Differential Vulnerability of Anterior White Matter in Nondemented Aging with Minimal Acceleration in Dementia of the Alzheimer Type: Evidence from Diffusion Tensor Imaging

Denise Head[1,2], Randy L. Buckner[1,2,3,4], Joshua S. Shimony[3], Laura E. Williams[1], Erbil Akbudak[3], Thomas E. Conturo[3], Mark McAvoy[3], John C. Morris[5] and Abraham Z. Snyder[3,5]

[1]Howard Hughes Medical Institute, Washington University, St Louis, MO, USA, [2]Department of Psychology, Washington University, St Louis, MO, USA, [3]Mallinckrodt Institute of Radiology, Washington University School of Medicine, St Louis, MO, USA, [4]Department of Anatomy & Neurobiology,Washington University School of Medicine, St Louis, MO, USA and [5]Department of Neurology, Washington University School of Medicine, St Louis, MO, USA

White matter microstructural integrity was assessed using diffusion tensor imaging (DTI) in 25 young adults, 25 nondemented older adults, and 25 age-matched older adults with dementia of the Alzheimer type (DAT). For each individual, measures of anisotropy and diffusivity were obtained from atlas-transformed images in the anterior and posterior callosum and in the frontal, parietal, temporal and occipital white matter. These data revealed age differences in anisotropy and diffusivity in all assessed regions. Age effects were greater in the anterior as opposed to the posterior corpus callosum and greater in the frontal white matter than in the temporal, parietal and occipital white matter, suggesting age-associated differences in white matter that exhibit a roughly anterior-to-posterior gradient. In contrast, individuals with early-stage dementia exhibited minimal, if any, additional change in anterior regions but did show greater deterioration of white matter in posterior lobar regions. Taken collectively, these results indicate that nondemented aging is characterized by significant changes in white matter most prominently in anterior brain regions. The dissociation between the regional effects of age and dementia status suggests that the mechanisms underlying age-associated cognitive decline are likely distinct from those underlying DAT.

Keywords: Alzheimer's disease, cognitive control, DTI, MCI, MRI, prefrontal

Introduction

Aging is associated with complex patterns of cognitive decline and alterations to brain structure and function (Wang and Kaufman, 1993; Kemper, 1994; Schaie, 1994; Raz, 2000; Albert and Killiany, 2001). Here, age-associated change in white-matter integrity was explored within the context of a multiple component model of brain aging. Specifically, we examined anatomical differences associated with nondemented aging in contrast to differences associated with dementia of the Alzheimer type (DAT). Relevant to this exploration is a growing literature that suggests multiple, often co-occurring, alterations in brain structure and function underlie the complex constellation of cognitive change observed in nondemented and demented aging (Gabrieli, 1996).

Older adults with dementia show marked cognitive decline that is both clinically significant and, even in early-stage DAT, quite distinct from cognitive change associated with nondemented aging (Albert, 1996; Rentz and Weintraub, 2000; Storandt *et al.*, 2002). Older adults without clinical signs of dementia nonetheless show differences in cognitive performance when contrasted with younger adults including slowed processing and disruption of executive functions associated with cognitive control (Craik and Byrd, 1982; Moscovitch and Winocur, 1992; Nyberg *et al.*, 1996; Salthouse, 1996; Luszcz and Bryan, 1999; Greenwood, 2000; Park *et al.*, 2001). One possibility is that DAT represents accelerated aging such that the same pattern of change in neural and cognitive processes occurs but is greater in rate and extent, eventually resulting in profound impairment. Alternatively, DAT may reflect distinct degenerative brain changes superimposed on the processes that normally occur in nondemented aging. There is evidence that aging and DAT are distinct rather than part of a continuum in terms of both cognitive loss and structural change (Albert, 1998; Morris, 1999; Ohnishi *et al.*, 2001).

In nondemented aging executive control processes tend to be reduced and the memory problems that may be present are mild and possibly related to executive deficits rather than an amnestic syndrome (Craik and Byrd, 1982; Moscovitch and Winocur, 1995; West, 1996; Perfect, 1997). In contradistinction, although attentional control changes can be detected (Parasuraman and Haxby, 1993; Balota and Faust, 2001), significant deficits in mnemonic functions with relative sparing of implicit and procedural memory typifies cognitive deterioration in the early stages of DAT (Storandt *et al.*, 1984; Moscovitch *et al.*, 1986; Welsh *et al.*, 1992; Albert, 1996; Fleischman and Gabrieli, 1998; Backman *et al.*, 2001). These distinct patterns of cognitive loss may reflect different causal mechanisms.

Evidence from histopathological and *in vivo* neuroimaging investigations using primarily cross-sectional designs suggests vulnerability of prefrontal gray and neostriatal structures to the deleterious effects of advancing age (Kemper, 1994; West, 1996; Raz, 2000; Good *et al.*, 2001; Jernigan *et al.*, 2001; Salat *et al.*, 2004). Recent longitudinal data also indicate greater changes in frontal (and parietal) regions (Resnick *et al.*, 2003). Age effects on the volume of the hippocampus tend to be in the mild-to-moderate range and not as striking as the effects observed in frontostriatal circuits (Raz, 2000). In contrast to nondemented aging, there is an allocortical-to-neocortical temporal progression of brain pathology in DAT as observed in histopathological studies. The entorhinal cortex and hippocampus appear to be affected in the earliest stages of the disease with subsequent involvement of temporal and parietal cortices. Eventually, frontal regions and the entire neocortex become affected (Braak and Braak, 1991, 1997; Price *et al.*, 1991; Price and Morris, 1999). Despite these observed distinctions, the relationship between nondemented and demented aging is still under debate (Huppert and Brayne, 1994; Whalley, 2002).

Alterations in white matter, including volume reductions, demyelination and white matter degeneration observed as

Cerebral Cortex April 2004;14:410–423; DOI: 10.1093/cercor/bhh003

white matter hyperintensities (WMH), are present in both nondemented older adults and individuals with DAT (Breteler *et al.*, 1994; Kemper, 1994; Waldemar *et al.*, 1994; Tang *et al.*, 1997; Raz, 2000; DeCarli and Scheltens, 2001; de Leeuw *et al.*, 2001; Jernigan *et al.*, 2001; O'Brien *et al.*, 2002; Bartzokis *et al.*, 2003). Persistent debate exists regarding the extent and regional variation of white matter damage in each population. In nondemented aging, white matter volume loss tends to be less than gray matter loss (Courchesne *et al.*, 2000; Raz, 2000; Good *et al.*, 2001) but see (Salat *et al.*, 1999; Jernigan *et al.*, 2001) but still with a predilection for anterior regions (Raz, 2000; Jernigan *et al.*, 2001). In addition, increased burden of WMHs tend to be greater in prefrontal regions (Gunning-Dixon and Raz, 2000; DeCarli and Scheltens, 2001). Support can be found in the literature for both a greater burden of WMH in DAT than in nondemented older adults and for similarities in the extent of WMH between the two groups (Kozachuk *et al.*, 1990; Leys *et al.*, 1990; Waldemar *et al.*, 1994; Scheltens *et al.*, 1995; Fazekas *et al.*, 1996). The equivocal contribution of WMH to DAT suggests it is at most a modulator of the disease but not central to its cause.

The corpus callosum, one of the most heavily myelinated regions of the brain, consists of fibers arising from large pyramidal neurons in layers III and V and is topographically organized longitudinally from rostrum to splenium (de Lacoste *et al.*, 1985; Pandya and Seltzer, 1986). *In vivo* assessments of the midsagittal area of the corpus callosum reveal mild nondemented age-related differences (Driesen and Raz, 1995) with additional decrements associated with DAT status (Lyoo *et al.*, 1997; Pantel *et al.*, 1999; Hensel *et al.*, 2002). Considering the topographical organization of the corpus callosum, atrophic changes in callosal regions may be expected to correspond to regional cortical atrophy. Thus, it would be expected that the specificity of nondemented aging and DAT effects on the corpus callosum might differ, reflecting the differing distribution of atrophy in these conditions. Consonant with this, the extant neuroimaging literature suggests aging effects predominantly in the frontal callosal fiber system (Weis *et al.*, 1991; Aboitz *et al.*, 1996; Janowsky *et al.*, 1996) but see Sullivan *et al.* (2002). Discrepancies, however, emerge from the literature assessing regional patterns of DAT effects. Although there is some evidence that the DAT effect may be greatest in the posterior fiber systems (Lyoo *et al.*, 1997; Teipel *et al.*, 1999), there are additional reports suggesting that anterior as well as posterior regions are particularly affected with some indications of relative sparing of the body of the corpus callosum (Begion *et al.*, 1994; Janowsky *et al.*, 1996; Pantel *et al.*, 1998, 1999; Teipel *et al.*, 1998, 1999, 2002). The composition of the DAT group may be an important determinant with the emergence of significant DAT effects on the corpus callosum not occurring until the mildly demented stage (Hensel *et al.*, 2002).

Diffusion tensor imaging (DTI) is a relatively recent advance that provides *in vivo* examination of white matter microstructure and has the potential for clarifying the inconsistencies in the literature. DTI takes advantage of the inherent properties of the motion of water. Specifically, the rate of diffusion is isotropic (equal in all directions) in unconstrained media such as the cerebrospinal fluid. In constrained media such as white matter tracts, water molecules move faster parallel than perpendicular to microscopic cellular or subcellular boundaries causing diffusion to be anisotropic. In DTI one can quantitate both the directionally averaged rate of diffusion (mean diffusivity) and the strength of the direction dependence of diffusion (anisotropy). DTI thus provides measures of the rate and directionality of water movement. Disruptions in the integrity of the white matter such as may occur in normal or pathological aging alter both anisotropy and mean diffusivity. Measured anisotropy will be lower in regions containing crossing fibers (Virta *et al.*, 1999). In addition, partial volume contamination (e.g. inclusion of non-white matter voxels) potentially impacts estimates of anisotropy (Virta *et al.*, 1999; Pfefferbaum and Sullivan, 2003). However, there is no reason to presume that such effects should differentially affect various populations.

Investigations in nondemented populations provide evidence that, within the context of global and regional increases in mean diffusivity and decreases in anisotropy (Gideon *et al.*, 1994; Chun *et al.*, 2000; Engelter *et al.*, 2000; Chen *et al.*, 2001; Nusbaum *et al.*, 2001; O'Sullivan *et al.*, 2001; Abe *et al.*, 2002; Sullivan and Pfefferbaum, 2003), anterior callosal and lobar fiber tracts may be more affected than posterior tracts (Pfefferbaum *et al.*, 2000; O'Sullivan *et al.*, 2001; Abe *et al.*, 2002). Diffusion-weighted MRI and DTI investigations of individuals with DAT (Sullivan and Pfefferbaum, 2003) note changes in whole brain white matter (Bozzali *et al.*, 2001) and posterior fiber tracts (Hanyu *et al.*, 1998; Sandson *et al.*, 1999; Rose *et al.*, 2000; Kantarci *et al.*, 2001; Takahashi *et al.*, 2002) with some evidence suggesting that the posterior fiber tracts are more affected than anterior fiber tracts (Sandson *et al.*, 1999; Kantarci *et al.*, 2001; Takahashi *et al.*, 2002). However, other reports note both anterior and posterior changes (Hanyu *et al.*, 1997, 1999; Bozzali *et al.*, 2002) or no significant changes (Bozzao *et al.*, 2001).

