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Longitudinal Study of Callosal Microstructure in the Normal Adult Aging Brain Using Quantitative DTI Fiber Tracking

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Abstract

We present a review of neuroimaging studies of normal adult aging conducted with Diffusion Tensor Imaging (DTI) and data from one of the first longitudinal studies using DTI to study normal aging. To date, virtually all DTI studies of normal adult aging have been cross-sectional and have identified several patterns of white matter microstructural sparing and compromise that differentiate regional effects, fiber type, and diffusivity characteristics: 1) fractional anisotropy (FA) is lower and mean diffusivity is higher in older than younger adults, 2) aging is characterized by an anterior-to-posterior gradient of greater-to-lesser compromise also seen in superior-to-inferior fiber systems, and 3) association fibers connecting cortical sites appear to be more vulnerable to aging than projection fibers. The results of this longitudinal study of the macrostructure and microstructure of the corpus callosum yielded a consistent pattern of differences between healthy, young (20s to 30s) and elderly (60s to 70s) men and women without change over 2 years. We then divided the fibers of the corpus callosum into the midsagittal strip and the lateral distal fibers in an attempt to identify the locus of the age-related differences. The results indicated that, on average, mean values of FA and longitudinal diffusivity (λL) were lower in the distal than midsagittal fibers in both groups, but the age effects and the anterior-to-posterior gradients were more pronounced for the distal than midsagittal fibers and extended more posteriorly in the distal than midsagittal fibers. Despite lack of evidence for callosal aging over 2 years, ventricular enlargement occurred and was disproportionately greater in the elderly relative to the young group, being 8.2% in the elderly but only 1.2% in the young group. Thus, different brain regions can express different rates of change with aging. Our longitudinal DTI data indicate that normal aging is associated with declining FA and increasing diffusivity in both λL (longitudinal diffusivity) and λT (transverse diffusivity), perhaps defining the normal ontological condition rather than a pathological one, which can be marked by low FA and low diffusivity.

There is little doubt that even healthy aging is marked by decline in sensory, motor, and selective cognitive functions, well delineated by hundreds of careful, quantitative, cross-sectional and longitudinal assessments (for volumes of reviews, Birren & Schaie, 2001; Craik & Salthouse, 2008). Less known are the neural mechanisms responsible for involutional changes in function, but quantitative in vivo neuroimaging studies conducted over the last quarter century provide critical leads to identify the selective brain structures and systems that contribute to functional decline.

We and others have recently reviewed the neuroimaging findings in normal adult aging (Madden, Bennet & Song, 2009; Sullivan & Pfefferbaum, 2007, 2009; Pfefferbaum & Sullivan, 2009, 2010; Zahr, Pfefferbaum & Sullivan, 2009) based on magnetic resonance imaging (MRI),

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capable of yielding quantification of macrostructural characteristics (notably, size and shape) of brain tissue, and diffusion tensor imaging (DTI), designed to yield quantification of microstructural characteristics of brain tissue, typically white matter axonal and myelin integrity. Many other reviews on the radiologically-identified structural characteristics of normal aging brain are also available, and most are cross-sectional in design. The goal of identifying specific brain mechanisms determining age-related declines in selective cognitive, sensory, and motor processes is a worthy neuropsychological goal in its own right and also forms an essential context for characterizing abnormalities of neurodegenerative diseases and other conditions affecting brain tissue integrity.

The purpose of this paper is to provide an overview of our current knowledge of white matter changes detected with neuroimaging across the adult age span. We focus on microstructural changes observed with DTI but start our review with a brief summary of macrostructural changes observed with MRI in order to give a context for both levels of analysis of neuromorphological ontological change. In addition, we present new data from a longitudinal DTI study of normal aging.

Differential Effects of Age on Brain Volume of Gray Matter and White Matter: MRI

Throughout development and aging, the brain undergoes extensive volume growth measurable with MRI. Quantitative cross-sectional MRI study of brain ontology in humans, ages 3 months to 70 years, implied growth of the cortical gray matter compartment until about age 5 years, followed by a linear volume decline (Pfefferbaum et al., 1994) until very old age when an accelerated decline occurs (Fotenos, Mintun, Snyder, Morris, & Buckner, 2008). A different pattern emerged for cortically subjacent white matter volume, which showed growth acceleration during adolescence to asymptote in the third decade; during the same time, CSF spaces, including sulci and ventricles, expanded continually (Pfefferbaum et al., 1994).

A majority of cross-sectional and longitudinal MRI studies in the adult age range report systematic age-related volume enlargement in CSF-filled spaces that occurs at the expense of cortical gray matter and with little volume change in white matter (cross-sectional Blatter et al., 1995; Courchesne et al., 2000; Good et al., 2001; Pfefferbaum et al., 1994; Raz et al., 1997; Smith, Chebrolu, Wekstein, Schmitt, & Markesbery, 2007; Sowell, Thompson, & Toga, 2004; Sullivan, Deshmukh, Desmond, Lim, & Pfefferbaum, 2000; Sullivan, Rosenbloom, Serventi, & Pfefferbaum, 2004; Taki et al., 2006; D. Tisserand, Van Boxtel, Gronenschild, & Jolles, 2001); (longitudinal Liu et al., 2003; Pfefferbaum, Sullivan, Rosenbloom, Mathalon, & Lim, 1998; Raz, Rodrigue, Kennedy, & Acker, 2007; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). A minority of studies has reported the opposite pattern of tissue shrinkage, with greater age-related volume decline in white matter than gray matter (Guttmann et al., 1998; Jernigan et al., 2001). When regional white matter volume does show age-related loss, it is typically small, estimated at 1% per year decline in midsagittal area of the corpus callosum of elderly men examined over a 4-year span (Sullivan, Pfefferbaum, Adalsteinsson, Swan, & Carmelli, 2002) and 2% per decade in a neuropathology study (Miller, Alston, & Corsellis, 1980); (but see Jernigan et al., 2001; Walhovd et al., 2005)]. In contrast to volumetric results, microstructural study of white matter with DTI appears to be more sensitive to aging's degenerative effects, as evidenced in the consistency of findings reported and reviewed below.

On MRI, neither the pons nor the corpus callosum show substantial age-related volume decline with age (Driesen & Raz, 1995; Raz, Gunning-Dixon, Head, Williamson, & Acker, 2001; Sullivan et al., 2002; Sullivan et al., 2004). Use of DTI to measure regional white matter fiber bundle volume revealed differential effects of age, with significant linear declines detected in the corona radiata, anterior cingulum, regions of the fornix and cerebellar peduncle and

nonlinear decline in the genu in healthy individuals, age 13 to 70 years (Pagani, Agosta, Rocca, Caputo, & Filippi, 2008). Visual inspection of corpora callosa of healthy elderly individuals can suggest excessive thinning, especially of the isthmus, in the elderly, that is actually the result of ventricular expansion and not necessarily callosal atrophy (Pfefferbaum, Sullivan, & Carmelli, 2001, 2004). Thus, caution must be exercised when interpreting callosal thinning in conditions, such as normal pressure hydrocephalus, marked by ventriculomegaly. Regional volume shrinkage, whether in gray matter or white matter, tends to accelerate in very old age (Raz et al., 2005; Salat, Kaye, & Janowsky, 1999) and may reflect heterogeneity arising from common occult conditions, such as preclinical or undetected dementia, hypertension, metabolic disorders, or alcoholism. Indeed, the Leukoaraiosis And DISability (LANDIS) study identified 569 elderly men and women with mild to severe subcortical white matter hyperintensities (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987) and found significant atrophy of the corpus callosum that was associated with poor scores on the Mini-Mental State Examination, a short physical performance battery, and walking speed (Ryberg et al., 2007) and selective relations between anterior but not posterior callosal atrophy and deficits in attention and executive functions (Jokinen et al., 2007).

