Published in final edited form as:

Neurobiol Aging. 2010 March ; 31(3): 464. doi:10.1016/j.neurobiolaging.2008.04.007.

Quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging:

Relations to timed performance

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Abstract

The integrity of white matter, as measured in vivo with diffusion tensor imaging (DTI), is disrupted in normal aging. A current consensus is that in adults advancing age affects anterior brain regions disproportionately more than posterior regions; however, the mainstay of studies supporting this anterior-posterior gradient is based primarily on measures of the corpus callosum. Using our quantitative fiber tracking approach, we assessed fiber tract integrity of samples of major white matter cortical, subcortical, interhemispheric, and cerebellar systems (11 bilateral and 2 callosal) on DTI data collected at 1.5 T magnet strength. Participants were 55 men (age 20-78 years) and 65 women (age 28-81 years), deemed healthy and cognitively intact following interview and behavioral testing. Fiber integrity was measured as orientational diffusion coherence (fractional anisotropy, FA) and magnitude of diffusion, which was quantified separately for longitudinal diffusivity (λ_L), an index of axonal length or number, and transverse diffusivity (λ_T), an index of myelin integrity. Aging effects were more evident in diffusivity than FA measures. Men and women, examined separately, showed similar age-related increases in longitudinal and transverse diffusivity in fibers of the internal and external capsules bilaterally and the fornix. FA was lower and diffusivity higher in anterior than posterior fibers of regional paired comparisons (genu versus splenium and frontal versus occipital forceps). Diffusivity with older age was generally greater or FA lower in the superior than inferior fiber systems (longitudinal fasciculi, cingulate bundles), with little to no evidence for age-related degradation in pontine or cerebellar systems. The most striking sex difference emerged for the corpus callosum, for which men showed significant decline in FA and increase in longitudinal and transverse diffusivity in the genu but not splenium. By contrast, in women the age effect was present in both callosal regions, albeit modestly more so in the genu than splenium. Functional meaningfulness of these age-related differences was supported by significant correlations between DTI signs of white matter degradation and poorer performance on cognitive or motor tests. This survey of multiple fiber systems throughout the brain revealed a differential pattern of age's effect on regional FA and diffusivity and suggests mechanisms of functional degradation, attributed at least in part to compromised fiber microstructure affecting myelin and axonal morphology.

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Disclosure statement: (a) There are no actual or potential conflicts of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the work submitted that could inappropriately influence (bias) their work. No author's institution has contracts relating to this research through which it or any other organization may stand to gain financially now or in the future. There are no other agreements of authors or their institutions that could be seen as involving a financial interest in this work. (b) Appropriate approval and procedures were used concerning human subjects and obtained prior to obtaining data.

Keywords

Brain; Aging; DTI; White matter; Fiber tracking; Diffusion

1. Introduction

With the advent of diffusion tensor imaging (DTI) in human applications, novel opportunities have emerged for in vivo characterization of qualitative features of the brain's white matter microstructure, such as fiber organization and myelin development. DTI studies have focused on examination of white matter because of the modality's sensitivity to the detection of tightly packed fibers in locally parallel orientation (Basser, 1995; Moseley et al., 1990), typifying white matter commissures, bundles, and fasciculi of the brain. DTI has revealed evidence of microstructural disruption of brain white matter in healthy adults as they age, even in regions appearing normal on conventional volume imaging (for reviews, Minati et al., 2007; Moseley, 2003; Pfefferbaum and Sullivan, 2005a; Sullivan and Pfefferbaum, 2003, 2007; Wozniak and Lim, 2006).

As stochastic descriptions of the movement of water molecules entrapped in fibers, DTI's metrics provide a quantitative method for characterizing the integrity of different features of white matter. The two principal DTI metrics are fractional anisotropy (FA), which is a measure of degree to which water diffusion has a common orientation, and diffusivity, which is a measure of the magnitude of water diffusion (Pierpaoli and Basser, 1996). Highly myelinated fiber bundles with a common orientation will have high anisotropy (usually measured as fractional anisotropy, FA). Breakdown of the myelin sheath, for example, with aging or disease can result in increases in extracellular fluid and transverse diffusivity (Song et al., 2002, 2005). Axonal damage has been associated with decreased FA and a disproportionate increase in longitudinal relative to transverse diffusivity (Song et al., 2003).

In general, studies on differences across the adult age range have quantified white matter integrity in focal brain regions and report average DTI metrics within those regions. Another analysis approach involves voxel-based morphometry, which attempts to identify selective regions throughout the brain where older groups differ from younger ones (reviewed by Sullivan and Pfefferbaum (2007)). Regardless of approach, the general consensus is that with advancing age, anisotropy in white matter declines and is accompanied by an increase in diffusivity (Chun et al., 2000; Head et al., 2004; Madden et al., 2004; Nusbaum et al., 2001; O'Sullivan et al., 2001; Pfefferbaum and Sullivan, 2003; Pfefferbaum et al., 2000b; Salat et al., 2005; Stebbins et al., 2001; but see Chepuri et al., 2002; Helenius et al., 2002). The age effects are regionally diverse and typically show an anterior-posterior gradient of anisotropy decline (Ardekani et al., 2007; Bhagat and Beaulieu, 2004; Bucur et al., 2007; Foong et al., 2000; Grieve et al., 2007; Head et al., 2004; Hsu et al., 2008; Kochunov et al., 2007; Madden et al., 2004, 2007; Nusbaum et al., 2001; O'Sullivan et al., 2001; Pfefferbaum et al., 2000b, 2005; Pfefferbaum and Sullivan, 2003; Salat et al., 2005; Sullivan et al., 2001; Takahashi et al., 2004; Yoon et al., 2007) and diffusivity rise (Chen et al., 2001; Engelter et al., 2000; Head et al., 2004; Helenius et al., 2002; Hsu et al., 2008; Naganawa et al., 2003; Pfefferbaum et al., 2005; Pfefferbaum and Sullivan, 2003) with age that was confirmed in a monkey model of aging (Makris et al., 2007). With a few exceptions (Hsu et al., 2008), this aging pattern is similar in men and women (Sullivan et al., 2001). A study of elderly twin men revealed that anterior regions of callosal white matter are under proportionately greater environmental than genetic control than are posterior regions (Pfefferbaum et al., 2001). Taken together, these studies indicate the relevance in comparing DTI metrics in multiple white matter fiber systems, separately in men and women, to reveal a complete picture of the pattern of sparing and loss of tissue integrity related to normal aging.

In addition to assessment of regional samples of white matter, DTI can provide visual depictions of white matter fiber systems (Lehericy et al., 2004; Stieltjes et al., 2001; Xu et al., 2002) and can be used to quantify FA and diffusivity along the length of identified fiber bundles (Gerig et al., 2005; Sullivan et al., 2006). This approach, referred to as quantitative fiber tracking, does not actually identify anatomically specific fibers or fiber bundles as detected histologically. Rather, it is a statistical representation of the voxel-to-voxel coherence of DTI-detectable water diffusion in white matter that is, nonetheless, increasingly being shown as representative of the underlying anatomy (Schmahmann et al., 2007). Whereas FA is a measure of the orientation of diffusion derived from the tensor's eigenvectors on an intravoxel basis, coherence-based measures, including tractography, provide an orientational measure on an intervoxel basis, that is, the degree to which the diffusion orientation of a voxel is similar to its neighbors (Pfefferbaum et al., 2000a), and serves the conceptual basis for quantitative fiber tracking (Fillard and Gerig, 2003; Gerig et al., 2005). Although the connectivity and coherence between different brain regions on vector and fiber tracking maps are readily apparent on visual inspection, these displays are not commonly quantified.

Quantitative fiber tracking has recently been used to characterize the developing brain in normal children and premature neonates (Barnea-Goraly et al., 2005; Gilmore et al., 2007), yet few studies have applied it to normal aging in adulthood. Recently, we observed lower FA, higher diffusivity, and fewer imaging-defined fibers in the anterior but not posterior segments of the corpus callosum in 10 elderly compared with 10 young, healthy men and women (Sullivan et al., 2006). Also observed were correlations between callosal fiber tracking metrics and performance on the Stroop color-word reading test. In a later study, which examined only the genu and splenium and based on DTI data from the 120 healthy adults in the current report, we observed a decline in FA and increase in diffusivity with age over a six-decade span that was greater in the genu than splenium of the corpus callosum (Pfefferbaum et al., 2007). A study focused on the fornix and cingulum, two fiber bundles connecting nodes of the limbic system, found age-related decline in FA and number of fibers and increase in diffusivity in the fornix but not the cingulum in 38 healthy individuals, age 18-88 years (Stadlbauer et al., 2008).

The functional ramifications of the DTI metrics have been regularly verified with observations of correlations between regionally-specific low FA or high diffusivity and poor cognitive (Bucur et al., 2007; Charlton et al., 2007; Grieve et al., 2007; Madden et al., 2007; O'Sullivan et al., 2001; Shenkin et al., 2003; Stebbins et al., 2001; Sullivan et al., 2006) or motor (Sullivan et al., 2001) test performance in humans and also a monkey model of aging (Makris et al., 2007). A recent study reported that decreased frontostriatal transverse diffusivity, suggestive of increasing myelination, correlated with speeded reaction time in a cognitive control (GO/NOGO) task engaged in by 21 individuals, age 7-31 years (Liston et al., 2006) and lending functional relevance to fiber tracking methods.

