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Diagnostic Utility of Cerebral White Matter Integrity in Early Alzheimer's Disease

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Abstract

We compared white matter integrity with brain atrophy in healthy controls and participants with very mild dementia (Clinical Dementia Rating 0 vs. 0.5) from the Brain Aging Project, a longitudinal study of aging and memory at the University of Kansas Medical Center. Structural magnetic resonance imaging and diffusion tensor imaging (DTI) including fractional anisotropy and mean diffusivity were performed on 27 patients with very mild dementia (Clinical Dementia Rating = 0.5) of the Alzheimer's type (DAT), and 32 cognitively normal subjects. Patient groups were compared across 6 volumetric measures and 14 DTI regions of interest. Very mildly demented patients showed expected disease-related patterns of brain atrophy with reductions in whole-brain and hippocampal volumes most prominent. DTI indices of white matter integrity were mixed. Right parahippocampus showed significant but small disease-related reductions in fractional anisotropy. Right parahippocampus and left internal capsule showed greater mean diffusivity in early DAT compared with controls. A series of discriminant analyses demonstrated that gray matter atrophy was a significantly better predictor of dementia status than were DTI indices. Brain atrophy was most strongly related to very mild DAT. Modest disease-related white matter anomalies were present in temporal cortex, and deep white matter had limited discriminatory diagnostic power, probably because of the very mild stage of disease in these participants.

Keywords

Alzheimer's disease; brain atrophy; diffusion tensor imaging (DTI); white matter disease

INTRODUCTION

White matter disease (WMD) is seen in neuropathologic examination in over 50% of confirmed cases of Alzheimer's disease (AD). In these moderate- to late-stage dementia of the Alzheimer's type (DAT) individuals, WMD appears global in nature, showing a non-specific pattern of distribution (Englund & Brun, 1990). In life, the prevalence of white matter hyperintensities visible by neuroimaging are increased in AD (Scheltens et al., 1992)

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Declaration of Interest
The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

and contribute to clinical-cognitive features of the disease (Burns et al., 2005; Snowdon et al., 1997). Theories of the underlying etiology of AD-related WMD include the following: (1) Wallerian degeneration (Stricker et al., 2009) of white matter most proximal to cortical regions with high-AD pathological burden; (2) a vascular disease process resulting in a non-specific pattern of axonal damage and gliosis (Englund, 1998); and (3) a primary myelin degeneration process resulting in a disconnection syndrome, where the first age-related breakdowns affect either genu and anterior cingulate (Xie et al., 2006) or superior longitudinal fasciculus (Medina et al., 2006; Takeshima et al., 2007).

Diffusion tensor imaging (DTI) measures water diffusion along or across white matter tracts, using a multidirectional gradient (Basser & Pierpaoli, 1998; Le Bihan, Turner, Douek, & Patronas, 1992). The resultant diffusion tensor provides information about the fractional anisotropy (FA; the amount of water moving along the tract's principle gradient) and mean diffusivity (MD; the distance of diffusion within a voxel during a set amount of time). DTI studies that investigate FA and MD in later-stage DAT generally find white matter changes in temporal cortex, corpus callosum, cingulate, and superior longitudinal fasciculus (for complete review see Chua, Wen, Slavin, & Sachdev, 2008). Studies that examine early-stage DAT (i.e., diagnoses consistent with mild cognitive impairment [MCI]) are more ambiguous. When white matter decrements are found, they often parallel the changes in later-stage DAT (Bozzali et al., 2002; Medina et al., 2006; Ray et al., 2006; Rose et al., 2000; Takahashi et al., 2002; Xie et al., 2006); however, location and magnitude of these decrements vary widely (Chua et al., 2008) probably in part because of the method of analyses (region of interest vs. voxel-based morphometry), samples, and diagnostic criteria.

Using a well-characterized population of healthy aging and very mild-stage dementia patients, we investigated early changes in DTI (FA and MD) across 14 white matter brain structures and compared DTI values with normalized volumetric indices of brain atrophy. We demonstrated that very mildly demented individuals (consistent with an MCI diagnosis) have typical Alzheimer-type cortical atrophy but lack much of the expected white matter changes seen in later-stage DAT. The most notable areas of disease-related white matter decrement were right-sided parahippocampus and left internal capsule.

MATERIALS & METHODS

All procedures and data collection have been approved by our local institutional review board according to ethical standards and practices.

