Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2024 November 01.

Published in final edited form as:

Alzheimers Dement. 2023 November ; 19(11): 5307–5315. doi:10.1002/alz.13352.

Hippocampal sclerosis of aging at post-mortem is evident on MRI more than a decade prior

Diana Ortega-Cruz[1,2], **Juan Eugenio Iglesias**[3,4,5], **Alberto Rabano**[2], **Bryan A. Strange**[1,2]

[1]Laboratory for Clinical Neuroscience, Center for Biomedical Technology, Universidad Politécnica de Madrid, IdISSC, 28223, Madrid, Spain.

[2]Alzheimer's Disease Research Unit, CIEN Foundation, Queen Sofia Foundation Alzheimer Center, 28031, Madrid, Spain.

[3]Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, 02129, Boston, MA, USA.

[4]Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, 02139, Boston, MA, USA.

[5]Centre for Medical Image Computing, University College London, WC1V 6LJ, London, UK.

Abstract

INTRODUCTION: Hippocampal sclerosis of aging (HS) is an important component of combined dementia neuropathology. However, the temporal evolution of its histologically-defined features is unknown. We investigated pre-mortem longitudinal hippocampal atrophy associated with HS, as well as with other dementia-associated pathologies.

METHODS: We analyzed hippocampal volumes from MRI segmentations in 64 dementia patients with longitudinal MRI follow-up and post-mortem neuropathological evaluation, including HS assessment in the hippocampal head and body.

RESULTS: Significant HS-associated hippocampal volume changes were observed throughout the evaluated timespan, up to 11.75 years before death. These changes were independent of age and Alzheimer's Disease (AD) neuropathology, and specifically driven by CA1 and subiculum atrophy. AD pathology, but not HS, significantly associated with the rate of hippocampal atrophy.

DISCUSSION: HS-associated volume changes are detectable on MRI earlier than 10 years before death. Based on these findings, volumetric cut-offs could be derived for *in vivo* differentiation between HS and AD.

Keywords

atrophy; dementia; hippocampal sclerosis of aging; hippocampus; longitudinal; magnetic resonance imaging; neuropathology

Correspondence: Diana Ortega-Cruz. Address: Laboratory for Clinical Neuroscience, Center for Biomedical Technology, Universidad Politécnica de Madrid. Crta M40, km38. 28223, Pozuelo de Alarcón, Madrid, Spain. diana.ortega@upm.es, Phone number: +34 680710623.

Conflicts

Declarations of interest: none

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

1. Introduction

Hippocampal sclerosis of aging (HS) is a pathological finding associated with worsened cognitive symptoms in dementia patients[1,2]. Since its first description by Dickson *et al.*[3], it has been defined by severe neuronal loss in CA1 and subiculum subfields of the hippocampus, which is particularly prevalent over 85 years of age[4]. This qualitatively-observed lesion is disproportionate to expected damage by other coexisting pathologies. HS normally coexists with one or several dementia neuropathologies: Lewy bodies (LB)[5,6], vascular pathology[7,8], Alzheimer's disease (AD)[9,10], and most commonly, limbic-predominant age-related TDP-43 encephalopathy (LATE)[11,12]. Indeed, 80–100% patients with HS present LATE pathology, and HS is found in up to 90% of LATE cases[13].

Despite its relevance within the dementia neuropathological spectrum, the contribution of HS is often overlooked. In several recent post-mortem studies on AD[14,15], TDP-43[16,17] and LB pathologies[18,19], HS was not evaluated. Conversely, other studies have highlighted its importance[20,21] and described histological findings proposed as early HS[5,22]. In line with this work, we recently characterized early pathological changes of HS, proposing this pathology forms a wider spectrum than initially defined[23]. Following this re-classification, the prevalence of HS could have been underestimated in previous studies, which reported a frequency of 3–30%[1,2,9].

The histological definition of HS has limited the search for biomarkers of this pathology. Preliminary evidence suggests that HS patients have lower Mini-Mental State Examination (MMSE) scores, longer symptom duration[10], and relatively preserved verbal and visuomotor functions[24,25] compared to AD. Moreover, HS has been associated with reduced hippocampal volumes in pre-mortem MRI[26]. However, the utility of these changes as biomarkers is limited by a current lack of understanding of the timespan of HS. Since this pathology can, up to now, only be evaluated post-mortem[27], its onset and duration remain unknown.

In this study, we aimed to characterize the timespan of hippocampal volume changes associated with HS. We studied data from dementia patients with pre-mortem MRI follow-up, spanning more than 10 years before death, and neuropathological evaluation. We describe longitudinal differences in hippocampal volume between subjects with HS (HS+) and without (HS-), following its classical definition, as well as according to our recently proposed evaluation including early stages[23]. Implementing a two-level HS assessment in the head and body of the hippocampus, we explore subfield volumetric changes in these two regions relative to HS. We also evaluate longitudinal volume differences as a function of other neuropathologies, thus dissociating their associated changes from those of HS, crucial for its *in vivo* identification.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2. Methods

2.1 Cohort

We studied data obtained between 2007 and 2020 from the Vallecas Alzheimer's Center Study (VACS), a nursing home for dementia patients who undergo neuroimaging follow-up. Although follow-up is semestral by protocol, actual frequency depends on the state of each individual. Out of 102 patients with at least one pre-mortem MRI acquisition and post-mortem donation to the BT-CIEN brain bank, 10 were excluded from analyses due to: a) no usable T1 scan (n=4); b) neuropathological diagnosis of Frontotemporal Dementia (n=3), given its independent association with hippocampal sclerosis[9]; c) unattainable hippocampus evaluation due to extreme atrophy (n=1) or hemorrhage (n=2).

2.2 Neuropathological evaluation

Brain extraction and processing followed previously described procedures[28]. After extraction, the left hemisphere was fixed and cut into coronal slices for tissue block dissection. Blocks were cut into 4μm sections for hematoxylin/eosin and immunostaining (against amyloid-β, phospho-tau AT100, total α-synuclein, and total TDP-43).