The dynamic nature of aging makes it particularly desirable to track its course with longitudinal examination. Such reports based on conventional MRI have been accumulating over the past decade (e.g., Fotenos et al., 2008; Kramer et al., 2007; Raz et al., 2005; Resnick et al., 2003); some suggest that cross-sectional study underestimates the toll of age on the brain (for review, Raz & Rodrigue, 2006). One longitudinal study showed that accelerated decline in whole brain volume correlated with higher socioeconomic status, which was interpreted as an indication that individuals with higher status have greater “reserve” than those with lower status and therefore express cognitive decline later despite accelerating signs of brain shrinkage (Fotenos et al., 2008). Yet another longitudinal study found no protective effects of educational attainment on preservation of brain volumes (Raz et al., 2005). Although the loci and extent of age-related tissue volume decline may differ from study to study, whether due to differences in study cohort, image acquisition parameters, or image data analysis, the most consistent finding is a salient, rapid decline of prefrontal tissue volume (Liu et al., 2003; Pfefferbaum et al., 1998; Raz et al., 2004; Resnick et al., 2003; Tang, Whitman, Lopez, & Baloh, 2001; Tisserand et al., 2002), possibly contributing to (if not accounting for) parallel declines in component processes of executive functioning, such as working memory(Leung, Gore, & Goldman-Rakic, 2002; Park et al., 1996), sequencing (Allain et al., 2007) and temporal ordering (Fuster, 2000), response inhibition (Müller-Oehring, Schulte, Raassi, Pfefferbaum, & Sullivan, 2007), error monitoring (Wang, Ulbert, Schomer, Marinkovic, & Halgren, 2005), stimulus evaluation response latency (Pfefferbaum, Ford, Wenegrat, Roth, & Kopell, 1984), and attention allocation (Madden, Pierce, & Allen, 1992), each drawing on adequate prefrontal functioning (sample of reviews, Buckner, 2004; Fuster, 2000; Tisserand & Jolles, 2003; Y. Wang et al., 2006). In contrast with the MRI literature, longitudinal DTI studies of microstructural integrity in normal aging are only recently emerging, and this report adds to this new area of study.

Differential Effects of Age on Regional White Matter Microstructure: DTI

MR diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) allow quantification of microscopic movement of water molecules modeled as Brownian motion *within* each voxel of an image (Basser, 1995; Moseley et al., 1990). Because of the linear organization of the brain’s fiber bundles, fasciculi, and commissures, DTI has been useful in characterizing the microstructural condition and constituents of white matter. The principles of DTI are presented in a number of overviews (e.g., Bammer, Acar, & Moseley, 2003; Le Bihan, 2003, 2007; Mori & Zhang, 2006; Pfefferbaum & Sullivan, 2005a) and are summarized next.

In regions with few or no constraints imposed by physical boundaries, such as cerebrospinal fluid (CSF) in the ventricles, water movement is random, that is, freely diffusing, and is therefore isotropic. By contrast, the water molecule path, for example, in a white matter fiber, is constrained by the physical boundaries, such as the axon sheath, causing the movement to be greater along the long axis of the fiber than across it and is anisotropic, typically measured as fractional anisotropy (FA) and ranging between 0 and 1 on a normalized scale (Pierpaoli & Basser, 1996). Thus, DTI is selectively sensitive to the detection of tightly packed fibers in parallel orientation of white matter systems.

The tensor is associated with three eigenvalues (λ_1, λ_2, λ_3), each corresponding to one of three mutually orthogonal orientational eigenvectors, describing the diffusion ellipsoid by its major axes (Figure 1). The eigenvalue average, which is equal to the trace of the tensor, reflects the magnitude of diffusion. The largest eigenvalue, λ_1, is the longitudinal diffusivity, λL, whereas λ_2 and λ_3 quantify transverse diffusivity, $\lambda T = (\lambda_2 + \lambda_3)/2$. The extent to which one eigenvalue, λ_1, dominates the other two, λ_2 and λ_3, determines the degree of anisotropy within a voxel. DTI data sets are commonly reduced to an anisotropy image and a mean diffusivity image, but the utility of decomposing mean diffusivity into λL and λT has been shown in studies of the developing neonate and children and normal aging as well as in tracking neurological conditions, including stroke (C. Wang et al., 2006), head injury (Sidaros et al., 2008;Wilde et al., 2006), multiple sclerosis (Bonzano et al., 2008), and alcohol (Pfefferbaum, Adalsteinsson, & Sullivan, 2006a,2006b) and drug dependence (Moeller et al., 2007).

Fractional anisotropy (FA)

In less than a decade, quantitative DTI has expanded our understanding of the toll aging takes on the brain's white matter microstructure. Quantitative DTI has revealed degradation of white matter microstructure (in terms of diffusion coherence on an intravoxel basis) undetectable with bulk volume (in terms of the average of many voxels of a specific tissue type) measures from conventional MRI in normal aging (Hugenschmidt et al., 2008; Pfefferbaum & Sullivan, 2003; Sullivan et al., 2001) and neuropathology (Herve et al., 2005; multiple sclerosis: Kolind et al., 2008; alcoholism Pfefferbaum & Sullivan, 2002; Sidaros et al., 2008; stroke: C. Wang et al., 2006; head injury Wilde et al., 2006). Most consistently observed has been a decline in FA and complementary increase in diffusivity in white matter with advancing age (Chun, Filippi, Zimmerman, & Ulug, 2000; Head et al., 2004; Madden et al., 2004; Nusbaum, Tang, Buchsbaum, Wei, & Atlas, 2001; O'Sullivan et al., 2001; Ota et al., 2006; Pfefferbaum, Sullivan, Hedehus, Lim et al., 2000; Salat et al., 2005; Stebbins et al., 2001). This aging pattern is similar in men and women (Ota et al., 2006; Sullivan et al., 2001), although regional variation may occur. Hsu et al. (Hsu et al., 2008) reported differential age-related declines in FA, where men showed a steeper decline in a global measure of FA and in FA of the right anterior limb of the internal capsule than women, whereas the FA decline was steeper in women than men in the right deep temporal white matter. Although the FA decline with age is linear from about 20 years onwards, the rise in diffusivity is not and accelerates in older age (Pfefferbaum, Rosenbloom, Adalsteinsson, & Sullivan, 2007).

