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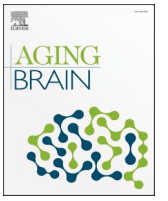

Longitudinal hippocampal atrophy in hippocampal sclerosis of aging

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ABSTRACT

Hippocampal sclerosis of aging (HS-A) is a common degenerative neuropathology in older individuals and is associated with dementia. HS-A is characterized by disproportionate hippocampal atrophy at autopsy but cannot be diagnosed during life. Therefore, little is known about the onset and progression of hippocampal atrophy in individuals with HS-A. To better understand the onset and progression of hippocampal atrophy in HS-A, we examined longitudinal hippocampal atrophy using serial MRI in participants with HS-A at autopsy (HS-A+, n = 8) compared to participants with limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) without HS-A (n = 13), Alzheimer's disease neuropathologic change (ADNC) without HS-A or LATE-NC (n = 16), and those without these pathologies (n = 7). We found that participants with HS-A had lower hippocampal volumes compared to the other groups, and this atrophy preceded the onset of dementia. There was also some evidence that rates of hippocampal volume loss were slightly slower in those with HS-A. Together, these results suggest that the disproportionate hippocampal atrophy seen in HS-A may begin early prior to dementia.

Introduction

Hippocampal sclerosis of aging (HS-A) is a neurodegenerative disease characterized by loss of neurons and gliosis in the hippocampus [1]. HS-A is found between 10 and 15% of the oldest-old population, being twice as common in those > 90 years of age than in those < 90, and is strongly associated with dementia [2–4]. Previous studies have found that patients with HS-A become impaired in hippocampus dependent cognitive functions including episodic memory, semantic memory, and perceptual speed in the years leading

Abbreviations: HS-A, Hippocampal sclerosis of aging; ADNC, Alzheimer's disease neuropathologic change; LATE-NC, Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; MCI, Mild cognitive impairment; TIV, Total intracranial volume.

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up to death [5]. Previous studies have found that patients harboring HS-A pathology, which is frequently unilateral, can have significant atrophy of the hippocampus [6–8] HS-A is often comorbid with other pathologies such as Alzheimer's disease neuropathologic change (ADNC) and limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC), which have also been found to be associated with hippocampal atrophy [9,10]. It is unclear when in the disease course atrophy of the hippocampus occurs, whether this precedes clinically meaningful cognitive decline, and how progression of atrophy over time compares to atrophy seen in those with ADNC or LATE-NC pathology without HS-A. To study the pattern and progression of atrophy and cognitive impairment in those with HS-A at autopsy, we performed a retrospective longitudinal study comparing hippocampal volumes of participants with HS-A (HS-A) to those without HS-A but with LATE-NC, ADNC, or neither pathologic change.

Methods

We used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI, https://adni.loni.usc.edu/), which was launched in 2003 and led by Principal Investigator Michael W. Weiner, MD. ADNI has been collecting serial MRI, PET, other biological markers, and clinical and neuropsychological assessment to study the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see https://www.adni-info.org. We included ADNI-1 participants with both 3D-T1w MRIs and autopsy data (April 2018 release). We chose ADNI-1 participants because of their similarly implemented T1w sequences across sites. To increase the number of HS-A group we also included the three participants with HS-A who were added in later ADNI neuropathology data freezes (December 2022 release). The MRI scans were processed with the longitudinal hippocampal segmentation stream in *FreeSurfer v6.0* [11]. All segmentations of the hippocampus were then checked for quality control, and segmentations with excessive inclusion of outside tissue (e.g. the ventricles) were excluded from analysis (12 segmentations across 8 participants were excluded). For our analyses we used either the sum of the total left and total right hippocampal volumes from the FreeSurfer hippocampal subfields (i.e. total hippocampal volume) or, to help account for the high rate of unilaterality in HS-A, the smaller of the total left or total right hippocampal volumes. For supplementary analyses, we also used the sum of the CA1 and subiculum volumes from the FreeSurfer hippocampal subfields, as these are the regions known to be involved in HS-A. All volumes were adjusted by participant total intracranial volume (TIV) from each MRI. HS-A was dichotomized by presence or absence, ADNC positivity was defined as high

Table 1
Demographics of all participants.

