Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke Association

A Division of American Heart Association

Diffusion-Weighted Imaging and Cognition in the Leukoariosis and Disability in the Elderly Study

Reinhold Schmidt, Stefan Ropele, José Ferro, Sofia Madureira, Ana Verdelho, Katja Petrovic, Alida Gouw, Wiesje M. van der Flier, Christian Enzinger, Leonardo Pantoni, Domenico Inzitari, Timo Erkinjuntti, Philip Scheltens, Lars O. Wahlund, Gunhild Waldemar, Egill Rostrup, Anders Wallin, Frederik Barkhof and Franz Fazekas

Stroke 2010, 41:e402-e408: originally published online March 4, 2010
doi: 10.1161/STROKEAHA.109.576629
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

Diffusion-Weighted Imaging and Cognition in the Leukoariosis and Disability in the Elderly Study

Reinhold Schmidt, MD; Stefan Ropele, PhD; José Ferro, MD, PhD; Sofia Madureira, PSyD; Ana Verdelho, MD; Katja Petrovic, MSc; Alida Gouw, MD; Wiesje M. van der Flier, MD; Christian Enzinger, MD; Leonardo Pantoni, MD, PhD; Domenico Inzitari, MD; Timo Erkinjuntti, MD, PhD; Philip Scheltens, MD, PhD; Lars O. Wahlund, MD, PhD; Gunhild Waldemar, MD, DMSc; Egill Rostrup, MD, MSc; Anders Wallin, MD, PhD; Frederik Barkhof, MD, PhD; Franz Fazekas, MD; on behalf of the LADIS study group

Background and Purpose—The mechanisms by which leukoariosis impacts on clinical and cognitive functions are not yet fully understood. We hypothesized that ultrastructural abnormalities of the normal-appearing brain tissue (NABT) assessed by diffusion-weighted imaging played a major and independent role.

Methods—In addition to a comprehensive clinical, neuropsychologic, and imaging work-up, diffusion-weighted imaging was performed in 340 participants of the multicenter leukoariosis and disability study examining the impact of white matter hyperintensities (WMH) on 65- to 85-year old individuals without previous disability. WMH severity was rated according to the Fazekas score. Multivariate regression analysis served to assess correlations of histogram metrics of the apparent diffusion coefficient (ADC) of whole-brain tissue, NABT, and of the mean ADC of WMH with cognitive functions.

Results—Increasing WMH scores were associated with a higher frequency of hypertension, a greater WMH volume, more brain atrophy, worse overall cognitive performance, and changes in ADC. We found strong associations between the peak height of the ADC histogram of whole-brain tissue and NABT with memory performance, executive dysfunction, and speed, which remained after adjustment for WMH lesion volume and brain atrophy and were consistent among centers. No such association was seen with the mean ADC of WMH.

Conclusions—Ultrastructural abnormalities of NABT increase with WMH severity and have a strong and independent effect on cognitive functions, whereas diffusion-weighted imaging metrics within WMH have no direct impact. This should be considered when defining outcome measures for trials that attempt to ameliorate the consequences of WMH progression. **(*Stroke*. 2010;41:e402-e408.)**

Key Words: cognition ■ imaging ■ leukoariosis

There is abundant evidence for a predominantly vascular etiology of leukoariosis in the elderly population, yet the role of white matter damage as a contributor to cognitive impairment and dementia is still not fully determined.[1] Cross-sectional and longitudinal studies in patients with leukoariosis report modest correlations between T2-lesion load and severity of cognitive impairment on a group level,[2–5] but individual patients can have widespread white matter damage on MRI without any cognitive dysfunction. In this context, it has to be considered that high signal intensity on standard MRI can reflect a spectrum of pathological abnormalities ranging from very mild tissue changes seen with punctate lesions to complete demyelination and axonal loss in the presence of small-vessel disease often seen with confluent abnormalities.[6] Thus, imaging techniques that allow a more direct assessment of the composition and integrity of white matter structures are promising tools to explain impaired cognition related to white matter abnormalities beyond what can be expected from lesion volumetry. One of these techniques is diffusion-weighted imaging (DWI).

In DWI, the average apparent diffusion coefficient (ADC), or mean diffusivity, represents a measure of tissue water

Received December 18, 2009; accepted January 11, 2010.

From Department of Neurology (R.S., S.R., K.P., C.E., F.F.), Medical University of Graz, Graz, Austria; Serviço de Neurologia (J.F., S.M., A.V., F.B.), Centro de Estudos Egas Moniz, Hospital de Santa Maria, Lisboa, Portugal; Department of Neurology (A.G., W.v.d.F., P.S., F.B.), Vrije Universiteit Medical Center, Amsterdam, the Netherlands; Department of Neurological and Psychiatric Sciences (A.G., L.P., D.I.), University of Florence, Florence, Italy; Memory Research Unit (T.E.), Department of Clinical Neurosciences, Helsinki University, Helsinki, Finland; Neurotec Department (L.O.W.), Section of Clinical Geriatrics, Karolinska Institute, Huddinge, Sweden; Memory Disorders Research Unit (G.W., E.R.), Department of Neurology, Copenhagen University Hospital, Copenhagen, Denmark; Institute of Clinical Neuroscience and Physiology (A.W.), University of Gothenburg, Gothenburg, Sweden; Department of Radiology (F.B.), Vrije Universiteit Medical Center, Amsterdam, the Netherlands.