The general goal of the present study was to examine the effects of aging and dementia on white-matter integrity using DTI. Two separate questions were addressed associated with (i) the anatomic distribution of alterations and (ii) whether alterations were associated with aging or dementia status. The anatomic distribution of aging and dementia effects was addressed by examining multiple, separate regions of interest (ROI) that spanned anterior and posterior brain structures. Regional analyses began with a targeted exploration of anterior versus posterior portions of the corpus callosum. The corpus callosum is anatomically well defined, allowing precise regions to be selected, and also contains coherent white-matter tracts with high anisotropy. Additionally, lobar regions were explored in secondary analyses. A final analysis used an exploratory map-wise approach to characterize the pattern of anatomic alterations. The second question, regarding the effects of aging versus dementia, was addressed by selecting three participant groups that differed in age and dementia status (young, nondemented older and DAT adults). Only individuals with early-stage DAT were included, allowing separation of nondemented age-associated effects from effects of DAT, which are known to be widespread at later stages.

Materials and Methods

Participants

Younger adults were undergraduate students at Washington University and were screened for neurologic illness or injury and use of psychoactive medications. Older adults were recruited from the Washington University Alzheimer's Disease Research Center (ADRC). Exclusion criteria included any neurologic illness or injury, current depression, medical conditions that might produce cognitive impair-

ment, and use of psychoactive medications. All participants were right-handed and native English speakers. Older adults were identified as demented or nondemented based on the Washington University Clinical Dementia Rating (CDR; Hughes *et al.*, 1982; Morris, 1993), which is an interview-based measure that examines the memory, orientation, judgment and problem solving, community affairs, home skills and hobbies and personal care of the participant. The interview is conducted with the participant and a collateral source. The diagnosis was established with this clinical assessment protocol in accordance with the NINCDS/ADRDA criteria. The validity of the CDR to distinguish between nondemented and demented individuals has been established by longitudinal and neuropathological follow-up studies (Berg *et al.*, 1998; Morris *et al.*, 2001).

The sample consisted of 25 younger adults, 25 nondemented older adults, and 25 individuals diagnosed with very mild-to-mild DAT. Sample characteristics are provided in Table 1. The DAT individuals had lower scores on the Mini-Mental State Examination (MMSE) than the nondemented older adults, $t(46) = 6.29$, $P < 0.001$. Nondemented older adults had slightly more years of education than individuals with DAT, $t(48) = 2.74$, $P < 0.01$.

All participants consented to participation in accordance with guidelines of the Washington University Human Studies Committee and were paid for their participation.

MR Acquisition

All imaging was performed using a Siemens 1.5 Tesla Vision scanner (Erlangen, Germany). Cushions and a thermoplastic mask were used during scanning to reduce head movement. The imaging protocol included high-resolution 3D T_1-weighted imaging (MP-RAGE), T_2-weighted turbo-spin echo (TSE) imaging, and echo-planar imaging-based tensor-encoded diffusion-weighted (DWI) scans. Three to four repetitions of sagittal MP-RAGE (T_R = 9.7 ms, T_E = 4 ms, FA = 10°, T_I = 20 ms, T_D = 200 ms, 128 × 128 matrix, voxel dimensions of 1 mm × 1 mm × 1.25 mm) were acquired. Two manually interleaved sagittal TSE multislice volumes (T_R = 6150 ms, T_E = 15 ms, 1 mm in-plane resolution, 2 mm thick slices with 2 mm gap) served as alignment intermediates in the registration of the diffusion data to each subject's MP-RAGE and ultimately, the standard atlas. The diffusion tensor imaging (DTI) protocol was similar to one previously described (sequence B in Shimony *et al.*, 1999). A custom, single-shot, spin-echo echo-planar imaging sequence (T_R = 7200 ms, T_E = 108 ms, 128 × 128 matrix, 36 contiguous 4 mm slices, acquired in plane resolution 2.5 mm² interpolated to 1.25 mm²) provided a combination of tetrahedral (b = 1004.91 s/mm²) and orthogonal (b = 334.97 s/mm²) sensitization plus one reference (unsensitized, or I_0) volume. For all encodings, the gradient duration, δ, and offset, Δ, were 19.0 ms and 42.83 ms, respectively.

Four untilted axial DTI scan repetitions were acquired in each subject for signal averaging. Inter- and intra-scan motion correction and averaging were accomplished off-line.

Image Processing

Image processing prior to ROI analysis included several image registration steps ultimately resulting in coregistered structural and diffusion-weighted data resampled to 1 mm³ voxels in the atlas space of Talairach and Tournoux (1988). The following describes the image registration steps carried out for each individual. First, a 12-parameter affine atlas transform was computed for one MP-RAGE. The atlas representative target image represented 12 (six female) young adult and 12 (nine female) nondemented old (mean age 75 years) subjects (Buckner *et al.*, 2000; Logan *et al.*, 2002). For each subject, the remaining MP-RAGE images were registered to the first (rigid body plus in-plane stretch) and atlas transforms for all MP-RAGE images were computed by transform composition (matrix multiplication). Each subject's averaged, atlas-transformed MP-RAGE then was produced using a single interpolation per scan. A similar strategy, i.e. transform composition followed by a single resampling step (Ojemann *et al.*, 1997) was used to align and atlas-transform the T_2-weighted and diffusion sensitized data. Alignment of diffusion sensitized data proceeded separately for each of the four acquisitions and included several steps. First, the 3D transform linking the TSE (conventional T_2 weighted) data and the I_0 volume was computed. Slice-based (2D) registration (allowing in-plane stretch to compensate for echo-planar imaging distortion) was used to align the DWI data onto I_0. For each DWI scan, the atlas transform obtained by transform composition (DWI → I_0 → TSE → MP-RAGE → atlas) included compensation for inter-scan head movement. The DWI data finally were resampled and averaged in atlas space.

The diffusion tensor was computed at each voxel in atlas space using standard least-squares techniques. Two tensor-derived rotational invariants were saved for subsequent ROI-based analysis. Mean diffusivity ($\bar{D}$) was calculated as the average of the three diagonal tensor elements. To measure anisotropy we calculated A_σ, as previously defined (Conturo *et al.*, 1996; Shimony *et al.*, 1999). This measure is similar to fractional anisotropy (FA) (Basser, 1995; Basser and Pierpaoli, 1996) and proportional to relative anisotropy (Basser and Pierpaoli, 1996; Pierpaoli and Basser, 1996). However, the obtained values of A_σ tend to be lower than FA values. A_σ is defined on a 0 (equal diffusion in all directions) to 1 (diffusion in only one direction) interval. Group-averaged A_σ and $\bar{D}$ images are presented in Figure 1.

Region-of-Interest (ROI) Measurement Procedure

All measurements were obtained using Analyze software (Version 4.0, Mayo Clinic) on the atlas-transformed anisotropy (A_σ) and diffusivity ($\bar{D}$) images of each individual participant. Images for each participant

Table 1
Sample characteristics

	Young	Nondemented old (CDR = 0)	DAT		
			Total	CDR = 0.5	CDR = 1
n	25	25	25	14	11
Mean age (years)	22 ± 2	77 ± 5	77 ± 6	76 ± 5	77 ± 6
Age range	19–28	69–88	69–87	69–86	69–87
Sex (F/M)	12/13	18/7	17/8	10/4	7/4
Mean education (years)	n/a	15 ± 3	13 ± 2	13 ± 2	12 ± 2
Education range (years)	n/a	8–20	8–16	8–16	8–14
MMSE	n/a	28.9 ± 1.2	22.9 ± 4.7	25.1 ± 3.2	19.8 ± 4.8
MMSE range	n/a	26–30	15–30	20–30	15–27

CDR = Clinical Dementia Rating, where CDR 0 = no dementia, CDR 0.5 and 1 = very mild and mild dementia, respectively. MMSE = Mini-Mental State Exam (Folstein and Folstein, 1975), where the range from best to worst performance is 30–0; DAT = dementia of the Alzheimer type; F = females; M = males; n/a = not available/applicable.

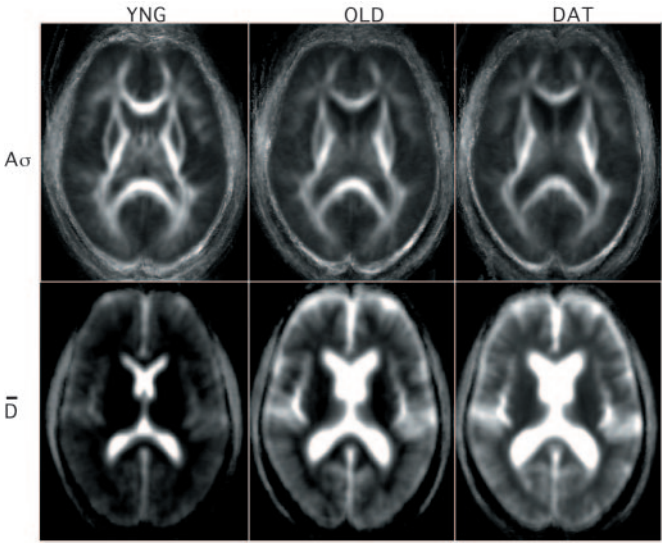

Figure 1. Group-averaged anisotropy (A_σ) [0 (dark) to 0.5 (white)] and mean diffusivity ($\bar{D}$) [0.65 (dark) to 1.5 (white) $\mu m^2/ms$] for the three subject groups. The A_σ and $\bar{D}$ images were computed from DWI data, transformed into a standard atlas space and then the A_σ and $\bar{D}$ images were averaged across the 25 individuals within each group. For all groups the selected slice corresponds to $Z = 12$ in the atlas of Talairach and Tournoux (1988).

were displayed on a 15-inch interactive display monitor (Cintiq 15x, Wacom) and each ROI was manually outlined on the screen with the accompanying grip pen. One operator (DH), blind to participant age and dementia status, manually outlined the ROIs. The method of manually determined, individualized ROIs was selected, in part, to minimize partial volume contamination. Examples of the tracings of the ROIs on an atlas-transformed individual participant are depicted in Figure 2 and specific rules are described below. Due to echo-planar image distortion, there was some misregistration in the frontal regions between the T_1-weighted MP-RAGE and the DTI images. Thus, it was not possible to define the regions-of-interest on other image data sets. Instead, ROIs were outlined on the anisotropy (A_σ) images directly. This procedure is analogous to that typically used for T_1-weighted images and is affected by changes in regional volume.

Corpus Callosum

The anterior corpus callosum (genu and rostrum) and the splenium were outlined separately on sagittal images. Measurement commenced on the midsagittal slice and continued on the next 10 lateral slices in both hemispheres for a total 21 slices. The anterior regions were defined as the anterior 25% of the callosum and the splenium as the posterior 25%. Due to artifacts in the images it was not possible to reliably determine an ROI for the body of the callosum.

Prefrontal White Matter (PFWM)

The PFWM was measured on 14–19 coronal slices. The most anterior slice on which the PFWM was measured was at the rostral point of the cingulate sulcus and the most posterior slice was the slice immediately anterior to the genu of the corpus callosum. These ranges were determined on the T_1-weighted images. The subcortical white matter adjacent to the frontal and cingulate gyri was included in this measure.

