Memory decline in elderly with cerebral small vessel disease explained by temporal interactions between white matter hyperintensities and hippocampal atrophy

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Abstract
White matter hyperintensities (WMH) constitute the visible spectrum of cerebral small vessel disease (SVD) markers and are associated with cognitive decline, although they do not fully account for memory decline observed in individuals with SVD. We hypothesize that WMH might exert their effect on memory decline indirectly by affecting remote brain structures such as the hippocampus. We investigated the temporal interactions between WMH, hippocampal atrophy and memory decline in older adults with SVD. Five hundred and three participants of the RUNDMC study underwent neuroimaging and cognitive assessments up to 3 times over 8.7 years. We assessed WMH volumes semi-automatically and calculated hippocampal volumes (HV) using FreeSurfer. We used linear mixed effects models and causal mediation analyses to assess both interaction and mediation effects of hippocampal atrophy in the associations between WMH and memory decline, separately for working memory (WM) and episodic memory (EM). Linear mixed effect models revealed that the interaction between WMH and hippocampal volumes explained memory decline (WM: β = .067; 95%CI[.024–.111]; p < .01; EM: β = .061; 95%CI [.025–.098]; p < .01), with better model fit when the WMH*HV interaction term was added to the model, for both WM (likelihood ratio test, χ²[1] = 9.3, p < .01) and for EM (likelihood ratio test, χ²[1] = 10.7, p < .01). Mediation models showed that both baseline WMH volume (β = –.170; p = .001) and hippocampal atrophy (β = .126; p = .009) were independently related to EM decline, but the effect of baseline WMH on EM decline was not mediated by hippocampal atrophy (p value indirect effect: 0.572). Memory decline in elderly with SVD was best explained by the interaction of WMH and hippocampal volumes. The relationship...
1 | INTRODUCTION

White matter hyperintensities (WMH) are frequently observed on neuroimaging in older adults (de Leeuw et al., 2001) and constitute an important radiological marker of cerebral small vessel disease (SVD) (Wardlaw et al., 2013). WMH have been associated with cognitive deficits in virtually every domain, including working memory (WM) and episodic memory (EM) (Debette & Markus, 2010; Prins & Scheltens, 2015). WM relies on prefrontal and parietal cortical regions that are largely affected in SVD (Baddeley, 2012; Metoki et al., 2017).

The role of WMH in EM deficits, however, is less well understood, as EM performance is mainly supported by structures in the medial temporal lobes and especially the hippocampus (Rolls, 2000; Squire & Zola-Morgan, 1991), which are typically unaffected by WMH (Lambert et al., 2016).

Several studies have reported associations between WMH and hippocampal volumes (de Leeuw, Barkhof, & Scheltens, 2004; den Heijer et al., 2012; Eckerstrom et al., 2011; Fiford et al., 2017; van der Flier et al., 2016), while others have reported that these pathologies are independent processes that both affect cognition adversely (Oosterman, Oosterveld, Rikker, Claassen, & Kessels, 2012; Vemuri et al., 2015). Thus far, studies have not thoroughly investigated the interactions of WMH, hippocampal atrophy and memory decline longitudinally. This is especially important as age is an important risk factor for all of these three phenomena and WMH progresses exponentially over time (van Leijsen et al., 2017).

There is increasing awareness that SVD exerts its clinical effects by affecting remote brain structures (Duering et al., 2012; Lambert et al., 2016), suggesting that disruptions in white matter connections due to WMH might lead to secondary hippocampal atrophy and a concomitant memory decline in patients with SVD. A recent cross-sectional neuroimaging study in patients with Alzheimer's disease (AD) showed that WMH contributed indirectly to memory deficits by contributing to temporal lobe atrophy (Swawardfager et al., 2018). Prospective studies, however, would be required to elaborate on the directionality of the associations.

In this article, we specifically examined the temporal interactions between WMH and hippocampal atrophy for these two memory systems longitudinally, using three neuroimaging and cognitive assessments over 9 years in an SVD cohort. Specifically, we tested two hypotheses as to how WMH and hippocampal atrophy might affect memory decline (Figure 1). First, we tested whether WMH and hippocampal atrophy interacted in predicting memory deficits. Second, we tested whether the effect of WMH on memory decline was mediated by hippocampal atrophy.

