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Imaging of Glial Cell Activation and White Matter Integrity in Brains of Active and Recently Retired National Football League Players

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Abstract

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IMPORTANCE—Microglia, the resident immune cells of the central nervous system, play an important role in the brain's response to injury and neurodegenerative processes. It has been proposed that prolonged microglial activation occurs after single and repeated traumatic brain injury, possibly through sports-related concussive and subconcussive injuries. Limited in vivo brain imaging studies months to years after individuals experience a single moderate to severe traumatic brain injury suggest widespread persistent microglial activation, but there has been little study of persistent glial cell activity in brains of athletes with sports-related traumatic brain injury.

OBJECTIVE—To measure translocator protein 18 kDa (TSPO), a marker of activated glial cell response, in a cohort of National Football League (NFL) players and control participants, and to report measures of white matter integrity.

DESIGN, SETTING, AND PARTICIPANTS—This cross-sectional, case-control study included young active (n = 4) or former (n = 10) NFL players recruited from across the United States, and 16 age-, sex-, highest educational level-, and body mass index-matched control participants. This study was conducted at an academic research institution in Baltimore, Maryland, from January 29, 2015, to February 18, 2016.

MAIN OUTCOMES AND MEASURES—Positron emission tomography-based regional measures of TSPO using [^{11}C]DPA-713, diffusion tensor imaging measures of regional white matter integrity, regional volumes on structural magnetic resonance imaging, and neuropsychological performance.

RESULTS—The mean (SD) ages of the 14 NFL participants and 16 control participants were 31.3 (6.1) years and 27.6 (4.9) years, respectively. Players reported a mean (SD) of 7.0 (6.4) years (range, 1–21 years) since the last self-reported concussion. Using [^{11}C]DPA-713 positron emission tomographic data from 12 active or former NFL players and 11 matched control participants, the NFL players showed higher total distribution volume in 8 of the 12 brain regions examined ($P < .004$). We also observed limited change in white matter fractional anisotropy and mean diffusivity in 13 players compared with 15 control participants. In contrast, these young players did not differ from control participants in regional brain volumes or in neuropsychological performance.

CONCLUSIONS AND RELEVANCE—The results suggest that localized brain injury and repair, indicated by higher TSPO signal and white matter changes, may be associated with NFL play. Further study is needed to confirm these findings and to determine whether TSPO signal and white matter changes in young NFL athletes are related to later onset of neuropsychiatric symptoms.

Increasing evidence supports the complex role of microglia, the resident immune cells of the central nervous system, in response to brain injury and neurodegenerative processes.[1] Widespread persistent microglial activation has been detected in a limited number of small in vivo brain imaging studies of individuals months to years after a single traumatic brain injury (TBI).[2,3] Nevertheless it is unclear whether prolonged microglial activation occurs after TBI or repeated TBI incurred through sports-related concussive and subconcussive injuries. New techniques designed to image markers of glial cell activation in vivo promise to help uncover whether sports-related TBI elicits acute and prolonged glial response.

The translocator protein 18 kDa (TSPO) is normally expressed at low levels in brain tissue but is increased in expression by activated microglia, as well as reactive astrocytes.[4] Therefore, TSPO is a proposed biomarker for brain injury and repair that can now be measured in living patients using radiotracers and positron emission tomographic (PET) imaging.[5,6] Recently, we characterized the use of [^{11}C]DPA-713 with PET to image the distribution of TSPO in health and disease,[7] including correction for the effect of a common, genetic polymorphism on [^{11}C]DPA-713 binding to TSPO.[8] In a cross-sectional pilot study of older former National Football League (NFL) players and control participants, TSPO PET signal was significantly higher in the right amygdala and bilateral supramarginal gyri of the players compared with control participants.[9]

In vivo study of brain tissue changes in athletes playing collision sports has largely focused on detection of white matter tract changes using diffusion tensor imaging (DTI), which is based on the estimates of water movement in brain tissue.[10] Previous studies suggest widespread changes in white matter diffusion indices over one season of high school participation in a collision sport.[11–13] White matter diffusion indices have also been reported in collegiate football players studied 6 months after concussion,[14] although changed white matter integrity may be clinically silent in high school and collegiate athletes with TBI.[11,13]

