

Regional White Matter Integrity Differentiates Between Vascular Dementia and Alzheimer Disease

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Background and Purpose—Considerable clinical and radiological overlap between vascular dementia (VaD) and Alzheimer disease (AD) often makes the diagnosis difficult. Diffusion-tensor imaging studies showed that fractional anisotropy (FA) could be a useful marker for white matter changes. This study aimed to identify regional FA changes to identify a biomarker that could be used to differentiate VaD from AD.

Methods—T1-weighted and diffusion-tensor imaging scans were obtained in 13 VaD patients, 16 AD patients, and 22 healthy elderly controls. We used tract-based spatial statistics to study regional changes in fractional anisotropy in AD, VaD, and elderly controls. We then used probabilistic tractography to parcel the corpus callosum in 7 regions according to its connectivity with major cerebral cortices using diffusion-tensor imaging data set. We compared the volume and mean FA in each set of transcallosal fibers between groups using ANOVA and then applied a discriminant analysis based on FA and T2-weighted imaging measures.

Results—FA reduction in forceps minor was the most significant area of difference between AD and VaD. Segmentation of the corpus callosum using tractography and comparison of FA changes of each segment confirmed the FA changes in transcallosal prefrontal tracts of patients with VaD when compared to AD. The best discriminant model was the combination of transcallosal prefrontal FA and Fazekas score with 87.5% accuracy, 100% specificity, and 93% sensitivity ($P < 0.0001$).

Conclusion—Integrating mean FA in the forceps minor to the Fazekas score provides a useful quantitative marker for differentiating AD from VaD. (*Stroke*. 2009;40:773-779.)

Key Words: Alzheimer disease ■ dementia ■ diffusion-weighted imaging ■ MRI ■ vascular dementia

Differentiating vascular dementia (VaD) from Alzheimer disease (AD) can be difficult. Vascular disease of the brain is a common cause of cognitive impairment that may lead to VaD.¹ The clinical diagnosis of VaD made using established criteria are not optimally specific and are insensitive.² The neuropsychological profile of patients with VaD generally shows more impairment in semantic memory, executive/attentional functioning, and visual-spatial and perceptual skills, whereas the clinical picture of AD is characterized by deficits in episodic memory.³ However, a recent study on neuropathologically confirmed cases of VaD and AD showed that the neuropsychological profile is a rather poor discriminator.⁴

There are studies such as MRC-FAS,⁵ NUN,⁶ Lille,⁷ and ours⁸ that indicate that VaD overlaps with AD, although pure forms, such as in CADASIL, certainly exist.^{9,10} In addition, white matter lesions seen on MRI do not correlate well with cognitive impairment in VaD¹¹ and cannot differentiate VaD from histologically confirmed AD.¹² Clearly, from a thera-

peutic standpoint, identifying the exact pathological components contributing to the dementia syndrome at the very early stages is important to guide therapy. Advances in neuroimaging techniques provide new tools to address this problem.

Diffusion-tensor imaging is a noninvasive method for visualization of white matter pathways in the human brain in vivo. Fractional anisotropy has been used extensively as a marker for white matter integrity, including in AD¹³ and VaD.¹⁴ However, no specific discriminator between AD and VaD has been identified. In this study, we used sophisticated image processing algorithms to identify the regional pattern of fractional anisotropy (FA) changes in VaD compared to AD and elderly controls (EC).

Subjects and Methods

Subjects

All data were obtained at the Alzheimer Center of the VU University Medical Center, Amsterdam, Netherlands. The cohort included VaD patients (n=13), AD patients (n=16), and healthy EC (n=22).

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Patients were carefully selected on the basis of clinical records and MRI findings after clinical diagnosis by a cognitive neurologist (P.S.) during 2004 to 2006. VaD patients were selected among those who received diagnosis of VaD. Only VaD patients who fully met the diagnostic criteria of VaD based on the NINDS-AIREN criteria¹⁵ and the radiological NINDS-AIREN criteria¹⁶ were invited to participate in this study. This selection procedure was necessary to ensure purity of the VaD group. Diagnostic criteria for AD conformed to those of NINCDS-ADRDA,^{16a} with Mini-Mental State Examination scores >18 and Clinical Dementia Ratings <2. These values correspond to what is known as mild AD. The Medical Ethics Committee of the VU University Medical Center Amsterdam approved the study. All subjects provided informed consent; patients were under supervision of their legal guardian if necessary. Participants were excluded if they had any significant neurological (except for the diseases undergoing study here in the patient groups and commonly found general medical conditions in the elderly, such as ischemic heart disease and hypertension) or psychiatric illnesses; a history of brain damage; or if they were using medication known to influence cerebral function (except for disease-related medication in the patient groups). T2-weighted fluid attenuation inversion recovery scans of each subject were reviewed by a neuroradiologist to assess the presence of vascular lesions.

