Multimodal MRI in Cerebral Small Vessel Disease
Its Relationship With Cognition and Sensitivity to Change Over Time

Arani Nitkunan, PhD; Tom R. Barrick, PhD; Rebecca A. Charlton, PhD; Chris A. Clark, PhD; Hugh S. Markus, FRCP

Background and Purpose—Cerebral small vessel disease is the most common cause of vascular dementia. Interest in using MRI parameters as surrogate markers of disease to assess therapies is increasing. In patients with symptomatic sporadic small vessel disease, we determined which MRI parameters best correlated with cognitive function on cross-sectional analysis and which changed over a period of 1 year.

Methods—Thirty-five patients with lacunar stroke and leukoaraiosis were recruited. They underwent multimodal MRI (brain volume, fluid-attenuated inversion recovery lesion load, lacunar infarct number, fractional anisotropy, and mean diffusivity from diffusion tensor imaging) and neuropsychological testing. Twenty-seven agreed to reattend for repeat MRI and neuropsychology at 1 year.

Results—An executive function score correlated most strongly with diffusion tensor imaging (fractional anisotropy histogram, $r = -0.640$, $P = 0.004$) and brain volume ($r = 0.501$, $P = 0.034$). Associations with diffusion tensor imaging were stronger than with all other MRI parameters. On multiple regression of all imaging parameters, a model that contained brain volume and fractional anisotropy, together with age, gender, and premorbid IQ, explained 74% of the variance of the executive function score ($P = 0.0001$). Changes in mean diffusivity and fractional anisotropy were detectable over the 1-year follow-up; in contrast, no change in other MRI parameters was detectable over this time period.

Conclusion—A multimodal MRI model explains a large proportion of the variation in executive function in cerebral small vessel disease. In particular, diffusion tensor imaging correlates best with executive function and is the most sensitive to change. This supports the use of MRI, in particular diffusion tensor imaging, as a surrogate marker in treatment trials. (Stroke. 2008;39:1999-2005.)

Key Words: cerebral small vessel disease ■ cognitive impairment ■ diffusion tensor imaging ■ MRI ■ surrogate marker

Cerebral small vessel disease (SVD) resulting in lacunar stroke causes one fourth of all ischemic stroke. It is also the most common cause of vascular dementia.1 Disease of the small perforating end arterioles results in lacunar infarcts with or without leukoaraiosis. Patients with lacunar stroke and leukoaraiosis have a relatively homogenous pattern of cognitive impairment with prominent impairment of executive function and information processing speed and relative sparing of memory.1

Despite its importance, there are few treatments that have been shown to be effective in SVD. Most therapies, including antiplatelet agents, have been evaluated in stroke as a whole without adequate subtyping to determine relative efficacy in SVD. There have been few studies examining the effect of secondary prevention on cognitive decline in patients with SVD. There are major challenges to conducting treatment trials for SVD. These include the relatively slow disease progression necessitating large patient populations. Although cognitive impairment was found in 83% of patients with lacunar stroke and leukoaraiosis, the rate of cognitive decline and progression to frank dementia is slow.2 The rate of recurrent stroke after lacunar stroke is also lower than after other stroke subtypes. These considerations make the use of surrogate markers to evaluate novel therapies before large clinical trials attractive. Neuropsychological decline itself, rather than progression to dementia, is one possible surrogate. However, neuropsychological testing is time-consuming and is complicated by a learning effect with repeat tests.

Interest in the use of imaging parameters as surrogate markers of cerebral SVD3 and vascular dementia4 is increasing. Fazekas et al proposed criteria for a surrogate marker for treatment trials.4 The first was that it must be able to predict the natural course of the disease; it should correlate with relevant clinical features, for example, cognitive function, in both cross-sectional and longitudinal studies.
A number of studies have correlated T2 lesion volume with clinical and cognitive parameters, but results have been conflicting.\textsuperscript{5–8} Recently, more promising results have been obtained with diffusion tensor imaging (DTI), which appears to be more sensitive to white matter damage in SVD. Two parameters are obtained; fractional anisotropy (FA) is a measure of the directionality of diffusion and a marker of white matter tract damage; mean diffusivity (MD) is a measure of the extent of diffusion and is sensitive to white matter ultrastructural damage. In SVD, DTI changes have been detected not only in lesions present on T2-weighted imaging, but also in normal-appearing white matter.\textsuperscript{9} SVD probably causes cognition impairment by disrupting cortical–cortical and cortical–subcortical pathways. Therefore, DTI changes, particularly FA, might be expected to correlate better with cognition than T2-weighted MRI.

