Relative contributions of mixed pathologies to cognitive and functional symptoms in brain donors exposed to repetitive head impacts

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Study conception and design: NS, YT, MA, TS.

Data acquisition, analysis, and interpretation: NS, YT, TM, AO, ZB, EY, JP, BM, MU, EN, BA, AS, RN, CN, RC, DD, BD, DK, RS, VA, BH, PB, JS, JM, AM, MA, TS.

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Abstract

Objective: Exposure to repetitive head impacts (RHI) is associated with later-life cognitive symptoms and neuropathologies including chronic traumatic encephalopathy (CTE). Cognitive decline in community cohorts is often due to multiple pathologies; however, the frequency and contributions of these pathologies to cognitive impairment in people exposed to RHI is unknown. Here, we examined the relative contributions of 13 neuropathologies to cognitive symptoms and dementia in RHI-exposed brain donors.
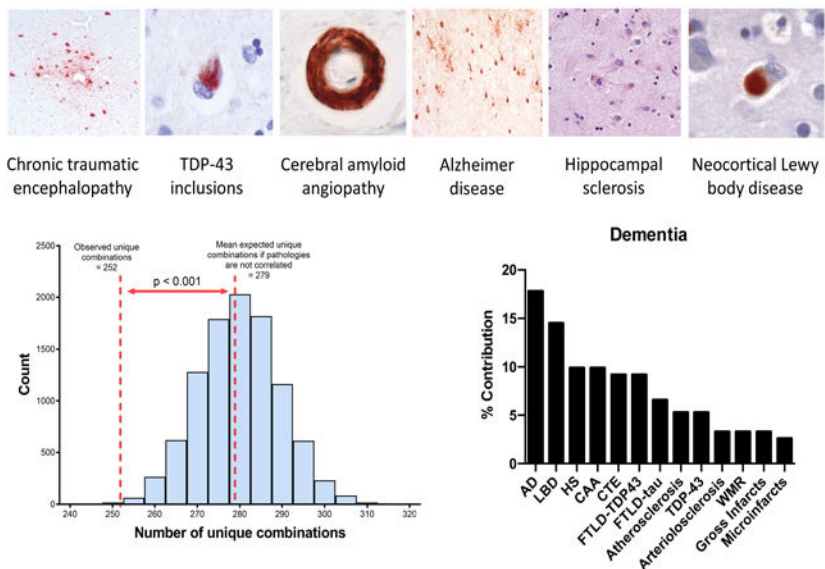
Methods: Neuropathologists examined brain tissue from 571 RHI-exposed donors and assessed for the presence of 13 neuropathologies, including CTE, Alzheimer disease (AD), Lewy body disease (LBD), and TDP-43 inclusions. Cognitive status was assessed by presence of dementia, Functional Activities Questionnaire (FAQ), and Cognitive Difficulties Scale (CDS). Spearman's rho was calculated to assess intercorrelation of pathologies. Additionally, frequencies of pathological co-occurrence were compared to a simulated distribution assuming no intercorrelation. Logistic and linear regressions tested associations between neuropathologies and dementia status and cognitive scale scores.

Results: The sample age range was 18–97 (median: 65.0 [IQR 46.0–76.0]). 77.2% of donors had at least one moderate-severe neurodegenerative or cerebrovascular pathology. Stage III-IV CTE was the most common neurodegenerative disease (43.1%), followed by TDP-43 pathology, AD, and hippocampal sclerosis. Neuropathologies were intercorrelated and there were fewer unique combinations than expected if pathologies were independent (p<0.001). The greatest contributors to dementia were AD, neocortical LBD, hippocampal sclerosis, CAA, and CTE.

Interpretation: In this sample of RHI-exposed brain donors with wide-ranging ages, multiple neuropathologies were common and correlated. Mixed neuropathologies, including CTE, underlie cognitive impairment in contact sport athletes.

Graphical Abstract

Pathological contributors to dementia after RHI

Chronic traumatic encephalopathy | TDP-43 inclusions | Cerebral amyloid angiopathy | Alzheimer disease | Hippocampal sclerosis | Neocortical Lewy body disease

Exposure to repetitive head impacts (RHI) is associated with the development of neurodegenerative disease and later-life cognitive symptoms. The most frequent neuropathologies found in a group with a history of RHI included chronic traumatic encephalopathy (CTE), TDP-43 inclusions, cerebral amyloid angiopathy, Alzheimer disease, hippocampal sclerosis, and neocortical Lewy body disease. Neuropathologies were intercorrelated and there were fewer unique combinations than expected if pathologies were independent (p<0.001). Mixed neuropathologies, including CTE, underlie dementia in contact sport athletes exposed to RHI.

