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Trajectories of cognitive decline differ in hippocampal sclerosis and Alzheimer's disease

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ABSTRACT

Hippocampal sclerosis (HS) is a prevalent cause of dementia in the oldest old but is generally misdiagnosed as Alzheimer's disease (AD) due to similarities in clinical presentation. To determine if clinical and cognitive features diverge over time, we compared results from longitudinal evaluations of participants in the University of California, San Diego, Alzheimer's Disease Research Center with autopsy-confirmed AD (n = 195), HS (n = 21), or both HS + AD (n = 18). Each group exhibited decline in all cognitive measures, with HS declining at a slower rate than AD on the Mini-Mental State Examination, immediate recall condition of a word-list learning test, and Dementia Rating Scale total and subtest scores (except memory). Five years before the final evaluation, more prominent semantic and visuospatial deficits were apparent in AD participants than in HS participants despite comparable global cognitive impairment. Groups did not differ on any measure of executive function. HS + AD differed from AD only on the Boston Naming Test. Overall, results suggest that HS dementia is associated with cognitive deficits that progress more slowly than, but generally mimic, those observed in AD.

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1. Introduction

Hippocampal sclerosis (HS) is characterized by severe neuronal loss and gliosis in the CA-1 and subiculum of the hippocampal formation (Dickson et al., 1994; Jellinger, 1994). Although predominantly studied in temporal lobe epilepsy, HS is increasingly recognized as the cause of dementia in up to 25% of the "oldest old" (Leverenz et al., 2002; Nelson et al., 2011, 2013; Zarow et al., 2012). Despite clear pathologic differences at autopsy, HS dementia presents with prominent memory loss (Dickson et al., 1994), as well as impairment in language, executive function, attention, visuospatial abilities, and perceptual speed (Corey-Bloom et al., 1997; Nag et al., 2015; Zarow et al., 2012), and is typically misdiagnosed as Alzheimer's disease (AD) in the clinic (Brenowitz et al., 2014; Leverenz et al., 2002; Nelson et al., 2011). Although patients with HS tend to be older and less functionally impaired than those with AD

(Brenowitz et al., 2014), no clinically differentiating features have been identified.

Comparisons of cognitive profiles between AD and HS participants have yielded inconsistent results: greater visuospatial, executive, and attention impairments in AD versus HS (Corey-Bloom et al., 1997); only greater executive impairment in AD (Leverenz et al., 2002); or no differences in cognition between the 2 (Zarow et al., 2008). Results indicating that patients with HS exhibit slower decline on the Mini-Mental State Examination (MMSE) than those with AD (Murray et al., 2014) suggest that these variable findings may be attributable to differences in trajectories of decline across various cognitive domains which are obscured in cross-sectional comparisons. In a single longitudinal study, Nelson et al. (2011) identified relatively preserved verbal fluency with similarly impaired word-list recall in HS compared with AD at baseline and 5.5–6.5 years before death. A modest group-level difference in the ratio of these measures was replicated in the National Alzheimer's Coordinating Center database (Brenowitz et al., 2014) but with too much overlap for individual discrimination. We now extend this work by comparing trajectories of decline in HS, AD, or HS + AD on a comprehensive panel of cognitive measures to determine if profiles of decline can assist in clinical differentiation.

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2. Materials and methods

2.1. Standard protocol approvals, registrations, and patient consents

The research protocol was reviewed and approved by the human subject's review board at the University of California, San Diego (UCSD). Informed consent to participate in the study was obtained at the point of entry into the Alzheimer's Disease Research Center (ADRC) longitudinal study from all patients or their caregivers consistent with California State law. Informed consent for autopsy was obtained at the time of death from the next of kin.

2.2. Participants

Cases for this study were selected from the brain bank of the Shiley-Marcos ADRC at UCSD. Cases were included if they had completed at least 2 longitudinal (approximately annual) clinical and neuropsychological evaluations between 1985 and 2018; received a pathologic diagnosis of HS, AD, or both (HS + AD); and did not have another neurodegenerative pathology that could account for cognitive decline. We excluded cases with the following concomitant pathologies: (1) frontotemporal lobar degeneration; (2) Parkinson's disease; (3) multiple sclerosis; and (4) tangle-only dementia. The presence of any Lewy body pathology also resulted in exclusion from the sample. Participants were also excluded if pathological data were incomplete, their last ADRC evaluation was more than 4 years from the date of death, or they died before the age of 65 years (Fig. 1). In contrast, the presence of vascular pathologies did not warrant exclusion as there may be a causal relationship with HS (Dickson et al., 1994; Leverenz et al., 2002; Nelson et al., 2016; Neltner et al., 2014). The prevalence of these vascular pathologies in each group is summarized in Table 1.

2.3. Clinical evaluation

Participants had annual standardized and detailed clinical, neurological, and neuropsychological assessments as previously
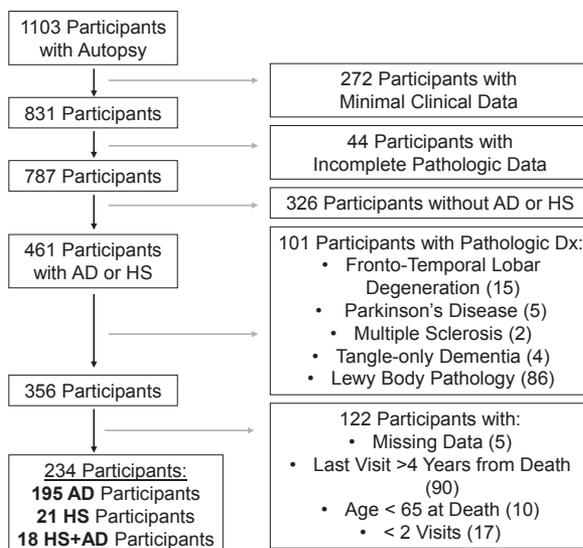

Fig. 1. Participant selection and exclusion. Flowchart of identification of participants for this analysis from the brain bank at the UCSD Shiley-Marcos Alzheimer's Disease Research Center. Exclusion criteria along with the number of subjects excluded are presented at each stage of selection. Abbreviations: AD, Alzheimer's disease; HS, hippocampal sclerosis.