Here we combined high-resolution brain [^{11}C]DPA-713 PET with assessment of white matter integrity, regional volumes, and neuropsychological performance in a new population of young active and former NFL players. Data from players were compared with data from control participants who were matched to players in age, sex, highest educational level, and body mass index (calculated as weight in kilograms divided by height in meters squared). We tested the hypothesis that players have higher [^{11}C]DPA-713 PET signal and altered white matter integrity compared with control participants. Rather than focusing on older former NFL players,[9] we focused on young players because they are temporally closer to NFL play and at less risk for cerebrovascular disease, which may also generate positive signal on TSPO PET.[15]

Methods

Human Participants

A Johns Hopkins institutional review board approved this study, which was conducted from January 29, 2015, to February 18, 2016. All participants provided written informed consent. National Football League players engaged in active play and those who were recently retired (defined as within 12 years of stopping play) were recruited through personal referrals by one of the authors (C.J.N.) and word of mouth. Male control participants were recruited through local advertising and completed a careful clinical interview to ensure stable health.

Clinical Assessment and Neuropsychological Testing

Participants underwent a standardized examination by a board-certified psychiatrist that included questions about past and current athletic pursuits (including participation in football and TBI for the NFL players) and medical and psychiatric history, as well as family history of neuropsychiatric illness (including dementia and affective illness). Details about

NFL play and past concussion, as defined by the Quality Standards Subcommittee of the American Academy of Neurology,[16] were obtained from the NFL players by self-report. Participants completed the 17-item Hamilton Depression Scale (HAM-D).[17] Control participants denied history of substance dependence, neurological disorder, subjective cognitive symptoms, participation in collegiate or professional collision sports, and TBI. Participants denied current use of anti-inflammatory treatment, including over-the-counter medications, and all were assessed for *TSPO* (rs6971) genotype as previously described.[7]

Participants completed a battery of neuropsychological tests (eTable 1 in the Supplement), from which we chose representative tests for this study (eAppendix 1 in the Supplement).

In Vivo Brain Imaging

Radiotracer Synthesis and PET Acquisition—[^{11}C]DPA-713 was synthesized as previously described[18] and met all US Pharmacopeia Chapter 823 acceptance testing criteria. Radiochemical purity at end of synthesis was greater than 99%, with mean (SD) specific activity of 342 (83) GBq per micromole (9245 [2255] mCi/μmol) at time of injection. The mean (SD) injected dose was 684.0 (53.1) MBq. Key details about the dynamic PET acquisition are included in eAppendix 2 in the Supplement and are identical to those previously described.[9]

Magnetic Resonance Imaging Acquisition—Participants underwent brain magnetic resonance imaging (MRI) on a Phillips Achieva 3-T scanner for structural T1-weighted imaging (3-dimensional MPRAGE) with 1 × 1 × 1-mm resolution and DTI. Diffusion tensor imaging parameters included single-shot echoplanar imaging; b-value of 700 seconds/mm^2; 32 diffusion-weighting orientations with 5 b0 images; 70 gapless whole-brain axial sections of 2.2-mm thickness; matrix of 96 × 96, field of view of 212 × 212 mm, and zero-filled to 256 × 256 mm. DtiStudio was used for data processing.[19] Motion and eddy current were monitored and corrected with an in-house affine transformation with a cost function based on tensor fitting.[20] Gradient tables were compensated for rotational motion. Tensor fitting was performed by a RESTORE-type in-house outlier rejection method.[21]

Data Analysis and Statistics

PET Data Analysis—The software package PMOD (version 3.3; PMOD Technologies Ltd) was used in the initial PET image processing and kinetic analysis. Interframe motion correction and PET-MRI coregistration were completed as previously described.[9] Cortical reconstruction and volumetric segmentation of T1-weighted MRIs were performed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). Twelve regions of interest (ROIs), identical to those used previously,[9] were selected for this study: right and left side hippocampus, parahippocampus, entorhinal cortex, amygdala, temporal pole, and supramarginal gyrus (eFigure 1 in the Supplement). Total cortical gray matter (GM) and total intracranial volume (ICV) were also defined using FreeSurfer for use in secondary analyses exploring the effect of (1) clinical characteristics on [^{11}C]DPA-713 binding in GM and (2) ROI volume normalized to ICV on regional binding.[18] The primary PET-based regional binding outcome was total distribution volume (V_T).[22]

Positron emission tomographic time-activity curves were generated for all participants using the ROI definitions. Based on the time-activity curves obtained, V_T within each ROI was estimated using Logan graphical analysis[23] (t^* = 30 minutes) with the metabolite-corrected arterial plasma input function. Plasma free fraction (f_P) was measured using rapid equilibrium dialysis as previously described[18] and V_T corrected for f_P (V_T/f_P) was calculated.

