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Age differences in callosal contributions to cognitive processes

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Abstract

In many cases bilateral cortical activation in older adults has been associated with better task performance, suggesting that a greater reliance on interhemispheric interactions aids performance. Interhemispheric communication is primarily mediated via the corpus callosum (CC), however with advancing age the anterior half of the CC undergoes significant atrophy. Here we determine whether there are age differences in the relationship between cross-sectional area of the CC and performance on cognitive tests of psychomotor processing speed and working memory. We found that older adults had significantly smaller callosal area in the anterior and mid-body of the CC than young adults. Furthermore, older adults with larger size in these callosal areas performed better on assessments of working memory and processing speed. Our results indicate that older adults with larger size of the anterior half of the CC exhibit better cognitive function, although their performance was still poorer than young adults with similar CC size. Thus, while the capability for interhemispheric interactions, as inferred from callosal size, may provide performance benefits for older adults, this capacity alone does not assure protection from general performance decline.

Keywords

Corpus callosum; aging; working memory; processing speed

1. INTRODUCTION

There is clear evidence that advancing age is associated with poorer performance on a wide range of speeded tasks (cf. Salthouse, 2000). Specifically, age-related performance declines have been observed in working memory tasks, processing speed, attention, and perceptual speed (Hedden et al., 2005; Salthouse, 2000). As noted by Salthouse (2000), it seems unlikely that causal mechanisms underlying these declines can be distinguished through behavioral research alone. Rather, inclusion of variables quantifying neural structure and

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function may be required to resolve the fundamental causes of age-related performance declines.

Transcallosal fibers connect largely homologous regions of the right and left hemispheres; thus, the corpus callosum (CC) mediates the transfer and integration of lateralized cognitive, motor, and sensory information between the hemispheres. Structural magnetic resonance imaging (MRI) has demonstrated that there is substantial interindividual variability in CC size and morphology for both young and older adults (Raz et al., 2010; Sullivan et al., 2010). One standard approach to studying callosal function involves parsing the callosum into segments using a geometric scheme (Witelson, 1989). Numerous studies relying on this approach have shown that variations in both CC macro- and microstructure partially explain individual differences in cognitive and motor function (Fling et al., *in press*; Stancak et al., 2003; Westerhausen et al., 2004).

Emerging evidence indicates that both the structure and physiological function of the corpus callosum exhibit age differences (Figure 1). The relative contributions of white matter morphology to age differences in cortical recruitment appear to be substantially more robust than those that result from gray matter (Colcombe et al., 2005). Declines in white matter volume with age begin later and appear to continue at a more accelerated rate than declines in gray matter volume (Courchesne et al., 2000; Ge et al., 2002; Jernigan et al., 2001); however it should be noted that these were cross-sectional studies. Moreover, the speed of white matter shrinkage appears to depend on vascular risk factors (Raz et al., 2005; Kennedy and Raz, 2009).

Numerous studies have reported that older adults have extensive reductions in both CC volume (Muller-Oehring et al., 2007; Langan, et al., 2010) and microstructural integrity (Fling et al., *In press*; Ota et al., 2006; Salat et al., 2005; Sullivan et al., 2010). These age-related differences follow an anterior to posterior gradient, such that white matter quality and quantity is poorest in anterior relative to posterior fiber bundles for older adults (Davis et al., 2009; O'Sullivan et al., 2001; Salat et al., 2004; Sullivan et al., 2010; Zahr et al., 2009). Furthermore, recent work has demonstrated that the relationship between callosal structure and interhemispheric function appears to shift in the aging brain (cf. Fling et al., 2011). Colcombe and colleagues (2005) therefore suggest that impaired interhemispheric communication may play a more significant role than the structure of local gray matter in age deficits in cognition, due to a limited potential for compensatory bilateral processing.

Age differences in brain activation patterns are often posited to be the result of changes in neural structure. Increased reliance on interhemispheric communication with age may serve a compensatory role in cognitive and motor performance. For example, older adults tend to engage both brain hemispheres for tasks that are associated with unilateral processing in young adults (for reviews see Reuter-Lorenz & Lustig, 2005; Seidler et al., 2010). In many cases these bilateral activation patterns have been associated with better task performance among older adults (Cabeza et al., 2002; Reuter-Lorenz & Cappell, 2008), suggesting that a greater reliance on interhemispheric interactions aids performance. Reuter-Lorenz and colleagues (1999) have shown that older adults benefit from bihemispheric processing across all levels of task complexity on a divided visual field letter-matching task, whereas young adults only demonstrate similar benefits on the most complex tasks. Interestingly, less lateralized task processing during both cognitive (Muller-Oehring et al., 2007) and motor (Langan et al., 2010) tasks has been shown to be associated with reductions in CC cross-sectional area in older adults. Thus, structural differences of the CC appear to impact cortical activity both at rest and during task performance, with significant implications for behavior.