Table 1
Participant demographics and pathology

	AD, n = 195	AD + HS, n = 18	HS, n = 21	p Value
Age at last visit, y, mean ± SD	78.1 ± 7.1	84.9 ± 5.2	85.2 ± 7.0	<0.001[c,d]
Age at death, y, mean ± SD	79.7 ± 7.0	86.6 ± 5.1	86.7 ± 7.1	<0.001[c,d]
Last visit to death interval, y, mean ± SD	1.6 ± 1.0	1.6 ± 1.0	1.5 ± 0.9	0.89
Age at symptom onset, y, mean ± SD	70.3 ± 8.1	76.5 ± 5.9	78.3 ± 7.1	<0.001[c,d]
Disease duration, y, mean ± SD	9.3 ± 3.6	10.3 ± 4.9	8.2 ± 3.6	0.25
Education, y, mean ± SD	14.7 ± 3.0	15.3 ± 2.4	15.3 ± 2.8	0.55
Gender, n (%)				
Male	115 (59%)	9 (50%)	14 (67%)	0.60
Female	80 (41%)	9 (50%)	7 (33%)	
[b]Apo E4 alleles,[a] n (%)				
0 alleles	65 (34%)	4 (22%)	12 (57%)	<0.05[c]
1 alleles	93 (48%)	13 (72%)	9 (43%)	
2 alleles	34 (18%)	1 (6%)	0 (0%)	
Clinical history, n (%)				
Hypertension	100 (51%)	9 (50%)	12 (57%)	0.87
Diabetes	20 (10%)	0 (0%)	4 (19%)	0.13
Stroke	30 (15%)	3 (17%)	3 (14%)	0.99
Braak stage, n (%)				<0.001[c,d,e]
I		-	6 (29%)	
II	-	-	2 (10%)	
III	-	-	4 (20%)	
IV	-	-	6 (29%)	
V	65 (33%)	13 (72%)	1 (5%)[b]	
VI	130 (67%)	5 (28%)	2 (10%)[b]	
CERAD Neuritic Plaque Score, n (%)				<0.001[c,e]
None	-	-	6 (29%)	
Mild	-	-	3 (14%)	
Moderate	43 (22%)	7 (39%)	8 (38%)	
Severe	152 (78 %)	11 (61%)	4 (19%)	
Vascular pathology[a], n (%)				
Arterial or lacunar infarct	30 (16%)	0 (0%)	2 (10%)	0.19
Microinfarct	15 (8%)	3 (17%)	6 (29%)	0.008[c]
Hemorrhage/microbleed	11 (6%)	1 (6%)	0 (0%)	0.70
Cerebral amyloid angiopathy (moderate/severe)	121 (63%)	12 (67%)	8 (38%)	0.08
Arteriosclerosis (moderate/severe)	27 (18%)	5 (42%)	6 (35%)	0.06
At least 1 of aforementioned pathologies	142 (73%)	13 (72%)	15 (71%)	0.99

p Values from Fisher's Exact test or analysis of variance test as appropriate.
Key: AD, Alzheimer's disease; CDR, Clinical Dementia Rating; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DLB, dementia with Lewy Bodies; HS, hippocampal sclerosis; MCI, mild cognitive impairment; POD, Pfeffer Outpatient Disability scale.
[a] Missing data: APOE genotype (n = 4, 1.7%), arterial or lacunar infarct (n = 2, <1%), microinfarcts (n = 1, <1%), hemorrhage or microbleed (n = 1, <1%), amyloid angiopathy (n = 2, <1%), arteriosclerosis (n = 56, 24%).
[b] Despite Braak Stages of V or VI, these 3 participants did not meet the diagnostic criteria for AD due to having "none" or "mild" CERAD neuritic plaque scores.
[c] Significant post hoc pairwise comparison between HS and AD.
[d] Significant post hoc pairwise comparison between HS + AD and AD.
[e] Significant post hoc pairwise comparison between HS + AD and HS.

described (Galasko et al., 1994; Salmon and Butters, 1992). Global cognitive function was assessed with the MMSE (Folstein et al., 1975) and the dementia rating scale (DRS) (Mattis, 1988) including its subscales for attention, initiation, conceptualization, construction, and memory. Memory was further assessed with the Wechsler Memory Scale (WMS) visual reproduction test immediate and delayed recall (adaptation) (Wechsler, 1945; Russell, 1975), the WMS-R logical memory test (Wechsler, 1987), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning Test (Morris et al., 1988), and the California Verbal Learning Test (CVLT) (Delis et al., 1987). Language was assessed with the Boston Naming

Test (BNT)-30 item version (Goodglass et al., 1983), the Letter Fluency Test (F-A-S) (Borkowski et al., 1967), and the Category Fluency Test ("animals", "fruits", and "vegetables") (Monsch et al., 1992). Executive function and attention were assessed with the Modified Wisconsin Card Sorting Test (Nelson, 1976), Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Substitution Test (Wechsler, 1981), Trail Making Test Parts A and B (measured as seconds/circle) (Reitan, 1958), and WAIS-R Digit Span Test (Wechsler, 1981). Visuospatial abilities were assessed with the Wechsler Intelligence Scale for Children-Revised (WISC-R) Block Design Test (Wechsler, 1974) and the copy condition of the WMS Visual Reproduction Test. Functional impairment was assessed using the Pfeffer Outpatient Disability (POD) (Pfeffer et al., 1981) scale or the Functional Assessment Questionnaire (in which case, scores were converted to appropriate corresponding POD scores).