Temporal Lobe White Matter (TLWM)

The TLWM was measured on 17–19 coronal slices beginning at the mammillary bodies and ending at the posterior commissure as determined on T_1-weighted images. An ovoid ROI was drawn in the area of the temporal stem and adjusted to avoid adjacent cerebrospinal fluid.

Parietal Lobe White Matter (PLWM)

The PLWM was estimated on 10 coronal slices with measurement beginning 10 mm posterior to the splenium and continuing posteriorly for another 10 mm. A line was drawn at the superior point of the lateral ventricles on the most anterior slice and applied to 10 consecutive slices. All white matter superior to this line was included in this measure and consisted of portions of the angular, superior parietal, and cuneate gyri.

Occipital Lobe White Matter (OLWM)

The OLWM was estimated on 15 axial images. The most superior slice on which the OLWM was measured was the last slice of the putamen and measurement continued for 10 mm inferior to this slice. A rectangular region of interest was placed on the white matter adjacent to the ventricles and below the level of the splenial fibers of the corpus callosum. The rectangular region was adjusted to avoid adjacent cerebrospinal fluid.

Exploratory Whole-brain Analysis

As a supplementary analysis, we examined the effects of nondemented aging and dementia status on a map-wise basis. The spatially normalized anisotropy and diffusivity images were first smoothed using a Gaussian kernel of 2 mm full-width at half-maximum. Between group-differences were explored for each voxel with independent samples *t*-tests based on a random effects model. Obtained *t*-scores were converted to equiprobable *Z*-scores and resulting maps were thresholded at a $P < 0.001$ level, uncorrected for multiple comparisons.

Results

Anisotropy and diffusivity values from each hemisphere were averaged to obtain a total regional value. Data were examined with a series of mixed general linear models with Tukey's HSD *post hoc* analyses. Group (young, nondemented old, and DAT) and sex were categorical variables and brain region (e.g. anterior callosum and posterior callosum) was a within-subject categorical variable. Anisotropy and diffusivity were analyzed separately.

Corpus Callosum

Initial targeted analyses focused on the anterior and posterior regions of the corpus callosum. These regions provide anatomically constrained targets with intrinsically high anisotropy of white matter. In the analysis of anisotropy (Fig. 3*A*,*B*), there was a significant main effect of Group [$F(2,69) = 13.21$, $P < 0.001$]. *Post hoc* Tukey's HSD tests indicated significant differences between the young and nondemented old ($P < 0.001$) and between the young and DAT groups ($P < 0.001$), but not between the nondemented old and DAT groups ($P = 0.90$). The Brain Region × Group interaction was also significant [$F(2,69) = 9.92$, $P < 0.001$] suggesting an anterior-to-posterior gradient. The anterior and posterior callosum were examined in separate univariate ANOVAs to decompose this interaction. The main effect of Group was significant in the anterior callosum [$F(2,69) = 22.57$, $P < 0.001$]. *Post hoc* analyses revealed significant differences between the young and nondemented ($P < 0.001$), but not between the nondemented old and DAT groups ($P = 0.87$) in the anisotropy of the anterior callosum. In the separate analysis of the posterior callosum there was again a main effect of Group, [$F(2,69) = 3.06$, $P = 0.05$]. *Post hoc* analyses indicated that neither the young and nondemented old groups ($P = 0.10$) nor the nondemented and DAT groups ($P = 0.95$) differed in anisotropy of the posterior callosum. The only significant difference was between the young and DAT groups ($P = 0.05$). These results suggest that the differential effects on

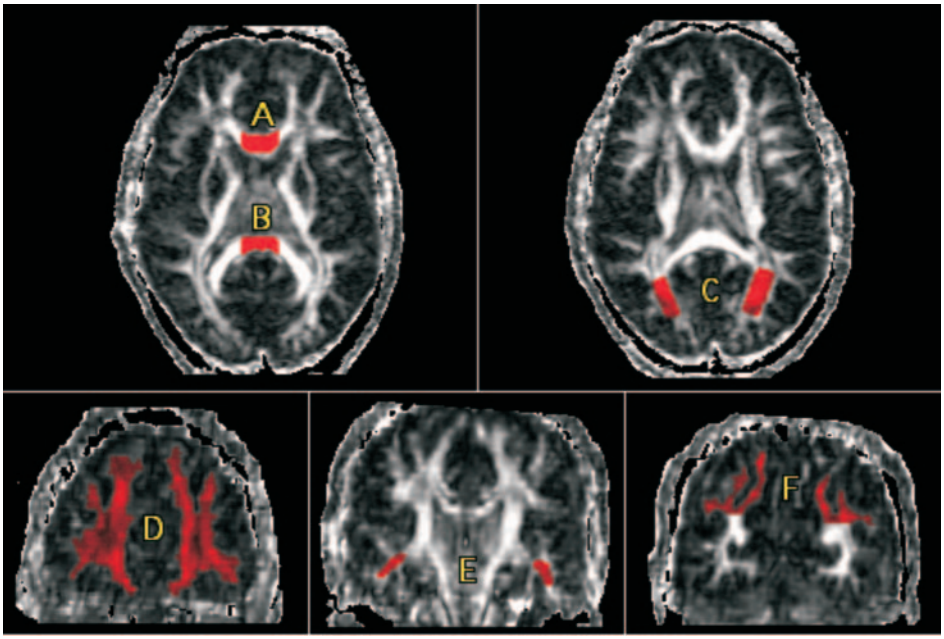

Figure 2. Examples of ROI demarcation on anisotropy images: (*A*) anterior corpus callosum; (*B*) posterior corpus callosum; (*C*) occipital lobe white matter; (*D*) frontal lobe white matter; (*E*) temporal lobe white matter; and (*F*) parietal lobe white matter

the callosum were associated with aging with minimal acceleration in DAT.

To further examine differential effects of age on the corpus callosum, the older adults (both nondemented old and DAT) were examined separately with age as a continuous variable (see Fig. 3*C*,*D*). The Brain Region × Age interaction was significant in the combined group of nondemented and DAT participants [$F(1,48) = 6.57$, $P < 0.05$], reflecting greater reductions with age in the anterior callosum ($r = -0.30$, $P < 0.05$) than in the posterior callosum ($r = 0.02$, NS). Note that this analysis is independent from the earlier analysis that compared young adults with older adults, providing a separate observation of the age-associated anterior-to-posterior gradient of change in the callosum. A similar pattern was observed when the nondemented old group was examined in isolation [$F(1,23) = 5.12$, $P < 0.05$; anterior callosum, $r = -0.42$, $P < 0.05$, and posterior callosum, $r = -0.08$, NS]. Although the overall pattern was similar in the DAT group, the Brain Region × Age interaction failed to reach significance [$F(1,23) = 2.15$, NS] and the age effects were not significant in either the anterior ($r = -0.20$, NS) or posterior callosum ($r = 0.09$, NS). There were no sex differences or interactions with sex in any of these analyses (all F values < 1.23).

Analysis of the mean diffusivity data revealed a significant main effect of Group [$F(2,69) = 23.74$, $P < 0.001$] with *post hoc* tests indicating significant differences between the young and nondemented old ($P < 0.001$) and DAT groups ($P < 0.001$), but not between the nondemented old and DAT groups ($P = 0.36$). Thus, there was increased diffusivity in the callosal regions in nondemented older adults and DAT individuals compared with younger adults, but individuals with DAT did not show significantly increased diffusivity in either the anterior or posterior callosum compared with nondemented older adults. These group effects did not significantly differ between the anterior and posterior callosum (Fig. 4*A*,*B*): Brain Region × Group interaction [$F(2,69) = 1.30$, NS].

To further examine differential effects of age on the corpus callosum, the older adults were examined separately with age as a continuous variable (see Fig. 4*C*,*D*). The Brain Region × Age interaction was significant [$F(1,48) = 7.30$, $P < 0.05$], reflecting greater increases in diffusivity with age in the anterior callosum ($r = 0.50$, $P < 0.001$) than in the posterior callosum ($r = 0.34$, $P < 0.05$), replicating the anterior-to-posterior gradient observed with anisotropy. When only the nondemented older adults were assessed, a nonsignificant trend towards a similar pattern was observed [$F(1,23) = 4.05$, $P = 0.06$], with the age effects significant in the anterior callosum ($r = 0.54$, $P < 0.01$), but not in the posterior callosum ($r = 0.31$, NS). Within the DAT group, there was also a nonsignificant trend [$F(1,23) = 3.56$, $P = 0.07$] for the anterior callosum ($r = 0.51$, $P < 0.01$) to show greater age-related increases in diffusivity than the posterior callosum ($r = 0.39$, $P = 0.06$). As in the anisotropy data, there were no sex differences or interactions with sex in any of these analyses (all F values < 1).

We also examined the effects of dementia severity by comparing individuals with very mild dementia (CDR = 0.5) to individuals with mild dementia (CDR = 1). There were no significant effects of dementia severity on the anisotropy of the anterior, $t(23) = 1.62$, NS, or posterior callosum ($t < 1$). Mean values for anterior and posterior callosum were 0.37 ± 0.07 and 0.50 ± 0.08, respectively, for CDR = 0.5 and 0.42 ± 0.06 and 0.52 ± 0.07, respectively, for CDR = 1. There were no significant effects of dementia severity on the diffusivity of the anterior or posterior callosum (ts < 1). Mean values for anterior and posterior callosum were 1.01 ± 0.12 and 0.88 ± 0.06, respectively, for CDR = 0.5 and 0.96 ± 0.10 and 0.89 ± 0.06, respectively, for CDR = 1.