Such evidence motivates the present examination of age differences in the relationship between cross-sectional area of the CC and performance on a variety of cognitive and speeded psychomotor tasks. The assessments used in the current study primarily rely upon anterior and sensorimotor cortical areas and are of relatively low complexity; thus we hypothesized that larger area in the anterior half of the CC would be associated with performance benefits for older, but not young adults.

2. METHODS

2.1 Participants

All participants were community-dwelling individuals recruited from the greater Ann Arbor area. Fifty-seven young adults (31 male; mean age 21.8 ± 3.2 years; range 18–30 years) were recruited from the population at the University of Michigan; all young adults were either undergraduate or graduate students and had completed an average of 14.9 years of education. Fifty-five older adults (27 male; 72.1 ± 5.2 years; range 65–80 years) also participated in this study and had completed an average of 15.3 years of education (all older adults completed high school). Participants were strongly right-handed as determined by the Edinburgh Handedness Inventory (M: 0.88; Oldfield, 1971).

2.2 Neuropsychological assessments and health questionnaire

Participants completed a series of questionnaires to assess general cognitive function including the Mini-Mental State Exam (MMSE; Folstein et al., 1975) and the Mattis dementia rating scale (Mattis, 1988). These assessments were administered to potentially exclude participants exhibiting signs of dementia and to confirm that older adult participants were representative of their age group. As in previous studies from our lab, a minimum MMSE score of 27 and a Mattis score of 123 were required for participation (Anguera et al., 2011). The Dysexecutive Questionnaire (DEX; Wilson et al. 1996) was also administered to all participants to determine whether individuals had difficulty with abstract thinking, planning, or other tasks associated with executive functioning. Finally, a health history questionnaire was provided to allow us to exclude participants with a history of stroke, diabetes, alcoholism, arthritis, or neurological disease.

All participants performed a battery of neuropsychological tests to assess specific cognitive processes. Short-term verbal working memory was assessed with the reading span task (a measure of the storage and processing aspects of verbal working memory, Daneman & Carpenter, 1980), as well as the forward and backward digit span tasks from the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1997). The forward and backward digit span tests are similar in that they both rely on attention and working memory, but the backward digit span also assesses planning and transformation of information within working memory (Schofield & Ashman, 1986). Finally, psychomotor processing speed was assessed by the digit-symbol substitution test (from the WAIS-R; Joy et al., 2004). For all of these neuropsychological assessments, a higher score indicates better performance.

2.3 Corpus callosum structural measures

All neuroimaging data were collected in the magnetic resonance imaging (MRI) scanner at the University of Michigan's functional MRI Laboratory (3.0T MRI scanner: General Electric, Waukesha, WI) with a standard GE head coil. Whole brain high-resolution structural MR images were collected using one of the following three T1-weighted gradient-echo pulse sequences acquired in the sagittal plane (field of view/repetition time/echo time/voxel size): sequence 1) 240×240 mm, 10.2ms, 3.4ms, $0.94 \times 0.94 \times 1.4$ mm (N = 28); sequence 2) 240×240 mm, 250ms, 3ms, $1.4 \times 1.4 \times 3.2$ mm (N = 34); or sequence 3) 220×220 mm, 200ms, 3.7ms, $1 \times 1 \times 1.2$ mm (N = 50). Using a custom MATLAB program that