The purpose of the present analysis was to examine in a large group of healthy men and women, spanning the adult age range, the effects of age and sex on multiple major fiber systems throughout the brain and brain stem. Fiber bundles examined were major bilateral tracts coursing through limbic (fornix, superior and inferior cingulum) and striatal (internal and external capsules) regions; supratentorial tracts (frontal and occipital forceps and superior and inferior longitudinal fasciculi); and infratentorial tracts (pontocerebellar and cerebellar hemisphere bundles). Also measured were interhemispheric connections, which were six anatomically-considered sectors the corpus callosum (after Pandya and Seltzer, 1986). We then tested the functional relevance of the DTI metrics by correlating them with tasks assessing cognitive and motor speed.

2. Methods

2.1. Participants

Participants were 120 healthy adults (55 men and 65 women) age 20-81 years, drawn from multiple recruitment efforts for ongoing longitudinal studies in our laboratory. All participants gave signed informed consent to participate in these laboratory studies and for continued use of the acquired data in follow-up analyses. DTI data based on the corpus callosum genu and splenium have appeared in our previous report (Pfefferbaum et al., 2007); here we expand the analysis by segmenting the corpus callosum into six anatomical regions of interest and add 21 separate fiber tracks widely distributed across the brain.

All participants underwent a series of structured interviews designed to characterize pertinent medical and psychiatric information. Clinical psychologists administered the Structured Clinical Interview for DSM-IV (First et al., 1998) to identify patients who met exclusionary criteria for lifetime schizophrenia or bipolar disorder, alcohol dependence or abuse, or non-alcohol substance dependence or abuse, and a structured history of alcohol consumption (Pfefferbaum et al., 1992; Skinner, 1982; Skinner and Sheu, 1982) to exclude participants whose quantity and frequency of drinking was in the hazardous range (4 drinks for women and 5 drinks for men per day for 30 consecutive days for any period of life). General cognitive status was assessed with the National Adult Reading Test (NART), which yields an intelligence quotient (IQ) with an average score of 100 (Nelson, 1982). Before analyzing the brain data, four research clinicians reviewed each participant's performance on each test of our standard clinical assessment. By concurrence, two women failed to meet study criteria for minimum achievement on standard tests of current cognitive status (Mini-Mental State Examination, Dementia Rating Scale, or the National Adult Reading Test). One man reported excessive alcohol drinking, and another man was found to have insulin dependent diabetes. Clinical review of the structural images revealed abnormalities in two additional men: one had a large vessel in a cerebellar hemisphere and the other had ventriculomegaly. The image quality of one woman was inadequate for quantitative analysis.

Additional interviews and examinations assessed handedness (Crovitz and Zener, 1962); socioeconomic status scale (SES), a two-factor scale based on education and occupation (Hollingshead and Redlich, 1958); and body mass index (height cm/weight kg²), an index of nutritional status. Means $\pm$ S.D. or frequency counts of these and other demographic values are presented in Table 1.

2.2. Imaging acquisition protocol

An initial spin-echo midsagittal localizer scan (13 contiguous, 4 mm thick, slices; TR/TE = 300/14 ms; matrix = 256 $\times$ 256, FOV = 24 cm) was used to identify landmarks for prescription of all subsequent coronal scans. The superior/inferior (S/I) center position of the coronal acquisitions was chosen as the most inferior extent of the midpoint of the isthmus of the corpus callosum, and the extent of the prescription in the anterior-posterior (A-P) orientation subtended the entire brain for all subjects. A coronal structural sequence used in this analysis was acquired with a 24 cm field of view: a dual-echo fast spin echo (FSE) sequence (47 contiguous, 4 mm thick slices; TR/TE1/TE2 = 7500/14/98 ms; matrix = 256 $\times$ 192). All images were zero-filled to 256 $\times$ 256 pixels in-plane by the scanner reconstruction software.

DTI was performed in the coronal plane with the same slice location parameters as the dual-echo FSE, using a single shot spin-echo echo-planar imaging technique with a 24 cm field of view (47 contiguous, 4 mm thick slices, TR/TE = 10,000/103 ms, matrix = 128 $\times$ 128, in-plane resolution = 1.875 mm²). The amplitude of the diffusion-sensitizing gradients was 1.46 Gauss/cm with 32 ms duration and 38 ms separation, resulting in a *b*-value of 860 s/mm². Diffusion

was measured along six non-collinear directions with alternating signs to minimize the need to account for cross-terms between imaging and diffusion gradients (Neeman et al., 1991). For each gradient direction, six images were acquired and averaged. For each slice, six images with no diffusion weighting ($b = 0 \text{ s/mm}^2$) were also acquired.

2.3. Image processing

The 47-slice, dual-echo FSE images were passed through the FSL brain extraction tool (BET) (Smith, 2002) to extract the brain and exclude dura, skull, scalp and other non-brain tissue. Eddy-current-induced image distortions due to the large diffusion encoding gradients cause spatial distortions in the diffusion-weighted DTI images that vary from one diffusion direction to the next. These artifacts were minimized by alignment with an average made of all 12 diffusion-weighted images with a 2-D 6-parameter affine correction on a slice-by-slice basis (Woods et al., 1998) to unwarp the eddy-current distortions in the diffusion-weighted DTI images for each direction. After eddy-current correction, the DTI data were aligned with the FSE data with a non-linear 3D warp (3rd order polynomial), which provided in-plane and through-plane alignment.

Using the averaged images with $b = 0$ and $b = 860 \text{ s/mm}^2$, six maps of the apparent diffusion coefficient (ADC) were calculated, each being a sum of three elements of the diffusion tensor. Solving the six equations with respect to ADC_{xx} , ADC_{xy} , etc. yielded the elements of the diffusion tensor. The diffusion tensor was then diagonalized, yielding eigenvalues λ_1 , λ_2 , λ_3 as well as eigenvectors that define the predominant diffusion orientations. Based on the eigenvalues from the tensor, fractional anisotropy (FA) was calculated on a voxel-by-voxel basis. The trace of the tensor matrix (the sum of the eigenvalues) and diffusivity expressed as apparent diffusion coefficient (ADC, the mean of the eigenvalues), like FA, were calculated on a voxel-by-voxel basis. Thus, each diffusion-weighted study was initially reduced to a set of three images for each slice (FA, diffusivity, and $b = 0$) to be used for analysis in conjunction with the anatomical images. FA was expressed as a percent, and ADC was expressed in units of $10^{-6} \text{ mm}^2/\text{s}$.

2.4. Warping to common coordinates

To achieve common anatomical coordinates across subjects, a group-average FA data set was constructed from the FA data from all 120 subjects with group-wise affine registration (Learned-Miller, 2006) followed by an iterative non-rigid averaging (Rohlfing et al., 2001; Rohlfing and Maurer, 2003).

2.5. Identification of white matter regions of interest

On a midsagittal slice of a group average FA image the corpus callosum was manually outlined and divided into six sectors from anterior to posterior based on the scheme of Pandya and Seltzer (1986). The fornix was also identified in the midline at its most anterior extent. Bilateral tract sources were identified with the following anterior-posterior locations: internal capsule at the knee of the internal capsule; external capsule at the knee of the internal capsule; frontal forceps 17 mm anterior to the genu; occipital forceps 15 mm posterior to the splenium; superior cingulate at anterior margin of pons; inferior cingulate at mid-temporal stem; superior longitudinal fasciculus at posterior pons; inferior longitudinal fasciculus at mid-temporal stem; pontocerebellar tract at mid-pons; and cerebellar hemispheres at mid-cerebellum (Fig. 1).

2.6. Fiber tracking

The fiber tracking routine (Mori et al., 1999; Xu et al., 2002), distributed by G. Gerig (www.cs.unc.edu), used a target-source convention that restricted the fibers to ones originating in source voxels and passing through target voxels. In common space the corpus callosum

target was expanded to 5.625 mm wide and each landmark was dilated with a morphological operator to produce a 9.375 mm cube as the fiber tracking target. Sources were defined as 5.625 mm thick planes: (a) 9.375 mm bilateral to the corpus callosum subtending the entire anterior-posterior extent of the brain; (b) 5.625 mm anterior and 5.625 mm posterior to the frontal and occipital forceps, superior and inferior cingulate, superior and inferior longitudinal fasciculi; (c) superior and inferior to the internal and external capsules. A cube surrounding the fornix, pontocerebellar tracts and cerebellar hemispheres served as sources for these targets. For each subject the targets and sources were mapped to that subject's native image space with a numerical inversion of the transformation to common space for fiber tracking. To compensate for any registration inaccuracy and ensure proper localization for each target, the FA image was multiplied by the eigenvector value for the orientation orthogonal to the expected tract orientation (e.g., the z-axis for the internal capsule) and then a search was performed within a $3 \times 3 \times 3$ voxel space allowing the target voxel to move ± 1 , 1.875 mm voxel in any direction. The targets, sources, and tensor images in native space were passed to the fiber tracking routine, the output of which is a 3D graphical model of the fiber paths, a table of locations and DTI metrics for each voxel in each fiber. Tracking parameters included white matter extraction threshold (minimum FA) of .17, fiber tracking threshold of .125, and maximum voxel-to-voxel coherence minimum transition smoothness threshold of .80 ($\sim 37^\circ$ maximum deviation between voxels), with essentially no limit on the number of fibers. Fiber length minimum (11.25 mm) and fiber length maximum (45 mm) assured that only the data reflecting the mid-region of the fiber bundle at the target location was used. The FA, ADC, and λ_1 , λ_2 , and λ_3 of each voxel comprising each fiber, for all fibers, were determined. We refer hereafter to the group of fibers coursing through each target region as "fiber bundles." The mean FA, ADC, longitudinal diffusivity ($\lambda_L = \lambda_1$) and transverse diffusivity ($\lambda_T = [\lambda_2 + \lambda_3]/2$) for each fiber bundle were the units of analysis. After fiber detection the fiber locations were transformed back to common coordinates for display (e.g., Fig. 4).