One of the most robust findings describing age-related differences in regional FA has been a distribution of low FA selective to frontal white matter in the elderly (Ardekani, Kumar, Bartzokis, & Sinha, 2007a; Bhagat & Beaulieu, 2004; Bucur et al., 2007; Foong et al., 2000; Grieve, Williams, Paul, Clark, & Gordon, 2007; Head et al., 2004; Madden et al., 2007; Madden et al., 2004; Nusbaum et al., 2001; O'Sullivan et al., 2001; Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Pfefferbaum & Sullivan, 2003; Pfefferbaum, Sullivan, Hedehus, Lim et al., 2000; D. H. Salat et al., 2005; Sullivan et al., 2001; Takahashi et al., 2004) that was confirmed in a monkey model of aging (Makris et al., 2007). This anterior-posterior gradient, where anterior fiber systems are more susceptible to age-related compromise than are posterior

systems, has been repeatedly replicated in the corpus callosum but also holds true for lateralized fiber bundles and endures whether measured with region-of-interest analysis (O'Sullivan et al., 2001; Pfefferbaum et al., 2005; Pfefferbaum & Sullivan, 2003; Sullivan et al., 2001), voxel-based approach (Ardekani, Kumar, Bartzokis, & Sinha, 2007b; Hsu et al., 2008; Salat et al., 2005), or quantitative fiber tracking (Pfefferbaum et al., 2007; Sullivan et al., 2001; Sullivan, Rohlfing, & Pfefferbaum, 2009).

Diffusivity

The typical aging pattern of white matter microstructure is characterized by a decrease in intravoxel anisotropy (FA) accompanied by an increase in diffusivity (Chen, Li, & Hindmarsh, 2001; Engelter, Provenzale, Petrella, DeLong, & MacFall, 2000; Head et al., 2004; Helenius et al., 2002; Naganawa, Sato, Katagiri, Mimura, & Ishigaki, 2003; Pfefferbaum et al., 2005; Pfefferbaum & Sullivan, 2003). Modeling age's effect on FA and diffusivity across 120 adults, 20 to 80 years, revealed a linear decline in FA and nonlinear increase in diffusivity with age that was greater in the genu than splenium of the corpus callosum (Pfefferbaum et al., 2007). Diffusivity can be inflated by partial voluming from non-white matter tissue, such as gray matter and cerebrospinal fluid, both characterized by lower FA and higher diffusivity than white matter (Bhagat & Beaulieu, 2004). Yet, even when controlling for partial voluming by eroding peripheral voxels of a particular region of interest, that is, by removing voxels in the periphery of white matter regions most likely to contain signal from non-white matter tissue, the complementary aging functions—FA decrease with diffusivity increase—are observable (Pfefferbaum & Sullivan, 2002; Pfefferbaum & Sullivan, 2003).

The magnitude of the FA-diffusivity relationship varies across brain regions and is greater in older than younger individuals (Pfefferbaum & Sullivan, 2003). This relationship suggests that decreased brain white matter intravoxel coherence is attributable, at least in part, to the accumulation of interstitial or intracellular fluid, or both fluid compartments (e.g., Norris, Niendorf, & Leibfritz, 1994; Pfefferbaum & Sullivan, 2005b; Rumpel, Ferrini, & Martin, 1998; Sehy, Ackerman, & Neil, 2002; Silva et al., 2002) and may reflect age-related loosening of myelin, dense cytoplasm, and formation of fluid-filled balloons, which were observed in area 46 white matter in nonhuman primate models of normal aging (Peters & Sethares, 2003).

Tractography

FA is a measure of the magnitude and orientation of diffusion derived from the tensor's eigenvalues on an *intravoxel* basis. By contrast, coherence 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. The use of voxel-to-voxel coherence measures serves the conceptual basis for quantitative fiber tracking (Fillard & Gerig, 2003; Gerig, Corouge, Vachet, Krishnan, & MacFall, 2005). Although the connectivity and coherence between different brain regions on vector and fiber tracking maps is readily apparent on visual inspection, these displays have only recently been subjected to quantification (Gerig et al., 2005; Mori et al., 2002; Xu, Mori, Solaiyappan, van Zijl, & Davatzikos, 2002; Xue, van Zijl, Crain, Solaiyappan, & Mori, 1999). Methods for quantitative analysis of structural connectivity of white matter include fiber-tract trajectories (Basser & Pierpaoli, 1998; Masutani, Aoki, Abe, Hayashi, & Otomo, 2003; Mori & van Zijl, 2002) and maps of the degree of "alignment" among neighboring vectors, that is, on a voxel-to-voxel basis, resulting in a measure of intervoxel coherence (Jones, Simmons, Williams, & Horsfield, 1999; Pfefferbaum, Sullivan, Hedehus, Adalsteinsson et al., 2000). In addition to providing useful visual depiction of empirically derived fiber tracts (Schmahmann et al., 2007), advantages of quantitative fiber tracking over focal region of interest analysis include the ability to measure the entire extent of a fiber tract and to characterize its integrity along its full extent.

In an initial study using quantitative fiber tracking in normal aging, we observed higher diffusivity and fewer imaging-defined fiber bundles in the anterior but not posterior segments of the corpus callosum, based on known interhemispheric projection sites (Pandya & Seltzer, 1986) in elderly compared with young, healthy men and women (Sullivan, Adalsteinsson, & Pfefferbaum, 2006). Examination of regionally distinct fiber bundles identified throughout the supratentorium and infratentorium replicated the anterior-posterior gradient of age-related degradation of white matter quality in a cohort of 120 healthy men and women, who spanned the adult age range from 20 to 81 years and extended the pattern to a superior-inferior gradient (Sullivan et al., 2009). In this case, quantitative fiber tracking revealed lower anisotropy and higher diffusivity in older than younger healthy individuals and in superior than inferior bundles (longitudinal fasciculi, cingulate bundles), but no age effect in pontine or cerebellar fiber systems. Robust sex differences were not identified in this study of adult aging nor were they forthcoming in a developmental study of regional fiber systems using quantitative tractography in children, age 6 to 17 years (Eluvathingal, Hasan, Kramer, Fletcher, & Ewing-Cobbs, 2007); however, sex differences have been reported in voxel-based analysis (Schneiderman et al., 2007).

Stadlbauer et al. (Stadlbauer, Salomonowitz, Strunk, Hammen, & Ganslandt, 2008) used fiber tracking to examine three different categories of fiber systems: association fibers, which included the superior longitudinal, inferior longitudinal, and inferior fronto-occipital fasciculi; callosal fibers; and projection fibers, which included corticobulbar and corticospinal tracts and thalamic fibers. The age-related declines in FA were graded from greatest in the association fibers, less so in the callosal fibers, and least in the projection fibers. Nonetheless, significant increases in mean diffusivity were present in all three, fiber systems, indicating that none was fully immune to involutional changes. Another fiber tracking study examined 38 healthy men and women, age 18 to 88 years, and found age-related FA decline and diffusivity increase in ADC and each of the three separate lambdas (eigenvalues) in the fornix but not the cingulate bundles (Stadlbauer, Salomonowitz, Strunk, Hammen, & Ganslandt, 2007). Using quantitative fiber tracking in groups of healthy young and elderly men and women, Zahr et al. (Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009) identified an anterior-posterior and superior-inferior gradient of age-related degradation in fiber bundles, notable in the genu, fornix, and uncinate fibers; functional relations were observed between Working Memory Problem Solving, and Motor factor scores and DTI metrics indicating regionally compromised fiber tracts.

