Gray matter reduction is correlated with white matter hyperintensity volume: A voxel-based morphometric study in a large epidemiological sample

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Both brain atrophy and T2-weighted white matter hyperintensities (WMH) are common findings in the brains of asymptomatic elderly individuals as well as in disease-specific brains. The study of the relationship between these two salient features is therefore important. To investigate such a relationship, we performed a brain magnetic resonance imaging (MRI) study on 397 asymptomatic individuals aged between 60 and 64 years, who were recruited randomly from a large community sample. WMH were delineated on T2-weighted fluid attenuation inversion recovery (FLAIR) whole brain scans using an automated procedure. The results showed that gray matter reduction, subarachnoid CSF (SA-CSF) increase and lateral ventricular dilation were significantly correlated with WMH load. Deep white matter hyperintensity (DWMH) had significant correlation with all three global atrophy indices, but periventricular white matter hyperintensity (PVWMH) was correlated only with gray matter volume. Voxel-based morphometric (VBM) analysis showed that regional gray matter reduction correlated more closely with WMH load of the proximate region than with WMH elsewhere. The results suggest that WMH have a relationship with brain atrophy in middle age, although the study cannot determine which process, i.e. the development of WMH or atrophy, is primary. The study also demonstrates that DWMH has a more significant relationship with structural brain changes, and may therefore be more functionally relevant than PVWMH. Further delineation of this relationship needs a longitudinal study of the changes in both WMH and indices of brain atrophy.

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Introduction

The brain undergoes progressive changes in adult life. There is a decline in brain size with increasing age (Hof and Morrison, 2004), the gradient of which increases in neurodegenerative disease. Elderly brains also accumulate foci of high signal intensity in the white matter on T2-weighted MRI, termed as leukoaraiosis or white matter hyperintensities (WMH) (Guttmann et al., 1998). These findings are already quite prominent in individuals in their 60s, with predominance in the periventricular region (Wen and Sachdev, 2004). In healthy elderly individuals, they are generally considered to be ischemic in origin, although the relative contribution of neurodegeneration is not known (Pantoni and Garcia, 1997). The high prevalence of WMH in the elderly has raised the issue of their pathological significance, with the suggestion that they may be normative findings (Awad et al., 1986). There is now converging evidence, however, that WMH indeed have a pathological significance. Possibly above a certain threshold, these lesions are associated with cognitive impairment (Roman, 1987) – (Sachdev et al., 2004a) and psychomotor abnormalities (Sachdev et al., 2005). The presence of subcortical hyperintense lesions has been associated with reduced cortical blood flow and volume (DeCarli et al., 1995; Miyazawa et al., 1997; Sultzer et al., 1995; Takahashi et al., 2000; Yao et al., 1990; Wen et al., 2004). WMH have also been linked to neuropsychiatric disorders such as major depression (Krishnan et al., 1997), bipolar disorder and late-onset schizophrenia (Sachdev and Brodaty, 1999).

WMH have also been associated with brain atrophy (DeCarli et al., 1995), but this relationship has been insufficiently examined. The usual emphasis is on subcortical atrophy, with the expectation that WMH are related to dilated ventricles, possibly due to white matter loss. The relationship of WMH with cortical gray matter has not been reported. This could occur for a number of reasons: WMH may indicate disruption of axons and consequent neuronal loss, or primary neuronal loss may secondarily lead to WMH. It is also
possible that WMH and cortical atrophy may have common risk factors such as hypertension or diabetes.

Our aim in this study was to determine if WMH were related with cortical and subcortical brain atrophy in otherwise healthy, community dwelling individuals. The study of the relationship between WMH and brain atrophy has previously been limited to clinic populations (Quarantelli et al., 2003). We hypothesized that WMH would be related to both cortical atrophy and ventricular dilatation, but DWMH would be more strongly associated with cortical atrophy and PVWMH with ventricular dilatation. We also expected that there would be some specificity in the correlation between WMH in a particular brain region and the cortical atrophy in that region.