Correspondence to Reinhold Schmidt, MD, Department of Neurology, Medical University of Graz, Auenbruggerplatz 22, 8036 Graz, Austria. E-mail reinhold.schmidt@medunigraz.at

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.109.576629**

mobility that depends on the structural barriers at cellular and subcellular levels.[7] Pathological processes that modify tissue integrity such as small-vessel disease are accompanied by an elevated ADC.[7] It has been suggested that in subjects with age-related white matter hyperintensities (WMH), an increase in ADC occurs not only in areas of T2 hyperintensity but also in normal-appearing white matter. Furthermore, mean diffusivity of normal-appearing white matter appeared more closely related to clinical deficits than the volume of visible white matter damage.[8–13] Such data have been reported in patients in CADASIL,[8] which is a genetic model of rapidly progressive small-vessel disease, and in single-center studies of individuals with age-related WMH.[9–13]

Our study extends previous work by using a multicenter approach and stratification for the severity of WMH to recruit a large sample of subjects with a wide range of white matter damage. We hypothesized that mean diffusivity in WMH and normal-appearing brain tissue (NABT) affects functioning in various cognitive domains and that these effects are independent of vascular risk factors, white matter lesion volume, and brain atrophy.

Subjects and Methods

Subjects

All subjects were participants of the multicenter leukoariosis and disability (LADIS) study. The rationale and design of the LADIS study have been described elsewhere.[14] In summary, elderly subjects between the ages of 65 and 84 years with MRI evidence of WMH but no or only mild disability according to the Instrumental Activities of Daily Living Scale[15] were enrolled in a hospital-based setting. To achieve a well-distributed range of WMH severity we stratified participants according to the modified Fazekas scale[16] with WMH categorization into 3 severity classes, ie, punctate, early confluent, and confluent. Further inclusion criteria were the presence of a regularly contactable informant and the agreement to sign an informed consent form. Exclusion criteria were likelihood of dropping out because of the presence of severe illnesses, eg, cardiac, hepatic, or renal failure, cancer, or other relevant systemic diseases; severe unrelated neurological diseases; leukoencephalopathy of nonvascular origin (immunologic, demyelinating, metabolic, toxic, infectious, other); severe psychiatric disorders; inability to give informed consent; and inability or refusal to undergo cerebral MRI.

For assessment of vascular risk factors at baseline, a structured data questionnaire was used together with a review of available records by trained medical personnel.[14] The risk factors used in this work were patient age, gender, presence of hypertension (treatment with antihypertensive medications or with values ≥140/90 mm Hg based on measurements taken on several separate occasions), history of diabetes mellitus (treatment with antidiabetic medications or at least 8-hour fasting plasma glucose ≥7.0 mmol/L or 126 mg/dL), atrial fibrillation (based on history or available clinical records such as an ECG), and history of myocardial infarction (documented by history, ECG, or cardiac enzymes). Years of education were also recorded.

MRI

Eight of the 11 LADIS centers participated in this substudy that required the acquisition of DWI in addition to the general scanning protocol used in the LADIS study. DWI was optional and some LADIS centers were not capable of performing a DWI sequence. In all centers contributing to the current study, imaging was performed on 1.5-T whole-body systems (ACS-Intera, Philips Medical Systems; Magnetom Vision, Siemens Medical Systems; Magnetom Sonata, Siemens Medical Systems; Signa, General Electric Medical System). The general MRI protocol included the following sequences: T1-weighted 3-dimensional magnetization-prepared rapid-acquisition gradient-echo (scan parameters, coronal or sagittal plane; echo time, 2–7 ms; repetition time, 9–26 ms; flip angle, 15°–30°; voxel size, $1\times1\times1-1.5$ mm^3), T2-weighted fast-spin echo (scan parameters, axial plane; echo time, 100–130 ms; repetition time, 4000–6600 ms; voxel size, $1\times1\times5$ mm^3; 19–31 slices), and fluid-attenuated inversion recovery (FLAIR; scan parameters, axial plane; echo time, 100–140 ms; repetition time, 6000–10 000 ms; inversion time, 2000–2400; voxel size, $1\times1\times5$ mm^3; 19–31 slices).

DWI was performed with a pulsed gradient spin-echo sequence with echo planar imaging readout (repetition time, 4000–6000 ms; echo time, 100–140 ms; matrix, 128×128; field of view, 250 mm; slice thickness, 5 mm; number of slices, 20–28). The voxel size was $1.95\times1.95\times5$ mm and it was identical across all centers.

The sequence was performed with 2 b factors ($b=0$ sec/mm^2 and $b=900–1000$ sec/mm^2), whereas the diffusion gradients were applied along the 3 principal directions. To provide ADC maps of comparable quality, every participating center was asked to optimize the protocol within the narrow frame of the proposed parameters according to local capabilities. Local variations of the DWI protocol mostly affected the repetition time, sampling bandwidth, partial Fourier imaging, and the number of averages. The total acquisition time of the DWI sequence varied as a function of the repetition time and the number of averages but was <2 minutes in each center.