2.4. Neuropathological evaluation

UCSD ADRC procedures at autopsy were as follows: The brain was divided sagittally, and the left hemibrain was fixed in 10% buffered formalin, whereas the right hemibrain was sectioned coronally and then frozen at −70 °C in sealed plastic bags. Routinely, tissue blocks from the right hemibrain of the midfrontal, inferior parietal, and superior temporal cortices; primary visual cortex in the occipital cortex; hippocampus; basal ganglia; substantia nigra; and cerebellum were removed and placed in 2% paraformaldehyde for subsequent thick sectioning by vibratome. Tissue blocks adjacent to the ones described previously were stored at −70 °C for subsequent immunoblot analysis for synaptic proteins and Aβ species (soluble and oligomers). Vibratome sections (40-μm thick) were stored in cryoprotective medium at −20 °C for subsequent immunochemical studies. The formalin-fixed left hemibrain was serially sectioned in 1 cm slices, and tissue blocks from the regions described previously were processed for histopathological examination by H&E and Thioflavin-S (Thio-S) to detect tau and β-amyloid deposits.

Brains were staged for degree of neurofibrillary tangle pathology by 1 pathologist (L.A.H) using a modification of the Braak staging scheme (Hansen and Terry, 1997). Estimates of neuritic plaque density were calculated using methods recommended by CERAD (Mirra et al., 1991). To match previously published analyses comparing HS and AD (Brenowitz et al., 2014; Nelson et al., 2011), AD was operationalized using the National Institute on Aging (NIA)-Reagan consensus criteria for the postmortem diagnosis of AD, wherein Braak stage V-VI with moderately to severely dense neuritic plaques corresponds to "high likelihood" that dementia is due to AD. HS was pathologically defined as cell loss and gliosis in CA1 and the subiculum of the hippocampus, out of proportion to AD pathology.

Participant brains were assessed for cerebral amyloid angiopathy and cerebrovascular disease. The severity of cerebral amyloid angiopathy was assessed semiquantitatively on thioflavin-S–stained preparations of the midfrontal cortex, superior temporal gyrus, inferior parietal cortex, and posterior hippocampus using a four-point scale ranging from 0 to 3 (absent, mild, moderate, and severe), using a method previously described (Olichney et al., 1996). The severity of arteriolosclerosis was scored separately on a similar semiquantitative four-point scale. Both were dichotomized as moderate/severe versus absent/mild for the purposes of comparison. Other pathologies were grouped as (1) large arterial and lacunar infarcts, (2) cortical microinfarcts, and (3) hemorrhages and microbleeds, and were simply dichotomized as present or absent.

2.5. Reference values

Reference values for each cognitive measure (presented as green shading on figures) were derived from a group of "robust" normal controls who were diagnosed as normal on their first evaluation and remained normal for the duration of their participation in the ADRC longitudinal study. There were 241 individual "robust" normal participants who completed a total of 1109 visits after the age of 65 years. Based on all of these visits, the "normal" reference range was defined as being within 1.5 standard deviations of the mean score for each measure. The "robust" normal participants were not used in any calculation, model, or statistics but purely served as a visual reference to guide interpretation of results.

2.6. Statistical methods

Demographics, clinical characteristics, and final cognitive performance were compared using a 3-group analysis of variance for continuous variables, followed by Tukey's honestly significant difference (HSD) post hoc analysis for significant results and a 3-group Fisher's exact test for categorical variables; post hoc pairwise Fisher Exact comparisons were performed for significant results.

Trajectories of cognitive decline associated with AD and HS neuropathology were analyzed using data from the final visit and up to 5 prior annual evaluations covering a period of up to 6 years. This approach was chosen because starting at the first evaluation and moving forward is confounded by the variance in the clinical status of participants at the entry into the study. With this approach, 100% of participants had data available at the last visit (by definition), 94% 1 year prior, 82% 2 years prior, 67% 3 years prior, 52% 4 years prior, and 38% 5 years prior. Data from a total of 1015 visits were available in this time window, with AD participants averaging 4.3 ± 1.4 visits, HS + AD averaging 4.8 ± 1.4, and HS averaging 4.0 ± 1.8 visits ($p = 0.24$).

Longitudinal linear mixed-effects models were used to assess how performance (expressed as raw scores) on each cognitive test declined with time to last evaluation. The participants' performance was modeled with fixed effects of pathologically confirmed diagnostic group, years of education, presence of an apolipoprotein E (APOE) ε4 allele, age at death, and interval from last evaluation to death, as well as each term's interactions by time (expressed as inverse time in years from the last visit). Participant-specific intercepts and slopes were included as random effects, which are assumed to follow a normal distribution with unknown variance. To account for floor effects on some of the measures, data after the first score of 0 were dropped on a by-participant and by-test basis. Each continuous variable was centered. All contrasts were in reference to AD. This parameterization allows for the estimation of the predicted performance for an average participant (varying only the pathologic diagnosis) via the group term, as well as the longitudinal decline each year via the group by time interaction term. Each of the covariates (education, age at death, APOE ε4, and interval from last evaluation to death) is able to influence both the final performance and the slope of decline.

All analyses were performed in R version 3.4.2 (R Core Team, 2013) using the *lme4* package (Bates et al., 2014) with restricted maximal likelihood estimation. Degrees of freedom for the fixed effects were estimated by the Satterwaite approximation as implemented in the package *lmerTest* (Kuznetsova et al., 2015).

3. Results

A total of 195 cases with autopsy-confirmed AD, 18 with HS + AD, and 21 with HS alone were identified (Table 1), and clinical data for the last visit (approximately 1.6 years before death for all groups; $p = 0.89$) and up to 5 additional prior annual visits were selected for modeling. Groups did not differ in gender distribution ($p = 0.60$) or education ($p = 0.55$). An APOE ε4 allele was present in

43% of HS cases, 66% of AD cases, and 78% of HS + AD cases ($p \leq$ 0.05), with a significant post hoc difference only between pure HS and pure AD (adjusted $p < 0.05$). HS and HS + AD participants were older than pure AD participants by approximately 7 years at symptom onset ($p < 0.001$), last visit ($p < 0.001$), and death ($p < 0.001$). The groups did not differ in the prevalence of self-reported history of hypertension ($p = 0.86$), diabetes ($p = 0.13$), or stroke ($p = 0.99$). Of the vascular pathologies assessed at autopsy, only prevalence of microinfarcts significantly differed between groups, with a greater proportion of HS than AD participants affected on pairwise post hoc testing (adjusted $p < 0.05$). However, the proportion of participants with at least 1 vascular pathology present was near 70% in all 3 groups ($p = 0.99$).

