White Matter Hyperintensities Are Associated With Impairment of Memory, Attention, and Global Cognitive Performance in Older Stroke Patients

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Background—The importance of white matter hyperintensities (WMH) for cognitive performance in older stroke patients is largely unknown. We hypothesized that processing speed and executive dysfunction will be associated with frontal WMH whereas impaired memory will be associated with temporal WMH.

Methods—Neuropsychological assessments using the Cambridge Cognitive Examination (CAMCOG) and the Cognitive Drug Research (CDR) were completed for 96 stroke survivors aged older than 75 and 23 age-matched controls. Magnetic resonance imaging whole-brain axial FLAIR images were undertaken to visualize WMH and an automated threshold technique was used to determine their volume.

Results—In comparison to controls, the stroke patients had significantly greater volume of WMH in all key areas. Within the stroke group, a consistent pattern of significant association was identified between total and frontal WMH volumes and attention and processing speed tasks (eg, choice reaction time [right: $R=0.24$, $P=0.02$; left: $R=0.26$, $P=0.01$]), but not with executive function. There were significant associations between memory and temporal WMH volumes (right: $R=0.27$, $P=0.008$; left: $R=0.20$, $P=0.047$).

Conclusion—In older stroke patients, cognitive processing speed and performance on measures of attention are significantly associated with WMH volume, particularly in the frontal lobe regions, whereas memory impairment is associated with the volume of temporal lobe WMH. (Stroke. 2004;35:1270-1275.)

Key Words: stroke ■ cognition ■ magnetic resonance imaging ■ aged

Twenty-five percent of stroke survivors have dementia as a direct result of a stroke event.1–3 However, the delayed development of incident dementia is up to 9 times greater than the incidence in an age-matched community population for ≈5 years after stroke.4 Prevalence rates are even higher among older stroke survivors.5,6 In addition, almost half of patients with early indications of cognitive impairment (usually referred to as vascular cognitive impairment) but without dementia at 5-year follow-up.7 To facilitate the identification of individuals at particular risk for progressive cognitive decline and hence target interventions for secondary prevention, it is imperative to understand the substrates of cognitive impairment.

Few studies have examined the detailed profile of cognitive impairment in stroke survivors,8,9 but global deficits are evident,8 with early impairment of attention and executive performance.9 One longitudinal study indicates that memory deficits may be an important predictor of cognitive decline.7

Neuroimaging and neuropathological studies suggest that diffuse white matter changes and microvascular disease are the main associations of dementia in patients with cerebrovascular disease,10,11 but less work has focused on the magnetic resonance imaging (MRI) correlates of specific neuropsychological functions. In healthy populations, executive dysfunction is associated with white matter hyperintensities (WMH).10,11 Within the context of cerebrovascular disease, the overall severity of WMH appears to be related to the speed of cognitive processing in patients with subcortical ischemic vascular dementia12 and with executive performance, but not global cognition, in people with more heterogeneous vascular dementia.13 A study focusing on stroke patients (with and without dementia) identified an association between the severity of periventricular WMH and executive dysfunction, although no association was seen between executive performance and WMH.14 These studies have not specifically evaluated the associations of memory dysfunction, although one would hypothesize that temporal lobe areas may be important.15–16

Even fewer studies have evaluated people with cerebrovascular disease who do not have dementia. A preliminary report

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in patients with mild cognitive impairment related to cerebrovascular disease did not identify any associations between cognition and WMH, although a larger community study identified an association between progressive cognitive impairment and global WMH.

Before the development of quantitative measures, WMH were assessed using visual rating scales. Early quantitative studies relied on manual tracing, which is subjective and requires a neuroanatomical expert. The development of fluid-attenuated inversion recovery (FLAIR) sequences has enabled semiautomated methods to be developed. Recently, WMH volumes were measured in patients with Alzheimer disease using FLAIR images and a semiautomated segmentation method based on intensity thresholding (FLAIR) sequences has enabled semiautomated methods to be developed. Recently, WMH volumes were measured in patients with Alzheimer disease using FLAIR images and a semiautomated segmentation method based on intensity thresholding to quantify WMH. Similarly, a combination of diffusion-weighted imaging, T1- and T2-weighted images have been used to identify tissue abnormalities in stroke patients.

In the current study, correlates between the volume of WMH (expressed as a percentage of brain volume) and key aspects of cognition in older stroke patients without dementia are undertaken.

