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Original article

Superficial white matter hyperintensities are associated with mild tissue alterations in vascular aging

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ABSTRACT

In the elderly, white matter hyperintensities (WMH) are usually rated as periventricular or deep. However, recent data suggest that superficial WMH may be associated with distinct mechanisms and may be associated with milder underlying tissue alterations. We developed and validated a new grading scale to differentiate superficial WMH from other WMH (either periventricular or deep). We evaluated individuals with high loads of WMH from MEMENTO, a multicenter memory-clinic study, to evaluate the links between superficial WMH and 1) MRI markers of cerebral small vessel disease (number of lacunes and microbleeds and normalized brain volume); 2) cognitive outcomes including global evaluation with Mini Mental State Examination (MMSE). Our analytical sample included 208 participants. Participants with higher grades of superficial WMH had larger normalized brain volumes (82.1 ± 1.3% vs 81.0 ± 1.1%, $P < 0.001$) and were more frequently women (85.0% vs 51.4%, $P = 0.01$). In total contrast but as expected, participants with higher grades of other WMH were older (79.8 ± 8.1 vs 75.5 ± 6.2 years, $P < 0.001$), had more often lacunes (41.7% vs

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7.1%, $P < 0.001$) and performed worse at the MMSE (26.8 ± 2.0 vs 28.1 ± 1.7, $P = 0.01$). Our results support the hypothesis that superficial WMH are distinct from other WMH and probably correspond to mild tissue alterations.

1. Introduction

White matter hyperintensities (WMH) are generally differentiated into periventricular and deep WMH, as defined by the widely used Fazekas scale [1]. In CADASIL, a monogenic cerebral small vessel disease (SVD) considered a pure model to study more frequent sporadic forms, superficial WMH, even when extensive, are not associated with worse clinical outcomes [2,3], in line with results previously obtained in sporadic SVD [4]. Extensive superficial WMH may even be associated with larger brain volumes and a report in a female patient suggested that this may be due to potentially reversible increase of water content [2,5]. The presence of multiple spots WMH in subcortical areas has also been associated with cerebral amyloid angiopathy (CAA) [6]. For large loads of other WMH, which would be considered as high grades of either periventricular or deep WMH in the Fazekas scale, often corresponding to severe tissue damage, their extent is strongly related to clinical severity [2,4]. Altogether, these results support that superficial WMH are related to distinct mechanisms than other WMH and should be evaluated separately.

However, in daily clinical practice, superficial WMH are rarely differentiated from periventricular and deep WMH.

From a cohort of elderly patients, at risk of Alzheimer's disease and with large loads of WMH we aimed at 1) evaluating the extent of superficial WMH with a specifically designed scale, 2) exploring their relationships with cardiovascular risk factors, other magnetic resonance imaging (MRI) markers of SVD, particularly brain volume, and clinical outcomes.

2. Material and methods

2.1. Study population

Participants were selected from MEMENTO, a large multicenter memory clinic-based cohort study designed for better understanding the natural history of Alzheimer's disease and/or SVD as soon as early subjective and cognitive manifestations. Blind to brain MRI assessment, 2,323 patients were included prospectively and consecutively from 2011 to 2014 in 26 French memory clinics. At inclusion, participants were not demented, and presented either light-to-moderate cognitive impairment (based on neuropsychological tests), or isolated cognitive complaints while being $\geq$ 60 years old. The ability to undergo brain MRI and absence of a recent stroke ($\leq$ 3 months) were part of eligibility criteria. Comprehensive details on MEMENTO inclusion criteria and procedures have been reported elsewhere [7].