In a previous cross-sectional study, we found strong correlations between DTI parameters and executive dysfunction in patients with sporadic SVD,\textsuperscript{10} and a correlation has also been reported between MD and Mini-Mental State Examination in patients with the genetic form of SVD, cerebral autosomal-dominant arteriopathy with subcortical ischemic leukoencephalopathy (CADASIL).\textsuperscript{10} Before using DTI as a surrogate marker, it is important to perform multimodal MRI studies to determine which combination of MRI parameters explains most cognitive function in a realistic imaging time. It is also important to determine the rate of change of DTI parameters over time. There are no longitudinal studies in sporadic SVD, although a 2-year follow-up study in CADASIL detected change in MD, which correlated with changes in clinical scores.\textsuperscript{11}

The aims of this study were to (1) confirm the strong association between executive function and DTI parameters in a new data set; (2) use multimodal MRI to determine which MR parameters correlate best with executive function; and (3) determine which MRI parameters are most sensitive to change during a 1-year prospective follow-up.

**Methods**

**Subjects**

Thirty-five patients presenting with lacunar stroke and with moderate or severe confluent leuкоaraiosis on MRI (defined as grade 2 or 3 on a modified Fazekas scale) were recruited.\textsuperscript{12} Patients with other causes of stroke apart from SVD were excluded: cardioembolic causes of stroke apart from SVD were excluded: cardioembolic, large cerebral artery stenosis (>50\%), large (>1.5 cm) subcortical infarcts, or any cortical infarcts. All participants were recruited at least 3 months after the date of the last stroke to avoid acute effects on MRI or neuropsychology. All participants were invited to return after 12 months (mean SD 12.4 1.5 months). Of the 35 patients, 27 reattended. Seven did not agree for the following reasons: did not want to be involved further (2), moved away (2), unwell (2), unable to be contacted (1), or no reason given (1).

All subjects were examined by the same neurologist at baseline and follow-up. Cerebrovascular risk factors, including hypertension, diabetes mellitus, hypercholesterolemia, smoking status, and body mass index were assessed at both time points. Hypertension was defined as antihypertensive treatment or systolic or diastolic blood pressure >140 or 90 mm Hg, respectively. Hypercholesterolemia was defined as drug-treated or cholesterol >5.2 mmol/L. Smoking was classified as current or previous smoker. Modified Rankin score was recorded as a measure of disability.\textsuperscript{13} The local research ethics committee approved the study and all subjects gave informed, written consent.

**MRI**

Imaging was performed on a 1.5-T GE Signa MRI scanner (General Electric, Milwaukie, Wis) with a maximum gradient strength of 22 mTm\textsuperscript{–1}. A standard quadrature head coil was used. The imaging protocol included the following sequences: (1) fluid-attenuated inversion recovery: repetition time/echo time = 9000/120, inversion time 2200 ms, 28 slices of 5-mm thickness; (2) spoiled gradient recalled echo T1-weighted: repetition time/echo time = 17/3; 92 slices of 1.5-mm thickness; and (3) DTI: single-shot echoplanar imaging in 12 diffusion-sensitized directions each with a b factor of 1000 s mm\textsuperscript{–2}, repetition time/echo time = 7000/80, acquisition matrix = 96×96; field of view = 24 cm, 2 interleaved series of 4 repeats, each containing 25 2.8-mm slices with a gap of 2.8 mm.

Of 27 patients who attended at both time points, one was unable to complete the protocol and therefore no T1-weighted volume or DTI scans were obtained and 2 had artifact on either or both DTI scans. There were no scanner upgrades or changes to software or hardware during the study period.