Brain structure-function relationships

The functional ramifications of the DTI metrics have been regularly verified with observations of correlations between 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) or motor (Sullivan et al., 2001) test performance in healthy aging men and women. Some studies provide evidence for selectivity of DTI-behavioral relationships. Low FA in frontal white matter correlated with low scores on tests of executive functions assessed with a visual odd-ball task (Madden et al., 2004). This study also revealed an age-related difference in regional FA relationships with reaction time, where the relationship in the older but not younger adults was selective to the internal capsule but not the splenium, whereas the younger adults showed the opposite relationship. We found a selective relation between performance on alternated finger tapping (but not the control condition of unimanual finger tapping) and FA in the splenium and perisplenial white matter in health men and women (Sullivan et al., 2001). A cross-sectional developmental DTI study of 92 children to young adults, age 9 to 24 years, found an age-related increase in FA of the splenium and that this increase, possibly reflecting further myelination, was also predictive of speed in the alternated finger tapping, which requires interhemispheric coordination of bimanual movements (Muetzel et al., 2008).

Other studies report nonspecific relationships. For example, Grieve et al. (Grieve et al., 2007) showed that low FA in three separate regions—frontal, temporal, and parietal white matter—correlated with faster maze completion time in a group of 87 healthy volunteers, age 20 to 73 years; attentional shifting accuracy was correlated with FA from frontal to occipital regions. Lower whole brain FA and mean diffusivity were predictive of working memory performance (Charlton et al., 2007; Charlton et al., 2006). Significant correlations were observed between high anterior white matter mean diffusivity and prolonged time to complete the Trail Making test, whereas high diffusivity was related to verbal fluency (O'Sullivan et al., 2001); unfortunately, selectivity of these relationships was not tested. A monkey model of aging provided evidence for age-related decrease in FA of association fibers, namely, the superior longitudinal fasciculus and cingulate bundle, and also the anterior corpus callosum, that also correlated with a cognitive set shifting task (Makris et al., 2007).

Brain structure-function relationships using quantitative fiber tracking have also been established in healthy adults. One report provided evidence for a relationship between Stroop word-color naming and central callosal FA integrity (Sullivan et al., 2006). In another study, fine finger movement speed correlated with FA and transverse diffusivity measured in three lateral fiber bundles supporting motor movement (internal capsules, external capsules, and cerebellar hemisphere bundles) but no commissural fiber tract metrics (Sullivan et al., 2009).

Longitudinal Study of Microstructure vs. Macrostructure of the Corpus Callosum

DTI studies of normal aging have largely relied on cross-sectional examination of healthy men and women drawn from either contrasting age groups (young vs. elderly adults) or a continuous age distribution. The lack of longitudinal results limits generalization of available studies (c.f., Raz et al., 2007; Rohlfing, Sullivan, & Pfefferbaum, 2006). The few studies reporting longitudinal results in normal aging do so secondarily, in that the target study groups were individuals with neurological conditions, including head injury (Sidaros et al., 2008) and amyotrophic lateral sclerosis (ALS) (Blain et al., 2007). In neither control group were age-related declines in FA or increases in diffusivity detected.

Here, we present new longitudinal DTI and MRI data collected over a 2-year interval in a sample of healthy young and elderly men and women. In follow-up to our initial study on the cross-sectional comparison of quantitative fiber tracking in this cohort (Sullivan et al., 2006), we predicted that DTI would reveal an anterior-posterior gradient of microstructural decline with age that would be even greater in the follow-up session in the older group. We also expected that DTI would be more sensitive to degenerative changes with age than size measures derived from MRI. We also examined anisotropy and diffusivity after dividing the callosal fibers into midsagittal and bilateral distal components. Given the consistency of ventricular expansion with age, we measured the ventricular system as a positive comparison brain structure at both times on MRI, anticipating that expansion over the inter-scanning interval would occur even if aging effects were not evident macroscopically on MRI or microscopically on DTI.

METHOD

Participants

The 10 men and 10 women who served in our earlier aging study were contacted, on average, 2 years later and invited to participate in a follow-up study. Re-contacting these 20 volunteers revealed that one man and one woman from the young group had moved too far away for a return visit and that two elderly volunteers had died; one man died of cancer unknown at MRI

1, and one woman was fatally hit as a pedestrian by a car. The remaining participants formed a balanced, two-group design of healthy, highly educated adults of 4 young and 4 elderly men and 4 young and 4 elderly women: 8 young (mean±SD=28.6±5.2, range=22 to 37 years at MRI 1; mean±SD=31.1±5.3, range=24 to 40 years at MRI 2; 17.9±1.6 years of education) and 8 older (mean±SD=72.7±5.2, range=65 to 79 years at MRI 1; mean±SD=74.6±5.1, range=67 to 81 years at MRI 2; 16.0±1.5 years of education). The younger subjects included laboratory members and men and women recruited from the local community. All older subjects were recruited from a larger ongoing study of normal aging and scored well within the normal range (above 25 out of 30) on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) at both scanning sessions: mean±SD=29.0±1.3, range=27 to 30 at MRI 1; mean ±SD=28.6±1.1, range=27 to 30 at MRI 2. The time between MRI 1 and MRI 2 was 2.5±.22 years for the young group and 1.9±.25 years for the elderly group.

DTI and MRI Acquisition

The DTI and structural data were acquired on a 3T MRI scanner: 1) structural Fast Spin Echo (FSE); 2) an Inversion Recovery Prepared SPoiled Gradient Recalled echo (IRPrepSPGR); 3) Diffusion Tensor Images (DTI) with 6 non-collinear diffusion directions repeated with opposite gradient polarity, and 4) a field map used for correction of spatial distortion due to main field (B_0) inhomogeneity. The SPGR data were aligned such that adjacent pairs of 1.25 mm thick SPGR slices subtended each 2.5 mm thick FSE and DTI slice.

DTI Analysis

DTI quantification was preceded by eddy current correction on a slice-by-slice basis by within-slice registration, which took advantage of the symmetry of the opposing polarity acquisition (Bodammer, Kaufmann, Kanowski, & Tempelmann, 2004) and also allowed for compensation of the diffusion effect created by the imaging gradients (Neeman, Freyer, & Sillerud, 1991), reducing the data to 6 non-collinear diffusion-weighted images per slice. Using the field maps, B_0-field inhomogeneity-induced geometric distortion in the eddy current-corrected images was corrected with PRELUDE (Phase Region Expanding Labeller for Unwrapping Discrete Estimates, (Jenkinson, 2003)) and FUGUE (FMRIB's Utility for Geometrically Unwarping EPIs (Jenkinson, 2001)). These "native" DTI data were used for fiber tracking. From the b=0 and 6 diffusion weighted images, 6 maps of the apparent diffusion coefficient (ADC) were calculated. Solving 6 simultaneous equations with respect to ADCxx, ADCxy, etc. yielded the elements of the diffusion tensor. The diffusion tensor was then diagonalized, yielding eigenvalues $\lambda_1, \lambda_2, \lambda_3$, as well as eigenvectors that define the predominant diffusion orientation. Based on the eigenvalues, FA and ADC were calculated on a voxel-by-voxel basis (Basser & Jones, 2002; Basser & Pierpaoli, 1998; Pierpaoli & Basser, 1996).