Neuropathological evaluation was performed following consensus criteria, and patients were stratified into low- and high-burden groups for each pathology. High probability of Alzheimer's Disease Neuropathological Change (ADNC) was determined based on National Institute on Aging (NIA) guidelines[29]. Cerebrovascular pathology assessment followed staging by Deramecourt *et al.*[30] (0–20), with a score of 8 or higher being classified as high-burden. LB pathology was assessed through Braak α-synuclein staging (0–6)[31], and high burden was assigned to values higher than 2 (pathology beyond the brainstem). TDP-43 proteinopathy was evaluated through LATE staging (0–3)[11], and patients with hippocampal inclusions (stage 2 or higher) were categorized as high-burden. HS was assessed following our recently proposed staging system (0-IV) including early stages[23], evaluated in both hippocampal head and body sections. Subjects presenting stages>0 in any of these two sections were classified as HS+. The classical HS definition was also employed[4], with head sections presenting severe neuronal loss in CA1 and subiculum (stage>II) classified as HS+.

2.3 MRI acquisition

T1-weighted images were acquired using a 3T scanner (General Electric) with a phased array eight-channel head coil, employing 3D sagittal Fast Spoiled Gradient Recalled (FSPGR) configuration with inversion recovery (repetition/echo/inversion times 7/3.2/750ms, resolution 1×0.469×0.469mm).

2.4 Longitudinal hippocampal segmentation

Whole hippocampal and subfield volumes were obtained by processing all T1-weighted scans from included subjects with the FreeSurfer 7.1.1 longitudinal workflow[32]. To overcome slight movement artifacts, subcortical segmentations were substituted by the segmentation from *SynthSeg*[33] prior to template creation. Segmentation of hippocampal subfields[34] was then obtained and visually inspected to discard those with inaccurate subfield delineation. Out of 92 subjects, 7 resulted in errors along the pipeline and 21

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

had all segmentations discarded, resulting in 64 subjects with accurate data. For timepoints with accurate segmentations in both hemispheres, left and right volumes were averaged for statistical analyses.

2.5 Statistics

RStudio 11.4.1106 was used for statistical analyses and plots. To compare between HS groups, for categorical, non-normal numeric, and normal numeric variables, we used Pearson's chi square, Kruskal-Wallis and t-tests respectively. To compare volumes at the timepoint closest to death, we modelled volume as a function of age at MRI, time to death, sex, and intracranial volume. We then added model residuals to volumes to obtain adjusted volume measures, which were compared using t-tests. Results from additional brain regions were FDR-corrected for multiple comparisons.

Linear mixed models with random intercept and slope were employed to model hippocampal volume as a function of time, assessing its interaction with the pathology of interest. In addition, age at death, sex and intracranial volume were included as independent variables. To account for differing times between last MRI and death, we verified all results were unaltered when including age at MRI instead.

3. Results

3.1 Cohort features

Among the 64 patients with accurate hippocampal segmentations, HS+ subjects presented expected differences: significantly longer disease duration, older age, and lower final severe-MMSE scores (Table 1). As expected, this group also presented higher ADNC and TDP-43 pathology burdens. Included pre-mortem MRI scans ranged between 1 and 11 per subject and covered a timespan of up to 11.75 years before death. Time between last included MRI and death was also significantly higher in HS+ patients, since scanning feasibility is directly affected by the patient's cognitive state.

3.2 Longitudinal hippocampal atrophy as a function of HS

As expected, whole hippocampal volume at the timepoint closest to death was significantly lower in the HS+ group (Figure S1). Volumes of other brain structures were also generally lower in HS+ subjects, but group differences were only significant in the amygdala (Figure S2). Next, we compared hippocampal volumes across time, correcting for age at death, sex, and intracranial volume. Including early and advanced stages (Figure 1A), HS+ patients displayed reduced hippocampal volumes compared to HS− ($F=31.7$, $p=0.006$). This difference was significant throughout the evaluated timespan, based on estimated marginal means (EMM) comparison (at −11.75 years, EMM difference between groups was 405±146 mm^3, $p=0.007$). Critically, the rate of volume decline was not significantly different between groups. Significantly lower volumes without different decline rates were also found following the classical HS definition (Figure 1B), showing this association is independent of classification criteria ($F=25.6$, $p=0.005$).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

These volume effects were still significant in a subset of the cohort including 26 HS+ subjects with closest ages at death to HS− subjects, further supporting the independence of results on age (Figure S3, Table S1). Moreover, correcting for age at MRI instead of at death did not alter these results. These effects were also independent of AD pathology burden (Figure 1C,1D). Furthermore, restricting analyses to subjects with high ADNC (n=44), differences between HS groups were still significant, following either HS staging (F=14.2, p=.015) or its classical definition (F=29.1, $p=2{\cdot}10^{-4}$).

3.3 Hippocampal subfield volume changes relative to HS

To test the regional specificity of hippocampal atrophy effects, we analyzed the association between HS stage and subfield volumes in both hippocampal head and body. The number of subjects at each stage, as well as demographic details, are shown in Table S2. Subfields were analyzed in two groups: CA1+subiculum, in which histological changes occur at earlier HS stages, and CA3+CA4, which may present changes in stage IV[23]. Throughout the evaluated timespan, CA1+subiculum volumes were significantly lower in both hippocampal head (Figure 2A) and body (Figure 2B) as a function of respective HS stages (head: F=5.8, p=0.035; body: F=8, p=0.003). Such association was not observed for CA3+4 volumes in the head (Figure 2C) or body (Figure 2D). Rates of volume change were not significantly different as a function of staging, nor between HS+ and HS− groups. We then evaluated CA1 and subiculum separately (Figure S4), evaluating longitudinal group differences through EMM comparisons. CA1 in the hippocampal head, and subiculum in the body, displayed significantly lower volumes in the HS+ group, as early as 11 and 9.5 years before death, respectively. These results were also significant following the classical HS definition.

Considering only the left hemisphere, in which neuropathological evaluation was performed, HS+ subjects displayed lower hippocampal and subfield volumes than HS-, but differences did not reach significance (Figure S5). The reduced sample size in these analyses (42 subjects with accurate left-hippocampus segmentations), limits their power to find significant longitudinal differences.

