White Matter Hyperintensities: Red Flags for Cognitive Impairment?

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Background: White matter hyperintensities (WMHs) on T2-weighted imaging are considered classic signs of cerebral small vessel disease (SVD). Although WMHs are prevalent in healthy ageing, they are also associated with cognitive decline and dementia. Potential mechanisms underlying this interaction have been proposed, but it remains unclear to what extent these mechanisms hold true in the context of different concomitant pathologies, such as the plaques and tangles found in Alzheimer's disease (AD). **Aims:** This article first evaluates the common approaches to assess WMH severity before addressing what is currently understood about the variable aetiology of WMHs. It then explores the interaction between WMHs and cognitive decline in the contexts of healthy ageing, mild cognitive impairment, and AD, culminating in a schematic representation of the current hypotheses and uncertainties regarding this complex interaction. In light of these interactions, the clinical potential of WMHs is appraised as clinical biomarkers. Finally, this article considers the outstanding limitations and future directions to improve the way we investigate and ultimately understand both WMHs and cognitive impairment in general. **Significance:** By examining the association between WMHs and cognition, this body of work supports the relevance of WMHs in the broader context of cognitive impairment and dementia. This, in turn, highlights the wider importance of WM structural integrity and cerebrovascular health for sustained cognitive performance throughout ageing.

Keywords: neuroimaging, dementia, biomarkers, magnetic resonance imaging, cerebrovascular disease.

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1 Introduction

White matter hyperintensities (WMHs), appearing as bright areas on T2-weighted magnetic resonance imaging (MRI), are traditional markers of cerebral small vessel disease (SVD). In addition to WMHs, other SVD markers include lacunes, cerebral microbleeds, and enlarged perivascular spaces [63], examples of which can be found in Shi and Wardlaw [62] and Lee et al. [38] (Figure 1.1). This article will focus on WMHs, which are prevalent in ageing and have been linked to dementia and cognitive decline. The terms leukoaraiosis and white matter lesion have been used in other studies, but for consistency, this article will refer to these MRI signs as WMHs when equivalence can be determined. Although they are best seen with T2-Fluid-Attenuated Inversion Recovery (T2-FLAIR) imaging, WMHs also appear hyperintense with T2-weighted and proton-density imaging. They most commonly develop around the lateral ventricles (i.e., periventricular) and in the deep, or subcortical, WM. Depending on their severity and location, WMHs may appear as punctate foci, thin periventricular lines, or extensive, confluent lesions.

WMHs and other signs of SVD are hallmark features of vascular cognitive impairment and vascular dementia. However, Alzheimer's disease (AD), a dementia characterised by beta-amyloid (Aβ) plaques and tau tangles, also involves SVD signs, including WMHs [33]. This indicates possible shared risk factors across dementia subtypes

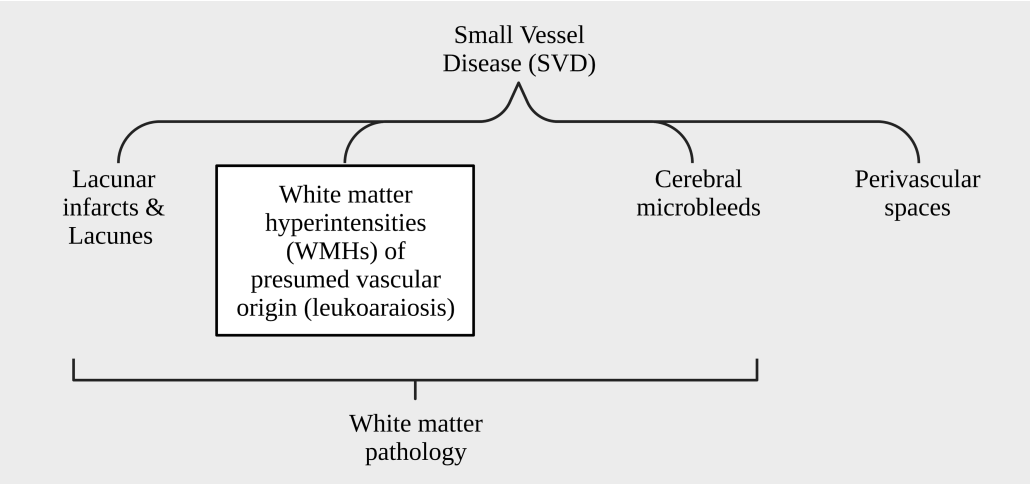

Figure 1.1: Types of small vessel disease (SVD). The term white matter pathology includes white matter hyperintensities (WMHs) of presumed vascular origin (leukoaraiosis), but it can also describe lacunes and cerebral microbleeds. Created with BioRender.com.

and points to a growing category of mixed dementia [32].

Considering the prevalence of cerebrovascular changes in cognitive impairment, I aim to explore the wider association between WMHs and cognitive decline. Given the recent developments in WMH quantification and our evolving understanding of WMH aetiology, an updated review that spans this nuanced interaction between WMHs and cognition is pertinent. I will first compare popular approaches for assessing WMHs. I will then consider the underlying pathology of WMHs before turning to evaluate their connection with cognitive decline in three contexts: cognitively-normal ageing, mild cognitive impairment (MCI), and AD. I will conclude by discussing the potential of WMHs as biomarkers and in the therapeutic context, as well as the current limitations and future directions for WMH investigations.

