

# Brain atrophy accelerates cognitive decline in cerebral small vessel disease

The LADIS study

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## ABSTRACT

**Objective:** To examine the independent contributions and combined interactions of medial temporal lobe atrophy (MTA), cortical and subcortical atrophy, and white matter lesion (WML) volume in longitudinal cognitive performance.

**Methods:** A total of 477 subjects with age-related WML were evaluated with brain MRI and annual neuropsychological examinations in 3-year follow-up. Baseline MRI determinants of cognitive decline were analyzed with linear mixed models controlling for multiple confounders.

**Results:** MTA and subcortical atrophy predicted significantly steeper rate of decline in global cognitive measures as well as compound scores for psychomotor speed, executive functions, and memory after adjusting for age, gender, education, lacunes/infarcts, and WML volume. Cortical atrophy independently predicted decline in psychomotor speed. WML volume remained significantly associated with cognitive decline even after controlling for the atrophy scores. Moreover, significant synergistic interactions were found between WML and atrophy measures in overall cognitive performance across time and the rate of cognitive decline. Synergistic effects were also observed between baseline lacunar infarcts and all atrophy measures on change in psychomotor speed. The main results remained robust after exclusion of subjects with clinical stroke or incident dementia, and after additional adjustments for progression of WML and lacunes.

**Conclusions:** Brain atrophy and WML are independently related to longitudinal cognitive decline in small vessel disease. MTA, subcortical, and cortical atrophy seem to potentiate the effect of WML and lacunes on cognitive decline. *Neurology*® 2012;78:1785-1792

## GLOSSARY

**AD** = Alzheimer disease; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **FLAIR** = fluid-attenuated inversion recovery; **LADIS** = Leukoaraiosis and Disability; **MMSE** = Mini-Mental State Examination; **MPRAGE** = magnetization-prepared rapid gradient echo; **MTA** = medial temporal lobe atrophy; **SVD** = small vessel disease; **VADAS** = Vascular Dementia Assessment Scale; **WML** = white matter lesion.

Cerebral small vessel disease (SVD) is the most frequent cause of vascular cognitive impairment.<sup>1,2</sup> The imaging hallmarks of SVD are ischemic white matter lesions (WML) and lacunar infarcts,<sup>3,4</sup> which both have been shown to contribute to longitudinal cognitive decline.<sup>5-7</sup> At an individual level, the clinical picture of SVD is variable, and the determinants of poor cognitive outcome are not completely understood. Beside vascular pathology, concomitant regional and generalized brain atrophy may have an impact on the clinical outcome.

Brain atrophy, as indicated by smaller gray matter and hippocampal volumes and larger CSF volumes, correlate with WML volume in subjects without dementia.<sup>8</sup> In patients with SVD, substantial hippocampal neuronal loss has been observed even in the absence of neuropathologic

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Supplemental Data



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evidence of Alzheimer disease (AD).<sup>9</sup> Earlier studies in subjects with cerebrovascular disease have shown that hippocampal and medial temporal lobe atrophy (MTA) are associated with cognitive impairment and specifically memory deficits.<sup>10–13</sup> Generalized brain atrophy has been suggested as a related processes contributing to cognitive impairment.<sup>5,10,11,14,15</sup>

Cross-sectional data from the Leukoaraiosis and Disability (LADIS) study have indicated that a combination of MTA and WML increases the risk of global cognitive impairment.<sup>16</sup> Longitudinal studies focusing on the consequences of brain atrophy on SVD-related cognitive decline are still sparse.<sup>5,17,18</sup> Particularly, the mediating effects and the interactions between atrophic changes and vascular pathology are largely unknown. The aims of the present study were to investigate in a sample of older individuals with age-related WML 1) whether baseline MTA and cortical or subcortical atrophy predict baseline and longitudinal cognitive performance independently of coexisting WML and infarcts, 2) whether these atrophic changes mediate the effect of WML on cognitive impairment, and c) whether the different imaging findings have synergistic effects on cognition.

