Regional White Matter Pathology in Mild Cognitive Impairment
Differential Influence of Lesion Type on Neuropsychological Functioning

Lisa Delano-Wood, PhD; Norm Abeles, PhD; Joshua M. Sacco, PhD; Christina E. Wierenga, PhD; Nikki R. Horne, MS; Andrea Bozoki, MD

Background and Purpose—Associations between regional white matter lesion pathology and neuropsychological performance across the aging spectrum are not well understood and, to date, research has been largely contradictory and inconclusive. The current study set out to clarify some of the inconsistencies in the literature by relating volumetric analyses of white matter lesions (deep white matter lesions and periventricular lesions) to neuropsychological performance in a large clinical sample of older adults diagnosed with mild cognitive impairment.

Methods—Seventy older adults with mild cognitive impairment were administered a comprehensive neuropsychological battery. White matter lesions identified on T2-weighted FLAIR images were quantified using a semi-automated volumetric approach (pixel thresholding).

Results—Results showed that, in contrast to performance on memory and naming tasks, total white matter lesions strongly predicted executive impairments, slowed processing speed, and visuospatial/construction difficulties. In addition, separate regression analyses demonstrated that results were primarily accounted for by deep white matter lesions (but not periventricular lesions), most likely due to frontal-subcortical circuitry disruption. Moreover, deep white matter lesions, but not periventricular lesions, significantly predicted overall poorer neuropsychological functioning after controlling for age, education, and level of depression.

Conclusions—Taken together, findings demonstrate a differential influence of lesion type on cognitive impairment in mild cognitive impairment and implicate deep white matter lesions as being most detrimental in terms of neuropsychological functioning. Clinical, theoretical, and methodological implications of these results are discussed. (Stroke. 2008;39:794-799.)

Key Words: cognition ■ deep white matter lesions ■ mild cognitive impairment ■ white matter hyperintensities ■ white matter lesions

Considered to be rare before the advent of MRI, white matter lesion (WML) pathology is now receiving considerable attention with respect to the understanding of neurobehavioral decline seen in aging and dementia. WMLs appear to be related to chronic microvascular disease and hypoperfusion, and they are known to increase with age. In addition, WML pathology is commonly seen in Alzheimer disease, and recent studies have shown that they appear to increase the risk of developing dementia. However, the role of WML in the pathology or disease severity of dementia has not been clearly established and whether WMLs represent a pathognomonic sign for brain disease remains a matter of debate.

Over the past several years, many studies have attempted to elucidate the neuropsychological significance of WML in healthy aging and dementia; however, for the most part, results have been mixed and unclear. For example, some recent studies have shown associations of WML and cognitive impairment in normal aging, particularly on tests that measure processing speed, whereas earlier studies have demonstrated no relationship between WML and cognition. Similarly, results from some studies have found significant correlations between WML and neuropsychological functioning in Alzheimer disease; however, other reports suggest no relationship among WML, cognition, and dementia severity. Thus, the association of WML with cognitive impairment in normal aging and dementia is still not fully elucidated. Discrepant findings may be due to numerous factors, including the use of insensitive measures of neuropsychological functioning, differential sensitivity of MRI methodologies, and inclusion of samples with a broad range of cognitive functioning.

Conflicting findings across the aging spectrum, particularly in the earliest clinical stages of Alzheimer disease, highlight...
the critical need for better characterization of white matter changes seen in mild cognitive impairment (MCI), a transitional stage between normal and demented aging that is based on a pathological model of cognitive change. However, although studies of MCI have been increasingly prevalent in the literature, few have examined WML within this population. Recently, Kumar et al reported that WMLs were not related to cognitive impairment in their MCI sample. However, the authors’ definition of MCI was restricted to memory impairment, and the authors acknowledge that their sample was younger and healthier than most MCI samples. Both of these factors may have attenuated any associations between WML and cognition. Mendonca et al also reported no association between neuropsychological impairment and WML in their MCI sample; however, authors of this study also applied MCI diagnostic criteria based solely on memory performance. In addition, WML was measured as a dichotomous variable (either present or absent) on the basis of CT scans, which are relatively insensitive to white matter abnormalities. In a recent volumetric study, van der Flier et al reported a significant relationship of WML with cognition (psychomotor speed, naming, and memory abilities); however, regional measures of WML (periventricular lesions [PVLs] and deep white matter lesions [DWMLs]) were not delineated, thus precluding any investigation of differential neuropsychological associations between these 2 lesion types. Overall, of the existing studies examining WML within MCI, many suffer from low sample sizes; a failure to distinguish between lesion types; MCI criteria that require specific memory impairment; and the use of visual rating scales versus more reliable volumetric methods in the quantification of WML burden. Furthermore, many studies of WML in MCI have not examined associations with neuropsychological functioning.

