The effect of white matter hyperintensities on verbal memory

Mediation by temporal lobe atrophy

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Abstract

Objective

To determine the relationship between white matter hyperintensities (WMH) presumed to indicate disease of the cerebral small vessels, temporal lobe atrophy, and verbal memory deficits in Alzheimer disease (AD) and other dementias.

Methods

We recruited groups of participants with and without AD, including strata with extensive WMH and minimal WMH, into a cross-sectional proof-of-principle study ($n = 118$). A consecutive case series from a memory clinic was used as an independent validation sample ($n = 702$; Sunnybrook Dementia Study; NCT01800214). We assessed WMH volume and left temporal lobe atrophy (measured as the brain parenchymal fraction) using structural MRI and verbal memory using the California Verbal Learning Test. Using path modeling with an inferential bootstrapping procedure, we tested an indirect effect of WMH on verbal recall that depends sequentially on temporal lobe atrophy and verbal learning.

Results

In both samples, WMH predicted poorer verbal recall, specifically due to temporal lobe atrophy and poorer verbal learning (proof-of-principle -1.53 , 95% bootstrap confidence interval [CI] -2.45 to -0.88 ; and confirmation -0.66 , 95% CI $[-0.95$ to -0.41] words). This pathway was significant in subgroups with (-0.20 , 95% CI $[-0.38$ to -0.07] words, $n = 363$) and without (-0.71 , 95% CI $[-1.12$ to -0.37] words, $n = 339$) AD. Via the identical pathway, WMH contributed to deficits in recognition memory (-1.82% , 95% CI $[-2.64\%$ to $-1.11\%]$), a sensitive and specific sign of AD.

Conclusions

Across dementia syndromes, WMH contribute indirectly to verbal memory deficits considered pathognomonic of Alzheimer disease, specifically by contributing to temporal lobe atrophy.

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Glossary

AD = Alzheimer disease; BPF = brain parenchymal fraction; CAA = cerebral amyloid angiopathy; CI = confidence interval; CVLT = California Verbal Learning Test; ICC = intraclass coefficient; LE = Lesion Explorer; LTL = left temporal lobe; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; SABRE = Semi-Automatic Brain Region Extraction; VCI = vascular cognitive impairment; WMH = white matter hyperintensities.

White matter hyperintensities (WMH) are a measure of brain frailty commonly coincident with Alzheimer disease (AD), presumed to represent damage to the cerebral small vessels.¹ While often shown to decrease attention, executive function, and psychomotor processing speed,² WMH are also associated with memory deficits in AD^{3,4} and in vascular cognitive impairment (VCI) due to stroke.⁵

The well-replicated effects of WMH on the frontal lobe suggest that the effect of WMH on memory may occur secondarily, as a consequence of poorer strategic information processing⁶; however, recent studies describe relationships between WMH and disproportionate atrophy of cortical and subcortical temporal lobe structures.^{3,7–9} Those findings suggest that WMH might also have a more primary effect on memory systems.¹⁰

Notwithstanding the effect of WMH on strategic information processing that influences memory performance,⁶ consideration of an independent primary contribution of WMH to the learning and memory deficits often considered to be pathognomonic of AD is warranted. Therefore, this study evaluates the relationship between WMH and poorer verbal memory function, hypothesizing an indirect effect that is mediated by left temporal lobe atrophy, both in participants with and without AD.

Methods

Study design

The volume of WMH (independent variable) was used as a measure of small vessel disease severity.¹ A proof-of-principle sample was designed specifically to include representative strata of minimal to extensive WMH, including those with and without AD. A consecutive sample of tertiary care cases presenting to a memory clinic was used to confirm the relevance of the hypothesized pathway. Participants were included if they had an MRI adequate for processing, and if they completed the memory assessment.

