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RESEARCH ARTICLE

Flortaucipir tau PET findings from former professional and college American football players in the DIAGNOSE CTE research project

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Abstract

INTRODUCTION: Tau is a key pathology in chronic traumatic encephalopathy (CTE). Here, we report our findings in tau positron emission tomography (PET) measurements from the DIAGNOSE CTE Research Project.

METHOD: We compare flortaucipir PET measures from 104 former professional players (PRO), 58 former college football players (COL), and 56 same-age men without exposure to repetitive head impacts (RHI) or traumatic brain injury (unexposed [UE]); characterize their associations with RHI exposure; and compare players who did or did not meet diagnostic criteria for traumatic encephalopathy syndrome (TES).

RESULTS: Significantly elevated flortaucipir uptake was observed in former football players (PRO+COL) in prespecified regions ($p < 0.05$). Association between regional flortaucipir uptake and estimated cumulative head impact exposure was only observed in the superior frontal region in former players over 60 years old. Flortaucipir PET was not able to differentiate TES groups.

DISCUSSION: Additional studies are needed to further understand tau pathology in CTE and other individuals with a history of RHI.

KEYWORDS
CTE, flortaucipir, football, PET, Tau

1 | BACKGROUND

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with exposure to repetitive head impacts (RHI), such as those experienced by contact/collision sport athletes and military combat veterans.[1,2] CTE is defined neuropathologically by the presence of neurofibrillary tangles (NFTs) in neurons, around small vessels, and in an irregular pattern at the depth of the cortical sulci[3,4] distinct from other tauopathy-related neurodegenerative diseases such as Alzheimer's disease (AD).[3,5] The clinical presentation of individuals with neuropathologically-confirmed CTE, referred to as traumatic encephalopathy syndrome (TES),[6] includes progressively worsening cognitive impairment (especially in episodic memory and executive functioning), neurobehavioral dysregulation (e.g., rage, short fuse, emotional lability), and in some instances, parkinsonism, and motor neuron disease.[6–9] Currently, CTE can only be definitively diagnosed *post mortem* based on neuropathological assessment. The lack of well-validated in vivo biomarkers specific for CTE NFT hampers clinical detection and diagnosis during life.[10] To address this challenge, the National Institute of Neurological Disorders and Stroke (NINDS) funded a multi-institutional and multidisciplinary study, referred to as the "Diagnostics, Imaging, and Genetics Network for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy (DIAGNOSE CTE) Research Project" to develop methods to detect, characterize, and DIAGNOSE CTE by evaluating a cohort of former professional and college American football players and a comparison group of same-age men without exposure to contact/collision sports or history of RHI or traumatic brain injury (TBI).[10]

Since tau is the central pathology that defines CTE, in vivo biomarkers that can assess tau pathology are essential for its detection and characterization. Tau-specific Positron emission tomography (PET) has emerged as a promising technique to detect and quantify NFTs in AD and other tauopathies.[11–13] The PET tracer [F18]-flortaucipir (FTP) was approved by the United States Food and Drug Administration (U.S. FDA) to measure NFTs in patients being evaluated for AD, a mixed 3-repeat-4-repeat (3R-4R) tauopathy. Although FTP has been found to have a high affinity for AD tau,[14,15] its affinity for tau isoforms in other tauopathies is weaker, especially in 4R tauopathies, such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).[16,17]

The detection of NFT in CTE has unique challenges. First, because tau deposition in earlier stages of CTE is patchy, with a focal sulcal depth distribution,[4,18] the overall uptake across any specific region of interest (ROI) is expected to be modest at best. Second, although CTE is a mixed 3R-4R tauopathy like AD, there are changes to the ratio of 3R:4R tau isoforms across disease stages, between neuronal and glial tau,[19] as well as across different regions.[20] Finally, growing research using cryo-electron microscopy has demonstrated that the molecular structure of tau filaments across different tauopathies are distinct,[5,21,22] and the 3R tau isoform which FTP is more sensitive in detecting is more predominant at late-stage CTE. Despite these challenges, in a previous investigation, higher FTP uptake was observed in a group of 26 former National Football League (NFL) players (all with cognitive, mood, and behavioral symptoms; ages 40–69) compared to a control group of 31 same-age participants (all asymptomatic and without a history of TBI).[23] Association between FTP uptake and exposure to RHI as measured by the years of playing football was also observed. However, no association was found between FTP uptake and cognitive function or neuropsychiatric symptoms.[23]

In this study, we examine further the ability of FTP PET to detect CTE tau pathology in former American football players and examine the relationships between FTP PET uptake and RHI exposure and clinical diagnosis. This study addresses previous limitations by including a much larger sample size, greater variability in RHI exposure (including in addition men who only played football up through college), greater variability in symptom severity in the former players (from asymptomatic to mild dementia), and an asymptomatic comparison group of same-age men without a history of playing contact/collision sports, other RHI exposure, concussion, or TBI.