According to MEMENTO study protocol, demographic variables were systematically collected, including age, sex, level of education, as well as cardiovascular risk factors such as hypertension (defined as anti-hypertensive drug intake or mean of three blood pressure measurements either $\geq$ 140 mmHg for systolic blood pressure or $\geq$ 90 mmHg for diastolic blood pressure) and current smoking, which were considered relevant covariates for this report. All patients underwent a comprehensive neuropsychological battery. In the present analyses we used Mini Mental State Examination (MMSE) as a reflect of global cognitive abilities [8] (best score = 30), trail-making test version A (TMT-A) as a marker of processing speed [9] (completion time measured in seconds), semantic and literal verbal fluency (animals and letter p, maximum words in 2 min) as markers of executive functions [10] and Free and Cued Selective Reminding Test (FCSRT) to evaluate memory [11] (sum of the total of the 3 recalls, best score = 48). The Short Physical Performance Battery (SPPB) was used to evaluate gait defect, a major complaint in SVD patients [12] (best score = 12).

2.2. Standard protocol approvals, registrations, and patient consents

The study protocol was approved by a local ethics committee and all patients gave their written informed consent to participate.

2.3. Magnetic resonance imaging, post-processing and grading of WMH

Neuroimaging acquisitions in the 26 centers were coordinated by the Center for Automated Treatment of Images (cati-neuroimaging.com). Brain MRI were mostly performed on 3 Tesla scanners (86%), 1.5 Tesla otherwise. The acquisition protocol included high-resolution 3D T1, 2D FLAIR (slice thickness = 2.5 or 5 mm) and 2D T2* sequences, as previously described [7].

Among the 2,323 Memento participants, 2,176 had exploitable MRI data. In the present study, further measurements of SVD neuroimaging markers were performed in 217 participants with the largest volumes of WMH (defined by the 90th percentile of WMH volume distribution measured automatically using the WHASA algorithm [13]). Indeed, below the 90th percentile, participants had low volumes of WMH on average (5.1 mL, interquartile range [2.5–9.1]) corresponding to limited extents of WMH and were considered irrelevant for the present analyses. Nine subjects were further excluded (7 had a large ischemic lesion; 1 had a subdural hematoma; 1 had a probable CAA-related inflammation), leaving a sample of 208 participants for analysis.

All MRI markers (WMH, lacunes, microbleeds, cortical superficial siderosis and perivascular spaces) were defined according to the STRIVE criteria blind to clinical data [14].

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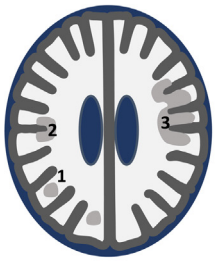
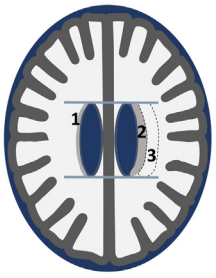
Lacunes and microbleeds numbers as well as the presence of cortical siderosis were recorded in each participant by two experienced readers (AA and EJ). Validated post-processing methods were used to obtain the brain volume normalized to the intracranial cavity volume (normalized brain volume) from 3DT1 sequences [15] following recent guidelines [16] and volumes of hippocampus on both sides [17].

Because the Fazekas scale does not distinguish superficial WMH from periventricular/deep WMH, and based on recent scoring developed in CADASIL [3], we designed a simple grading scale, to identify and grade superficial WMH, regardless of clinical data and other MRI markers. In line with above-mentioned data suggesting that both high loads of periventricular and deep (but not superficial) WMH are associated with more severe clinical outcomes, we graded them as a whole under the term ''other'' WMH. We designed our scale with basic principles to optimize its reproducibility and allow its use in daily clinical practice: 1) rating based on a single pre-determined slice; 2) three grades by WMH type; 3) limit the influence of potentially associated lesions. The grading was performed on the axial plane. The lateral ventricles were used as a reference to improve the reproducibility of the slice location. The reference was defined as the upmost slice containing lateral ventricle voxels with the actual signal of the cerebrospinal fluid (without partial volume effect with brain tissue). Superficial WMH within or in contact with gyral white matter were first rated. In line with the Fazekas scale [1], we distinguished punctiform WMH, limited confluence WMH and clearly confluent WMH. After grading superficial WMH, we virtually discarded them from the slice to grade other WMH. To control for the potential influence of posterior WMH which are associated with CAA and likely to artificially increase the grade of deep WMH [18], we only considered them in the area between two straight lines passing through the ends of lateral ventricles (see details in Fig. 1 and examples in Fig. 2). We called this new grading scale the SO (superficial and other WMH) grading scale. The intra-rater agreement of our grade was assessed on a randomly selected subsample of 20 patients rated twice, four weeks apart. Inter-rater agreement was evaluated on the same subsample. Weighted kappa was 0.92 (intra-rater) and 0.77 (inter-rater) for superficial WMH and 0.91 (intra-rater) and 0.73 for other WMH.

