

Regional White Matter Hyperintensity Influences Grey Matter Atrophy in Mild Cognitive Impairment

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Abstract. The association between cerebrovascular disease pathology (measured by white matter hyperintensities, WMH) and brain atrophy in early Alzheimer's disease (AD) remain to be elucidated. Thus, we investigated how WMH influence neurodegeneration and cognition in prodromal and clinical AD. We examined 51 healthy controls, 35 subjects with mild cognitive impairment (MCI), and 30 AD patients. We tested how total and regional WMH is related to specific grey matter volume (GMV) reductions in MCI and AD compared to controls. Stepwise regression analysis was further performed to investigate the association of GMV and regional WMH volume with global cognition. We found that total WMH volume was highest in AD but showed the strongest association with lower GMV in MCI. Frontal and parietal WMH had the most extensive influence on GMV loss in MCI. Additionally, parietal lobe WMH volume (but not hippocampal atrophy) was significantly associated with global cognition in MCI while smaller hippocampal volume (but not WMH volume) was associated with lower global cognition in AD. Thus, although WMH volume was highest in AD subjects, it had a more pervasive influence on brain structure and cognitive impairment in MCI. Our study thus highlights the importance of early detection of cerebrovascular disease, as its intervention at the MCI stage might potentially slow down neurodegeneration.

Keywords: Alzheimer's disease, cognition, grey matter, white matter hyperintensity

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease associated with the accumulation of neurofibrillary tangles and neuritic plaques in the brain, resulting in cumulative neuronal damage [1]. Neurobiological changes follow certain atrophy patterns, occurring first in trans-entorhinal regions, entorhinal cortex, and hippocampus, before spreading out into the amygdala and basolateral temporal lobe, and eventually into neocortical regions

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[2]. Studies show that small-vessel cerebrovascular disease (CeVD) and the prevalence of its markers [3–5], particularly white matter hyperintensities (WMH), indicate that CeVD is an important risk factor for the clinical expression of AD [6, 7]. Indeed, increased WMH burden has been associated with medial temporal lobe atrophy and cognitive impairment in AD [8–10]. Specifically, AD subjects show associations between WMH and global reductions in grey matter volume (GMV) together with frontal and parietal-lobe specific structural alterations [11]. However, the exact pathophysiological process of how WMH and AD neuropathology interact to accelerate degeneration in AD remains to be elucidated. Therefore, it is of interest to study the effect of WMH on atrophy patterns and cognition in AD.

Previous studies have demonstrated that WMH plays a role in grey matter (GM) structural changes and cognitive decline even in the prodromal stage of AD, known as mild cognitive impairment (MCI) [12–18]. MCI is characterized by cognitive impairment but without functional impairment that interferes with daily life [19–22]. Cross-sectional studies illustrate associations between high WMH and decline in perceptual speed and executive function in healthy controls and MCI [13, 19, 23]. Moreover, high WMH volume has been associated with greater risk of progression to MCI [22]. However, the associations between regional WMH distribution and cognition have been mixed. For instance, while some showed higher temporal lesion load associated with global cognition in healthy and patient groups [12], others found higher frontal and temporal WMH as being related to worse cognition in middle-aged healthy adults [24]. Some studies have also highlighted the influence of frontal WMH on executive function in the healthy elderly but temporal WMH influence on memory in AD [25]. Nonetheless, their relationship across different phases of disease requires further study [26].

Previous studies indicate that larger total WMH volume is associated with smaller total GMV [20, 27] and baseline WMH is likely to predict the rate of global GMV decline in healthy elderly [28] and MCI patients [29]. Moreover, it has been suggested that in comparison to region-of-interest based approaches, whole-brain voxel-wise analysis provides greater sensitivity to focal alterations in brain anatomy [30]. Indeed, the association between regional WMH volume as well as other cerebrovascular markers such as lacunes and regional GMV has been a subject of recent investigation [30–32]. While some studies

show cross-sectional and longitudinal associations between cerebrovascular disease markers and GM loss in temporal, frontal, and parietal cortices [14, 16, 29, 30, 32, 33], others show no such associations between WMH and cortical thinning [31]. However, previous studies have not simultaneously examined the influence of lobe-wise WMH on whole-brain voxel-wise GMV and their contribution to cognition in healthy controls, MCI, and AD.

In light of these uncertainties, we investigated differences in whole-brain GMV and effect of total and regional WMH on voxel-wise GMV in AD, MCI, and age-matched healthy controls. Based on previous findings regarding the influence of WMH on GMV decline and disease progression, we hypothesized that regional WMH volumes will be mainly associated with GMV loss in frontal, temporal, and parietal lobes in AD and MCI patients. Furthermore, based on mixed findings regarding the influence of lobe-wise WMH on global and domain-specific cognition across the disease spectrum, we evaluated the differential contribution of regional WMH and region-specific GMV loss to cognitive impairment in AD and MCI.

METHODS

Participants

Between April 2013 and April 2016, 165 participants were recruited from tertiary neurology centers in Singapore [34, 35]. Inclusion criteria included diagnosis of MCI based on the NIA-AA criteria [36] or AD based on the NIA-AA criteria [37]. Subjects with MCI were required to have cognitive symptoms, deficits on neuropsychological evaluation, a clinical dementia rating (CDR) score of 0.5, and to not meet criteria for dementia. AD subjects were required to have a CDR of 1. Healthy control subjects were required to have a Mini-Mental State Examination (MMSE) score of 27 or above and a CDR of 0. Exclusion criteria included: 1) a history of alcohol or drug abuse; 2) a current or known history of major depression; 3) comorbid neurodegenerative disease such as Parkinson's disease; 4) CeVD such as cerebral amyloid angiopathy and prior stroke; 5) neuropsychiatric conditions such as psychosis; 6) presence of contraindications to MRI. Of the 165 participants, 49 of them did not have a FLAIR image. As such, in this study, we only included participants with both T1-weighted and FLAIR images ($n = 116$). Subjects' demographics and cognitive characteristics are sum-

Table 1
Demographics and clinical characteristics of patients and control subjects

	HC (n = 51)	MCI (n = 35)	AD (n = 30)	Group Statistics
Age	66.23 (5.66)	66.25 (5.92)	69.07 (7.89)	F = 2.18, df = 115
Gender M:F, N	26/25	14/21	19/11	$\chi^2 = 3.52, p = 0.172$
Ethnicity C:M:I:O, N	49/1/1/0	34/0/1/0	24/2/2/2	$\chi^2 = 10.57, p = 0.103$
Education (y)	12.82 (3.67)	10.86 (3.45)	10.33 (3.73) ^{A,B}	F = 5.49, df = 115*
Handedness R:L:Ambidextrous, N	48/1/2	32/2/1	30/0/0	$\chi^2 = 3.46, p = 0.486$
Diabetes Mellitus, No:Yes	44/7	30/5	24/6	$\chi^2 = 0.625, p = 0.732$
Hypertension, No:Yes	28/23	19/15	17/13	$\chi^2 = 2.36, p = 0.670$
Hyperlipidemia, No:Yes	20/31	16/19	13/17	$\chi^2 = 0.379, p = 0.827$
Scanner Type (Tim Trio/ Prisma Fit, N)	20/31	16/19	18/12	$\chi^2 = 3.29, p = 0.193$
Total WMH load	0.30 (0.41)	0.35 (0.54)	0.62 (0.58) ^B	F = 3.596, df = 98*
Frontal WMH load	1.51 (2.05)	2.16 (3.45)	3.93 (5.77) ^B	F = 3.946, df = 114*
Parietal WMH load	0.62 (1.47)	1.00 (1.95)	2.79 (4.70) ^{B,C}	F = 5.831, df = 110*
Temporal WMH load	0.25 (0.44)	0.34 (0.52)	0.92 (1.42) ^{B,C}	F = 6.231, df = 107*
Occipital WMH load	0.32 (0.34)	0.33 (0.37)	0.78 (0.86) ^{B,C}	F = 8.038, df = 107*
CDR	0.00 (0.00)	0.32 (0.25)	0.62 (0.31) ^{A,B,C}	F = 85.17, df = 115*
MMSE	28.59 (1.60)	27.46 (1.75)	24.00 (4.09) ^{B,C}	F = 31.96, df = 115*
z score Episodic Memory	0.42 (0.69)	-0.57 (0.91)	-1.93 (1.61) ^{A,B,C}	F = 46.01, df = 113*
z score Executive Function	0.60 (0.48)	-0.16 (0.80)	-2.26 (2.08) ^{A,B,C}	F = 55.42, df = 112*
z score Attention	0.46 (0.71)	-0.20 (0.62)	-0.50 (0.92) ^{A,B}	F = 17.70, df = 113*
z score Language	0.55 (0.57)	-0.16 (0.75)	-0.87 (0.91) ^{A,B,C}	F = 37.36, df = 114*
z score Visuospatial	0.42 (0.35)	-0.43 (1.52)	-1.23 (1.19) ^{A,B,C}	F = 23.05, df = 112*

^AHC > MCI, ^BHC > AD, ^CMCI > AD, $p < 0.05$. Values represent mean (SD). Superscript letters indicate whether group mean was significantly different healthy controls and MCI (A), between healthy controls and AD (B) and between MCI and AD (C), based on *post-hoc* comparisons ($p < 0.05$) following one-way ANOVA. Chi-square tests were carried out on gender, handedness, and ethnicity covariates as well as on the three cardiovascular risk factors namely diabetes mellitus, hypertension, and hyperlipidemia. HC, healthy controls; MCI, mild cognitive impairment; AD, Alzheimer's disease; C, Chinese; M, Malay; I, Indian; O, Other; R, Right; L, Left; WMH, white matter hyperintensities; CDR, Clinical Dementia Rating scale; MMSE, Mini-Mental State Examination. * $p < 0.05$.

marized in Table 1. A total of 116 subjects were included in the study, i.e., healthy controls ($n = 51$), MCI ($n = 35$), and AD ($n = 30$). Subjects were well matched in their demographics, such as age, gender, ethnicity, education, and handedness. This study was approved by the SingHealth institutional ethics review board and written informed consent was obtained for all participants.