Proof-of-principle sample

This cross-sectional sample was designed to elucidate relationships between subcortical ischemic vascular disease and cognitive performance. Five groups of participants (table 1), aged 50–85, were recruited between 2007 and 2013: (1) patients with extensive WMH (≥ 4 focal lesions each ≥ 5 mm in diameter or periventricular WMH extending at least 5 mm from the ventricular border consistent with Fazekas scale

periventricular hyperintensity score ≥ 2) who presented to a stroke prevention clinic within 3 months of TIA with no residual physical symptoms, (2) patients with AD who had minimal WMH (Fazekas scale periventricular hyperintensity score ≤ 1 and ≤ 3 focal hyperintensities none of which were ≥ 3 mm in diameter), (3) patients with AD who had extensive WMH (as per same criteria above), (4) healthy elderly volunteers similar in age to the former groups with minimal WMH (as per same criteria above), and (5) patients with symptomatic coronary artery disease without a neurologic diagnosis recruited from a cardiac rehabilitation clinic.¹¹ All participants undertook MRI at 3.0T for the purpose of this study, were fluent in English, had hearing adequate for cognitive testing, and had Mini-Mental State Examination (MMSE) score >19 . Participants with other neurologic diagnoses or those presenting with cortical infarcts or cortical hyperintensities (>3 hyperintense foci, or any lesion >3 mm in diameter) were excluded. Participants with unstable medical conditions or other neurologic or psychiatric histories were excluded, with the exception of mild depressive symptoms.

Confirmation sample

Baseline cross-sectional data were used from the Sunnybrook Dementia Study, an observational study of prospectively collected (1992–2014) consecutive patients from a real-world tertiary care clinic that includes non-mutually exclusive diagnoses of dementia or mild cognitive impairment (MCI) due to AD, VCI or other/mixed causes, and healthy elderly controls.¹² Cortical stroke and other neurodegenerative signs were not excluded from this sample, in order to determine if the effects of WMH on memory were robust and generalizable.

Standard protocol approvals, registrations, and patient consents

This study received approval from an institutional ethical standards committee. Written informed consent was obtained from all patients, or from their substitute decision makers with patient assent. The Sunnybrook Dementia Study is registered at clinicaltrials.gov (NCT01800214).

Assessments

Verbal memory assessment

Verbal memory was assessed using the California Verbal Learning Test (CVLT); the proof-of-principle sample used the 2nd edition, while the confirmation sample used the 1st edition. In both versions, a list of 16 words is read 5 times, the participant is asked to recall the list immediately after each

Table 1 Proof-of-principle sample characteristics (n = 118)

Group	Healthy elderly	CAD	Extensive WMH	AD with minimal WMH	AD with extensive WMH
Total, n	27	51	17	12	11
Age, y, mean ± SD	71.5 ± 7.8	65.7 ± 7.2	76.2 ± 9.5	74.5 ± 9.1	77.1 ± 7.3
Sex, % male	48.1	84.3	52.9	66.7	36.4
Education, y, mean ± SD	16.0 ± 3.2	16.2 ± 3.1	12.9 ± 3.2	12.9 ± 4.6	15.5 ± 2.7
TIC, mL, mean ± SD	1,235 ± 128	1,263 ± 116	1,232 ± 142	1,234 ± 91	1,241 ± 188

Abbreviations: AD = Alzheimer disease; CAD = coronary artery disease; TIC = total intracranial capacity; WMH = white matter hyperintensity.

trial, and the total number of words recalled correctly over the 5 learning trials is recorded as a measure of verbal learning. The CVLT also assesses to what degree different learning strategies are used. The word list is divided into 4 categories, and the degree to which participants group words into categories during recall is recorded as “semantic clustering,” a strategic information processing strategy that engages frontal-subcortical circuits.^{13,14} After a distractor task and a 20-minute delay, the participant is asked to recall the list freely from memory, which is recorded as delayed free recall. Next, recognition memory is assessed in a forced choice trial wherein participants discriminate between words that were on the list from those that were not. The number correctly retained is compared to those incorrectly guessed. Providing the words as memory cues subverts retrieval demands and therefore offers a more precise measure of the inability to retain information.