RESEARCH IN CONTEXT

1. **Systematic review**: Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with exposure to repetitive head impacts (RHIs) and defined neuropathologically by the presence of hyperphosphorylated neurofibrillary tangles. We previously reported in a moderate-sized cohort of former professional football players and controls that elevated tau can be detected by flortaucipir PET in the player group; however, another recent study failed to observe this. Here, in a larger cohort that also included former college players, we confirmed the modestly elevated flortaucipir uptake in former football players. The flortaucipir uptake was also associated with the estimated exposure to RHIs but only in participants 60 years and older. The flortaucipir PET was not able to differentiate clinical groups in former players.
2. **Interpretation**: Elevated flortaucipir uptake can be detected in patients with RHI exposure, although this requires a sufficient sample size. There is also a delay between RHI exposure and the accumulation of tau pathology, which contributed to the conflicting results in the literature.
3. **Future directions**: Future studies are needed to identify optimal CTE tau biomarkers, clarify the relationship between tau markers and different indicators of RHI in former football players and other groups, and the extent to which they predict subsequent clinical progression and *post mortem* CTE pathology.

TABLE 1 Summary of cohort characteristics

	PRO ($N = 104$)	COL ($N = 58$)	UE ($N = 56$)	p-Value
Age (years) Mean ± SD (min, max)	58.7 ± 7.9 (45,74)	53.1 ± 7.3 (45,74)	59.5 ± 8.4 (45,74)	<0.0001
Race (*n* [%] Black/African-American)	45 (43.2%)	11 (19.0%)	21 (37.5%)	0.008
APOE-e4 carriers (*n* [%])	30 (30%)	20 (35%)	10 (19%)	0.16
Education (years) Mean ± SD (min, max)	16.6 ± 1.2 (15,21)	16.9 ± 1.4 (15,22)	17.5 ± 3.4 (13,30)	0.04
MoCA total score Mean ± SD (min, max)	24.4 ± 3.5 (12,30)	25.2 ± 3.2 (11,30)	26.6 ± 2.3 (17,30)	<0.001

Note: One-way ANOVA was performed to examine continuous cohort variables for exposure group level differences, and $\chi 2$ test was used to determine group difference for categorical variables, including percentage of Black or African American participants.
Abbreviations: APO-E, apolipoprotein E; COL, former college football players; MoCA, Montreal Cognitive Assessment; PRO, former professional football players; SD, standard deviation; UE, participants with no football exposure.

2 | METHODS

2.1 | Participants

The design of the DIAGNOSE CTE Research Project has been previously described.[10] Briefly, the overall study enrolled 240 participants, ages 45–74, including 120 former professional football players (PRO) and 60 former college football players (COL) regardless of their cognitive and clinical status, and 60 control participants without RHI exposure, TBI, or combat military history and who denied symptoms at telephone screening (unexposed, UE). Specific inclusion and exclusion criteria are reported elsewhere.[10] Participants were evaluated at one of four Participant Evaluation Sites: (1) Boston (Boston University Chobanian & Avedisian School of Medicine, 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 in Phoenix, AZ). The study was approved by the Institutional Review Boards at all sites, and written informed consent was obtained for all participants. Eight participants who were part of our previous study[23] were excluded from this analysis to avoid circularity as the primary regions we examined as described below were defined statistically using data including these participants. Participants without FTP PET data were also excluded, resulting in a total of 218 participants (104 PRO, 58 COL, and 56 UE) included in this analysis (Table 1).

2.2 | Brain imaging

T1 MRIs were acquired on 3T Siemens Skyra scanners across the four study sites using MPRAGE sequence with 1 mm^3 isotropic resolution.[10] FTP PET data were acquired following a bolus injection of approximately 259 MBq (7 mCi) of the PET tracer on a PET/CT scanner (GE Discovery 710 or Siemens mCT) at one of the four participating sites in dynamic mode with 5-min frames. Most FTP scans were acquired with an 80–100 min post-injection window while three participants only had data up to 90 min after injection. All PET data were reconstructed with CT-based attenuation correction and standard random and scatter corrections. The use of flortaucipir in this study was carried out through an Investigational New Drug (IND #131,391) from the U.S. FDA. FTP doses were requested through and provided at no cost by Avid Radiopharmaceuticals (Philadelphia, PA, USA). Quality control and imaging calibration procedures were completed prior to study initiation by Invicro (Needham, MA, USA) to certify the scanners used in this study at each site.

The T1-weighted MRI data were analyzed using FreeSurfer v6 (Martinos Center for Biomedical Imaging, Charlestown, Massachusetts, USA) to define anatomical regions of interest (ROIs) by the Brigham and Women's Hospital team. FTP PET analysis was conducted at Banner Alzheimer's Institute using an in-house pipeline.[24,25] The analysis included scanner harmonization filtering to reach a common 8-mm resolution,[26] between frame motion correction, target frame summation, PET-to-MR coregistration, and regional standardized uptake value ratio (SUVR) extraction based on the FreeSurfer generated anatomical ROIs with bilateral inferior cerebellar cortex as the reference region.[27] Fully bias field corrected and intensity normalized T1-MRI from the FreeSurfer pipeline (T1.mgz) was also spatially normalized using the Statistical Parametric Mapping (SPM) to generate the individual-to-template space nonlinear transformation and transform PET data into the MNI template space. The FTP PET data in template space were also renormalized using cerebellum crus one region (5128 voxels) as the reference for prespecified regional analysis to be consistent with our prior work.[23] Three prespecified statistical ROIs, bilateral superior frontal region (2887 voxels), bilateral medial temporal region (1283 voxels), and left parietal region (252 voxels)[23] (referred to as prespecified statistical ROIs henceforth), were included as the primary ROIs. These prespecified statistical ROIs were voxel clusters defined in our previous study of 26 formal professional football players and 31 control subjects where former players had statistically significantly higher FTP SUVR than controls[23] (Figure S1). For 13 participants missing MR data, the summed FTP PET data were transformed to the

template space using a separate PET only SPM pipeline with a pre-established FTP template. For these participants, only the prespecified statistical ROI measures were extracted.