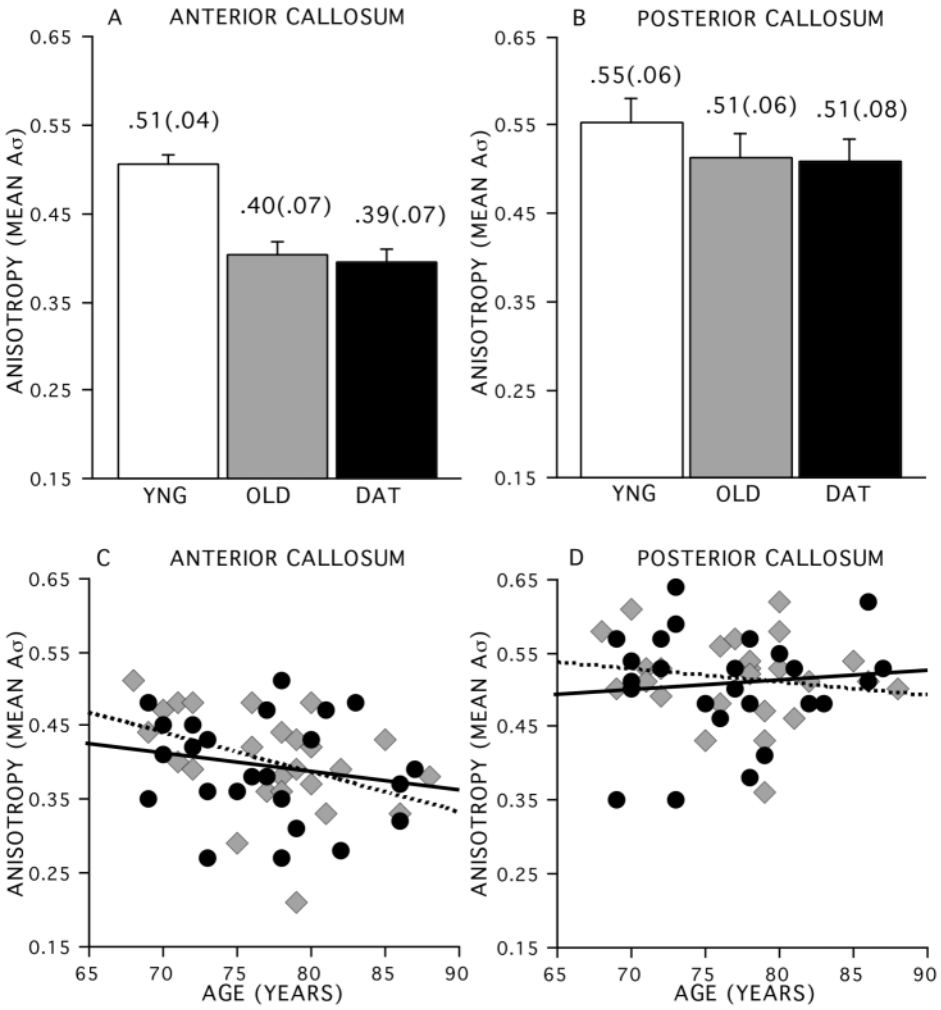

Figure 3. Comparison of anisotropy in the corpus callosum between young (white bars), nondemented older adults (gray bars) and demented older adults (black bars). (*A*) Anterior corpus callosum with mean (SEM). (*B*) Posterior corpus callosum with mean (SEM). (*C*) Scatterplot of anisotropy in the anterior corpus callosum in nondemented older adults (gray diamonds) and demented older adults (black circles). (*D*) Scatterplot of anisotropy in the posterior corpus callosum in nondemented older adults (gray diamonds) and demented older adults (black circles). The dashed and black linear regression lines apply, respectively, to the nondemented and demented older adult groups. Numbers indicate bar values with SD in parentheses.

Overall, there were age differences in the anisotropy and diffusivity of both the anterior and posterior corpus callosum with age effects tending to be greater in the anterior region. In relation to the anterior-to-posterior gradient of age-related differences in the callosum, three of the four possible analyses (young versus nondemented older adults for anisotropy and diffusivity data, relationship with age in older adults for anisotropy and diffusivity data) converged on this gradient, with the exception being failure to reach significance in the comparison of young adults with older adults for the diffusivity data. Importantly, individuals with DAT did not show significantly lower anisotropy or increased diffusivity compared with nondemented old adults, and thus the observed differences were reflective of aging independent of dementia status. Furthermore, the effect of age and dementia status was similar for both men and women.

Lobar Regions

Data for the lobar regions were also examined with a series of mixed general linear models with Tukey's HSD *post hoc* analyses. Group (young, nondemented old, and DAT) and sex were categorical variables and brain region (frontal, temporal, parietal and occipital) was a within subject categorical variable. Anisotropy and diffusivity data were analyzed separately and results are presented in Figures 5 and 6, respectively.

In the analysis of anisotropy there was a significant main effect of Group, $F(2,69) = 78.83$, $P < 0.001$. *Post hoc* analyses indicated significant differences between young and nondemented old groups ($P < 0.001$) and between young and DAT groups ($P < 0.001$) but not between the nondemented old and DAT groups ($P = 0.12$). There was also a significant Brain Region × Group interaction, $F(6,136) = 2.49$, $P < 0.05$. Separate univariate analyses of each lobar region were performed to decompose this interaction. In all analyses the main effect of Group was significant: frontal, $F(2,69) = 73.02$, $P < 0.001$; temporal, $F(2,69) = 30.75$, $P < 0.001$; parietal $F(2,69) = 41.14$, $P < 0.001$; and occipital, $F(2,69) = 30.53$, $P < 0.001$. *Post hoc* analyses indicated significant differences between the young and nondemented old groups in all analyses: frontal ($P < 0.001$), temporal ($P < 0.001$), parietal ($P < 0.001$), and occipital

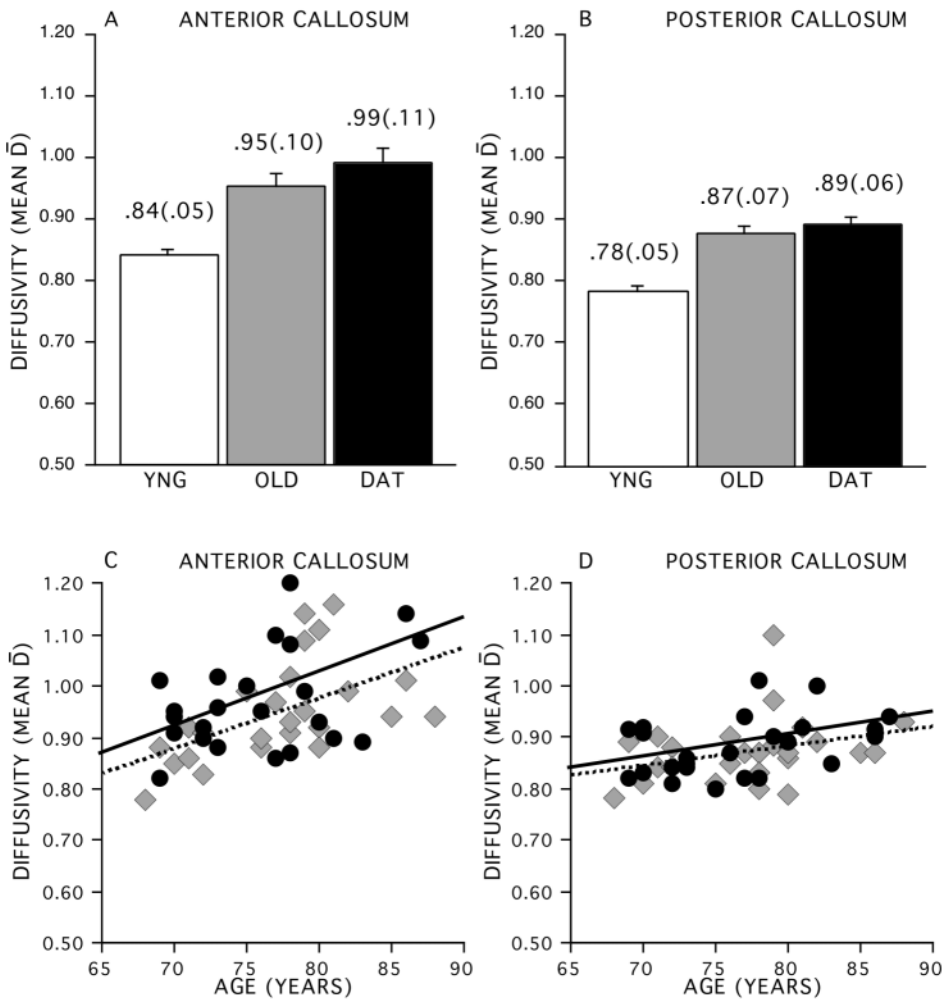

Figure 4. Comparison of diffusivity in the corpus callosum between young (white bars), nondemented older adults (gray bars) and demented older adults (black bars). (*A*) Anterior corpus callosum with mean (SEM). (*B*) Posterior corpus callosum with mean (SEM). (*C*) Scatterplot of diffusivity in the anterior corpus callosum in nondemented older adults (gray diamonds) and demented older adults (black circles). (*D*) Scatterplot of diffusivity in the posterior corpus callosum in nondemented older adults (gray diamonds) and demented older adults (black circles). The dashed and black linear regression lines apply, respectively to the nondemented and demented older adult groups. D is in units of μm^2/ms.

($P < 0.001$). Comparison of the magnitudes of the age effects using Cohen's *d* and confidence intervals (CI) revealed larger young versus nondemented old age differences in the anisotropy of the frontal region ($d = 2.46$; CI = 2.19–2.74) than in the temporal ($d = 1.93$; CI = 1.70–2.16), parietal ($d = 1.48$; CI = 1.28–1.68) or occipital regions ($d = 1.93$; CI = 1.70–2.16). Additionally, the age differences in occipital anisotropy were significantly smaller than in the temporal and parietal regions. In contrast, *post hoc* analyses indicated that there was a nonsignificant trend for differences between the nondemented old and DAT groups in anisotropy of the parietal region ($P < 0.06$) but nonsignificant differences in the frontal ($P = 0.99$), temporal ($P = 0.21$), and occipital regions ($P = 0.34$). There were no sex differences or interactions with sex in any of these analyses (all *F* values < 2.6, NS). Overall, the anisotropy of the frontal, temporal, parietal and occipital regions showed significant age differences, and the differences were larger in magnitude in the frontal as compared with other lobar regions. There were no significant effects of DAT on anisotropy and there were no differences between men and women.

Analysis of the diffusivity data also revealed a main effect of Group [$F(2,69) = 93.55$, $P < 0.001$]. *Post hoc* analyses indicated significant differences between all groups: young versus nondemented old ($P < 0.001$), young versus DAT ($P < 0.001$) and nondemented old versus DAT ($P < 0.001$). A significant Brain Region × Group interaction, $F(6,136) = 8.97$, $P < 0.001$, was also observed. Separate univariate analyses of each lobar region were performed to decompose this interaction. In all analyses the main effect of Group was significant: frontal, $F(2,69) = 40.76$, $P < 0.001$; temporal, $F(2,69) = 71.61$, $P < 0.001$; parietal, $F(2,69) = 37.65$, $P < 0.001$; and occipital, $F(2,69) = 20.51$, $P < 0.001$. *Post hoc* analyses indicated significant differences between the young and nondemented old groups in all analyses: frontal ($P < 0.001$), temporal ($P < 0.001$), parietal ($P < 0.001$), and occipital ($P < 0.05$). Comparison of the magnitudes of the age effects revealed larger age differences in the diffusivity of the frontal region ($d = -3.08$; CI = –3.42 to –2.74) than in the temporal ($d = -2.15$; CI: –2.40 to –1.90), parietal (–1.93; CI: –2.16 to –1.70) or occipital regions ($d = -1.11$; CI = –1.30 to –0.93). In addition, age differences in occipital diffusivity were smaller than in the temporal and parietal regions. In contrast, differences between the nondemented old and DAT groups were significant for the diffusivity of the temporal ($P < 0.001$), parietal ($P < 0.01$) and occipital regions ($P < 0.01$) but not for

