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Lesion location matters: The relationships between white matter hyperintensities on cognition in the healthy elderly

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Abstract

White matter hyperintensities (WMH) are associated with cognitive decline. We aimed to identify the spatial specificity of WMH impact on cognition in non-demented, healthy elderly. We quantified WMH volume among healthy participants of a community dwelling cohort ($n = 702$, age range $60 – 82$ years, mean age $= 69.5$ years, 46% female) and investigated the effects of WMH on cognition and behavior, specifically for executive function, memory, and motor speed performance. Lesion location influenced their effect on cognition and behavior: Frontal WMH in the proximity of the frontal ventricles mainly affected executive function and parieto-temporal WMH in the proximity of the posterior horns deteriorated memory, while WMH in the upper deep white matter—including the corticospinal tract—compromised motor speed performance. This study exposes the subtle and subclinical yet detrimental effects of WMH on cognition in healthy elderly, and strongly suggests a causal influence of WMH on cognition by demonstrating the spatial specificity of these effects.

Introduction

Rapidly aging populations are burdening societies around the globe. While healthcare costs increase with age, cognitive skills generally decline. While not every person develops clinically manifest dementia, many elderly experience some form of cognitive deterioration. Most people also exhibit white matter hyperintensities (WMH) on brain MRI.[1] In this project, we studied WMH—usually a correlate of vascular changes in the aging brain—to quantify the effects on cognition.[2] WMH volume increases over a lifetime, highlighting its progressive importance with advancing age.[1] While the exact causal mechanisms of WMH formation remain elusive, major risk factors for the development of WMH are hypertension,[3,4] smoking,[5] and cardiovascular disease.[6] Extensive literature describes the negative effects of WMH on cognitive functioning.[7,8] However, while it is agreed that WMH have

detrimental effects on cognition, there is a clinicoradiological discrepancy between the extent of the white matter disease and cognitive impairment.[8] Indeed, some individuals exhibit extensive white matter disease while preserving a high level of cognitive functioning. Moreover, comprehensive meta-analyses have

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indicated that—among the cognitive domains—attention, executive function, and memory are specifically affected by WMH.[9,10]

Several studies suggest that the strategic position of the lesions is more predictive for cognitive outcome than general WMH volume. While earlier studies utilized case-control to investigate the relationship between lesion location and cognition, more recent studies have investigated localized WMH effects with ROI/voxel-based analyses.[11,12]

Building on this literature, the current study deploys a population-based epidemiological large-cohort study and focuses on healthy non-demented elderly participants. We quantified WMH volume and investigated the effect of total WMH volume as well as their location-specific impact on cognition. By identifying the spatial strategic effects of WMH on cognition in a large sample of healthy elderly participants, the current study elucidates the subtle relationship between WMH and subclinical cognitive decline.

Methods

Study population

This study took place within the framework of the population-based study of the Leipzig Research Centre for Civilization Diseases (LIFE). All participants were randomly chosen and invited via the city registry office according to the study protocol from the LIFE-Adult-Study.[13] After providing informed consent, all participants underwent a 3 Tesla MRI brain scan, structured interviews, neuropsychological tests, and a set of medical assessments.[13] Financial compensation was provided, the study protocol was in accordance with the Declaration of Helsinki and approved by the ethics committee at the University of Leipzig. Our results are based on participants over the age of 60 years. After excluding individuals with an intake of psychoactive drugs ($n = 242$), neuroradiological incidental findings ($n = 3$), neurological diseases ($n = 8$), difficulties during data processing ($n = 62$), and missing cognitive data ($n = 188$), a cohort of 702 participants was included in the current study. Note that cerebral microbleeds and perivascular spaces were not taken into account. A flow chart visualizes the selection process of participants (see Figure 1) and Table 1 provides an overview of demographics of our cohort.

MRI data acquisition

All MRI scans were performed at 3 Tesla on a MAGNETOM Verio scanner (Siemens, Erlangen, Germany). The body coil was used for RF transmission and a 32-channel head coil was used for signal reception. T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) and fluid-attenuated inversion recovery (FLAIR) images were acquired as part of a standardized protocol: MPRAGE (FA = 9°, TR = 2300 ms, TI = 900 ms, TE = 2.98 ms, 1 mmisotropic resolution, AT = 5.10 min); FLAIR (TR = 5000 ms, TI = 1800 ms, TE = 395 ms, 1 mmisotropic resolution, AT = 7.02 min).

