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Cerebral small-vessel disease and decline in information processing speed, executive function and memory

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Cerebral small-vessel disease is common in older people and may contribute to the development of dementia. The objective of the present study was to evaluate the relationship between measures of cerebral small-vessel disease on MRI and the rate of decline in specific cognitive domains in participants from the prospective, population-based Rotterdam Scan Study. Participants were 60–90 years of age and free from dementia at baseline in 1995–1996. White matter lesions (WML), cerebral infarcts and generalized brain atrophy were assessed on the baseline MRI. We performed neuropsychological testing at baseline and repeatedly in 1999–2000 and in 2001–2003. We used random-effects models for repeated measures to examine the association between quantitative MRI measures and rate of decline in measures of global cognitive function, information processing speed, executive function and memory. There were a total of 2266 assessments for the 832 participants in the study, with an average time from the initial to last assessment of 5.2 years. Increasing severity of periventricular WML and generalized brain atrophy and the presence of brain infarcts on MRI were associated with a steeper decline in cognitive function. These structural brain changes were specifically associated with decline in information processing speed and executive function. The associations between MRI measures of cerebral small-vessel disease and cognitive decline did not change after additional adjustment for vascular risk factors or depressed mood. After exclusion of participants with an incident stroke, some of the associations of periventricular WML, brain infarcts and generalized brain atrophy with measures of information processing speed and executive function were no longer significant. This may indicate that stroke plays an intermediate role in the relationship between cerebral small-vessel disease and cognitive decline. Our results suggest that in older people cerebral small-vessel disease may contribute to cognitive decline by affecting information processing speed and executive function.

Keywords: ischaemic leucoaraiosis; lacunar infarction; MRI; executive function; cognitive function

Abbreviations: *APOE* = apolipoprotein E gene; MMSE = Mini-Mental State Examination; WML = white matter lesions

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Introduction

There is increasing evidence that cerebral small-vessel disease contributes to the development of cognitive decline and dementia (Kalaria, 2002; Roman, 2003). Cerebral small-vessel disease can be visualized on MRI as white matter lesions (WML) and lacunar infarcts (Pantoni and Garcia, 1997; Lammie, 2000). Generalized brain atrophy on MRI is a characteristic finding in Alzheimer's disease (Fox *et al.*, 1999; Scahill *et al.*, 2002), but is also associated with vascular risk factors and small-vessel disease (Walters *et al.*, 2003). The presence of brain infarcts and the severity of WML and generalized brain atrophy on MRI are associated with an increased risk of dementia (Kuller *et al.*, 2003; Vermeer *et al.*, 2003). A diagnosis of dementia is often preceded by a preclinical phase of many years (Elias *et al.*, 2000). During

this phase, people already perform less well on psychometric tests (Masur *et al.*, 1994; Fabrigoule *et al.*, 1998). A sharp decline in psychometric performance is observed at the time that the first clinical changes in cognitive functioning and behaviour start to interfere with activities of daily living (Rubin *et al.*, 1998).

Establishing a temporal relationship between cerebral small-vessel disease and cognitive decline in the general population may provide evidence for a causal role of cerebral small-vessel disease in the aetiology of dementia. It will also help in answering the question of whether small-vessel disease affects information processing speed and executive function differentially, since the typical cross-sectional findings in individuals with WML and lacunar infarcts are suggestive of disconnection of frontosubcortical structures (Wolfe *et al.*, 1990; de Groot *et al.*, 2000). In the Rotterdam Scan Study, participants underwent repeated neuropsychological testing with a 30-min test battery that includes tests for information processing speed, executive function and memory. The objective of the present study was to evaluate the relationship between measures of cerebral small-vessel disease on MRI and the rate of decline in global cognitive function, information processing speed, executive function and memory in a large sample of community-dwelling older people.