Fiber Tracking

To achieve common anatomical coordinates across subjects, FA data for each subject were aligned with a laboratory standard average brain FA template (Rohlfing, Zahr, Sullivan, & Pfefferbaum, 2008) using nonrigid registration (Rohlfing, Brandt, Menzel, & Maurer, 2004; Rohlfing & Maurer, 2003). The midsagittal corpus callosum (the target region of interest for fiber tracking) was identified with an interactive program on the laboratory standard, as were parallel planes 10mm bilaterally (the sources for fiber tracking). For fiber tracking, the target and sources were then warped to the corresponding locations on the native basis images for each subject with a numerical inversion of the subject-to-standard transformation. The tensor matrix, targets, and sources were passed to the fiber tracking routine in native space.

Fiber tracking was performed with the software distributed by Gerig et al. (Gerig et al., 2005) based on the method of Mori and colleagues (Mori & van Zijl, 2002; Xu et al., 2002; Xue et al., 1999). Fiber tracking parameters included white matter extraction threshold

(minimum FA) of .17, minimum fiber length of 37.5 mm, maximum fiber length of 187.5 mm, fiber tracking threshold of .125 (that is, .125 is the minimum FA of a voxel allowable in a fiber tract), and maximum voxel-to-voxel coherence minimum transition smoothness threshold of .80 (~37° maximum deviation between fiber segments from neighboring voxels), with no limit on the number of fibers. Identified fibers were required to pass through both sources to ensure identification of callosal fibers that extended to both hemispheres. The mean FA and ADC of all voxels comprising each fiber, for all fibers, were determined. After fiber detection the fiber locations were transformed back to common standard coordinates for display and further analysis. In common space, the midsagittal corpus callosum was divided geometrically into 6 regions of interest (Figure 2) but guided by the callosal anatomical projections described by (Pandya & Seltzer, 1986). For each callosal region the number of fibers, the mean fiber length, FA, ADC, λL, and λT were determined. We refer hereafter to the fibers coursing through each of the six callosal regions as "fiber bundles" following the Pandya and Selzer convention: prefrontal, premotor, precentral, postcentral, posterior parietal, and temporal-occipital (Figure 2).

MRI Quantification

The volume of the ventricular system and the midsagittal volume of the corpus callosum were determined by a parcellation method (Pfefferbaum, Rosenbloom et al., 2006). To achieve common anatomical coordinates for brain structure, the IRPrepSPGR data for each subject were aligned with a laboratory standard average structural template (Rohlfing et al., 2008) using nonrigid registration (Rohlfing et al., 2004; Rohlfing & Maurer, 2003). The entire ventricular system and the midsagittal plus two bilateral, 1 mm thick, immediately parasagittal slices of the corpus callosum were outlined with a semiautomated routine on the laboratory standard. The regions of interest were then warped to the native locations on the native IRPrepSPGR for each subject using numerical inversion of the initial transformation, and the volumes computed by voxel count.

Statistical Analysis

Primary analyses were based on group-by-brain region-by-time analysis of variance (ANOVA) and follow-up analyses used t-tests. For single-level variables, such as age, repeated measures with one within-group factor was used. For multiple-level variables, such as 6 callosal sectors for FA or 2 cerebral hemispheres for ventricular volume, repeated measures with multiple within-group factors was used with Greenhouse-Geiser (GG) correction where appropriate.

RESULTS

DTI Metrics of Fiber Tracking

Mean±S.E. for FA, ADC, λL, and λT for the two age groups at each scanning session are presented in Figure 2.

Fractional anisotropy (FA)—The group-by-sector-by-time ANOVA examining group differences in FA of the 6 callosal sectors over time revealed a group-by-sector interaction ($F(5,70)=10.084$, $p=.0001$ GG). Follow-up analysis indicated significantly lower FA in the elderly than young group in the four anterior sectors ($p=.0001$ to $.0477$). The premotor sector only showed a modest decline over time in both groups ($p=.0501$).

Diffusivity—The group-by-sector-by-time ANOVA for the diffusivity (ADC) identified one significant interaction: group-by-sector ($F(5,70)=8.2254$, $p=.0002$ GG). Follow-up analyses indicated significantly higher ADC in the elderly than young group in five of the six sectors ($p=.0044$ to $.0008$), the exception being the posterior parietal sector. Change over time was not significant in either age group. The pattern of group differences observed for ADC, with the

elderly showing greater diffusivity than the young in five callosal sectors, was the same for λL (F(5,70)=5.508, p=.0021 GG) and λT (F(5,70)=9.467, p=.0001 GG). In follow-up testing, the p-values of the group differences for λL ranged from .0026 to .0429, and for λT ranged from .0049 to .0001.

Midsagittal vs. distal fibers—In a further analysis, we divided the fibers of the corpus callosum into the midsagittal strip and the lateral distal fibers in an attempt to identify the location of the age differences. Accordingly, we conducted group-by-sector-by-time ANOVA for each DTI metric of the midsagittal and distal fibers. For FA, the group-by-sector interactions were significant for both sets of fibers (midsagittal: (F(5,70)=5.134, p=.0032 GG; distal: (F (5,70)=13.452, p=.0001 GG). Follow-up analyses together with inspection of Figure 3 reveal a more extensive effect of age in the distal than midsagittal fibers, extending from prefrontal to postcentral sectors for the distal fibers but only to the two most anterior sectors for the midsagittal fibers. Further, mean FA of the midsagittal fibers ranged from .55 to .75 but only . 40 to .55 for FA of the distal fibers.

As observed for FA, the age effects and the anterior-to-posterior gradients were more pronounced for the distal than midsagittal fibers, although a time effect was not forthcoming (Figure 3). Again, the group-by-sector-by-time ANOVAs for each diffusivity measure showed a similar set of effects for the midsagittal and distal fibers: ADC: midsagittal: (F(5,70)=3.126, p=.04 GG; distal: (F(5,70)=6.101, p=.0017 GG; λL: midsagittal: (F(5,70)=2.954, p=.0419 GG; distal: (F(5,70)=2.606, p=.0682 GG; and λT: midsagittal: (F(5,70)=3.833, p=.0173 GG; distal: (F(5,70)=9.031, p=.0001 GG. On average, mean values of FA, ADC, and λL were lower and mean λT values higher in the distal than midsagittal fibers in both groups.

MRI Volumes of Macrostructure

Mean±S.E. of the volumes of the corpus callosum and lateral ventricles for the two age groups at each scanning session are presented in Figure 4.

Corpus Callosum—Unlike the callosal DTI measures, the MRI measures of callosal volume did not differ significantly by group (F(1,14)=1.957, p=.1836) nor time (F(1,14)=.144, p=. 7102) and showed no group-by-time interaction (F(1,14)=.0093, p=.9245).