**Neuropsychological Assessment**

A battery of tests assessing a range of cognitive abilities was administered. Premorbid intelligence was estimated using the National Adult Reading Test–Restandardised. Current intelligence was assessed using the Vocabulary and Matrix Reasoning subtests from the Wechsler Abbreviated Scale for Intelligence. The Mini-Mental State Examination was included because it is frequently used clinically as a measure of general abilities. Attention was measured using the Digit Span Forwards Raw Score from the Wechsler Memory Scale III. Immediate and delayed verbal memory was measured by the Memory Logical Immediate and Delayed Recall subtests of Wechsler Memory Scale III. Executive function was measured using tests from the Delis-Kaplan Executive Function System, which were Verbal Fluency (letter fluency) and the Trails Switching subtest (based on the Trail Making Test part B). Digit Span Backwards from the Wechsler Memory Scale III was used as a measure of working memory, a component of executive function. The Trails Motor Speed subtest from the Delis-Kaplan Executive Function System was included as a measure of speed. These tests were chosen to investigate those domains impaired in SVD, particularly executive function, and allow construction of a composite executive function score (see subsequently) as our primary cognitive parameter.

**Image Analysis and Postprocessing**

Images were analyzed on a Sun workstation (Sun Microsystems, Mountain View, Calif). All image analysis was performed blind to the subject’s identity.

Brain volume was calculated using a fully automatic program, SIENAX (Structural Image Evaluation, using Normalization, of Atrophy).\textsuperscript{14} This program reports brain volume relative to normalized skull size, reducing head size-related variability between subjects. Brain volume change was calculated using SIENA (Structural Image Evaluation, using Normalization, of Atrophy; www.fmrib.ox.ac.uk) on T1-weighted images. This fully automated program output percentage brain volume change.

A semiautomatic program was used to determine whole brain white matter hyperintensity lesion volume on fluid-attenuated inversion recovery images as described previously.\textsuperscript{15} Percentage lesion volume was determined as a ratio of lesion volume to nonnormalized brain volume.

A single observer (H.S.M.) evaluated fluid-attenuated inversion recovery and T1-weighted images to identify lacunar infarcts. A lacunar infarct was defined as a distinct area 3 to 15 mm in diameter with the same signal characteristics as cerebrospinal fluid on fluid-attenuated inversion recovery and T1-weighted images.

DTI data were analyzed using an automated global measure. The T2-weighted image obtained from DTI (b=0 image) was coreg-
tered with the T1-weighted volume scan using MATLAB 6.0 (MathWorks, Natick, Mass) and SPM2 (Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm). The T1-weighted volume scan was automatically segmented into gray and white matter and cerebrospinal fluid to obtain a mask of brain tissue (including all visible lesions). Voxels were included in the mask if the probability of being gray matter and the probability of being white matter was >0.5. This mask was checked visually for errors in voxel classification. A histogram of MD and FA was computed for each subject with a bin width equal to 0.00004 mm²/s and 0.01 and a fixed upper limit of 0.004 mm²/s and 1.0, respectively, for each DTI voxel below the brain mask. To correct for differences in brain volume, each histogram was normalized to the total number of voxels corresponding to the brain tissue. For each histogram, the normalized frequency of pixels at the peak height, the median, and the mode were obtained. For the cross-sectional part of the study, only the former was analyzed over the median or the mode because its distribution is non-Gaussian and has been consistently reported in a range of other studies on multiple sclerosis, CADDASIL, and aging.

Follow-up DTI data were processed in the same manner as baseline data. To ensure that the same part of the brain was sampled for each subject regardless of time, the T2-weighted images and T1-weighted images derived at follow-up were coregistered to the T2-weighted images from the baseline. This realigned data were used to obtain the FA and MD histogram parameters for each subject.

Statistical Analysis
All statistical analysis was performed using SPSS. Paired t tests or Wilcoxon signed rank test were performed on the 27 patients who attended at both time points to determine if there was a change in vascular risk factors and modified Rankin score.

The distribution of MR parameters was normal apart from percentage lesion volume and lacunar infarcts, which required transformation by log and by square root, respectively. MR parameters were correlated with neuropsychological scores and modified Rankin score. To reduce the number of comparisons between MR parameters and cognitive scores, 2 composite scores were determined using principal component analysis. Age-corrected scores are used for all tests apart from Mini-Mental State Examination and the individual digit span tests because this is not available. A composite global cognition score was calculated using digit span total (forward + backward), verbal fluency, Trails Switching corrected (Trails switching subtest was corrected for speed by subtracting the Trails motor score), and both immediate and delayed recall from the logical memory test. An executive function score was calculated using digit span backwards, verbal fluency, and Trails Switching corrected.

