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Diffusion tensor imaging of adult age differences in cerebral white matter: relation to response time

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Diffusion tensor imaging (DTI) measures the displacement of water molecules across tissue components, thus providing information regarding the microstructure of cerebral white matter. Fractional anisotropy (FA), the degree to which diffusion is directionally dependent, is typically higher for compact, homogeneous fiber bundles such as the corpus callosum. Previous DTI studies in adults have demonstrated an age-related decline in white matter FA, but whether the relation between FA and behavioral performance varies as a function of age has not been determined. We investigated adult age differences in FA, and age-related changes in the relation between FA and response time (RT), in a visual target-detection task. The results confirmed that, independently of age, FA is higher in the corpus callosum than in other brain regions. We also observed an age-related decline in FA that did not vary significantly across the brain regions. For both age groups, a lower level of integrity of the cerebral white matter (as indexed by FA), in specific brain regions, was associated with slower responses in the visual task. An age-related change in this relation was evident, however, in that the best predictor of RT for younger adults was FA in the splenium of the corpus callosum, whereas for older adults the best predictor was FA in the anterior limb of the internal capsule. This pattern is consistent with measures of the task-related cortical activation obtained from these same individuals and suggests an age-related increase in the attentional control of responses mediated by corticostriatal or corticothalamic circuits.

Keywords: White matter; Diffusion tensor imaging; Fractional anisotropy

Investigations of brain structure and function have yielded important information for understanding age-related changes in perceptual and cognitive functioning. The postmortem examination of brain tissue and structural neuroimaging data obtained in vivo, especially from magnetic resonance imaging (MRI), have revealed notable age-related changes in the structure of the brain, even in the absence of significant disease. There is a gradual decrease in total brain mass, beginning in younger adulthood, which in later adulthood is evident as gyral atrophy, widening of sulci, and enlargement of the lateral ventricles (Raz, 2000, in press; Uylings and de Brabander, 2002). The decrease in gray matter volume with age is predominantly linear and appears to result from the shrinkage of neuronal somata or the loss of neuronal processes, especially from cortical layer I, rather than the death of neurons themselves (Haug, 1985; Peters, 2002; Peters et al., 1998). The changes with age in white matter volume, assessed by MRI, are more often reported to be nonlinear, with the volume remaining relatively constant during middle adulthood but declining more precipitously after the sixth decade (Courchesne et al., 2000). A recent histological analysis of normal adult human brains, however, suggested a more steady loss of myelinated axons throughout adulthood (a decrease of approximately 10% per decade), with the small-diameter axons being most vulnerable (Marner et al., 2003). The age-related decline in volume of gray matter varies by cortical region, being more pronounced in prefrontal and parietal lobes than in the temporal and occipital lobes, whereas the decline in white matter volume is widespread throughout the brain (Resnick et al., 2003).

Age-related changes in cortical activation in response to perceptual and cognitive demands have been widely investigated with positron emission tomography and functional MRI (fMRI; Cabeza, 2001; Grady and Craik, 2000; Madden et al., in press-a Reuter-Lorenz, 2002). Less is known regarding the potential contribution of age-related changes in cerebral white matter to cognitive performance. For example, T_2-weighted images of healthy older adults frequently exhibit an increased number of white matter signal hyperintensities, which are associated with decreased performance in tests relying on perceptual speed and attentional control (Gunning-Dixon and Raz, 2000). Diffusion tensor imaging (DTI) is a potentially valuable methodology for addressing this issue because DTI can map the microstructure of cerebral white matter in vivo (Le Bihan, 1995, 2003).

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Diffusion tensor imaging is an MRI technique that measures both the rate and directionality of the displacement distribution of water molecules across tissue components on a voxel-by-voxel basis. Because diffusion is a three-dimensional process, the molecular movement of water is not likely to be the same in all directions, depending on the orientation of obstacles (e.g., tissue, proteins in the extracellular matrix) that limit movement. The diffusion per voxel is represented quantitatively by three parameters: mean diffusivity (the overall mean-squared displacement of molecules), fractional anisotropy (FA; the degree to which molecular displacements are directionally dependent), and the main direction of diffusivity.

The FA measure is particularly useful as a measure of the functional integrity and specific organization of myelinated axonal fibers. This measure ranges from zero, representing diffusion that is equal in all directions, to 1.0, representing complete directional dependence. Diffusion of water is faster along the longitudinal axis of a group of aligned fibers than in the perpendicular (transverse) axis. Thus, anisotropy tends to be higher in the white matter compared with the gray matter due to the presence of myelinated fiber bundles, and it is greater for white matter structures that contain the largest numbers of fibers running in parallel, such as the corpus callosum (Shimony et al., 1999). Furthermore, FA is higher in compact white matter structures such as the corpus callosum than in less compact white matter regions.

