White Matter Lesions Are Prevalent but Differentially Related With Cognition in Aging and Early Alzheimer Disease

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Background: White matter lesions (WMLs) are prevalent in nondemented aging and in Alzheimer disease (AD). Their relationship with cognition in the earliest stages of AD is unknown.

Objective: To assess the relationship between WMLs and cognition in nondemented aging and in early-stage AD.

Design: Cross-sectional study.

Setting: Alzheimer Disease Research Center, St Louis, Mo.

Participants: Participants were nondemented (n=88) or had very mild (n=48) or mild (n=20) AD.

Main Outcome Measures: Regression coefficients for deep WMLs and periventricular WMLs (PVWMLs) as predictors of cognition, after controlling for age, educational achievement, brain atrophy, and infarctlike lesions.

Results: White matter lesions were present in nondemented aging and in early-stage AD, with no group differences in deep WML burden and a modest PVWML burden increase in the AD group. The prevalence of infarctlike lesions was equivalent between groups. Age and hypertension were related to deep WML burden and PVWML burden. Deep WML burden and PVWML burden were associated with reduced global cognition in AD but not in nondemented aging. A PVWML × AD status interaction for global cognition suggests that the relationship between PVWMLs and cognition is modified by AD. In AD, global cognitive reductions were related to impairments in visual memory, processing speed, and executive function.

Conclusions: White matter lesions are prevalent in nondemented aging and in early-stage AD, and their presence influences cognitive impairment in the earliest stages of AD. Individuals with early-stage AD may be more vulnerable to the cognitive effect of WMLs than nondemented aging individuals with similar WML burden.

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HYPERINTENSE SIGNAL ABNORMALITIES ARE COMMONLY FOUND IN THE CEREBRAL WHITE MATTER ON T2-WEIGHTED MAGNETIC RESONANCE IMAGING IN NONDEMENTED AGING AND IN ALZHEIMER DISEASE (AD). A QUANTITATIVE REVIEW OF THE INFLUENCE OF WHITE MATTER LESIONS (WMLs) ON COGNITION IN HEALTHY OLDER PERSONS FOUND THAT WMLs WERE ASSOCIATED WITH REDUCED MEMORY, PROCESSING SPEED, AND EXECUTIVE FUNCTION. WHITE MATTER LESIONS ARE CONSISTENTLY ASSOCIATED WITH AGE, HYPERTENSION, AND OTHER CARDIOVASCULAR RISK FACTORS AND ARE COMMONLY CONSIDERED PART OF THE SPECTRUM OF VASCULAR-RELATED INJURY, DESPITE NONSPECIFIC UNDERLYING PATHOLOGIC CHANGES. PATHOLOGICAL EVIDENCE SUGGESTS THAT WMLs MAY PLAY A ROLE IN THE CLINICAL SYMPTOMS OF AD. INDIVIDUALS WITH MORE WMLs HAVE A HIGHER RISK OF DEVELOPING AD. IN ADDITION, INDIVIDUALS WITH WMLs AND CEREBRAL INFARCTLIKE LESION REQUIRE A LOWER NEUROPATHOLOGICAL AD BURDEN TO DEMONSTRATE COGNITIVE IMPAIRMENT AND DEMENTIA THAN INDIVIDUALS WITHOUT THESE LESIONS. NEUROIMAGING STUDIES ON THE CLINICAL SIGNIFICANCE OF WMLs IN AD HAVE REPORTED MIXED RESULTS. ALTHOUGH SOME STUDIES HAVE REPORTED THAT INDIVIDUALS WITH AD HAVE ELEVATED WMLs COMPARED WITH NONDEMENTED AGING INDIVIDUALS, THIS PATTERN HAS NOT BEEN UNIFORMLY OBSERVED. IN ADDITION, THE RELATIONSHIP BETWEEN WMLs AND COGNITION IN AD REMAINS UNCLEAR. SOME STUDIES SUGGEST THAT SUBJECTS WITH AD AND WMLs PERFORM WORSE THAN NONDEMENTED AGING INDIVIDUALS ON COGNITIVE TASKS, AND OTHERS FIND NO RELATIONSHIP BETWEEN WMLs AND COGNITION. THESE STUDIES HAVE BEEN LIMITED BY SAMPLES WITH A RANGE OF VERY MILD TO SEVERE AD, SUBJECT SELECTION BASED ON IMAGING CHARACTERISTICS, AND INSENSITIVE PRIMARY MEASURES OF COGNITION SUCH AS THE MINI-MENTAL STATE EXAMINATION (MMSE). THEREFORE, THE CLINICAL SIGNIFICANCE OF WMLs IN AD REMAINS UNCLEAR, PARTICULARLY IN THE EARLIEST CLINICAL STAGES OF THE DISEASE.
We examined WMLs in a sample of nondemented aging control subjects vs subjects with early-stage AD to determine the relative contribution of WMLs to the cognitive symptoms of early-stage AD. We also assessed whether the WML burden was increased in subjects with early-stage AD compared with nondemented aging controls.

