseases), or psychiatric (e.g. chronic depression) disorders. All participants were right-handed, did not use a hearing aid and had normal or corrected-to-normal visual acuity. The study was approved by Academia Sinica Institutional Review Board and all participants gave informed consent prior to their participation.

General procedures

Before MRI scanning, each participant completed the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and the Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005) in a separate experimental session to measure global cognitive/mental abilities. In addition, we also adapted a battery of neuropsychological tests used to assess age-related cognitive differences, including digit symbol coding, symbol search, block design, picture completion, matrix reasoning, arithmetic, letter-number sequencing, forward and backward digit span, vocabulary, similarity tests (from the third version of the Wechsler Adult Intelligence Scale (Wechler, 1997a), forward and backward spatial span, immediate and delayed face recognition, visual reproduction tests (from the third version of the Wechsler Memory Scale (Wechler, 1997b), and part A and B of the trail making tests (Reitan & Wolfson, 1985). For the visual reproduction test, each participant was initially shown a single geometric figure for 10 s, after which it was removed from view: the participant was then asked to draw the figure from memory. Scoring was based on the degree to which the participant was able to correctly replicate the figures. Performance on the trail making tests (A and B) was judged in terms of the number of seconds required to complete the test. Neuropsychological and imaging data was collected on 2 separate days (at least 1 week apart).

Imaging acquisition and preprocessing

Image acquisition was performed on a 3.0 T MRI scanner (Siemens Magnetom Tim Trio, Erlangen, Germany) equipped with a 12-channel head coil. The structural T1-weighted image was collected with the following parameters: repetition time (TR) = 3500 ms, echo time (TE) = 3.5 ms, matric size = 256 × 256 with voxel size = 1 × 1 × 1 mm^3. In total, 192 contiguous axial slices that were aligned to the anterior and posterior commissure line were obtained to cover the entire brain. The diffusion-weighted images were acquired using a single-shot spin-echo EPI sequence in the axial-plane with the following parameters: TR = 11,000 ms, TE = 104 ms; number of excitation = 3; matric size = 128 × 128, field of view = 26 cm; slice thickness = 2.0 mm; 70 slices; b-value = 1000 s/mm^2; 30 isotropic diffusion directions and three non-diffusion weighted T2 images.

DTI analysis

Raw DTI images were preprocessed using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) diffusion toolbox (Raz, Rodrigue, & Haacke, 2007), part of the Functional Magnetic.

Resonance Imaging of the Brain software library (FSL; Morrison & Hof, 1997). The raw DTI image was corrected for the effects of head movement and the distortion caused by eddy currents. A brain extraction tool was used to remove all non-brain parts of the image by using Brain Extraction Tool (BET, Smith, 2002). The WM pathways were reconstructed with TRActs Constrained by UnderLying Anatomy (TRACULA), a tool available in FreeSurfer for automatically reconstructing 18 WM pathways from diffusion weighted images using probabilistic tractography (Yendiki et al., 2011). From these images, fractional anisotropy (FA) values were calculated by fitting a diffusion tensor model to the data at each voxel of the images. The Tract-Based Spatial Statistics (TBSS) pipeline (Scahill et al., 2003) was then used to register and normalize all participants' FA images to the MNI standard space. A mean FA image was created and thinned to create a mean FA skeleton that represented an alignment-invariant tract representation common to the group. An FA threshold of 0.2 was used

to exclude non-skeletal voxels (Scahill et al., 2003; Yang et al., 2016). The aligned FA data of each participant within 18 WM fibers that were served as defined regions of interest (ROIs)[1]. was then projected onto the skeleton. The average FA in each ROI was calculated for subsequent statistical analyses.

Mediation analysis

If our data show associations between age, integrity of regional WM fibers, and cognitive performance, we would perform the mediation analysis with a free Matlab-based toolbox developed by Dr. Wager and colleagues (http://www.columbia.edu/cu/psychology/tor/). Based on the conceptual framework of a mediation effect (MacKinnon, Fairchild, & Fritz, 2007), the age group (older vs. younger group) was selected as the predictor, performance on the cognitive test as the outcome, and the FA values in specific WM as the mediator.

Mediation analyses were conducted in a sequential series of steps. An initial regression analysis was performed to identify which age-related WM tracts associated with age group differences in each neurocognitive test. Step 2, age-group (older group = 1, younger group = −1) was regressed onto cognitive performance to estimate the simple age group–cognition association. Step 3, the FA values from age-related WM tracts and age group were entered into a regression model. This step addressed the question of whether the WM mediated the effect of aging on cognitive performance, which should be manifested as a reduction in explained variance by age compared to the step 2.