Methods

Participants

The Rotterdam Scan Study is a prospective, population-based cohort study, designed to study causes and consequences of age-related brain changes on MRI in the elderly. The characteristics of the 1077 participants have been described previously (de Groot *et al.*, 2000). All participants were free of dementia at baseline. Baseline examination in 1995–1996 comprised a structured interview, neuropsychological tests, physical examination and blood sampling, and all participants underwent an MRI scan of the brain. Each participant gave informed consent to the protocol, which was approved by the medical ethics committee of the Erasmus Medical Center Rotterdam.

In 1999–2000, we reinvited 973 of the 1077 participants for a second examination with a protocol similar to that of the baseline examination; of those invited, 787 participated (81%). The remaining 104 participants were not reinvited for the following reasons: 82 had died, 17 had been institutionalized, four had moved abroad, and one could not be reached. In 2001–2003, we reinvited 844 of the 1077 participants for a third examination that comprised an interview, physical examination and neuropsychological tests; of those invited, 653 participated (response 77%). The remaining 233 participants were not reinvited for the following reasons: 187 had died, 29 had been institutionalized, 11 had moved and could not be reached, and for six participants the invitation was postponed for logistical reasons. The present study is based on 832 participants who had at least one follow-up neuropsychological assessment.

MRI procedure

We made axial T1-, T2- and proton density-weighted scans on 1.5-tesla MRI scanners (MR Gyroscan; Philips, Best, The Netherlands, and MR VISION; Siemens, Erlangen, Germany). The slice thickness was 5 or 6 mm (scanner-dependent) with an interslice gap of 20% (de Leeuw *et al.*, 2001). WML severity was graded for periventricular and subcortical areas separately. Periventricular WML were scored semiquantitatively (range 0–9). For subcortical WML, a total volume was approximated, based on number and size (range 0–29.5 ml) (de Groot *et al.*, 2001). Cerebral infarcts were defined as focal hyperintensities on T2-weighted images, 3 mm in size or larger, and with a corresponding prominent hypointensity on T1-weighted images (Vermeer *et al.*, 2003). Generalized brain atrophy was scored on T1-weighted images. Cortical atrophy was rated on a semiquantitative scale (range 0–15) using reference scans. Subcortical atrophy was measured as the ventricle : brain ratio (range 0.21–0.45) (den Heijer *et al.*, 2002).

Cognitive decline

Participants underwent the following neuropsychological tests at the baseline and follow-up examinations: the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975), the Stroop test (Golden, 1976; Houx *et al.*, 1993), the Letter–Digit Substitution Task (Jolles *et al.*, 1995; Lezak, 1995), a verbal fluency test (animal categories) (Welsh *et al.*, 1994) and a 15-word verbal learning test (based on Rey's recall of words) (Brand and Jolles, 1985). The neuropsychological tests, test demands and latent skills measured are given in Table 1. The reading and naming part of the Stroop test and the Letter–Digit Substitution Task are considered to be primarily measures of information processing speed, whereas the colour word interference part of the Stroop test and the verbal fluency task are considered to be measures of executive function. We used parallel versions of the same tests at the follow-up examinations. In order to obtain a more robust outcome measure for cognitive decline, we used the individual neuropsychological tests to construct a compound score for global cognitive function (Cognitive Index). For each participant, we calculated z scores (individual test score minus mean test score divided by the standard deviation) for the tests at baseline and follow-up using the mean and standard deviation of the baseline tests. The compound score for global cognitive function was the average of the z scores of the Stroop test (sum of the reading, colour naming and interference subtask), the Letter–Digit Substitution Task (number of correct digits in 1 min), the verbal fluency test (number of animals in 1 min), and the immediate and delayed recall of the 15-word verbal learning test.

Incident stroke

In 1999–2000 and in 2001–2003, we reinterviewed participants about symptoms of stroke using a structured questionnaire. In addition, we continuously monitored the medical records of all 832 participants at the general practitioner's office to obtain information on the occurrence of stroke until April 1, 2002. For all reported strokes, we recorded information about signs and symptoms, date of onset, duration, and hospital stay. If participants had been hospitalized for a stroke, we retrieved discharge letters and radiology reports from the hospital where they had been treated. An experienced neurologist assessed the day of onset and classified the stroke by reviewing all available information. Stroke was defined as an episode of relevant focal deficits with acute onset, documented by neurological examination, and lasting for >24 h. On the basis of radiological findings strokes were further subdivided into haemorrhagic and ischaemic stroke subtypes (Vermeer *et al.*, 2003).