**METHODS Participants.** In total, 639 subjects were recruited in the LADIS Study, a prospective longitudinal multicenter study investigating the role of the age-related WML in transition to functional disability. A detailed description of the study has been published elsewhere.<sup>19,20</sup> The inclusion criteria were age 65 to 84 years, changes in cerebral white matter of any degree according to the revised Fazekas scale (mild/moderate/severe),<sup>19</sup> no or mild impairment in instrumental activities of daily living, and presence of a contactable informant. The exclusion criteria were presence of severe illness likely leading to dropout, severe unrelated neurologic disease, leukoencephalopathy of nonvascular origin, severe psychiatric disorders, and inability or refusal to undergo MRI.

All subjects underwent brain MRI and comprehensive neurologic and neuropsychological evaluations at study entry. The clinical assessments were repeated at yearly intervals at 3 subsequent follow-up visits (4 assessments in total), whereas MRI was replicated at the final visit.

**Standard protocol approvals and patient consents.** The local ethics committees of each participating center approved the study, and all subjects gave written informed consent.

**MRI analysis.** MRI of the brain was carried out at baseline and after 3 years according to the same protocol at each study center comprising the T1-weighted magnetization-prepared rapid gradient echo (MPRAGE), T2-weighted fast spin echo, and fluid-attenuated inversion recovery (FLAIR) sequences as detailed

before.<sup>21,22</sup> The images were analyzed centrally and all ratings were blinded to clinical information.

Brain atrophy was evaluated by a single rater at baseline on FLAIR images with a template-based rating scale ranging from 1 = no atrophy to 8 = severe atrophy separately for cortical (sulcal) and subcortical (ventricular) regions (figures e-1 and e-2 on the *Neurology*<sup>®</sup> Web site at [www.neurology.org](http://www.neurology.org), respectively). In case of asymmetry, the side with a more severe atrophy was used for rating. The sum of cortical and sulcal atrophy score was taken as a measure of global atrophy. The same template has been used in previous publications of the LADIS Study.<sup>22,23</sup> Reliability analysis revealed >0.90 (weighted Cohen  $\kappa$ ) intrarater agreement for both cortical and subcortical atrophy. Inter-rater agreement was 0.70 for cortical and 0.83 for subcortical atrophy.<sup>22,23</sup> MTA was rated also by a single rater on the T1-weighted images resliced in the coronal plane according to the Scheltens scale ranging from 0 to 4 on the left and right hemispheres.<sup>24</sup> The average of these 2 scores was used in the present study. Intrarater agreement for MTA was 0.85.<sup>16</sup>

WML volume was evaluated on the baseline axial FLAIR images in periventricular, subcortical, and infratentorial regions using a semiautomated method.<sup>21</sup> The lesions were marked and borders were set by using local thresholding on each slice. Areas of hyperintensity on T2-weighted images around infarctions and lacunes were not included. After all lesions were delineated, the total volume of WML was calculated automatically. At follow-up, progression of WML was evaluated according to the modified Rotterdam progression scale (range 0–7).<sup>25</sup>

The lacunar and nonlacunar infarcts were recorded according to their number at baseline and at follow-up. Lacunes were defined as cavities with a diameter of 3 to 10 mm with signal intensities similar to CSF in all scan sequences by using a combination of FLAIR, MPRAGE, and T2 images in order to distinguish lacunes from Virchow Robin spaces and microbleeds.<sup>25</sup> The nonlacunar infarcts included the larger cortical/lobar infarcts related to a blockage of a large cerebral artery.

Of the total sample ( $n = 639$ ), cortical and subcortical atrophy ratings were available in 530, MTA 582, WML volume 615, lacunes 637, and nonlacunar infarcts in 636 subjects. Complete baseline MRI data for the purposes of the present analysis were available in 477 subjects. Missing data resulted from insufficient image quality or incomplete dataset in some cases. The subjects with complete MRI data did not differ from the other subjects of the sample in terms of age, gender, or baseline Mini-Mental State Examination (MMSE) score ( $p > 0.05$ ), but they had more years of education (10.0 vs 8.4,  $t = -4.5$ ,  $p < 0.001$ ). Of the 477 subjects, follow-up MRI data were available for 289 subjects. As reported before, the cases with both MRI scans were younger, had more years of education, higher baseline cognitive scores, and more often vascular risk factors as compared to those who only underwent baseline scan.<sup>25</sup>

