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Diffusion Alterations at the Gray Matter/White Matter Boundary in Traumatic Encephalopathy Syndrome

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Abstract

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with exposure to repetitive head impacts (RHI). In CTE, hyperphosphorylated tau (p-tau) aggregates are found in neurons at the depth of cortical sulci close to the gray matter/white matter (GM/WM) boundary. To date, CTE can only be diagnosed postmortem by neuropathological examination. Traumatic encephalopathy syndrome (TES) is the clinical syndrome purported to be associated with CTE pathology. The aim of this study is to investigate microstructural properties at the GM/WM boundary in individuals with a history of exposure to RHI and clinical features of CTE (i.e., TES). Diffusion magnetic resonance imaging (dMRI), TES diagnoses, and cerebrospinal fluid (CSF) biomarkers were acquired from 165 male former American football players (age: 57.29 ± 8.23 years) from the DIAGNOSE CTE Research Project, a multicenter, observational cohort study. Fractional anisotropy (FA) was measured at the GM/WM boundary of the whole brain. In addition, a widely used method (tract-based spatial statistics [TBSS]) was applied to measure FA of central WM. We used analyses of covariance to test associations between FA and TES. Furthermore, we used linear regressions to test associations between FA and nine CSF biomarkers (i.e., p-tau-181, -217, -231, total tau, amyloid β $[A\beta]_{1-40}$, $A\beta_{1-42}$, glial fibrillary acidic protein [GFAP], neurofilament light [NfL], and soluble triggering receptor expressed on myeloid cells-2 [sTREM2]). We report an association between higher FA at the GM/WM boundary and higher levels of certainty for CTE pathology ($F(1, 147) = 5.781$, 95% confidence interval (CI) = 0.0003–0.003, $p = 0.035$) as well as neurobehavioral dysregulation ($F(1, 148) = 7.559$, 95% CI = 0.001–0.009, $p = 0.020$), and functional dependence/dementia ($F(1, 148) = 5.046$, 95% CI = 0.0004–0.006, $p = 0.039$). In addition, we report an association between higher FA at the GM/WM boundary and higher CSF p-tau-181 ($\beta = 0.272$, 95% CI = 0.078–0.466, $p = 0.029$) and p-tau-217 ($\beta = 0.295$, 95% CI = 0.102–0.488, $p = 0.027$). FA of the central WM was not associated with TES diagnoses. Taken together, these findings suggest that dMRI at the GM/WM boundary could be used to investigate microstructural alterations suggestive of tau pathology-associated neurodegeneration in individuals with TES, the clinical presentation of CTE. Future studies are needed to validate this approach and to identify clinically useful cutoff values for dMRI metrics.

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Keywords: American football; chronic traumatic encephalopathy; diffusion MRI; diffusion tensor imaging; repetitive head impacts; tauopathy

Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with exposure to repetitive head impacts (RHI).[1,2] Early stages of CTE are characterized by the accumulation of hyperphosphorylated tau (p-tau) primarily around small vessels in the depth of cortical sulci[2] before tau pathology spreads across the brain in later stages.[2,3] To date, CTE can only be diagnosed postmortem by neuropathological examination. Objective biomarkers would make a diagnosis possible in the living.

Individuals with a history of RHI exposure who are later diagnosed with CTE at postmortem show diverse and nonspecific symptoms several years before death. These symptoms include cognitive impairment (e.g., memory and executive dysfunction), neuropsychiatric abnormalities (e.g., behavioral and emotional dysregulation), and motor impairments (e.g., parkinsonism).[1] The term traumatic encephalopathy syndrome (TES) has been used to describe the clinical manifestation of CTE pathology. The National Institute of Neurological Disorders and Stroke (NINDS) consensus diagnostic criteria for TES were published in 2021.[4] Associations between TES and potential *in vivo* biomarkers of CTE such as neuroimaging or fluid biomarkers could aid in the validation of TES diagnostic criteria and may allow diagnosis of CTE in the living.

Diffusion magnetic resonance imaging (dMRI) is a noninvasive MRI technique that quantifies diffusion characteristics of water in the tissue, thereby providing insights into brain microstructure.[5,6] Fractional anisotropy (FA) is a commonly reported dMRI metric reflecting the directionality of diffusion. FA has been shown to be sensitive to microstructural alterations associated with current and previous exposure to RHI[7–9] and neurodegenerative diseases.[10,11] Thus, it may be sensitive to microstructural alterations related to CTE. More specifically, a recent systematic review of dMRI in active contact sport athletes reported an association between lower FA and RHI in almost half of the 17 studies included.[8] However, one-fourth of these studies found increased FA following RHI,[8] emphasizing the complex association between RHI exposure and dMRI measures. Studies in former American football players are rare. One study reported lower FA in the right internal capsule.[12] In another study, more concussions were associated with lower FA among former college players but with higher FA among former professional players.[13] Two articles based on the same study reported associations between lower FA in the corpus callosum and younger age at first exposure to RHI[9] as well as worse cognitive performance.[7]

While previous studies on RHI focused on the central white matter (WM), the peripheral WM underneath cortical gray matter (GM) has not been systematically investigated. Importantly, this part of the WM directly borders the predominant location of tau pathology in CTE. To date, only one study has combined postmortem dMRI analysis with histopathological analysis of the brains of 10 deceased individuals with confirmed CTE.[14] In this

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study, an association was reported between lower FA and axonal disruption in the WM bordering tau-positive GM sulci,[14] suggesting that WM alterations are associated with CTE pathology. It is nonetheless not known if microstructural alterations at the GM/WM boundary are associated with TES in individuals who are at risk for CTE.[14]

Furthermore, several studies have pointed out the potential of fluid biomarkers in the study of CTE by reflecting pathological processes in the brain that could allow earlier diagnosis and monitoring of disease progress.[15,16] Combining MRI with fluid biomarkers may thus provide additional insights regarding the underlying pathophysiology of MRI findings.

The aim of this study is to investigate microstructural properties at the GM/WM boundary in individuals with a history of substantial RHI exposure. First, we compare former American football players diagnosed with TES with former players without TES. We then test associations between FA at the GM/WM boundary and cerebrospinal fluid (CSF) levels of biomarkers of brain injury and tauopathy. As this is the first empirical study to analyze the GM/WM boundary, we also apply a commonly used approach to investigate central WM in the brain.