Table 1 Description of neuropsychological tests

Neuropsychological test	Test demand	Latent skill measured
Stroop test		
Reading (Part 1; s)	Reading colour names	Speed of reading (automated process)
Naming (Part 2; s)	Naming colours	Speed of colour naming (less automated process)
Colour Word Interference (Part 3; s)	Naming colours of colour names printed in incongruous ink colour	Interference of automated process with less automated process and attention
Letter–Digit Substitution Task (no. of items/min)	Writing down numbers underneath corresponding letters	Speed and efficiency of processing in working memory
Verbal fluency (no. of animals/min)	Mentioning items from a predefined category (animals) in 1 min	Efficiency of searching in long-term memory
15-word verbal learning test		
Total in three trials (no. of words)	Immediate recall of words directly after visual presentation	Verbal learning
Delayed recall (no. of words)	Delayed recall of words 15 min after visual presentation	Retrieval from verbal memory

Ascertainment of dementia

All participants were free of dementia at baseline. We screened all participants for dementia at follow-up with the MMSE (Folstein *et al.*, 1975) and the Geriatric Mental State Schedule (Copeland *et al.*, 1976). Participants with an MMSE score of 25 or lower or with a GMS score of 1 or more were evaluated using the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) diagnostic interview (Roth *et al.*, 1986). Participants who were suspected of having dementia based on their CAMDEX performance were examined by a neurologist, and underwent additional neuropsychological testing. In addition, we continuously monitored the medical records of all participants at the general practitioner's office and at the Regional Institute for Outpatient Mental Health Care (RIAGG) to obtain information on interval cases of dementia until April 1, 2002 (Vermeer *et al.*, 2003).

Other baseline measurements

The following baseline variables were used as possible confounders: age (continuously per year); sex; educational status (UNESCO, 1976), depressed mood [defined as a Center of Epidemiologic studies Depression Scale (CES-D) score of 16 or higher] (Radloff, 1977), apolipoprotein E (*APOE*) genotype (Wenham *et al.*, 1991) (dichotomized into carriers and non-carriers of the *APOE* ε4 allele). Incident stroke during follow-up was assessed through self-report and checking of medical records, and verified by a neurologist (Vermeer *et al.*, 2003).

Data analysis

To examine the association between quantitative MRI measures and the rate of cognitive decline we used random-effects models for repeated measures (PROC MIXED with residual maximum likelihood method; SAS Systems for Windows, release 6.12; SAS Institute, Cary, NC, USA). Random-effects modelling of longitudinal data can be conceptualized as a method in which regression coefficients to account for within-subject change of scores across time are simultaneously estimated for all individuals in the sample, and, in the same analysis, between-subject predictors of these within-subject change indices are evaluated (Mungas *et al.*, 2002). This approach utilizes all available data and accounts for within-person correlation across time, which results in increased statistical power for estimating effects (Beckett, 1994; Diggle *et al.*, 1994). We included random-effect terms to account for differences between participants in cognitive performance at baseline and in the rate of cognitive decline. To account for effects on baseline cognitive performance we included terms for age, sex and education. Age was the only demographic variable that was related to cognitive decline in preliminary analyses, so we included a term to account for the effect of age on the rate of cognitive decline.

First, we evaluated the association between MRI measures and cognitive performance at baseline and the rate of cognitive decline, by adding terms for the MRI measures and terms for the interaction of MRI measures with time to the models. We analysed periventricular and subcortical WML, and subcortical and cortical brain atrophy in quintiles of their distributions to study the shape of the associations, and continuously per standard deviation. Brain infarcts were analysed as present versus absent. Secondly, we adjusted for vascular risk factors and depressed mood by adding terms for these factors and terms for the interaction of these factors with time to the model. Thirdly, we examined possible interaction of MRI measures with APOE genotype in relation to cognitive decline, by including effects for the interaction of the MRI measures with presence versus absence of the *APOE* ε4 allele in the models. Finally, we repeated the analyses on the association between MRI measures and cognitive decline after exclusion of participants with incident stroke and incident dementia during follow-up.