**Neuropsychological assessment.** The neuropsychological test battery consisted of the MMSE,<sup>26</sup> the modified Vascular Dementia Assessment Scale—cognitive subscale (VADAS),<sup>27</sup> the Stroop test,<sup>28</sup> and the Trail-making test.<sup>29</sup> Global cognitive function was assessed with the total scores of the MMSE and VADAS. Domain-specific cognitive functions were evaluated with 3 composite scores constructed by averaging the related standardized raw scores.<sup>30</sup> Speed and motor control score included the Trail-making test part A (time), and the maze (time) and digit cancellation (number of correct responses) subtasks from the VADAS. Executive functions score was compounded of the subtraction scores from the Trail-making (B time – A time) and the

Stroop test (Stroop III time – Stroop II time) as well as the Symbol Digit Modalities Test (number correct responses) and verbal fluency (animal names in 1 minute) from the VADAS. Memory functions score included the VADAS word recall, delayed recall, word recognition, and digit span. Low values indicate inferior performance in the MMSE and compound scores, but the VADAS scale is reversed.

Of the 477 subjects participating in the present study, the baseline MMSE score was available in 476, VADAS 451, speed 466, executive functions 437, and memory 471 subjects. Due to death, dropout, or subject's inability to complete the entire test battery, the data were reduced during follow-up. At the final evaluation, neuropsychological data were available as follows: MMSE 344, VADAS 313, speed 325, executive functions 299, and memory 325.

**Statistical analysis.** The MRI predictors of longitudinal cognitive performance were investigated with linear mixed models, which are able to analyze complex correlation structures and take all available data into account without assuming equal numbers of observations at each measurement. The assessment year (baseline, first, second, and third follow-up year) served as a within-subject variable. Covariance structure was unstructured. The 5 neuropsychological scores were set as dependent variables separately. In all models, age, gender, years of education, as well as baseline lacunes (0, 1–3, >3) and nonlacunar infarcts (0, ≥1) were controlled. The predictor variables included WML volume, MTA, and global atrophy entered simultaneously. The contribution of cortical and subcortical atrophy was analyzed separately by controlling for WML volume and MTA. Logarithmic transformation was applied for WML volume due to substantial positive skewness. For each dependent variable, we first analyzed the main effects of the MRI predictors on baseline cognitive performance. In the same models, MRI predictor × time interactions were explored to reveal the influence of atrophic changes on the rate of cognitive change. Further, the interactions of the different MRI predictors on overall cognitive performance across time were analyzed by using centered variables in separate models. Finally, 3-fold interactions (2 MRI predictors together with time) were considered to show the combined effects of the MRI findings on the rate of cognitive decline. The results were analyzed with PASW Statistics 18.0.2 mixed module.

**RESULTS** The demographic, clinical, and MRI characteristics of the subjects are summarized in table 1. The means and intercorrelations of the atrophy scores and WML volume (mL) are given in table 2.

**Baseline cognitive performance.** After controlling for age, gender, education (years), lacunes (no/few/many), nonlacunar infarcts (no/yes), WML volume, and global atrophy, the linear mixed models revealed a significant main effect of MTA on MMSE, VADAS, speed, executive functions, and memory ( $F = 10.7\text{--}65.8$ ,  $p < 0.01$ ), indicating the independent association of MTA on baseline cognitive performance. Global atrophy was independently associated with baseline VADAS ( $F = 4.2$ ,  $p = 0.041$ ), speed ( $F = 8.5$ ,  $p < 0.004$ ), and executive functions ( $F = 7.8$ ,  $p = 0.005$ ), but not with MMSE or memory ( $p > 0.05$ ). Specifically, subcortical atrophy was related to baseline MMSE ( $F = 4.2$ ,  $p = 0.041$ ), VADAS ( $F = 4.9$ ,  $p = 0.028$ ), speed ( $F = 12.8$ ,  $p <$