INTRODUCTION

Neurodegenerative disease pathologies rarely occur in isolation[1] and the importance of mixed neuropathologies underlying cognitive decline in older adults is increasingly recognized.[1–6] In previous clinical-pathological studies of older adults from the Religious Orders Study and the Rush Memory and Aging Project (ROSMAP), Boyle et al. found that out of 9 neuropathologies examined, 78% of participants exhibited two or more upon post-mortem examination.[5] There were 236 distinct combinations of pathologies, each occurring in <6% of the sample.[5,7] Alzheimer Disease (AD) was the most frequent pathology in this sample and also had the strongest effect on cognitive decline of all of the pathologies examined.[5] After AD, Lewy Body disease (LBD) and hippocampal sclerosis (HS) were the biggest contributors to cognitive decline, although the contribution of individual pathologies varied greatly at the individual level and depended on the combination present.[5] It is in part because of the heterogeneity of underlying neuropathologies that attempts at treating and preventing AD and AD related dementias may have been met with limited success.[1,8,9]

Chronic traumatic encephalopathy (CTE) is a neurodegenerative tauopathy that is uniquely characterized by the aggregation of hyper-phosphorylated tau (p-tau) in neurons around small blood vessels and at the depths of the sulci. CTE can currently only be diagnosed

at autopsy using published neuropathological diagnostic criteria.[10,11] CTE is caused by exposure to repetitive head impacts (RHI) such as those from contact sports.[12–14] Research diagnostic criteria that describe the clinical syndrome of CTE have been proposed, known as traumatic encephalopathy syndrome (TES). The core clinical features of TES include cognitive impairment (particularly in episodic memory and executive functions) and neurobehavioral dysregulation (e.g., short fuse, impulsivity). There remains uncertainty of the clinical presentation of CTE in part because of the significant heterogeneity in symptom presence, severity, and presentation (e.g., type, age of onset, course). Such heterogeneity may partially be a result of mixed pathologies.

CTE has been associated with multiple other neuropathologies. In those with CTE, common comorbid pathologies include moderate-severe arteriolosclerosis (47%),[15] moderate-severe white matter rarefaction (WMR) (46%),[15] transactive response DNA-binding protein 43 (TDP-43) inclusions (43%),[16] cerebral amyloid angiopathy (CAA) (29%),[17] HS (23%),[16] AD (13%),[18] and neocortical LBD (5%).[17,19] Beta-amyloid deposition was found in 52% of brain donors with CTE as predominantly diffuse plaques, while neuritic plaques were less common.[20] In addition to CTE, RHI, as measured by years of play, has been associated with multiple neuropathologies, including neocortical LBD,[19] frontal CAA,[17] hippocampal TDP-43 inclusions,[16] and WMR.[15] Other studies in small numbers of soccer, rugby, and American football players have also shown frequent comorbid pathologies including AD, CTE, and TDP-43.[21,22] All of these pathologies can contribute to dementia. Therefore, the contributions of CTE and other pathologies to cognitive impairment in participants with a history of RHI warrant further investigation.

A systematic examination of co-morbidities and the unique contribution of neuropathologies to cognitive symptoms has yet to be examined in RHI exposed individuals. Here, we investigated the frequency of 13 neuropathological comorbidities in 571 brain donors exposed to RHI. We then examined their unique contributions to informant-reported cognitive and functional symptoms, including antemortem dementia.

METHODS

Brain Donors

The sample included 571 brain donors from the Understanding Neurologic Injury and Traumatic Encephalopathy (UNITE) brain bank who played contact sports during life and had a complete neuropathological examination. Inclusion criteria for brain donors in the UNITE study have been published previously.[23] As an overview, inclusion requires a history of RHI (e.g., from contact sports, military service, physical violence, or other sources) and tissue quality sufficient for neuropathological diagnosis using immunohistochemistry. More recently, the criteria were expanded to include a history of moderate to severe traumatic brain injury. For this study, participants were limited to those who played contact sports in order to limit the heterogeneity in brain injury exposure. In most cases, the brain donors' next-of-kin contacted the CTE Center at the time of the donors' passing to arrange for brain donation; in other cases, they were referred by medical examiners or recruited by the Concussion Legacy Foundation. Informed consent for brain donation and study enrollment

was obtained from the brain donors' next-of-kin, and approval for all study procedures was obtained from the Boston University Medical Campus Institutional Review Board.

Retrospective Clinical Assessments

Retrospective clinical data were obtained through online surveys and telephone interviews with informants of the brain donor as well as review of medical records. These methods have been described elsewhere.[23] Researchers and informants were blind to the neuropathological results. Clinicians with expertise in traumatic brain injury (TBI) and/or neurodegenerative diseases conducted semi-structured interviews and research assistants conducted structured interviews that included administration of standardized clinical scales adapted for informant-based, post-mortem, retrospective administration. The Functional Activities Questionnaire (FAQ) was used to assess instrumental activities of daily living in the year prior to the brain donors' death.[24] It is a 10-item measure and scores range from 0–30, with higher scores representing worse daily function. The Cognitive Difficulties Scale (CDS) is a 39-item instrument that asks about difficulties related to attention, memory, perception, and psychomotor abilities prior to death.[25] Responses are made on a 0 (not at all) to 4 (very often) Likert scale and scores are summed to form a global composite (higher scores reflect greater reported cognitive symptoms). Finally, antemortem dementia status was adjudicated through a diagnostic consensus conference of expert clinicians who were blinded to brain donors' pathological diagnoses. We used adapted DSM-IV-TR criteria for the diagnosis of dementia and the diagnosis was informed by the structured interview conducted by research assistants, the unstructured interview conducted by clinicians, as well as the online surveys. The clinical history (i.e., symptoms, symptom course) and other pertinent history (e.g., medical, family, substance use history) was summarized at the consensus conference.

