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Linking Type and Extent of Head Trauma to Cavum Septum Pellucidum in Older Adults With and Without Alzheimer Disease and Related Dementias

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Abstract

Background and Objectives

Cavum septum pellucidum (CSP) is a common but nonspecific MRI finding in individuals with prior head trauma. The type and extent of head trauma related to CSP, CSP features specific to head trauma, and the impact of brain atrophy on CSP are unknown. We evaluated CSP cross-sectionally and longitudinally in healthy and clinically impaired older adults who underwent detailed lifetime head trauma characterization.

Methods

This is an observational cohort study of University of California, San Francisco Memory and Aging Center participants (healthy controls [HCs], those with Alzheimer disease or related dementias [ADRDs], subset with traumatic encephalopathy syndrome [TES]). We characterized traumatic brain injury (TBI) and repetitive head impacts (RHI) through contact/collision sports. Study groups were no RHI/TBI, prior TBI only, prior RHI only, and prior RHI + TBI. We additionally looked within TBI (1, 2, or 3+) and RHI (1–4, 5–10, and 11+ years). All underwent baseline MRI, and 67% completed a second MRI (median follow-up = 5.4 years). CSP measures included grade (0–4) and length (millimeters). Groups were compared on likelihood of CSP (logistic regression, odds ratios [ORs]) and whether CSP length discriminated groups (area under the curve [AUC]).

Results

Our sample included 266 participants (N = 160 HCs, N = 106 with ADRD or TES; age 66.8 ± 8.2 years, 45.3% female). Overall, 123 (49.8%) participants had no RHI/TBI, 52 (21.1%) had TBI only, 41 (16.6%) had RHI only, 31 (12.6%) had RHI + TBI, and 20 were classified as those with TES (7.5%). Compared with no RHI/TBI, RHI + TBI (OR 3.11 [1.23–7.88]) and TES (OR 11.6 [2.46–54.8]) had greater odds of CSP. Approximately 5–10 years (OR 2.96 [1.13–7.77]) and 11+ years of RHI (OR 3.14 [1.06–9.31]) had higher odds of CSP. CSP length modestly discriminated participants with 5–10 years (AUC 0.63 [0.51–0.75]) and 11+ years of prior RHI (AUC 0.69 [0.55–0.84]) from no RHI/TBI (cut point = 6 mm). Strongest effects were noted in analyses of American football participation. Longitudinally, CSP grade was unchanged in 165 (91.7%), and length was unchanged in 171 (95.5%) participants.

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Glossary

ADRC = Alzheimer's Disease Research Center; **ADRD** = Alzheimer disease and related dementia; **AUC** = area under the curve; **BrANCH** = Brain Aging Network for Cognitive Health; **BU-HIEA** = Boston University Head Impact Exposure Assessment; **CSP** = cavum septum pellucidum; **CTE** = chronic traumatic encephalopathy; **HC** = healthy control; **LOC** = loss of consciousness; **OR** = odds ratio; **OSU TBI-ID** = Ohio State University TBI Identification method; **PPG** = Program Project Grant; **PTA** = posttraumatic amnesia; **RHI** = repetitive head impact; **TBI** = traumatic brain injury; **TES** = traumatic encephalopathy syndrome; **UCSF** = University of California, San Francisco.

Discussion

Among older adults with and without neurodegenerative disease, risk of CSP is driven more by duration (years) of RHI, especially American football, than number of TBI. CSP length (≥6 mm) is relatively specific to individuals who have had substantial prior RHI. Neurodegenerative disease and progressive atrophy do not clearly influence development or worsening of CSP.

Introduction

Cavum septum pellucidum (CSP) is a relatively common neuroimaging finding of an anterior separation ("cyst") of the 2 otherwise fused membranes comprising the septum pellucidum. Presence of CSP can be congenital due to incomplete closure of the septum pellucidum during development, but CSP also is observed in higher rates among individuals with prior head trauma. CSP was detected in vivo as far back as the 1930s when Forster (1933) used air encephalography to identify CSP in a patient who had just experienced a traumatic brain injury (TBI). Throughout the 1960s and 1970s, CSP was noted in studies of boxers experiencing neurologic changes and speculated to be the result of repetitive head impacts (RHI) sustained throughout their careers.[1-3] Conclusions drawn over 50 years ago largely ring true for many today who believe "changes in septum pellucidum probably *cause* no neurologic deficit," but that "demonstration of a cavum, by implicating boxing [or other sources of RHI] as its probable cause, is helpful diagnostically."[3]

Clinicians and researchers have long questioned the sensitivity and specificity of CSP to prior RHI or TBI. CSP has been observed in 50%–90% of individuals with prior RHI such as boxers, American football, or rugby athletes, while rates in "unexposed" groups can range from 20% to 50%.[4-8] Autopsy series of patients with chronic traumatic encephalopathy (CTE), a neurodegenerative tauopathy highly specific to prior RHI, report CSP frequency up to 65%.[9,10] It is also unclear whether neurodegenerative disease and progressive atrophy alone may contribute to developing CSP, or worsening CSP over time, even in the absence of RHI/TBI. Addressing these gaps requires evaluating CSP in relation to multiple types of head trauma exposure in older adults spanning the cognitive continuum from clinically normal to suspected Alzheimer disease and related dementia (ADRD).

Specific CSP characteristics such as longer length, rather than presence/absence, may be more specific to prior head trauma. Longer CSP length has been shown in studies of former boxers,[6] American football players,[4] and pediatric patients following single symptomatic TBI.[11] Longer CSP is also observed in patients with psychiatric conditions such as schizophrenia.[12] A key limitation of existing studies describing such variable frequencies in CSP presence or length among both RHI/TBI and non-RHI/TBI groups is inadequate characterization of relevant types of head trauma ranging from subclinical RHI to severe TBI. Relying on methods with low sensitivity to prior RHI/TBI risks overestimating CSP frequency in presumed "unexposed" individuals.

We evaluated CSP presence, grade, and length in healthy and clinically impaired older adults who underwent detailed characterization of lifetime exposure to both RHI and TBI. Most participants were not recruited based on prior athletic or military experience, known RHI/TBI exposure, or known CSP, thereby representing a sample more generalizable to broader aging and dementia research cohorts. CSP changes over time were evaluated in participants who completed longitudinal neuroimaging. A selected cohort with suspected CTE (diagnosed traumatic encephalopathy syndrome, or TES[13]) was used for comparison and to enhance representation of individuals with more extensive prior RHI. The main goal of our study was to determine associations between prior RHI/TBI and CSP characteristics in older adults. We specifically aimed to identify the *type* and *extent* of head trauma most strongly associated with CSP and CSP characteristics (e.g., grade, length) that were most specific to prior RHI/TBI.

