Independent Cognitive Effects of Atrophy and Diffuse Subcortical and Thalamico-Cortical Cerebrovascular Disease in Dementia

Richard H. Swartz, MD, PhD; Donald T. Stuss, PhD; Fuqiang Gao, MD; Sandra E. Black, MD

Background and Purpose—Brain atrophy, cortical infarction, and subcortical ischemic vasculopathy have all been associated with cognitive dysfunction. The interrelationships between these pathologies and their independent contributions to cognitive function remain unclear. Despite the high frequency of Alzheimer disease (AD) in those with clinically diagnosed vascular dementia, and the frequent findings of vascular disease in those with clinically diagnosed AD, many studies of brain-behavior relationships in dementia consider these populations separately. The present study sought to identify the correlates of independent domains of cognitive impairment in an unselected sample across a large range of severity and overlap of AD and VaD.

Methods—Two hundred five individuals from the Sunnybrook Dementia Study recruited from a university Memory clinic had detailed neuropsychological testing and MRI quantification using a multi-step postprocessing algorithm. A factor analysis of the cognitive protocol yielded a 3-factor solution, provisionally labeled: (1) short-term memory and language, (2) attention and working memory, and (3) mental flexibility.

Results—A factor analysis of brain measures identified 3 independent factors with measures of (1) brain atrophy, (2) subcortical vascular disease, and (3) strategic infarcts (anterior-medial thalamus and cortical infarcts). After accounting for the effects of age and education, measures of brain atrophy were the strongest correlates of all cognitive domains. Small vessel disease was independently associated with general severity, impaired short-term memory/language, and reduced mental flexibility, but not with poor working memory, presumably through disruption of frontal-subcortical connections. In contrast, strategic infarcts to anterior-medial thalamus and cortical gray matter were associated with poor short-term and working memory, but not with impairments in mental flexibility or global severity measures.

Conclusions—These data support the hypothesis that the thalamico-cortical network subserves both short-term and working memory. The findings also suggest that each type of pathology (atrophy, small vessel disease, and strategic infarcts) contribute independently to the pattern of cognitive disabilities associated with dementia. Particular attention to cerebrovascular disease in deep white or gray matter structures of the thalamico-cortical system is certainly warranted. (Stroke. 2008;39:822-830.)

Key Words: atrophy ■ cognition ■ dementia ■ thalamus ■ white matter hyperintensity

Alzheimer disease (AD) and vascular dementia (VaD) are the 2 most common causes of dementia1 and often co-exist.2 Despite the high frequency of AD pathology in those with clinically diagnosed vascular dementia, and the frequent findings of vascular disease in those with clinically diagnosed AD, many imaging studies of brain-behavior relationships in dementia consider these populations separately.

Studies of the cognitive consequences of vascular disease have yielded contradictory results. In otherwise healthy elderly individuals, those with global atrophy and WMHI often show reduced speed of information processing and impaired executive function compared with those with neither atrophy nor WMHI.3,4 Those with AD and WMHI show greater visuospatial dysfunction,5 attention/concentration impairment,6 slower cognitive processing, and greater executive dysfunction6 than those with AD alone, but other studies find no neuropsychological differences between these 2 groups.7–9 Functional imaging studies show different activation patterns in those with and without WMHI, suggesting that an equivalent level of cognitive impairment results from different mechanisms in AD with and without WMHI.7,10

In contrast to subtle and often controversial cognitive correlates of CVD-related MRI hyperintensities, MRI measures of atrophy have shown stronger and more consistent relationships with cognitive impairment. In individuals with
cognitive impairment, medial temporal lobe atrophy is correlated with both impairments in verbal memory\(^{11-13}\) and greater general impairment.\(^{12}\) Global brain atrophy also correlates with severity of cognitive impairment.\(^{14,15}\)

Few studies have evaluated the effects of atrophy and CVD independently. In one group of AD patients, gray matter volume and WMHI were independently correlated with global cognitive severity.\(^{16}\) However, another study of 76 AD patients with WMHI found no association of WMHI with severity of cognitive impairment or dementia, after controlling for atrophy and demographic factors.\(^ {17}\) This study excluded individuals with lacunar infarcts (n = 84) and normalized whole brain atrophy but not WMHI to total intracranial capacity (TIC). Fein et al suggested that hippocampal and cortical atrophy are the strongest correlates of cognitive impairment in individuals with lacunes.\(^{18}\) All 3 studies used global measures of cognitive impairment, without specifically examining memory or executive function. One other study suggests that hippocampal and cortical atrophy remain the strongest predictors of a wide range of cognitive functions, with WMHI only associated with timed tasks. However, in that study measures of atrophy were also correlated with the measures of CVD.\(^{15}\)