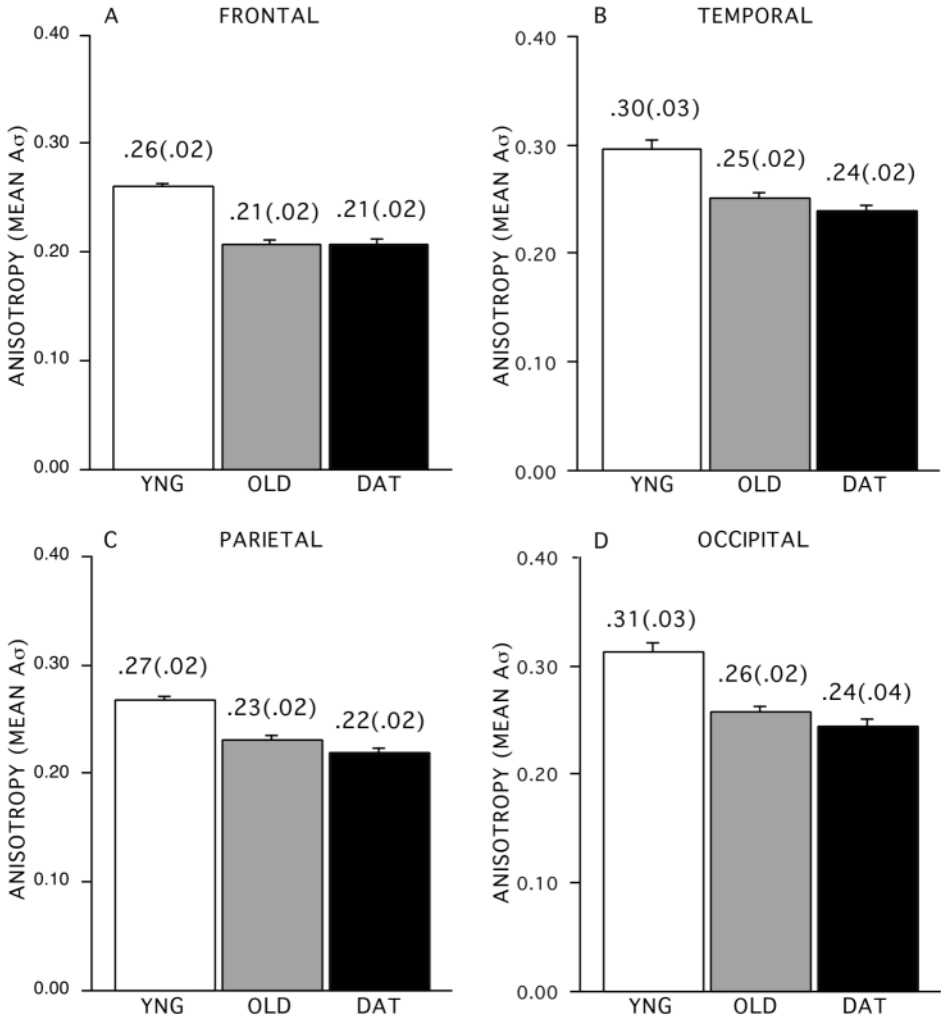

Figure 5. Comparison of anisotropy in the lobar regions between young (white bars), nondemented older adults (gray bars) and demented older adults (black bars). (*A*) Frontal lobe white matter, (*B*) temporal lobe white matter, (*C*) parietal lobe white matter, (*D*) occipital lobe white matter.

the frontal region ($P = 0.73$). Neither the main effect of sex nor the Brain Region × Sex interaction was significant in any of the analyses (all F values < 2.4, NS).

Thus, the age effects on diffusivity were similar to those observed on anisotropy with significant age differences emerging for all lobar regions and greater effects in frontal than other lobar regions. The effects of dementia status were not significant in the anisotropy or diffusivity of the frontal regions; however, there were significant effects on the diffusivity of the temporal, parietal and occipital regions. Furthermore, there were no significant effects of dementia severity on the anisotropy of any of the lobar regions (all ts < 1.21). There were no significant effects of dementia severity on the diffusivity of the frontal (t < 1), temporal (t < 1), parietal ($t(23) = 1.36$, NS) or occipital white matter, $t(23) = 1.52$, NS.

Correlations Between Anisotropy and Diffusivity

We examined the correlations between anisotropy and diffusivity in all regions within each group taking into account the effects of age. The correlations for the younger adults were: anterior corpus callosum, $r = -0.56$; posterior corpus callosum, $r = -0.29$; frontal, $r = -0.26$; temporal, $r = -0.09$, parietal, $r = -0.16$, occipital, $r = -0.11$; for the nondemented older adults: anterior corpus callosum, $r = -0.67$; posterior corpus callosum, $r = -0.74$; frontal, $r = -0.65$; temporal, $r = -0.63$, parietal, $r = -0.25$, occipital, $r = 0.08$; and for the DAT group: anterior corpus callosum, $r = -0.81$; posterior corpus callosum, $r = -0.39$; frontal, $r = -0.45$; temporal, $r = -0.59$, parietal, $r = -0.72$, occipital, $r = -0.47$. All correlations $r > 0.45$ were significant at $P < 0.05$.

Exploratory Whole-brain Analysis

Results of the group-wise t-test comparisons of the anisotropy data were largely consistent with the targeted ROI analyses in indicating an anterior-to-posterior gradient of nondemented age-related differences (see Fig. 7). DAT-specific effects were minimal and mostly confined to posterior regions.

Discussion

This study characterizes the anatomic distribution of alterations in white matter associated with nondemented and demented aging. Significant age-related reductions in white

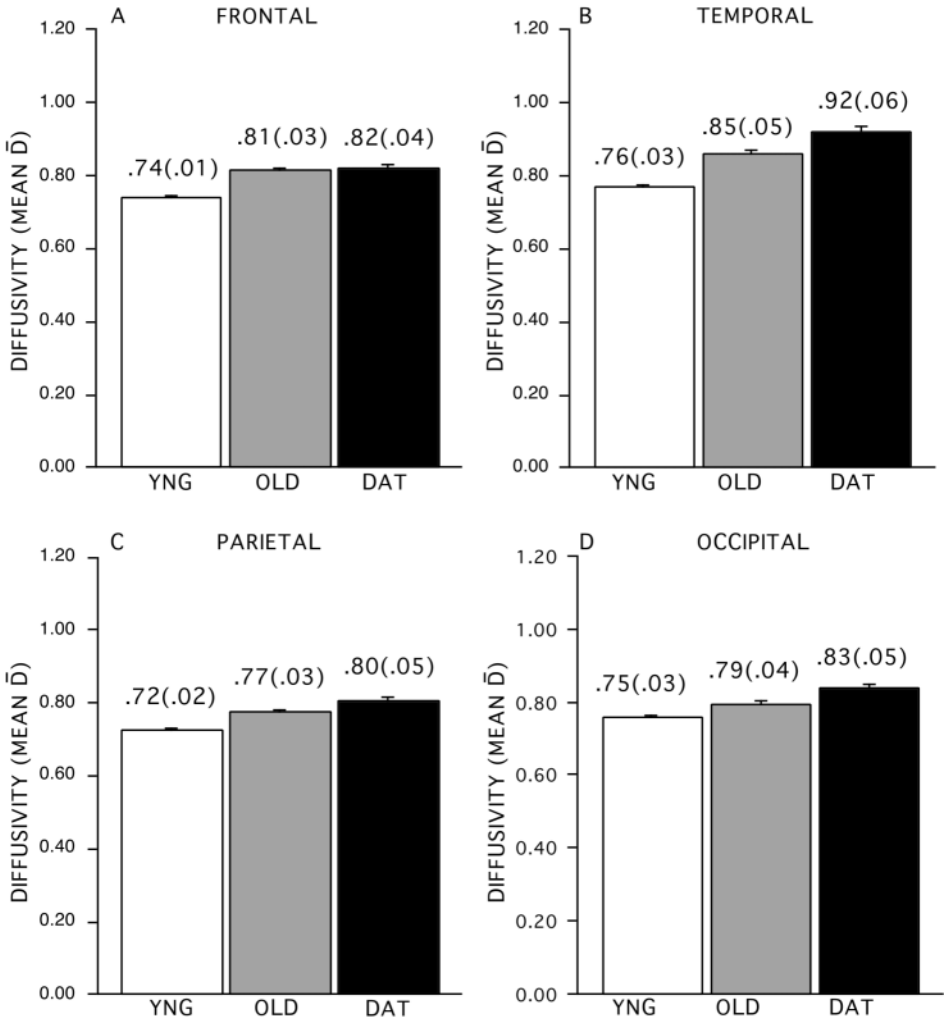

Figure 6. Comparison of diffusivity in the lobar regions between young (white bars), nondemented older adults (gray bars) and demented older adults (black bars). (*A*) Frontal lobe white matter, (*B*) temporal lobe white matter, (*C*) parietal lobe white matter, (*D*) occipital lobe white matter.

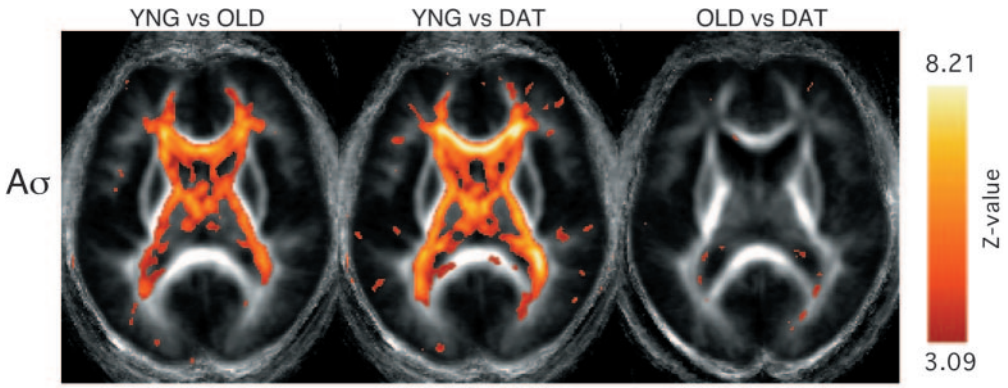

Figure 7. Z-maps of group comparisons of anisotropy on a voxel-by-voxel basis. All voxels are significant at the $Z = 3.09$, $P < 0.001$ level, uncorrected for multiple comparisons. Color bar represents range of Z values. The axial section corresponds to $z = 10$ above the plane of the anterior commissure–posterior commissure (Talairach and Tournoux, 1988).

matter integrity were observed, as indexed by DTI anisotropy measures. Notably, three of the four regional analyses of the corpus callosum indicated that the anterior callosum was more affected by advanced age than the posterior callosum. An anterior-to-posterior gradient in the effect of age was also observed in the lobar white matter. Minimal additional differences were observed for anterior regions in the demented individuals. Mild, but significant, dementia-associated changes were noted in posterior lobar regions. This same pattern of results was observed in the supplementary map-wise compari-

sons. Thus, the present results suggest that (i) nondemented aging is associated with a clear decline in white matter integrity, (ii) age-associated differences are especially characteristic of anterior brain regions, and (iii) anterior white-matter changes are not accelerated in early-stage DAT. These results are discussed in the context of related studies as well as a general model that multiple, often co-occurring, alterations in brain structure and function underlie cognitive decline in aging and dementia.

