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White matter hyperintensities and hippocampal atrophy in relation to cognition: The 90+ Study

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Abstract

Objectives: To study the interactive effect of white matter hyperintensities (WMH) and hippocampal atrophy on cognition in the oldest-old.

Design: Ongoing longitudinal study.

Setting: Southern California, brain MRI-scans conducted between May 2014 and December 2017.

Participants: Individuals from ***The 90+ Study*** with a valid brain MRI-scan (N=141, 94 cognitively normal and 47 with cognitive impairment).

Measurements: Cognitive testing was performed every six months with a mean follow-up of 2.0 years and included the following tests: Mini-Mental State Examination (MMSE), modified MMSE (3MS), California Verbal Learning Test (CVLT) immediate recall over four trials and delayed recall, Digit Span Backward, Animal Fluency, Trail Making Test (TMT) A, B and C. We used one linear mixed model for each cognitive test to study the baseline and longitudinal association of WMH and hippocampal volume with cognition. Models were adjusted for age, gender and education.

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Author Contributions: All authors have made substantial contributions to the manuscript. MC, CK, PS and NL created the design and concept of the study. NL performed the data analyses and MC assisted with the data analyses. EF, PM and CD performed the MRI analyses. NL drafted the first and final versions of the manuscript. All authors contributed to and approved the final version.

Conflict of Interest: The authors do not have any conflicts of interest.

Results: Mean age was 94.3 (SD=3.2) years. At baseline, higher WMH volumes were associated with worse scores on the 3MS, CVLT immediate and delayed recall and TMT B. Lower hippocampal volumes were associated with worse baseline scores on all cognitive tests, except for the Digit Span Backward. Longitudinally, higher WMH and lower hippocampal volumes were associated with faster decline in the 3MS and MMSE and lower hippocampal volume was also associated with faster decline in the CVLT immediate recall. There was no association between WMH and hippocampal volume and no interaction between WMH and hippocampal volume in their association with baseline cognition or cognitive decline.

Conclusion: We show that WMH and hippocampal atrophy have an independent, negative effect on cognition, which make these biomarkers relevant to evaluate in the diagnostic work-up of oldest-old individuals with cognitive complaints. However, the predictive value of WMH for cognitive decline seems to be less evident in the oldest-old compared to younger elderly.

Keywords

white matter hyperintensities; hippocampal atrophy; cognitive functioning; oldest-old

1. Introduction

Cognitive functioning in individuals aged 90 years and older (the oldest-old) is determined by multiple factors. Neuropathological studies in this age group show that the presence of multiple pathologies, including Alzheimer's disease (AD) and vascular pathology, is associated with an increased dementia risk[1,2]. The association between cognitive impairment and individual pathologies seems to become weaker at older ages[3]. It remains however unknown how these different pathologies interact in the oldest-old.

White matter hyperintensities (WMH), which are considered to represent underlying cerebral small vessel disease[4], and hippocampal atrophy substantially increase with age and are both important predictors of cognitive decline in young elderly[5–7]. An additive effect of WMH and hippocampal atrophy on cognition has been reported in young elderly[8] and the effect of WMH on cognition might be mediated by hippocampal atrophy[9]. In the oldest-old, multiple pathologies seem to be important and WMH and hippocampal atrophy might have a synergistic effect on cognition.

To test these hypotheses, we aimed to determine the association between WMH and hippocampal atrophy with cognitive functioning and cognitive decline in the oldest-old. Second, we aimed to test whether the effect of WMH and hippocampal atrophy on cognition is synergistic and whether the effect of WMH on cognition is mediated by hippocampal atrophy.

2. Methods

2.1. Study sample

The study sample consisted of individuals from ***The 90+ Study***, an ongoing longitudinal study of aging and dementia in Southern California. This study was initiated in January 2003 and originally enrolled survivors from the Leisure World Cohort Study (LWCS)[10]. Over

time, open recruitment beyond the LWCS was initiated which specifically focused on individuals willing to have brain imaging who were capable of giving consent and lived within driving distance of the imaging center[11]. Brain MRI scans in ***The 90+ Study*** began in May 2014 and 169 individuals had a brain MRI-scan between May 2014 and December 2017. We excluded 28 individuals because of an invalid fluid attenuation inversion recover (FLAIR) sequence, leaving 141 individuals for the present study. Thirty-one (22.0%) of the included individuals were from the original LWCS.

All individuals provided informed consent and the study was approved by the University of California, Irvine, institutional review board.