**METHODS**

**PARTICIPANTS**

Participants were enrolled in the Washington University Memory and Aging Project and underwent brain magnetic resonance imaging between June 15, 2000, and August 15, 2003. Recruitment was based on media appeals for healthy and cognitively impaired individuals. Participants were nondemented (Clinical Dementia Rating [CDR] 0) or had a clinical diagnosis of AD in the very mild (CDR 0.5) or mild (CDR 1) dementia stage; participants who had a CDR 0.5 or CDR 1 together represent early-stage AD. At study enrollment, participants were free of non-AD disorders that could potentially cause dementia such as major depression, clinical history of stroke, Parkinson disease, and brain trauma. Twelve participants were excluded because of incomplete imaging protocols. Two participants were excluded because of the incidence of symptomatic infarctlike lesions during their longitudinal evaluation. Symptomatic infarctlike lesions were defined as the collateral source’s report of a clinical stroke or transient ischemic attack and neuroimaging evidence of an infarctlike lesion in an appropriate territory to explain the clinical symptoms. One hundred fifty-six participants were included in the study.

**CLINICAL ASSESSMENT**

The status of nondemented aging vs early-stage AD was based on clinical methods, without reference to psychometric performance. Experienced clinicians conducted semistructured interviews with each participant and with a collateral source who was knowledgeable about the participant. Diagnostic criteria for AD required the gradual onset and progression of impairment in memory and in at least 1 other cognitive and functional domain, comparable to standard diagnostic criteria for probable AD. These criteria have been validated and have a diagnostic accuracy for AD of 93%. In addition, longitudinal investigations have demonstrated that subjects with early-stage AD predictably progress to worse stages of cognitive impairment and that neuropathological examination of even CDR stage AD predictably progressed to worse stages of cognitive impairment and that neuropathological examination of even CDR stage AD predictably progressed to worse stages of cognitive impairment.

**NEUROPSYCHOLOGICAL EVALUATION**

An annual psychometric battery was administered to all participants approximately 2 weeks after the clinical assessment. This battery included the MMSE, Short Blessed Test, Trail-Making Test (A and B), Boston Naming Test, Crossing-off, Benton Visual Retention Test (forms C and D), Wechsler Memory Scale Logical Memory (immediate and delayed), Wechsler Memory Scale Associate Memory, Wechsler Memory Scale Digit Span Backward, Wechsler Adult Intelligence Scale–Revised Information, Wechsler Adult Intelligence Scale–Revised Block Design, Wechsler Adult Intelligence Scale–Revised Digit Symbol, and Word Fluency (letters s and p). A principal components analysis of these measures in a sample of 82 nondemented older adults produced a single factor accounting for 34% of the variance. Cognitive factor scores for the present sample were computed and standardized using the weights, means, and standard deviations from the earlier sample of 82 nondemented older adults. The cognitive factor score broadly assesses cognition and is minimally susceptible to floor or ceiling effects. The MMSE was used as a secondary measure of global cognitive function. Psychometric test results were not used in the clinical diagnosis or severity staging of dementia.

**NEUROIMAGING**

All imaging was performed using a 1.5-T vision scanner (Siemens, Erlanger, Germany). Four 1 × 1 × 1.25-mm T1-weighted (MP-RAGE) images were acquired in each individual (repetition time, 9.7 milliseconds; echo time, 4 milliseconds, flip angle, 10°; inversion time, 20 milliseconds; and delay time, 200 milliseconds). In addition, T2-weighted images were acquired using a turbo spin-echo sequence (repetition time, 6150 milliseconds; and echo time, 15 milliseconds), providing data at 1 × 1 × 2-mm resolution. Proton density imaging was not performed. All image data were mutually coregistered, transformed to the atlas space of Talairach and Tournoux, and resampled to 1-mm³ voxels as previously described.