Based on a standard three-variable path model with a bootstrap test for the statistical significance of the product *a*b*, a single-level version of the mediation path model was used to get further insight of linkage between the age group, structural WM integrity, and cognitive performance. Path *a* coded the link in which the predictor variable must be related to the mediator. Path *b* coded the link in which the mediator must be directly related to the outcome, controlling for age group. The mediation effect (*a*b*) must be significant, which amounts to a statistical test on the product of the *a* and *b* path coefficients. The test for the predictor–outcome relationship would be significantly reduced by the inclusion of the mediator in the path model. We refer the total predictor–outcome relationship as the *c* effect, and control the direct effect for the mediator as *c′*. The *a*b* effect was to test the significance of *c* − *c′*.

Statistical analysis

The chi-square test for categorical variables and independent *t* test for continuous variables were used to compare the demographic characteristics of the two age groups.

The analysis of variance evaluated the effects of the neuropsychological and structural imaging data between younger and older groups. Group was the between-subject factor and each behavioral and imaging measure was the dependent variable. If the two age groups had significant difference in terms of sex ratio and educational level, these factors were used as covariates in an analysis of covariance. Bonferroni-corrected follow-up analysis was applied to adjust the significance level in multiple comparisons, and a *p* value of less than 0.003 (the neuropsychological outcomes: 0.05/18 tests = 0.003; the DTI outcomes: 0.05/18 tracts = 0.003) was considered statistically significant. Although adjusted *p* values are needed for multiple comparisons, such corrections are actually wasteful of statistical power (Nakagawa, 2004), likely leading to a type II error (Feise, 2002). We therefore also calculated the effect sizes (Cohen's *d* and eta squared (η^2)), to index the magnitude of group differences on each dependent variable and to reduce the false negative error rate.

To assess the relationship between the WM integrity and cognitive performance, multiple linear regressions were performed to identify whether the FA values in specific WM fibers was significantly associated with cognitive performance measures. Cognitive performance showing significant between group differences were entered into the regression models as dependent variables, while including age group, age-related WM integrity differences, and their interaction as independent variables. Covariates included sex and years of education. The interaction between age group and the specific WM fibers was of particular interest in terms evaluating whether the relationship between cognitive performance and the FA differed for the older and the younger groups. Pearson correlations between the FA and the cognitive performance for each group were then obtained to further explore significant age by group interactions revealed by linear regression. All statistical analyses were performed using the PASW software package version 18 (SPSS, Inc., Chicago, IL, USA). Fisher *r* to *z* transformations were conducted for each correlation. A *z*-test of significance was used with the resulting statistics to determine whether the correlation between the FA and cognitive performances significantly differed between the two age groups. Probability for entry in multiple regressions was set as .05. Adjusted R^2 value, standardized coefficient (β), and incremental R^2 provided better estimation of the contribution for each predictor in the model.

Results

Demographic and behavioral results

Table 1 summarizes the demographic and neuropsychological results for the two age groups. Older participants had fewer

Table 1. Demographic and neuropsychological results of younger and older participants

	Older group		Younger group		
	Mean	SD	Mean	SD	*P*
Age	64.72	4.10	22.89	2.16	<.01
Sex (M/F)	7/9		5/13		.33
Year of education	14.72	1.81	16.38	1.54	.01
MMSE	28.17	1.47	28.94	1.24	.11
MOCA	27.72	1.57	28.31	1.01	.21
Digit-symbol coding test	68.22	16.89	96.94	9.72	<.01*
Symbol search test	29.28	5.41	46.50	5.11	<.01*
Block design test	32.06	10.03	52.44	7.30	<.01*
Picture completion test	18.17	3.88	20.94	1.48	.01
Matrix reasoning test	13.50	5.76	21.75	2.91	<.01*
Arithmetic test	15.56	3.73	18.38	2.03	.02
Trail making test– A	13.33	5.53	10.25	3.61	.15
Trail making test– B	33.83	8.78	22.81	17.53	.09
Letter-number sequencing test	9.11	2.93	14.06	3.40	<.01*
Digit span (forward) test	13.22	1.77	15.12	1.09	.01
Digit span (backward) test	6.83	1.95	11.63	2.85	<.01*
Spatial span (forward) test	8.94	1.96	10.44	1.90	.06
Spatial span (backward) test	7.83	1.54	8.94	2.08	.27
Vocabulary test	43.33	15.48	52.00	5.10	.18
Similarity test	19.17	4.44	23.69	2.63	.02
Visual reproduction test	77.67	12.74	92.81	9.96	<.01*
Immediate face recognition test	33.67	4.09	40.25	3.32	<.01*
Delayed face recognition test	33.33	3.80	38.31	3.34	<.01*

Abbreviations: M/F, Male/Female; MMSE, Mini-mental state examination; MOCA, the Montreal cognitive assessment