Neuropsychological assessments

All patients underwent clinical, neuropsychological, and MRI assessments. Clinical evaluations were also conducted, including comprehensive physical examination by neurologists and medical history from the patient and reliable informant [37]. The neuropsychological battery was performed by trained psychologists who evaluated global cognition as well as specific cognitive domains, namely episodic memory, executive function, attention, visuospatial abilities, and language abilities. Global cognition was assessed using the MMSE [38] and Montreal Cognitive Assessment [39]. Episodic memory was assessed

using 10-word delayed recall [40] and WAIS-IV delayed visual reproduction [41]; executive function was assessed using color trails 2 [42] and frontal assessment battery [43]; attention/working memory was assessed using coding [44] and digit span forward tests [42]; language was assessed using verbal fluency and the 30-word Boston naming test [45]; and visuospatial was assessed using the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) constructional praxis test [40] and block design test [42]. Performance on the individual tasks was transformed into z-scores based on normative scores [46–51]. A composite summary index for each cognitive domain was then derived from the corresponding averages of the tests.

Image acquisition

MRI scans were performed at Duke-NUS Medical School, Singapore on a 3T Tim Trio System (Siemens, Erlangen, Germany) ($n = 54$) or a 3T Prisma Fit System (Siemens, Erlangen, Germany)

($n=62$) after scanner upgrade. We obtained high-resolution T1-weighted MPRAGE (Magnetization-Prepared Rapid Gradient Echo) sequences (192 continuous sagittal slices, TR/TE/TI=2300/2.28/900 ms, flip angle=9°, FOV=256 × 240 mm², matrix=256 × 240, isotropic voxel size=1.0 × 1.0 × 1.0 mm³, bandwidth=240 Hz/pixel) and FLAIR (Fluid Attenuated Inversion Recovery) sequences (192 continuous sagittal slices, TR/TE/TI=5000/387.0/1800 ms, flip angle=15°, FOV=256 × 256 mm², matrix=256 × 256, isotropic voxel size=1.0 × 1.0 × 1.0 mm³) on both scanners using the same parameters. Scan images were reviewed at acquisition and subjects with motion artifacts and gross pathological findings were excluded.

Following procedures reported by Weir and Zuo [52, 53], we quantified the test-retest reliability for MPRAGE on Tim Trio and Prisma Fit in an independent cohort of 23 young healthy controls (11 females, 28.7 ± 6.0 years old, 94.5 ± 24.0 days between scans), and achieved a voxel-correspondent intra-class correlation of 0.96 ± 0.04 for GM, 0.97 ± 0.04 for white matter (WM), and 0.88 ± 0.10 for cerebrospinal fluid (CSF).

White matter hyperintensity derivation

From the FLAIR images, WMH was quantified using an in-house automatic procedure. First, SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) was used to segment GM, WM, and CSF of the T1-weighted images. Combining GM and WM images, we obtained subject-specific brain masks which were used to remove non-brain regions from the FLAIR images. Finally, WMH segmentation and quantification were performed, which involved: 1) modal pixel intensity determined by FLAIR image and 2) threshold-based segmentation using a threshold of 1.45 times the modal pixel intensity. Regional WMH volume for the frontal, parietal, temporal, and occipital lobes were also calculated [54]. Manual visual inspection was performed following the quantification of WMH volume. The total and regional WMH volumes were log transformed to ensure normality.

Volume-based morphometry

We applied the voxel-based morphometry protocol using the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm8/>) in Statistical Parametric Mapping (SPM12) (<http://www.fil.ion.ucl.ac.uk/spm/>). This SPM voxel-based morphometry analysis [55] was

used to derive subject-level GM, WM, and CSF masks using SPM tissue probability maps from T1-weighted structural data, similar to our previous approach [56], including 1) segmentation of individual T1-weighted images into GM, WM, and CSF using an adaptive Maximum A Posterior (MAP) technique that does not require *a priori* tissue probabilities [57]; 2) creating a study-specific template using non-linear DARTEL registration [58]; 3) normalization of each GM/WM segmented map to the customized template in MNI space; 4) modulation by multiplying voxel values by only the nonlinear components of the Jacobian determinants derived from the spatial normalization step, to account for individual brain sizes; 5) smoothing the normalized GM and WM maps with an 8 mm isotropic Gaussian kernel.

Group differences in GMV: To examine group differences, we built a voxel-wise Analysis of Covariates (ANCOVA) general linear model with GMV as the dependent variable, group membership, and total and lobe-wise WMH as the independent variables-of-interest and scanner type, education and ethnicity as covariates. In a secondary analysis, we further controlled for age, gender, and handedness covariates in addition to ethnicity, education, and scanner covariates. The GM regions which showed significant group differences were examined using a threshold of uncorrected $p < 0.001$ and a minimum cluster size of 100 voxels [30, 32]. Significant clusters in the GM were anatomically identified using the Automated Anatomical Labelling atlas labels.

Associations between GMV and WMH: We also assessed the differential effects of regional WMH on GMV across groups. For this analysis, we set up contrasts to assess which regions showed associations between GMV and total WMH and lobe-wise WMH in AD, MCI, and control groups separately. Scanner type, education, and ethnicity were included as nuisance covariates. The GM regions that showed significant association with total/regional WMH were reported using a threshold of uncorrected $p < 0.001$ and a minimum cluster size of 100 voxels.

Statistical analyses

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 24.0 (SPSS, Inc; Chicago, IL, USA). Normality for continuous variables was examined using Skewness-Kurtosis and visual inspection of histogram. One-way analysis of variance (ANOVA) was used to examine the differences between groups and chi-square was

Table 2

Regions showing group differences in grey matter volume before (a) and after (b) controlling for total white matter hyperintensity volume

Contrast	Regions	Peak	Cluster	MNI	Age, gender,	Age, gender,	Age, gender,
		t-statistics	size	coordinates	handedness Peak t-statistics	handedness Cluster size	handedness MNI coordinates
a) Before controlling for total WMH volume							
HC - AD	Right superior temporal gyrus; right middle temporal gyrus; right hippocampus; right amygdala	5.45	5455	45, -14, -14	5.35	3872	45, -14, -14
	Left middle occipital gyrus	5.09	699	-28, -81, 8	4.62	551	-28, -81, 8
	Left hippocampus; left amygdala; left superior temporal pole	5.05	4607	-15, -10, -12	4.61	1704	-15, -10, -12
	Right precuneus	4.74	406	12, -56, 38	4.68	330	12, -56, 38
	Right middle frontal gyrus	4.24	291	32, 29, 20	3.94	135	32, 29, 20
	Left middle temporal gyrus	4.36	878	-51, -39, -9	4.00	376	-51, -39, -9
MCI - AD	Left hippocampus; left amygdala; left parahippocampus; left superior temporal pole	4.98	4405	-18, -8, -14	4.42	2555	-16, -9, -14
	Right hippocampus; right superior temporal gyrus; right middle temporal gyrus; right amygdala	4.78	5825	44, -15, -14	4.40	3042	44, -14, -15
b) After controlling for total WMH volume							
HC - AD	Left middle occipital gyrus	4.91	510	-30, -84, 4	4.82	461	-30, -84, 4
	Right superior temporal gyrus; right middle temporal gyrus	4.51	1359	45, -15, -16	4.58	1404	44, -15, -15
MCI - AD	Left amygdala; left hippocampus	3.88	641	-22, 4, -18	3.83	522	-22, 4, -18
	Left hippocampus; left amygdala; left parahippocampus	4.26	1813	-21, -36, 3	4.25	901	-21, -36, 3
	Right hippocampus; right middle temporal gyrus; right superior temporal gyrus; right parahippocampus	4.10	1419	44, -15, -15	4.06	1121	44, -15, -15

Grey matter regions showing atrophy in AD compared to healthy controls and MCI, before and after controlling for total WMH volume. Columns labelled "age, gender, handedness" represent the grey matter volume reduction results after further controlling for age, gender, and handedness covariates. WMH, white matter hyperintensity; HC, healthy controls; MCI, mild cognitive impairment; AD, Alzheimer's disease.

used to assess differences between categorical variables. Significance was set at a two-tailed probability value of $p < 0.05$.

To investigate the associations between GMV, regional WMH, and cognition, we performed stepwise multiple linear regression analysis. The independent variables comprised GMV from regions that showed significant group differences in AD compared to controls, total or regional WMH volume while cognitive scores were the main dependent variable. The tested cognitive measures included global cognition (MMSE, Montreal cognitive assessment) and five domain-specific cognition scores (episodic memory, executive function, attention, language, and visuospatial function). The multiple regression analysis was controlled for age, gender, education, handedness, ethnicity, and scanner type. Multiple comparisons correction was carried out across these seven models with a multiple comparisons corrected p -value of $p < 0.0071$.

RESULTS

AD subjects show less widespread reductions in temporal GMV after controlling for WMH

Total WMH volume was highest in AD subjects compared to both MCI ($p = 0.030$) and controls ($p = 0.003$). Before controlling for total WMH, AD subjects showed significantly reduced GMV compared to healthy controls and MCI in frontal, temporal, and parietal regions: right middle frontal gyrus, right superior temporal gyrus, bilateral middle temporal gyrus, bilateral hippocampus and amygdala, left parahippocampus, and right precuneus (Table 2). After controlling for WMH, AD subjects showed less widespread GM atrophy; temporal regions including the left hippocampus, left amygdala, and right superior and middle temporal gyrus showed reductions in GMV (Table 2 and Fig. 1). MCI subjects did not show any difference in GMV compared to controls.