Automated assessment of WMH

Prior to segmentation, all images were carefully checked by a radiologist for incidental findings. Participants with hemorrhagic, ischemic, or lacunar infarctions, or other neuroradiological incidental findings were excluded from the analysis. Lesion TOADS—a computer-based WMH segmentation algorithm that was previously validated for patients with multiple sclerosis—was used to automatically determine WMH volume on T1-weigthed MPRAGE and FLAIR images.[14] As WMH differ in their pattern, intensity, and extent to those of multiple sclerosis, we adapted the algorithm to the needs of age-related WMH in our cohort in a two-step iterative process and revalidated it the algorithm on our cohort. Given the large variety of WMH, their appearance on FLAIR images had a wider range of intensities across participants. Therefore, from the first segmentation given by LesionTOADS (step 1), we renormalized the contrast of input FLAIR images to better separate WMH from healthy tissue, modeling the FLAIR intensity inside the brain as a mixture of Gaussian and outlier distributions (step 2). The intensity boundary between tissue intensity and WMH is estimated from setting the ratio of segmented WMH to brain volume as an outlier ratio, and performing the LesionTOADS step again on the re-normalized intensities. This method ensures that the relative intensities of the FLAIR in different images are similar across a large cohort of subjects. Binary WMH maps of all participants were nonlinearly co-registered to a standardized Montréal Neurological Institute (MNI) template (1 mm isometric) by applying the transformation matrix obtained from co-registering the MPRAGE of the respective participant to the template with ANTS[15]: a state-of-the-art registration technique.[16] We afterwards carefully inspected every standardized image. This registration technique ensures a low amount of warping while aligning accurately the main morphological features of the brain (ventricles, white matter tracts, subcortex, overall shape and size of the cerebral cortex). As depicted in Figure 1, we excluded lesion segmentation of 27 participants. Reasons included erroneous skull-stripping, motion or
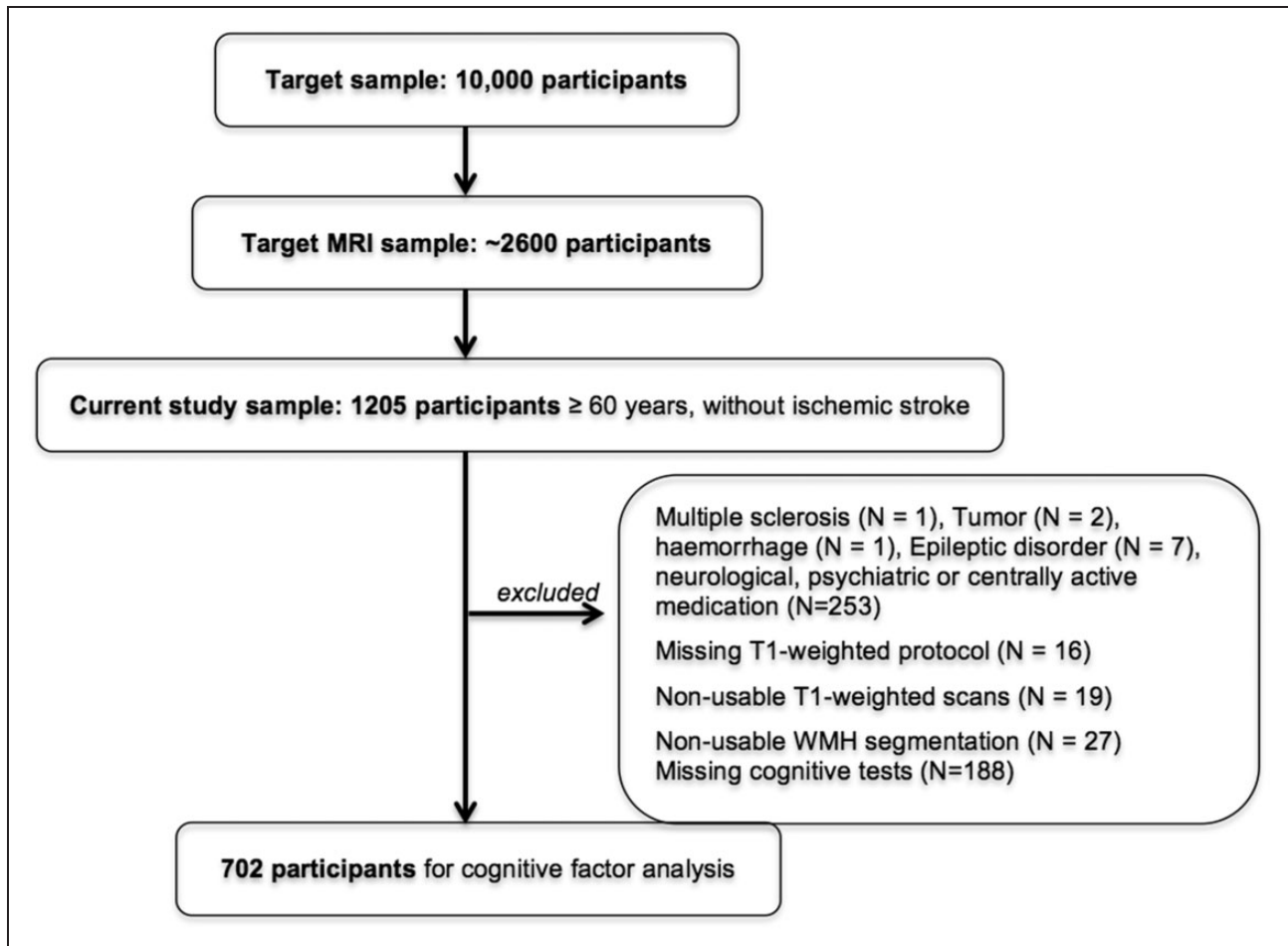
Figure 1. Flow chart visualizing of the selection process of participants.