2.2. Brain MRI acquisition and analyses

All individuals were scanned on the same GE Discovery 750W 3T scanner (General Electric Healthcare, Milwaukee, WI). For the present study, the high-resolution T1-weighted fast-spoiled gradient recalled echo (3D T1) and FLAIR sequence were used. To calculate WMH, we used the four tissue segmentation method, previously described and used in the Alzheimer's Disease Neuroimaging Initiative (ADNI)[12]. Hippocampal segmentation was performed using a standard atlas based diffeomorphic approach[13]. Details about the brain MRI acquisition and analyses are provided in the Supplementary Text S1.

2.3. Cognitive tests

Every six months, individuals in ***The 90+ Study*** perform a battery of cognitive tests administered by trained neuropsychologists[14]. For the present study, we used the Mini-Mental State Examination (MMSE)[15] and modified MMSE (3MS)[16] as measures for global cognitive functioning, the short nine-item version of the California Verbal Learning Test version II (CVLT-II)[17] for memory, the WAIS-III Digit Span Backward [18] for working memory, Trail Making Test (TMT) A[19] and C[20] for processing speed and Animal Fluency[21] and TMT B[19] for executive functioning. The immediate recall of the CVLT-II was a sum score over four trials and the delayed recall was administered after ten minutes.

On the cognitive tests, floor scores were assigned when an individual did not understand the instructions for administration, quit the test before finishing, or became confused during the test. For the TMT A, B and C floor scores were also assigned when an individual was unable to complete the test in the time allowed (200 seconds for TMT A and C and 350 seconds for TMT B). MMSE and 3MS scores were assigned a proportional score if fewer than 5 (MMSE) or 13 (3MS) points were missing.

2.4. Cognitive status evaluation

Neurological examiners used information from their neurological evaluation in combination with the MMSE and 3MS score to determine cognitive status by applying the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* criteria[22]. Individuals who had some cognitive or functional loss but not of sufficient severity to meet the DSM-IV criteria for dementia, were diagnosed with Cognitive Impairment–No Dementia (CIND)[23]. In the analyses, cognitive impairment was defined as a diagnosis of CIND or dementia.

2.5. Additional variables

We recorded the highest level of education attained and categorized it in three groups: less than college, some college or a college degree and education beyond a college degree. Comorbidities which were considered as potential confounders in the analyses (hypertension, diabetes mellitus (DM), hypercholesterolemia, stroke, transient ischemia infarction (TIA), heart disease (which included coronary artery disease, myocardial infarction, atrial fibrillation or other arrhythmias, heart valve disease, congestive heart failure, coronary artery bypass, or pacemaker placement) or depression), were based on self-reported history and medication use.

2.6. Statistical analyses

WMH and hippocampal volume were normalized by total intracranial volume (TIV) to correct for differences in head size and WMH volume was log-transformed to normalize population variance.

The association between WMH and hippocampal volume and their interaction with cognitive functioning at baseline and during follow-up was tested by linear mixed models. Baseline (time = 0) was defined as the visit closest to the MRI-scan. We included all visits within one year before the MRI-scan and all visits after the MRI-scan.

We analyzed the effects of WMH and hippocampal volume on cognitive functioning by adding the following variables to one linear mixed model: WMH volume, hippocampal volume, time (in years), the interaction between WMH volume and time and the interaction between hippocampal volume and time. The estimate of the effect of WMH or hippocampal volume reflects the baseline effect of WMH or hippocampal volume on cognitive functioning. The estimate of the interaction between WMH or hippocampal volume and time reflects the longitudinal effect of WMH or hippocampal volume on cognitive decline. In order to test whether the effect of WMH and hippocampal volume on cognitive functioning and cognitive decline was dependent on each other we also added a three-way interaction of WMH volume, hippocampal volume with time to the model. We added a random intercept to the model and compared models with and without a random slope. The model including a random slope showed a better fit based on the Akaike information criterion (AIC) for seven of the nine cognitive tests and was therefore used for all analyses. Models were adjusted for the fixed effects of age at time of the MRI-scan, gender, education and the significant comorbidity variables (defined as significant when there was an association between the comorbidity and WMH or hippocampal volume and cognition). We tested the association between hippocampal volume and WMH volume using a linear regression model adjusted for age at time of the MRI-scan, gender and education. If this association was significant, mediation analysis would be performed.

We performed secondary analyses to adjust for a potential learning effect, to assess the influence of cognitive diagnosis on the association of WMH and hippocampal volume with cognitive functioning and to explore the role of missing and floored cognitive data. Details about the secondary analyses are provided in the Supplementary Text S1.

The p-value threshold for significance was set at 0.05. All analyses were performed in R-Studio version 1.1.414 with R version 3.4.3[24]. The 'lme4' and 'lmerTest' packages were used for the linear mixed models[25,26].