The asterisks indicated $p < .003$ (a correction for 18 neuropsychological measures tested)

years of education than the younger participants (older adults: $M = 14.72$, $SD = 1.81$, younger adults: $M = 16.38$, $SD = 1.54$, $p = .01$, $d = .99$), however, young and older participants had equivalent verbal ability as measured on Vocabulary test, as shown in Table 1. Younger and older participants had a minimum score of 26 on the MMSE and MOCA, with no significant between-group differences in the MMSE [t (32) = −1.65, $p = .11$, $d = 0.45$] and the MOCA [t (32) = −1.29, $p = .21$, $d = 0.45$]. For the neuropsychological data, our results indicated an age group difference on *processing speed* (digit symbol coding test: [F (1, 33) = 29.94, $p < .01$, $\eta^2 = 0.49$]; symbol search test: [F (1, 33) = 44.62, $p < .01$, $\eta^2 = 0.58$]), visuospatial ability (block design test: [F (1, 33) = 30.68, $p < .01$, $\eta^2 = 0.50$]; picture completion test: [F (1, 33) = 8.32, $p = .01$, $\eta^2 = 0.21$]), fluid intelligence (matrix reasoning test: [F (1, 33) = 31.93, $p < .01$, $\eta^2 = 0.50$]; arithmetic test: [F (1, 33) = 5.69, $p = .02$, $\eta^2 = 0.16$]), *working memory* (letter number sequencing: [F (1, 33) = 17.62, $p < .01$, $\eta^2 = 0.36$]; digit span forward: [F (1, 33) = 7.44, $p = .01$, $\eta^2 = 0.19$]; digit span backward: [F (1, 33) = 26.14, $p < .01$, $\eta^2 = 0.46$]), *language abilities* (similarity: [F (1, 33) = 6.31, $p = .02$, $\eta^2 = 0.17$), and both *immediate and delayed recall measures* (visual reproduction: [F (1, 33) = 12.88, $p < .01$, $\eta^2 = 0.29$]); immediate face recognition: [F (1, 33) = 20.70, $p < .01$, $\eta^2 = 0.40$]; delayed face recognition: [F (1, 33) = 12.14, $p < .01$, $\eta^2 = 0.28$]). Bonferroni-corrected *post hoc* comparison showed that participants with the older participants scored lower on these measures than those with the younger participants (although the corrected p is not significant, the magnitude of group differences was large on the picture completion ($d = 0.94$), arithmetic ($d = 0.94$), digit span forward ($d = 1.30$), and similarity tests ($d = 1.24$)). This pattern of spared crystallized intelligence (vocabulary test) with age and lower fluid intelligence (speed, executive function, and working memory) is typical of most cognitive aging samples in the literatures that focus on normal aging (Park et al., 2002) (Table 1).

Structural imaging results

Controlling for years of education, group-wise comparison of the WM structural integrity (index by the FA) between younger and older participants showed significant effects of age on FA in brain fibers of the anterior CC (i.e. the forceps minor) [F (1, 33) = 16.44, $p < .01$, $\eta^2 = 0.35$], the right cingulum-angular [F (1, 33) = 5.07, $p = .03$, $\eta^2 = 0.14$], and the right uncinate fasciculus [F (1, 33) = 7.23, $p = .01$, $\eta^2 = 0.19$] (Table 2). Bonferroni-corrected follow-up analysis demonstrated that the older participants had significantly reduced FA values compared to the younger participants in anterior CC [t (32) = −4.72, $p < .001$, $d = 1.52$]. Although the corrected p is not significant, the older participants had reduced the FA values in the right uncinated fasciculus [t (32) = −3.09, $p = .004$, $d = 1.05$] and greater the FA values in the right cingulum-angular [t (32) = 2.50, $p = .02$, $d = 0.85$] compared to the younger participants with large effects (Figure 1).

Associations between structural integrity and neurocognitive performance

We were specifically interested in age group differences in the relationship between WM structural integrity and neurocognitive function. Therefore, age group and regional FA differences (the anterior CC, the right cingulum-angular and the right uncinate fasciculus) were then used to predict cognitive performance using multiple linear regressions. Our regression model showed a significant age group-by-forceps minor FA interaction in performance on the block design test [standardized $\beta = 4.25$, t (33) = 2.11, $p = .04$]. Post hoc analysis indicated that a positive correlation between the FA values in the forceps minor and performance on the block design test in older adults was relatively high (Pearson $r = 0.53$), whereas no such effect was found in younger adults (Pearson $r = -0.12$) (Figure 2A). Fisher test upon transformed r-values confirmed that this correlation was significantly stronger for older participants than those with the younger group ($z = 1.88$, $p = .03$).