2 | METHODS

2.1 | Study population

This study is part of the RUN DMC study, a prospective cohort study among 503 nondemented older adults with SVD, aged between 50 and 85 years, that investigates risk factors and clinical consequences of SVD. Symptoms of SVD include both acute symptoms, such as transient ischemic attack (TIA) or lacunar syndromes, and subacute manifestations such as cognitive and motor (gait) disturbances (Roman, Erkinjuntti, Wallin, Pantoni, & Chui, 2002). As the onset of SVD is often insidious, clinically heterogeneous, and typically with mild symptoms, the selection of participants with SVD was based on neuroimaging characteristics, including WMH and lacunes (Erkinjuntti, 2002). The detailed study protocol has been published previously (van Norden et al., 2011). In short, 503 independently living older adults with SVD, without dementia, were included for baseline assessment in 2006. Inclusion criteria were age between 50 and 85 years and presence of SVD on neuroimaging (i.e., WMH and/or lacunes). Subsequently, the above mentioned acute and subacute clinical symptoms of SVD were assessed. Of these 503 participants, 361 underwent repeated MRI assessment at first follow-up in 2011, and 296 participants at second follow-up in 2015 (van Leijsen et al., 2017). Of those, seven participants were excluded because of insufficient scan quality at baseline, 15 participants at first follow-up, and seven at second follow-up, yielding a sample of 496 participants for neuroimaging analyses at baseline, 346 at first follow-up, and 289 at second follow-up. Thus, in total 1,131 observations could be used for linear mixed effect analyses. In total, 263 participants underwent repeated cognitive and neuroimaging assessments of sufficient quality at all three time-points and could be used for longitudinal analyses (Supporting Information Figure S1). The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study and all participants gave written informed consent.

2.2 | Cognitive function

Cognitive performance was measured using an extensive neuropsychological test battery during all three waves of data collection (van
Uden et al., 2015). In the present study, we used the immediate and delayed recall of the Rey Auditory Verbal Learning Test (RAVLT) (Van der Elst, van Boxtel, van Breukelen, & Jolles, 2005) and Rey Complex Figure Task (RCFT) (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2002) as well as Speed–Accuracy Trade-Off (SAT) scores of the 2-letter and 3-letter subtasks of the Paper–Pencil Memory Scanning Task (PPMST) (Van Der Elst, Van Boxtel, Van Breukelen, & Jolles, 2007). To account for possible learning effects, parallel versions of the RAVLT and RCFT were used for the second follow-up assessment. Performance across tests was made comparable by transforming the raw test scores into z-scores, where higher z-scores indicate better performance. Raw scores of all three time-points were transformed into z-scores based on the mean and standard deviation (SD) of the baseline study population. We subsequently calculated compound scores for WM and EM. WM is a compound score of the SAT scores of the 2-letter and 3-letter subtasks of the PPMST (Van Der Elst et al., 2007). EM is a compound score of the mean of the z-scores of the three learning trials and the delayed recall of the RAVLT and the mean of the z-scores of the immediate recall trial and the delayed recall trial of the RCFT. Cognitive decline over time was calculated for each participant individually, by subtracting baseline scores from the follow-up scores.

2.3 | Vascular risk factors

We assessed the presence of hypertension, smoking, alcohol use, body mass index, diabetes, and hypercholesterolemia using standardized questionnaires, as described previously (van Norden et al., 2011). Hypertension was defined as the use of antihypertensive agents and/or systolic blood pressure greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg. Diabetes was defined as treatment with diabetic medication and hypercholesterolemia as the use of lipid-lowering drugs (van Norden et al., 2011).

