Published in final edited form as:

Alzheimers Dement. 2008 November ; 4(6): 381–389. doi:10.1016/j.jalz.2008.07.001.

White Matter Integrity Linked To Functional Impairments in Aging and Early Alzheimer's Disease

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Abstract

Background—Alzheimer's disease (AD) is associated with changes in cerebral white matter (WM) but the functional significance of such findings is not yet established. We hypothesized that diffusion tensor imaging (DTI) might reveal links between regional WM changes and specific neuropsychologically and psychophysically defined impairments in early AD.

Methods—Older adult control subjects (OA, n=18) and mildly impaired AD patients (n=14) underwent neuropsychological and visual perceptual testing along with DTI of cerebral WM. DTI yielded fractional anisotropy (FA) and mean diffusivity (<D>) maps for nine ROIs in three brain regions that were then compared to the performance measures.

Results—AD patients showed non-significant trends toward lower FAs in the posterior region's callosal and sub-cortical ROIs. However, posterior callosal FA was significantly correlated with verbal fluency and figural memory impairments, whereas posterior subcortical FA was correlated with delayed verbal memory, figural memory, and optic flow perceptual impairments.

Conclusions—WM changes in early AD are concentrated in posterior cerebral areas with distributions that correspond to specific functional impairments. DTI can be used to assess regional pathology related to individual's deficits in early AD.

Introduction

Alzheimer's disease (AD) is a clinically diverse neurodegenerative disorder associated with prominent impairments of memory, attention, and perception. The histological description of AD neuropathology was described one hundred years ago (1) and the molecular composition of AD lesions is the subject of intensive scrutiny (2). Tremendous effort is directed at developing methods for the early diagnosis of AD in the hope that early interventions in high-risk populations will provide the greatest opportunities for effective treatment.

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MRI based diffusion tensor imaging (DTI) can assess the integrity of WM tracts that sustain early damage in AD, possibly reflecting the selective vulnerability of cortico-cortical connections (3) (4). DTI studies of AD have revealed significant changes in sub-cortical parietal (5) (6) (7) (8), temporal (9) (10) (11), and callosal WM. The loss of WM integrity in AD has been linked to global cognitive decline (12) (13) (9) (14) with evidence for more specific links between delayed verbal recall and WM changes in the left centrum semiovale, temporal, and hippocampal regions (15) (16).

Our previous work demonstrated links between functional impairment in AD and neuropsychological, psychophysical, and neurophysiological changes (17). We developed a model of impaired information processing in AD linking functional changes to conduction delays in posterior cortico-cortical networks (18) known to show early AD pathology (3;4). We hypothesized that OA and AD patients differ with respect to the relationship between neuropsychological and perceptual impairment and posterior cortical WM integrity. We find evidence that WM integrity in posterior cortical areas is related to functional losses that are specific to early AD, whereas WM integrity in frontal and middle cortical areas is related to functional losses shared by both OA and early AD patients.

Method

Subject Groups

We studied 14 patients with Alzheimer's disease (AD) (eight men, six women) and 18 normal older adult (OA) control subjects (nine men, nine women) without ophthalmologic or other neuropsychiatric disorders (Table 1). All subjects had normal, or corrected to normal, visual acuity and contrast sensitivity without significant group differences. We recruited mildly impaired AD patients, Mini-Mental State Examination (MMSE) ≥ 20 from the clinical programs of the University of Rochester Alzheimer's Disease Center. Probable Alzheimer's disease diagnosis was based on National Institutes of Neurological Diseases and Stroke criteria (19) and included the documentation of a verbal memory impairment as well as a deficit in at least one of the following domains: aphasia, agnosia, apraxia, or disorganization/dysexecutive capabilities. OA subjects were recruited from programs for the healthy elderly or were the spouses of AD patients. Informed consent was obtained from all subjects before their enrollment. All procedures were approved by the University of Rochester Medical Center, Research Subjects Review Board.

Subject Testing

All tests were administered in the Visual Orientation Laboratory of the Strong Memorial Hospital, Rochester, New York in two 90 minute sessions:

Session 1: Neuropsychological Tests—We used a battery of eight neuropsychological tests to provide standardized assessments of cognitive function in all OA and AD subjects. Verbal Paired Associates Test I from the Wechsler Memory Scale – Revised (WMS-R) (20) was used to evaluate immediate and delayed recall for word pairs. The WMS-R Figural Memory test was used to evaluate immediate visual recognition memory. Categorical Name Retrieval test of animal names in one minute was used as a test of verbal fluency. The Money Road Map test (21) was used as a test of topographic orientation with subjects using a pencil to trace a route on a map while identifying left and right turns. The Judgment of Line Orientation test (22) was used to evaluate the visual processing of spatial relations. The Facial Recognition test (22) was used to evaluate the visual processing of complex figures. The MMSE (23) was administered by one of the investigators in the course of making the clinical diagnosis of AD within four weeks of laboratory testing and was not repeated for this study.

Session 2: Basic Visual Tests—All subjects underwent visual testing to assess the comparability of subject groups. Monocular visual acuity was tested to confirm acuity of at least 20/40. The better eye was used for all subsequent testing that included monocular contrast sensitivity testing at five spatial frequencies from 0.5 to 18 cycles/° (VisTech Consultants, Inc.). Contrast sensitivity functions were obtained under the standard lighting conditions as required for conversion to equivalent acuity units. All subjects generated CSF curves that satisfied criteria for using the approach to equivalent acuity units and yielded contrast sensitivities in the normal range (see <http://www.ageingeye.net/cataract/Vistech2.pdf>).