2.4. *Statistical analysis*

Statistical analyses were performed with the R software (https://www.r-project.org/, version 3.5.3). Descriptive analyses relied on the mean, median, standard-deviation, or range depending on variable type and distribution. Data were collected at baseline and cross-sectional analyses are presented. We investigated the relationships between superficial or other WMH with cardiovascular risk factors, MRI markers or clinical outcomes with analysis of variance (ANOVA) or analysis of covariance (ANCOVA) depending on the set of predictors (only ordinal or categorical or also continuous) when outcomes were continuous or with logistic regression in

WMH type	Definition, Visual assessment and score	Schematic representation
Main guidelines : • Score Superficial (S) WMH first, then Other (O) WMH. • WMH scored into Superficial pattern should be excluded from Other WMH scoring, unless it can't be dissociated. • When there are different lesions for the same WMH type, always choose the worst score.		
Superficial (S)	WMH located in gyral white matter or on contact with cortical grey matter 1 : no lesions or focal lesions located in a gyrus [mono or multifocal] 2 : beginning of confluence in two consecutive gyri 3 : confluent lesions in multiple gyri	
Other (O)	WMH located in periventricular regions, that could extend to deep locations. Score only WMH located between the two lines 1 : absence or pencil-thin lining/homogenous "halo" in continuity with lateral ventricles. 2 : heterogenous "halo" in continuity with lateral ventricles. 3 : confluent hyperintensities extending into the deep white matter	

Adapted from Fazekas et al, AJR, 1987

Figure 1 – The Superficial and Other white matter hyperintensities grading scale.

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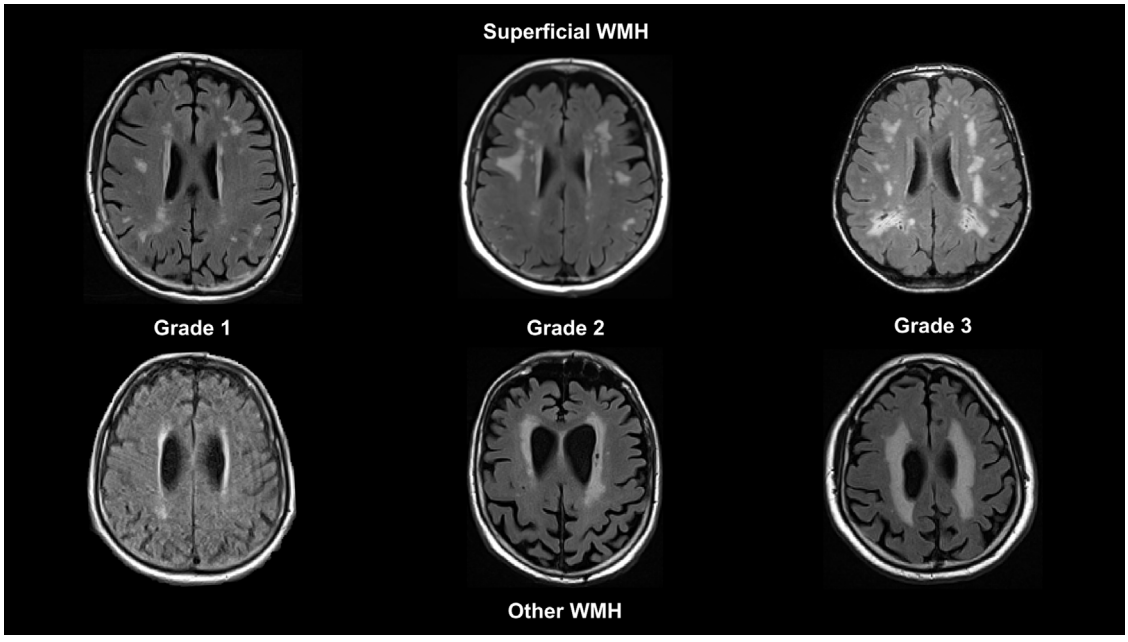