Several DTI investigations have reported an age-related decrease in FA in healthy individuals (Moseley, 2002). Pfefferbaum et al. (2000) assessed FA (among other measures) for five regions of interest (ROIs) in a sample of 31 healthy men between 23 and 76 years of age. Consistent with previous findings (Shimony et al., 1999), FA was higher in the genu and splenium of the corpus callosum than in the frontal and parietal pericallosal regions and in the centrum semiovale. There was, in addition, a negative correlation between FA and age for all of the ROIs, which was significant statistically for all of the ROIs except the splenium. Pfefferbaum et al. concluded that the age-related decline in FA represented a decline in white matter integrity, possibly involving mild demyelination and loss of myelinated axons. Sullivan et al. (2001) compared these 31 men to 18 women between 23 and 79 years of age and found a similar pattern of age-related change for each group. In addition, Sullivan et al. found that FA values for the splenium and parietal pericallosal regions were positively correlated with perceptual-motor performance (alternating finger tapping). These regional FA values were in fact better predictors of performance in this task than age.

O'Sullivan et al. (2001) also examined the relation between DTI measures (mean diffusivity and FA) and neuropsychological test performance. This study included a sample of 10 younger adults and 20 older adults, and the authors divided the white matter of each hemisphere into anterior, middle, and posterior ROIs using the posterior margin of the genu and the anterior margin of the splenium as borders. Consistent with the results of Pfefferbaum et al. (2000) and Sullivan et al. (2001), increased age was associated with a decline in FA and an increase in mean diffusivity, and the age difference in both of these measures was most pronounced in the anterior ROI. Correlations performed within the older adult group indicated that mean diffusivity in the anterior ROI was correlated with a neuropsychological measure of attention (Trail Making), whereas FA in the middle region was correlated with verbal fluency.

As one consequence of age-related changes in white matter, the relative importance of particular white matter pathways for behavioral performance may vary as a function of age. Thus, a direct comparison between younger and older adults should reveal a difference, either within or across brain regions, in the correlation between FA and behavioral performance. Sullivan et al. (2001) compared FA and age as predictors of perceptual-motor performance, and O'Sullivan et al. (2001) examined the correlation between FA and neuropsychological test scores only within the older adult group. It has not yet been determined whether the relation between FA and behavioral performance differs for younger and older adults, and we addressed this issue in the present experiment.

In this study, we set out to measure adult age differences in mean FA and age-related changes in the relation between FA and one form of behavioral performance, a visual target detection (oddball) task. This behavioral measure was obtained during an fMRI scanning session in which diffusion tensor images were also acquired, and previous analyses of the fMRI data demonstrated task-dependent cortical activation in prefrontal, deep gray matter, and occipital regions (Madden et al., in press-b). In the present DTI analyses, we consequently placed ROIs in six white matter regions relevant to the cortical activation: the genu and splenium of the corpus callosum, a frontal pericallosal ROI, the white matter within the superior frontal gyrus, the anterior limb of the internal capsule, and a posterior visual ROI. The behavioral performance measure was response time (RT) for correct responses in the oddball task.

We expected that, independently of age effects, FA would be higher in the genu and splenium of the corpus callosum than in the ROIs outside the callosum (Pfefferbaum et al., 2000; Shimony et al., 1999). In addition, we predicted that an age-related decline in mean FA would occur and would be more pronounced in those ROIs with direct connections to the prefrontal cortex (genu, frontal pericallosal, white matter of superior frontal gyrus, and anterior limb of the internal capsule) than in the more posterior regions (O'Sullivan et al., 2001; Pfefferbaum et al., 2000; Sullivan et al., 2001). With regard to the relation between FA and RT, previous research leads to different predictions depending on which task demands are most prominent. The oddball task has an attentional component, in terms of holding the response assignments in working memory and selecting the appropriate response. The data of O'Sullivan et al. (2001) lead to the prediction that these attentional demands would be reflected in a more prominent correlation between FA and RT for anterior ROIs, such as the genu and frontal pericallosal regions, than for more posterior regions. The oddball task also involves purely perceptual-motor demands such as viewing displays and initiating a motor response, however, and thus the results of Sullivan et al. (2001) lead to the prediction of a more pronounced association between FA and performance for more posterior regions, such as the splenium of the corpus callosum, than for more anterior regions.

