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ORIGINAL PAPER

Contact sport participation and chronic traumatic encephalopathy are associated with altered severity and distribution of cerebral amyloid angiopathy

Oliver J. Standring[1,2] · Jacob Friedberg[1,2] · Yorghos Tripodis[4] · Alicia S. Chua[4] · Jonathan D. Cherry[1,2,3] · Victor E. Alvarez[1,2,3,5] · Bertrand R. Huber[1,2,3] · Weiming Xia[5] · Jesse Mez[1,3] · Michael L. Alosco[1,3] · Raymond Nicks[1,5] · Ian Mahar[1,3] · Morgan J. Pothast[1,2,5] · Hannah M. Gardner[2] · Gaoyuan Meng[2,5] · Joseph N. Palmisano[1,6] · Brett M. Martin[1,6] · Brigid Dwyer[3,7] · Neil W. Kowall[1,2,3] · Robert C. Cantu[1,8,9,10,11] · Lee E. Goldstein[1,12,13,14] · Douglas I. Katz[3,7] · Robert A. Stern[1,3,8,10] · Ann C. McKee[1,2,3,5,14] · Thor D. Stein[1,2,5,14]

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Abstract

Cerebral amyloid angiopathy (CAA) consists of beta-amyloid deposition in the walls of the cerebrovasculature and is commonly associated with Alzheimer's disease (AD). However, the association of CAA with repetitive head impacts (RHI) and with chronic traumatic encephalopathy (CTE) is unknown. We evaluated the relationship between RHI from contact sport participation, CTE, and CAA within a group of deceased contact sport athletes ($n=357$), a community-based cohort ($n=209$), and an AD cohort from Boston University AD Center ($n=241$). Unsupervised hierarchal cluster analysis demonstrated a unique cluster ($n=11$) with increased CAA in the leptomeningeal vessels compared to the intracortical vessels ($p<0.001$) comprised of participants with significantly greater frequencies of CTE (7/11) and history of RHI. Overall, participants with CTE ($n=251$) had more prevalent ($p<0.001$) and severe ($p=0.010$) CAA within the frontal leptomeningeal vessels compared to intracortical vessels. Compared to those with AD, participants with CTE had more severe CAA in frontal than parietal lobes ($p<0.001$) and more severe CAA in leptomeningeal than intracortical vessels ($p=0.002$). The overall frequency of CAA in participants with CTE was low, and there was no significant association between contact sport participation and the presence of CAA. However, in those with CAA, a history of contact sports was associated with increased CAA severity in the frontal leptomeningeal vessels (OR = 4.01, 95% CI 2.52–6.38, $p<0.001$) adjusting for AD, *APOE ε4* status, and age. Participants with CAA had increased levels of sulcal tau pathology and decreased levels of the synaptic marker PSD-95 (p's <0.05), and CAA was a predictor of dementia (OR = 1.75, 95% CI 1.02–2.99, $p=0.043$) adjusting for age, sex, and comorbid pathology. Overall, contact sport participation and CTE were associated with more severe frontal and leptomeningeal CAA, and CAA was independently associated with worse pathological and clinical outcomes.

Keywords Chronic traumatic encephalopathy · Alzheimer's disease · Cerebral amyloid angiopathy · Repetitive head impacts · Mild traumatic brain injury · American football

Introduction

Cerebral amyloid angiopathy (CAA) is characterized by the deposition of beta-amyloid (Aβ) within the vessel walls of cerebral arteries, arterioles, and capillaries [10, 11]. CAA is common in older adults and has been reported in up to 98% of Alzheimer disease (AD) cases [5]. Increasing age and genetic factors impact CAA pathology such as the presence of the *apolipoprotein E (APOE) allele ε4* [11, 42, 44]. CAA is primarily found within leptomeningeal vessels and superficial intracortical vessels and is generally more common in

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✉ Thor D. Stein
tdstein@bu.edu

Extended author information available on the last page of the article

the posterior cerebral cortex (parietal and occipital lobes) than the frontal lobes [4, 43, 53–56]. Beta amyloid (Aβ) deposition in the blood vessel wall leads to progressive weakening and dysfunction of the vessel wall with rupture and subsequent intracerebral hemorrhage (ICH). CAA is a leading cause of ICH in elderly individuals [3, 26, 55]. Independent of other pathologies, CAA is associated with age as well as impaired cognitive function and dementia likely due to a combination of hemorrhage, ischemia, and synaptic damage [11, 27].

Recent studies have suggested an association between traumatic brain injury (TBI) and repetitive head impacts (RHI) and neurodegenerative diseases [1, 20, 39, 41]. RHI and contact sport participation, such as American football, boxing, and ice hockey, are associated with the development of chronic traumatic encephalopathy (CTE). In addition to concussions and severe TBI, head impacts in contact sports that do not result in clinical symptoms (subconcussive injury) may still result in neuronal injury [33, 51]. The total number of years of contact sport participation is associated with the pathological stage of CTE and with severity of tau pathology [2, 12, 34, 35, 38]. For American football players, head collisions predominantly involve the anterior aspect of the skull, and a recent analysis of a helmet-to-helmet collision in football predicted that the greatest strain occurs in the frontal convexities and at the depths of sulci [9, 17, 21]. This correlates with the anatomical areas affected earliest and most severely by tau pathology in CTE and may result in a more frontal distribution of other pathologies, including CAA [34, 49].

Previous studies examining single TBI have not shown a significant relationship to CAA [16, 30]. However, the relationship between RHI and the development of small vessel disease is largely unknown. Amateur football players were found to have blood–brain barrier (BBB) disintegrity by dynamic contrast-enhanced MRI analysis after a single season of play compared to non-contact sport athletes [61]. RHI may also predispose individuals to small vessel vascular pathology such as CAA.

We hypothesized that participants with CTE or a history of RHI would have an altered distribution of CAA as well as increased prevalence and severity of CAA. We also performed a hypothesis free approach to look at the distribution of CAA using hierarchal clustering. Additionally, we hypothesized that CAA was associated with the presence of dementia independent of other pathologies, including CTE.