Figure 2 – Different grades of superficial and other white matter hyperintensities. Those brain MRI represent the grading of six different participants from the MEMENTO study and illustrate the 3 grades for both superficial and other WMH. WMH: white matter hyperintensities.

case of binary outcomes. Models were systematically adjusted for age and sex. Further adjustment for level of education was systematic for cognitive outcomes. The normality of residuals was checked for every model. Given a low proportion of missing data (except for T2* sequences which were lacking in 20 subjects for technical issues), incomplete data were excluded from analyses (details provided in Table 1). Level of significance was set at 0.05 two-sided for all analyses.

3. Results

In the final analytical sample, mean age was 76.7 ± 6.2 years. Women represented 55% of the sample. The median WMH volume was 37.1 mL (IQR = [15.2–59]), with the following distributions for superficial WMH (grade 1: 148 patients (71.2%); grade 2: 40 (19.2%), grade 3: 20 (9.6%)) and other WMH (grade 1: 113 patients (54.3%); grade 2: 83 (40.0%); grade 3: 12 (5.8%)) (Table 1). Twenty-four individuals (11.5%) had at least one lacune. T2* sequences were available for 188 individuals among whom 31 (14.9%) had at least one microbleed and only four (1.9%) had cortical superficial siderosis.

On average, superficial and other WMH grades increased with each other, but their correlation coefficient was low to moderate ($r = 0.23$, $P < 0.001$).

Higher grades of superficial WMH were more frequent in women (odds ratio (OR) = 3.35, 95% confidence interval [1.48; 9.59], $P = 0.01$) but were not associated with age, hypertension or smoking (Fig. 3). Higher grades of superficial WMH were associated with the presence of lacunes, independent of age and sex: OR 3.3 [1.5; 9.6]. Higher grades of superficial WMH were associated with larger brain volumes independent of age and sex (F2, 203 = 7.1, $P = 0.001$) (Fig. 4), normalized brain volumes in grade 3 being 0.8% larger than in grade 1. Grades of superficial WMH were not associated with the presence of microbleeds (either deep or lobar) or cortical siderosis nor with the volume of hippocampus. Likewise, they were not associated with either enlarged perivascular spaces (EPVS) scores in basal ganglia or in the white matter.

In total contrast, patients with higher grades of other WMH were older, after controlling for sex (two-way ANOVA, $F_{2,204} = 6.46$, $P = 0.001$), patients with grade 3 being on average 4.4 years older than patients with grade 1. Higher grades of other WMH were associated with the presence of lacunes (OR 5.7 [2.02; 16.2], $P = 0.001$), independent of age and sex (Fig. 3). There was no significant association between grades of other WMH and microbleeds or cortical siderosis. There was an effect of grades of other WMH on normalized brain volume, independent of age and sex (two-way ANCOVA, $F_{2,202} = 8.42$, $P < 0.0001$). However, additional group comparisons showed that grades 2 corresponded to lower normalized brain volumes than both grade 1 and grade 3 which were not significantly different from each other. Higher grades of other WMH were associated with lower right and left hippocampal volumes, independent of age and sex ($F_{2,198} = 3.68$, $P = 0.03$ and $F_{2,195} = 7.02$, $P = 0.001$ respectively) (Fig. 4).

