Background and Purpose—The relationship between subcortical ischemic vascular disease (SIVD) and cognition in normal elderly is unclear, in part because of methodological inconsistencies across studies. To clarify this relationship, the current study investigated a well characterized cognitively normal elderly sample (≥55 years) with quantitative MRI and psychometrically robust neuropsychological measures within a multivariate model. Converging evidence suggests that SIVD selectively impairs frontal-executive tasks by disrupting frontal-subcortical circuits. We therefore hypothesized that MRI markers of SIVD would be selectively associated with worse executive functioning.

Methods—We studied 94 participants who were cognitively and functionally normal. Volumetric measures of white matter signal hyperintensity (WMH), subcortical lacunes, hippocampal volume, and cortical gray matter were obtained to predict performance on composite measures of executive functioning and episodic memory.

Results—Hierarchical regression demonstrated that after controlling for demographic variables, MMSE, and total intracranial volume, the total number of subcortical lacunes was the only significant predictor, with a greater number of lacunes associated with poorer executive performance. Hippocampal volume best predicted episodic memory performance.

Conclusions—Results suggest that SIVD in the form of silent lacunes corresponds to poorer executive functioning even in otherwise normal elderly, which is consistent with the hypothesis that SIVD preferentially disrupts frontal-subcortical circuits. The clinical importance of these findings is highlighted by the fact that 33% of the normal elderly participants in this study had lacunar infarcts. (Stroke. 2008;39:397-402.)

Key Words: cerebral lacunes ■ cognition ■ elderly ■ magnetic resonance imaging

Subcortical ischemic vascular disease (SIVD) is widespread among the elderly with asymptomatic lacunes reported in 11% to 28% of normal individuals.1–3 The prevalence of subcortical white matter hyperintensities (WMH) ranges from 30% to 100% across studies of healthy nondemented populations.4–9 Despite this high prevalence of SIVD among normal elderly, its specific impact on cognition remains unclear.

Previous studies of the effect of these MRI markers in cognitively normal elderly suffer from various limitations. Cognitive assessment has typically included mainly or exclusively global measures such as the MMSE, which lacks sensitivity to detect subtle cognitive changes, particularly those such as executive functioning thought to be mediated by the frontal lobes where SIVD is often most prevalent.10,11 Executive function describes a set of cognitive abilities that control and regulate other abilities and behaviors and are necessary for goal-directed behavior, abstract thinking, and conceptualizing. They include the ability to initiate and stop actions, to monitor and change behavior as needed, and to plan future behavior when faced with novel tasks and situations.

Additional limitations of previous studies of SIVD include qualitative MRI methods, such as semiquantitative visual rating scales that yield highly variable nonvolumetric values,12 which decrease the sensitivity for demonstrating structure/function relationships.13 Also, “normal” elderly samples are frequently poorly characterized with terms such as cognitively normal, functionally normal, and medically healthy being used interchangeably. Finally, cooccurring neuropathological factors such as coexistent lacunes and WMH have been rarely controlled for with multivariate models.1,4,14,15

The current study attempted to address these limitations by investigating the relationship between SIVD and cognition.
within a well-characterized sample of cognitively and functionally normal elderly using quantitative structural MRI and psychometrically complete composite scales of cognition. We examined the independent contribution of lacunes, along with structural volumes of WMH, hippocampi, and cortical gray matter, to global cognitive functioning. We hypothesized that MRI volumetric markers of SIVD would be selectively associated with frontally mediated cognitive abilities such as executive function even in cognitively normal individuals.

**Subjects and Methods**

Subjects were recruited from 3 academic dementia centers as part of a previously described longitudinal study of ischemic cerebrovascular disease and aging. The institutional review boards at all participating institutions approved the study, and subjects provided written informed consent. Participants received a comprehensive clinical and cognitive evaluation that included a general history, neurologic examination, appropriate laboratory tests that consisted of serum chemistry, blood cell count, vitamin B12 level, thyroid function tests, comprehensive neuropsychological testing, and assignment of a Clinical Dementia Rating (CDR) by a trained rater. The CDR is a measure of function that has been previously validated in dementia populations and correlated with pathology. In addition, participants received a standardized MRI scan of the brain as described below. At the completion of this clinical evaluation, a consensus diagnostic conference rated each participant as cognitively normal, cognitively impaired but not demented, or demented.

Subjects were included in the present analyses if they were normal elderly (ie, ≥55) as defined by: (1) designation of cognitively normal by the clinical team after completion of the evaluation; (2) CDR score of 0; (3) Mini Mental State Examination (MMSE) scores equal to or greater than 26; and (4) scores within normal limits across the comprehensive battery of neuropsychological testing. The median number of days between neuroimaging and neuropsychological testing was 33 (IQR = 17.0 to 86.25).