The slices of all axial sequences were positioned to cover the central part of the brain and to run parallel to a line defined by the most inferior–anterior part of the corpus callosum and the most inferior–posterior part of the corpus callosum.

Image Analysis

Assessment of WMH severity used for this study was performed centrally by a single rater who was blinded to all clinical information. WMH were rated visually on axial FLAIR images using a modification of the Fazekas scale.[16] This scale grades WMH severity into mild, moderate, and severe categories. Typical examples for each grade have been displayed elsewhere.[17] To determine the intrarater reliability of this rating scheme, 18 randomly selected scans were scored twice, which resulted in a weighted Cohen κ of 0.84.

In addition to WMH rating, volumetric analysis of WMH was also performed centrally on the axial FLAIR images. Using a seed-growing technique with local thresholding, the contour of WMH was delineated and WMH masks and corresponding volumes were calculated.[18]

DWI metrics were analyzed for the whole-brain tissue (WBT), which included normal-appearing white matter, white matter lesions and gray matter, the NABT including normal-appearing white matter and gray matter but no white matter lesions, and areas of WMH. Because WMH were identified on FLAIR images, all parameter maps were registered with the FLAIR images after they had been calculated from the raw data.

To calculate ADC maps, the images with the high b values were averaged over all 3 principal directions to obtain a rotationally invariant image. The ADC was then determined by the slope of the line, which was defined by the natural logarithm of the averaged image with the high b value and the logarithm of the T2-weighted image ($b=0$ sec/mm^2). The ADC maps were then registered with the FLAIR scans, and the T2-weighted scan ($b=0$ sec/mm^2) was used to calculate the transformation matrix. Registration was performed with an affine 12-parameter model using a correlation ratio-based cost function and trilinear interpolation (http://www.fmrib.ox.ac.uk/fsl/). This model can only partly account for nonlinear EPI distortion. A possible way around this problem is tract-based registration; however, for this study, we had no flip angle data available. To obtain NABT masks, WMH were masked out and nonbrain tissue was removed with a brain extraction tool (FSL, FMRIB Analysis Group). To reduce partial volume effects at the border of WMH, the WMH masks were dilated by 1 pixel before NABT masks were generated. Likewise, WMH masks were eroded by 1 pixel when determining lesional ADC.

For assessing WBT and NABT, we used a histogram analysis and calculated the relative peak height, the peak position, and the average ADC. To correct for differences in individual brain volumes, the histograms were normalized by the total number of voxels included in the histogram analysis. For the assessment of WMH we calculated the mean ADC.

To assess brain atrophy, 1 observer (R.S.) rated ventricular and sulcal atrophy separately by using a template-based rating scale ranging from 1 (no atrophy) to 8 (severe atrophy). The sum of both ratings was used as a global measure of atrophy. This template also has been used in previous publications of the study group.[18,19] Intrarater reliability was assessed on the basis of double readings of 50 randomly selected scans. Similarly, inter-rater reliability was assessed from the readings of the same scans by 3 other persons. For the current observer (R.S.), the intrarater κ value was >0.9 for both sulcal and ventricular atrophy; The inter-rater κ value was 0.70 for sulcal and 0.83 for ventricular atrophy.[19]

Neuropsychological Testing

Neuropsychological assessment followed the LADIS protocol.[20] The test battery included the Vascular Dementia Assessment Scale cognitive subscale,[21] the Stroop test,[22] Trail-Making test.,[23] and the Mini Mental State Examination.[24] Vascular Dementia Assessment Scale cognitive subscale includes all items of the Alzheimer Disease Assessment Scale[25] plus the symbol digit test, the digit span, a maze test, and tests of digit cancellation and verbal fluency.

We measured cognitive performance by cognitive domains using standardized results of Vascular Dementia Assessment Scale subtests for the domains language, constructional abilities, and orientation. Memory, executive function, and speed were assessed by computing compound measures from all test results within a given domain. The Mini Mental State Examination was considered as a measure of global cognitive function.

Statistical Analysis

We used the Statistical Package for Social Sciences (SPSS 16.0; SPSS) for data analysis. To allow for direct comparisons of ADC histogram analyses and of neuropsychological tests results between centers, we generated z scores. A z score defines where a score is within the distribution of scores. A z score of $+1$ corresponds to a score 1 SD above the mean score. The z scores of neuropsychological tests for which higher scores represented poorer performance were inverted ($-z$) for calculation of compound measure scores.

The memory score was the sum of the z scores of immediate word recall (inverted) plus delayed word recall (inverted) plus word recognition (inverted) plus digit span. Executive functions were represented by the sum of z scores of Stroop 3 to 2 (inverted) plus Trail-Making test B minus Trail-Making test A (inverted) plus symbol digit score plus verbal fluency.

The speed score was the sum of the z scores of Trail-Making test A (inverted) plus maze (inverted) plus digit cancellation. The results of the Mini Mental State Examination were also transferred to z scores.

Categorical variables among the white matter lesion grades were compared by the χ^2 test. Assumption of normal distribution for continuous variables was assessed by Lilliefors statistics. Normally distributed continuous variables were compared by 1-way analysis of variance, whereas the Kruskal-Wallis test was used for comparison of non-normally distributed variables. Multivariate regression analysis assessed the relative contribution of ADC measures on performance in different cognitive domains. Regression analyses were adjusted in 3 models.