**Patients and Methods**

Stroke patients aged 75 years or older were recruited from consecutive patients on representative hospital-based stroke registers in Tyneside and Wearside. These patients were free of dementia (DSM IV criteria) and free of disabilities precluding computerized cognitive testing (eg, aphasia, hemiparesis of writing hand). Stroke was defined using the World Health Organization definition. The cohort was comprehensively assessed at 3 months after stroke, allowing time for the resolution of delirium. The evaluation included a medical history, assessment of neurological deficits, a full blood screen, and CT scan. Age-matched elderly controls were recruited from spouses or carers of patients.

The Local Research Ethics Committees granted ethical approval for the study. After full explanation and discussion, patients and healthy age-matched volunteers gave their consent to the evaluations, with additional assent from the next of kin.

**Neuropsychological Evaluations**

The Cambridge Cognitive Examination (CAMCOG) is a standardized paper-and-pencil test for global cognition with subscores for memory and executive function.

The Cognitive Drug Research (CDR) computerized battery has been widely used to evaluate attention/processing speed and executive function in elderly controls and dementia patients. Specific tasks include choice reaction time (CRT), digit vigilance, and memory scanning (numerical working memory).

**MRI Methods**

MRI used a 1.5 T GE Signa system (General Electric) within 3 months of the neuropsychological assessment. Whole-brain FLAIR images were acquired in the axial plane (TR=10 000 ms, TE=125 ms, TI=2100 ms, slice thickness=5 mm, interslice gap=0.3 mm) and transferred to a personal computer (converted to Analyze using MRicron). Code written in-house using Matlab (The Mathworks Inc) and SPM99 (Functional Imaging Laboratory, University College London) routines were used to quantify WMH. Images were reviewed before study inclusion. Seven patients were excluded because of movement, poor tolerability, or concurrent malignancy. The method of WMH volume measure has been described in detail previously and validated using a manually adjusted contour threshold technique.

FLAIR images were spatially normalized to the T1-weighted Montreal Neurological Institute (MNI) template, which approximates Talairach space, using a 12-parameter affine transformation and nonlinear iterations. Images were then resampled to a voxel size of 2×2×2 mm³ using bilinear interpolation and automatically segmented using a cluster analysis into gray matter, white matter, cerebrospinal fluid, and a fourth partition consisting of skull, fat, and voxels with a high degree of partial voluming. The “brain extract” function of SPM99 involves a series of conditional erosions and dilations and was used to create a brain mask. The outer surface of the brain mask was further eroded to ensure that only brain tissue was included after masking. Regions within the brain mask were then set to 1 and the previous probability cerebrospinal fluid map of SPM99 was used to set the ventricles to 1.

![Figure 1. Axial FLAIR image showing thresholding technique for WMH.](image1)

![Figure 2. Axial image of brain mask.](image2)
An iterative process of convolving the extracted brain with a 1-pixel-wide Gaussian and thresholding to remove pixels of intensity <0.7 was repeated 6 times. This eroded brain mask was then transformed from MNI space to the orientation of the FLAIR image, using the SPM deformation toolbox, using information from the scanner about the relative orientation of the FLAIR slices. This brain mask was used to remove nonbrain regions. The FLAIR images were then segmented, slice-by-slice, and WMH were identified as pixels with an intensity >1.45-times that of the modal pixel intensity. This threshold was chosen empirically after visual inspection showed good representation of the actual WMH on the FLAIR images (Figure 1). Those pixels not directly connected to 2 other WMH pixels were identified as isolated bright pixels and removed. This step removed isolated bright pixels, which were mostly not actual WMH. The WMH map was reviewed visually and any remaining nonbrain structure removed by manual editing.

A region of interest map (created in MNI space) was transformed onto the FLAIR image of each subject. This permitted quantification of WMH volume in the 4 lobes of the brain (Figure 2). The percentage of WMH in the brain was calculated by dividing the volume of segmented WMH by the volume of the brain as determined from the SPM99 segmentation. This was undertaken to control for intersubject differences in brain size. This semiautomated process for identifying WMH has been previously validated by comparison with a manual region of interest approach with excellent concordance (correlation >0.95).26

**Statistics**

Primary evaluations examined correlations between processing speed (CRT) and frontal WMH volume, and memory and temporal WMH volume using Pearson R test. Secondary evaluations were undertaken using the same statistical method, examining the regional associations of global cognitive deficits and examining the correlations of memory, processing speed, other aspects of attention, and executive performance with the severity of WMH. All evaluations used the SPSS computerized statistical package (version 10).

**Results**

One hundred three patients were evaluated. Seven MRI scans were excluded (see Methods), hence the final study population included 96 stroke patients older than 75. They had a mean age of 80.2 (±4.1), and 54 (56%) were female, 68 (71%) had a history of hypertension, and the mean Mini-Mental State Examination (MMSE) score was 26.5 (±2.48). Nineteen had predominantly cortical infarcts.