The specific pattern of age-related change in the relation between FA and RT is difficult to predict in the absence of any previous evidence. O'Sullivan et al. (2001) proposed that the age-related decline in prefrontal FA contributes to a disconnection among prefrontal cortical networks, which suggests that the relation between FA and RT, for prefrontal regions, may also be more pronounced for older adults than for younger adults. Analyses of the fMRI data obtained concurrently with the oddball task, however, indicated that prefrontal cortical activation in this particular task was comparable for the two age groups (Madden et al., in press-b). The older adults exhibited less activation of the extrastriate occipital cortex (fusiform and lateral occipital gyri), but greater activation of deep gray matter regions (e.g., caudate, putamen, thalamus, and insula), than younger adults. This pattern may reflect an age-related increase in reliance on the basal ganglia

and corticostriatal circuits involved in visuomotor learning and response regulation (Graybiel, 2000; Huettel et al., 2002; Poldrack et al., 1999). In addition, the activation of the deep gray matter structures, among 12 cortical regions of interest, was the best predictor of RT in the oddball task for the older adults, whereas the prefrontal activation was the best predictor for younger adults. Thus, white matter regions involving the corticostriatal connections between deep gray matter structures and prefrontal cortex, such as the anterior limb of the internal capsule, may have a prominent role in older adults' performance in this task.

Materials and methods

Subjects

The research procedures were approved by the Institutional Review Board of the Duke University Medical Center, and all subjects gave written informed consent. All of the subjects were right-handed, community-dwelling individuals who participated in the fMRI study reported by Madden et al. (in press-b), and demographic data are included in that article. There were 16 subjects (eight women) in each of two age groups: younger adults between 19 and 25 years of age (M = 20.9 years) and older adults between 60 and 70 years of age (M = 64.7 years). Subjects were screened by questionnaire for health problems, and all subjects reported being free of significant disease such as atherosclerosis and hypertension. Subjects also reported that they were not taking medication potentially affecting cognition or cerebral blood flow, such as antidepressants or anti-hypertensive agents. The two age groups were comparable in the number of years of education (younger adults' M = 15.2 years; older adults' M = 15.8 years). In addition to the DTI scans, the imaging session included high resolution T_1-weighted and T_2-weighted structural images, and T_2^*-weighted functional imaging. A neuroradiologist (one of the authors, J.M.P.) reviewed the T_2-weighted images for cortical atrophy, ventricular enlargement, and white matter signal hyperintensities and found all of the subjects to be within normal limits. Due to technical problems, the DTI data for one younger subject were lost, yielding a final sample size of 15 subjects for the younger adults' DTI data.

Imaging protocol

Scanning was conducted on a 1.5-T GE NVi SIGNA scanner with 41 mT/m gradients for fast image acquisition. Head motion was minimized with a vacuum-pack system molded to fit each subject. The T_1-weighted imaging used a gradient-echo sequence with TR = 450 ms, TE = 3.5 ms, flip angle = 90°, NEX = 1, FOV = 24 cm, 256 × 256 image matrix, and in-plane resolution = 0.94 mm^2. The T_1-weighted images were prescribed from sagittal localizer images (spanning the midline) to be parallel to the line connecting the anterior and posterior commissures, resulting in 14 contiguous near-axial oblique slices, 5 mm thick, with no interslice gap. Diffusion tensor imaging used a spin echo echo-planar sequence with TR = 15,000 ms, TE = 112 ms, flip angle = 90°, NEX = 1, b = 1000 s/mm^2, FOV = 20 cm, and 128 × 64 image matrix, four signal averages, acquiring 30 straight axial slices 6 mm thick, with no interslice gap.

Diffusion was measured in six directions, plus one image with no diffusion weighting. The direction scheme followed that of Basser and Pierpaoli (1998). The directions were (x, y, z) = (0, 0, 0), (1, 1, 0), (1, −1, 0), (1, 0, 1), (1, 0, −1), (0, 1, 1), (0, 1, −1), where 1 indicates a gradient applied in that direction. The actual gradient strengths were adjusted for each direction to yield the desired b value. Diffusion-weighed images were processed using custom MATLAB (Mathworks, Natick, MA) scripts that calculated the diffusion tensor eigenvalues ($D1$, $D2$, $D3$) in each voxel. The fractional anisotropy (FA) was calculated from Eq. (1):

$$\mathrm{FA} = [(3/2)((D1-\mathrm{Dav})^2+(D2-\mathrm{Dav})^2+(D3-\mathrm{Dav})^2)]^{1/2}/\mathrm{DM}, \quad (1)$$

where Dav = ($D1$ + $D2$ + $D3$)/3 and DM = ($D1^2$ + $D2^2$ + $D3^2$)$^{1/2}$.