3. Results

Characteristics of the 141 individuals included are shown in Table 1. Individuals were on average 94.3 years at baseline (range 90.0–102.6 years), 96 (68.1%) were female, 135 (95.7%) Caucasian and 50 (35.5%) completed some education beyond a college degree. Ninety-four individuals were cognitively normal at baseline (66.7%), 37 (26.2%) were diagnosed with CIND and 10 (7.1%) with dementia. The mean follow-up time was 2.0 years (interquartile range 1.1 – 2.8 years). Evaluation of the comorbidities showed that none of these were associated with WMH or hippocampal volume, except for hypertension which was positively associated with hippocampal volume (estimate 0.02, p-value: 0.04) but not with any of the cognitive tests. Therefore, we did not include any comorbidities as covariates in the analyses.

3.1. Association of WMH and hippocampal volume with cognitive functioning

At baseline, higher WMH volumes were associated with worse scores on the 3MS, CVLT-II immediate and delayed recall, Digit Span Backward and TMT B (Table 2, Figure 1, Supplementary Figure S1).

Lower hippocampal volumes were associated with worse scores on all cognitive tests at baseline, except for the Digit Span Backward (Table 2, Figure 2, Supplementary Figure S2). At follow-up, higher WMH volumes were associated with faster decline in the 3MS and MMSE (Table 2, Figure 1, Supplementary Figure S1). None of the other tests showed an association between rate of decline and WMH volume.

Lower hippocampal volumes were associated with faster decline in the 3MS, MMSE and CVLT-II immediate recall (Table 2, Figure 2, Supplementary Figure S2). The rate of decline on the other tests were not associated with hippocampal volume.

3.2. Interaction effect of WMH and hippocampal volume on cognitive functioning

The two-way interaction of WMH and hippocampal volume and the three-way interaction of WMH, hippocampal volume and time were not significant for any of the cognitive tests, meaning that the associations between WMH or hippocampal volume with cognition and cognitive decline were not dependent on each other (Figure 3, Supplementary Figure S3). However, the group with both high WMH and low hippocampal volume consistently showed the worse scores on each cognitive test, which was not always the case for the highest percentile of WMH and hippocampal volume separately (Figure 1 and 2, Supplementary Figure S1 and S2). In addition, we did not find an association between WMH and hippocampal volume at baseline (estimate: −0.00, p-value: 0.85).

3.3. Secondary analyses

Results of the secondary analyses are presented in Supplementary Text S2. Most importantly, after stratification for diagnosis, the association between hippocampal volume and 3MS or MMSE was only present in cognitively impaired individuals (Supplementary Table S1). Furthermore, most of the missing and floored cognitive data points were in individuals with a high WMH or low hippocampal volume (Supplementary Table S2).

4. Discussion

In individuals aged 90 years and older, we found that WMH and hippocampal atrophy were associated with worse cognitive scores at baseline and with a higher rate of decline in tests of global cognition. Hippocampal atrophy was also associated with a higher rate of decline in tests of memory. The effects of WMH and hippocampal atrophy on cognition and cognitive decline were independent of each other and we found no association between WMH and hippocampal volume.

4.1. Association of WMH and hippocampal atrophy with cognitive functioning

To the best of our knowledge, there are no previous studies in the oldest-old that tested the association between WMH or hippocampal atrophy with specific cognitive domains. Our finding that WMH was associated with global cognition at baseline and at follow-up and with memory at baseline, is in line with studies conducted in younger elderly[7]. The association of WMH with frontal lobe functions was less strong compared to those in younger elderly, as WMH was associated with baseline Digit Span Backward and TMT B, but not with TMT A and TMT C, and WMH was not associated with decline in frontal lobe functions over time[7,27]. It is possible that the higher WMH volumes[5,7] and lower cognitive test scores in older individuals[28], limited the range of WMH and cognitive test scores and thereby the chance to find an association between WMH and cognition. It is also possible that in the oldest-old, the association between WMH and frontal lobe dysfunction is obscured by other frontal lobe pathologies in the oldest-old such as decline of dopamine levels with aging[29]. In addition, the TMT A, B and C might not be the most accurate tests to assess cognitive functioning in the oldest-old as they highly depend on visual acuity and hand motor skills which are often impaired in this age range. The high number of missing data points for the Digit Span Backward and TMT A, B, and C, especially in individuals with a high WMH volume, might also explain the lack of an association between WMH and decline in cognitive functions of the frontal lobe. Last, our mean follow-up of two years was generally shorter than the mean follow-up of other studies[7]. However, a meta-analysis of 14 longitudinal studies relating WMH to cognitive decline did not find a difference in effect size between studies with a mean follow-up of ≥ 5 years and studies with a shorter follow-up[7].