	HS-A no LATE-NC (+/− ADNC) (N = 8)	**LATE-NC no HS-A (+/− ADNC) (N = 13)**	**ADNC no HS-A or LATE-NC (N = 16)**	**No HS-A, LATE-NC, or ADNC (N = 7)**	**P-value**
Male	6 (75.0%)	10 (76.9%)	11 (68.8%)	7 (100%)	0.50
Bachelor's degree or More	7 (87.5%)	8 (61.5%)	11 (68.8%)	3 (42.9%)	0.36
Age at first MRI Mean [Min,Max]	80.6 [72.8, 86.8]	78.5 [69.0,87.7]	75.2 [63.9,87.1]	81.2 [72.4,85.5]	0.06
Age at last MRI Mean [Min,Max]	84.0 [79.9, 87.9]	81.1 [72.2,89.9]	78.4 [68.0,90.3]	85.5 [79.6,91.9]	**0.01**
Age at Death Mean [Min,Max]	88.6 [80.0, 96.0]	85.4 [77.0,97.0]	80.8 [69.0,94.0]	88.7 [81.0,95.0]	**0.01**
Vol. of Both Hipp. at first MRI (%TIV) Mean (SD)	0.315 (0.0671)	0.312 (0.0341)	0.341 (0.0385)	0.359 (0.0823)	0.18
Vol. of Both Hipp. at last MRI (%TIV) Mean (SD)	0.290 (0.0564)	0.293 (0.0303)	0.310 (0.0402)	0.339 (0.0740)	0.17
Vol. of Smallest Hipp. at first MRI (%TIV) Mean (SD)	0.140 (0.0346)	0.149 (0.0184)	0.165 (0.0190)	0.170 (0.0416)	0.07
Vol. of Smallest Hipp. at last MRI (%TIV) Mean (SD)	0.132 (0.0282)	0.139 (0.0168)	0.149 (0.0196)	0.161 (0.0358)	0.10
Rate of Hippocampal Vol. Loss (%TIV/ year) Mean (SD)	−0.007 (0.0077)	−0.010 (0.0090)	−0.011 (0.0055)	−0.004 (0.0031)	0.25
Rate of Smallest Hipp. Vol. Loss (%TIV/ year)	−0.002 (0.0034)	−0.006 (0.0042)	−0.005 (0.0030)	−0.002 (0.0020)	**0.04**
Rate of CDR-SB Change Mean (SD)	0.077 (0.744)	1.63 (1.59)	2.25 (1.63)	0.605 (0.848)	**<0.05**
Baseline Cognition					0.18
Cognitively Normal	2(25.0%)	0 (0%)	1 (6.3%)	1 (14.3%)	
MCI	3 (37.5%)	9 (69.2%)	9 (56.3%)	6 (85.7%)	
Dementia	3 (37.5%)	4 (30.8%)	6 (37.5%)	0 (0%)	
Cognition at Last MRI					0.09
Cognitively Normal	2 (25.0%)	0 (0%)	1 (6.3%)	0 (0%)	
MCI	1 (12.5%)	5 (38.5%)	2 (12.5%)	4 (57.1%)	
Dementia	5 (62.5%)	8 (61.5%)	13 (81.3%)	3 (42.9%)	
Severe ADNC	4 (50.0%)	9 (69.2%)	16 (100%)	0 (0%)	**<0.05**
Presence of LATE-NC	8 (100%)	13 (100%)	0 (0%)*	0 (0%)	**<0.05**

Abbreviations: ADNC: Alzheimer's disease neuropathologic change, HS-A: hippocampal sclerosis of aging, LATE-NC: limbic-predominant age-related TDP-43 encephalopathy neuropathologic change, MCI: Mild cognitive impairment.
*2 participants in the ADNC group did not have LATE-NC data available.

likelihood ADNC based on NIA-AA criteria, and LATE-NC was defined as positive if TDP-43 was present in the hippocampus, entorhinal/inferior temporal cortex, or the neocortex [1,12,13]. We separated the participants into 4 groups: those with HS-A regardless of LATE-NC and ADNC status (HS-A), those with LATE-NC pathology but no HS-A with or without ADNC (LATE-NC), those with ADNC but no HS-A or LATE-NC (ADNC), and those with no HS-A, LATE-NC, or ADNC (no pathology). Participants with frontotemporal lobar degeneration with TDP-43 (FTLD-TDP, N = 2) were excluded from analysis. Of note, participants from any of the groups could harbor other pathologies including vascular or Lewy Body pathology.