Lateral Ventricles—The group-by-hemisphere-by-time ANOVA revealed significant effects of group (F(1,14)=48.681, p=.0001) and hemisphere (F(1,14)=9.515, p=.0081). Examples of age differences in ventricular volumes are presented in Figure 5. A group-by-time interaction (F(1,14)=8.921, p=.0098) revealed a disproportionately greater expansion of the lateral ventricles in the elderly than young group. Even though the significant hemisphere effect indicated that the right ventricle was larger than the left, this pattern held similarly for young and elderly individuals, and an absence of a group-by-hemisphere-by-time interaction (F(1,14) =1.115, p=.3090) indicated lack of a laterality effect in aging.

DISCUSSION

The results of this longitudinal study of the macrostructure and microstructure of the corpus callosum yielded a consistent pattern of differences between healthy, young (20s to 30s) and elderly (60s to 70s) men and women without change over 2 years. The microstructural result is consistent with other longitudinal DTI observations in controls, showing no change over 12 months (Sidaros et al., 2008) or over an average of 8 months (Blain et al., 2007). Even in a group of 215 elderly men (age 70 to 82 years) examined over a 4-year interval, we detected <1% decrease per year in the midsagittal area of the corpus callosum, whereas the lateral ventricles expanded 2.9% annually (Sullivan et al., 2002). Although this time interval may

have been too brief for detection of structural features of callosal aging, the interval was adequate for detection of ventricular enlargement, which was disproportionately greater in the elderly relative to the young group: the increase in the lateral ventricles was 8.2% in the elderly compared with 1.2% in the young group. Thus different brain regions express different rates of change with aging.

The analyses based on dividing the corpus callosum into a midsagittal component and a bilateral distal component revealed a pattern of anisotropy and diffusivity age differences similar to those observed across the entire extent of fibers tracked but more dramatic for the distal than midsagittal fibers. Specifically, the age effects and the anterior-to-posterior gradients were more robust for the distal than midsagittal fibers and extended more posteriorly in the distal than midsagittal fibers. On average, FA and λL values were lower in the distal than midsagittal fibers in both groups. The higher FA of the midsagittal fibers may reflect a greater linearity of microstructure than in the distal fibers, but the consistency of group differences and small variance indicate surprising homogeneity of fibers identified as they emerge from the midsagittal corpus callosum. Although fibers that extend into the centrum semiovale should be more susceptible to partial voluming from boggy tissue characteristic of white matter hyperintensities, the low diffusivity in the distal relative to the midsagittal fibers dispels this possibility. Indeed, the consistency of the age effects and replicability of the measurements over 2 years provide predictive validity and reliability to quantitative fiber tracking in studies of normal aging.

The frontal microstructural effect of age observed in the DTI results at both scan session comports with the mainstay of cross-sectional reports on the effects of normal age, indicating greater age-related compromise of frontal relative to posterior brain white matter. This anterior-posterior gradient may reflect the normal developmental pattern, where frontal sites develop relatively late (Sowell, Thompson, Holmes, Jernigan, & Toga, 1999), show the greatest vulnerability to functional decline in normal aging (Gunning-Dixon & Raz, 2003; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998), and are under proportionately greater environmental than genetic control than are posterior regions (Pfefferbaum et al., 2001).

The regionally differential effects of age in white matter FA and diffusivity across brain regions is likely attributable to the structure of the underlying fibers (Barkovich, 2000; Peters & Sethares, 2003), which influence the homogeneity of fiber orientations within each voxel. This variation with age may also contribute to some reports of fewer fiber representations identified with DTI (Stadlbauer et al., 2008; Sullivan et al., 2006). This speculation must be tempered, however, by the actual size of white matter fibers imaged. Given the diameters of axons, for example in the corpus callosum ranging from 0.4 to 5 μm, with the preponderance less than 1 μm, it is estimated that a cross-section of the genu of the human corpus callosum contains approximately 400,000 fibers per mm^2 (Aboitiz, Scheibel, Fisher, & Zaidel, 1992). A single voxel of a DTI study using relatively high resolution ($2\times2\times2$ mm^3) for current standards could contain 1.6 million fibers in a cross-section. Additionally, the number of fibers identified can be influenced by the size of the brain from the simple fact that larger brains have more voxels from which fibers can be mathematically constructed.

Taken together, the last decade of DTI studies has identified several patterns of white matter microstructural sparing and compromise in normal adult aging that differentiate regional effects, fiber type, and diffusivity characteristics: FA is lower and diffusivity is higher in older than younger adults. These aging patterns are regional, characterized by an anterior-to-posterior gradient of greater-to-lesser compromise also seen in superior-to-inferior fiber systems. Association fibers connecting cortical sites may be more vulnerable to aging than projection fibers, which are corticospinal and corticothalamic systems; commissural fiber systems show an anterior-posterior gradient, which is paralleled by postmortem investigations. These studies

reveal degradation of white matter microstructure, including degradation of myelin and microtubules (Kemper, 1994) and axon deletion (Aboitiz, Rodriguez, Olivares, & Zaidel, 1996; Meier-Ruge, Ulrich, Bruhlmann, & Meier, 1992), especially of myelinated fibers of the precentral gyrus and small connecting fibers of the anterior corpus callosum. Whether the freely diffusing water molecules characterized with DTI are from the intracellular or extracellular compartments remains controversial (e.g., Sen & Basser, 2005). Although the general pattern is that FA declines with advancing age in healthy adults, it must also be recognized that surprisingly high FA is not necessarily a sign of exceptional health. Indeed, selective deletion of uniformly-orientated white matter fibers from a tissue sample of crossing fibers (as can occur with Wallerian degeneration) causes abnormally high anisotropy (Pierpaoli et al., 2001). Therefore, interpretation of FA results requires guidance by knowledge of the underlying regional architecture, especially white matter, given current applications (Pierpaoli et al., 2001; Shimony et al., 1999; Virta, Barnett, & Pierpaoli, 1999).

Further refinement of the observed aging patterns is revealed by consideration of the separate contributions from the ellipsoid components of the apparent diffusion coefficient (i.e., mean diffusivity). Animal models of stroke, fiber crushing, and dysmyelination indicate that decline in longitudinal diffusivity, λL, reflects axonal injury, whereas increase in transverse or radial diffusivity, λT, reflects damaged myelin. In particular, data from a shiver mouse model suggests that dysmyelination results in decreased FA because of increased λT, leaving λL unaffected (Song et al., 2002). By contrast, traumatic injury results in decreased FA typically because of both increased λT and decreased λL (Nevo et al., 2001). Human developmental studies of neonates through late adolescence or young adulthood report increasing FA and initially decreasing λT, together indicative of myelination. Curiously, studies of the normal human aging adult report declining FA and increasing diffusivity in both λL and λT, perhaps defining the normal ontological condition rather than a pathological one.

Given the assertion that white matter lesions measured on structural MRI "account for *all* age-related declines in speed but not in intelligence" (Rabbitt et al., 2007), neuropsychological studies of normal aging need to consider the condition of white matter supporting connectivity of gray matter structures, which function as a circuit and underlie complex cognitive, sensory, and motor abilities. Quantitative DTI and fiber tracking can contribute to the characterization of these white matter fiber systems, serve as correlates and predictors of selective functional abilities, and suggest mechanisms of compromise and decline with age and disease. Ideally, conclusions about brain structure-function relationships require support from formal tests of double or multiple dissociations to establish selectivity of such relationships (c.f., Bates, Appelbaum, Salcedo, Saygin, & Pizzamiglio, 2003; Teuber, 1955).