In addition, we found a significant age group-by-the right cingulum-angular FA interaction in performance on the block design [standardized $\beta = 3.39$, t (33) = 3.06, $p = .01$] and the matrix reasoning [standardized $\beta = 3.10$, t (33) = 2.36, $p = .03$] tests. Post hoc analysis indicated that a positive correlation between the FA values in the right cingulum-angular and performance on the block design test in older adults was relatively high (Pearson $r = 0.63$), whereas no such effect was found in younger adults (Pearson $r = 0.02$) (Figure 2B). Fisher test upon transformed r-values confirmed that this correlation was significantly stronger for the older than younger group ($z = 1.90$, $p = .03$). In contrast, a negative correlation between the right cingulum-angular FA and performance on the matrix reasoning test in younger adults was a large effect size (Pearson $r = -0.53$), whereas a medium to large effect was evident in older adults (Pearson $r = 0.45$) (Figure 2C). Fisher test upon transformed r-values confirmed that this correlation was significantly stronger in the younger than older adults ($z = 2.84$, $p < .01$). However, there was no significant interaction effect of age group and the right uncinate fasciculus FA on performance in the immediate face recognition test [standardized $\beta = 1.59$, t (33) = 0.79, $p = .43$].

Table 2. Regional mean skeleton fractional anisotropy-values of the study participants

	Older group Mean	SD	Younger group Mean	SD	P
Forceps major	.59	.02	.60	.02	.43
Forceps minor	.52	.03	.56	.02	<.01*
Left anterior thalamic radiation	.47	.03	.48	.01	.26
Right anterior thalamic radiation	.46	.03	.47	.02	.26
Left cingulum-angular	.44	.04	.43	.03	.24
Right cingulum-angular	.50	.04	.48	.04	.03
Left cingulum/cingulate gyrus	.60	.04	.59	.03	.25
Right cingulum/cingulate gyrus	.55	.04	.53	.03	.21
Left Corticospinaltract	.59	.03	.60	.02	.99
Right Corticospinaltract	.57	.03	.59	.02	.26
Left inferior longitudinal fasciculus	.48	.03	.49	.03	.53
Right inferior longitudinal fasciculus	.47	.03	.49	.02	.14
Left superior longitudinal fasciculus parietal part	.49	.03	.50	.02	.35
Right superior longitudinal fasciculus parietal part	.50	.03	.50	.02	.91
Left superior longitudinal fasciculus temporal part	.50	.03	.52	.02	.42
Right superior longitudinal fasciculus temporal part	.49	.03	.50	.02	.59
Left uncinate fasciculus	.44	.03	.46	.02	.14
Right uncinate fasciculus	.42	.02	.44	.02	.01

The asterisk indicated $p < .003$ (a correction for 18 white matter fibers tested)

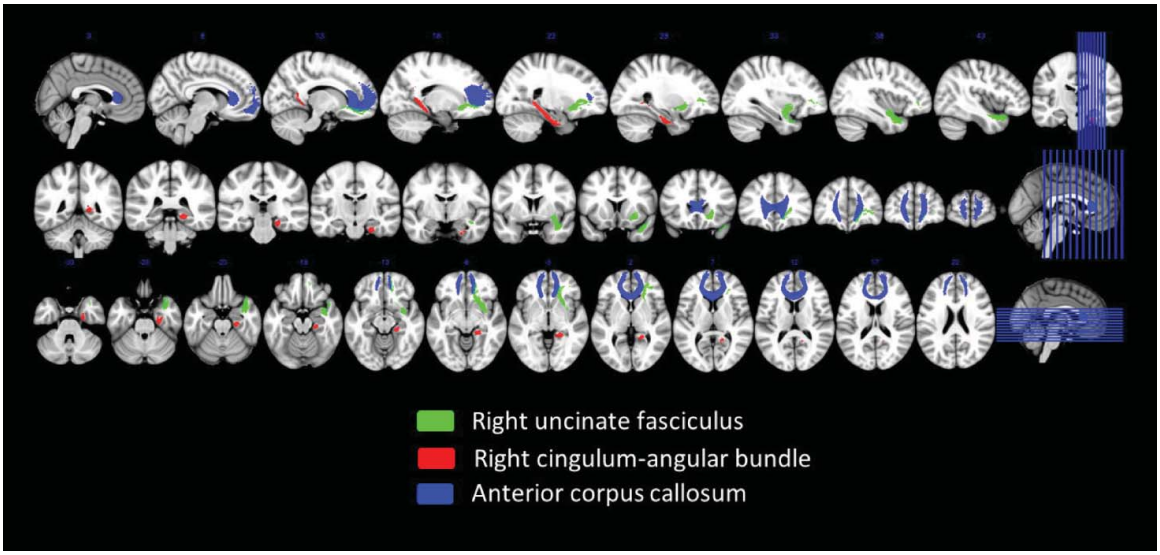

Figure 1. The regions of interest (ROIs) of white matter fibers where show significant age-related differences in microstructural integrity.
The ROIs of white matter fibers depicting microstructural integrity featuring ager-related differences in FA values after controlling for years of education. Significant reduction for FA values in older adults were found in anterior corpus callosum [F (1, 33) = 16.44, $p < .01$, $\eta 2 = 0.35$] and right uncinate fasciculus [F (1, 33) = 7.23, $p = .01$, $\eta 2 = 0.19$], whereas increase for FA values in older adults were reported in right cingulum-angular [F (1, 33) = 5.07, $p = .03$, $\eta 2 = 0.14$].