Materials and Methods

Ethics approval

This study was approved by the Institutional Review Boards from all sites. Written informed consent was obtained from all study participants before study enrollment according to the Declaration of Helsinki. This article follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Study design and participants

This study is part of the multisite Diagnostics, Imaging, and Genetics Network for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy (DIAGNOSE CTE) Research Project.[17] One of the aims of the DIAGNOSE CTE Research Project is to identify biomarkers for the *in vivo* diagnosis of CTE. The study protocol includes demographic questionnaires, neuropsychological tests, evaluation of exposure to RHI, neurological and psychiatric examinations, neuropsychiatric questionnaires, lumbar puncture and blood draw, MRI, and positron emission tomography (PET). The four study sites of DIAGNOSE were: (1) Boston (Boston University with MRI scans conducted at Brigham and Women's Hospital); (2) Las Vegas (Cleveland Clinic Lou Ruvo Center for Brain Health); (3) New York (New York University Langone Health); and (4) Scottsdale/Phoenix (Mayo Clinic Arizona with PET scans conducted at Banner Alzheimer's Institute).

One hundred and eighty former American football players (120 former professional players and 60 former collegiate football players) were recruited. The inclusion criteria were: (1) male sex; (2) age between 45 and 74 years; (3) English as the primary language; (4) no contraindications for neuroimaging or lumbar puncture; and (5) consent to all procedures and willingness to have available a study partner (i.e., a spouse, a life partner, a close friend, or a family member). Not all individuals exposed to RHI will develop CTE or neuropsychiatric impairments. A known risk factor is the cumulative exposure to RHI including RHI frequency and intensity as well as younger age of first exposure.[17–19] Thus, the former professional football players were required to have played a minimum of 12 years of organized football with ≥3 years at the professional level. The former collegiate football players were required to have played >6 years of organized football, with >3 years at the college varsity level at similar high head impact playing positions. Participants from all groups were excluded for the following reasons: (1) history of stroke or significant neurological condition; (2) severe vision or hearing impairment; (3) inability to provide informed consent to participate; (4) currently clinically significant infectious, endocrine, metabolic, pulmonary, renal, hepatic disease, or cancer; and (5) body weight >400 pounds (≈181 kg). Of note, we did not include the control group in our analyses as the focus of this study lies on TES and potential associations with dMRI at the GM/WM boundary; by definition, individuals without substantial RHI exposure cannot meet criteria for TES.

Study enrollment for baseline evaluations began in 2016 and was completed in February 2020 (before the surge of the COVID-19 pandemic). Detailed inclusion and exclusion criteria and study methodology for the DIAGNOSE CTE Research Project have been described elsewhere.[17]

MRI

Image acquisition. Non-contrast cranial MRI was conducted at four study sites in the United States using a Siemens 3T Magnetom Skyra MRI scanner (Siemens Healthineers, Erlangen, Germany) with software version VE11 and a 20-channel head coil. We used two structural MRI sequences: a T1-weighted (T1w) Magnetization-Prepared-Rapid-Gradient-Echo sequence (TR = 2,530 ms, TE = 3.36 ms, T1 = 1,100 ms, 7° flip angle, 256 FOV, $1 \times 1 \times 1$ mm^3 voxel size) and a T2-weighted (T2w) Sampling-Perfection-with-Application-optimized-Contrasts-by-using-flip-angle-Evolution (SPACE) sequence (TR = 3,200 ms, TE = 412 ms, 256 FOV, $1 \times 1 \times 1$ mm^3 voxel size). In addition, we used a multi-shell dMRI GeneRalized Autocalibration Partial Parallel Acquisition (GRAPPA) sequence (TR = 11,000 ms, TE = 105 ms, 30 gradient directions at b = 2,500/mm^2, 30 at b = 1,000 sec/mm^2, 6 at b = 500 sec/mm^2, 3 at b = 200 sec/mm^2, and 5 interleaved b0 images, 256 FOV, $2 \times 2 \times 2$ mm^3 voxel size).

Image processing. *Preprocessing of structural and diffusion MRI.* Our analyses required T1w, T2w, and dMRI data. Of the 180 former American football players, 6 had missing data for T1w, T2w, or dMRI, and thus were excluded. Next, T1w, T2w, and dMRI data were inspected for image quality and artifacts such as motion or ghosting using 3D slicer (http://www.slicer.org; version 4.5, Surgical Planning Laboratory, Brigham and Women's Hospital, Boston, MA), independently by two trained raters (T.L.T.W., L.P.). Nine cases with insufficient quality in T1w, T2w, or dMRI were excluded, leaving 165 cases (8% excluded).

Processing of structural MRI. T1w and T2w data were processed and masked using custom tools developed by the Psychiatry Neuroimaging Laboratory (https://github.com/pnlbwh/luigi-pnlpipe, https://github.com/pnlbwh/pnlNipype) as well as FreeSurfer version 7.1 (https://surfer.nmr.mgh.harvard.edu). The brain images were then parcellated according to the Destrieux neuroanatomical atlas.[20–24]

Processing of diffusion MRI. dMRI data were preprocessed using a custom pipeline (https://github.com/pnlbwh/pnlNipype). Specifically, images were first brain-masked using a deep learning-based tool (https://github.com/pnlbwh/CNN-Diffusion-MRIBrain-Segmentation).[25] They were then corrected for geometric distortions due to participant motion and eddy currents[26,27] as well as susceptibility artifacts due to EPI acquisition.[28] Images were then harmonized across the four data acquisition sites using an established procedure based on rotationally invariant spherical harmonics (https://github.com/pnlbwh/dMRIharmoniziation).[29,30] FA maps were estimated using a least-squares fit model. In addition, we applied a method described by Pasternak et al.[31] to calculate free water (FW) maps for each case. The FW model separates diffusion properties into a tissue-specific component and an FW component. We used the tissue-specific component to calculate tissue-specific FA, which eliminates the influence of freely diffusing water molecules, for example, due to CSF or neuroinflammation.[31]

Diffusion MRI at the GM/WM boundary. B0 maps from the dMRI data were registered to the FreeSurfer space of the same individual using boundary-based registration[32,33] (FreeSurfer command: bbregister, option –t2 to indicate the b = 0 contrast is similar to a T2w image). Based on the resulting transformation, FA images in the original dMRI space were then registered to the same individual's FreeSurfer "white" left and right hemisphere surfaces (FreeSurfer command: mri_vol2surf). Based on the Destrieux neuroanatomical atlas,[20] we extracted the FA value of the voxel line below the cortical GM and the area for each of the brain regions (Fig. 1A). Based on the mean FA and the size of each brain region, we calculated weighted sums of the FA of the whole brain as well as all gyri and all sulci. Higher FA represents more directed diffusion. In the central WM, this is commonly interpreted as reflecting more densely packed WM fibers. However, several studies have reported higher FA values that are associated with neurotrauma and potential tissue damage.[8] Moreover, studies on dMRI of the GM/WM boundary are sparse.