2.4 | Neuroimaging protocols

MR images were acquired at three time-points on 1.5-Tesla MRI (2006: Siemens, Magnetom Sonata; 2011 and 2015: Siemens, Magnetom Avanto) and included the following whole brain scans: T1-weighted 3D MPRAGE sequence (isotropic voxel size 1.0 mm$^3$), a FLAIR sequence (2006: voxel size 0.5 x 0.5 x 5.0 mm, interslice gap 1.0 mm; 2011 and 2015: voxel size 0.5 x 0.5 x 2.5 mm; interslice gap 0.5 mm) and a DTI sequence (2006: isotropic voxel size 2.5 mm$^3$, 4 unweighted scans, 30 diffusion weighted scans at $b = 900$ s/mm$^2$; 2011 and 2015: isotropic voxel size 2.5 mm$^3$, 8 unweighted scans, 60 diffusion weighted scans at $b = 900$ s/mm$^2$). Full acquisition details have been described previously (van Leijsen et al., 2017; van Leijsen et al., 2018; van Norden et al., 2011) and can be found in the Supporting Information Methods.

2.5 | Brain volumetry

We assessed grey matter (GMV), white matter (WMV), and CSF volumes using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) unified segmentation routines on the T1 MPRAGE images corrected for WMH, as has been described in detail elsewhere (van Leijsen et al., 2017).

2.6 | White matter hyperintensities

WMH volumes were calculated by a semi-automatic WMH segmentation method, which has been described previously (Ghafoorian et al., 2016). Segmentations were visually checked for segmentation errors by one trained rater, blinded for clinical data. WMH volumes were corrected for inter-scan-differences in ICV and then normalized to baseline ICV. We calculated individual annualized WMH progression rates using linear mixed effects (LME) models based on all available time-points. The individual WMH progression rates were extracted and used for further analyses.

2.7 | Hippocampal volumes

Hippocampal volume segmentations were automatically processed with the longitudinal stream (Reuter, Schmansky, Rosas, & Fischl, 2012) in FreeSurfer 5.3 (http://surfer.nmr.mgh.harvard.edu/). In short, the T1-weighted images from all three time-points were first processed separately using the standard processing stream. Subsequently, an unbiased within-subject template was created from all time-points for each subject using the longitudinal processing stream,
and several processing steps were then initialized with common information from the within-subject template, to increase the reliability of the segmentation of brain regions over time (Reuter et al., 2012). For those participants who were only able to complete one or two neuroimaging assessments, we ran the same longitudinal pipeline using the available T1-weighted images, to ensure that all images underwent the same processing steps (Bernal-Rusiel et al., 2013). All segmentations were visually checked for segmentation accuracy at each time-point and manually adjusted when necessary. We used LME models to estimate individual annualized hippocampal atrophy rates based on all available time-points, with negative values reflecting more hippocampal atrophy. The individual hippocampal atrophy rates were extracted and used for further analyses.

2.8 | Statistical analysis

Change in WMH, HV and cognitive performance over time was tested using repeated measures ANOVA. We visualized the change in both working memory and episodic memory over time according to quartiles of baseline WMH and hippocampal volumes. We analyzed WMH and hippocampal volumes in quartiles of their distribution and tested continuous linear trend per stratum. We additionally displayed the change in working and episodic memory according to the interaction between WMH and hippocampal volumes. We therefore identified low WMH volume (WMH+), high WMH volume (WMH-), high hippocampal volume (HV+), and low hippocampal volume (HV-) based on median split of baseline volumes, thereby creating four groups: WMH+/HV+, WMH-/HV+, WMH+/HV-, and WMH-/HV-. Differences between these groups were calculated using one way ANOVA with post hoc Bonferroni-correction.

