Cerebral White Matter Lesions and Cognitive Function: The Rotterdam Scan Study

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Cerebral white matter lesions (WMLs) have been associated with cognitive dysfunction. Whether periventricular or subcortical WMLs relate differently to cognitive function is still uncertain. In addition, it is unclear whether WMLs are related to specific cognitive domains such as memory or psychomotor speed. We examined the relationship between periventricular and subcortical WMLs and cognitive functioning in 1,077 elderly subjects randomly sampled from the general population. Quantification of WMLs was assessed by means of an extensive rating scale on 1.5-T magnetic resonance imaging scans. Cognitive function was assessed by using multiple neuropsychological tests from which we constructed compound scores for psychomotor speed, memory performance, and global cognitive function. When analyzed separately, both periventricular and subcortical WMLs were related to all neuropsychological measures. When periventricular WMLs were analyzed conditional on subcortical WMLs and vice versa, the relationship between periventricular WMLs and global cognitive function remained unaltered whereas the relationship with subcortical WMLs disappeared. Subjects with most severe periventricular WMLs performed nearly 1 SD below average on tasks involving psychomotor speed, and more than 0.5 SD below average for global cognitive function. Tasks that involve speed of cognitive processes appear to be more affected by WMLs than memory tasks.

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Cerebral white matter lesions (WMLs) have been associated with cognitive impairment in demented and nondemented elderly subjects.[1–3] There have been several reports associating WMLs to speed of cognitive processes.[4–6] The subcortical structures of the brain are thought to be especially important for the speed of cognitive processes and memory function.[7–9] The white matter of the subcortical structures can be distinguished into the area just under the cortex and the area surrounding the ventricles. The subcortical region has a high density of short looped U-fibers, which connect adjacent cortical areas, whereas the periventricular region contains many long association fibers that connect the cortex with subcortical nuclei such as the striatum and more distant cortical areas.[10] White matter lesions in these separate regions might affect cognition in different ways. In most research performed to date, the different locations of WMLs have been rated and combined into a single score,[1,11] or only one of the two regions has been considered.[6,12–14] Studies that analyzed periventricular and subcortical WMLs separately are limited and inconclusive with regard to their distinctive relationship with cognition.[5,15–17]

The aim of the present study was to determine whether the location and severity of WMLs are reflected in different aspects of cognitive function in an elderly population. The study was conducted in 1,077 nondemented Dutch subjects, aged 60 to 90 years.

Subjects and Methods

Study Population

The Rotterdam Scan Study was designed to study determinants and cognitive correlates of age-related brain changes in the elderly. In 1995 to 1996, a random sample of 1,904 subjects, aged between 60 and 90 years, was invited by strata of age and sex, from participants of two large ongoing cohort studies, the Rotterdam Study and the Zoetermeer Study. The Rotterdam Study is a prospective population-based study among 7,983 elderly subjects, aged 55 years and older, designed to study determinants of chronic diseases in the elderly.[18] The Zoetermeer Study, also a population-based study, is concerned with prevalence of various chronic diseases.[19] Both studies have been described in detail elsewhere.[18,19]

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Because 187 of the invited 1,904 subjects had contraindications for the study (dementia, contraindications for magnetic resonance imaging [MRI] scanning, or blindness), 1,717 were eligible. Assessment of dementia was performed by a stepped approach, analogous to the protocol used in the Rotterdam Study.[20] Participants were screened with the Mini-Mental State Examination (MMSE) and the Geriatric Mental Schedule, organic section, and those who scored below the cutoff of 26 on the MMSE or above 0 on the Geriatric Mental Schedule were further evaluated by more extensive neuropsychological tests, and, if indicated, informant interview and checking of medical records. Complete data were obtained in 1,077 participants (response, 62.7%). The study was approved by the Medical Ethics Committee of Erasmus University, and written consent was obtained from each participant. Compared with nonparticipants, the participants of the study were younger (mean age difference, 3.8 years; $p < 0.001$) and more educated (5% more subjects with university-level education; $p = 0.05$). Baseline systolic blood pressure measurements, for subjects originally invited from the Zoetermeer Study, were significantly lower in participants compared with nonparticipants (age- and sex-adjusted difference, 2.4 mm Hg; $p = 0.03$), whereas this was not significant for subjects originally invited from the Rotterdam Study. Baseline MMSE scores were available for subjects originally invited from the Rotterdam Study and were higher in participants compared with nonparticipants (age- and sex-adjusted mean difference, 0.4 points; $p < 0.001$).