Psychophysical Visual Motion Stimuli—Subjects underwent psychophysical testing to determine their visual motion coherence thresholds for horizontal and radial (inward/outward) motion using left/right two-alternative forced-choice discrimination paradigm. Horizontal motion stimuli consisted of leftward or rightward moving dots. Radial motion stimuli consisted of dots moving in a radial pattern either out from or in to a center of motion on the horizontal meridian, 20° to the left or right of the centered fixation point. The horizontal and radial motion patterns were intermixed with random dot motion. The percentage of coherently and randomly moving dots varied between trials for the determination of motion coherence thresholds. Individual dots were randomly assigned to coherent or random motion in each frame. All stimuli contained 2000 white dots ($.4^\circ \times .4^\circ$, 2.69 cd/m²) projected on a dark background and covering the central $40^\circ \times 60^\circ$ of the visual field with the same dot density, luminance, contrast, and average dot speed (30°/s).

Psychophysical Testing Paradigm—Subjects sat facing an 8 ft $\times$ 6 ft rear-projection tangent screen on which a TV projector (Electrohome, Ontario) presented a 60 Hz frame rate animated sequence. Motion coherence thresholds were obtained using the technique of parameter estimation by sequential testing (24) (25) run initially for 20 trials with a seed value based on pilot data from that subject group (80% coherence for Alzheimer's disease subjects and 50% coherence for young and older normal groups). Each subject's preliminary threshold was used to seed a subsequent series of 50 trials to yield their final threshold. Threshold was the percentage of dots in coherent motion in stimuli ((coherently moving dots / (coherently moving dots + random dots)) * 100) yielding 82.5% correct responses, reflecting Weibull fits to psychophysical responses.

Trials began with an audible tone and a centered fixation spot (0.5°). Eye position was continuously monitored by infrared oculometry (ASL, Inc) which was used to interrupt and delete all trials in which gaze moved beyond the central 10°. All subjects maintained stable fixation during testing with few aborted trials. During central fixation, a visual motion stimulus was presented for 1 s and was followed by a pair of audible tones prompting the subject's left or right button press to indicate the direction of horizontal motion or the center of motion in radial motion within 4 s. Subjects were asked to make their best guess if unsure of the correct response.

MR Imaging Protocol

MRI Acquisition—All MR examinations were performed on a GE Signa 1.5 T MR scanner with echo-speed gradients (GEMS, Milwaukee, WI). All subjects were screened to ensure that they did not have any metallic implants, shrapnel, pacemakers, etc. before they took part in magnetic resonance studies. A quadrature head coil was used for all image acquisitions. All subjects were scanned with the following pulse sequences: (1) A three-orientation scout imaging sequence for localization; (2) 3D Coronal fast SPGR sequence for whole brain anatomy, with variable bandwidth and enhanced dynamic range, TR/TE/FA=19/min/25°, 256 $\times$ 256 matrix size, slice thickness=1.2mm, FOV=24cm, loc/slab=128; (3) Whole brain DTI imaging in coronal orientation, with a single-shot pulsed-gradient spin-echo echo-planar

imaging sequence and the following parameters: TR/TE = 4000/116 ms, matrix size = 128×128, FOV = 24 cm, thickness=7mm, with no gaps, and with 2 repetitions in each diffusion orientation. Diffusion weighting was applied in 20 different non-collinear orientations with diffusion sensitizing factor $b=1000 \text{ s/mm}^2$. In addition three images with $b=0$ were also acquired. Images cover anatomic structures including the sub-cortical WM in the bilateral, frontal and posterior parietal areas, bilateral fronto-posterior parietal superior bundles, bilateral anterior and posterior cingulum, and the anterior (genu) and posterior (splenium) portion of CC.

DTI Processing

Before tensor calculation, DTI images were corrected for intra-protocol motion artifacts and eddy current distortions introduced by diffusion weighting gradients.

DTI parameters—From all diffusion-weighted images, the general diffusion tensor was first diagonalized, and the eigenvalues λ_1 , λ_2 , and λ_3 for every image pixel were calculated. As index of degree of anisotropy, we are using fractional anisotropy (FA, dimensionless, ranging from 0.0 for perfectly isotropic diffusion, to 1.0 for perfectly anisotropic diffusion), which is defined as

$$FA = \sqrt{\frac{2}{3}} \frac{\sqrt{(\lambda_1 - \langle D \rangle)^2 + (\lambda_2 - \langle D \rangle)^2 + (\lambda_3 - \langle D \rangle)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}},$$

where $\langle D \rangle$ is the average of the trace of the diffusion tensor:

$$\langle D \rangle = \frac{1}{3}(\lambda_1 + \lambda_2 + \lambda_3).$$

Regions of interest (ROI) Procedures

All measurements were obtained with a home made software based on the b_0 and directional colored FA images for each subject. Images were displayed on standard computer monitor and each ROI was manually outlined using a mouse guided crosshair. We manually delineated each subject's ROIs from b_0 and FA maps in part to minimize partial volume effects and in part due to the lack of detectable anatomical landmarks on T1 images for some WM tracts (e.g., superior longitudinal fasciculus, internal capsule). Manual delineation of the ROIs was performed by two of the authors (H. N. and V. K.) who were unaware of the subjects' diagnoses but yielded inter-rater reliability between .85 and .91 across all ROIs. Subsequent analyses did not show any significant differences between their DTI measures (i.e., number of voxels per ROI, magnitude of DTI measures).