Mediation analysis results

As the age group (older group = 1, younger group = −1) were negatively correlated with both the FA values in the forceps minor [standardized $\beta = -0.64$, t (33) = −4.66, $p < .01$] and performance on the block design test [standardized $\beta = -0.76$, t (33) = −6.70, $p < .01$], and better performance on the block design test was coupled with increased FA values of the forceps minor [standardized $\beta = 0.73$, t (33) = 5.97, $p < .01$], we performed a bootstrapped mediation analysis to investigate the relation between these variables. This analysis revealed that the FA value in the forceps minor was a significant mediator of the age group–performance on the block design test relation (Figure 3). Reduced FA in the forceps minor was associated with more age-related decline in performance on the block design test ($a = -0.03$, SE = 0.01, $p < .01$; $b = 124.04$, SE = 37.43, $p < .01$; $c = -10.18$, SE = 1.46, $p < .01$; $c' = -6.82$, SE = 1.75, $p < .01$; $a*b = -3.35$, $Z = -2.17$, $p = .03$). However, the FA values of the right cingulum–angular was not a significant mediator in predicting the age group–performance on the block design test relation ($a = 0.01$, SE = 0.01, $p = .21$; $b = 89.85$, SE = 41.73, $p = .03$; $c = -10.18$, SE = 1.46, $p < .01$; $c' = -10.82$, SE = 1.44, $p < .01$; $a*b = 0.66$, $Z = 1.54$, $p = .12$). Neither the right cingulum–angular nor the right uncinate fasciculus significantly mediated age group–performance on the matrix reasoning test relation ($a = 0.01$, SE = 0.01, $p = 0.21$; $b = 16.61$, SE = 22.08, $p = .42$; $c = -4.12$, SE = 0.75, $p < .01$; $c' = -4.26$, SE = 0.82, $p < .01$; $a*b = 0.14$, $Z = 1.04$, $p = .30$) and age group–performance on the immediate face recognition test relation ($a = -0.01$, SE = 0.01, $p < .01$; $b = -60.48$, SE = 34.44, $p = .08$; $c = -3.29$, SE = 0.62, $p < .01$; $c' = -3.38$, SE = 0.63, $p < .01$; $a*b = 0.63$, $Z = 1.07$, $p = .28$), respectively.

Discussion

The current study provides evidence for linkage between changes in the WM integrity and age-related cognitive decline. At the behavioral level, older adults had markedly poorer performance on multiple cognitive measures compared to younger adults. At the neural level, age-related WM changes were evident within interhemispheric and traversing fibers of the frontal regions, and the cingulum-angular fibers.

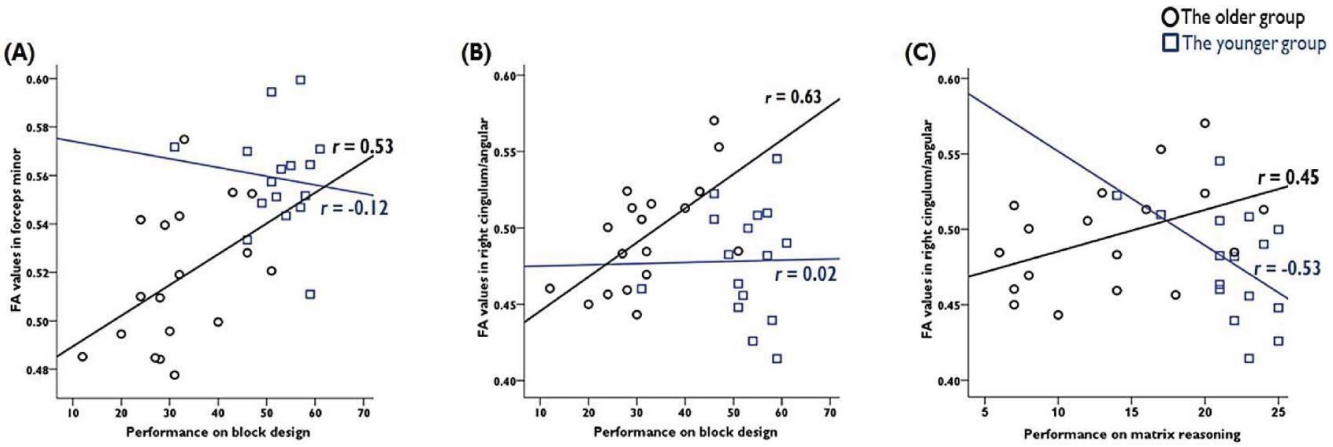

Figure 2. Correlations between regional white matter integrity (indexed by FA) and neuropsychological measures. The FA values in both (A) the forceps minor and (B) the right cingulum/angular positively correlated with performance on the block design test for the older participants, but not for the younger participants. (C) The FA values in the right cingulum/angular negatively correlated with performance on the matrix reasoning test only for the younger participants, but not for the older participant.