Bowler and Hachinski have argued that both types of WML should be analyzed separately, and this appears to be critically important given recent suggestions that PVL and DWML may differ in their pathogenesis and clinical significance. Recently, an immunohistochemistry study by Simpson et al showed that the lesion types differ in their cellular pathology. Specifically, the authors demonstrated PVLs appear to be primarily associated with cerebrospinal fluid leakage into the white matter and subsequent loss of ependymal lining in the ventricles. In contrast to PVLs, which appear to be most strongly related to age, DWMLs seem to be reflective of underlying vascular risk and the presence of vascular disease. Despite a call for studies to investigate both types of WML, few studies have made this differentiation. Given this, coupled with the lack of studies that have examined WML in MCI, the primary aims of this study were to (1) explore the relationship between WML and cognition in a heterogeneous MCI sample; and (2) characterize specific patterns of cognitive impairment associated with both PVL and DWML. It is expected that increased WML volumes will be associated with greater overall cognitive impairment and, in contrast to DWML, PVL will be more strongly related to age. In addition, given that DWML may interrupt critical neuropsychological pathways that facilitate complex neuropsychological functioning, we hypothesized that DWML, but not PVL, will be associated with greater overall neuropsychological impairment, particularly in cognitive domains thought to be dependent on frontal–striatal circuits (executive functioning, processing speed, and visuospatial/construction).

Materials and Methods

Participants

Data were obtained from a clinical sample of 70 older adults who were recruited from the Michigan State University Geriatric Neurology Clinic, an outpatient subspecialty of the Michigan State University Neurology and Radiology Department. Participants were excluded from the study if there was any evidence of current or past diagnoses of neurological or psychiatric disorder, stroke, thyroid disease, diabetes, known head injury, or any significant visual or auditory impairment that precluded them from participating in neuropsychological testing. All participants provided written informed consent and the procedures in the present study were approved by the Michigan State University Committee on Research Involving Human Subjects.

Materials and Procedures

A diagnosis of MCI was based on the following criteria recently defined by Petersen and Morris: (1) subjective patient memory complaints; (2) normal activities of daily living; (3) absence of dementia; (4) Mini-Mental State Examination score of 24 or greater; and (5) mild quantifiable cognitive impairment. Although no reliable cutoff for defining impairment in MCI has yet been delineated, Busse et al demonstrated that a more liberal cutoff (ie, 1 SD below the mean) is optimal because it offers higher sensitivity than the traditional cutoff of 1.5 SD. Thus, given our aim to be broadly inclusive, we attempted to compromise using a cutoff of 1.2 SD (after applying norms adjusted for age, education, and gender), signifying a level of performance worse than 88.5% of the population (indicative of mild to moderate impairment). All neuropsychological scores were standardized with a z-score transformation on the
basis of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) or other normative data of the neuropsychological tests.\textsuperscript{30} Scores that reflected number of errors or response times were multiplied by \(-1\) so that negative z-scores consistently reflected poor performance. All participants were categorized into 4 subgroups (single-domain amnestic MCI, \(n = 12\); single-domain nonamnestic MCI, \(n = 12\); multiple-domain amnestic MCI, \(n = 28\)); and multiple-domain nonamnestic MCI, \(n = 18\)) based on neuropsychological test scores.\textsuperscript{28}

**Neuropsychological Test Battery**

Neuropsychological classification of MCI was conducted independently of the WML quantitative analyses and all cognitive tasks were administered to each participant individually by a technician who was blind to the participant’s medical status and MRI results. In addition to the Mini-Mental State Examination (MMSE)\textsuperscript{31}, a general measure of overall cognitive status, participants were administered the CERAD\textsuperscript{30}, a reliable, well-standardized battery that includes 7 individual tests designed to tap several domains, including memory, praxis/visuospatial construction, and language. Specific CERAD tasks included verbal fluency (animal fluency), object naming (15 items); constructional praxis (figure copying), and memory tests (word list learning, delayed free recall, and recognition). Delayed visual memory was assessed by recall of geometric figure presented earlier. The CERAD was designed to detect impairment in mildly impaired populations, and recent studies have begun to use the battery in their MCI diagnosis determination.\textsuperscript{32,33} To strengthen our diagnostic populations, and recent studies have begun to use the battery in their memory was assessed by recall of geometric figure presented earlier.