Model 1 included gender, age, years of education, center, hypertension, diabetes, and cardiac disease. Model 2 extended model 1 by the addition of white matter lesion volume and model 3 extended model 2 by the addition of the brain atrophy score. Analyses were performed on the entire cohort and by center.

Results

Eight centers of the LADIS consortium contributed a total of 340 patients with DWI scans. The number of patients per center ranged from 20 to 61. Table 1 describes the patient characteristics for the whole group and are broken down by WMH grade.

The subgroup taking part in the ADC study did not significantly differ from the entire LADIS cohort with respect to age, gender, education, frequency of vascular risk factors, and WMH scores.[26] As can be seen from Table 1, increasing WMH scores were associated with higher frequency of hypertension, a greater WMH volume, more brain atrophy, and worse overall cognitive performance. Executive functions and speed were most affected. Increasing WMH severity also related to significant changes in the ADC histogram metrics of WBT, NABT, and in the mean ADC of WMH (Table 1). Specifically, mean ADC and ADC peak position increased in WBT and NABT, whereas ADC peak height decreased. Mean ADC of WMH increased with higher WMH scores.

The ADC in areas of WMH correlated with ADC measures in WBT (mean ADC, $r=0.37$; $P<0.0001$; peak height, $r=-0.33$; $P<0.0001$; peak position, $r=0.50$; $P<0.0001$) and NABT (mean ADC, $r=0.38$; $P<0.0001$; peak height, $r=-0.34$; $P<0.0001$; peak position, $r=0.49$, $P<0.0001$). When assessing the relation between ADC metrics in WBT, NABT, and the mean ADC of WMH with cognitive performance, significant associations were seen with scores assessing memory, executive function, and speed of performance (Table 2). No associations were seen with test results on language, constructional abilities, and orientation. As can be seen in Table 2, associations with performance in tests of memory, executive function, and speed with ADC histogram metrics were similarly strong whether obtained from WBT or NABT, whereas the associations with mean ADC of WMH were only marginal for memory and speed and lost significance after correction for WMH volume (model 2). In model 3, which adjusted for age, gender, study center, education, risk factors, white matter lesion volume, and brain atrophy, the global mean ADC and peak position of WBT and NABT remained significantly associated with speed only, whereas peak height correlated with memory performance, executive dysfunction, and speed. The associations between relative peak height in WBT and NABT and memory, executive functioning, and speed were consistent among centers. This is illustrated for NABT in the Figure. In the fully adjusted model, lower Mini Mental State Examination scores also correlated significantly with lower peak height in WBT ($\beta=0.19$; SE, 0.09; $P=0.02$) and in NABT ($\beta=0.19$; SE, 0.08; $P=0.02$).

Discussion

In this large multicenter study in subjects with various degrees of age-related WMH, we found that ADC indices in unsegmented WBT related to executive dysfunction, slower processing speed, and memory impairment, a pattern that has been implicated with leukoariosis.[1,27,28] The associations were also reflected on Mini Mental State Examination results,

Table 1. Patient Characteristics, MRI Measures, and Cognitive Findings

Characteristic	Whole Group (n=340)	WMH Grade 1 (n=155)	WMH Grade 2 (n=108)	WMH Grade 3 (n=77)	*P*
Age, yr	73.9±5.1	73.3±5.1	74.1±5.3	74.8±4.7	0.09
Female	183 (53.8%)	82 (52.9%)	66 (61.1%)	35 (45.5%)	0.10*
Years of education	10.0±4.1	10.0±4.2	10.2±4.2	9.8±4.3	0.74§
Hypertension	238 (70%)	91 (58.7%)	80 (74.1%)	67 (87.0%)	<0.001*
Diabetes	47 (13.8%)	19 (12.3%)	16 (14.8%)	12 (15.6%)	0.74*
Atrial fibrillation	25 (7.4%)	8 (5.2%)	10 (9.3%)	7 (9.1%)	0.36*
Myocardial infarction	47 (13.8%)	22 (14.2%)	12 (11.1%)	13 (16.9%)	0.53*
WMH volume, cm‡	20.2±21.0	6.4±5.0	19.1±9.5	49.8±23.6	<0.001§
Brain atrophy score	8.1±2.6	7.3±2.5	8.4±2.7	9.3±2.3	<0.001‡
Cognition (*z* scores)					
Memory	0.04±0.69	0.11±0.66	0.00±0.72	−0.03±0.71	0.26†
Executive function	0.13±0.7	0.25±0.66	−0.18±0.64	−0.18±0.79	<0.001†
Speed	0.04±0.83	0.21±0.73	0.05±0.72	0.31±1.03	<0.001§
Construction	0.50±0.73	0.45±0.58	0.59±0.93	0.50±0.68	0.80§
Language	0.17±0.43	0.14±0.44	0.12±0.33	0.29±0.51	0.01§
Orientation	0.39±1.21	0.22±0.96	0.54±1.50	0.53±1.21	0.06§
Mini Mental State Examination	27.54±2.33	27.88±1.95	27.46±2.46	27.06±2.77	0.06
Apparent diffusion coefficient (*z* scores)					
Whole brain tissue (WBT) ADC					
Mean§	0.0±0.99	−0.24±0.95	0.06±1.00	0.39±0.91	<0.001†
Peak height¶	0.0±0.99	0.29±0.97	−0.08±094	−0.48±0.88	<0.001†
Peak position‖	0.0±0.99	−0.33±0.89	0.12±0.92	0.51±1.03	<0.001†
NABT ADC					
Mean§	0.0±0.99	−0.23±0.96	0.05±1.00	0.38±0.91	<0.001†
Peak height¶	0.0±0.99	0.30±0.97	−0.07±0.93	−0.51±0.89	<0.001†
Peak position‖	0.0±0.99	−0.34±0.87	0.12±0.94	0.52±1.02	<0.001†
WMH ADC					
Mean§	0.0±0.99	−0.28±0.97	−0.03±0.87	0.61±0.94	<0.001†