The consensus clinical diagnosis for participants in each group was possible or probable AD in over 85% of cases at the final visit (Table 2) and over 70% at the first visit used for modeling (Table 3). There were no differences between groups ($p = 0.49$ and $p = 0.44$). At the first modeled visit, the groups did not differ in the use of antidepressant medications, antipsychotic medications, or N-methyl-D-aspartic acid antagonists, although a higher proportion of the participants of the HS + AD group were taking acetylcholinesterase inhibitors than those in the AD group (Table 3; adjusted $p < 0.05$).

3.1. Decline in global cognitive measures

Our primary analysis used the MMSE and the Mattis DRS, which were the most commonly administered tests with the most complete data. At the last visit, AD and HS + AD participants were more impaired than pure HS on these measures (Table 2; $p < 0.01$). Tukey's post hoc analysis revealed significant differences between HS and AD, as well as HS and HS + AD groups on every measure (adjusted $p < 0.05$), but there were no differences between AD and HS + AD.

Mixed-effects linear regression was used to assess the trajectories of decline for the participants. All 3 groups exhibited decline over their last 5 years of evaluations (Fig. 2A). For a demographically average individual with all else held constant, HS participants declined $3.3 \pm 1.4\%$ of the maximal score per year slower than AD participants on the MMSE ($p = 0.02$) and $2.9 \pm 1.2\%$ slower on the total Mattis DRS ($p = 0.02$).

The DRS includes 5 subdomains that assess attention, initiation, conceptualization, construction, and memory. HS participants declined $3.1 \pm 1.4\%$ ($p = 0.03$) slower per year on attention, $3.1 \pm 1.3\%$ ($p = 0.02$) slower on initiation, $5.4 \pm 1.9\%$ ($p = 0.004$) slower on construction, and $3.5 \pm 1.5\%$ ($p = 0.02$) slower on conceptualization. HS did not differ from AD in the rate of decline on the memory subscale ($p = 0.51$). The mixed HS + AD group did not differ from pure AD on any DRS subscale.

The model predictions (Fig. 2B–D), plotted over the raw data, indicate that at their final visit, all groups were impaired relative to the reference range of scores obtained from cognitively intact control participants (green shading), with AD and HS + AD more severely impaired than HS on all measures (all $p < 0.05$). Five years before their final visit, all 3 groups were near the normal range on all measures, except DRS memory, which was significantly more impaired in AD participants than in HS participants ($p = 0.03$). A similar pattern is observed when actual scores from the first modeled visit were examined (Table 3; HS > AD on DRS memory, $p < 0.03$).

3.2. Decline in domain specific cognitive tests

As a secondary analysis, we explored trajectories of decline on specific cognitive measures that had data available for at least 50% of visits, using the same model parameterizations. Because most of these measures had less complete data than the MMSE and DRS, models were underpowered to detect differences in slope; instead, inferences are drawn from model predictions at specific time points (Fig. 3).

Memory was assessed using the CERAD Word List (available for 66% of visits), the California Verbal Learning Test (52% of visits), Visual Reproduction Test (56% of visits), and the Logical Memory Test (56% of visits). The CERAD Word List Immediate Recall had sufficient data to demonstrate a significant $2.8 \pm 1.1\%$ slower decline in HS participants than AD participants ($p = 0.01$). At the

Table 2
Global cognitive performance at the last visit by pathologic diagnosis

	AD, n = 195	AD + HS, n = 18	HS, n = 21	p Value
Clinical diagnosis at last visit, n (%):				
Probable/possible AD	173 (89%)	17 (94%)	18 (86%)	0.49
MCI	2 (1%)	0 (0%)	1 (5%)	
DLB	17 (9%)	1 (6%)	1 (5%)	
Other	3 (1%)	0 (0%)	1 (5%)	
CDR at last visit[a], n (%)				
0	0 (0%)	0 (0%)	0 (0%)	<0.001[b,d]
0.5	5 (4%)	0 (0%)	3 (21%)	
1.0	15 (12%)	3 (23%)	7 (50%)	
2.0	61 (49%)	4 (31%)	4 (29%)	
3.0	44 (35%)	6 (46%)	0 (0%)	
POD at last visit[a], mean ± SD	16.7 ± 3.9	18.0 ± 3.3	11.9 ± 6.3	<0.001[b,d]
MMSE, mean ± SD (/30)	10.5 ± 8.0	10.7 ± 7.7	18.4 ± 6.1	<0.001[b,d]
DRS total, mean ± SD (/144)	63.4 ± 37.9	59.7 ± 41.3	101.0 ± 26.1	<0.001[b,d]
DRS attention, mean ± SD (/37)	23.2 ± 11.3	23.2 ± 12.2	32.5 ± 5.9	0.002[b,d]
DRS initiation, mean ± SD (/37)	11.1 ± 9.8	11.0 ± 11.2	21.9 ± 9.6	<0.001[b,d]
DRS construction, mean ± SD (/6)	2.2 ± 2.1	1.8 ± 1.6	4.1 ± 1.6	<0.001[b,d]
DRS conceptualization, mean ± SD (/39)	19.7 ± 13.0	17.9 ± 13.6	30.5 ± 9.0	0.001[b,d]
DRS memory (/25)	7.1 ± 4.8	5.7 ± 5.5	12.0 ± 4.9	<0.001[b,d]

p Values from Fisher Exact or ANOVA tests as appropriate.
Key: AD, Alzheimer's disease; CDR, Clinical Dementia Rating; DLB, dementia with Lewy Bodies; DRS, Mattis Dementia Rating Scale; HS, hippocampal sclerosis; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; POD, Pfeffer Outpatient Disability scale; SD, standard deviation.
[a] Missing data: CDR (n = 82, 35%), POD (n = 47, 20%).
[b] Significant post hoc pairwise comparison between HS and AD.
[d] Significant post hoc pairwise comparison between HS + AD and HS.