Methods

A total of 807 autopsy participants were examined from three different study groups utilizing previously described procedures [1, 40]. The Understanding Neurological Injury and Traumatic Encephalopathy (UNITE) group consisted of 357 participants with a history of exposure to contact sports such as football, ice hockey, boxing, soccer, rugby, and martial arts at either the professional or amateur level [37]. For most brain donations, the next-of-kin contacted the brain bank to donate tissue at or near the time of death. The second cohort consisted of 241 participants from Boston University's Alzheimer's Disease Center (BUADC) with and without cognitive impairment who underwent annual cognitive evaluations using the National Alzheimer's Disease Coordinating Center (NACC) Uniform Data Set (UDS) protocol [32]. The third cohort consisted of 209 participants from the Framingham Heart Study (FHS), a longitudinal, community-based study. Consents for brain donation and research participation were provided by donor next of kin. Institutional review boards from the Boston University Medical Center approved brain donation, post-mortem clinical record review, neuropathological evaluation, and clinical interviews with donor family members.

Clinical assessment

For UNITE study participants, information pertaining to RHI history, athletic or military service history, history of cognitive, mood, and behavior changes, and clinical status prior to death were all collected via post-mortem interviews with informants through online surveys and review of medical records as described previously [37]. All interviews were performed by neurologists and neuropsychologists trained to assess for RHI exposure and neurodegenerative diseases. In addition, medical records were examined to provide a comprehensive determination of clinical symptoms. For the FHS participants, an athletic history assessment identical to UNITE was performed with the donor's next-of-kin [21]. Athletic history was not available for BU ADC participants. For all studies, the presence of dementia was determined in a subset of participants by a panel of clinicians after review of medical and study records. A diagnosis of dementia was determined based on modified Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria and included reported evidence of neurobehavioral dysfunction and functional impairment. All interviews were conducted independently and blinded to the results of neuropathological examination.

Pathological assessment

Neuropathological assessment was performed following procedures and criteria previously established for the UNITE study [37, 58]. The neuropathological diagnosis for CTE was made using only pathologic criteria as established by the National Institute of Neurological Disorders and Stroke consensus [32, 35]. Alzheimer's disease was

diagnosed based on the National Institute of Aging Reagan criteria and included intermediate or high probability [40]. CAA was assessed in four cortical regions: dorsolateral frontal (Brodmann area 6, 8), superior temporal (BA 20, 21, 22), inferior parietal (BA 39, 40), and calcarine (BA 17, 18) cortices. CAA evaluation and scoring were performed as described by Vonsattel et al. on a semi-quantitative 0–3 scale determined by the extent of Aβ deposition within a blood vessel using Aβ immunohistochemistry [59]. If no Aβ-positive vessels were seen within a given region it was given a score of 0. The presence of Aβ within smooth muscle cells in a normal vessel was classified as mild CAA and given a score of 1. Replacement of the tunica media by Aβ without evidence of hemorrhage was classified as moderate CAA and given a score of 2. Vessel wall deposition of Aβ with evidence of blood leakage or vessel wall fragmentation was defined as severe CAA and given a score of 3 [59]. Examples of each CAA score are shown in Supplemental Fig. 1. Leptomeningeal and intracortical vessels were scored separately. A global CAA severity score was determined using NIA-AA guidelines [40]. In brief, no CAA was scored as 0, mild CAA or