In accordance with studies performed in young elderly[30], we found an association between hippocampal atrophy and lower memory scores at baseline and at follow-up. This strengthens the evidence that the hippocampus plays a central role in memory, also in the oldest-old. Earlier literature in younger elderly has mainly focused on hippocampal volume as a valuable measurement to discriminate between individuals with normal cognition, MCI

and AD-type dementia[31], and on the capability of hippocampal atrophy to predict conversion to AD-type dementia in MCI patients[32]. Our results in the oldest-old are rather in line with the predictive value of hippocampal atrophy in younger MCI patients, as we found an association of hippocampal atrophy with global cognitive functioning and global cognitive decline which was only present in individuals with cognitive impairment. We also found an association between hippocampal atrophy and frontal lobe functions at baseline, but not with decline over time. Whether such an association exists in younger individuals is not yet clear, given the lack of studies on this topic.

4.2. Interaction effect of WMH and hippocampal volume on cognitive functioning

There are different mechanisms proposed for how cerebrovascular pathology and neurodegeneration may jointly affect cognition[33]. In younger elderly, it has been suggested that cerebrovascular pathology lowers the threshold for other pathologies to affect cognitive functioning[34]. However, we did not find an interaction between WMH and hippocampal atrophy on their association with cognition, meaning that WMH and hippocampal atrophy are two independent pathways towards cognitive decline in the oldest-old. The lack of interaction between WMH and hippocampal atrophy also makes a synergistic effect of both biomarkers on cognition less likely.

Another proposed mechanism is that the effect of WMH on cognition might be mediated by hippocampal atrophy[9], as shown in studies with younger elderly[8,35–38]. However, consistent with findings in a 85-year old population of the Ginkgo Evaluation of Memory Study[39], we found no association between WMH and hippocampal volume. It suggests that WMH and hippocampal atrophy do not share an underlying pathology in the oldest-old. In the oldest-old, hippocampal atrophy is often associated with hippocampal sclerosis and argyrophilic grain disease, which are tauopathies unrelated to vascular problems[40]. Furthermore, in the oldest-old other neurobiological alterations, such as increased oxidative stress and neuroinflammation, might lead to age-related hippocampal atrophy[41]. This process might be independent of vascular changes in the brain.

4.3. Strengths and limitations

This study has several strengths that should be mentioned. It is the first study on WMH and hippocampal volume in relation to cognitive functioning in the oldest-old. ***The 90+ Study*** is one of the largest imaging studies in the oldest-old. Brain MRI-scan segmentation is done according to ADNI protocols which make direct comparison with other studies possible[12,42]. Cognitive testing in the study includes several cognitive domains and is performed frequently, every six months, providing a relatively large number of data points even with short follow-up times. To limit potential selection bias towards the healthier oldest-old, we did not exclude individuals with dementia or a history of stroke at baseline which made our study sample more representative of the general 90+ population. Some of our results were not present in only the cognitively normal individuals which might be due to a limited scoring range of the cognitive tests in these individuals.

Another potential limitation is that our study sample was mostly Caucasian, highly educated and most of the participants were volunteers who were physically able to undergo a brain

scan and cognitively able to consent to the procedure. This may have led to a study sample with a higher mean level of cognition and less brain pathologies compared to the general population. Our results might therefore not be generalizable to other more diverse groups. As we did not have follow-up MRI-scans, we were not able to test the effect of progression of WMH or hippocampal atrophy in our study. The effect of progression of WMH or hippocampal atrophy on cognitive decline might be stronger than the effect of the presence of WMH or hippocampal atrophy on cognitive decline[7,43]. Furthermore, follow-up MRI-scans would have enabled us to further examine a possible interactive effect of WMH and hippocampal atrophy progression on cognition and to adjust for incident brain pathologies such as infarcts. The effect of other potential confounders, such as sensory deficits and newly developed comorbidities during follow-up, is probably minimal but also need to be considered when interpreting the results.

We did not report about dementia subtypes because diagnostic criteria for dementia subtypes are not validated in the oldest-old, multiple pathologies underlie a dementia diagnosis in this cohort[1]and the focus of the present study was on cognition and cognitive decline instead of dementia diagnosis.

We did not take location of the WMH (periventricular or subcortical) into account. It has been suggested that the association between WMH and cognition is only present for WMH located in periventricular areas[44,45]. However, periventricular, subcortical and total WMH are also highly correlated which makes a distinction arbitrary[12]. Furthermore, atrophy in other brain regions than the hippocampus, were not considered in the present study. WMH might especially be associated with frontotemporal cortical atrophy[46]. Future research should therefore also include the association of atrophy and WMH in specific brain regions with cognitive functioning.