2.7. Neuropsychological tests

The test used to question whether the regional DTI metrics had apparent functional significance involved speed motor or cognitive skills or postural stability. Higher scores indicated better performance for all functional measures. The Fine Finger Movement Test required subjects to turn a knurled pin with their forefinger and thumb, unimanually and then bimanually (Corkin et al., 1986). Three, 30-s trials for each condition were administered. The score was the number of rotations made per condition; for data reduction, the mean score of the four conditions was used in correlational analysis with the DTI metrics. The Digit Symbol Test of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) required subjects to fill in a grid of boxes with a symbol that was associated with single-digit numbers as quickly as possible; the score was the total number of correct boxes completed in 90 s. Two measures of an ataxia battery (Fregly et al., 1972) were analyzed, each performed with eyes closed: (1) stand heel-to-toe with arms folded across the chest for two, 60 s trials; (2) stand on one foot at a time for two, 30 s trials and scores for correlational analysis were expressed as the mean of left and right leg scores.

2.8. Statistical analysis

The effects of age and sex were tested for each fiber tracking region and for each DTI metric (FA, MD, λ_L , and λ_T) with a two-step procedure. For the first set of analyses, we used repeated measures analysis of variance (ANOVA) to test for sex differences by hemisphere for each bilateral fiber bundle, with the objective of averaging left and right hemisphere measures for regions not showing significant sex-by-hemisphere interactions. Such averages would halve the number of potential analyses required to test for age effects. For the six segments of the corpus callosum, we used repeated measures ANOVA (sex-by-six segments) to test for sex and interaction effects. Follow-up analyses used *t*-tests. For the second set of analyses, we

focused on age and sex effects. Accordingly, relations between variables were tested with Pearson product-moment correlations (r), with the prediction that lower FA and higher diffusivity would be correlated with older age and poorer test performance. Differences between correlations for men versus women were assessed with slopes tests. In a set of analysis, we examined whether regional DTI metrics were predictive of test performance and applied family-wise Bonferroni correction for 17 comparisons (11 bilateral and 6 commissural measures), for which p -values $\leq .006$ were considered significant.

3. Results

3.1. Effects of sex and hemisphere on normal variation in bilateral fiber systems

Repeated measures ANOVAs examined laterality differences between men and women in the 10 bilateral fiber systems and sought sex-by-hemisphere interactions. ANOVA statistics are presented in Table 2. None of the interactions met statistical significance with correction for multiple comparisons (family-wise Bonferroni correction for 10 comparisons for $\alpha = .05$, $p = .005$). Only two regional group effects were significant after multiple test correction: frontal forceps FA was greater in the men than the women ($p = .0026$), and the cerebellar hemisphere diffusivity measures were greater in the women than men (ADC $p = .0001$, λL $p = .0001$, and λT $p = .0002$). Given the absence of systematic sex-by-hemisphere interactions in the bilateral fiber systems, subsequent analyses used the mean FA or diffusivity of the left and right hemispheres, as presented in Fig. 2. The fornix, which was not divided bilaterally, showed marginal sex differences in FA, which was 3.8% greater in men than women ($t(118) = 2.165$, $p = .0324$) and no sex differences in ADC ($t(118) = .733$, $p = .4648$), λL ($t(118) = .413$, $p = .6804$), or λT ($t(118) = .848$, $p = .3979$).

3.2. Effects of sex and sector on normal variation in callosal fiber sectors

Repeated measures ANOVAs examined differences between men and women across the six callosal fiber sectors for each DTI metric. Mean $\pm$ S.E. for each measure by sex are presented in Fig. 3. For FA, although the group effect was not significant ($F(1,118) = .575$, $p = .4498$), the effects of region ($F(5,590) = 260.615$, $p = .0001$) and the sex-by-region interaction were significant ($F(5,590) = 4.984$, $p = .0002$). The regional effect reflected an anterior to posterior gradient, with lower FA anteriorly than posteriorly. Follow-up t -tests indicated that women had significantly lower FA than the men by 2.8% in the splenium, the most posterior sector ($t(118) = 2.889$, $p = .0046$). ADC showed a region effect ($F(5,590) = 59.355$, $p = .0001$) and a sex-by-region interaction ($F(5,590) = 3.029$, $p = .0104$), indicating greater diffusivity in the anterior sectors of the women, likely attributable to presence of more older women than men in the samples. For λL , only the region effect was significant ($F(5,590) = 18.528$, $p = .0001$), where diffusivity tended to be higher in the posterior than anterior sectors; neither the group effect ($F(1,118) = 1.578$, $p = .2115$) nor interaction was significant ($F(5,590) = 1.172$, $p = .3215$). λT showed a region effect ($F(5,590) = 155.109$, $p = .0001$) and a sex-by-region interaction ($F(5,590) = 4.211$, $p = .0009$) but not a group effect ($F(1,118) = .023$, $p = .8807$); regional diffusivity of λT indicated higher transverse diffusivity anteriorly than posteriorly.

3.3. Effects of age and sex on normal variation in regional DTI metrics: bilateral fibers

Fig. 4 displays the scatterplots, regression lines, correlation coefficients, and p -values of the regional FA and diffusivity correlations with age separately for men and women. Tests of differences between regression slopes of men versus women for each bilateral fiber system failed to identify differences in the relationship between any DTI metric and age. Decreases in FA with age were typically modest, with the most prominent age effect in the frontal forceps.

In general, the diffusivity measures complemented FA by showing increases in diffusivity with age that were similar in men and women; however, the diffusivity-age correlations were more

pronounced than those observed in FA. The three diffusivity measures in the fornix, internal and external capsules, and superior longitudinal fasciculi were greater in older than younger men and women. Neither the pontocerebellar tracts nor the cerebellar hemisphere fibers showed significant positive slopes with age.

3.4. Effects of age and sex on normal variation in callosal fiber systems

Fig. 5 displays the scatterplots, regression lines, correlation coefficients, and p -values of the regional callosal FA and diffusivity correlations with age separately for the men and women. In general, the correlations between DTI metrics and age were greater for the women than the men. In the women, FA declined significantly with age in five of the six callosal sectors; the exception was the sensory-motor sector. Although regressions of the men between FA and age were negative, the FA decline was significant only in the parietal and temporal sectors. For diffusivity, ADC, λL , and λT measures were significantly higher ($p \leq .05$) with older age in women in all six callosal sectors. For men, diffusivity increase with age was significant for ADC in all sectors except the splenium, for λL in the anterior four sectors (genu, premotor, sensory-motor, and parietal), and for λT in the genu, premotor, parietal, and temporal sectors. Tests between regression slopes identified a significant difference for λT ($p = .045$) and a trend for λL of the splenium ($p = .0666$), indicating that the increases in diffusivity with age were greater in women and men.

3.5. Test performance associations with regional fiber bundle FA and diffusivity

We examined whether regional DTI metrics were predictive of test performance. Applying family-wise Bonferroni correction for 17 comparisons (11 bilateral and 6 commissural measures) with predicted directions per brain measure, p -values $\leq .006$ were considered significant. All correlations and p -values are presented in Table 3. Fine finger movement scores correlated significantly with three lateral fiber bundles (internal capsules, external capsules, and cerebellar hemisphere bundles) and no commissural fiber tract metrics. Two multiple regression analyses tested whether the internal or external capsule FA and then λT were independent predictors of fine finger movement scores (Fig. 6). Unlike measures of the external capsule (FA $p = .71041$; λT $p = .7061$), the internal capsule FA ($p = .007$) and λT ($p = .0358$) made significant, independent contributions to prediction of performance.

Digit Symbol scores correlated with FA or diffusivity in several lateral fiber bundles (fornix, internal and external capsules, frontal forceps, superior longitudinal fasciculus) and in three of the six callosal sectors (genu, parietal, temporal). The most robust correlations were between Digit Symbol scores and the temporal callosal sector (Fig. 6). For ataxia, higher scores correlated with higher FA in the frontal forceps (Fig. 6).

Because each of the performance measures correlated negatively with age, we used multiple regression analysis to test whether the DTI-performance correlations were mediated by age alone or alternatively, could be attributable to local fiber integrity. In no case did age make an independent contribution to the relationship with fine finger movement scores beyond the independent contributions from the DTI measures of fiber integrity. By contrast, age was the predominant factor in predicting Digit Symbol and ataxia scores, with one exception: FA or diffusivity in the temporal callosal sector and age each contributed significantly to the prediction of Digit Symbol performance.

4. Discussion

DTI anisotropy and diffusivity measures derived from quantitative fiber tracking enabled in vivo examination of the effect of aging on the microstructural integrity of major supratentorial, infratentorial, and commissural fiber systems in the healthy men and women. Orientation (FA)

and magnitude (ADC) of diffusion indexed fiber integrity and varied by bundle location. The lowest FA was observed in the inferior cingulum bundle and the highest in the pontocerebellar tract; by far the highest diffusivity (ADC, λ_L , and λ_T) was in the fornix. Without regard to age effects, only two fiber bundles exhibited significant sex differences, which were small: FA in the frontal forceps of the men was 3.8% higher than in the women, and diffusivity in the cerebellar hemisphere bundles was 2.7% for λ_L to 4.6% for λ_T greater in the women than the men. The sex effects observed were bilateral because in no region was the sex-by-hemisphere interaction for anisotropy or diffusivity significant; that is, any laterality difference observed was the same for men and women.