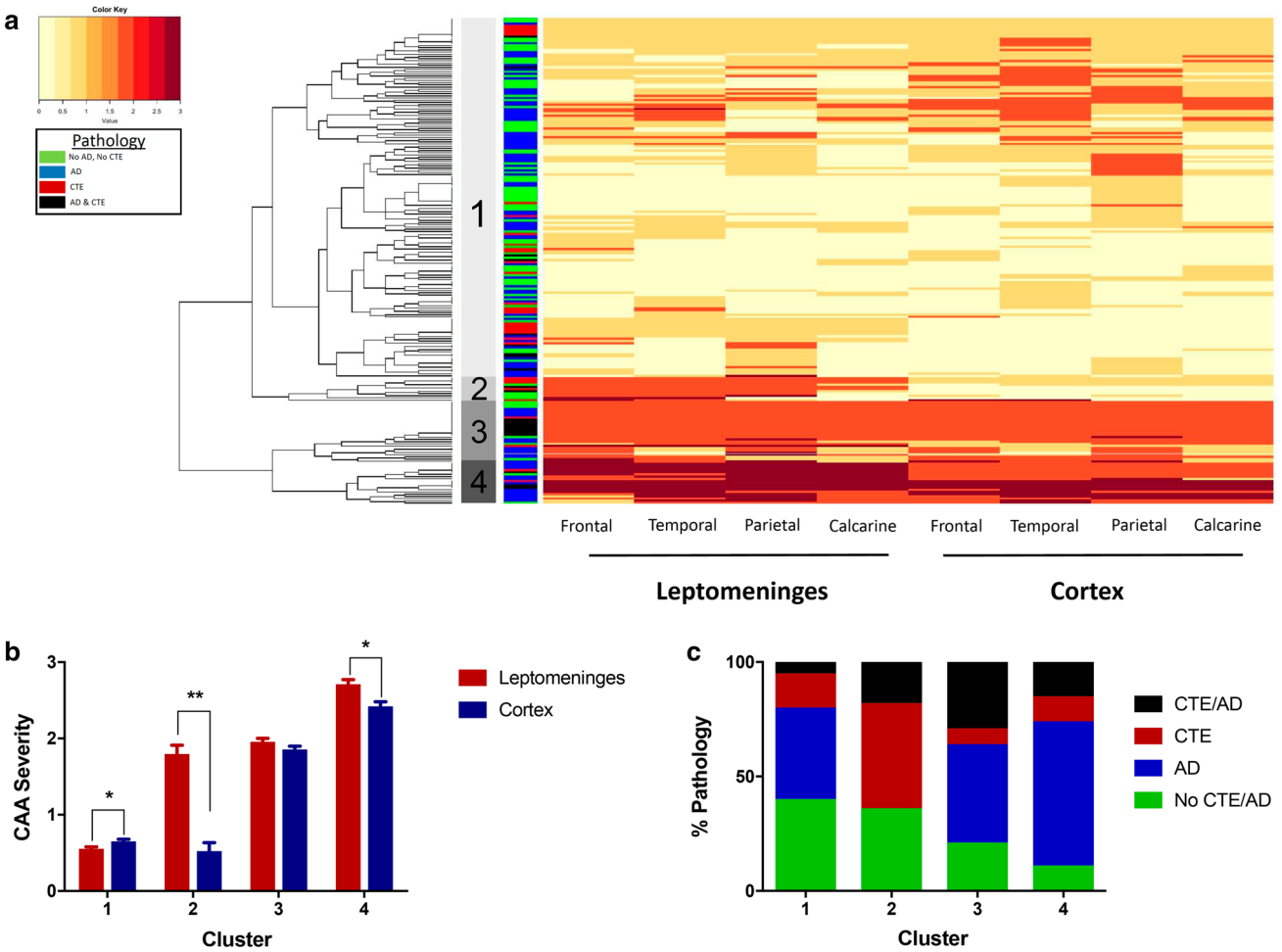

Fig. 1 Distribution of cerebral amyloid angiopathy by hierarchical cluster algorithm. **a** An unbiased hierarchical cluster heatmap shows the distribution and severity of CAA in all participants with CAA and without missing data ($n = 222$). The orange color scale indicates the semi-quantitative severity of CAA (0–3). The four major clusters are indicated by the shaded gray bars to the right of the dendrogram. Pathologic diagnoses are shown in the adjacent green (No AD/CTE), blue (AD), red (CTE), and black (AD & CTE) colored column and in panel C. **b** The mean severity of CAA across all regions is shown for each cluster in both the leptomeningeal (red) and cortical (blue) vessel compartments. Analysis of the clusters using a mixed linear mixed effects model showed that cluster 2 had significantly more severe disease in the leptomeninges across all regions compared to the cortex (**$p < 0.001$). Cluster 4 and cluster 1 also showed significant differences (*$p = 0.001$) but had much smaller mean differences than cluster 2. **c** The composition of the clusters differed significantly by pathology ($p < 0.001$; χ^2 analysis). The proportion of individuals with CTE was significantly higher in Cluster 2 compared to cluster 1 and cluster 4 ($p < 0.001$). Cluster 1 and cluster 4 had a significantly higher percentage of individuals with AD than cluster 2 ($p < 0.001$). There was no difference in the proportion of No CTE/No AD individuals throughout the clusters and the only significant difference in CTE & AD individuals was between clusters 1 and 3 ($p < 0.001$)

scattered Aβ-positive vessels = 1; moderate CAA in multiple brain regions = 2; severe CAA in widespread brain regions = 3.

Immunohistochemistry

Tissue was fixed in periodate–lysine–paraformaldehyde, tissue blocks were paraffin-embedded, and sections were cut at 10 µm for immunohistochemistry. Antigen retrieval for Aβ was performed with formic acid treatment for 2 min. Sections were incubated overnight at 4 °C with antibodies to phosphorylated PHF-tau (AT8; Pierce Endogen, Rockford IL; 1:2000) and Aβ (4G8; BioLegend, San Diego, CA; 1:100,000). Sections were washed three times with PBS (pH 7.4), and subsequently treated with biotinylated secondary antibody and labeled with a 3-amino-9-ethylcarbazol HRP substrate kit (Vector Laboratories). The sections were then counterstained with Gill's Hematoxylin (Vector Laboratories H-3401) and coverslipped using Permount mounting medium. For tau pathology quantification, slides immunostained for ptau (AT8) were scanned at 20× magnification with a Leica Aperio Scanscope (Leica Biosystems, Richmond, IL) as previously described [13]. ImageScope (Leica Biosystems) was used to highlight the gray matter at the bottom third of the sulcus. Leica's image analysis and automated counting software (Aperio positive pixel count, Version 9) was calibrated for staining intensity to detect AT8-immunoreactivity within the region of interest. Counts were normalized to the area measured and are presented as positive pixels per mm^2 within the sulcal depth.

Biochemical pathology measurements

Frozen tissue homogenate was prepared using ice cold 5 M guanidine hydrochloride in Tris-buffered saline (20 mM Tris–HCl, 150 mM NaCl, pH 7.4 TBS) as previously described [50]. The lysate was diluted with 1% Blocker A (Meso Scale Discovery (MSD), Rockville, MD, #R93BA-4) in wash buffer according to the assays for Aβ 1–40 and 1–42 (MSD #K15200E-2) and PSD-95 (MSD #K250QND). Standards with known concentrations were used for Aβ. For PSD-95, arbitrary values were assigned to a reference brain lysate, which was run as a standard curve with every plate. All standards and samples were run in duplicate. Sulfo-tag conjugated anti-mouse secondary antibody was used for signal detection by the MSD SECTOR Imager 2400. Measurements were made on participants with available tissue (No CTE/AD: No CAA, $n = 73$, CAA, $n = 110$; CTE: No CAA, $n = 59$; CAA, $n = 36$).

APOE genotyping

DNA was extracted from brain tissue and APOE genotype determined using two single nucleotide polymorphisms (National Center for Biotechnology Information SNPs rs429358 and rs7412) as described previously [50].

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (IBM Corp, Armonk, NY), Prism v6 and v7 (GraphPad Software, La Jolla, CA), and SAS version 9.4 (SAS Institute Inc., Cary, NC). To determine interrater reliability for CAA scoring between the three rating pathologists (ACM, BRH, and TDS), three participants with each score (0–3) as determined by one pathologist were blindly rated by the other two pathologists and an intraclass correlation coefficient statistic was performed to determine consistency among raters. To cluster similar distributions of CAA according to individual semi-quantitative scores in selected regions, an unbiased hierarchical cluster analysis was performed using the unbiased cluster function in R-Studio 3.4.1 (The R Foundation for Statistical Computing). The dendrogram illustrates this clustering with participants on the same branch with similar distributions and those further away with increasingly dissimilar distributions. Mean differences by cluster were analyzed using a linear mixed effects model allowing for subject-specific and location-specific random effects. For the analysis of variation between subject groups and analysis of prevalence data, we used a Chi-square test for proportions and ANOVA with Bonferroni correction for continuous variables. Age-adjusted estimated marginal means were determined for immunoassay measurements of Aβ and PSD-95. PSD-95 values that were outside 1.5× the interquartile range were eliminated as outliers and included No CTE/AD with CAA ($n = 2$), CTE without CAA ($n = 2$), and CTE with CAA ($n = 1$). Quantitative protein measurements and location severity were analyzed by two-way ANOVA with Holm–Sidak correction for multiple comparisons (GraphPad Prism 8). The relationships between CAA, CTE, contact sport exposure, and dementia were analyzed using logistic regression (dementia or CAA as binary outcomes) or cumulative logit proportional odds (CAA severity as ordinal outcomes) using SPSS (v.24, IBM). To account for differences between autopsy groups, propensity scores based on age, AD, and *APOE ε4* status for the exposed and unexposed group were calculated in SAS version 9.4 and

logistic and ordinal regressions were weighted with the calculated propensity scores.