that has previously been described (Fling et al., in press; Langan et al., 2010), we manually outline the corpus callosum (CC) from the mid-sagittal slice of a high-resolution T1 image, which is subsequently divided into seven regions as previously described by Witelson (1989). Based upon recent diffusion tensor tractography work from Hofer & Frahm (2006), these seven regions approximately correspond to distinct anatomical connections of the caudal/orbital prefrontal, inferior premotor cortices (region 1), prefrontal cortices (2), premotor cortices (3), pre-supplementary motor and supplementary motor areas (4), primary motor cortices (5), primary somatosensory cortices (6), superior temporal, posterior parietal, occipital and inferior temporal cortices (7) (Figure 2). Although Hofer and Frahm (2006) outline a scheme with five CC segments, we maintained all seven CC regions from the Witelson (1989) segmentation to increase the sensitivity for determining relationships between regions of the callosal midbody and task performance. Despite the inclusion of 7 regions, connectivity of callosal regions was interpreted relative to Hofer & Frahm (2006). The same custom MATLAB program was utilized to calculate intracranial area (ICA); an outline was drawn along the interior border of the skull with a straight line connecting the nasion and the inion. The same mid-sagittal slice was used to measure the CC and ICA for each participant. Four independent raters made all callosal measurements and inter-rater reliability was assessed with both Krippendorff's alpha (Hayes and Krippendorff, 2007) and intraclass correlation coefficient (ICC). The mean callosal cross-sectional area across raters was used in subsequent analyses.

2.4 Data analysis

We used SPSS 18.0 to run statistical analyses on metrics of cognitive and motor performance. Independent sample *t*-tests were used to compare group performance on all neuropsychological tests and handedness; all *t*-tests were two-tailed, unless otherwise noted. Mixed model repeated measures ANOVA was used to analyze CC cross-sectional area: CC region was included as the within-subjects variable and age group and gender as the between-subjects variables. Intracranial area and structural MR acquisition parameters (TR/TE/and voxel size) were included as covariates in this statistical analysis, since three different image acquisitions were used for different subsets of the participants (all with the same MRI scanner). Significance was set at $\alpha = 0.05$. The Huynh-Feldt epsilon was computed to test for sphericity; we evaluated tests using the adjusted degrees of freedom in cases of sphericity violation. Significant main effects were subjected to post-hoc independent (age group, gender) and paired *t*-tests (CC region). We also performed linear regression to assess relationships between cognitive task performance. This resulted in our computing a composite cognitive score using the Z scores for performance on the digit symbol substitution, reading span, and forward and backward digit span tasks. To assess relationships between size of callosal regions and task performance we used a general linear model with cognitive task performance as the dependent variable and age group and size of callosal region as predictors while controlling for ICA. All data are presented as mean (\pm standard error) unless otherwise noted.

3. Results

3.1 Neuropsychological assessments

Young adults performed significantly better than older adults on all assessments of working memory and processing speed ($P < 0.05$ for all tasks; Table 1). In addition, performance on all cognitive variables was significantly correlated ($P < 0.01$; Table 2). Therefore, we computed one composite variable for all cognitive measures, which we use in all subsequent regression analyses.

3.2 Callosal size

Inter-rater reliability of the CC cross-sectional area measurements within region 1 (rostrum) was poor (Krippendorff's alpha < 0.3; ICC < 0.4). However, measurements within the remaining 6 CC regions (2–7) were highly reliable (Krippendorff's alpha > 0.92; ICC > 0.88). Due to the large variability among measures of CC region 1 both within and across raters, this region was excluded from further analyses.

For callosal cross-sectional area a main effect of CC region ($F_{5,535} = 10.3$, $P < 0.001$) and an age group \times CC region interaction were found ($F_{5,535} = 6.6$, $P < 0.001$), as well as a main effect of age group ($F_{1,107} = 6.4$, $P < 0.05$). Further, the use of three different MRI acquisition parameter sets had no significant effect on measures of callosal size ($P > 0.4$), nor were there any significant interactions between MR sequence and CC region, or age group ($P > 0.35$). Post-hoc independent sample t-tests indicated that older adults had significantly smaller cross-sectional area in callosal regions 2 ($t = 3.4$, $P < 0.001$) and 4 ($t = 4.4$, $P < 0.001$; Figure 3) than young adults. These regions contain transcallosal fibers that connect pre-frontal cortices (CC2) and supplementary motor areas (CC4). Although not significant when corrected for multiple comparisons ($\alpha = 0.05/6$) we also note a similar trend within CC region 5 ($t = 2.1$, $P < 0.04$), a region containing fibers that connect the primary motor cortices. Furthermore, the results revealed no main effect of gender ($F_{1,107} = 0.3$, $P < 0.8$), no gender \times CC region interaction ($F_{5,535} = .47$, $P < 0.7$), no gender \times age group interaction ($F_{1,107} = .46$, $P < 0.5$), and no CC region \times gender \times age interaction ($F_{5,535} = 2.0$, $P > 0.1$).