Four trained operators, who were blinded to subject age, independently outlined six ROIs directly on the tensor images on a slice-by-slice basis for each subject. The operators used individual slices from each subject's T_1-weighted series as a visual reference, although the T_1-weighted and tensor images were acquired at different angles and were not coregistered. The ROIs, illustrated in Fig. 1, were the genu and splenium of the corpus callosum, frontal white matter just lateral to the genu of the corpus

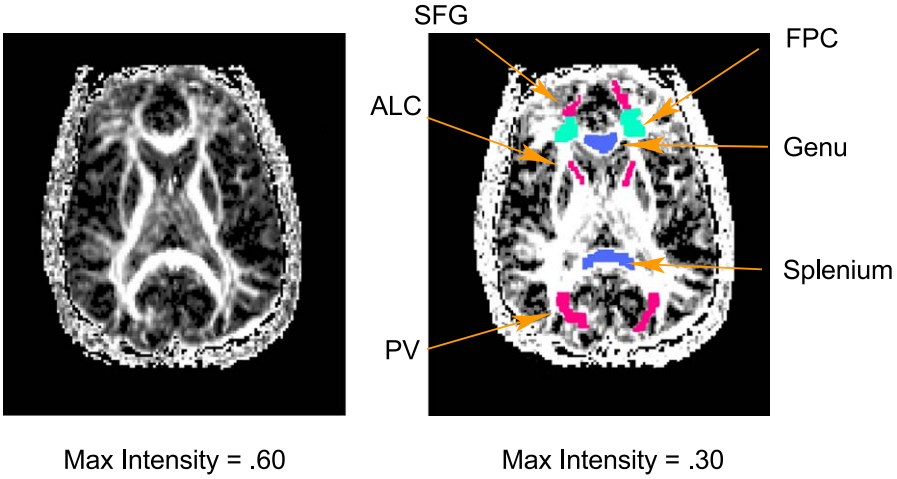

Fig. 1. Example of diffusion tensor image set at normal image intensity (left panel) and at a lower maximum image intensity (right panel), with regions of interest. SFG = superior frontal gyrus; FPC = frontal pericallosal region; ALC = anterior limb of internal capsule; PV = posterior visual region.

callosum (frontal pericallosal ROI), subcortical white matter within the superior frontal gyrus (superior frontal ROI), the anterior limb of the internal capsule, and medial occipital white matter sampled to include the subcortical white matter associated with the cuneus and lingual gyri (posterior visual ROI). Before drawing the regions, operators set the maximum FA image intensity to a low value (0.30) so that all voxels with FA values greater than this criterion were saturated and appeared homogeneously as pure white. This threshold helped minimize the influence of voxels with higher FA values, thus reducing the dependence of ROI definition on FA values. Operators then drew each ROI to include all saturated (white) pixels within the specified neuroanatomical boundaries.

The genu and splenium of the corpus callosum, and the anterior limb of the internal capsule, were clearly visible on the T_1-weighted images, and standard anatomical landmarks were used to define these regions. The frontal pericallosal and superior frontal ROIs were defined on image slices containing the genu of the corpus callosum. The frontal pericallosal ROI targeted the anterior centrum semiovale, where fibers of passage associated with dorsolateral prefrontal cortical areas and related subcortical structures would be expected to course. This ROI was bounded by gray matter at the fundi of the frontal sulci anteriorly and laterally (it did not sample subcortical white matter within frontal gyri), by the anterior horn of the lateral ventricles medially, and by insular cortex posteriorly. To sample from a prefrontal gyrus that could be recognized reliably in every subject, we defined an ROI to include the white matter contained within the superior frontal gyrus. This ROI was drawn generally on the same slices as the frontal pericallosal ROI, comprising the white matter between the latter ROI and the gray matter of the superior frontal gyrus. The posterior visual ROI was defined in slices that contained the thalamus. This ROI targeted the medially located white matter associated with the cuneus and lingual gyrus, with the parieto-occipital sulcus as its anterior boundary.

Two operators drew the genu and splenium, and two other operators drew the other four regions. Each pair of operators drew regions on separate image sets that included both younger and older adults. In addition, each pair of operators drew regions on the relevant DTI slices for the same set of four subjects, including either two or three older adults. This allowed us to assess the consistency with which different operators drew ROIs over the same neuroanatomical regions. To do so, we used custom MATLAB scripts to measure the percentage common voxels among operators (i.e., the degree of spatial overlap), as described by Caviness et al. (1996) and Nieto-Castanon et al. (2003). For the genu and splenium (total of 13 observations), the mean percentage of common voxels ranged from 80% to 89% across the data for the four shared subjects. For the other four regions (total of 66 observations), the mean percentage of common voxels ranged from 71% to 76% across the four shared subjects.