Results

Participant groups

Participants were grouped based on the presence or absence of CTE or AD pathology. Pathologic groups differed in age, gender, and comorbid pathologies (Table 1). The CTE cohort was significantly younger than other cohorts, and the CTE & AD and the No CTE/No AD groups were younger than the AD group. The CTE and CTE & AD groups also had a higher composition of men than the other groups and were significantly more likely to have participated in contact sports. The prevalence of CAA was highest in the AD and CTE & AD groups. The interrater reliability for CAA scoring between raters was found to be intraclass correlation coefficient = 0.920 (95% CI 0.834–0.962, $p < 0.001$), which shows excellent agreement.

Hierarchical clustering shows distinct CAA distribution groups

To determine patterns of CAA distribution in an unbiased manner, a hierarchical clustering algorithm grouped participants with CAA and without missing data ($n = 222$) by severity of CAA within the leptomeningeal and intracortical vessels in the four cortical regions, resulting in

Table 1 Demographic, clinical, and pathological measures between pathology groups

	No CTE/No AD	AD	CTE	CTE and AD	*p* value
Sample size (*n*)	282	230	251	44	
Cohort					< 0.001[b]
FHS	137 (48.6%)	70 (30.4%)	0 (0%)	2 (4.5%)	< 0.05*,**,***,****,*****,******
UNITE	66 (23.4%)	5 (2.2%)	246 (98.0%)	40 (90.9%)	< 0.05*,**,***,****,*****
BUADC	79 (28.0%)	155 (67.4%)	5 (2.0%)	2 (4.5%)	< 0.05*,**,***,****,*****
Age at death (S.E.M)	74.6 (1.5)	84.3 (0.7)	59.7 (1.2)	75.5 (1.7)	< 0.001[a],*,**,***,****,*****,******
Sex m/f (%male)	176/106 (62.4%)	135/95 (58.7%)	251/0 (100%)	43/1 (97.7%)	< 0.001[b],**,***,****,*****
RHI y/n (%exposed)	76/92 (45.2%)	13/54 (19.4%)	249/0 (100%)	44/0 (100%)	< 0.001[b],*,**,***,****,*****
Exposure years (S.E.M.)	4.12 (0.51)	1.58 (0.50)	16.1 (0.4)	15.9 (1.4)	< 0.001[a],*,**,***,****,*****
CAA with/without (% with)	153/129 (54.3%)	220/10 (95.7%)	72/179 (28.7%)	36/8 (81.8%)	< 0.001[b],*,**,***,****,*****,******
CAA severity score *n* (%)					< 0.001[b]
1	98 (64.1%)	86 (39.1%)	49 (68.1%)	13 (36.1%)	< 0.05*,***,****,******
2	44 (28.8%)	84 (38.2%)	15 (20.8%)	15 (41.7%)	< 0.05****
3	11 (7.2%)	50 (22.7%)	8 (11.1%)	8 (22.2%)	< 0.05*,***
CTE stage % (*n*)					< 0.001[b]
Stage I			37 (14.7%)	3 (6.8%)	
Stage II			54 (21.5%)	4 (9.1%)	
Stage III			97 (38.6%)	11 (25.0%)	
Stage IV			63 (25.1%)	26 (59.1%)	< 0.05******
Neocortical LBD	20/262 (7.1%)	33/197 (14.3%)	13/238 (5.2%)	6/38 (13.6%)	0.002[b],*,****
Remote cortical microinfarcts	74/173 (30.0%)	62/149 (29.4%)	28/189 (12.9%)	7/29 (19.4%)	< 0.001[b],**,*****
Macro-hemorrhages	3/235 (1.3%)	0/203 (0%)	5/195 (2.5%)	1/33 (2.9%)	0.139[b]
Dementia	73/157 (31.7%)	172/18 (90.5%)	123/109 (53.0%)	36/2 (94.7%)	< 0.001[b],*,**,***,****,*****

Data are presented as mean (S.E.M.) years for age at death and contact sport exposure and as # yes/# no (%) unless otherwise indicated

AD Alzheimer disease, *CTE* chronic traumatic encephalopathy, *LBD* Lewy body disease, *RHI* repetitive head impacts

*$p < 0.05$ for comparison between No CTE/No AD and AD

**$p < 0.05$ for comparison between No CTE/No AD and CTE

***$p < 0.05$ for comparison between No CTE/No AD and CTE & AD

****$p < 0.05$ for comparison between AD and CTE

*****$p < 0.05$ for comparison between AD and CTE & AD

******$p < 0.05$ for comparison between CTE and CTE & AD

[a]ANOVA with Bonferroni correction

[b]χ^2 test for proportions between all pathology groups

four distinct clusters (Fig. 1a). Further analysis of these clusters showed that both cluster 2 and cluster 4 had significantly more leptomeningeal than intracortical CAA with cluster 2 showing a dramatic predominance of CAA in the leptomeninges compared to the cortex (Fig. 1b, p's < 0.001). The frequency of CTE was greatest in cluster 2: 64% of individuals in cluster 2 had CTE, and 100% had a history of contact sport participation (p's < 0.001, Table 2, RHI data were missing in one participant). Cluster 2 did not include any individuals with exclusively AD and CAA, despite that pathology comprising 40.5% of the overall cohort. (Fig. 1c, Table 2). Overall, CTE and a history of RHI were overrepresented in cluster 2 which had a predominance of leptomeningeal CAA. However, the small sample size of cluster 2 ($n = 11$) limits the conclusions that can be made from this analysis. We, therefore, next set out to directly test hypotheses about altered CAA with RHI and CTE.

Distribution by pathology

We hypothesized that the distribution of CAA would be altered in CTE such that there would be greater involvement of the frontal lobe compared to an aging AD population. The unbiased hierarchical clustering analysis further suggested increased leptomeningeal disease in CTE. In participants with AD, intracortical ($p < 0.001$) and leptomeningeal ($p = 0.012$) CAA were more frequent in the parietal lobe compared to the frontal lobe (Fig. 2a). In addition, CAA severity scores were significantly greater in the parietal lobe compared to the frontal lobe in AD (cortical $p < 0.001$; leptomeningeal $p = 0.006$, Fig. 2b). In AD, comparison of CAA between the leptomeningeal and intracortical vessels showed no differences in frequency and decreased CAA severity in the leptomeninges compared to the cortex. In contrast, the CTE group had increased CAA frequency in both the frontal and parietal leptomeninges (frontal $p < 0.001$, parietal $p = 0.015$) and increased CAA severity score in the frontal leptomeninges compared to both frontal and parietal cortices (p's $= 0.010$). There were