Table 3
Global cognitive performance at first modeled visit by pathologic diagnosis

Acetylcholinesterase	AD, n = 195	AD + HS, n = 18	HS, n = 21	p Value
Interval from first modeled visit to last visit, y, mean ± SD	4.0 ± 1.3	4.3 ± 1.2	4.1 ± 1.7	0.15
Clinical diagnosis at first modeled visit, n (%)				0.44
Cognitively normal	10 (5%)	1 (6%)	1 (5%)	
Probable/possible AD	161 (83%)	15 (83%)	15 (71%)	
MCI	10 (5%)	1 (6%)	3 (14%)	
DLB	7 (4%)	1 (6%)	0 (0%)	
Other	7 (4%)	0 (0%)	2 (10%)	
CDR at last visit[a], n (%):				0.04[d]
0	4 (4%)	0 (0%)	1 (6%)	
0.5	24 (23%)	0 (0%)	7 (41%)	
1.0	63 (59%)	11 (73%)	9 (53%)	
2.0	15 (14%)	4 (27%)	0 (0%)	
3.0	0 (0%)	0 (0%)	0 (0%)	
Medications used[a], n (%):				
AChE inhibitors	59 (30%)	12 (67%)	9 (43%)	0.007[c]
NMDA antagonists	9 (5%)	3 (17%)	0 (0%)	0.06
Antipsychotics	10 (5%)	1 (6%)	0 (0%)	0.68
Antidepressants	47 (24%)	4 (22%)	5 (24%)	0.99
POD at first modeled visit, mean ± SD	10.2 ± 5.2	12.2 ± 5.7	7.4 ± 5.3	0.02[d]
MMSE[a], mean ± SD (/30)	21.7 ± 5.4	22.1 ± 3.8	24.4 ± 2.5	0.07
DRS total[a], mean ± SD (/144)	112.2 ± 20.1	113.9 ± 12.4	121.7 ± 10.4	0.09
DRS attention, mean ± SD (/37)	33.8 ± 3.9	35.3 ± 1.4	35.5 ± 1.5	0.06
DRS initiation, mean ± SD (/37)	26.1 ± 7.8	26.4 ± 6.2	29.4 ± 5.2	0.17
DRS construction, mean ± SD (/6)	4.6 ± 1.5	4.5 ± 1.2	4.8 ± 1.3	0.80
DRS conceptualization, mean ± SD (/39)	33.0 ± 5.9	33.5 ± 3.4	34.2 ± 2.6	0.63
DRS memory (/25)	14.6 ± 5.4	14.2 ± 5.3	17.8 ± 4.7	0.03[b]

p Values from Fisher's Exact test or analysis of variance tests as appropriate.
Key: AChE, acetylcholinesterase; AD, Alzheimer's disease; CDR, Clinical Dementia Rating; DLB, dementia with Lewy Bodies; DRS, Mattis Dementia Rating Scale; HS, hippocampal sclerosis; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NMDA, N-methyl-D-aspastate; POD, Pfeffer Outpatient Disability scale; SD, standard deviation.
[a] Missing data: MMSE (n = 3, 1 %), DRS (n = 8, 3%), medications (n = 1, <1%), CDR (n = 95, 41%), POD (n = 14, 6%).
[b] Significant post hoc pairwise comparison between HS and AD.
[c] Significant post hoc pairwise comparison between HS + AD and AD.
[d] Significant post hoc pairwise comparison between HS + AD and HS.

final visit, HS participants were significantly less impaired than AD participants on all 5 memory measures (all $p < 0.05$). Five years before the final visit, HS were significantly less impaired than AD only on Logical Memory immediate recall ($p < 0.01$) and Visual Reproduction Test immediate recall ($p < 0.01$). These groups showed comparable performance on CERAD Word List immediate recall and recognition, as well as CVLT immediate recall, at this earlier time point. The delayed recall conditions of these tests were at floor for participants in all 3 groups and could not be modeled.

Attention was assessed using the Digit Span test (58% of visits). HS participants performed significantly better than AD participants at both the final visit ($p < 0.05$) and 5 years before ($p < 0.01$).

Executive function was assessed using the Digit Symbol Substitution test (53% of visits), the Wisconsin Card Sorting Test (53% of visits), and the Trail Making Test Parts A and B (56% of visits). HS, AD, and HS + AD participants did not differ in performance on these measures at any time point.

Visuospatial ability, assessed via the Block Design test (82% of visits), was less impaired in HS participants than AD participants at the final visit ($p < 0.001$) and 5 years before ($p < 0.05$).

Language was assessed using Verbal Fluency (85% of visits) and the BNT (86% of visits). At the final visit, HS participants performed significantly better than AD participants on the Category Fluency test ($p < 0.001$), the F-A-S Letter Fluency test ($p < 0.05$), and the BNT ($p < 0.01$); however, 5 years before, they performed better only on the Category Fluency test ($p < 0.05$).

3.3. Trajectories of functional impairment

In addition to less severe cognitive impairment, HS participants were also less functionally impaired at their final evaluation than either AD or HS + AD participants as judged both by their global Clinical Dementia Rating score ($p < 0.001$) and their POD scale score ($p < 0.001$) (Table 2). HS participants were also less impaired than HS + AD participants on the Clinical Dementia Rating and POD at the first modeled visit (Table 3, both $p < 0.05$). Our longitudinal modeling approach applied to POD scores (available for 86% of visits) demonstrated nearly identical slopes of increasing functional impairment across groups, with HS participants significantly less impaired than AD participants at both final visit ($p < 0.001$) and 5 years before ($p < 0.05$). HS + AD participants were also more impaired than AD participants at the final visit ($p < 0.05$).

3.4. Age-matched validation

When we repeated the aforementioned analyses with a subset of AD participants matched for age to the HS and HS + AD participants, the pattern of findings was unchanged for all global cognitive and functional tests (data not shown). Results in domain-specific measures were also similar although with fewer significant effects due to a reduced number of participants in the models.