Diffusion MRI of the WM skeleton. In addition, we used tract-based spatial statistics (TBSS)[34] to study FA at the WM skeleton (Fig. 1B). We used an established pipeline (https://github.com/pnlbwh/TBSS) based on the Enhancing Neuro Imaging Genetics through Meta-Analysis Diffusion Tensor Imaging (ENIGMA-DTI) working group's protocol (http://enigma.ini.usc.edu/ongoing/dti-working-group). We only used FA of the whole-brain WM skeleton.

Traumatic Encephalopathy Syndrome

The NINDS consensus diagnostic criteria were published in 2021 and represent clinical criteria for a diagnosis of TES as well as more specific core clinical features and supportive features of TES. Details of the NINDS consensus diagnostic criteria have previously been published.[4] We applied the NINDS consensus diagnostic

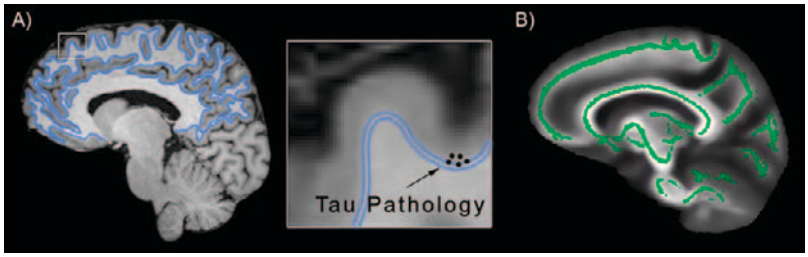

FIG. 1. Visualization of the gray matter/white matter (GM/WM) boundary and the central WM. **(A)** Depiction of the GM/WM boundary, where tau pathology may accumulate in chronic traumatic encephalopathy (CTE). Tissue-specific fractional anisotropy (FA) was extracted from one voxel line below the cortex. **(B)** Tract-based spatial statistics (TBSS) depicting FA at the central WM that might be less specific to tau pathology in CTE.

criteria to our sample through multidisciplinary diagnostic consensus conferences.[17]

Based on the NINDS criteria,[4] TES is defined by: (1) substantial exposure to RHI; (2) cognitive impairment (involving episodic memory and/or executive functioning), neurobehavioral dysregulation (explosiveness, impulsivity, rage, violent outbursts, and emotional lability), or both; (3) a progressive worsening of clinical features; and (4) symptomology not fully accounted for by other disorders, although other neuropsychiatric illnesses or neurodegenerative diseases do not exclude TES. In addition, for individuals with a diagnosis of TES, their level of functional dependence/dementia is determined, that is, no dementia, subtle/functional limitations, mild dementia, moderate dementia, or severe dementia. A provisional level of certainty for CTE pathology (i.e., suggestive of CTE, possible CTE, and probable CTE) is also derived based on the amount of RHI exposure, presence of cognitive impairment, level of functional dependence/dementia, and supportive features such as delayed onset, motor signs, and psychiatric symptoms (please see the original publication for the detailed criteria and cutoff values[4]).

Investigation of the binary diagnosis of TES, the provisional level of certainty for CTE pathology, as well as the clinical features "cognitive impairment," "neurobehavioral dysregulation," and "level of functional dependence/dementia" were selected *a priori*. Information on cognitive impairment and thus also on TES diagnosis and level of certainty was missing for one study participant.

Fluid Biomarkers

CSF was collected via lumbar puncture. CSF samples were processed, aliquoted, and stored at −80°C at the four study sites and then shipped on dry ice overnight to VA Puget Sound, where they were stored at −70°C. Samples were shipped to the University of Gothenburg, Sweden, where the measurements were performed. Concentrations of the p-tau epitope CSF p-tau-181, total tau (t-tau), as well as amyloid β ($A\beta$)$_{1–40}$ and $A\beta_{1–42}$ (markers of Alzheimer's disease [AD]), were measured by Lumipulse (Fujirebio, Ghent, Belgium), as previously described.[35] CSF p-tau-217 concentration was measured using the ALZpath Single Molecule Array (Simoa) assay (ALZpath, Carlsbad, CA).[36] CSF p-tau-231 concentration was measured using an in-house Simoa assay.[37] CSF glial fibrillary acidic protein (GFAP; a marker of astroglial injury) concentration was measured using a commercially available Simoa assay (Quanterix, Billerica, MA). CSF neurofilament light (NfL; a marker of neurodegeneration) concentration was measured using an in-house enzyme-linked immunosorbent assay.[38] CSF soluble triggering receptor expressed on myeloid cells-2 (sTREM2; a microglial marker) concentration was measured using an in-house immunoassay.[39] All CSF assays were performed in one batch. Intra-assay coefficients of variation were below 10%.

Statistical Analyses

All statistical analyses were conducted using the software R, version 4.1.1. We used analyses of covariance to test associations between FA at the GM/WM boundary as well as the central WM and TES. In the case of group differences with more than two groups, we performed Tukey post hoc analyses for group-wise comparisons. In addition, we used linear regressions to test associations between FA at the GM/WM boundary and CSF biomarkers. We controlled for the effects of age in years at the time of the MRI scan, body mass index (BMI), years of education, imaging site, binary apolipoprotein E4 (APOE4) carrier status, and racial identity, which have previously been shown to influence neuroimaging and/or clinical metrics.[25,40–42] Race, for example, was previously shown to be associated with BMI, systolic blood pressure, GM volumes, and tau levels of former professional football players.[40] Most participants self-identified as Black/African American or White individuals with insufficient representation of other racial or ethnic groups to analyze them separately (see Table 1). We thus recoded race into two groups: White and Black or African American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and multiple races combined. Whenever there were significant associations for the whole brain, we performed post hoc pairwise comparisons to assess whether gyri or sulci were the main contributors to the association. All results were corrected for multiple comparisons using false discovery rate. After correction, p values <0.05 were considered statistically significant. For regression analyses, we report standardized beta weights.

Results

Sample characteristics

We included a total of 165 former American football players (age: 57.29 ± 8.23 years; time since active play: 29.21 ± 8.49 years). Among all football players, 106 were diagnosed with TES. For detailed sample characteristics, see Table 1.