Table 2 Clinical and exposure measures between clusters

Cluster	1	2	3	4	p value
Sample size (n)	164	11	28	19	
Age at Death (S.E.M)	84.7 (1.0)	72.5 (3.3)	82.4 (2.2)	84.7 (2.5)	$<0.001^{a,*,*****}$
Sex m/f (%male)	89/73 (54.9%)	10/1 (83.3%)	19/9 (67.9%)	13/6 (68.4%)	0.062
Pathology group (n)					<0.001
No CTE/No AD	65 (39.6%)	4 (36.4%)	6 (21.4%)	2 (10.5%)	
AD	66 (40.2%)	0 (0%)	12 (42.9%)	12 (63.2%)	$<0.05^{a,*,*****}$
CTE	24 (14.6%)	5 (45.5%)	2 (7.1%)	2 (10.5%)	$<0.05^{a,*,****}$
CTE & AD	9 (5.5%)	2 (18.2%)	8 (28.6%)	3 (15.8%)	$<0.05^{a,**}$
RHI y/n (%)	42/79 (34.7%)	10/0 (100%)	12/7 (63.2%)	8/4 (66.7%)	$<0.001^{a,*}$
Exposure years	5.4 (0.8)	16.7 (2.0)	7.6 (1.8)	7.9 (0.7)	
LBD y/n (%)	52/112 (31.7%)	3/8 (27.3%)	12/16 (42.9%)	4/15 (21.1%)	0.443
CTE y/n (%)	33/131 (20.1%)	7/4 (63.6%)	10/18 (35.7%)	5/13 (26.3%)	$<0.001^{a,*}$
Stage I	1 (3%)	0 (0%)	1 (10%)	0 (0%)	
Stage II	3 (9.1%)	2 (28.6%)	0 (0%)	0 (0%)	
Stage III	16 (48.5%)	2 (28.6%)	2 (20%)	1 (20%)	
Stage IV	13 (39.4%)	3 (42.9%)	7 (70%)	4 (80%)	
Dementia	99/54 (64.7%)	8/3 (72.7%)	21/6 (77.8%)	16/3 (84.2%)	0.224

Participants with complete CAA data in all brain regions were used in hierarchical clustering analysis ($n = 222$).Values are presented as mean (S.E.M.) years for age at death and contact sport exposure; mean years of exposure are for subjects with sports exposure > 0

AD Alzheimer disease, *CTE* chronic traumatic encephalopathy, *LBD* Lewy body disease, *RHI* repetitive head impacts

*$p < 0.05$ for comparison between clusters 1 and 2

**$p < 0.05$ for comparison between clusters 1 and 3

***$p < 0.05$ for comparison between 1 and 4

****$p < 0.05$ for comparison between clusters 2 and 3

*****$p < 0.05$ for comparison between clusters 2 and 4

[a] χ^2 test for proportions

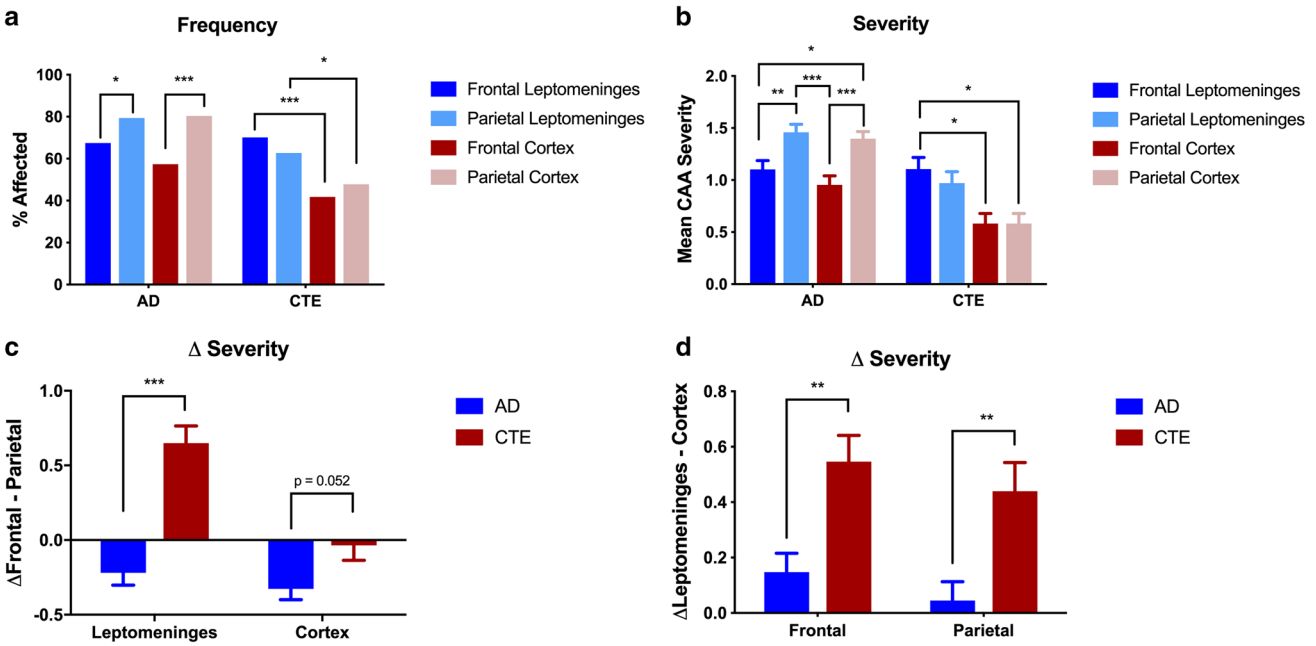

Fig. 2 Distribution of CAA by pathology group. **a** Participants with AD had a significantly increased frequency of CAA in the parietal lobe in both the cortex and the leptomeninges as compared to the frontal lobe. In contrast, participants with CTE had increased CAA frequency in the leptomeninges in both the frontal and parietal lobes compared to the cortex; $*p < 0.05$, $***p < 0.001$, χ^2 tests. **b** Participants with AD had increased CAA severity in the parietal lobe (including in both the cortex and leptomeninges) compared to the frontal lobe compartments. In contrast, participants with CTE had increased CAA severity in the leptomeninges of the frontal lobe compared to the frontal or parietal cortices. **c** CAA severity was significantly increased in the frontal lobe of participants with CTE compared to AD in the leptomeninges ($p < 0.001$) and trended towards increased CAA in the frontal cortex ($p = 0.052$). **d** CAA severity was significantly increased in the leptomeninges of participants with CTE compared to those with AD in both the frontal and the parietal lobes (p's = 0.002). For **b**–**d**, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, ANOVA with Holm–Sidak correction for multiple comparisons