Methods

Participants were from the University of California, San Francisco Memory and Aging Center enrolled in the Alzheimer's Disease Research Center (ADRC), Program Project Grant (PPG) on frontotemporal dementia, or Brain Aging Network for Cognitive Health (BrANCH). All participants underwent detailed neurologic and neuropsychological

evaluations and diagnosis by multidisciplinary consensus conference. Healthy controls (HCs) were BrANCH participants characterized as clinically normal, functionally independent, community-dwelling older adults without cognitive concerns. ADRC and PPG participants spanned the diagnostic continuum of ADRDs including Alzheimer disease and frontotemporal dementia spectrum conditions (eTable 1). We additionally identified a subset of the ADRC participants evaluated specifically for concerns related to prior repetitive head trauma and subsequently diagnosed with TES. TES diagnosis is intended to aid antemortem identification of CTE pathology based on the extent of prior RHI and symptom profiles. Individuals meeting criteria for TES can be further classified based on the degree of certainty for underlying CTE (suggestive, possible, or probable CTE).[13]

Head Trauma Exposure Assessment

All study participants completed comprehensive evaluations of lifetime head trauma exposure including symptomatic injuries (TBI) and RHI from contact and collision sports or military service. TBI history was assessed with the Ohio State University TBI Identification method (OSU TBI-ID), and RHI was assessed with the Boston University Head Impact Exposure Assessment (BU-HIEA). In brief, the OSU TBI-ID quantifies the frequency and injury details of prior TBI involving loss of consciousness (LOC) or posttraumatic amnesia (PTA).[14,15] The BU-HIEA characterizes the type and duration of sport participation and military-related exposure (years of service, combat experience, blast exposure, etc).[16] The BU-HIEA further queries symptomatic head trauma without corresponding LOC/PTA, often called "concussion." For this study, we required the presence of LOC *or* PTA to count toward the prior TBI total. TBI severity was based on LOC duration and is noted for descriptive purposes as mild (LOC 0–30 minutes) or moderate to severe (LOC >30 minutes). Moderate-to-severe TBI was rare and did not factor into specific analyses or group assignments. Features of TBI symptoms and severity do not factor into RHI determinations.

The OSU TBI-ID and BU-HIEA were used to create 4 main study groups to allow for better understanding how type of head trauma may relate to CSP characteristics: no RHI/TBI, TBI only, RHI only, and RHI + TBI (Table 1). The no RHI/TBI group reported no prior participation in contact or collision sports, no prior military service, no prior TBI with LOC or PTA, and further denied any symptomatic head trauma without LOC/PTA (i.e., concussion). In addition, a separate fifth group of participants with diagnoses of TES had to meet threshold for proposed diagnostic certainty levels of either possible or probable CTE.[13]

To determine dose-response relationships between types of head trauma exposure and CSP characteristics, we created exposure groups for number of prior TBI (1, 2, or 3+ TBI) and duration (years) or RHI exposure (1–4, 5–10, 11+ years). RHI duration was calculated as the sum of all years participating in

Table 1 Descriptions and Inclusion Criteria for Exposure Categories

Exposure category	Inclusion criteria	Additional stratifications
No RHI/TBI	Denied participation in any contact or collision sports (BU-HIEA) Denied military service involving any high-risk training activities or blast exposure (BU-HIEA) Denied history of any TBI with LOC or PTA (OSU TBI-ID) Denied history of any symptomatic head trauma including concussion without LOC/PTA (BU-HIEA)	Reference group for all analyses
TBI only	Denied participation in any contact or collision sports (BU-HIEA) Denied military service involving any high-risk training activities or blast exposure (BU-HIEA) Reported history of at least 1 prior TBI with LOC or PTA (OSU TBI-ID)	Groups: 0, 1, 2, 3+ prior TBI
RHI only	Previously participated in at least 1 contact or collision sport (BU-HIEA) OR Prior military service with multiple blast exposures (BU-HIEA) Denied history of any TBI with LOC or PTA (OSU TBI-ID)	1–4 y (minimal) 5–10 y (substantial) 11+ y (extensive) Separate analyses specific to American football duration also conducted
RHI + TBI	Previously participated in at least 1 contact or collision sport (BU-HIEA) OR Prior military service with multiple blast exposures (BU-HIEA) AND Reported history of at least 1 prior TBI with LOC or PTA (OSU TBI-ID)	n/a
TES	Consensus determination of criteria met for TES with either possible or probable CTE level of diagnostic certainty	n/a

Abbreviations: BU-HIEA = Boston University Head Impact Exposure Assessment; CTE = chronic traumatic encephalopathy; LOC = loss of consciousness; OSU TBI-ID = Ohio State University TBI Identification method; PTA = posttraumatic amnesia; RHI = repetitive head impact; TBI = traumatic brain injury; TES = traumatic encephalopathy syndrome.
Inclusion criteria note the type of exposure required to be reported or denied and the corresponding questionnaire in parentheses. Qualifying contact or collision sports included American football, ice hockey, boxing, and soccer. Data were examined for participants reporting information about other sports played to determine whether RHI classification was warranted (e.g., mixed martial arts, rugby) on a case-by-case basis. The "Additional Stratifications" column includes descriptions of more granular exposure groupings used for a subset of follow-up analyses.

contact/collision sports (American football, boxing, ice hockey, and soccer) and specifically for American football participation because this was the most common contact/collision sport in our sample and it is currently the only sport with proposed thresholds reflecting increased risk of long-term negative effects of RHI. RHI duration groups reflect these recent consensus recommendations for minimal, substantial, and extensive exposure.[13] Participants with TES were included in analyses focused on RHI and American football duration (detailed TBI with LOC/PTA history unknown for TES group).

Brain MRI Acquisition and Automated Reorientation

Participants underwent structural magnetic resonance imaging at the University of California, San Francisco (UCSF) Neuroscience Imaging Center using either a Siemens Trio Tim or Prisma Fit 3T scanner. Magnetization-prepared rapid gradient-echo sequences were used to obtain whole-brain T1-weighted images. Parameters for both Trio and Prisma scanners had nearly identical parameters but slightly different echo times (Trio: 2.98 milliseconds; Prisma: 2.9 milliseconds). An automated pipeline was developed to ensure all images were in a standardized orientation where the anterior-posterior axis in the sagittal plane bisected the corpus callosum through the genu anteriorly and splenium posteriorly (see eMethods for more details).

CSP Measurement

CSP was defined as a cyst (space) observed within the pre-fornix septum. T1-weighted brain MRIs for each participant were evaluated to determine CSP presence/absence, CSP grade, and CSP length. CSP grade and length measurement followed previously described approaches.[4] CSP grades were based on visual inspection of the widest point of septum pellucidum separation, typically seen on the anterior-most slice viewed in the coronal plane, and coded as 0 ("absent"), 1 ("borderline/equivocal"), 2 ("mild," width less than septum thickness), 3 ("moderate," width greater than septum thickness but less than half intraventricular width), or 4 ("severe," width at least half intraventricular width). CSP length in millimeters was based on the number of sequential coronal slices that separation was visible (slice width = 1 mm). For a CSP to be counted as "present," we required a length of at least 3 mm to limit the influence of near ubiquitously observed very small CSP and to improve generalizability to MRI parameters with thicker brain slices (i.e., >1 mm) in different clinical or research settings.