Four chief methodological problems have limited previous approaches to the role of CVD in cognitive impairment. First, most studies use group comparisons. When these groups are based on diagnostic categorizations (eg, AD versus VaD), the results may be affected by overlapping pathology. Some degree of AD pathology is common in individuals with VaD,\(^ {2,19}\) and cases of VaD without any coexisting AD pathology are rare,\(^ {20}\) whereas diagnoses of AD often do not account for cerebrovascular pathology.\(^ {2}\) Second, studies that compare patients with and without WMHI within diagnostic groups (AD or normal controls) vary considerably in the methods used (ie, quantitative analysis versus rating scales), in definition of groups (ie, which lesions or hyperintensities are used to separate the groups), and in cognitive outcome measures used (ie, global severity, memory or executive function). Third, these analyses, although demonstrating cognitive differences between groups, do not assess independent contributions of different brain measures. In most cases, groups with lacunes or WMHI also have greater global atrophy than those without,\(^ {15,21}\) so it is difficult to draw conclusions regarding independent contributions of atrophy and WMHI. Finally, many previous studies fall short of sample sizes sufficient for multivariate analyses.

Thus, this study explores relationships between quantitative brain measures and patterns of cognitive impairment in a large memory clinic sample. Based on previous group comparisons, we hypothesized that volumes of CVD and atrophy would independently correlate with measures of cognitive impairment. Specifically, WMHI would correlate with frontally-mediated tasks, whereas brain atrophy measures would correlate with memory and global cognitive performance.

**Materials and Methods**

**Participants**

Participants were consecutive eligible patients from a university memory clinic and community volunteers (part of the Sunnybrook Dementia Study). All patients received a screening neurological examination, routine laboratory evaluations, detailed cognitive testing, and technically adequate MRI within 12 weeks of each other, and were fluent in English. Secondary causes of dementia (other than vascular disease) and history of other neurological or psychiatric illnesses were exclusionary. The protocol was approved by the institutional Research Ethics Board, and written informed consent was obtained from all subjects or their substitute decision-makers.

For descriptive purposes, diagnostic criteria were applied by an experienced clinician. Dementia was defined using DSM-IV criteria.\(^ {22}\) Individuals with dementia were categorized by standardized criteria as either possible or probable AD,\(^ {23}\) or probable VaD.\(^ {24,25}\) Individuals with cognitive impairment not meeting criteria for dementia were designated cognitive impairment, no dementia (CIND).\(^ {26}\) Elderly normal controls were community-dwelling, with no history of psychiatric or neurological diseases and had no subjective or objective cognitive impairment. MR evidence of WMHI was not exclusionary.

**Neuropsychological Testing**

Neuropsychological tests were chosen to ensure a sufficient range of tasks and difficulty within a reasonably short administration time. The Functional Rating Scale (FRS)\(^ {27}\) (range 8 = normal, independent function, to 40 = severely impaired, dependent) was used to assess functional impairments. The Mattis Dementia Rating Scale (DRS), which ranges from 0 to 144, was used as a test of general cognitive function.\(^ {28}\) Tests of specific cognitive domains included: the California Verbal Learning Test (CVLT)\(^ {29}\) to test learning and short-term verbal memory, the Forward and Backward Digit Span tests from the Weschler Memory Scale-Revised (WMS-R)\(^ {30}\) to test working memory, the FAS fluency\(^ {29}\) to assess both language and executive functions,\(^ {30}\) the Wisconsin Card Sorting Test (WCST) to assess frontal systems,\(^ {31}\) the Benton Line Orientation task\(^ {29}\) to test visuospatial orientation and attention, and the Boston Naming Test\(^ {29}\) as a language measure.