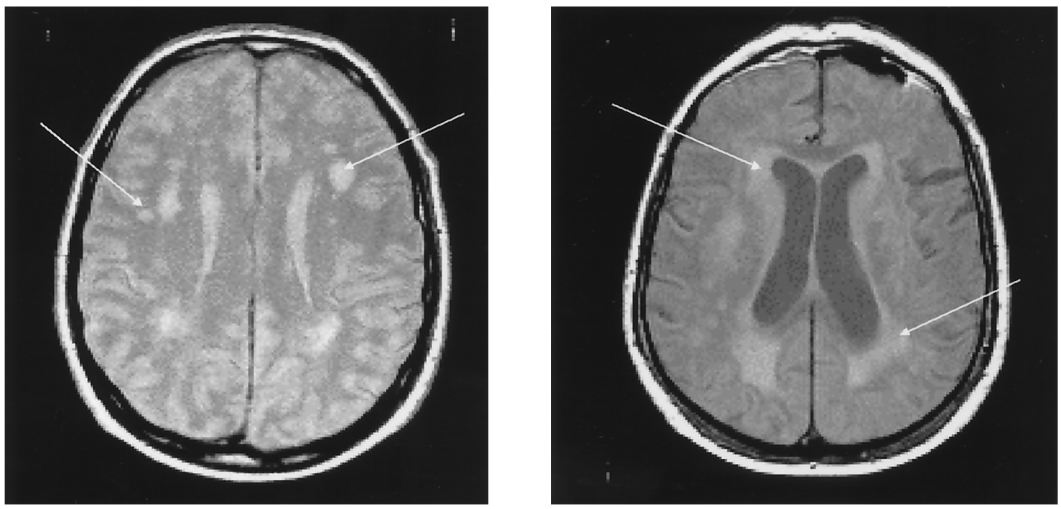
MRI Scanning

MRI scanning was performed on 1.5-T scanners (Gyroscan, Philips NT, Best, The Netherlands, or Magnetom Vision, Siemens AG, Erlangen, Germany). The scanning protocol included a series of axial proton-density (repetition time [TR], 2,200 msec, echo time [TE], 20 msec; number of excitations, 1; matrix, 192 × 256; flip angle, 80°), T2-weighted (TR, 2,200 msec; TE, 80 msec; number of excitations, 1; matrix, 192 × 256; flip angle, 80°) and T1-weighted (for Gyroscan: TR, 485 msec; for Vision: TR, 700 msec; TE, 14 msec; number of excitations, 1; matrix, 192 × 256; flip angle, 70°) images. Sections were 5 or 6 mm thick (scanner dependent) with an interslice gap of 20%. After optimization of the images on the scanner screen, data were archived on magnetic optical disk and laser hard copies were printed with a reduction factor of 2.7.

White Matter Lesions Rating Scale

Presence, severity, and location of morphological brain characteristics were rated according to a protocol designed for the Rotterdam Scan Study. WMLs were considered present in cases of hyperintense lesions on both proton-density and T2-weighted images but not hypointense on T1-weighted images. When the largest diameter of the WML was adjacent to the ventricle, it was defined as periventricular, otherwise as subcortical (for an example, see Fig 1). Periventricular WMLs were rated semiquantitatively as 0 (none), 1 (pencil-thin lining), 2 (smooth halo), or 3 (large confluent) for three separate regions; adjacent to frontal horns (frontal caps), adjacent to the wall of the lateral ventricles (bands), and adjacent to the occipital horns (occipital caps). The total periventricular WML score was calculated by adding the region-specific scores (range, 0–9). Subcortical WMLs were categorized, according to their maximum diameter (as appearing on the hard copy), as small (1–3 mm), medium (3–10 mm), or large (>10 mm). The number of subcortical WMLs was rated per size category for the frontal, parietal, occipital, and temporal lobes. Distinction between lobes was according to anatomical landmarks. We approximated a total subcortical WML volume (in milliliters on hard copy) by assuming subcortical WMLs spherical with diameters of 2, 6, or 12 mm (according to their size category) and adding these volumes. Other features recorded from the MRI images were brain atrophy (cortical and subcortical) and the presence and number of strokes. Cortical atrophy was rated visually on a four-point severity scale. Subcortical atrophy was measured by the ventricle-to-brain ratio (mean of the biventricular width at the level of the frontal, and occipital horns and at