Interrater and Intrarater Reliabilities

Before reviewing any MRIs, all raters were provided standardized methods for measuring CSP grade and length along with examples of different CSP grades. Scans were reviewed by 2 independent raters blinded to head trauma exposure history and clinical diagnosis to establish interrater reliability for each CSP characteristic. Each rater also reevaluated a subset of 10 scans twice to establish intrarater reliability. Scans representing the spectrum of CSP grades and lengths were chosen for intrarater reliability by the lead author. Discrepancies in CSP presence/absence or grade were adjudicated by a third independent reviewer. Final determination of CSP length reflected the average measured length between the 2 independent reviewers.

Additional Measurements

Prior studies have incorporated measurement of pre-fornix length and total septum length to account for individual differences in head/ventricle size influencing CSP characteristics.[4] Both were measured in our study but not found to affect study results. All study results therefore represent CSP grade and length unadjusted for pre-fornix or total septum length.

Other studies have also separately measured cavum vergae, which has been variably defined and measured across studies. Cavum vergae refers to separation in the post-fornix septum either as an extension of the CSP (CSP et vergae) or emanating from the splenium, analogous to the pre-fornix separation of the CSP emanating from the genu. We do not specifically evaluate cavum vergae independently from CSP measurements, though CSP et vergae would be accounted for in the overall measurement of the CSP length in our study, which includes all separation along the length of the entire septum (both pre-fornix and post-fornix).

Statistical Analyses

Analyses were performed using IBM SPSS (version 28). Analysis of variance and the χ^2 test were used to compare study groups on demographic characteristics. Interrater and intrarater reliabilities were evaluated using weighted Cohen κ and Pearson correlation (R^2). All analyses included sex as a covariate. RHI was evaluated for combined contact/collision sport exposure and specifically for American football participation. The HC and ADRD participants were combined for most analyses with stratified results provided as supplemental data. Likelihood of CSP presence and mild or worse grade (2+) were determined using logistic regression with odds ratios (ORs) and 95% CIs (dummy-coded study groups with no RHI/TBI as the reference group). Group differences in CSP length (log transformed) were analyzed with analysis of covariance. Planned post hoc analyses were limited to pairwise comparison with the no RHI/TBI reference group (least significant difference and Cohen *d* effect size). We additionally compared TES with the subgroup of no RHI/TBI with ADRD to assess more directly RHI effects among those with clinical impairment. Correlations with continuous variables were determined using the Spearman ρ. Area under the curve (AUC) analyses were used to determine how accurately CSP length discriminated between study groups (0.60–0.69 = "poor," 0.70–0.79 = "fair," 0.80–0.89 = "good," and ≥0.90 = "excellent"). The Youden index informed the CSP length that optimally balanced sensitivity and specificity to a given type or extent of head trauma exposure. Repeated measures analysis of covariance were planned for evaluating longitudinal changes in CSP in participants with a second brain MRI. We additionally provide qualitative descriptions of CSP features that emerged during our review.

Table 2 Descriptive Statistics for the Overall Study Sample and Stratified by Head Trauma Exposure Group

	Overall	No RHI/TBI	TBI only	RHI only	RHI + TBI	TES
N	266	123	52	41	30	20
Age, y	66.8 (8.2)	68.2 (7.6)	68.0 (8.5)	67.0 (8.3)	61.9 (6.9)	61.7 (9.2)
Sex, female, n (%)	121 (45.3)	82 (66.7)	29 (55.8)	9 (22.0)	1 (3.3)	0 (0)
Race/ethnicity, n (%)						
White/Caucasian	240 (89.9)	109 (88.6)	45 (86.5)	38 (92.7)	28 (93.3)	19 (95.0)
Black/African American	6 (2.2)	2 (1.6)	2 (3.8)	0 (0.0)	1 (3.3)	1 (5.0)
Asian	11 (4.0)	7 (5.7)	2 (3.8)	2 (4.8)	0 (0.0)	0 (0.0)
Other/multiracial	8 (3.0)	4 (3.2)	2 (3.8)	1 (2.4)	1 (3.3)	0 (0.0)
Unknown/refused	2 (0.7)	1 (0.8)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Diagnosis group						
HC	160 (60.2)	87 (70.7)	34 (65.4)	26 (63.4)	13 (43.3)	0 (0)
ADRD	106 (39.8)	36 (29.3)	18 (34.6)	15 (36.6)	17 (56.7)	20 (100)
Exposure details						
Prior TBI[a]						
0	164 (66.7)	123 (100)	0 (0)	41 (100)	0 (0)	—
1	48 (19.5)	0 (0)	34 (65.4)	0 (0)	14 (45.2)	—
2	19 (7.7)	0 (0)	13 (25.0)	0 (0)	6 (19.4)	—
3+	15 (6.2)	0 (0)	5 (9.6)	0 (0)	10 (32.3)	—
RHI[b]						
0 y	176 (68.2)	123 (100)	52 (100)	1 (3.0) [blast]	0 (0)	0 (0)
1–4 y	27 (10.1)	0 (0)	0 (0)	14 (42.4)	13 (43.3)	0 (0)
5–10 y	30 (11.6)	0 (0)	0 (0)	13 (39.4)	10 (33.3)	9 (45.0)
11+ y	23 (8.9)	0 (0)	0 (0)	5 (15.2)	7 (23.3)	11 (55.0)
CSP characteristics						
Present, n (%)	156 (58.6)	64 (52.5)	27 (51.9)	25 (61.0)	22 (73.3)	18 (90.0)
Grade						
0	44 (16.5)	20 (16.3)	10 (19.2)	9 (22.0)	4 (13.3)	1 (5.0)
1	131 (49.2)	72 (58.5)	26 (50.0)	17 (41.5)	13 (43.3)	3 (15.0)
2	67 (25.1)	25 (20.3)	13 (25.0)	8 (19.5)	10 (33.3)	11 (55.0)
3	23 (8.6)	6 (4.9)	3 (5.8)	7 (17.1)	3 (10.0)	4 (20.0)
4	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.0)
Length, mm	4.1 (5.1)	3.0 (2.7)	3.6 (4.9)	4.1 (4.9)	5.1 (5.5)	10.2 (10.7)
Length, ≥6 mm	44 (16.5)	8 (6.5)	6 (11.5)	9 (22.0)	9 (29.0)	12 (60.0)