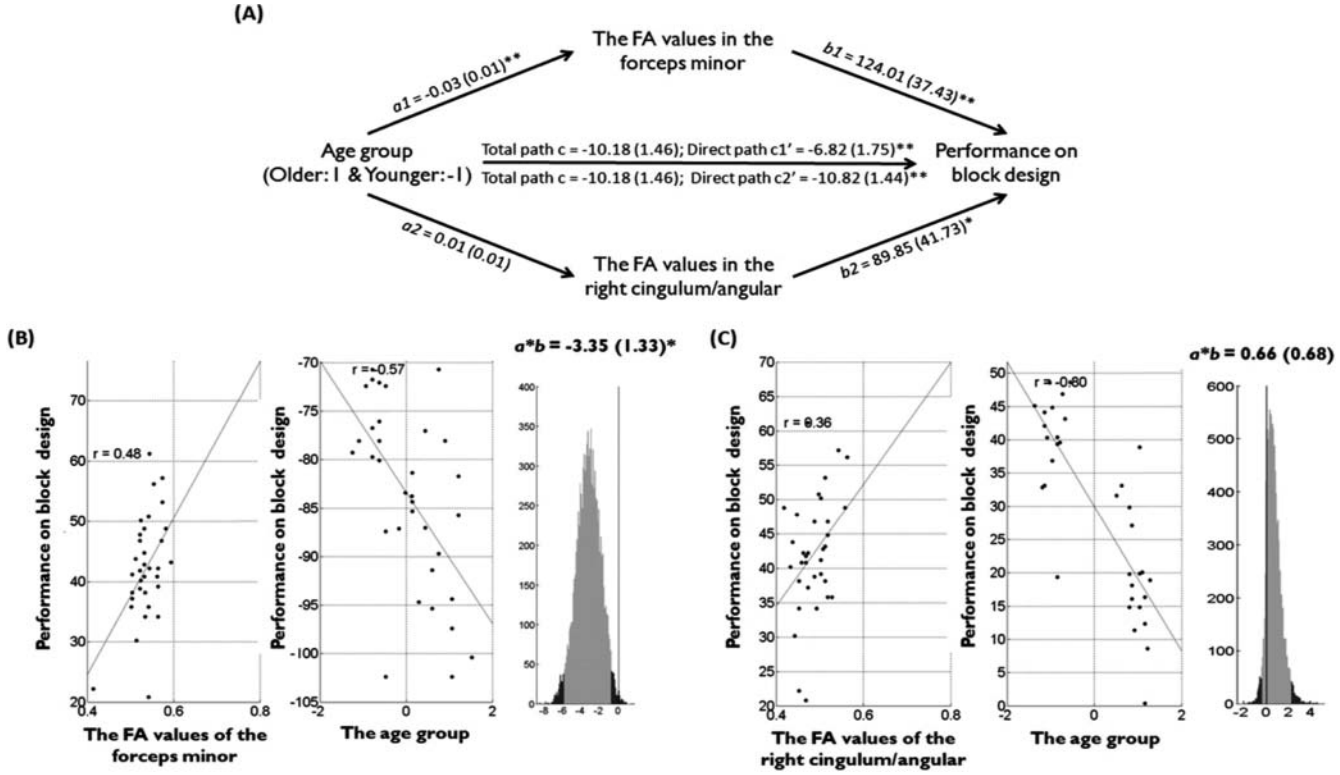

Figure 3. Mediation analysis results. (A) Path diagram showing the relationships between the age group, the FA values in the regional white matter tracts, and performance on block design in the path model. The predictor region in the age group is shown at left, which predicts the FA values in the forceps minor at top and the FA values in the right cingulum-angular (bottom). These are *a* paths for each mediator. The mediator factors connections to the outcome (performance on block design) are the *b* paths. They are calculated controlling for the age group and for the mediator factor, as is standard in mediation models. Path *c* and *c′* indicated the total and direct (controlling for the mediator) effect of age group on performance on block design test, respectively. The paths (path *a*, *b*, *c*, and *c′*) and mediation effects (path *a*b*) are labeled with path coefficients, and their standard errors are shown in parenthesis. $^{**}p < 0.01$, $^{*}p < 0.05$, two-tailed. (B) Partial regression scatterplots for the FA values in the forceps minor—performance on block design relation (left panel) and for the age group—performance on block design relation (center panel). The right panel shows an example of a bootstrapped mediation effect (path *a*b*) for the FA values in the forceps minor. (C) Partial regression scatterplots for the FA values in the right cingulum-angular—performance on block design relation (left panel) and for the age group—performance on block design relation (center panel). The right panel shows an example of a bootstrapped mediation effect (path *a*b*) for the FA values in the right cingulum-angular.