**MR Imaging**

Brain images were acquired using a 1.5-T Signa MR imager (GE Medical Systems) using a protocol compliant with the consensus recommendations for Vascular Cognitive Impairment.\(^ {32}\) A 12-minute, standard interleaved spin-echo acquisition was performed in the axial plane covering the whole brain including cerebellum. T2 and proton-density (PD) weighted MR images were acquired using 3-mm-thick slices (TE = 30, 80 ms; TR = 3000 ms, 0.5 excitations, field of view = 20x20 cm, matrix 256x192). In addition, a 10-minute, 3D, axially acquired T1-weighted MR scan (TE/TR = 5/35 ms; flip angle = 35°; 1 excitation; voxel dimensions = 0.86 x 0.86 x 1.3; field of view = 20 x 20 cm; matrix 256x192) was used to measure the medial temporal region using ANALYZE.\(^ {33,34}\) Images were transferred to a Sun workstation for postprocessing.

**MRI Postprocessing**

Volumetric brain measures were extracted from MRI using a reliable protocol of segmentation followed by manual and automated postprocessing described previously.\(^ {35}\) Volumes were generated for the sulcal CSF (sCSF) and ventricular CSF (vCSF), brain parenchyma, basal ganglia hyperintensities, thalamic hyperintensities, and periventricular and deep WMHI. Lesions within the anterior one-third or medial one-half of the thalamus were further subclassified as anterior-medial thalamic hyperintensities, and lesions in the lateral one-half and posterior two-thirds of the thalamus were classified as posterior-lateral thalamic hyperintensities.\(^ {36}\) Cortical strokes were manually defined by a research neuroradiologist (F.G.). Medial temporal lobe atrophy was indexed by the thinnest linear width on T1-weighted MRI.\(^ {33,34}\) For individuals who had suffered posterior cerebral artery strokes involving the medial temporal lobe, the thinnest point of the contralateral unaffected medial temporal lobe was used. Analyses were performed in random order, by raters blind to all demographic, clinical, and neuropsychological data.
Data were imported to a statistical software package for further analyses. Volumes were individually normalized to total intracranial capacity (TIC).

### Statistical Analysis

The distributions of all brain imaging measures across the sample were explored and transformations were performed to meet the assumption of normality when necessary. Correlations between normalized transformed brain measures were evaluated using bivariate Pearson correlation coefficients. A factor analysis was performed using the brain measures to identify independent variables. Volumes of hyperintensities in the periventricular and deep white matter, basal ganglia, posterior-lateral and anterior-medial thalamus, volume of strokes affecting the cerebral cortex, vCSF and sCSF volumes, and medial temporal lobe thickness were entered as variables and a principal components factor analysis with varimax rotation was applied. Only those factors with eigenvalues greater than 1 were retained.

Correlations between cognitive test scores were evaluated using bivariate Pearson correlation coefficients and a factor analysis was performed to identify a smaller number of independent variables. DRS total score and the FRS were not entered into the factor analysis, so that they could be used as measures of general severity and improvement when necessary. Neuropsychological subtest scores (including the subtests of the DRS) were entered into a principal components factor analysis with varimax rotation. Only factors with eigenvalues greater than 1 were retained.

Brain-behavior relationships were explored using multiple linear regression models. Analyses were performed for general cognitive status (DRS total score), functional status (FRS), and for each behavior factor. Two-block linear regression models were performed. In the first block, the effects of age and education were entered. In the second block, independent brain factors were used as predictor variables in step-wise models. Bonferroni corrections were used for both the cutoff for significance of F change in the step-wise modeling (alpha=0.05/3=0.016, because 3 variables were entered into the step-wise analysis) and for the criterion for significance of the total models (alpha=0.05/6=0.0083). All analyses accounted for the effects of age.

### Results

Two hundred five individuals recruited over 6 years met criteria for this study (see Table 1 for population demographics). Twenty-five with possible/probable AD and 1 with CIND were taking cholinesterase inhibitors as these had just come to market. An additional 14.6% took 1 or more of vitamin E, hormone replacement therapy, or nonsteroidal antiinflammatory drugs (but not cholinesterase inhibitors).