Regarding the relationships between clinical outcomes and superficial WMH, we only found an effect with MMSE after adjustment for age, sex and level of education (two-way ANCOVA $F_{2,199} = 3.2$, $P = 0.04$). However, the effect was explained by lower MMSE scores in grade 2 than in both grade 1 and grade 3, while scores in grade 1 and in grade 3 were not statistically different. In total contrast, we found strong relationships between high grades of other WMH and clinical outcomes. Higher grades of other WMH were associated with

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Table 1 – Grades of white matter hyperintensities, cardiovascular risk factors, MRI markers and clinical outcomes.

	Superficial WMH			Other WMH		
	Grade 1 (n = 148)	Grade 2 (n = 40)	Grade 3 (n = 20)	Grade 1 (n = 113)	Grade 2 (n = 83)	Grade 3 (n = 12)
Cardiovascular risk factors						
Age, mean, SD (range)	76.6, 5.8 (59–90)	77.4, 6.5 (60–90)	77.4, 8.2 (60–91)	**75.3, 6.2 (59–86)**	**78.2, 5.5 (64–90)**	**79.8, 8.1 (62–91)**
Female sex, n (%)	**76 (51.4)**	**21 (52.5)**	**17 (85.0)**	55 (57.5)	43 (51.8)	6 (50.0)
Hypertension, n (%)	76 (51.4)	23 (57.5)	7 (35.0)	57 (50.4)	43 (51.8)	6 (50.0)
Smoking, n (%)	10 (6.8)	1 (2.5)	1 (5.0)	7 (6.2)	5 (6.0)	0
MRI markers						
Lacunes, n (%)	**11 (7.4)**	**9 (22.5)**	**4 (20.0)**	**8 (7.1)**	**11 (13.3)**	**5 (41.7%)**
Microbleeds, n (%)[a]	18/136 (12.2)	9/35 (22.5)	4/16 (20.0)	16/102 (14.2)	11/75 (13.3)	4/11 (33)
Cortical siderosis, n (%)[a]	2.7% (4)	0	0	4 (3.5)	0	0
Normalized brain volume, mean (SD)	**81.0 (1.1)**	**81.7 (1.1)**	**82.1 (1.3)**	81.3 (1.1)	80.7 (1.2)	81.4 (1.2)
Hippocampal volume, right cm^3, mean, (SD)[a]	2.7 (0.4)	2.6 (0.4)	2.7 (0.4)	**2.7 (0.3)**	**2.6 (0.4)**	**2.4 (0.4)**
Hippocampal volume, left cm^3, mean, (SD)[a]	2.5 (0.4)	2.5 (0.5)	2.5 (0.4)	**2.6 (0.4)**	**2.4 (0.5)**	**2.3 (0.5)**
Clinical outcomes						
MMSE (mean, median, range)	27.9, 28 (21–30)	27.1, 28 (20–30)	27.9, 28 (25–29)	**28.1, 28 (21–30)**	**27.4, 28 (20–30)**	**26.8, 27 (23–29)**
Verbal fluency, words in 2 min						
Literal (letter p)[a]	19.7 (7.7)	19.8 (7.1)	19.2 (6.8)	**20.9 (7.9)**	**18.2 (6.9)**	**18.3 (5.1)**
Semantic (animals)[a]	25.6 (8.6)	25.9 (8.0)	28.1 (8.0)	**27.2 (8.3)**	**24.6 (8.8)**	**23.6 (6.4)**
FCSRT, sum of the 3 recalls	41.1 (8.7)	41.5 (7.0)	44.4 (3.4)	41.5 (7.9)	41.4 (8.6)	42.7 (5.4)
TMT-A in seconds[a]	53.6 (18.1)	52.6 (20.1)	60.1 (44.0)	52.4 (24.6)	55.2 (19.5)	61.3 (12.6)
SPPB score[a]	9.8 (2.2)	10.3 (1.9)	(2.9)	**10.2 (1.9)**	**9.7 (2.2)**	**9.2 (4.0)**

The links between dependent variables (cardiovascular risk factors, imaging markers and clinical outcomes) and grades of white matter hyperintensities were investigated with analysis of variance or analysis of covariance for continuous outcomes or with logistic regression for binary outcomes (Section 2.4). Models were adjusted for age and sex systematically, and further adjusted for level of education for predicting clinical outcomes. Significant relationships are shown in bold. MMSE: mini mental state examination; FCSRT: Free and Cued Selective Reminding Test; TMT-A: Trail making test version A; SPPB: Short Physical Performance Battery.