Our results further revealed that the effects of aging on particular WM tracts had differential influences on specific cognitive domains; in particular, integrity of the anterior portion of CC (i.e. the forceps minor) mediates age-related changes in visuospatial performance in healthy older adults.

As expected, advanced age was associated with poor performance on all neuropsychological tests, except for verbal knowledge, trail making (A and B), and spatial span tests, with the largest declines for processing speed (symbol search), visuospatial ability (block design), and fluid intelligence (matrix reasoning) tests. Decades of cognitive aging research shows that knowledge based intelligence remains relatively stable over the lifespan, but that fluid intelligence such as processing speed, reasoning and memory performance is reduced with advanced age (Park & Reuter-Lorenz, 2009; Park et al., 2002; Salthouse, 2004, 2012). More recent work has demonstrated age-related decline in performance on a range of fluid intelligence tasks, such as block design, letter digit, episodic memory, matrix reasoning, and processing speed (Burgmans et al., 2011; Daffner et al., 2005; Salami et al., 2012; Steffener et al., 2014; Kristen & Raz, 2009). A recent DTI-based study using structural equation modeling found that longitudinal changes in the WM microstructure were coupled with changes in fluid intelligence (Ritchie et al., 2015) supporting the notion that disconnection of brain regions, in particular those in frontal regions, is among the causes of age-related cognitive decline (Bennett & Madden, 2014; Bugg, Zook, DeLosh, Davalos, & Davis, 2006; Park & Reuter-Lorenz, 2009). Here, although the difference in performance on some neuropsychological tests (i.e. the Trail making-B and spatial span tests) between the two age groups was not significant, the effect sizes ranged from medium to large (Trail making-B test: $d = 0.79$; Forward spatial span test: $d = 0.7$). The non-significant but nearly large effect size of this finding is most likely due to the small sample size.

Our DTI findings coincide with results from a number of structural imaging studies that elderly adults showed significantly reduced FA in the forceps minor compared to younger adults (Bennett et al., 2010; Salat et al., 2005; Sullivan & Pfefferbaum, 2006; Sullivan et al., 2010). The age-related differences in WM tracts in healthy elderly may involve several neurobiological processes, including microvascular damage, degeneration of myelin sheaths around axons, decreasing axonal density, and breakdown of the cytoskeleton (Goh, 2011; Madden et al., 2012; Sullivan & Pfefferbaum, 2006). Previous studies have revealed that interhemispheric communication between frontal regions is especially susceptible to advanced age (Persson et al., 2006; Salami et al., 2012; Sullivan & Pfefferbaum, 2006) and loss of integrity in the late-myelinated fibers (e.g. the genu of the CC) likely results in degradation of cortical function (Inoue et al., 2008; Kochunov et al., 2007). Our study also shows a greater FA reduction in the frontal callosum fibers with advanced age, whereas the FA values in the vast majority of other WM fibers are relatively stable. These findings lend support to the WM retrogenesis hypothesis that the last brain regions to myelinate

(phylogenetically and ontogenetically) are the first to decline with normal aging processes (Bennett & Madden, 2014; Bugg et al., 2006; Cox et al., 2016).

As has been reported previously (Kerchner et al., 2012; Salami et al., 2012; Wen et al., 2011), our regression model demonstrated that the effects of aging on particular WM tracts had an impact on visuospatial performance, with the forceps minor correlated positively with performance gains on the block design task in older adults, but not in younger adults. In addition to visuospatial ability, the block design task involves higher-order cognitive functions, including perceptual reasoning and problem solving (Lezak, Howieson, & Loring, 2004). Hence, the visuospatial performance in older adults observed in the study may stem from the efficiency of interhemispheric communication via the frontal callosum fibers which is critical for visuospatial information processing (Salami et al., 2012; Wen et al., 2011). Importantly, the results of mediation analysis further revealed that decreased WM integrity of the forceps minor mediates age-related cognitive decline in task measuring visuospatial ability. Zahr and colleagues found that diffusion properties of the genu of the CC can mediate age-related changes in multiple cognitive domains, including working memory, motor performance, and problem solving (Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009). Previous reviews of DTI-based studies have also revealed that the strength of relationships between age and cognitive performance were weaker when analyses statistically controlled for integrity in the genu of the CC (Bennett & Madden, 2014; Madden et al., 2009). The multimodal imaging studies in aging combined DTI with fMRI measures noted that older adults compared to younger adults had greater functional connectivity between bilateral prefrontal regions and older adults' task-related connectivity was correlated positively with the WM integrity in the genu of the CC (Davis, Kragel, Madden, & Cabeza, 2012), even after controlling for age (Schulze et al., 2011). The current study, combining correlation and mediation analyses, illuminates how age-related change in WM integrity influence cognitive function in advanced aging and supports the role of white matter microstructure in age-related cognitive decline and preservation.