4.4. Conclusion

We showed that in the oldest-old, WMH and hippocampal atrophy were independently associated with cognitive functioning. These results implicate that both WMH and hippocampal volume are important features to evaluate in the diagnostic work-up of oldest-old individuals with cognitive complaints. Furthermore, to restrain the number of oldest-old with cognitive impairment in the near future, preventive studies should focus on the risk and protective factors for WMH and hippocampal atrophy in this age group.

We found that WMH and hippocampal atrophy do not have a synergistic effect on cognition but independently affect cognitive functioning in the oldest-old. However, the effect of WMH on cognition seems to be less evident than in younger elderly because the number of cognitive tests that we found to be affected by WMH was limited. This might suggest that other, potentially yet unknown, factors need to be considered to further elucidate what determines cognitive functioning and drives cognitive decline in the oldest-old.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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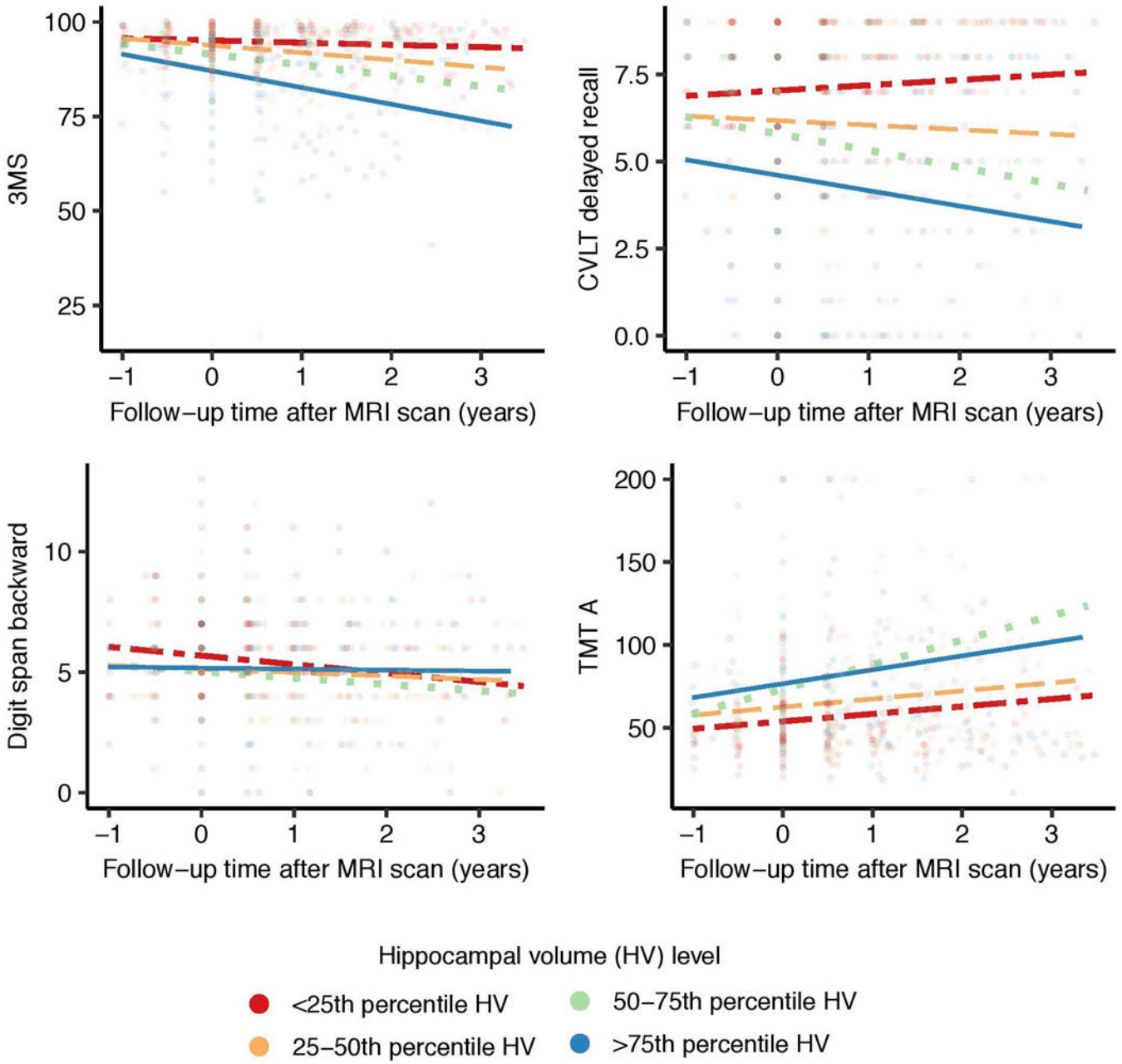