2 Assessing WM Pathology

There are various qualitative and quantitative approaches to measure WMH severity (Figure 2.1). At one end of this spectrum are the original visual rating scale, the Fazekas scale [16], and more recent scales, including the Schelten's scale [61] and the age-related white matter changes (ARWMC) scale [74]. These visual ratings are relatively quick to perform, are less affected by lower-quality scans (e.g., lower field strengths), and do not require advanced computing resources. Moreover, these scales may categorise WMHs in clinically-relevant ways (e.g., by proximity to the lateral ventricles or by brain lobe). Although qualitative ratings are subjective, less precise, and dependent on an expert radiologist's opinion, they are still commonly used in clinical and research settings.

By contrast, fully automated approaches like BIANCA (Brain Intensity AbNormality Classification Algorithm) yield probabilistic lesion maps, which can be used to calculate WMH volumes [23]. Volumetric measures correlate well with subjective ratings [18] and are more sensitive to subtle, longitudinal differences. BIANCA tends to be less biased than subjective WMH ratings, although its accuracy is subject to that of its training dataset of manually-labelled lesions [23]. This automated approach is higher-throughput and supports multimodal analyses for improved accuracy. BIANCA has been widely adopted in the research domain [2], although it has not yet been extensively adopted in clinical settings. Other sophisticated approaches, including deep learning algorithms for WMH classification [57], are also accurate but currently too memory-intensive

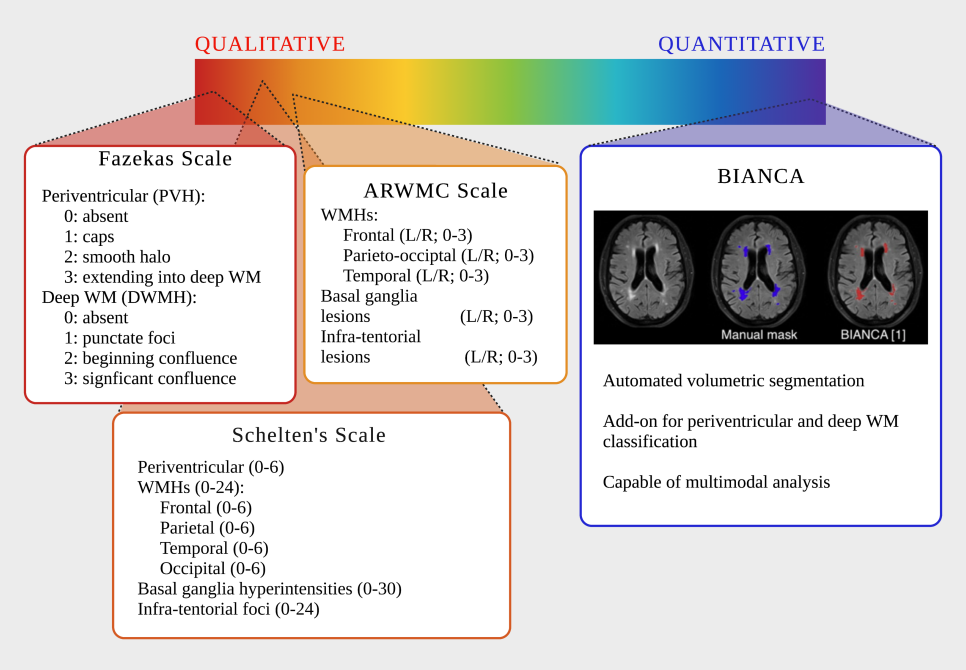

Figure 2.1: White matter hyperintensity (WMH) rating scales: spectrum from qualitative to quantitative. Three qualitative rating scales are included: the Fazekas scale, Schelten's scale, and ARWMC scale. A popular quantitative approach, BIANCA, is also shown along with some of its features. ARWMC, age-related white matter changes; L/R, left/right lateralised ratings; BIANCA, Brain Intensity AbNormality Classification Algorithm. BIANCA example image reproduced from Griffanti et al. [23]. Created with BioRender.com.

for widespread clinical use. Therefore, BIANCA is a more promising tool for clinical applications since it is relatively less computationally demanding.

3 WMH Aetiology Is Heterogeneous

The aetiology of WMHs is heterogeneous, even within those of presumed vascular origin (Figure 3.1). Microvascular disruption may include ischaemia, hypoperfusion, or blood-brain barrier disruption [21]. Despite their similar hyperintense appearance on T2-FLAIR imaging, post-mortem histological analyses have revealed diverse underlying structural changes in WMHs, ranging from minor changes in the extracellular matrix to substantial demyelination and axonal loss [21]. Concomitant pathologies, such as amyloid angiopathy, also promote the appearance of WMHs [21]. In controls, WMHs were associated with demyelination, likely reflecting an ischaemic origin, but WMHs in AD were also associated with axonal loss, likely reflecting Wallerian degeneration [47]. Pathological origins may also be region-dependent, with periventricular WMHs more commonly linked to ischaemia [42]. Multimodal T1-weighted [48] and diffusion tensor [49] imaging may distinguish WMH types, but nevertheless, this mixed aetiology of WMHs likely contributes to the poor correlation between clinical symptomatology and radiological phenotype [21].