**MRI Protocol and Quantification of White Matter Lesions**

All MRI was performed on a 1.5-T Signa scanner (General Electric, Milwaukee, Wis) and WML volumes were estimated from T2-weighted axial fluid-attenuated inversion recovery (FLAIR) images (field of view=20×20 cm; matrix=256×256; flip angle=90°, TE=142 ms, TR=10000 ms, 5-mm slice thickness with no interslice gap). A semiautomated volumetric approach was used using the FLAIR images, a methodology recently shown to be the most reliable approach for the analysis of WML when compared with other image types and traditional quantitative visual rating scales.\textsuperscript{37} WML volumes were obtained based on 17 to 21 axial images per subject using GE’s Advantage Workstation software (version 4.2) and WMLs were measured according to protocols established elsewhere.\textsuperscript{1,3} Hyperintense regions, defined as circumscribed areas of increased signal intensity within the white matter, were measured on axial slices beginning at the most inferior slice on which the inferior horn of the lateral ventricles could be seen. WMLs were coded according to their presence, volume, and type (PVL and DWML). If the largest diameter was adjacent to the ventricular lining, WML were considered to be PVL; otherwise, they were considered to be in the deep white matter. All questionable cases were resolved by consulting an experienced neuroradiologist.

Because two operators completed the WML measurements, inter-rater reliability coefficients were computed based on a random sample of 5 traced brains. The intraclass correlation formula for 2 random raters\textsuperscript{38} was used, and the resulting reliability estimates for all regions of interest and types of WML exceeded 0.85. As described in detail by Raz et al,\textsuperscript{1} the total volume of each region in cubic centimeters was calculated by multiplying the summed pixel cross-sectional area in square centimeters by slice thickness in centimeters, and WML volumes were normalized to the intracranial cavity volume for each participant. See the Figure for an illustration of WML measurement on an axial slice of a randomly chosen participant’s FLAIR.

**Statistical Analyses**

Composite scores were computed for memory (CERAD word list delayed and visual memory scores; \(r = 0.38, P < 0.05\)) as well as executive functioning (Trail B and the Stroop Color–Word Test Interference score; \(r = 0.69, P < 0.001\)). Significant correlations between the tests that comprise each composite score supported this approach. Given a recent study that demonstrated that the CERAD word list learning trials are associated with low sensitivity and specificity in MCI,\textsuperscript{39} this particular subtest was omitted from our memory composite score. In addition, a composite variable was computed from the means of all neuropsychological tests to evaluate the relationship between WML and overall neuropsychological functioning (NP). Pearson product-moment correlations and multiple hierarchical regressions were used to examine the role of WMLs on cognitive functioning and to further characterize the independent role of PVL and DWML on cognitive performance. Finally, when appropriate, adjustments for multiple comparisons were made in the reported analyses. All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, 2004).

**Results**

Table 1 provides descriptive statistics and intercorrelations for demographic and clinical variables of interest for the sample. As can be expected, higher age was associated with lower scores on the MMSE (\(r = -0.39, P < 0.05\)) as well as poorer overall neuropsychological functioning (NP; \(r = -0.41, P < 0.05\)). In addition, as can be seen in Table 2, age was positively associated with PVL (\(r = 0.27, P < 0.05\)) but was not significantly related to DWML (\(r = 0.15, P > 0.05\)). For the analyses presented subsequently, MCI subgroups were collapsed across groups given that they did not differ significantly in terms of any WML index (total WML, DWML, or PVL). However, qualitatively, the multiple-domain nonamnestic group demonstrated the highest volumes of total WML and DWML.