Results

Table 2 gives the baseline characteristics of the study population. People without a follow-up examination were older, less educated, performed worse on the MMSE and had a lower Cognitive Index, and had more severe periventricular WML and cortical atrophy at baseline, compared with people with a follow-up examination (Table 2). Two hundred and thirty participants (28%) had two neuropsychological assessments, and 602 (72%) had three assessments, contributing to a total of 2266 assessments. Average time

Table 2 Characteristics of the study population

Characteristic	People with a follow-up examination (n = 832)	People without a follow-up examination (n = 245)	P-value for difference*
Age (yr)	71	76	<0.01
Women (%)	53	48	0.12
Primary education only (%)	32	44	0.03
Systolic blood pressure (mmHg)	146 (21)	150 (23)	0.46
Diastolic blood pressure (mmHg)	79 (12)	78 (12)	0.91
Hypertension (%)	48	62	0.07
Diabetes (%)	6	11	0.07
Depressed mood, no CES-D-positive (%)	58 (7)	21 (9)	0.44
MMSE score	28 (2)	27 (3)	<0.01
Cognitive Index	0.0 (0.72)	−0.5 (0.78)	<0.01
APOE ε4 carriers (%)†	27	26	0.74
Periventricular WML (score)	2.2 (2.1)	3.2 (2.4)	0.02
Subcortical WML (ml)	1.2 (2.5)	2.1 (4.0)	0.16
Subcortical atrophy (VBR‡)	0.31 (0.035)	0.33 (0.036)	0.53
Cortical atrophy (score)	5.2 (2.7)	6.8 (3.0)	0.01
Cerebral infarcts (%)	23	29	0.92

Values are unadjusted means (SD) or percentages. *Age- and sex-adjusted difference in mean or percentage; †*APOE* genotype was not determined in 79 of the 832 people with a follow-up examination and in 27 of the 245 people with a follow-up examination; ‡ventricle: brain ratio.

from the initial to the last assessment was 5.3 years (SD 1.2; range 2.8–7.9). The mean annual decline on the Cognitive Index was 0.022 points (95% confidence interval 0.029–0.014) and on the MMSE 0.031 points (95% confidence interval 0.057–0.005).

Higher age was associated with a higher rate of cognitive decline. For each year of increase in age, the annual rate of decline on the Cognitive Index increased by 0.004 points (95% confidence interval 0.003–0.005) and decline on the MMSE increased by 0.012 points (95% confidence interval 0.009–0.016). The figure shows the association between MRI measures and decline on the Cognitive Index. Increasing severity of WML and generalized brain atrophy and the presence of brain infarcts were associated with decline on the Cognitive Index (Fig. 1). Per standard deviation increase in periventricular WML severity, the annual rate of decline on the MMSE increased by 0.035 points (95% confidence interval 0.003–0.066). Annual decline on the MMSE for people with brain infarcts was 0.085 points (95% confidence interval 0.02–0.15) larger than for people without brain infarcts on MRI. Other MRI measures were not associated with decline on the MMSE (data not shown).