The UNITE study has evolved over time. Prior to January 2014, only the FAQ was administered for assessing cognitive and functional symptoms, and after 2014, the CDS was added. Demographics, educational attainment, athletic history (type of sports played, level, position, age of first exposure and duration), military history, and traumatic brain injury history were queried during a telephone interview (pre-2014) and/or using an online questionnaire (2014 and on).

Neuropathological Examination

Brain tissue was processed according to previously-published, established procedures.[26,27] Neuropathological diagnoses were made blinded to all clinical information about the brain donor. Established criteria were used to diagnose the presence of neurodegenerative pathology including frontotemporal lobar degeneration with tau or TDP-43 inclusions (FTLD-tau; FTLD-TDP), neocortical LBD, CAA, HS, and WMR.[28–32] National Institute of Neurological Disorders and Stroke and National Institute of Biomedical Imaging and Bioengineering (NINDS-NIBIB) consensus criteria were used to diagnose CTE,[10,11] and stages I-IV were assigned using McKee criteria.[33,34] CTE stages III-IV were considered in this study since they have previously been shown to be associated with dementia and to match the disease severity of other diseases such as AD.[33,34] Involvement of the hippocampus by CTE pathology in stages III-IV was distinguished from other tauopathies such as primary age-related tauopathy by the preferential involvement of CA2 and CA4.[35]

CTE in the presence of comorbid AD was determined by the presence of a clear focus of perivascular neurofibrillary tangles with a predilection for greater involvement of the sulcal depths by tau pathology. NIA-Reagan criteria were used to diagnose AD of intermediate or high likelihood.[36] TDP-43 inclusions were assessed within the amygdala, entorhinal cortex, hippocampus, and dorsolateral frontal cortex and marked positive if present in any of those regions. Most TDP-43 inclusions were limbic predominant and indistinguishable from limbic-associated TDP-43 encephalopathy-neuropathologic change (LATE-NC); however, TDP-43 deposition has been shown to occur at a younger age and is associated with RHI in CTE.[37] Brain tissue was also evaluated for the presence of vascular pathology including gross infarcts, microinfarcts, moderate-severe atherosclerosis, and moderate-severe arteriolosclerosis. Pathologies were dichotomized as present or not (CTE stage III or IV, intermediate or high AD, neocortical LBD, HS, FTLD, TDP-43 inclusions, and gross and micro-infarcts). For pathologies rated on a none-mild-moderate-severe scale (CAA, WMR, atherosclerosis, and arteriolosclerosis), scores were dichotomized as moderate/severe vs none/mild. Primary age-related tauopathy, age-related tau astrogliopathy (ARTAG), argyrophilic grain disease, and LBD other than neocortical are either rare or have not been found to be significant contributors to dementia in previous studies and therefore were not included in our analyses in order to improve power.

Statistical analyses

To assess the intercorrelation of pathologies, the number of unique combinations of pathologies observed in our sample was compared to a distribution of combinations in 10,000 simulated datasets assuming no intercorrelation. The simulated datasets were representative of our sample in terms of sample size and frequencies of each neuropathology. Spearman's rho was also used to assess correlations between each pathology. We used independent logistic regressions to examine the relationship between each pathology and dementia status. Pathologies were assessed separately because of the high degree of correlation between pathologies and therefore the given β's do not account for any correlations. Using the regression coefficients, we calculated the percent contribution of each pathology to dementia status to examine the effect of each individual pathology in relation to the other pathologies assessed (β for each pathology / sum of βs for all pathologies). This approach gives the relative contribution of each pathology, but not the fraction of total variance in dementia status. Similarly, we used independent linear regressions to examine the relationships between each pathology and score on the FAQ and the CDS. We used multivariable regression to estimate the total variance in dementia status and FAQ and CDS scale scores explained by all neuropathologies. All regression models were adjusted for age, Black/African American race, and education level. A p-value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of brain donors

Brain donors ranged in age from 18 to 97 (median 65.0 [IQR 46.0–76.0]). Nearly all (565 [98.9%]) of the brain donors were male. Based on informant report, 87 (15.2%) were Black/African American, 466 (81.6%) of the brain donors were White, and 18 (3.2%) were other

races. All brain donors previously played contact sports (mean 14.5 years of play [SD 7.5]), and 513 (89.8%) played football. Most of the brain donors had played their primary sport at the professional (n=238 [46.1%]) or college (n=171 [33.1%]) level. 139 (24.3%) of the brain donors had served in the military, and 23 (4.0%) had served in combat. About half of the brain donors (300 [52.5%]) had dementia at the time of their death. The mean FAQ score was 14.2 (SD 12.1) and the mean CDS score was 88.1 (SD 48.6). Additional descriptive data are provided in Table 1.