FA and TES

Higher FA at the GM/WM boundary was associated with a higher level of certainty for CTE pathology ($F(1, 147) = 5.781$, 95% confidence interval (CI) = 0.0003–0.003, $p = 0.035$; Fig. 2 and Table 2). Tukey post hoc analysis showed that group differences in FA were significant between the categories with the highest and the lowest level of certainty for CTE pathology (probable CTE vs. no TES; Estimate = −0.516, 95% CI = −1.013 to −0.018,

Table 1. Detailed Sample Characteristics

Measure	*Football players (n = 165)*
Demographic information	
Age (years)	Mean: 57.29, SD: 8.23
Time since active play (years)	Mean: 29.21, SD: 8.49
Total years of active play (years)	Mean: 15.96, SD: 4.34
Duration of education (years)	Mean: 16.75, SD: 1.49
Body mass index (BMI) (kg/m^2)	Mean: 32.61, SD: 4.71
APOE4 carrier	Yes: 44, No: 115
Racial identity	American Indian or Alaska Native: 0 Asian: 0 Black or African American: 56 Native Hawaiian, Pacific Islander: 0 White: 106 Multiple races: 3
Traumatic encephalopathy syndrome (TES)	
TES diagnosis	Yes: 106, No: 58
Levels of certainty for CTE pathology	TES and probable CTE: 55 TES and possible CTE: 20 TES and suggestive of CTE: 31 No TES: 58
Cognitive impairment	Yes: 97, No: 67
Neurobehavioral dysregulation	Yes: 95, No: 70
Dementia	Severe dementia: 0 Moderate dementia: 0 Mild dementia: 15 Subtle/functional limitations: 53 No dementia: 97

BMI: normal = 18.5–24.9 kg/m^2, overweight = 25.0–29.9 kg/m^2, obese = ≥30 kg/m^2. Information on apolipoprotein E4 (APOE4) carrier status is missing for six individuals. Information on cognitive impairment and thus diagnosis of TES as well as level of certainty for chronic traumatic encephalopathy (CTE) pathology is missing for one individual. SD, standard deviation.

$p = 0.039$; Fig. 2; for detailed demographic characteristics for each level of certainty, see Supplementary Table S1).

Higher FA at the GM/WM boundary was associated with neurobehavioral dysregulation ($F(1, 148) = 7.559$, 95% CI = 0.001–0.009, $p = 0.020$; Fig. 2). In addition, higher FA at the GM/WM boundary was associated with the level of functional dependence/dementia ($F(1, 148) = 5.046$, 95% CI = 0.0004–0.006, $p = 0.039$; Fig. 2). Tukey post hoc analysis showed that group differences in FA were significant between the categories with no and subtle functional dependence/dementia (Estimate = –0.423, 95% CI = –0.826 to –0.020, $p = 0.038$; Fig. 2).

Additional analyses distinguishing between FA at the gyri versus the sulci showed that FA at the gyri was significantly associated with all three variables (i.e., level of certainty for CTE pathology, neurobehavioral dysregulation, and dementia), whereas FA at the sulci was only associated with neurobehavioral dysregulation (Table 2).

There were no statistically significant associations between FA at the GM/WM boundary and binary TES diagnosis or cognitive impairment (Table 2). For additional analyses on associations between FA at the GM/WM boundary and more detailed measures of neurobehavioral dysregulation and cognitive function, see Supplementary Materials.

In contrast, FA of the WM skeleton was not associated with any diagnosis or diagnostic criterion related to TES (Table 2).

For detailed analyses on TES and FA at the GM/WM boundary of 12 lobes/regions (6 per hemisphere: frontal, temporal, parietal, occipital, insula, limbic), as well as regions of the Destrieux atlas corresponding to the superior frontal, dorsolateral frontal, and inferior frontal lobes, see Supplementary Table S2.

FA at GM/WM boundary and fluid biomarkers

Higher FA at the GM/WM boundary was significantly associated with higher CSF levels of p-tau-181 ($\beta = 0.272$, 95% CI = 0.078–0.466, $p = 0.029$). This association was similar for sulci ($\beta = 0.257$, 95% CI = 0.058–

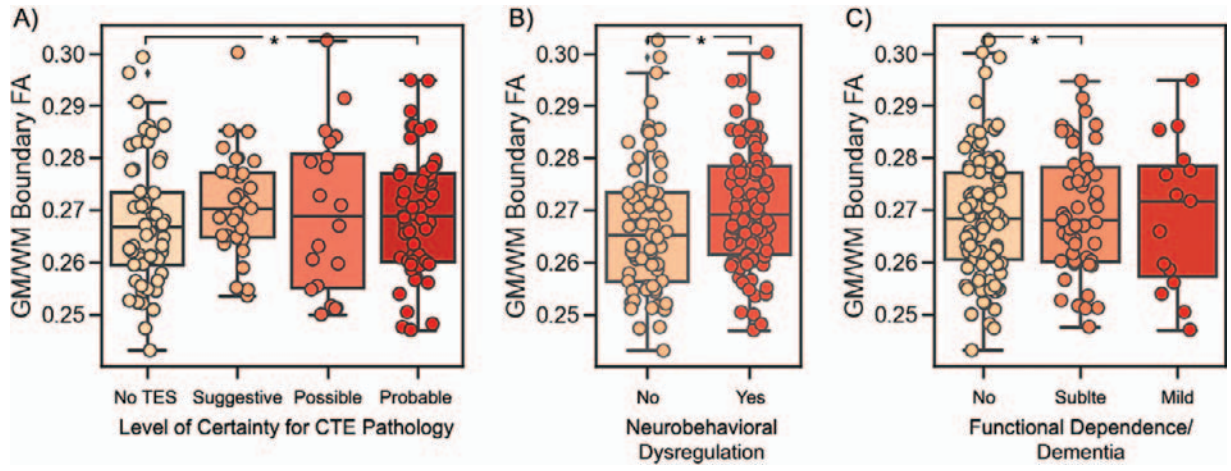

FIG. 2. Diffusion magnetic resonance imaging at the gray matter/white matter (GM/WM) boundary in traumatic encephalopathy syndrome (TES). Associations between fractional anisotropy (FA) at the GM/WM boundary and **(A)** the level of certainty for chronic traumatic encephalopathy (CTE) pathology, **(B)** neurobehavioral dysregulation, and **(C)** functional dependence/dementia.