Age Is Associated with White Matter Differences Particularly in Anterior Brain Regions

While DTI white matter measures showed widespread alterations associated with nondemented aging, anterior regions showed particular vulnerability. The results augment an accumulating body of DTI investigations pointing to the relevance of anterior structures (O'Sullivan *et al.*, 2001) including the genu of the corpus callosum (Pfefferbaum *et al.*, 2000; Abe *et al.*, 2002). A greater susceptibility of anterior regions is also consistent with extant investigations on a broad range of structural and functional brain indices. Age-related volumetric shrinkage of prefrontal and striatal regions (Raz, 2000) is concomitant with reductions in dopaminergic and glutamatergic functioning (Volkow *et al.*, 1996, 2000; Grachev *et al.*, 2001). Greater effects of age in anterior regions are also apparent in declines in regional cerebral blood flow and glucose metabolism (Meyer *et al.*, 1994; Bentourkia *et al.*, 2000). Post-mortem analyses provide additional evidence that aging induces large alterations in anterior gray and white matter regions (Kemper, 1994). It is important to note that, despite efforts to minimize partial volume contamination, such effects may have contributed to the present results as indexed by the strong correlations between anisotropy and diffusivity. The greater susceptibility of the anterior regions to macrostructural volume loss with age may lead to an increased presence of partial volume effects. As our results are generally consistent with extant literature, they are unlikely to predominantly reflect artifact (e.g. partial volume effects). Our results likely reflect a biologic pattern observed at multiple levels of analysis, the nature of which will require more detailed and extensive histopathological examination.

The findings of greater age differences in anterior regions for both the callosal and lobar measurements is consistent with the anatomic organization of the white matter as the fibers from the frontal lobe course through the anterior regions of the corpus callosum. Anterior callosal vulnerability may contribute to, or arise from, the age-related decline in frontal cortical volume and function (Pfefferbaum *et al.*, 2000). One possibility is that age-related atrophy of the anterior corpus callosum may result from primary subcortical lesions to fiber tracts crossing the frontal white matter, as a relation between WMH and area measurements of callosum has been reported (Teipel *et al.*, 2002).

The pathophysiological basis of DTI effects remains uncertain. Decreases in anisotropy in the anterior callosum may reflect axonal fiber loss in small diameter myelinated fibers, demyelination, increased water content, or any combination of these factors. Increases in mean diffusivity appear to be coincident with decreases in anisotropy, but mean diffusivity and anisotropy may be affected by different mechanisms (Virta *et al.*, 1999). It should also be noted that the genu contains a relatively large proportion of small diameter lightly myelinated fibers that may be subject to greater degeneration than large diameter fibers (Tang *et al.*, 1997).

Our data are consistent with the possibility that the temporal progression of age-related brain differences in white matter inversely recapitulates developmental myelogenesis (i.e. areas last myelinated being first affected by aging (Kemper, 1994) as the anterior corpus callosum becomes myelinated at a later stage than the posterior corpus callosum (Brody *et al.*, 1987; Kinney *et al.*, 1988). Cerebrovascular damage (small vessel disease) represents one possible mechanism of white matter change in the elderly individuals. The preponderance of WMH in nondemented older adults, which may in part relate to cerebrovascular risk factors, is in anterior regions (Pantoni and Garcia, 1997; DeCarli and Scheltens, 2001).

Anterior White Matter Differences Are Not Greater in Early-stage DAT

The anterior-to-posterior gradient characteristic of nondemented aging was not accentuated in DAT. Specifically, changes in anisotropy and diffusivity in the corpus callosum were not significantly different in nondemented versus demented older adults. Failure to find acceleration of white matter microstructural damage is consistent with some past reports (Bozzao *et al.*, 2001), although inconsistent with others (Bozzali *et al.*, 2002). Our results are also consistent with a very recent report (Yoshiura *et al.*, 2003), which suggests that increased sensitivity for detection of groups differences may be increased by the use of considerably stronger diffusion-sensitizing gradients. These discrepancies possibly relate to the range of dementia severity in the various population samples. In our sample, individuals at the earliest stages of DAT were studied allowing changes specific to DAT to be identified prior to the occurrence of widespread atrophy in later stages. The lack of DAT-specific effects may also relate to the technique of defining the ROIs on the anisotropy images. This method could potentially increase the probability of type II error if there is group-dependent edge-dependent inhomogeneity of anisotropy. However, a similar finding of stability of the posterior callosum was observed for area measurements (Teipel *et al.*, 1999) and, as these authors note, the posterior callosum contains minimal fibers from the medial temporal region (Pandya and Seltzer, 1986) and consequently may not show changes until later stages. Thus, our data suggest that the cognitive differences between the DAT and nondemented groups, as reflected by the MMSE, are not attributable to additional degradation of anterior white matter.

In contrast to more extensive age effects in frontal lobe white matter, dementia status was associated with additional vulnerability in posterior fiber tracts. DAT-related effects on diffusivity were observed in parietal, temporal and occipital regions, although this was not reflected in changes in posterior corpus callosum. The significant DAT-specific effects were observed primarily as changes in mean diffusivity with nonsignificant trends for anisotropy. The effects were small in both measures and the failure to find statistically significant results in the anisotropy data as compared with the diffusivity data may reflect limited statistical power rather than biology. The anatomical distribution agrees with previous pathological studies (Braak and Braak, 1991, 1997).

Relation Between Anterior White Matter Differences and Deficits in Executive Control

One of the functional consequences of anterior white matter degeneration may be a deficit in executive control (Boone *et al.*, 1992; DeCarli *et al.*, 1995; DeCarli and Scheltens, 2001; O'Sullivan *et al.*, 2001). The frontostriatal network is likely a critical neural substrate for executive functions (Rubin, 1999; Fuster, 2002; Shimamura, 2002) and changes in executive (cognitive) control have been noted in many reviews of nondemented aging (Zacks and Hasher, 1994; Moscovitch and Winocur, 1995; Craik and Grady, 2002). There is evidence that the lateral prefrontal gray matter mediates age-associated executive decline (Raz *et al.*, 1998; Schretlen *et al.*, 2000; Head *et al.*, 2002). An interesting area of future investigation will be to explore more thoroughly the relation between age-related differences in anterior white matter and the many kinds of executive processes that are affected in aging. Many of the studies in a related literature on age-associated differences in functional activation patterns, observed using positron emission tomography (PET) and functional MRI, have noted activation increases and atypical bilateral recruitment of frontal regions in nondemented older adults (Cabeza *et al.*, 1997; Madden *et al.*, 1999; Reuter-Lorenz *et al.*, 2000; Cabeza, 2002; Logan *et al.*, 2002; Reuter-Lorenz, 2002). It remains to be determined whether bilateral recruitment is a response to, or consequence of, differences in anterior white matter and associated structural declines.

Relation to a Multiple Component Framework of Cognitive Aging

Our results demonstrate a dissociation between nondemented aging and DAT. The extant DAT literature emphasizes volumetric change in the medial temporal lobes (Jack and Petersen, 2000) associated with a constellation of clinically significant impairments including early memory loss (Albert, 1996; Kohler *et al.*, 1998; Rentz and Weintraub, 2000) and later executive dysfunction (Balota *et al.*, 2000). The available data thus imply that there are at least two distinct sets of pathophysiological processes that characteristically lead to cognitive decline during aging.

Recognizing that an individual's cognitive status may reflect multiple coexisting pathologies, our goal should to be to dissociate and characterize these factors, identify risk factors, and ultimately, understand how these multiple factors independently, or interactively, influence cognition.

Notes

We thank the Washington University ADRC for clinical assistance and participant recruitment, Glenn Foster for assistance with MRI data collection and Martha Storandt for valuable comments on an earlier draft. This study was supported by NIH grants AG05681, AG03991, MH57506, NS06833 and NS39538, the Alzheimer's Association, the James S. McDonnell Foundation program in cognitive neuroscience, and the Howard Hughes Medical Institute.

Address correspondence to Denise Head, HHMI at Washington University, Psychology Department Campus Box 1125, One Brookings Drive, St Louis, MO 63130, USA.

References

Abe O, Aoki S, Hayashi N, Yamada H, Kunimatsu A, Mori H, Yoshikawa T, Okubo T, Ohtomo K (2002) Normal aging in the central nervous system: quantitative MR diffusion-tensor analysis. Neurobiol Aging 23:433–441.

Aboitz F, Rodriguez E, Olivares R, Zaidel E (1996) Age-related changes in fibre composition of the human corpus callosum: sex differences. Neuroreport 7:1761–1764.

Albert M (1996) Cognitive and neurobiologic markers of early Alzheimer's disease. Proc Natl Acad Sci USA 93:13547–13551.

Albert M (1998) Normal and abnormal memory: aging and Alzheimer's disease. In: Handbook of the aging brain (Wang E, Snyder DS, eds), pp. 1–13. San Diego, CA: Academic Press.

Albert M, Killiany RJ (2001) Age-related cognitive change and brain–behavior relationships. In: Handbook of the Psychology of Aging (Birren JE, ed.), pp. 161–185. San Diego, CA: Academic Press.

Backman L, Small BJ, Fratiglioni L (2001) Stability of the preclinical episodic memory deficit in Alzheimer's disease. Brain 124:96–102.

Balota DA, Faust ME (2001) Attention in dementia of the Alzheimer type. In: Handbook of neuropsychology, 2nd edn (Boller F, Cappa SF, eds), pp. 51–80. Amsterdam: Elsevier Science.

Balota DA, Dolan PO, Duchek JM (2000) Memory changes in healthy older adults. In: The Oxford Handbook of Memory (Craik FIM, ed.), pp. 395–409. London: Oxford University Press.

Bartzokis G, Cummings JL, Sultzer D, Henderson VW, Nuechterlein KH, Mintz J (2003) White matter structural integrity in healthy aging adults and patients with Alzheimer disease. Arch Neurol 60:393–398.

Basser PJ (1995) Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. NMR Biomed 8:333–344.

Basser PJ, Pierpaoli C (1996) Microstuctural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Resonon B 111:209–216.

Bentourkia M, Bol A, Ivanoiu A, Labar D, Sibomana M, Coppens A, Michel C, Cosnard G, De Volder AD (2000) Comparison of regional cerebral blood flow and glucose metabolism in the normal brain: effect of aging. J Neurol Sci 181:19–28.

Berg L, McKeel DW, Miller JP, Storandt M, Rubin EH, Morris JC, Baty J, Coats M, Norton J, Goate AM, Price JL, Gearing M, Mirra SS, Saunders AM (1998) Clinicopathologic studies in cognitively healthy aging and Alzheimer disease: relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. Arch Neurol 55:326–335.

Begion A, Eberling JL, Richardson BC, Roos MS, Wong STS, Reed BR, Jagust WJ (1994) Human corpus callosum in aging and Alzheimer's disease. Neurobiol Aging 15:393–397.

Boone KB, Miller BL, Lesser IM, Mehringer CM, Hill-Gutierrez E, Goldberg MA, Berman NG (1992) Neuropsychological correlates of white-matter lesions in healthy elderly subjects. Arch Neurol 49:549–554.

Bozzali M, Franceshi M, Falini A, Pontesilli S, Cercignani M, Magnani G, Scotti G, Comi G, Filippi M (2001) Quantification of tissue damage in AD using diffusion tensor and magnetization transfer MRI., Neurology 57:1135–1137.

Bozzali M, Falini A, Franceschi M, Cercignani M, Zuffi M, Scotti G, Comi G, Filippi M (2002) White matter damage in Alzheimer's disease assessed *in vivo* using diffusion tensor magnetic resonance imaging. J Neurol Neurosurg Psychiatry 72:742–746.

Bozzao A, Floris R, Baviera ME, Apruzzese A, Simonetti G (2001) Diffusion and perfusion MR imaging in cases of Alzheimer's disease: correlations with cortical atrophy and lesion load. Am J Neuroradiol 22:1030–1036.