**Table 1** Characteristics of the subjects (n = 477)<sup>a</sup>

Characteristics	Values
<b>Demographics</b>	
Age, y, mean (SD)	73.8 (5.0)
Female	259 (54)
Education, y, mean (SD)	10.0 (3.5)
<b>Clinical characteristics</b>	
MMSE score, mean (SD)	27.4 (2.4)
Arterial hypertension	320 (67)
Diabetes	67 (14)
History of clinical stroke	134 (28)
Incident clinical stroke	32 (7)
Conversion to dementia <sup>b</sup>	69 (15)
<b>MRI findings</b>	
WML, mild/moderate/severe	209 (44)/155 (33)/113 (24)
WML progression score, mean (SD), range	2.0 (1.8), 0–7
Lacunes, no/few/many	261 (55)/155 (33)/61 (13)
Incident lacunes, present <sup>c</sup>	48 (17)
Nonlacunar infarcts, present	45 (9)
Incident nonlacunar infarcts, present <sup>c</sup>	24 (8)

Abbreviations: DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MMSE = Mini-Mental State Examination; WML = white matter lesions.

<sup>a</sup> If not otherwise reported, values are number of cases (%).

<sup>b</sup> Dementia was evaluated at each follow-up visit according to DSM-IV criteria.

<sup>c</sup> Follow-up MRI data available for 289 of 477 subjects.

0.001), and executive functions ( $F = 7.9$ ,  $p = 0.005$ ). However, cortical atrophy had no independent main effect on any of the baseline cognitive measures ( $p > 0.05$ ). WML volume remained independently associated with all other baseline cognitive measures ( $F = 5.8\text{--}41.3$ ,  $p < 0.05$ ), except the memory score, even after adjusting for the atrophy scores and other confounders.

**Longitudinal cognitive change.** Atrophy score × time interactions are presented in table 3 (model I), demonstrating the predictive value of these scores on the rate of cognitive change during follow-up. MTA significantly predicted longitudinal decline in all cognitive scores, whereas global atrophy predicted decline in MMSE, VADAS, speed, and executive functions, but not in memory. The association of global atrophy with cognitive decline was accounted most by subcortical atrophy, as its interaction with time was significant for all cognitive variables, but cortical atrophy × time interaction was significant only for speed. Examples of these effects are illustrated in figure 1, where the subjects are categorized into 2 groups according to the median atrophy scores. After

**Table 2** Means and intercorrelations of WML and brain atrophy in the study sample

	Mean (SD)	Range	Pearson correlations (p value)			
			MTA	Global atrophy	Subcortical	Cortical
WML volume, mL	21.4 (22.8)	0.9-156.1	0.37 (<0.001)	0.23 (<0.001)	0.34 (<0.001)	0.02 (0.612)
MTA average	1.0 (0.8)	0-4		0.42 (<0.001)	0.47 (<0.001)	0.22 (<0.001)
Global atrophy	8.0 (2.5)	2-15			0.86 (<0.001)	0.80 (<0.001)
Subcortical	3.9 (1.6)	1-8				0.38 (<0.001)
Cortical	4.1 (1.4)	1-8				

Abbreviations: MTA = medial temporal lobe atrophy; WML = white matter lesions.

controlling for MTA, global atrophy, and other confounders, WML volume still significantly predicted longitudinal decline in MMSE ( $F = 8.7, p < 0.001$ ), VADAS ( $F = 5.6, p < 0.001$ ), speed ( $F = 21.2, p < 0.001$ ), and executive functions ( $F = 11.4, p < 0.001$ ), but not memory ( $F = 1.3, p = 0.276$ ).

**Interactions of the MRI predictors.** Significant synergistic (potentiating) interactions were found between WML volume and atrophy scores across time in MMSE and executive functions, and also between the different atrophy scores in MMSE, executive functions, and memory (table 3, model II; figure 2).