2.3 | Estimated cumulative RHI exposure and TES diagnostic grouping

In this study, the cumulative head impact index based on measurements of linear acceleration (CHII-G) was used to estimate the lifetime cumulative g-force that participants experienced due to football RHI.[28,29] CHII-G is a composite score based on a combination of self-reported measures of exposure,[28] projected onto data aggregated into a positional exposure matrix (PEM) based on published helmet accelerometer studies, stratified by position and level of play.[29] All participants were diagnosed through multidisciplinary diagnostic consensus conferences using the NINDS Consensus Diagnostic Criteria for TES (including the Provisional Levels of Certainty for CTE Pathology).[6,10] The consensus conference panelists included 16 clinician-researchers (all DIAGNOSE CTE Research Project investigators) representing multiple disciplines (neurology, neuropsychology, psychiatry, neurosurgery), from seven institutions. Panelists were presented with the participant's medical history (including neurologic and psychiatric); football history (and other RHI exposure); self- and informant-reported complaints of cognitive, mood, and/or behavior problems, as well as functional dependence status; neurological/motor evaluation findings; and standardized neuropsychological and neuropsychiatric test results (the specific tests and assessment methods have been described previously[10]) Based on this information, the panelists used the TES criteria and adjudicated the following diagnostic categories pertinent to the current study: (1) No TES, (2) TES with *suggestive* level of certainty for CTE pathology, and (3) TES with *possible* or *probable* level of certainty for CTE pathology. A diagnosis of TES[6] requires (1) substantial RHI exposure from contact sports, military service, or other causes; (2) core clinical features of cognitive impairment (in episodic memory and/or executive functioning, substantiated by performance on formal neuropsychological testing, > 1.5 SDs below norms) and/or neurobehavioral dysregulation (e.g., rage, emotional dyscontrol, short fuse); (3) progressive course; and (4) that the core clinical features are not fully accounted for other neurologic, psychiatric, or medical disorders. The Provisional Levels of Certainty for CTE Pathology are determined based on specific RHI exposure thresholds, core clinical features (e.g., cognitive impairment is required for possible or probable levels of certainty), functional status, and additional supportive features, including delayed symptom onset after retirement from football, motor signs, and psychiatric features.[6]

2.4 | Statistical analysis

One-way analysis of variance (ANOVA) was performed to examine continuous cohort variables for exposure group-level differences, and the χ^2 test was used to determine group differences for categorical variables, including the percentage of Black or African American participants.

Exposure group-level differences in FTP PET-measured tau pathology were examined in both regional and voxel-wise analysis. The primary regional analysis focused on the three prespecified statistical ROIs to replicate our previous findings and examine the relationship between FTP uptake and exposure to football. Exploratory analysis was also performed for a preselected subset of eight anatomical ROIs (to limit the impact of type I error due to multiple comparisons) that are known to be susceptible to tau pathology in aging, Alzheimer's disease, and/or CTE, including entorhinal cortex, parahippocampal gyrus, superior frontal cortex, superior parietal cortex, hippocampus, amygdala, inferior parietal cortex, and inferior temporal cortex. Group-level comparison of regional FTP SUVR adjusted for age and race was performed using analysis of covariance (ANCOVA) followed by post hoc pair-wise comparisons in the framework of ANCOVA.

For the voxel-wise analysis to examine the spatial extent of the FTP measured tau burden group differences, voxel-wise general linear model analysis on the spatially normalized FTP SUVR images was performed between the groups. The primary comparison was made between all former players (PRO+COL) and UE followed by additional comparisons for PRO versus UE and COL versus UE. To avoid potential biases caused by analysis variation, only those FTP scans with data over the full 80- to 100-min post-injection window that had successful FreeSurfer runs were included in the voxel-wise analysis. A Monte-Carlo simulation approach introduced previously[23] was used to assess the omnibus significance for the voxel-wise SUVR differences between groups. Referred to as the majority-count statistics (MCS) in this report, this statistical significance examination is a way to assess the significance free from the multiple comparisons concern. MCS capitalizes on the argument that the likelihood of observing wide-spread tau load increase in one contrast direction (e.g., higher SUVR in PRO than in UE) versus minimal load in the opposite direction (e.g., lower SUVR in PRO than in UE) should be very low if no group difference exists. In other words, the number of voxels where one group has higher SUVR than the other group should be statistically the same for the opposite direction if no group SUVR difference exists. A detailed description of MCS can be found in our previous study.[23] Additionally, we applied family-wise error (FWE) corrections to adjust for the voxel-wise multiple comparisons with localization power.