MRI methodology and processing

Brain MRI was obtained at 3.0T (Discovery MR750; General Electric, Cleveland, OH) in the proof-of-principle sample and at 1.5T (Signa, General Electric) in the confirmation sample (e-Methods, links.lww.com/WNL/A159). Images were processed using Lesion Explorer (LE; sabre.brainlab.ca; figure 1), a comprehensive, highly reliable (global intraclass coefficient [ICC] 0.99; regional ICC 0.98; Similarity Index 0.97; scan-rescan reliability for all tissue types ICC >0.9) and previously validated (LE vs kNN ICC 0.97, LE vs Age-Related White Matter Change scale $r = 0.86$) tri-feature segmentation and parcellation procedure for regionalized brain volumetrics.^{15–17} Briefly, segmentation utilizes coregistered T1, proton density, and T2 images to obtain regionalized volumes of normal-appearing gray matter (NAGM), normal-appearing white matter (NAWM), ventricular CSF (vCSF) and sulcal CSF (sCSF), WMH, and subcortical silent infarcts (lacunes). Skull and other nonbrain structures were removed with Brain-Sizer, a LE component, to obtain supratentorial volume (total intracranial capacity), including subarachnoid CSF immediately below the dura mater. The tissue segmentation fits localized voxel intensities to 4 Gaussian curves and the Semi-Automatic Brain Region Extraction (SABRE) component of LE parcellates the brain into standardized volumes of interest including the left temporal lobe (LTL).¹⁶ The third component of LE

segments WMH using proton density/T2 sequences and further segments lacunar-like infarcts within each hyperintensity using information from the initial T1 segmentation. Thus, WMH volume was obtained. The result is a personalized segmentation map, which is ideally suited to assess regional tissue volumes unconfounded by atrophy or WMH. Atrophy was inferred as the brain-parenchymal fraction (BPF) calculated from tissue class estimates specifically within the LTL as delineated by SABRE (figure 1):

$$\frac{\text{NAWM}_{\text{LTL}} + \text{NAGM}_{\text{LTL}}}{\text{NAWM}_{\text{LTL}} + \text{NAGM}_{\text{LTL}} + \text{vCSF}_{\text{LTL}} + \text{sCSF}_{\text{LTL}}}$$

The volumes of WMH and lacunes were not included in the denominator to avoid inflating estimates of the association of WMH volume with atrophy, or in the numerator to avoid inflating estimates of healthy tissue.

Clinical diagnoses

To identify dementia or MCI due to AD, or VCI, clinical diagnoses were made, by consensus of 2 independent clinicians, using prevailing criteria, behavioral neurology assessments, clinical reports of SPECT and MRI scans, the MMSE, and the Dementia Rating Scale. MCI was diagnosed by Petersen-Albert criteria.^{18,19} McKhann criteria^{20,21} were used to diagnose AD, also compatible with National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria.²⁰ VCI was diagnosed according to clinical²² and National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche en l’Enseignement en Neurosciences research criteria.²³ Other diagnoses were made by prevailing clinical criteria (e-references, links.lww.com/WNL/A160).

Statistical methods

WMH volumes were log-transformed. To test the mediation hypotheses, a bias-corrected bootstrapping procedure was used for inferential estimation of indirect effects. The method makes no assumptions about normality in the sampling distribution and offers better control of type I error compared to other methods such as the Sobel method.^{24,25} Confidence intervals (CIs) were estimated using 10,000 replications and

MRI-derived 3D segmentation and regional parcellation generated by lesion explorer. Top row: axial slices of skull-stripped coregistered MRI from (A) T2-weighted, (B) T1-weighted, and (C) proton density. Middle row: (D) demarcation of the Semi-Automatic Brain Region Extraction (SABRE) regional parcellation of the left temporal lobe region overlaid on axial T1, (E) tri-feature tissue segmentation for gray (light gray) and white matter (dark gray), ventricular (yellow) and sulcal CSF (blue), and white matter hyperintensities (purple), (F) white matter hyperintensities (purple) overlaid on proton density. Bottom row: 3D surface volume rendering of (G) SABRE regional parcellation (left temporal lobe in red). (H) Transparent surface shows white matter hyperintensities (purple).

indirect effects were considered significant when the 95% bias corrected bootstrapped interval did not contain zero.

It was hypothesized that a serial mediation effect runs from WMH to left temporal atrophy^{3,8,9} to verbal learning to verbal recall (the left temporal lobe was examined due to correlation with verbal memory in previous studies).²⁶ This indirect effect was estimated by multiplying the coefficients from 3 sequential linear regression models representing the pathway links ($a \times b \times c$). The models simultaneously estimate 2 shorter pathways, from WMH to left temporal atrophy to verbal recall ($a \times b_2$), and from WMH to verbal learning to verbal recall ($a_2 \times c$), and the direct effect between WMH and verbal recall adjusted for the indirect pathways ($d' = d - a \times b \times c - a \times b_2 - a_2 \times c$). Total intracranial capacity, age, years of formal education, and sex were added to the model as covariates, regressed at once on mediators and outcomes. Path coefficients were estimated in SPSS (version 22; SPSS Inc., Chicago, IL) using the PROCESS macro.²⁷