The effect of age on regional DTI metrics varied by fiber bundle and was far more dramatic than observed sex differences. Of the 17 fiber bundles examined, only for the splenium were the regression slopes of DTI metrics with age significantly different in men from women; specifically, the slope for transverse diffusivity was steeper in women than men, suggesting that the splenia of women age faster than those of men through myelin degradation. The overall pattern of age-related differences indicated that anterior fiber systems (frontal forceps and callosal genu) showed more consistent age effects than their posterior counterparts (occipital forceps and callosal splenium), and superior lateral systems (superior cingulum and longitudinal fasciculus) were more consistently affected than their inferior counterparts (inferior cingulum and longitudinal fasciculus). The increase in diffusivity of the superior fiber systems was more apparent in the transverse than longitudinal diffusivity, suggestive of myelin compromise. In contrast to supratentorial fiber systems, the two infratentorial systems examined (pontocerebellar and cerebellar hemisphere bundles) showed no signs of aging whatsoever, a finding consistent with a fiber tracking study of children and young adults (Liston et al., 2006) and a region-of-interest study of adult aging (Yoon et al., 2007). As has been speculated, demonstrated, and replicated with region-of-interest and voxel-based analyses (for reviews, Minati et al., 2007; Moseley, 2003; Pfefferbaum and Sullivan, 2005a; Sullivan and Pfefferbaum, 2003, 2007; Wozniak and Lim, 2006), these patterns of normal aging provide support for subtle disruption of frontal systems in explaining age-related decline in selective cognitive and motor functions (Craik and Salthouse, 2008; Fazekas et al., 2005; Raz and Rodrigue, 2006). Degradation of anterior commissural fibers may curtail deployment of bilateral compensatory mechanisms to enhance performance when age-related decline reduces performance efficiency by the preferred gray matter system (c.f., Dennis and Cabeza, 2008).

The functional relationships observed with measures of regional white matter microstructure lend validity to the DTI metrics reported. Fine finger movement speed was related to the integrity of fibers of the internal and external capsules, which are systems interconnecting striatal and motor cortical regions subserving motor control. The internal capsule fibers course through its genu, lending speculation to the possibility that the fiber system measured reaches toward the supplementary motor area, possibly about the level of the hand region, given the somatotopic organization of the internal capsule with respect to the primary and supplementary motor areas (Schmahmann et al., 2004). Such motor systems may be more resistant to the effects of age than fibers of the anterior limb of the internal capsule because of latter's predominant connections with prefrontal sites. The focal nature of this primarily motor fiber system makes it an ideal correlate of basic motor functions, as observed in our DTI-fine finger movement correlations.

Also relevant to motor performance are the cerebellar hemisphere fiber bundles; here, greater transverse diffusivity, an index of myelin integrity, contributed to slower finger movement. This speeded movement task does not require interhemispheric transfer of information for good performance, and indeed, the integrity of the corpus callosum did not relate to performance on this task. Regarding the test of postural stability (stand on one foot), we have noted in previous studies that declining stability in normal aging does not necessarily have a cerebellar substrate

as occurs in pathological conditions, such as chronic alcoholism (Sullivan et al., 2006). Instead, age-related imbalance and ataxia occurs with degradation of supratentorial white matter. In particular, geriatric studies report greater incidence of falling in older men and women with white matter hyperintensities in centrum semiovale and periventricular tissue, detectable on MRI (Baloh et al., 2003; Cahn et al., 1996; Tell et al., 1998) (reviewed in Butler et al., 2006) and DTI (Sullivan et al., 2001). Regarding Digit Symbol performance, which requires speeded scribing with enhancement from good working memory and selective attention (Sassoon et al., 2007), the fiber systems correlating with performance involved executive, memory, and attentional systems (internal and external capsules, fornix, frontal forceps, and superior longitudinal fasciculus). As an eye-hand coordinated task, probably requiring interhemispheric information transfer for matching numerical and nonsense symbols (c.f., Rosenbloom et al., in press), it is also reasonable that better performance was related to evidence for greater callosal integrity; in this case, the regions making the greatest contribution to performance were the genu, parietal, and temporal sectors. Taken together, these performance-white matter relationships support the contention that degradation of white matter systems in normal aging may be a greater contributor to slowed performance than degradation of gray matter (e.g., Rabbitt et al., 2007), although a direct test of this hypothesis will require joint assessment of gray matter and white matter.

Only a few other studies used quantitative fiber tracking to test the effect of age on brain white matter systems, but each study was limited in scope. Our earlier study, based on DTI data collected at 3 T, a different dataset from the one reported herein, focused on the corpus callosum and revealed an anterior-posterior gradient for low to high FA and the opposite pattern for the three diffusivity measures (Sullivan et al., 2006). This gradient was forthcoming in the present study as well. Another study, also conducted at 3 T, compared two fiber tracts of the limbic system and found age-related modest decline in FA and definitive increase in diffusivity in fornix but not cingulate bundles, which did not differentiate the superior from the inferior extension (Stadlbauer et al., 2008). In the current study, this pattern was replicated in the fornix and inferior cingulate bundle but not fully in the superior cingulate bundle, which showed similar FA declines and diffusivity increases with age parallel in men and women but statistically significant in the women. Although the DTI data in the present study were collected at a lower magnetic field strength (1.5 T) than the other reports (3 T), the data were adequately robust to conduct the fiber tracking routine. On average, and therefore irrespective of age-related decline, FA ranged from 36% in the fornix and inferior cingulum to 52% in the pontocerebellar bundle and from 56% in the genu to 68% in the splenium. The diffusivity measures for the fornix were exceptionally high. Unique to the fornix is the fact that it is the only structure measured essentially surrounded by CSF, enhancing the possibility of exaggerating the influence of partial voluming (i.e., the inclusion of CSF rather than white matter in the voxel). Further, the observed fornix values may have been contaminated by CSF pulsation, again because of its location in the ventricles. In defining the confines of a fiber system, we imposed restrictions on the length of each tract to assure fidelity of tract identification. Because of the inability to identify and quantify the full extent between gray matter structural targets due to the change in orientational diffusivity as the signal transitions from white matter to gray matter (occurring at any magnet field strength), fiber tracking from gray matter node to node is especially challenging and was not attempted here.

In essence, fiber tracking uses local samples of white matter meeting a minimum FA value of 17% and a maximum eigenvector permitting no more than a 37° difference in orientational anisotropy from voxel to voxel. These criteria can minimize the problem of partial voluming effects, which arises when non-white matter signal is included into the region examined. Even when partial voluming is controlled for by rarifying a white matter sample by eroding the outer perimeter, the likely location of partial voluming, age-related increases in diffusivity and decreases in FA are significant (Pfefferbaum and Sullivan, 2003). Thus, the analysis criteria

applied in fiber tracking serve as a form of erosion of voxels with a high potential of containing non-white matter signal. The resulting regionally differential increase in water motility with age is likely attributable to age-related increases in extracellular spaces (Sen and Basser, 2005) but cannot currently be definitively discerned in vivo (e.g., Norris et al., 1994; Pfefferbaum and Sullivan, 2005b; Rumpel et al., 1998; Sehy et al., 2002; Silva et al., 2002). It may also reflect breakdown of myelin sheathing, trapping of fluid between thin or lysed sheaths and between fibers and bulbous swelling of oligodendrocytes observed postmortem in normal aging human and nonhuman primates (Peters and Sethares, 2002, 2003; Peters et al., 2001).

The age-related increase in diffusivity was typically distributed in both λ_L and λ_T . This pattern differs from acute animal models of axonal injury and demyelination. For instance, 12 weeks of cuprizone treatment in a mouse resulted in demyelination and produced a decrease in λ_L followed by an increase in λ_T in the corpus callosum (Sun et al., 2006). The decrease in λ_L was transient and almost fully recovered at the time the increase in λ_T occurred. As modeled by Sen and Basser (2005), “the bath or the extraaxonal fluid mainly determines the overall diffusion coefficient..” (p. 2936). Thus, the cause of the decrease in λ_L in the acute mouse cuprizone model, while unknown, might be due to transient extraaxonal processes inhibiting or disrupting linear water motility, e.g., inflammatory response. In the case of normal adult aging, which is a non-acute condition, we observed increases in both λ_L and λ_T , which could be explained by decreased packing within a voxel, allowing for increased diffusivity in all orientations. The likely age-related increase in extraaxonal fluid could be due to thinning of myelin or decrease in axonal diameter or both. The possibility of decreased axonal packing in white matter structures with advancing age is also supported by the observation that white matter volume shows little decrease with advancing age (Blatter et al., 1995; Courchesne et al., 2000; Good et al., 2001; Pfefferbaum et al., 1994; Raz et al., 1997; Smith et al., 2007; Sowell et al., 2004; Sullivan et al., 2000, 2004; Taki et al., 2006), whereas other MR imaging metrics, e.g., ADC and T2 (Pfefferbaum and Sullivan, 2003), which are sensitive to free water content, increase.