Behavioral task

During the fMRI imaging runs, immediately before diffusion tensor imaging, subjects performed a visual target detection (oddball) task. Stimulus presentation is described in more detail in Madden et al. (in press-b). Briefly, subjects viewed a series of 1080 displays, each of which contained one item, either a standard (a filled square), a target (a filled circle), or a novel (a photograph of an everyday object, e.g., telephone, bicycle). Subjects made the same manual (button press) response to standards (87% of trials) and novels (6% of trials) but pressed a different response button at the appearance of targets (7% of trials). Thus, the task involved responding to two types of infrequent (oddball) events: novels, which required the same response as standards but were of greater visual complexity, and targets, which were similar in visual complexity to standards but required a different response.

Results

Region size and FA

The sizes of the ROIs are presented in Table 1. These data represent the number of voxels in each ROI, obtained for each subject, summed across image slice and hemisphere. We performed an analysis of variance (ANOVA) on these data using age group as a between-subjects variable and the six ROIs as levels of a within-subjects variable. Although the mean number of voxels was numerically lower for older adults than for younger adults in each ROI, the main effect of age group was not significant, $F(1, 29) = 3.05$, $P = 0.091$. The ROI main effect was significant, $F(5, 145) = 96.48$, $P < 0.0001$, as a result of the fact that the mean number of voxels varied across the ROIs. The Age Group × ROI interaction was not significant ($F < 1.0$).

The mean FA values for the regions are presented in Fig. 2. An ANOVA of these data, including age group and ROI as variables, yielded a significant effect of age group, $F(1, 29) = 6.20$, $P < 0.05$, which occurred because mean FA was higher for younger adults ($M = 0.568$, SD = 0.123) than for older adults ($M = 0.550$, SD = 0.130). This age difference remained significant when white matter volume (i.e., region size summed across ROI) was added as a covariate, $F(1, 28) = 6.44$, $P < 0.05$. The ROI main effect was also significant, $F(5, 145) = 661.41$, $P < 0.0001$, reflecting variation in mean FA across the regions. Paired comparisons of the ROIs, using a Bonferroni correction for multiple comparison (critical $t = 2.98$, $P = 0.05$), demonstrated that the ordering of the mean FA values, from highest to lowest, was: splenium, genu, anterior limb of the internal capsule, posterior visual ROI, frontal pericallosal ROI, and superior frontal ROI. All of the paired comparisons among the ROIs were significant, with two exceptions: the posterior visual ROI versus frontal pericallosal ROI, and the frontal pericallosal ROI versus the superior frontal ROI.

The mean FA value was numerically lower for older adults than for younger adults in each of the regions. Simple main effect tests indicated that the age difference was significant at $P < 0.05$ only

Table 1
Region size as a function of age group

Region	Younger adults ($n = 15$)	Older adults ($n = 16$)
Genu	96.67 (40.03)	83.56 (35.37)
Splenium	178.53 (76.46)	167.38 (64.21)
SFG	211.80 (54.67)	196.88 (66.32)
FPC	392.67 (128.19)	310.38 (100.89)
ALC	70.73 (33.27)	63.06 (26.87)
PV	429.27 (137.93)	395.44 (130.39)

Note. Values are mean number of voxels summed across image slice and hemisphere for each subject; standard deviations are in parentheses. SFG = superior frontal gyrus; FPC = frontal pericallosal region; ALC = anterior limb of internal capsule; PV = posterior visual region.

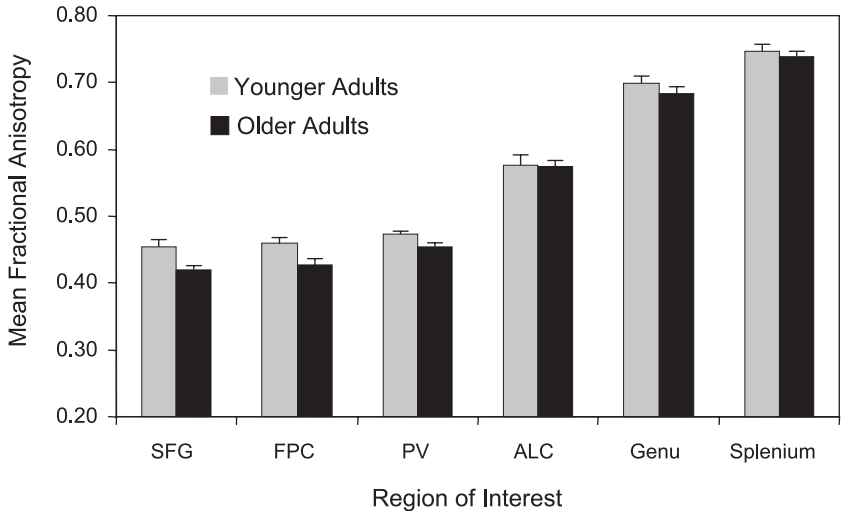

Fig. 2. Mean fractional anisotropy (+SE) as a function of age group and region of interest. SFG = superior frontal gyrus; FPC = frontal pericallosal region; ALC = anterior limb of internal capsule; PV = posterior visual region.

for the frontal pericallosal, superior frontal, and posterior visual ROIs. The Age Group × ROI interaction, however, was not significant, $F(5, 145) = 1.59$, $P = 0.168$.