3.4 Longitudinal hippocampal atrophy as a function of other pathologies

Given the absence of an effect of HS on hippocampal atrophy rates, we evaluated whether other neuropathologies presented such association. Whole hippocampal volumes across time were analyzed separately as a function of AD, vascular, LB and TDP-43 pathologies, dividing patients into low- and high-burden groups. Considering the prevalence of co-pathologies (Table S3) and that ADNC is a major determinant of hippocampal atrophy and cognitive decline, ADNC burden was added as a covariate in models for the rest of pathologies, as done previously with HS. Groups displaying high ADNC probability (F=13.4, p=0.004) and TDP-43 burden (F=14.6, p=0.022) showed significantly lower volumes compared to their respective low-burden groups (Figure 3). In addition, ADNC severity displayed a significant interaction with time (p=.016), with faster decline rates in the high ADNC group. These results were independent of TDP-43 burden, which showed no significant effect on decline rate, independently of ADNC (Figure S6). No significant volume differences were found between burden groups for vascular and LB pathologies.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Considering baseline and final MMSE scores, cognitive decline followed a similar trend as hippocampal volume: HS+ subjects showed lower scores, with comparable decline rates, while high ADNC was associated with lower scores and faster decline (Figure S7). For subjects with more than one included MRI, correlations between hippocampal volume and MMSE scores at basal and final timepoints were significant, except for HS+ subjects in their final timepoint, which displayed a floor effect in cognition. This is in line with cognitive differences between HS groups being significant only at the final evaluation (Table 1), while volumes are already different at the earliest timepoint. Such cognitive worsening in HS+ subjects is partially explained by a longer dementia duration, as suggested by its inverse correlation with MMSE (Figure S7).

4. Discussion

We studied longitudinal hippocampal volume changes as a function of HS, a pathology for which no biomarkers currently exist. Previous work by our group[23] and others[26,35] revealed an association between HS and hippocampal atrophy, but the timespan of these changes remained unknown. We found lower hippocampal volumes in HS+ compared to HS− subjects throughout the evaluated timespan, up to 11.75 years before death. Volume decline rates did not differ between groups, suggesting volume reduction manifests prior to this evaluated timespan. Importantly, this trend was independent of age and ADNC burden. Our findings were also independent of the classification of early HS cases, indicating volume effects are driven by advanced stages, which present the HS classical cell loss signature.

Hippocampal atrophy is a well-established AD marker[36,37]. Yet, vascular[38,39], TDP-43[21] and LB pathologies[40,41] are also associated with reduced hippocampal volumes, thus questioning its specificity for ADNC. Hippocampal atrophy rate has also been described as a useful AD predictor[42,43], which is reinforced by our results. However, in contrast to our findings, larger-cohort studies found TDP-43 pathology to associate with faster hippocampal atrophy[44], independently of AD[45,46]. Although our reported effects in symptomatic dementia suggest the impact of ADNC on atrophy rate is greater than that of TDP-43, its specificity is challenged by previous work and the intricate association between these pathologies.

Our subfield analyses revealed early HS-associated hippocampal atrophy is driven by CA1 and subiculum, consistent with its histological pattern. More specifically, CA1 in the hippocampal head displayed this reduction earliest. One distinguishing feature of our work is the evaluation of HS at two histological sections along the hippocampal long axis[47], allowing region-specific subfield analyses. Previous studies assessed HS in a single hippocampal section, either unspecified[4,7,20] or parallel to the lateral geniculate body[3,22], prompting variable results. The reported early reduction in CA1 head volume points towards the anterior hippocampus as a key region in the pathology, highlighting its relevance for HS assessment.

Exploring volumetric differences in other brain regions at the timepoint closest to death, we found significantly lower amygdala volumes in HS+ subjects. In previous work, we

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

found grey matter density differences relative to HS extending to the amygdala as well[23]. While this is consistent with TDP-43 pathology distribution, whether the amygdala presents additional histopathological alterations specific to HS is currently unknown, representing a relevant question for future research.

Together with our two-level HS assessment, other strengths of this study include an extensive neuropathological evaluation and unified MRI acquisition and processing pipelines. Moreover, segmentation accuracy was enhanced using *SynthSeg*[33], robust to movement artifacts, prior to hippocampal segmentation. This work also entails several limitations, including the lack of data from pre-dementia onset or from cognitively healthy individuals. Differing times between last MRI and death represent another limitation, which we mitigated by using several time and age corrections. A modest sample size, combination of left and right hemisphere data, and a unilateral pathological evaluation are other limitations, as they impede accounting for HS asymmetry[4,27]. Our results can serve as foundation for larger studies to define volumetric ranges in individuals with HS and AD, and explore if HS-associated volume changes are observed at pre-dementia stages. These early volumetric differences could be combined with recently described FDG-PET medial-temporal hypometabolic changes in HS[48] and TDP-43[49,50], to reinforce the distinction of these pathologies from AD.

5. Conclusion

We describe reduced hippocampal volumes in HS+ dementia patients that are detectable earlier than a decade before death, independently of age. HS did not affect volume decline rates, which following a comprehensive pathological evaluation, were only found to significantly associate with ADNC burden. These results suggest AD pathology has the strongest effect on hippocampal atrophy during symptomatic dementia, and stimulate efforts to understand HS as a determining pathology throughout life, with early effects in pre-mortem MRI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors wish to thank the participants of the VACS cohort and their family members, as well as the CIEN Foundation staff. Especially, we thank Paloma Ruiz and Laura Saiz for their work at BT-CIEN. We also thank Eva Alfayate and Felipe García from the neuroimaging department.

