Changes in total cerebral blood flow and morphology in aging

Spilt, A.

Not all age-related white matter hyperintensities are the same, a magnetization transfer imaging study

Chapter 9

Not all age-related white matter hyperintensities are the same, a magnetization transfer imaging study

Aart Spilt
Rutger Goekoop
Rudi G.J. Westendorp
Gerard J. Blauw
Anton J.M. de Craen
Mark A. van Buchem

Purpose
To assess whether the presumed histological heterogeneity of age-related white matter hyperintensities (WMH) is reflected in quantitative magnetization transfer imaging (MTI) measures.

Materials and methods
From a group of patients participating in a double blind placebo controlled multicenter study on the effect of pravastatin (PROSPER) we selected 56 subjects with white matter hyperintensities (WMH). WMH were classified as periventricular WMH (PVWMH) and deep WMH (DWMH). PVWMH were subclassified as irregular or smooth, depending of the aspect of their border. The signal intensity of all WMH on T1 weighted images was scored as iso- or hypointense. The mean magnetization transfer ratio (MTR) value of the different types of WMH was assessed and compared. As control group we selected 19 subjects with none or limited WMH.

Results
Mean MTR of PVWMH (mean (SE)) (frontal: 31.2% (0.2%), occipital: 32.2% (0.2%)) was lower than that of DWMH (33.7% (0.5%)). The mean MTR of frontal PVWMH (31.2% (0.2%)) was lower than that occipital PVWMH (32.2% (0.2%)). As compared to occipital PVWMH, frontal PVWMH more often had a smooth lining (82% frontal versus 8% occipital) and an area with low signal intensity on T1 weighted images (76% frontal versus 35% occipital). MTR did not differ between smooth (31.1% (0.3%)) and irregular (31.6% (0.5%)) PVWMH.

Conclusion
Age-related WMH are heterogeneous, despite their similar appearance on T_2-weighted images. By taking into account the heterogeneity of age-related WMH, both in terms of etiology as in terms of severity of tissue destruction, a better understanding on the causes and consequences of these lesions may be obtained.

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Introduction

White matter hyperintensities (WMH) are striking abnormalities that are often found on T_2 weighted and fluid attenuated inversion recovery (FLAIR) images in the elderly. WMH occur in about 30% of healthy subjects over sixty years old and their prevalence shows a steady rise with increasing age[3]. WMH can be divided in two subtypes according to their location. Periventricular WMH (PVWMH) aligning the lateral ventricles and the deep WMH (DWMH) in the remaining white matter. The most important and consistent risk factor for WMH is age; other established risk factors are: female sex[4], aortic atherosclerosis[5], and elevated systolic blood pressure[6]. The correlation between WMH and cognitive functioning is not yet clear. In some studies correlations are found[139], whereas in other studies no such relations are observed[140]. In studies where WMH are sub classified, different functional correlates have been found for PVWMH and DWMH. PVWMH are correlated with cognitive decline[7], and DWMH are correlated with late onset depression[141].

In correlative radiologic-pathological studies it has been demonstrated that WMH, although having a uniform appearance on MR, are histologically heterogeneous. Braffman et al. found WMH in the elderly to represent white-matter infarctions, white matter gliosis or plaques of demyelination[124]. Based on their radiological appearance Fazekas et al. distinguished PVWMH with a smooth delineation and those with an irregular border with the surrounding normal appearing white matter[142]. At autopsy, samples were taken from the periventricular white matter, and histological findings were compared between PVMWH with an irregular and those with a smooth border. Histologically, smoothly delineated periventricular lesions were characterized by subependymal gliosis, demyelination and discontinuation of the subependymal lining. These abnormalities were felt to be of non-ischemic origin. On the other hand, irregular lesions showed microcystic infarcts and patchy rarefaction of myelin and were considered to be of ischemic origin [142].

Despite histological differences, all WMH look similar on conventional T_2 and proton-density weighted images as well as on FLAIR images. Magnetization transfer imaging (MTI) has proven to be able to reflect histologic differences better than conventional MR techniques. Using MTI, the amount of magnetization transfer in tissues can be assessed and quantitatively reflected by a magnetization transfer ratio (MTR). Different histological changes are differently reflected in MTR values. Edema and demyelination give rise to different MTR values[127] and in the multiple sclerosis (MS) literature good correlation has been found between the degree of demyelination and axonal loss on the one hand and MTR measures on the other hand[137]. Age-related

WMH were studied with MTI by Wong et al.[135], who found lower MTR values in PVWMH as compared to normal white matter[135]. Hanyu et al.[136] found a correlation between the MTR values of age-related PVWMH and cognitive functioning.