Sample

Data from all available participants enrolled in the University of Kansas's Brain Aging Project between May 2006 and January 2008 (Wave 1 of the longitudinal study) without a Clinical Dementia Rating (CDR 0, $n = 32$; cf. Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1993) and participants with very mild DAT (CDR 0.5, $n = 27$) aged 60 and above were used in the current report. These participants are a subset of the Brain Aging Project cohort that has provided data published in previous reports (Burns et al., 2007, 2008a; Burns, Mayo, Anderson, Smith, & Donnelly, 2008b; Honea et al., 2009). Study exclusions include neurologic disease other than AD, diabetes mellitus (defined as a clinical diagnosis and use of an antidiabetic agent), history of ischemic heart disease (acute coronary artery event, angina), schizophrenia, clinically significant depressive symptoms, abnormalities in B12, rapid plasma reagin, or thyroid function, use of antipsychotic and investigational medications, and significant visual or auditory impairment, systemic illness, or orthopedic issues that could impair completion of the study (cf. Table 1). Because this study focused on comparing health versus disease, two patients staged as CDR 0.5 but with an “uncertain” diagnosis of dementia were also excluded.

Clinical Assessment

The clinical assessment included a semistructured interview with the participant and with a collateral source knowledgeable about the participant (CDR; Hughes et al., 1982; Morris, 1993). Diagnostic criteria for DAT require the gradual onset and progression of impairment in memory and in at least one other cognitive and functional domain. The presence or absence of dementia and its severity if present were determined using the CDR. These methods have a diagnostic accuracy for DAT of 93% (Berg et al., 1998), are sensitive to detection of the earliest stages of DAT by focusing on intraindividual change rather than comparison with group norms (Storandt, Grant, Miller, & Morris, 2006), and are accurate in identifying the subset of individuals meeting criteria for MCI who have early-stage DAT (Morris, 2006). Only CDR 0 and 0.5 individuals were enrolled into the current study. Medications, past medical history, education, and demographic information were collected from the collateral source by the nurse clinician. A standard physical and neurologic examination was performed to assess abnormalities in visual fields, cranial nerves, motor strength, sensation, reflexes, plantar responses, coordination, praxis, and gait. Global cognitive functioning was measured by the mini-mental state examination (MMSE; scores vary from 0 to 30; Folstein, Folstein, & McHugh, 1975) and a standardized global composite score derived from factor analysis of the National Alzheimer's Coordinating Center's Uniform Data Set cognitive assessment battery (Logical Memory I & II, Digit Span Forward, Digit Span Backward, Category Fluency–Animals & Vegetables, Trail Making A & B, Boston Naming Test, and Digit Symbol; composite scores vary from 0 to 1). High scores on both measures indicate better performance.

Magnetic Resonance Imaging Acquisition

Magnetic resonance imaging (MRI) scans were obtained on a Siemens 3.0-T Allegra MRI scanner. High-resolution T1-weighted anatomical images were acquired (magnetization prepared rapid gradient echo; $1 \times 1 \times 1$ mm^3 voxels, repetition time = 2,500 ms, echo time = 4.38 ms, inversion time = 1,100 ms, field of view = 256 × 256, flip angle = 8°). Single-shot echo-planar imaging sequence was used to obtain diffusion images with the following parameters: repetition time = 6,300 ms and echo time = 84 ms. Diffusion gradients were applied in 12 noncollinear directions with two b-values ($b = 0$ and $b = 1{,}000$ s/mm^2). Thirty-four 3-mm sections were acquired at an in-plane resolution of 128 × 128.

Whole-Brain Volumetry

Whole-brain volume (gray plus white parenchyma within the entire intracranial volume down to approximately the superior arch of C1) is computed for each image session, using a validated comprehensive set of imaging tools from FMRIB Software Library (http://www.fmrib.ox.ac.uk/fsl). The images were preprocessed and skull-stripped using Brain Extraction Tool. The skull-stripped images were then segmented into white matter, gray matter, and cerebrospinal fluid using FMRIB's Automated Segmentation Tool (FAST) after registering them to a MNI 152 template. Image processing was conducted utilizing the Laboratory of Neuroimaging Pipeline (http://www.pipeline.loni.ucla.edu). White matter, gray matter, and whole-brain (sum of white and gray matters) volumes were normalized by statistically controlling for total intracranial volume and gender. Normalized brain volumes minimize gender differences and produce an estimate of brain atrophy. As expected, normalized whole-brain volumes were not related to gender [77.1% (3.3) in women vs. 76.9% (3.4) in men; $p = .76$], lending validity to the normalization procedure.