Braak H, Braak E (1991) Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 82:239–259.

Braak H, Braak E (1997) Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 18:351–357.

Breteler MMB, van Amerongen NM, van Swieten JC, Claus JJ, Grobbee DE, van Gijn J, Hofman A, van Harskamp F (1994) Cognitive correlates of ventricular enlargement and cerebral white matter lesions on magnetic resonance imaging: the Rotterdam study. Stroke 25:1109–1115.

Brody BA, Kinney HC, Kloman AS, Gilles FH (1987) Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. J Neuropath Exp Neurol 46:283–301.

Buckner RL, Snyder AZ, Sanders AL, Raichle ME, Morris JC (2000) Functional brain imaging of young, nondemented and demented older adults. J Cogn Neurosci 12 Suppl 2:24–34.

Cabeza R (2002) Hemispheric reduction in older adults: the HAROLD model. Psychol Aging 17:85–100.

Cabeza R, Grady CL, Nyberg L, McIntosh AR, Tulving E, Kapur S, Jennings JM, Houle S, Craik FIM (1997) Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. J Neurosci 17:391–400.

Chen ZG, Li Ti-Q, Hindmarsh T (2001) Diffusion tensor trace mapping in normal adult brain using single-shot EPI technique. Acta Radiol 42:447–458.

Chun T, Filippi CG, Zimmerman RD, Ulug AM (2000) Diffusion changes in the aging human brain. Am J Neuroradiol 21:1078–1083.

Conturo T, McKinstry RC, Akbudak E, Robinson BH (1996) Encoding of anisotropic diffusion with tetrahedral gradients: a general mathematical diffusion formalism and experimental results. Magn Reson Med 35:399–412.

Courchesne E, Chisum HJ, Townsend J, Cowles A, Covington J, Egaas B *et al.* (2000) Normal brain development and aging: quantitative analysis of *in vivo* MR imaging in healthy volunteers. Radiology 21:672–682.

Craik FIM, Byrd M (1982) Aging and cognitive deficits: the role of attentional resources. In: Aging and cognitive process (Craik FIM, Trehub S, eds), pp. 191–211. New York: Plenum.

Craik FIM, Grady CL (2002) Aging, memory, and frontal lobe functioning. In: Principles of frontal lobe function (Stuss DT, Knight RT, eds), pp. 528–540. London: Oxford University Press.

DeCarli C, Scheltens P (2001) Structural brain changes. In: Vascular cognitive impairment (Erkinjuntti T, Gauther, eds), pp. 1–24. London: Martin Dunitz.

DeCarli C, Murphy DGM, Tranh M, Grady CL, Haxby JV, Gillette JA, Salerno JA, Gonzales-Aviles A, Horwitz B, Rapoport SI, Schapiro MB (1995) The effect of white matter hyperintensity volume on brain structure, cognitive performance, and glucose metabolism of glucose in 51 healthy adults. Neurology 45:2077–2084.

de Lacoste MC, Kirkpatrick JB, Ross ED (1985) Topography of the human corpus callosum. J Neuropathol Exp Neurol 44:578–591.

de Leeuw F-E, de Groot JC, Achten E, Oudkerk M, Ramos LMP, Heijboer R, Hofman A, Jolles J, van Gijn J, Breteler MMB (2001) Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam scan study. J Neurol Neurosurg Psychiatry 70:9–14.

Driesen NR, Raz N (1995) The influence of sex, age, and handedness on corpus callosum morphology: a meta-analysis. Psychobiology 23:240–247.

Engelter ST, Provenzale JM, Petrella JR, DeLong DM, MacFall, JR (2000) The effect of aging on the apparent diffusion coefficient of normal-appearing white matter. Am J Radiol 175:425–430.

Fazekas F, Kapeler P, Schmidt R, Offenbacher H, Payer F, Fazekas G (1996) The relation of cerebral magnetic resonance signal hyperintensities to Alzheimer's disease. J Neurol Sci 142:121–125.

Fleischman DA, Gabrieli JD (1998) Repetition priming in normal aging and Alzheimer's disease: a review of findings and theories. Psychol Aging 13:88–119.

Fuster JM (2002) Physiology of executive functions: the perception–action cycle. In: Principles of frontal lobe function (Stuss DT, Knight RT, eds), pp. 96–126. London: Oxford University Press.

Gabrieli JDE (1996) Memory systems analyses of mnemonic disorders in aging and age-related diseases. Proc Natl Acad Sci USA 93:13534–13540.

Gideon P, Thomsen C, Henriksen O (1994) Increased self-diffusion of brain water in normal aging. J Magn Reson Imag 4:185–188.

Good CD, Johnsrude IS, Ashburner J, Henson RNA, Friston KJ, Frackowiak RSJ (2001) A voxel-based morphometric study of agein in 465 normal adult human brains. Neuroimage 14:21–36.

Grachev ID, Swarnkar A, Szeverenyi NM, Ramachandran TS, Apkarian AV (2001) Aging alters the multichemical networking profile of the human brain: an *in vivo* ^{1}H-MRS study of young versus middle-aged subjects. J Neurochem 77:292–303.

Greenwood PM (2000) The frontal aging hypothesis evaluated. J Int Neuropsychol Soc 6:705–726.

Gunning-Dixon FM, Raz N (2000) The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. Neuropsychology 14:224–232.

Hanyu H, Shindo H, Kakizaki D, Abe K, Iwamoto T, Takasaki M (1997) Increased water diffusion in cerebral white matter in Alzheimer's disease. Gerontology 43:343–351.

Hanyu H, Sakurai H, Iwamoto T, Takasaki M, Shindo H, Abe K (1998) Diffusion-weighted MR imaging of the hippocampus and temporal white matter in Alzheimer's disease. J Neurol Sci 156:195–200.

Hanyu H, Asano T, Sakurai H, Imon Y, Iwamoto T, Takasaki M, Shindo H, Abe K (1999). Diffusion-weighted and magnetization transfer imaging of the corpus callosum in Alzheimer's disease. J Neurol Sci 167:37–44.

Head D, Raz N, Gunning-Dixon F, Williamson A, Acker JD (2002) Age-related differences in the course of cognitive skill acquisition: the role of regional cortical shrinkage and cognitive resources. Psychol Aging 17:72–84.

Hensel A, Wolf H, Kruggel F, Riedel-Heller SG, Nikolaus C, Arendt T, Gertz HJ (2002) Morphometry of the corpus callosum in patients with questionable and mild dementia. J Neurol Neurosurg Psychiatry 73:59–61.

Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL (1982) A new clinical scale for the staging of dementia. Br J Psychiatry 140:566–572.

Huppert FA, Brayne C (1994) What is the relationship between dementia and normal aging? In: Dementia and normal aging (Huppert FA, Brayne C, O'Connor DW, eds), pp. 3–11. Cambridge: Cambridge University Press.

Jack CR, Petersen RC (2000) Structural imaging approaches to Alzheimer's disease. In: Early diagnosis and treatment of Alzheimer's disease (Scinto LFM, Daffner KR, eds), pp. 127–148. Totowa, NJ: Humana Press.

Janowsky JS, Kaye JA, Carper RA (1996) Atrophy of the corpus callosum in Alzheimer's disease versus healthy aging. J Am Geriatr Soc 44:798–803.

Jernigan TL, Archibald SL, Fennema-Notestine C, Gamst AC, Stout JC, Bonner J, Hesselink JR (2001) Effects of age on tissues of the cerebrum and cerebellum. Neurobiol Aging 22:581–594.

Kantarci K, Jack CR, Xu YC, Campeau NG, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Kokmen E, Tangalos EG, Petersen RC (2001) Mild cognitive impairment and Alzheimer disease: regional diffusivity of water. Radiology 219:101–107.

Kemper TL (1994) Neuroanatomical and neuropathological changes during aging and dementia. In: Clinical neurology of aging (Albert ML, Kusefel J, eds), pp. 3–67. New York: Oxford.

Kinney HC, Brody BA, Kloman AS, Gilles FH (1988) Sequence of central nervous system myelination in human infancy. II. Patterns of myelination in autopsied infants. J Neuropathol Exp Neurol 47:217–234.

Kohler S, Black SE, Sinden M, Szekely C, Kidron D, Parker JL, Foster JK, Moscovitch M, Wincour G, Szalai JP, Bronskill MJ (1998) Memory impairments associated with hippocampal versus parahippocampal-gyrus atrophy: an MR volumetry study in Alzheimer's disease. Neuropsychologia 36:901–914.

Kozachuk WE, DeCarli C, Schapiro MB, Wagner EE, Rapoport SI, Horwitz B (1990) White matter hyperintensities in dementia of Alzheimer's type and in healthy subjects without cerebrovascular risk factors: a magnetic resonance imaging study. Arch Neurol 47:1306–1310.

Leys D, Soetaert G, Petit H, Fauquette A, Pruvo J-P, Steinling M (1990) Periventricular and white matter magnetic resonance imaging hyperintensities do not differ between Alzheimer's disease and normal aging. Arch Neurol 47:524–527.

Logan JM, Sanders AL, Snyder AZ, Morris JC, Buckner RL (2002). Under-recruitment and non-selective recruitment: dissociable neural mechanisms associated with aging. Neuron 33:827–840.

Luszcz MA, Bryan J (1999) Toward understanding age-related memory loss in late adulthood. Gerontology 25:2–9.

Lyoo IK, Satlin A, Lee CK, Renshaw PF (1997) Regional atrophy of the corpus callosum in subjects with Alzheimer's disease and multi-infarct dementia. Psychiatry Res Neuroimag 74:63–72.

Madden DJ, Turkington TG, Provenzale JM, Denny LL, Hawk TC, Gottlob LR, Coleman RE (1999) Adult age differences in the functional neuroanatomy of verbal recognition memory. Hum Brain Mapp 7:115–135.

Meyer JS, Kawamura J, Terayama Y (1994) Cerebral blood flow and metabolism with normal and abnormal aging. In: Clinical neurology of aging, 2nd edn (Albert M, Knoefel JE, eds), pp. 214–234. London: Oxford University Press.

Morris JC (1993) The clinical dementia rating scale (CDR): current version and scoring rules. Neurology 43:2412–2414.

Morris JC (1999) Is Alzheimer's disease inevitable with age? Lessons from clinicopathologic studies of healthy aging and very mild Alzheimer's disease. J Clin Invest 104:1171–1173.

Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, Berg L (2001) Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 58:397–405.

Moscovitch M, Winocur G (1992) The neuropsychology of memory and aging. In: The handbook of aging and cognition (Craik FIM, Salthouse TA, eds), pp. 315–360. Hillsdale: Lawrence Erlbaum Associates.

Moscovitch M, Winocur G (1995) Frontal lobes, memory, and aging. Ann NY Acad Sci 769:119–150.

Moscovitch M, Winocur G, Lachlan D (1986) Memory as assessed by recognition and reading time in normal and memory-impaired people with Alzheimer's disease and other neurological disorders. J Exp Psychol Gen 115:331–347.

Nusbaum AO, Tang CY, Buchsbaum MS, Wei TC, Atlas SW (2001) Regional and global changes in cerebral diffusion with normal aging. Am J Neuroradiol 22:136–142.