Four had thalamic infarcts, 29 had subcortical basal ganglia infarcts (SCBG), 5 had a combination of cortical and thalamic infarcts, 17 had a combination of cortical and SCBG infarcts, 10 had a combination of thalamic and SCBG infarcts, and 2 patients had cortical, SCBG, and thalamic infarcts. The remaining patients had infarcts in the cerebellum or capsular regions.

An additional 23 subjects without strokes, transient ischemic attacks (but not excluded because of hypertension or cardiovascular risk factors), or dementia and who scored at least 25 on the MMSE: and 85 on the CAMCOG were evaluated as controls. They had a similar age and gender balance as the stroke population (Table 1). In comparison to the controls, the stroke patients had significantly greater impairment of global cognition, memory, executive performance, reaction times, and other aspects of attention, and they were less likely to have hypertension (all P<0.0001; Table 1). The total volume of WMH and the volumes in the temporal lobe and frontal lobe areas were also greater in the

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**TABLE 1. Demographic Characteristics and Cognitive and MRI Results**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Stroke (N=96)</th>
<th>Control (N=23)</th>
<th>Evaluation</th>
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<tbody>
<tr>
<td>Age</td>
<td>80.2 (SD: 4.1)</td>
<td>80.4 (SD: 5.6)</td>
<td>t=0.21, P=0.83</td>
</tr>
<tr>
<td>Gender</td>
<td>54 (56%) F</td>
<td>11 (48%) F</td>
<td>χ² 0.53, P=0.47</td>
</tr>
<tr>
<td>Hypertension mm Hg</td>
<td>68 (71%)</td>
<td>6 (26%)</td>
<td>χ² 17.8, P&lt;0.0001</td>
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<tr>
<td>Neuropsychology</td>
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<td>Global cognition (total CAMCOG)</td>
<td></td>
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<tr>
<td>Memory (CAMCOG)</td>
<td>84.7 (SD: 6.6)</td>
<td>93.6 (SD: 4.3)</td>
<td>t=4.78, P&lt;0.0001</td>
</tr>
<tr>
<td>Executive function (CAMCOG)</td>
<td>20.8 (SD: 3.3)</td>
<td>22.5 (SD: 1.5)</td>
<td>t=3.7, P&lt;0.0001</td>
</tr>
<tr>
<td>Choice reaction time (ms)</td>
<td>735.6 (SD: 277.7)</td>
<td>504.7 (SD: 73.1)</td>
<td>t=7.1, P&lt;0.0001</td>
</tr>
<tr>
<td>Fluctuating attention (ms)</td>
<td>204.8 (SD: 159.0)</td>
<td>95.4 (32.8)</td>
<td>t=6.1, P&lt;0.0001</td>
</tr>
<tr>
<td>Number vigilance (accuracy)</td>
<td>91.8 (SD: 16.5)</td>
<td>99.4 (SD: 1.9)</td>
<td>t=4.3, P&lt;0.0001</td>
</tr>
<tr>
<td>Memory scanning (ms)</td>
<td>1270.2 (SD: 686.3)</td>
<td>849.7 (SD: 205.4)</td>
<td>t=5.1, P&lt;0.0001</td>
</tr>
</tbody>
</table>

WMH indicates white matter hyperintensities.

Hypertension associated with slowed choice reaction time (t=2.4, P=0.03) and temporal WMH (t=2.2, P=0.04), with a trend toward association with total WMH (t=2.0, P=0.06) in controls. No significant associations between hypertension and any cognitive or WMH variables in stroke patients. In a subanalysis comparing stroke patients (n=28) and controls (n=18) without hypertension, all differences remained significant (P<0.01) except memory (t=2.3, P=0.03) and number vigilance (t=1.7, P=0.09), despite small numbers.
stroke patients (all $P<0.0001$; Table 1). The stroke patients had a total brain volume of 1052 mm$^3$ (SD 112) and the controls had a volume of 1106 mm$^3$ (SD 136).

**Correlations Within Stroke Group**

Age was correlated with the total volume of WMH ($R=0.23$, $P<0.02$), but there was no association with hypertension ($T=0.8$ $P=0.44$) or gender ($T=1.6$ $P=0.11$). Therefore, all correlations were undertaken as partial correlations controlling for age. Significant associations were identified between right ($R=0.26$ $P=0.01$) and left ($R=0.26$ $P=0.01$) frontal WMH volumes and CRT, but no association was evident between executive dysfunction and WMH volumes in either the right ($R=-0.12$ $P=0.21$) or the left ($R=-0.14$ $P=0.17$) frontal regions. There was an association between left frontal WMH volume and working memory ($R=0.24$ $P=0.02$).

