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

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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...
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.8 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.8,9,13 This scale grades WMH severity 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.

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 Scale14 were enrolled in a hospital-based setting. To achieve a well-distributed range of WMH severity we stratified participants according to the modified Fazekas scale16 with WMH affecting visualization in various cognitive domains and that these effects are independent of vascular risk factors, white matter lesion volume, and brain atrophy.

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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, 1×1×1–1.5 mm³), T2-weighted fast-spin echo (scan parameters, axial plane; echo time, 100–130 ms; repetition time, 4000–6000 ms; voxel size, 1×1×5 mm³; 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, 1×1×5 mm³; 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 1.95×1.95×5 mm³ and it was identical across all centers. The sequence was performed with 2 b factors (b=0 sec/mm² and b=900–1000 sec/mm²), 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 modified Fazekas scale.8 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/mm²). The ADC maps were then registered with the FLAIR scans, and the T2-weighted scan (b=0 sec/mm²) 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. 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 $k$ value was $>0.9$ for both sulcal and ventricular atrophy; The inter-rater $k$ value was $0.70$ for sulcal and $0.83$ for ventricular atrophy.

**Neuropsychological Testing**

Neuropsychological assessment followed the LADIS protocol. The test battery included the Vascular Dementia Assessment Scale cognitive subscale, the Stroop test, Trail-Making test, and the Mini Mental State Examination. Vascular Dementia Assessment Scale cognitive subscale includes all items of the Alzheimer Disease Assessment Scale 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 subscores 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 $\chi^2$ 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. 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 leukoaraiosis. The associations were also reflected on Mini Mental State Examination results,
WMH volume is likely to have more impact on brain integrity relations not only to lesional mean ADC but also to ADC increase in diffusivity. However, WMH severity seem-

worse neuropsychologic test results with increasing WMH remained preserved despite adjustment for WMH volume. At first glance this appears in contradiction with reportedly significant associations existed with ADC measures of segmented NABT after masking WMH. The associations between ADC metrics in NABT and cognitive functioning 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 that corrected the association between diffusion imaging variables and cognitive functioning for both WMH lesion load and brain atrophy. These authors also described that diffusivity in normal-appearing white matter was more strongly related to cognition than WMH volume and atrophy, and they also found 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.
associations not only with executive dysfunction but also with performance on memory tasks.

ADC has been considered as a measure of white matter integrity, 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, has a substantial impact on peak height, but our analyses were corrected for atrophy. Consequently, the most likely expla-

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)

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<th>WBT Mean Global ADC</th>
<th>Peak Height</th>
<th>Peak Position</th>
<th>NABT Mean Global ADC</th>
<th>Peak Height</th>
<th>Peak Position</th>
<th>WMH Mean ADC</th>
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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 multi-center basis as shown by our results.

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Disclosure
None.

References
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on behalf of the LADIS study group

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老年白质疏松及残疾患者弥散加权成像与认知功能的研究

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

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背景和目的：白质疏松对临床和认知功能的影响机制目前仍不十分清楚。我们认为弥散加权成像中发现的正常表现脑组织(NABT)的超微结构异常可能是一个重要和独立的因素。

方法：除了全面收集临床和神经精神特征及影像学资料外，还对参加多中心白质疏松和残疾研究的340名患者进行磁共振弥散加权成像分析，旨在发现白质高信号(WMH)对65岁到85岁无既往残疾的老年人的影响。根据Fazekas评分来评估WMH的严重程度。通过多变量回归分析来了解认知功能与全脑和NABT的表观弥散系数(ADC)参数之间以及与WMH的ADC均值之间的关系。

结果：WMH评分越高与高血压越多、WMH体积越大、脑萎缩越多、总体认知功能越差以及ADC改变有关。研究发现即使校正了WMH病变体积和脑萎缩这两个因素，全脑组织和NABT的ADC参数之间以及与WMH的ADC均值之间仍存在相关性。

结论：NABT超微结构的异常和WMH的严重程度呈正相关，是影响认知功能的一个很强而且独立的因素，而WMH的弥散加权成像参数没有直接影响。在试图干预WMH进展的试验中，应在定义结局指标时考虑到上述结论。

关键词：认知，影像，白质疏松
Stroke May 2010

者 WMH 严重程度进行分层，基于先前的研究进行一步的研究。我们假设 WMH 和正常表现的脑组织 (NABT) 中的平均弥散率是除了血管危险因素、白质损害体积和脑萎缩以外影响各种认知领域的独立危险因素。