Table 1. Demographics of the participants and distribution of visually and automatically assessed WMH volume.

Number of subjects	702
Age range in years	60–82
Mean age (SD) in years	68.49 (4.58)
Sex (female) in %	46.01
Fazekas rating 0, 1, 2, 3 in %	22.2, 55.3, 21.9, 1.6
Mean number of 1 mm iso-voxels WMH (SD)	4249 (6661)
Mean number of 1 mm iso-voxels WM (SD)	412,054 (43,759)
MMSE (SD)	28.59 (1.28)

SD: standard deviation; WM: white matter; WMH: white matter hyperintensity; MMSE: mini mental status examination.

inhomogeneity artifacts, mis-registration of the T1-weighted and FLAIR data, or incorrect warping onto the MNI template. For standard space lesion maps across participants, WMH maps were added to create a WMH frequency map with FSL.[17] Brain images were visualized with the Mango viewer (http://ric.uthscsa.edu/mango/mango.html).

Cognitive assessment

Cognitive performance was assessed with a set of standard neuropsychological tests.[13] Results of the Wortschatztest (a German vocabulary test), the extended version of the Consortium to Establish a Registry of Alzheimer's Disease (CERADplus) test battery,[18] the Structured Interview for Diagnosis of Dementia of Alzheimer type, as well as Multi-Infarct Dementia and Dementia of other Etiology according to DSM-III-R, DSM-IV, and ICD-10,[19] were available for analysis. All subtest results were carefully checked for missing values and data recording errors.

Statistical analysis

Associations between log-transformed normalized (by WM volume) total WMH volume and cognition have

been assessed using separate multiple regression models with cognitive domains as the dependent variable, and age, sex, and years of education as confounders. Significance threshold was set to $\alpha < 0.05$ (one-sided) and corrected for the number of cognitive domains tested with Bonferroni correction ($\alpha < 0.0167$). Significant associations are marked with an asterisk, in the results section. Statistical analyses were performed with R.[20]

Topographical relevance analysis of WMH for cognition

In order to identify regions where WMH occurrence is robustly related to worse performance in a specific cognitive domain, we used an ad hoc analysis routine. Here, we scaled binary WMH map (in standard space) of each participant with the standardized adjusted performance of the subject in that cognitive domain (after controlling for other domains as well as age, sex, and education based on the following formula: standardized adjusted performance of cognitive factor X = raw scores of cognitive factor X – [b1 × raw scores of cognitive factor Y + b2 × raw scores of cognitive factor Z + b3 × age + b4 × sex + b5 × education]). The sum of all scaled WMH maps for each cognitive factor were then assessed in voxel space and with a threshold (>10) to identify regions in WM, where WMH occurrence increases the probability of worse performance on each cognitive domain. Note that two participants were discarded from this analysis because of failed registration into standard space.

Results

WMH volume distribution

Characteristics of the study cohort ($n = 702$) are provided in Table 1. WMH volume segmented by LesionTOADS reflects the visual assessment of WMH volume represented by the visual rating (see Supplementary Figure 3(b)) and increases with age, as expected. Supplementary Figure 4 illustrates the WMH frequency distribution respectively in a characteristic lesion pattern with highest lesion frequency located adjacent to the lateral ventricles symmetrically.