*χ test.
†ANOVA.
‡Kruskal-Wallis test.
§Higher values indicates higher diffusivity in the analyzed tissue compartment.
¶Lower values indicate less tissue with normal diffusivity values in the analyzed tissue compartment.
‖A shift to higher values indicates a global increase of diffusivity in the analyzed tissue compartment.

presenting a global measure of cognitive functioning. Our analyses in segmented brain tissue clearly demonstrate that changes in mean diffusivity of NABT are responsible for cognitive dysfunction. This is supported by the fact that mean ADC of WMH was not related to poorer test performance whereas significant associations existed with ADC measures of segmented NABT after masking WMH. The associations between ADC metrics in NABT and cognitive functioning remained preserved despite adjustment for WMH volume. At first glance this appears in contradiction with reportedly worse neuropsychologic test results with increasing WMH severity and the assumption of more extensive tissue destruction in higher WMH grades, which is supported by an increase in diffusivity.[6,26] However, WMH severity seemingly relates not only to lesional mean ADC but also to ADC histogram metrics of NABT. Not surprisingly, the integrity of NABT constituting a much larger portion of the brain than the WMH volume is likely to have more impact on brain functioning and correlations with neuropsychologic variables were quite similar whether WMH were included (WBT) or not (NABT). Whether changes in NABT are directly related to WMH severity or a parallel phenomenon caused by the same upstream parameters still remains to be clarified. By all means, the close relationship between WMH grading and DWI findings in NABT suggests WMH severity as seen on conventional MRI to be an indirect marker of NABT integrity.

Furthermore, our findings indicate that the integrity of NABT as reflected by histogram metrics contributes to cognitive impairment of subjects with WMH independent of brain atrophy. There is only 1 other study[29] that corrected the association between diffusion imaging variables and cognitive functioning for both WMH lesion load and brain atrophy. These authors[29] also described that diffusivity in normal-appearing white matter was more strongly related to cognition than WMH volume and atrophy, and they also found

Table 2. Associations Between ADC Histogram Metrics in Whole Brain Tissue (WBT), Normal Appearing Brain Tissue (NABT), Mean ADC of WMH and Cognitive Performance (Only Domains With Significant Associations are Shown)

	WBT			NABT			
Cognitive Function	Mean Global ADC	Peak Height	Peak Position	Mean Global ADC	Peak Height	Peak Position	WMH Mean ADC
Memory							
Model 1							
β	−0.12	0.14	−0.06	−0.12	0.15	−0.06	−0.07
SE	0.04	0.04	0.04	0.04	0.04	0.04	0.04
P	0.02	<0.0001	0.12	0.001	<0.001	0.12	0.002
Model 2							
β	−0.11	0.15	−0.05	−0.11	0.16	−0.05	−0.06
SE	0.04	0.04	0.04	0.04	0.04	0.04	0.04
P	0.005	<0.0001	0.23	0.004	<0.0001	0.24	0.1
Model 3							
β	−0.11	0.19	−0.04	−0.11	0.21	−0.03	−0.06
SE	0.06	0.05	0.05	0.06	0.06	0.05	0.05
P	0.07	0.001	0.45	0.06	<0.0001	0.5	0.2
Executive function							
Model 1							
β	−0.07	0.11	−0.08	−0.08	0.12	−0.09	−0.04
SE	0.04	0.04	0.04	0.04	0.04	0.04	0.04
P	0.06	0.002	0.02	0.04	0.001	0.01	0.22
Model 2							
β	−0.04	0.08	−0.04	−0.04	0.09	−0.05	0.004
SE	0.04	0.04	0.04	0.04	0.04	0.04	0.04
P	0.30	0.03	0.26	0.26	0.02	0.22	0.92
Model 3							
β	−0.006	0.12	−0.02	−0.005	0.13	0.002	0.01
SE	0.05	0.05	0.05	0.05	0.05	0.02	0.02
P	0.91	0.02	0.63	0.92	0.01	0.89	0.76
Speed							
Model 1							
β	−0.21	0.21	−0.18	−0.21	0.21	−0.17	−0.11
SE	0.04	0.04	0.04	0.05	0.04	0.04	0.04
P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.01
Model 2							
β	−0.19	0.18	−0.14	−0.19	0.17	−0.13	−0.06
SE	0.05	0.05	0.05	0.05	0.05	0.05	0.05
P	<0.0001	<0.0001	0.002	<0.0001	<0.0001	0.005	0.22
Model 3							
β	−0.18	0.23	−0.13	−0.15	0.21	−0.11	−0.02
SE	0.06	0.05	0.05	0.06	0.06	0.05	0.05
P	0.002	<0.0001	0.008	0.01	<0.0001	0.03	0.62

associations not only with executive dysfunction but also with performance on memory tasks.