<table>
<thead>
<tr>
<th>Table 1. Descriptives and Intercorrelations Among Demographic Variables for MCI Sample</th>
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<tbody>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Education</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
</tr>
<tr>
<td>MMSE</td>
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<tr>
<td>Overall NP</td>
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</tbody>
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Note: Mean for total NP=0 because this variable represents a composite score. Sex: females coded 1, males coded 0. N=70.

*\(P<0.05\).
Table 2. Bivariate Correlations Between WML and Demographic, Clinical, and Neuropsychological Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>PVL</th>
<th>DWML</th>
<th>Total WML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.27*</td>
<td>0.15</td>
<td>0.21</td>
</tr>
<tr>
<td>Sex</td>
<td>0.01</td>
<td>0.18</td>
<td>0.10</td>
</tr>
<tr>
<td>Education</td>
<td>−0.12*</td>
<td>−0.35*</td>
<td>−0.33*</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
<td>0.42†</td>
<td>0.56‡</td>
<td>0.52†</td>
</tr>
<tr>
<td>MMSE</td>
<td>−0.39</td>
<td>0.07</td>
<td>−0.03</td>
</tr>
<tr>
<td>VS (figure copying)</td>
<td>−0.38</td>
<td>−0.44†</td>
<td>−0.35†</td>
</tr>
<tr>
<td>Trail A</td>
<td>−0.20</td>
<td>−0.37*</td>
<td>−0.29*</td>
</tr>
<tr>
<td>BNT</td>
<td>−0.15</td>
<td>−0.05</td>
<td>−0.09</td>
</tr>
<tr>
<td>Fluency (animals)</td>
<td>−0.21</td>
<td>−0.18</td>
<td>−0.20</td>
</tr>
<tr>
<td>Memory</td>
<td>−0.12</td>
<td>−0.09</td>
<td>−0.11</td>
</tr>
<tr>
<td>EF</td>
<td>−0.42‡</td>
<td>−0.56‡</td>
<td>−0.51†</td>
</tr>
</tbody>
</table>

Note: N=70. Correlations between WML variables (PVL, DWML, and total WML) and neuropsychological variables (MMSE, VS, Trail A, BNT, Fluency, Memory, and EF) are adjusted for age, sex, education, and depression. PVL indicates Visuospatial/Construction; BNT, Boston Naming Test; EF, Executive Functioning (composite score).

*P<0.05. †P<0.01.

The sample as a whole demonstrated slightly higher levels of DWML versus PVL (DWML: mean=5.3, SD=3.4; PVL: mean=2.3, SD=2.4). Although no relationship was found between total WML volume and MMSE performance (r=−0.03, P>0.05), poorer overall NP was significantly related to total WML burden (r=−0.36, P<0.05), PVL volume (r=−0.33, P<0.05), and DWML volume (r=−0.44, P<0.05). Linear regression analysis was performed to determine if total WML and specific lesion types (DWML and PVL) accounted for a significant amount of variance in neuropsychological test performance (eg, whether WML volumes were predictive of cognition). Results showed that total WML significantly predicted overall NP after controlling for age, education, gender, and depression (β=−0.53; ΔR²=0.22, P<0.02). After adjusting for multiple comparisons and important demographic variables (age, gender, education, and depression), separate linear regression analyses demonstrated that total WML was strongly predictive of executive functioning (β=−0.63; ΔR²=0.22, P<0.001), processing speed (β=−0.54; ΔR²=0.16, P<0.001), and visuospatial/construction (β=−0.44; ΔR²=0.12, P=0.004).

Given the high correlations between the predictors (PVL and DWML; r=0.74, P=0.001), separate regressions were conducted on each lesion type. Age, education, gender, and depression were entered into the first block and lesion type was entered in block 2. Results showed that PVL volume did not significantly add to the prediction of overall NP functioning (ΔR²=0.009, P>0.05). However, the prediction of overall NP functioning incremental to that of the predictors in step 1 was significant for DWML (ΔR²=0.043, P<0.001). A series of standard multiple regressions were performed with DWML entered as the independent variable and each of the neuropsychological variables as dependent variables after controlling for age, education, gender, and depression. As expected, DWML strongly predicted poorer executive functioning (β=−0.65; ΔR²=0.25, P<0.001), Trail A (β=−0.56, ΔR²=0.18, P<0.001), and visuospatial/construction (β=−0.53, ΔR²=0.17, P<0.001). However, DWML was not found to significantly predict naming or memory (all probability values >0.05). The same series of multiple regressions were then performed with PVL entered as the dependent variable. After controlling for age, education, gender, and depression, PVL was not predictive of performance on any neuropsychological variables.