Funding

This work has been supported by the Queen Sofia Foundation and the CIEN Foundation. DOC was supported by “la Caixa” Foundation (ID 100010434), with fellowship code LCF/BQ/DR20/11790034. BAS and JEI were supported by a MISTI Global Seed Fund (0000000246). JEI was supported by the ERC (Starting Grant 677697), the NIH (1RF1MH123195, 1R01AG070988, 1UM1MH130981), and ARUK (ARUK-IRG2019A-003).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

References

1. Amador-Ortiz C, Ahmed Z, Zehr C, Dickson D. Hippocampal sclerosis dementia differs from hippocampal sclerosis in frontal lobe degeneration. Acta Neuropathol. 2007;113(3):245–252. doi:10.1007/s00401-006-0183-4 [PubMed: 17195931]
2. Nelson PT, Fardo DW, Van Eldik LJ, et al. Hippocampal Sclerosis of Aging, a Prevalent and High-Morbidity Brain Disease. Acta Neuropathol. 2013;126(2):161–177. doi:10.1007/s00401-013-1154-1 [PubMed: 23864344]
3. Dickson DW, Davies P, Bevona C, et al. Hippocampal sclerosis: a common pathological feature of dementia in very old (≥80 years of age) humans. Acta Neuropathol. 1994;88(3):212–221. doi:10.1007/BF00293396 [PubMed: 7810292]
4. Nelson PT, Schmitt FA, Lin Y, et al. Hippocampal sclerosis in advanced age: Clinical and pathological features. Brain. 2011;134(5):1506–1518. doi:10.1093/brain/awr053 [PubMed: 21596774]
5. Aoki N, Murray ME, Ogaki K, et al. Hippocampal sclerosis in Lewy body disease is a TDP-43 proteinopathy similar to FTLD-TDP Type A. Acta Neuropathol. 2015;129(1):53–64. doi:10.1007/s00401-014-1358-z [PubMed: 25367383]
6. Trieu T, Sajjadi S, Kawas C, Nelson P, Corrada M. Risk factors of hippocampal sclerosis in the oldest old: The 90+ Study. Neurology. 2018;91(19):e1788–e1798. doi:10.1212/WNL.0000000000006455 [PubMed: 30315072]
7. Neltner JH, Abner EL, Baker S, et al. Arteriolosclerosis that affects multiple brain regions is linked to hippocampal sclerosis of ageing. Brain : a journal of neurology. 2014;137:255–267. doi:10.1093/brain/awt318 [PubMed: 24271328]
8. Sieben A, Van Langenhove T, Vermeiren Y, et al. Hippocampal Sclerosis in Frontotemporal Dementia: When Vascular Pathology Meets Neurodegeneration. J Neuropathol Exp Neurol. 2021;80(4):313–324. doi:10.1093/jnen/nlab010 [PubMed: 33638350]
9. Brenowitz WD, Monsell SE, Schmitt FA, Kukull WA, Nelson PT. Hippocampal sclerosis of aging is a key Alzheimer's disease mimic: clinical-pathologic correlations and comparisons with both alzheimer's disease and non-tauopathic frontotemporal lobar degeneration. J Alzheimers Dis. 2014;39(3):691–702. doi:10.3233/JAD-131880 [PubMed: 24270205]
10. Lopez OL, Kofler J, Chang Y, et al. Hippocampal sclerosis, TDP-43, and the duration of the symptoms of dementia of AD patients. Annals of clinical and translational neurology. 2020;7(9):1546–1556. doi:10.1002/acn3.51135 [PubMed: 32735084]
11. Nelson PT, Dickson DW, Trojanowski JQ, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. Brain : a journal of neurology. 2019;142(6):1503–1527. doi:10.1093/brain/awz099 [PubMed: 31039256]
12. Amador-Ortiz C, Lin W, Ahmed Z, et al. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. Ann Neurol. 2007;61(5):435–445. doi:10.1002/ana.21154 [PubMed: 17469117]
13. Besser LM, Teylan MA, Nelson PT. Limbic Predominant Age-Related TDP-43 Encephalopathy (LATE): Clinical and Neuropathological Associations. J Neuropathol Exp Neurol. 2020;79(3):305–313. doi:10.1093/jnen/nlz126 [PubMed: 31845964]
14. Alosco ML, Sugarman MA, Besser LM, et al. A Clinicopathological Investigation of White Matter Hyperintensities and Alzheimer's Disease Neuropathology. J Alzheimers Dis. 2018;63(4):1347–1360. doi:10.3233/JAD-180017 [PubMed: 29843242]
15. Mattsson-Carlgren N, Grinberg LT, Boxer A, et al. Cerebrospinal Fluid Biomarkers in Autopsy-Confirmed Alzheimer Disease and Frontotemporal Lobar Degeneration. Neurology. 2022;98(11):e1137–e1150. doi:10.1212/WNL.0000000000200040 [PubMed: 35173015]
16. Hunter S, Hokkanen SRK, Keage HAD, et al. TDP-43 Related Neuropathologies and Phosphorylation State: Associations with Age and Clinical Dementia in the Cambridge City over-75s Cohort. J Alzheimers Dis. 2020;75(1):337–350. doi:10.3233/JAD-191093 [PubMed: 32280087]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

17. Uemura MT, Robinson JL, Cousins KAQ, et al. Distinct characteristics of limbic-predominant age-related TDP-43 encephalopathy in Lewy body disease. Acta Neuropathol. 2021;143(1):15–31. doi:10.1007/s00401-021-02383-3 [PubMed: 34854996]

18. Gibson LL, Grinberg LT, ffytche D, et al. Neuropathological correlates of neuropsychiatric symptoms in dementia. Alzheimer's Dement. 2022. doi:10.1002/alz.12765

19. Chen Z, Gan J, Yang Y, Meng Q, Han J, Ji Y. The vascular risk factors and vascular neuropathology in subjects with autopsy-confirmed dementia with Lewy bodies. Int J Geriatr Psychiatry. 2022;37(3). doi:10.1002/gps.5683

20. Barker WW, Luis CA, Kashuba A, et al. Relative Frequencies of Alzheimer Disease, Lewy Body, Vascular and Frontotemporal Dementia, and Hippocampal Sclerosis in the State of Florida Brain Bank. Alzheimer Disease & Associated Disorders. 2002;16(4)