Fig 1. An example of subcortical (left) and periventricular (right) white matter lesions.



the level of the body of the caudate nuclei divided by the corresponding brain width at those levels).

Two independent readers from a pool of four experienced physicians examined all scans. In case of disagreement of more than one point, a consensus reading was held; in other instances, scores were averaged. Intrarater and interrater studies showed good to excellent agreement. Weighted κ values for periventricular WML severity grades were between 0.79 and 0.90. Interreader- and intrareader-intraclass correlation coefficients for total subcortical WML volume were 0.88 and 0.95, respectively. Of all subjects, only 5% had no WMLs at all, whereas 20% were free of periventricular WMLs and 7% had no signs of subcortical WMLs; 73% of all subjects had both periventricular and subcortical WMLs. Pearson's correlation coefficient between periventricular and subcortical WMLs was 0.6.

Measurement of Cognitive Function

Cognitive function was assessed with neuropsychological tests that were considered to be sensitive and suitable for use in this study population. These tests took no longer than 30 minutes to complete. The tests were aimed to assess the speed of cognitive processes, memory function, and global cognitive function and were chosen because of their robustness in detecting age-related impairment and sensitivity to subcortical dysfunction.[21] To evaluate speed of mental processes, the following four tests were used: an abbreviated Stroop test consisting of three subtasks, the Paper-and-Pencil Memory Scanning Task consisting of four subtasks,[22,23] the Letter-Digit Substitution Task, which is a modified version of the Symbol Digit Modalities Test,[24] and a verbal fluency test in which as many animals as possible had to be named within 60 seconds. Memory function was evaluated by a 15-word verbal learning test, a test used to evaluate the ability to acquire and retain new verbal information based on Rey's auditive recall of words.[25] As measures of global cognitive function, we used a combination of above-mentioned tests[26] as well as the widely used MMSE.[27] Most of these tests have been used in other large-scale studies of cognition.[28,29] The tests were performed in quiet rooms and administered by trained investigators; a stopwatch was used in timed tests.

Performance across tests was made comparable by transforming the raw test scores into Z scores as described elsewhere.[26] We calculated compound scores for psychomotor speed, memory performance, and global cognitive function by averaging the relevant Z scores. Some of the tasks we used for psychomotor speed have executive or frontal components, in particular the more complicated tasks of the Stroop test and the verbal fluency task. To assess psychomotor speed as purely as possible, we only included the simplest part of the Stroop test (reading subtask), the simplest version of the Paper-and-Pencil Memory Scanning Test (one-letter subtask), and the Letter-Digit Substitution Task in a compound score for psychomotor speed. The sign of the speed score was inverted so that it indicated above average performance when positive and below average performance when negative. A compound score for memory function was calculated by taking the mean of two Z scores from the 15-word verbal learning test, one for the added scores on three learning trials of this test, and one for the delayed recall of this test. As an overall measure of cognitive function, a compound score was used, referred to as the Cognitive Index. It was calculated as the mean of the Z scores on the one-letter subtask of the Paper-and-Pencil Memory Scanning Task, the reading subtask of the Stroop test, the Letter-Digit Substitution Task, the added score on the learning trials of the 15-word verbal learning test, and the delayed recall of this last test. If, during testing, the test assistant encountered problems, a code was given for test status, reflecting reliability of the test result. Separate codes were given for lack of motivation, presence of a cognitive or physical handicap, or deviation from the instructions. For 99% of all subjects, a score for psychomotor speed and memory performance could be calculated of which 92.9% completed all tests without any recording of test problems. Lack of motivation possibly interfered with testing in 2.6% of subjects, deviation from the test instructions in 0.7%, technical difficulties in 0.4% (such as a broken pencil or stopwatch failure), and a physical or cognitive handicap (such as color blindness or dyslexia) in 3.8%. A combination of these possible problems occurred in 5.7% of subjects.