对象和方法

对象

所有的患者都参加了多中心白质疏松和残疾研究 (LADIS)。LADIS 研究的原理和设计已有报道 [14]。总得来说，本研究基于医院纳入 65 岁至 84 岁之间磁共振显示有 WMH 表现但没有或仅有轻度残疾 (根据工具性日常生活活动能力量表) 的老年患者。为了使 WMH 严重程度有一个良好的分布，我们基于改良 Fazekas 评分 [16] 把有 WMH 的患者分成 3 个等级：点状，早期融合和融合型。进一步的纳入标准是患者能够被有规律的联系到并签署了知情同意书。排除标准包括容易因为严重的疾病而脱落的患者，如心脏、肝脏或者肾脏衰竭，肿瘤或其他相关系统性疾病；严重的非神经系统相关的疾病；非血管源性感染及其它；严重的精神疾病；不能签署知情同意书；有头痛 MRI 禁忌症或拒绝行头颅 MRI 检查。

通过训练有素的医务人员对资料进行回顾，用标准化的问卷提取基线血管危险因素。危险因素包括患者年龄、性别、高血压 (接受抗高血压药物治疗或者血压多次测量值≥140/90 mmHg)、糖尿病史 (接受降糖治疗或者至少 8 小时空腹血糖≥7.0 mmol/L 或 126 mg/dL)、房颤 (有既往病史或有临床证据如 ECG 和心肌梗塞) (有既往病史，ECG 或心肌酶谱)。同样记录患者的教育年限。

MRI

11 个 LADIS 中心中有 8 个中心参加了在总的扫描序列外加入 DWI 序列的亚组研究。DWI 序列是可选择性的，某些中心没有实施 DWI 序列扫描的条件。所有参加当前试验的中心均采用 1.5T 整体系统 (ACS-Intera, Philips Medical Systems; Magnetom Vision, Siemens Medical Systems; Magnetom Sonata, Siemens Medical Systems; Signa, General Electric Medical System)。主要 MRI 方案包括以下序列：T1 加权三维磁化预置快速获得的梯度回波 (扫描参数，轴平面；回波时间，100-130 ms；重复时间，4000-6000 ms；体素大小，1×1×5 mm³) 和液体衰减反转恢复序列 (FLAIR；扫描参数，轴平面；回波时间，100-140 ms；重复时间，6000-10 000 ms；反转时间，2000-2400；体素大小，1×1×5 mm³)。

DWI 是通过有回波层面成像读数的脉冲梯度自旋回波序列来表现 (重复时间，4000-6000 ms；回波时间，100-140 ms；矩阵，128×128；视野，250 mm；切片厚度，5 mm；层数，20-28)。在各个中心体素大小一致，为 1.95×1.95×5 mm。

该序列以 2b 因子来运行 (b=0 sec/mm² 和 b=900-1000 sec/mm²)，而弥散梯度则在三个主方向上进行。为了使各个中心提供的 ADC 图像质量之间有可比性，要求所有参加的中心根据自身能力在方案建议的参数中作小范围的调整。各中心之间 DWI 方案的不一致最可能影响的是重复时间、采样带宽、部分 Fourier 成像以及平均值的数目。DWI 序列完成需要的时间受重复时间和平均值数目的影响而不同，但在各个中心均小于 2 分钟。

所有轴位序列的层面均放置在包含大脑中心部分的位置，平行于胼胝体的大部分下部 - 前部到大部分下 - 后部这条线。

图像分析

WMH 严重程度的评定集中由单个评估人在全盲状态下进行。WMH 在轴位 FLAIR 影像上通过改良 Fazekas 评分 [16]，被分为轻度、中度和重度。各个级别分类的典型例子已有报道 [17]。为了测试该等级设计的施测者测量信度，随机选择了 18 个扫描图像，对其进行两次评分，结果为加权 Cohen κ 值 0.84。

除了对 WMH 进行分级外，还集中对轴位 FLAIR 图像的 WMH 进行了容积分析。运用 seed-growing 技术和局部阈值来界定 WMH 的轮廓和计算 WMH 区域及相应的体积 [18]。

对全脑组织 (WBT)，NABT 及 WMH 区域的 DWI 参数进行分析。WBT 包括正常表现的白质、白质病变灶和灰质，而 NABT 包括正常表现的白质和灰质，但不包括白质病变灶和 WMH 区域。因为 WMH 是在 FLAIR 图像上被识别，所有参数图像在对原始数据进行计算后登记入 FLAIR 图像中。