To determine which MR parameters were most informative in predicting neuropsychological function, multivariate analysis was run using multiple linear regression with backward elimination. The 4 imaging parameters, age, gender, and premorbid IQ were entered into the model together with the composite executive function score as the dependent variable. A similar analysis was carried out for Rankin score.

Changes in MRI parameters between the 2 time points were assessed using paired t tests for parametric data or Wilcoxon signed rank test for nonparametric parameters. For ease of comparison, percentage difference for each of the parameters was also calculated.

To identify factors that would predict the possible significant changes seen in the imaging parameters between the 2 time points, multivariate analysis was run with changes in the imaging parameter as the dependent variable and the following independent baseline variables: age, gender, systolic blood pressure, lesion volume, and imaging parameter.

Neuropsychological data were compared between the 2 time points using paired t tests or Wilcoxon signed rank as appropriate. Partial correlation coefficients were obtained between changes in the 2 composite scores and changes in the DTI parameters while controlling for baseline age.

Table 1. Demographic Characteristics of the 35 Patients With SVD Who Attended at Baseline and the Subset of 27 Who Attended at Both Time Points

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Whole Population at Baseline</th>
<th>Subtest Who Attended at Baseline</th>
<th>1-Year Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>35</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Baseline age, mean (SD)</td>
<td>68.8 (9.3)</td>
<td>68.9 (8.7)</td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>24 (69%)</td>
<td>19 (70%)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive, %</td>
<td>97%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) systolic blood pressure</td>
<td>155 (19)</td>
<td>159 (18)</td>
<td>155 (15)</td>
</tr>
<tr>
<td>Mean (SD) diastolic blood pressure</td>
<td>87 (9)</td>
<td>88 (9)</td>
<td>84 (11)</td>
</tr>
<tr>
<td>Treated diabetes mellitus, n (%)</td>
<td>10 (29%)</td>
<td>9 (33%)</td>
<td></td>
</tr>
<tr>
<td>Treated hypercholesterolemia, n (%)</td>
<td>23 (66%)</td>
<td>20 (63%)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) body mass index, kg/m²</td>
<td>28.0 (5.0)</td>
<td>28.1 (4.7)</td>
<td>27.9 (5.0)</td>
</tr>
<tr>
<td>Smoker (current or ex), n (%)</td>
<td>24 (68.6%)</td>
<td>18 (66.6%)</td>
<td></td>
</tr>
<tr>
<td>Rankin score (SD)</td>
<td>1.46 (1.2)</td>
<td>1.33 (1.3)</td>
<td>1.31 (1.4)</td>
</tr>
</tbody>
</table>

Immediate Reproducibility
To assess reproducibility of each imaging parameter, 10 volunteers were scanned twice in quick succession (within a couple of hours). Subjects were removed from the scanner and repositioned before repeat scanning. The mean (SD) percentage difference was calculated for each measure: percentage lesion load 0.68 (7.93), percentage brain volume change 0.057 (0.19), median MD 0.48 (3.45), MD at peak height 0.50 (3.05), peak height of MD graph 0.85 (5.08), median FA 1.73 (7.57), FA at peak height 2.06 (8.50), and peak height of FA graph 10.5 (8.25).

Results
Demographic characteristics of the whole SVD population at baseline and of the 27 patients in whom repeat imaging was performed are shown in Table 1. There was no change in any risk factors except for a small decrease in diastolic blood pressure (mean, -4.5 mm Hg, P = 0.03). No patients experienced transient ischemic attack or stroke during follow-up. There were no differences in baseline demographic characteristics or imaging parameters between those who attended at both time points and those who dropped out.

Cross-sectional Results
Correlations between each MRI parameter and cognitive measures are shown in Table 2. After controlling for age, gender, and premorbid IQ, the composite executive function score correlated most strongly with peak height of FA histogram (r = -0.640, P = 0.004) and brain volume (r = 0.501, P = 0.034). It did not correlate with lesion load or number of lacunar infarcts. Global cognition score correlated with brain volume alone (r = 0.507, P = 0.032). Episodic memory and current IQ did not correlate with any imaging parameter.