Figure 1. Association of WMH volume with cognitive decline

Lines are the predicted trajectories for women with age 94.0 years (median age of study sample) and a college education level. Higher percentiles mean higher WMH volumes. 3MS: modified Mini-Mental State Examination; CVLT: California Verbal Learning Test; TMT: Trail Making Test; WMH: white matter hyperintensities

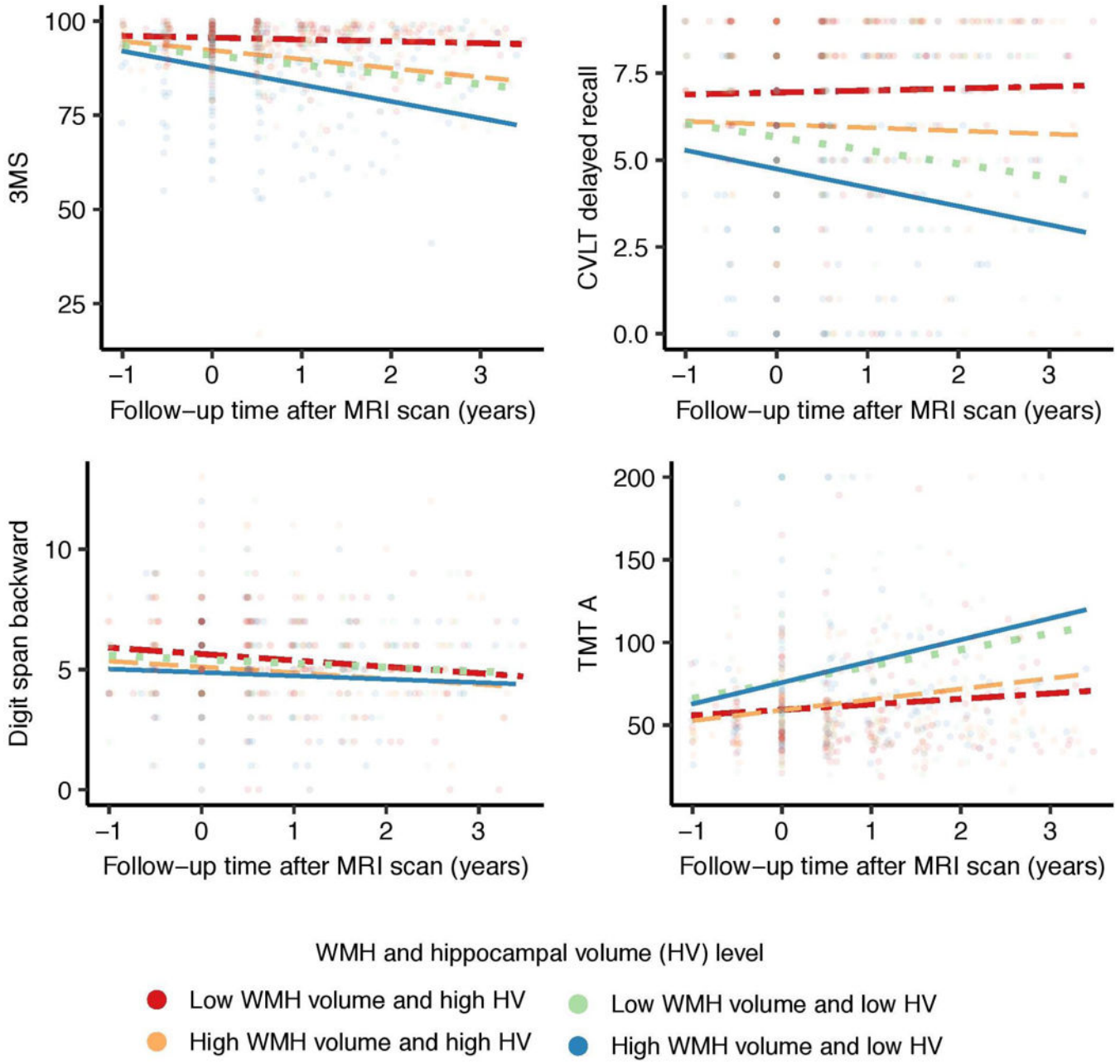

Figure 2. Association of hippocampal volume with cognitive decline

Lines are the predicted trajectories for women with age 94.0 years (median age of study sample) and a college education level. Higher percentiles mean lower hippocampal volumes. 3MS: modified Mini-Mental State Examination; CVLT: California Verbal Learning Test; HV: hippocampal volume; TMT: Trail Making Test