There is more radiological evidence that suggests that age-related WMH have different histological substrates. In our experience, PVWMH in elderly patients often are hypointense on T_1 weighted images as compared to the surrounding brain parenchyma.

The aim of this study was to assess whether the presumed histological heterogeneity of age-related WMH is reflected in quantitative MTI measures. For that purpose we compared MTR values in PVWMH and DWMH, compared MTR values between smooth and irregular PVWMH, between frontal and occipital PVWMH, and between PVWMH with normal or hypointense signal on T_1 weighted images.

Materials and methods

Patients

Patients included in this study were selected from the first 184 participants of a double blind placebo controlled multicenter study on the effect of pravastatin on the occurrence of cerebrovascular events in elderly (70-82 years of age) people with cardiovascular risk factors (PROSPER-trial; for detailed description see Shepherd et al.[42]). In these patients T_2 weighted images were screened for the presence of WMH, defined as areas with increased signal intensity in the white matter as compared to surrounding white matter. These areas were classified as WMH when they showed no mass effect, and could not be related to other types of pathology than aspecific white matter hyperintensities. Selection out of this patient group was based on the presence of DWMH and/or PVWMH. Subjects with periventricular lesions smaller than 0.5 mm (measured with a calliper on hardcopies of the T_2 weighted images) were excluded from the analysis. DWMH needed to be larger than five by five pixels in order to be included. Subjects with evidence of cerebral pathology besides aspecific WMH (such as infarction, tumours) on MR imaging were also excluded. This resulted in a group of 56 patients with WMH. As a control group, 19 individuals were chosen from the same group of 184 participants of the PROSPER trial of age and sex comparable to those of the study-group, showing no WMH or a very limited load (Scheltens score of I or less; corresponding to less than 5 mm thickness of PVWMH) of WMH[126]).

Image acquisition

All imaging was performed on a 1.5T ACS-NT15 Philips MR system equipped with a Powertrak 6000 gradient system (Philips Medical Systems, Best, The Netherlands). The following T_1 weighted spin echo sequence was used: repetition time/echo time (TR/TE) 600/20 msec, matrix 256, with a field of view (FOV) of 220, scan percentage of 80% and a rectangular FOV of 75%. Slice thickness was 6 mm with an interslice gap of 0.6 mm. A dual turbo spin echo sequence (3000/27 and 120 (TR/TE1 and TE2 in msec), echo train length 10, 3 mm slice thickness and no interslice gap, 256 matrix size with a FOV of 220 mm, 80% scan percentage) was used for WMH assessment. Magnetization transfer imaging (MTI) was performed using a 3D gradient echo pulse sequence (106/6, 12° flip angle, 5 mm slice thickness, 256 matrix size with a 220 mm FOV and 50% scan percentage). Two consecutive sets of axial images were acquired: the first was performed without a radio frequency saturation pulse, and the second in combination with a radio frequency saturation pulse (sinc-shaped, 1,100 Hz downfield of the H_2O resonance)[127].