To investigate whether tau burden is associated with exposure to RHI, linear regression analysis was performed within the PRO+COL group with CHII-G as the response variable, regional FTP SUVRs for the three prespecified statistically defined ROIs as the independent variable, and age and race as covariates. To examine whether FTP PET can differentiate the two TES diagnostic groups described above in former football players, ANCOVAs were performed between the two groups for FTP SUVR in each of the three prespecified ROIs again with age and race as covariates. Exploratory analyses were also performed in the subset of former football players (PRO+COL) older than 60 (N = 54, 45 PRO, 9 COL) to examine the tau association with RHI exposure and its ability to differentiate clinical groups, as in our recent

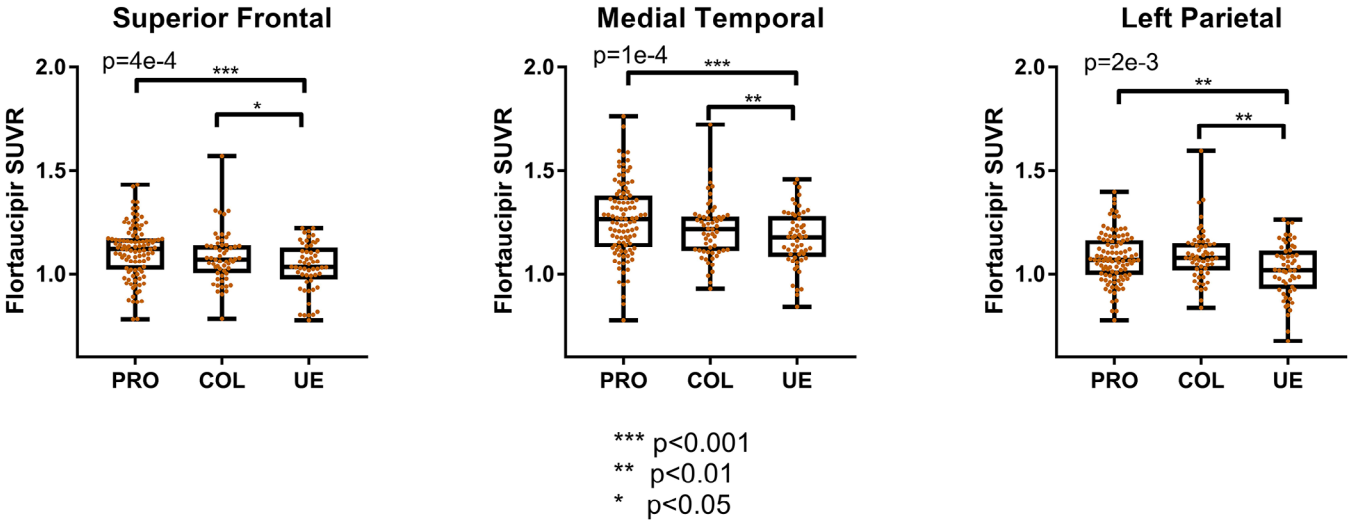

FIGURE 1 Comparison of flortaucipir SUVR in prespecified statistical ROIs among football exposure groups controlling for age and race. The *p*-value for the ANCOVA test was indicated for each plot, significance level of post hoc pair-wise comparison was also reported. ANCOVA, analysis of covariance; COL, former college football players; PRO, former NFL players; ROIs, regions of interest; SUVR, standardized uptake value ratio; UE, asymptomatic participants with no football exposure;

investigations of white matter changes in this cohort, increased white matter lesion was only observed in participants older than 60.[30]

3 | RESULTS

Demographics for each of the three exposure groups are summarized in Table 1, example FTP SUVR images are shown in Figure S2. A statistically significant (ANCOVA $p < 0.01$) exposure group difference in regional FTP SUVR was observed for all three prespecified statistical ROIs controlling for age and race (Figure 1). In pair-wise post hoc comparisons, the PRO group had higher regional FTP SUVRs than the UE group for all three statistical ROIs ($p < 0.01$). The COL group also had higher regional FTP SUVRs than the UE group ($p < 0.05$). The combined group of all former football players (PRO+COL) also had higher FTP SUVRs than the UE group for all three regions ($p < 0.05$). No statistical differences were observed between the PRO and COL groups. In the exploratory analysis with anatomically defined regions, significant group difference in the same direction in the three-way comparison ($p < 0.05$) in FTP SUVR was observed in six of the eight preselected regions including entorhinal cortex, parahippocampal gyrus, superior frontal cortex, superior parietal cortex, hippocampus, and amygdala (Figure S3). The PRO group also had higher FTP SUVRs than the UE group in the same six regions in pair-wise comparisons ($p < 0.02$).

In the voxel-wise analysis, a total of 202 participants (99 PRO, 51 COL, and 52 UE) with consistent imaging data acquisition and preprocessing were included and controlled for age and race. The raw statistical significance (Z-score) map of the one-tailed test for the PRO+COL group having greater FTP SUVRs than the UE group is shown in the left panel of Figure 2 with a threshold of $p < 0.005$ not corrected for multiple comparisons which were dealt with using MCS. The map of the opposite direction is shown in the right panel. We observed 24016 voxels where the FTP SUVR was higher in former players than in UE, in comparison to only 1100 voxels where FTP SUVR was lower in former players than in UE. Given the difference in the number of voxels between the two directions, the omnibus significance assessed by MCS is $p < 0.001$. After FWE correction 43 voxels in the superior frontal cortex, medial temporal cortex, and precuneus remained significant in the expected direction while no voxels remained significant in the opposite direction. Similar findings were observed in the PRO versus UE and COL versus UE comparisons (Figure S4).