Abbreviations: ADRD = Alzheimer disease and related dementia; CSP = cavum septum pellucidum; HC = healthy control; LOC = loss of consciousness; PTA = posttraumatic amnesia; RHI = repetitive head impact; TBI = traumatic brain injury; TES = traumatic encephalopathy syndrome.
[a] Details of all injuries with LOC/PTA unavailable for the TES group (denominator = 247). Of 152 total TBI with LOC or PTA reported across the cohort, 73 (48.0%) involved LOC, 8 of which were classified as moderate to severe (LOC >30 minutes), including 5 ADRD (4 "TBI only," 1 "RHI + TBI") and 3 HC participants (2 "TBI only," 1 "RHI + TBI").
[b] In 11 cases, participant had known RHI exposure, but details of participation years or ages was unknown; denominator = 258 (no RHI/TBI, N = 123; TBI only, N = 52; RHI only, N = 33; RHI + TBI, N = 30; and TES, N = 20). One participant listed as "0 years" of RHI in the "RHI only" group had documented repeated blast exposure during military service.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the institutional review board at UCSF (IRBs #10-02076 and #10-00619). All participants provided written informed consent during study recruitment.

Data Availability

Qualified researchers from academic, not-for-profit institutions can request deidentified data associated with this study through the UCSF Memory and Aging Center after obtaining IRB approval from the UCSF Human Research Protection Program and completing a resource request (memory.ucsf.edu/research-trials/professional/open-science).

Results

Our sample included 266 participants (age 66.8 ± 8.2 years, 45.3% female; Table 2) including 160 (60.2%) HCs, 86 (32.3%) individuals with ADRD, and 20 (7.5%) with TES. Of the 247 participants not classified as TES, 123 (49.8%) were no RHI/TBI, 52 (21.1%) were TBI only, 41 (16.6%) were RHI only, and 31 (12.6%) were RHI + TBI. As expected, male individuals were overrepresented in the head trauma groups especially the RHI, RHI + TBI, and TES groups. Both the ADRD (64.3 ± 8.6) and TES groups (61.7 ± 9.2) were younger than HCs (68.7 ± 7.3).

CSP Measurement Reliability

For both interrater and intrarater reliabilities, there was substantial agreement for CSP grade (weighted $\kappa = 0.62$ and 0.79, $ps < 0.001$), and CSP length measurement was strongly correlated ($R^2 = 0.71$ and 0.84, $ps < 0.001$; eTable 2). Between raters, there was perfect agreement on CSP grades in 72% of cases. Among the 28% with disagreement, ratings never differed by more than 1 grade level. Based on the frequency of CSP grades and to account for interrater variability in CSP grading, we grouped CSP grade as 0–1 ("none/equivocal"; N = 175) and 2+ ("mild-to-moderate," N = 91; only 1 participant rated as grade 4) for subsequent analyses.

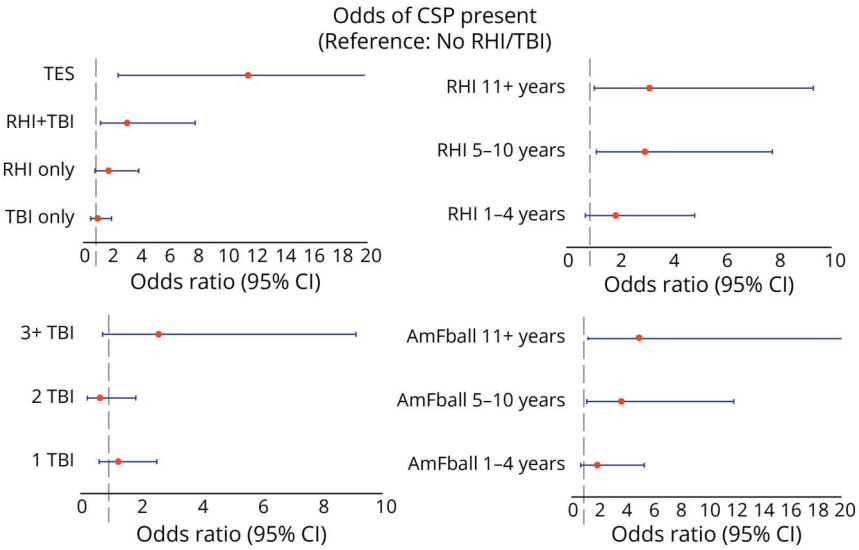
Frequency of CSP

CSP was present in 156 (58.6%) participants. Compared with no RHI/TBI, only the RHI + TBI (OR 3.11 [1.23–7.88], $p = 0.017$) and TES groups (OR 11.6 [2.46–54.8], $p = 0.002$) had significantly greater odds of CSP (Figure 1). Results were similar when comparing the TES group with the subgroup of no RHI/TBI with ADRD (OR 7.7 [1.3–47.8], $p = 0.03$). RHI duration was related to odds of CSP. Compared with no RHI/TBI, participants with 5–10 years (OR 2.96 [1.13–7.77], $p = 0.027$) and 11+ years of RHI (OR 3.14 [1.06–9.31], $p = 0.039$) had higher odds of CSP. Frequency of prior TBI was not significantly associated with higher odds of CSP. The greatest odds of CSP compared with no RHI/TBI were observed when specifically evaluating years of American football participation (5–10 years: OR 3.71 [1.14–12.02], $p = 0.03$; 11+ years: OR 5.02 [1.24–20.30], $p = 0.024$). ORs tended to be nominally higher for ADRD than HC participants (eTable 3). Of note, there were no participants in the HC group with 11+ years of American football participation.

CSP Grade

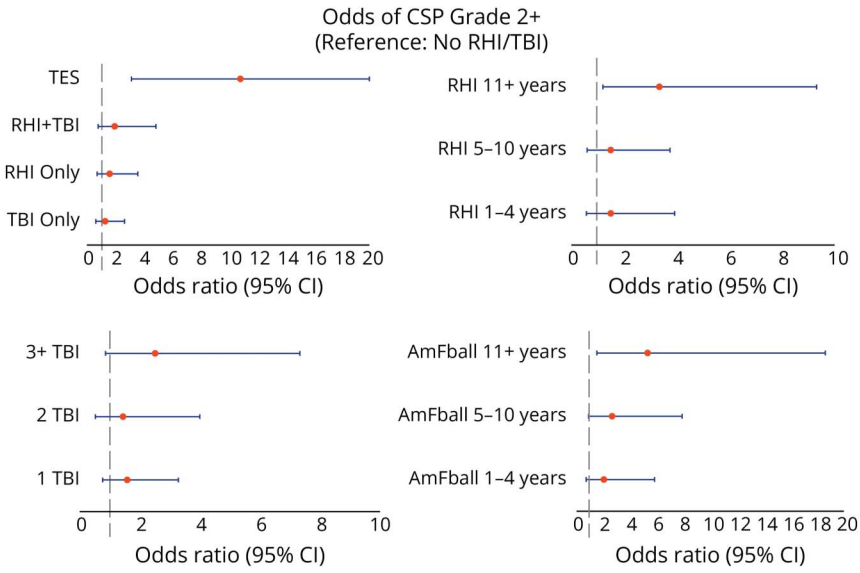
A mild-to-moderate (grade 2+) CSP was present in 91 (34.1%) participants. Compared with no RHI/TBI, only the TES group had significantly greater odds of grade 2+ CSP (OR 10.9 [3.15–37.5], $p < 0.001$; Figure 2). Results were similar when comparing the TES group with the subgroup of no RHI/TBI with ADRD (OR 9.0 [1.8–44.9], $p = 0.007$). Regarding RHI duration, only the 11+ years of RHI group had significantly greater odds of grade 2+ CSP compared