MRI Acquisition

MRI examinations were conducted on a 1.5-T Sonata system (Sonata; Siemens AG) and included a T1-weighted 3-dimensional gradient sequence (repetition time=2700 ms; echo time=3.97 ms; flip angle=8°; 160 coronal slices; voxel size: 1×1.5×1 mm). Diffusion-tensor imaging was measured using an echo planar imaging sequence with the following specifications: repetition time=8500 ms; echo time=86 ms; voxel size, 2 mm isotropic; 59 consecutive slices; acquisition matrix 128 mm×128 mm (field of view=256 mm); 6/8 partial Fourier; 60 diffusion directions with b value=700 s/mm²; and 10 images with no diffusion weighting (b=0 s/mm²). The bandwidth was 1860 Hz/pixel.

Image Analysis

Image analyses were performed using tools from FSL (FMRIB Software Library, <http://www.fmrib.ox.ac.uk/fsl>).¹⁷ Brain Extraction Tool was used for brain extraction of T1-weighted images.¹⁸ FMRIB's Linear Image Registration Tool was used to derive affine transformation matrices between diffusion and T1-weighted images.¹⁹ Effects of eddy currents and head motion were reduced by registering all diffusion-weighted images to a nondiffusion-weighted reference image using fully affine 12-degrees-of-freedom registration. Analyses of diffusion images were performed using tools from FMRIB's Diffusion Tool (FMRIB Diffusion Toolkit). Probabilistic modeling of diffusion parameters and tractography were performed using previously described methods.²⁰

Voxel-Wise FA Analysis

Statistical analysis of the FA data were performed using tract-based spatial statistics, which has been described elsewhere in detail.¹⁷ Briefly, FA images were created by fitting the diffusion-tensor to the raw diffusion data and then brain-extracted.¹⁸ The next analysis steps were performed separately for the EC, VaD, and AD groups. All subjects' FA data were aligned into a common space using the nonlinear registration as implemented in Image Registration Tool Kit.²¹ Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to all groups. Each subject's aligned FA data were then projected onto this skeleton and the resulting data were fed into cross-subject statistics. Group differences in global FA integrity were calculated by comparing mean FA values within the skeleton mask (thresholded at a mean FA value of 0.2). Nonparametric 2-sample Mann-Whitney *U* tests were used to test for significant differences between groups. Voxel-wise statistics were performed using a permutation-based inference tool for nonparametric statistical thresholding ("Randomize" tool, part of FMRIB's Software Library).²² All voxel-wise group

comparisons were performed using simple 2-sample *t* tests on group mean FA skeleton (thresholded at a mean FA value of 0.25) and the number of permutation tests was set to 5000.

Transcallosal Tractography

Probabilistic tractography between the corpus callosum and 7 major cerebral cortical regions performed using FDT (FMRIB Diffusion Toolkit)²⁰ was performed on the diffusion data. Each subject's brain was first aligned with the Montreal Neurological Institute brain using a 6-degrees-of-freedom transformation (ie, without changing the brain volume). Tissue-type segmentation¹⁸ then was performed and a midsagittal section of the corpus callosum (CC) (seed mask) was obtained from the estimated white matter. Cortical masks (target masks) included prefrontal cortical (PFC) region, premotor cortical region, M1, S1, posterior parietal cortical region, temporal cortical region, and occipital cortical region of each hemisphere and were obtained from probabilistic maps of cortical regions (Harvard-Oxford Cortical Structural Atlas, part of FMRIB's Software Library Viewer). Only voxels present in at least 70% of subjects were retained. Cortical masks were then registered to the T1-weighted images of each subject and masked with the gray matter maps obtained by tissue-type segmentation.¹⁸ The resulting images were binarized and used as the target mask for tractography.