Other Measurements

The following characteristics were considered as possible confounding variables: age, sex, level of education (according to UNESCO),[30] and mood disturbances (determined with the Center of Epidemiologic Studies Depression Scale).[31] These data were obtained during a 2-hour visit of each participant to the local research facilities. Additional neuroimaging findings, considered as confounding variables in the relation between WMLs and cognitive function, were cortical and subcortical atrophy, and the presence and number of any strokes.

Statistical Analysis

The relationships of periventricular and subcortical WMLs with cognitive performance were assessed by means of multivariate regression with adjustment for age, sex, and educational level. WMLs were analyzed in quintiles of severity to allow for a nonlinear relationship with cognitive function. Analyses of covariance were performed to obtain adjusted mean cognitive performance by quintiles of WML severity. Additional adjustments were made for the presence of depressive symptoms, severity of brain atrophy, and number of strokes. For the test of trend of the analysis of covariance results, quintiles of WML severity were considered as a continuous variable in a multiple linear regression model, with adjustment for the same variables as in the analysis of covariance. To study the relation between cognitive function and subcortical WMLs, conditional on the severity of periventricular WMLs and vice versa, periventricular and subcortical WMLs were entered simultaneously in the multivariate model.

Results

Characteristics of the 1,077 participants of the study are given in Table 1. As expected, age was related to the severity of both periventricular and subcortical WMLs. After adjustment for age, women tended to have more WMLs than men (difference in mean periventricular WML score = 0.2, $p = 0.07$; and in mean subcortical WML volume = 0.16, $p = 0.35$).

Table 1. Characteristics of the Rotterdam Scan Study Participants by Age Category and Sex

Characteristics	Age Category (yr)			Sex	
	60–69	70–79	80–89	Male	Female
No. of subjects	465	416	196	522	555
Age	65.2 (2.6)	74.7 (2.8)	83.7 (2.7)	72.1 (7.2)	72.4 (7.7)
Only primary education (%)	30.1	33.7	49.0	27.4	42.2
MMSE score (range)	27.8 (21–30)	27.4 (19–30)	26.8 (19–30)	27.6 (19–30)	27.3 (19–30)
Total subcortical WML volume	0.6 (1.6)	1.4 (2.6)	3.3 (4.6)	1.3 (2.9)	1.5 (2.9)
No. of large WMLs	0.4 (1.5)	1.0 (2.5)	2.8 (4.6)	1.0 (2.8)	1.1 (2.8)
No. of medium WMLs	1.6 (3.0)	2.9 (4.3)	5.0 (5.0)	2.4 (3.7)	3.0 (4.5)
No. of small WMLs	15.5 (17.3)	22.8 (22.1)	26.6 (18.9)	18.2 (18.3)	22.4 (21.4)
Total periventricular WML score	1.4 (1.6)	2.6 (2.1)	4.2 (2.4)	2.3 (2.1)	2.5 (2.3)
Score frontal caps	0.6 (0.6)	0.9 (0.8)	1.4 (0.8)	0.8 (0.7)	0.9 (0.8)
Score bands	0.6 (0.6)	0.9 (0.8)	1.5 (0.9)	0.8 (0.8)	0.9 (0.8)
Score occipital caps	0.3 (0.6)	0.7 (0.9)	1.3 (1.0)	0.7 (0.9)	0.7 (0.9)
With previous stroke on MRI (%)	6.7	16.8	17.9	14.4	11.0
Cortical atrophy score	0.8 (0.4)	1.2 (0.5)	1.7 (0.5)	1.2 (0.6)	1.0 (0.6)
Ventricle-to-brain ratio	0.30 (0.03)	0.32 (0.03)	0.33 (0.04)	0.32 (0.04)	0.31 (0.04)

Numbers are mean (SD).