为了计算 ADC 图像，在三个主方向上对高 b 值的图像进行平均来获得旋转不变的图形。通过由高 b 值的平均图像的自然对数和 T2 加权图像的自
然对数计算的斜率来获得 ADC ($b=0$ sec/mm$^2$)。通过 FLAIR 扫描登记 ADC 图像，通过 T2 加权的扫描来计算变换矩阵。通过 12-参数模型基于比率相关性的代数函数和三线性插值来进行登记 (http://www.fmrib.ox.ac.uk/fsl/). 该模型只能部分地解释非线性 EPI 失真。通过基于序列的登记可能会解决这个问题；然而，在当前研究中我们没有可用的倾倒角的数据。为了获得 NABT 模型，WMH 被屏蔽，非脑部组织也通过脑部提取工具 (FSL, FMRIIB Analysis Group) 移除了。为了减少体积对 WMH 边界的影响，在 NABT 模型产生之前对 WMH 模型扩大了 1 个像素。在决定病灶 ADC 时 WMH 模型减少 1 个像素。

我们运用直方图分析以及对相应峰高、峰位和平均值的计算来评价。一个研究者 (R.S) 通过基于模板的评估量表分别对脑室和脑沟萎缩进行从 1 (无萎缩) 到 8 (严重萎缩) 的评价。这两项的总和被作为脑萎缩的总体评分。

该模板在本研究过去发表的成果中有记录 [18,19]。通过对 50 张随机选择的影像进行两次读片来评价施测者测量信度。同样地，施测者间信度通过其他三人对相同影像的读片来评价。对当前研究者 (R.S.)，脑沟和脑室萎缩两者的施测者测量信度的 k 值大于 0.9。脑沟和脑室的施测者间信度的 k 值分别为 0.70 和 0.83[19]。

### 神经精神测定


我们通过血管性痴呆评估量表对认知领域评定的标准变化结果来测量认知功能的言语、构造和定位能力。记忆、执行能力和速度通过计算所有测试的综合结果来评定。迷你精神状态测试是对整个认知功能的检测。

### 统计分析

我们采用社会科学统计软件包 (SPSS 16.0; SPSS) 进行统计分析。为了使各中心中的直方图 ADC 值和神经精神测试结果可直接进行比较，我们生成 z 分数。z 值用来定义分数的分布位置。一个 +1 的 z 值对应于平均值之上的 1 个标准差值。在神经精神测试中高分表示表现差，z 值在测定复合测定分数时是倒置的 (-z)。

记忆分数是即时语言回顾 (倒置的)、延时语言回顾 (倒置的)、词汇识别 (倒置的) 以及数字广度的 z 值的总和。执行功能是 Stroop 3 到 2(倒置的)、Trail-Making B 试验减去 Trail-Making A 试验的倒置的)、符号数字分值以及语言流畅性的 z 值的总和。

速度评分是 Trail-Making A 试验 (倒置的) 、迷津试验 (倒置的) 以及数字撤销试验的 z 值的总和。迷你精神状态测试的结果同样也被转化成 z 值。

运用卡方检验对白质病灶的分级变量进行比较。正态分布的连续变量采用 Lilliefors 统计进行检验。正态分布的变量采用单向变量分析而非正态分布的变量则采用 Kruskal-Wallis 检验。多因素回归分析不同认知区域的表现和相应 ADC 分布的关系。回归分析在三个模型中都进行了校正。

模型 1 包括性别、年龄、教育年限、研究中心、高血压、糖尿病和心脏疾病。模型 2 在模型 1 的基础上加上了白质病灶体积，模型 3 在模型 2 的基础上增添了脑萎缩评分。按整个队列和每个中心进行了分析。

### 结果

8 个 LADIS 中心共收集了 340 例有 DWI 影像的患者。每个中心患者人数从 20 到 61 不等。表 1 展示的是全组及 WMH 分级组中患者的特征。

与整个 LADIS 队列相比，参加 ADC 研究的亚组在年龄、性别、教育、血管危险因素的比例以及 WMH 分数方面均没有显著差异 [20]。在表 1 中可以看出 WMH 分数越高与高血压越多、WMH 体积越大、脑萎缩越多、总体认知功能越差相关。执行功能和速度受到的影响最大。WMH 严重程度的增加还与 WBT 和 NABT 中 ADC 直方图中参数以及 WMH 的 ADC 均值的剧烈变化有关 (图 1)。特别是，平均 ADC 和 ADC 峰位在 WBT 和 NABT 中都有增高，而 ADC 的峰高却有下降。WMH 的 ADC 均值随 WMH 评分增高而增大。