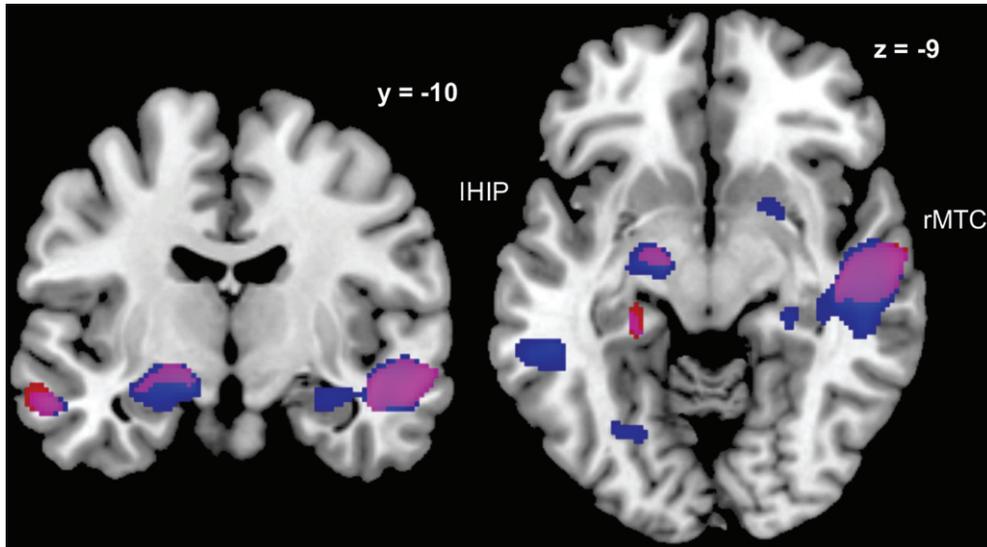


Fig. 1. Group differences in grey matter volume after controlling for total white matter hyperintensity volume. AD subjects showed reduced grey matter volume (purple) in the bilateral hippocampus, middle temporal and superior temporal cortices following correction for total WMH volume. Clusters in blue represent areas of grey matter atrophy in AD subjects prior to controlling for WMH volume. Results are shown at the uncorrected $p < 0.001$ height threshold with an extent threshold of 100 voxels. Results are displayed on representative sections of the MNI template brain. In coronal and axial slices, the left side of the image corresponds to the left side of the brain. R Mid Temp, right middle temporal cortex; IHIP, left hippocampus.

Total WMH volume has the greatest negative impact on frontal and temporal grey matter in MCI

Total WMH volume had the largest negative influence on GMV in MCI subjects, specifically in temporal and frontal regions ($p < 0.001$; minimum cluster size = 100 voxels; Fig. 2). We found an overlap between regions atrophied in AD and those showing association between total WMH and reduced GMV in MCI (Supplementary Figure 1).

Frontal and parietal WMH have the largest negative impact on voxel-wise GMV in MCI

Frontal and parietal WMH had the largest negative impact on GMV in MCI (Supplementary Figure 2). Specifically, frontal WMH showed associations with frontal and temporal GMV reductions: bilateral middle frontal gyrus, left precentral gyrus, left superior, middle and inferior temporal gyri, bilateral superior medial frontal gyrus, bilateral parahippocampus, bilateral hippocampus, left insula, and right middle and inferior orbitofrontal gyri (Table 3). After further controlling for age, gender, and handedness, frontal WMH showed associations with frontal and

temporal GMV reductions: bilateral middle frontal gyrus, left superior, middle and inferior temporal gyri, bilateral superior medial frontal gyrus, left parahippocampus, left hippocampus (Table 3A, Fig. 3). Furthermore, parietal WMH was associated with frontal and temporal GMV reductions: bilateral superior medial frontal gyrus, bilateral medial and right superior orbitofrontal gyri, right middle frontal gyrus, left precentral gyrus, left inferior and superior temporal gyri, left hippocampus, and left amygdala (Table 3). After further controlling for age, gender, and handedness, parietal WMH was associated with mainly frontal GMV reductions: bilateral superior medial frontal gyrus, right medial orbitofrontal gyri, left precentral and postcentral gyri (Table 3B and Fig. 4).

In healthy controls, frontal and parietal regional WMH was associated with reductions in frontal, temporal, and parietal GMV. On the one hand, frontal WMH was associated with GMV reductions in bilateral middle and right superior frontal gyri, right superior and middle orbitofrontal gyri, right superior temporal gyrus, and right supramarginal gyrus before and after controlling for age, gender, and handedness (Table 3A, Fig. 3). On the other hand, parietal WMH was associated with left supplementary motor area

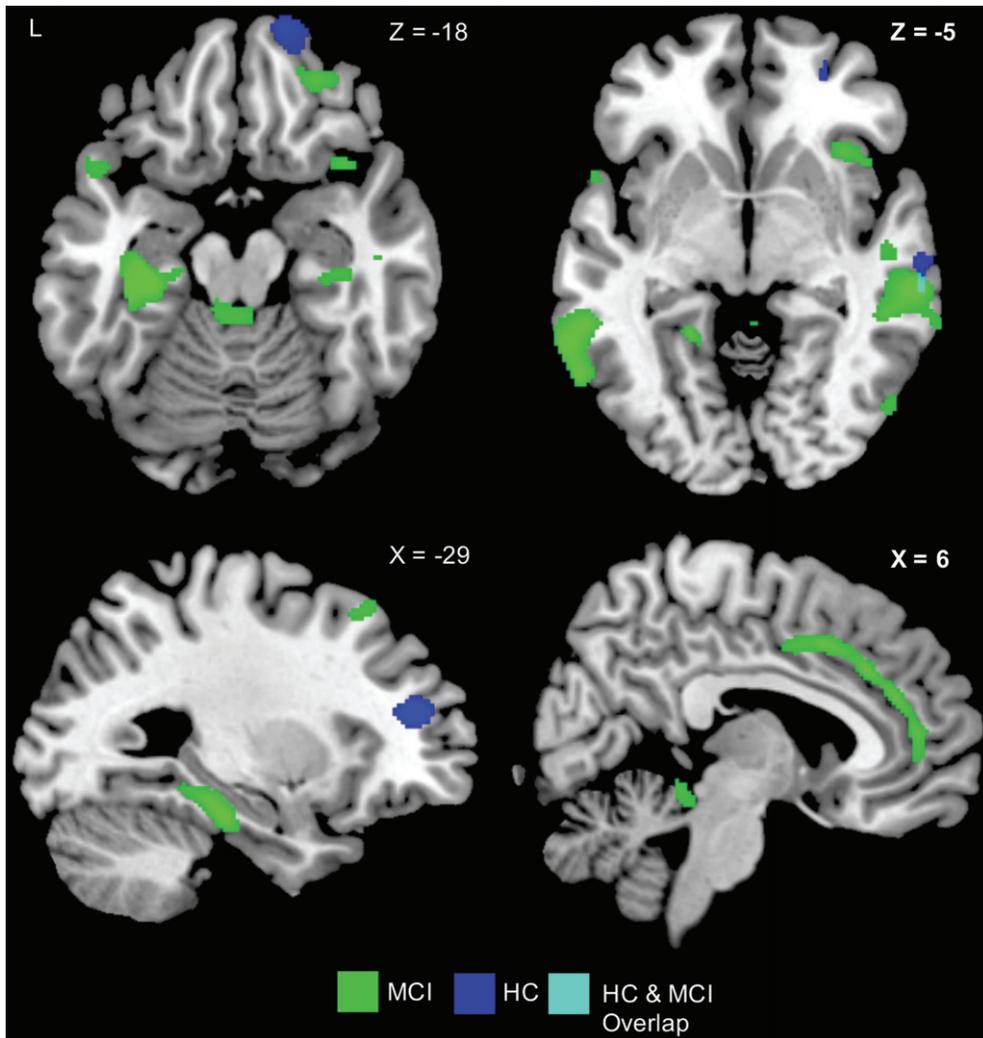


Fig. 2. Impact of total white matter hyperintensity volume on grey matter volume in AD, MCI and healthy controls. Total WMH volume showed an association with grey matter volume in MCI (green) and healthy controls (blue) after controlling for age, gender, handedness, ethnicity, education and scanner covariates. MCI subjects showed the most widespread decreases in grey matter volume across the frontal and temporal lobes while controls showed reduced grey matter volume mainly in frontal and middle temporal regions. Subjects with AD did not show any reduced grey matter volume associated with total WMH. Results are displayed on representative sections of the MNI template brain. The left side of the image corresponds to the left side of the brain. WMH, white matter hyperintensity; AD, Alzheimer's disease; MCI, mild cognitive impairment; HC, healthy controls.

and left superior frontal gyrus atrophy (Table 3B). After further controlling for age, gender, and handedness parietal lobe WMH was associated with GMV reduction in left precuneus and left middle cingulum regions in healthy controls (Table 3B, Fig. 4).

In AD subjects, frontal and parietal regional WMH were associated with right middle and inferior orbitofrontal gyrus GMV reductions but only prior to additionally controlling for age, gender and handedness covariates (Table 3A, B).

Occipital and temporal WMH show smaller influence on voxel-wise GMV in healthy controls and MCI compared to frontal and parietal WMH

Although occipital and temporal WMH showed a negative influence on GMV, the effect of temporal WMH was not as widespread as that of frontal and parietal regional WMH.