[a] Missing values for 20 (cortical siderosis, microbleeds due to technical issues of the T2* sequence), 3 (right hippocampal volume), 6 (left hippocampal volume), 2 (literal fluency), 3 (semantic fluency), 1 (trail making test version A) and 7 subjects (SPPB) respectively.

lower MMSE, independent of age, sex and level of education (two-way ANCOVA $F_{2,199} = 4.3$, $P = 0.01$), scores in grade 3 being on average 0.8 points lower than in grade 1. Higher grades of other WMH were associated with both lower letter p and animal fluencies (two-way ANCOVA $F_{2,197} = 4.02$, $P = 0.02$ and two-way ANCOVA $F_{2,196} = 3.06$, $P = 0.049$), scores in grade 3 being respectively lower on average by 1.1 and 1.9 points than in grade 1. Finally, higher grades of other WMH were associated with lower SPPB scores (two-way ANCOVA $F_{2,192} = 3.12$, $P = 0.046$), scores in grade 3 being lower than in grade 1 by 1.0 point. We found no relationship between grades of other WMH and TMT-A nor with FCSRT.

4. Discussion

Our results support the hypothesis that superficial WMH are related to mild tissue damage, with possibly distinct mechanisms including increased water content. Indeed, by contrast to "non superficial" (periventricular and deep) WMH, the grade of superficial WMH was not significantly associated with cognitive or gait outcomes. Furthermore, higher grades of superficial WMH were associated with larger brain volumes and were more frequent in women, while higher grades of periventricular and deep WMH were associated with lower hippocampus volume.

One could consider that the absence of relationships between superficial WMH and clinical outcomes is easily explained by a lack of statistical power and/or by the location in superficial areas which might have a lower detrimental effect on clinical outcomes. However, if periventricular and deep WMH, on one hand, and subcortical WMH, on another hand, were the expression of the same underlying mechanisms, we would expect patients with higher grades of superficial WMH to show relationships with other disease parameters like those in periventricular and deep WMH. This would not explain larger normalized brain volumes in higher grades of superficial WMH nor why they are more frequent in female patients. This finding is in line with results reported in CADASIL where superficial WMH were associated with larger brain volumes and with mild clinical outcomes [2,3,19,20].

The striking predominance of women amongst patients with the largest superficial WMH is intriguing. In CADASIL, women have less severe forms of the disease in general [21], but whether this is related to the extent of superficial WMH will require further investigations. Still in CADASIL, the water content of lesions underlying superficial WMH appears larger than those of lesions underlying other WMH when measured with relaxometry at 7 Tesla [19]. In line, we reported the case of a patient whose extent of superficial WMH was temporarily reduced while taking valpromide suggesting large variations of water between compartments [5]. More generally, our