Discussion

This study set out to examine the relationship between WML and cognition in a heterogeneous group of older adults diagnosed with MCI. Results demonstrate that DWML, but not PVL, strongly predicted performance on tests of executive functioning, speed of processing, and visuospatial/constructional skills after adjusting for important demographic variables. In contrast, DWML did not predict performance on tests of verbal memory or language. Given these results, coupled with the strong associations reported in the literature among DWML, microangiopathy, and hypoperfusion,6 it may be that early manifestations of vascular cognitive impairment associated with DWML lead to dysexecutive deficits in cognition thought to be dependent on the integrity of frontal–subcortical circuits.40 Indeed, DWMLs are more frequently identified at the level of the dorsolateral prefrontal cortex, and concomitant cognitive deficits may be the result of small vessel disease disrupting frontal–subcortical pathways.41 Our results are consistent with other recent studies that have shown that PVL, but not DWML, may represent an age-related phenomenon.5,21 Overall, our results corroborate the hypothesis that these 2 lesion types may differentially impact clinical presentation, and additional research is needed to more clearly elucidate whether WML subtypes arise from dissociable paths of pathogenesis.

Our findings stand in contrast to some earlier studies examining the effect of lesion types on cognitive functioning in aging populations.7,9,23 For example, although the majority of our results are similar to those of Prins et al.,7 we did not find a relationship between PVL or DWML and memory performance. Prins and colleagues administered a much more difficult test of verbal memory (15-word verbal learning test), which may have been more sensitive than the memory measure that we used. It is thus plausible that our lack of findings in terms of memory performance is linked to ceiling effects. In addition, in contrast to our findings, other studies have demonstrated that PVLs, but not DWMLs, are related to cognitive impairment, particularly processing speed.7,42 Possible explanations for differing findings between their results and ours include methodological differences in terms of sample selection, imaging techniques, and WML quantification.

Similar to other studies that have not found associations between WML and measures of global cognition,9,44 our results indicated that total WML volume was not associated with MMSE performance. It is known that the MMSE is not sensitive to subtle neuropsychological impairment and the measure largely taps verbal and memory functions, cognitive domains that are not typically related to WML. These results suggest that studies investigating the relationship between...
WML and cognition may fail to find a significant association if only brief screening measures are used. Future studies should select, a priori, neuropsychological measures that tap domains known to be sensitive to white matter changes (e.g., speed of processing and executive function).

To our knowledge, the results presented here represent one of the few existing studies to associate volumetric analyses of WML subtypes and neuropsychological impairment in a large, heterogeneous clinical sample of patients with MCI. It should be noted, however, that some of the neuropsychological measures used in this study were designed as screening instruments in the assessment of cognitive deficits of aging and disease. Thus, the range of neuropsychological performance was likely restricted, and this may have resulted in less sensitivity to detect brain–behavior relationships. In addition, the current study used a volumetric methodology in the measurement of WML burden and thus little can be inferred regarding the extent and pattern of microstructural white matter changes in the pathology of MCI. Moreover, we did not use a measure of vascular burden or stroke risk, and future studies are needed to further clarify the association between vascular risk and WML subtypes. However, given that the selection criteria restricted the range of white matter abnormalities observed in this study, these results may represent a conservative estimate of the role of WML in MCI.

Summary
The results of this study indicate that, when controlling for the effects of age, education, gender, and depression, DWMLs (but not PVLs) appear to be associated with specific neuropsychological deficits dependent on frontal–subcortical circuitry, including executive functioning, processing speed, and visuospatial/construction. Future studies should attempt to disentangle the effects of vascular pathology, aging, and early Alzheimer disease pathology on the relationship between WML and neuropsychological functioning. In addition, the use of newer techniques such as diffusion tensor imaging should aid in better identification of white matter pathology across the aging spectrum. Finally, given the imaging should aid in better identification of white matter lesions in patients with early Alzheimer disease pathology on the relationship between WML and neuropsychological functioning should aid in better identification of white matter lesions in patients with early Alzheimer disease pathology.

Discussion
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Disclosures
None.

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