Table 2. Associations Between Fractional Anisotropy at the Gray Matter/White Matter Boundary Versus White Matter Skeleton and Traumatic Encephalopathy Syndrome Diagnoses

	GM/WM boundary			*Central WM*
	Whole brain	*Gyri*	*Sulci*	*Whole brain*
TES diagnosis	$F(1, 149)$: 3.565, p: 0.061			$F(1, 149)$: 0.593, p: 0.443
Level of certainty for CTE pathology	$F(1, 149)$: 6.159, **p: 0.028**	$F(1, 149)$: 7.532, **p: 0.014**	$F(1, 149)$: 3.490, p: 0.064	$F(1, 149)$: 0.319, p: 0.443
Cognitive impairment	$F(1, 149)$: 3.058, p: 0.082			$F(1, 149)$: 0.460, p: 0.911
Neurobehavioral dysregulation	$F(1, 149)$: 7.877, **p: 0.017**	$F(1, 149)$: 9.612, **p: 0.005**	$F(1, 149)$: 4.550, **p: 0.035**	$F(1, 149)$: 0.251, p: 0.911
Dementia	$F(1, 149)$: 5.291, **p: 0.034**	$F(1, 149)$: 6.365, **p: 0.025**	$F(1, 149)$: 3.280, p: 0.072	$F(1, 149)$: 0.012, p: 0.911

Significant p values are marked in bold.
CTE, chronic traumatic encephalopathy; GM, gray matter; TES, traumatic encephalopathy syndrome; WM, white matter.

0.456, $p = 0.012$) and gyri ($\beta = 0.263$, 95% CI = 0.070–0.455, $p = 0.012$). In addition, higher FA at the GM/WM boundary was significantly associated with higher CSF levels of p-tau-217 ($\beta = 0.295$, 95% CI = 0.102–0.488, $p = 0.027$). This association was, again, comparable for sulci ($\beta = 0.301$, 95% CI = 0.104–0.500, $p = 0.006$) and gyri ($\beta = 0.259$, 95% CI = 0.064–0.454, $p = 0.010$).

There were no significant associations between FA at the GM/WM boundary and p-tau-231 ($\beta = 0.135$, 95% CI = –0.071 to 0.340, $p = 0.353$), t-tau ($\beta = 0.041$, 95% CI = –0.144 to 0.226, $p = 0.661$), GFAP ($\beta = 0.218$, 95% CI = 0.009–0.426, $p = 0.123$), NfL ($\beta = 0.086$, 95% CI = –101 to 0.273, $p = 0.466$), sTREM2 ($\beta = 0.066$, 95% CI = –139 to 0.272, $p = 0.588$), $A\beta_{1-42}$ ($\beta = 0.167$, 95% CI = –0.022 to 0.355, $p = 0.185$), and $A\beta_{1-42}/A\beta_{1-40}$ ($\beta = –0.099$, 95% CI = –0.295 to 0.097, $p = 0.466$). For exploratory analyses on FA at the GM/WM boundary and additional inflammatory biomarkers, see Supplementary Table S3. Of note, those with missing CSF variables were younger, had a higher BMI, and had a slightly lower FA (Supplementary Table S4).

Discussion

This study found an association between higher FA at the GM/WM boundary and higher level of certainty for CTE pathology in former American football players. Furthermore, higher FA at the GM/WM boundary was also associated with higher CSF levels of p-tau-181 and -217. Taken together, these findings suggest that dMRI of the GM/WM boundary could be used to investigate microstructural alterations associated with tauopathy in living individuals with TES, the clinical presentation of CTE.

Here, we report microstructural alterations (i.e., higher FA) at the GM/WM boundary associated with worse symptoms in former American football players with a history of exposure to RHI. In the context of this study, there are three potential mechanisms that appear as possible causes of microstructural alterations at the GM/WM boundary: (1) a history of extensive exposure to RHI and sport-related concussion; (2) neurodegenerative processes not specific to CTE; and (3) CTE-specific tau pathology. In what follows, we discuss these three potential mechanisms.

To date, research on diffusion characteristics of the GM/WM boundary in sport-related concussion and RHI is sparse. In the past, most studies in RHI have analyzed dMRI at the central WM in youth or young adult samples still engaged in contact sports.[8] In several of these studies, RHI exposure was associated with lower FA, which, in turn, was interpreted as axonal damage.[8] However, as pointed out by a recent systematic review on dMRI in sport-related RHI, one in four studies in youth and young adult samples reported higher FA in the central WM.[8,43–46] These studies attributed the findings to adaptive growth processes such as axonal budding or inflammatory processes. Similarly, higher FA in the WM following mild traumatic brain injury or sport-related concussion has been attributed to inflammatory processes and associated with poor long-term outcomes.[47–51]

Among former American football players, one study with a small sample size reported lower FA in the central WM compared with controls.[12] Higher exposure to RHI and sport-related concussion in former American football players has been associated with both, lower and higher FA in central WM areas.[7,13] As inflammatory processes can persist chronically,[52] we corrected our analyses for FW and thus extracellular edema. However, inflammatory processes also include the invasion of immune cells and astrogliosis. In consequence, the number of cells in a given voxel can increase, which could potentially restrict diffusion and, in turn, may be responsible for an increase in FA.[53–56] However, chronic inflammatory processes have more commonly been associated with decreases in FA.[8,57] In addition, we did not find associations between FA and inflammatory CSF biomarkers such as GFAP or sTREM2 in our study, which further argues against invasion of immune cells as the underlying mechanism. Also, we did not find an association between an estimate of cumulative RHI exposure and FA (see Supplementary Materials). Thus, exposure to RHI and sport-related concussion alone does not seem to fully explain our findings.

WM alterations may also be due to nonspecific neurodegenerative processes. For example, higher FA has been reported in other neurodegenerative tauopathies (e.g.,

AD).[58–60] Of note, in AD, FA has been shown to follow nonlinear trajectories with higher FA in early stages followed by a decrease in FA as the disease progresses.[61,62] The early stages of AD are characterized by cellular damage and inflammation rather than demyelination. Thus, similar to what has been described in AD and other neurodegenerative diseases, higher WM FA in individuals with TES could potentially be due to inflammatory processes. As mentioned above, we did not find associations between FA and inflammatory CSF biomarkers. However, higher FA at the GM/WM boundary was associated with higher levels of CSF p-tau-181 and -217. Whereas both biomarkers have also been observed in AD,[63,64] diagnostic criteria of TES require that symptoms are not accounted for by another disease such as AD.[4] In fact, as previously reported, there were no group differences in amyloid PET uptake between the American football players included in our study and controls.[65] Furthermore, we did not find associations between FA and the AD biomarkers $A\beta_{1-42}$ and $A\beta_{1-42}/A\beta_{1-40}$. Thus, AD seems to be an unlikely cause of the findings reported here.