Nyberg L, Backman L, Erngrund K, Olofsson U, Nilsson L (1996) Age differences in episodic memory, semantic memory, and priming relationships to demographic, intellectual, and biological factors. J Gerontol Psychol Sci 51B: P234–P240.

O'Brien JT, Wiseman R, Burton EJ, Barber B, Wesnes K, Saxby B, Ford GA (2002) Cognitive associations of subcortical white matter lesions in older people. Ann NY Acad Sci 977:436–444.

Ohnishi T, Matsuda H, Tabira T, Asada T, Uno M (2001) Changes in brain morphology in Alzheimer disease and normal aging: is Alzheimer disease an exaggerated aging process? Am J Neuroradiol 22:1680–1685.

Ojemann JG, Akbudak E, Snyder AZ, McKinstry RC, Raichle ME, Conturo TE (1997) Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. Neuroimage 6:156–167.

O'Sullivan M, Jones DK, Summers PE, Morris RG, Williams SCR, Markus HS (2001) Evidence for cortical 'disconnection' as a mechanism of age-related cognitive decline. Neurology 57:632–638.

Pandya DN, Seltzer B (1986) The topography of commissural fibers. In: Two hemispheres–one brain: functions of the corpus callosum (Lepore F, Ptito M, Jasper HH, eds), pp. 47–73.

Pantel J, Schroder J, Essig M, Minakaran R, Schad LR, Friedlinger M, Jauss M, Knopp MV (1998) Corpus callosum in Alzheimer's disease and vascular dementia — a quantitative magnetic resonance study. J Neural Transm 54:129–136.

Pantel J, Schroder J, Jauss M, Essig M, Minakaran R, Schonknecht P, Schneider G, Schad LR, Knopp MV (1999) Topography of callosal atrophy reflects distribution of regional cerebral volume reduction in Alzheimer's disease. Psychiatry Res Neuroimag 90:181–192.

Pantoni L, Garcia JH (1997) Pathogenesis of leukoaraiosis. Stroke 28:652–659.

Parasuraman R, Haxby JV (1993) Attention and brain function in Alzheimer's disease: a review. Neuropsychology 7:242–272.

Park DC, Polk T, Mikels J, Taylor SF, Marshuetz C (2001) Cerebral aging: integration of brain and behavioral models of cognitive function. Dialogues Clin Neurosci 3:151–165.

Perfect T (1997) Memory aging as frontal lobe dysfunction. In: Cognitive models of memory (Conway M, ed.), pp. 315–339. Cambridge: MIT Press.

Pfefferbaum A, Sullivan EV (2003) Increased brain white matter diffusivity in normal adult aging: relationship to anisotropy and partial voluming. Magn Reson Med 49:953–961.

Pfefferbaum A, Sullivan EV, Hedehus M, Lim KO, Adalsteinsson E, Moseley M (2000) Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. Magn Reson Med 44:259–268.

Pierpaoli C, Basser PJ (1996) Toward a quantitative assessment of diffusion anisotropy. Magn Reson Med 36:893–896.

Price JL, Davis PB, Morris JC, White DL (1991) The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. Neurobiol Aging 12:295–312.

Price JL, Morris JC (1999) Tangles and plaques in nondemented aging and 'preclinical' Alzheimer's disease. Ann Neurol 45:358–368.

Raz N, Gunning-Dixon F, Head D, Dupuis JD, Acker JDE (1998) Neuroanatomical correlates of cognitive aging: evidence from structural magnetic imaging. Neuropsychology 12:95–114.

Raz N (2000) Aging of the brain and its impact on cognitive performance: integration of structural and functional findings. In: Handbook of aging and cognition, vol. 2 (Craik, FIM, Salthouse TA, eds), pp. 1–90. Mahwah, NJ: Erlbaum.

Rentz DM, Weintraub S (2000) Neuropsychological detection of early probable Alzheimer's disease. In: Early diagnosis and treatment of Alzheimer's disease (Scinto LFM, Daffner KR, eds), pp. 169–190. Totowa, New Jersey: Humana Press.

Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C (2003) Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. J Neurosci 23:3295–3301.

Reuter-Lorenz PA (2002) New visions of the aging mind and brain. Trends Cogn Sci 6:394–400.

Reuter-Lorenz PA, Jonides J, Smith EE, Hartley A, Miller A, Marshuetz C, Koeppe RA (2000) Age differences in frontal lateralization of verbal and spatial working memory revealed by PET. J Cogn Neurosci 12:174–187.

Rose SE, Chen F, Chalk JB, Zelaya FO, Strugnell WE, Benson M, Semple J, Doddrell DM (2000) Loss of connectivity in Alzheimer's disease: an evaluation of white matter tract integrity with colour coded MR diffusion tensor imaging. J Neurol Neurosurg Psychiatryry 69:528–530.

Rubin DC (1999) Fronto-striatal circuits in cognitive aging: evidence for caudate involvement. Aging Neuropsychol Cogn 6:241–259.

Salthouse TA (1996) The processing speed theory of adult age differences in cognition. Psychol Rev103:403–428.

Salat DH, Kaye JA, Janowsky JS (1999) Prefrontal gray and white matter volumes in healthy aging and Alzheimer disease. Arch Neurol 56:338–344.

Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RSR, Busa E, Morris JC, Dale AM, Fischl B (2004) Thinning of the cerebral cortex in aging. Cereb Cortex (in press).

Sandson TA, Felician O, Edelman RR, Warach S (1999) Diffusion-weighted magnetic resonance imaging in Alzheimer's disease. Dement Geriatr Cogn Disord 10:166–171.

Schaie KW (1994) The course of adult intellectual development. Am Psychol 49:304–313.

Scheltens P, Barkhof F, Leys D, Wolters EC, Ravid R, Kamphorst W (1995) Histopathologic correlates of white matter changes on MRI in Alzheimer's disease and normal aging. Neurology 45:883–888.

Schretlen D, Pearlson GD, Anthony JC, Aylward EH, Augustine AM, Davis A, Barta P (2000) Elucidating the contributions of processing speed, executive ability and frontal lobe volume to normal age-related differences in fluid intelligence. J Int Neuropsychol Soc 6:52–61.

Shimony JS, McKinstry RC, Akbudak E, Aronovitz JA, Snyder AZ, Lori NF, Cull TS, Conturo TE (1999) Quantitative diffusion-tensor anisotropy brain MR imaging: normative human data and anatomic analysis. Radiology 212:770–784.

Shimamura AP (2002) Memory retrieval and executive control process. In: Principles of frontal lobe function (Stuss DT, Knight RT, eds), pp. 528–540. London: Oxford University Press.

Storandt M, Botwinick J, Danziger WL, Berg L, Hughes CP (1984) Psychometric differentiation of mild senile dementia of the Alzheimer type. Arch Neurol 41:497–499.

Storandt M, Grant EA, Miller P, Morris JC (2002) Rates of progression in mild cognitive impairment and early Alzheimer's disease. Neurology 59:1034–1041.

Sullivan EV, Pfefferbaum A (2003) Diffusion tensor imaging in normal aging and neuropsychiatric disorders. Eur J Radiol 45:244–255.

Sullivan EV, Adalsteinsson E, Hedehus M, Ju C, Moseley M, Lim KO, Pfefferbaum A (2001) Equivalent disruption of regional white matter microstructure in ageing healthy men and women. Neuroreport 12:99–104.

Sullivan EV, Pfefferbaum A, Adalsteinsson E, Swan GE, Carmelli D (2002) Differential rates of regional brain change in callosal and ventricular size: a 4-year longitudinal MRI study of elderly men. Cereb Cortex 12:438–445.

Takahashi S, Yonezawa H, Takahashi J, Kudo M, Inoue T, Tohgi H (2002) Selective reduction of diffusion anisotropy in white matter of Alzheimer disease brains measured by 3.0 Tesla magnetic resonance imaging. Neurosci Lett 332:45–48.

Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. New York: Thieme Medical Publishers.

Tang Y, Nyengaard JR, Pakkenberg B, Gundersen HJG (1997) Age-induced white matter changes in the human brain: a stereological investigation. Neurobiol Aging 18:609–615.

Teipel SJ, Hampel D, Alexander GE, Schapiro MB, Horwitz B, Teichberg D, Daley E, Hippius J, Moller H-J, Rapoport SI (1998) Dissociation between corpus callosum atrophy and white matter pathology in Alzheimer's disease. Neurology 51:1381–1385.

Teipel SJ, Hampel D, Pietrini P, Alexander GE, Horwitz B, Daley E, Moller H-J, Schapiro MB, Rapoport SI (1999) Arch Neurol 56:467–473.

Teipel SJ, Bayer W, Alexander GE, Zebuhr Y, Teichberg D, Kulic L, Schapiro MB, Moller H-J, Rapoport SI, Hampel H (2002) Progression of corpus callosum atrophy in Alzheimer disease. Arch Neurol 59:243–248.

Virta A, Barnett A, Pierpaoli C (1999) Visualizing and characterizing white matter fiber structure and architecture in the human pyramidal tract using diffusion tensor MRI. Magn Reson Imag 17:1121–1133.

Volkow ND, Wang G, Fowler JS, Logan J Gatley SJ, MacGregor RR, Schlyer DJ, Hitzemann, Wolf AP (1996) Measuring age-related changes in dopamine D_2 receptors C-raclopride and F-N-methylspiroperidol. Psychiatry Res Neuroimag 67:11–16.

Volkow ND, Logan J, Fowler JS, Wang G-J, Gur RC, Wong C, Felder C, Gatley J, Ding Y-S, Hitzemann R, Pappas N (2000) Association between age-related decline in brain dopamine activity and impairment in frontal and cingulate metabolism. Am J Psychiatry 157:75–80.

Waldemar G, Christiansen P, Larsson HBW, Hogh, P, Laursen J, Lassen NA, Paulson OB (1994) White matter magnetic resonance hyperintensities in dementia of the Alzheimer type: morphological and regional cerebral blood flow correlates. J Neurol Neurosurg Psychiatry 57:1458–1465.

Wang J, Kaufman AS (1993) Changes in fluid and crystallized intelligence across the 20 to 90 year age range on the K-BIT. J Psychoeduc Assess 11:29–37.

Weis S, Jellinger K, Wenger E (1991) Morphometry of the corpus callosum in normal aging and Alzheimer's disease. J Neural Transm Suppl 33:35–38.

Welsh KA, Butters N, Hughes JP, Mohs RC, Heyman A (1992) Detection and staging of dementia in Alzheimer's disease. Arch Neurol 49:448–452.

West RL (1996) An application of prefrontal cortex function theory to cognitive aging. Psychol Bull 120:272–292.

Whalley LJ (2002) Brain ageing and dementia: what makes the difference? Br J Psychiatry 181:369–371.

Yoshiura T, Mihara F, Tanaka A, Ogomori K, Ohyagi Y, Taniwaki T, Yamada T, Yamasaki T, Ichimiya A, Kinukawa N, Kuwabara Y, Honda H (2003) High *b* value diffusion-weighted imaging is more sensitive to white matter degeneration in Alzheimer's disease. Neuroimage 20:413–419.

Zacks RT, Hasher L (1994) Directed ignoring: inhibitory regulation of working memory. In: Inhibitory process in attention, memory and language (Dagenbach D, Carr TH, eds), pp. 241–264. San Diego, CA: Academic Press.