Single and Combined Effects of Cerebral White Matter Lesions and Lacunar Infarctions on Cognitive Function in an Elderly Population

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Background. This study is to investigate the association between single and combined vascular brain changes (white matter lesions [WMLs], lacunar infarctions) and the cognitive domains of memory, processing speed, and motor function in the elderly adults.

Methods. In a sample of 268 participants aged 65–83 years of the MEMO (Memory and Morbidity in Augsburg Elderly) population-based study in Augsburg, Germany, cerebral magnetic resonance imaging (MRI) was performed and a detailed neuropsychological test battery applied. Analysis of covariance determined the effects of vascular brain changes on domains of cognitive functioning.

Results. Strong associations of large WMLs and of MRI-defined lacunar infarction with three different domains of cognitive function even after adjustment for age, gender, and education were found. The combined occurrence of both lesions affected about one in 10 participants and was associated with a strong decrease in cognitive function in all domains. The difference between the groups with only one lesion type (either large WMLs or MRI-defined infarction) and participants affected by both was significant in the domains of processing speed and memory, even after adjustment for important confounders such as age, gender, education, and comorbidities. The effects of both lesion types on cognitive function were not more than additive.

Conclusions. Our study shows that both large WMLs and MRI-defined lacunar infarction contribute to impairments in different cognitive domains. The results suggest that their combined occurrence is associated with stronger reductions in cognitive function than each of the two brain lesion types alone.

Key Words: White matter lesions—Brain infarcts—Cognitive function—Elderly.

Common age-related changes such as subcortical lesions of the white matter (WMLs) are observed on magnetic resonance imaging (MRI) of the brain of healthy older individuals and in patients with neurodegenerative diseases, for example, dementia (1,2). White matter lesions (WMLs) increase in prevalence with age and may have a vascular etiology (3). With few exceptions (4), studies report that increased WML load correlates with cognitive impairment (5,6), but studies disagree as to the size of the effect and the cognitive domains involved (4). Among the cognitive functions that seem to be affected by WMLs, speed and attention appear particularly impaired (7–9), although impairment in memory and executive and motor function also has been reported (5,8,10,11).

WMLs are often related to other morphologic changes detectable by brain imaging such as lacunar infarctions (12). The combined appearance of WMLs and lacunar infarctions is conceptualized as cerebral small-vessel disease (13). Recent clinical studies in hospitalized patients with acute stroke due to lacunar infarctions found that the WMLs appear to be mostly associated with executive dysfunction (14,15).

Although consequences of WMLs and lacunar infarctions have been examined in several studies (16–20), it is still unclear if their impact on cognitive performance differs between their single and combined occurrence in an elderly individual. First evidence suggested that WMLs and lacunar infarctions were independently associated with general cognitive function in a sample of independently living elderly adults; however, this research was limited by the use of a general cognitive measures (Mini-Mental State Examination, MMSE) rather than specific cognitive domains (21). The clinical relevance especially of the frequent punctuate lesions or those of moderate size (22) is also a matter of debate. Further, it is unknown if WMLs and lacunar infarctions cause impairments in different cognitive domains.

The aim of this study was to investigate the association between single and combined vascular brain changes (WMLs and lacunar infarctions) and the cognitive domains of memory, processing speed, and motor function in a population-based study of the elderly adults.

Materials and Methods

Design

The MEMO Study (Memory and Morbidity in Augsburg Elderly) (23) is a follow-up project of the 1989–1990 World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease Project, Augsburg, Germany (24).
restricted to participants 65 years or older. Sampling of participants in MEMO was done by age groups (65–69, 70–74, and 75+) to represent a broad age range between 65 and 83 years. The overall response rate among those eligible was 60.6%, yielding a total of 385 participants of whom 268 received an MRI scan without contraindications. Informed consent was obtained from all study participants. The study was approved by the Ethics Committee of the University of Münster, Germany.

Measurements
Participants were assessed with a standardized face-to-face interview including a comprehensive neuropsychological test battery and a standardized neurological examination by trained physicians. Depressive symptoms were assessed using the Center for Epidemiologic Studies—Depression scale, a 20-item, self-report scale designed to measure depressive mood experienced during the previous week (25). Considering characteristics of the German education system, 10 years of education (years at school plus years on special job training) was regarded as standard and more than 10 years as higher education.

Cognitive Test Battery
The cognitive test battery consisted of tests assessing short-term memory, attention, cognitive motor speed and is described in detail elsewhere (26–28). In brief, measures of immediate recall were derived from the 3-word recall tests on the basis of the Tulving and Colotla lag measures (29) that were used in the Betula Study (30). Higher test results in the recall tests are associated with better memory performance. Word fluency was assessed by the use of the production component of the semantic memory test (31,32). Lower scores in this test of word fluency are regarded as an indication of poorer cognitive performance.