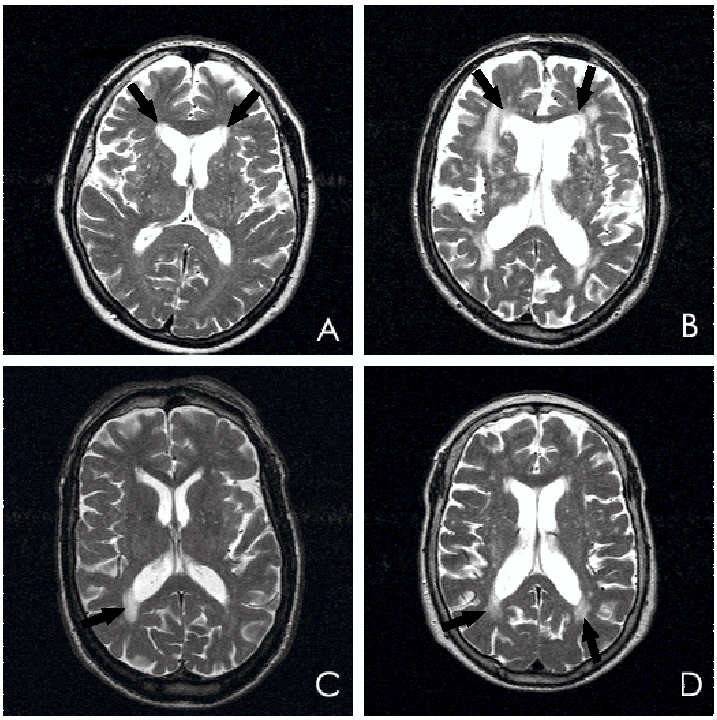

Figure 1 Different types of PVWMH. Examples of frontal PVWMH with a smooth lining (A, right and left) and frontal PVWMH with an irregular lining (B, right and left); and examples of occipital PVWMH with a smooth (C, right) and irregular (D, right and left) lining.

Lesion classification and segmentation

Periventricular lesions were detected and classified in irregular or smooth lesions (Figure 1) according to Fazekas et al.[142]. Smooth delineation was defined as having a smooth delineation with normal appearing white matter in all slices showing the PVWMH. Left and right PVWMH were considered separately. The classification of PVWMH was assessed in a consensus meeting by three of the authors (MAVB, RG and AS). This was done for occipital and frontal periventricular lesions separately. On T_1 weighted images the presence of periventricular hypointense lesions were assessed (Figure 2). They were defined as lesions with a signal intensity on T_1 lower than the surrounding white matter but higher than CSF. After categorizing, one rater outlined manually the PVWMH and DWMH in the patient group on the MT images acquired with saturation pulse (MS; which have a proton-density contrast) using 3DVIEWNIX image processing software (Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA). In the patient and control group, normal appearing periventricular white matter and deep white matter were manually outlined. Deep NAWM was outlined in the semioval center by placing four 5 by 5 pixels large regions of interest. The same regions of interest were used for sampling periventricular NAWM. No samples were taken from periventricular NAWM if periventricular lesions were present. For all outlined regions volume and mean MTR were calculated. MTR was defined as the percentage of change in signal intensity between the scans with and without the saturation pulse, as shown in the following equation[127]: $MTR = [(M_0 - M_S)/M_0] \times 100\%$.

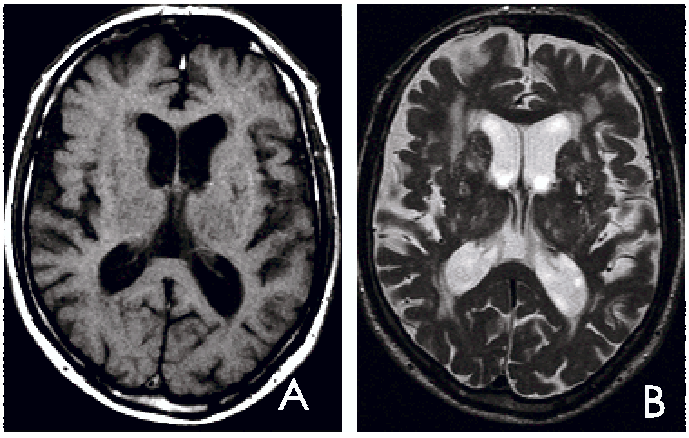

Figure 2 Example of a PVWMH with the charateristic high signal intensity on a T2 weighted image (A) with a low signal intensity on a T1-weighted image (B) (arrow).

Analysis

Data are presented as means (SE). Means were compared with t-tests. P-values below 0.05 were considered statistically significant.

Table 1 Baseline characteristics of study population.

	Subjects with WMH	Control subjects
n	56	19
Sex (M/F)	25/31	16/3
Age (year; [SD])	76 (3)	73 (3)
MTR of NAWM (%, [SE])	35.6 (0.1)	35.7 (0.2)

WMH = White matter hyperintensities.
MTR = Magnetization transfer ratio
NAWM = Normal appearing white matter

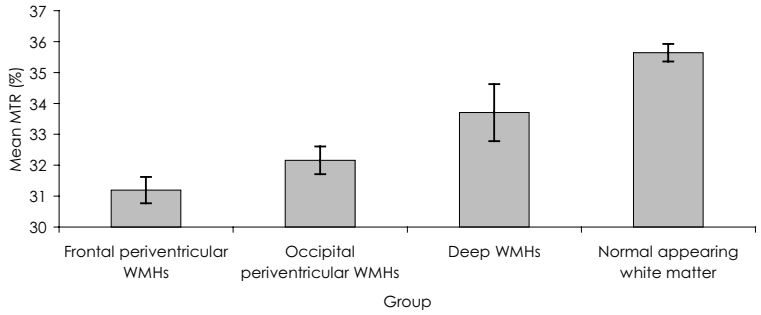

Figure 3 Mean MTRs with 95% confidence intervals for the four different regions in the subjects with white matter hyperintensities.