Multivariate analysis with backward elimination was performed to determine which combination of MR parameters...
Table 2. Pearson’s Correlation Coefficients Between Different Cognitive Scores and MRI Parameters After Controlled For Age, Gender, and Premorbid IQ*

<table>
<thead>
<tr>
<th>MR Parameter</th>
<th>Composite Neuropsychology Score</th>
<th>Composite Executive Function Score</th>
<th>Memory Score—Immediate Recall</th>
<th>Current IQ</th>
<th>Modified Rankin Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized brain volume</td>
<td>0.507†</td>
<td>0.501†</td>
<td>0.347</td>
<td>0.398</td>
<td>−0.026</td>
</tr>
<tr>
<td>Percentage lesion volume</td>
<td>−0.213</td>
<td>−0.320</td>
<td>−0.122</td>
<td>−0.143</td>
<td>0.237</td>
</tr>
<tr>
<td>No. of lacunar infarcts</td>
<td>−0.342</td>
<td>−0.278</td>
<td>−0.256</td>
<td>0.417</td>
<td>0.147</td>
</tr>
<tr>
<td>Median FA at peak height</td>
<td>−0.116</td>
<td>0.494†</td>
<td>−0.368</td>
<td>0.169</td>
<td>−0.525†</td>
</tr>
<tr>
<td>FA at peak height</td>
<td>−0.196</td>
<td>−0.0003</td>
<td>−0.214</td>
<td>−0.033</td>
<td>−0.155</td>
</tr>
<tr>
<td>Peak height FA</td>
<td>−0.142</td>
<td>−0.640‡</td>
<td>0.101</td>
<td>−0.049</td>
<td>0.496†</td>
</tr>
<tr>
<td>Median MD at peak height</td>
<td>−0.520†</td>
<td>−0.251</td>
<td>−0.486†</td>
<td>−0.242</td>
<td>0.272</td>
</tr>
<tr>
<td>MD at peak height</td>
<td>0.418</td>
<td>−0.007</td>
<td>−0.489†</td>
<td>−0.255</td>
<td>0.206</td>
</tr>
<tr>
<td>Peak height MD</td>
<td>0.485†</td>
<td>0.374</td>
<td>0.387</td>
<td>0.126</td>
<td>−0.067</td>
</tr>
</tbody>
</table>

*The correlation with the modified Rankin score is corrected for age and gender.
†P<0.05.
‡P<0.005.

Discussion

Best described the variance in executive function. For this analysis, only one DTI parameter was used because FA and MD were highly correlated. Peak height of FA histogram was used rather than MD because it correlated most strongly with executive function in the previous analysis. Age, gender, and premorbid IQ were also entered in the model. The final model contained only peak height of FA histogram and premorbid IQ and this explained 74% of the variance of the composite executive function score (P=0.0001, Table 3).

Modified Rankin score correlated only with peak height of the FA histogram (r=0.496, P=0.016). It did not correlate with brain volume, lesion load, or lacunar infarcts. Applying a similar multivariate model with the modified Rankin score as the dependent variable resulted in only the peak height of the FA histogram remaining within the model explaining 56% of the variance (P=0.001).

Longitudinal Results

Over the 1-year follow-up, there were significant changes in DTI parameters with an increase in median MD and MD at peak height and a reduction in peak height of FA histogram (Table 4; Figure 1). In contrast, there were no significant changes in lesion load or brain volume. There were no differences in any cognitive tests between the 2 time points at 1-year follow-up. In contrast, conventional MRI sequences, including T2 lesion volume. Furthermore, in a prospective longitudinal study, changes in DTI parameters could be detected over 1-year follow-up. In contrast, conventional MRI sequences, including lesion load and brain volume, did not change significantly, and no change in neuropsychological scores could be demonstrated.