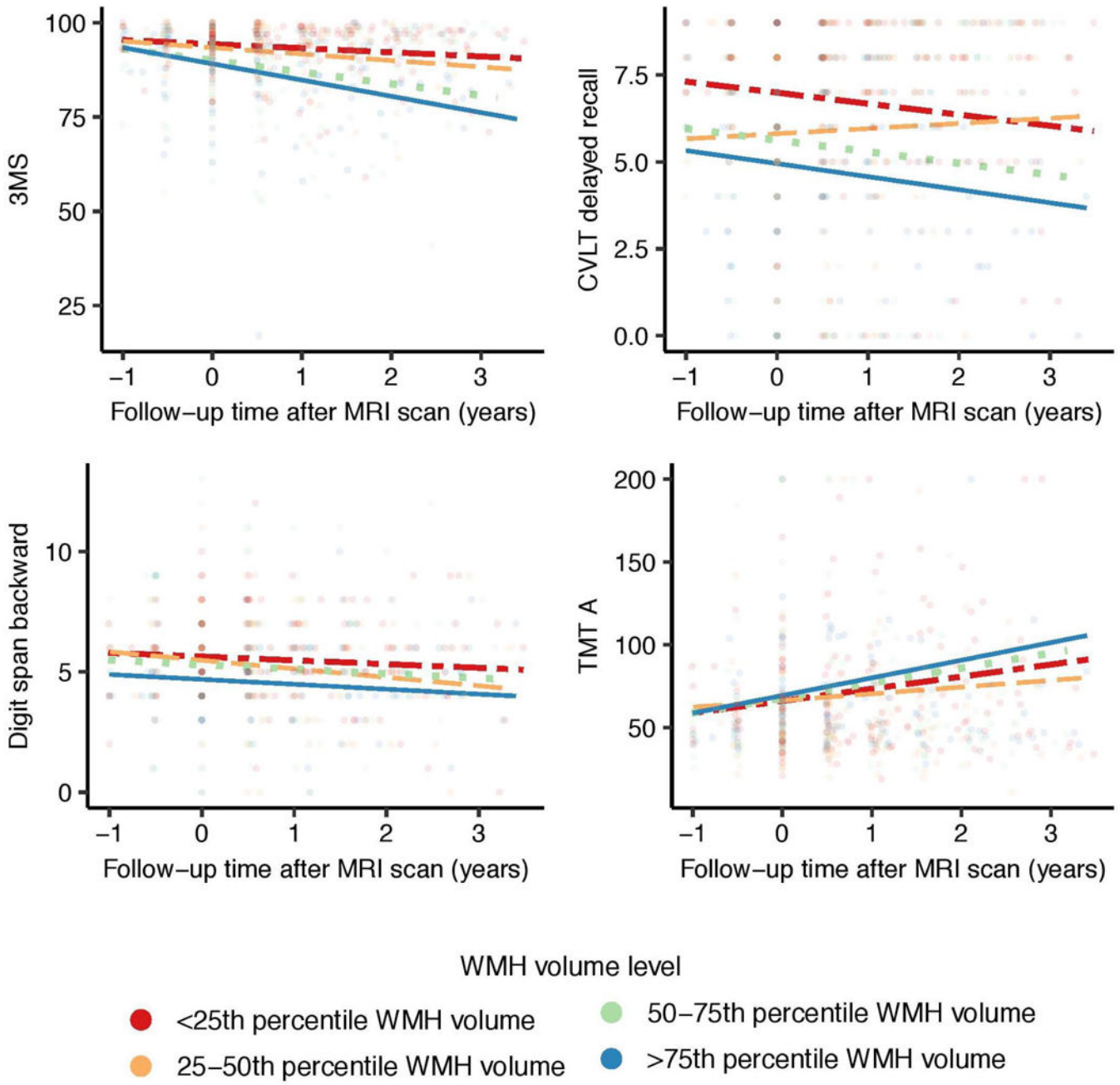

Figure 3. Association of WMH and hippocampal volume with cognitive decline

Lines are the predicted trajectories for women with age 94.0 years (median age of study sample) and a college education level. Low and high WMH and hippocampal volume are defined according to the median volumes. 3MS: modified Mini-Mental State Examination; CVLT: California Verbal Learning Test; HV: hippocampal volume; TMT: Trail Making Test; WMH: white matter hyperintensities

Table 1.