3.3 Relationships between callosal size and performance

For the regions where CC cross-sectional area significantly differed between groups (CC2 and CC4), we assessed whether size of CC region predicted performance on the composite cognitive variable in a differential fashion between age groups. We report a significant main effect for group ($\chi^2_{1,104} = 552.6$; $P < 0.001$), size of CC2 ($\chi^2_{98,104} = 3561.6$; $P < 0.001$), and size of CC4 ($\chi^2_{86,95} = 279.8$; $P < 0.001$). Further, we observed a significant interaction for age group \times CC2 size ($\chi^2_{5,104} = 200.9$; $P < 0.001$) and for age group \times CC4 size ($\chi^2_{8,95} = 31.7$; $P < 0.01$). When investigating linear regression between the cognitive composite variable and size of CC2 (while controlling for ICA) when separated by age group, a positive relationship was observed in older adults ($r = 0.32$) whereas no relationship was found in young adults ($r = 0.05$; see Figure 4A). Similarly the relationship between the cognitive composite variable and the size of CC4 revealed a positive relationship in older adults ($r = 0.29$), while little to no relationship was observed in young adults ($r = 0.04$; Figure 4B). Thus, size of CC2 and CC4 are positively correlated with cognitive performance in older adults and unrelated to cognitive performance in young adults.

Finally, to demonstrate the callosal region specificity of these relationships we also correlated the cognitive composite variable with size of CC7, a region that was actually larger in the older adult group (OA: 188.7mm²; YA: 185.7mm²). We chose this as a control region because CC7 is an area containing fibers that connect cortical regions serving a minimal role during the current tasks (e.g. occipital cortices). We report no relationship between size of CC7 and cognitive performance in either the young adult ($r = 0.03$) or older adult ($r = -0.09$) group, supporting the specificity of the effects reported for CC2 and CC4.

4. Discussion

We report that adults over the age of 65 have reduced size within the genu and anterior truncus of the corpus callosum when controlling for intracranial area (ICA). For all participants, performance on cognitive tasks assessing psychomotor processing speed and

working memory were all highly correlated with one another, and as a result we computed a composite score of cognitive function. Consistent with our hypothesis, we observed a positive relationship between the size of the genu and anterior truncus of the corpus callosum with our cognitive composite measure in older, but not young adults. The observed result of age-group and callosal region specific relationships between callosal size (controlled for intracranial cranial area) and task performance implies that our findings are not driven by general callosal atrophy, but rather reflect age effects specific to certain callosal regions.

Age differences in the relationship between neural activity and cognitive function have been studied extensively in recent years (for reviews see Reuter-Lorenz and Lustig, 2005; Reuter-Lorenz and Park, 2010). Additionally, research has shown that changes in neural structure play a significant role in age-related performance declines. Solely investigating the genu and the splenium of the CC, Kennedy and Raz (2009) found that poorer white matter microstructure of the genu (which is approximately equivalent to CC2 in the current study) was associated with decreased processing speed and working memory performance in older adults. In addition to fibers within this anterior CC region, our results indicate that fibers passing through CC4 also play an important role during tasks assessing psychomotor speeded response and working memory. This particular callosal region contains transcallosal fibers projecting into the medial motor areas including cingulate motor and supplementary motor areas (Hofer and Frahm, 2006). These medial motor areas have previously been implicated in tasks assessing psychomotor processing speed (Venkatraman et al., 2010) and working memory (Jansma et al., 2001; Mu et al., 2005). The findings of the current study, coupled with those of Kennedy and Raz (2009), suggest that older adults with larger macrostructure and better microstructure of the genu and anterior truncus of the CC experience relatively spared cognitive function, potentially through the preserved capability of interhemispheric interactions. For example, Sullivan and colleagues (2001) noted that age-related declines in the corpus callosum were associated with reduced interhemispheric communication efficiency.

Cabeza (2002) originally proposed the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model, describing the finding that older adults demonstrate decreased prefrontal cortex lateralization across different memory and cognitive tasks. Older adults exhibit similar over-recruitment when performing motor tasks (cf. Seidler et al., 2010 for a comprehensive review). Evidence suggests that over-recruitment patterns in older adults may reflect either i) compensatory activation where additional brain areas are positively associated with task performance (Cabeza, 2002; Heuninckx et al., 2008; Mattay et al., 2002; Naccarato et al., 2006; Reuter-Lorenz and Lustig, 2005) or ii) de-differentiation suggesting that brain structure-function relationships become less precise with age (Li & Lindenberger, 1999; Logan et al., 2002; Park et al., 2004; Riecker et al., 2006). In support of the de-differentiation hypothesis, increased bilateral activation in older adults has been suggested to be the result of decreased interhemispheric inhibition via the corpus callosum.