All statistical analyses were carried out in R 3.4.2 (https://www.r-project.org/). To test whether WMH and hippocampal volumes interacted in predicting memory deficits (Figure 1 – Hypothesis I), we fitted linear mixed effects (LME) models with memory performance as the dependent variable using “lme4” version 1.1–14 in R (Bates, Machler, Bolker, & Walker, 2015). All analyses were performed separately for working and episodic memory. LME models allow for the simultaneous modeling of fixed (population-average) and random (subject-specific) effects, allowing us to examine memory decline in the entire population while accounting for individual differences in rates of memory decline. We fitted four models: (1) a null model including baseline age, sex and the level of education at baseline. Time between baseline and follow-up assessments was added as a fixed effect and a subject-specific random intercept and slope, such that the fixed effect coefficient estimates group-level memory decline per year, while the random terms are the individual trajectories of memory decline over time. In addition, we included a quadratic term for time, as WMH were found to progress nonlinearly over time (van Leijen et al., 2017). In the second model (2), we additionally added WMH volumes of all available time-points and the interaction between WMH and time-squared, indicating the effect of nonlinear WMH progression on memory decline. In the third model (3), we added hippocampal volumes of all available time-points and the interaction between HV and linear time to the null model, to estimate the effect of hippocampal atrophy over time on memory decline. (4) In the fully specified model we additionally added an interaction term between WMH and HV. We compared model fit between the four models using a likelihood ratio test, and we evaluated the change in Akaike information criterion (AIC) and Bayesian information criterion (BIC). For both indexes, smaller values indicate better fit.

We performed additional analyses on the temporal interactions between WMH, HV, and memory decline. For this, we first used LME models to estimate individual annualized WMH progression and hippocampal atrophy rates based on all available time-points. The individual WMH progression and hippocampal atrophy rates were extracted and used for further analyses. Using “lavaan” version 0.5–23.1097 in R (Rosseel, 2012), we estimated the effects of baseline WMH volume, WMH progression, baseline hippocampal volume and hippocampal atrophy on memory decline, separately for working and episodic memory decline. We also tested the effect of the interaction term between baseline WMH and hippocampal volumes on memory decline. Analyses were adjusted for baseline age, sex and level of education at baseline. We compared model fit between the models with and without the interaction term using a likelihood ratio test.

To test whether interactions between WMH and HV in predicting memory deficits were specifically attributed to hippocampal atrophy, we performed the same analyses with global gray matter atrophy instead of hippocampal atrophy. Hence, we compared four models: in the first model (1), we added WMH and the interaction between WMH and quadratic time only. In the second model (2), we additionally added HV, the interaction between HV and time, and the interaction term between WMH and HV. In the third model (3), we added GMV, the interaction term between WMH and GMV, and the interaction term between HV and GMV. In the fourth model (4), we additionally added an interaction term between WMH and HV.

We also tested the effect of the interaction term between baseline WMH and hippocampal volumes on memory decline. Analyses were adjusted for baseline age, sex and level of education at baseline. We compared model fit between the models with and without the interaction term using a likelihood ratio test.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Baseline characteristics</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td>Study population (n = 503)</td>
</tr>
<tr>
<td>Age, years</td>
<td>65.7 ± 8.8</td>
</tr>
<tr>
<td>Male sex, number of participants</td>
<td>284 (56.5)</td>
</tr>
<tr>
<td>MMSE score</td>
<td>28.1 ± 1.6</td>
</tr>
<tr>
<td>Education, years</td>
<td>9.8 ± 1.8</td>
</tr>
<tr>
<td><strong>Vascular risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension, number of participants</td>
<td>369 (73.4)</td>
</tr>
<tr>
<td>Hypercholesterolemia, number of participants</td>
<td>237 (47.1)</td>
</tr>
<tr>
<td>Diabetes, number of participants</td>
<td>75 (14.9)</td>
</tr>
<tr>
<td>Smoking, ever, number of participants</td>
<td>353 (70.2)</td>
</tr>
<tr>
<td>Alcohol, glasses/week</td>
<td>7.9 ± 9.3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.1 ± 4.1</td>
</tr>
<tr>
<td><strong>Imaging characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Total brain volume, ml</td>
<td>1,060.9 ± 80.1</td>
</tr>
<tr>
<td>Grey matter volume, ml</td>
<td>606.2 ± 52.6</td>
</tr>
<tr>
<td>White matter volume, ml</td>
<td>454.7 ± 46.0</td>
</tr>
<tr>
<td>Microbleeds, number of participants</td>
<td>83 (16.5)</td>
</tr>
<tr>
<td>Lacunes, number of participants</td>
<td>132 (26.2)</td>
</tr>
<tr>
<td>WMH volume, ml</td>
<td>3.6 (1.2–11.4)</td>
</tr>
<tr>
<td>Hippocampus volume, ml</td>
<td>7.6 ± 1.0</td>
</tr>
</tbody>
</table>

Data represent number of participants (%), mean ± SD or median (IQR).
between GMV and time, and an interaction term between WMH and GMV to the first model, to estimate the effect of global gray matter atrophy on memory decline. We additionally fitted a fourth model (4), in which we added both HV and GMV together with their interaction terms, to estimate the relative strengths of hippocampal and global gray matter atrophy in explaining memory decline.