Subjects and methods

Subjects
The study sample was drawn from the Path Through Life (PTL) project and comprised 2551 individuals aged 60–64 years who were residents of the city of Canberra and the adjacent town of Queanbeyan, Australia. They were recruited randomly through the electoral roll. Enrolment to vote is compulsory for Australian citizens. The response rate was 58.3% for the total sample. Subjects were asked at the initial interview if they would be willing to undergo a MRI scan. Those who were unwilling during the initial interview were significantly (p < 0.05) more likely to be female, of non-English speaking background, less educated, with poorer physical health and lower cognitive scores. The 622 participants who indicated willingness for a scan were approached, and 478 (218 males, 179 females) were chosen for the study and comprised 2551 individuals aged 60–64 years who were residents of the city of Canberra and the adjacent town of Queanbeyan, Australia. They were recruited randomly through the electoral roll. Enrolment to vote is compulsory for Australian citizens. The response rate was 58.3% for the total sample. Subjects were asked at the initial interview if they would be willing to undergo a MRI scan. Those who were unwilling during the initial interview were significantly (p < 0.05) more likely to be female, of non-English speaking background, less educated, with poorer physical health and lower cognitive scores.

Table 1

Table 1: Descriptive characteristics of the study sample by sex

<table>
<thead>
<tr>
<th>Variables</th>
<th>Male (n = 218)</th>
<th>Female (n = 179)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>397 62.66 (1.41)</td>
<td>395 62.67 (1.44)</td>
<td>0.920</td>
</tr>
<tr>
<td>Education (years)</td>
<td>395 14.45 (2.49)</td>
<td>395 13.62 (2.70)</td>
<td>0.002</td>
</tr>
<tr>
<td>Right-handed (%)</td>
<td>395 182 (90.5)</td>
<td>395 153 (96.2)</td>
<td>0.035</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>387 212 (175)</td>
<td>175</td>
<td>0.011</td>
</tr>
<tr>
<td>Definite (%)</td>
<td>100 (47.17)</td>
<td>58 (33.14)</td>
<td></td>
</tr>
<tr>
<td>Probable (%)</td>
<td>50 (23.58)</td>
<td>44 (25.14)</td>
<td></td>
</tr>
<tr>
<td>Normotensive (%)</td>
<td>62 (29.25)</td>
<td>73 (41.72)</td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>395 216</td>
<td>179</td>
<td>0.447</td>
</tr>
<tr>
<td>Definite yes (%)</td>
<td>23 (10.6)</td>
<td>15 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Not diabetes (%)</td>
<td>193 (89.4)</td>
<td>164 (91.6)</td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>395 216</td>
<td>179</td>
<td>0.000</td>
</tr>
<tr>
<td>Current (%)</td>
<td>17 (7.87)</td>
<td>13 (7.26)</td>
<td></td>
</tr>
<tr>
<td>Past (%)</td>
<td>97 (44.91)</td>
<td>42 (23.46)</td>
<td></td>
</tr>
<tr>
<td>Nonsmoking (%)</td>
<td>102 (47.22)</td>
<td>124 (69.28)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>347 185</td>
<td>162</td>
<td>0.254</td>
</tr>
<tr>
<td>Yes (%)</td>
<td>88 (47.57)</td>
<td>87 (53.70)</td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>97 (52.43)</td>
<td>75 (46.30)</td>
<td></td>
</tr>
<tr>
<td>Heart disease (%)</td>
<td>395 216</td>
<td>179</td>
<td>0.042</td>
</tr>
<tr>
<td>Yes (%)</td>
<td>31 (14.35)</td>
<td>14 (7.82)</td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>185 (85.65)</td>
<td>165 (92.18)</td>
<td></td>
</tr>
<tr>
<td>Stroke, self-report</td>
<td>395 216</td>
<td>179</td>
<td>0.370</td>
</tr>
<tr>
<td>Yes (%)</td>
<td>7 (3.24)</td>
<td>9 (5.03)</td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>209 (96.76)</td>
<td>170 (94.97)</td>
<td></td>
</tr>
<tr>
<td>MMSE (SD)</td>
<td>396 29.23 (1.21)</td>
<td>29.39 (1.10)</td>
<td>0.173</td>
</tr>
</tbody>
</table>

Note. p values are for t tests of continuous variables and chi-square tests of discrete variables between males and females.