For each individual, the tractography algorithm was run between every voxel inside the CC and each cortical mask. The voxels within the CC were classified according to their connectivity with the cortical targets. Such connectivity-based classification was performed separately for each hemisphere (using the same CC seed mask) and the result was averaged for each region between hemispheres. The resulting regions often overlap.²³ To eliminate this potential problem, probability of connectivity of each voxel was normalized and hard segmentation was performed to find the most probable border between adjacent regions.²³

Volume measurements of white matter, gray matter, and CC regions were normalized for differences in total intracranial volume among subjects by means of an analysis of covariance approach, which adjusts observed volumes by an amount proportional to the difference between an individual's observed intracranial volume and the mean intracranial volume for all subjects.²⁴ This approach results in a more Gaussian distribution than does the usual "ratio adjustment" approach, in which an individual brain volume is divided by total cranial volume,²⁵ which tends to yield positively skewed values.²⁴

Statistical Analyses

Subsequent to volume correction, we calculated the region and mean FA for each CC region. In addition, volumes of the total brain tissue, gray matter, and white matter were also calculated. Univariate ANOVA, with Bonferroni post hoc comparisons, were used for investigating differences in volume and FA values of each CC region across the groups. The level of statistical significance was set at <0.01. To assess more precisely the differences of all measures between AD and VaD patients, effect sizes (*d*) of these measures were determined.²⁶ Measures that showed large effect sizes (*d*>0.8) were used in discriminant analysis with leave-one-out cross-validation test with a stepwise approach (criterion for removal was set to *P*=0.10).

Results

Demographic and Neuropsychological Data

Table 1 shows demographic data of our subjects. There were no differences across groups with respect to age, education, intelligence quotient, alcohol intake, and number of cigarettes smoked. There was a strong difference between the Mini-Mental State Examination and Clinical Dementia Ratings scores of patients compared with EC (*P*<0.0001), but no difference was seen between AD and VaD patients, demon-

Table 1. Summary of Group Demographic Characteristics (Mean±SD)

Characteristics	EC (N=22)	AD (N=16)	VaD (N=13)	Group Effect $F_{(2,48)}$ (<i>P</i>)
Age	70.7±6.0	69.5±6.7	74.3±7.0	2.12 (0.13)
Sex, female:male	13:9	9:7	4:10	
Education, yr	14.7±3.2	14.4±3.1	13.3±4.7	0.41 (0.67)
IQ (NARD)	110.7±18.7	102.5±19.7	99.7±17.3	1.40 (0.27)
CDR	0.0±0.0	0.81±0.44	1.15±0.52	21.8 (<0.0001)
Fazekas score	0.0±0.0	0.88±0.88	2.85±0.38	27.7 (<0.0001)
MMSE	28.7±1.4	22.9±3.2	22.1±3.3	28.8 (<0.0001)
Alcohol use per wk	9.1±8.8	0.3±11.1	8.8±8.6	0.03 (0.97)
Cigarettes per wk	9.1±21.2	0.0±0.0	17.1±44.3	1.7 (0.19)

CDR indicates Clinical Dementia Ratings; MMSE, Mini-Mental State Examination; NARD, National Adult Reading Test.

strating that these 2 groups were not distinguishable on the basis of these scores only.

Across the AD and control groups, white matter abnormalities were observed in 25 out of 40 subjects. These consisted of punctiform white matter lesions in x, early confluent lesions in y, and confluent white matter lesions in z subjects.²⁷ Between-group comparison of Fazekas score showed significant ($P<0.0001$) effect of the groups that was attributed to difference between AD and VaD (Table 1).

Quantitative Volumetry

There were significant differences across groups in total brain tissue, gray matter, and white matter volumes (Table 2). Post hoc comparisons showed that in VaD patients the total brain tissue, white matter, and gray matter volumes were significantly reduced compared with EC, but not compared with AD. The volume of gray matter was also significantly reduced in AD patients compared with EC, whereas total brain tissue and white matter volume were not significantly different between these 2 groups.

Total CC volume was not significantly different across groups. Analyses of CC regions showed no difference in total

CC volume across groups but significant reduction of transcallosal PFC volume in VaD when compared with EC. No significant difference was found between AD and EC in the volume of CC regions.

FA Analysis

Mean FA values of the white matter in each group are shown in Table 3. White matter FA value in the VaD was significantly less than in EC; however, only a trend was observed when VaD was compared with AD. There was no significant difference between mean white matter FA of EC and AD. A similar pattern of difference was seen in the FA value of CC across the groups. CCFA in VaD was significantly less than in EC, but showed no difference when compared with AD.