Frequency of neuropathologies

The majority of brain donors (441 [77.2%]) met diagnostic criteria for at least one moderate-severe neurodegenerative or cerebrovascular pathology. The most common neurodegenerative disease observed was stage III-IV CTE (246 [43.1%]). Less common, but still frequent, neurodegenerative pathologies included TDP-43 inclusions (137 [24.0%]), AD (107 [18.7%]), and HS (96 [16.8%]). Neocortical LBD (34 [6.0%]), FTLD with TDP-43 inclusions (24 [4.2%]), and FTLD with tau inclusions (24 [4.2%]) were less common. Moderate-severe WMR was observed frequently in our sample (251 [44.0%]), as was moderate-severe cerebrovascular disease including arteriolosclerosis (292 [51.1%]), CAA (123 [21.5%]), and atherosclerosis (108 [18.9%]). Chronic macroscopic infarcts were observed in 77 (13.5%) brain donors and chronic microscopic infarcts were observed in 110 (19.3%) brain donors. Figure S1 displays the frequencies of each unique combination of neuropathologies. The frequency of each unique combination of pathologies ranged from 1–17 people, with the most common combination (arteriolosclerosis + WMR) occurring in only 3% of the sample. The most common combinations of pathologies observed were arteriolosclerosis + WMR and CTE with varying combinations of arteriolosclerosis, WMR, TDP-43 inclusions, and CAA (Table 2).

Intercorrelation of neuropathologies

Pathologies frequently occurred in combination in our sample. 357 (62.5%) brain donors had at least two moderate-severe neuropathologies present and 290 (50.8%) had at least three. As shown in Table 3 and Figure 1, the neuropathologies assessed were intercorrelated. Figure 1 shows the expected distribution (mean 278.9 [SD 9.6]) of numbers of unique combinations of independent pathologies, modeled in a simulation of 10,000 datasets representative of our sample in terms of sample size and relative frequencies of each pathology. We observed 252 unique combinations of pathologies in our RHI-exposed sample, which is less than would be expected if the pathologies were completely independent (p<0.001). Table 3 shows the Spearman's rho correlation between each neuropathology, demonstrating further that most of the pathologies assessed were intercorrelated. When age was accounted for in the analysis, CTE was still significantly correlated with TDP-43 inclusions and HS (Table S3).

Association of neuropathologies with dementia and cognitive scales

We used independent logistic regression to examine the relationship between each pathology and dementia status. Using the regression coefficients, we calculated the percent contribution of each pathology to dementia status to examine the effect of each individual pathology in relation to the other pathologies assessed. We found that the most influential contributors to dementia status in our sample included the following in rank order: AD

(17.8%; β=0.27; p<0.001), neocortical LBD (14.5%; β=0.22; p<0.001), HS (9.9%; β=0.15; p<0.001), CAA (9.9%; β=0.15; p<0.001) and stage III-IV CTE (9.2%; β=0.14; p<0.001).

Similarly, we used independent linear regressions to examine the relationships between each pathology and variation in scores on the FAQ and the CDS. The pathologies contributing most to variance in FAQ scores were AD (20.7%; β=10.50; p<0.001), FTLD-TDP (11.7%; β=5.93; p=0.002), CAA (11.3%; β=5.74; p<0.001), neocortical LBD (11.1%; β=5.64; p<0.001), HS (9.2%; β=4.66; p<0.001), TDP-43 inclusions (8.2%; β=4.16; p<0.001), atherosclerosis (7.1%; β=3.60; p<0.001), and stage III-IV CTE (6.4%; β=3.26; p<0.001); and the pathologies contributing most to variance in CDS scores were AD (23.8%; β=36.63; p<0.001), CAA (16.0%; β=24.62; p<0.001), neocortical LBD (14.7%; β=22.65; p=0.003), FTLD-TDP (9.2%; β=14.21; p=0.13), HS (8.2%; β=12.55; p=0.02), WMR (6.4%; β=9.77; p=0.01), and stage III-IV CTE (6.6%; β=10.1; p=0.02). The regression coefficients and calculated percent contribution to dementia status and cognitive scale scores for each pathology relative to the effect of all pathologies are shown in Table 4. The relative percent contributions to dementia status and cognitive scale scores for each significant pathology are displayed in Figure 2.

We used multivariable regression to estimate the total variance in dementia status and cognitive scale scores explained by all neuropathologies. Taken together, all neuropathologies assessed accounted for 46% of variance in dementia status, 57% of variance in FAQ scores, and 39% of variance in CDS scores.

Sensitivity analyses for sex, hypertension, and diabetes were computed because these variables have been previously shown to affect risk for cognitive decline and dementia. The sensitivity analyses showed that inclusion of sex, hypertension, or diabetes diagnosis in these regression models did not impact the results. In addition, we calculated the percent contributions to dementia status and cognitive scale scores for each pathology stratified by age <60 years (Table S1) and 60 years (Table S2). The results were similar such that for those age <60 years, AD, neocortical LBD, CAA, CTE, and FTLD-TDP were all significantly associated with dementia while in those age 60 years, AD, neocortical LBD, HS, CAA, and CTE were significantly associated with dementia.

DISCUSSION

In this group of participants with contact sports exposure, multiple neuropathologies were common and correlated. High stage CTE was the most frequent neurodegenerative pathology and was commonly present with cerebrovascular pathology, WMR, and TDP-43 inclusions. These findings demonstrate that in patients with a history of RHI, dementia status and cognitive scores were associated with multiple neurodegenerative and cerebrovascular pathologies with the greatest variance explained by AD, neocortical LBD, HS, CAA, TDP-43 inclusions, and CTE, respectively.