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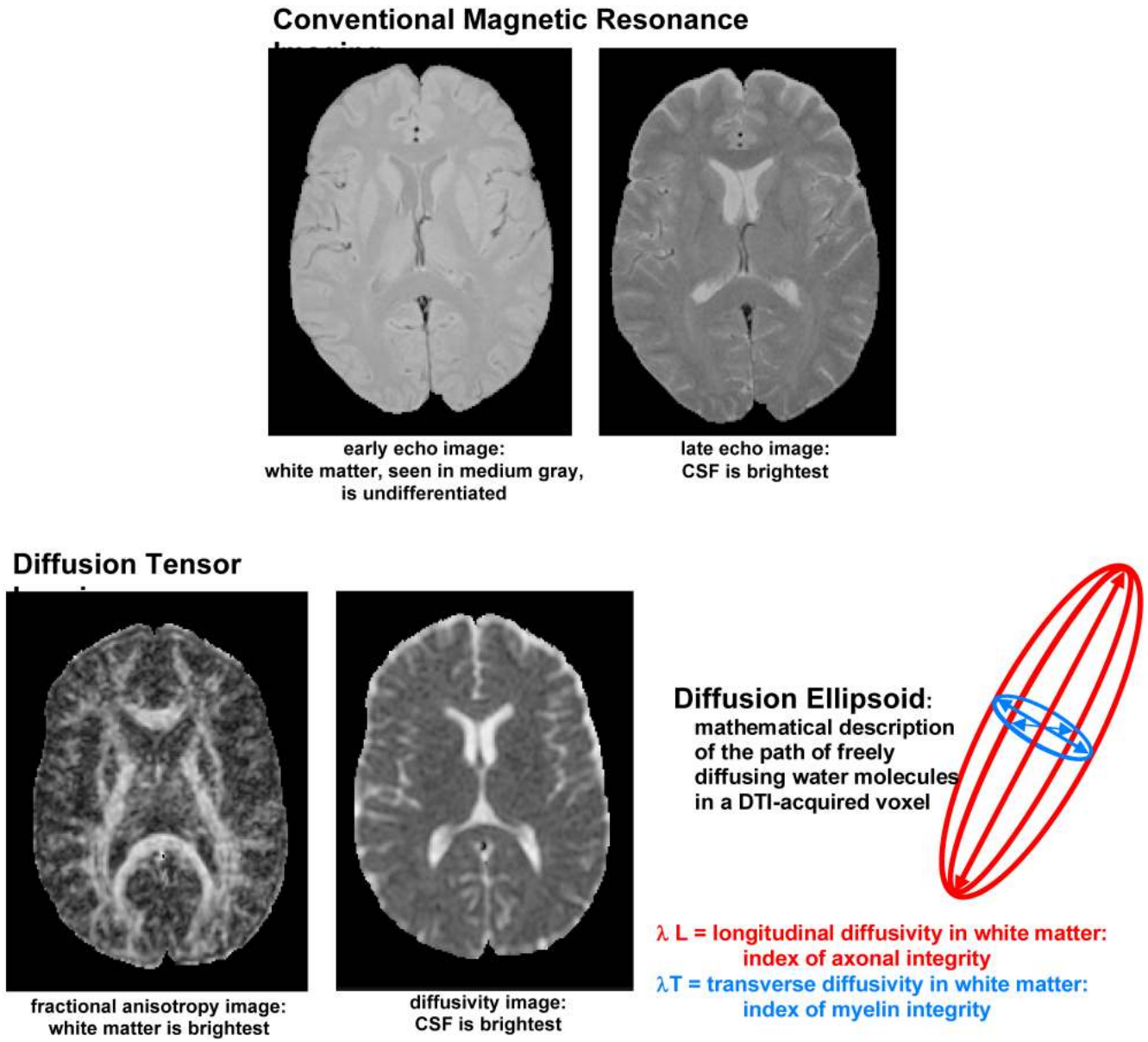

Figure 1.

Axial images at the level of the lateral ventricles. Top two images. Examples of conventional magnetic resonance images from a fast spin-echo sequence (FSE). On the left is an early-echo image, which differentiates gray matter (light gray) and white matter (darker gray), both of which are relatively homogeneous in intensity. On the right is a late-echo image, on which CSF is brightest. Bottom two images: Examples of images from a diffusion tensor imaging sequence. On the left is a fractional anisotropy (FA) image, on which white matter is the brightest. On the right is a diffusivity image, on which CSF is brightest. The diffusion ellipsoid model displays in red the preferred orientation of the longitudinal diffusion, λL, and in blue the two minor axes of diffusion, the mean of which is λT.