To test whether hippocampal atrophy mediated the association between WMH and memory decline (Figure 1, Hypothesis II), we performed mediation analyses using “lavaan” version 0.5–23.1097 in R (Rosseel, 2012). For this, we first used LME models to estimate individual annualized hippocampal atrophy rates based on all available time-points. The individual hippocampal atrophy rates were extracted and used for further analyses. Using lavaan, we estimated the direct

FIGURE 2  Age-related working and episodic memory performance by white matter hyperintensities and hippocampal volumes. (a) Spaghetti plots showing the trajectories of working memory performance (left) and episodic memory performance (right) over time. (b) Age-related working memory performance by white matter hyperintensities (left) and hippocampal volumes (right). (c) Age-related episodic memory performance by white matter hyperintensities (left) and hippocampal volumes (right). Dots are color-coded by age, with baseline age of participants ranging from 50 years in light blue to 85 years in dark blue [Color figure can be viewed at wileyonlinelibrary.com]
effect of baseline WMH volume on memory decline and the indirect effect of baseline WMH volume on memory decline via hippocampal atrophy, separately for working and episodic memory decline.

3 | RESULTS

Baseline characteristics of the study population are presented in Table 1. Mean age at baseline was 65.7 (SD 8.8) years and 57% of the participants were male. WMH and hippocampal volumes and cognitive performance over time is shown in Supporting Information Table S1. Higher WMH volumes were related to both lower WM and lower EM performance (WM: β = −.295; 95%CI [−.348 − .241]; p < .001; EM: β = −.271; 95% CI [−.324 − .217]; p < .001) and higher hippocampal volumes were related to both higher WM and higher EM performance (WM: β = 0.307; 95%CI [0.253−.359]; p < .001; EM: β = 0.392; 95%CI [0.341−.440]; p < .001), modified by age (Figure 2). Change in both working memory and episodic memory over time according to quartiles of baseline WMH and hippocampal volumes as well as their interaction was graphically displayed in Figure 3. We observed more decline in the WMH+/HV- group compared to both WMH-/HV+ and WMH+/HV+ groups.

3.1 | Memory decline explained by interactions between WMH and hippocampal atrophy

The results of the mixed effect models are shown in Table 2. Both models with WMH only and HV only provided significantly better fits in comparison to the null model, for both WM (WMH only vs. null model: likelihood ratio test, χ²(2) = 7.3, p < .05; HV only vs. null model: χ²(2) = 9.8, p < .01) and for EM (WMH only vs. null model: χ²(2) = 28.3, p < .001; HV only vs. null model: χ²(2) = 74.4, p < .001). The models with HV alone fitted better than the models with WMH alone, not only for EM (likelihood ratio test, χ²[0] = 46.1, p < .001), but also for WM (likelihood ratio test, χ²[0] = 2.4, p < .001). Importantly, including the WMH+HV interaction term significantly improved the model, for both WM (likelihood ratio test model with both WMH & HV vs. full model with WMH+HV interaction term, χ²[1] = 9.3, p < .01) and for EM (likelihood ratio test model with both WMH & HV vs. full model with WMH+HV interaction term, χ²[1] = 10.7, p < .01). The WMH+HV interaction term was significantly associated with memory function (WM: β = 0.132; 95%CI [0.024−0.111]; p < .01; EM: β = 0.061; 95%CI [0.025−0.098]; p < .01). More hippocampal atrophy was associated with lower EM performance (β = 0.171; 95%CI [0.009−0.25]; p < .001).