Results

MTR values were calculated in WMH of 56 people. The average age of this group was 76 year (sd: 3 yr) with 25 men and 31 women. In total 93 frontal PVWMH, 52 occipital PVWMH, 20 DWMH, and 104 regions with NAWM were outlined in the population with WMH. The control group comprised 19 subjects with an average age of 73 years (sd: 3 yr), 16 men and three women. In this group 38 regions with normal appearing deep white matter were outlined, 22 regions normal appearing frontal periventricular white matter, and 38 regions occipital normal appearing periventricular white matter. Table 1 shows the lack of difference (P=0.47) in MTR of NAWM between the study group (35.6% (0.1%)) and the control group (35.7% (0.2%)). Within the study group no differences in MTR were observed between deep (35.7% (0.2%)) and periventricular NAWM; and neither between frontal (36.0% (0.2%); P=0.13) and occipital (35.6% (0.2%); P=0.46) periventricular NAWM.

In the study group a significant difference in mean MTR was found between DWMH and PVWMH (Figure 3). The MTR of DWMH (33.7% (0.5%)) was higher than that of PVWMH (frontal: 31.2% (0.2%), P<0.001; occipital: 32.2% (0.2%), P<0.005). The mean MTR of frontal PVWMH was lower than that of occipital PVWMH (31.2% (0.2%) vs. 32.2% (0.2%); P<0.005) (Table 2).

Table 2 Magnetization transfer ratio of periventricular and deep normal appearing white matter and white matter hyperintensities.

	Periventricular				Deep	
	Frontal		Occipital			
	n	MTR(%, [SE])	n	MTR(%, [SE])	n	MTR(%, [SE])
NAWM	22	36.0 (0.2)	38	35.6 (0.2)	38	35.7 (0.2)
WMH	93	31.2 (0.2)	52	32.2 (0.2)*	20	33.7 (0.5)†

†P < 0.005 for difference between periventricular (frontal and occipital combined) and DWMH.
*P < 0.005 for difference between frontal WMH and occipital WMH.
WMH = White matter hyperintensities.
MTR = Magnetization transfer ratio
NAWM = Normal appearing white matter

Table 3 Magnetization transfer ratio values of smooth and irregular lesions in frontal and occipital white matter hyperintensities.

	Smooth	Irregular
Frontal		
n	76	17
MTR (%, [SE])	31.1 (0.3)	31.6 (0.5)
Number hypointense on T1 (%)	57 (75%)	14 (82%)
Occipital		
n	4	48
MTR (%, [SE])	32.1 (0.6)	32.2 (0.2)
Number hypointense on T1 (%)	1 (25%)	17 (35%)

MTR = Magnetization transfer ratio

A different proportion of frontal and occipital PVWMH was found to be smooth (Table 2). Sixty-seven of the 93 (82%) frontal PVWMH were smooth, whereas only four of the 52 (8%) occipital PVWMH were smooth. Mean MTR values of irregular and smooth PVWMH were not different (31.6% (0.5%) for irregular frontal versus 31.1% (0.3%) for smooth frontal (P=0.21) and 32.2% (0.2%) for irregular occipital versus 32.1% (0.6%) for smooth occipital (P=0.48)).

The periventricular hypointensities on the T_1 weighted images all had a smooth lining, regardless of the lining of the WMH on T_2 weighted images. In table 3 the proportions of PVWMH with a hypointense appearance on T_1 are shown. The majority of the frontal PVWMH had a low signal intensity on T_1 weighted images (76%), whereas only 35% of occipital PVWMH were hypointense on T_1 weighted images. No correlation was observed between the presence of hypointense signal on T_1 and irregularity of the PVWMH on T_2 weighted images.