Image acquisition

Imaging was performed on a 1.5 T Gyroscan MRI scanner (ACS-NX, Philips Medical Systems, Best, Netherlands) for T1-weighted 3D structural and T2-weighted FLAIR sequence MRI. A 2D scout mid-sagittal cut for AC–PC plane alignment was first acquired (TR/TE/NEX = 500/16/1.5; slice thickness = 5 mm). Then 3D structural MRI was acquired in coronal orientation using a T1-weighted FFE sequence (TR/TE/NEX = 28.05/2.64/2; flip angle = 30; matrix size = 256 × 256; FOV = 260 × 260 mm; slice thickness = 2.0 mm, inter-slice distance = 1.0 mm), yielding over-continuous coronal slices 1.5 mm thick and an in-plane spatial resolution of 1.016 × 1.016 mm/pixel. The FLAIR sequence was acquired in coronal orientation (TR/TE/TI/NEX = 11000/140/2600/2; matrix size = 256 × 256; FOV = 230 × 230 mm; slice thickness = 4.0 mm with no gap between slices) with in-plane spatial resolution of 0.898 × 0.898 mm/pixel. The total time of each subject’s scanning session was approximately 20 min.

Image processing

The WMH in each individual’s FLAIR images were detected and measured by an automated procedure, using a set of in-house computer algorithms and programs, but with the oversight of a trained operator (Wen and Sachdev, 2004). SPM2 (Wellcome Department of Cognitive Neurology, University College London, UK) was used for segmenting the whole brain into GM and WM volumes and CSF. Lateral ventricles were traced manually by a trained research assistant on T1-weighted anatomical MRIs and their volumes were calculated. The statistical technique of voxel-based morphometry (VBM) from SPM2 was used to examine the relationship between WMH volumes and localized changes of gray matter.

Automatic detection and measurement of WMH volumes

Details of the algorithm and correlations between the results from the automated method and visual rating are described...
elsewhere (Wen and Sachdev, 2004). In brief, we constructed an age-specific FLAIR template in Montreal Neurological Institute (MNI)-space (Evans et al., 1994). Spatial normalization of the coregistered FLAIR and T1-weighted MRIs was then performed using FLAIR templates. The detection and grading of WMH from each normalized FLAIR image with the coregistered T1-weighted image as reference were carried out. Each WMH map generated by the computer algorithm was visually inspected and the false classification of WMH was manually removed from the map (Wen and Sachdev, 2004).

WMH maps thus generated were binary images, the voxel values of which indicated either the presence or absence of WMH on that location. Linear and nonlinear transforms were applied onto each individual MRI in warping them into MNI-space. The WMH thus measured is the normalized and relative WMH lesion load rather than the absolute volume.

Separation of periventricular (PVWMH) and deep (DWMH) white matter hyperintensities

Since all the WMH were detected in the “standard” space, we traced these ROIs using the standard space template to form various ROI masks so that an automatic separation of WMH into DWMH and PVWMH could be achieved. Any WMH extracted from the ROIs of anterior horn, posterior horn and periventricular body as defined in the Supplementary Figure (available on-line) were regarded as PVWMH, with the remaining being DWMH. The periventricular region defined as up to 10 mm deep from the ventricular wall of the standard brain as shown in a previous publication (Wen and Sachdev, 2004). The choice of 10 mm was based on an examination of the brains visually, and a consensual decision made by the investigators that this included the majority of the variance in the PVWMH. All 397 scans were checked for the coverage of the relevant ROIs over the ventricles by superimposing the scans with the mask image. We confirmed that all brains had their ventricles inside the designated ROIs (anterior horn, posterior horn and periventricular body), which guaranteed that PVWMH would not be taken as DWMH.