MMSE = Mini-Mental State Examination; WML = white matter lesion; MRI = magnetic resonance imaging.

Increasing severity of both periventricular WMLs and subcortical WMLs correlated consistently with worse performance across all tests of cognitive function (Table 2). Additional adjustments for score on the Center of Epidemiologic Studies Depression Scale, degree of cerebral atrophy, and number of cerebral infarcts did not alter these results.

The relation between WMLs in quintiles of severity and global cognitive function is shown in Figure 2. The Cognitive Index was related to severity of both subcortical WMLs ($p_{trend} < 0.001$) and periventricular WMLs ($p_{trend} < 0.001$) (see Fig 2, top). As subcortical and periventricular WMLs are highly correlated, we assessed the relation between cognitive function and subcortical WMLs, conditional on the presence of periventricular WMLs and vice versa. The relationship with

Table 2. The Relation Between WML Severity and Neuropsychological Test Outcome

Neuropsychological Test	Difference in Test Result per Unit Increase of WML	
	Subcortical WML 95% CI (Range: 0;29.5), ml	Periventricular WML in Grades, 95% CI (Range: 0;9)
Mini-Mental State Examination (score)	−0.01 (−0.06;0.04)	−0.07 (−0.14;−0.01)
Stroop test		
Reading (part 1 in sec)	0.15 (0.03;0.27)	0.26 (0.10;0.41)
Naming (part 2 in sec)	0.30 (0.15;0.44)	0.48 (0.29;0.68)
Interference (part 3 in sec)	0.42 (−0.08;0.93)	1.06 (0.39;1.73)
Paper-and-Pencil Memory Scanning Task		
1 letter (sec)	0.29 (0.08;0.50)	0.49 (0.20;0.78)
2 letters (sec)	0.61 (0.26;0.95)	1.03 (0.57;1.49)
3 letters (sec)	0.63 (0.23;1.03)	0.92 (0.39;1.46)
Letter Digit Substitution Task		
No. of letters/min	−0.20 (−0.34;−0.06)	−0.43 (−0.61;−0.25)
Verbal fluency		
No. of animals/min	−0.14 (−0.25;−0.03)	−0.26 (−0.41;−0.12)
15-word verbal learning test		
Total in 3 trials (no. of words)	−0.09 (−0.21;0.02)	−0.23 (−0.38;−0.07)
Delayed recall (no. of words)	−0.05 (−0.11;0.01)	−0.14 (−0.21;−0.06)
Recognition (no. of words)	−0.05 (−0.10;−0.00)	−0.10 (−0.17;−0.03)
Cognitive Index (*z* score)	−0.02 (−0.04;−0.01)	−0.05 (−0.07;−0.03)
Simple psychomotor speed (*z* score)	−0.03 (−0.05;−0.01)	−0.05 (−0.08;−0.03)
Memory performance (*z* score)	−0.02 (−0.04;0.00)	−0.05 (−0.07;−0.02)

Numbers are regression coefficients and 95% CI, controlling for age, sex, educational level, and test status.

WML = white matter lesion; CI = confidence interval.