Hippocampal Volumetry

Hippocampal volumes were determined using procedures adapted from Jack et al. (1997) Preprocessing steps include reorienting the brain to the anterior commissure–posterior

commissure plane to minimize head tilt and rotation, normalization of the image to a study-specific atlas using statistical parametric mapping (SPM2), and reformatting the images perpendicular to the principle axis of the hippocampal formation. Normalization to a study-specific atlas occurs using an affine transformation (SPM2) and minimizes variations in hippocampal volume related to head size. The normalization process has the expected effect of inflating the normalized hippocampal volume so that the hippocampi of nonnormalized scans are an average 33% smaller. After preprocessing, the hippocampus was traced by two raters using Analyze software (AnalyzeDirect, Inc., Lenexa, KS) with a view of all three planes available on a second monitor. Interrater reliability intraclass correlation coefficient (ICC) was 0.974. Intrarater reliability ICC for rater 1 was 0.980 and 0.987 for rater 2.

DTI Postprocessing

The DTI data were processed using MedINRIA program (http://www-sop.inria.fr/asclepios/software/MedINRIA). FA maps were generated for each subject from the diffusion data. Regions of interest (ROIs) were hand drawn on color-coded FA maps at specific locations. Six bilateral pairs of ROIs were drawn on axial slices at the following locations: posterior limb of the internal capsule, posterior cingulate, parahippocampal gyrus, superior longitudinal fasciculus, and frontal and temporal regions. The genu and splenium ROIs were placed on the center of the anterior and the posterior corpus callosum. The tracer was blinded to subject information and was trained to draw ROIs at specified regions. The tracer had an intrarater reliability ICC of 0.965 for all DTI measurements. Means and standard deviations (*SD*) for apparent diffusion coefficient and FA were the recorded statistics at each ROI. To account for potential variation due to head size, gender, and white matter fiber thickness, all DTI images were normalized by statistically controlling for total intracranial volume and gender (analogous to volumetric measures).

Statistical Analyses

Disease versus control group comparisons across quantitative measures were conducted using the student's *t*-test with a one-tailed threshold for significance ($\alpha = .05$). While two-tailed tests look for any change (increase or decrease), we know from extensive prior literature that AD results in brain atrophy (cf. Chua et al., 2008); thus we followed standard analytic prescriptions of Cohen, Cohen, West, and Aiken (2002) and used the one-tailed test to detect expected decreases in brain volumetry. Chi-square test of independence was used for nominal variables. Pearson correlation coefficients assessed simple relationships between variables. Discriminant analysis and receiver operator characteristic curves were used to assess the power of brain indices to predict clinical status (CDR 0 vs. CDR 0.5).

RESULTS

Demographics

This cohort of older adults ($N = 59$) was well matched with regard to age (mean = 71.6 years, $SD = 6.4$), education (mean = 15.5 years, $SD = 2.9$), and gender (male-to-female ratio = 34/25). Although there was a slightly higher ratio of men to women in the DAT group, no differences between nondemented and very mildly demented groups on any of these demographics were significant (Table 1). However, individuals with very mild DAT had mild global cognitive dysfunction with a mean MMSE difference of 1.9 points and a two *SD* difference score on the global composite score.

Brain Volumetrics

Comparison of the healthy controls versus the very mildly demented groups revealed the expected disease-related brain atrophy (Table 2). Normalized brain volumes of whole brain, total white matter, total gray matter, and hippocampus showed significant brain atrophy that was widely distributed and present in areas known to be affected by AD. Further, amount of brain atrophy was highly correlated with diagnostic status. Discriminant analyses and receiver operator characteristic curves across indices of brain atrophy showed good sensitivity and specificity for most individual measures; however, the best discriminator between early DAT and controls was right-sided hippocampal atrophy. No combination of these measures improved fit above right-sided hippocampal atrophy alone. Notably, the poorest measure of diagnostic status was total white matter volume.

Diffusion Tensor Imaging

The mean values of FA were mixed across the healthy controls and the very mildly demented groups (Table 3). Lower-tailed *t*-tests of these normalized values revealed a significant difference for right parahippocampal gyrus. The mean values of MD were also mixed (Table 3). Upper-tailed *t*-tests revealed significant differences for right parahippocampus and left internal capsule. All significant DTI indices remained after controlling for age and education. Discriminant analyses using any of these three DTI measures yielded poor results (accuracy ≤ 66%; Area Under the Curve (AUC) ≤ 63%). When entered (stepwise) as additional variables in the previous discriminant analysis using right-sided hippocampal volume, DTI indices failed to contribute to the discrimination over and above the volumetric measures (F to include <3.84, $p > .05$). Intercorrelation between our best diagnostic measure (right-sided hippocampal volume) and proximal white matter projections [right-sided parahippocampal FA ($r = .30$, $p = .01$), right-sided parahippocampal MD ($r = –.16$, $p > .05$)] revealed that gray matter volume and white matter FA were positively associated in the right-sided hippocampal region.