Intensity of WMH

Because the abnormal white matter signal varied in its intensity, we categorized it into “low” and “high” intensity lesions. The former usually appears as a milky fuzziness, whereas the latter as a white opacity to the naked eye. Because the neuropathological validity of this distinction has not been demonstrated, we present the total hyperintense lesions volume for the subsequent analyses. The numbers and sizes of nonconnected discrete WMH were also of interest and were calculated automatically by a computer program that estimated the diameter of each WMH, assuming it to be a sphere.

Volume measurement and statistical analysis

GM, WM and CSF were segmented using SPM2. Subarachnoid CSF (SA-CSF) (calculated as the difference between the total CSF and volume of lateral ventricles) was used as an index of cortical atrophy. To account for variable head sizes, total intracranial volume (TIV) was used for normalizing GM, WM, CSF, SA-CSF and lateral ventricle CSF (LV-CSF). The statistical analyses of this section were performed using the SPSS package (Version 12; SPSS Inc., Chicago, IL, USA). We observed that all subjects had at least some WMH and the normalized WMH volumes ranged from 352 mm$^3$ (0.352 ml) to 50408 mm$^3$ (50.408 ml), strongly skewed towards the lower end ($n = 397$; skewness = 4.229; kurtosis = 30.741). Natural logarithm transform of WMH volumes ($n = 397$; skewness = 0.218; kurtosis = 0.155) was hence used in the subsequent analyses. The interaction between WMH volumes and brain atrophy was tested in linear correlation analysis by examining the relationships between WMH volumes, including the total WMH, DWMH and PVWMH vs. normalized GM, WM, SA-CSF and LV-CSF with sex as a control factor. DWMH comprised WMH of frontal, temporal, parietal and occipital lobes and PVWMH of anterior horn, posterior horn and periventricular body as defined in Wen and Sachdev (2004).

Voxel-based morphometry (VBM)

Deformation-based morphometry such as VBM represents an analysis of the deformation fields that spatially normalizes images into a “standard” space. However, differences in brain anatomy may not be completely encoded by these deformations; local structural differences may persist after spatial normalization. VBM was introduced to characterize these differences (Friston and Ashburner, 2004). VBM was not a substitute for the analyses of the global measures such as the volumes of total gray matter, SA-CSF and lateral ventricle in our study. VBM complemented our investigation by specifying regional gray matter changes in relation to WMH load. VBM was carried out using an optimized method as reported by Good et al. (2001a,c). The 3D structural T1-weighted MR images were processed using SPM2 with Matlab 6.5 (Math-Works, Natick MA, USA). Regional designation of gray matter changes, such as lobes and Brodmann area numbers, was determined by the Talairach Daemon (Lancaster et al., 2000). As the various preprocessing steps implicit in VBM, such as brain extraction, spatial normalization, segmentation, modulation and smoothing have been detailed by Good et al. (2001a,b,c) and Ashburner and Friston (2000), we will briefly describe these steps and the processing components pertinent to this study here.

Scan selection. The T1-weighted structural scans available ($n = 477$) were spatially normalized to the MNI-template. They were all segmented into GM, WM and CSF in their native space. The results of spatial normalization and segmentation were then visually checked and rated. The only criterion for the inclusion/exclusion of the scans was the spatial normalization and tissue segmentation quality and the rater was blind to any other information or identity of the scans. There was no bias found between the ones selected or removed for the study. Finally, the scans of 397 subjects with high quality in both spatial normalization and segmentation results were chosen for the study, which meant 17% of the total scans were excluded from the sample due to our stringent selection criteria for ensuring the reliability and robustness of the results. The identity of the subjects was not known to the operator in making the selection.