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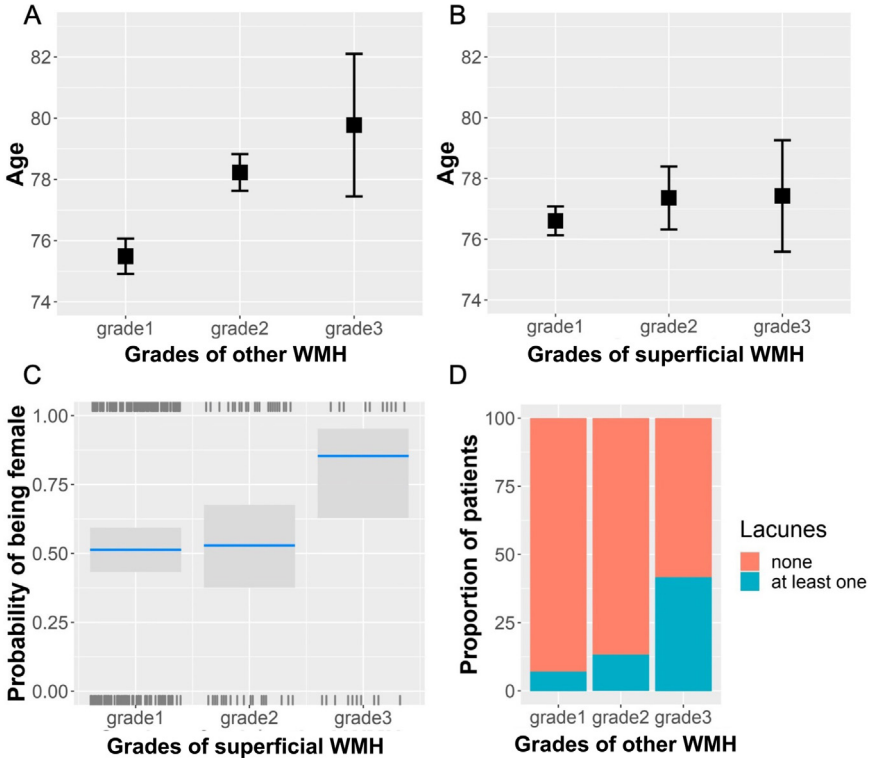

Figure 3 – Illustration of the main relationships between white matter hyperintensities and cardiovascular risk factors and other MRI markers. A. Higher grades of other WMH are observed in older individuals, while we found no difference in age across grades of superficial WMH (B), but a strong association with female sex (C). Higher grades of other WMH were strongly associated with the presence of lacunes (D). WMH: white matter hyperintensities.

results question the fact that these superficial WMH are part of the SVD spectrum. One may hypothesize that sex affects microvascular regulation, leading to water influx in the brain in some conditions, including variations in the hormonal status along the lifespan in women.

We observed that higher grades of non-subcortical, "other" WMH, were associated with older age, presence of lacunes, lower hippocampal volumes and worse performances on cognitive testing. Altogether these results suggest that they correspond to tissue lesions related to hypertensive microangiopathy, known to be potentially severe [22]. The similar frequency of hypertension in all three other WMH grades might appear surprising. One possible explanation is selection bias, that hypertensive patients with severe SVD are more likely to suffer from stroke, gait alterations or cardiovascular events and thus, are less likely to attend a memory clinic.

Even if superficial WMH are mostly related to early radiological stages of CAA, when clinical deficits are not yet noticeable, we would expect to find an association between the extent of superficial WMH and hippocampal atrophy mediated by concomitant Alzheimer's disease. We did not find such an association, while it was obvious for periventricular and deep WMH, in line with the hypothesis of vulnerable microvasculature of the hippocampus [23]. Finally, we did not find any association between grades of superficial WMH and specific markers of CAA, such as lobar cerebral microbleeds, cortical superficial siderosis or enlarged perivascular spaces in the white matter. Despite our findings, in the presence of other prominent markers of CAA, such as numerous lobar microbleeds or superficial siderosis, the presence of superficial WMH, particularly through multiple spots, should probably be considered another MRI marker of CAA.

Our study has some limitations. First of all, our results were obtained in a subsample of MEMENTO, questioning the possibility to generalize our results to the different forms of SVD. The threshold for inclusion (>90th percentile of WMH volume) in the present analyses was somehow arbitrary. While we could not formally exclude an influence of the choice of the threshold on our results, we obtained similar results when estimating superficial and other WMH by their automated measure (data not shown), which renders this bias unlikely. In addition, patients with WMH volume under the 90th percentile were grade 1 on both superficial and other WMH, and including more so closely related patients regarding the measured variable would unlikely alter our results. Conversely, our grading scheme is mostly usable in patients with high enough loads of WMH, which may restrict its use in daily clinical practice. However, the interest of grading patients with very low burdens of WMH may appear of limited interest. Further studies may help refine our approach for earlier forms of SVD. We also chose not to correct for multiple testing given our small sample size. However, the number of significant tests far exceeds those expected if significant relationships were only related to chance (11/20, i.e. 55% vs 5%). Finally, the cross-sectional nature of the study prevents obtaining insights on the direction of the observed relationships.