21. Josephs KA, Whitwell JL, Knopman DS, et al. Abnormal TDP-43 immunoreactivity in AD modifies clinicopathological and radiological phenotype. Neurology. 2008;70(19):1850. doi:10.1212/01.WNL.0000304041.09418.B1 [PubMed: 18401022]

22. Hokkanen SRK, Hunter S, Polvikoski TM, et al. Hippocampal sclerosis, hippocampal neuron loss patterns and TDP-43 in the aged population. Brain Pathology. 2018;28(4):548–559. doi:10.1111/bpa.12556 [PubMed: 28833898]

23. Ortega-Cruz D, Uceda-Heras A, Iglesias JE, Zea-Sevilla M, Strange B, Rabano A. A novel histological staging of hippocampal sclerosis that is evident in gray matter loss in vivo. Alzheimer's Dement. 2023. doi:10.1002/alz.12942

24. Lippa CF, Dickson DW. Hippocampal sclerosis dementia: Expanding the phenotypes of frontotemporal dementias? Neurology. 2004;63(3):414–415. doi:10.1212/01.WNL.0000136241.71716.72 [PubMed: 15304570]

25. Onyike CU, Pletnikova O, Sloane KL, Sullivan C, Troncoso JC, Rabins PV. Hippocampal sclerosis dementia: an amnesic variant of frontotemporal degeneration. Dementia & neuropsychologia. 2013;7(1):83–87. doi:10.1590/S1980-57642013DN70100013 [PubMed: 24363834]

26. Woodworth DC, Nguyen HL, Khan Z, Kawas CH, Corrada MM, Sajjadi SA. Utility of MRI in the identification of hippocampal sclerosis of aging. Alzheimer's and Dementia. 2021;17(5):847–855. doi:10.1002/alz.12241

27. Zarow C, Sitzer T, Chui H. Understanding hippocampal sclerosis in the elderly: Epidemiology, characterization, and diagnostic issues. Curr Neurol Neurosci Rep. 2008;8(5):363–370. doi:10.1007/s11910-008-0057-3 [PubMed: 18713571]

28. Martínez-Martín P, Avila J. Alzheimer Center Reina Sofia Foundation: Fighting the Disease and Providing Overall Solutions. Journal of Alzheimer's disease : JAD. 2010;21(2):337–348. doi:10.3233/JAD-2010-101149 [PubMed: 20693620]

29. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol. 2012;123(1):1–11. doi:10.1007/s00401-011-0910-3 [PubMed: 22101365]

30. Deramecourt V, Slade JY, Oakley AE, et al. Staging and natural history of cerebrovascular pathology in dementia. Neurology. 2012;78(14):1043–1050. doi:10.1212/WNL.0b013e31824e8e7f [PubMed: 22377814]

31. Braak H, Del Tredici K, Rüb U, de Vos R,AI, Jansen Steur E,NH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24(2):197. doi: 10.1016/s0197-9 [PubMed: 12498954]

32. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage. 2012;61(4):1402–1418. doi:10.1016/j.neuroimage.2012.02.084 [PubMed: 22430496]

33. Billot B, Greve DN, Puonti O, et al. SynthSeg: Segmentation of brain MRI scans of any contrast and resolution without retraining. Med Image Anal. 2023;86:102789. doi:10.1016/j.media.2023.102789 [PubMed: 36857946]

34. Iglesias JE, Augustinack JC, Nguyen K, et al. A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: Application to adaptive segmentation of in vivo MRI. Neuroimage. 2015;115:117–137. doi:10.1016/J.NEUROIMAGE.2015.04.042 [PubMed: 25936807]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

35. Dawe RJ, Bennett DA, Schneider JA, Arfanakis K. Neuropathologic correlates of hippocampal atrophy in the elderly: a clinical, pathologic, postmortem MRI study. PLoS One. 2011;6(10):e26286. doi:10.1371/journal.pone.0026286 [PubMed: 22043314]

36. Risacher LS, Saykin JA, Wes DJ, Shen L, Firpi AH, McDonald CB. Baseline MRI Predictors of Conversion from MCI to Probable AD in the ADNI Cohort. Current Alzheimer Research. 2009;6(4):347–361. doi:10.2174/156720509788929273 [PubMed: 19689234]

37. Jack CRJ, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535–562. doi:10.1016/j.jalz.2018.02.018 [PubMed: 29653606]

38. van de Pol L, Gertz H, Scheltens P, Wolf H. Hippocampal atrophy in subcortical vascular dementia. Neurodegener Dis. 2011;8(6):465–469. doi:10.1159/000326695 [PubMed: 21613775]

39. Fein G, Di Sclafani V, Tanabe J, et al. Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. Neurology. 2000;55(11):1626–1635. doi:10.1212/wnl.55.11.1626 [PubMed: 11113215]

40. Chow N, Aarsland D, Honarpisheh H, et al. Comparing hippocampal atrophy in Alzheimer's dementia and dementia with lewy bodies. Dement Geriatr Cogn Disord. 2012;34(1):44–50. doi:10.1159/000339727 [PubMed: 22922563]

41. Elder GJ, Mactier K, Colloby SJ, et al. The influence of hippocampal atrophy on the cognitive phenotype of dementia with Lewy bodies. Int J Geriatr Psychiatry. 2017;32(11):1182–1189. doi:10.1002/gps.4719 [PubMed: 28425185]

42. Apostolova LG, Mosconi L, Thompson PM, et al. Subregional hippocampal atrophy predicts Alzheimer's dementia in the cognitively normal. Neurobiol Aging. 2010;31(7):1077–1088. doi:10.1016/j.neurobiolaging.2008.08.008 [PubMed: 18814937]

43. den Heijer T, van der Lijn F, Koudstaal PJ, et al. A 10-year follow-up of hippocampal volume on magnetic resonance imaging in early dementia and cognitive decline. Brain. 2010;133(Pt 4):1163–1172. doi:10.1093/brain/awq048 [PubMed: 20375138]