Customized templates. There are several reasons to use study-specific templates due to mainly the possible differences between the demographics of the study participants and the subjects contributing to the templates, and the possible systematic differences introduced by each scanner such as the scanner-specific nonuniformities in image intensity and inhomogeneities in B0 field. Because the participants’ ages in our study were between 60 and 64, while the default prior probability maps and T1-weighted template are based on young healthy subjects, customized gray and white matter and cerebral spinal fluid templates were created from
the subjects of the study. This process involved spatially normalizing the structural T1-weighted scans (397 scans) to the MNI-template, segmenting each normalized image into gray and white matter and CSF compartments, and smoothing each gray and white matter segment with an 8-mm FWHM Gaussian kernel. The smoothed segments were averaged to form gray and white matter and CSF templates, respectively.

**Normalization, segmentation, modulation and smoothing.** Segmentation of MR images into GM, WM and CSF compartments was carried out after the original images were affine transformed. GM, WM and CSF images resulting from the segmentation process contain voxels with values representing the probabilities of voxels being a particular tissue type (or CSF). The process of modulation incorporated as part of optimized VBM (Good et al., 2001a,b,c) was designed to correct for the volume changes introduced by spatial normalization. As a result of nonlinear spatial normalization, the volumes of certain brain regions may grow, whereas others may shrink. To preserve the tissue volume, we included the modulation step in the data process. The normalized, segmented, modulated images were finally smoothed with a 12-mm FWHM Gaussian kernel.

**Results**

The mean and standard deviation (SD) of total WMH volume for these 397 subjects were 4.773 ml and 4.519 ml, respectively. If the total WMH was divided into DWMH and PVWMH, the means (SD) for these two partitions were 1.745 (2.941) and 3.019 (1.973) ml, respectively, suggesting that, in this age group, PVWMH contributed about two thirds of the total WMH.

**Global atrophy indices and WMH**

The relationship between global atrophy and WMH was investigated using linear correlation analysis. Four segmented and normalized volumes, i.e. total gray matter (cortical and subcortical), white matter, lateral ventricles and SA-CSF, were examined in relation to WMH volumes (see **Table 2**). We examined these linear correlations initially for the whole group, controlling for sex, and subsequently for male and female subgroups separately (Fig. 1).

The DWMH and PVWMH were both significantly correlated with gray matter reduction, but only DWMH had a significant correlation with SA-CSF increase and lateral ventricular dilation. As shown in **Table 2**, WMH vs. atrophy correlation coefficients are different for men and women. We compared two correlations with the following statistics if both correlations were significant ($p < 0.05$). If there were two correlations, $r_1$ and $r_2$ based on samples $N_1$ and $N_2$, we transformed the two correlations into $Z_1$ and $Z_2$ using $Z_i = \frac{1}{2} \ln \left( \frac{1 + r_i}{1 - r_i} \right)$, then calculated the $z$-statistic using $z = \frac{z_1 - z_2}{\sqrt{\frac{1}{N_1 - 1} + \frac{1}{N_2 - 1}}}$. Two notable features of these relationships were: (a) stronger correlations ($z = 1.6232, p < 0.05$ for GM reduction) between WMH volumes and atrophy were found in women; (b) DWMH (GM reduction, SA-CSF increase and lateral ventricular dilation were all significant) volumes had higher correlations with brain atrophy measures than PVWMH (only GM reduction was significant). Conversely, we found that white matter volumes were not correlated with total WMH or DWMH.

![Table 2](image)

<table>
<thead>
<tr>
<th>Correlation coefficient $r$ and significance</th>
<th>Male ($n = 218$)</th>
<th>Female ($n = 179$)</th>
<th>Male and female combined ($n = 397$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWMH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray matter</td>
<td>0.211; 0.002</td>
<td>0.130; 0.067</td>
<td>0.160; 0.037</td>
</tr>
<tr>
<td>Subarachnoid CSF</td>
<td>0.399; 0.000</td>
<td>0.182; 0.007</td>
<td>0.248; 0.001</td>
</tr>
<tr>
<td>Lateral ventricle</td>
<td>0.325; 0.000</td>
<td>0.173; 0.011</td>
<td>0.248; 0.001</td>
</tr>
<tr>
<td>PVWMH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray matter</td>
<td>0.246; 0.000</td>
<td>0.170; 0.011</td>
<td>0.204; 0.005</td>
</tr>
<tr>
<td>Subarachnoid CSF</td>
<td>0.376; 0.000</td>
<td>0.204; 0.011</td>
<td>0.376; 0.000</td>
</tr>
<tr>
<td>Lateral ventricle</td>
<td>0.273; 0.000</td>
<td>0.132; 0.007</td>
<td>0.273; 0.000</td>
</tr>
</tbody>
</table>