Fujiyama and colleagues (2009) found that older adults have a reduced ability to modulate inhibitory function in a task-dependent manner in comparison to young adults. Further, recent work by Muller-Oehring and colleagues (2007) investigating visual attentional processes indicates that callosal degeneration plays a pivotal role in the reduced functional cerebral lateralization seen in healthy aging. Specifically, they propose that selective degradation of the genu, as observed in the current study, leads to less robust interhemispheric inhibition, thus reducing lateralization and allowing interhemispheric crosstalk to influence cortical processing. Supporting this, we have recently shown that older adults with smaller CC size and poorer microstructure demonstrate task-specific performance declines on bimanual motor tasks requiring increased interhemispheric

inhibition (Fling et al., In press). The current results fit in well with this literature demonstrating that older adults who maintain callosal size in specific regions that are prone to degradation demonstrate preserved performance on both cognitive and motor tasks. Thus, declines in callosal size and integrity, coupled with decreases in the inter-connectedness of the two hemispheres of the brain suggest that age-related cognitive and motor impairments may be due, at least in part, to reductions in interhemispheric inhibition. However, one notable limitation of the current study is a lack of measurement of vascular risk. As previously described, vascular risk is a mediator of age-related changes and differences in white matter integrity and volume (Raz et al., 2005; Kennedy & Raz, 2009).

Furthermore, the older adults exhibited lower scores on the MMSE, DEX, and Mattis dementia rating scale than the young adults. While the differences were slight and certainly are not atypical for studies comparing these two age groups, it may be that these differences in general cognitive status influenced the results. However, given the specificity of age differences in CC2 and CC4, and the fact that size of CC7—which did not exhibit significant age differences in size nor significant relationships with cognitive performance—we think it unlikely that such generalized factors are at play.

Our finding of age-specific relationships between callosal size and performance indicate older adults with larger macrostructure of the anterior half of the CC experience relatively spared performance on tasks related to psychomotor processing speed and working memory. Nevertheless, while the capability for interhemispheric interactions, as inferred from callosal size, may provide performance benefits for older adults, this capacity alone does not assure protection from general performance decline. That is to say, older adults with similar callosal size to young adults still exhibited reductions in performance. Further research is required to dissociate which task parameters are associated positively or negatively with CC size and microstructure, bihemispheric processing and task performance in young and older adults.

- Age-related callosal decline has the capability to influence cognitive performance.
- Older adults have selective loss of size in anterior callosal regions.
- We correlate size of callosal sub-regions with cognition in a large sample size.
- Increased anterior callosal size is favorable for older, but not young adults.

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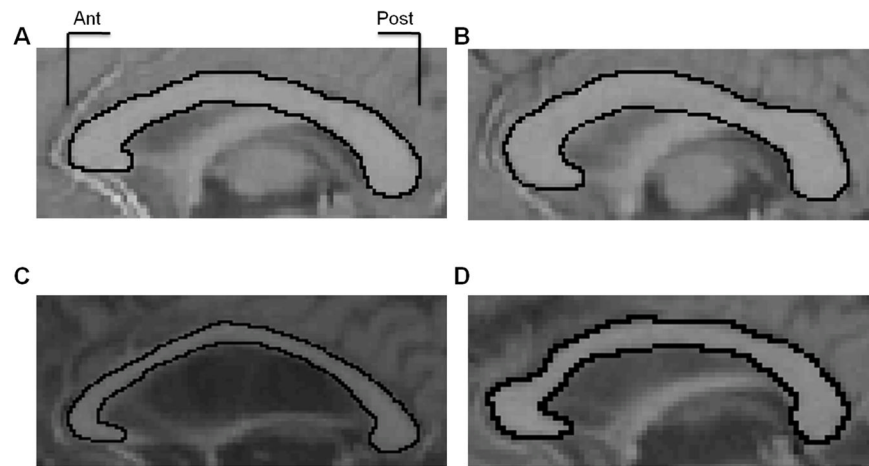


Figure 1. Two representative examples of the corpus callosum viewed on a mid-sagittal slice from young adult participants (**A**, **B**), and two older adult participants (**C**, **D**). These images are displayed to demonstrate overall age differences in callosal size, as well as region-specific decreases within the anterior and mid-body of the corpus callosum. Ant = anterior; Post = posterior.