44. Josephs KA, Dickson DW, Tosakulwong N, et al. Rates of hippocampal atrophy and presence of post-mortem TDP-43 in patients with Alzheimer's disease: a longitudinal retrospective study. Lancet Neurol. 2017;16(11):917–924. doi:10.1016/S1474-4422(17)30284-3 [PubMed: 28919059]

45. Josephs KA, Martin PR, Weigand SD, et al. Protein contributions to brain atrophy acceleration in Alzheimer's disease and primary age-related tauopathy. Brain. 2020;143(11):3463–3476. doi:10.1093/brain/awaa299 [PubMed: 33150361]

46. Buciuc M, Wennberg AM, Weigand SD, et al. Effect Modifiers of TDP-43-Associated Hippocampal Atrophy Rates in Patients with Alzheimer's Disease Neuropathological Changes. J Alzheimers Dis. 2020;73(4):1511–1523. doi:10.3233/JAD-191040 [PubMed: 31929165]

47. Strange BA, Witter MP, Lein ES, Moser EI. Functional organization of the hippocampal longitudinal axis. Nature Reviews Neuroscience. 2014;15(10):655–669. doi:10.1038/nrn3785 [PubMed: 25234264]

48. Botha H, Mantyh WG, Murray ME, et al. FDG-PET in tau-negative amnestic dementia resembles that of autopsy-proven hippocampal sclerosis. Brain. 2018;141(4):1201–1217. doi:10.1093/brain/awy049 [PubMed: 29538658]

49. Buciuc M, Botha H, Murray ME, et al. Utility of FDG-PET in diagnosis of Alzheimer-related TDP-43 proteinopathy. Neurology. 2020;95(1):e23. doi:10.1212/WNL.0000000000009722 [PubMed: 32518145]

50. Grothe MJ, Moscoso A, Silva-Rodríguez J, et al. Differential diagnosis of amnestic dementia patients based on an FDG-PET signature of autopsy-confirmed LATE-NC. Alzheimer's Dement. 2022. doi:10.1002/alz.12763

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

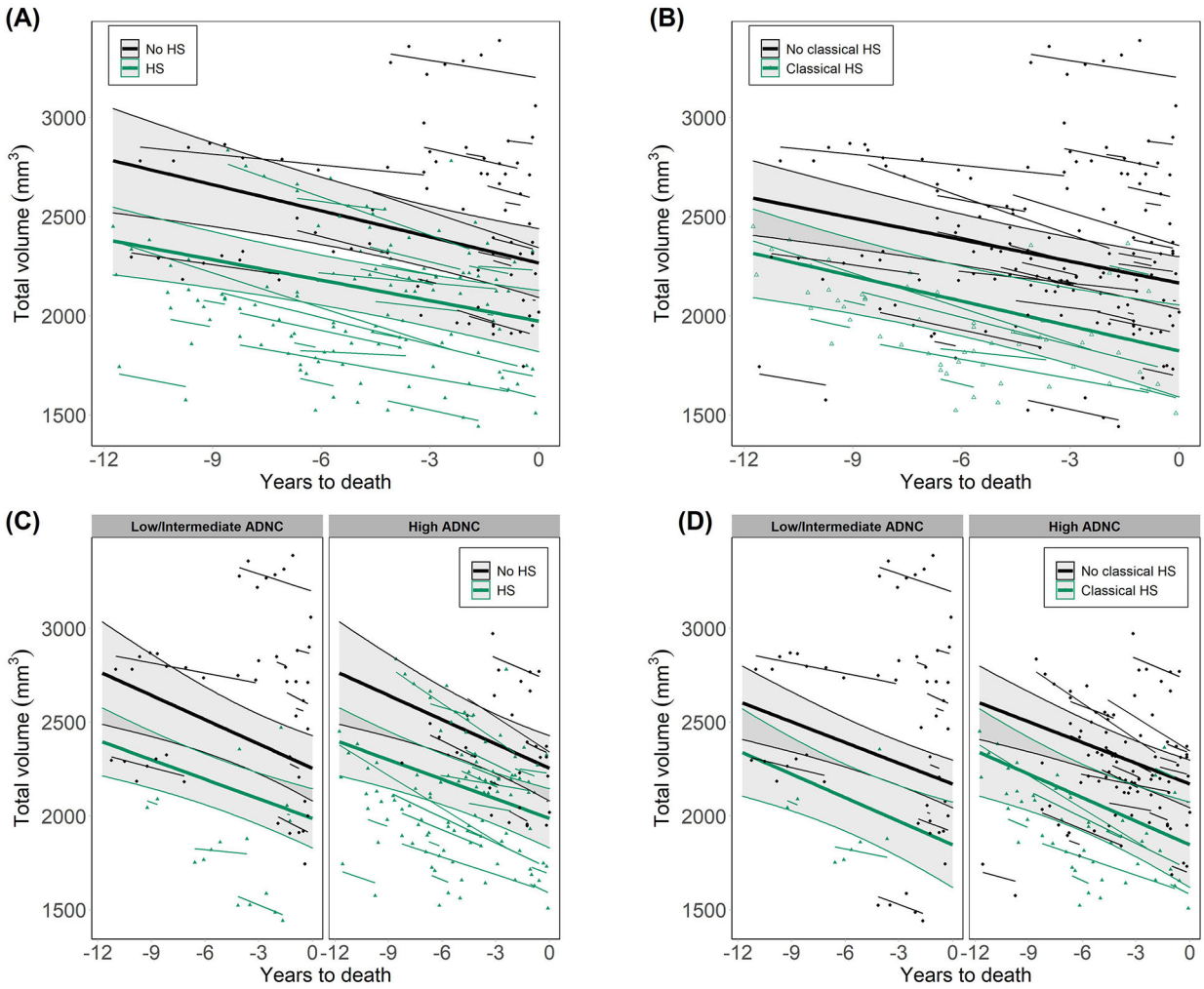

Figure 1. Longitudinal progression of hippocampal volumes as a function of HS.