在 WMH 区域的 ADC 与 WBT 中测量的 ADC( 平均 ADC, $r=-0.37$, $P<0.0001$; 峰高, $r=-0.33$, $P<0.0001$)；峰值, $r=0.50$, $P<0.0001$; 和 NABT (平均 ADC, $r=-0.38$, $P<0.0001$; 峰高, $r=-0.34$;
表 1 患者特征、MRI 分级和认知发现

<table>
<thead>
<tr>
<th>特征</th>
<th>全组 (n=340)</th>
<th>WMH 等级 1(n=155)</th>
<th>WMH 等级 2(n=108)</th>
<th>WMH 等级 3(n=77)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄, 岁</td>
<td>73.9±5.1</td>
<td>73.3±5.1</td>
<td>74.1±5.3</td>
<td>74.8±4.7</td>
<td>0.09</td>
</tr>
<tr>
<td>女性</td>
<td>183 (53.8%)</td>
<td>82 (52.9%)</td>
<td>66 (61.1%)</td>
<td>35 (45.5%)</td>
<td>0.10*</td>
</tr>
<tr>
<td>教育年限</td>
<td>10±0.4</td>
<td>10±0.4</td>
<td>10.2±4.2</td>
<td>9.8±4.3</td>
<td>0.74§</td>
</tr>
<tr>
<td>高血压</td>
<td>238 (70%)</td>
<td>91 (58.7%)</td>
<td>80 (74.1%)</td>
<td>67 (87.0%)</td>
<td>-0.001*</td>
</tr>
<tr>
<td>糖尿病</td>
<td>47 (13.8%)</td>
<td>19 (12.3%)</td>
<td>16 (14.8%)</td>
<td>12 (15.6%)</td>
<td>0.74*</td>
</tr>
<tr>
<td>房颤</td>
<td>25 (7.4%)</td>
<td>8 (5.2%)</td>
<td>10 (9.3%)</td>
<td>7 (9.1%)</td>
<td>0.36*</td>
</tr>
<tr>
<td>心肌梗塞</td>
<td>47 (13.8%)</td>
<td>22 (14.2%)</td>
<td>12 (11.1%)</td>
<td>13 (16.9%)</td>
<td>0.53*</td>
</tr>
<tr>
<td>WMH 体积, cm²</td>
<td>20.2±21.0</td>
<td>6.4±5.0</td>
<td>19.1±9.5</td>
<td>49.8±23.6</td>
<td>-0.001‡</td>
</tr>
<tr>
<td>脑萎缩分数</td>
<td>8.1±2.6</td>
<td>7.3±2.5</td>
<td>8.4±2.7</td>
<td>9.3±2.3</td>
<td>-0.001‡</td>
</tr>
</tbody>
</table>

认知 (z 评分)

| 记忆 | 0.04±0.69 | 0.11±0.66 | 0.00±0.72 | -0.03±0.71 | 0.26†   |
| 执行功能 | 0.13±0.7 | 0.25±0.66 | -0.18±0.64 | -0.18±0.79 | -0.001† |
| 速度 | 0.04±0.83 | 0.21±0.73 | 0.05±0.72 | 0.31±1.03 | -0.001§ |
| 构建 | 0.50±0.73 | 0.45±0.58 | 0.59±0.93 | 0.50±0.68 | 0.80§   |
| 语言 | 0.17±0.43 | 0.14±0.44 | 0.12±0.33 | 0.29±0.51 | 0.01§   |
| 定向 | 0.39±1.21 | 0.22±0.96 | 0.54±1.50 | 0.53±1.21 | 0.06§   |

表观弥散系数 (z 评分)

| 记忆 | 0.04±0.69 | 0.11±0.66 | 0.00±0.72 | -0.03±0.71 | 0.26† |
| 执行功能 | 0.13±0.7 | 0.25±0.66 | -0.18±0.64 | -0.18±0.79 | -0.001† |
| 速度 | 0.04±0.83 | 0.21±0.73 | 0.05±0.72 | 0.31±1.03 | -0.001§ |
| 构建 | 0.50±0.73 | 0.45±0.58 | 0.59±0.93 | 0.50±0.68 | 0.80§ |
| 语言 | 0.17±0.43 | 0.14±0.44 | 0.12±0.33 | 0.29±0.51 | 0.01§ |
| 定向 | 0.39±1.21 | 0.22±0.96 | 0.54±1.50 | 0.53±1.21 | 0.06§ |