The rates of hippocampal volume loss and cognitive decline were determined using linear regressions for each participant. To compare the HS-A group to each of the other groups, we used multiple linear regressions with group membership as the independent variable and either initial or final hippocampal volume, or rate of hippocampal volume loss as the dependent variable, adjusting for age, cognition, and time between MRI and death. We also performed similar analyses examining Clinical Dementia Rating sum of the boxes (CDR-SB) as a measure for severity of cognitive impairment in relation to hippocampal volumes. In addition, we performed linear mixed effect regressions with random slope and intercept with hippocampal volumes as the outcome and age, cognition, and interval between MRI and death as covariates. We also performed a similar analysis using CDR-SB as outcome and hippocampal volumes as predictors, with only random intercept as the model failed to converge with random slope. To further examine the relationship between cognition and hippocampal volume across groups, we performed linear regressions using the hippocampal volume at last MCI visit before conversion to dementia for individuals who did convert, as well as for the average hippocampal volume for each participant at MCI and dementia. All analyses were performed using R (v4.1.2). The data used is publicly available from the ADNI database.

Results

Participant characteristics are shown in Table 1. HS-A participants had an average baseline age of 80.6 years and an average age at death of 88.6 years. At baseline, two HS-A participants were cognitively normal, three had MCI, and three had dementia. At final visit, two HS-A participants remained with normal cognition, one remained with MCI, two converted to (and three remained with)