DISCUSSION

In a well-characterized cohort of healthy aging controls and very mildly demented individuals, we found significant disease-related global brain atrophy, with the right hippocampus most severely affected. This is congruent with our previous studies(Bu, 2001; Burns et al., 2007; Burns et al., 2008b). Although white matter integrity in the right parahippocampus and the left internal capsule was reduced in the very mildly demented group, the magnitude of decrement was small and gray matter atrophy was a significantly better predictor of diagnostic status (85% diagnostic accuracy) than was FA or MD (both ≤63%). Thus, the clinical features of this very early-stage DAT group were related to both global and region-specific (hippocampal) gray matter atrophy but only modestly associated with white matter pathology.

Our DAT participants were in the mildest stages, comparable to MCI, and demonstrated significant global and regional brain atrophy, consistent with a number of studies suggesting that hippocampal atrophy is the most sensitive structural index of early DAT (Fotenos, Snyder, Girton, Morris, & Buckner, 2005; Thompson et al., 2003). Age-matched healthy controls were relatively spared from atrophic processes. In contrast, FA and MD white matter values were similar between the controls and participants with DAT, and their diagnostic power was poor. These FA and MD data add to the large variability in the reported location and magnitude of white matter pathology reported in the early DAT literature (Chua et al., 2008). For instance, two recent papers (Chua et al., 2008; Muller et al., 2005) reported excellent discrimination between controls and amnestic MCI using FA; however, the brain regions cited as different across AD and nondemented participants differ

greatly (splenium vs. right hippocampus) across the studies. Disparate findings across centers highlight the inconsistency of DTI indices and cast doubt on the utility of DTI to detect early DAT disease processes because of a lack of consistent discriminatory power.

Overall, these data are consistent with the finding that gray matter is more vulnerable to AD than white matter (Fotenos et al., 2005; Thompson et al., 2003). The very mildly demented individuals reported here have clinical symptoms of early-stage AD and demonstrate cognitive, functional, and neuroimaging (volumetric decrements in gray matter) consistent with this diagnosis but failed to show widespread white matter change. While white matter integrity was reduced most in the right parahippocampal region (consistent with Rose et al., 2006), this area is strongly interconnected with and close in proximity to the right hippocampus. Asymmetrical gray matter atrophy with a right-greater-than-left pattern has been found consistently across volumetric studies of AD (cf. meta-analysis by Shi, Liu, Zhou, Yu, & Jiang, 2009). In the present study, gray matter atrophy in right hippocampus was a superior predictor of disease status than was FA or MD. Moreover, right parahippocampal FA and MD correlated with right hippocampal atrophy measures, suggesting that observed white matter changes in the later clinical stages of AD may be in part due to Wallerian degeneration from primary neurodegeneration in cortical gray matter, resulting in later white matter decrement. However, longitudinal follow-up of the current individuals is needed to examine the cascade of disease-related process in gray matter atrophy and white matter disintegration. Serial white matter volumetric analyses may disambiguate the timing of gray versus white neuropathological events. The relatively high level of white matter integrity observed in our participants with DAT is likely to be due to their very mild stage. When these patients progress, we expect to see greater white matter change. Although small white matter decrements could produce the large gray matter atrophy witnessed in this region (Gouw et al., 2008; Muller et al., 2005), our data are more consistent with the literature suggesting that AD predominantly affects gray matter early in the disease course. This very early right-sided hippocampal gray matter degeneration may later affect local white matter integrity, thus interfering with patients with very mild DAT to represent information visually while encoding (Aguirre, Zarahn, & D'Esposito, 1998; Cornwell et al., 2010). Finally, we did not find any support for regional-specific changes in cingulate and splenium in this study. These areas have been implicated by recent reviews as susceptible to early DAT-related changes and thus interpreted as an aid to early DAT diagnosis (Fellgiebel et al., 2005; Fellgiebel et al., 2004; Medina et al., 2006; Zhang et al., 2007); however, in this study, our very mildly demented participants actually had slightly better DTI values in these regions than did our healthy controls, further limiting the discriminative power of these indices in very early stage DAT.