Relation between RT and FA

To examine the relation between RT in the target detection task and FA, we conducted a stepwise regression analysis in which RT for correct responses was the dependent variable and FA from each of the regions, with the associated age group interaction, was the predictor variable. Because the RTs for the three task conditions (standards, targets, and novels) were positively correlated (r = 0.73–0.90 for each age group), we used the mean RT across the three task conditions as the dependent variable. Differences in performance among the task conditions are discussed by Madden et al. (in press-b). Although accuracy was comparable for the two age groups (older adults' M = 94%, SD = 0.054; younger adults' M = 96%, SD = 0.028), mean RT was significantly higher for older adults (M = 470 ms, SD = 66) than for younger adults (M = 413 ms, SD = 57), $t(30) = 2.60$, $P < 0.05$. The age group variable was forced into the regression model at the first step, and other predictor variables entered the model sequentially from the strength of their relation to the dependent variable (mean RT), covaried for the effects of variables entered previously. Model estimation ended when no other variable met the criterion for entry ($P = 0.15$).

Table 2
Stepwise regression of response time using regional FA values as predictors

Variable	t	P	Beta	r^2	Model R^2
Age group	−0.14	0.894	−0.488	0.163	
Splenium × Age group	2.85	0.008	9.280	0.100	
ALC × Age group	−3.13	0.004	−8.411	0.111	
ALC	−2.20	0.037	−0.367	0.099	0.472

Note. Response time is the mean of median response time for the three task conditions. FA = fractional anisotropy; ALC = anterior limb of internal capsule. The criterion for entry into the model was set at $P = 0.15$; $t = t$ value for variable at final step; P = probability level for variable at final step; Beta = standardized estimate of regression coefficient; r^2 = variance accounted for by individual variable at entry into the model; Model R^2 = variance accounted for by all variables at final step.

The final model, presented in Table 2, accounted for 47% of the variance in RT, $F(4, 26) = 5.81$, $P < 0.01$. The FA for the anterior limb of the internal capsule was a significant predictor, as was the age group interaction effects for the anterior limb of the internal capsule and splenium. These latter two effects indicate that the relation between FA and RT differed as a function of age group in these two regions. We therefore examined the correlation between FA and RT for these two regions separately. The results are presented in Fig. 3. For the anterior limb of the internal capsule, the correlation between FA and RT was significant for older adults but not for younger adults, whereas for the splenium, the correlation was significant for younger adults but not for older adults. For both regions, the correlations were negative, indicating that individuals with lower FA values exhibited slower responses in the visual target detection task. For the anterior limb of the internal capsule, FA accounted for 30% of the variance in the older adults' RTs. For the splenium, FA accounted for 29% of the variance in the younger adults' RTs.

Discussion

The results of this investigation lead to three conclusions regarding the functional neuroanatomy of cerebral white matter. First, the structural composition of white matter varies across regions of the brain. Consistent with previous studies (Pfefferbaum et al., 2000; Shimony et al., 1999), we demonstrated significantly higher FA values for the genu and splenium of the corpus callosum than for white matter ROIs located outside of the callosum (Fig. 2), which reflects the anatomical structure of the callosum in densely packed, homogeneously oriented fiber tracts. We also found that, within the callosum, FA for the splenium was significantly higher than for the genu. Chepuri et al. (2002) also reported this pattern and proposed that several variables could be responsible, including a tighter packing of axons, less permeable myelin sheaths, and fewer obliquely oriented axons, in the splenium relative to the genu.