Fractional anisotropy (FA) and mean diffusion rate $\langle D \rangle$ from DTI of white matter (WM) were measured in the ROIs which were defined with respect to the CC and thus standardized across the participants. The rules for location of each ROI are described below. For all ROIs we used a low pass filter to select only pixels with $\langle D \rangle \leq 1.7$. All ROIs were manually outlined from coronal sections (Figure 1).

Sub-cortical White Matter (SWM)—SWM was evaluated in 2 regions from a single slice. In both cases, the cortical ribbon was defined by a line drawn on b_0 maps which followed the border between WM and cortex grey matter (i.e., the line between light and dark grey) (Figure 1, bottom panels). In the rostral region, WM boundary was drawn above tentorium. To reduce

the effects of gray matter and cerebrospinal fluid we used a high pass filter based on FA values so that the pixels with $FA < 0.15$ were excluded from the ROIs.

Anterior SWM was defined in the slice anterior to the most anterior section showing the corpus callosum (CC). On average, the anterior SWM slice was comprised of 1800 voxels. Posterior SWM was defined in the slice posterior to the most posterior section showing the CC. On average, the posterior SWM slice was comprised of 2800 voxels.

White Matter Tracts—FA and $\langle D \rangle$ from DTI images were measured in the following regions of interest (ROI): 1. Bilateral superior longitudinal fasciculus as a part of frontoparietal network connectivity. 2. Bilateral anterior and posterior cingulum involved bidirectional projections. 3. Anterior (genu), mid-body, and posterior (splenium) portions of the CC (Fig 1. A, B, C). Locations of the ROIs for all WM tracts were standardized across all the subjects to the midpoint of the anterior CC, the mid-body CC, and the posterior CC.

Callosal White Matter—We defined three ROIs in CC (anterior, mid-body and posterior CC) which were outlined on direction colored coronal FA maps of the CC (Figure 1 A, B, C). Anterior CC was defined as the three adjacent slices centered at the middle of the genu and, on average, comprised 230 voxels. Mid-body CC was defined as the three adjacent slices centered at the middle of the longitudinal extent of the CC and, on average, comprised 130 voxels. Posterior CC was defined as the three adjacent slices centered in the middle of the splenium and, on average, comprised 450 voxels.

Intra-hemispheric Association White Matter Tracts—In addition to studying inter-hemispheric WM, we also measured DTI signal in two intra-hemispheric tracts: the cingulum (CIN) and the superior longitudinal fasciculus (SLF). These tracts were studied in both hemispheres and in middle and posterior segments. After finding very similar measurements from both sides, we averaged the measures from the left and right CIN to obtain a single CIN measurement, and we averaged the measures from the left and right SLF to obtain a single SLF measurement. Measurements for middle and posterior portions of these tracts, known to include distinct cortico-cortical fiber bundles, yielded different values and were treated separately. The outline for cingulum was a circular cross-section just above the midline of CC. For outlining the SLF we used MRI Atlas of Human White Matter (26) which locates the SLF laterally to the CC. On average, the cingulum was comprised of 120 voxels, 60 voxels for the middle and posterior ROIs, whereas the SLF was comprised of 300 voxels, 150 voxels for the middle and posterior ROIs.

Statistical Analyses

Statistical analyses were conducted using commercial software SPSS (27). Differences between the AO and AD groups on neuropsychological and perceptual tests were evaluated by Student's t-tests for non-paired data as well as with nonparametric Mann-Whitney tests. We used a multivariate ANOVA with outcome variables of FA and $\langle D \rangle$ and between subjects factors of ROI (nine levels) and subject group (two levels). We also applied Student's t-tests to compare each ROI between the two subject groups with Bonferroni correction for multiple comparisons. Pearson's correlation coefficient (r) was used to evaluate the relationship between FA and $\langle D \rangle$ at each ROI and to evaluate the relationship between FAs and $\langle D \rangle$ s across all ROIs.

Multiple linear regression was used to evaluate possible relationships between performance measures, considering neuropsychological and perceptual tests separately, and the FA DTI measures from all ROIs. We used the forward stepwise model selection method with significance levels of 0.05 for variable entry and 0.10 for variable retention. We adjusted for

the impact of multiple analyses by using the Bonferroni-Holm procedure for confirming significance in sequential testing (28). The procedure provides statistical comparisons of our two subject groups across the multiple regions of interest without assumptions about the underlying distribution of DTI measures in these populations. This procedure uses sequential comparisons between groups by consecutively adjusting critical p values until the observed p value exceeds adjusted p value. In this manner Bonferroni-Holm procedure limits the probability of making even one type 1 error, an erroneous conclusion that the groups differ when they do not. In this sense, it is a conservative approach as it sacrifices sensitivity to type 2 errors, concluding that the groups do not differ when they do. We chose this approach in consideration of our small sample size. All reported results satisfied this additional requirement for ascertaining statistical significance. Neuropsychological test scores were available for all but one AD patient, while the radial motion perceptual scores were not available for one control subject and two AD patients.