*Two-tailed Pearson correlation coefficients $r$ and significance were used.*

*Two-tailed partial correlation coefficients $r$ and significance were used (controlling for gender).*

*Natural log of WMH volumes were used.*

**Table 2** Correlations between white matter hyperintensity volumes and gray matter, subarachnoid CSF and lateral ventricle volumes.
Regional gray matter changes using VBM

Regionally specific relationships between gray matter volume and WMH load were assessed using multiple regression analyses, with modulated gray matter volume as the response variable, natural logarithm of WMH volumes as the explanatory variable and total GM volume age as covariates. In the first set of analyses, the WMH volumes in the frontal, temporal, parietal and occipital lobes were used individually to examine the cortical gray matter changes. The cumulative WMH load such as the total WMH, PVWMH and DWMH were also used in the same manner. The second set of analyses accounted for sex, and the male and female subgroups were analyzed separately. The resulting t statistics were thresholded at \( p = 0.05 \), and corrected for multiple comparisons using the false discovery rate (FDR) (Nichols and Hayasaka, 2003; Genovese et al., 2002).

The results showed that although there was a strong association between the total WMH load and lobar WMH load, the correlation between the regional GM reduction and the WMH load of the same region was more prominent (Figs. 2 and 3). For example, while total WMH correlated significantly with GM reduction in nearly every lobe, temporal WMH load correlated only with the GM reduction in the temporal lobe (Fig. 2). It can be observed from Fig. 3 that regional GM reduction tends to be more strongly influenced by the WMH load of the same region than another regional WMH. The data also showed that DWMH correlated more strongly with cortical GM reduction than PVWMH. This is depicted in Fig. 3 which shows more cells with warmer colors in the DWMH column in lobar areas than the PVWMH column. Furthermore, it can also be seen in Fig. 3 that the correlation between total brain WMH load and brain atrophy was predictably in between the two. We have looked into the negative correlations as well for all the VBM analyses. We have not detected any significant negative association, i.e. WMH related to increased gray matter volume/density.

In relation to sex, men and women showed different patterns of correlation between regional gray matter reduction and regional WMH load. We found that women in general showed significant correlations between WMH load and GM reduction in more areas in nearly every lobe (Fig. 3), which coincided with the results using global measures as shown in Table 2. Fig. 3 summarizes the results from seven multiple regression analyses in the VBM framework for each group of subjects. The color in each cell represents the \( t \) score of the region which showed significant correlations (false discovery rate: \( p < 0.05 \)) between GM reduction and WMH load in the region or globally, with blue indicating a lack of a significant correlation. We would like to point out that although the warm colors indicate a significant correlation, they in general have relatively low \( t \) values which suggest that the correlations were moderate.

We used subject’s age as covariates in the VBM models, even though our sample had a relatively narrow age range (max age difference was five years). Our statistical analyses demonstrated a significant impact of age on the total gray matter volume, i.e. a significant total gray matter reduction with advancing age. The differences between the VBM results with or without controlling for age were also apparent: the models with age as covariates produced fewer number of areas of significant correlations between WMH and GM.

Discussion

The results of this study suggest that the brain’s WMH load is significantly correlated with the various indices of brain atrophy examined—reduction in GM volume, increase in subarachnoid CSF and lateral ventricular dilation. There was some regional specificity in this relationship, with the closest associations being between the GM reduction and WMH load in the same lobe. A noteworthy finding was that DWMH volumes had stronger...
relationship with all atrophy indices than PVWMH, despite the fact that DWMH accounted for only one-third of total WMH.