There were significant associations between memory and both right ($R=0.27$ $P=0.008$) and left ($R=0.20$ $P=0.048$) temporal WMH volumes (Table 2A). There was a consistent pattern of associations between attention and WMH volume (Table 2B), including an association between total WMH volume and both processing speed (CRT $R=0.25$ $P=0.016$) and number vigilance ($R=0.24$ $P=0.02$).

**Regression Analyses**

Additional linear regression analyses were undertaken to determine the independent contribution of WMH volumes to specific cognitive deficits. These analyses were undertaken for each cognitive domain where significant associations were identified in the correlational analysis (total CAMCOG score, memory, vigilance, CRT, CRT SD, working memory), using cognitive performance as the dependent variable. For each evaluation, total WMH volume and the key potential confounders (age, gender, hypertension, medial temporal atrophy measured with Scheltens scale, size of cortical infarctions) were included as independent variables, together with any specific regional WMH volumes identified from the correlations. WMH volumes were significantly associated with each cognitive domain independently of the potential confounding factors. There were no significant associations with hypertension (Table 3).
to stroke patients without dementia, indicating the importance of these lesions as a substrate of vascular cognitive impairment.

Contrary to the hypothesis, but consistent with the only previous study in stroke patients, there was no association between WMH and overall executive performance. There was an association between WMH and memory scanning (which does involve executive processing), although this test also measures reaction time, which probably explains the association.

The association between memory impairments and the severity of temporal lobe WMH is novel, but consistent with the key role of temporal lobe areas in memory, and preliminary neuropathological observations identifying microvascular disease in areas containing key hippocampal tracts in vascular dementia patient.

Severe WHM were associated with global cognitive impairment. These findings are potentially important because they indicate that in stroke patients without dementia, WMH are a substrate of a broad range of core cognitive functions and emphasize the potential value of WMH as a target for preventing dementia in these individuals, with stringent control of blood pressure or cholinergic therapies among the exciting opportunities for clinical trials.

References

Threshold
The 25th percentile was WMH of 1.2% (mild) of the total brain volume, the median was 2.4% (moderate), and the 75th percentile was 4.5% (severe). Patients with moderate WMH had greater impairments of processing speed and attention than patients with mild WMH (CRT: $t=2.4, P=0.017$; digit vigilance $t=3.0, P=0.004$) but did not have greater impairment of global cognition or memory. However, the individuals with the most severe WMH had a greater impairment of global cognition and memory (total CAMCOG $t=2.3, P=0.02$; memory $t=2.2, P=0.03$).

Discussion
Cognitive processing speed and performance on other measures of attention were associated with total WMH and frontal WMH volume in older stroke patients. Memory impairment was associated with the volume of temporal lobe WMH. These associations remained significant in regression analyses that incorporated potential confounders (age, gender, hypertension, medial temporal atrophy, cortical infarctions), suggesting that it does represent an independent effect. Although the strength of individual correlations is modest, with an effect size explaining 5% to 10% of the variance, the consistent pattern of associations strongly suggests that this is a helpful finding.

This study uses a sensitive method of quantifying WMH volumes, which correlates well with visual ratings. The technique provides a reliable and less subjective means of measuring lesion volumes. Although FLAIR images provide good visualization of lesions, a limitation was the inability to measuring lesion volumes. Although FLAIR images provide good visualization of lesions, a limitation was the inability to

<table>
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<th>Cognitive Domain</th>
<th>Regression Model</th>
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<tr>
<td>Total CAMCOG</td>
<td>Age $t=2.6, P=0.01$, left frontal WMH vol $t=2.9, P=0.005$</td>
</tr>
<tr>
<td>Memory</td>
<td>Right temporal lobe WMH vol $t=2.2, P=0.03$</td>
</tr>
<tr>
<td>Choice reaction time</td>
<td>Gender $t=2.2, P=0.03$, total WMH vol $t=4.5, P&lt;0.0001$, left frontal WMH vol $t=2.0, P=0.05$</td>
</tr>
<tr>
<td>Vigilance</td>
<td>Right frontal $t=3.2, P=0.002$</td>
</tr>
<tr>
<td>Fluctuating attention</td>
<td>Total WMH vol $t=2.8, P=0.006$, right temporal $t=2.6, P=0.01$</td>
</tr>
<tr>
<td>Working memory</td>
<td>Total WMH vol $t=6.2, P&lt;0.0001$, left frontal $t=3.3, P=0.001$</td>
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