Occipital WMH was associated with GMV reductions in right superior and middle temporal gyri,

Table 3

Negative association between lobe-wise (frontal – A; parietal – B; occipital – C; temporal – D) white matter hyperintensity and gray matter volume

Regions	Peak t-statistics	Cluster size	MNI coordinates	Age, gender, handedness Peak t-statistics	Age, gender, handedness Cluster size	Age, gender, handedness MNI coordinates	
A) Association between frontal lobe WMH and reduced GMV							
HC	Left middle/superior frontal gyrus	6.19	1010	–30, 48, 15	5.34	421	–30, 46, 16
	Right middle frontal gyrus; right superior frontal gyrus; right superior orbitofrontal gyrus; right middle orbitofrontal gyrus	5.18	1933	27, 48, 4	4.50	537	28, 50, 2
	Bilateral anterior cingulum	4.56	1358	2, 34, 4			
	Right superior temporal gyrus; right supramarginal gyrus	4.21	1650	60, –20, 14	4.06	521	58, –36, 22
MCI	Right middle frontal gyrus; bilateral middle and anterior cingulum; right inferior triangular frontal gyrus; bilateral superior medial frontal gyrus	5.46	1190	44, 32, 26	4.19	1111	32, 42, 15
	Right middle temporal gyrus; right superior temporal gyrus	4.99	3486	62, –28, –3	4.31	687	62, –28, –4
	Left middle frontal gyrus; left inferior triangular frontal gyrus	4.84	1244	–48, 28, 33	4.60	533	–44, 33, 36
	Left parahippocampus; left hippocampus; left inferior temporal gyrus	4.78	2613	–26, –38, –10	3.87	508	–21, –45, –4
	Left middle temporal gyrus; left supramarginal gyrus; left angular gyrus	4.46	1984	–58, –42, –3	4.50	1464	–60, –60, –10
	Right middle orbitofrontal gyrus; right inferior orbitofrontal gyrus	4.43	1344	34, 45, –14	–	–	–
	Left inferior operculum frontal gyrus; left superior temporal pole; left insula	4.16	802	–46, 8, 4	–	–	–
	Right parahippocampus; right hippocampus	4.33	1018	28, –32, –15	–	–	–
	Left postcentral gyrus; left precentral gyrus	3.86	675	–36, –24, 42	–	–	–
AD	Right inferior orbitofrontal gyrus; right middle orbitofrontal gyrus	4.47	961	34, 34, –12	–	–	–
B) Association between parietal lobe WMH and reduced GMV							
HC	Left supplementary motor area; left superior frontal gyrus	4.36	780	–2, 15, 63	3.63	281	–10, 22, 63
	Left middle cingulum; left precuneus	–	–	–	4.28	500	–3, –32, 45
MCI	Bilateral superior medial frontal gyrus; right medial orbitofrontal gyrus; bilateral anterior cingulum	5.11	2179	10, 52, 14	4.88	1143	10, 52, 14
	Right middle frontal gyrus	4.87	544	32, 50, 2	–	–	–
	Left postcentral gyrus; left precentral gyrus	4.31	1311	–58, –21, 50	3.85	606	–28, 8, –22
	Left superior temporal pole; left hippocampus; left inferior orbitofrontal gyrus; left amygdala	4.15	1995	–22, 6, –16	–	–	–
	Left hippocampus; left inferior temporal gyrus	4.15	715	–36, –26, –15	–	–	–
	Bilateral medial orbitofrontal gyrus; right superior orbitofrontal gyrus	4.03	2369	10, 27, –26	–	–	–
AD	Right inferior orbitofrontal gyrus; right middle orbitofrontal gyrus	4.09	788	36, 34, –12	–	–	–
C) Association between occipital lobe WMH and reduced GMV							
HC	Right superior temporal gyrus; right middle temporal gyrus	5.13	858	66, –20, –4	4.71	578	66, –20, –4
	Right superior temporal gyrus; right supramarginal gyrus	4.31	974	60, –28, 20	3.89	344	60, –28, 20
	Right medial orbitofrontal gyrus; right superior frontal gyrus	3.99	531	6, 45, –3	–	–	–

(Continued)

Table 3
(Continued)

Regions	Peak t-statistics	Cluster size	MNI coordinates	Age, gender, handedness Peak t-statistics	Age, gender, handedness Cluster size	Age, gender, handedness MNI coordinates
MCI Bilateral superior medial frontal gyrus; bilateral medial orbitofrontal gyrus; right anterior cingulum gyrus	5.38	2405	3, 54, 9	5.11	1478	3, 54, 9
Left hippocampus; left inferior temporal gyrus; left parahippocampus	5.07	1813	-39, -18, -27	4.76	1029	-39, -18, -27
Right middle frontal gyrus; right inferior triangular frontal gyrus; right insula; right inferior orbitofrontal gyrus	4.41	2999	48, 33, 0	4.08	1010	48, 33, 0
Right middle temporal gyrus; right superior temporal gyrus	4.32	750	68, -39, 4	4.10	306	69, -39, 4
Left middle frontal gyrus; left inferior triangular frontal gyrus	4.11	800	-42, 18, 33	-	-	-
Left middle frontal gyrus	4.06	428	-28, 22, 50	-	-	-
AD None						
D) Association between temporal lobe WMH and reduced GMV						
HC Right inferior temporal gyrus	4.06	847	42, -9, -45	3.96	694	42, -9, -46
MCI Right medial orbitofrontal gyrus; right medial superior frontal gyrus	4.74	570	12, 50, -2	4.32	279	14, 50, -3
Right middle frontal gyrus; right superior frontal gyrus	4.40	733	34, 52, 9	4.00	339	34, 52, 9
Left inferior operculum frontal gyrus; left inferior triangular frontal gyrus; left middle frontal gyrus	4.14	468	-39, 20, 32	3.95	144	-39, 20, 32
AD None						

Grey matter regions showing negative association with lobe-wise WMH volume. Columns labelled "age, gender, handedness" represent areas showing such negative associations after further controlling for age, gender, and handedness covariates. WMH, white matter hyperintensity; GMV, gray matter volume; HC, healthy controls; MCI, mild cognitive impairment; AD, Alzheimer's disease.

right supramarginal gyrus, right medial orbitofrontal gyrus, and right superior frontal gyrus in healthy controls and remained largely the same after additionally controlling for age, gender and handedness in the model; and bilateral superior medial frontal and orbitofrontal gyri, bilateral middle and inferior triangular frontal gyri, left inferior temporal gyrus, left parahippocampus and hippocampus in MCI (Table 3C). After further controlling for age, gender, and handedness, occipital WMH negatively influenced GMV in bilateral superior medial frontal and orbitofrontal gyri, right middle frontal and inferior triangular frontal gyri, left parahippocampus, and hippocampus in MCI (Table 3C).

Temporal WMH had the largest negative impact on right inferior temporal GMV in healthy controls; and right medial orbitofrontal gyrus, right medial superior frontal gyrus, and right middle and superior frontal gyri in MCI (Table 3D). These results remained after further controlling for age, gender and handedness covariates. There was no impact of occipital and temporal regional WMH on GM structure in AD.

Parietal WMH and hippocampal volume predict global cognition

Of all the features including GMV, regional WMH, and cognition that were included in the step-wise regression model, only parietal lobe WMH was selected as a significant predictor of MMSE scores in MCI ($p=0.025$, $R^2=0.145$) (Fig. 5A) whereas hippocampal GMV significantly predicted MMSE scores in AD ($p=0.003$, $R^2=0.213$) (Fig. 5B). There was no association between lobar WMH and global cognition in AD.

On the other hand, we found no association between lobar WMH or GMV and domain-specific cognition in MCI. In contrast, AD subjects showed positive associations between episodic memory and hippocampal GMV ($p=0.029$, $B=0.449$) as well as executive function and precuneus GMV ($p=0.020$, $B=0.464$). There were no associations between domain-specific cognition and lobe-wise WMH volume in AD.