DTI Data Analyses—Diffusion tensor imaging data were analyzed by automated white matter segmentation using MriStudio software.[24,25] Briefly, an atlas with defined white matter regions (JHU "Eve" Atlas) was warped to each patient image using large deformation diffeomorphic metric mapping implemented in Diffeo-Map software. Fractional anisotropy (FA) and mean diffusivity (MD) values of the 8 predefined white matter structures (eFigure 2 in the Supplement) were then measured using RoiEditor. These white matter regions were selected because they contain long fibers that collectively project from subcortical structures to widespread cortical tissue. Long axonal projections are potentially more vulnerable to axonal injury from rapid biomechanical forces induced by hits to the head.[26] While studies implicate varied sites of white matter change after sports-related concussion,[27] we focused on right and left side anterior, superior, and posterior corona radiata, as well as posterior thalamic radiation (PTR), because postseason changes in corona radiata and PTR have been observed in young athletes playing collision sports.[11,12,28] Using a 3-dimensional atlas-based approach, we overcame the limitation of tract-based methods in defining thalamic radiations, which are difficult to define using a 2-dimensional plane.[29]

Statistical Analysis

Statistical analyses of the primary PET outcome measure, regional V_T, were performed with multivariate general linear modeling using SPSS Statistics (version 22.0; IBM Corp). We modeled the V_T values obtained from the 12 selected ROIs based on their relationship to between-participant factors, including cohort (NFL player or control) and *TSPO* genotype (C/C: high affinity binder and C/T: mixed affinity binder) as independent fixed factors. Participants with genotype T/T were excluded from this analysis of PET data owing to the low affinity of [^{11}C]DPA-713 for TSPO in individuals with T/T genotype. Similar analyses were repeated for regional values, V_T/f_P.

All other statistical analyses were performed using R (R Foundation for Statistical Computing).[30] Demographic and clinical characteristics of NFL players vs control participants were compared using 2-sample *t* tests for continuous variables and Fisher exact test for categorical variables. Data were expressed as mean (SD) unless otherwise noted.

The threshold for significance in all statistical tests involving regional V_T and regional volume measures was set as $P < .004$, taking into account the 12 ROIs using Bonferroni correction ($0.05/12 \approx 0.0042$). The threshold for significance in all statistical tests involving the 8 white matter regions tested was set as $P < .006$ (approximately 0.05/8). Statistical significance was otherwise defined as $P < .05$, except where otherwise noted.

Results

Study Population

Demographic characteristics and clinical characteristics of the NFL players and control participants are in Table 1. A total of 14 NFL players (4 active and 10 recently retired; ages 24–39 years) and 16 control individuals (ages 21–37 years) participated. The 10 former NFL players ended NFL play in a period that spanned a range of 1 to 144 months prior to participation. Players reported a mean (SD) of 7.0 (6.4) years (range, 1–21 years) since the last self-reported concussion. Other self-reported details about NFL play are listed in eTable 2 in the Supplement. On the HAM-D, 1 of the 14 players scored a 14, consistent with moderate depressive symptoms, and 1 player scored an 11, indicating mild depressive symptoms. All other participants were without depressive symptoms (HAM-D < 8). A summary of the number of participants in each cohort with data from [^{11}C]DPA-713 PET imaging, structural MRI, DTI, and neuropsychological testing is in eTable 3 in the Supplement.

Neuropsychological Assessment of Former NFL Players and Control Participants

Three control participants did not undergo neuropsychological assessment. Neuropsychological test results from the 1 player with a HAM-D score of 14 were excluded owing to his scores on a performance validity measure (Word Memory Test).[31] There were no differences in neuropsychological test scores between the remaining 13 players and 13 control participants after correction for multiple comparisons (Table 2).

Structural MRI and Volumetric Analyses

No evidence of structural abnormality was present on T1-weighted MRI. Quantitative analysis of the MRI-based segmentation results for the 12 ROIs showed no significant difference between young NFL players and control participants in regional volume normalized to ICV (eTable 4 in the Supplement).

[^{11}C]DPA-713 PET Imaging

Three control participants lacked arterial input function measurement, 1 control participant was excluded for T/T *TSPO* genotype, and 2 individuals (1 control and 1 player) had insufficient PET imaging due to scanner malfunction. One player (with C/C genotype) reported taking a creatine supplement and had unusually low binding across all brain regions (eTable 5 in the Supplement). Positron emission tomographic data from this outlier were removed from primary analyses because of previously published evidence that creatine use may lower TSPO PET signal.[32] No other participants reported use of creatine supplements.