The results of the interaction analyses on decline in WM and EM are shown in Figure 4. Lower baseline hippocampal volumes (β = 0.132; p < .001) and higher baseline WMH volumes (β = −.164; p < .001) were associated with more EM decline. More hippocampal atrophy was associated with more EM decline (β = 0.120; p < .001). Including the WMH+HV interaction term significantly improved the model, for both WM (likelihood ratio test, χ²(1) = 6.0, p < .05) and EM (likelihood ratio test, χ²(1) = 10.1, p < .01).

![Graphical displays of working memory and episodic memory over time according to baseline WMH and hippocampal volumes and their interaction. Decline in working memory (top) and episodic memory (bottom), according to quartiles of baseline WMH volumes and quartiles of baseline hippocampal volumes. Right: Decline in working and episodic memory according to the interaction between WMH and hippocampal volumes. Based on median split of baseline WMH volume (low WMH volume (WMH−) and high WMH volume (WMH+) and baseline hippocampal volume (high hippocampal volume (HV+) and low hippocampal volume (HV−)), we identified 4 groups: WMH+/HV+, WMH-/HV+, WMH+/HV−, and WMH-/HV−. Bars represent decline in z-scores and whiskers represent standard errors. p Trends for continuous linear trend per stratum are displayed in the corners. *** p < .001; ** p < .01; * p < .05](image-url)
<table>
<thead>
<tr>
<th></th>
<th>Working memory</th>
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<tbody>
<tr>
<td></td>
<td>Null (1)</td>
<td>WMH only (2)</td>
<td>HV only (3)</td>
<td>Full (4)</td>
</tr>
<tr>
<td><strong>Baseline age (years)</strong></td>
<td>−.046***</td>
<td>−.043***</td>
<td>−.041***</td>
<td>−.038***</td>
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<tr>
<td></td>
<td>(−.054, −.038)</td>
<td>(.052, −.034)</td>
<td>(.051, −.032)</td>
<td>(.048, −.028)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>.191**</td>
<td>.198***</td>
<td>.152</td>
<td>.173**</td>
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<tr>
<td></td>
<td>(.057, .324)</td>
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<td>.131***</td>
<td>.135***</td>
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<td>(.094, .170)</td>
<td>(.092, .169)</td>
<td>(.093, .169)</td>
<td>(.097, .173)</td>
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<tr>
<td><strong>Follow-up time (linear)</strong></td>
<td>−.092***</td>
<td>−.095***</td>
<td>−.171***</td>
<td>−.119**</td>
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<tr>
<td></td>
<td>(−.119, −.064)</td>
<td>(−.123, −.068)</td>
<td>(−.247, −.096)</td>
<td>(−.200, −.038)</td>
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<td><strong>Follow-up time (quadratic)</strong></td>
<td>.003</td>
<td>.005**</td>
<td>.003</td>
<td>.004</td>
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<tr>
<td></td>
<td>(−.001, .006)</td>
<td>(.001, .009)</td>
<td>(.0004, .006)</td>
<td>(.0001, .007)</td>
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<tr>
<td><strong>WMH volume</strong></td>
<td>−.016</td>
<td>−.534**</td>
<td>−.013</td>
<td>−.487***</td>
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<tr>
<td></td>
<td>(−.070, .038)</td>
<td>(−.869, −.199)</td>
<td>(−.060, .033)</td>
<td>(−.772, −.202)</td>
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<td><strong>WMH progression (quadratic)</strong></td>
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<td>−.0004</td>
<td>−.002***</td>
<td>−.001*</td>
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<td>(−.003, −.001)</td>
<td>(−.002, −.0001)</td>
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<td><strong>Hippocampal volume</strong></td>
<td>.029</td>
<td>−.057</td>
<td>−.069***</td>
<td>−.006</td>
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<td>(−.052, .111)</td>
<td>(−.156, .042)</td>
<td>(.002, .137)</td>
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<td><strong>Hippocampal atrophy (linear)</strong></td>
<td>.011*</td>
<td>.004</td>
<td>.025***</td>
<td>.017***</td>
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<tr>
<td><strong>WMH + HV interaction</strong></td>
<td>.067**</td>
<td>(0.24, .111)</td>
<td>.061**</td>
<td>(0.25, .098)</td>
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<tr>
<td></td>
<td>(−1.186,406)</td>
<td>(−1.182,732)</td>
<td>(.239,2813)</td>
<td>(2.443,130)</td>
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<td><strong>Log likelihood</strong></td>
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<td>2.379,352</td>
<td>2.075,909</td>
<td>2.126,340</td>
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<td><strong>AIC</strong></td>
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<td>2.387,039</td>
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<td><strong>BIC</strong></td>
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<td>2.449,845</td>
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**Fixed effects results from linear mixed effect models explaining memory function, separately for working and episodic memory. In the null model, (1) we estimated the effects of age as well as the linear and quadratic effects of temporal progression on memory. We then adopted a data-driven approach to determine the role of baseline WMH as well as nonlinear WMH progression (2) and baseline HV as well as linear hippocampal atrophy (3) in contributing to memory deficits. In the full model (4) we estimated the effect of the interaction between WMH and HV on memory. Data represent standardized estimates with confidence intervals and statistical significance: *p < .05; **p < .01; ***p < .001. Models were compared using likelihood ratio tests, with smaller AIC and BIC values indicating better model fit. WMH = white matter hyperintensities; HV = hippocampal volume.**
Additional analyses on global gray matter atrophy revealed a significant interaction effect of WMH*GMV for WM (β = .090; 95%CI [.004–.177]; p < .05), though the addition of both hippocampal and gray matter atrophy to the model rendered the WMH*GMV interaction term nonsignificant (β = .027; 95%CI [-.077–.131]; p > .05) where the WMH*HV interaction term remained significant (β = .059; 95%CI [.007–.111]; p < .05). There was no significant interaction effect of WMH*GMV for EM (β = .073; 95%CI [-.001–.147]; p > .05).