Tract-based spatial statistics analysis showed that the pattern of FA changes in VaD was clearly different from AD. Contrasting EC and AD showed reduced FA mainly in the medial temporal white matter and uncinate fasciculus (Figure). However, VaD patients showed FA reduction more extensively in periventricular area, corona radiata, forceps minor, frontal white matter, and inferior fronto-occipital fasciculi (Figure). Contrasting AD with VaD showed FA

Table 2. Comparison of TBVotal Brain Volume, Gray Matter Volume, White Matter Volume, and CC Regions Using ANOVA With Bonferroni Correction

	EC	AD	VaD	ANOVA§	Post hoc
TBV (cm ³)	1072±127	994±90	912±94	F=9, $P<0.0001$	VaD-EC, $P=<0.0001$ VaD-EC, $P<0.0001$
GM (cm ³)	652±20	591±25	584±24	F=50.3, $P<0.0001$	AD-EC, $P<0.0001$
WM (cm ³)	421±20	416±23	398±9	F=6.5, $P=0.003$	VaD-EC, $P=0.003$
CC Regions					
PFC	430±61	395±46	356±50	F=7.7, $P=0.001$	VaD-EC, $P=0.001$
PMC	114±18	106±16	101±22	F=2.3, $P=0.11$	
PPC	175±46	180±31	185±41	F=0.27, $P=0.76$	
Temp	82±26	106±35	94±37	F=2.7, $P=0.08$	
Occ	55±15	61±17	53±16	F=1.1, $P=0.35$	
S1	35±10	29±15	26±6	F=2.7, $P=0.08$	
M1	28±12	26±8	29±13	F=0.21, $P=0.81$	
Total CC	920±85	906±60	847±80	F=3.9, $P=0.03$	VaD-EC, $P=0.03$

Gender and age were taken as covariants. Note that the CC regions are 1 voxel thick in sagittal plain.

Occ indicate occipital; GM, grey matter, PMC, premotor cortical region; PPC, posterior parietal cortical region; Temp, temporal; WM, white matter.

Table 3. Comparison of Mean FA Value of each CC Region Using ANOVA $F_{(2,48)}$ With Bonferroni Correction

Region	EC (N=22)	AD (N=16)	VaD (N=13)	ANOVA	Post hoc
Total CC	0.46±0.05	0.44±0.05	0.40±0.04	F=4.9, P=0.01	P<0.01 (VaD-EC) P<0.0001 (VaD-EC) P<0.0001 (VaD-AD)
PFC	0.54±0.05	0.52±0.04	0.45±0.04	F=15.4, P<0.0001	P<0.001 (VaD-EC)
PMC	0.54±0.06	0.51±0.06	0.46±0.06	F=7.9, P=0.001	P<0.001 (VaD-EC)
PPC	0.61±0.05	0.58±0.07	0.53±0.08	F=5.8, P=0.006	P<0.004 (VaD-EC)
Temp	0.64±0.06	0.64±0.07	0.58±0.07	F=3.8, P=0.03	NS
Occ	0.62±0.08	0.64±0.09	0.58±0.07	F=1.8, P=0.17	NS
S1	0.54±0.08	0.48±0.08	0.44±0.08	F=7.8, P=0.001	P<0.01 (VaD-EC)
M1	0.51±0.08	0.48±0.07	0.43±0.08	F=4.7, P=0.014	P<0.009 (VaD-EC)

Gender and age were taken as covariants. Only significant results are shown.

Comparison of FA values (mean±SD).

NS indicates not significant.

changes mainly in the forceps minor, superior and inferior longitudinal fasciculus, as well as in the anterior and inferior fronto-occipital fasciculus (Figure and Table 4). Details of regional FA changes in AD in comparison with young and old healthy volunteers have been reported elsewhere.²⁸

Regional analysis of mean FA values of CC regions showed significant group differences in all CC regions, except those regions predominantly containing occipital and temporal fibers (Table 3). Posthoc comparisons showed that PFC FA was significantly reduced in VaD patients compared with EC and AD patients. Premotor cortical region, parietal cortical region, M1, and S1 showed significantly reduced FA in VaD patients compared with EC, but not compared with AD patient. There was no difference in FA between AD patients and EC for any of these regions. Adding the Fazekas score as covariant in the group comparison analysis showed no difference in the result of this group analysis. In addition, linear regression model between FA values and Fazekas score showed no correlation.

Discrimination of VaD From AD

We compared effect size of each variable. Volume of PFC region, and total CC, mean FA values of the PFC, premotor

Table 4. Cluster Size and Coordinates of Local Maxima in Major White Matter Tracts When FA Map in AD Was Compared to FA Map in VaD Group Using TBSS

	Size	X	Y	Z	T
Forceps minor	119	98	151	86	4.41
Right superior longitudinal fasciculus	278	70	93	110	4.17
Left superior longitudinal fasciculus	250	126	105	99	4.04
Left inferior fronto-occipital fasciculus	468	123	61	78	4.10
Left anterior thalamic radiation	107	113	160	67	4.07

The most significant clusters are within forceps minor. In addition, significant clusters are found in other major white matter connected to prefrontal cortex.