Two raters (J.M.B. and J.A.C.) blinded to dementia status, age, and clinical information assessed deep WMLs (DWMLs), periventricular WMLs (PVWMLs), and infarctlike lesions (Figure 1). White matter lesions were assessed using methods by Scheltens et al. White matter lesions were defined as hyperintensity on T2-weighted images with corresponding T1-weighted hypointensity clearly discernible from the background. Periventricular WMLs were defined as WMLs located adjacent to the ventricle, while all other subcortical WMLs were considered DWMLs. Deep WMLs were rated semiquantitatively on a scale ranging from 0 to 6 in frontal, parietal, temporal, and occipital lobes. Total DWML burden represents the sum of the 4 regions (range, 0-24). Using these methods, interrater and intrarater intraclass coefficients exceeded 0.78. Periventricular WMLs were rated in the left and right frontal horns, posterior horns, and ventricular bodies on a semiquantitative scale ranging from 0 to 3. Each region’s PVWML score was based on visual inspection of the T2-weighted images with corresponding T1-weighted hypointensity clearly discernible from the background. Periventricular WMLs were defined as WMLs located adjacent to the ventricle, while all other subcortical WMLs were considered DWMLs. Deep WMLs were rated semiquantitatively on a scale ranging from 0 to 6 in frontal, parietal, temporal, and occipital lobes. Total DWML burden represents the sum of the 4 regions (range, 0-24). Using these methods, interrater and intrarater intraclass coefficients exceeded 0.78. Periventricular WMLs were rated in the left and right frontal horns, posterior horns, and ventricular bodies on a semiquantitative scale ranging from 0 to 3. Each region’s PVWML score.
vascular spaces, we use the term
the potential to incorrectly classify infarctlike lesions and peri-
segmentation algorithm.29,31
the atlas-registered brain mask based on a validated open-source
estimated by using the gray and white voxels–all voxels ratio in
farcts
ume), and presence of infarctlike lesions.
to determine the effect of WML burden on cognitive perfor-
correlations tested for associations between neuroimaging mea-
s were determined using
Differences in continuous demographic and imaging variables
were determined using t tests. Mann-Whitney U test was used
to compare categorical frequency distributions. Spearman rank
correlations tested for associations between neuroimaging mea-
sures and clinical variables. Linear regression analyses were used
to determine the effect of WML burden on cognitive performance
measures after controlling for the effects of age, educa-
tional achievement, brain atrophy (normalized whole-brain vol-
ume), and presence of infarctlike lesions.

STATISTICAL ANALYSIS

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tional achievement, brain atrophy (normalized whole-brain vol-
ue), and presence of infarctlike lesions.

PARTICIPANT CHARACTERISTICS

Table 1 gives the demographic, clinical, and neuroim-
ageing features of the 156 individuals in the study, in-
cluding 88 nondemented aging participants and 68 par-
ticipants with early-stage AD (48 were very mildly
demented and 20 were mildly demented). There were no
significant differences in age or sex between the nonde-
mented aging and AD groups, although a trend was ob-
served for more women in the nondemented aging group.
The AD group had fewer years of formal education, had
elevated systolic blood pressure, and were more likely
to have an apolipoprotein E genotype than the nonde-
mented aging group. No differences were observed in the
histories of hypertension, stroke, diabetes mellitus, heart
disease, tobacco use, or use of a lipid-lowering agent. The
mean MMSE score for the AD group was 24.2.

WML BURDEN

Periventricular WML burden was modestly higher in the
AD group (Table 1 and Figure 2). Deep WML burden
did not differ between the groups. Adjusting for age, sex,
education, and brain atrophy did not change the re-
sults. The overall infarctlike lesion prevalence in the co-
hort was 42.3% and was comparable between the 2 groups.

Figure 3 shows the similar relationship between age and
WMLs in the nondemented aging (DWML \( r = 0.26 \)
and PVWML \( r = 0.42 \)) and AD (DWML \( r = 0.27 \)
and PVWML \( r = 0.40 \)) groups (DWML \( P < .05 \)
and PVWML \( P < .001 \) for both groups). Deep WML and PVWML
burdens were related to a history of hypertension (DWML
mean ± SD burden of 13.7 ± 3.6 in individuals with hyper-
tension vs 12.2 ± 3.0 without hypertension, \( P < .01 \); and
PVWML burden of 9.3 ± 4.9 with hypertension vs 7.7 ± 3.8
without hypertension, \( P < .05 \)) but not sex, heart disease,
apolipoprotein E genotype, or use of a lipid-lowering agent.
A history of diabetes mellitus was associated with increased
DWML burden (mean ± SD DWML burden of 14.1 ± 1.9 for
subjects with diabetes mellitus vs 12.6 ± 3.5 for nondiabetics),
although this relationship remained only a trend (\( P = .09 \)) after controlling for