4. Discussion

We examined the profiles of cognitive decline in 234 participants with longitudinal neuropsychological testing who had neuropathologically confirmed diagnoses of HS, AD, or both HS + AD and no other neurodegenerative pathologies that could account for cognitive decline. Consistent with previously published work (Brenowitz et al., 2014; Leverenz et al., 2002), participants with HS were less functionally and cognitively impaired than those with AD or HS + AD proximal to death (Table 2). Less cognitive impairment
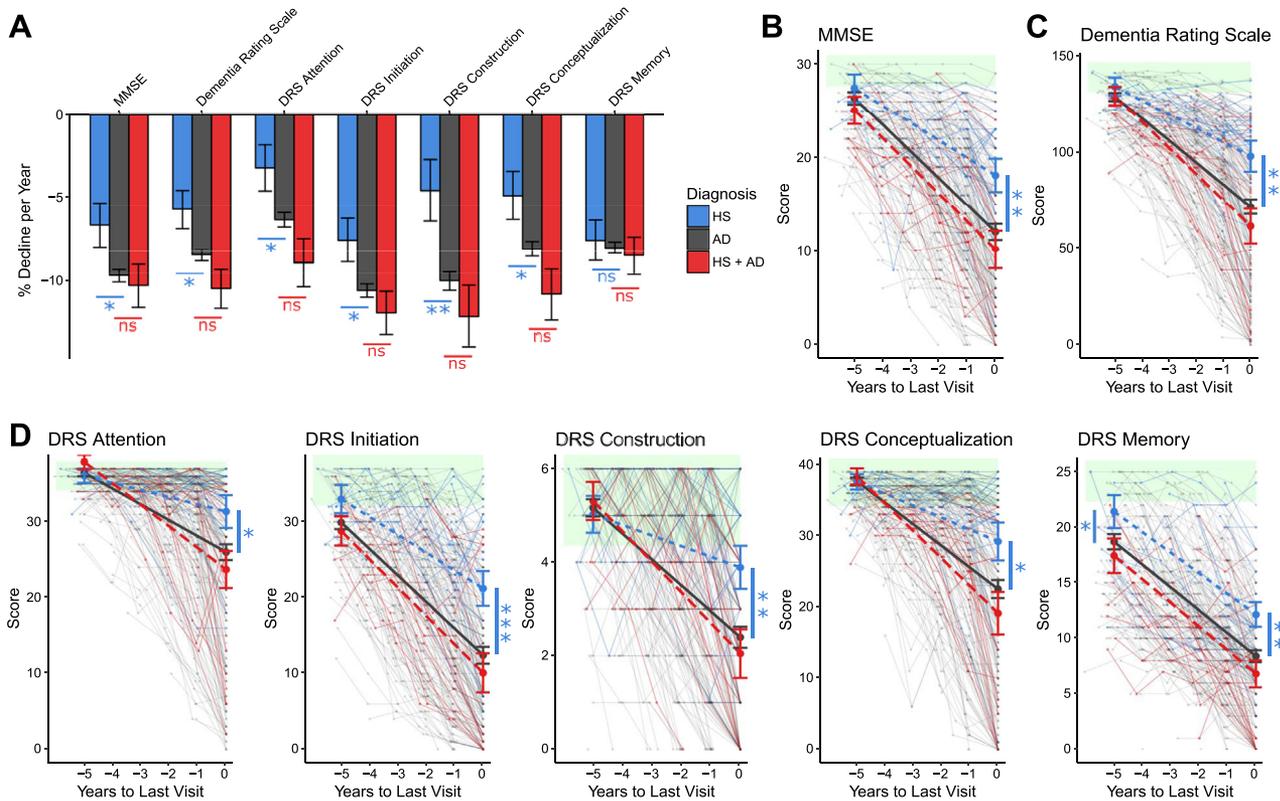
Fig. 2. (A) Trajectories of global cognitive decline by pathologic diagnosis. Linear mixed modeling of the trajectories of cognitive decline due to hippocampal sclerosis (blue), Alzheimer's disease (gray), or both pathologies (red). Average rates of cognitive decline per year (expressed as percentage of maximal score), stratified by eventual pathology, are presented for each cognitive measure. Spaghetti plots of data used for modeling, overlaid with model predictions in bold, are presented for the (B) MMSE, (C) total DRS, and (D) each of the DRS subscales. Green shading represents the reference range for normal performance, defined as being within 1.5 standard deviations of mean performance of ADRC robust normal controls. Comparisons of modeled performance (in reference to AD) were made at the last visit and 5 years before. $^*p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$, as calculated using the Satterwaite approximation for degrees of freedom. Abbreviations: AD, Alzheimer's disease; ADRC, Alzheimer's Disease Research Center; DRS, dementia rating scale; HS, hippocampal sclerosis; MMSE, Mini-Mental State Examination. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

at the last visit apparently reflects slower decline in HS than AD because the groups showed comparable performance 5 years before on both the MMSE and DRS global cognitive measures (Fig. 1). A similar pattern was observed on the DRS attention, initiation, conceptualization, and construction subscales. DRS memory subscale performance, in contrast, showed similar slopes of decline for HS and AD but with a persistent longitudinal profile of less severe memory impairment in HS.

Longitudinal performance on domain-specific neuropsychological tests showed that HS produced a slower rate of decline than AD on measures of language (BNT, F-A-S fluency) and memory for word lists (i.e., CERAD Word List, CVLT). In each case, the HS and AD groups did not differ 5 years before the final visit, but HS were less impaired than AD at the last visit. HS and AD declined at similar rates on 2 additional memory tests (i.e., Visual Reproduction and Logical Memory) and tests of category fluency, attention (Digit Span), and visuospatial ability (Block Design), even though HS were less impaired than AD on these measures overall (i.e., less impaired both 5 years before the last visit and at the last visit). There was no difference in overall impairment or rate of decline on tests of executive function (i.e., Digit Symbol Substitution, Trail Making Test parts A and B); the HS and AD groups did not differ 5 years before the last visit or at the last visit.