All variables except sulcal CSF and medial temporal lobe thickness required logarithmic transformations to meet the assumption of normality. Because volumes of zero were possible for one or more measurement, a constant was added to each variable transformed. The resulting distributions were evaluated for improvement using the Kolmogorov-Smirnov test of normality and using comparison of skewness and kurtosis values for each distribution before and after transformation. For posterior-lateral thalamic and anterior-medial thalamic hyperintensity volumes, many participants had scores of zero, so complete normalization was not possible, but the transformation improved normality (skewness and kurtosis both approaching zero). All other measures met assumptions of normality after transformation. Therefore, the

### Table 1. Summary of Demographic Measures for Each Diagnostic Group; Averages and Standard Deviations Are Included

<table>
<thead>
<tr>
<th>Measure</th>
<th>Normal</th>
<th>CIND</th>
<th>Possible/Probable AD</th>
<th>VaD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>34</td>
<td>30</td>
<td>126</td>
<td>15</td>
<td>205</td>
</tr>
<tr>
<td>Age, y</td>
<td>67±8.7</td>
<td>69±7.7</td>
<td>73±9.8</td>
<td>78±8.1</td>
<td>71±9.6</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>41</td>
<td>57</td>
<td>50</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>Education, y</td>
<td>15±2.7</td>
<td>14±3.4</td>
<td>14±3.7</td>
<td>14±4.1</td>
<td>14±3.5</td>
</tr>
<tr>
<td>Duration, y</td>
<td>n/a</td>
<td>2.8±1.9</td>
<td>4.2±2.8</td>
<td>5.1±5.6</td>
<td>4.0±3.1</td>
</tr>
<tr>
<td>MMSE*</td>
<td>29±1.3</td>
<td>27±2.2</td>
<td>22±4.8</td>
<td>22±3.8</td>
<td>24±4.9</td>
</tr>
</tbody>
</table>

*MMSE indicates Folstein Mini-Mental Status Examination.

### Table 2. Pearson Correlation Coefficients for Brain Imaging Measurements

<table>
<thead>
<tr>
<th>Measure</th>
<th>sCSF</th>
<th>MTLT</th>
<th>DW</th>
<th>PV</th>
<th>PLT</th>
<th>AMT</th>
<th>BG</th>
<th>vCSF</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTLT</td>
<td>-0.38**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DW</td>
<td>0.14</td>
<td>-0.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV</td>
<td>0.17</td>
<td>-0.29**</td>
<td>0.76**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT</td>
<td>0.15</td>
<td>-0.04</td>
<td>0.51**</td>
<td>0.56**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMT</td>
<td>0.07</td>
<td>0.08</td>
<td>0.31**</td>
<td>0.34**</td>
<td>0.55**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BG</td>
<td>0.17</td>
<td>-0.08</td>
<td>0.55**</td>
<td>0.64**</td>
<td>0.63**</td>
<td>0.40**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vCSF</td>
<td>0.33**</td>
<td>-0.47**</td>
<td>0.38**</td>
<td>0.53**</td>
<td>0.32**</td>
<td>0.20**</td>
<td>0.32**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0.14</td>
<td>0.13</td>
<td>0.20*</td>
<td>0.23*</td>
<td>0.31**</td>
<td>0.26**</td>
<td>0.23*</td>
<td>0.25**</td>
<td></td>
</tr>
</tbody>
</table>

*Correlation is significant at 2-tailed P<0.005.
**Correlation is significant at 2-tailed P<0.0005.

Volumes normalized to total intracranial capacity and log transformed except for sCSF and MTLT.
transformed volumes of vCSF, cortical stroke, and all hyperintensities were used for all analyses.

Brain volumes were highly correlated with each other (Table 2). Correlations between all volumes of hyperintensities were statistically significant ($P<0.005$; Pearson correlation coefficient between 0.2 to 0.8). Of all the CVD measures, the strongest correlation occurred between periventricular WMHI and deep WMHI (Figure; $r=0.87$, Pearson $R^2=0.76$). Two atrophy measures, sCSF and medial temporal lobe thickness, were correlated with each other and vCSF, but rarely correlated with the CVD measures. In contrast, ventricular volume was significantly correlated with all measurements.

In the factor analysis, 3 factors emerged (eigenvalues >1), accounting for 69% of the variance. Table 3 shows factor loadings for all brain measures, reflecting the correlations of each variable with the final factor. The first factor (40.7% of total variance) reflected measures of small vessel disease. The second factor (17.5% of total variance) reflected strategic lesions, including large vessel cortical strokes and anterior-medial thalamic lesions.