Figure 1 Forest Plots Showing Odds of Having a CSP Present (Minimum 3 mm Length Required)



The reference group for all comparisons was no RHI/TBI. The vertical dashed line represents an OR of 1.0. Orange circles represent the point estimate OR. Point estimates to the right of the dashed line (OR >1.0) suggest a greater odds of having CSP than the no RHI/TBI group. Blue bars represent the 95% CI of the OR. Bars that do not cross the vertical dashed line are statistically significant ($p < 0.05$). For the TES and AmFball 11+ year groups, there was a wide CI with a high upper limit. The x-axis was truncated to avoid visual distortion of the forest plots. Raw CI values are provided in the main text and/or listed in eTable 3. AmFball = American football; CSP = cavum septum pellucidum; RHI = repetitive head impact; TBI = traumatic brain injury; TES = traumatic encephalopathy syndrome.

Figure 2 Forest Plots Showing Odds of Having at Least a Grade 2–Rated CSP



The reference group for all comparisons was no RHI/TBI. The vertical dashed line represents an OR of 1.0. Orange circles represent the point estimate OR. Point estimates to the right of the dashed line (OR >1.0) suggest a greater odds of having CSP than the no RHI/TBI group. Blue bars represent the 95% CI of the OR. Bars that do not cross the vertical dashed line are statistically significant ($p < 0.05$). For the TES group, there was a wide CI with a high upper limit. The x-axis was truncated to avoid visual distortion of the forest plots. Raw CI values are provided in the main text and/or listed in eTable 3. CSP = cavum septum pellucidum; RHI = repetitive head impact; TBI = traumatic brain injury.

with the no RHI/TBI group (OR 3.34 [1.20–9.32], p = 0.021). Focusing on American football, the greatest odds were again seen in the 11+ years of American football group (OR 5.32 [1.52–18.6], p = 0.009), and there was a trend for 5–10 years of American football (OR 2.66 [0.90–7.90], p = 0.078).

CSP Length

At the group level, there was a stepwise increase in average CSP length from no RHI/TBI, TBI only, RHI only, RHI + TBI, to TES (Figure 3). Both the TES ($p < 0.001$, $d = 1.3$) and RHI + TBI groups ($p = 0.039$, $d = 0.46$) had significantly longer CSP than no RHI/TBI, and the TES group had longer CSP than the subgroup of no RHI/TBI with ADRD ($p < 0.001$, $d = 1.3$). For RHI duration, participants with 5–10 years RHI ($p = 0.042$; $d = 0.47$) and 11+ years RHI ($p = 0.003$, $d = 0.74$) had longer CSP than no RHI/TBI. Specifically for American football duration, both 5–10 years ($p = 0.015$, d = 0.65) and 11+ years ($p < 0.001$, $d = 1.1$) had longer CSP than no RHI/TBI. No significant or trend-level differences in CSP length were noted based on the frequency of prior TBI. CSP length for study subgroups by exposure type are summarized in eTable 4.

Across the whole sample, longer RHI duration ($\rho = 0.20$, p = 0.001) and specifically years of American football participation ($\rho = 0.23$, $p < 0.001$) were significantly but weakly associated with longer CSP (Figure 4). Frequency of TBI was not significantly associated with CSP length ($\rho = 0.09$, $p = 0.18$).

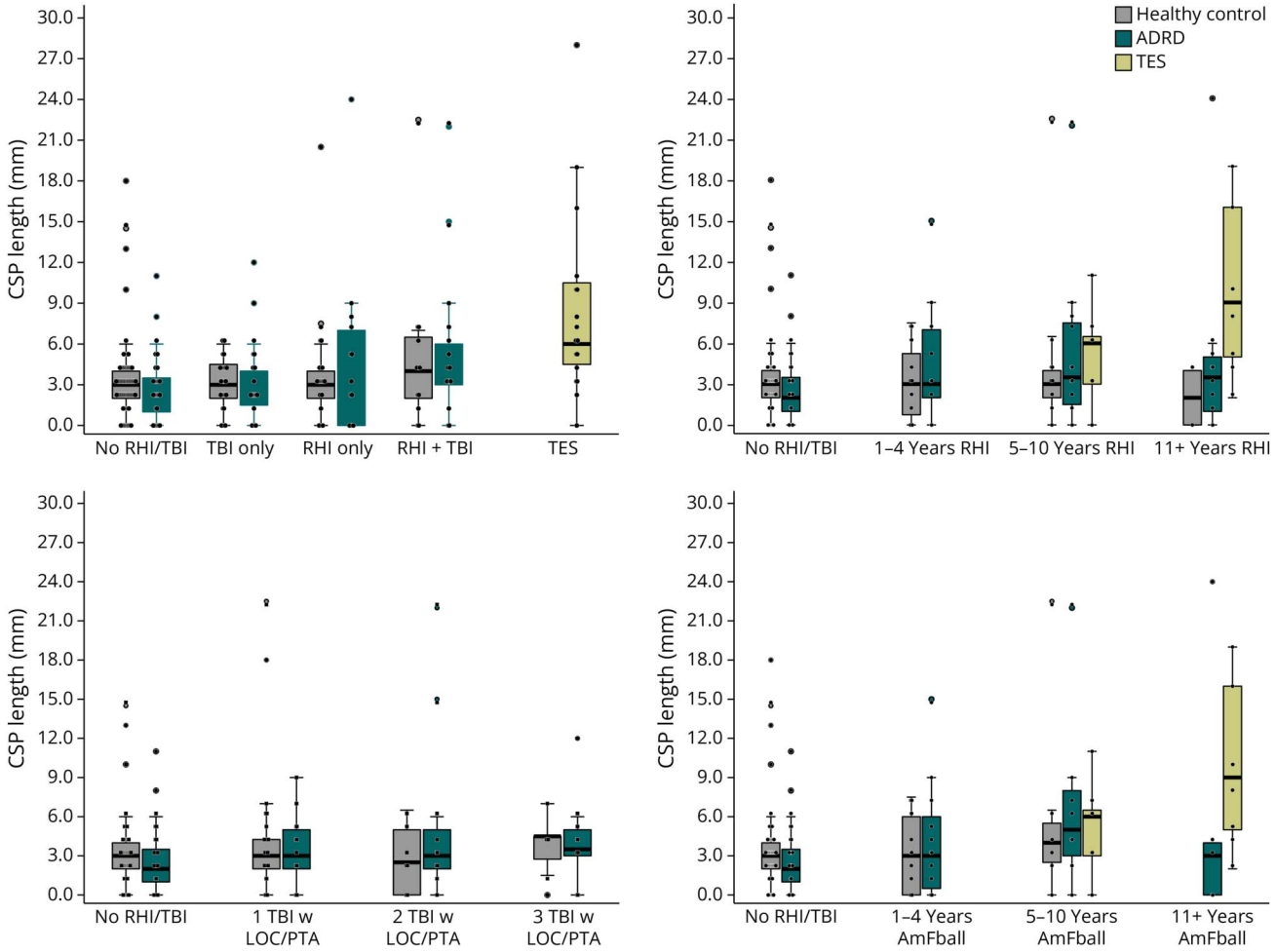
CSP length showed good discriminability of TES from all with no RHI/TBI (AUC = 0.83 [0.71–0.95], $p < 0.001$; Youden index = 6 mm, sensitivity = 63%, specificity = 93%) and no RHI/TBI with ADRD (AUC = 0.84 [0.72–0.96], $p < 0.001$; Youden index = 6 mm, sensitivity = 63%, specificity = 91%) and significant but poor discriminability of RHI + TBI and no RHI/TBI (AUC = 0.64 [0.52–0.76], $p = 0.02$; Youden index = 4 mm, sensitivity = 55%, specificity = 71%; Figure 5). Compared with no RHI/TBI, CSP length also discriminated participants with 5–10 years of prior RHI (AUC = 0.63 [0.51–0.75], $p = 0.03$; Youden index = 6 mm, sensitivity = 33%, specificity = 93%) and 11+ years of prior RHI (AUC = 0.69 [0.55–0.84], $p = 0.004$; Youden index = 4 mm, sensitivity = 68%, specificity = 72%). Discrimination improved when specifically evaluating years of American football participation both for participants with 5–10 years (AUC = 0.69 [0.55–0.84], $p = 0.005$; Youden index = 6 mm, sensitivity = 48%, specificity = 93%) and 11+ years (AUC = 0.75 [0.59–0.92], $p = 0.002$; Youden index = 5 mm, sensitivity = 60%, specificity = 86%). Based on the frequency of prior TBI, there was a trend for significant discriminability of 3+ TBI from no RHI/TBI (AUC = 0.64 [0.48–0.80], $p = 0.065$; Youden index = 4 mm, sensitivity = 59%, specificity = 73%).