Intercorrelation of pathologies secondary to RHI

RHI may be a common cause for multiple neurodegenerations. Clinically, RHI has been linked to cognitive impairment, depression, and behavioral dysregulation[18,33,38,39] as well

as probable REM sleep behavior disorder.[40] Pathologically, years of contact sport play, a proxy for RHI, has been associated with CTE,[13] neocortical LBD,[19] WMR,[15] more severe frontal and leptomeningeal CAA,[17] and HS and TDP-43 inclusions.[16] Here we found that multiple neuropathologies were intercorrelated and that the number of unique pathology combinations was significantly less than predicted if they were independent in this RHI-exposed group. RHI may be one common cause of multiple neuropathologies. Future studies should examine the effects of RHI, age, and vascular risk factors on the intercorrelation of neuropathologies in different cohorts.

Potency of pathologies

The relative potency of the various neuropathologies on dementia and cognitive scores varied. In other community aging autopsy groups, AD was the most frequent pathology, and AD, neocortical LBD, and HS accounted for the largest percentage of cognitive impairment.[5,7] However, unlike in community aging groups, in our RHI-exposed group, CTE was the most frequent neurodegenerative pathology, and AD was less frequent. In addition, neocortical LBD, HS, and CAA were much less frequent than CTE. However, as in community-based groups, when present, AD and neocortical LBD were most strongly associated with dementia. CTE had a similar effect size to HS and CAA, two well-known contributors to dementia and cognitive impairment. Overall, AD, neocortical LBD, HS, CAA, and CTE explained most of the pathology-related variance in dementia and cognitive scores in this RHI-exposed group.

Heterogeneity and frequency of mixed pathologies

Heterogeneity and the presence of multiple neuropathologies is common with advanced age. Here we show that even in a relatively young group of RHI-exposed participants, multiple concurrent neuropathologies are common and varied. This has been previously reported in smaller groups of RHI exposed individuals, including the common comorbidity of HS and TDP-43.[16,21,41] In CTE, TDP-43 inclusions can occur in a variety of regions, including at the sulcal depths in the frontal cortex which may represent a CTE-specific form, but more commonly in limbic regions in the pattern described for limbic age-related TDP-43 encephalopathy.[16] In addition, we found that CAA showed an association with dementia and cognitive impairment. Our previous study showed that RHI and CTE are associated with more severe frontal leptomeningeal CAA than occurs in aging and AD[17] and therefore CAA may partially mediate the association of RHI with dementia. Similarly, neocortical LBD has been linked to a history of traumatic brain injury[42] and RHI[19] and recent data suggests that high stage CTE is associated with HS.[16] The clinical syndrome of CTE, Traumatic encephalopathy syndrome (TES), is evolving[43] and the specific causes of the TES phenotypes are uncertain and likely to include tau and non-tau pathologies. Overall, the common presence of mixed pathologies in an RHI exposed group should inform future studies identifying the salient clinical features associated with pathology.

A combination of environmental and genetic factors likely determines the pathologies that develop later in life. Common genetic risk factors such as *Apolipoprotein E*[44] and *Transmembrane Protein 106B*[45] alter the risk for many neurodegenerative pathologies including the severity of CTE. Determining interactions between RHI and genetic risk

factors on the development of neurodegenerative disease requires large numbers of individuals and is an ongoing focus in the field.

Importance of factors beyond known pathologies

The average age of the RHI-exposed group was relatively young (median 65 years at death), yet 77.2% had at least one moderate to severe pathology. Nevertheless, this is much less than the reported 94% with at least one neuropathology in an older community group (Religious Orders Study and the Memory and Aging Project (ROSMAP), average age 90 years at death)[5] highlighting the importance of age in the development of these pathologies. However, even in the much younger RHI-exposed group the combination of neuropathologies explained 46% of the dementia status, 57% of variance in FAQ scores, and 39% of variance in CDS scores, which is similar to previous reports in ROSMAP.[7] Factors that contribute to resilience and resistance to the development of neuropathologies likely at least partially underlie the variance in cognition not explained by the neuropathological combinations. These may include environmental factors previously linked to dementia such as depression, air pollution, physical inactivity, diabetes, hypertension, hearing loss, obesity, excessive alcohol consumption, lack of social contact, and insomnia.[46,47] Non-traditional and new measures of pathology such as white matter integrity, synaptic density, and neuroinflammatory measures may mediate some of these effects and require further study.[48,49]

Limitations

Our sample was primarily comprised of male former American football players who completed at least some college. Although the majority were White, 15% were Black/African American which is high for a brain bank. Nevertheless, these findings may not be generalizable to non-athletes, female athletes, athletes who played other contact sports, athletes with other racial/ethnic backgrounds, or athletes who completed fewer years of education. Brain donors were enrolled in this study at post-mortem, so we did not have access to longitudinal cognitive data, and instead relied on retrospective informant reports of cognitive and functional impairment. The median age of the RHI-exposed group in this study was young compared to other published autopsy groups and the potential modifying effects of age on the association of pathology and cognitive impairment are not well understood. Further, although previously RHI was not found to be associated with ARTAG,[50] the role of RHI in the development of primary age-related tauopathy and ARTAG and the association with cognitive impairment requires additional study. Although we were underpowered to examine effects of moderate-severe TBI, comparison of the effects of RHI and TBI is a high priority for future studies. The substantial amount of correlation among pathologies makes statistical modeling difficult. Future studies should examine the roles of age, vascular risk factors, and RHI on the intercorrelations of neuropathologies. In addition, neurobehavioral dysregulation is a common feature among brain donors with CTE, but its specific association with CTE p-tau pathology is uncertain. Future studies that examine associations between neuropathology and mood and behavior symptoms as well as those including longitudinal assessments of cognitive and neurobehavioral functioning are warranted to confirm and extend these findings.