Cluster size and coordinates of local maxima in major white matter tracts when AD was compared to VaD group.

TBSS indicates tract-based spatial statistics.

cortical region, and temporal regions, as well as Fazekas score, showed a significant effect size of ≥ 0.8 . When each of these areas was entered as an independent variable in single discriminant analysis, they each showed discriminatory power ($P<0.05$). However, in a combined discriminant analysis model, PFC region and Fazekas score together (with age and sex covariants) provided the most accurate discriminate between AD and VaD patients (specificity=100%; sensitivity=87.5%; overall accuracy=93%; $\chi^2=33.87$; degrees of freedom=2; $P<0.0001$).

Discussion

This study aimed to use diffusion data for differentiating VaD from AD. We first looked for voxel-wise FA changes of the entire brain that showed the most significant change in the forceps minor. We then examined transcallosal regions that confirmed that the most significant change occurs in the transcallosal prefrontal tracts. We found that this marker together with Fazekas score provides sensitive and specific markers for differentiating AD from VaD.

To our best knowledge, this is the first report in which changes in specific tracts are identified as an accurate biomarker for differentiation VaD from AD. This is important because previous studies showed that ischemic white matter lesions seen on fluid attenuation inversion recovery images do not necessarily correlate with dementia.²⁹ Our study in association with that of others⁹ suggests that location of the ischemic damage is crucial for the development of dementia in VaD. In addition, Fazekas score as covariant in group analysis had no significant effect on the result of the analysis, suggesting that the brain damage in vascular dementia is likely to be attributable to white matter damage that is beyond detection by visual inspection. This highlights the importance of quantification using diffusion-tensor imaging data.

Quantifying Diffusion-Tensor Imaging

We used fractional anisotropy as a surrogate marker for white matter integrity. Fractional anisotropy changes has been associated with inflammatory or degenerative damage to the nerves.^{30,31} In our study, tract-based spatial statistics showed that forceps minor, corona radiata, and fronto-occipital tracts were particularly compromised in VaD subjects when com-

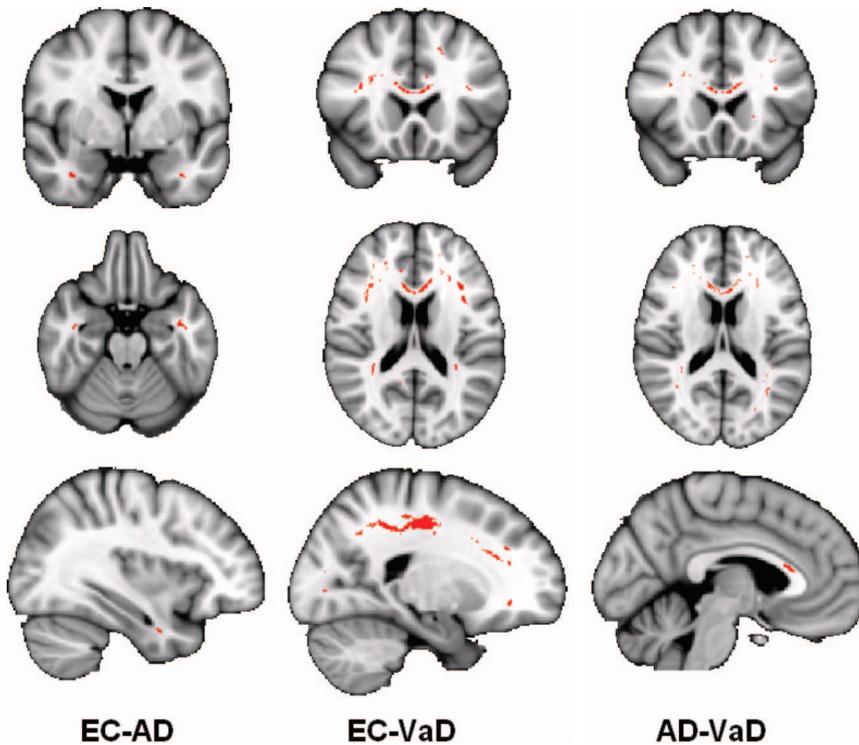


Figure. Tract-based spatial statistics analysis and subsequent permutation analysis showed reduced FA in AD compared to controls (left) and in anterior CC, frontal, and parietal white matter in VaD compared to controls. However, when AD was compared with VaD, the most significant area of difference was in the transcallosal prefrontal tracts ($P < 0.0001$, corrected).

pared with AD or EC. This is most likely attributable to ischemia-induced pathology in the periventricular area, and frontal and parietal white matter in VaD. This finding guided us to find the corpus callosum region of interest that shows maximum changes across subjects.