Results

Performance Measures

AD patients scored significantly lower on all the neuropsychological tests ($p < .01$), confirming their cognitive impairment (Table 1). AD patients also performed significantly worse on tests of motion perception with significantly elevated thresholds for left- or rightward horizontal motion ($p = .04$), outward left- or right-sided center of motion radial optic flow ($p = .007$), and interleaved in- and outward radial optic flow with left- or right-sided center of motion ($p < .0005$) (Figure 2), replicating our previous findings (29) (30) (17). The neuropsychological and psychophysical measures were not correlated, supporting the view that these approaches assess separate aspects of AD impairment.

DTI Analyses

We obtained the FA and $\langle D \rangle$ measures at each ROI by averaging across the corresponding voxels. We tested for mean differences between the left and right hemisphere ROIs for the cingulum and the superior longitudinal fasciculus and did not find significant differences. Thus, we averaged DTI values from the left and right side to derive composite measures for unilateral fiber tracts.

Differences between the AD and OA groups were assessed using MANOVA separately for FA and $\langle D \rangle$ applied to the nine ROIs. As expected, results yielded significant ROI effects [$F(5.14, 159.2) = 168.09, p < .001$] for FA and [$F(4.65, 144) = 199.06, p < .001$] for $\langle D \rangle$. However, analyses for group differences did not show significant results neither for FA [$F(9, 22) = .97, p < .49$] for $\langle D \rangle$ [$F(9, 22) = .96, p < .49$]. When testing for the group differences, MANOVA also showed that our observed power was only .40 for both dependent measures. There were no significant ROI by group interactions for FA or $\langle D \rangle$. Student's t-tests comparing groups at each ROI yielded: posterior sub-cortical FA of $t = 2.65$ ($p = .01$) and $\langle D \rangle$ of $t = 2.03$ ($p = .05$), and posterior CC FA of $t = 2.7$ ($p = .01$). Bonferroni correction for multiple comparisons yielded a critical p value of .006, showing that these group differences were not statistically significant (Figure 3). Thus, we conclude that DTI measures of WM integrity do not detect significant differences between OA and early AD patients.

We assessed the regional specificity of DTI measures by examining correlations across ROIs in FA and $\langle D \rangle$ (Table 2). These analyses revealed a high degree of regional specificity of FA with significant correlations only between nine of the 36 combinations of ROIs with seven of those nine cases relating contiguous ROIs. In contrast, $\langle D \rangle$ and its constituent measures of axial and radial diffusivity, showed extensive patterns of significant correlation across ROIs: $\langle D \rangle$, all 36 combinations; axial diffusivity, 33 of 36; radial diffusivity, 26 of 36. This evidence

of collinearity of <D> across ROIs led us to focus on the more regionally specific FA measures in subsequent analyses.

Linking Performance and DTI

To evaluate the functional significance of WM integrity we used stepwise multiple linear regressions to characterize the relationships between FA and performance on neuropsychological and perceptual tests for the OA and AD groups and across subject groups using the Bonferroni-Holm procedure to adjust for multiple tests (Table 3). These analyses showed that for elderly subjects decreased FA in the anterior callosal and middle cingular ROIs was correlated ($p < .01$) with poorer performance, increased thresholds, on in/out radial motion processing. In contrast, AD patients' decreased FA in the anterior and middle CC and anterior subcortical ROIs was strongly correlated with poorer performance, decreased scores, on tests of Figural memory ($p < .002$) and Facial recognition ($p < .001$). Thus, both groups showed behavioral declines linked to overlapping anterior cerebral regions but in different cognitive domains.

The differences between the OA and AD groups are more readily discerned in stepwise multiple regressions across groups. This analysis revealed that the DTI measures that distinguished the groups were decreased FA in the posterior callosal and posterior sub-cortical ROIs and that that these values were robustly associated with poorer performance on tests of delayed verbal recall, verbal fluency, figural memory, and in/out radial motion processing. Thus, the within each group, functional capacities varied mainly with anterior FA, but between the two groups, functional capacities varied mainly with posterior FA.

Discussion

The major finding of this study is that anterior and middle WM integrity is linked to functional decline both in OA and AD subjects. In contrast, posterior cerebral WM integrity is linked to functional losses that distinguish OA from AD subjects. In OA subjects, middle cerebral WM integrity is correlated with group variability in visual motion processing capacities. In AD patients, anterior and middle cerebral WM integrity is correlated with group variability in stationary visual form processing. However, we should emphasize that the differences between the OA and AD groups, includes variation in those domains as well as in verbal memory and fluency, all of which are correlated with changes in posterior cerebral WM integrity (Table 3).

Our findings are consistent with evidence of WM deterioration, seen as declining FA, in anterior cortical regions during healthy aging (31) (32). Such studies highlight aging effects in the anterior corpus callosum with the relative sparing of posterior portions and smaller declines in the splenium (33) that result in an apparent peak of FA decline in the genu at the level of the anterior commissure (34). In other hands, age-related decline in FA has been found in the genu but not in the splenium or in adjacent fronto-parietal cortical areas (35). The relationship between WM changes and FA alterations are not well-understood. DTI signals reflect the mobility of water in tissue with decreases in FA potentially mediated by increased extra-cellular fluid following the Wallerian degeneration of axonal fibers secondary to neuron loss (36). WM changes might also be a primary pathophysiological event, with secondary gray matter degeneration (37). Our findings highlight recognition that discrete WM changes are not required to reveal links between WM integrity and function.