Lastly, the observed WM alterations at the GM/WM boundary may also be due to CTE-specific tau pathology. This is supported by the fact that we studied FA at the GM/WM boundary in individuals at risk for CTE and that FA was associated with clinical features of CTE such as neurobehavioral dysregulation.[4] It is further supported by a previous study reporting evidence of axonal disruption in the WM bordering tau-positive cerebral sulci based on a histopathology study of 10 confirmed cases of CTE.[14] This study, however, found lower FA bordering tau-positive sulci,[14] whereas in our analyses the sulci did not stand out as the primary driver of the results. Moreover, the role of p-tau-181 and -217 in CTE is not yet fully elucidated. Thus, the association between higher FA at the GM/WM boundary and higher levels of CSF p-tau-181 and -217 may also be due to CTE-specific tauopathy.[66] However, it is important to emphasize the substantial overlap of FA between all levels of certainty for CTE pathology. Thus, no diagnostically useful cutoff values have emerged.

Taken together, our findings suggest that dMRI of the GM/WM boundary could provide additional insights into microstructural alterations in individuals at risk for CTE even when TBSS/dMRI of the central WM is negative. Although dMRI of the central WM is more established in RHI than dMRI of the GM/WM boundary, the latter approach may be more promising given the predominant location of CTE tauopathy, which is close to the boundary. However, future studies are needed to validate our approach and to clarify the role of higher FA many years after exposure to sport-related RHI. In addition, clear cutoff values for FA at the GM/WM boundary that would allow a differentiation between TES and no TES did not emerge in our study.

There are several limitations to our findings. First, the analyses are cross-sectional. Thus, the predictive value of dMRI at the GM/WM boundary for individual disease progression remains unknown. Second, this study uses the clinical criteria for TES and does not include postmortem neuropathology information. Thus, it is unknown if the participants in this study have CTE p-tau pathology. Third, diagnostic criteria for TES have only recently been established and require further validation. Fourth, our analyses do not include a control group. Thus, no comparison with asymptomatic participants without a history of RHI is possible. Fifth, study participants were all male former American football players who were active in the 1970s to 2000s. Thus, the findings cannot be generalized to today's football players, other sources of RHI exposure, or to females. Last, CSF p-tau levels are missing for around 40 of the 166 participants included here, mostly due to unsuccessful lumbar punctures.

Conclusion

We report an association between microstructural alterations at the GM/WM boundary and clinical features of CTE pathology in former college and professional American football players. Additionally, higher FA at the GM/WM boundary was associated with higher CSF p-tau-181 and -217. Taken together, these findings suggest that dMRI at the GM/WM boundary could be used to investigate microstructural alterations in individuals at risk for CTE. However, future studies are needed to validate this approach and identify clinically useful cutoff values for dMRI metrics.

Transparency, Rigor, and Reproducibility

This article follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for observational studies. Details on the study design and acquired data were published previously.[17] The study was approved by the Institutional Review Boards from all sites. Written informed consent was obtained from all study participants before study enrollment according to the Declaration of Helsinki. Preliminary results were previously presented at an international scientific conference. Analyses are based on a unique sample of former professional American football players. Inclusion and exclusion criteria for study participants are described in detail in this article. Initially, 180 individuals were recruited at four data acquisition sites across the United States. Analyses presented here are based on 165 former professional American football players. The reasons for excluding 15 (8%) individuals are provided in detail in the methods section of this article. We developed a novel algorithm to investigate

dMRI metrics at the GM/WM boundary, thereby applying an approach that is linked more directly to the pathophysiology of RHI and CTE. Image processing steps are described in detail in this article, and processing tools are made publicly available via GitHub. Diffusion MRI data were harmonized between sites prior to processing and analysis. Furthermore, we controlled all statistical analyses for the effects of several potential confounders, including age, BMI, years of education, imaging site, binary APOE4 carrier status, and racial identity. Moreover, results were corrected for multiple comparisons using false discovery rate. We include multiple post hoc analyses on measures such as cognitive function, neurobehavioral dysregulation, and RHI exposure to provide more detailed information on our study sample and main findings. Results are interpreted and put into context based on a recent systematic review article.[8] Data from the DIAGNOSE CTE Research Project will be available to qualified investigators through the Federal Interagency Traumatic Brain Injury Research Informatics System: https://fitbir.nih.gov/content/access-data. Data will also be available to qualified investigators through a project-specific data-sharing portal. Interested investigators should contact Dr. Robert A. Stern: bobstern@bu.edu.