Longitudinal CSP Grade and Length Changes

A subset of 179 participants completed a second brain MRI (median [IQR] follow-up = 5.4 [2.4–9.1] years, range 0.3–13.1 years). CSP grade was unchanged in 165 (91.7%) participants with a relatively similar frequency of lower (N = 6, 3.3%) or higher (N = 9, 5.0%) grade rating at follow-up. Each individual participant underwent additional review, and all instances of discrepant CSP grade suggested nearly identical CSP appearance (eFigure 1). There was no reported interim head trauma in any case.

Despite general progression of brain atrophy (eResults), CSP length was unchanged (within 2 mm) in 171 (95.5%)

Figure 3 Box-and-Whisker Plots Showing Differences in CSP Length Between Study Groups



Data are visually stratified by clinical diagnostic group (healthy controls vs ADRD) and the specific subset of participants meeting criteria for TES when applicable. Upper left: TES ($p < 0.001$, $d = 1.3$) and RHI + TBI ($p = 0.039$, $d = 0.46$) had significantly longer CSP than no RHI/TBI. Upper right: participants with 5–10 years RHI ($p = 0.042$; $d = 0.47$) and 11+ years RHI ($p = 0.003$, $d = 0.74$) had longer CSP than no RHI/TBI. Bottom right: both 5–10 years ($p = 0.015$, $d = 0.65$) and 11+ years ($p < 0.001$, $d = 1.1$) of AmFball had longer CSP than no RHI/TBI. Bottom left: no group differences in CSP length based on the number of prior TBI with LOC/PTA. One participant with CSP length of 45 mm (11+ years RHI/AmFball with TES) is not shown to avoid y-axis distortion. Descriptive data for each group are summarized in eTable 4. ADRD = Alzheimer disease and related dementia; AmFball = American football; CSP = cavum septum pellucidum; LOC = loss of consciousness; PTA = posttraumatic amnesia; RHI = repetitive head impact; TBI = traumatic brain injury; TES = traumatic encephalopathy syndrome

participants with equal frequency of shorter (N = 4, 2.2%) and longer (N = 4, 2.2%) length at follow-up (eFigure 2). Too few participants exhibited change in CSP length to perform formal longitudinal analyses. We reviewed the 8 participants with CSP length change of at least 2 mm. Two participants with longer CSP at follow-up were initially characterized as CSP grade 0/length 0 mm and grade 1/length 3 mm at follow-up. In both cases, additional inspection of the baseline MRI suggested there was a small CSP with similar appearance to the follow-up scan and that the discrepancy likely reflected interrater variability. The other 2 participants with longer CSP at follow-up increased from 21 mm to 28 mm and 23 mm to 44 mm, respectively. In both, we suspect the discrepancy was related to incomplete dorsal closure of the septum pellucidum that was more apparent at follow-up. No participants reported RHI or TBI occurring during the interim period between MRIs. In all 4 cases where CSP length was shorter at follow-up, the participant had a small and equivocal CSP at baseline that was then rated as absent at follow-up.

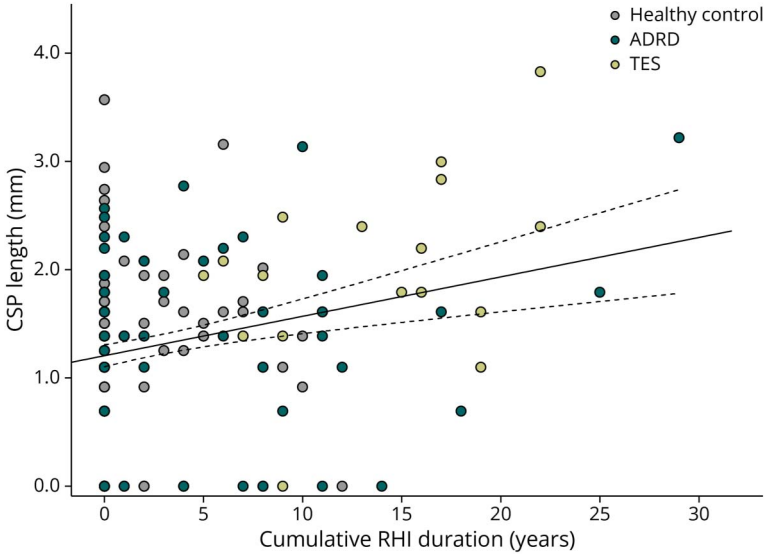
Qualitative CSP Observations

We provide examples and descriptions detailing CSP phenotypes that emerged during our review (eFigure 3). These include (1) CSP with thick appearing bands on coronal view and a relatively high CSP grade (3), but relatively short length (<6 mm) and inconsistent head trauma history, (2) CSP with a tattered and fenestrated appearance that we suspect may increase the likelihood of trauma-induced CSP, and (3) CSP with incomplete CSP separation that may increase the likelihood for measurement variability.