CONCLUSIONS

In an RHI-exposed group, CTE and multiple other pathologies are common and correlated. Cognitive impairment is often associated with multiple neuropathologies, and diagnosis and eventual treatment should target the frequent combinations of pathologies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

DATA AVAILABILITY

Data elements from the Understanding Neurologic Injury and Traumatic Encephalopathy study are available from the publicly available FITBIR data set. Other raw data from this study are available upon reasonable request to the corresponding author.

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Summary for Social Media if Published

1.   @bu_cte

2.   Exposure to repetitive head impacts (RHI) is associated with later-life cognitive symptoms and neuropathologies including chronic traumatic encephalopathy (CTE). Cognitive decline is often due to multiple pathologies.

3.   The frequency and contributions of these pathologies to cognitive impairment in people exposed to RHI is unknown. Here, we examined the relative contributions of 13 neuropathologies to cognitive symptoms and dementia in RHI-exposed brain donors.

4.   Mixed neuropathologies, including CTE, underlie cognitive impairment in contact sport athletes exposed to repetitive head impacts.

5.   Cognitive impairment is often associated with multiple neuropathologies, and diagnosis and eventual treatment should target the frequent combinations of pathologies.

Figure 1:
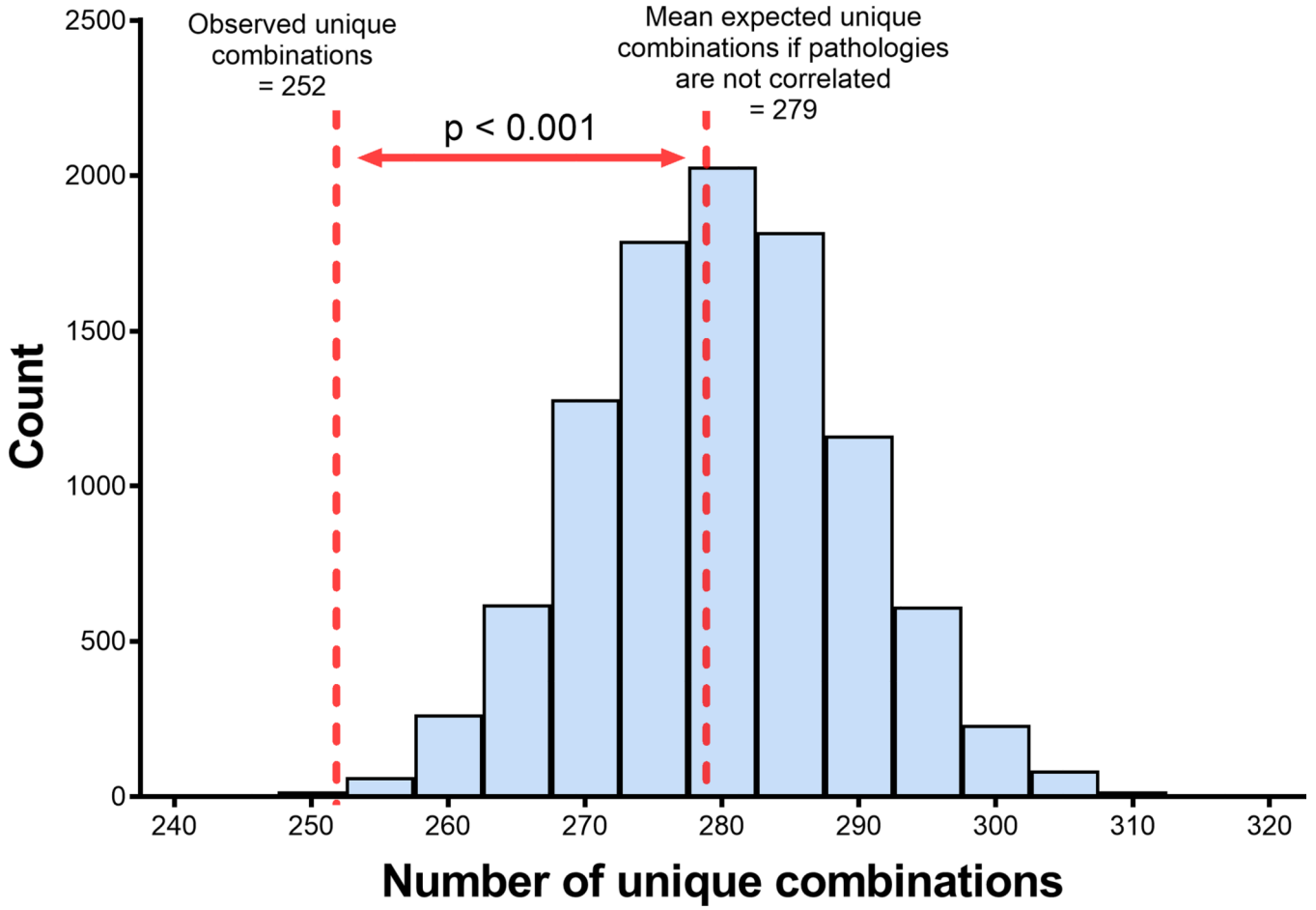Actual and expected unique number of combinations of neuropathologies.
The distribution of numbers of unique combinations of pathologies assuming each is independent is shown from a simulation of 10,000 datasets that are representative of our brain donors in sample size and frequencies of individual pathologies. The dashed lines represent the observed and predicted numbers of unique pathologies observed in our sample.
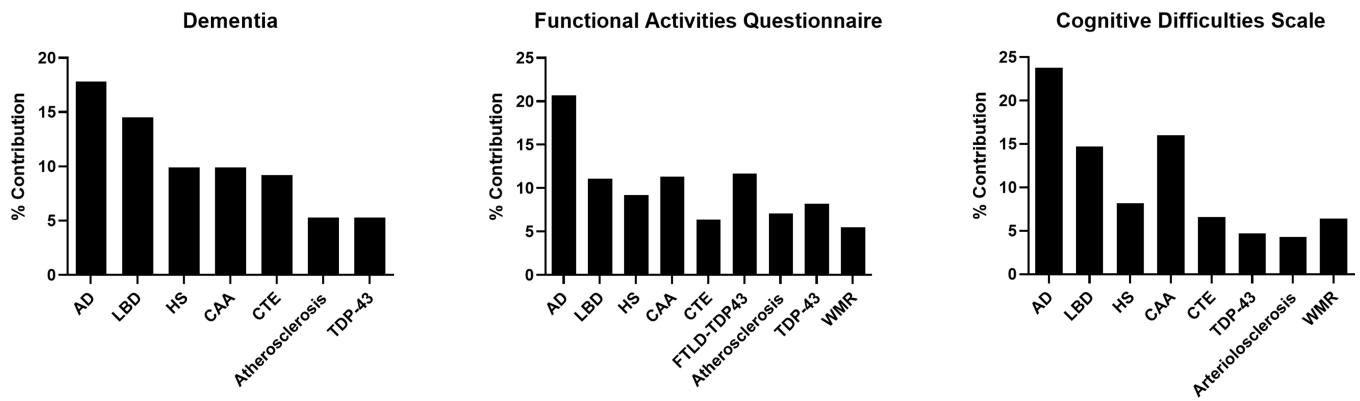
Figure 2:

The relative percent contribution of each neuropathology to variance in dementia status or cognitive scale scores.

The percent contribution of each pathology relative to the total effect of all the pathologies on the variance in dementia status and cognitive scale scores is shown. FAQ = functional activities questionnaire; CDS = cognitive difficulties scale; AD = Alzheimer's disease; LBD = neocortical Lewy body disease; HS = hippocampal sclerosis; CAA = cerebral amyloid angiopathy; CTE = chronic traumatic encephalopathy stages III-IV; FTLD = frontotemporal lobar degeneration; TDP-43 = transactive response DNA-binding protein 43; WMR = white matter rarefaction.

Table 1.

Descriptive characteristics of brain donors (n=571)

Variable	Mean (SD) or n (%)
Age at death, years, median (IQR) (range)	65.0 (46.0–76.0) (18–97)
Education level	
Some high school or high school diploma/GED	38 (6.7)
Some college or college degree	383 (67.1)
More than college or graduate degree	150 (26.3)
Male sex	565 (98.9)
Race	
White	466 (81.6)
Black/African American	87 (15.2)
Other race	18 (3.2)
Contact sports	
Football	513 (89.8)
Soccer	63 (11.0)
Wrestling	54 (9.5)
Hockey	45 (7.9)
Boxing	36 (6.3)
Lacrosse	22 (3.9)
Rugby	18 (3.2)
Mixed martial arts	5 (0.9)
Military	139 (24.3)
Combat	23 (4.0)
Dementia	300 (52.5)
FAQ score	14.2 (12.1)
CDS score	88.1 (48.6)
Neurodegenerative pathology	
CTE (stages III-IV)	246 (43.1)
TDP-43 inclusions	137 (24.0)
Alzheimer Disease	107 (18.7)
Hippocampal sclerosis	96 (16.8)
Neocortical Lewy bodies	34 (6.0)
FTLD-TDP	24 (4.2)
FTLD-tau	24 (4.2)
Cerebrovascular pathology	
Arteriolosclerosis (mod-sev)	292 (51.1)
CAA (mod-sev)	123 (21.5)
Microinfarcts	110 (19.3)
Atherosclerosis (mod-sev)	108 (18.9)
Gross Infarcts	77 (13.5)
White matter rarefaction (mod-sev)	251 (44.0)

FAQ = Functional Activities Questionnaire; CDS = Cognitive Difficulties Scale; CTE = chronic traumatic encephalopathy; FTLD = frontotemporal lobar degeneration; TDP-43 = transactive response DNA-binding protein 43; CAA = cerebral amyloid angiopathy.