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Supplementary Material

Supplementary Data

References

1. Montenigro PH, Baugh CM, Daneshvar DH, et al. Clinical subtypes of chronic traumatic encephalopathy: Literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. Alzheimers Res Ther 2014;6(5):68; doi: 10.1186/s13195-014-0068-z
2. McKee AC, Stern RA, Nowinski CJ, et al. The spectrum of disease in chronic traumatic encephalopathy. Brain 2013;136(Pt 1):43–64; doi: 10.1093/brain/aws307
3. Katsumoto A, Takeuchi H, Tanaka F. Tau pathology in chronic traumatic encephalopathy and Alzheimer's disease: Similarities and differences. Front Neurol 2019;10:980; doi: 10.3389/fneur.2019.00980
4. Katz DI, Bernick C, Dodick DW, et al. National institute of neurological disorders and stroke consensus diagnostic criteria for traumatic encephalopathy syndrome. Neurology 2021;96(18):848–863; doi: 10.1212/wnl.0000000000011850
5. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B 1996;111(3):209–219; doi: 10.1006/jmrb.1996.0086
6. Le Bihan D, Mangin JF, Poupon C, et al. Diffusion tensor imaging: Concepts and applications. J Magn Reson Imaging 2001;13(4):534–546; doi: 10.1002/jmri.1076
7. Kochsiek J, O'Donnell LJ, Zhang F, et al. Exposure to repetitive head impacts is associated with corpus callosum microstructure and plasma total tau in former professional American football players. J Magn Reson Imaging 2021;54(6):1819–1829; doi: 10.1002/jmri.27774
8. Koerte IK, Wiegand TLT, Bonke EM, et al. Diffusion imaging of sport-related repetitive head impacts-A systematic review. Neuropsychol Rev 2023;33(1):122–143; doi: 10.1007/s11065-022-09566-z
9. Stamm JM, Koerte IK, Muehlmann M, et al. Age at first exposure to football is associated with altered corpus callosum white matter microstructure in former professional football players. J Neurotrauma 2015;32(22):1768–1776; doi: 10.1089/neu.2014.3822
10. Hall JR, Johnson LA, Zhang F, et al.; HABLE Study. Using fractional anisotropy imaging to detect mild cognitive impairment and Alzheimer's disease among Mexican Americans and non-Hispanic Whites: A HABLE study. Dement Geriatr Cogn Disord 2021;50(3):266–273; doi: 10.1159/000518102
11. Teipel SJ, Grothe MJ, Filippi M, et al.; EDSD study group. Fractional anisotropy changes in Alzheimer's disease depend on the underlying fiber tract architecture: A multiparametric DTI study using joint independent component analysis. J Alzheimers Dis 2014;41(1):69–83; doi: 10.3233/jad-131829
12. Adler CM, DelBello MP, Weber W, et al. MRI evidence of neuropathic changes in former college football players. Clin J Sport Med 2018;28(2):100–105; doi: 10.1097/jsm.0000000000000391
13. Clark MD, Varangis EML, Champagne AA, et al. Effects of career duration, concussion history, and playing position on white matter microstructure and functional neural recruitment in former college and professional football athletes. Radiology 2018;286(3):967–977; doi: 10.1148/radiol.2017170539
14. Holleran L, Kim JH, Gangolli M, et al. Axonal disruption in white matter underlying cortical sulcus tau pathology in chronic traumatic encephalopathy. Acta Neuropathol 2017;133(3):367–380.
15. Shahim P, Gill JM, Blennow K, et al. Fluid biomarkers for chronic traumatic encephalopathy. Semin Neurol 2020;40(4):411–419; doi: 10.1055/s-0040-1715095
16. Zetterberg H, Blennow K. Chronic traumatic encephalopathy: Fluid biomarkers. Handb Clin Neurol 2018;158:323–333; doi: 10.1016/b978-0-444-63954-7.00030-6
17. Alosco ML, Mariani ML, Adler CH, et al.; DIAGNOSE CTE Research Project Investigators. Developing methods to detect and diagnose chronic traumatic encephalopathy during life: Rationale, design, and methodology for the DIAGNOSE CTE Research Project. Alzheimers Res Ther 2021;13(1):136; doi: 10.1186/s13195-021-00872-x
18. Montenigro PH, Alosco ML, Martin BM, et al. Cumulative head impact exposure predicts later-life depression, apathy, executive dysfunction, and cognitive impairment in former high school and college football players. J Neurotrauma 2017;34(2):328–340; doi: 10.1089/neu.2016.4413
19. Alosco ML, Kasimis AB, Stamm JM, et al. Age of first exposure to American football and long-term neuropsychiatric and cognitive outcomes. Transl Psychiatry 2017;7(9):e1236; doi: 10.1038/tp.2017.197
20. Destrieux C, Fischl B, Dale A, et al. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. Neuroimage 2010;53(1):1–15; doi: 10.1016/j.neuroimage.2010.06.010
21. Del Re EC, Gao Y, Eckbo R, et al. A new MRI masking technique based on multi-atlas brain segmentation in controls and schizophrenia: A rapid and viable alternative to manual masking. J Neuroimaging 2016;26(1):28–36; doi: 10.1111/jon.12313
22. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 1999;9(2):179–194; doi: 10.1006/nimg.1998.0395
23. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 1999;9(2):195–207; doi: 10.1006/nimg.1998.0396
24. Fischl B, van der Kouwe A, Destrieux C, et al. Automatically parcellating the human cerebral cortex. Cereb Cortex 2004;14(1):11–22; doi: 10.1093/cercor/bhg087
25. Cetin-Karayumak S, Zhang F, Zurrin R, et al. Harmonized diffusion MRI data and white matter measures from the Adolescent Brain Cognitive Development Study. Sci Data 2024;11(1):249; doi: 10.1038/s41597-024-03058-w
26. Andersson JLR, Graham MS, Zsoldos E, et al. Incorporating outlier detection and replacement into a non-parametric framework for movement and distortion correction of diffusion MR images. Neuroimage 2016;141:556–572; doi: 10.1016/j.neuroimage.2016.06.058
27. Andersson JLR, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage 2016;125:1063–1078; doi: 10.1016/j.neuroimage.2015.10.019
28. Albi A, Meola A, Zhang F, et al. Image registration to compensate for EPI distortion in patients with brain tumors: An evaluation of tract-specific effects. J Neuroimaging 2018;28(2):173–182; doi: 10.1111/jon.12485
29. Mirzaalian H, Ning L, Savadjiev P, et al. Multi-site harmonization of diffusion MRI data in a registration framework. Brain Imaging Behav 2018;12(1):284–295; doi: 10.1007/s11682-016-9670-y
30. Cetin Karayumak S, Bouix S, Ning L, et al. Retrospective harmonization of multi-site diffusion MRI data acquired with different acquisition parameters. Neuroimage 2019;184:180–200; doi: 10.1016/j.neuroimage.2018.08.073
31. Pasternak O, Sochen N, Gur Y, et al. Free water elimination and mapping from diffusion MRI. Magn Reson Med 2009;62(3):717–730; doi: 10.1002/mrm.22055
32. Ghajari M, Hellyer PJ, Sharp DJ. Computational modelling of traumatic brain injury predicts the location of chronic traumatic encephalopathy pathology. Brain 2017;140(2):333–343; doi: 10.1093/brain/aww317
33. Greve DN, Fischl B. Accurate and robust brain image alignment using boundary-based registration. Neuroimage 2009;48(1):63–72; doi: 10.1016/j.neuroimage.2009.06.060
34. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. Neuroimage 2006;31(4):1487–1505; doi: 10.1016/j.neuroimage.2006.02.024
35. Gobom J, Parnetti L, Rosa-Neto P, et al. Validation of the LUMIPULSE automated immunoassay for the measurement of core AD biomarkers in cerebrospinal fluid. Clin Chem Lab Med 2022;60(2):207–219; doi: 10.1515/cclm-2021-0651
36. Ashton NJ, Brum WS, Di Molfetta G, et al. Diagnostic accuracy of a plasma phosphorylated Tau 217 immunoassay for Alzheimer disease pathology. JAMA Neurol 2024;81(3):255–263; doi: 10.1001/jamaneurol.2023.5319
37. Ashton NJ, Pascoal TA, Karikari TK, et al. Plasma p-tau231: A new biomarker for incipient Alzheimer's disease pathology. Acta Neuropathol 2021;141(5):709–724; doi: 10.1007/s00401-021-02275-6
38. Gaetani L, Höglund K, Parnetti L, et al. A new enzyme-linked immunosorbent assay for neurofilament light in cerebrospinal fluid: Analytical validation and clinical evaluation. Alzheimers Res Ther 2018;10(1):8; doi: 10.1186/s13195-018-0339-1
39. Gisslén M, Heslegrave A, Veleva E, et al. CSF concentrations of soluble TREM2 as a marker of microglial activation in HIV-1 infection. Neurol Neuroimmunol Neuroinflamm 2019;6(1):e512; doi: 10.1212/nxi.0000000000000512