no significant differences between the superior temporal and calcarine cortices in participants with CTE while participants with AD had significantly increased CAA severity in the superior temporal gyrus compared to the calcarine gyrus (Supplemental Fig. 2). Subsequent analysis shows similar location distributions when analyzed by contact sport exposure history instead of pathology, such that participants with a history of contact sports, regardless of pathology, showed the same significant differences seen in the CTE group and those without a contact sport history demonstrated CAA frequency and severity similar to that of the AD group (data not shown). Direct comparison between CAA in AD and CTE further highlights the differences in distribution. The difference of CAA severity was determined for each participant between the frontal and parietal lobes (Δfrontal-parietal). Participants with CTE had a significant increase in Δfrontal-parietal CAA severity compared to those with AD in the leptomeninges ($p < 0.001$) and trended towards an increase in the intracortical vessels ($p = 0.052$; Fig. 2c). Similarly, the difference in CAA severity between the leptomeningeal and intracortical vessels (Δleptomeninges-cortex; Fig. 2d) showed a significant increase in leptomeningeal CAA in those with CTE compared to participants with AD in both the frontal and the parietal lobes (p's = 0.002).

To test whether differences were also present between cohorts, we compared the FHS and UNITE groups (ADC was excluded due to almost unanimous CAA prevalence), adjusting for age, *APOE ε4*, and AD. Logistic regressions showed that compared to the FHS cohort, the UNITE group was less likely to develop CAA overall (OR = 0.49, 95% CI 0.28–0.84, $p = 0.010$), but was more likely to develop CAA in the frontal leptomeninges (OR = 2.12, 95% CI 1.21–3.71, $p = 0.009$).

Contact sport participation and CAA severity

To test the relationship between contact sport participation and CAA in the frontal leptomeninges, logistic (CAA presence) and cumulative logit proportional odds (CAA severity ordinal outcomes) were conducted controlling for age, *APOE ε4*, and AD in a pooled group of participants where contact sport history was ascertained from the FHS and UNITE studies. Due to differences in the groups used for this pooled analysis, we generated propensity scores by matching individuals by age, AD, and *APOE ε4* status. The

sample size was 469 for these analyses due to missing data for *APOE* genotype. To distinguish effects for the presence of CAA (yes/no) versus the severity of CAA (1–3 severity score) we examined each separately. A logistic regression demonstrated that the presence of CAA in the frontal leptomeninges was not significantly associated with a history of contact sport participation (OR = 0.79, 95% CI 0.60–1.04, $p = 0.089$) when the model was weighted by the calculated propensity scores. However, within those participants with CAA, a weighted cumulative logit proportional odds model showed that a history of contact sport participation was associated with increased odds of more severe CAA in the frontal leptomeninges (OR = 4.01, $p < 0.001$, Table 3). Years of contact sport participation was also associated with increased odds of more severe CAA in the frontal leptomeninges (OR = 1.06 per year of play, $p < 0.001$). Sensitivity analyses showed that adjusting for CTE stage gave similar results (contact sport play OR = 3.67, 95% CI 1.72–7.82, $p < 0.001$), suggesting that the association between contact sports and CAA severity is not due in increasing CTE severity.

Table 3 History of contact sport participation predicts increased severity of CAA in frontal leptomeninges

	Severity of CAA $n = 143$		
	OR	95% CI	p value
Contact sport participation (y/n)	4.01	2.52–6.38	< 0.001

Weighted cumulative logit proportional odds regression analysis was performed in participants with CAA > 0 for CAA severity outcome (odds for an increase in severity score 1–3), adjusting for propensity score matching participants by age, AD, and APOE ε4 status

CAA was associated with increased neurodegenerative proteins and decreased PSD-95 density

We next quantified levels of $A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$, and PSD-95 in participants with and without CTE and with frozen tissue available (NoCTE/AD: $n = 183$; CTE: $n = 95$; Fig. 3). As expected, $A\beta_{1\text{-}40}$, a major component of the amyloid in CAA was significantly increased in those with CAA within the CTE group when comparing age-adjusted means ($p < 0.001$, Fig. 3a). In addition, $A\beta_{1\text{-}42}$ was increased in participants