To determine the scope of relevance, sensitivity analyses were carried out in those who met and did not meet clinical criteria for possible or probable AD, in those who did not meet clinical criteria for VCI, and in women and men separately. To determine if imaging and cognitive measures were specific as mediators, substitutions into the hypothesized pathway were tested; verbal learning with semantic clustering (a component of strategic information processing), left temporal atrophy with atrophy of other lobes (to determine if the results might be explained, for instance, by frontal atrophy), and delayed free recall with recognition memory (to probe more AD-specific memory deficits).

Results

Proof-of-principle sample

Volumes of WMH differed between groups (figure 2A), as did the BPF in the left temporal lobe; the group with extensive WMH but without AD had temporal lobe atrophy comparable to that of the AD groups (figure 2B), and the AD group with

Figure 2 Brain volumetrics and memory measures from the proof-of-principle sample

(A) White matter hyperintensity volumes (WMH), (B) left temporal lobe brain parenchymal fraction, (C) California Verbal Learning Test, 2nd ed. (CVLT-II) verbal learning trials, (D) CVLT-II long delayed free recall trials in the proof-of-principle sample. WMH volume ($F_{1,117} = 22.591$, $p < 0.001$), left temporal brain parenchymal fraction ($F_{1,117} = 17.534$, $p < 0.001$), verbal learning ($F_{1,117} = 20.57$, $p < 0.001$), and verbal recall ($F_{1,117} = 40.057$, $p < 0.001$) differed significantly between groups. AD = Alzheimer disease; CAD = coronary artery disease.

extensive WMH had greater left temporal atrophy than the AD group with minimal WMH. Verbal learning and delayed free recall also differed between groups; despite comparable temporal lobe atrophy to the high WMH group without AD, both AD groups had significantly poorer verbal learning and recall scores (figure 2, C and D). Within the entire sample, WMH volume correlated inversely with left temporal lobe BPF ($r = -0.659$, $p < 0.001$), and with verbal learning ($r = -0.393$, $p < 0.001$) and recall ($r = -0.413$, $p < 0.001$).

In the path model, just one indirect pathway was significant as hypothesized, wherein WMH volume was associated with poorer verbal recall, mediated serially by left temporal lobe

atrophy and verbal learning (figure 3A). There was no direct effect independent of the hypothesized pathway, nor were any other pathways significant.

Confirmation sample

Of 815 records, 729 patients provided a CVLT and demographic data, and 702 of those had MRI sufficient for processing. For a breakdown of the sample by diagnosis and correlations between MRI measures, see tables e-1, e-2, and e-3 ([links.ww.com/WNL/A160](https://www.ww.com/WNL/A160)). Total WMH volume was inversely correlated with left temporal lobe BPF ($r = -0.385$, $p < 0.001$) and with verbal learning ($r = -0.201$, $p < 0.001$) and recall ($r = -0.187$, $p < 0.001$). WMH in each lobe were

Figure 3 Path models show direct and indirect relationships between white matter hyperintensity (WMH) volume and verbal memory performance

Path model tested in (A) proof-of-principle sample (n = 118) and (B) confirmation sample (n = 702). Thick lines are part of a significant pathway. Thin lines are part of a nonsignificant pathway. For each connection, the coefficient (a, b, c, a_2 and b_2), its standard error, and significance (p) are shown. The mediation effect of the hypothesized serial pathway ($a \times b \times c$) and its 95% CI are shown in red, the mediation effect of learning alone ($a_2 \times c$) in green, and the mediation effect of atrophy alone ($a \times b_2$) in blue. Direct effects are shown in orange; d is the direct effect adjusted only for covariates and d' is the direct effect adjusted for covariates and indirect effects. Covariate effects on mediators or outcomes with $p < .05$ are shown in grey. SE = standard error; TIC = total intracranial capacity.

associated with left temporal atrophy (table e-2), justifying the use of the whole brain measure in mediation models. Correlations between total WMH volume and each lobar atrophy measure are presented in table e-3, showing the strongest correlations in the temporal lobes.

In the path model, only the hypothesized serial mediation pathway was significant, as in the proof-of-principle sample. The other indirect pathways were not significant, and the direct relationship between WMH and verbal recall was attenuated by the indirect effects (figure 3B).