Regional FTP SUVR was not significantly associated with CHII-G in the PRO+COL group for any of the prespecified ROIs. However, in the sensitivity analysis, there was an association in the superior frontal region in PRO+COL participants over age 60 years ($p = 0.03$, Figure 3D). Regional FTP SUVRs were not significantly different between former players with a TES diagnosis from those who did not (Figure 4A–C). In addition, regional FTP SUVRs were also not significantly different between former players with a TES diagnosis at a suggestive level of CTE pathology and those who had a possible or probable level of CTE pathology (Figure 4D–F). The results were similar in the sensitivity analyses that only included participants over 60 years, and FTP SUVR was not able to differentiate TES diagnostic groups.

4 | DISCUSSION

In this study, we examined tau PET imaging with the FTP tracer in former professional and college American football players from the DIAGNOSE CTE Research Project cohort. Significantly higher FTP SUVR was observed in the former football players compared to the unexposed controls in all three prespecified ROIs (bilateral superior frontal, bilateral medial temporal, and left parietal), controlling for age and race. Higher FTP SUVR was also observed in six anatomically

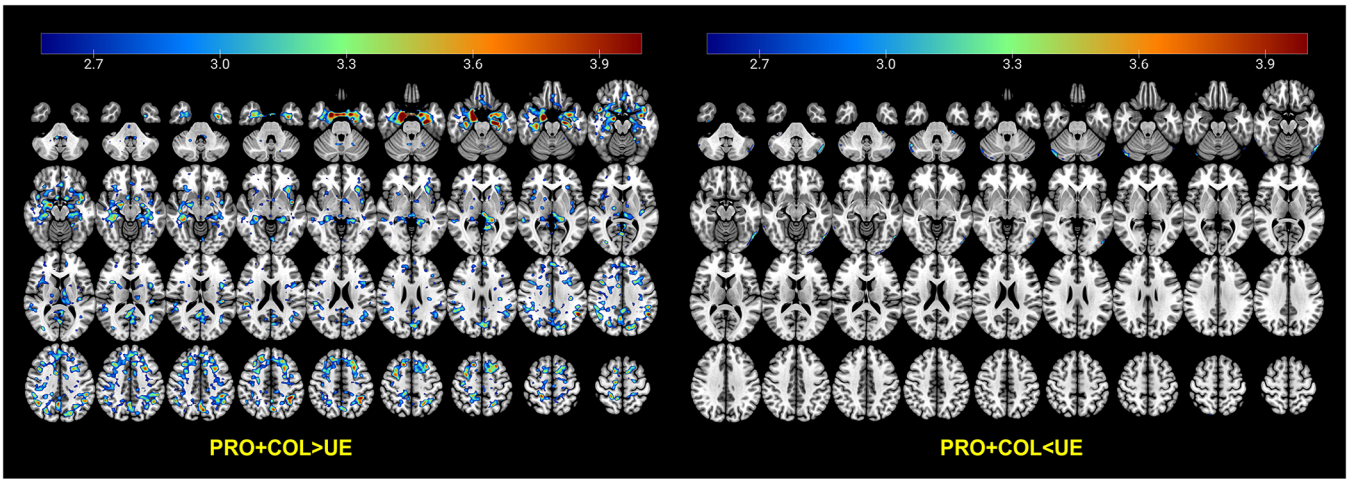

FIGURE 2 Voxel-wise comparison of FTP uptake between football exposure groups PRO+COL versus UE. Voxel-wise Z-score map for one-tailed test for each direction is shown at a threshold of $p = 0.005$ uncorrected for voxel-wise multiple comparisons which were dealt with using MCS, age and race are controlled for in all analyses. A total of 24,016 voxels were above this threshold in the expected direction (PRO+COL > UE) in contrast to 1100 voxels in the opposite direction (PRO+COL < UE). MCS analysis with $N = 1000$ iterations found overall significantly elevated FTP uptake in former American football players (PRO+COL) than control participants (UE) ($p < 0.001$). Additionally, 43 voxels remained significant after the FWE correction. COL, former college American football players ($N = 51$); FTP, flortaucipir; FWE, family-wise error; MCS, majority count statistics; PRO, former professional American football players ($N = 99$); UE, control participants not exposed to head injuries ($N = 52$)