Table 2:

Most common combinations of pathologies

Pathology combination	n (%)
Arteriolosclerosis + WMR	17 (3.0)
CTE + Arteriolosclerosis + WMR	11 (1.9)
CTE + Arteriolosclerosis	10 (1.8)
CTE + WMR	9 (1.6)
CTE + TDP-43	6 (1.1)
AD + Arteriolosclerosis + WMR	5 (0.9)
Arteriolosclerosis + Microinfarcts + WMR	5 (0.9)
CTE + TDP-43 + Arteriolosclerosis + WMR	4 (0.7)
CTE + Arteriolosclerosis + WMR + CAA	4 (0.7)

CTE= chronic traumatic encephalopathy, WMR= white matter rarefaction, AD= Alzheimer disease, CAA= cerebral amyloid angiopathy

Table 3:

Intercorrelations of neuropathologies

	CTE	TDP-43	AD	HS	LBD	FTLD-TDP	FTLD-tau	Art	CAA	Micro infarcts	AS	Infarcts
CTE	--											
TDP-43	.39**	--										
AD	.15**	.22**	--									
HS	.35**	.40**	.16**	--								
LBD	.03*	.10*	.15**	.09*	--							
FTLD-TDP	.10*	-.07	.06	.33**	.06	--						
FTLD-tau	.05	.07	.01	.05	.10*	.04	--					
Art	.31**	.21**	.23**	.23**	.06	.02	.14**	--				
CAA	.16**	.23**	.34**	.25**	.19**	.06	-.04	.25**	--			
Micro infarcts	.14**	.15**	.07	.12**	.09*	.03	.08	.22**	.10*	--		
AS	.23**	.24**	.15**	.22**	.09*	.06	.12**	.24**	.15**	.29**	--	
Infarcts	.18**	.12**	.18**	.14**	.01	.07	.02	.25**	.06	.30**	.28**	--
WMR	.23**	.18**	.24**	.13**	.03	.13**	.03	.40**	.18**	.22**	.14**	.25**

AD = Alzheimer's disease; Art = Arteriolosclerosis; AS = Atherosclerosis; LBD = neocortical Lewy body disease; HS = hippocampal sclerosis; CAA = cerebral amyloid angiopathy; CTE = chronic traumatic encephalopathy stages III-IV; FTLD = frontotemporal lobar degeneration; TDP-43 = transactive response DNA-binding protein 43; WMR = white matter rarefaction.

*
Correlation is significant at the 0.05 level (2-tailed), based on Spearman's rho.

**
Correlation is significant at the 0.01 level (2-tailed), based on Spearman's rho.

Table 4:

The effect and relative contribution of each pathology on dementia and cognitive scale scores

	DEMENTIA				FAQ				CDS			
	β	% cont.	SE	p-value	β	% cont.	SE	p-value	β	% cont.	SE	p-value
AD	.27	17.8	.04	<.001	10.50	20.7	.94	<.001	36.63	23.8	4.70	<.001
LBD	.22	14.5	.07	<.001	5.64	11.1	1.61	<.001	22.65	14.7	7.51	.003
HS	.15	9.9	.04	<.001	4.66	9.2	1.08	<.001	12.55	8.2	5.14	.02
CAA	.15	9.9	.04	<.001	5.74	11.3	.98	<.001	24.62	16.0	4.67	<.001
CTE	.14	9.2	.04	<.001	3.26	6.4	.89	<.001	10.1	6.6	4.31	.02
FTLD-TDP	.14	9.2	.08	.09	5.93	11.7	1.94	.002	14.21	9.2	9.32	.13
FTLD-tau	.10	6.6	.08	.19	.94	1.9	1.89	.62	-6.58	-4.3	8.86	.46
Athero-sclerosis	.08	5.3	.04	.05	3.60	7.1	1.05	<.001	9.00	5.9	5.01	.07
TDP-43	.08	5.3	.04	.04	4.16	8.2	.96	<.001	7.17	4.7	4.63	.12
Arteriolo-sclerosis	.05	3.3	.04	.14	1.31	2.6	.92	.15	6.60	4.3	4.31	.13
WMR	.05	3.3	.03	.15	2.77	5.5	.82	<.001	9.77	6.4	3.92	.01
Gross Infarcts	.05	3.3	.05	.31	1.59	3.1	1.16	.17	2.79	1.8	5.54	.62
Micro-infarcts	.04	2.6	.04	.40	.65	1.3	1.02	.52	4.31	2.8	4.84	.37

Multiple linear regressions adjusting for age, Black/AA race, and education level were performed separately for each pathology. The percent contribution (% cont.) shows the contribution of each pathology relative to the total effect of all pathologies. FAQ = functional activities questionnaire; CDS = cognitive difficulties scale; AD = Alzheimer's disease; LBD = neocortical Lewy body disease; HS = hippocampal sclerosis; CAA = cerebral amyloid angiopathy; CTE = chronic traumatic encephalopathy stages III-IV; FTLD = frontotemporal lobar degeneration; TDP-43 = transactive response DNA-binding protein 43; WMR = white matter rarefaction.