Sensitivity analyses

Substituting verbal learning with semantic clustering (n = 655) revealed the identical serial mediation pathway between WMH and long-delayed free recall; however, in this model, a significant $a \times b_2$ pathway was also observed, indicating that effects of WMH on verbal learning other than semantic clustering also had a significant effect on verbal recall (figure e-1A, [links.lww.com/wnl/A161](https://www.lww.com/wnl/A161)).

Substituting left temporal atrophy with left frontal atrophy (n = 702) demonstrated no significant effects on verbal

learning or verbal memory downstream of WMH volumes mediated by left frontal atrophy (figure e-1B, links.lww.com/wnl/A161), although an a_2c indirect effect was significant, confirming effects of WMH on verbal learning and memory other than those mediated by left frontal lobe atrophy. Similarly, substituting each lobar atrophy measure into the model indicated that only right and left temporal (but not frontal, occipital, or parietal) atrophy mediated effects of WMH volume on verbal memory (table e-4, links.lww.com/WNL/A160).

When delayed free recall was replaced with recognition memory ($n = 689$), the hypothesized indirect pathway was observed ($a \times b \times c = -1.82\%$, 95% CI -2.64% to -1.11%). A second indirect pathway was also significant ($a \times b_2 = -0.69\%$, 95% CI -1.40% to -0.23%), indicating that processes other than verbal learning also contributed to deficits in recognition memory related to WMH (i.e., forgetting learned information after a delay).

Subgroup analyses

For subgroup analyses, the confirmation sample was grouped into patients who met clinical criteria for AD and those who did not, and patients who met clinical criteria for VCI and those who did not (table 2). The AD and VCI subgroups were not mutually exclusive (93 patients met both criteria).

The hypothesized serial mediation pathway was significant in subgroups with (figure e-1C, links.lww.com/wnl/A161) and without AD (figure e-1D, links.lww.com/wnl/A161), and in a subgroup not diagnosed clinically with VCI ($a \times b \times c = -0.680$, 95% CI -1.010 to -0.332 words). The identical indirect pathway was significant in men ($a \times b \times c = -0.498$, 95% CI -0.885 to -0.188 words, $n = 324$) and women ($a \times b \times c = -0.802$, 95% CI -1.220 to -0.431 words, $n = 378$).

In a subgroup with AD without VCI, when substituting delayed free recall with recognition memory ($n = 263$), only the hypothesized serial mediation pathway was significant, indicating that WMH contributed to recognition memory specifically via temporal lobe atrophy and verbal learning in AD (figure e-1E, links.lww.com/wnl/A161).

Post hoc model

To discount the notion that an underlying factor correlated with both WMH and left temporal atrophy might have led to a spurious path effect, an alternative model was tested in which left temporal lobe atrophy leads to WMH volume, which leads to verbal learning and verbal recall. No evidence for this pathway was found (mediation effect -0.190 , 95% CI -1.017 to 0.533 words), indicating that the mediation effect is specific to the hypothesized sequential order.

Table 2 Confirmation sample characteristics grouped by AD and VCI^a

Group	Subgroups by AD		Subgroups by VCI		All
	AD	Non-AD	VCI	Non-VCI	
Total, n	363	339	140	562	702
Demographics					
Age, y	72.0 ± 9.3	69.4 ± 9.4	74.5 ± 7.7	69.8 ± 9.6	70.7 ± 9.4
Sex, % male	46.8	45.4	45.0	46.4	46.2
Education, y	13.8 ± 3.7	14.4 ± 3.7	13.5 ± 3.4	14.2 ± 3.8	14.1 ± 3.7
Neuroimaging					
TIC, mL	1,215 ± 135	1,210 ± 122	1,207 ± 131	1,214 ± 129	1,212 ± 129
WMH volume, mL	8.9 ± 13.4	6.3 ± 11.1	16.3 ± 19.4	5.5 ± 8.7	7.7 ± 12.4
Left temporal atrophy (BPF)	0.76 ± 0.05	0.80 ± 0.06	0.76 ± 0.05	0.78 ± 0.06	0.78 ± 0.06
Left frontal atrophy (BPF)	0.70 ± 0.05	0.72 ± 0.06	0.70 ± 0.05	0.71 ± 0.06	0.71 ± 0.06
CVLT measures					
Verbal learning (words)	21.2 ± 9.6	35.5 ± 15.0	24.5 ± 11.6	28.9 ± 14.8	28.0 ± 14.4
Semantic clustering	1.0 ± 0.7	1.5 ± 1.1	1.2 ± 0.8	1.3 ± 1.0	1.3 ± 0.9
Verbal recall (words)	1.8 ± 2.5	6.6 ± 4.5	3.1 ± 3.4	4.4 ± 4.5	4.1 ± 4.3
Recognition memory (%)	68.2 ± 14.0	82.0 ± 16.5	72.8 ± 15.0	75.4 ± 17.1	74.9 ± 16.7