WMH volume and cognition

An exploratory factor analysis was employed to assess the structure of the cognitive data and to reduce its dimensions in the cohort of 702 participants (for details see supplementary material). The factor analysis resulted in four cognitive and behavioral domains, i.e. "executive function," "memory," "motor speed performance," and "visuoconstructive abilities." The average MMSE score was 28.59 (standard deviation = 1.28). Multiple linear regression corrected for age, sex, and education showed negative, but subtle association between WMH volume and executive function ($r = -0.07$, $p = 0.013$), memory ($r = -0.07$, $p = 0.016$), and motor speed performance ($r = -0.09$, $p = 0.006$) in our cohort of non-demented, elderly participants. We did not find an association between WMH volume and visuoconstructive abilities in our sample of cognitively intact healthy elderly ($r = -0.002$, $p = 0.34$).

Topographical relevance of WMH for cognitive function

Regarding a topographical relationship between WMH and different cognitive and behavioral domains, we found that WMH in the frontal white matter adjacent to the frontal horns were much more pronounced in participants with worse performance in executive function, while participants with high cognitive performance in executive functions had less WMH in the frontal, periventricular white matter. Participants with decreased memory function had prevailing WMH in the bilateral parieto-temporal white matter junctions adjacent to the posterior horns of the lateral ventricles, while participants with higher memory performance showed less WMH in this location. Participants with worse motor speed performance showed an increased amount of WMH in the upper deep white matter—including the corticospinal tract—while participants with better motor speed performance had less lesions, respectively. All WMH locations with detrimental negative effects on cognition are bilateral with a symmetrical pattern (Figure 2). Unthresholded maps with the full range of location-specific impact on cognition are available on a meta-analysis database (http://neurovault.org/collections/66/). A separate voxel-wise lesion symptom mapping analysis (VLSM, FDR-corrected, $p < 0.01$) confirmed the pattern. WHM in the frontal white matter were related to negative executive function, WMH in the parieto-temporal white matter were related to negative memory function, and WMH in the upper deep white matter were related to negative motor speed performance (Supplementary Figure 6).

Discussion

Based on a single sample of well-characterized non-demented elderly subjects ($n = 702$), we demonstrate the subtlety of the relationship between global WMH load and cognitive and behavioral functions. Furthermore, we localize the effects of WMH on cognitive and behavioral functions in the healthy elderly
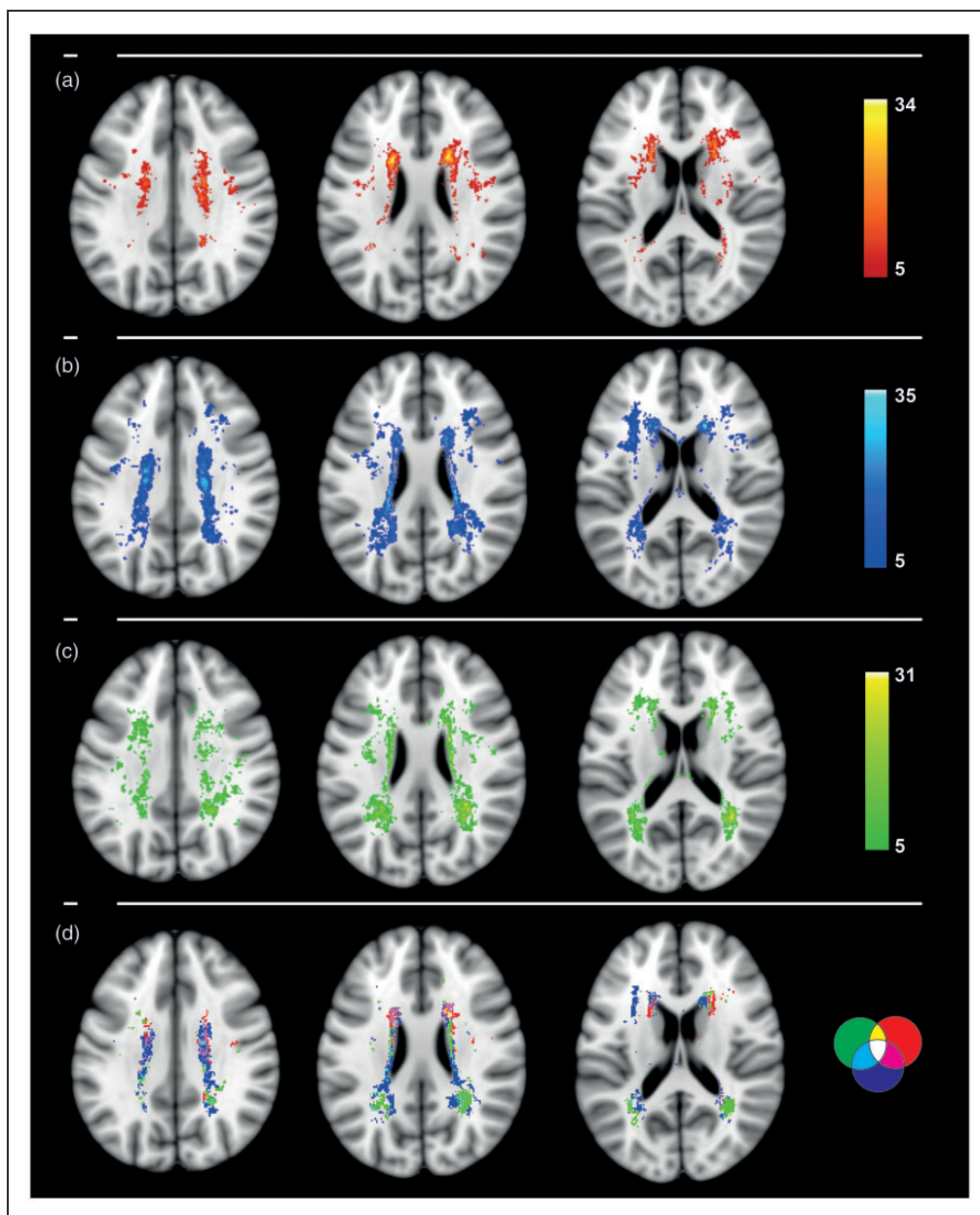
Figure 2. WMH frequency maps of negative impact on cognition: thresholded above 5 on (a) executive function, (b) motor speed performance, and (c) memory; (d) all three cognitive factors thresholded above 10 with red for executive function, green for memory, and blue for motor speed performance with logical color coding of intersecting clusters.