The current study reported that older participants showed greater FA values in the right cingulum-angular tract than younger participants. Our regression model further demonstrated that the right cingulum-angular tract FA correlated with performance on both block design and matrix reasoning tasks. The right cingulum-angular WM tract has been identified to connect the hippocampus, parahippocampus, and parietal cortex and play an important role in episodic memory, spatial processing, and attention-shifting tasks (Beckmann, Johansen-Berg, & Rushworth, 2009; Torta & Cauda, 2011). Recent DTI-based studies have shown the cingulum-angular WM tract to be degraded in normal aging and individuals with neurodegenerative conditions who exhibit worsening performance on executive and visuospatial functions (Gazes et al., 2016; Lee et al., 2015; Lin et al., 2014). Here, our findings showed similar association between WM tract integrity and cognition, suggesting that increased structural integrity within the cingulum-angular tract may potentially play a supporting role to compensate for age-related declines in cognitive functioning (Angel, Fay, Bouazzaoui, & Isingrini, 2011; Huang, Polk, Goh, & Park, 2012; Metzler-Baddeley et al., 2012).

Additionally, we found that older adults showed reduced WM integrity in the uncinate fasciculus compared to young adults, consistent with previous findings (Davis et al., 2009; Hasan et al., 2009) and seem to support the retrogenesis hypothesis that the last brain regions to be myelinated would be the most vulnerable to aging (Bartzokis, 2004; Hedden & Gabrieli, 2004). The uncinate fasciculus, one of the late-myelinating fibers, connects the inferior frontal gyrus and the orbital frontal cortex with the anterior portions of the temporal lobe (Ebeling & Von Cramon, 1992; Schmahmann, Smith, Eichler, & Filley, 2008). Results from developmental studies found an inverted U-shaped curve for the FA in advanced age, with positive linear age trends in healthy children and young adults, and negative age trends in older adults (Jones et al., 2006; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Sullivan et al., 2010). However, recent DTI-based work revealed that age-related WM changes are nonlinear (Grydeland, Walhovd, Tamnes, Westlye, & Fjell, 2013; Sexton et al., 2014), and may peak much later than the average age of the younger adults (Kochunov et al., 2012). In the current study, the sample size in each age group was relatively small and did not recruit the middle-aged adults. Such design may restrict interpretation of the current results and limit out capacity to investigate variation in the WM integrity with advanced age.

This study has some limitations that warrant discussion. First, the major limitations are that the sample size in each age group was relatively small and inter-individual variation might have differential effects on cognitive and neurological measures. Importantly, several our behavioral, neurophysiological, and their correlation results showed the non-significant but nearly large effect size. These findings have been due to a relatively small sample size, and therefore a large number of participants are necessary to verify the current study results. Second, this study did not recruit participants with middle-aged group. This may affect our understanding of the relationships between longitudinal changes in brain structure and cognitive performance across the lifespan. Finally, we used FA to represent WM integrity; whereas previous research suggests that other diffusivity measures (e.g. mean diffusivity, and axial and radial diffusivity) are more sensitive than the FA to age-related neurobiological differences (Bennett & Madden, 2014; Cox et al., 2016). Future studies should collect data from large sample sizes across different age groups, use a variety of diffusivity measures, and focus on individual differences in both behavioral and neural domains.

In conclusion, this study demonstrated that multiple cognitive domains and the WM microstructure were altered in healthy older adults. We identified age-related differences in specific WM tract integrity contribute to cognitive decline associated with advanced age. Our results show that cognitive tasks within the visuospatial domain can be mediated by integrity of frontal interhemispheric fibers. Given that mediation analysis is useful to investigate the role of intermediate variables in relationship between a predictor and an outcome, our findings push forward our understanding of cognitive aging by applying mediation-analysis approach on neuroimaging data (Atlas et al., 2010; Lindquist, 2012) to reveal that the variation in the WM microstructure of specific brain fiber is a significant mediator of the age-performance on neurocognitive functions, and by providing a more integrative view of the relationships between aging, cognition, and measures of cortical integrity.

Note

1. Forceps major, Forceps minor, Left anterior thalamic radiation, Right anterior thalamic radiation, Left cingulum-angular, Right cingulum-angular, Left cingulum/cingulate gyrus, Right cingulum/cingulate gyrus, Left corticospinaltract, Right corticospinaltract, Left inferior longitudinal fasciculus, Right inferior longitudinal fasciculus, Left superior longitudinal fasciculus parietal part, Right superior longitudinal fasciculus parietal part, Left superior longitudinal fasciculus temporal part, Right superior longitudinal fasciculus temporal part, Left uncinate fasciculus, Right uncinate fasciculus

Disclosures Statement

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