Performance on individual neuropsychological tests 5 years before the final visit provides a look at the differential effects of early HS and AD pathology on various cognitive processes at a time when the global mental status is equivalent and near normal levels in the 2 groups. Despite comparable impairment on the CVLT and

CERAD Word List memory tests at that point, AD was more impaired than HS on the immediate recall conditions of the Logical Memory and Visual Reproduction tests (Fig. 2). This discrepancy suggests that these 2 latter tasks engage cognitive processes beyond episodic memory that may be affected more prominently in early AD than in early HS. One possibility, for example, is that the Logical Memory test engages both memory and semantic processing (as the story provides a semantic structure), and language deficits are greater in early AD than in early HS. This is consistent with our finding that AD was more impaired than HS on category fluency but not letter fluency tests, a pattern that is thought to reflect a semantic language deficit (Monsch et al., 1992). Similarly, the Visual Reproduction test may engage both memory and visuospatial abilities (to process the geometric forms), and visuospatial deficits are greater, as shown by our results with the Block Design test, in early AD than in early HS.

A number of our findings are consistent with previous cross-sectional studies that have compared patterns of cognitive deficits in HS and AD. As reported by Corey-Bloom et al. (1997), we found that performance on tests of attention and visuospatial abilities was less impaired in HS than in AD throughout the course of disease. Consistent with Nelson et al. (2011), we found that 5 years before the last visit, HS participants were less impaired than AD participants on the category fluency test, whereas the 2 groups were equally impaired on the CERAD Word List memory test; however, we used the immediate recall condition, whereas Nelson et al. used delayed recall. This pattern was not maintained over time, however, as HS showed slower decline than AD on the CERAD memory test
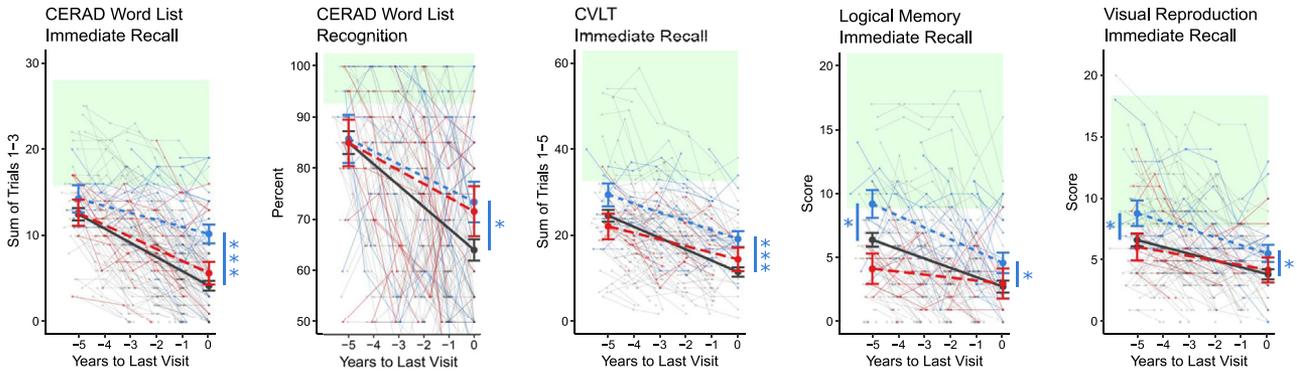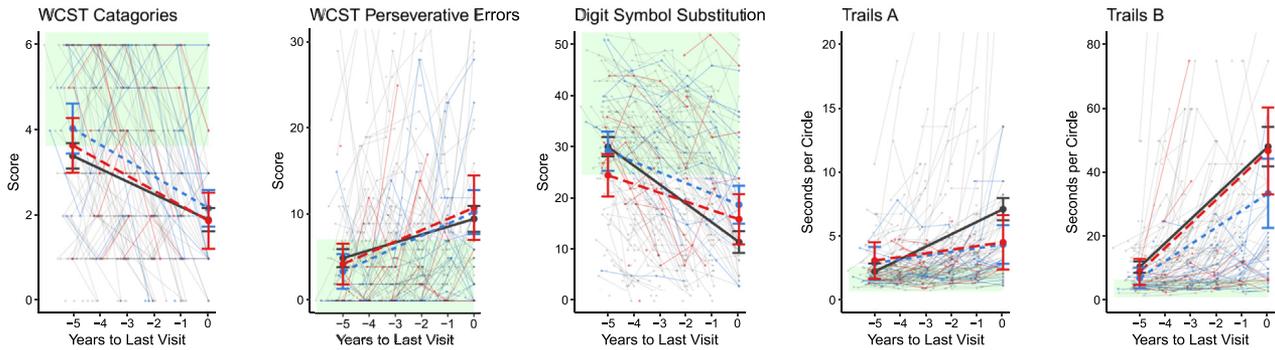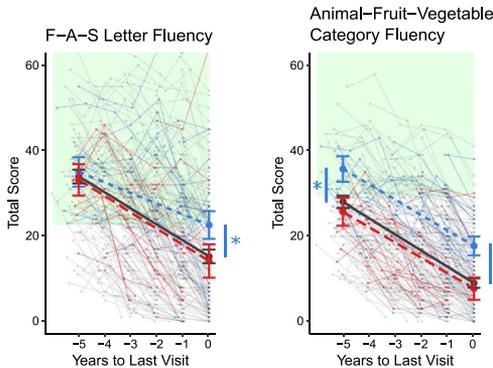
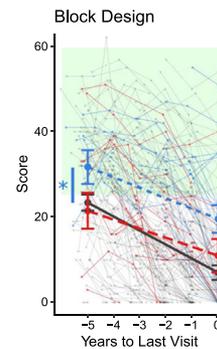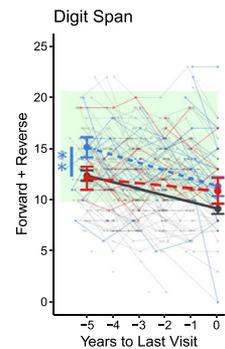**Fig. 3.** Trajectories of cognitive decline on domain-specific measures by pathologic diagnosis. Linear mixed modeling of decline in domain-specific measures due to hippocampal sclerosis (blue), Alzheimer's disease (gray), or both pathologies (red). Green shading represents the reference range for normal performance, defined as being within 1.5 standard deviations of mean performance of ADRC robust normal controls. Comparisons of modeled performance (in reference to AD) were made at the last visit and 5 years before. $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$, as calculated using the Satterwaite approximation for degrees of freedom. Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CVLT, California Verbal Learning Test; WCST, Wisconsin Card Sorting Test; (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

and declined at the same rate as AD on the category fluency test, thus causing the ratio of CERAD memory (either immediate or delayed) to category fluency to not differ in HS and AD groups in the later stages of disease. In contrast to Corey-Bloom et al. (1997) and other investigators (Leverenz et al., 2002), we did not detect differences on measures of executive function at any time point.