Additionally, WMHs may represent the most extreme presentation on a continuum of WM pathology [53]. Other MRI-detectable WM changes (e.g., cerebral microbleeds [19]) are associated with WMHs. Altered microstructural integrity, detected as changes in fractional anisotropy and mean diffusivity on diffusion-weighted

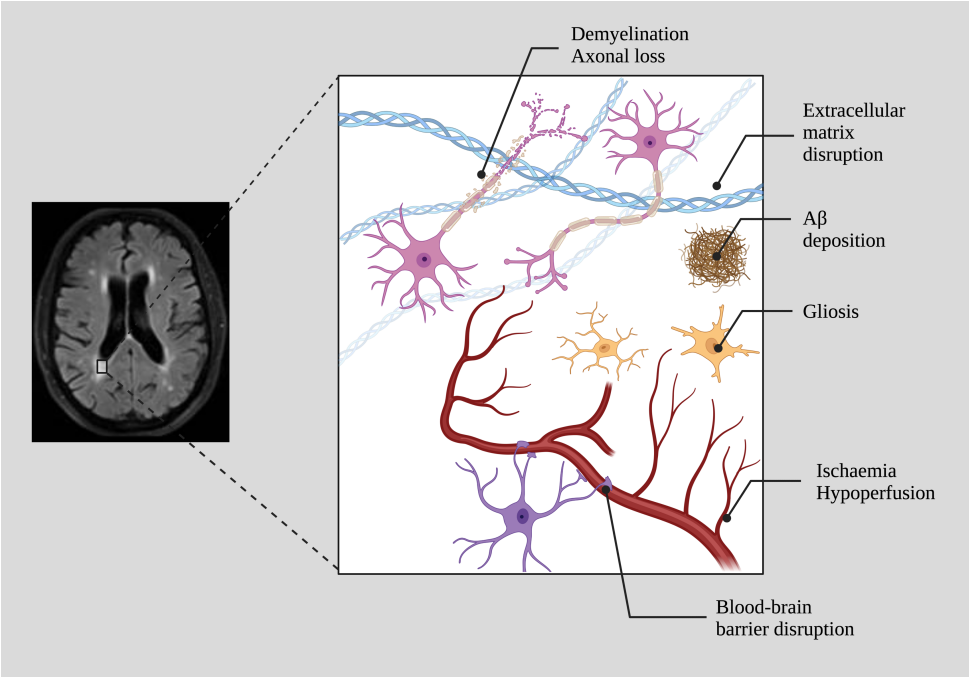

Figure 3.1: Pathological changes that may contribute to the manifestation of white matter hyperintensities (WMHs). Depending on the region and disease context, a mixture of these changes may contribute to the appearance of WMHs on MRI. Aβ, beta-amyloid. T2-FLAIR image reproduced from Griffanti et al. [23]. Created with BioRender.com.

imaging, often precede WMH development [26, 41]. Although Zeng et al. [78] reported that these microstructural changes are only apparent with severe WMHs, subtle WM changes may long precede WMH development and thus are not significantly different between controls and mild cases. Widespread integrity changes throughout the WM [67] may further contribute to the poor clinico-radiological correlation observed.

4 WMHs in Cognitively-Normal Ageing

WMHs are some of the most commonly-detected changes in cognitively-normal elderly populations [77]. In adults over 65, WMH prevalence has been estimated around 96% [45]. Age consistently correlates with automated [24, 23] and qualitative [78] measures of WMH burden. Despite this prevalence, it remains unclear how WMHs in healthy ageing differ from those observed in cognitive decline and dementia.

Aside from age, cardiovascular risk factors are also associated with WMH incidence in the general population. Leeuw et al. [40] found that the presence and severity of midlife aortic atherosclerosis was linearly associated with the presence of periventricular WMHs 20 years later. They did not, however, find any associations with late-life atherosclerosis or subcortical WMHs. Hypertension, particularly if uncontrolled during midlife, is also consistently reported as predictive of WMH severity [24] and progression [39, 60, 72]. Overall, these studies reinforce the significance of midlife cardiovascular health and earlier interventions regarding subsequent WMH appearance.

Table 5.1: Cross-sectional studies on white matter hyperintensities (WMHs) in relation to cognitive impairment. Relevant studies were selected using PubMed. MCI, mild cognitive impairment; AD, Alzheimer's disease; ARWMC, age-related white matter changes; MoCA, Montreal Cognitive Assessment.