Further examination of changes in the CC using segmentation of the transcallosal tracts based on diffusion-tensor imaging tractography showed FA reduction in prefrontal and sensorimotor interhemispheric tracts in VaD (but not in AD) compared with EC. This suggests loss of integrity of transcallosal tracts, most likely attributable to multiple ischemic insults. Our findings support previous reports which showed that, in VaD patients, FA diminishes in the anterior part of the CC.³² We extended these findings by demonstrating a selective damage of the prefrontal and premotor interhemispheric tracts. Prefrontal connections play an important role in frontal network function,³ information processing, set shifting, executive function, and memory that are often impaired in VaD patients. It is likely that small white matter lesions in the frontal lobe cause minor cognitive deficits at the early stages, but that the presence of rich interhemispheric prefrontal connections provides access to the contralateral neural systems that can compensate for the loss of cognitive function. However, once these interhemispheric connections are severely damaged, this potential no longer exists and clinical features of dementia on a background of small vessel disease develop.

Some authors^{14,33} reported decrease in volume and mean FA in the anterior part of the CC in VaD. Others found that the apparent diffusion coefficients are significantly higher in the anterior portions of CC in VaD compared with healthy controls and to AD patients.³⁴ High apparent diffusion coefficient values are thought to be associated with axonal degeneration.³⁵

Quantitative Structural Morphometry

Cortical gray matter in AD (similarly to VaD) was significantly diminished when compared with EC. However, white matter volume in AD was similar to EC and larger than in VaD. This is consistent with the clinical notion that VaD is predominantly a subcortical, and AD a cortical, dementia.³ Reduction of cortical mass in VaD is likely to be secondary to substantial white matter damage through Wallerian degeneration.

Comparison of CC regions between groups showed a general trend of reduction of the areas subserving prefrontal and sensorimotor tracts in AD and VaD. However, the degree of tissue loss in VaD patients seems to be more pronounced than in AD. This was particularly evident in the region including the prefrontal fibers. This finding is supported by previous studies in which anterior part of the CC was reported to undergo degenerative process both in AD and VaD.³²

Other studies of regional changes in CC have arrived at varying conclusions. For example, some authors³⁶ identified significantly smaller posterior midbody, isthmus, and splenium of the corpus callosum compared with controls; another³⁷ found atrophy of the rostral body and midbody regions. In our study, the total volume of the CC was not significantly reduced in VaD patients compared with EC at a statistical threshold of $P < 0.01$. However, volume of PFC region (and not other CC regions) showed significant reduction in VaD comparison to AD and controls. These findings are in contrast with previous studies.^{38,39} This discrepancy could be attributable to image analysis techniques used to identify CC regions, registration methods, inclusion criteria of patients (eg, early vs advanced stage), and statistical level of significance used. In general, we found that affine registration is unsuitable for accurate

study of the CC. In addition, we aligned all brains and created CC masks in the midsagittal plane to ensure that masks were exactly in the same anatomic location. Furthermore, general sparing of the CC volume in our study can be explained by the fact that our patient groups were at early stages of their disease, whereas the aforementioned postmortem studies^{38–40} were performed on advanced cases.

Discriminating VaD From AD

Discriminant analysis with leave-one-out cross-validation test showed that mean FA in PFC of CC and Fazekas score together provided the best discriminator, with overall accuracy of 93% and 100% specificity. Reduction of FA values in premotor cortical region, S1, M1, temporal cortical region, and parietal cortical region were not associated with volume reductions in these regions (unlike PFC region). FA volume dissociation phenomenon is consistent with the notion that FA changes precede white matter atrophy⁴¹ and are therefore a more sensitive marker for differentiating VaD from AD.

Summary

In this study we showed that tractography-based analysis combined with tract-based spatial statistics has proved to be a useful technique to identify specific regional changes in white matter integrity. Using this approach, we showed that mean FA in transcallosal prefrontal connections may be a useful marker to differentiate AD from VaD.

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Disclosures

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