Tasks from the Stroop color-word-tests were used for assessing speed, attention, and executive functioning (Stroop subtest III) in the present study (33). More time needed to perform the Stroop test is associated with lower cognitive performance.

The Letter-Digit-Substitution Test (34) was another task that was included to assess processing/cognitive speed and attention (35). Lower values were regarded as an expression of lower cognitive capability.

A test of motor speed, the Purdue Pegboard test (36–38) was included as a tool to assess processing and central executive functions. Lower values were assumed as poorer motor speed.

MRI Scans
MRI scanning was performed in 268 participants (69%) without contraindications. In all, 117 individuals did not receive an MRI due to contraindications (artificial eye lenses or incorporated metal artifacts including pace maker, n = 69), claustrophobia (n = 16), dissent (n = 11), or other reasons (n = 21). MEMO participants with MRI were significantly younger (mean age 72.3 vs 73.7) than those without MRI. All MRI scans were performed on a Phillips 1.5-T machine at the Department of Radiology and Neuroradiology, Central Hospital of Augsburg. The MRI protocol included proton density (PD) and T1- and T2-weighted images acquired with spin echo sequences with 20 axial slices, 5- or 6-mm thick with an interslice gap of 1 or 1.2 mm, respectively. MRI reading was done by a single reader using an established rating scale (39,40). A detailed description of the reading protocol which is also used by the Rotterdam Study is described elsewhere (41). In brief, WMLs were focal signal hyperintensities on PD and T2-weighted scans, which were not seen or exhibited only faint hypointensity on T1-weighted images. Subcortical WMLs were hyperintense foci separated from the lateral ventricle. They were graded by size (small <3 mm, medium 3–10 mm, and large >10 mm) and number. The total volume of subcortical WMLs was assessed by multiplying each lesion by a size-dependent constant (0.0042 for small lesions, 0.114 for medium lesions, and 0.95 for large lesions) and by subsequent summation of the results. WMLs were considered periventricular if they were abutting the lateral ventricle; otherwise, they were considered subcortical. Periventricular WMLs were graded semiquantitatively on a severity scale (0–3) at the horns and the body of the lateral ventricle, with the total periventricular WML score being the sum of these three scores. In this analyses subcortical WMLs were categorized as a dichotomous variable indicating presence or absence of large (>10 mm) WMLs. Lacunar infarction on MRI was defined as the presence of a hypointense (T1, PD) or hyperintense (T2) lesion of ≥2 mm on the MRI scan. These two variables, (a) large WMLs (>10 mm) and (b) MRI-defined lacunar infarction, were finally combined into a single variable consisting of 4 categories: (a) no large WMLs, no MRI-defined lacunar infarction; (b) only MRI-defined lacunar infarction; (c) only large WMLs; and (d) large WMLs plus MRI-defined lacunar infarction. In addition, periventricular WMLs were categorized in a score ranging from 0 (no lesion) to 9 (extensive, confluent lesions).

Statistical Analysis
Group differences of continuous variables were tested with Student’s t test (Table 1). Analysis of variance (ANOVA) was used to analyze the individual associations of large WMLs (>10 mm: yes vs no) and MRI-defined lacunar infarction (yes vs no) with the different test scores (Tables 2–3). Additionally, we analyzed if the associations between both brain lesion and cognitive domains were independent by combining both lesion variables and also an interaction term into the respective ANOVA models. Subsequently, ANOVA was also applied to analyze the relations between cognitive
test results and a variable containing four categories of single and combined large WMLs (>10 mm) and MRI-defined lacunar infarction (Table 3). Analyses were adjusted first for age, gender, and education and subsequently also for depression, hypertension, diabetes, myocardial infarction, and transient ischemic attack/stroke (Model 2, Table 3). Bonferroni correction for multiple comparisons set the significance level at \( p < .02 \) for three summary test scores. Analyses were performed using SPSS software (version 14.0; Chicago, IL).

**Principal Components Analysis**

A principal components analysis using a varimax rotation of all results from single tests of the neuropsychological test battery was done after their transformation to standardized \( z \) scores. Variables with a factor loading of 0.4 and higher were regarded as valid and significant contributors to one of the resulting three factors. The first factor was defined as overall memory, the second was labeled processing speed, and the third one was named motor function. Details of the principal component analysis are published elsewhere (27,28).