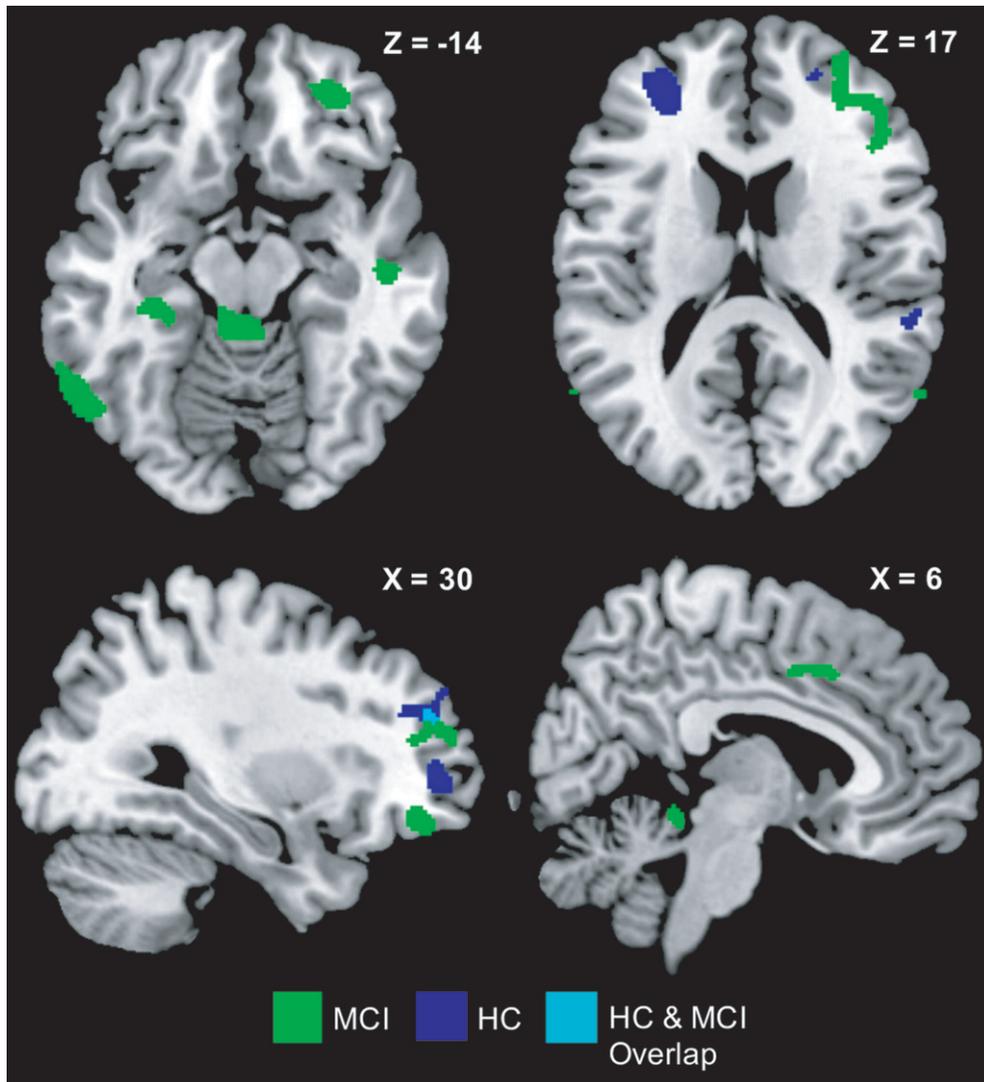


Fig. 3. Impact of frontal lobe white matter hyperintensity volume on grey matter volume in AD, MCI, and healthy controls. Greater frontal WMH related to lower grey matter volume in MCI (green) and healthy controls (blue) after controlling for age, gender, handedness, ethnicity, education, and scanner covariates. MCI subjects showed the most widespread WMH-associated decreases in grey matter volume of the bilateral frontal and temporal lobes while controls also showed WMH-related grey matter volume reductions in the bilateral frontal and right temporal regions. Subjects with AD did not show any reduced grey matter volume associated with total WMH. Results are displayed on representative sections of the MNI template brain. In the axial slices, the left side of the image corresponds to the left side of the brain. WMH, white matter hyperintensity; AD, Alzheimer's disease; MCI, mild cognitive impairment; HC, healthy controls.

DISCUSSION

A whole brain voxel-wise approach was used to assess the influence of regional WMH volume on GM structure in prodromal and clinical AD. We observed that AD patients exhibited less extensive GM atrophy after controlling for total WMH volume. Importantly, greater regional, i.e., frontal and parietal WMH volumes were associated with the largest negative and most extensive effect on GMV in

MCI subjects, compared to AD and healthy controls. Additionally, parietal lobe WMH was associated with lower MMSE scores only in MCI subjects while decreased hippocampal volume was associated with lower MMSE scores only in AD subjects. Our findings thus lend support to the proposition that AD and CeVD-related alterations begin in prodromal stages of disease and are likely to be important co-morbid conditions that influence cognitive decline.

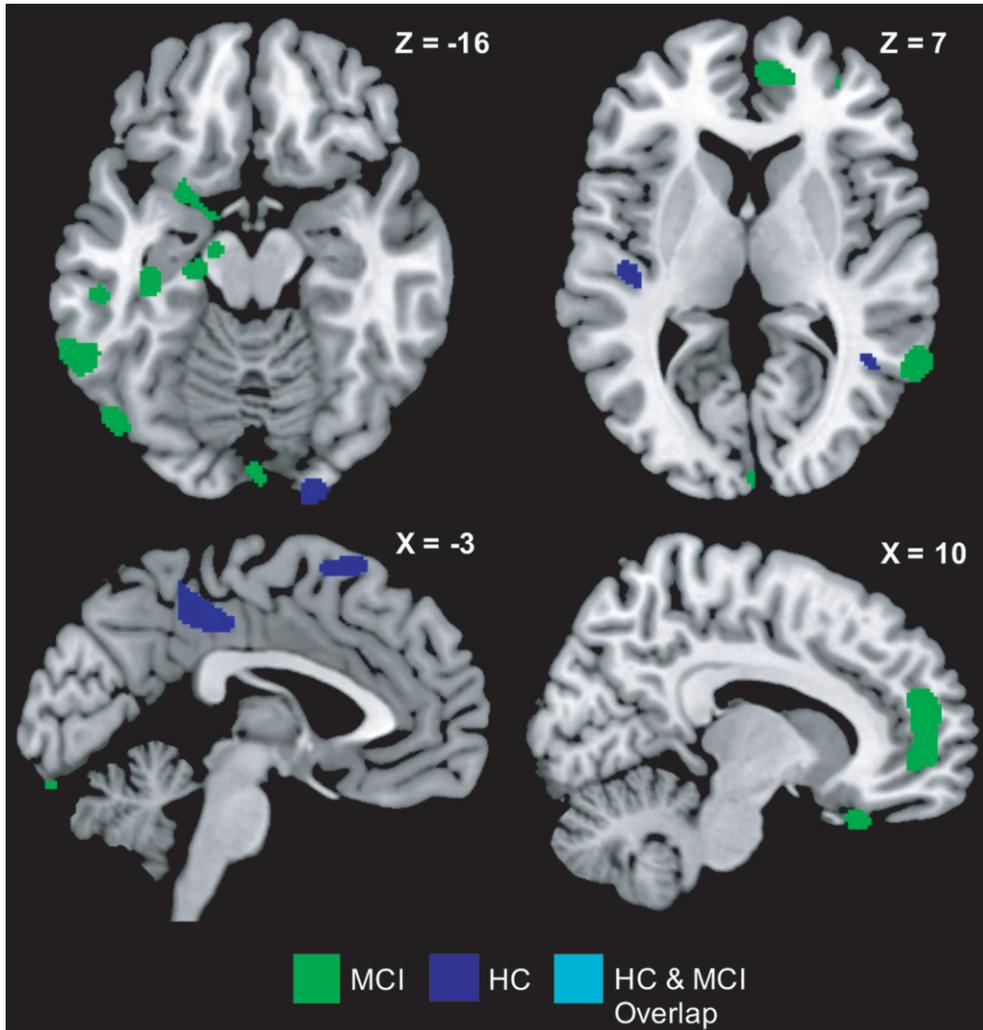


Fig. 4. Impact of parietal lobe white matter hyperintensity volume on grey matter volume in AD, MCI and healthy controls. Parietal WMH volume showed an association with grey matter volume in MCI (green) and healthy controls (blue) after controlling for age, gender, handedness, ethnicity, education, and scanner covariates. MCI subjects showed changes in grey matter volume across the bilateral frontal, left temporal regions while controls showed reduced grey matter volume mainly in left precuneus and left middle cingulum regions. Subjects with AD did not show any reduced grey matter volume associated with total WMH. Results are displayed on representative sections of the MNI template brain. In the axial slices, the left side of the image corresponds to the left side of the brain. WMH, white matter hyperintensity; AD, Alzheimer's disease; MCI, mild cognitive impairment; HC, healthy controls.

The influence of cerebrovascular disease on neurodegeneration

Previous studies indicate that WMH volume accounts for 23% of the variance of cortical GM atrophy [59] and has the greatest contribution to AD [60]. Similarly, we found that total WMH volume was highest and associated with reduced GMV in AD. Additionally, corroborating with our findings, negative associations between WMH and GMV have been previously observed in the healthy elderly [20]. More importantly, WMH may be associated

pathologically to AD since total WMH volume was associated with reduced GMV in the hippocampus, amygdala, and temporal regions in AD in our study. Eminently, neuropathological evidence does show diffuse and focal WM lesions, including WMH, in AD [61]. Although the direction of this association between WMH and cortical degeneration is under conjecture, our findings showed less extensive atrophy when total WMH was controlled for. It is likely that WMH, a marker of CeVD pathology, has additive effects with AD pathology resulting in greater GMV loss. Indeed, concurrent AD and CeVD pathology in

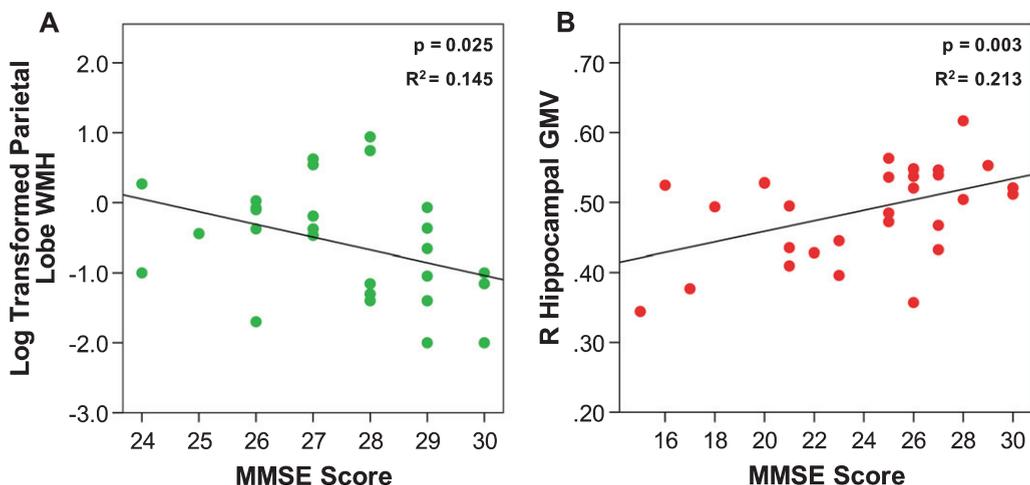


Fig. 5. AD and MCI subjects showed distinct associations with global cognition. In MCI subjects only, higher parietal lobe WMH was associated with reduced MMSE scores while in AD subjects only, lower hippocampal grey matter volume was associated with decline in MMSE scores. MMSE, Mini-Mental State Examination; WMH, white matter hyperintensity; GMV, grey matter volume; R, right; AD, Alzheimer's disease; MCI, mild cognitive impairment.

prodromal stages has been shown to indicate accelerated disease progression [62–65]. Additionally, WM disruption within areas of WMH may interrupt axonal projections to cortical regions resulting in cortical neuronal loss by retrograde degeneration [59]. Thus, when GMV is corrected for WMH, the amount of GMV is lower because both GMV and WMH are on the same pathological continuum. Therefore, the presence of WMH may result in more pronounced detrimental effects of underlying AD pathology.