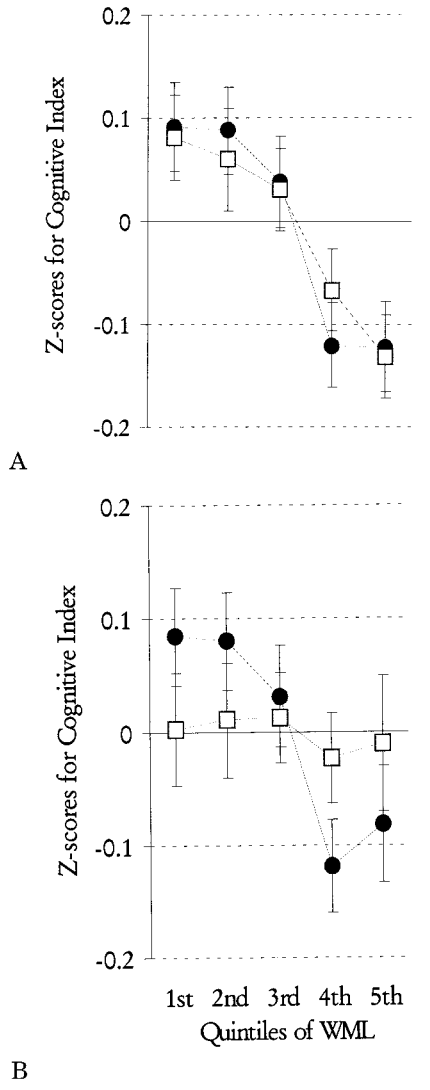


Fig 2. The relation between white matter lesion (WML) severity and cognitive function (expressed as mean z scores (+SEM) for Cognitive Index adjusted for age, sex, educational level, and test status). Locations in separate models (A); both locations in the same model (B). ● = periventricular WMLs; □ = subcortical WMLs.

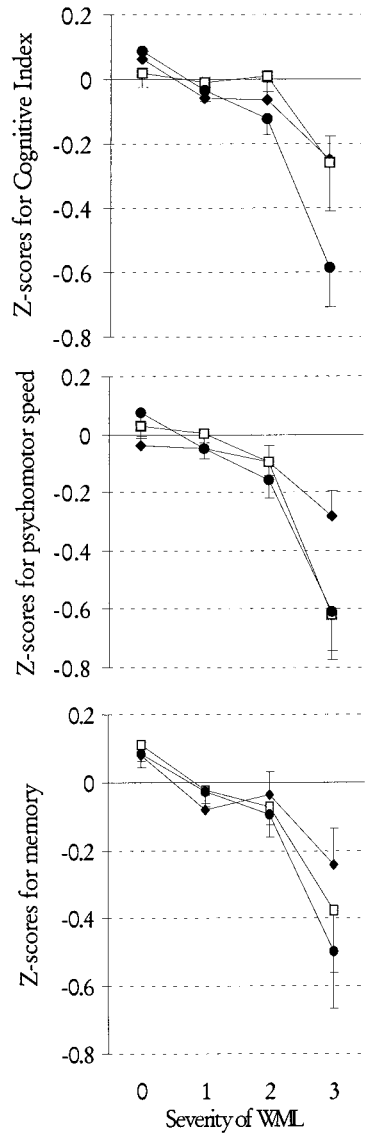


Fig 3. The relation between severity of periventricular white matter lesions (WMLs) at three locations and cognitive function (expressed as mean z scores (+SEM) for cognitive performance adjusted for age, sex, education, and test status). ◆ = occipital caps; □ = frontal caps; ● = lateral bands.

the Cognitive Index remained virtually the same for periventricular WMLs ($p_{trend} = 0.001$) but largely disappeared for subcortical WMLs ($p_{trend} = 0.68$) (see Fig 2, bottom). The analyses of psychomotor speed and memory showed similar results. For subjects with the most severe periventricular WMLs (score 9), psychomotor speed performance was −0.85 SD (95% confidence interval [CI], −1.30 to −0.40) below average; but for less severe periventricular WMLs (score 3), this difference was only −0.15 SD (95% CI, −0.28 to −0.02). For memory, these scores were −0.46 SD (95% CI, −0.99 to 0.07) and −0.19 SD (95% CI, −0.34 to −0.04), respectively.

When periventricular WMLs were analyzed (conditional on subcortical WML severity) for frontal, occipital, and lateral regions separately (Fig 3), more severe WMLs in all three periventricular regions were related with poorer Cognitive Index scores and poorer memory scores (all $p_{trend} < 0.01$). Only the lateral bands of periventricular WMLs showed a significant relationship with psychomotor speed scores ($p_{trend} < 0.001$). For subcortical WMLs, we separately analyzed total lesion volume per lobe and the number of subcortical WMLs per size category. When analyzed conditional on periventricular WML severity, no relation was found between subcortical WMLs and any of the three cognitive compound scores.