**RESULTS**

**Sample Characteristics**

Almost three of four participants (72%), among the 268 participants with MRI, had at least punctuate subcortical WMLs. About one in three had WMLs between 3 and 10 mm in diameter (34.3%) or larger than 10 mm in diameter (37.7%). Among the 41 participants with MRI-defined lacunar infarction, a total of 56 stroke lesions were detected. Most of them had a single lacunar infarction, whereas 11 participants had two and 2 individuals three strokes. The majority of these strokes (54%, \( n = 30 \)) were very small (2–3 mm in diameter) and another 23.2% were of small size (<20 mm), both fulfilling accepted criteria of lacunar infarctions. About one in 10 participants (8.6%) had large WMLs and at least one lacunar infarction at the same time. Table 1 presents participants’ characteristics according to presence or absence of large WMLs and MRI-defined ischemic infarction.

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Large WMLs (&gt;10 mm)</th>
<th>MRI-Defined Ischemic Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (N=101)</td>
<td>No (N=167)</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>74.1</td>
<td>71.1*</td>
</tr>
<tr>
<td>Women (%)</td>
<td>47.5</td>
<td>47.9</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>10.9</td>
<td>9.0</td>
</tr>
<tr>
<td>Body mass index (mean kg/m²)</td>
<td>27.5</td>
<td>28.1</td>
</tr>
<tr>
<td>Mean systolic blood pressure (mm Hg)</td>
<td>143.4</td>
<td>144.5</td>
</tr>
<tr>
<td>Mean diastolic blood pressure (mm Hg)</td>
<td>82.2</td>
<td>82.1</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>53.5</td>
<td>43.7</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>10.9</td>
<td>7.2</td>
</tr>
<tr>
<td>History of myocardial infarction (%)</td>
<td>11.0</td>
<td>5.4</td>
</tr>
<tr>
<td>History of clinical TIA/stroke (%)</td>
<td>17.8</td>
<td>2.4†</td>
</tr>
</tbody>
</table>

Notes: WML = white matter lesions; MRI = magnetic resonance imaging; TIA = transient ischemic attack.

* \( p \) value <.01 for age difference yielded by Student’s \( t \) test.

† \( p \) value <.001 for group differences yielded by \( \chi^2 \) test.

In Table 2 results of single tests and cognitive domains (summary scores) are shown according to presence or absence of both brain lesion types. Participants with large (>10 mm) WMLs had significantly worse scores in the word fluency test after Bonferroni correction compared with those without this lesion type even after adjustment for age, gender, education, and Bonferroni correction. MRI-defined lacunar infarction had significant worse results in Stroop tests 2 after adjustment and Bonferroni correction.

Cognitive performance was significantly poorer in participants with either large WMLs or lacunar infarction across all cognitive summary scores (except for large WMLs affecting motor function; Table 2). After adding both lesion types to the same ANOVA model without an interaction term, a significant \( (p = .03) \) relationship between large WMLs and the memory domain (and nonsignificance for infarction) was found. In contrast MRI-defined infarction remained significantly related to the domains of processing speed \( (p = .05) \) and motor function \( (p = .02) \) but not large WMLs. However, for all three cognitive domain scores, the interaction term between WMLs and MRI-defined infarction in the respective model was nonsignificant.

In Table 3 mean scores in cognitive domains according to the four possible combinations of the two brain lesions are shown in two models of adjustment. Whereas Model 1 considers age, gender, and education as confounders, Model 2 additionally includes a number of potential confounders such as cardiovascular variables and depression.

The table shows significant differences in the memory and processing speed domains between the category of large WMLs plus MRI stroke and no lesions. The differences in the domain of motor function were of borderline significance. Evaluation of the adjusted means of each lesion type category showed large differences especially between those
without any lesions and those with both lesions combined. For all three cognitive domains this contrast was more than one standard deviation (SD).

In additional analysis we tested if the differences between single categories were statistically significant. The differences in cognitive performance across all domains between individuals with only one lesion (regardless if WMLs or MRI defined lacunar infarction) and those with no lesions were all nonsignificant. However, the considerable differences between those individuals with one lesion and those who had both lesion types reached statistical significance in the processing speed (F value: 4.63; p = .03) domain, but not for the memory domain (F value: 2.79; p = .09) and for motor function (F value: 0.07; p = .79). This pattern of significance was the same for each single lesion (either large WMLs or lacunar infarction).

Finally, we reanalyzed our data using the upper quartile of the distribution of WML volume as the cutoff instead of the dichotomous variable large WMLs. This did not materially change our results.

We also analyzed the associations between neuropsychological test scores and periventricular WMLs. Subcortical WMLs and periventricular WMLs were significantly correlated (partial coefficient = 0.449; p < .0001, adjusted for age and gender). Results of linear regression analyses between periventricular WMLs and single cognitive tests as well as composite cognitive measures (memory, processing speed, motor function) remained nonsignificant after Bonferroni correction for multiple comparisons.