In conclusion, our survey of white matter fiber systems throughout much of the brain indicated regional variation in microstructural integrity, with greater contribution to these differences from age than sex and from diffusivity (marking the condition of axons and myelin) than anisotropy (marking the organization of parallel fibers). Frontal, limbic, striatal, and superior fiber systems of the supratentorium were most consistently affected by advancing age in adulthood, whereas infratentorial systems were robust to normal aging. An anterior-posterior gradient was replicated in the commissural fiber sectors. The pattern of age-related decline of FA mirrors postmortem investigations, which reveal degradation of white matter microstructure, including degradation of myelin (measured in vivo with λ_T) (Kemper, 1994) and axon deletion (measured in vivo with λ_L) (Aboitiz et al., 1996; Meier-Ruge et al., 1992), especially of myelinated fibers of the precentral gyrus and small connecting fibers of the anterior corpus callosum. The greater susceptibility of superior than inferior and anterior than posterior fiber bundles to the throes of aging suggests a neural systems basis for dampening of components of motor control and selective attention, marking performance by healthy elderly men and women (e.g. Johannsen et al., 1997; Müller-Oehring et al., 2007; Nielsen-Bohlman and Knight, 1995; Pfefferbaum et al., 1984; Rabbitt et al., 2007 for review Craik and Salthouse, 2008). Declining function with normal aging may preferentially arise from impoverished connections between nodes of a neural system rather than, or in addition to, deterioration of the gray matter nodes themselves, thus curtailing but not prohibiting youthful performance by the elderly.

Acknowledgments

We would like to thank our research assistants (Jeffrey Eisen, Donna Murray, Marya Schulte, Andrea Spadoni, Carla Raassi, Daniel J. Pfefferbaum, Ted Sullivan, Alexander Jack, Julia Sandler, Carrie McCloskey), and research clinicians (Stephanie A. Sassoon, Ph.D., Anne O'Reilly, Ph.D., Anjali Deshmukh, M.D.) for their work in subject recruitment, clinical evaluation, medical examination, scheduling, screening, data collection, and data entry. This work was supported by the National Institute on Aging (AG017919) and National Institute on Alcohol Abuse and Alcoholism (AA010723 and AA012388).

References

- Aboitiz F, Rodriguez E, Olivares R, Zaidel E. Age-related changes in fibre composition of the human corpus callosum: sex differences. *Neuroreport* 1996;7(11):1761–1764. [PubMed: 8905659]
- Ardekani S, Kumar A, Bartzokis G, Sinha U. Exploratory voxel-based analysis of diffusion indices and hemispheric asymmetry in normal aging. *Magn. Reson. Imaging* 2007;25(2):154–167. [PubMed: 17275609]
- Baloh RW, Ying SH, Jacobson KM. A longitudinal study of gait and balance dysfunction in normal older people. *Arch. Neurol* 2003;60(6):835–839. [PubMed: 12810488]
- Barnea-Goraly N, Menon V, Eckert M, Tamm L, Bammer R, Karchemskiy A, Dant CC, Reiss AL. White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. *Cereb. Cortex* 2005;15(12):1848–1854. [PubMed: 15758200]
- Basser PJ. Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. *NMR Biomed* 1995;8(78):333–344. [PubMed: 8739270]
- Bhagat YA, Beaulieu C. Diffusion anisotropy in subcortical white matter and cortical gray matter: changes with aging and the role of CSF-suppression. *J. Magn. Reson. Imaging* 2004;20(2):216–227. [PubMed: 15269946]
- Blatter DD, Bigler ED, Gale SD, Johnson SC, Anderson C, Burnett BM, Parker N, Kurth S, Horn S. Quantitative volumetric analysis of brain MRI: normative database spanning five decades of life. *Am. J. Neuroradiol* 1995;16(2):241–245. [PubMed: 7726068]
- Bucur B, Madden DJ, Spaniol J, Provenzale JM, Cabeza R, White LE, Huettel SA. Age-related slowing of memory retrieval: contributions of perceptual speed and cerebral white matter integrity. *Neurobiol. Aging*. 2007
- Butler, EE.; Druizin, M.; Sullivan, EV. Gait changes and adaptations in adulthood: pregnancy, aging, and alcoholism. In: Rose, J.; Gamble, JG., editors. *Human Walking*. 3rd ed.. Lippincott, Williams and Wilkins; Philadelphia, MD: 2006. p. 131-147.
- Cahn DA, Malloy PF, Salloway S, Rogg J, Gillard E, Kohn R, Tung G, Richardson ED, Westlake R. Subcortical hyperintensities on MRI and activities of daily living in geriatric depression. *J. Neuropsychiatry Clin. Neurosci* 1996;8:404–411. [PubMed: 9116476]
- Charlton R, Landau S, Schiavone F, Barrick TR, Clark CA, Markus HS, Morris RG. A structural equation modeling investigation of age-related variance in executive function and DTI measured white matter damage. *Neurobiol. Aging*. 2007 doi:10.1016/j.neurobiolaging.2007.03.017.
- Chen ZG, Li TQ, Hindmarsh T. Diffusion tensor trace mapping in normal adult brain using single-shot EPI technique. A methodological study of the aging brain. *Acta Radiol* 2001;42(5):447–458. [PubMed: 11552881]
- Chepur NB, Yen YF, Burdette JH, Li H, Moody DM, Maldjian JA. Diffusion anisotropy in the corpus callosum. *Am. J. Neuroradiol* 2002;23(5):803–808. [PubMed: 12006281]
- Chun T, Filippi CG, Zimmerman RD, Ulug AM. Diffusion changes in the aging human brain. *Am. J. Neuroradiol* 2000;21(6):1078–1083. [PubMed: 10871018]
- Corkin, S.; Growdon, JH.; Sullivan, EV.; Nissen, MJ.; Huff, FJ. Assessing treatment effects from a neuropsychological perspective. In: Poon, L., editor. *Handbook of Clinical Memory Assessment in Older Adults*. American Psychological Association; Washington, DC: 1986. p. 156-167.
- Courchesne E, Chisum HJ, Townsend J, Cowles A, Covington J, Egaas B, Harwood M, Hinds S, Press GA. Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. *Radiology* 2000;216(3):672–682. [PubMed: 10966694]

- Craik, FIM.; Salthouse, TA. The Handbook of Aging and Cognition. 3rd ed.. Psychology Press; New York: 2008. p. 657
- Crovitz HF, Zener KA. Group test for assessing hand and eye dominance. *Am. J. Psychol* 1962;75:271–276. [PubMed: 13882420]
- Dennis, NA.; Cabeza, R. Neuroimaging of healthy cognitive aging. In: Craik, FIM.; Salthouse, TA., editors. The Handbook of Aging and Cognition. 3rd ed.. Psychology Press; New York: 2008. p. 1-54.
- Engelter ST, Provenzale JM, Petrella JR, DeLong DM, MacFall JR. The effect of aging on the apparent diffusion coefficient of normal-appearing white matter. *Am. J. Roentgenol* 2000;175(2):425–430. [PubMed: 10915688]
- Fazekas F, Ropele S, Enzinger C, Gorani F, Seewann A, Petrovic K, Schmidt R. MTI of white matter hyperintensities. *Brain* 2005;128:2926–2932. [PubMed: 15958507]
- Fillard, P.; Gerig, G. Analysis tool for diffusion tensor MRI; Proceedings of Medical Image Computing and Computer-assisted Intervention Lecture Notes in Computer Science; Saint-Malo, France, Springer. 2003; p. 967-968.
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) Version 2.0. Biometrics Research Department, New York State Psychiatric Institute; New York, NY: 1998.
- Foong J, Maier M, Clark C, Barker G, Miller D, Ron M. Neuropathological abnormalities of the corpus callosum in schizophrenia: a diffusion tensor imaging study. *J. Neurol. Neurosurg. Psychiatry* 2000;68(2):242–244. [PubMed: 10644799]
- Fregly AR, Graybiel A, Smith MS. Walk on floor eyes closed (WOFEC): a new addition to an ataxia test battery. *Aerosp. Med* 1972;43(4):395–399. [PubMed: 5045439]
- Gerig, G.; Corouge, I.; Vachet, C.; Krishnan, KR.; MacFall, JR. Quantitative analysis of diffusion properties of white matter fiber tracts: a validation study; 13th Proceedings of the International Society for Magnetic Resonance in Medicine; Miami, FL. 2005; Abstract no. 1337
- Gilmore JH, Lin W, Corouge I, Vetsa YS, Smith JK, Kang C, Gu H, Hamer RM, Lieberman JA, Gerig G. Early postnatal development of corpus callosum and corticospinal white matter assessed with quantitative tractography. *Am. J. Neuroradiol* 2007;28(9):1789–1795. [PubMed: 17923457]
- Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult brains. *NeuroImage* 2001;14:21–36. [PubMed: 11525331]
- Grieve SM, Williams LM, Paul RH, Clark CR, Gordon E. Cognitive aging, executive function, and fractional anisotropy: a diffusion tensor MR imaging study. *Am. J. Neuroradiol* 2007;28(2):226–235. [PubMed: 17296985]
- Head D, Buckner RL, Shimony JS, Williams LE, Akbudak E, Conturo TE, McAvoy M, Morris JC, Snyder AZ. Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. *Cereb. Cortex* 2004;14(4):410–423. [PubMed: 15028645]
- Helenius J, Soinne L, Perkio J, Salonen O, Kangasmaki A, Kaste M, Carano RA, Aronen HJ, Tatlisumak T. Diffusion-weighted MR imaging in normal human brains in various age groups. *Am. J. Neuroradiol* 2002;23(2):194–199. [PubMed: 11847041]
- Hollingshead, A.; Redlich, F. Social Class and Mental Illness. John Wiley and Sons; New York: 1958. p. 398-407.
- Hsu JL, Leemans A, Bai CH, Lee CH, Tsai YF, Chiu HC, Chen WH. Gender differences and age-related white matter changes of the human brain: a diffusion tensor imaging study. *NeuroImage* 2008;39(2):566–577. [PubMed: 17951075]
- Johannsen P, Jakobsen J, Bruhn P, Hansen SB, Gee A, Stodkilde-Jorgensen H, Gjedde A. Cortical sites of sustained and divided attention in normal elderly humans. *NeuroImage* 1997;6(3):145–155. [PubMed: 9344819]
- Kemper, TL. Neuroanatomical and neuropathological changes during aging and dementia. In: Albert, ML.; Knoefel, JE., editors. Clinical Neurology of Aging. 2nd ed.. Oxford University Press; New York: 1994. p. 3-67.
- Kochunov P, Thompson PM, Lancaster JL, Bartzokis G, Smith S, Coyle T, Royall DR, Laird A, Fox PT. Relationship between white matter fractional anisotropy and other indices of cerebral health in normal