Reference	Sample Size	Methods	Key Findings	Strengths	Limitations
Kaskikallio et al. [35]	86 [42 older controls, 44 MCI/AD; 79 of which were R-handed]	Multistage WMH segmentation algorithm; measures of semantic and phonological fluency	• Excluding L-handed individuals, frontal, parieto-occipital, and right temporal WMH volumes correlated with semantic fluency performance • In the whole sample, after multiple comparison correction, no associations were found between WMHs and semantic fluency • No group-specific associations were significant for controls or MCI/AD	• Ran analyses including and excluding L-handed subjects • Used the Benjamini-Hochsberg procedure to control for Type I errors • Controlled for age and education • Region-wise analysis	• The verbal fluency tasks used may not be very sensitive to the word-finding difficulties associated with cognitive decline • Sample size limited their statistical power
Kaskikallio et al. [34]	148 [56 older controls, 40 MCI, 52 AD]	Visually-rated MRI data (ARWMC Scale)	• Frontal and parieto-occipital WMHs affected processing speed (generally and in the AD group specifically) • Left frontal WMHs affected visual memory • No effects of WMHs were observed for verbal-logical memory or verbal functions	• Controlled for age and education • Region-wise analysis (including hemispheric analysis) • 9 neuropsychological assessments of 4 cognitive domains	• Did not control for cortical atrophy (although this may be advantageous if the effects of WMHs are indeed mediated through atrophy) • Did not examine executive function • Groups differed in age and education (possible confounding effects) • Did not correct for multiple comparisons

Reference	Sample Size	Methods	Key Findings	Strengths	Limitations
Wei et al. [76]	161 [113 with WMHs (35 cognitively normal), 48 controls]	Fazekas scale to assess WMH presence	• Individuals with WMHs (combined normal cognition and vascular cognitive impairment) had lower cognitive performance scores (assessed with MoCA and an executive function battery) than controls	• No significant difference in age, sex, or cardiovascular risk factors across groups • Fully automated processing	• Excluded participants with non-vascular dementia • Hospital-based (possible selection bias) • No correlational analyses with WMH load
Zeng et al. [78]	321 [all cognitively normal]	Fazekas scale and quantitative assessment of WMHs; 6 cognitive domains measured	• Negative association between WMH severity and working and episodic memory (starting at Fazekas grades 3 and 4) • Periventricular WMHs appeared first (in milder cases) • Only Fazekas grades 3 and 4 had significant changes in FA or significant cognitive differences • Fazekas grade 3 may be predictive for future cognitive decline	• Sampled community-dwelling individuals • Adjusted for age (Model 2) and additional factors (Model 3)	• Cognitive assessments may have lacked sensitivity to subtle changes • Strong assumption that disease progression is represented in this cross-sectional data • Excluded participants with MCI or AD
Defrancesco et al. [12]	60 [all MCI]	Modified Fazekas scale and Schelten's scale	• Baseline periventricular WMHs were negatively associated with psychomotor speed, executive function, attention, and cognitive flexibility • Baseline subcortical WMHs were negatively associated with visual memory	• Avoids selection biases (recruitment based on patient initiative) • Detailed neuropsychological evaluation	• Small sample size • Recruitment style may not represent wider population

Reference	Sample Size	Methods	Key Findings	Strengths	Limitations
Kramer et al. [36]	39 [27 controls, 12 cognitively normal with subcortical lacunes]	Group comparison (lacunes vs controls); WMH volume	• Subjects with lacunes had significantly greater WMH volume and subtle impairments in executive functioning and visual memory • 2 out of 3 executive function measures correlated with WMH extent	• Bonferroni correction to correct for multiple comparisons across executive function tests • No significant difference between patients' and controls' age or education level	• Very small sample size • Subcortical lacunes were the focus for group assignment (but used interchangeably with WMHs, defined as hyperintense on proton-density imaging) • Did not correct for multiple comparisons across other cognitive domains • Lacked the power to investigate the effects of lacune location or number
Mungas et al. [51]	157 [90 controls, 37 MCI, 30 dementia; with and without WMHs]	Quantitative assessment of subcortical lacunes and WMH volumes	• Subcortical lacunes did not independently relate to cognitive measures • WMHs independently predicted performance on timed tasks, indicating a possible effect on cognitive speed • Cortical grey matter and hippocampal volumes predicted cognitive performance	• Volumetric approach with automated segmentation • Subclassified lacunes by subcortical region • Measured cortical grey matter and hippocampal volumes to control for these factors • Age and education were included as covariates	• Groups (controls, MCI, dementia) significantly differed in age and education level • Did not examine effects of WMH location • Correlational, limiting ability to infer causality

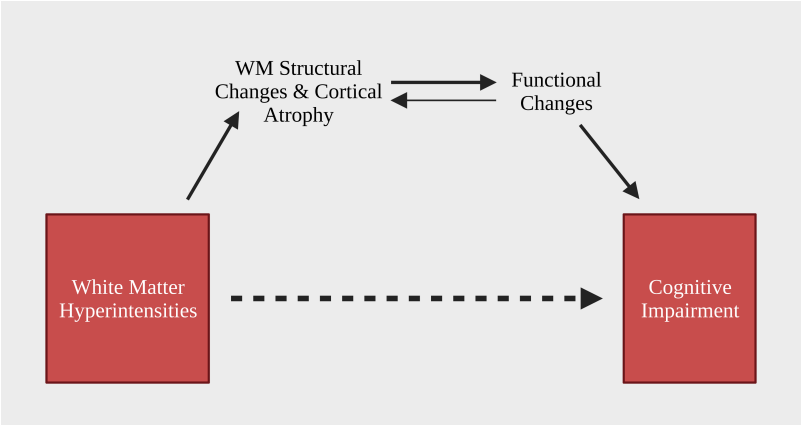

Figure 5.1: Possible interaction between WMHs and cognitive impairment. The nature of the interactions contributing to the co-occurrence of white matter hyperintensities and cognitive decline remains unclear. This interaction may be mediated by structural WM changes and cortical atrophy, which in turn contribute to functional network changes and cognitive decline. Further work is necessary to shed light on any additional mediators or direct interactions (dashed arrow). Created with BioRender.com.