This study has a number of strengths and weaknesses. We present neuroimaging data from a moderate-sized sample ($N = 59$) of older adults who underwent thorough clinical assessment of neurocognitive function and physical health. Although this sample is relatively large by comparison with other neuroimaging studies, more participants are needed to determine the objective utility of DTI in early DAT. The DTI data presented here were gathered using a 12-direction structural MRI scan sequence. Although it is doubtful that any additional directionality would increase the magnitude of the effects witnessed here, it is possible that a higher resolution gradient sequence may capture white matter change in additional regions. These data are limited by the 3 × 3 mm voxel size; thus our resolution is somewhat diminished and may affect our sensitivity to detect very small white matter decrement. Finally we have not examined what role periventricular and deep-cortical white matter hyperintensities play in these participants. Follow-up studies of these participants will quantify how white matter anomalies interact with anisotropy and diffusivity over time.

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TABLE 1

Demographics

	Nondemented	DAT (CDR 0.5)
CDR	0 (*n* = 32)	0.5 (*n* = 27)
Age	70.3 (6.3)	73 (6.5)
Education	16.2 (3.0)	14.7 (2.9)
Gender (M/F)	16/16	18/9
MMSE	29.4 (0.84)	27.5 (2.25)**
Global cognitive composite	0.15 (0.80)	−1.91 (0.19)**
Cholesterol	185.7 (30.1)	182.3 (44.9)
Treated for hypertension	*n* = 5 (16%)	14 (50%)*
Depression diagnosis (remote history > 1 year)	*n* = 3 (9%)	*n* = 6 (21%)
Geriatric Depression Scale	0.88 (0.91)	2.0 (1.7)*

Note: Study exclusions included diabetes mellitus, history of ischemic heart disease, schizophrenia, clinically significant depressive symptoms, abnormalities in B12, rapid plasma reagin, or thyroid function, use of antipsychotic medications, and significant visual or auditory impairment, systemic illness, or orthopedic issues that could impair completion of the study.

* $p < .01$.

** $p < .001$.

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TABLE 2

Normalized brain volumes in cubic centimeters

	Healthy controls	DAT (CDR 0.5)					
	Mean (*SD*)	Mean (*SD*)	Dementia status[a]	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC (*SD*)
Whole-brain volume	1120.5 (74.3)	1047.4 (86.5)	−.44**	56%	81%	69%	.75 (.06)***
White matter (total)	501.1 (44.8)	478.4 (45.1)	−.24*	26%	84%	58%	.57 (.08)
Gray matter (total)	619.4 (41.5)	568.9 (54.6)	−.48**	70%	72%	71%	.75 (.06)***
Hippocampus (left + right)	89.6 (10.4)	68.3 (14.7)	−.67**	74%	91%	83%	.91 (.04)***
Right	44.9 (49.0)	33.1 (81.5)	−.69**	74%	94%	85%	.92 (.04)***
Left	44.6 (58.7)	35.19 (7.5)	−.60**	67%	81%	75%	.86 (.05)***

[a] Spearman's rho.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

TABLE 3

Diffusion tensor indices

	Fractional anisotropy		Diffusivity	
	Healthy controls Mean (*SD*)	**DAT (CDR 0.5) Mean (*SD*)**	**Healthy controls Mean (SD)**	**DAT (CDR 0.5) Mean (SD)**
Genu	0.57 (.06)	0.58 (.09)	2.70 (.36)	2.70 (.78)
Splenium	0.59 (.07)	0.63 (.07)	2.61 (.35)	2.47 (.31)
Left internal capsule	0.64 (.05)	0.64 (.06)	2.18 (.09)	2.26 (.15)[a,*]
Right internal capsule	0.62 (.06)	0.64 (.06)	2.19 (.10)	2.21 (.14)
Left cingulate	0.49 (.07)	0.50 (.05)	2.27 (.16)	2.29 (.15)
Right cingulate	0.53 (.08)	0.53 (.06)	2.30 (.15)	2.24 (.16)
Left frontal	0.48 (.09)	0.44 (.07)	2.43 (.18)	2.48 (.17)
Right frontal	0.42 (.08)	0.41 (.08)	2.49 (.22)	2.50 (.21)
Left parietal	0.42 (.07)	0.43 (.09)	2.26 (.16)	2.30 (.17)
Right parietal	0.44 (.07)	0.48 (.08)	2.24 (.13)	2.26 (.13)
Left superior longitudinal fasciculus	0.59 (.08)	0.58 (.08)	2.28 (.18)	2.31 (.21)
Right superior longitudinal fasciculus	0.59 (.09)	0.60 (.08)	2.38 (.19)	2.41 (.21)
Left parahippocampus	0.52 (.08)	0.51 (.08)	2.74 (.64)	2.62 (.59)
Right parahippocampus	0.53 (.09)	0.50 (.09)[a]	2.50 (.39)	2.78 (.80)[a,*]

[a] One-tailed $t > 2.01$.

* $p < .05$.