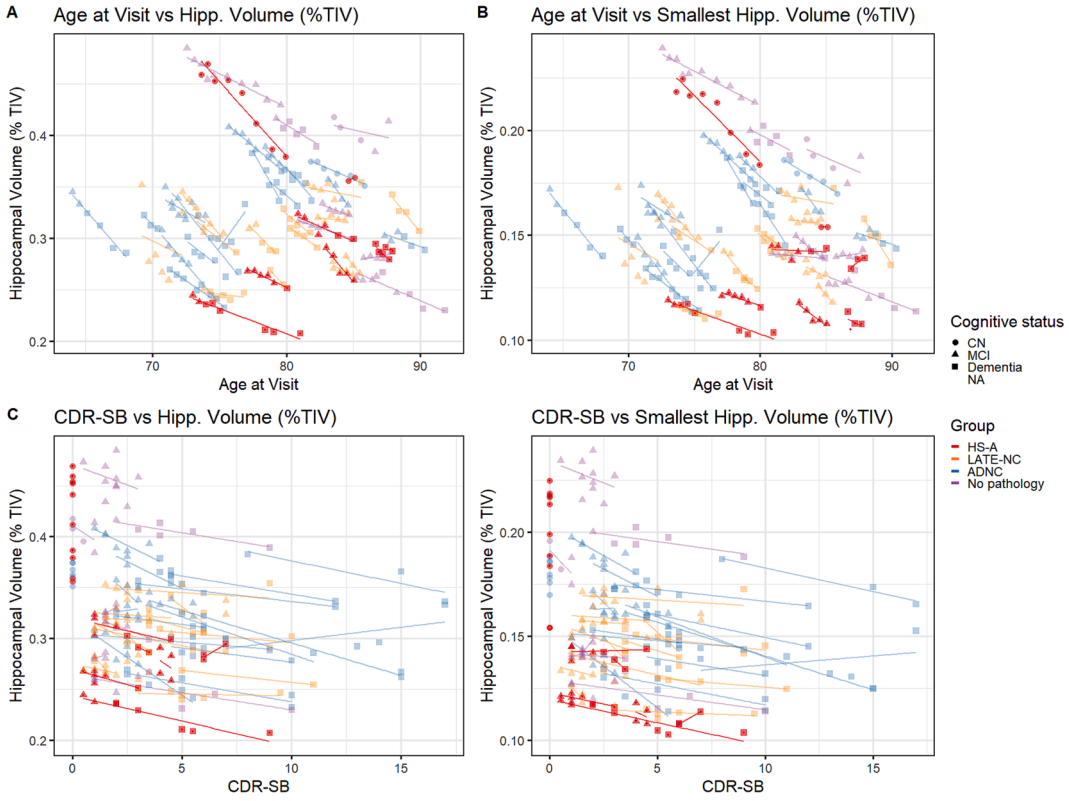

Fig. 1. Total hippocampal volume (A) and smallest hippocampal volume (B) as percentage of total intracranial volume (%TIV) plotted against age at visit. Total hippocampal volume (C) and smallest hippocampal volume (D) as percentage of total intracranial volume (%TIV) plotted against CDR-SB. HS-A participants are shown in red, ADNC participants are shown in blue, LATE-NC participants are shown in orange, and no pathology participants are shown in purple. Marker shapes denote cognition at time of visit. Abbreviations: HS-A: Hippocampal sclerosis of aging, ADNC: Alzheimer's disease neuropathologic change, LATE-NC: limbic-predominant age-related TDP-43 encephalopathy neuropathologic change, CN: cognitively normal, MCI: mild cognitive impairment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dementia. All HS-A participants also had LATE-NC pathology. Hippocampal volumes were on average the smallest in the HS-A group followed by the LATE-NC, then the ADNC, and finally the no pathology group. Also, half of the participants in the HS-A and over two thirds of the LATE-NC groups had concomitant severe ADNC. Cognitive status was roughly comparable between the HS-A, ADNC, and LATE-NC groups, with most individuals progressing to dementia through follow up.

Fig. 1A shows a graph plotting the total hippocampal volumes of all participants against age at visit. Visually, hippocampal volume appeared to decrease approximately linearly with age in all groups and across most participants. There were two HS-A participants who maintained high hippocampal volume, as well as normal cognition, throughout follow up, indicating that HS-A is not universally associated with drastically lower volumes. Additionally, when using smallest hippocampal volume several HS-A participants showed considerably lower volumes compared to the other groups and in compariosn with the plot of total hippocampal volumes, suggesting a stronger association with HS-A when using smallest vs total hippocampal volumes (Fig. 1B). A similar graph was plotted using the volume of the CA1 and subiculum subfields (Supplemental Fig. 1A), which followed the same trends as the graphs showing results for the whole hippocampus.

From linear regression models, the difference in initial total hippocampal volume was significantly lower in those with HS-A compared to ADNC (0.036, 95% CI [0.014, 0.058], $p = 0.005$), no pathology (0.11, 95% CI [0.027, 0.19], $p = 0.040$), but only trended towards significance when comparing to the LATE-NC ($p = 0.10$) group. The difference in final total hippocampal volume was significant when comparing the HS-A group to the ADNC group (0.030, 95% CI [−0.010, 0.050], $p = 0.009$) and trended towards significance for the no pathology group (0.088, 95% CI [0.014, 0.16], $p = 0.058$). Difference in final total hippocampal volume was not significant for the LATE-NC group, but was close to trend level ($p = 0.12$).

Rates of hippocampal volume loss were highest in the ADNC group (−0.011% TIV/year), followed by the LATE-NC group (−0.010% TIV/year), the HS-A group (−0.007% TIV/year), and then the no pathology group (−0.004% TIV/year). None of the linear regression models examining rate of hippocampal volume loss reached significance (HS-A vs LATE-NC: $p = 0.6$, vs ADNC: $p = 0.6$, vs no pathology $p = 0.4$).

When using the smallest hippocampal volumes in the linear regression models, the difference between initial volume was significant when comparing HS-A to each of the groups (LATE-NC: 0.022, 95% CI [0.0032, 0.041], $p = 0.037$; ADNC: 0.036, 95% CI [0.014, 0.058], $p = 0.005$; no pathology: 0.054, 95% CI [0.024, 0.084], $p = 0.006$). For final volume, the difference between HS-A and no pathology (0.027, 95% CI [0.0034, 0.042], $p = 0.027$), as well as ADNC (0.030, 95% CI [0.0095, 0.050], $p = 0.01$) maintained significance, while LATE-NC (0.018, 95% CI [−0.0019, 0.038], $p = 0.097$) and no pathology (0.0400, 95% CI [0.0044, 0.076], $p = 0.055$) trended towards significance.