5 WMHs and Cognitive Impairment

In the general population, WMHs are associated with subjective and objective measures of cognitive impairment [25]. Numerous cross-sectional studies support this association (Table 5.1).

However, the cognitive domains affected by WMHs remain controversial. Impairments in information processing speed and executive functioning are most commonly cited [12, 50]. In a large prospective study, the presence and progression of periventricular WMHs were associated with a baseline reduction and accelerated decline in mental processing speed [28]. A recent meta-analysis similarly found the greatest WMH effect sizes for the following frontal lobe functions: attention, executive function, and processing speed [4]. While some have proposed that memory is not associated with WMHs, others have reported impaired episodic and working memory in association with severe WMHs [78] or even mild WMHs [65]. Despite these domain-specific findings, Overdorp et al. [52] reported only an independent effect of WMHs on global cognition. However, this study regressed out medial temporal atrophy, which may be an over-adjustment if neurodegeneration is a mediator for the effects of WMHs, as proposed by Rizvi et al. [58].

Beyond simply the presence of WMHs, growing attention has been paid to their location. WMHs are non-uniformly distributed, with periventricular and frontal WMHs developing before subcortical and dorsal ones [27, 78]. Periventricular WMHs tend to associate more strongly with cognitive impairments [14], and WMH location influences which cognitive domains are affected [12]. While frontal WMHs were associated with executive dysfunction, parieto-temporal WMHs were linked with memory impairments in one study [37]. This likely contributes to the aforementioned variability between studies. The absence of region-wise analysis by Overdorp et al. [52] may, therefore, also contribute to the insensitivity to domain-specific changes.

Since most studies are correlational, causality is difficult to assess, especially in the presence of concomitant and multifactorial pathologies. Although supported by animal models of cerebrovascular disease [6], the causality of WMH-related changes in cognitive impairment is difficult to determine in clinical settings. In practice, expert opinion considers severe WMHs preceding cognitive impairment suggestive of vascular dementia [55]. However, this assumption does not indicate mechanisms, mediators, or the general involvement of WMHs in cognitive decline. Considering that WMHs are associated with accelerated cortical atrophy, Rizvi et al. [58] propose that

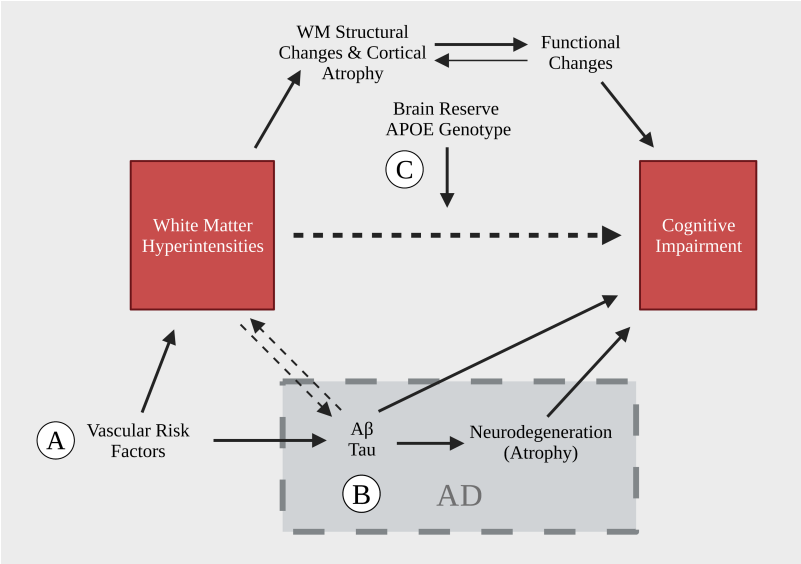

Figure 6.1: WMHs and cognitive decline in the context of Alzheimer's disease (AD). A) Vascular risk factors contribute to both the development of WMHs and AD hallmark pathologies like Aβ deposition. B) The classical AD aggregates of Aβ and hyperphosphorylated tau may bi-directionally interact with WMH development, in addition to contributing to cognitive impairment in other ways. C) The extent of brain reserve and the AD risk gene APOE may moderate the strength of the association between WMHs and cognitive impairment. Aβ, beta-amyloid. Created with BioRender.com.

WMH-related changes may drive neurodegeneration with global and localised changes in cortical thickness mediating the relationship between WMHs and cognitive decline. Jokinen et al. [30], on the other hand, found that WMHs and atrophy have independent but synergistic effects on cognition. Functional connectivity changes linked to WMHs suggest another potential mechanism of executive dysfunction [65, 66]. Clarifying the links between WMHs and cognition is crucial (Figure 5.1).