**MRI**

MRI acquisition occurred between 1995 and 2001. MRI variables of interest included total WMH volume, cortical gray matter volume, total hippocampal volume, and number of subcortical lacunes. MR studies were performed on a 1.5-T MR scanner (Siemens Medical Systems, Erlangen Germany). A sagittal T1-weighted localizer image was obtained, followed by oblique axial double spin-echo images aligned parallel to the planum sphenoidale with the following parameters: 3000/20/80 (repetition time/echo times of first and second signal, respectively), single excitation (NEX = 1), in-plane resolution of 1×1.4 mm², and 3-mm-thick sections with no section gap, covering the entire brain from the inferior cerebellum to the vertex. Furthermore, a volumetric T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence was acquired with the following parameters: 10/4/300 (repetition time/echo time/inversion time), NEX = 1, an inplane resolution of 1×1 mm², and 1.4-mm-thick partitions. The scalp and skull were first extracted from the images, followed by estimation and removal of radio frequency field inhomogeneity with a low pass filter on each image section.

Proton density and T2-weighted MR images from the double spin-echo sequence and T1-weighted images from MPRAGE were used together as inputs for segmenting the brain into gray matter, white matter, and CSF based on a k-means cluster analysis algorithm as described in more detail in a study by Cardenas and colleagues (2001). FLAIR sequences were not acquired as full brain coverage with FLAIR could not be obtained because the number of slices was limited on this MRI system and interleaved acquisitions to offset partial coverage were often degraded by motion.

All segmented brains were then further edited by trained operators, both blinded to demographic and clinical information, into areas of ventricular and sulcal CSF, cortical gray matter (CGM), subcortical gray matter (SCGM), and WMH. In addition, total intracranial volume (TIV) was computed by summing over all voxels within the intracranial vault.

Lacunes were defined as small (>2 mm) areas of subcortical gray and white matter with increased signal relative to CSF on proton density MRI. Isointense lesions on proton density MRI at the level of the anterior commissure or inferior putamen were termed perivascular spaces; outside that region, they were defined as cavitated lacunes if they were ≥3 mm at maximum width. Lacunes were further classified into the following anatomical subregions: subcortical white matter, caudate, putamen, globus pallidus, and thalamus.

As previously described, semi-automated hippocampal volumetry was carried out using a commercially available high dimensional brain mapping tool (Medtronic Surgical Navigation Technologies), that has been recently validated and compared with manual tracing of the hippocampus.

**Cognitive Function**

Participants received a standardized battery of neuropsychological tests that took approximately 1 hour to administer. All personnel involved in test administration were trained in scoring procedures, and cross-center observation and cross-scoring of test protocols were used to assure data quality. Select tests were used to compile 2 composite scales of memory and executive function to be used as the cognitive outcome measures in this study. The Memory Scale was comprised of items from the Memory Assessment Scale, specifically the immediate recall trials (1 and 3), delayed free recall, and delayed cued recall trials. Donor items for the Executive Scale included the Initiation-Perseveration subscale of the Mattis Dementia Rating Scale (MDRS), letter fluency (FAS), Digit Span Backward, and Visual Memory Span Backward.

The composite scales were developed using Item Response Theory (IRT) analytic methods in an effort to ensure that they be psychometrically matched (ie, equivalent reliability and sensitivity) and possess linear properties (ie, equivalency along an ability range). In other words, a given change in ability in one part of the ability continuum will result in the same change in the scale score as would an equal change in ability in a different part of the ability continuum. Details of the construction and characteristics of these particular scales have been previously described. Briefly, they were developed based on a larger sample of 400 older participants with cognitive function ranging from normal to demented. Both measures demonstrated high reliability (>0.90) from about −2.0 SD below the mean of the overall development sample to 2.0 SD above the mean, and did not have appreciable floor or ceiling effects. Additionally, the scales were near-normally distributed, which presents advantages for statistical analyses.

The Memory and Executive measures were transformed so that scores were referenced to the distribution of the cognitively normal group in the development sample from this project and so that the scale of measurement corresponded to a traditional scale with a mean of 100 and SD of 15. Thus, a score of 85 represents 1 SD below the mean of the cognitively normal individuals from the development sample.