The entire neuropsychological test battery was completed by 190 of the 205 individuals. Seven normal controls had incomplete batteries, and 8 of the 171 individuals with cognitive impairment either refused or were unable to complete one or more of the Boston naming,3 Benton line orientation,5 FAS fluency,2 and digit span1 tests. Six of these had probable AD and 2 had probable VaD. Because individuals with incomplete neuropsychological data ($n=1$ incomplete test = 15) were equally or more severely impaired compared with those in the same diagnostic categories with complete data, missing values were replaced with the average for the diagnostic group (AD, VaD, NC).37,38

As expected, cognitive test scores were highly correlated with each other. The factor analysis identified 4 salient variables (eigenvalues >1), which accounted for 71.3% of the variance in the sample (Table 4). One variable (FAS fluency) contributed equally (loadings $<0.05$ apart39) to factors 1 and 2. Factor 1 (45.4% of total variance) reflected short-term memory and language skills. Factor 2 (12.4% of total variance) reflected tests of working memory and attention. Factor 3 (8.7% of total variance) encompassed 4 of the 5 WCST measures, a problem solving task requiring abstraction and set shifting, considered a test of “mental flexibility.” WCST perseveration to previous category was poorly correlated with most other tests and emerged as a separate factor (Factor 4 in Table 4, 5.3% of total variance).

Because 4 factors were identified, 6 brain-behavior regression models were performed (DRS, FRS, and each cognitive factor). Age and education were forced into all models in the first block and the brain factors were evaluated step-wise in the second block. The first 5 models were significant ($P<0.0005$), whereas the model for neuropsychological factor 4 (WCSTpc) was not significant. Regression models demonstrated that both global cognitive (DRS total) and functional (FRS) impairments are independently related to brain atrophy and small vessel disease. Table 5 shows the results of these 2 regression models.

The 3 significant regression models for the cognitive factors are presented in Table 6. Measures of atrophy, small vessel disease, and strategic infarct were all independently related to short-term memory and language (Factor 1). However, the atrophy factor was the strongest predictor, accounting for 10 times the variance in short-term memory and language compared with the small vessel and strategic infarct factors (Table 6). Working memory/attention was associated with both atrophy and strategic infarcts. In con-

Table 3. Factor Analysis of Volumetric Brain Measures

<table>
<thead>
<tr>
<th>Factor Description</th>
<th>Brain Measure</th>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small vessel disease</td>
<td>Deep WMHI</td>
<td>0.83</td>
<td>0.16</td>
<td>-0.01</td>
</tr>
<tr>
<td></td>
<td>Periventricular WMHI</td>
<td>0.86</td>
<td>0.29</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Posterior-lateral thalamic HI</td>
<td>0.74</td>
<td>0.03</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Basal ganglia HI</td>
<td>0.80</td>
<td>0.08</td>
<td>0.18</td>
</tr>
<tr>
<td>Atrophy</td>
<td>vCSF</td>
<td>0.40</td>
<td>0.68</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>sCSF</td>
<td>-0.03</td>
<td>0.76</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>Medial temporal lobe</td>
<td>-0.12</td>
<td>-0.80</td>
<td>0.35</td>
</tr>
<tr>
<td>Strategic lesions</td>
<td>Anterior-medial thalamic HI</td>
<td>0.51</td>
<td>-0.10</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>Large vessel stroke</td>
<td>0.12</td>
<td>0.12</td>
<td>0.84</td>
</tr>
</tbody>
</table>

The strongest factor loadings are shown in bold; if one variable loaded equally ($\pm 0.05$) on 2 factors, both are bold.
Contrast, mental flexibility (Factor 3) was only significantly related to small vessel disease.

### Discussion

Conflicting evidence exists regarding the relative contribution of CVD to cognitive impairment in aging and dementia, which reflects methodological difficulties. In the present study the independent effects of brain atrophy and CVD volumes on behavioral scores were explored across the entire sample. The analysis was not restricted to global cognitive function; rather, it encompassed multiple neuropsychological domains, and detailed analysis of correlations between measures was undertaken.

The current results may help to resolve some controversial issues in the literature. First, correlation between multiple brain measures may account for some of the confusion regarding the impact of CVD in dementia. Studies suggesting WMHI do not influence cognitive impairment after accounting for atrophy\(^{15,17}\) have used ventricular size or cortical gray matter volumes to index atrophy. Our results suggest that these variables also correlate with CVD. Several studies have tried to compare the effects of subcortical versus periventricular WMHI.\(^{40,41}\) Our results confirm and extend those of one previous study,\(^{42}\) and suggest that the 2 variables, along with other subcortical hyperintensities, are very highly inter-correlated. Studies attempting to elucidate their relative contributions to cognitive impairment must be undertaken with caution.