We also observed that regions showing atrophy in AD overlapped with regions where reduced GMV associated with total WMH in MCI and healthy controls including the bilateral hippocampus and right middle temporal cortex (Supplementary Figure 1). This offers some insights regarding the early influence of CeVD such that structures that are affected by WMH in prodromal disease stages could provide information on regions that later show the greatest atrophy in AD or regarding further progression to AD [15, 18, 31]. Our findings highlight the importance of distinguishing subjects with high and low WMH load in order to better ascertain extent and pattern of atrophy in AD.

Region-specific WMH influence GMV in prodromal AD

Previous studies have shown that the majority of WMH occur in the frontal lobe and the parietal lobe,

similar to the deposition pattern observed in our study [66]. While some studies show the largest effect of WMH on GM atrophy in AD subjects [10, 59], others show that vascular pathology alongside AD pathology is associated with greater hippocampal atrophy in MCI [14, 67]. Such mixed results could be due to hypothesis-driven region-of-interest approaches where all voxels in a region-of-interest are averaged, possibly causing essential signals, especially at early disease stages, to also be averaged out [68]. Here, using a whole-brain voxel-wise approach, we observed that WMH-related effects on atrophy were more profound in MCI and revealed a novel finding that frontal and parietal WMH had the largest negative influence on GMV compared to temporal and occipital WMH. Whole-brain voxel-wise analysis is more sensitive to alterations in GM regions specific to the different disease course [69]. For instance, in our study, both frontal and parietal lobe WMH volume influenced hippocampal, frontal, and temporal GMV in MCI. Similarly, recent studies exhibit associations between high WMH burden, especially in frontal and temporal lobes, and more severe atrophy in AD-related regions. This may be explained as the influence of both vascular pathology and disruptions in WM pathways that link such distant regions in the brain [33, 70]. One postmortem study has also shown that greater axonal and myelin loss were found in WMH in both AD and healthy controls [66]. In addition, previous studies have shown that parietal lobe WMH is associated with more severe

disease progression and predictive of MCI conversion to AD over time [3, 12, 13, 16, 71]. On the other hand, studies also point towards the involvement of neurodegenerative factors such as cortical atrophy as well as tau and amyloid- β deposition in the accumulation of WMH via Wallerian degeneration of anatomically connected WM bundles [72–75]. In this regard, postmortem studies do indicate that parietal lobe WMH in AD are associated with demyelination and axonal loss rather than ischemic damage in aged controls [74]. However, due to the lack of amyloid and tau imaging in our current study, no directionality can be presently inferred regarding the association between cortical atrophy and WMH accumulation. Furthermore, although we did not observe significant differences in GMV between MCI and controls, unlike previous studies [76, 77], we have established patterns of GMV reductions (similar to atrophy patterns in AD) as an effect of region-specific WMH, thus indicating that WMH-related derogatory effects on structure appear to be evident early in disease.

Relationship between WMH volume and cognition

We observed that parietal WMH volume was associated with global cognition as measured by MMSE in MCI subjects only. However, such a relationship between WMH and domain-specific cognition was not observed. Such mixed associations between WMH and cognition have also been observed previously in the healthy elderly and MCI [13, 27]. Indeed, studies do indicate that the presence of WMH can itself cause disruptions in fibers connecting spatially distant cortical areas, in turn leading to greater cognitive impairment in concurrent AD and CeVD pathology [78, 79]. Furthermore, such WMH-cognition associations were missing in AD patients. In contrast, consistent with previous findings, hippocampal volume was related to global cognition in AD [80, 81]. This suggests that region-specific WMH volume may contribute to cognitive impairment in MCI rather than in the dementia stage, where atrophy might play a greater role.

Strengths and limitations

The strengths of this study include comprehensive assessments of structural brain measures and neuropsychological assessments and voxel-wise GMV analysis that allows detection of subtle changes in brain volume. Additionally, we assessed the influence

of regional WMH on both brain structure and cognition to help provide greater insights into the influence of CeVD on the brain at the healthy control, MCI, and AD stages. However, our study was limited by the cross-sectional study design which prevented us from investigating the effect of WMH on the progression of atrophy patterns. Given the moderate sample size, our voxel-wise GMV findings did not survive corrections for multiple comparisons though stringent height and cluster-level thresholding were performed to minimize false positives. Moreover, we did not have information regarding the amyloid status of our subjects, thus we were unable to assess the influence of such AD risk factors on the relationship between WMH and brain structure. In addition, the MCI group had a mixture of amnesic and non-amnesic MCI subjects; such heterogeneity might confound the relationship between WMH, GMV and cognition. Thus, future work will involve understanding the interaction between AD risk factors, WMH and GMV and age-dependent associations with cognition in prodromal and clinical AD [82].

CONCLUSIONS

In conclusion, we used voxel-wise brain analysis to study the effect of total and regional WMH volumes on GMV in healthy controls, MCI, and AD subjects. We demonstrated that total WMH volume had the largest negative effect on GMV in MCI. Interestingly, the regional distribution of WMH, specifically in the frontal and parietal lobes, also had the largest influence on GMV in MCI. We demonstrated that parietal WMH volume was associated with global cognitive deficits in MCI only. Taken together, the total volume and location of WMHs are important determinants of their clinical relevance [83, 84]. Hence, early detection of WMH and timely intervention could potentially attenuate regional cortical atrophy and cognitive impairment at the MCI stage. Management and modification of risk factors for CeVD are thus likely to be important therapeutic goals in AD.

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <http://dx.doi.org/10.3233/JAD-180280>.