Rate of volume loss for the smallest hippocampus was greatest in the ADNC group (−0.0056 %TIV/year), followed by LATE-NC (−0.0049 %TIV/year), no pathology (−0.0023 %TIV/year), then the HS-A groups (−0.0016 %TIV/year). Linear regression models comparing the volume loss rates of smallest hippocampus between groups found a trend in difference when comparing HS-A to LATE-NC (−0.0035, 95% CI [−0.0072, 0.0002], $p = 0.082$), but no significant difference when comparing to ADNC ($p = 0.16$) or no pathology ($p = 0.8$).

Linear mixed effects regressions with total hippocampal volume as outcome with random slope and intercept only trended towards significance when comparing the HS-A group to the no pathology group (−0.039, 95% CI [−0.079, 0.0015], $p = 0.085$), and were not significant when comparing to other groups (LATE-NC: $p = 0.3$; ADNC: $p = 0.8$). In similar models including an interaction term between age and group, we found significant differences in volume loss rate only when comparing the HS-A group to the LATE-NC group (HS-A vs LATE-NC: −0.0052, 95% CI [−0.010, −0.0007], $p = 0.002$; HS-A vs ADNC: $p = 0.8$; HS-A vs no pathology: $p = 0.14$).

Linear mixed effect models examining the volume of the smallest hippocampus followed similar trends to those examining total hippocampal volume, with the difference in volume reaching significance only when comparing the HS-A group to the no pathology group (no pathology: −0.035, 95% CI [−0.059, −0.010], $p = 0.014$; LATE-NC: $p = 0.3$; ADNC: $p = 0.8$). In models including interaction between age and group, we found that the rate of volume loss trended towards significance only when comparing HS-A to no pathology (−0.0019 %TIV/year, 95% CI [−0.0037, −0.0012], $p = 0.064$), and did not reach significant for other groups (LATE-NC: $p = 0.3$; ADNC: $p = 0.6$).

Fig. 1C shows a graph of hippocampal volumes against the corresponding CDR-SB score. A similar graph was plotted using the volume of the CA1 and subiculum subfields as %TIV (Supplemental Fig. 1B) and this showed similar trends to graphs of total hippocampal volume. Decreasing hippocampal volume was associated with increasing CDR-SB score (plotted as downward on the y-axis to denote decline) in all groups. We found that HS-A participants generally had lower hippocampal volumes (both for the smallest hippocampus and total hippocampal volume) for a given CDR-SB score compared to the other groups.

We also compared the rate of cognitive decline, measured by increase in CDR-SB score, between groups. We found that the ADNC group had the highest average rate of decline (2.3/year), followed by the LATE-NC group (1.6/year), the no pathology group (0.61/year), and the HS-A group (0.077/year). The rate of increasing CDR-SB score reached or approached significance in the model comparing the HS-A group to all other groups (LATE-NC: 1.45, 95% CI [0.13, 2.74], $p = 0.046$; ADNC: 2.1, 95% CI [0.61, 3.5], $p = 0.012$; no pathology: 0.96, 95% CI [−0.041, 1.96], $p = 0.093$). Linear mixed effect models examining the difference in CDR-SB score between groups trended towards or reached significance when comparing HS-A to all groups except no pathology (LATE-NC: −2.6, 95% CI [−2.77, −2.45], $p = 0.080$; ADNC: −7.1, 95% CI [−11.9, −2.3], $p = 0.01$; no pathology: $p = 0.5$).

In linear regression models examining the total hippocampal volume at last MCI visit before conversion to dementia, we found the difference between groups trended towards significance when comparing HS-A ($n = 3$) to LATE-NC ($n = 4$, 0.046, 95% CI [0.015, 0.077], $p = 0.064$) and ADNC ($n = 6$, 0.074, 95% CI [0.0057, 0.14], $p = 0.087$). There was no significant difference in volume when comparing the HS-A group to the no pathology group ($n = 3$, $p = 0.5$). In similar analysis examining volume of the smallest hippocampus, the difference was significant when comparing HS-A to ADNC (0.042, 95% CI [0.012, 0.073], $p = 0.043$), trended towards

significance for LATE-NC (0.022, 95% CI [−0.017, 0.211], p = 0.096), and was not significant for no pathology (p = 0.443).