**Table 3** Baseline MRI predictors of longitudinal cognitive performance in 3-year follow-up<sup>a</sup>

	MMSE	VADAS	Speed	Executive	Memory
<b>Model I</b>					
MTA × time	7.3 (<0.001) <sup>b</sup>	4.5 (0.004) <sup>b,d</sup>	13.3 (<0.001) <sup>b,c,d</sup>	18.4 (<0.001) <sup>b,c,d</sup>	13.2 (<0.001) <sup>b,c,d</sup>
Global atrophy × time	3.6 (0.013) <sup>b</sup>	3.3 (0.022) <sup>b,d</sup>	6.1 (<0.001) <sup>b,c</sup>	4.0 (0.008) <sup>b</sup>	NS <sup>b</sup>
Subcortical × time	6.4 (<0.001) <sup>b</sup>	4.9 (0.002) <sup>b,c,d</sup>	8.0 (<0.001) <sup>b,c,d</sup>	3.3 (0.019) <sup>b</sup>	3.1 (0.027) <sup>b,d</sup>
Cortical × time	NS	NS	3.2 (0.024)	NS <sup>c</sup>	NS
<b>Model II</b>					
MTA × WML	6.8 (0.009)	NS	NS	6.1 (0.014)	NS
Global atrophy × WML	NS	NS	NS	5.4 (0.020)	NS
Subcortical × WML	NS	NS	NS	4.3 (0.038)	NS
Cortical × WML	NS	NS <sup>c</sup>	NS	NS	NS
Global atrophy × MTA	NS	NS	NS	6.0 (0.014) <sup>c</sup>	4.9 (0.028) <sup>b</sup>
Subcortical × MTA	4.6 (0.033) <sup>c</sup>	NS	NS	5.3 (0.022) <sup>c,d</sup>	5.1 (0.024) <sup>b</sup>
Cortical × MTA	NS	NS	NS	NS	NS
<b>Model III</b>					
MTA × WML × time	NS	NS	NS	NS	NS
Global × WML × time	4.1 (0.007) <sup>b</sup>	NS	NS <sup>b</sup>	NS <sup>d</sup>	NS <sup>d</sup>
Subcortical × WML × time	4.0 (0.008) <sup>b</sup>	NS	NS	NS	NS
Cortical × WML × time	NS	NS	NS <sup>b</sup>	NS <sup>c,d</sup>	NS <sup>c,d</sup>
Global × MTA × time	5.1 (0.002) <sup>b,d</sup>	2.9 (0.035) <sup>b</sup>	2.8 (0.039) <sup>b,c</sup>	NS	NS <sup>b</sup>
Subcortical × MTA × time	4.3 (0.005) <sup>b,d</sup>	NS	NS	NS <sup>b,c</sup>	NS
Cortical × MTA × time	NS <sup>d</sup>	NS	NS <sup>c</sup>	NS	NS

Abbreviations: DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MMSE = Mini-Mental State Examination; MTA = medial temporal lobe atrophy; VADAS = Vascular Dementia Assessment Scale-cognitive subscale; WML = white matter lesions.