3.2 | Mediation of the associations between WMH and memory decline by hippocampal atrophy

The results of the causal mediation analyses are shown in Figure 5, separately for WM and EM decline. Decline in WM performance over time was not associated with baseline WMH volume (β = −.022; p = .707) or hippocampal atrophy (β = .056; p = .306) after adjusting for age, sex, and education. The direct effects of both baseline WMH volume (β = −.170; p = .001) and hippocampal atrophy (β = 0.126; p = .009) on EM decline were significantly different from zero. The effect of baseline WMH on EM decline was not mediated by hippocampal atrophy (p value indirect effect: 0.572).

4 | DISCUSSION

We observed that memory decline in individuals with SVD was best explained by an interaction of WMH and hippocampal atrophy, rather than these two variables independently. In addition, we showed that the association between WMH and episodic memory decline was not causally mediated by hippocampal atrophy. Finally, we demonstrated
that these effects were specific to hippocampal atrophy, rather than general grey matter atrophy. Together, our findings suggest that memory decline in patients with SVD is a heterogeneous condition to which different pathologies contribute.

Our findings that memory decline could be best explained by the interaction of WMH and hippocampal atrophy are consistent with imaging studies showing an additive effect of WMH and hippocampal atrophy on the level of cognitive decline (Godin et al., 2010; Prins & Scheltens, 2015; van der Flier et al., 2005), although there are also studies that have reported that AD and vascular pathologies are independent processes (Vemuri et al., 2015). These variable findings might be due to differences in the relative proportion of cerebrovascular and AD pathologies, with both pathologies being present in many older adults with dementia (Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study, 2001). Our study adds to these findings by describing the temporal interactions between both pathologies and memory decline longitudinally, over a long follow-up of almost 9 years. We found that memory decline could be best explained by the interaction of WMH and hippocampal atrophy and that the associations between WMH and hippocampal atrophy were not causally mediated by hippocampal atrophy, suggesting that WMH and hippocampal atrophy synergistically affect memory decline. Moreover, we found that this effect of hippocampal atrophy was not just the result of global brain atrophy, as the effect of hippocampal atrophy was stronger than the effect of global gray matter atrophy.