(A) HS groups defined as a function of HS staging including early and advanced stages (HS+ for those at stage>0)[23]. (B) HS groups determined by the classical definition of the pathology, by which only advanced cases with severe cell loss are included within the HS+ group. (C) HS groups defined as a function of HS staging, compared within groups of high and low/intermediate ADNC. After including ADNC grouping in the statistical model, the effect of HS was still significant (F=30.7, p=.015), with lower volumes in HS+ compared to HS− patients at 11.75 years before death. (D) HS groups determined by the classical definition of the pathology, compared within ADNC burden groups, with the effect of HS remaining significant after including this variable (F=26.1, p=.006). ADNC: Alzheimer's disease neuropathological change. HS: hippocampal sclerosis of aging.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

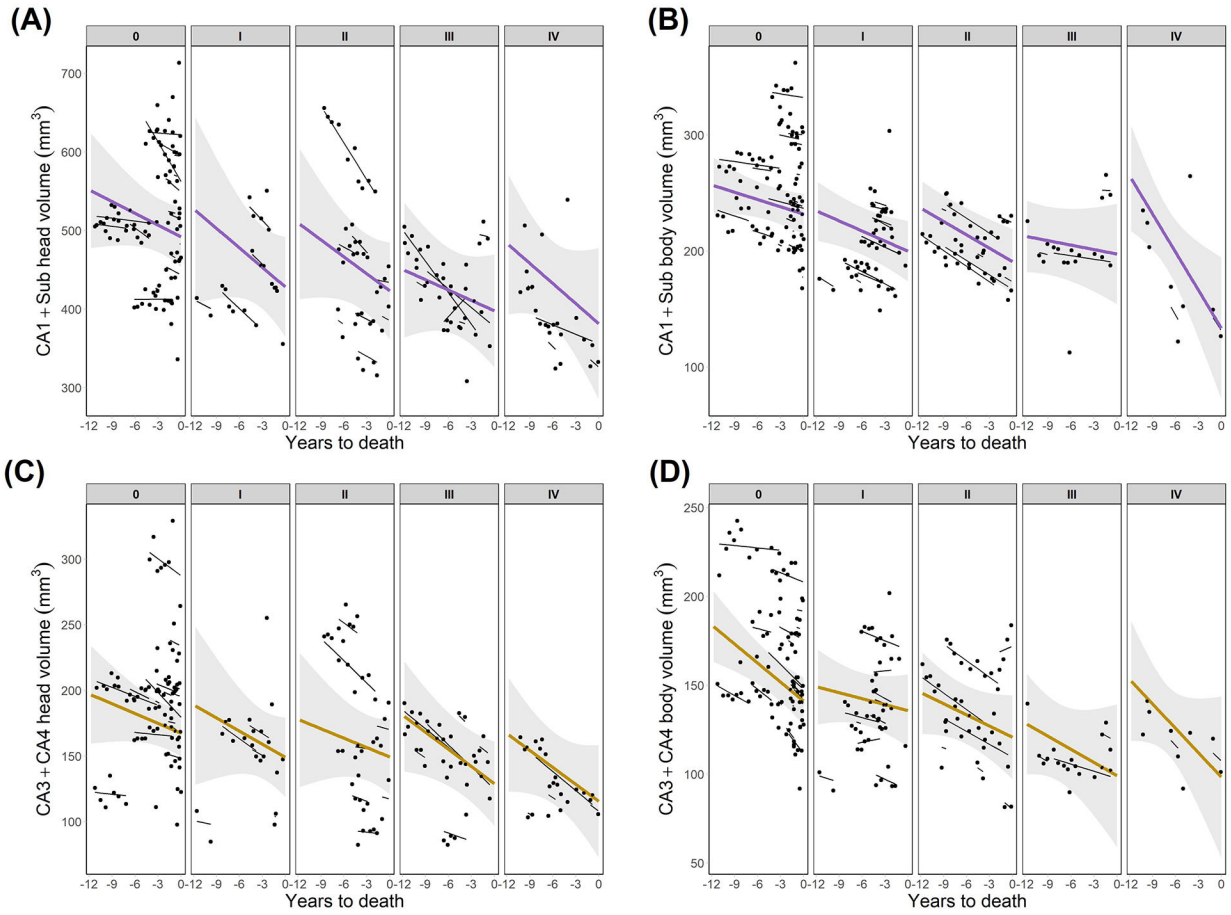

Figure 2. Longitudinal progression of hippocampal subfields volumes as a function of HS staging.

(A) Volumes of CA1+subiculum in the head of the hippocampus. (B) Volumes of CA1+subiculum in the hippocampal body. (C) CA3+CA4 volumes in the head of the hippocampus. (D) CA3+CA4 volumes in the hippocampal body. CA1+Sub: CA1+subiculum.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