In PVWMH with a low signal on T_1, the area with a hypointense signal on T_1 was invariably smaller than the area with a high signal intensity on T_2 weighted images.

Discussion

Our study confirmed the finding by others [133-137] that the MTR of WMH is lower than the MTR of NAWM in the elderly. In addition we found that the MTR of PVWMH is lower than the MTR of DWMH. Of interest are also the differences that we observed between the frontal PVWMH and occipital PVWMH: frontal PVWMH showed a lower MTR than the occipital PVWMH, and they showed more often a smooth lining and an area with low signal intensity on the T_1 weighted images. However, we did not find a difference in MTR between smooth and irregular periventricular lesions.

In this study, MTR analysis demonstrated significant differences between PVWMH and DWMH: lower MTR values were observed in PVWMH than in DWMH. This finding corroborates an observation by Tanabe and co-workers who reported similar differences in MTR values between periventricular and deep WMH in subcortical ischemic vascular dementia[134]. It could be argued that these findings are merely based on an artefact, due to the inclusion of periventricular pixels with partial volume effects of CSF in the periventricular region of interest, which might give rise to artificially low MTR values of PVWMH. But, if this would have been the case then we would have also expected a difference between the deep and periventricular NAWM in the control subjects, which was not observed. We rather believe that these MTR changes reflect histologic differences between deep and periventricular WMH.

Two explanations for histological differences between DWMH and PVWMH can be put forward. First, assuming that lesions in both locations are due to ischemia, the pathophysiological mechanisms that lead to ischemia in these locations may be different and the severity of the resulting ischemia could be different. The periventricular white matter is an arterial border zone that is supplied by long perforating arteries, and is supposed to be particularly vulnerable for decreases in cerebral blood flow[143]. The observed stronger association between cardiovascular risk factors with PVWMH as compared to DWMH also suggests a difference in aetiology[144]. It is conceivable that perfusion can be jeopardized by more mechanisms (drops in blood pressure, diffuse small vessel disease, atherosclerosis, emboli) in the periventricular than the deep white matter (atherosclerosis, emboli), resulting in a higher accumulation of ischemic damage in the periventricular location.

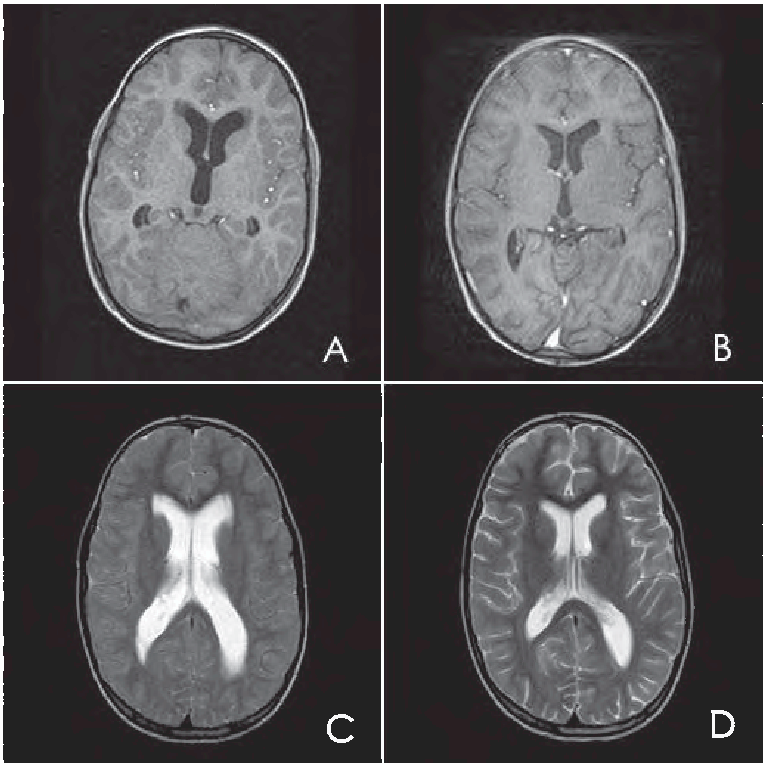

Figure 4 Subject (8 year old) with an obstructive hydrocephalus secondary to infratentorial mass before (A: T1-weighted image; C: T2-weighted image) and after placement of a ventricoperitoneal shunt (B: T1-weighted image; D: T2-weighted image). Notice the location and lining of the areas with increased signal intensityhypointensities on T1-weighted images in the periventricular white matter before drainage (A), disappearing after drainage (B).