Secondly, an age-related decline in white matter integrity is evident for healthy older adults who are without an atypical degree of cortical atrophy or number of white matter hyperintensities in the accompanying T_2-weighted images. This conclusion is based on the

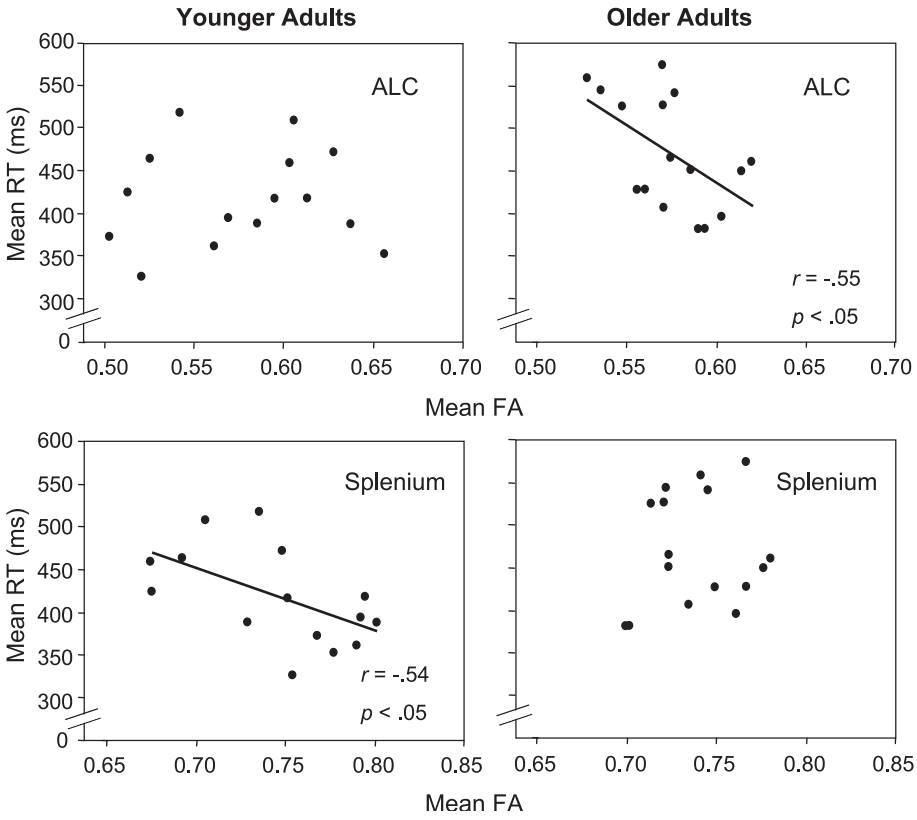

Fig. 3. Correlation between mean response time (RT) and mean fractional anisotropy (FA) for the anterior limb of the internal capsule (ALC) and splenium as a function of age group. Line of best fit is presented for significant correlations.

significant age group main effect in the ANOVA of the FA values. The age difference in white matter volume was not significant, and the age-related decline in FA remained significant when covaried for white matter volume. This result confirmed our initial prediction and is similar to findings of O'Sullivan et al. (2001), Pfefferbaum et al. (2000), and Sullivan et al. (2001), who also reported an age-related decline in FA in healthy older adults. O'Sullivan et al. emphasized that the participants in their study did not exhibit diffuse hyperintensities in T_2-weighted images (see also Engelter et al., 2000). Thus, the age-related decline in FA is likely to reflect microstructural changes in the cerebral white matter, such as a frank loss of myelinated axons (Marner et al., 2003) and more subtle disruptions of myelin sheaths and the cytoskeletal components of axons (Peters and Sethares, 2002), which are not evident in T_1- and T_2-weighed images.

Our data differ from those of O'Sullivan et al. (2001), Pfefferbaum et al. (2000), and Sullivan et al. (2001), however, in that we did not observe a differential age-related decline in FA for the more anterior regions of the brain, which is a trend that all three of the previous studies reported. Although the ANOVA of our FA values yielded significant main effects for age group and ROI, in contrast to our initial prediction, there was no interaction among these variables, indicating that the age-related decline in white matter integrity is widely distributed throughout the brain rather than regionally specific. There is a trend evident in Fig. 2 for the age-related decline in FA to be more pronounced in those regions with the lower values of FA overall, which included the posterior visual ROI as well as more anterior regions (the frontal pericallosal ROI and white matter of the superior frontal gyrus). Thus, an Age Group × ROI interaction may be detected when statistical power is higher. It is also possible that there is an overall age-related decline in FA, which is magnified to some degree in those regions with relatively lower FA. Resnick et al. (2003) made a similar point regarding age-related volumetric decline, which they proposed is regionally specific for gray matter but widespread throughout the brain for white matter.

Thirdly, the present results demonstrate that the relation between FA and behavioral performance differs for younger and older adults. The present experiment provides the first direct comparison between younger and older adults in the relation between the functional integrity of cerebral white matter and behavioral performance. In the regression model for predicting mean RT in the oddball task (Table 2), there was a correlation between FA and RT for both the splenium and the anterior limb of the internal capsule that varied significantly as a function of age group. As is evident in Fig. 3, FA in the splenium was a predictor of RT for younger adults but not for older adults, whereas FA in the anterior limb of the internal capsule was a predictor of RT for older adults but not for younger adults. Both of the correlations were negative, suggesting that lower levels of white matter integrity (i.e., FA) are associated with slower responding (i.e., higher RT), consistent with the effect of decreased myelination on axonal conduction velocity (Felts et al., 1997; McDonald and Sears, 1970).