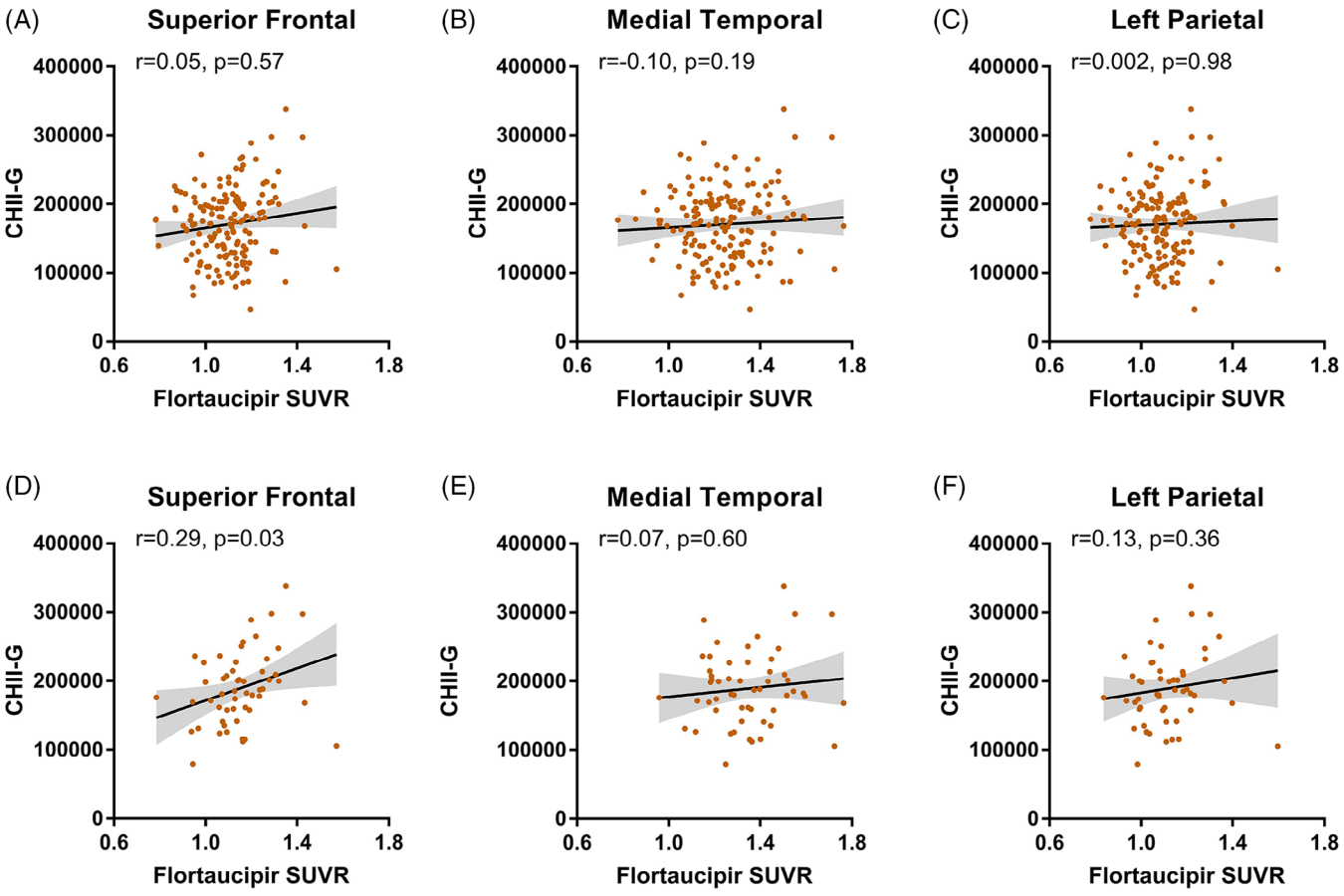

FIGURE 3 Association between regional FTP SUVR and CHII-G in the full COL+PRO group (A, B, C) and the subset of COL+PRO participants over age 60 years (D, E, F). All analyses controlled for age and race. CHII-G, cumulative head impact index based on measurements of linear acceleration; COL, former college football players; FTP, flortaucipir; PRO, former NFL players; SUVR, standardized uptake value ratio; UE, participants with no football exposure