**Data Analysis**

Statistical data analyses were performed using SPSS version 12.0 for windows. Hierarchical multiple regression analyses were used to evaluate the relationship between the MRI variables of interest and the 2 cognitive scales (ie, to assess how well each of those variables predict both executive functioning and memory performances while accounting for the contribution of the other MRI variables). Hierarchical regression was used so that the researchers could control the order of entry of the predictor variables to determine how well the MRI variables of interest could predict cognitive performance over and above the effects of demographic factors (age, education, and sex), MMSE, and total intracranial volume. The same procedure was used to predict both executive functioning and memory. Specifically, in the first step of each model, demographic variables and MMSE were entered as independent variables to predict cognitive perfor-
Table 1. Demographic, Cognitive, and MRI Variables of the Study Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72.88</td>
<td>7.21</td>
<td>55–88</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.20</td>
<td>2.86</td>
<td>8–20</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>45.70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total intracranial volume, cm³</td>
<td>1307.52</td>
<td>122.52</td>
<td>1021.15–1561.97</td>
</tr>
<tr>
<td>Cortical gray matter, cm³</td>
<td>511.39</td>
<td>45.46</td>
<td>413.28–632.74</td>
</tr>
<tr>
<td>White matter volume</td>
<td>4.58</td>
<td>0.59</td>
<td>3.40–6.13</td>
</tr>
<tr>
<td>No. of lacunes</td>
<td>0°*</td>
<td>(0, 1)*</td>
<td>0–8</td>
</tr>
<tr>
<td>Presence of 1 or more lacunes</td>
<td>33.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive functioning scale</td>
<td>98.57</td>
<td>14.67</td>
<td>59.64–131.62</td>
</tr>
<tr>
<td>Memory scale</td>
<td>106.04</td>
<td>14.87</td>
<td>69.18–141.08</td>
</tr>
<tr>
<td>No. of days between MRI and cognitive testing</td>
<td>33° (17.00, 86.25)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Medians and interquartile ranges are reported for nonnormally distributed variables.

Results

Demographic, cognitive, and neuroimaging characteristics of the sample are described in Table 1. The sample consisted of 94 participants with a mean age of 72.88 (SD=7.2) and an average of 15.2 (SD=2.8) years of education. Forty-six percent of the sample was male (n=43), and the average MMSE score was 29.2 (SD=0.98). Thirty-one participants (33.0%) had evidence of at least 1 lacunar infarct on MRI.

After controlling for demographic variables, MMSE, and total intracranial volume in step 1 and step 2, MRI variables explained an additional 10.2% of the variance in the Executive scale (F Change[4,84]=2.76; P=0.033) as shown in Table 2. The total number of lacunes was the only independently significant MRI variable to contribute to executive functioning (β=−0.222; P=0.046). WMH was not significantly associated (β=−0.207; P=0.083). The Figure demonstrates the negative linear relationship between lacunes and executive functioning performance (R²=0.20; P<0.0001) and describes the number of participants that evidenced from 0 to 8 total lacunes. Post hoc group comparisons revealed that participants without lacunes performed significantly better on the executive functioning composite measure than participants with lacunes (103.67 [SD=12.0] versus 95.72 [SD=16.3]; P<0.009).

We conducted additional post hoc analyses to determine the relationship between lacune anatomical location (ie, caudate, putamen, globus pallidus, thalamus, and subcortical white matter), and executive functioning. Across the sample, 15 total lacunes were found in the caudate, 17 in the putamen, 2 in the globus pallidus, 23 in the thalamus, and 25 in subcortical white matter. Nonparametric correlations (Spearman’s rho) demonstrated no significant associations between any of the anatomical subregions and the Executive scale (P>0.10).

Regression results for memory functioning are summarized in Table 3. After controlling for demographic variables, MMSE, and total intracranial volume, only hippocampal volume contributed significantly to memory performance (β=0.247; P=0.047).

Discussion

The current study sought to examine the relationship between SIVD and cognition in a carefully screened population of cognitively normal elderly and found that total number of subcortical lacunes was an independent predictor of executive functioning. Specifically, a greater number of lacunes predicted poorer performance on composite measures of execu-
tive functioning in normal elderly, even when controlling for demographic variables and the presence of other MRI measures of interest. In addition, post hoc analyses revealed that the executive functioning scores of participants without lacunes were significantly higher than those with lacunes, suggesting that presence of lacunes was clinically discriminating. Hippocampal volume best predicted memory performance in normal individuals.

One possible mechanism underlying the relationship between subcortical lacunes and executive dysfunction may be related to cortical hypometabolism. FDG-PET studies have demonstrated lacunes to be associated with frontal hypometabolism, particularly within the prefrontal cortex, which in turn relates to poorer executive functioning.\(^{23,24}\) Frontal hypometabolism may in fact be a result of strategically located infarcts (ie, in the basal ganglia, thalamus, and/or frontal white matter), which directly damage frontal-subcortical circuits, thereby leading to reduced connectivity to the prefrontal cortex, reduced metabolism, and ultimately executive dysfunction. When we examined the relationship between executive functioning and specific lacune location, we did not find any significant associations. However it is important to note that the anatomical data were significantly positively skewed and restricted in range, which likely limited the robustness of these analyses.