We also performed linear regressions with the hippocampal volume averaged over visits with participants at MCI or at dementia in separate models, adjusted for average age and interval between MRI and death. For MCI, the difference in total hippocampal volume trended towards or reached significance when comparing between HS-A (n = 4) to each other group (LATE-NC: n = 8, 0.046, 95% CI [0.0026, 0.090], p = 0.068; ADNC: n = 9, 0.077, 95% CI [0.028, 0.13], p = 0.015; no pathology: n = 7, 0.098, 95% CI [0.015, 0.18], p = 0.054). For dementia, difference in hippocampal volume was significant for HS-A (n = 5) compared to LATE-NC (n = 13, 0.036, 95% CI [0.011, 0.061], p = 0.021) and ADNC (n = 8, 0.064, 95% CI [0.018, 0.11], p = 0.017), but not no pathology though only 3 participants in no pathology group had dementia (p = 0.34). When examining the volume of the smallest hippocampus, the average MCI volume was significantly different when comparing the HS-A group to all others (LATE-NC: 0.030, 95% CI [0.008, 0.052], p = 0.027; ADNC: 0.0047, 95% CI [−0.018, 0.028], p = 0.004; no pathology: 0.055, 95% CI [0.016, 0.093], p = 0.028). The average dementia volume of the smallest hippocampus was significantly different when comparing HS-A to ADNC (0.034, 95% CI [0.011, 0.057], p = 0.012) but was only trending for the comparison to LATE-NC (p = 0.10) and not significant compared to no pathology (p = 0.2).

Discussion

In this study we performed a retrospective investigation of the longitudinal pattern of hippocampal atrophy seen in participants with HS-A and compared that against participants with other pathological changes including individuals with LATE-NC without comorbid HS-A, individuals with ADNC but no comorbid HS-A or LATE-NC, and individuals with none of the three pathologies. We found that hippocampal atrophy was more severe in those with HS-A, appearing to begin early and continuing insidiously through the course of cognitive impairment. We found this using both initial and final available hippocampal volumes, and when using the smallest of the right or left hippocampal volumes. Our results are in line with the findings of a recent similar study, which found that individuals with hippocampal atrophy had significantly lower hippocampal volumes up to a decade before death [14]. This other study was performed in a group where all participants had dementia, and there was a very high rate (over 50%) of HS-A; however, in our study we compared participants with HS-A to other pathologically defined groups, not just ADNC but also LATE-NC without HS-A and those without ADNC or LATE-NC, in a sample that spanned normal cognition to dementia. This allowed us to examine HS-A in relation to cognition and changes in cognitive status. Namely, we also found that, compared with other degenerative pathologies, participants with HS-A had a more exaggerated hippocampal atrophy for a given level of cognitive impairment. In addition, we found that the differences in hippocampal atrophy were better detected when examining only the volume of the smallest hippocampus rather than total bilateral hippocampal volume. HS-A commonly presents unilaterally, and here we show that this may mean disproportionate atrophy in the hippocampus in one hemisphere vs. the other [8,15]. Thus, examining total hippocampal volume alone could mask the extent of the atrophy in the affected hemisphere of individuals with HS-A and therefore, it is important to consider the laterality of the presentation of HS-A in its assessment. Also, we found some limited evidence that participants with HS-A appeared to have a relatively slower rate of hippocampal atrophy, accompanied as well by what appeared to be a slower cognitive decline. The recent study by Ortega et al found that HS-A was not related to the rate of hippocampal atrophy, but ADNC was, which somewhat mirror our results here.