Table 3. Results of 3 Multivariate Models With the Backward Elimination Method With 3 Different Dependent Variables*

<table>
<thead>
<tr>
<th>Dependent Variable Used</th>
<th>Independent Variables Remaining in Model</th>
<th>Adjusted R² (P Value)</th>
<th>Unstandard Coefficient B</th>
<th>P Value</th>
<th>95% CI for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite neuropsychology score</td>
<td>Premorbid IQ</td>
<td>0.517 (0.0002)</td>
<td>0.053</td>
<td>0.001</td>
<td>0.030–0.077</td>
</tr>
<tr>
<td></td>
<td>Brain volume</td>
<td></td>
<td>0.003</td>
<td>0.086</td>
<td>0–0.006</td>
</tr>
<tr>
<td>Composite executive function score</td>
<td>Peak height FA</td>
<td>0.739 (0.0001)</td>
<td>−112–38</td>
<td>0.008</td>
<td>−192–33</td>
</tr>
<tr>
<td></td>
<td>Premorbid IQ</td>
<td></td>
<td>0.025–0.014</td>
<td>0.085</td>
<td>−0.004–0.053</td>
</tr>
<tr>
<td>Rankin score</td>
<td>Peak height FA</td>
<td>0.559 (0.001)</td>
<td>161</td>
<td>0.001</td>
<td>68.8–254</td>
</tr>
</tbody>
</table>

*The most significant model contained peak height of FA and premorbid IQ and explained 74% of the variance of the executive function score.
detected. These findings demonstrate that using an MR-based model, a considerable amount of variance in executive function in SVD can be explained and that the strongest predictor of variance in both cognition and disability are DTI parameters. These findings are consistent with DTI being the most sensitive parameter to monitor white matter damage in patients with SVD. It is likely to reflect the fact that DTI parameters are more sensitive to ultrastructural damage and also that the DTI parameters used measure change throughout the white matter rather than just in areas with lesion.

Over the 1-year follow-up, changes were detected in DTI parameters. Cross-sectional studies have shown that DTI parameters change with age and an age-related decline could potentially account for some of the changes we observed. To investigate this, we compared the results of this study with those from a study of normal ageing in which the same MRI protocol was used and in which repeat MRI was performed at 2 years rather than 1 year. In 80 age- and gender-matched subjects (mean age, 68.6 years; gender, 58%; male gender, 58%; P = 0.3), a reduction in FA and an increase in MD at peak height were detected, but the annual rate of change was significantly less than in the cohort of patients with SVD in this article than in the healthy control subjects. (control subjects versus patients with SVD—mean median MD [mm²/s × 10⁻³] 0.94 versus 2.98, P = 0.001; peak height FA 5.67 versus 10.79, P = 0.005; R.A. Charlton, H. Markus, unpublished data).

Over the 1-year follow-up, no changes were also found in cognition or disability. In view of this lack of change, it is not surprising that there were no correlations between MRI parameters and executive function. This lack of detectable change is likely to reflect a number of factors. First, disease progression is slow emphasizing the need for surrogate markers to evaluate therapies. Second, measurement error with cognitive testing is higher and cognitive testing is further complicated by a learning effect, which may reduce changes over time, although over a 1-year period, one would not expect this to be so great. The Rankin disability scale itself is fairly insensitive to change and has only a few large categories, which result in poor sensitivity to change. Third, the sample size may be too small to detect a significant change. To definitively prove the use of DTI as a surrogate marker, larger studies with longer follow-up are required to show a correlation between changes in DTI parameters and cognitive testing.

Executive dysfunction is one of the most prominent features of SVD. Therefore, we assessed correlations with this cognitive domain. In a model incorporating a variety of imaging parameters as well as age and premorbid IQ, we were able to explain 82% of variance in executive function. This very high variance supports the use of MRI parameters as a surrogate marker for treatment trials. In large multicenter treatment trials, it is advantageous to have as short an imaging protocol as possible. Therefore, we explored how much variance could be explained if fewer imaging parameters were incorporated in the model. A model incorporating brain volume, lesion volume, and FA explained 79% of the variance. This was only slightly reduced to 76% when lesion volume was excluded. There was a further small reduction to 74% when brain volume was excluded. Therefore, using a DTI parameter alone with premorbid IQ explained 74% of the variance in the executive function. These data can be used to plan future treatment trials and suggest that a short, simple MRI sequence may contribute nearly as much information as more prolonged multimodal scanning. Consistent with these results, similar associations were found with the Rankin score. Again, FA was the main contributor explaining the variance in disability score. Alone it explained 56% of the variance compared with 62% explained when all parameters were included in the model.