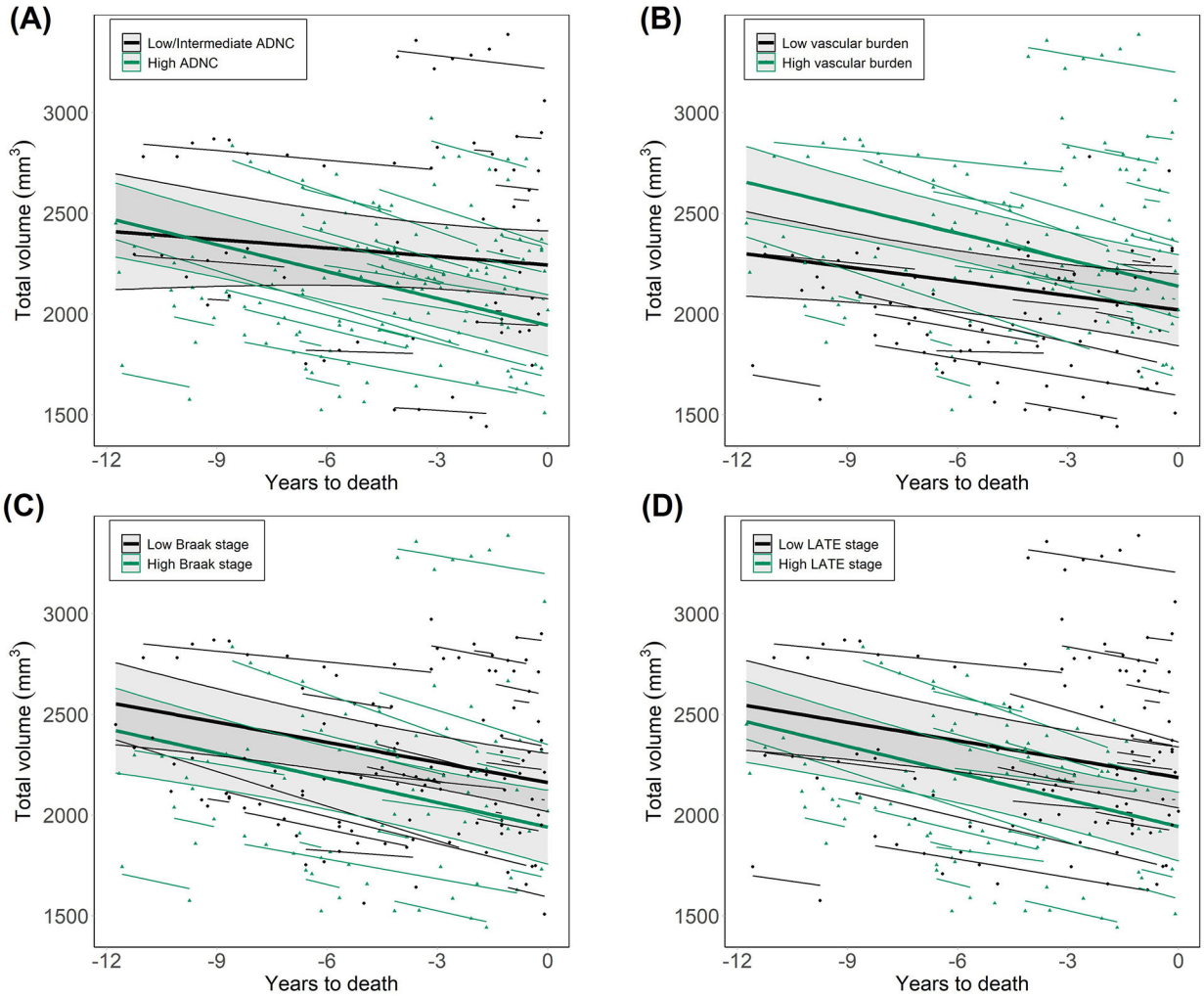

Figure 3. Longitudinal volumes of the whole hippocampus as a function of other neuropathologies in dementia.

(A) Differences between groups of low/intermediate and high probability of ADNC. Significant volume differences between these groups were found (F=13.4, p=0.004), as well as significantly different slopes (p=.016, estimated slopes (mm3/year): −14 for low/intermediate, −44.5 for high ADNC). To evaluate the effects of pathologies considered in B, C and D, the contribution of ADNC was taken into account by adding it as a covariate in these models. (B) Groups of low and high vascular pathology burden, following the evaluation proposed by Deramecourt *et al.*[30], showed no significant between-group volume differences (F=7.8, p=.294). (C) Groups of low and high Lewy body pathology burden, as a function of Braak staging for α-synuclein. Differences between these groups showed a tendency to significance (F=4.7, p=.084). (D) Comparisons between groups of low and high TDP-43 pathology burden (F=14.6, p=0.022), evaluated through LATE staging. ADNC: Alzheimer's disease neuropathological change. LATE: limbic age-related TDP-43 encephalopathy.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1.

Demographic, follow-up and neuropathological data for subjects included in volume analyses in this study.

	Whole cohort	HS− (n=26)	HS+ (n=38)	p value
Demographics	**Mean ± SD or %**			
Sex (%Females)	81.3	73.1	86.8	0.166 ([a])
Estimated age at symptom onset *	76.5 ± 6	75 ± 6.5	77.6 ± 5.5	0.354([b])
Age at death	88.4 ± 6.6	84.6 ± 6.6	90.9 ± 5.3	**10−4** ([c])
sMMSE score at admission	19.1 ± 9.2	20.5 ± 9.3	18.3 ± 9.1	0.287 ([b])
sMMSE score prior to death	10.4 ± 10.6	14.9 ± 11	7.4 ± 9.3	**0.005**([b])
Follow-up	**Mean ± SD**			
Time in nursing home (years)	4.7 ± 3.4	3.3 ± 3.3	5.7 ± 3.2	**0.004**([b])
Time between last MRI and death (years)	3 ± 3.1	1.6 ± 2.2	4 ± 3.3	**4·10−4** ([b])
Number of MRI scans included	3.2 ± 2.7	3 ± 2.5	3.3 ± 2.9	0.849 ([b])
Neuropathology burden	**%**			
High ADNC	68.8	46.2	84.2	**0.001**([a])
High vascular pathology	60.9	73.1	52.6	0.1 ([a])
Lewy bodies beyond brainstem (Braak>2)	40.6	34.6	44.7	0.418 ([a])
TDP-43 inclusions in hippocampus (LATE>1)	50	11.5	76.3	**6·10−7** ([a])
Early or advanced HS	59.4	0	100	-
Classical HS	29.7	0	50	**2·10−5** ([a])

NOTE. This cohort was composed by a predominantly female population of advanced age at death. The three right-most columns show values and comparison between groups with and without HS, with early and advanced stages included within the HS+ group. Results for comparison between groups do not change when stratifying groups by the classical HS definition. Significantly longer disease duration in the HS+ group is reflected by longer time in the nursing home.

Group comparisons by:

[a] Pearson's chi-2 test.

[b] Kruskal-Wallis test.

[c] T-test.

* Age at symptom onset is estimated by neurologists based on medical records and interviews with caretakers.

Abbreviations: ADNC: Alzheimer's Disease Neuropathological Change; HS: hippocampal sclerosis of aging; LATE: limbic age-related TDP-43 encephalopathy; MRI: Magnetic Resonance Imaging; SD: standard deviation; sMMSE: severe Mini-Mental State Examination; TDP-34: TAR DNA-binding protein 43.