The data for the splenium are similar to the Sullivan et al. (2001) finding of a relation between splenium FA and perceptual-motor performance. The splenium is the conduit for the interhemispheric transfer of visual information, and the relation between splenium FA and RT suggests that, for younger adults, the efficiency of visual

sensory processing is a prominent influence on their performance in this visual target detection task. The data for the anterior limb of the internal capsule were somewhat unexpected, given the O'Sullivan et al. (2001) finding that FA in prefrontal ROIs correlated with a neuropsychological measure of attention. Our findings are not completely disparate from those of O'Sullivan et al. because the anterior limb of the internal capsule contains the axons of thalamic neurons in the mediodorsal and anterior nuclear complex that project to the prefrontal cortex, as well as the axons of prefrontal cortical neurons that provide feedback to the associated thalamic nuclei (Behrens et al., 2003). Furthermore, the anterior limb of the internal capsule should also contain the axons of prefrontal neurons that project into the anterior striatum, which envelopes this portion of the capsule (Ferry et al., 2000).

The fact that the ROI in the anterior limb of the internal capsule, rather than our other prefrontal-related ROIs, captured the relationship between FA and behavioral performance (i.e., RT) suggests that older adults' performance in this task is influenced more by the integrity of the white matter circuits connecting the prefrontal cortex and subcortical structures (e.g., anterior striatum and the mediodorsal thalamus), than by the integrity of the white matter circuits within the prefrontal cortex itself. Corticostriatal circuits have been implicated in attentional processing in the context of visuomotor control and response regulation (Graybiel, 2000; Huettel et al., 2002; Poldrack et al., 1999). The older adults' correlation between FA and RT, for the internal capsule ROI, suggests an age-related increase in the attentional control of responses in this task mediated by prefrontal corticostriatal circuits. More generally, the results suggest that those regions exhibiting an age difference in the relation between FA and behavior do not necessarily exhibit an age-related decline in FA.

The present DTI results complement the earlier findings regarding fMRI activation in these same samples of younger and older adults (Madden et al., in press-b). The previous report noted that activation of extrastriate cortical regions was greater for younger adults than for older adults, whereas the activation of deep gray matter nuclei was greater for older adults than for younger adults. In addition, the fMRI analyses indicated that activation of deep gray matter regions was the best predictor of older adults' target detection RT, whereas prefrontal activation was the best predictor for younger adults. The present analyses demonstrated that, for both age groups, the white matter ROI that was the best predictor of RT was near the cortical region exhibiting the age-related increase in activation: the splenium and extrastriate regions in the case of younger adults, and the anterior limb of the internal capsule and deep gray matter nuclei in the case of older adults. The combined results from the fMRI and DTI data suggest that older adults' performance in the target detection task depends on both cortical activation and white matter integrity within corticostriatal circuits. For younger adults, in contrast, performance depends more directly on the white matter integrity of posterior regions mediating visual processing, although there is an additional influence of prefrontal activation, perhaps as the result of top-down attentional control (Hopfinger et al., 2000; Kastner and Ungerleider, 2000). The age-related increase in the role of corticostriatal regions may be a compensatory response to a decline in the efficiency of visual cortical processing.

In summary, these findings from DTI confirm previous results regarding white matter integrity and provide new information regarding age-related change in this aspect of the brain structure. We confirmed the variation in FA across brain regions observed by previous researchers in terms of both higher FA within the corpus callosum than in other ROIs and higher FA in the splenium of the corpus callosum than in the genu. We also replicated the age-related decline in FA that has been observed previously, although the present results suggest an age effect that is general throughout the brain rather than regionally specific. Finally, the present analyses provide the first test of age differences in the relation between FA and behavioral performance. The integrity of cerebral white matter as indexed by FA was correlated significantly with RT for both younger and older adults. An age-related change in this relation was evident, however, in that the best predictor of RT was FA in the splenium for younger adults but was FA in the anterior limb of the internal capsule for older adults. This pattern is consistent with the task-related cortical activation observed for these same individuals, as obtained from fMRI, and suggests an age-related increase in the attentional control of responses mediated by corticostriatal or corticothalamic circuits. In developing a more complete account of age-related changes in brain function, it will consequently be valuable to consider the role of white matter integrity as well as task-specific cortical activation.

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