- aging: tract-based spatial statistics study of aging. *NeuroImage* 2007;35(2):478–487. [PubMed: 17292629]
- Learned-Miller EG. Data driven image models through continuous joint alignment. *IEEE Trans Pattern Anal. Mach. Intell* 2006;28:236–250. [PubMed: 16468620]
- Lehericy S, Ducros M, Van de Moortele PF, Francois C, Thivard L, Poupon C, Swindale N, Ugurbil K, Kim DS. Diffusion tensor fiber tracking shows distinct corticostriatal circuits in humans. *Ann. Neurol* 2004;55(4):522–529. [PubMed: 15048891]
- Liston C, Watts R, Tottenham N, Davidson MC, Niogi S, Ulug AM, Casey BJ. Frontostriatal microstructure modulates efficient recruitment of cognitive control. *Cereb. Cortex* 2006;16(4):553–560. [PubMed: 16033925]
- Madden DJ, Spaniol J, Whiting WL, Bucur B, Provenzale JM, Cabeza R, White LE, Huettel SA. Adult age differences in the functional neuroanatomy of visual attention: a combined fMRI and DTI study. *Neurobiol. Aging* 2007;28(3):459–476. [PubMed: 16500004]
- Madden DJ, Whiting WL, Huettel SA, White LE, MacFall JR, Provenzale JM. Diffusion tensor imaging of adult age differences in cerebral white matter: relation to response time. *NeuroImage* 2004;21(3):1174–1181. [PubMed: 15006684]
- Makris N, Papadimitriou GM, van der Kouwe A, Kennedy DN, Hodge SM, Dale AM, Benner T, Wald LL, Wu O, Tuch DS, Caviness VS, Moore TL, Killiany RJ, Moss MB, Rosene DL. Frontal connections and cognitive changes in normal aging rhesus monkeys: A DTI study. *Neurobiol. Aging* 2007;28(10):1556–1567. [PubMed: 16962214]
- Meier-Ruge W, Ulrich J, Bruhlmann M, Meier E. Age-related white matter atrophy in the human brain. *Ann. N. Y. Acad. Sci* 1992;673:260–269. [PubMed: 1485724]
- Minati L, Grisoli M, Bruzzzone MG. MR spectroscopy, functional MRI, and diffusion-tensor imaging in the aging brain: a conceptual review. *J. Geriatr. Psychiatry Neurol* 2007;20(1):3–21. [PubMed: 17341766]
- Mori S, Crain BJ, Chacko VP, van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Ann. Neurol* 1999;45:265–269. [PubMed: 9989633]
- Moseley M. Diffusion tensor imaging and aging - a review. *NMR Biomed* 2003;15:553–560. [PubMed: 12489101]
- Moseley ME, Mintorovitch J, Cohen Y, Asgari HS, Derugin N, Norman D, Kucharczyk J. Early detection of ischemic injury: comparison of spectroscopy, diffusion-, T2-, and magnetic susceptibility-weighted MRI in cats. *Acta Neurochirurgica Suppl* 1990;51:207–209.
- Müller-Oehring EM, Schulte T, Raassi C, Pfefferbaum A, Sullivan EV. Local-global interference is modulated by age, sex and anterior corpus callosum size. *Brain Res* 2007;1142:189–205. [PubMed: 17335783]
- Naganawa S, Sato K, Katagiri T, Mimura T, Ishigaki T. Regional ADC values of the normal brain: differences due to age, gender, and laterality. *Eur. Radiol* 2003;13(1):6–11. [PubMed: 12541104]
- Neeman M, Freyer JP, Sillerud LO. A simple method for obtaining cross-term-free images for diffusion anisotropy studies in NMR microimaging. *Magn. Reson. Med* 1991;21(1):138–143. [PubMed: 1943671]
- Nelson, HE. The National Adult Reading Test (NART). Nelson Publishing Company; Windsor, Canada: 1982.
- Nielsen-Bohlman L, Knight RT. Prefrontal alterations during memory processing in aging. *Cereb. Cortex* 1995;5(6):541–549. [PubMed: 8590826]
- Norris DG, Niendorf T, Leibfritz D. Healthy and infarcted brain tissues studied at short diffusion times: the origins of apparent restriction and the reduction in apparent diffusion coefficient. *NMR Biomed* 1994;7(7):304–310. [PubMed: 7718430]
- Nusbaum AO, Tang CY, Buchsbaum MS, Wei TC, Atlas SW. Regional and global changes in cerebral diffusion with normal aging. *Am. J. Neuroradiol* 2001;22(1):136–142. [PubMed: 11158899]
- O'Sullivan M, Jones D, Summers P, Morris R, Williams S, Markus H. Evidence for cortical “disconnection” as a mechanism of age-related cognitive decline. *Neurology* 2001;57:632–638. [PubMed: 11524471]

- Pandya, DN.; Seltzer, B. The topography of commissural fibers. In: Lepore, F.; Ptito, M.; Jasper, HH., editors. *Two Hemispheres-One Brain: Functions of the Corpus Callosum*. Alan R. Liss, Inc.; New York: 1986. p. 47-74.
- Peters A, Sethares C. Aging and the myelinated fibers in prefrontal cortex and corpus callosum of the monkey. *J. Comp. Neurol* 2002;442(3):277–291. [PubMed: 11774342]
- Peters A, Sethares C. Is there remyelination during aging of the primate central nervous system? *J. Comp. Neurol* 2003;460(2):238–254. [PubMed: 12687688]
- Peters A, Sethares C, Killiany RJ. Effects of age on the thickness of myelin sheaths in monkey primary visual cortex. *J. Comp. Neurol* 2001;435(2):241–248. [PubMed: 11391644]
- Pfefferbaum A, Adalsteinsson E, Sullivan EV. Frontal circuitry degradation marks healthy adult aging: evidence from diffusion tensor imaging. *NeuroImage* 2005;26(3):891–899. [PubMed: 15955499]
- Pfefferbaum A, Ford J, Wenegrat B, Roth WT, Kopell BS. Clinical application of the P3 component of event-related potentials: I. Normal aging. *Electroencephalogr. Clin. Neurophysiol* 1984;59:85–103. [PubMed: 6200311]
- Pfefferbaum A, Lim KO, Zipursky RB, Mathalon DH, Rosenbloom MJ, Lane B, Ha CN, Sullivan EV. Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: a quantitative MRI study. *Alcohol.: Clin. Exp. Res* 1992;16(6):1078–1089. [PubMed: 1471762]
- Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Arch. Neurol* 1994;51:874–887. [PubMed: 8080387]
- Pfefferbaum A, Rosenbloom MJ, Adalsteinsson E, Sullivan EV. Diffusion tensor imaging with quantitative fiber tracking in HIV infection and alcoholism comorbidity: synergistic white matter damage. *Brain* 2007;130:48–64. [PubMed: 16959813]
- Pfefferbaum, A.; Sullivan, EV. Diffusion MR imaging in neuropsychiatry and aging. In: Gillard, J.; Waldman, A.; Barker, P., editors. *Clinical MR Neuroimaging: Diffusion, Perfusion and Spectroscopy*. Cambridge University Press; Cambridge: 2005a. p. 558-578.
- Pfefferbaum A, Sullivan EV. Disruption of brain white matter microstructure by excessive intracellular and extracellular fluid in alcoholism: evidence from diffusion tensor imaging. *Neuropsychopharmacology* 2005b;30:423–432. [PubMed: 15562292]
- Pfefferbaum A, Sullivan EV. Increased brain white matter diffusivity in normal adult aging: relationship to anisotropy and partial voluming. *Magn. Reson. Med* 2003;49:953–961. [PubMed: 12704779]
- Pfefferbaum A, Sullivan EV, Carmelli D. Genetic regulation of regional microstructure of the corpus callosum in late life. *Neuroreport* 2001;12:1677–1681. [PubMed: 11409738]
- Pfefferbaum A, Sullivan EV, Hedehus M, Adalsteinsson E, Lim KO, Moseley M. In vivo detection and functional correlates of white matter microstructural disruption in chronic alcoholism. *Alcohol.: Clin. Exp. Res* 2000a;24(8):1214–1221. [PubMed: 10968660]
- Pfefferbaum A, Sullivan EV, Hedehus M, Lim KO, Adalsteinsson E, Moseley M. Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. *Magn. Reson. Med* 2000b;44(2):259–268. [PubMed: 10918325]
- Pierpaoli C, Basser PJ. Towards a quantitative assessment of diffusion anisotropy. *Magn. Reson. Med* 1996;36:893–906. [PubMed: 8946355]
- Rabbitt P, Scott M, Lunn M, Thacker N, Lowe C, Pendleton N, Horan M, Jackson A. White matter lesions account for all age-related declines in speed but not in intelligence. *Neuropsychology* 2007;21(3):363–370. [PubMed: 17484599]
- Raz N, Gunning FM, Head D, Dupuis JH, McQuain J, Briggs SD, Loken WJ, Thornton AE, Acker JD. Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cereb. Cortex* 1997;7(3):268–282. [PubMed: 9143446]
- Raz N, Rodrigue KM. Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neurosci. Biobehav. Rev* 2006;30:730–748. [PubMed: 16919333]
- Rohlfing, T.; Brandt, R.; Maurer, CR., Jr.; Menzel, R. In: Staib, L., editor. *Bee brains, B-splines and computational democracy: generating an average shape atlas*; IEEE Workshop on Mathematical Methods in Biomedical Image Analysis 2001, Kauai, HI; IEEE Computer Society, Los Alamitos, CA. 2001; p. 187-194.