Abbreviations: AD = dementia or mild cognitive impairment thought to be attributable to Alzheimer disease; BPF = brain parenchymal fraction; CVLT = California Verbal Learning Test; TIC = total intracranial capacity; VCI = dementia or cognitive impairment thought to be attributable to vascular lesions. Values are mean ± SD unless noted otherwise.

^a Categorical diagnoses are not mutually exclusive (mixed diagnoses were included in this sample).

Discussion

In 2 independent samples, WMH were related to poorer verbal memory, confirming a distinct underappreciated contribution to dementia.⁴ In the first sample, cortical stroke was excluded to infer specific effects of subcortical small vessel disease, a common co-pathology in AD that lowers the dementia threshold.²⁸ The effect of WMH was confirmed in an unselected, heterogeneous, consecutive, real-world case series, including patients across spectra of common, mixed, and rarer dementia syndromes. This validation strategy is conservative since significance rose above statistical noise introduced by multiple intervening pathologies, indicating robust effects broadly relevant across neurodegenerative disorders.

WMH volume was associated particularly with temporal lobe atrophy, and its effect on memory was due to this relationship; WMH volume was associated with poorer verbal memory only insofar as temporal lobe atrophy was seen. Previously, effects of WMH may have been underestimated because they are eclipsed when controlling for atrophy; however, here we show that WMH contribute to that atrophy. The results clarify the network effects of WMH underlying verbal memory deficits; however, further effects of strategically located lesions can contribute by interrupting circuits important for memory performance regardless of their size.²⁹

Verbal memory deficits related to WMH volume arose at the learning stage, although additional effects on delayed free recall were seen in those without AD, likely reflecting effects of WMH on retrieval of learned information. Temporal atrophy mediated the observed effects of WMH on learning, including reduced use of semantic clustering, a strategy consistent with previously observed effects of WMH on memory performance via information processing/executive function.⁶ Although semantic clustering acted as a mediator, additional effects of WMH on verbal recall were seen that could not be explained by this executive strategy.

Often WMH have been considered inconsequential in AD, in part because their contribution to memory deficits has not been understood. In AD, WMH contributed, via the hypothesized serial mediation pathway, to variance underlying recognition memory, a sensitive and specific neuropsychological sign of AD, even though no direct effects of WMH on recognition memory were observed. Since WMH contributed to the identical memory deficits as the more canonical features of AD, the present in vivo findings add to the evidence that WMH can constitute a core feature of the AD dementia syndrome. Autopsy studies confirm that late-onset dementia is often a product of multiple synergistic pathologies.³⁰ In a recent series of those aged 90+, the presence of ischemic findings contributed additively to the likelihood of a dementia diagnosis, increasing the risk 4-fold above that attributable to amyloid or tau pathology alone.³¹ Even “pure” autosomal dominant AD cases show increased

propensity for WMH, mostly likely due to cerebral amyloid angiopathy (CAA) in those cases that precedes the dementia syndrome.³²

Among those clinically diagnosed with AD in life, at least 50% will have significant small vessel disease at autopsy.^{33,34} On pathology, WMH are often related to damage to the small cerebral vessels, which can arise heterogeneously with atherosclerosis, arteriolosclerosis, venous collagenosis and vessel tortuosity related to vascular risk factors and remodeling phenomena, CAA, demyelination and axonal loss, blood-brain barrier disruption, or deterioration of the ventricular ependymal lining.^{35–37} Although these causes cannot be differentiated here, collectively they may lead to diffuse chronic hypoperfusion injury to the temporal lobe directly, or to atrophy secondary to disruption of temporal lobe network connectivity.²⁹ Therefore, strategies to protect the small vessels, prevent insults to the white matter, or manipulate downstream molecular pathways that lead to temporal lobe atrophy might be necessary to prevent and treat many AD cases.^{38,39}