6 Interactions Between WMHs and AD

In the context of Alzheimer's Disease (AD), both vascular factors and disease-specific mechanisms may contribute to the formation of WMHs. Cardiovascular risk factors, which directly promote WMH development, also increase dementia risk (Figure 6.1A; [44]). These vascular factors influence the amyloid pathway, with blood-brain barrier disruption increasing the risk of Aβ deposition [3, 29]. Aβ may also contribute to WMH development in addition to its traditional involvement in AD (Figure 6.1B; [47, 73]). Although a recent study showed no association between global amyloid burden and WMHs [20], periventricular WMHs have been linked with PET measures of Aβ [22]. Overall, this provides preliminary support for a bidirectional interaction between Aβ and WMH pathology in AD.

WMHs may also relate to hyperphosphorylated tau, the other trademark aggregate in AD, which parallels cognitive decline more closely. In a small post-mortem study on varying degrees of AD pathology, only hyperphosphorylated tau immunoreactivity independently predicted WMH severity [46]. Although this suggests an association of tau with WMHs, a much larger study on non-demented individuals reported no association between regions with elevated tau burden on PET and WMH burden [22]. This does not refute the possibility of disease-specific WMH-tau interactions, but larger-scale investigations are necessary to determine the extent of

any such interactions.

WMHs and AD-specific features (i.e., Aβ, tau, and neurodegeneration) may have additive or synergistic effects contributing to cognitive decline. The heightened prevalence of signs of cerebrovascular disease, including WMHs, in AD compared to other neurodegenerative disorders supports an interaction [69]. Even among patients with AD, those with severe frontal WMHs had slower information processing speed than those with milder WMHs [34]. Other AD-related factors, such as APOE genotype, may modify the relationship between WMHs and cognitive decline (Figure 6.1C). Specifically, the cognitive effects of the APOE4 allele may weaken or overpower any interaction with WMHs [55]. Reserve, including brain reserve and cognitive reserve, can also influence the strength of the interaction between changes like WMHs and cognitive decline [64]. Therefore, beyond contributing to the development of WMHs, these disease-specific mechanisms may mediate or overshadow any direct interactions between WMHs and cognitive impairment.

7 WMHs as Biomarkers

Longitudinal studies suggest that both WMH baseline severity and progression may be linked to risk of future cognitive decline (Table 7.1). This supports their prognostic value as MRI markers to identify individuals likely to develop cognitive impairment. Although group-level differences may be present, however, the high degree of within-group variability currently precludes the use of WMHs as a selective biomarker at the individual level. Furthermore, the ability of WMHs to predict conversion to specific subtypes of dementia is also unclear. While Verdelho et al. [71] found that WMH severity generally predicted cognitive decline to dementia, subtype analysis revealed that AD was only predicted by medial temporal atrophy, whilst vascular dementia was also predicted by WM changes. More promisingly, Brickman et al. [7] found that both baseline parietal WMH severity and parietal WMH progression independently predicted conversion to AD in a study of 300 non-demented individuals.

Given their association with both cognitive decline and dementia, WMHs could theoretically also improve diagnostic accuracy. Although considered in the diagnosis of vascular dementia [43], including WMHs in the diagnostic criteria for other dementia subtypes currently offers little benefit because they tend to be more closely related to disease progression as opposed to disease status. Rather than a signal of impending diagnosis, WMHs may more accurately be an indication of additional risk factors for disease development, including vascular status. Although the variable aetiology of WMHs complicates this interpretation, the possibility of disease-specific mechanisms highlights their unique value as relatively comprehensive biomarkers of neurological state.

Moreover, there is an ever-present drive to develop better objective measures of therapeutic efficacy in clinical trials. WMHs hold potential in this context as a covariate or a surrogate marker of cerebrovascular disease progression [1, 53]. For this application, however, the possibility of additional disease-specific mechanisms obscures direct interpretations in the context of neurodegenerative disease.

8 Therapeutic Value of WMHs

Given the association between WMHs and cognitive impairment, it is worth examining their therapeutic implications. Detection of WMHs may inform strategies for both primary (i.e., prior to overt cognitive impairment) and secondary (i.e., after the presentation of mild cognitive impairment) prevention. Thus far, WMH-related therapies have centred on targeting cardiovascular risk factors to slow WMH progression and the associated cognitive outcomes. The other disease-specific origins of WMH development, however, remain more difficult to target.

Epidemiological evidence supports the influence of good cardiovascular health and effective treatment on WMH severity. A large prospective cohort study demonstrated that, while individuals with successfully-treated hypertension had moderately increased risks of WMHs compared to normotensive individuals, those with

Table 7.1: Longitudinal studies on the predictive value of white matter hyperintensities (WMHs) for disease progression and cognitive decline. Relevant studies were selected using PubMed. AD, Alzheimer's disease; MCI, mild cognitive impairment; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; MMSE, Mini-Mental State Examination; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; SIVD, subcortical ischaemia vascular disease.