Baseline characteristics of the study sample

	Total sample (N=141)
Age, mean (SD) years	94.3 (3.2)
Females, N (%)	96 (68.1)
Caucasian, N (%)	135 (95.7)
Education, N (%)	
< College	29 (20.6)
College	62 (44.0)
> College	50 (35.5)
Cognitive status at baseline	
Cognitively normal, N (%)	94 (66.7)
CIND, N (%)	37 (26.2)
Dementia, N (%)	10 (7.1)
Follow-up time, mean (IQR) years	2.0 (1.1–2.8)
Dementia during follow-up, N (%[1])	25 (19.1)
WMH volume as % of TIV, mean (SD)[2]	0.1 (0.9)
Hippocampal volume as % of TIV, mean (SD)	0.5 (0.0)
Comorbidities[3]	
Hypertension, N (%)	117 (83.0)
Diabetes mellitus, N (%)	18 (12.8)
Hypercholesterolemia, N (%)	70 (49.6)
Stroke, N (%)	13 (9.2)
TIA, N (%)	28 (19.9)
Heart disease[4], N (%)	56 (39.7)
Deceased during follow-up[5], N (%)	54 (38.3)

Abbreviations: CIND: Cognitive Impairment–No Dementia; IQR: interquartile range; N: number; TIV: total intracranial volume; WMH: white matter hyperintensities

[1]Percentage of study sample without dementia at baseline (N=131);

[2]Natural log transformed;

[3]Based on self-report and for hypertension, diabetes mellitus and hypercholesterolemia also on the use of medication;

[4]Includes coronary artery disease, myocardial infarction, atrial fibrillation or other arrhythmias, heart valve disease, congestive heart failure, coronary artery bypass, or pacemaker placement;

[5]Deseased individuals were on average followed 1.7 years, they were included in both the cross-sectional and longitudinal analyses

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Table 2.

Association of WMH and hippocampal volume with cognitive functioning

		Baseline effect[1]				Longitudinal effect[2]			
		WMH volume		Hippocampal volume		WMH volume		Hippocampal volume	
Cognitive test	**N[3]**	**Estimate (SE)**	**P-value**	**Estimate (SE)**	**P-value**	**Estimate (SE)**	**P-value**	**Estimate (SE)**	**P-value**
3MS	136	−1.52 (0.69)	0.03	57.35 (12.76)	<0.01	−1.02 (0.42)	0.02	28.06 (8.16)	<0.01
MMSE	141	−0.36 (0.23)	0.12	19.02 (4.26)	<0.01	−0.40 (0.17)	0.03	8.29 (3.38)	0.02
CVLT immediate recall[4]	137	−1.41 (0.51)	<0.01	37.62 (9.40)	<0.01	−0.34 (0.26)	0.18	12.65 (5.03)	0.01
CVLT delayed recall	137	−0.64 (0.21)	<0.01	17.13 (3.82)	<0.01	0.01 (0.10)	0.91	4.02 (2.06)	0.05
Digit Span Backward	116	−0.33 (0.17)	0.05	4.63 (3.16)	0.15	−0.04 (0.08)	0.66	−0.79 (1.70)	0.64
Animal Fluency	140	−0.16 (0.42)	0.70	21.57 (7.70)	<0.01	−0.14 (0.16)	0.38	1.57 (3.15)	0.62
Trail Making Test A	121	1.92 (3.00)	0.52	−165.42 (56.59)	<0.01	0.45 (1.49)	0.76	−41.54 (29.11)	0.16
Trail Making Test B	119	24.45 (8.75)	<0.01	−465.99 (164.75)	<0.01	−1.89 (2.98)	0.53	−11.7 (59.74)	0.85
Trail Making Test C	117	1.37 (1.57)	0.38	−81.28 (29.79)	<0.01	1.19 (1.50)	0.43	−44.6 (28.97)	0.13

Abbreviations: 3MS: modified MMSE; CVLT: California Verbal Learning Test; MMSE: Mini-Mental State Examination; WMH: white matter hyperintensities; TMT: Trail Making Test

Estimates and standard errors (SE) of each cognitive test are determined in one linear mixed model that includes the following variables: WMH volume, hippocampal volume, time (in years), age, gender, education, the interaction between WMH volume and time and the interaction between hippocampal volume and time

[1]The estimate for the baseline effect shows the change in cognitive test score at baseline per unit increase in WMH or hippocampal volume value

[2]The estimate for the longitudinal effect shows the annual change in cognitive test score that is attributable to each unit increase in WMH or hippocampal volume value

[3]Number of individuals included in the analyses per cognitive test

[4]Immediate recall is determined by the sum of the recall over four trials