Discussion

CSP is common in the general population but more frequently occurs in individuals with prior TBI or from RHI

Figure 4 Scatterplot Showing the Positive Correlation Between More Cumulative Years of RHI Exposure From Contact/Collision Sports and Longer CSP Length



Dashed lines represent the 95% CI of the linear fit line. Across the whole sample, longer RHI duration (ρ = 0.20, p = 0.001) and specifically years of American football participation (ρ = 0.23, p < 0.001; data not shown) were significantly but weakly associated with longer CSP. Frequency of TBI was not significantly associated with CSP length (ρ = 0.09, p = 0.18; data not shown). CSP = cavum septum pellucidum; RHI = repetitive head impact; TBI = traumatic brain injury.

during activities such as contact or collision sports. We demonstrated that not all types or amount of RHI/TBI increase the odds of having a CSP and that considering CSP length improves specificity to prior RHI/TBI. At a group level, greatest odds of having CSP and more severe CSP (higher grade, longer length) was seen in those with a combination of both prior RHI and TBI. Further analysis of RHI and TBI exposure separately suggested that RHI from contact and collision sports was more strongly and consistently associated with presence, higher grade, and longer length of CSP than prior TBI, in a dose-response manner. Strongest effects were noted when focusing on years of American football participation. A CSP that was 6 mm or longer was highly specific to at least 5 years of prior RHI, which corresponds with proposed thresholds for "substantial" RHI in recent research criteria for TES diagnosis and required exposure for a possible CTE classification. We further showed that neurodegenerative disease or progressive atrophy alone does not seem to alter CSP characteristics longitudinally.

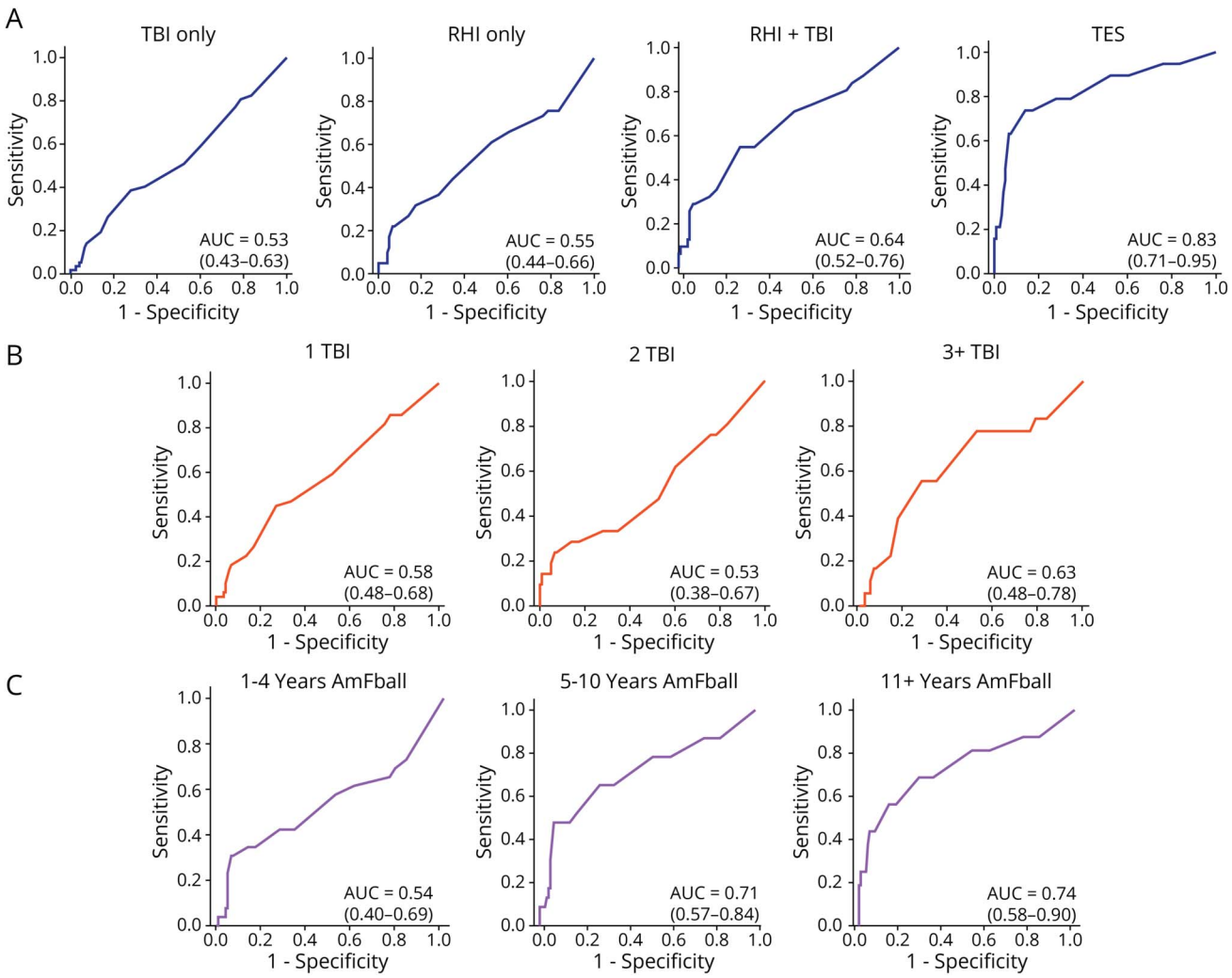
A major strength of our study design was the detailed characterization of both prior RHI and TBI. This increased the likelihood that our comparison group of participants without RHI/TBI had not experienced lifetime head trauma. Regardless, CSP was present in more than 50% of participants in the no RHI/TBI group, highlighting the limited utility of interpreting *any* CSP irrespective of grade and length as potentially suggesting prior head trauma.[8] We note that had we considered the smallest of septum pellucidum separations (i.e., <3 mm length), the frequency of cohort-wide CSP prevalence would have been 83%, including 84% of the no RHI/TBI group. Variability in minimum thresholds for determining CSP presence may contribute to inconsistent frequencies across studies.