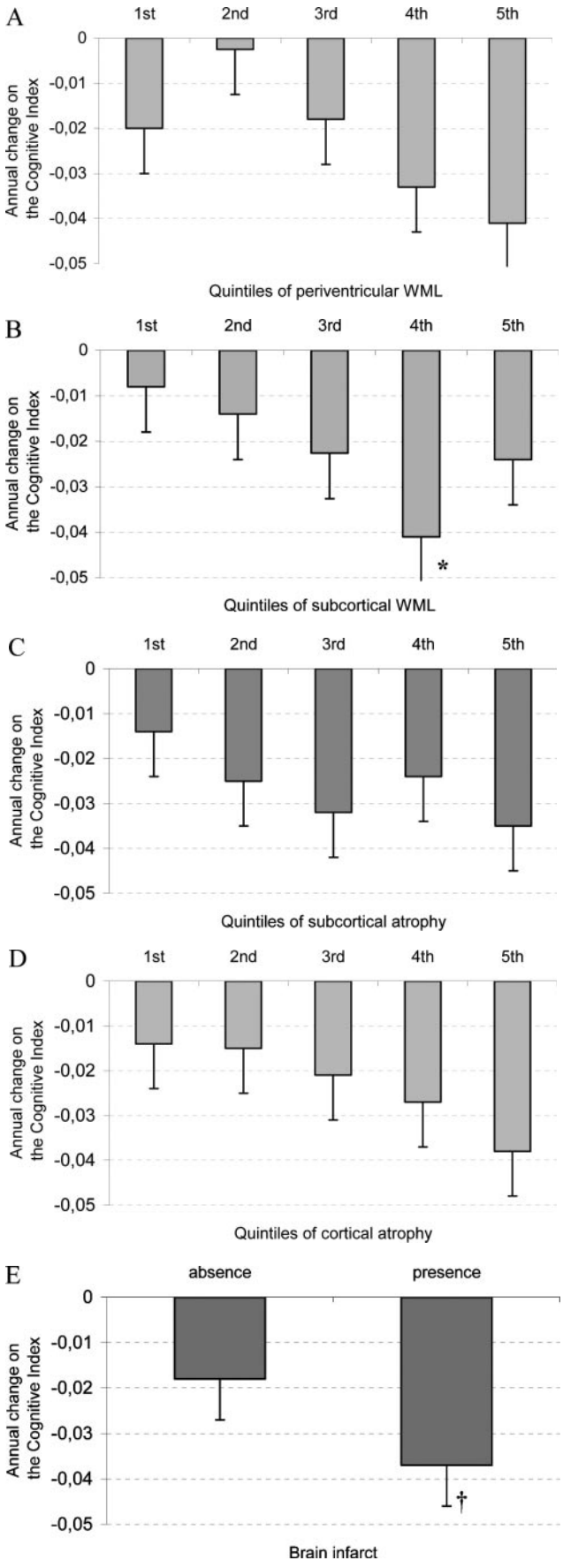
In Table 3 we present the association of age and MRI measures with each individual neuropsychological test. Higher age was associated with steeper decline in performance on all neuropsychological tests (Table 3). Increasing severity of periventricular WML, subcortical and cortical brain atrophy, and the presence of brain infarcts were to a varying degree associated with steeper decline in performance on the subtasks of the Stroop test, the Letter–Digit Substitution Task and verbal fluency (Table 3). None of the MRI measures were associated with decline in performance on the immediate and delayed recall of the 15-word verbal learning test (Table 3). Additional adjustment for vascular risk factors or depressed mood did not change the estimates. No statistically significant interactions were present between MRI measures and the presence of the *APOE* ε4 allele, in relation to cognitive decline (data not shown).

During follow-up, 42 participants had a stroke. After exclusion of participants with an incident stroke, the associations of periventricular WML with the naming subtask of the Stroop test, of brain infarcts with the naming subtask of the Stroop test, of subcortical atrophy with the colour word interference subtask of the Stroop test, and of subcortical atrophy with verbal fluency were no longer significant. After exclusion of participants who developed dementia (n = 23) during follow-up, the associations of periventricular WML with the naming subtask of the Stroop test, of brain infarcts with the naming subtask of the Stroop test, of brain infarcts with verbal fluency, and of subcortical atrophy with verbal fluency were no longer significant (data not shown).

Discussion

In this large population-based study, we found that periventricular WML, brain infarcts and generalized brain atrophy on MRI were associated with the rate of decline in cognitive function. These structural brain changes on MRI, which are thought to be caused by small-vessel disease, were specifically associated with decline in information processing speed and executive function.