<table>
<thead>
<tr>
<th>Feature</th>
<th>Nondemented Aging (n = 88)</th>
<th>Early-Stage Alzheimer Disease (n = 68)</th>
<th>P Value</th>
<th>Total Cohort (N = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>76.9 ± 8.2</td>
<td>77.4 ± 7.1</td>
<td>.68</td>
<td>77.2 ± 7.7</td>
</tr>
<tr>
<td>Female sex</td>
<td>62 (70.5)</td>
<td>38 (55.9)</td>
<td>.06</td>
<td>100 (64.1)</td>
</tr>
<tr>
<td>Educational achievement, y</td>
<td>14.6 ± 2.9</td>
<td>13.3 ± 3.1</td>
<td>&lt;.01</td>
<td>14.0 ± 3.1</td>
</tr>
<tr>
<td>Mini-Mental State Examination score</td>
<td>29.0 ± 1.2</td>
<td>24.2 ± 3.8</td>
<td>&lt;.001</td>
<td>26.9 ± 3.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35 (39.8)</td>
<td>28 (41.2)</td>
<td>.95</td>
<td>63 (40.4)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>135.8 ± 19.2</td>
<td>143.0 ± 21.1</td>
<td>&lt;.05</td>
<td>138.9 ± 20.3</td>
</tr>
<tr>
<td>Diastolic</td>
<td>72.2 ± 10.3</td>
<td>74.4 ± 10.4</td>
<td>.22</td>
<td>73.2 ± 10.4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (11.4)</td>
<td>6 (8.8)</td>
<td>.61</td>
<td>16 (10.3)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>30 (34.1)</td>
<td>24 (35.3)</td>
<td>.82</td>
<td>54 (34.6)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>36 (40.9)</td>
<td>30 (44.1)</td>
<td>.84</td>
<td>66 (42.3)</td>
</tr>
<tr>
<td>Apolipoprotein E genotype†</td>
<td>21/76 (27.6)</td>
<td>31/56 (55.4)</td>
<td>&lt;.001</td>
<td>52 (39.4)</td>
</tr>
<tr>
<td>Lipid-lowering agent</td>
<td>26 (29.5)</td>
<td>12 (17.6)</td>
<td>.09</td>
<td>38 (24.4)</td>
</tr>
<tr>
<td>Deep WML burden‡</td>
<td>12.4 ± 3.0</td>
<td>13.3 ± 3.7</td>
<td>.12</td>
<td>12.8 ± 3.4</td>
</tr>
<tr>
<td>Periventricular WML burden‡</td>
<td>7.5 ± 4.2</td>
<td>9.5 ± 4.6</td>
<td>&lt;.01</td>
<td>8.4 ± 4.5</td>
</tr>
<tr>
<td>Infarctlike lesion prevalence</td>
<td>36 (40.9)</td>
<td>30 (44.1)</td>
<td>.69</td>
<td>66 (42.3)</td>
</tr>
</tbody>
</table>

Abbreviation: WML, white matter lesion.
*Data are given as mean ± SD or as number (percentage) unless otherwise indicated.
†Apolipoprotein E genotype represents subjects with 1 or more alleles.
‡Semiquantitative burden, with higher scores representing more WMLs.
hypertension. Using Spearman rank correlation analyses, systolic and diastolic blood pressures were not associated with DWML or PVWML burden. Deep WML and PVWML burdens were highly correlated ($r = 0.64$, $P < .001$).

**WMLs AND COGNITION**

Table 2 summarizes the relationship between WMLs and global cognition in nondemented aging and early-stage AD after adjusting for confounding variables of age, educational achievement, brain atrophy, and infarctlike lesions. In the AD group, DWMLs and PVWMLs were related to the cognitive factor score, the primary measure of global cognition. Adding hypertension and apolipoprotein E genotype to the model did not change the results. This relationship between WMLs and cognition was absent in the nondemented aging group. A PVWMLs × AD status interaction effect was present for the cognitive factor score ($P < .01$), indicating that the relationship between PVWMLs and cognition is different across groups (Figure 4). This interaction remained present after adjusting for age, education, brain atrophy, and infarctlike lesions ($P < .01$). There was no interaction effect for DWMLs × AD status for the cognitive factor score. Performance on secondary measures of global cognition, the MMSE and the Short Blessed Test, was related to PVWMLs but not DWMLs in participants with AD.