We can not confirm the anterior regionality of WM changes in aging as we did not study younger comparison groups. Our focus is on the relationship between DTI measurements of WM deterioration and functional decline in aging. We have found a link between anterior and middle WM integrity and optic flow perception in aging that may reflect the attentional modulation of posterior extrastriate visual motion processing (38) (39) (40). This hypothesis

is consistent with our finding electrophysiological evidence of posterior cortical disinhibition, consistent with the loss of top-down anterior cortical control, in the earliest stages of late-life cognitive decline (41). A similar interpretation has been offered for DTI evidence of links between frontal WM changes and declining executive function in aging monkeys (42). Thus, anterior WM changes may be linked to functional losses in aging, including declines in the top-down behavioral modulation of visual motion processing, that have potentially important links to ambulation (29), driving (30), and navigation (17).

A somewhat different picture emerges from our study of AD patients who show links between anterior and middle cerebral WM changes and declines in the capacity to process stationary visual form stimuli. These correlations with facial recognition and figural memory scores may reflect the relationship between higher-order visual associative function and impaired verbal mediation common in early AD (43) (44). The lack of links to visual motion processing in AD patients could be the product of there being different visual sub-types of AD (45). Alternatively, the more substantial decline of AD patients on our visual motion tests may result from mechanisms of impairment other than those related to the deterioration of frontal attentional mechanisms (Table 2). This interpretation is consistent with direct impact of AD on posterior cortical function, possibly related to deficits in global motion integration (30).

While we can not confirm the finding that AD is associated with more significant WM alterations in posterior cortical areas (46) (12) (47) (48), our data trend in that direction. A posterior parietal concentration of WM changes in AD is harmonious with the posterior predilection for other pathological features of this disease (49) (50). We emphasize that, despite the lack of significant regional specificity of WM changes in our data, we find evidence of strong links between posterior cortical WM changes and functional decline in AD. Analyses across our OA and AD groups reveals significant links between posterior cortical WM changes and impaired performance on tests of verbal and figural memory as well as verbal fluency and optic flow perceptual thresholds. Thus, our findings are consistent with evidence of defects in posterior cortical networks of AD patients both at rest (51) (52) and during mnemonic (53), attentional (54), and perceptual (55) activation.

The cortico-cortical connections that are the substrate of the posterior cortical networks may be specifically disrupted in AD as reflected in the FA of splenium of the CC (56). This is consistent with evidence for the specific vulnerability of cortico-cortical projection neurons in AD (57) that are the most prominent contributors to the inter-hemispheric pathways in the corpus callosum (58). This selective vulnerability may account for aspects of AD impairment that can be viewed as cortical disconnection syndromes (4) (59) reflecting the exclusive interaction of higher-order association areas with other cortical areas. Thus, the decreased integrity of posterior WM tracts may play a critical role in the functional competence of cognitive networks in AD.

Our study has several limitations. Cross-sectional, observational studies can not establish clear evidence of functional or structural changes with disease progression. Furthermore, partial volume effects might differentially bias DTI measures in the somewhat atrophied brains of AD patients as compared to healthy OA subjects. Finally, doubling the number of OA and AD subjects would increase the probability of finding significant effects from .4 to .8 with group differences of the magnitude seen in this study. Thus, the small sample size of this preliminary work underpowered our analyses, suggesting the conservative approach to statistical inference implemented here and encouraging our further work in this area.

We infer the existence of significant links between specific aspects of functional decline and WM integrity in early AD. The specificity of links between behavioral deficits and WM integrity may reflect our limiting our sample to patients with mild disease before more severe

and widespread symptoms emerge. This highlights the potential utility of these methods for the early detection of AD. Further work is needed to confirm the links between WM integrity and decline in memory, cognitive, and perpetual function.