Only approximately 6% of the no RHI/TBI participants had CSP 6 mm or longer compared with 30% of the RHI + TBI group and 60% of participants in the TES group. A longer CSP is therefore more specific than sensitive to prior RHI/TBI. Observing a CSP 6 mm or longer on MRI should raise suspicion that the individual has sustained prior head trauma, likely some form of RHI, especially in the absence of any known neurodevelopmental condition that might explain a prominent but congenital CSP.

We did not observe clear differences between HCs and patients with ADRD in the degree to which RHI/TBI was associated with CSP characteristics. Our sample size likely was underpowered to appropriately evaluate the diagnostic subgroups at the higher end of RHI/TBI exposure for controls and ADRD separately or with interaction models. The clinical ramifications of an observed CSP remain uncertain, but future work guided by our findings that focuses on specific CSP features and RHI/TBI thresholds (e.g., CSP ≥6 mm, 5+ years of RHI) may clarify diagnostic or prognostic value.

Results from the Professional Fighters Brain Health Study suggest that longer CSP length relates to lower cognitive scores and brain volume among active and retired boxers and mixed martial artists.[17] Lower brain volume correlates were observed in medial temporal and limbic brain regions such as the thalamus, hippocampus, and amygdala and midline structures such as the basal ganglia and corpus callosum. These regions generally seem susceptible to the effects of RHI/TBI[18,19] and, perhaps unsurprisingly, many are spatially adjacent to the anterior and inferior horns of the lateral ventricle and the septum pellucidum. If an individual has sustained sufficient RHI/TBI to lead to a notable CSP, it may be reasonable to assume that adjacent limbic and midline

Figure 5 AUC Analyses Showing the Group Discrimination Accuracy of CSP Length



Data are shown for (A) the main study group classifications by type of exposure and for analyses based on extent/frequency of particular types of head trauma exposure (B = number of prior TBI; C = years of American football participation). The reference group for all models was no RHI/TBI. Youden index calculations suggested that CSP of at least 6 mm provided an optimal balance of sensitivity and specificity to prior head trauma, most notably for individuals with either 5–10 years or 11+ years of AmFball participation or those meeting criteria for TES. AmFball = American football; AUC = area under the curve; CSP = cavum septum pellucidum; RHI = repetitive head impact; TBI = traumatic brain injury; TES = traumatic encephalopathy syndrome.

structures that more directly relate to clinical symptoms are at high risk of being affected also. This could be especially true for structures attached to the septum pellucidum, such as the fornix and corpus callosum.[18,20] Planned future analyses will evaluate structural and cognitive correlates in our older adult sample with and without ADRD.

We provide further evidence against the hypothesis that neurodegenerative disease or progressive atrophy alone leads to CSP or worsens CSP over time. Only 2% of our longitudinal sample (4/179) had a longer CSP at follow-up, which may be more related to measurement variability. Our ADRD cohort included patients with conditions that often involve profound and rapid atrophy over time such as frontotemporal dementia spectrum disorders. Despite MRIs separated by several years and evidence of clear and expected progression of brain volume loss, CSP features were essentially identical. This was also true for HCs, some of whom completed MRIs separated by more than 10 years.

Beyond quantitative CSP characteristics, there is speculation that qualitative CSP features such as a fenestrated or "ratty" appearance may more clearly point to a traumatic etiology.[4,9,19] This has proven difficult to operationalize, though we observed this phenomenon within our cohort and other CSP "phenotypes" that emerged that we suspect are less consistently attributable to RHI/TBI (eFigure 3). Fenestrated CSP is often described in autopsy cohorts of patients diagnosed with CTE,[9] a neurodegenerative disease essentially observed only in individuals who have had substantial prior RHI. The evidence linking CSP to RHI outweighs the evidence linking CSP to CTE pathology, but a notable CSP

might increase suspicion that RHI has contributed in some way to a neurodegenerative process with or without CTE present. More research is needed in older adults across the ADRD spectrum.

Except for the TES subgroup, our study uniquely focused on older adults who were not selected because of their head trauma history. This improves generalizability to aging cohorts with and without cognitive impairment. Our cohort was a convenience sample of participants that completed comprehensive head trauma exposure surveys and was not prospectively recruited based on head trauma exposure. Reliance on self-report to determine prior RHI/TBI is an inherent limitation of this research field, but prior work suggests the methods we used significantly improve on typical screening questionnaires, and contact/collision sport history is almost never queried in detail.[15,16] Years of RHI is a proxy for cumulative exposure to subclinical and milder impacts, but there is variability across types of exposure (i.e., different sports, sport vs blast exposure) and within sports, such as different risks associated with position or style.[21] The distinction between participants in the TES group and participants in the ADRD group with prior RHI + TBI is relatively subjective and may partly reflect evolving diagnostic frameworks. Of note, the RHI or TBI history in both the HC and ADRD cohorts, which were at times substantial, were not always known before our prospective administration of the OSU TBI-ID and BU-HIEA and therefore would not have factored into multidisciplinary consensus diagnosis. RHI and TBI are much more common among male individuals, and more work is needed to better understand whether the association with structural brain changes such as CSP differs between male and female individuals. Moderate-to-severe TBI was rare in this cohort, so most conclusions related to CSP risk associated with TBI are likely limited to milder forms of TBI. The TES group was relatively small and CIs related to odds of CSP were wide, so larger TES samples are needed to improve the point estimation of the risk of CSP relative to other populations. Our sample was predominantly non-Hispanic White/Caucasian older adults. Findings need to be replicated in samples with better representation of sociodemographically diverse older adults with potentially different social determinants of brain health, including disproportionate exposure to RHI/TBI throughout life.[22] It was more common for participants in the ADRD cohort than the HCs to receive assistance from study partners when completing head trauma surveys, which may increase the risk of underreporting bias. However, these concerns are somewhat alleviated by RHI/TBI exposure frequency being similar or higher in the ADRD cohort than in controls.

Among older adults with and without suspected neurodegenerative disease, a combination of both RHI *and* symptomatic TBI is associated with the greatest odds of having a CSP. Risk of CSP may be driven more by prior RHI, especially American football participation, than isolated episodes of symptomatic mild TBI. Focusing on CSP features such as length (≥6 mm) improves specificity to individuals who have had substantial prior RHI. Neurodegenerative disease and progressive atrophy do not clearly influence development or worsening of CSP.

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Disclosure

L. Iaccarino is currently a full-time employee of Eli Lilly and Company/Avid Radiopharmaceuticals and a minor shareholder of Eli Lilly and Company. His contribution to the work presented in this article was performed, while he was affiliated with the University of California San Francisco. All other authors deny conflicts of interest or disclosures related to the content of this study. Go to Neurology.org/N for full disclosures.

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Continued

Appendix *(continued)*

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Appendix *(continued)*

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