Given that the cognitive factor score combines performance on multiple psychometric tasks, we further examined the relationship between WMLs and performance on specific cognitive tasks (Table 2). Results of these analyses indicate that the observed relationship between overall global cognitive impairment and WMLs in early-stage AD was driven primarily by reductions in visual memory, processing speed, and executive function. In nondemented aging, PVWMLs were modestly associated with reduced associate memory and processing speed (Crossing-off), although multiple comparisons increase the risk of spurious associations. In nondemented aging, deep WMLs were not associated with performance on any measures.

**COMMENT**

Our results suggest that WMLs are prevalent in nondemented aging and in early-stage AD and that the earliest clinical stages of AD are influenced by the presence of...
WMLs, independent of brain atrophy and infarctlike lesions. The cross-sectional nature of our study limits the ability to infer causality, but the results suggest that individuals in the early stages of AD may be more vulnerable to the cognitive influence of WMLs than non-demented aging individuals. Pathological studies demonstrate that AD and vascular-related lesions interact to increase the likelihood of expressing clinically significant cognitive decline. Our results conceptually replicate and extend these pathological observations by providing neuroimaging evidence suggesting that the co-occurrence of AD and vascular-related lesions is associated with greater cognitive impairment than either condition alone. The most parsimonious explanation is that WMLs are distinct from pathological changes associated with AD but, when combined with AD pathological changes, increase the level of cognitive impairment.

### Table 2. Relationship Between Global Cognition and White Matter Lesions (WMLs)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Nondemented Aging</th>
<th>Early-Stage Alzheimer Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive factor score</td>
<td>−.12</td>
<td>−.32†</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>.07</td>
<td>−.18</td>
</tr>
<tr>
<td>Short Blessed Test</td>
<td>.07</td>
<td>.27 (P = .08)</td>
</tr>
<tr>
<td>Specific cognitive tasks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wechsler Memory Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logical Memory, immediate</td>
<td>−.12</td>
<td>−.15</td>
</tr>
<tr>
<td>Logical Memory, delayed</td>
<td>−.13</td>
<td>−.08</td>
</tr>
<tr>
<td>Associate Memory</td>
<td>.18</td>
<td>−.05</td>
</tr>
<tr>
<td>Digit Span Backward</td>
<td>.01</td>
<td>−.27 (P = .06)</td>
</tr>
<tr>
<td>Benton Visual Retention Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Form C</td>
<td>.02</td>
<td>−.42§</td>
</tr>
<tr>
<td>Form D</td>
<td>−.01</td>
<td>−.22</td>
</tr>
<tr>
<td>Wechsler Adult Intelligence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scale–Revised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information</td>
<td>−.10</td>
<td>−.30†</td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>−.03</td>
<td>−.24†</td>
</tr>
<tr>
<td>Block Design</td>
<td>−.10</td>
<td>−.12</td>
</tr>
<tr>
<td>Trail-Making Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>.20</td>
<td>26†</td>
</tr>
<tr>
<td>B</td>
<td>.11</td>
<td>.15</td>
</tr>
<tr>
<td>Crossing-off</td>
<td>−.21 (P = .07)</td>
<td>−.22 (P = .07)</td>
</tr>
<tr>
<td>Word Fluency (letters s and p)</td>
<td>.07</td>
<td>−.26†</td>
</tr>
<tr>
<td>Animal Naming Test</td>
<td>−.03</td>
<td>−.40†</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>−.12</td>
<td>−.36†</td>
</tr>
</tbody>
</table>

*Data are given as standardized β values, representing the correlation of the WML burden with each cognitive measure after adjusting for age, educational achievement, brain atrophy, and infarctlike lesions. P values in parentheses represent trends.

†P < .01.
‡P < .05.
§P < .001.

Figure 4. The relationship between periventricular white matter lesion (WML) burden and cognition differs in nondemented aging vs early-stage Alzheimer disease (AD). In the early stages of AD, increased periventricular WML burden was associated with decreased cognition, while no significant relationship was observed in nondemented aging. Regression lines before controlling for age, education, and other neuroimaging variables represent Pearson product moment correlation r = −0.21 (P = .05) in nondemented aging and r = −0.35 (P = .004) in early-stage AD.