ADC has been considered as a measure of white matter integrity,[30] but only the relative peak height of the ADC histogram in NABT was consistently and strongly related to cognitive performance, whereas no such relationships existed with peak position or mean ADC. The main contribution to the ADC histogram of NABT comes from white matter, which largely governs the peak position and the peak height. The relative peak height reflects the number of voxels in normal-appearing white matter in relation to the total number of voxels contributing to the histogram. Any change in tissue composition will inevitably change peak height. Brain atrophy, which is known to occur with white matter disease,[31] has a substantial impact on peak height, but our analyses were corrected for atrophy. Consequently, the most likely expla-

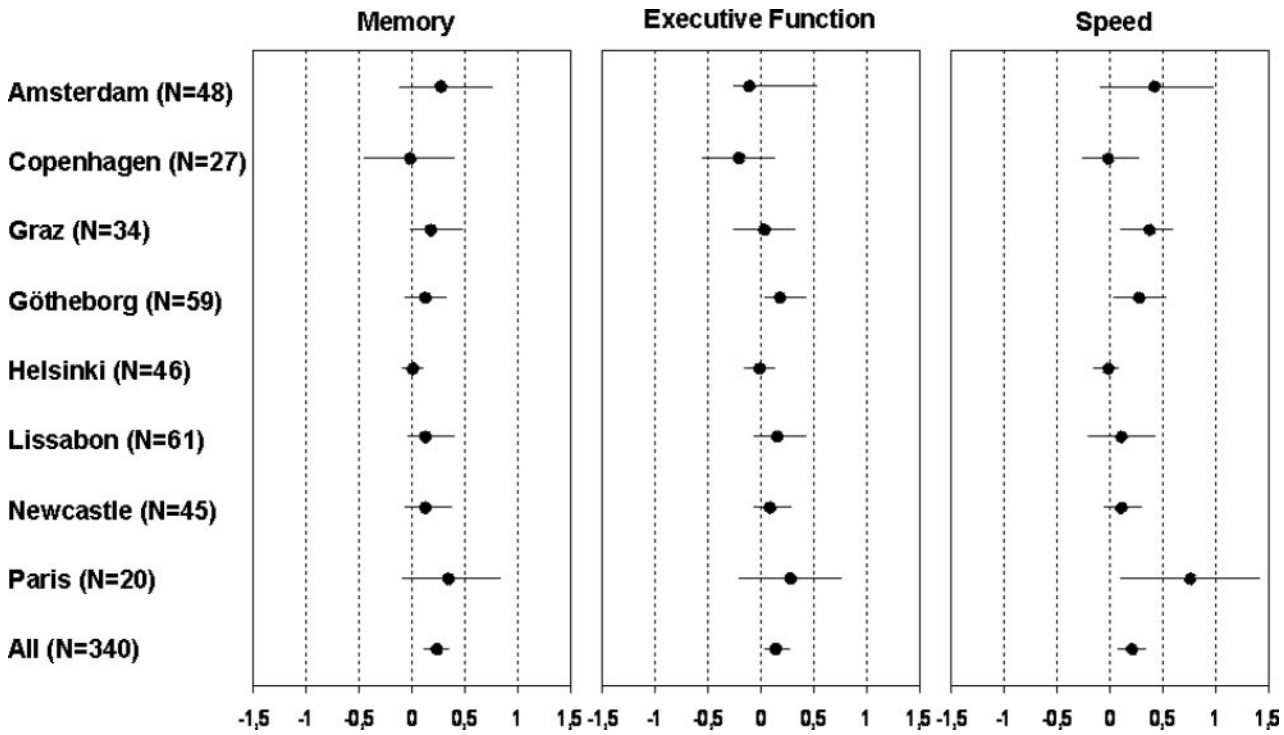

Figure. Associations between relative peak height in NABT and memory, executive functioning, and speed in participating centers. Multiple linear regression analysis between *z* scores of NABT and cognitive domains adjusted for gender, age, years of education, hypertension, diabetes, cardiac disease, volume of white matter lesions, and brain atrophy score by center. Dot on x-axis indicates β coefficient and line indicates 95% confidence interval. There is a direct relationship between peak height of NABT and performance in the 3 cognitive domains. The association of combined results was significant and the direction of the associations was largely consistent among centers.

nation for the observed associations between cognition and ADC peak height are focal alterations of tissue composition or structure in the normal-appearing white matter. Diffuse white matter changes would have resulted in changes of peak position, which indicates the ADC of the largest contributing tissue component. Thus, these findings can add to our etiologic understanding of age-related white matter damage because they argue against a diffuse pathological process as the origin of WHM. They support the view that both visible and invisible microstructural small-vessel disease-related damage in the aging brain is focal, with invisible abnormalities being a crucial factor in the evolution of cognitive impairment.[32,33] Whether these abnormalities precede WMH or are a consequence of the same pathogenic mechanisms or even occur secondarily to WMH cannot be resolved with this study but should be explored in the future.