Reference	Sample Size	Follow-Up (Mean)	Methods	Key Findings	Strengths	Limitations
Bilello et al. [5]	158 [57 AD, 66 MCI, 35 controls]	1–1.5 years	Automatic WMH segmentation and voxel-wise atrophy measures at baseline	• In AD patients, WMHs in the corpus collosum and fornices correlated with cognitive decline (CERAD score) • No significant correlations between WMHs and cognitive decline in the MCI or control groups	• Combines WMH and grey matter volumes in sophisticated voxel-wise analysis • Groups did not significantly differ in age or education	• Did not investigate individual cognitive domains • Did not address patient conversion
Defrancesco et al. [12]	60 [all MCI; 31 → AD]	1.5 years	Retrospective analysis; modified Fazekas scale and Scheltens scale	• Converters had higher Fazekas scores and more periventricular WMHs • WMH location impacts which cognitive domains are affected • WMH severity was not associated with memory decline • Vascular changes were not predictive for conversion from MCI to AD (i.e., risk factor but not early symptom of conversion)	• Avoids selection biases (recruitment based on patient initiative) • Single-centre, therefore reduced inter-investigator variability • Age did not affect results of regression analysis	• Retrospective analysis introduces possible bias (higher conversion rate) • Small sample size • Significant age difference between converters and non-converters

Reference	Sample Size	Follow-Up (Mean)	Methods	Key Findings	Strengths	Limitations
Carmichael [9]	804 [cognitively normal, MCI, or AD]	1 year	WMH volume (3 timepoints)	• Higher baseline WMH volume associated with worse baseline performance and greater change in both MMSE and ADAS-Cog	• Large study • Model included many covariates (age, ApoE genotype, cardiovascular risk score, atrophy, etc.) • WMH progression included • Similar parameters to a clinical trial	• Convenience sample • Linear models were fitted to non-linear trajectories for cognitively-normal individuals • MMSE is not very sensitive to subtle changes (as may be expected after 1 year) • Short time period for detectable changes
Jokinen et al. [31]	639 [age 65-84]	3 years	Subcortical ischaemic vascular disease (SIVD), based on WMHs and lacunar infarcts	• SIVD patients had steeper cognitive decline (executive function, psychomotor speed, and global cognition) • SIVD patients had a greater risk of developing dementia (3-fold)	• Large study • Included a battery of neuropsychological assessments (examining different domains) • Controlled for age, education, and medial temporal atrophy • Included 2 WM pathologies	• Did not stratify by severity of WM pathology

Reference	Sample Size	Follow-Up (Mean)	Methods	Key Findings	Strengths	Limitations
Dijk et al. [14]	668 [age 60-90]	3.4 years	Semi-quantitative 9-point scale for periventricular WMHs; volume estimates for subcortical WMHs	• Progression of periventricular WMHs associated with decline in information processing speed, global cognitive function, and MMSE score • Subcortical WMH progression was not associated with cognitive decline	• Large study • Repeated MRI scanning allowed tracking of WMH progression • 5 neuropsychological tests used to create compound scores • Prospective study design	• Those who followed up tended to be younger and healthier with better cognitive function (possible selection bias) • Semiquantitative approach less objective than volumetric measures
Pantoni et al. [54]	639 [age 65-84]	3 years	Fazekas scale for WMHs; extent of disability measured with the Disability Assessment for Dementia	• Association between baseline WMH severity and functional impairment • Impairment in executive function correlated with increasing WMH severity • WMH severity associated with higher autonomy → disability transition rates	• Large sample • Multi-centre and multinational	• Risk of inter-rater variability • Non-specific disability measurement • Single MRI scan (no analysis of WMH progression)

Reference	Sample Size	Follow-Up (Mean)	Methods	Key Findings	Strengths	Limitations
Prins et al. [56]	832 [non-demented at baseline]	5.2 years	Baseline periventricular WMHs (9-point scale) and subcortical WMHs (volume estimates); neuropsychological evaluation (3 timepoints)	• Periventricular WMH severity, infarcts, and generalised atrophy each predicted steeper decline in information processing speed and executive function • No associations were observed with rate of memory decline • With stroke cases excluded, many associations no longer significant (i.e., stroke involved in the interaction between SVD and cognitive decline)	• Large study • Used a global index of cognitive function, which they propose to be more robust	• A higher percentage of those who dropped out had memory decline • Excluding participants with incident stroke is an over-adjustment
De Groot et al. [11]	563 [non-demented elderly]	7.3 years	Semi-qualitative scale for periventricular and subcortical WMHs; MMSE for cognitive assessment	• Subjects with severe periventricular WMHs declined three times faster than average • Subcortical WMHs not independently associated with cognitive decline • No association between baseline MMSE score and WMH severity	• Long follow-up period • Sampled from general population • Controlled for age, education, atrophy, and infarcts • Reported results with and without correcting for baseline MMSE	• MMSE relatively insensitive to subtle cognitive changes • Those with less severe WMHs tended to participate longer (possible bias) • Single MRI scan (no analysis of WMH progression)

poorly-controlled hypertension had substantially higher relative risks [39]. A more recent longitudinal study showed that treated individuals, even if their hypertension was not successfully controlled, had less WMH progression compared to untreated patients [72]. This supports the importance of hypertension treatment and overall good cardiovascular health to slow WMH progression. Despite these findings, randomised controlled trials of cardiovascular interventions for slowing WMH progression are limited but ongoing [75].