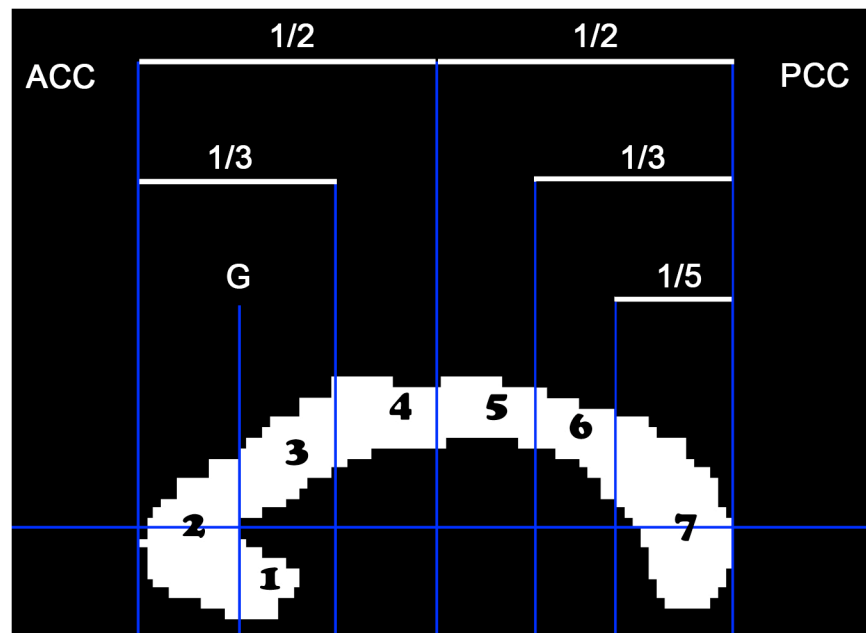


Figure 2. Geometric segmentation of the corpus callosum based on Witelson (1989). The cross sectional area of the midsagittal CC was parsed into 7 regions: (1) rostrum, (2) genu, (3) rostral truncus, (4) anterior intermediate truncus, (5) posterior intermediate truncus, (6) isthmus, (7) splenium. ACC = anterior border of corpus callosum; PCC = posterior border of corpus callosum; G = genu.

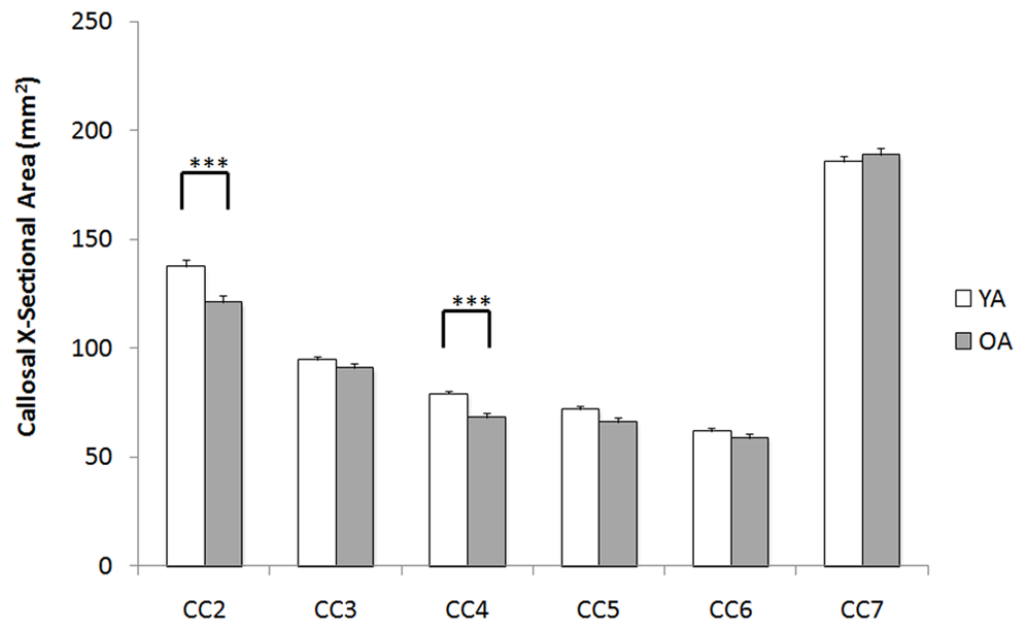


Figure 3.