Reference List

1. Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR. An English translation of Alzheimer's 1907 paper, "Über eine eigenartige Erkrankung der Hirnrinde". Clin Anat 1995;8(6):429–431. [PubMed: 8713166]
2. Roberson ED, Mucke L. 100 years and counting: prospects for defeating Alzheimer's disease. Science 2006 Nov 3;314(5800):781–784. [PubMed: 17082448]
3. Hof PR, Bouras C, Constantinidis J, Morrison JH. Balint's syndrome in Alzheimer's disease: specific disruption of the occipito-parietal visual pathway. Brain Research 1989;493:368–375. [PubMed: 2765903]
4. Morrison JH, Hof PR, Bouras C. An anatomic substrate for visual disconnection in Alzheimer's disease. Annals of the New York Academy of Sciences 1991;640:36–43. [PubMed: 1776757]
5. Sugihara S, Kinoshita T, Matsusue E, Fujii S, Ogawa T. Usefulness of diffusion tensor imaging of white matter in Alzheimer disease and vascular dementia. Acta Radiol 2004 Oct;45(6):658–663. [PubMed: 15587425]
6. Kantarci K, Jack CR Jr, Xu YC, et al. Mild cognitive impairment and Alzheimer disease: regional diffusivity of water. Radiology 2001 Apr;219(1):101–107. [PubMed: 11274543]
7. Yoshiura T, Mihara F, Tanaka A, et al. High b value diffusion-weighted imaging is more sensitive to white matter degeneration in Alzheimer's disease. Neuroimage 2003 Sep;20(1):413–419. [PubMed: 14527601]
8. Naggara O, Oppenheim C, Rieu D, et al. Diffusion tensor imaging in early Alzheimer's disease. Psychiatry Res 2006 Apr 30;146(3):243–249. [PubMed: 16520023]
9. Bozzali M, Falini A, Franceschi M, et al. White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging. Journal of Neurology Neurosurgery and Psychiatry 2002;72(6):742–746.
10. Takahashi S, Yonezawa H, Takahashi J, Kudo M, Inoue T, Tohgi H. Selective reduction of diffusion anisotropy in white matter of Alzheimer disease brains measured by 3.0 Tesla magnetic resonance imaging. Neurosci Lett 2002 Oct 25;332(1):45–48. [PubMed: 12377381]
11. Kantarci K, Jack CR Jr, Xu YC, et al. Mild cognitive impairment and Alzheimer disease: regional diffusivity of water. Radiology 2001 Apr;219(1):101–107. [PubMed: 11274543]
12. Rose SE, Chen F, Chalk JB, et al. Loss of connectivity in Alzheimer's disease: an evaluation of white matter tract integrity with colour coded MR diffusion tensor imaging. Journal of Neurology, Neurosurgery & Psychiatry 2000 Oct;69(4):528–530.
13. Yoshiura T, Mihara F, Ogomori K, Tanaka A, Kaneko K, Masuda K. Diffusion tensor in posterior cingulate gyrus: correlation with cognitive decline in Alzheimer's disease. NeuroReport 2002 Dec 3;13(17):2299–2302. [PubMed: 12488815]
14. Kalus P, Slotboom J, Gallinat J, et al. Examining the gateway to the limbic system with diffusion tensor imaging: the perforant pathway in dementia. Neuroimage 2006 Apr 15;30(3):713–720. [PubMed: 16337815]
15. Fellgiebel A, Muller MJ, Wille P, et al. Color-coded diffusion-tensor-imaging of posterior cingulate fiber tracts in mild cognitive impairment. Neurobiol Aging 2005 Aug;26(8):1193–1198. [PubMed: 15917103]
16. Naggara O, Oppenheim C, Rieu D, et al. Diffusion tensor imaging in early Alzheimer's disease. Psychiatry Res 2006 Apr 30;146(3):243–249. [PubMed: 16520023]
17. Kavcic V, Fernandez R, Logan DJ, Duffy CJ. Neurophysiological and perceptual correlates of navigational impairment in Alzheimer's disease. Brain 2006;129:736–746. [PubMed: 16461482]
18. Kavcic V, Duffy CJ. Attentional dynamics and visual perception: Mechanisms of spatial disorientation in Alzheimer's disease. Brain 2003;126:1173–1181. [PubMed: 12690056]
19. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department

- of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34(7):939–944. [PubMed: 6610841]
20. Wechsler, D. Wechsler Memory Scale, Revised Manual. San Antonio, TX: The Psychological Corp; 1987.
 21. Money, J. A Standardized Road Map Test of Direction Sense. Academic Therapy Publications: San Rafael, CA; 1976.
 22. Benton, A.; Hamsher, K.; Varney, NR.; Spreen, O. Contributions to neuropsychological assessment: a clinical manual. New York: Oxford University Press; 1983.
 23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975 Nov;12(3):189–198. [PubMed: 1202204]
 24. Pentland A. Maximum likelihood estimation: The best PEST. *Perception & Psychophysics* 1980;28(4):377–379. [PubMed: 7465322]
 25. Harvey LO. Efficient estimation of sensory thresholds with ML-PEST. *Spatial Vision* 1997;11(1):121–128. [PubMed: 9304762]
 26. Mori, Sususu; Wakana, Setsu; Nagae-Poetcher, Lidia M.; Van Zijl, Peter CM. MRI Atlas of Human White Matter Elsevier. 2005.
 27. SPSS Inc. SPSS 12.0. Upper Saddle River, NJ: Prentiss Hall, Inc.; 2002.
 28. Howell, DC. Fundamental Statistics for the Behavioral Sciences. Vol. 5th ed.. Belmont, CA: Brooks/Cole - Thomson Learning Inc.; 2007.
 29. Tetewsky S, Duffy CJ. Visual loss and getting lost in Alzheimer's disease. *Neurology* 1999;52:958–965. [PubMed: 10102412]
 30. O'Brien HL, Tetewsky S, Avery LM, Cushman LA, Makous W, Duffy CJ. Visual mechanisms of spatial disorientation in Alzheimer's disease. *Cerebral Cortex* 2001 Nov;11(11):1083–1092. [PubMed: 11590117]
 31. Head D, Buckner RL, Shimony JS, et al. Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. *Cereb Cortex* 2004 Apr;14(4):410–423. [PubMed: 15028645]
 32. Sullivan EV, Adalsteinsson E, Pfefferbaum A. Selective age-related degradation of anterior callosal fiber bundles quantified in vivo with fiber tracking. *Cereb Cortex* 2006 Jul;16(7):1030–1039. [PubMed: 16207932]
 33. Pfefferbaum A, Sullivan EV, Hedehus M, Lim KO, Adalsteinsson E, Moseley M. Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. *Magn Reson Med* 2000 Aug;44(2):259–268. [PubMed: 10918325]
 34. Pfefferbaum A, Adalsteinsson E, Sullivan EV. Frontal circuitry degradation marks healthy adult aging: Evidence from diffusion tensor imaging. *Neuroimage* 2005 Jul 1;26(3):891–899. [PubMed: 15955499]
 35. Abe O, Aoki S, Hayashi N, et al. Normal aging in the central nervous system: quantitative MR diffusion-tensor analysis. *Neurobiol Aging* 2002 May;23(3):433–441. [PubMed: 11959406]
 36. Pierpaoli C, Barnett A, Pajevic S, et al. Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. *Neuroimage* 2001 Jun;13(6 Pt 1):1174–1185. [PubMed: 11352623]
 37. Bartzokis G. Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. *Neurobiol Aging* 2004 Jan;25(1):5–18. [PubMed: 14675724]
 38. Treue S, Maunsell JH. Attentional modulation of visual motion processing in cortical areas MT and MST. *Nature* 1996;382(6591):539–541. [PubMed: 8700227]
 39. O'Craven KM, Rosen BR, Kwong KK, Treisman A, Savoy RL. Voluntary attention modulates fMRI activity in human MT-MST. *Neuron* 1997 Apr;18(4):591–598. [PubMed: 9136768]
 40. Dubin MJ, Duffy CJ. Behavioral influences on cortical neuronal responses to optic flow. *Cereb Cortex* 2007 Jul;17(7):1722–1732. [PubMed: 17008413]
 41. Fernandez R, Kavcic V, Duffy CJ. Neurophysiologic analyses of low- and high-level visual processing in Alzheimer disease. *Neurology* 2007 Jun 12;68(24):2066–2076. [PubMed: 17562827]