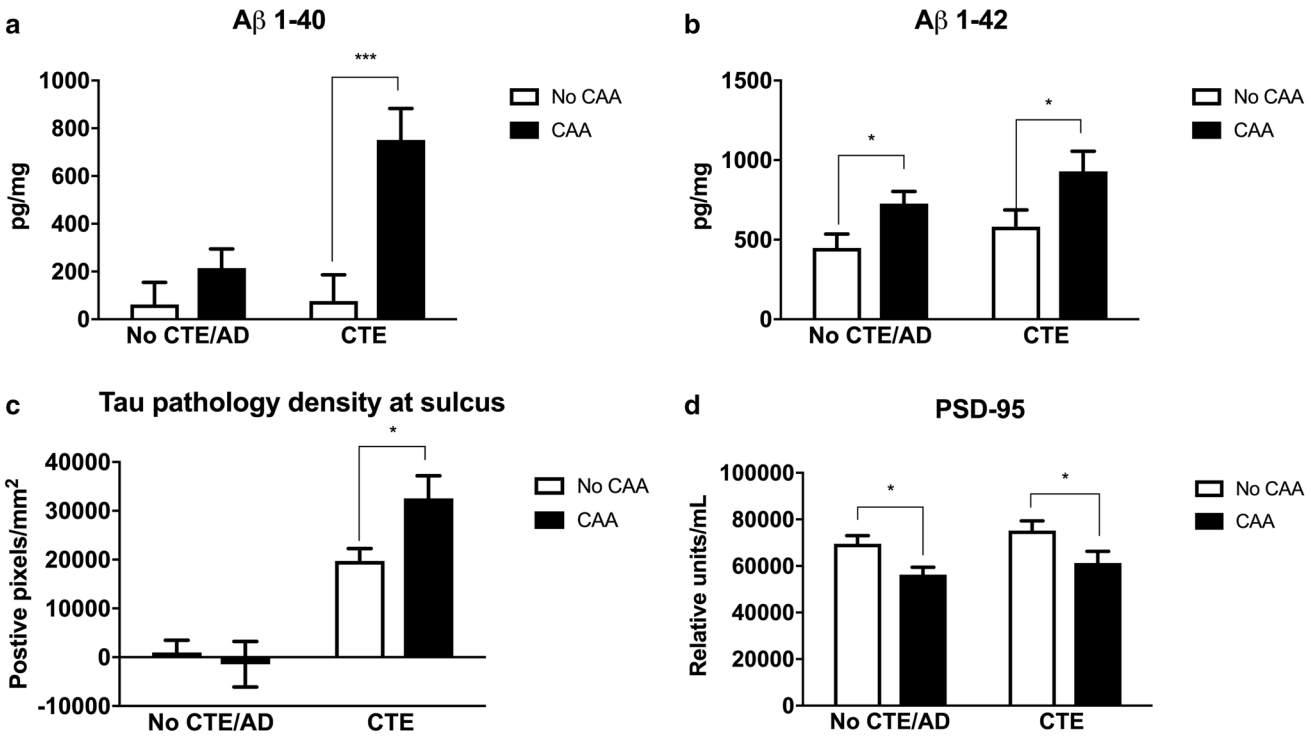

Fig. 3 CAA was associated with altered Aβ, sulcal tau pathology, and synaptic density. $A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$, tau pathology (AT8 density), and PSD-95, a marker of synaptic density, were measured by immunoassay in the dorsolateral frontal cortex, and age-adjusted means are shown. **a** Multiple comparison testing (Holm–Sidak) showed that $A\beta_{1\text{-}40}$ was significantly increased in those with CTE and CAA compared to only CTE. **b** $A\beta_{1\text{-}42}$ was significantly increased in those with CTE and CAA and in those without CTE or AD. **c** Tau pathology as measured by AT8 density was significantly increased within the sulcal depth in participants with CTE and CAA compared to those with CTE alone. **d** CAA was associated with a significant decrease in the age-adjusted means of PSD-95 density in participants without CTE or AD as well as in those with CTE. Age-adjusted means with standard error are shown (*$p < 0.05$, ***$p < 0.001$, ANOVA with Holm–Sidak correction for multiple comparisons)

with CAA with and without CTE (p's = 0.037, Fig. 3b). Age-adjusted AT8 density, a marker of ptau burden, was significantly increased within the sulcus ($p = 0.033$) in those with CTE and CAA as compared to only CTE (Fig. 3c). Given this increased pathology in participants with CAA, we hypothesized that PSD-95 (a marker for synaptic density) would be decreased in those with CAA. In fact, the age-adjusted mean of PSD-95 density was significantly decreased in those with CAA compared to those without CAA with and without CTE (p's < 0.05, Fig. 3d). For PSD-95, mean values were similar, but less significant when outliers were included in the analysis (adjusted $p = 0.072$).

Pathological associations with dementia

We next tested the association of CAA with dementia adjusting for comorbid pathology. A logistic regression demonstrated that moderate to severe CAA was significantly associated with increased odds for ante-mortem dementia (OR 1.75, $p = 0.043$) adjusting for age, sex, CTE stage (stages 0-IV), neocortical Lewy body disease (LBD), AD, and cohort (Table 4). A sensitivity analysis demonstrated a similar effect of CAA on dementia (OR 1.84, CI 1.04–3.26, $p = 0.037$) when adjusting for the presence of cortical microinfarcts.

Discussion

This study examined the relationships between neuropathological diagnoses, RHI exposure from contact sport participation, and CAA. Unbiased hierarchical cluster analysis showed a unique cluster of individuals with leptomeningeal dominant CAA, most of whom had CTE and all of whom had a history of contact sport participation. Subsequent analysis by pathology showed that those with CTE had more CAA in leptomeningeal vessels than in intracortical vessels and had greater involvement of the frontal lobe. In contrast, participants with AD showed more CAA in the parietal lobe compared to the frontal lobe in both leptomeningeal and intracortical vessels. Ordinal logistic regression analysis showed that a history of contact sport play was not significantly associated with the overall presence of CAA, but was associated with more severe CAA in the frontal leptomeninges, adjusting for age, *APOE ε4*, and AD. The presence of CAA, in turn, was associated with increased levels of neurodegenerative proteins, decreased levels of PSD-95, and the presence of dementia. Overall, contact sport participation did not appear to affect the risk of developing CAA, but did modulate the severity and distribution of CAA when present.

Accumulating evidence suggests that prolonged contact sport participation and exposure to RHI are associated with multiple neurodegenerative conditions [1, 34, 38, 39, 50, 60]. However, the role of RHI in the development of small vessel disease is largely unknown. Human post-mortem analyses of individuals exposed to a single TBI demonstrated disruption of the BBB by the presence of extravasated serum proteins in brain tissue, even years after the injury [24, 51] and similar results have been described in a case of CTE [19]. Another study found that Aβ burden was increased in individuals with a history of TBI [47]. Animal models have shown an association between TBI and damage to the meningeal cerebrovasculature, including intravascular leakage into the CSF after TBI [15, 31, 46] and marked disruption of the BBB following single and repetitive blast and concussion exposure [22, 51]. A study of two separate and pooled autopsy cohorts did not find an association between TBI with or without loss of consciousness and the presence of CAA [16]. However, the distribution and severity of CAA was not delineated in this study.

The distribution of CAA has been characterized in multiple aging populations, largely focusing on the topographical distribution between different cortical regions [4, 55, 56]. In AD, CAA predominates in the parietal and occipital lobes [4, 43, 53–56] and may favor the leptomeningeal over the intracortical vessels [4, 6]. We also found CAA significantly increased in the parietal lobe compared to the frontal lobe in AD. In contrast, CAA in the CTE group was more severe in frontal than parietal lobes. Moreover, CAA in the RHI and CTE groups was predominantly leptomeningeal. The leptomeningeal vessels may be particularly susceptible to tissue strain associated with RHI as they are tethered to the pia mater and travel within sulci [21]. Cortical capillary involvement by CAA is a distinct subtype that is related to *APOE ε4* [25, 52]. In addition, dysphoric CAA has been related to tau pathology [45]. Although CAA in participants with RHI and CTE predominantly involved the leptomeningeal vessels and dysphoric angiopathy was not a prominent feature, further study of capillary CAA and dysphoric angiopathy in association with RHI and CTE is warranted.