Previous studies have found that participants with HS-A had greater deformation of hippocampal CA1 and subiculum subfields and smaller hippocampi when compared to those with ADNC and that concomitant presence of LATE-NC and/or that HS-A was more strongly associated with hippocampal atrophy than ADNC alone [7,16]. Our group has reported that participants with HS-A had greater atrophy of the CA1 and subiculum subregions of the hippocampus, even when a substantial proportion of participants with HS-A were at a pre-dementia stage [6]. One potential explanation for this observation is that the hippocampal atrophy in HS-A starts early in the course of cognitive impairment. The findings of the current study support the notion that profound hippocampal atrophy is an early event in those with HS-A pathology, a finding supported by the recent study from Ortega et al. [14]. While concomitant ADNC was common in those with HS-A, not all participants with HS-A had ADNC, and those with ADNC but no HS-A did not have as low hippocampal volumes but did seem to have a slightly greater rate of loss. Moreover, we found greater hippocampal atrophy in HS-A participants compared to the other groups at a given degree of cognitive impairment, both as measured by CDR scores as well across MCI and dementia stages. This is consistent with our previous findings that HS-A was the neuropathology most strongly associated with hippocampal atrophy near death, even after accounting for cognition [17].

LATE-NC was present in all HS-A cases, a finding consistent with the reported high prevalence of LATE-NC pathology in brains harboring HS-A [3,4,8]. Our findings suggests that low hippocampal volumes observed early in the HS-A group may be more strongly associated with the presence of HS-A than LATE-NC per se. One potential explanation is that HS-A represents the most advanced stage of LATE-NC pathology accompanied by the highest levels of neurodegeneration. It should be noted, however, that presence of LATE-NC is not a ubiquitous finding in all cases of HS-A. Future studies are needed to compare the degree of hippocampal atrophy in HS-A participants with and without LATE-NC pathology.

There are limited studies examining longitudinal atrophy in HS-A, and as such this study represents a valuable contribution to the field. While other studies examining HS-A have generally found faster rates of hippocampal atrophy in those with HS-A and LATE-NC with concurrent ADNC, we found that the HS-A group had visually slower rates of atrophy compared to the other pathology groups, though the results did not always reach statistical significance [14,18,19]. A potential explanation for the slower atrophy in HS-A individuals is that those with HS-A (and LATE-NC) had higher rates of hippocampal decline earlier in the disease stage and the rate decreased after the bulk of atrophy had already occurred, while those with ADNC and no LATE-NC or HS-A, who tended to be younger, were at an earlier disease stage and therefore, had increased rates of hippocampal atrophy. This explanation is supported by previous work on the ADNI dataset, which found that individuals with AD and MCI had decreasing rates of hippocampal atrophy in old age compared to cognitively normal individuals, who had increasing rates of hippocampal atrophy at older age [20].

Limitations of this study include the small sample size which limits the power of statistical analyses and limited our ability to account for other neuropathologic changes beyond ADNC and LATE-NC that could potentially affect hippocampal volumes. Additionally, because HS-A is only assessed at autopsy and those with HS-A tend to die at older ages, it is difficult to fully account for the effect of age. Both the small sample size and the age effects may explain why we found stronger results using initial and final hippocampal volumes as opposed to the linear mixed effect models. Also, many of the no pathology participants had cognitive impairment and hippocampal atrophy, despite not having any of the three pathologies of interest, meaning it is possible that degenerative and vascular pathologies not accounted for in the study have been partially responsible for low hippocampal volumes and cognitive scores in the "pathology negative" group. However, some previous studies have not found an association between Lewy bodies or vascular pathologies and hippocampal atrophy [17,21–24]. The age range of the participants was also relatively limited, with a low number of oldest-old participants, which is the age range with highest prevalence of HS-A and for which there have been limited neuroimaging studies specifically targeting this age group [24,25].

Conclusion

In this study, we found that participants with HS-A had smaller hippocampi across multiple visits spanning several years, when compared to participants with ADNC or LATE-NC without HS-A, particularly when examining participant volumes for the smaller of the left and right hippocampi. This atrophy was detectable early in the course of cognitive impairment and for a given degree of cognitive impairment participants with HS-A had greater hippocampal atrophy compared to participants with other pathologies.

CRediT authorship contribution statement

Janice X. Li: Writing – original draft, Writing – review & editing, Formal analysis. **Hannah L. Nguyen:** Formal analysis. **Tianchen Qian:** Methodology. **Davis C. Woodworth:** Writing – original draft, Writing – review & editing, Conceptualization, Methodology. **S. Ahmad Sajjadi:** Writing – review & editing, Conceptualization, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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