42. Makris N, Papadimitriou GM, van der KA, et al. Frontal connections and cognitive changes in normal aging rhesus monkeys: a DTI study. *Neurobiol Aging* 2007 Oct;28(10):1556–1567. [PubMed: 16962214]
43. Laatu S, Revonsuo A, Jaykka H, Portin R, Rinne JO. Visual object recognition in early Alzheimer's disease: deficits in semantic processing. *Acta Neurologica Scandinavica* 2003;108:82–89. [PubMed: 12859283]
44. Vogel A, Gade A, Stokholm J, Waldemar G. Semantic memory impairment in the earliest phases of Alzheimer's disease. *Dement Geriatr Cogn Disord* 2005;19(23):75–81. [PubMed: 15572875]
45. Fujimori M, Imamura T, Yamashita H, Hirono N, Mori E. The disturbances of object vision and spatial vision in Alzheimer's disease. *Dementia & Geriatric Cognitive Disorders* 1997 Jul;8(4):228–231. [PubMed: 9213067]
46. Naggara O, Oppenheim C, Rieu D, et al. Diffusion tensor imaging in early Alzheimer's disease. *Psychiatry Res* 2006 Apr 30;146(3):243–249. [PubMed: 16520023]
47. Medina D, Toledo-Morrell L, Urresta F, et al. White matter changes in mild cognitive impairment and AD: A diffusion tensor imaging study. *Neurobiol Aging* 2006 May;27(5):663–672. [PubMed: 16005548]
48. Brun A, Englund E. Regional pattern of degeneration in Alzheimer's disease: neuronal loss and histopathological grading. *Histopathology* 1981;5:549–564. [PubMed: 7286917]
49. Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cerebral Cortex* 1991;1:103–116. [PubMed: 1822725]
50. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica* 1991;82:239–259. [PubMed: 1759558]
51. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci U S A* 2001 Jan 16;98(2):676–682. [PubMed: 11209064]
52. Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci U S A* 2004 Mar 30;101(13):4637–4642. [PubMed: 15070770]
53. Grady CL, McIntosh AR, Beig S, Keightley ML, Burian H, Black SE. Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. *J Neurosci* 2003 Feb 1;23(3):986–993. [PubMed: 12574428]
54. Buck BH, Black SE, Behrmann M, Caldwell C, Bronskill MJ. Spatial- and object-based attentional deficits in Alzheimer's disease. Relationship to HMPAO-SPECT measures of parietal perfusion. *Brain* 1997 Jul;120(Pt 7):1229–1244. [PubMed: 9236633]
55. Rombouts SA, Goekoop R, Stam CJ, Barkhof F, Scheltens P. Delayed rather than decreased BOLD response as a marker for early Alzheimer's disease. *Neuroimage* 2005 Jul 15;26(4):1078–1085. [PubMed: 15961047]
56. Huang H, Zhang J, Jiang H, et al. DTI tractography based parcellation of white matter: application to the mid-sagittal morphology of corpus callosum. *Neuroimage* 2005 May 15;20(1):195–205. [PubMed: 15862219]
57. Hof PR, Morrison JH. Quantitative analysis of a vulnerable subset of pyramidal neurons in Alzheimer's disease: II. Primary and secondary visual cortex. *The Journal of Comparative Neurology* 1990;301:55–64. [PubMed: 1706358]
58. Aboitiz, F.; Ide, A.; Olivares, R. Corpus Callosum Morphology in Relation to Cerebral Asymmetries in the Postmortem Human. In: Zaidel, E.; Ilacboni, M., editors. *The Parallel Brain: The Cognitive Neuroscience of the Corpus Callosum*. Cambridge, USA: The MIT Press; 2003. p. 33-46.
59. Delbeuck X, Van der LM, Collette F. Alzheimer's disease as a disconnection syndrome? *Neuropsychol Rev* 2003 Jun;13(2):79–92. [PubMed: 12887040]

ROIs Relative to Structural Landmarks

Figure 1.