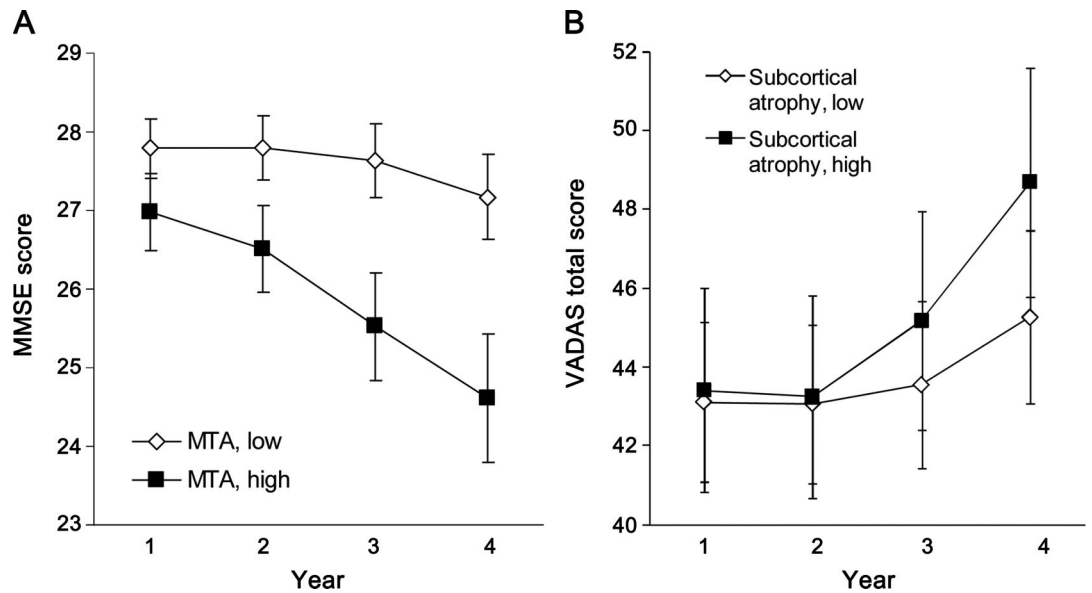
<sup>a</sup> Linear mixed models ( $F$  [p value]) adjusted for age, gender, education, lacunes, infarcts, and other MRI co-findings (see text for details). Cognitive performance was assessed in 4 evaluations at yearly intervals. Model I: independent predictive value of atrophy scores to the rate of cognitive decline during follow-up. Model II: synergistic interactions between the MRI findings in overall cognitive performance across time. Model III: synergistic interactions between the MRI findings in the rate of cognitive decline during follow-up.

<sup>b</sup> Significant after exclusion of cases with prior or incident clinical stroke.

<sup>c</sup> Significant after exclusion of cases who converted to dementia (DSM-IV) during follow-up.

<sup>d</sup> Significant after additional controlling for incident lacunes and WML progression score; data available only for 289 (61%) subjects.

**Figure 1** Relationship between baseline atrophy scores and the rate of global cognitive decline



Graphs represent model adjusted means with 95% confidence intervals in the Mini-Mental State Examination (MMSE) (A) and the modified Vascular Dementia Assessment Scale-cognitive subscale (VADAS) (B). Higher values indicate better performance in MMSE, but worse performance in VADAS. The atrophy scores are categorized into 2 groups according to the median value: medial temporal lobe atrophy (MTA) low = 0-1, high = 2-4; subcortical atrophy low = 1-4, high 5-8.

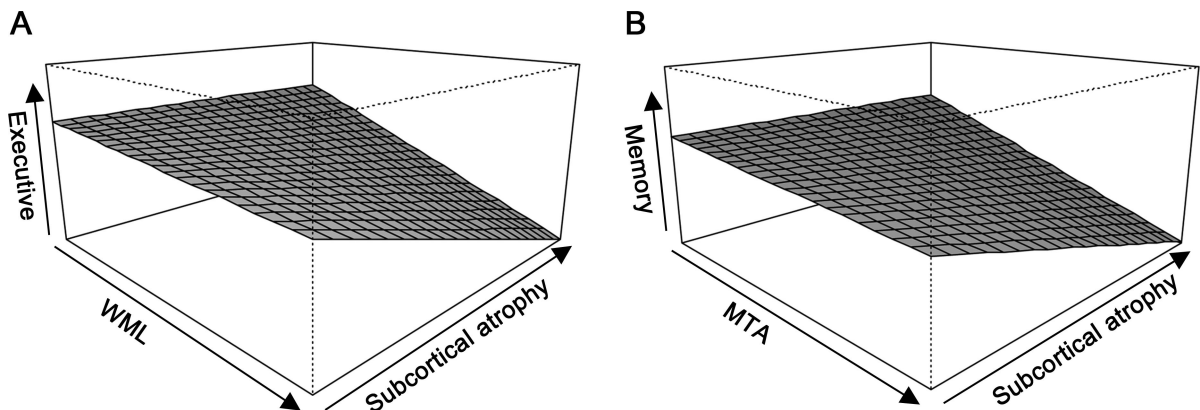
Furthermore, 3-fold interactions revealed synergistic MRI × MRI × time effects on cognitive decline (table 3, model III). Significant interactions were also found between lacunes and all 4 atrophy measures in decline of speed performance ( $F = 2.3-3.6$ ,  $p < 0.05$ ).