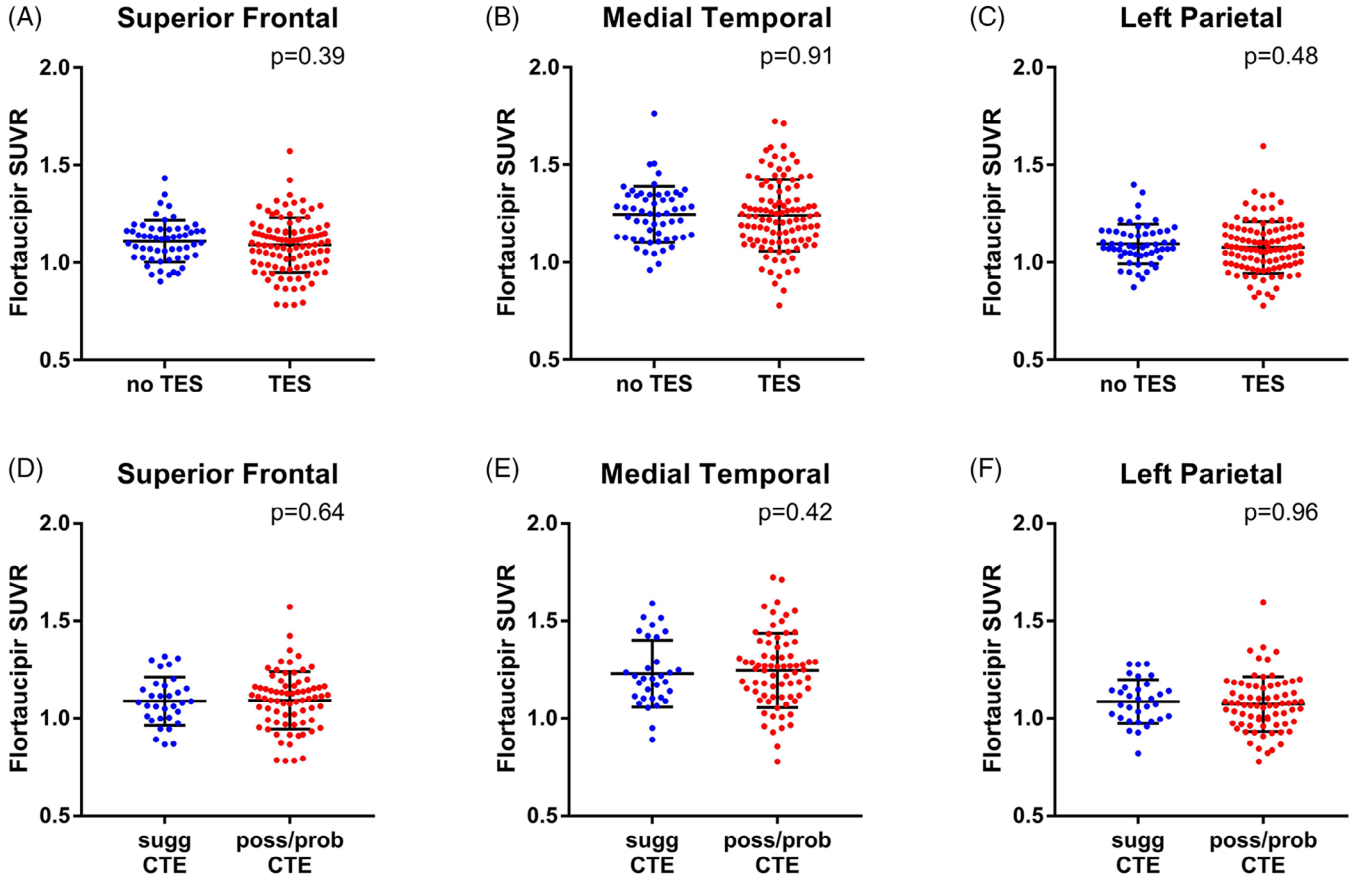

FIGURE 4 Comparison of FTP SUVRs in the prespecified regions between former American football players (PRO+COL) with or without a TES diagnosis (A, B, C); and comparison of FTP SUVRs in the prespecified regions between former players with a TES diagnosis and suggestive level of CTE pathology (sugg CTE) and former players with a TES diagnosis and possible or probable level of CTE pathology (poss/prob CTE) (D, E, F). COL, former college football players; CTE, chronic traumatic encephalopathy; FTP, flortaucipir; PRO, former NFL players; SUVR, standardized uptake value ratio; TES, traumatic encephalopathy syndrome

defined brain regions in former football players compared to controls. The voxel-wise analysis also revealed widespread elevation in FTP SUVR in the PRO group compared to the UE as well as for the combined player group versus UE. The spatial extent of the elevated FTP SUVRs included 39% of the voxels in the bilateral superior frontal region, 67% of voxels in the bilateral medial temporal region, and 25% of voxels in the left parietal region.

Tau burden measured by regional FTP SUVR did not show a significant association with estimated cumulative RHI exposure as measured by CHII-G in the full PRO+COL group. However, the association was significant when only former players older than 60 years were examined but only in the superior frontal region. This may suggest that there is a significant delay between exposure to RHI and the accumulation of tau pathology measurable by FTP PET, as would be expected in a progressive tauopathy. This may also reflect the specificity of FTP binding to 3R tau isoforms expected in later-stage CTE. FTP SUVR in our prespecified regions was not able to differentiate players who met diagnostic criteria for TES from those who did not. Similarly, there were no differences in FTP SUVR when comparing former players with lower versus higher levels of certainty of CTE pathology, based on the TES criteria. These patterns remained the same when only older participants were examined.

The group level differences and the spatial patterns of elevated FTP SUVR observed in this study are in line with our previous study in a smaller cohort.[23] We extended the findings to demonstrate CTE-related tau pathology also affects former football players at the college level. The previous study reported the association of FTP SUVR with years of football play[23] which was not confirmed in our current study. Another recent study[31] failed to observe differences in FTP SUVR between former professional football players and controls, and the discrepancy is attributable to the younger age and smaller sample size of that study given the moderate differences in FTP uptake and the delayed manifestation of tau pathology as we discussed earlier. A recent study of the incidence rate of CTE-related pathology in military personnel did not observe increased pathology in those who were exposed to blasts or other miliary-related TBI, while those with exposure to contact sports had a higher incidence rate of CTE pathology.[32] This may be attributable to the fact that the exposure to head injury due to blasts or other military-related events was more likely to be incidental and less frequent than those playing contact sports.

In a small subset of six participants of this cohort, we have previously reported a moderately strong association between FTP SUVR and *post mortem* pathological measures of tau density.[33] Those findings, along with this current study suggest that FTP–as a first-generation tau PET tracer with substantial off-target binding – could be useful for detecting CTE-related tau pathology but may not be optimal. As described previously, although CTE is characterized by a mixture of 3R and 4R tau isoforms, their relative contribution to the overall tauopathy shifts from predominantly 4R in the early stages to 3R as the disease progresses[20] making FTP less optimal for detecting CTE related tau aggregates at the early stages and different tracers are likely needed for detecting CTE related tau pathology at different stages due to the stage related variability in the underlying tau pathologies.[34] Moreover, because early-stage CTE p-tau deposition is patchy, with a perivascular, sulcal depth distribution,[4,18] tau tracer uptake across specific ROIs would not be expected to be as robust as is seen in early-stage AD pathology, for example.[35] This is also confirmed in this study where only patchy and moderately elevated FTP SUVR was observed in former football players and does not follow the typical spatial pattern of tau deposition in clinical/preclinical AD patients. Examination of other tau PET tracers[36–38] is warranted, as is the development of tracers specifically targeting CTE tau based on knowledge gained through recent cryo-EM findings,[21,22] as well as studies of molecular docking and dynamics simulations.[31] PET imaging of other pathways such as neuroinflammation[39] in the individuals exposed to substantial RHI is warranted. Advanced quantification techniques[40,41] may also improve the ability to use tau PET imaging to assess CTE-related tauopathies.