REFERENCES

- [1] Frisoni GB, Fox NC, Jack CR Jr, Scheltens P, Thompson PM (2010) The clinical use of structural MRI in Alzheimer disease. *Nat Rev Neurol* **6**, 67-77.
- [2] Braak H, Braak E (1995) Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging* **16**, 271-278; discussion 278-284.
- [3] Brickman AM, Zahodne LB, Guzman VA, Narkhede A, Meier IB, Griffith EY, Provenzano FA, Schupf N, Manly JJ, Stern Y, Luchsinger JA, Mayeux R (2015) Reconsidering harbingers of dementia: Progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. *Neurobiol Aging* **36**, 27-32.
- [4] Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Perez JM, Evans AC, Alzheimer's Disease Neuroimaging Initiative (2016) Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nat Commun* **7**, 11934.
- [5] Ramirez J, McNeely AA, Berezuk C, Gao F, Black SE (2016) Dynamic progression of white matter hyperintensities in Alzheimer's disease and normal aging: Results from the Sunnybrook Dementia Study. *Front Aging Neurosci* **8**, 62.
- [6] Tosto G, Zimmerman ME, Carmichael OT, Brickman AM, Alzheimer's Disease Neuroimaging Initiative (2014) Predicting aggressive decline in mild cognitive impairment: The importance of white matter hyperintensities. *JAMA Neurol* **71**, 872-877.
- [7] Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, Decarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge R, Pantoni L, Speck O, Stephan BC, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norring B, Gorelick PB, Dichgans M; Standards for Reporting Vascular changes on nEuroimaging (STRIVE v1) (2013) Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* **12**, 822-838.
- [8] Jang JW, Kim S, Na HY, Ahn S, Lee SJ, Kwak KH, Lee MA, Hsiung GY, Choi BS, Youn YC (2013) Effect of white matter hyperintensity on medial temporal lobe atrophy in Alzheimer's disease. *Eur Neurol* **69**, 229-235.
- [9] Kandiah N, Chander RJ, Ng A, Wen MC, Cenina AR, Assam PN (2015) Association between white matter hyperintensity and medial temporal atrophy at various stages of Alzheimer's disease. *Eur J Neurol* **22**, 150-155.
- [10] Yoshita M, Fletcher E, Harvey D, Ortega M, Martinez O, Mungas DM, Reed BR, DeCarli CS (2006) Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. *Neurology* **67**, 2192-2198.
- [11] Ha SY, Youn YC, Kim S, Hsiung GY, Ahn SW, Shin HW, Park KY, Park TH, Kim SS, Kee BS, Kwon OS (2012) A voxel-based morphometric study of cortical gray matter volume changes in Alzheimer's disease with white matter hyperintensities. *J Clin Neurosci* **19**, 1506-1510.
- [12] Bilello M, Doshi J, Nabavizadeh SA, Toledo JB, Erus G, Xie SX, Trojanowski JQ, Han X, Davatzikos C (2015) Correlating cognitive decline with white matter lesion and brain atrophy magnetic resonance imaging measurements in Alzheimer's disease. *J Alzheimers Dis* **48**, 987-994.
- [13] Boyle PA, Yu L, Fleischman DA, Leurgans S, Yang J, Wilson RS, Schneider JA, Arvanitakis Z, Arfanakis K, Bennett DA (2016) White matter hyperintensities, incident mild cognitive impairment, and cognitive decline in old age. *Ann Clin Transl Neurol* **3**, 791-800.
- [14] Bos I, Verhey FR, Ramakers I, Jacobs HIL, Soinen H, Freund-Levi Y, Hampel H, Tsolaki M, Wallin AK, van Buchem MA, Oleksik A, Verbeek MM, Olde Rikkert M, van der Flier WM, Scheltens P, Aalten P, Visser PJ, Vos SJB (2017) Cerebrovascular and amyloid pathology in predementia stages: The relationship with neurodegeneration and cognitive decline. *Alzheimers Res Ther* **9**, 101.
- [15] Guzman VA, Carmichael OT, Schwarz C, Tosto G, Zimmerman ME, Brickman AM, Alzheimer's Disease Neuroimaging Initiative (2013) White matter hyperintensities and amyloid are independently associated with entorhinal cortex volume among individuals with mild cognitive impairment. *Alzheimers Dement* **9**, S124-131.
- [16] Lambert C, Sam Narean J, Benjamin P, Zeestraten E, Barrick TR, Markus HS (2015) Characterising the grey matter correlates of leukoaraiosis in cerebral small vessel disease. *Neuroimage Clin* **9**, 194-205.
- [17] Peters F, Villeneuve S, Belleville S (2014) Predicting progression to dementia in elderly subjects with mild cognitive impairment using both cognitive and neuroimaging predictors. *J Alzheimers Dis* **38**, 307-318.
- [18] Staekenborg SS, Koedam EL, Henneman WJ, Stokman P, Barkhof F, Scheltens P, van der Flier WM (2009) Progression of mild cognitive impairment to dementia: Contribution of cerebrovascular disease compared with medial temporal lobe atrophy. *Stroke* **40**, 1269-1274.
- [19] Au R, Massaro JM, Wolf PA, Young ME, Beiser A, Seshadri S, D'Agostino RB, DeCarli C (2006) Association of white matter hyperintensity volume with decreased cognitive functioning: The Framingham Heart Study. *Arch Neurol* **63**, 246-250.
- [20] Crane DE, Black SE, Ganda A, Mikulis DJ, Nestor SM, Donahue MJ, MacIntosh BJ (2015) Gray matter blood flow and volume are reduced in association with white matter hyperintensity lesion burden: A cross-sectional MRI study. *Front Aging Neurosci* **7**, 131.
- [21] Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. *J Intern Med* **256**, 183-194.
- [22] Smith EE, Egorova S, Blacker D, Killiany RJ, Muzikansky A, Dickerson BC, Tanzi RE, Albert MS, Greenberg SM, Guttman CR (2008) Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. *Arch Neurol* **65**, 94-100.
- [23] Smith EE, Salat DH, Jeng J, McCreary CR, Fischl B, Schmahmann JD, Dickerson BC, Viswanathan A, Albert MS, Blacker D, Greenberg SM (2011) Correlations between MRI white matter lesion location and executive function and episodic memory. *Neurology* **76**, 1492-1499.

- [24] Bunce D, Anstey KJ, Cherbuin N, Burns R, Christensen H, Wen W, Sachdev PS (2010) Cognitive deficits are associated with frontal and temporal lobe white matter lesions in middle-aged adults living in the community. *PLoS One* **5**, e13567.
- [25] Ramirez J, McNeely AA, Scott CJ, Stuss DT, Black SE (2014) Subcortical hyperintensity volumetrics in Alzheimer's disease and normal elderly in the Sunnybrook Dementia Study: Correlations with atrophy, executive function, mental processing speed, and verbal memory. *Alzheimers Res Ther* **6**, 49.
- [26] Bolandzadeh N, Davis JC, Tam R, Handy TC, Liu-Ambrose T (2012) The association between cognitive function and white matter lesion location in older adults: A systematic review. *BMC Neurol* **12**, 126.
- [27] Arvanitakis Z, Fleischman DA, Arfanakis K, Leurgans SE, Barnes LL, Bennett DA (2016) Association of white matter hyperintensities and gray matter volume with cognition in older individuals without cognitive impairment. *Brain Struct Funct* **221**, 2135-2146.
- [28] Taki Y, Kinomura S, Sato K, Goto R, Wu K, Kawashima R, Fukuda H (2011) Correlation between degree of white matter hyperintensities and global gray matter volume decline rate. *Neuroradiology* **53**, 397-403.
- [29] Tosto G, Zimmerman ME, Hamilton JL, Carmichael OT, Brickman AM, Alzheimer's Disease Neuroimaging Initiative (2015) The effect of white matter hyperintensities on neurodegeneration in mild cognitive impairment. *Alzheimers Dement* **11**, 1510-1519.
- [30] Duan D, Li C, Shen L, Cui C, Shu T, Zheng J (2016) Regional gray matter atrophy coexistent with occipital periventricular white matter hyperintensities. *Front Aging Neurosci* **8**, 214.
- [31] Dickie DA, Karama S, Ritchie SJ, Cox SR, Sakka E, Royle NA, Aribisala BS, Hernandez MV, Maniega SM, Pattie A, Corley J, Starr JM, Bastin ME, Evans AC, Deary IJ, Wardlaw JM (2016) Progression of white matter disease and cortical thinning are not related in older community-dwelling subjects. *Stroke* **47**, 410-416.
- [32] Grau-Olivares M, Arboix A, Junque C, Arenaza-Urquijo EM, Rovira M, Bartres-Faz D (2010) Progressive gray matter atrophy in lacunar patients with vascular mild cognitive impairment. *Cerebrovasc Dis* **30**, 157-166.
- [33] Habes M, Erus G, Toledo JB, Zhang T, Bryan N, Launer LJ, Rosseel Y, Janowitz D, Doshi J, Van der Auwera S, von Sarnowski B, Hegenscheid K, Hosten N, Homuth G, Volzke H, Schminke U, Hoffmann W, Grabe HJ, Davatzikos C (2016) White matter hyperintensities and imaging patterns of brain ageing in the general population. *Brain* **139**, 1164-1179.
- [34] Tan YJ, Ng ASL, Vipin A, Lim JKW, Chander RJ, Ji F, Qiu Y, Ting SKS, Hameed S, Lee TS, Zeng L, Kandiah N, Zhou J (2017) Higher peripheral TREM2 mRNA levels relate to cognitive deficits and hippocampal atrophy in Alzheimer's disease and amnesic mild cognitive impairment. *J Alzheimers Dis* **58**, 413-423.
- [35] Yatawara C, Lim L, Chander R, Zhou J, Kandiah N (2016) Depressive symptoms influence global cognitive impairment indirectly by reducing memory and executive function in patients with mild cognitive impairment. *J Neurol Neurosurg Psychiatry* **87**, 1375-1383.
- [36] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 270-279.
- [37] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.
- [38] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.
- [39] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* **53**, 695-699.
- [40] Skinner J, Carvalho JO, Potter GG, Thames A, Zelinski E, Crane PK, Gibbons LE, Alzheimer's Disease Neuroimaging Initiative (2012) The Alzheimer's Disease Assessment Scale-Cognitive-Plus (ADAS-Cog-Plus): An expansion of the ADAS-Cog to improve responsiveness in MCI. *Brain Imaging Behav* **6**, 489-501.
- [41] Drozdick LW, Holdnack JA, Weiss LG, Zhou X (2013) Chapter 1 - Overview of the WAIS-IV/WMS-IV/ACS. In *WAIS-IV, WMS-IV, and ACS: Advanced Clinical Interpretation*, Holdnack JA, Drozdick LW, Weiss LG, Iverson GL, ed. Academic Press.
- [42] Weintraub S, Wicklund AH, Salmon DP (2012) The neuropsychological profile of Alzheimer disease. *Cold Spring Harb Perspect Med* **2**, a006171.
- [43] Dubois B, Slachevsky A, Litvan I, Pillon B (2000) The FAB: A Frontal Assessment Battery at bedside. *Neurology* **55**, 1621-1626.
- [44] Joy S, Kaplan E, Fein D (2004) Speed and memory in the WAIS-III Digit Symbol-Coding subtest across the adult lifespan. *Arch Clin Neuropsychol* **19**, 759-767.
- [45] Ivanova I, Salmon DP, Gollan TH (2013) The multilingual naming test in Alzheimer's disease: Clues to the origin of naming impairments. *J Int Neuropsychol Soc* **19**, 272-283.
- [46] Chong MS, Lim WS, Chan SP, Feng L, Niti M, Yap P, Yeo D, Ng TP (2010) Diagnostic performance of the Chinese Frontal Assessment Battery in early cognitive impairment in an Asian population. *Dement Geriatr Cogn Disord* **30**, 525-532.
- [47] Lee CKY, Collinson SL, Feng L, Ng T-P (2012) Preliminary normative neuropsychological data for an elderly Chinese population. *Clin Neuropsychol* **26**, 321-334.
- [48] Ng A, Chew I, Narasimhalu K, Kandiah N (2013) Effectiveness of Montreal Cognitive Assessment for the diagnosis of mild cognitive impairment and mild Alzheimer's disease in Singapore. *Singapore Med J* **54**, 616-619.
- [49] Sahadevan S, Tan NJ, Tan T, Tan S (1997) Cognitive testing of elderly Chinese people in Singapore: Influence of education and age on normative scores. *Age Ageing* **26**, 481-486.
- [50] Wechsler D (2008) *Wechsler Adult Intelligence Scale - Fourth Edition*, Pearson Assessment, San Antonio, TX.
- [51] Wechsler D (2009) *Wechsler Memory Scale - Fourth Edition*, Pearson Clinical, San Antonio, TX.