NABT ADC

| 均值 § | 0.0±0.99 | -0.24±0.95 | 0.06±1.00 | 0.39±0.91 | <0.001† |
| 峰高 ¶ | 0.0±0.99 | 0.29±0.97 | -0.08±0.94 | -0.48±0.88 | <0.001† |
| 峰位 || | 0.0±0.99 | -0.33±0.89 | 0.12±0.92 | 0.51±1.03 | <0.001† |

WMH ADC

| 均值 § | 0.0±0.99 | -0.28±0.97 | -0.03±0.87 | 0.61±0.94 | <0.001† |

* x2 检验。
† ANOVA。
‡ Kruskal-Wallis 检验。
§ 值越高表示在被分析的组织中弥散率越高。
¶ 值越低表示在被分析的组织中有正常弥散率的组织越少。
|| 转变为正值表示在被分析的组织中弥散率增高。

P< 0.0001; 峰位, r=0.49，P<0.0001) 相关。在评估 
WBT、NABT 中 ADC 参数和 WMH 的 ADC 均值 
与认知表现之间的关系时发现, 其与记忆、执行能力 
和动作敏捷的评分显著相关 (表 2)。在语言、造 
型能力和定向方面没有相关性。在表 2 中可以看到, 
无论在 WBT 或 NABT 中 ADC 直方图参数与记忆、 
执行能力以及速度同样有很强的相关性，而 WMH 
中的平均 ADC 仪与记忆和速度有微弱的关系，在校 
正了 WMH 体积后则没有关系 (模型 2)。在模型 3 中, 
当校正了年龄、性别、研究中、教育、危险因素、 
白质病灶体积和脑萎缩后, 总体的平均 ADC、WBT 
和 NABT 的峰位同样与速度有显著的关系，然而 
峰高和记忆、执行能力失常以及速度有关。WBT 和 
NABT 的峰高和记忆、执行功能和速度之间的相关性 
在各个中心是一致的。在 NABT 的图中有展示。

在全部校正的模型中, 低迷你精神状态测试分数同 
样和 WBT (β=0.19; SE，0.09; P=0.02) 和 NABT 中 
(β=0.19; SE，0.08; P=0.02) 的低峰高有关。

讨论

在这个研究年龄相关的不同程度 WMH 的大型 
多中心研究中, 我们发现未分段的 WBT 中 ADC 指 
标与执行功能失用、缓慢的处理速度以及记忆力损 
害有关，这些表现与白质疏松有关[1,27,28]。

这种联系同样反映在对认知水平进行总体评测 
的迷你精神状态测试中。通过对各部分脑组织的分 
析清楚的显示了 NABT 的平均弥散率的改变可能 
形成认知功能障碍。这也被下面这一点支持：WMH 
的平均 ADC 与测验表现不良没有关系，而与去除 
WMH 后的 NABT 区域的 ADC 有很强的相关性。即
表 2 全脑组织 (WBT)、正常表现脑组织 (NABT)、WMH 的平均 ADC 和认知能力之间的关系 (只显示了有显著意义的项目)

<table>
<thead>
<tr>
<th>认知功能</th>
<th>WBT 平均全面 ADC</th>
<th>峰高</th>
<th>峰位</th>
<th>NABT 平均全面 ADC</th>
<th>峰高</th>
<th>峰位</th>
<th>WMH 平均ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>模型 1</td>
<td>β</td>
<td>0.12</td>
<td>0.14</td>
<td>-0.16</td>
<td>-0.12</td>
<td>0.15</td>
<td>-0.06</td>
</tr>
<tr>
<td></td>
<td>SE</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.02</td>
<td>&lt;0.0001</td>
<td>0.12</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.12</td>
</tr>
<tr>
<td>模型 2</td>
<td>β</td>
<td>-0.11</td>
<td>0.15</td>
<td>-0.05</td>
<td>-0.11</td>
<td>0.16</td>
<td>-0.05</td>
</tr>
<tr>
<td></td>
<td>SE</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.005</td>
<td>&lt;0.0001</td>
<td>0.23</td>
<td>0.0004</td>
<td>&lt;0.0001</td>
<td>0.24</td>
</tr>
<tr>
<td>模型 3</td>
<td>β</td>
<td>-0.06</td>
<td>0.05</td>
<td>0.05</td>
<td>0.06</td>
<td>0.06</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>SE</td>
<td>0.07</td>
<td>0.001</td>
<td>0.45</td>
<td>0.06</td>
<td>&lt;0.0001</td>
<td>0.5</td>
</tr>
</tbody>
</table>