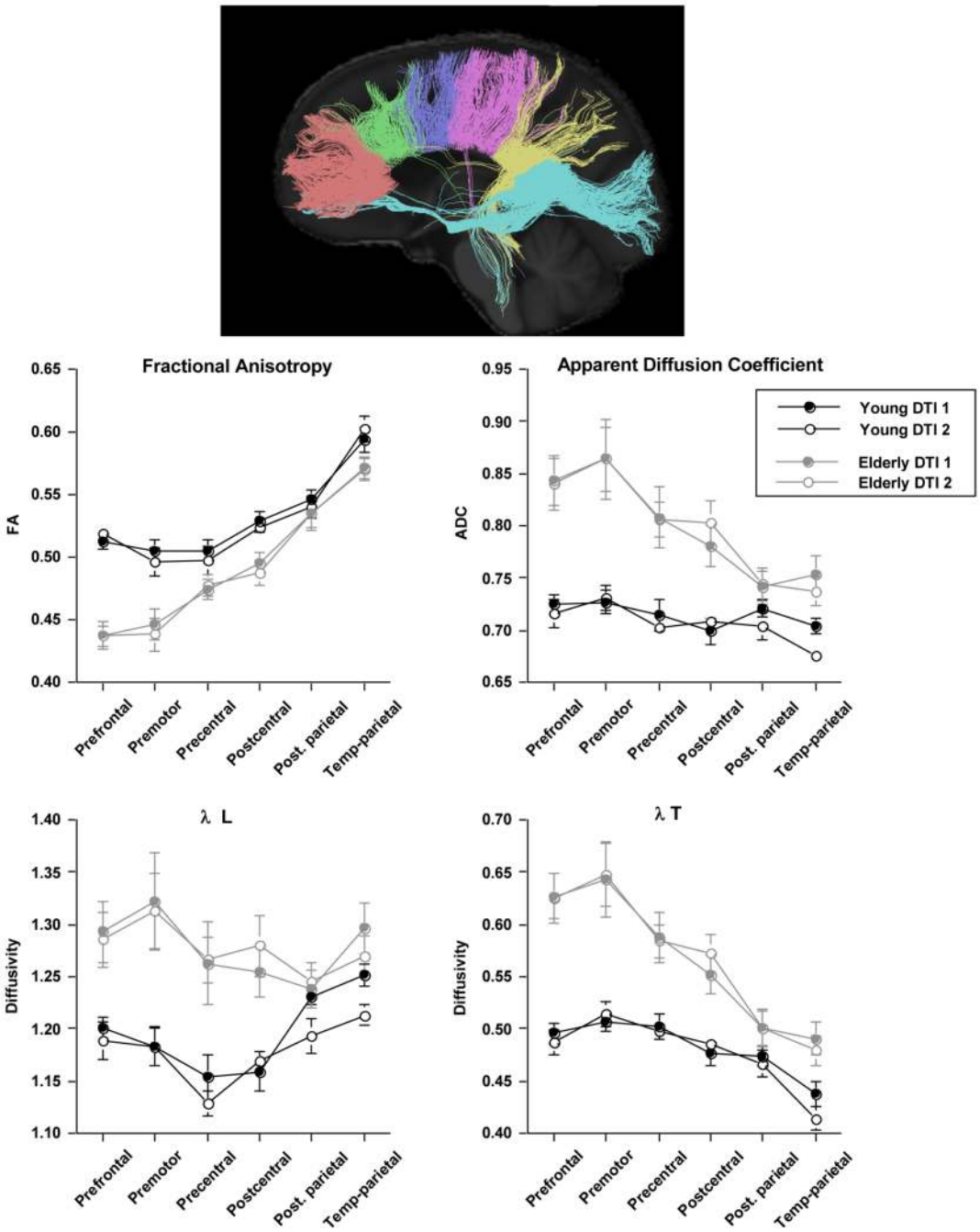

Figure 2.

Top sagittal image: Example of fiber tracking of the corpus callosum of a 23 year-old healthy woman. The colors represent six different fiber bundles based on divisions described by Pandya and Selzer (Pandya & Seltzer, 1986) identified with fiber tracking based on the DTI-derived FA. From anterior (far left) to posterior (far right), the bundles are deemed prefrontal, premotor, precentral, postcentral, posterior parietal, and temporal-occipital. Bottom data figures: Mean ±S.E. of the six callosal sectors for the young and elderly groups at each MRI session of the four principal metrics of DTI: fractional anisotropy (upper left), apparent diffusion coefficient (upper right), λL (lower left), and λT (lower right). The elderly group had lower FA and higher

diffusivity than the young group at both scanning sessions, and the group differences were greatest in the anterior sectors.

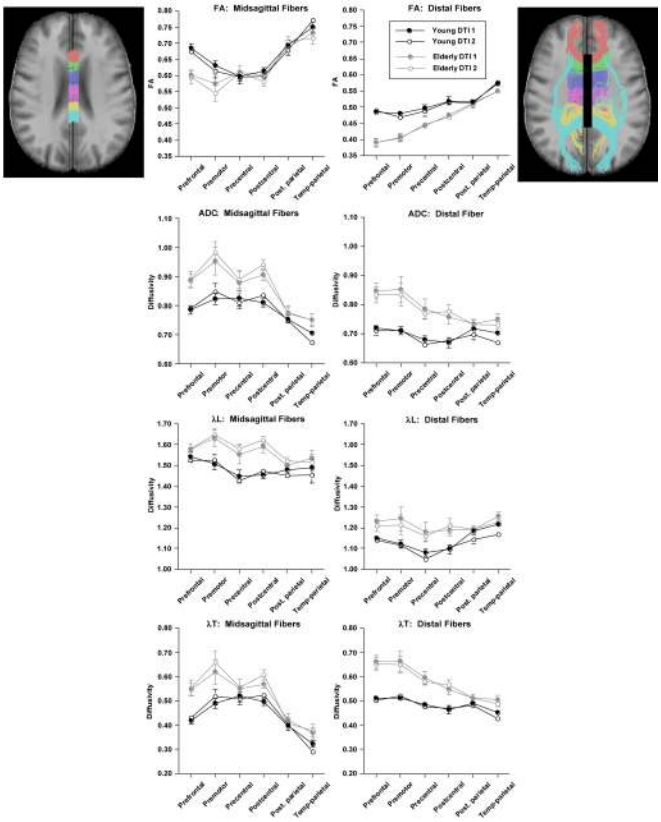

Figure 3.

Top axial image on left: Example of fiber tracking of the midsagittal corpus callosum. The colors represent six different fiber bundles defined in Figure 2. Left column of line plots: Mean ±S.E. of FA, ADC, λL, and λT of the midsagittal callosal fibers. Top axial image on right: Example of fiber tracking of the distal fibers of the corpus callosum. Right column of line plots: Mean±S.E. of FA, ADC, λL, and λT of the distal callosal fibers.

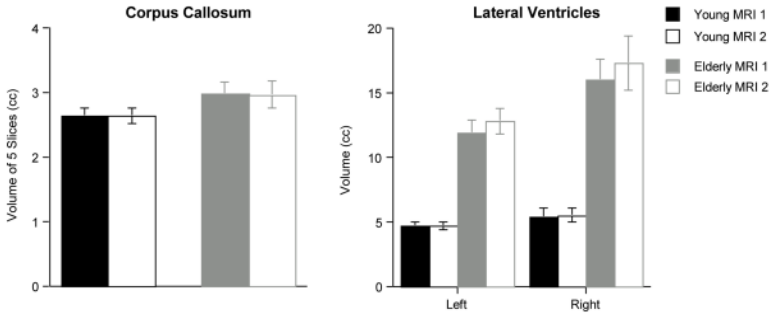

Figure 4.

Mean±S.E. of the volumes of the corpus callosum and lateral ventricles for the young and elderly groups at each MRI session. While the callosal volumes showed no detectable change in either group over the 2-year follow-up period (group-by-time interaction ($F(1,14)=.0093$, $p=.9245$), the lateral ventricles expanded disproportionately in the elderly relative to the young group (group-by-time interaction ($F(1,14)=8.921$, $p=.0098$).

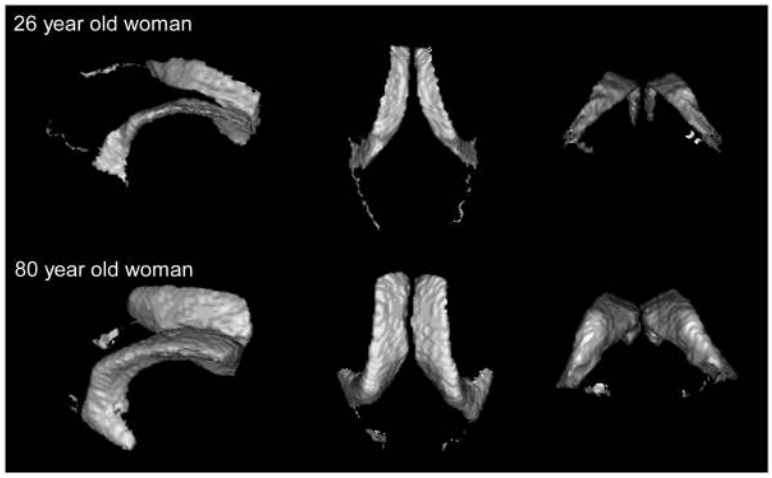

Figure 5.
Three-dimensional rendering of three views of the ventricular system: oblique sagittal view on left (frontal to occipital is right to left); axial view in middle (frontal to occipital is top to bottom); coronal view on right. All views reveal that the ventricles of the elderly women are substantially greater than those of the younger woman.