- [52] Weir JP (2005) Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. *J Strength Cond Res* **19**, 231-240.
- [53] Zuo XN, Kelly C, Adelstein JS, Klein DF, Castellanos FX, Milham MP (2010) Reliable intrinsic connectivity networks: Test-retest evaluation using ICA and dual regression approach. *Neuroimage* **49**, 2163-2177.
- [54] Smart SD, Firkbank MJ, O'Brien JT (2011) Validation of automated white matter hyperintensity segmentation. *J Aging Res* **2011**, 391783.
- [55] Ashburner J, Friston KJ (2000) Voxel-based morphometry—the methods. *Neuroimage* **11**, 805-821.
- [56] Ng KK, Lo JC, Lim JK, Chee MW, Zhou J (2016) Reduced functional segregation between the default mode network and the executive control network in healthy older adults: A longitudinal study. *Neuroimage* **133**, 321-330.
- [57] Rajapakse JC, Giedd JN, Rapoport JL (1997) Statistical approach to segmentation of single-channel cerebral MR images. *IEEE Trans Med Imaging* **16**, 176-186.
- [58] Ashburner J (2007) A fast diffeomorphic image registration algorithm. *Neuroimage* **38**, 95-113.
- [59] Capizzano AA, Acion L, Bekinschtein T, Furman M, Gomila H, Martinez A, Mizrahi R, Starkstein SE (2004) White matter hyperintensities are significantly associated with cortical atrophy in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **75**, 822-827.
- [60] Brickman AM, Muraskin J, Zimmerman ME (2009) Structural neuroimaging in Alzheimer's disease: Do white matter hyperintensities matter? *Dialogues Clin Neurosci* **11**, 181-190.
- [61] Kalaria RN (2016) Neuropathological diagnosis of vascular cognitive impairment and vascular dementia with implications for Alzheimer's disease. *Acta Neuropathol* **131**, 659-685.
- [62] Freeze WM, Jacobs HI, Gronenschild EH, Jansen JF, Burgmans S, Aalten P, Clerx L, Vos SJ, van Buchem MA, Barkhof F, van der Flier WM, Verbeek MM, Rikkert MO, Backes WH, Verhey FR (2017) White matter hyperintensities potentiate hippocampal volume reduction in non-demented older individuals with abnormal amyloid-beta. *J Alzheimers Dis* **55**, 333-342.
- [63] van Straaten EC, Harvey D, Scheltens P, Barkhof F, Petersen RC, Thal LJ, Jack CR Jr, DeCarli C, Alzheimer's Disease Cooperative Study Group (2008) Periventricular white matter hyperintensities increase the likelihood of progression from amnesic mild cognitive impairment to dementia. *J Neurol* **255**, 1302-1308.
- [64] Silbert LC, Dodge HH, Perkins LG, Sherbakov L, Lahna D, Erten-Lyons D, Woltjer R, Shinto L, Kaye JA (2012) Trajectory of white matter hyperintensity burden preceding mild cognitive impairment. *Neurology* **79**, 741-747.
- [65] Chong JSX, Liu SW, Loke YM, Hilal S, Ikram MK, Yu X, Tan BY, Venketasubramanian N, Chen CLH, Zhou J (2017) Influence of cerebrovascular disease on brain networks in prodromal and clinical Alzheimer's disease. *Brain* **140**, 3012-3022.
- [66] Gouw AA, van der Flier WM, Fazekas F, van Straaten EC, Pantoni L, Poggesi A, Inzitari D, Erkinjuntti T, Wahlund LO, Waldemar G, Schmidt R, Scheltens P, Barkhof F, Group LS (2008) Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: The Leukoaraiosis and Disability study. *Stroke* **39**, 1414-1420.
- [67] Fiford CM, Manning EN, Bartlett JW, Cash DM, Malone IB, Ridgway GR, Lehmann M, Leung KK, Sudre CH, Ourselin S, Biessels GJ, Carmichael OT, Fox NC, Cardoso MJ, Barnes J, Alzheimer's Disease Neuroimaging Initiative (2017) White matter hyperintensities are associated with disproportionate progressive hippocampal atrophy. *Hippocampus* **27**, 249-262.
- [68] Poldrack RA (2007) Region of interest analysis for fMRI. *Soc Cogn Affect Neurosci* **2**, 67-70.
- [69] Frisoni GB, Testa C, Zorzan A, Sabatoli F, Beltramello A, Soininen H, Laakso MP (2002) Detection of grey matter loss in mild Alzheimer's disease with voxel based morphometry. *J Neurol Neurosurg Psychiatry* **73**, 657-664.
- [70] Habes M, Erus G, Toledo JB, Bryan N, Janowitz D, Doshi J, Volzke H, Schminke U, Hoffmann W, Grabe HJ, Wolk DA, Davatzikos C (2018) Regional tract-specific white matter hyperintensities are associated with patterns to aging-related brain atrophy via vascular risk factors, but also independently. *Alzheimers Dement (Amst)* **10**, 278-284.
- [71] Brickman AM, Provenzano FA, Muraskin J, Manly JJ, Blum S, Apa Z, Stern Y, Brown TR, Luchsinger JA, Mayeux R (2012) Regional white matter hyperintensity volume, not hippocampal atrophy, predicts incident Alzheimer disease in the community. *Arch Neurol* **69**, 1621-1627.
- [72] Ma M (2013) Role of calpains in the injury-induced dysfunction and degeneration of the mammalian axon. *Neurobiol Dis* **60**, 61-79.
- [73] McAleese KE, Firkbank M, Dey M, Colloby SJ, Walker L, Johnson M, Beverley JR, Taylor JP, Thomas AJ, O'Brien JT, Attems J (2015) Cortical tau load is associated with white matter hyperintensities. *Acta Neuropathol Commun* **3**, 60.
- [74] McAleese KE, Walker L, Graham S, Moya ELJ, Johnson M, Erskine D, Colloby SJ, Dey M, Martin-Ruiz C, Taylor JP, Thomas AJ, McKeith IG, De Carli C, Attems J (2017) Parietal white matter lesions in Alzheimer's disease are associated with cortical neurodegenerative pathology, but not with small vessel disease. *Acta Neuropathol* **134**, 459-473.
- [75] Scott JA, Braskie MN, Tosun D, Maillard P, Thompson PM, Weiner M, DeCarli C, Carmichael OT, ADNI (2016) Cerebral amyloid is associated with greater white-matter hyperintensity accrual in cognitively normal older adults. *Neurobiol Aging* **48**, 48-52.
- [76] Barbeau EJ, Ranjeva JP, Didic M, Confort-Gouny S, Felician O, Soulier E, Cozzone PJ, Ceccaldi M, Poncet M (2008) Profile of memory impairment and gray matter loss in amnesic mild cognitive impairment. *Neuropsychologia* **46**, 1009-1019.
- [77] Hamalainen A, Tervo S, Grau-Olivares M, Niskanen E, Penanen C, Huuskonen J, Kivipelto M, Hanninen T, Tapiola M, Vanhanen M, Hallikainen M, Helkala EL, Nissinen A, Vanninen R, Soininen H (2007) Voxel-based morphometry to detect brain atrophy in progressive mild cognitive impairment. *Neuroimage* **37**, 1122-1131.
- [78] Kim JH, Hwang KJ, Kim JH, Lee YH, Rhee HY, Park KC (2011) Regional white matter hyperintensities in normal aging, single domain amnesic mild cognitive impairment, and mild Alzheimer's disease. *J Clin Neurosci* **18**, 1101-1106.
- [79] Vemuri P, Lesnick TG, Przybelski SA, Knopman DS, Preboske GM, Kantarci K, Raman MR, Machulda MM, Mielke MM, Lowe VJ, Senjem ML, Gunter JL, Rocca WA, Roberts RO, Petersen RC, Jack CR Jr (2015) Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. *Brain* **138**, 761-771.

- [80] Peng GP, Feng Z, He FP, Chen ZQ, Liu XY, Liu P, Luo BY (2015) Correlation of hippocampal volume and cognitive performances in patients with either mild cognitive impairment or Alzheimer's disease. *CNS Neurosci Ther* **21**, 15-22.
- [81] Velayudhan L, Proitsi P, Westman E, Muehlboeck JS, Mecocci P, Vellas B, Tsolaki M, Kloszewska I, Soininen H, Spenger C, Hodges A, Powell J, Lovestone S, Simmons A, dNeuroMed Consortium (2013) Entorhinal cortex thickness predicts cognitive decline in Alzheimer's disease. *J Alzheimers Dis* **33**, 755-766.
- [82] Hong Z, Ng KK, Sim SK, Ngeow MY, Zheng H, Lo JC, Chee MW, Zhou J (2015) Differential age-dependent associations of gray matter volume and white matter integrity with processing speed in healthy older adults. *Neuroimage* **123**, 42-50.
- [83] Prins ND, Scheltens P (2015) White matter hyperintensities, cognitive impairment and dementia: An update. *Nat Rev Neurol* **11**, 157-165.
- [84] Biesbroek JM, Weaver NA, Hilal S, Kuijf HJ, Ikram MK, Xu X, Tan BY, Venketasubramanian N, Postma A, Biessels GJ, Chen CP (2016) Impact of strategically located white matter hyperintensities on cognition in memory clinic patients with small vessel disease. *PLoS One* **11**, e0166261.