Several methodological issues should be addressed. This study was performed in a large number of older people from the general population, who were not demented at baseline and were followed for 5 years on average. The use



of random-effects models in combination with the large sample size has led to precise estimates. However, people who participated in this study were younger, more educated, had a higher MMSE score and Cognitive Index at baseline, and had less severe periventricular WML and cortical atrophy compared with people who did not undergo a follow-up examination. This attrition is likely to have resulted in underestimation of the association between structural brain changes on MRI and the rate of cognitive decline. This should be taken into account when generalizing our results to the general population at large.

Previously, other population-based studies reported on the relationship between indicators of cerebral small-vessel disease on MRI and cognitive decline. Garde and colleagues reported on the relationship between WML severity and decline in intelligence measured with the Wechsler Adult Intelligence Scale (WAIS) (Garde *et al.*, 2000). We previously reported on the association between WML and decline on the MMSE (De Groot *et al.*, 2002), and between silent brain infarcts and decline in cognitive function (Vermeer *et al.*, 2003). The Cardiovascular Health Study reported that subcortical brain atrophy was associated with decline on a Modified MMSE, whereas brain infarcts, high WML grade and high sulci width were not (Kuller *et al.*, 1998). They defined cognitive decline as a decline of five points or more on the Modified MMSE examination in 3 years, and used this as a dichotomous variable in the analyses. This will have reduced statistical power, and may explain the absence of a statistically significant relation with cerebral infarcts, WML and sulci width. Furthermore, WML were analysed as severe versus non-severe, and no distinction was made between WML severity in the periventricular and subcortical regions. Our observation that WML and infarcts affect the speed of information processing and executive function is in line with previous findings from studies in non-demented older people. WML and infarcts were related to decline in executive function and measures of focused attention derived from the Cognitive Drug Research (CDR) system (O'Brien *et al.*, 2002), and WML and atrophy were associated with decline in performance on the Digit Symbol Substitution test (Swan *et al.*, 2000).

Although the presented associations between MRI measures and cognitive decline were significant, the size of the effects was modest and may not be regarded as clinically relevant. We would like to argue that, despite the size of the effects, our findings are relevant from an aetiological point of view and may be regarded as proof of principle. One way to appreciate our findings is to look at the effects in relative

Fig. 1 Association of periventricular WML (**A**), subcortical WML (**B**), subcortical atrophy (**C**) and cortical atrophy (**D**) in quintiles and presence of cerebral infarcts (**E**) with rate of cognitive decline, expressed as mean change per year on the Cognitive Index, adjusted for age, sex and level of education. Bars are standard errors. *Significantly different from first quintile; †significantly different from absence.

Table 3 Association of age and MRI measures with decline in performance on neuropsychological tests

Variable	Stroop Reading*		Stroop Naming*		Stroop CWI*		LDST†		Fluency†					
	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*	15-WVLT IR†	*P*	15-WVLT DR†	*P*
Age (per year increase)	0.03	<0.01	0.03	<0.01	0.14	<0.01	−0.04	<0.01	−0.02	<0.01	−0.02	<0.01	−0.01	<0.01
Periventricular WML (per SD increase)	0.07	0.16	0.08	0.04	0.03	0.85	−0.03	<0.01	−0.02	0.68	−0.04	NE	−0.01	0.63
Subcortical WML (per SD increase)	−0.02	0.74	−0.01	0.84	0.18	0.34	−0.05	0.19	0.03	0.46	−0.07	NE	−0.00	0.85
Brain infarcts (yes versus no)	0.14	0.18	0.17	0.04	0.28	0.43	−0.09	0.28	−0.16	0.05	0.05	NE	0.03	0.51
Subcortical atrophy (per SD increase)	0.10	0.02	0.09	<0.01	0.36	0.02	−0.06	0.12	−0.07	0.05	−0.02	NE	−0.01	0.75
Cortical atrophy (per SD increase)	0.19	<0.01	0.14	<0.01	0.66	<0.01	−0.16	<0.01	−0.05	0.18	−0.02	NE	−0.01	0.63