Table 4 CAA was an independent predictor of dementia

	$n = 690$		
	OR	(95% CI)	p value
AD	10.8	(6.1–19.2)	< 0.001
LBD, neocortical	7.73	(2.55–23.4)	< 0.001
CTE stage	1.70	(1.44–2.00)	< 0.001
CAA	1.75	(1.02–2.99)	0.043

Logistic regression was performed adjusting for age, sex, and cohort

CTE Chronic traumatic encephalopathy (stage 0–IV), *AD* Alzheimer disease, *LBD* Lewy body disease, neocortical type, *CAA* Cerebral amyloid angiopathy severe (severity score 2–3)

One functional consequence of CAA may be the loss of vessel elasticity and the subsequent inhibition of perivascular clearance of solutes out of the brain parenchyma into CSF [18, 23, 48, 62]. Thus, CAA may contribute to the buildup of both Aβ and tau proteins within the brain parenchyma. We found that within participants with CTE, the presence of CAA was associated with significantly increased $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$, sulcal tau pathology, and decreased PSD-95 (synaptic density marker) (Fig. 3). Although CAA may precipitate tau accumulation via vessel dysfunction, it is also possible that tau accumulation may lead to vessel damage and subsequent CAA [36]. Future studies examining the temporal and spatial relationship between CAA and tau accumulation in CTE are necessary.

Consistent with the association between CAA and decreased PSD-95, CAA was a significant predictor of dementia even when adjusting for AD, LBD, CTE, and study group (Table 4). Similarly, a previous study showed that CAA significantly increased risk of AD dementia controlling for AD pathology such as plaques and tangles, suggesting an independent contribution to clinical dementia [8]. As CAA is associated with increased risk for spontaneous hemorrhage, dementia may be partially due to hemorrhagic tissue damage [7, 29]; however, CAA may also independently predict dementia as cognitive decline often precedes overt hemorrhage in subjects with CAA [14, 57]. Our findings show an association between CAA and dementia when adjusting for a history of microinfarcts supporting a role for other mechanisms in CAA-associated dementia such as persistent inflammation, vasoconstriction-related ischemia [28, 63], and decreased synaptic density.

Limitations

There were several limitations to this study. Autopsy groups differed in composition and recruitment. Individuals in the UNITE group were largely self-selected or referred by the next-of-kin after death and do not represent all individuals who have a history of contact sport play. The FHS brain cohort is a subset of the larger FHS cohort, and although it is a community-based study population, autopsy-based selection bias was present as evidenced by high disease prevalence. Although the three cohorts were distinct, data were carefully harmonized. Neuropathological evaluation was performed for all three studies by the same experienced neuropathologists using standard research protocols, and dementia diagnoses were obtained by expert clinicians using established guidelines. Methods for determination of RHI exposure were standardized across FHS and UNITE; however, the data depended on retrospective review that might have introduced bias. In attempts to account for differences in age, sex, pathology, and autopsy group, we adjusted for these variables when appropriate and performed a propensity analysis to appropriately group comparisons when testing for the association of contact sport participation on the development and severity of CAA. Future studies within larger community-based aging cohorts with RHI history as well as prospective studies will be necessary to confirm and expand these findings. Although we used PSD-95 as a marker for synaptic density, there are more precise ways to measure synaptic density such as electron microscopy and super-resolution microscopy, which warrant future study. In addition, the mechanisms underlying the putative vascular injury due to RHI remain to be elucidated.

Conclusions

Both a history of contact sport participation and years of play were significantly associated with increased severity, but not frequency, of CAA in the frontal leptomeninges. In CTE, CAA was primarily leptomeningeal with increased involvement of the frontal relative to parietal cortex compared to participants with AD. Overall, RHI may alter the distribution and severity of CAA and thus lead to increased risk of dementia through multiple pathways.

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Compliance with ethical standard

Conflict of interest Lee E. Goldstein is a paid consultant to Johnson & Johnson (New Brunswick, NJ) / Janssen Research & Development, LLC (Raritan, NJ) and Rebiscan, Inc. (Cambridge, MA). He has received funding from the WWE and Ivivi Health Sciences. Robert A. Stern has received research funding from the NFL, the NFL Players Association, and Avid Radiopharmaceuticals, Inc. (Philadelphia, PA,

USA). He is a member of the Mackey-White Committee of the NFL Players Association. He is a paid consultant to Amarantus BioScience Holdings, Inc. (San Francisco, CA, USA) and Avanir Pharmaceuticals, Inc. (Aliso Viejo, CA). He receives royalties for published neuropsychological tests from Psychological Assessment Resources, Inc. (Lutz, FL, USA), as well as compensation from expert legal opinion. He has also provided consultation for Biogen (Cambridge, MA). Robert C. Cantu is a paid consultant to the NFL Head Neck and Spine Committee, NOCSAE, and Concussion Legacy Foundation, and he receives royalties from book publications and compensation from expert legal opinion.

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Affiliations

Oliver J. Standring[1,2] · Jacob Friedberg[1,2] · Yorghos Tripodis[4] · Alicia S. Chua[4] · Jonathan D. Cherry[1,2,3] · Victor E. Alvarez[1,2,3,5] · Bertrand R. Huber[1,2,3] · Weiming Xia[5] · Jesse Mez[1,3] · Michael L. Alosco[1,3] · Raymond Nicks[1,5] · Ian Mahar[1,3] · Morgan J. Pothast[1,2,5] · Hannah M. Gardner[2] · Gaoyuan Meng[2,5] · Joseph N. Palmisano[1,6] · Brett M. Martin[1,6] · Brigid Dwyer[3,7] · Neil W. Kowall[1,2,3] · Robert C. Cantu[1,8,9,10,11] · Lee E. Goldstein[1,12,13,14] · Douglas I. Katz[3,7] · Robert A. Stern[1,3,8,10] · Ann C. McKee[1,2,3,5,14] · Thor D. Stein[1,2,5,14]

1 Alzheimer's Disease and CTE Center, Boston University School of Medicine, Boston University, Boston, MA 02118, USA

2 VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130, USA

3 Department of Neurology, Boston University School of Medicine, Boston, MA 20118, USA

4 Department of Biostatistics, School of Public Health, Boston University, Boston, MA 20118, USA

5 Department of Veterans Affairs Medical Centers, Bedford, MA 01730, USA

6 Biostatistics and Epidemiology Data Analytics Center, Boston University School of Public Health, Boston, USA

7 Braintree Rehabilitation Hospital, Braintree, MA 02118, USA

8 Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, MA 20119, USA

9 Concussion Legacy Foundation, Boston, MA 02115, USA

10 Department of Neurosurgery, Boston University School of Medicine, Boston, MA 02118, USA

11 Department of Neurosurgery, Emerson Hospital, Concord, MA 01742, USA

12 Departments of Psychiatry, Ophthalmology, Boston University School of Medicine, Boston, USA

13 Departments of Biomedical, Electrical and Computer Engineering, Boston University College of Engineering, Boston, USA

14 Department of Pathology and Laboratory Medicine, Boston University School of Medicine, Boston, MA 02118, USA