All significant main effects and interactions were in the expected direction, i.e., more severe MRI findings predicted inferior/steeper decline of cognitive performance. Additional controlling for hypertension had no effect on the longitudinal results. However, adjusting for incident lacunes (0, ≥1) and WML progression as well as exclusion of cases with

clinical stroke or incident dementia (*DSM-IV*) partly changed the observed effects (table 3).

**DISCUSSION** We investigated the individual and joint effects of baseline regional and global brain atrophy on longitudinal cognitive decline among older individuals with age-related WML. The key finding of the study was that MTA, subcortical, and cortical atrophy independently predicted steeper decline of cognitive performance during the 3-year follow-up. Cognitive decline was accelerated by the synergistic interactions between the different atrophy measures and WML.

**Figure 2** Combined effects of white matter lesions (WML) and brain atrophy on executive (A) and memory (B) performance



Both the main effects and the interactions of WML, medial temporal lobe atrophy (MTA), and subcortical atrophy on cognitive performance were statistically significant.

Of the atrophy measures, MTA had the strongest individual contribution to cognition, as it independently predicted both baseline performance and longitudinal decline in a wide range of cognitive domains including global cognitive function, psychomotor speed, executive functions, and memory. The role of MTA in global cognitive decline has been suggested by earlier studies in cross-sectional<sup>1,10,11</sup> and longitudinal<sup>31</sup> settings. In subjects with vascular changes, MTA has been strongly associated with memory impairment,<sup>11–13</sup> but also with deficits in other domains such as mental speed<sup>12</sup> and executive functions.<sup>1,13</sup>

Independently of MTA and WML volume, global brain atrophy was also associated with baseline performance and the rate of cognitive decline. This effect was more strongly accounted by subcortical than cortical atrophy. In fact, subcortical atrophy significantly predicted change in all cognitive measures, whereas cortical atrophy was only associated with decline in psychomotor speed. The results converge with previous cross-sectional and longitudinal studies suggesting the role of brain atrophy in SVD-related cognitive impairment.<sup>10,11,13,15,18,32,33</sup> However, many of these studies have evaluated only cortical atrophy or the whole brain volume, and the differences between cortical and subcortical atrophy regarding cognitive decline have not been elucidated. Subcortical atrophy may be of special interest, as it reflects shrinkage of white matter and the deep gray matter structures, which are critical for the integrity of the frontal-subcortical functional networks.<sup>34</sup> In a cross-sectional study of patients with atherosclerotic disease, larger ventricular volume has been associated with worse executive and memory performance, whereas cortical gray matter volume was only related to executive functions after adjusting for vascular lesions.<sup>35</sup> Moreover, both subcortical and cortical atrophy have been associated with longitudinal decline in measures of speed and executive functions, but not in those of memory.<sup>5</sup>

Some of the previous studies have suggested that the effect of WML on cognitive decline is overridden by the stronger influence of brain atrophy.<sup>17,33</sup> The present data do not support this hypothesis, as WML volume still remained significantly associated with baseline and longitudinal measures of global cognitive function, speed, and executive functions even after controlling for MTA, global atrophy, and other confounders. In our sample, WML correlated significantly with MTA as well as global and subcortical atrophy, but not specifically with cortical atrophy. Previous studies have reported correlations of WML with both subcortical and cortical atrophy.<sup>8,36</sup> Even though WML and brain atrophy are obviously inter-

related processes, our results suggest that they independently and differentially contribute to cognitive impairment.

Of particular interest is the finding that brain atrophy and WML had synergistic interactions in cognitive functioning. WML in combination with either MTA or subcortical atrophy had potentiating detrimental effects on global cognitive function and executive functions. Moreover, the different types of atrophic changes—MTA and subcortical atrophy together—had synergistic interactions in global cognitive function, executive functions, and importantly also in memory impairment. The synergistic effects of WML, MTA, and global atrophy were evident both in overall cognitive performance and in change over time, suggesting that the influence of the brain changes in cognitive decline taken together is greater than the sum of their individual effects.