**DISCUSSION**

In this population-based study of the elderly adults we found strong associations of large WMLs and of MRI-defined lacunar infarction with three different domains of cognitive function even after adjustment for age, gender, and education. The combined occurrence of both lesions affected about one in 10 participants and was associated with a strong decrease of more than 1 SD in cognitive function in all analyzed domains.

The difference between the groups with only one lesion (either large WMLs or MRI-defined infarction) and participants affected by both was considerable and significant in the domains of processing speed and memory, even after adjustment for important confounders such as age, gender, education, and comorbidities. Formal interaction testing revealed that the effects of both lesion types on cognitive function were not more that additive.

Although several studies suggested a relationship between both WMLs and lacunar infarction and cognitive decline (42–45), it is not clear whether WMLs represent a marker of vascular and normal brain changes rather than an independent causative factor. Postmortem studies of WMLs suggest that punctuate WMLs may represent widened perivascular spaces without substantial lacunar tissue damage, whereas early confluent and confluent lesions correspond to incomplete ischemic destruction, possibly with focal transition to true strokes (46). In a prospective study by Schmidt and colleagues (47) it was demonstrated that punctuate WMLs were
neither ischemic nor progressive for a period of 6 years, whereas early confluent and confluent lesions were both ischemic and progressive during a period of time, requiring further clarification of their clinical significance.

WMLs were related to memory deficits in our study, which is in line with previous reports (16). Large (>10 mm) WMLs showed especially worse scores in the word fluency test, which might indicate that verbal fluency may also represent executive function. Because this test was included in the memory domain with other verbal memory measures, the relation between executive function and WMLs might have diluted by the more “pure” memory measures. We also observed a weak association of large WMLs with processing speed and the single tests determining this domain. de Groot and colleagues (5) observed an impairment of global cognitive function and especially psychomotor speed in cases with severe WMLs. Similarly, Ylikoski and colleagues (9) found a slowing of mental processing and attention deficits in affected individuals. The severity of WMLs has shown to be gradually associated with a decline in cognitive function (48). In contrast, Boone and colleagues (8) suggested a threshold effect rather than a linear reduction in cognitive function with increasing severity of WMLs. By using a dichotomized WML definition in our study, we restricted case status to those individuals with the more severe large WMLs of more than 10 mm diameter and found significantly worse results in several cognitive tests compared with those without lesions. We interpret our results in this context rather as a support for a possible threshold effect at a cutoff of 10 mm WML diameter size. In all but one prior study, analyses of the associations between WMLs and cognitive function were done without taking the combination of large WMLs and MRI-defined lacunar infarction into account. Thus, these studies might have overestimated the effect of each lesion type alone on cognitive function because they misclassified individuals with two combined lesion types. Further, the considerable worse cognitive status of the latter group was masked by this misclassification.

The only other study that considered both brain lesion types separately (21) was restricted to tests of global cognitive function, the MMSE, and Alzheimer Disease Assessment Scale. In this study independent effects of WMLs and lacunar strokes were found on the mini-mental status scores. Our study had the ability to analyze cognitive function in more detail by applying a complete neuropsychological test battery and take differential effect of both lesion types into account.

Lacunar infarction is closely related to focal neurological deficits. In line with this, our results indicate the strongest effects of lacunar infarctions on motor function. Other studies confirm the possible negative effect of lacunar infarctions on cognitive function (19,49).

Our study has several strengths and limitations. It provides a detailed description of the impact of large WMLs and MRI-defined lacunar infarction on cognitive function in an elderly general population. Diagnoses of WMLs and ischemic cerebral lesions on brain imaging were done following a standardized MRI reading protocol. All personnel involved in the assessment of test scores and the MRI scans were extensively trained prior to the study. Our findings are limited by the relatively small number of individuals, especially in the group of combined large WMLs and MRI-defined lacunar infarction. We restricted the analyses to subcortical WMLs because periventricular lesions were strongly correlated to these and had less strong relations to individual test scores. To assess the interaction of WMLs, MRI-defined lacunar infarction, and cognitive domains in more detail, a larger number of participants and a prospective study design are needed.
Our study shows that both large WMLs and MRI-defined lacunar infarction contribute to impairments in different cognitive domains. The results suggest that their combined occurrence affects about one in 10 older adults and is associated with stronger reductions in cognitive function than each of the two brain lesion types alone. Identifying individuals with subclinical vascular brain changes such as lacunar infarctions and large WMLs can help to understand the development of marked cognitive impairments in old age. In this process it is also important to evaluate if differences in risk factors contribute to the occurrence of single versus combined brain lesions.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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