The findings suggest that WMH are associated with loss of brain volume. This must be understood in the context of the neuropathology of these MRI-visible lesions. WMH on T2-weighted FLAIR sequences are nonspecific findings that may represent diffuse rarefaction, demyelination, axonal loss, changes in glial cell numbers and morphology or some other pathology (Fazekas et al., 1993). For volume loss to be a prominent feature of WMH, demyelination and/or axonal loss must be prominent in the pathology. Microinfarction has been described in large WMH, and this may be another process of volume loss. That this process is occurring significantly in individuals in their early 60s, living in the community emphasizes the need to examine brain aging from a different perspective—as a process that begins much before the sometimes arbitrary age cut-off of 65 years.

The cross-sectional nature of this study makes it difficult to deduce the direction of causality in the relationship between WMH and atrophy. There are three possibilities: (i) white matter pathology is primary, with loss of gray matter being secondary to consequent neuronal cell loss, and together these contribute to ex-vacuo dilatation of the ventricles; (ii) WMH are representative of white matter change secondary to atrophy of the gray matter and (iii) both white and gray matter changes are due to shared pathoetiological processes, in particular, cerebral ischemia. The regional specificity of the WMH-gray matter relationship suggests a correspondence between white matter change in gray volume loss in that region. If cerebral ischemia is the basis of this pathology, white matter is likely to be more severely affected because of its greater vulnerability to ischemia (Pantoni and Garcia, 1997). White matter lesions are therefore likely to be the first events in the causal chain. We therefore consider it likely that WMH represent a primary pathology which leads to injury to the neuronal cell body. Loss of gray matter volume does not necessarily imply loss of neurons, but may reflect a reduction in dendritic arborization or the overall size of the neuron. Ventricular dilatation is likely to be due to loss of white matter. Sulcal dilatation may, on the other hand, occur both with white matter or gray matter loss. We point out that the coexistence of these two common MRI findings and how they were correlated with each other were the focus of this study. The discussion on the possible associations between the risk factors listed in Table 1 and brain atrophy and WMH was not within the scope of this paper, and will be the subject of a separate study.

The differential relationship of DWMH and PVWMH with atrophy in our study is worthy of discussion. These two subcategories of WMH were strongly correlated ($r = 0.646; p < 0.001$) in this study, which is consistent with other reports (DeCarli et al.,
2005). It has been reported that there is a decreasing gradient of WMH as one moves away from the wall of the lateral ventricle, with the corollary that the distinction between DWMH and PVWMH may not be meaningful (DeCarli et al., 2005). Our data suggest that the distinction is clinically relevant, and should not be abandoned. PVWMH accounted for about two-thirds of the total WMH load in our subjects, but DWMH showed a stronger relationship with atrophy indices, including ventricular volume. Various studies have pointed to etiological and neuropathological differences between DWMH and PVWMH. The caps and lines of PVWMH are neuropathologically related to myelin pallor or rarefaction without other convincing evidence of ischemia (Fazekas et al., 1993; Scheltens et al., 1995). One of the mechanisms of their development is fluid shifts to and from the ventricles. DWMH are generally associated with microangiopathy, and the ischemic nature of these is much more convincing (Fazekas et al., 1993; Scheltens et al., 1995; Takao et al., 1999). Other etiological factors may be differentially related to the two subcategories, e.g. homocysteine was reported to be a determinant of DWMH but not PVWMH (Sachdev et al., 2004b). The severity of tissue damage is therefore more extensive with DWMH and this may explain the relationship seen in this study. The functional consequences of the two are somewhat different in relation to cognition (de Groot et al., 2001a,b; Ylikoski et al., 1993), motor function (Sachdev et al., 2005) and emotions (Steffens et al., 2002). These arguments support the distinction between DWMH and PVWMH, at least until a better understanding of their pathogenesis is available.