Our findings indicate that HS is a progressive pathological process that results in gradual cognitive decline, albeit at a rate slower than that in AD. The involvement of all cognitive domains in HS suggests that the effects of HS pathology are not localized to the hippocampus, as the name might imply, but likely involve diffuse

neocortical regions either directly or through disruption of networks that support the affected cognitive functions. Worse deficits in AD than HS on tasks that require visuospatial and semantic processing may reflect greater disruption of frontotemporal semantic (Binder and Desai, 2011; Mascali et al., 2018) and occipito-parietal visual networks (Deng et al., 2016) that are known to be altered by AD. In contrast, the striking similarity in performance of HS and AD participants on 5 measures from 3 different tests of executive function indicates that HS results in similar disruptions to frontal executive networks as AD. Indeed, these executive measures are the only measures to not demonstrate less impairment in HS at

the final visit, suggesting that relative to the levels of impairment in other cognitive functions, executive deficits may actually be more prominent in individuals with HS than in those with AD.

Despite some of the group differences we observed at various time points in the course of disease, the overall similarity of cognitive impairments between HS and AD makes it difficult to confidently distinguish these pathologies on clinical grounds alone. As Nelson et al. (2011) suggested, overlap in the distribution of scores on those cognitive measures that did show group differences means that no measure tested had the discriminatory power necessary for individual classification.

Some investigators suggest that the presence of dementia with a clinical and cognitive profile consistent with AD and neuroimaging evidence of neurodegeneration in an elderly person (e.g., over the age of 80), but in the absence of positive positron emission tomography (PET) imaging or cerebrospinal fluid (CSF) biomarkers of amyloid or tau pathology, suggests the presence of HS (Botha et al., 2018). However, without a positive biomarker for HS, such a diagnosis must remain speculative and may rise only to the level of "probable" or "possible" HS. A pattern of circumscribed medial temporal lobe hypometabolism on fluorodeoxyglucose (FDG) PET imaging has been proposed as a potential marker of HS (Botha et al., 2018) but has yet to be validated. The presence of the transactive response (TAR) DNA-binding protein-43 (TDP-43) has been proposed as a possible pathological marker of the disease, but there is considerable overlap in TDP-43 deposition across AD and other neurodegenerative diseases (e.g., amyotrophic lateral sclerosis, frontotemporal lobar degeneration), and there is currently no PET imaging ligand or CSF marker to measure TDP-43 deposition in the brain. Our results, in conjunction with those of Nelson et al. (2011), show that the pattern of cognitive deficits at a single time point may provide some supportive positive evidence for the diagnosis of HS, but this does not rise to the level where it would be useful for identifying an individual patient, and any diagnostic use of the pattern may depend on the stage of disease. Without a positive biomarker of HS pathology, it will remain very difficult to differentiate the disease from AD.

We observed very few differences between AD and HS + AD groups on cognitive measures in terms of overall severity or rate of decline. These results suggest that the contributions of the 2 pathologies to the development of dementia are not simply additive. As the AD and AD + HS groups had a similar degree of AD pathology (i.e., all were Braak stage V-VI and had moderate-to-severe neuritic plaque density), the addition of HS pathology might be expected to increase the severity of cognitive impairment or the rate of cognitive decline, but this was not the case. The interpretation of these results is limited, however, as the temporal order of onset of the pathologies is not known, and HS + AD participants were more likely than AD participants to be taking acetylcholinesterase inhibitors at the first modeled visit. The only measure that demonstrated a difference between AD and HS + AD groups was the BNT, traditionally considered a measure of cortical (rather than hippocampal) function. This is further evidence for the wide-ranging effects of HS on cognitive functions beyond those thought to be regulated by the hippocampus.

Strengths of this work include the relatively large number of participants compared to most previous studies, the longitudinal nature of the analysis, and the consistency of neuropsychological, clinical, and pathological evaluation. We report performance on a broad range of well-established cognitive instruments, allowing comparison to existing literature. In addition, when we restricted the analysis to AD participants who were age-matched to HS participants, the results were essentially unchanged.

There are also some limitations. First, previous work suggests that HS occurs unilaterally in some cases, yet the ADRC neuropathology protocol assesses only the left hemisphere. Second, given the legacy nature of this study, TDP-43 immunostaining was not routinely performed at the time of autopsy for the vast majority of cases. Though TDP-43 protein inclusions in the hippocampus have been reported in 70%—90% of HS cases (Leverenz et al., 2002; Nelson et al., 2011), this has proved to be a nonspecific pathological marker for HS that also occurs in 20%—60% of cases with pure AD (Amador-Ortiz et al., 2007; Josephs et al., 2014) and is not part of the diagnostic criteria for either disease. Furthermore, a recent study examining the effects of neural pathologies on cognition found that TDP-43 and HS pathologies independently affect distinct cognitive domains, suggesting that they may not be manifestations of the same pathologic process (Wilson et al., 2013). Nonetheless, the association of TDP-43 with cognitive decline is intriguing (both in the context of HS and dementia in general), and we will examine the complex relationship between TDP-43 and cognition in future studies.

5. Conclusion

HS and AD both result in progressive impairments in all cognitive domains, although HS generally appears to decline at a slower rate. Compared with HS, AD disproportionally affects semantic and visuospatial abilities at an early stage of overall cognitive impairment. In contrast, by the final evaluation, HS demonstrated less impairment in all domains except for executive function. Despite these group-level differences, the differing trajectories of decline and the extensive overlap in cross-sectional scores between groups meant that no cognitive measure had the discriminatory power to differentiate HS and AD clinically.

Disclosures

Acknowledgements

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