WMLs, independent of brain atrophy and infarctlike lesions. The cross-sectional nature of our study limits the ability to infer causality, but the results suggest that
tion, a valid biomarker of AD neuropathological changes, hippocampal volume, predicts the development of poststroke dementia and is the most predictive magnetic resonance imaging correlate of cognitive function in participants with subcortical ischemic vascular disease. Our data suggest that vascular dementia criteria requiring the combined presence of cognitive impairment and cerebrovascular disease may introduce a systematic selection bias for individuals most vulnerable to the cognitive effect of vascular-related injury, such as those with concomitant early neuropsychological changes of AD.

The differential relationship between WMLs and cognition in nondemented aging and in early-stage AD may be related to the phenomenon of cognitive reserve. The theory of cognitive reserve postulates the existence of protective factors to account for the observation that some individuals are resilient to the clinical expression of brain lesions, while others are not. Proposed markers of cognitive reserve include higher education levels, occupation, brain size, and functional imaging measures. The presence of early-stage AD neuropathological changes in the brain may reduce the brain's ability to compensate for the presence of WMLs and, in turn, accentuate the relationship between WMLs and cognition.

Inconsistencies in the literature regarding the association between WMLs and cognition are in part related to differences in study methods (ie, WML assessment and patient characteristics), as well as differences in data analysis. For instance, in our primary analysis (Table 2), the volumetric measure of brain atrophy was comparable to WMLs in predicting general cognition (brain atrophy $\beta = .39$ in the DWML model vs $\beta = .36$ in the PVWML model). This seems inconsistent with recent findings that hippocampal and gray matter volumes are stronger predictors of cognition than WMLs. That report, however, differed from ours because it assessed a cohort combining nondemented subjects and cognitively impaired individuals with subcortical ischemic vascular disease, while our primary analysis was confined to single groups of subjects with nondemented aging or early-stage AD. Combining our nondemented aging and AD groups (data not shown), we found similar results, with whole-brain atrophy as the strongest predictor of cognition ($\beta = .50$), while WML associations were weaker (DWML $\beta = -.27$ and PVWML $\beta = -.30$) ($P < .001$ for all). Therefore, well-defined differences in brain volume between controls and subjects with AD are likely responsible for the greater explanatory value of volumetric measures with cognition when analyses are conducted on combined control and AD groups. Conversely, confining the analysis to either group (ie, controls or AD) may result in reduced variability that might attenuate the demonstration of structural-functional relationships. Nevertheless, WML burden appears to be inversely related to cognitive performance, and our data suggest that this relationship is accentuated in AD.

This study has several limitations. The cross-sectional observational nature of the study limits the ability to infer causality. We plan to extend our findings with longitudinal analyses to determine the relative effect of WML progression on cognition. The sample consists of research participants who may not be representative of the general population. The imaging protocol did not include proton density scans, complicating the differentiation of infarctlike lesions from perivascular spaces. The slightly higher prevalence of infarctlike lesions in our sample (42.3%) compared with that reported in the literature (≤33%) may be related in part to possible inclusion of perivascular spaces as infarctlike lesions. We subjected all suspected infarctlike lesions to a second level of review, and our results are consistent with the literature in terms of clinical associations (ie, hypertension). In addition, our imaging protocol provides high-resolution images that increase the sensitivity of detecting abnormal signals. Any difficulty in distinguishing perivascular spaces from infarctlike lesions or WMLs would be likely to attenuate associations with cognition. Furthermore, our T2-weighted sequence has a long repetition time, which may affect our ability to detect the full spectrum of WMLs. As in any study in which multiple analyses are performed on the same data, there is an increased chance of type I errors and spurious observations. The probability of a type I error is most likely for tests resulting in $P$ values that are close to .05, and the likelihood decreases with decreasing $P$ values. Last, we used clinical methods as the gold standard for determining a diagnosis of AD. Although these clinical criteria have been validated and are highly accurate, they remain imperfect in predicting pathological changes in AD.

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Author Contributions: Study concept and design: Burns and Buckner. Acquisition of data: Burns, Church, and Buckner. Analysis and interpretation of data: Burns, Church, Johnson, Xiong, Marcus, Fotenos, Snyder, Morris, and Buckner. Drafting of the manuscript: Burns. Critical revision of the manuscript for important intellectual content: Burns, Church, Johnson, Xiong, Marcus, Fotenos, Snyder, Morris, and Buckner. Statistical analysis: Burns, Johnson, and Xiong. Obtained funding: Morris and Buckner. Administrative, technical, and material support: Church, Marcus, Fotenos, Snyder, Morris, and Buckner. Study supervision: Burns, Morris, and Buckner.

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