A strength of our study is the large sample size with an equal distribution of subjects with various grades of WMH. This is different from population-based samples in which the most severe grades of WMH are often under-represented.

A limitation of the study is that ADC values come from diffusion weighting in only 3 independent directions and represent measures of mean diffusivity. Because diffusion is not an isotropic process in neuronal tissue, a more detailed diffusion analysis could have been expected from diffusion tensor imaging with at least 6 independent directions of the diffusion gradient. This would have allowed additional assessment of radial and axial diffusivity and, subsequently, fractional anisotropy, although interpretation of radial and axial diffusivity in terms of underlying tissue structure is not necessarily straightforward.[34] Unfortunately, the acquisition of such data was not possible in all centers at the start of the LADIS study.

Another limitation is that we did not segment gray and white matter separately. Reliable segmentation can only be performed with conventional MRI scans with adequate contrast and resolution and with a nonlinear registration technique. Because these conditions were not fulfilled in the current multicenter setting, we refrained from segmentation to avoid misclassification errors and introduction of noise into the histogram analysis. It is important to point out, however, that although the histogram analysis was performed for NABT, this analysis mainly provides information on normal-appearing white matter, simply because it drives the histogram peak representing white matter. Our study is cross-sectional and interpretation of current results regarding cause and effect is limited.

Conclusion

In conclusion, DWI studies like ours clearly direct further research in the field of age-related brain damage toward ultrastructural abnormalities of NABT because they have now been consistently shown to more closely relate to the actual cognitive function of older persons than the amount of tissue destruction visible in standard MR acquisitions. In this context DWI adds not only to the potential for quantitative assessment of tissue changes but also allows the appreciation

of changes of the entire brain, and thus of a much larger portion of cerebral tissue than WMH, which are consequences of or evolve in parallel to WMH. Any interventional trial attempting to ameliorate the clinical consequences of progressing WMH should also include DWI as an outcome measure, which can be reliably accomplished on a multicenter basis as shown by our results.

Acknowledgments

The authors thank all participants and investigators for their contribution to this study.

Sources of Funding

The LADIS Study was supported by the European Union within the V European Framework Programme "Quality of life and management of living resources" (1998–2002), contract QLRT–2000-00446 as a concerted action.

Disclosure

None.