Estimates are regression coefficients (*P*-value) for annual decline in performance on neuropsychological tests. All models are controlled for age, sex, education and the interaction of age with time. *Higher scores indicate worse performance; †lower scores indicate worse performance. CWI = Colour Word Interference; LDST = Letter–Digit Substitution Task; 15-WVLT IR = 15-word verbal learning test immediate recall (total in three trials); 15-WVLT DR = 15-word verbal learning test delayed recall; NE = could not be estimated.

terms. We showed, for example, that each standard deviation increase in severity of periventricular white matter lesions had the same effect on decline in performance on the naming subtask of the Stroop test as being approximately 2.5 years older.

None of the structural MRI measures were associated with the rate of decline in memory. Memory decline is a pivotal symptom in dementia and is particularly related to medial temporal atrophy (Mungas *et al.*, 2001). We previously reported that (silent) brain infarcts, periventricular WML and subcortical brain atrophy increase the risk of dementia (Vermeer *et al.*, 2003). The present results suggest that WML, infarcts and generalized brain atrophy contribute to dementia mainly by affecting non-memory-related cognitive function. However, selective dropout of participants with memory decline should also be taken into account. Of the 832 people who participated in the present study, 23 (3%) developed dementia during follow-up, compared with 25 (10%) of the 245 people who did not participate. Participants not only had a lower incidence of dementia compared with non-participants but also performed better on memory tasks at baseline [age- and sex-adjusted difference in 15-word verbal learning test immediate recall, 1.11 (P = 0.03), and in 15-word verbal learning test delayed recall 0.43 (P = 0.02)].

Different pathophysiological mechanisms may underlie the associations of periventricular WML, cerebral infarcts and generalized brain atrophy with cognitive decline, and, more specifically, decline in information processing speed and executive function. In our study, the vast majority (89%) of brain infarcts were lacunar and were located in the basal ganglia and subcortical region (Vermeer *et al.*, 2002). Both lacunar infarcts and WML are thought to result from arteriolosclerosis. Occlusion of the arteriolar lumen leads to lacunar infarcts, while critical stenosis of multiple medullary arterioles leads to hypoperfusion and widespread incomplete infarction of the cerebral white matter (Pantoni and Garcia, 1997; Roman *et al.*, 2002). Lacunar infarcts and WML are thought to interrupt prefrontal subcortical loops, which leads to impaired prefrontal lobe functioning, including impaired information processing (Cummings, 1998; Roman *et al.*, 2002; Tekin and Cummings, 2002). We observed that exclusion of participants with incident stroke attenuated the association of WML and brain infarcts with decline in information processing speed and executive function, which suggests that new infarcts play an intermediate role (Vermeer *et al.*, 2003). It may also indicate that small-vessel disease has to rise to the level of stroke in order to cause cognitive decline. Excluding participants with incident stroke can be considered as overadjusting when stroke is an intermediate in the association between small-vessel disease and cognitive decline. Progression of WML may mediate the association between WML and cognitive decline, since WML severity is a strong predictor of WML progression (Schmidt *et al.*, 2003). Apart from having a direct effect on cognitive function, lacunes and WML may also be an

indicator of Alzheimer's disease encephalopathy. WML and lacunes are frequently found in patients with Alzheimer's disease, and evidence suggests that these lesions interact with typical Alzheimer's disease pathology, such as amyloid plaques and neurofibrillary tangles (Kalaria, 2002). Generalized brain atrophy may result from both Alzheimer's disease and cerebrovascular disease (Fox *et al.*, 1999; Mungas *et al.*, 2002). Neuronal loss in cortical associative areas, as well as cerebrovascular damage to white matter fibre tracts connecting these areas, may explain cognitive decline associated with generalized atrophy.

In conclusion, we showed that measures of cerebral small-vessel disease on MRI in non-demented older people are associated with decline in cognitive function by affecting information processing speed and executive function.

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