We also studied WML severity in relation to the MMSE score, as another test for global cognitive function. Only periventricular WMLs showed significant associations with the MMSE score ($p_{trend} = 0.009$) conditional on other locations of WMLs. This relationship did not change, after additional adjustment for score on the Center of Epidemiologic Studies Depression Scale, degree of cerebral atrophy and number of strokes.

Discussion

This population-based study in a large sample of elderly subjects is the first to find that separate regions of WMLs relate to different cognitive domains. We observed, on the basis of multiple neuropsychological tests, that mainly periventricular WMLs, rather than subcortical WMLs, were associated with cognitive impairment.

It could be suggested that, although the response rate in this study was reasonable, response bias might have affected our results. Participants from this study were younger and had lower blood pressure than nonparticipants. Because old age and high blood pressure are established risk factors for the presence and severity of WMLs, the group with the most severe WMLs is probably underrepresented in our study. Baseline MMSE scores (1990–1993) could only be compared between participants to nonparticipants of the Rotterdam Study, but it is likely that the comparisons would be the same if we had been able to include the Zoetermeer Study. Participants had higher baseline MMSE scores than nonparticipants. Most likely the selection can only have impeded the detection of the association between WMLs and cognitive function. Our findings, thus, would constitute a conservative estimation of the relation between WML severity and cognitive function.

We found a relation between periventricular, but not subcortical, WMLs and cognitive function. However, we cannot exclude that subcortical WMLs affect cognitive function, to an extent that remains below threshold of detection by the neuropsychological tests that we used. Why periventricular and subcortical WMLs have a different relationship with cognitive function is as yet not clear. Subcortical WMLs probably disrupt mainly short corticocortical connections consisting of arcuate U-fibers, which have a high density in the areas just underlying the gray matter, whereas the periventricular WMLs affect areas with a high density of long associating tracts that connect more distant cortical areas with each other.[10,32] The performance on the multiple neuropsychological tests that we used depends on the connections between many cortical areas, not necessarily adjacent, and thus depends mainly on the long associating tracts. This might explain why cognitive function is especially impaired in individuals with periventricular WMLs. The cognitive function most affected by WMLs was psychomotor speed, in agreement with previous studies.[4,5,33] Our findings are in line with the notion that mainly the speed of cognitive processes is diminished in subcortical dementia.[7,34] Schmidt and colleagues[6] suggested that only complex mental processes were affected by WMLs, leaving simple tasks unaltered. In contrast, we found that the affected speed components also involved simple timed psychomotor tasks. This finding is also compatible with a relationship between WMLs and pure motor speed. Unfortunately, we have not been able to incorporate measures for pure motor speed in our study.

There have been only three studies in volunteers on the neuropsychological correlates of WMLs with separate analyses for subcortical and periventricular WMLs.[5,15,16] Only one of these studies was population based.[5] The studies by Ylikoski and associates[5] and Fukui and co-workers[16] showed speed of cognitive function to be related with periventricular WMLs but not with subcortical WMLs. Baum and collaborators[15] have reported the contrary. The relation between cognition and subcortical WMLs has never been reported, conditional on the presence or severity of periventricular WMLs and vice versa. To have an idea about the relation of a distinct brain characteristic with cognitive function, it is important to control for other features. Our study suggests that subcortical WMLs have only a marginal independent relation with cognitive function as opposed to periventricular WMLs.

In conclusion, this study suggests that WMLs are related to impairment of cognitive functions, in particular those that involve a speed component. By means of the compound scores for cognition, we were able to relate more robust measures of cognition to WMLs than with separate tests. The reported relations remained stable when relations were studied with periventricular WMLs, conditional on subcortical WML, even when we adjusted for other brain abnormalities (atrophy and stroke) and for other characteristics that could influence cognitive outcome measures such as educational level and the presence of depressive symptoms. Although our findings are biologically plausible and very robust, they need further confirmation in prospective studies.

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