### Table 4. Factor Analysis of Neuropsychological Test Scores

<table>
<thead>
<tr>
<th>Description</th>
<th>Brain Measure</th>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
<th>Factor 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term memory and language</td>
<td>CVLT acquisition</td>
<td>0.91</td>
<td>0.25</td>
<td>0.24</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>CVLT short delay, free recall</td>
<td>0.91</td>
<td>0.01</td>
<td>0.17</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>CVLT short delay, cued recall</td>
<td>0.87</td>
<td>0.15</td>
<td>0.15</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>DRS memory</td>
<td>0.83</td>
<td>0.27</td>
<td>0.18</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Boston naming</td>
<td>0.65</td>
<td>0.31</td>
<td>0.18</td>
<td>−0.02</td>
</tr>
<tr>
<td></td>
<td>MMSE</td>
<td>0.64</td>
<td>0.58</td>
<td>0.14</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>DRS initiation</td>
<td>0.59</td>
<td>0.49</td>
<td>0.19</td>
<td>−0.03</td>
</tr>
<tr>
<td>Phonemic fluency (FAS)</td>
<td></td>
<td>0.52</td>
<td>0.51</td>
<td>0.20</td>
<td>0.08</td>
</tr>
<tr>
<td>Working memory and attention</td>
<td>DRS attention</td>
<td>0.25</td>
<td>0.74</td>
<td>0.03</td>
<td>−0.07</td>
</tr>
<tr>
<td></td>
<td>Digit span—fowards</td>
<td>0.05</td>
<td>0.72</td>
<td>0.08</td>
<td>−0.03</td>
</tr>
<tr>
<td></td>
<td>Digit span—backwards</td>
<td>0.20</td>
<td>0.70</td>
<td>0.13</td>
<td>−0.04</td>
</tr>
<tr>
<td></td>
<td>DRS conceptualization</td>
<td>0.46</td>
<td>0.61</td>
<td>0.10</td>
<td>−0.01</td>
</tr>
<tr>
<td></td>
<td>DRS construction</td>
<td>0.13</td>
<td>0.58</td>
<td>0.14</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Benton line orientation</td>
<td>0.32</td>
<td>0.56</td>
<td>0.24</td>
<td>0.19</td>
</tr>
<tr>
<td>Mental flexibility</td>
<td>WCST # correct</td>
<td>0.22</td>
<td>0.17</td>
<td>0.93</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>WCST # categories</td>
<td>0.39</td>
<td>0.26</td>
<td>0.70</td>
<td>0.14</td>
</tr>
<tr>
<td>WCST non-perseverative errors</td>
<td>−0.15</td>
<td>−0.08</td>
<td>−0.78</td>
<td>−0.58</td>
<td></td>
</tr>
<tr>
<td>WCST previous response perseveration</td>
<td>−0.19</td>
<td>−0.15</td>
<td>−0.90</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Previous category perseveration</td>
<td>−0.01</td>
<td>−0.04</td>
<td>0.14</td>
<td>0.98</td>
<td></td>
</tr>
</tbody>
</table>

The strongest factor loadings are shown in bold; if one variable loaded equally (\(\pm 0.05\)) on 2 factors, both are bold.

### Table 5. Whole Sample Regression Model of DRS Total Score and FRS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Predictor Variables</th>
<th>R² Change</th>
<th>(P_\text{change})</th>
<th>Beta</th>
<th>(P_{\text{Beta}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global severity (DRS TOTAL) model</td>
<td>Age</td>
<td>0.04</td>
<td>0.025</td>
<td>0.148</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>Education</td>
<td></td>
<td></td>
<td>0.146</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Atrophy factor</td>
<td>0.25</td>
<td>&lt;0.001</td>
<td>−0.581</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Small vessel factor</td>
<td>0.04</td>
<td>0.001</td>
<td>−0.208</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Strategic infarct factor</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Functional impairment (FRS) model</td>
<td>Age</td>
<td>0.05</td>
<td>0.008</td>
<td>−0.130</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>Education</td>
<td></td>
<td></td>
<td>−0.143</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>Atrophy factor</td>
<td>0.24</td>
<td>&lt;0.001</td>
<td>0.578</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Small vessel factor</td>
<td>0.06</td>
<td>&lt;0.001</td>
<td>0.266</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Strategic infarct factor</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