with a novel routine as well as with well-established VLSM. This study expands upon the existing literature, which to the largest extent has been conducted on patient data. By investigating participants from a community-dwelling large cohort study strictly focusing on healthy elderly individuals, we bring further light into the relationship between lesion location and cognitive deficits. In line with the existing literature and with a meta-analysis spanning over 30 studies investigating the relationship between WMH and cognition, we find consistent negative relations between WMH volume and

executive function, memory, and motor speed performance.[10] For visuoconstructive abilities, we did not find an association with WMH volume in our cohort. On the one hand, this might be due to a low sensitivity of the cognitive tests to sufficiently identify visuoconstructive differences in healthy elderly. On the other hand, visuoconstruction might in fact be spared from the detriment of WMH in healthy elderly. Note that our participants exhibited a high level of cognitive functioning (mean MMSE 28.59, SD 1.28) which emphasizes the subtlety of the WMH-effects on cognition.

Furthermore, it exemplifies the clinicoradiological discrepancy between the extent of the white matter disease and cognitive impairment in healthy elderly. With respect to the clinicoradiological discrepancy, it has been suggested that WMH induce compensatory mechanisms such as changes of cerebral blood flow found in a longitudinal study,[21] hinting towards an individual tolerance of WMH load before cognitive function is measurably impaired. Moreover, the incongruence between the extent of WMH volume and cognitive dysfunction could be explained by 'cognitive reserve'—a model which conceptualizes the resilience of the individual brain to neuropathological damage by recruiting alternative neuronal capacities.[22] By controlling for years of education, this study only marginally corrects for 'cognitive reserve'.

Another general problem of MRI-based WMH studies is the lack of histopathological specification of WMH. Neuropathological studies have described heterogeneous structural correlates of WMH,[8] which implies that different pathologies result in different lesions that appear similarly on FLAIR images. If different lesion etiologies have specific effects on cognition, it cannot be accounted for on FLAIR images. Furthermore, WMH are just one aspect of brain aging. While signal transmission in the white matter is crucial for cognition, other structural correlates such as gray matter have their own contribution to cognition independent of WMH volume and were not accounted for in this study.