ROIs for DTI. Middle: Sagittal T2s indicate genu-splenial plane (dashed) and anterior-posterior levels. Top: Coronal FA maps by fiber orientation: red, left-right; green, anterior-posterior; blue, dorsal-ventral. Bottom: Coronal T2s show anterior and posterior planes. (A=anterior, M=middle, P=posterior, CC=corpus callosum, Cin=cingulum, SLF=superior longitudinal fasciculus.)

Figure 2.

Visual dot motion for determining coherence thresholds: A. left/right horizontal motion, B. outward radial patterns with left or right focus of expansion, C. Interleaved inward and outward patterns with left or right center of motion. D. Visual motion perceptual thresholds from OA and AD subjects.

Figure 3. Fractional anisotropy measures for nine ROIs in OA and AD subjects. Mean + S.E.M. (ordinate) for each ROI (abscissa) for older adults (OA) (open bar) and AD patients (filled bar).

Table 1

Subject group demographics, neuropsychological test scores, and visual motion thresholds.

	OA (n = 18)	AD (n = 14)
Demographics		
Age (years)	75.39 (7.09)	74.93 (+/- 5.91)
MMSE (max. 30)	28.94 (+/- 1.16)	24.08** (+/- 3.07)
Education (years)	15.67 (+/- 2.81)	14.46 (+/- 2.18)
Neuropsychological Tests		
Delayed Recall	7.06 (+/- .94)	2.58** (+/- 1.68)
Verbal Paired Assoc.	18.61 (+/- 3.24)	6.75** (+/- 4.33)
Figural Memory	7.00(+/- 1.03)	4.38** (+/- .96)
Verbal Fluency	22.89 (+/- 3.72)	4.75** (+/- 4.75)
Money Road Map	30.56 (+/- 2.23)	24.92** (+/- 3.62)
Facial Recognition	47.22 (+/- 3.57)	41.23** (+/- 5.76)
Line Orientation	25.61 (+/- 3.29)	21.50** (+/- 4.11)
Visual Motion Thresholds		
Horizontal motion	13.65 (+/- 4.95)	24.82* (+/- 9.28)
Out left/right radial motion	15.82 (+/- 8.10)	30.82** (+/- 25.58)
In/Out left/right radial motion	19.71 (+/- 19.74)	68.82** (+/- 40.16)

*
p < .05**
p < .01

Table 2
Correlations between two DTI measures across nine ROIs

<D>									
FA	SUB-A	SUB-P	CC-A	CC-M	CC-P	CIN-M	CIN-P	SLF-M	SLF-P
SUB-A		0.79**	0.73**	0.39*	0.61**	0.63**	0.45*	0.76**	0.61**
SUB-P	-0.01		0.74**	0.51**	0.60**	0.72**	0.56**	0.77**	0.68**
CC-A	.60**	0.10		0.59**	0.69**	0.61**	0.36*	0.62**	0.50**
CC-M	-0.19	-0.10	-0.15		0.61**	0.66**	0.47**	0.61**	0.51**
CC-P	0.14	0.07	0.33	-0.23		0.59**	0.48**	0.65**	0.62**
CIN-M	.42*	0.08	.50**	-0.15	0.04		0.72**	0.78**	0.70**
CIN-P	0.31	-0.13	.38*	0.10	0.06	.45**		0.59**	0.76**
SLF-M	0.10	-0.25	0.03	0.12	0.05	0.23	0.12		0.67**
SLF-P	.37*	-.47**	0.30	0.09	0.23	0.29	.64**	.38*	

Table 3
Regression coefficients relating neuropsychological and psychophysical findings to DTI FA in nine ROIs.

	OA		AD		Across Groups	
	R ² _{adj.} (p)	β coefficients	R ² _{adj.} (p)	β coefficients	R ² _{adj.} (p)	β coefficients
Neuropsychological Tests						
Verbal Paired Associates						
Delayed Verbal Recall					.17 (.01)	Post-Sub (β = .44)
Verbal Fluency					.19 (.008)	Post-CC (β = .47)
Line Orientation						
Figural Memory			.57 (.002)	Ant-Sub (.78)	.31 (.002)	Post-Sub (β = .37) Post-CC (β = .44)
Facial Recognition			.68 (.001)	Ant-CC (.52) Mid-CC (.91)		
Money Road Map						
Visual Motion Thresholds						
Horizontal Motion						
Outward Radial Motion						
In/Out Radial Motion	.34 (.01)	Mid-Cin (−.62)			.22 (.006)	Post-Sub (β = −.49)