Raw corpus callosum cross-sectional area of regions 2–7 (region 1 is excluded due to lack of measurement reliability). Older adults (OA) had significantly smaller callosal area than young adults (YA) in CC region 2 (** $P < 0.01$) and region 4 (***) ($P < 0.001$) while controlling for intracranial area. Data are mean + 1 S.E.M. X-sectional = cross-sectional.

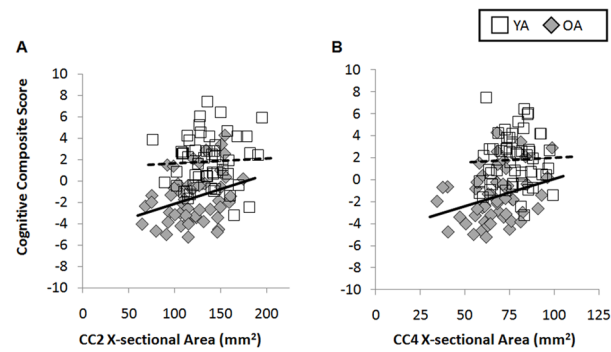


Figure 4.

A) Relationships between size of CC2 and the cognitive composite variable in each age group. While older adults demonstrate a positive relationship ($r = 0.32$), no relationship is observed in young adults ($r = 0.05$). **B)** Relationships between size of CC4 and the cognitive composite variable in each age group. Again older adults demonstrate a positive relationship ($r = 0.29$), whereas there is no association observed in young adults ($r = 0.04$). Dashed lines represent linear regression fit to young adult data. Solid lines indicate linear regression fit to older adult data. X-sectional = cross-sectional.

Table 1

Group values for all assessments. YA – young adults; OA – older adults; S.E.M. –standard error of the mean; MMSE – mini-mental state exam; Mattis – Mattis dementia rating scale; DEX – dysexecutive questionnaire; FDS – forward digit span; BDS – backward digit span.

	YA (N = 57)	OA (N = 55)	Significance	
	Mean	Mean	<i>t</i>	<i>p</i>
Edinburgh	0.86 (0.02)	0.89 (0.2)	-1.88	0.08
Education	14.9 (1.3)	15.3 (2.6)	-0.9	0.16
MMSE	29.7 (0.09)	29.1 (0.2)	3.0	0.004
Mattis	141.8 (0.2)	140.2 (0.5)	3.0	0.003
DEX	18.9 (1.1)	15.6 (1.1)	2.1	0.037
Digit Symbol	90.0 (1.5)	64.4 (1.7)	11.4	0.001
Reading Span	32.8 (0.6)	26.0 (0.8)	6.6	0.001
FDS Trial	12.4 (0.3)	10.4 (0.3)	4.4	0.001
BDS Trial	8.3 (0.3)	7.0 (0.3)	3.2	0.002

Table 2

Correlation matrix for all callosal regions and cognitive assessments, while controlling for intracranial area. All data in the table are Pearson r values. Because performance on all cognitive variables were significantly correlated, a cognitive composite score of performance on all four tasks is also included. FDS – forward digit span; BDS – backward digit span; Cog Comp = cognitive composite score.

	CC3	CC4	CC5	CC6	CC7	Age	Digit Sym.	Read. Span	FDS	BDS	Cog Comp
CC2	0.25**	0.56***	0.5***	0.3***	0.25**	-0.32***	0.30***	0.3***	0.1	0.12	0.25**
CC3		0.40***	0.35***	0.35***	0.54***	-0.11	0.05	0.002	0.15	-0.08	0.04
CC4			0.7***	0.40***	0.33***	-0.42***	0.38***	0.33***	0.16	0.1	0.31***
CC5				0.66***	0.34***	-0.24**	0.23*	0.18*	0.01	0.06	0.15
CC6					0.29***	-0.11	0.01	0.15	0.03	0.1	0.1
CC7						-0.11	-0.03	-0.04	-0.05	-0.14	-0.08
Age							-0.75***	-0.52***	-0.40***	-0.28**	-0.62***
Digit Sym.								0.61***	0.42***	0.37***	0.77***
Reading Span									0.48***	0.48***	0.82***
FDS										0.54***	0.78***
BDS											0.76***

* $P < 0.05$;

** $P < 0.01$;

*** $P < 0.001$