The amount of independent variance explained by each predictor variable in the final model is shown (\(R^2\) change), along with the significance of the change in the model (\(F\) change significance), the standardized beta for each variable in the final model, and the significance of the variable weighting (\(P_{\text{Beta}}\)). Age and education were forced into each model in the first step so there is only one \(R^2\) change for the 2 variables, but the beta for each variable is provided. n.s. indicates not significant.
Independent factors reflecting brain atrophy, small vessel disease, and strategic infarcts were identified in the present study. Anterior-medial thalamic hyperintensities contributed equally to both small vessel disease and strategic infarct factors. The vascular supply to this region is mediated by small perforating vessels that can be affected by the same pathological processes that predispose to other small vessel disease-related changes, such as periventricular WMHI. In addition, the anterior and dorsomedial thalamus have multiple important interconnections with structures involving memory including the hippocampus, mamillary bodies, and posterior cingulate. Strokes in these regions are therefore strategically located to cause cognitive problems. Individuals with lesions here can have cognitive impairment in the absence of any other CVD or AD pathology. Thus, this variable was likely related to the small vessel disease factor by common causation and to the strategic infarct factor by common consequence.

It is important to note that white matter hyperintensities are not necessarily infarctions. The pathological correlates of these hyperintensities are diverse and range from complete infarcts to astrocytic swelling (clasmatoendodrosis). Thus, although we have tentatively labeled one of the factors “small vessel disease” there may be other underlying features which predispose to the development of all these MRI changes beyond small vessel ischemia.

The variables that emerged after analysis of neuropsychological tests reflected underlying cognitive skills affected by AD and CVD, including short-term memory/language, working memory, and mental flexibility. The factors were named with descriptive nomenclature, rather than with neuropsychological terminology, because each factor involves contributions from multiple tests or subtests. The first factor reflected short-term memory and language abilities, 2 domains commonly impaired in AD. Stuss et al showed that these domains are also highly correlated in individuals with frontal lobe injury. The tests of short-term memory used in this analysis (e.g., CVLT, DRS memory) were largely verbal, thus partially accounting for the correlation with language tests.

The second factor reflected scores on the DRS attention, the digit span task, the DRS conceptualization and construction subscores, and the Benton line orientation task. These tests require the short-term storage, manipulation, and utilization of mental representations. The 2 visuospatial tasks (DRS construction and Benton line orientation) similarly require storage, manipulation, and utilization abilities, but using visuospatial representations rather than language or numbers. These tests were the weakest contributors to the factor score, suggesting that the factor is more closely related to the attention and working memory components of the tasks than to visuospatial abilities. This factor was hence labeled “working memory and attention” as a way of describing the cognitive requirements underlying these tasks.

The third factor was related to most of the WCST scores. The WCST assesses the ability to identify salient features for categorization of cards (by the number, color or shape of figure on the cards), the ability to recognize when the categorization rules have changed and the ability to identify the new rule for sorting cards. Because participants are not informed when decision rules are altered, all participants exhibit perseveration to the previous category each time the rule is switched. Thus, even normal controls have several of these types of “errors.” It was not surprising, therefore, that the fourth factor (perseveration to previous category) was an
Independent measure, unrelated to other measures of cognitive impairment, or to brain volumes. In contrast, the total number of nonperseverative errors, the number of perseverations to previous (erroneous) responses, and the total number of correct categorizations all reflect the ability (or inability) to shift categorization rules, or “mental flexibility.”

Because factor analyses require large samples and multiple tests, they are not frequently used in clinical neuropsychological studies. Two previous studies have used factor analyses to explore cognitive dysfunction in AD. The first study identified 3 factors reflecting working memory, memory-language abilities, and visuospatial functions in a group of mild AD. The second identified 4 factors in AD, reflecting the cognitive domains of attention/registration, verbal fluency/reasoning, graphomotor/praxis, and recent memory. The factors in both studies are similar to those reported here; however, neither study explored the relationship of these cognitive impairments with in vivo measures of CVD and atrophy and both studies were restricted to AD populations. Thus it is reassuring that our study showed an additional factor related to mental flexibility given the additional burden of vascular disease in this sample.