In vascular cognitive impairment, the cognitive benefits of slowing WMH progression are evident [17], but the benefits in other forms of cognitive impairment are less clear. WMH pathology may have a late effect on cognitive decline [78], which opens up a therapeutic window to slow WMH progression prior to cognitive changes. A six-year randomised control trial demonstrated no differences in dementia incidence with a cardiovascular intervention program compared to usual treatment, but this study also failed to show any differences in cardiovascular disease incidence, likely due to the high standard of care in the usual treatment arm [10]. Another recent trial did not observe a significant dementia risk reduction with intensive hypertension treatment, but they did report an associated reduction in mild cognitive impairment as a non-primary outcome [68]. Although these reports do not rule out the value of WMH-directed cardiovascular interventions, they are far from conclusive. Considering the importance of midlife factors on later dementia onset, however, these treatments may also be targeted too late in disease progression.

9 Limitations and Future Directions

Despite the consistent association between WMHs and cognitive impairment, the correlational nature of our analyses limits our ability to infer mechanisms or causality. Currently, cortical atrophy [58] and WM microstructural changes [76] have been proposed as mediators, while factors like brain reserve are modifiers [8]. Other controversy surrounds the scale of WM changes (i.e., global or tract-specific) that influence cognitive decline [67, 78]. Further work is necessary to clarify the nature of any interaction between WMHs and cognitive decline, including how AD-specific pathologies contribute to or modify this interaction. Bearing in mind that WMHs are simply visible signs of underlying pathologies, the upstream pathological mechanisms (e.g., cardiovascular factors) must be targeted to have any meaningful impact. Nevertheless, this does not negate the suggested value of WMHs as biomarkers.

Objective and sensitive measures of cognitive impairment are difficult to consistently achieve. To standardise our working definition of cognitive impairment, the DSM-5 outlines six neurocognitive domains with subdomains (Table 9.1). This framework, however, does not include objective assessments for each domain, and thus assessments vary between studies. The standard choices (Table 9.1) often lack sensitivity for subtle cognitive decline. Meanwhile, other cognitive assessments, including the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), remain popular choices to easily assess cognitive function, but they, too, lack sensitivity and do not directly correspond to the cognitive domains.

Greater standardisation across the field is necessary to enable better comparison across studies and effective meta-analyses. Terms to describe WM pathology are often vaguely defined and interchanged. Standardisation of rating scales is also necessary, which can be achieved by a greater shift towards quantitative approaches. Even volumetric measures currently lack complete standardisation (e.g., in the definition of periventricular [24]). As our computing resources improve, so should our optimisation of standardised, automated pipelines and machine-learning approaches to segment and stratify WMHs with greater accuracy and consistency. Optimising these approaches, in conjunction with multimodal neuroimaging, may also allow clinically-relevant subcategorization of WMHs, such as based on T1 intensity [48].

Our current categorisation of dementia subtypes, in particular the delineation of vascular dementia, often leads to misdiagnosis. The widespread contribution of cerebrovascular disease across dementia subtypes calls into question our current distinction between vascular dementia and other dementia subtypes like AD. Instead,

Table 9.1: DSM-5 neurocognitive domains and subdomains. Some commonly-used objective assessments are listed for each. Italicised domains are particularly relevant in the context of WMH-related cognitive decline. See Sachdev et al. [59] and Eramudugolla et al. [15].

DSM-5 Neurocognitive Domain	Example Subdomains	Example Assessments
Complex Attention	• Processing speed • Divided attention • Selective attention	• Trail Making Test A • Simple Reaction Time • Choice Reaction Time
Executive Function	• Planning • Decision-making • Cognitive flexibility	• Colour-word inference (Stroop test) • Trail Making Test B • Digit Span Backwards
Learning and Memory	• Free recall • Recognition memory • Implicit learning	• California Verbal Learning Test
Language	• Object naming • Word finding • Fluency	• Letter Fluency • Boston Naming Test
Perceptual-Motor Function	• Visual perception • Perceptual-motor coordination	• Purdue Pegboard Test • Benton Visual Retention Copy
Social Cognition	• Recognition of emotions • Theory of mind • Insight	

common risk factors and pathomechanisms may point to a growing category of mixed dementia [32]. By looking at WMHs in the context of other WM pathologies (e.g., microbleeds and infarctions), we may be able to (i) unpick the case-by-case contribution of cerebrovascular factors to WMH formation and (ii) separate this mechanism from other disease-specific processes. This, in turn, may better inform our understanding of the wider contribution of cerebrovascular changes in cognitive decline [13, 70]. Clarifying the extent to which vascular mechanisms are shared across dementia subtypes may further shape our diagnostic practices, clinical trial recruitment, and therapeutic strategies.

10 Conclusions

The general association between WMHs and cognitive impairment is evident, and more recent studies indicate possible region-specific effects on certain cognitive domains. Given the correlational nature of current research and the lack of standardisation in the field, however, any inference of specific pathological mechanisms is obscured. The latest evidence highlights the varied origins of WMHs in different contexts. While the vascular origin of WMHs is widely supported, WMH-related studies in the context of AD also point to distinct disease-specific mechanisms. Nevertheless, these findings highlight the wider relevance of WM pathology in cognitive impairment

and dementia, even across dementia subtypes. By further elucidating the details of this interaction, including the role of disease-specific mediators and moderators, we may better understand the potential of WMHs as biomarkers and any therapeutic implications.

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