In summary, we confirmed our previous finding of modestly elevated PET measurements of tau tangle burden in empirically predefined ROIs in a larger number of former American football players and controls and related the findings to three levels of RHI exposure in the former professional players, former college players, and unexposed controls. Additional studies are needed to clarify the extent to which these or other measurements of PET or fluid biomarker measurements of tau tangle pathology are associated with different indicators of RHI former football players and other groups, the extent to which they distinguish between those who do or do not meet criteria for TES, and the extent to which they predict subsequent clinical progression and *post mortem* CTE pathology.

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CONFLICT OF INTEREST STATEMENT

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W.B.B. receives royalties or license fees from Springer Publishing, consulting fees for legal cases involving concussion & CTE, he also receives payments and travel support for speakership at American Academy of Clinical Neuropsychology (AACN) and National Academy of Neuropsychology. D.W.D. consults for Amgen, Atria, CapiThera Ltd., Cerecin, Ceruvia Lifesciences LLC, CoolTech, Ctrl M, Allergan, AbbVie, Biohaven, GlaxoSmithKline, Lundbeck, Eli Lilly, Novartis, Impel, Satsuma, Theranica, WL Gore, Genentech, Nocira, Perfood, Praxis, AYYA Biosciences, Revance, Pfizer; receives honoraria from American Academy of Neurology, Headache Cooperative of the Pacific, Canadian Headache Society, MF Med Ed Research, Biopharm Communications, CEA Group Holding Company (Clinical Education Alliance LLC), Teva (speaking), Amgen (speaking), Eli Lilly (speaking), Lundbeck (speaking), Pfizer (speaking), Vector Psychometric Group, Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix Communications, Medica Communications LLC, MJH Lifesciences, Miller Medical Communications, WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, Cambridge University Press; has Non-profit board membership at American Brain Foundation, American Migraine Foundation, ONE Neurology, Precon Health Foundation, International Headache Society Global Patient Advocacy Coalition, Atria Health Collaborative, Arizona Brain Injury Alliance, Domestic Violence HOPE Foundation/Panfila; receives research support from Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Henry Jackson Foundation, Patient Centered Outcomes Research Institute (PCORI); owns stock options of Aural analytics, Axon Therapeutics (shares/board), ExSano, Palion, Man and Science, Healint, Theranica, Second Opinion/Mobile Health, Epien, Nocira, King-Devick Technologies, EigenLyfe, AYYA Biosciences, Cephalgia Group, Atria Health; owns shares and/or serves on board of Matterhorn, Ontologics, King-Devick Technologies, Cephalgia Group. 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J.L.C. has ownership of Neuropsychiatric Inventory (NPI) copyright, has provided consultation to AB Science, Acadia, Alkahest, AlphaCognition, ALZPath, Annovis, AriBio, Artery, Avanir, Biogen, Biosplice, Cassava, Cerevel, Clinilabs, Cortexyme, Diadem, EIP Pharma, Eisai, GatehouseBio, GemVax, Genentech, Green Valley, Grifols, Janssen, Karuna, Lexeo, Lilly, Lundbeck, LSP, Merck, NervGen, Novo Nordisk, Oligomerix, Otsuka, PharmacotrophiX, PRODEO, Prothena, ReMYND, Renew, Resverlogix, Roche, Signant Health, Suven, Unlearn AI, Vaxxinity, VigilNeuro, Zai Laboratories pharmaceutical, assessment, and investment companies; owns stock or stock options of ADAMAS, Acumen, Alkahest, Alzheon, AnnovisBio, Behren Therapeutics, BIOasis, MedAvante, and United Neuroscience; served on Data Safety Monitoring or Advisory Board of Acadia, Biogen, Genentech, Grifols, Janssen, Karuna, Otsuka, reMYND, Roche, Signant Health; he is Chief Scientific Advisor – CNS Innovations, LLC. R.A.S. Receives royalties from Psychological Assessment Resources, Inc., consults for Biogen and Lundbeck, he is unpaid member of NFL Players Association Mackey-White Health and Safety Committee, Court-Appointed Member of NCAA Student-Athlete Concussion Injury Litigation, Medical Scientific Committee; owns Stock Options of King-Devick Technologies, Inc. E.M.R. is a compensated scientific advisor for Scientific Advisor, Alzheon, Aural Analytics Denali, Enigma, Retromer Therapeutics, Vaxxinity, a co-founder of ALZPath. He is Chairman of the Board, Flinn Foundation, Chairman of the Board, Arizona Alzheimer's Consortium. The remaining authors have no relevant conflicts of interest to disclose. Author disclosures are available in the supporting information.

CONSENT STATEMENT

The study was approved by the Institutional Review Boards at all sites, and written informed consent was obtained for all participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX

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