- Rohlfing T, Maurer CR. Nonrigid image registration in shared-memory multiprocessor environments with application to brains, breasts, and bees. *IEEE Trans. Inform. Technol. Biomed* 2003;7(1):16–25.
- Rosenbloom MJ, Sassoos SA, Fama R, Sullivan EV, Pfefferbaum A. Frontal callosal fiber integrity selectively predicts psychomotor performance in chronic alcoholism. *Brain Imaging Behav.* in press.
- Rumpel H, Ferrini B, Martin E. Lasting cytotoxic edema as an indicator of irreversible brain damage: a case of neonatal stroke. *Am. J. Neuroradiol* 1998;19:1636–1638. [PubMed: 9802484]
- Salat DH, Tuch DS, Greve DN, van der Kouwe AJW, Hevelone ND, Zaleta AK, Rosen BR, Fischl B, Corkin S, Rosas HD, Dale AM. Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiol. Aging* 2005;26:1215–1227. [PubMed: 15917106]
- Sassoos SA, Fama R, Rosenbloom MJ, O'Reilly A, Pfefferbaum A, Sullivan EV. Component cognitive and motor processes of the Digit Symbol Test: differential deficits in alcoholism, HIV infection and their comorbidity. *Alcohol.: Clin. Exp. Res* 2007;31:1315–1324. [PubMed: 17550370]
- Schmahmann JD, Pandya DN, Wang R, Dai G, D'Arceuil HE, de Crespigny AJ, Wedeen VJ. Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. *Brain* 2007;130(Pt 3):630–653. [PubMed: 17293361]
- Schmahmann JD, Rosene DL, Pandya DN. Motor projections to the basis pontis in rhesus monkey. *J. Comp. Neurol* 2004;478(3):248–268. [PubMed: 15368534]
- Sehy JV, Ackerman JJ, Neil JJ. Evidence that both fast and slow water ADC components arise from intracellular space. *Magn. Reson. Med* 2002;48(5):765–770. [PubMed: 12417990]
- Sen PN, Basser PJ. A model for diffusion in white matter in the brain. *Biophys. J* 2005;89(5):2927–2938. [PubMed: 16100258]
- Shenkin SD, Bastin ME, MacGillivray TJ, Deary IJ, Starr JM, Wardlaw JM. Childhood and current cognitive function in healthy 80-year-olds: a DT-MRI study. *Neuroreport* 2003;14(3):345–349. [PubMed: 12634481]
- Silva MD, Omae T, Helmer KG, Li F, Fisher M, Sotak CH. Separating changes in the intra- and extracellular water apparent diffusion coefficient following focal cerebral ischemia in the rat brain. *Magn. Reson. Med* 2002;48(5):826–837. [PubMed: 12417997]
- Skinner, HA. Development and Validation of a Lifetime Alcohol Consumption Assessment Procedure. Addiction Research Foundation; Toronto, Canada: 1982.
- Skinner HA, Sheu WJ. Reliability of alcohol use indices: the life-time drinking history and the MAST. *J. Stud. Alcohol* 1982;43:1157–1170. [PubMed: 7182675]
- Smith CD, Chebrolu H, Wekstein DR, Schmitt FA, Markesbery WR. Age and gender effects on human brain anatomy: a voxel-based morphometric study in healthy elderly. *Neurobiol. Aging* 2007;28(7):1075–1087. [PubMed: 16774798]
- Smith S. Fast robust automated brain extraction. *Hum. Brain Mapp* 2002;17:143–155. [PubMed: 12391568]
- Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *NeuroImage* 2003;20(3):1714–1722. [PubMed: 14642481]
- Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Demyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *NeuroImage* 2002;17(3):1429–1436. [PubMed: 12414282]
- Song SK, Yoshino J, Le TQ, Lin SJ, Sun SW, Cross AH, Armstrong RC. Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage* 2005;26(1):132–140. [PubMed: 15862213]
- Sowell ER, Thompson PM, Toga AW. Mapping changes in the human cortex throughout the span of life. *Neuroscientist* 2004;10(4):372–392. [PubMed: 15271264]
- Stadlbauer A, Salomonowitz E, Strunk G, Hammen T, Ganslandt O. Quantitative diffusion tensor fiber tracking of age-related changes in the limbic system. *Eur. Radiol* 2008;18(1):130–137. [PubMed: 17701181]
- Stebbins G, Carrillo MD, Medina D, de Toledo-Morrell L, Klingberg T, Poldrack RA, Moseley M, Karni O, Wilson RS, Bennett DA, Gabrieli JDE. Frontal white matter integrity in aging and its relation to

- reasoning performance: a diffusion tensor imaging study. *Soc. Neurosci. Abstr* 2001;27:1204. Abstract 456.3.
- Stieltjes B, Kaufmann WE, van Zijl PC, Fredericksen K, Pearlson GD, Solaiyappan M, Mori S. Diffusion tensor imaging and axonal tracking in the human brainstem. *NeuroImage* 2001;14(3):723–735. [PubMed: 11506544]
- Sullivan EV, Adalsteinsson E, Hedehus M, Ju C, Moseley M, Lim KO, Pfefferbaum A. Equivalent disruption of regional white matter microstructure in aging healthy men and women. *Neuroreport* 2001;12(22):99–104. [PubMed: 11201100]
- Sullivan EV, Adalsteinsson E, Pfefferbaum A. Selective age-related degradation of anterior callosal fiber bundles quantified in vivo with fiber tracking. *Cereb. Cortex* 2006;16(7):1030–1039. [PubMed: 16207932]
- Sullivan EV, Deshmukh A, Desmond JE, Lim KO, Pfefferbaum A. Cerebellar volume decline in normal aging, alcoholism, and Korsakoff's syndrome: relation to ataxia. *Neuropsychology* 2000;14(3):341–352. [PubMed: 10928737]
- Sullivan EV, Pfefferbaum A. Diffusion tensor imaging in normal aging and neuropsychiatric disorders. *Eur. J. Radiol* 2003;45:244–255. [PubMed: 12595109]
- Sullivan EV, Pfefferbaum A. Neuroradiological characterization of normal adult aging. *Br. J. Radiol* 2007;80:S99–S108. Spec No2. [PubMed: 18445750]
- Sullivan EV, Rosenbloom MJ, Serventi KL, Pfefferbaum A. Effects of age and sex on volumes of the thalamus, pons, and cortex. *Neurobiol. Aging* 2004;25:185–192. [PubMed: 14749136]
- Sun SW, Liang HF, Trinkaus K, Cross AH, Armstrong RC, Song SK. Noninvasive detection of cuprizone induced axonal damage and demyelination in the mouse corpus callosum. *Magn. Reson. Med* 2006;55(2):302–308. [PubMed: 16408263]
- Takahashi T, Murata T, Omori M, Kosaka H, Takahashi K, Yonekura Y, Wada Y. Quantitative evaluation of age-related white matter microstructural changes on MRI by multifractal analysis. *J. Neurol. Sci* 2004;225(12):33–37. [PubMed: 15465083]
- Taki Y, Kinomura S, Sato K, Goto R, Inoue K, Okada K, Ono S, Kawashima R, Fukuda H. Both global gray matter volume and regional gray matter volume negatively correlate with lifetime alcohol intake in non-alcohol-dependent Japanese men: a volumetric analysis and a voxel-based morphometry. *Alcohol.: Clin. Exp. Res* 2006;30(6):1045–1050. [PubMed: 16737464]
- Tell GS, Lefkowitz DS, Diehr P, Elster AD. Relationship between balance and abnormalities in cerebral magnetic resonance imaging in older adults. *Arch. Neurol* 1998;55:73–79. [PubMed: 9443713]
- Wechsler, D. Manual for the Wechsler Adult Intelligence Scale Revised. The Psychological Corporation; New York: 1981.
- Woods RP, Grafton ST, Holmes CJ, Cherry SR, Mazziotta JC. Automated image registration: I. General methods and intra-subject, intramodality validation. *J. Comput. Assist. Tomogr* 1998;22(1):139–152. [PubMed: 9448779]
- Wozniak JR, Lim KO. Advances in white matter imaging: a review of in vivo magnetic resonance methodologies and their applicability to the study of development and aging. *Neurosci. Biobehav. Rev* 2006;30(6):762–774. [PubMed: 16890990]
- Xu D, Mori S, Solaiyappan M, van Zijl PC, Davatzikos C. A framework for callosal fiber distribution analysis. *NeuroImage* 2002;17:1131–1143. [PubMed: 12414255]
- Yoon B, Shim YS, Lee KS, Shon YM, Yang DW. Region-specific changes of cerebral white matter during normal aging: A diffusion-tensor analysis. *Arch. Gerontol. Geriatr.* 2007

Fig. 1.

Fiber tracts were identified on the group-average FA image in common space with single point landmarks in three dimensions on axial or coronal slices. Three orthogonal views of FA were displayed and could be moved simultaneously by a human operator. This example presents the landmark for the left superior cingulate bundle.