Synergistic interactions were also observed between baseline lacunar infarcts and the different atrophy measures in longitudinal decline of psychomotor speed suggesting similar potentiating mechanisms as between WML and atrophy. Very few studies have addressed the interaction of brain atrophy with vascular pathology before. Recently, a cross-sectional study demonstrated that the association of cortical and subcortical atrophy with executive performance became stronger with the presence of severe WML, but no interactions were found in memory performance.<sup>35</sup> A longitudinal study has reported a cumulative effect of baseline WML and hippocampal volume on the severity of cognitive decline.<sup>37</sup>

A limitation of the present study is that we used a template-based visual rating scale to assess brain atrophy instead of volumetric measurements. Visual scales may not be as sensitive as structural volumetry, but they are cost-effective, usable in clinical practice, and have been proved to reach good reliability and correspondence to volumetric measurements.<sup>38,39</sup> In our evaluations, we separated subcortical and cortical atrophy, but were not able to evaluate specific cortical regions. Another disadvantage of the study is that brain atrophy was only evaluated at baseline and measures of progression were only available for lacunes and WML for a subgroup of the sample. Furthermore, as in any follow-up study of aging and cognition, a considerable amount of data were lost during follow-up due to death, subject dropout from the study, or inability to complete the entire neuropsychological evaluation causing a possible bias toward cases with better clinical picture.<sup>40</sup> Some imaging data were also lost because of insufficient image quality.

Among the strengths of the study are the prospective longitudinal design and the large sample of sub-

jects, who at baseline were free from functional disability and were stratified into all levels of WML. The comprehensive clinical evaluations included a detailed neuropsychological assessment carried out at 4 annual visits. Several confounding factors including the demographic and clinical variables were controlled. Additional analyses revealed that clinical stroke played no major role in the observed results, whereas the effects of atrophy were more prominent in the subjects who converted to dementia during follow-up. Progression of lacunes and WML also modified the effects to some extent, although the main results remained robust.

In ischemic SVD, brain atrophy and WML are interrelated processes, which independently contribute to decline across multiple cognitive domains. Specifically, brain atrophy amplifies the effects of WML and lacunes on cognition, exceeding the sum of the individual effects of these pathologies. The poorest outcome seems to be determined by a combination of vascular lesions, MTA, and subcortical atrophy. The results highlight the complex interplay between vascular and degenerative pathologies leading to progressive cognitive impairment in older individuals with age-related WML. The pathophysiologic mechanisms of these brain changes remain unresolved. Atrophy may result from neurodegenerative processes such as AD, but it may also derive from cerebral ischemia caused by the SVD itself. We suggest that in SVD, regional and global atrophic changes deserve equal attention beside vascular pathology.

#### AUTHOR CONTRIBUTIONS

All authors made critical revisions of the manuscript for important intellectual content. In addition, the most central work of each author for the study was as follows. H. Jokinen: responsible investigator and corresponding author, neuropsychological data acquisition, design and conceptualization of the study, statistical analysis and interpretation, drafting and finishing of the manuscript. J. Lipsanen: expertise in statistical analysis and interpretation, preparation of figure 2. R. Schmidt: design of the LADIS study, responsible for the MRI methods, evaluation of brain atrophy. F. Fazekas: design of the LADIS study, responsible for the MRI methods. A. Gouw: MRI data analysis, evaluation of brain infarcts and lacunes. W.M. van der Flier: MRI data analysis, evaluation of lacunes and medial temporal lobe atrophy. F. Barkhof: responsible for the MRI methods, design of the LADIS study. S. Madureira: construction of the neuropsychological test battery, neuropsychological data acquisition. A. Verdelho: neuropsychological and clinical data acquisition. J.M. Ferro: construction of the neuropsychological test battery, design of the LADIS study. A. Wallin: design of the LADIS study. L. Pantoni: coordination and design of the LADIS study. D. Inzitari: study coordinator, member of the LADIS steering committee, design of the LADIS study. T. Erkinjuntti: member of the LADIS steering committee, study conceptualization and design, design of the LADIS study.

#### DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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