In contrast to the highly significant association between FA and executive function score, there was no relationship between T2 lesion volume and executive function. This is consistent with previous studies in patients with established leukoaraiosis, in which only weak or absent correlations have been reported. This is likely to reflect the fact that T2 high signal can represent a variety of pathologies, only some of which cause axonal destruction. Consistent with other studies, we found a significant relationship between brain volume and executive function, although this did not persist in multivariate analysis. We found no association between the number of lacunar infarcts and executive function. This is consistent with other studies in sporadic SVD. This suggests that DTI may be a useful parameter for surrogate trials of therapeutic approaches in cerebral SVD.

| Table 4. Paired t Tests Comparing Differences in MR Parameters Between the 2 Time Points |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|
| MRI Parameter                   | Baseline        | 1-Year Follow-Up| Mean Percent Change Over 1 Year | P               |
| Percentage lesion load          | 3.72 (2.69)     | 3.76 (2.45)     | 1.08             | 0.104           |
| Normalized brain volume, cc*    | 1532 (85)       | 1526 (91)       | −0.91            | 0.419           |
| Median MD, mm²/s × 10⁻³         | 0.947 (0.059)   | 0.975 (0.069)   | 2.96             | 0.0001          |
| MD at peak height, mm²/s × 10⁻³ | 0.785 (0.031)   | 0.801 (0.040)   | 2.04             | 0.0005          |
| Peak height MD                  | 0.0931 (0.017)  | 0.0920 (0.021)  | −1.18            | 0.632           |
| Median FA                       | 0.1971 (0.013)  | 0.1929 (0.018)  | −2.13            | 0.264           |
| FA at peak height               | 0.1317 (0.013)  | 0.1367 (0.015)  | 3.80             | 0.062           |
| Peak height FA                  | 0.0438 (0.004)  | 0.0465 (0.005)  | 10.73            | 2 × 10⁻⁵        |

*Percentage brain volume change is calculated using SIENA. However, the normalized brain volumes and p values of its difference were calculated using SIENAX.
DTI histogram analysis produces a number of related parameters, results of which are shown in Table 2. We have found that peak height FA tends to correlate best with executive function in studies of normal aging and SVD, and this parameter was therefore used in this study.

The findings in sporadic SVD are supported by those in CADASIL. Cross-sectional studies in CADASIL have also found stronger correlations between DTI parameters and both Mini-Mental State Examination and Rankin score than with conventional MRI parameters. A 2-year study in CADASIL detected changes in MD and these correlated with

Figure 1. Average FA and MD graphs for the 2 time points.

Figure 2. Changes of (A) median MD, (B) MD at peak height, and (C) peak height of FA graph with time. Each line represents an individual patient.
Rankin score, Barthel index, and cognition. No values were given on FA, which we found to correlate more strongly than MD in our data sets. The correlations with cognition in this CADASIL study are likely to reflect the more rapid rate of decline seen in this patient population and the 2-year follow-up period.

In conclusion, our data demonstrate that DTI is a sensitive marker to white matter damage in SVD, correlates better with both executive function and disability scores than other MRI parameters, and can detect longitudinal change over a relatively short time period. Larger studies with longer follow-up are now required to confirm these findings. If these include therapeutic interventions, it will be possible to demonstrate whether DTI surrogate markers predict clinical response to therapies.

Acknowledgments
We thank Dominick J.O. McIntyre and Yuji Shen for help with analysis.

Source of Funding
This work was funded by The Health Foundation and Research Into Ageing.

Disclosures
None.

References
Multimodal MRI in Cerebral Small Vessel Disease: Its Relationship With Cognition and Sensitivity to Change Over Time
Arani Nitkunan, Tom R. Barrick, Rebecca A. Charlton, Chris A. Clark and Hugh S. Markus

*Stroke*. 2008;39:1999-2005; originally published online April 24, 2008;
doi: 10.1161/STROKEAHA.107.507475

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/39/7/1999

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/