References

1. Desmond DW. Cognition and white matter lesions. *Cerebrovasc Dis.* 2002;13(Suppl 2):53–57.
2. Schmidt R, Fazekas F, Offenbacher H, Dusek T, Zach E, Reinhart B, Grieshofer P, Freidl W, Eber B, Schumacher M, Koch M, Lechner H. Neuropsychologic correlates of MRI white matter hyperintensities: A study of 150 normal volunteers. *Neurology*. 1993;43:2490–2494.
3. Longstreth WT Jr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, Enright PL, O'Leary D, Fried L. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The cardiovascular health study. *Stroke*. 1996;27:1274–1282.
4. de Groot JC, de Leeuw FE, Oudkerk M, van Gijn J, Hofman A, Jolles J, Breteler MM. Cerebral white matter lesions and cognitive function: The Rotterdam scan study. *Ann Neurol*. 2000;47:145–151.
5. Au R, Massaro JM, Wolf PA, Young ME, Beiser A, Seshadri S, D'Agostino RB, DeCarli C. Association of white matter hyperintensity volume with decreased cognitive functioning: The Framingham heart study. *Arch Neurol*. 2006;63:246–250.
6. Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, Radner H, Lechner H. Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology*. 1993;43:1683–1689.
7. Le Bihan D, Turner R, Douek P, Patronas N. Diffusion mr imaging: Clinical applications. *AJR Am J Roentgenol*. 1992;159:591–599.
8. Holtmannspotter M, Peters N, Opherk C, Martin D, Herzog J, Bruckmann H, Samann P, Gschwendtner A, Dichgans M. Diffusion magnetic resonance histograms as a surrogate marker and predictor of disease progression in cadasil: A two-year follow-up study. *Stroke*. 2005;36:2559–2565.
9. O'Sullivan M, Morris RG, Huckstep B, Jones DK, Williams SC, Markus HS. Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoariosis. *J Neurol Neurosurg Psychiatry*. 2004;75:441–447.
10. Shenkin SD, Bastin ME, Macgillivray TJ, Deary IJ, Starr JM, Rivers CS, Wardlaw JM. Cognitive correlates of cerebral white matter lesions and water diffusion tensor parameters in community-dwelling older people. *Cerebrovasc Dis*. 2005;20:310–318.
11. Della Nave R, Foresti S, Pratesi A, Ginestroni A, Inzitari M, Salvadori E, Giannelli M, Diciotti S, Inzitari D, Mascalchi M. Whole-brain histogram and voxel-based analyses of diffusion tensor imaging in patients with leukoaraiosis: Correlation with motor and cognitive impairment. *AJNR Am J Neuroradiol*. 2007;28:1313–1319.
12. Nitkunan A, Barrick TR, Charlton RA, Clark CA, Markus HS. Multimodal MRI in cerebral small vessel disease: Its relationship with cognition and sensitivity to change over time. *Stroke*. 2008;39:1999–2005.
13. Viana-Baptista M, Bugalho P, Jordao C, Ferreira N, Ferreira A, Forjaz Secca M, Esperanca-Pina JA, Ferro JM. Cognitive function correlates with frontal white matter apparent diffusion coefficients in patients with leukoariosis. *J Neurol*. 2008;255:360–366.
14. Pantoni L, Basile AM, Pracucci G, Asplund K, Bogousslavsky J, Chabriat H, Erkinjuntti T, Fazekas F, Ferro JM, Hennerici M, O'Brien J, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Inzitari D. Impact of age-related cerebral white matter changes on the transition to disability—the LADIS study: Rationale, design and methodology. *Neuroepidemiology*. 2005;24:51–62.
15. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9:179–186.
16. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. Mr signal abnormalities at 1.5 t in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol*. 1987;149:351–356.
17. Inzitari D, Simoni M, Pracucci G, Poggesi A, Basile AM, Chabriat H, Erkinjuntti T, Fazekas F, Ferro JM, Hennerici M, Langhorne P, O'Brien J, Barkhof F, Visser MC, Wahlund LO, Waldemar G, Wallin A, Pantoni L. Risk of rapid global functional decline in elderly patients with severe cerebral age-related white matter changes: The LADIS study. *Arch Intern Med*. 2007;167:81–88.
18. van Straaten EC, Fazekas F, Rostrup E, Scheltens P, Schmidt R, Pantoni L, Inzitari D, Waldemar G, Erkinjuntti T, Mantyla R, Wahlund LO, Barkhof F. Impact of white matter hyperintensities scoring method on correlations with clinical data: The LADIS study. *Stroke*. 2006;37:836–840.
19. Ryberg C, Rostrup E, Sjostrand K, Paulson OB, Barkhof F, Scheltens P, van Straaten EC, Fazekas F, Schmidt R, Erkinjuntti T, Wahlund LO, Basile AM, Pantoni L, Inzitari D, Waldemar G. White matter changes contribute to corpus callosum atrophy in the elderly: The LADIS study. *AJNR Am J Neuroradiol*. 2008;29:1498–1504.
20. Madureira S, Verdelho A, Ferro J, Basile AM, Chabriat H, Erkinjuntti T, Fazekas F, Hennerici M, O'Brien J, Pantoni L, Salvadori E, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Inzitari D. Development of a neuropsychological battery for the leukoariosis and disability in the elderly study (LADIS): Experience and baseline data. *Neuroepidemiology*. 2006;27:101–116.
21. Ferris SH. General measures of cognition. *Int Psychogeriatr*. 2003;15(Suppl 1):215–217.
22. Stroop J. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18:643–662.
23. Reitan R. Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8:271–276.
24. Folstein M, Folstein S, McHugh P. Mini mental state: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.
25. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141:1356–1364.
26. Ropele S, Seewann A, Gouw AA, van der Flier WM, Schmidt R, Pantoni L, Inzitari D, Erkinjuntti T, Scheltens P, Wahlund LO, Waldemar G, Chabriat H, Ferro J, Hennerici M, O'Brien J, Wallin A, Langhorne P, Visser MC, Barkhof F, Fazekas F. Quantitation of brain tissue changes associated with white matter hyperintensities by diffusion-weighted and magnetization transfer imaging: The ladis (leukoaraiosis and disability in the elderly) study. *J Magn Reson Imaging*. 2009;29:268–274.
27. Desmond DW. The neuropsychology of vascular cognitive impairment: Is there a specific cognitive deficit? *J Neurol Sci*. 2004;226:3–7.
28. Price CC, Jefferson AL, Merino JG, Heilman KM, Libon DJ. Subcortical vascular dementia: Integrating neuropsychological and neuroradiologic data. *Neurology*. 2005;65:376–382.
29. Vernooij MW, Ikram MA, Vrooman HA, Wielopolski PA, Krestin GP, Hofman A, Niessen WJ, Van der Lugt A, Breteler MM. White matter microstructural integrity and cognitive function in a general elderly population. *Arch Gen Psychiatry*. 2009;66:545–553.
30. Kubicki M, Westin CF, Nestor PG, Wible CG, Frumin M, Maier SE, Kikinis R, Jolesz FA, McCarley RW, Shenton ME. Cingulate fasciculus integrity disruption in schizophrenia: A magnetic resonance diffusion tensor imaging study. *Biol Psychiatry*. 2003;54:1171–1180.
31. Schmidt R, Ropele S, Enzinger C, Petrovic K, Smith S, Schmidt H, Matthews PM, Fazekas F. White matter lesion progression, brain atrophy, and cognitive decline: The Austrian stroke prevention study. *Ann Neurol*. 2005;58:610–616.
32. Pantoni L, Garcia JH. Pathogenesis of leukoariosis: A review. *Stroke*. 1997;28:652–659.
33. Schmidt R, Petrovic K, Ropele S, Enzinger C, Fazekas F. Progression of leukoariosis and cognition. *Stroke*. 2007;38:2619–2625.
34. Wheeler-Kingshott CA, Cercignani M. About "axial" and "radial" diffusivities. *Magn Reson Med*. 2009;61:1255–1260.