Small vessel disease was an independent predictor of impaired global function, short-term memory and language, and mental flexibility. These cognitive impairments are key components of the cognitive decline in AD and VaD. Indeed, a prospective longitudinal community-based study found that those who develop AD within 2 years show the largest declines in memory and executive function. The Wisconsin Card Sort test activates large areas of the frontal cortex in functional imaging studies of normal volunteers. WCST impairments are related to frontal lobe atrophy, and the test is sensitive to the effects of frontal lobe damage in individuals with focal lesions. Thus, small vessel disease-related hyperintensities in the periventricular and subcortical white matter may be interrupting frontal-subcortical networks and impairing frontal lobe function.

In contrast, large vessel cortical strokes and anterior-medial thalamic hyperintensities were related to working memory and short-term memory-language functions. This is consistent with findings in individuals with isolated thalamic lesions that result in amnestic syndromes. The anterior-medial thalamus is a key component of a limbic circuit that also involves the hippocampus, anterior cingulate, and mammillary bodies. Disruption of this network, and other thalamico-cortical relays, result in impaired short-term memory and working memory/attention function.

The regression models demonstrate that relatively little variation in behavior is independently accounted for by small vessel disease or strategic infarcts. This might be in part attributable to the patient sample; for example, large vessel infarcts were less common in this population that might be expected in a stroke clinic cohort. Replication of the relationships seen here using multiple different populations including a prospective post-stroke population and a vascular dementia population is warranted. In this study, CVD accounted for less than 20% of the explained variability in any model. If, however, treatments for controlling or preventing vascular disease are widely applied, it might be possible to reduce the frequency or severity of short-term memory/language dysfunction in a small but significant proportion of individuals. Recent results from treatment of late-life hypertension show that if 1000 individuals undergo effective blood pressure control for 5 years, 19 new cases of dementia (2% of the sample) might be prevented. Although a small change, a 2% risk reduction in a large at-risk population, such as those over age 65, could result in tremendous benefits.

Summary
This study systematically analyzed the interrelationships between volumetric measures of brain atrophy and cerebrovascular disease to clarify the independent contributions of these pathologies. The large sample size, volumetric analyses, and statistical analyses that these data allow provided a unique approach to cerebrovascular disease in aging, cognitive impairment, and dementia that resolves several areas of controversy in previous research. The results of this study show that periventricular and deep white matter hyperintensities are highly intercorrelated, and studies attempting to separate their effects must be undertaken with caution. Small vessel disease and strategic thalamico-cortical infarcts do contribute independently to global cognitive and functional impairments and to difficulties in mental flexibility, short-term memory/language, and working memory, over and above the effects of brain atrophy. These consequences are likely mediated by disruption of separate frontal-subcortical and thalamico-cortical networks. These results provide a biological rationale for empirical findings in which prospective treatment of CVD risk factors (eg, therapy for high cholesterol and high blood pressure) reduce the incidence of dementia. Thus, treatments aimed at preventing CVD may play a significant role in preventing the onset, or ameliorating the severity, of cognitive decline in older age. This study also confirms the importance of brain atrophy for cognitive impairment in both vascular and degenerative disease populations. Because both AD pathology and CVD are associated with brain atrophy, preventing CVD should be considered complementary to therapies aimed at slowing AD neuropathology, and the 2 therapeutic strategies may produce synergistic effects.

Acknowledgments
We owe a debt to Dr J.P. Szalai (in memoriam) for his sound statistical advice and to Dr D.J. Sahlas for his constructive comments on the manuscript. We appreciate the ongoing dedication of the invaluable staff in the LC Campbell Cognitive Neurology Research Unit and remain especially grateful to the patients and their caregivers for their participation and support.

Sources of Funding
This study was funded by the Canadian Institute of Health Research grant # MT-13129 to S.E.B and D.S. Personal support was provided from the C.I.H.R. with an MD/PhD studentship to R.H.S.

Disclosures
None.

References


Independent Cognitive Effects of Atrophy and Diffuse Subcortical and Thalamico-Cortical Cerebrovascular Disease in Dementia
Richard H. Swartz, Donald T. Stuss, Fuqiang Gao and Sandra E. Black

Stroke. 2008;39:822-830; originally published online February 7, 2008;
doi: 10.1161/STROKEAHA.107.491936

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/39/3/822

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/