Another possibility is that the relationship between executive functioning and subcortical lacunes is somehow mediated or driven exclusively by arterial hypertension, which several studies have demonstrated to be associated with WMH, lacunes, and cognitive dysfunction, particularly in the domains of verbal memory, attention, and abstract reasoning.\(^{25,26}\) We cannot rule out this possibility entirely, as reliable measures of hypertension were not available to use as covariates in our analyses. However, the fact that lacunes were specifically related to executive dysfunction and not also memory impairment makes the contribution of hypertension a less likely explanation as it would be expected to affect both cognitive areas equally.

Although WMH was not a statistically significant independent predictor of either executive functioning or memory when controlling for the presence of other cooccurring pathological variables, it did demonstrate a nonsignificant trend with greater volume associated with poorer executive functioning. The lack of statistical significance was similar to findings obtained in an autopsy series of prospectively studied elderly individuals.\(^{27}\) In that study, once the presence of lacunes was accounted for in a multivariate model, WMH was no longer a significant predictor of cognition. However, this phenomenon contrasts with the results of several struc-
tural neuroimaging studies that found the opposite occurrence (ie, WMH but not lacunes was related to cognitive performance in the elderly, when controlling for both).16,28 Both of those studies compared groups of subjects with and without lacunes along a spectrum of cognition based on their CDR alone, perhaps limiting their sensitivity to detect subtle cognitive differences. In addition, previous studies have investigated the volume of lacunes, not the total number, perhaps masking the linearity of the relationship.28 Our study using detailed cognitive assessments and rigorous MRI measures points to number of lacunes as the most significant predictor of executive dysfunction in these normal individuals.

Although the significant association between hippocampal volume and memory performance in the current study is consistent with previous studies of individuals with mild cognitive impairment29 and patients with dementia,30,31 this relationship has not been as consistently established in cognitively normal elderly.32 The lack of a significant contribution from either lacunes or WMH to memory highlights the selectivity of SIVD to other areas of cognition, particularly executive functioning.

The current study had several advantages. First, we used comprehensive and psychometrically robust measures of cognition that were reliable, fairly normally distributed, and did not have ceiling effects. Second, this study used quantitative MRI variables, which have been shown to yield more reliable associations than subjective qualitative ratings. Third, carefully characterizing a well screened cognitively and functionally normal elderly sample decreased the likelihood that concomitant neurodegenerative disease was impacting cognition and simultaneously masking any effects of SIVD markers. The fact that significant effects were demonstrated in a cognitively and functionally normal sample decreased the likelihood that concomitant neurodegenerative disease was impacting concomitant neurodegenerative disease was impacting cognition and simultaneously masking any effects of SIVD markers. The fact that significant effects were demonstrated in a cognitively and functionally normal sample decreased the likelihood that concomitant neurodegenerative disease was impacting cognition and simultaneously masking any effects of SIVD markers. The fact that significant effects were demonstrated in a cognitively and functionally normal sample decreased the likelihood that concomitant neurodegenerative disease was impacting cognition and simultaneously masking any effects of SIVD markers. The fact that significant effects were demonstrated in a cognitively and functionally normal sample decreased the likelihood that concomitant neurodegenerative disease was impacting cognition and simultaneously masking any effects of SIVD markers. The fact that significant effects were demonstrated in a cognitively and functionally normal sample decreased the likelihood that concomitant neurodegenerative disease was impacting cognition and simultaneously masking any effects of SIVD markers. The fact that significant effects were demonstrated in a cognitively and functionally normal sample decreased the likelihood that concomitant neurodegenerative disease was impacting cognition and simultaneously masking any effects of SIVD markers. The fact that significant effects were demonstrated in a cognitively and functionally normal sample decreased the likelihood that concomitant neurodegenerative disease was impacting cognition and simultaneously masking any effects of SIVD markers.

One major limitation of this study is that we used whole brain gray matter as a predictor variable, which did not significantly contribute to cognition in this group. This is a limitation because it is possible that some regional gray matter atrophy might correlate with cognition, but when the entire brain gray matter is used as a whole, the effects of regional change are lost. Another limitation relates to the observational nature of the study design and specifically the unpredictable and frequently unbalanced distribution of key variables of interest, which in this case is the presence of lacunes. Finally, it is important to mention that there were a number of patients in this study without evidence of lacunes, who had lower executive scores. This suggests the possibility that the assumption of more lesions equaling greater dysfunction as measured by linear regression may not fully explain the complex relationship.

The cognitive dysfunction demonstrated in these normal individuals suggests that these MRI markers, particularly lacunes, may not be truly “silent,” especially with reference to higher order executive abilities. These findings may also have important implications for the independent performance of instrumental activities of daily living (IADLs; eg, medication management), given the recognized association between executive dysfunction and IADL dependence.33 In addition, individuals who present with a high burden of lacunes on MRI might be considered for neuropsychological evaluation or intervention, even in the absence of evidence of gross neurological dysfunction. Prospective trials of aggressive vascular risk factor modification in these patients may help prevent further decline in these individuals.

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Disclosures
None.

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