A second explanation for the observed differences in MTR between DWMH and PVWMH is not based on differences in vascularization between these brain areas, but on differences in interstitial fluid dynamics. Since the brain is devoid of a lymphatic system, interstitial fluid is transported through the extracellular space of the brain and through the ependymal lining to the ventricles [145,146]. Once in the ventricles, the ependymal lining prevents the CSF from leaking into brain parenchyma. Since in elderly subjects with PVWMH partial disappearance of the ependymal lining of the ventricles has been observed, it is conceivable that increased interstitial water resulting from ependymal dyscontinuation contributes to the high signal intensity on T_2 weighted MR images[142]. The similarity between the distribution of age-related PVWMH and the reversible periventricular high signal intensity on T_2 weighted images that can be observed in patients with obstructive hydrocephalus (see Figure 4) supports this hypothesis. The observed lower MTR values in PVWMH

as compared to DWMH could thus be based on the additional contribution of increased interstitial fluid concentration on MTR values in the periventricular white matter which is absent in the deep white matter.

Apart from differences in MTR values between DWMH and PVWMH, differences were also observed between frontal and occipital PVWMH, suggesting there are also differences in histological composition of PVWMH in these locations.

Differences between frontal and occipital PVWMH are also suggested by the observation in our study that frontal PVWMH more often have a smooth lining than occipital PVWMH. This observation can be explained by what is known about the natural history of WMH. WMH in the periventricular location occur early on in life in almost every individual, often long before the appearance of DWMH. These periventricular lesions have a smooth lining and are most pronounced around the frontal horns and along the laterosuperior border of the bodies of the ventricles[122,147]. Later and in a more limited number of individuals, the PVWMH in these locations may further grow, start showing an irregular border and may confluence with concomitant DWMH, and PVWMH may also start being more pronounced in other locations, such as around the occipital horns of the lateral ventricles [122,147]. These observations suggest that age-related PVWMH around the frontal and occipital horns have different aetiologies.

PVWMH in the frontal location more often showed low signal intensity on T_1 weighted images than occipitally, corroborating the suggestion of differences in tissue composition between these two locations based on our MTI analysis. These hypointense areas may partly be explained by more severe tissue destruction in this location, but the specific shape of the hypointense areas around the frontal horns and its relation with the areas with high signal on T_2 weighted images rather suggests a different pathogenesis. The frontal hypointense areas invariably had the appearance of smoothly delineated frontal caps irrespective of the delineation of the same lesions on T_2 weighted images (Figure 2). And often the frontal hypointense areas were smaller than the hyperintense areas in the same location and in the same patients (Figure 2). The morphological similarity between the frontal periventricular hypointense lesions and the frontal hyperintense caps that are prevalent in most adults suggests 1) that these lesions are based on the same aetiology, and 2) that this aetiology differs from that of the occipital and larger, irregular frontal PVWMH. Based on our observations we hypothesize that frontal PVWMH are partly caused by increased interstitial fluid accumulation and partly by ischemia, whereas in the development of occipital and large, irregular frontal PVWMH there is less influence of interstitial fluid dynamics. This hypothesis is

supported by observations from Fazekas who demonstrated that irregular PVWMH on MRI correlated with more severe ischemic changes on histology than smooth PVWMH [142].

We found no difference in MTR values between smooth and irregular periventricular lesions. This seems contradictory to the observations from Fazekas, who, on histology, found more ischemic tissue destruction in PVWMH with an irregular border on MRI than in smoothly delineated PVWMH. However, the larger contribution of increased interstitial fluid in smooth lesions may, in terms of MTR values, have compensated for the more severe tissue destruction in irregular lesions.

In conclusion, the findings in this study demonstrate that age-related WMH despite their similar appearance on T_2 weighted images are heterogeneous. In most studies aimed at assessing the causes and the functional consequences of age-related WMH, all WMH are treated equally by assessing the total volume of WMH based on T_2 weighted images. In general, such studies show poor, if any, correlations between the load of WMH on the one hand, and measures of cognitive functioning or risk factors on the other hand. By taking into account the heterogeneity of age-related WMH, both in terms of aetiology as in terms of severity of tissue destruction, a better understanding on the causes and consequences of these lesions may be obtained.