Studies have investigated the effect of WMH location with region-based as well as with voxel-wise techniques.[23] Region-based approaches with large and rather arbitrary sections were helpful to demonstrate regional differences, yet these studies were limited to uncovering localized effects beyond the predefined areas. Smith et al.,[12] who employed a voxel-wise technique to disentangle the relation between WMH and cognitive deficits, have provided interesting results relating frontal WMH to executive deficits, and temporo-occipital WMH to disturbance of episodic memory in a cohort of 147 subjects with cognitive deficits ranging from dementia to normal cognition.[12] Our study expands upon these findings by incorporating 702 healthy and non-demented elderly participants after rigorously excluding participants with progressive cognitive deficits and medication influencing cognition (i.e. psychoactive medication). All WMH clusters occurred in regions of high WMH density (Supplementary Figure 4) and thus reflect many subjects.

WMH clusters that related to poor executive function were predominantly located in the frontal white matter adjacent to the anterior ventricles, with peak voxels in the anterior limb of the corona radiata (anterior thalamic radiation according to the JHU White-Matter atlas), which is known to connect the prefrontal cortex with the thalamus and has high relevance for executive function.[24] Given the high plausibility of relating these lesions to executive function, we conclude that our findings corroborate similar findings of previous studies.[11,12] Moreover, we assume that the previous studies that did not find a relationship between executive function and frontal WMH may not have done so because of limitations such as large WM parcels and smaller sample sizes.[25,26]

WMH in the parieto-temporal white matter were prevailing in participants with poorer memory performance, which might be explained by WMH clusters interfering with the inferior and superior longitudinal fasciculus as well as the retrosplenial cingulum—white matter tracts which are known to be associated with memory function.[27] As WMH in the deeper temporal white matter were sparse in our participants (see WMH frequency map in Supplementary Figure 4), we could not evaluate the assumed impact of these WMH for memory with sufficient power.

Motor speed performance was decreased with WMH clusters in the upper deep white matter interestingly incorporating parts of the corticospinal tract. Previous studies have assessed the disruptive characteristics of WMH on both connectivity and structural integrity.[28,29] Our observations strongly support the assumption of WMH having a causal effect on cognitive deficits and further specify the location-wise impact of WMH on distinct cognitive functions.

To our knowledge, this is the first large cohort study to relate spatial specificity of WMH to subtle cognitive differences in a non-demented sample of healthy elderly from the general population.

Limitations of the study are the cross-sectional nature of the data and the lack of histopathology. With respect to the underlying pathophysiology of WMH, on the one hand, it can be safely assumed that the predominant majority of WMH in our cohort were of ischemic origin. On the other hand, given the fact that MRI findings are rather non-specific—no definite etiological assessment can be made about individual lesions in different subjects. To address the interesting question whether WMH of different origins have different effects on gray matter and cognitive function, further analysis with pathophysiological differentiation of lesions will be required for example by comparing patients with distinct lesion pathologies such as multiple sclerosis, vasculitis, etc. Combinations of innovative techniques such as quantitative MR-imaging, high-gradient diffusion weighted imaging, and MR-spectroscopy could further help to differentiate between distinct lesion etiology. A general challenge of studies with elderly participants is the non-linear registration of aged brains that often exhibit a

significant amount of deformation. However, by using a recommended high-performance algorithm and through quality-checking, we assured a high standard of registration. Furthermore, while LesionTOADS is a state-of-the-art segmentation algorithm as demonstrated in the ISBI segmentation challenge,[30] potential difficulties are systematic errors such as mis-segmentation of artefacts around the ventricles. While systematic false positives reduce correlations with WMH volumes, it does not affect the topographical analysis of WMH and cognitive functions. More refined WMH segmentation algorithms are under development. Another disadvantage of voxel-wise techniques to assess lesion impact is the relative scarcity of WMH in the peripheral white matter. Larger cohorts or statistical methods accounting for the structure of WM tracts might help to tackle this in future studies.

Conclusions

In non-demented, healthy elderly subjects, WMH are associated with cognitive decline. While total WMH volume is associated with deterioration in several cognitive domains, WMH location is associated with specific cognitive deficits in healthy elderly subjects.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' contributions

Conceived and designed the study: LL, SKM, PLB; Acquired the data: LL, MLS, ML, AV, KA; Performed the analysis: LL, SKM; Wrote the paper: LL, PLB; Provided valuable advice during analysis and contributed writing the manuscript: SKM, JK, CJS, AVW, MLS, AV.

Supplementary material

Supplementary material for this paper can be found at the journal website: http://journals.sagepub.com/home/jcb

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