40. Alosco ML, Tripodis Y, Koerte IK, et al. Interactive effects of racial identity and repetitive head impacts on cognitive function, structural MRI-derived volumetric measures, and cerebrospinal fluid Tau and Aβ. Front Hum Neurosci 2019;13:440; doi: 10.3389/fnhum.2019.00440
41. Kirton JW, Dotson VM. The interactive effects of age, education, and BMI on cognitive functioning. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2016;23(2):253–262; doi: 10.1080/13825585.2015.1082531
42. Atherton K, Han X, Chung J, et al. Association of APOE genotypes and chronic traumatic encephalopathy. JAMA Neurol 2022;79(8):787–796; doi: 10.1001/jamaneurol.2022.1634
43. Mayinger MC, Merchant-Borna K, Hufschmidt J, et al. White matter alterations in college football players: A longitudinal diffusion tensor imaging study. Brain Imaging Behav 2018;12(1):44–53; doi: 10.1007/s11682-017-9672-4
44. Brett BL, Koch KM, Muftuler LT, et al. Association of head impact exposure with white matter macrostructure and microstructure metrics. J Neurotrauma 2021;38(4):474–484; doi: 10.1089/neu.2020.7376
45. Churchill NW, Hutchison MG, Di Battista AP, et al. Structural, functional, and metabolic brain markers differentiate collision versus contact and non-contact athletes. Front Neurol 2017;8:390; doi: 10.3389/fneur.2017.00390
46. Nilsson KJ, Flint HG, Gao Y, et al. Repetitive head impacts in youth football: Description and relationship to white matter structure. Sports Health 2019;11(6):507–513; doi: 10.1177/1941738119865264
47. Babcock L, Yuan W, Leach J, et al. White matter alterations in youth with acute mild traumatic brain injury. J Pediatr Rehabil Med 2015;8(4):285–296; doi: 10.3233/prm-150347
48. Borich M, Makan N, Boyd L, et al. Combining whole-brain voxel-wise analysis with *in vivo* tractography of diffusion behavior after sports-related concussion in adolescents: A preliminary report. J Neurotrauma 2013;30(14):1243–1249; doi: 10.1089/neu.2012.2818
49. Meier TB, Bergamino M, Bellgowan PS, et al. Longitudinal assessment of white matter abnormalities following sports-related concussion. Hum Brain Mapp 2016;37(2):833–845; doi: 10.1002/hbm.23072
50. Sasaki T, Pasternak O, Mayinger M, et al. Hockey concussion education project, Part 3. White matter microstructure in ice hockey players with a history of concussion: A diffusion tensor imaging study. J Neurosurg 2014;120(4):882–890; doi: 10.3171/2013.12.Jns132092
51. Ware AL, Yeates KO, Tang K, et al.; Pediatric Emergency Research Canada A-CAP Study Team. Longitudinal white matter microstructural changes in pediatric mild traumatic brain injury: An A-CAP study. Hum Brain Mapp 2022;43(12):3809–3823; doi: 10.1002/hbm.25885
52. Koerte IK, Lin AP, Willems A, et al. A review of neuroimaging findings in repetitive brain trauma. Brain Pathol 2015;25(3):318–349; doi: 10.1111/bpa.12249
53. Babcock KJ, Abdolmohammadi B, Kiernan PT, et al. Interface astrogliosis in contact sport head impacts and military blast exposure. Acta Neuropathol Commun 2022;10(1):52; doi: 10.1186/s40478-022-01358-z
54. Verboon LN, Patel HC, Greenhalgh AD. The immune system's role in the consequences of mild traumatic brain injury (concussion). Front Immunol 2021;12:620698; doi: 10.3389/fimmu.2021.620698
55. Brun A, Englund E. A white matter disorder in dementia of the Alzheimer type: A pathoanatomical study. Ann Neurol 1986;19(3):253–262; doi: 10.1002/ana.410190306
56. McKee AC, Abdolmohammadi B, Stein TD. The neuropathology of chronic traumatic encephalopathy. Handb Clin Neurol 2018;158:297–307; doi: 10.1016/b978-0-444-63954-7.00028-8
57. Wiegand TLT, Sollmann N, Bonke EM, et al. Translational neuroimaging in mild traumatic brain injury. J Neurosci Res 2022;100(5):1201–1217; doi: 10.1002/jnr.24840
58. Adluru N, Destiche DJ, Lu SY, et al. White matter microstructure in late middle-age: Effects of apolipoprotein E4 and parental family history of Alzheimer's disease. Neuroimage Clin 2014;4:730–742; doi: 10.1016/j.nicl.2014.04.008
59. Bergamino M, Walsh RR, Stokes AM. Free-water diffusion tensor imaging improves the accuracy and sensitivity of white matter analysis in Alzheimer's disease. Sci Rep 2021;11(1):6990; doi: 10.1038/s41598-021-86505-7
60. Benitez A, Jensen JH, Thorn K, et al. Greater diffusion restriction in white matter in preclinical Alzheimer disease. Ann Neurol 2022;91(6):864–877; doi: 10.1002/ana.26353
61. Collij LE, Ingala S, Top H, et al. White matter microstructure disruption in early stage amyloid pathology. Alzheimers Dement (Amst) 2021;13(1):e12124; doi: 10.1002/dad2.12124
62. Wolf D, Fischer FU, Scheurich A, et al.; Alzheimer's Disease Neuroimaging Initiative. Non-linear association between cerebral amyloid deposition and white matter microstructure in cognitively healthy older adults. J Alzheimers Dis 2015;47(1):117–127; doi: 10.3233/jad-150049
63. Asken BM, Tanner JA, VandeVrede L, et al. Plasma P-tau181 and P-tau217 in patients with traumatic encephalopathy syndrome with and without evidence of Alzheimer disease pathology. Neurology 2022;99(6):e594–e604; doi: 10.1212/wnl.0000000000200678
64. Thijssen EH, La Joie R, Strom A, et al.; Advancing Research and Treatment for Frontotemporal Lobar Degeneration investigators. Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: A retrospective diagnostic performance study. Lancet Neurol 2021;20(9):739–752; doi: 10.1016/s1474-4422(21)00214-3
65. Stern RA, Trujillo-Rodriguez D, Tripodis Y, et al.; DIAGNOSE CTE Research Project Investigators. Amyloid PET across the cognitive spectrum in former professional and college American football players: Findings from the DIAGNOSE CTE Research Project. Alzheimers Res Ther 2023;15(1):166; doi: 10.1186/s13195-023-01315-5
66. Muraoka S, Lin W, Takamatsu-Yukawa K, et al. Enrichment of phosphorylated Tau (Thr181) and functionally interacting molecules in chronic traumatic encephalopathy brain-derived extracellular vesicles. Aging Dis 2021;12(6):1376–1388; doi: 10.14336/ad.2020.1007