Fig. 2.

Mean $\pm$ S.E.M. of each DTI metric for each bilateral fiber bundle. In general, the men and women differed little from each other but did show regional variation.

Fig. 3.

Mean $\pm$ S.E.M. of each DTI metric for callosal sector. In general, the men and women differed little from each other but did show regional variation, with the anterior sectors showing lower FA and higher diffusivity than posterior sectors.

(a)

External Capsule **Fornix** **Internal Capsule**

Fig. 4.

(a-c) Correlations between DTI metrics [fractional anisotropy, FA (top, left); apparent diffusion coefficient, ADC (bottom, left); longitudinal diffusivity, λ_L , a marker of axonal integrity (bottom, middle); transverse diffusivity, λ_T , a marker of myelin integrity (bottom, right)] and age are plotted separately for 55 men (black dots and regression line) and 65 women (gray dots and regression line) for each fiber bundle tracked (shown in color). The decrease in FA and increase in diffusivity is especially prominent in the frontal and superior fiber bundles. (a) Includes fiber bundles of the limbic and striatal systems; (b) are bilateral supratentorial fiber systems and (c) are infratentorial fiber systems.

Fig. 5. Correlations of FA (top, left), ADC (top, right), λL (bottom, left), and λT (bottom, right) of each callosal sector tracked (shown in color) with age for 55 men and 65 women. The decrease in FA and increase in diffusivity is especially prominent in the anterior sectors.

Fig. 6.

Examples of scatterplots of significant correlations (from Table 3) between regional DTI metrics and different tests of motor function and psychomotor speed.

Table 1

Demographic characteristics of the men and women studied

Variable	Men (N = 55)			Women (N = 65)		
	Mean	S.D.	N	Mean	S.D.	N
Age	48.3	14.4	55	53.6	13.7	65
NART IQ	113.3	6.3	42	114.1	6.1	57
Education	16.1	2.4	55	15.8	2.3	65
Handedness	22.3	10.5	52	23.1	14.9	63
Socioeconomic status	24.4	13.5	50	25.9	11.2	64
Body mass index	26.9	4.5	53	25.1	4.4	64
Lifetime alcohol consumption (kg)	72.0	81.0	53	36.6	60.6	65
Smoking frequencies never/past/current	32/12/3		47	39/15/0		54

Values are not available for all subjects. Right handedness = 14-32; left handedness = 50-70.

Table 2

Repeated measures ANOVAs for bilateral DTI fiber metrics: effect of sex

Fiber system	Sex (d.f. = 1,118)		Hemisphere (d.f. = 1,118)		S × H (d.f. = 1,118)	
	F	p	F	p	F	p
FA						
Frontal forceps	9.49	.003	1.10	.30	.22	.64
Occipital forceps	.30	.59	8.73	.0038	3.18	.08
Internal capsule	5.74	.0181	307.64	.0001	2.38	.13
External capsule	4.79	.0305	22.04	.0001	.90	.34
Superior cingulum	.39	.53	175.57	.0001	.07	.80
Inferior cingulum	2.63	.11	.01	.93	3.24	.07
Superior longitudinal fasciculus	1.27	.26	6.95	.0095	.05	.82
Inferior longitudinal fasciculus	.24	.63	13.92	.0003	.29	.59
Pontocerebellar tract	.79	.38	1.62	.2063	.33	.56
Cerebellar hemispheres	1.51	.22	1.67	.1986	.37	.55
ADC						
Frontal forceps	.83	.36	6.02	.0156	.28	.60
Occipital forceps	2.91	.09	2.18	.1424	.00	.99
Internal capsule	1.50	.22	81.94	.0001	4.44	.037
External capsule	4.58	.0344	7.89	.0058	1.86	.18
Superior cingulum	.01	.93	9.94	.002	.76	.38
Inferior cingulum	1.86	.17	.20	.65	.53	.47
Superior longitudinal fasciculus	.19	.67	31.54	.0001	.27	.60
Inferior longitudinal fasciculus	1.41	.24	14.90	.0002	.90	.34
Pontocerebellar tract	3.86	.052	19.14	.0001	.04	.85
Cerebellar hemispheres	17.94	.0001	12.06	.0007	.28	.60
λL						
Frontal forceps	.47	.50	10.19	.0018	.13	.72
Occipital forceps	2.35	.13	.61	.44	1.89	.17
Internal capsule	.05	.83	.39	.53	2.65	.11
External capsule	.74	.39	.51	.47	.71	.40

Fiber system	Sex (d.f. = 1,118)		Hemisphere (d.f. = 1,118)		S × H (d.f. = 1,118)	
	F	p	F	p	F	p
Superior cingulum	.01	.92	129.36	.0001	.73	.40
Inferior cingulum	.29	.59	1.34	.25	.03	.85
Superior longitudinal fasciculus	.05	.83	19.44	.0001	.99	.32
Inferior longitudinal fasciculus	2.18	.14	8.84	.0036	.83	.36
Pontocerebellar tract	2.88	.09	36.53	.0001	.01	.93
Cerebellar hemispheres	8.36	.005	17.40	.0001	.08	.78
λT						
Frontal forceps	3.27	.07	1.35	.25	.28	.60
Occipital forceps	1.56	.21	9.34	.0028	2.48	.12
Internal capsule	3.74	.0554	192.73	.0001	4.37	.04
External capsule	6.39	.0128	20.61	.0001	1.57	.21
Superior cingulum	.03	.87	33.25	.0001	.31	.58
Inferior cingulum	2.96	.09	.00	.99	1.35	.25
Superior longitudinal fasciculus	.52	.47	13.60	.0003	.01	.90
Inferior longitudinal fasciculus	.67	.42	16.54	.0001	.82	.37
Pontocerebellar tract	3.52	.06	9.10	.0031	.12	.73
Cerebellar hemispheres	17.38	.0001	6.01	.0157	.41	.52

Bold numbers indicate significant results determined with family-wise Bonferroni correction for 10 comparisons with $\alpha = .05$ requires $p = .005$.

Table 3
Pearson correlations (*r*) between regional tractography metrics and neuropsychological test scores

Fiber tract	Fine finger movements			Digit Symbol—raw score			Ataxia—stand on one foot		
	FA	λL	λT	FA	λL	λT	FA	λL	λT
Fornix	.11	.01	-.03	.07	-.33	-.35	-.02	-.08	-.90
Internal capsule	.24	.95	.75	.47	.0003	.0001	.85	.44	.36
	.35	-.06	-.36	.14	-.28	-.30	.15	.01	-.17
External capsule	.0001	.52	.0001	.13	.0022	.0014	.13	.95	.10
	.25	-.14	-.31	.13	-.27	-.28	.08	-.15	-.18
Frontal forceps	.007	.14	.0009	.16	.004	.0025	.43	.15	.08
	.19	-.08	-.21	.30	.02	-.26	.32	.14	-.18
Occipital forceps	.042	.42	.029	.0013	.80	.0053	.04	.18	.076
	.21	-.03	-.24	.25	.08	-.23	.04	.08	-.03
Superior cingulate bundle	.025	.78	.01	.0084	.38	.0146	.68	.41	.77
	.02	-.17	-.03	.23	-.05	-.23	.02	-.09	-.07
Inferior cingulate bundle	.88	.19	.73	.0145	.56	.012	.81	.38	.46
	.09	-.08	-.12	.04	.05	-.004	-.14	.02	.11
Superior longitudinal fasciculus	.32	.43	.21	.68	.61	.97	.16	.85	.28
	.24	-.06	-.24	.23	-.09	-.29	.13	-.03	-.14
Inferior longitudinal fasciculus	.01	.54	.013	.0123	.33	.0016	.21	.78	.16
	.03	-.002	-.01	-.01	-.07	-.07	-.03	-.08	-.06
Pontocerebellar bundle	.73	.98	.89	.92	.45	.44	.73	.43	.57
	.14	-.09	-.13	-.04	.07	.11	.05	.18	.09
Cerebellar hemisphere bundle	.153	.35	.16	.65	.48	.26	.61	.075	.40
	.09	-.22	-.29	.05	-.01	-.05	.05	.01	-.07
Corpus callosum	.35	.022	.0016	.62	.93	.56	.61	.90	.49
	.10	-.10	-.16	.19	-.18	-.26	.15	-.04	-.18
Genu	.31	.28	.10	.0463	.0536	.006	.14	.71	.076
	.08	-.02	-.08	.15	-.23	-.24	.16	-.07	-.18
Premotor	.38	.81	.38	.11	.0121	.0108	.12	.48	.079

Fiber tract	Fine finger movements			Digit Symbol—raw score			Ataxia—stand on one foot		
	FA	λL	λT	FA	λL	λT	FA	λL	λT
Sensory-motor	-.04	.03	.03	.08	-.15	-.13	.07	-.11	-.11
	.64	.78	.73	.41	.12	.18	.48	.28	.27
Parietal	-.03	.08	.04	.30	-.20	-.30	.17	-.10	-.16
	.72	.41	.67	.0014	.0341	.0011	.10	.34	.12
Temporal	.04	-.07	-.07	.40	-.26	-.44	.22	.01	-.19
	.69	.46	.45	.0001	.0058	.0001	.0279	.96	.063
Splenium	.14	-.05	-.13	.08	-.23	-.23	.16	.01	-.15
	.16	.58	.19	.39	.0144	.015	.12	.96	.14

Bold numbers indicate significant results determined with family-wise Bonferroni correction for 17, 1-tailed comparisons $p = .006$.