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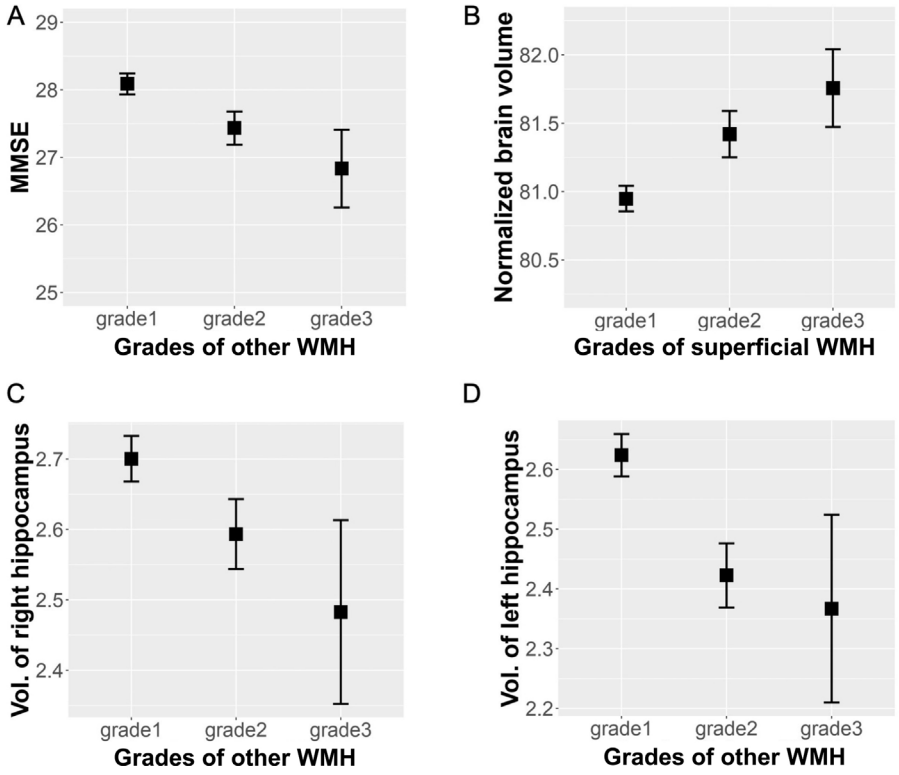

Figure 4 – Main relationships between white matter hyperintensities and morphological MRI markers and clinical outcomes. A. Higher grades of other WMH are associated with lower MMSE scores. B. Higher superficial white matter grades are associated with larger normalized brain volumes. In contrast, other WMH grades are associated with smaller hippocampal volumes on both sides (C and D). WMH: white matter hyperintensities; MMSE: mini-mental state examination.

Despite some remaining uncertainty regarding the exact interpretation of our results, the present study already strongly supports the interest of differentiating, even in daily clinical practice, superficial from non-superficial WMH, which actually seem associated with both different underlying processes and different evolutive profile.

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Author contributions

Dr Agnes Aghetti analyzed and interpreted data, drafted the manuscript for intellectual content.

Dr Vincent Bouteloup supported the analysis of the data, drafted the manuscript for intellectual content.

Dr Jessica Lebenberg supported the analysis of the data, drafted the manuscript for intellectual content.

Dr Marie Chupin organized CATI MRI harmonization, collection, analysis and quality control.

Emmanuelle Gourieux performed CATI WMH automated analysis and quality control.

Dr Jean-François Mangin organized CATI analysis and revised the manuscript for intellectual content.

Dr Geneviève Chêne conceptualized study, revised the manuscript for intellectual content.

Dr Carole Dufouil conceptualized study, revised the manuscript for intellectual content.

Dr Eric Jouvent conceptualized study, analyzed and interpreted data, revised the manuscript for intellectual content.

Disclosure of interest

The authors declare that they have no competing interest.

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