As a limitation, few cognitively healthy controls were included, limiting generalizability to “normal aging”; however, since multiple dementias were included, the validation approach was conservative with respect to our main objectives. As a further limitation, fluid biomarker confirmation of AD was not available, precluding assessment of “additive” effects of WMH with other AD-related markers.^{29,40} Analyses included only patients with complete data, possibly introducing bias at imaging (e.g., motion in the scanner), or cognitive testing. The lower sensitivity of MRI at 1.5T to WMH may have contributed to different numerical estimates between the proof-of-principle and confirmation samples; regardless, the identical hypothesized pathway was validated. The results show that WMH-based anatomical network disruption contributes to verbal memory deficits across dementia syndromes, implicating small vessel disease as an important underlying etiology.

Author contributions

W.S.: design of the study, analysis and interpretation of data, drafting and revising the manuscript. H.C.-M.: analysis and interpretation of data, drafting and revising the manuscript. M.M.: conception of the study, interpretation of the data, revising the manuscript. J.R.: interpretation of the data, drafting and revising the manuscript. N.H.: design of the study, interpretation of the data, revising the manuscript. J.D.E.: design of the study, revising the manuscript. M.S.: revising the manuscript for intellectual content. P.C.: analysis of the data, revising the manuscript. D.Y.: analysis of the data, revising the manuscript. S.M.N.: analysis of the data, revising the manuscript. C.J.M.S.: analysis of the data, drafting and revising the manuscript. M.F.H.: analysis of the data, drafting and revising the manuscript. D.J.S.: conception and design of the study. A.K.: conception and design of the study, revising the manuscript. P.I.O.: conception of the study, revising the

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The effect of white matter hyperintensities on verbal memory

Mediation by temporal lobe atrophy

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Study question

What is the relationship between the volume of white matter hyperintensities (WMH) and verbal memory deficits in individuals with and without a diagnosis of Alzheimer disease (AD) or other dementias?

Summary answer

WMH predicted poorer verbal recall, mediated serially by left temporal lobe atrophy and poorer verbal learning, across dementia syndromes.

What is known and what this article adds

WMH on MRI are thought to indicate the presence of cerebral small vessel damage, and they have been associated with deficits in multiple cognitive domains. This study reports that WMH contribute to verbal memory deficits across dementia syndromes, specifically by contributing to temporal lobe atrophy.

Participants and setting

The study included a proof-of-principle sample of 118 persons that was specifically designed to include representative strata of minimal and extensive WMH, and an independent validation sample of 702 consecutive tertiary care patients drawn from the Sunnybrook Dementia Study, including both AD and non-AD dementias.

Design, size, and duration

The design included a cross-sectional proof-of-principle study followed by validation in a separate sample. Structural MRI was used to assess WMH and temporal lobe atrophy inferred from brain parenchymal fractions. Verbal learning and memory was assessed using the California Verbal Learning test. Path modeling with inferential bootstrapping was used to assess the pathway mediating a relationship between WMH and verbal memory.

Primary outcomes

The primary outcome was the relationship number of words retained after a delay.

Main results and the role of chance

In both the proof-of-principle and validation samples, WMH predicted poorer verbal recall in a manner mediated by

Path model showing significant serial mediation effect in red ($a \times b \times c$), with other pathways ($a \times b_2$ and $a_2 \times c$) and adjusted direct effect (d') not significant.

temporal lobe atrophy and poorer learning in sequence (estimate [95% bootstrap confidence interval] -1.53 [-2.45 to -0.88] and -0.66 [-0.95 to -0.41] words, respectively). WMH also contributed to deficits in recognition memory via this pathway (-1.82% [-2.64% to -1.11%]). The path model was valid regardless of dementia syndrome (AD vs non-AD).

Bias, confounding, and other reasons for caution

The analysis was cross-sectional, and limited by unavailability of biomarker confirmation of AD. In addition, analyses only included patients with complete data, resulting in possible bias.

Generalizability to other populations

Generalizability of the results to normal aging populations is limited by the inclusion of relatively few cognitively normal control participants in the validation sample.

Study funding/potential competing interests

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A draft of the short-form article was written by A. Symons, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.