An important feature of this study is the use of VBM for analysis. Due to the fact that WMH of each lobe were strongly correlated to each other, from the lowest between frontal and occipital (0.249, \( p = 0.000 \)) to the highest between frontal and parietal (0.824, \( p = 0.000 \)), the influence of WMH within any particular region to gray matter reduction was multi-regional and complex. The results from multiple regression models of VBM for the regional WMH loads as well as total DWMH and PVWMH and their sum-total (Total WMH), showed not only the gray matter reduction of the region but also of other regions which showed somewhat weaker correlations nevertheless. Regional analyses further supported the findings using global indices that females had stronger correlation between WMH load and cerebral atrophy than males. Another large epidemiological study of WMH has shown a higher prevalence in women compared to men aged over 60 years (Sijens et al., 2001), which may be due to a larger age-related decrease of the brain choline level in women (Sijens et al., 2003). The drastic changes in circulating hormone concentrations due to menopause in women around age 50 years could be one cause (Lamberts, 2002; Raz et al., 2004), but this assertion requires further investigations to be validated. Compared with the results arrived at with these two different methods, the regional analysis using VBM demonstrated anatomical specificities.
There have been discussions on potential limitations of VBM elsewhere (Ashburner and Friston, 2000; Good et al., 2001b; Ashburner and Friston, 2001). For instance, there can be contributions from artifactual sources such as imperfections in the spatial normalization that themselves show a regional specificity (Good et al., 2001c). Therefore, some significant correlations from the multiple regression analyses (t scores and thus p values) shown in the areas (either lobar or Brodmann) could also be artifact-related effects. The information attained using the VBM method should therefore be considered along with that from global measures. Characterizing the cortical surfaces quantitatively (Tilak Ratnanather et al., 2004; Thompson et al., 2003) and then mathematically modeling the relationship between WMH and overlying cortex may lead to more robust and reliable insights into the association between them.

One of the strengths of this study is that the sample comprised a large community-based asymptomatic cohort. These subjects did not suffer from a neurological disorder and the WMH in their brains are likely to be at an early stage. Considering the stage of their development, the finding of a relationship with atrophy therefore has particular significance. The main limitation of the study is that it is cross-sectional and the casual nature of the relationship cannot be inferred. A repeat assessment of this cohort is planned in 4 years' time, which will address this deficiency. Another limitation is imposed by the manner in which PVWMH and DWMH were delineated. In the periventricular region, WMH often extend from the ventricle wall into deep white matter with no natural demarcation (DeCarli et al., 2005). Therefore, two complexities may occur. First, a demarcation line may go through a confluent WMH and portion of its volume was counted as PVWMH and the rest DWMH, which then rendered the division of WMH into PVWMH and DWMH somewhat capricious. The same ambiguity happened when dividing total brain WMH into each lobe. Second, individuality in lateral ventricle shape and size influenced the inclusion or exclusion of a particular WMH cluster (a group of connected WMH voxels) for PVWMH or DWMH. Our argument for retaining the separation of DWMH and PVWMH is based on the possible clinical relevance suggested by our data, such as the stronger correlations of GM atrophy with DWMH than PVWMH, even though DWMH accounted for only about one-third of the total WMH. We concede that further efforts at refining the demarcation of DWMH and PVWMH are needed so that the differentiation of the impact of DWMH and PVWMH will be more meaningful.

In conclusion, the results of this study show that WMH are related to volumes of gray matter and CSF and therefore brain atrophy. We cannot determine which process is primary, but the nature of the change leads us to argue that WMH may be the primary lesions that lead to ventricular and sulcal dilatation and loss of cortical gray matter. Alternatively, these may be independent processes that have shared etiology. The study also demonstrates that DWMH may be more significant in producing structural brain changes, and may therefore be more functionally relevant. Further delineation of this relationship needs a longitudinal study of the changes in both WMH and indices of brain atrophy.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuroimage.2005.08.057.

References