Interestingly, we observed an interaction between WMH and hippocampal atrophy for WM, although the relative involvement of the hippocampus itself was lower for WM performance than for EM performance. While it has been argued that WM processing should not rely on the hippocampus (Baddeley, 2012; Squire & Zola-Morgan, 1991), and we hypothesized that WM performance would be related to WMH specifically, some degree of long-term encoding has been demonstrated during WM tasks related to the specific task demands (Bergmann, Rijpkema, Fernandez, & Kessels, 2012). That is, WM tasks are rarely "process pure," but may also include components that promote incidental long-term encoding (e.g., maintaining the target items in the PPMT over a longer period of time).

Several mechanisms might be proposed for the association between WMH and memory decline. WMH might exert their clinical effects in a direct way by disconnecting white matter tracts, or indirectly through incident stroke (Vermeer et al., 2003) or by affecting remote brain structures (Duering et al., 2012; Lambert et al., 2016). Alternatively, vascular risk factors might lead to cognitive decline in patients with SVD through other mechanisms, such as inflammatory responses, hormonal dysregulation, or damage to neurotransmitter systems (Kimura et al., 2000; Roman & Kalaria, 2006; Strachan, Reynolds, Marioni, & Price, 2011). Finally, memory decline in patients with SVD might also be explained by the interaction of SVD pathology with other neurodegenerative pathologies, such as seen in AD (Breteler, 2000; Kalaria, 2002; Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study, 2001; Prins & Scheltens, 2015). Our observations that WMH and hippocampal atrophy interact in explaining memory decline in patients with SVD support this hypothesis. This is in line with a study in patients with AD showed that reduced network integrity was associated with SVD severity, specifically in networks important for cognition (Nestor et al., 2017). Animal studies have suggested that neurovascular dysfunction could potentiate the production of amyloid beta (Koncz & Sachdev, 2018), suggesting that cerebrovascular pathology might be a risk factor for AD, although longitudinal evidence on the directionality of associations between vascular and Alzheimer's pathology in humans remains limited.

The presence of an interaction effect in the absence of a causal mediation effect suggests that WMH and hippocampal atrophy are independent processes that synergistically affect memory decline. These findings suggest that age-related memory decline is a heterogeneous condition in which different pathologies contribute to the memory decline observed in elderly with SVD.

Major strengths of this study include the large number of participants with SVD included in the study and the longitudinal design of our study with three neuroimaging assessments over 9 years, which enabled us to study temporal interactions between WMH progression, hippocampal atrophy, and memory decline beyond cross-sectional associations. Several methodological issues and limitations deserve consideration. First, slight changes in neuroimaging protocols between baseline and first follow-up might be a potential source of bias. To minimize effects of changes in FLAIR sequence we resliced follow-up FLAIR images to match the slice thickness of baseline images using linear interpolation. Besides, we calculated WMH volumes for odd and even slices separately to determine the effects of change in slice thickness of the FLAIR sequence. This revealed similar results. Furthermore, hippocampal volumes were calculated using subject templates as part of the longitudinal segmentation pipeline, reducing the risk of bias in longitudinal volume calculations. Another limitation might be that learning effects have led to an underestimation of memory decline in our study population. We limited these possible learning effects by the use of alternative versions of the memory tasks during the second follow-up assessment. Due to the long-term follow-up of our study a proportion of the participants was unable to complete the entire follow-up. This attrition bias might have led to an underestimation of the effects, since those lost to follow-up had more severe WMH, smaller hippocampal volumes and were cognitively more impaired already at baseline. However, by mixed effects models we could also take into account the participants with one or more missing values, thereby limiting the effect of the attrition bias. Finally, as we did not have pathological confirmations on cerebrovascular or AD pathologies, we used WMH and hippocampal volumes as markers of these two diseases.

In conclusion, memory decline in elderly with SVD was best explained by the interaction of WMH with hippocampal atrophy. The relationship between WMH and memory was not causally mediated by hippocampal atrophy, suggesting that memory decline during aging is a heterogeneous condition in which different pathologies contribute to the memory decline observed in elderly patients with SVD.

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CONFLICT OF INTEREST

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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