使在纠正了 WMH 体积后，NABT 里 ADC 参数和认知功能仍存在相关性。表面上看这与已报道的神经精神测定越差 WMH 更严重以及在 WMH 高等级中有更广泛的组织损伤（与弥散率的增加有关) 相矛盾。然而，WMH 的严重程度看上去不仅与病灶平均 ADC 有关，还与 NABT 的 ADC 直方图参数有关。意料之外的是，NABT 的完整性比 WMH 体积在大脑中所占的比例更大，似乎对脑功能有更大的影响，而不管 WMH 是否被包含在内 (WBT) 或者没有 (NABT)，它与神经精神变量的关系也很相似。
与 WMH 体积和脑萎缩相比，正常表现的白质中的弥散率与认知功能关系更加密切。他们同时发现这种联系不仅同执行功能有关还和记忆任务表现有关。ADC 可以衡量白质的完整性[30]，但仅仅是在 NABT 中 ADC 直方图的峰高和认知表现有很好的一致性和相关性，而峰位或平均 ADC 则与之无关。NABT 的 ADC 直方图的主要分布来自白质，而白质主要控制着峰位和峰高。相关的峰高反映了直方图中在整个体素数量中的正常表现的白质中体素的数量。组织构成中任何的变化不可避免的会改变峰高。脑萎缩是一种发生在白质的疾病[31]，对峰高有重要影响，但是我们的研究已经对脑萎缩进行了纠正。对观察到的认知和 ADC 峰高之间的关系最可能的解释是在正常表现的白质中出现了组织构成和结构的局部改变。弥散白质改变会导致峰位的改变，暗示 ADC 是最大的组织组成因素。因此，这些发现增加了我们对年龄相关白质损伤病因的了解。这些发现不支持弥散病理过程最初来源于 WMH 这个观点，而支持这样的观点：在年老大脑中看得见和看不见的微结构小血管病变是很重要的，而看不见的异常病变是认知损害进展的一个主要原因[32,33]。这些异常是发生在 WMH 之前或之后，还是继发于 WMH，在本研究中尚无法得知，应在以后的研究中进一步探讨。

本研究的一大优势在于样本量大且各个等级的 WMH 分布均匀。这不同于会忽视 WMH 非常重的患者的基于人群的研究。

本研究的局限性在于 ADC 值仅来自三个独立方向的弥散加权，而测量的是平均弥散率。在神经元组织中弥散不是一个各向同性的过程，因此至少有 6 个独立方向的弥散权数的弥散张量成像可以得到一个更加具体的弥散分析。这样可以对径向和轴向弥散率进行额外的分析，接着分析分数的各向异性。尽管潜在的组织结构而言，径向和轴向弥散率并不一定是直接的[34]。不幸的是，在 LADIS 研究之初并不能从所有中心中得到这些数据。

另外一个局限是我们在没有细分灰质和白质，可靠的分类只能由足够的对比度和分辨率的传统磁共振扫描和非线性登记技术来完成。由于当前的多中心中不具备这些条件，我们没有进行细分以避免错误的分类和在直方图分析中引进干扰。然而，非常重要的地方是，尽管是为 NABT 做的直方图分析，这一分析主要提供的是正常表现的白质的信息，因为该信息代表白质的峰值。本研究是横断面的研究，对因果关系的分析很有限。
结论

DWI 研究（如同我们的研究）明确了进一步研究的方向，即通过 NABT 超微结构的改变来研究年龄相关的脑损伤。因为和标准 MRI 中显示的可见病变组织相比，NABT 超微结构的变化和老年人实际认知功能有更强的相关性。这样，DWI 不仅可用于定量评估组织变化，还可以评估整个大脑的变化，和 WMH 相比有更大的脑组织比例，NABT 超微结构的改变可能是 WMH 的结果或者与 WMH 同步进展。任何试图减轻进展性 WMH 临床结局的干预试验都应将 DWI 作为一个结局指标，这已经被本多中心研究证实是可靠的。

参考文献