In 2-way analysis of variance, with genetic group (C/C vs C/T) and cohort (players vs control participants) as independent fixed factors, V_T values between 12 NFL players and 11 control participants differed significantly in the left and right hippocampus, left entorhinal cortex, left and right parahippocampal cortex, left and right supramarginal gyrus, and left temporal pole (Figure 1; eTable 5 in the Supplement). Correction of V_T for plasma free fraction (V_T/f_P) did not change the results. Data from the 9 former players alone compared with control participants also revealed higher V_T values in players in these regions (eTable 6

in the Supplement). Multivariate regressions using data from participants, controlling for genotype, showed no significant effect of ROI volume normalized to total ICV on V_T in each of the 12 ROIs. Exploratory analyses of the effects of demographic and NFL play-related characteristics on [^{11}C]DPA-713 V_T in GM showed NFL players had higher V_T in GM compared with control participants, but there was no significant effect of age, race/ethnicity, body mass index, or years of education on V_T in GM (eTable 7 in the Supplement). Among the NFL cohort, there was also no observed effect of actively playing (vs being a former player), duration of retirement, years of play in the NFL, number of NFL games played, number of self-reported concussions, age at first self-reported concussion, or years since last self-reported concussion on V_T in GM.

Diffusion Tensor Imaging

Diffusion tensor imaging data from 1 player and 1 control participant were excluded owing to severe motion artifact and claustrophobia limiting scan time, respectively. Of the 13 NFL players and 15 control participants with DTI data, FA values were significantly lower in the right posterior thalamic radiation of NFL players compared with control participants (Table 3). Mean diffusivity values in the left anterior corona radiata were significantly higher in NFL players compared with control participants. Fractional anisotropy and MD values in the other white matter ROIs did not differ from those of control participants.

Discussion

Recent research supports an expanded role for microglia, the resident immune cells of the central nervous system, across the human lifespan and in disease.[33–35] Because activated microglia can influence synaptic remodeling and white matter recovery after TBI,[36,37] characterization of glial activation close to the time of NFL play may elucidate the relationship between microglial response, tissue micro-structural organization, and symptoms. The increased expression of TSPO by activated glia (microglia and reactive astrocytes) is the basis of several promising PET-based imaging methods to measure brain injury and repair in vivo.[6,38–42]

The current study extends our earlier findings of higher regional [^{11}C]DPA-713 V_T values in older former NFL players compared with control participants[9] to a new cohort of younger NFL players compared with matched control participants (Figure 1). We measured TSPO binding in the same temporal and parietal cortical regions as well as the mesial temporal lobe structures as in our previous study. Visual inspection of [^{11}C]DPA-713 parametric PET images implicates high binding in the thalamus and midbrain regions in young NFL players as well (Figure 2). The collective results from this and our previous study suggest potential vulnerability of the supramarginal gyrus to injury from TBI in football that warrants further investigation. Furthermore, higher TSPO signal in the left temporal pole and mesial temporal lobe structures of young NFL players compared with control participants provides in vivo evidence of hypothesized vulnerability of these regions to biomechanical forces incurred through sports-related TBI.[26]

We aimed to assess TSPO signal in parallel with white matter organization, regional volume, and neuropsychological performance. Looking across the widespread white matter area

covered by bilateral subsections of the coronal radiata and bilateral PTR, we observed lower FA, a nonspecific but potential indicator of lower white matter integrity, in the right PTR of the NFL players compared with control participants. Mean diffusivity, often observed as inverse of FA and reflecting the magnitude of white matter change,[10] was higher in NFL players compared with control participants in the left anterior corona radiata. Irrespective of these white matter diffusion findings, we did not see a difference in regional volumes normalized to ICV, nor difference in performance on selected neuropsychological tests between these cohorts of young individuals. Marked pathological changes to susceptible brain regions and associated cognitive, affective, and behavioral symptoms may take decades to emerge after participation in collision sport.[26,43] Together our results support emerging evidence from mouse studies of persistent microglial activation after head trauma that may increase susceptibility to later cognitive deficits.[44,45] Therefore, therapeutic and preventive interventions before onset of clinical decline may be possible.

Strengths and Limitations

A strength of this study is the focus on relatively young NFL players who are closer to the time of play and are less likely to have cerebrovascular disease, which is independently associated with inflammation and white matter changes. Still, the players in this study reported a mean (SD) of 7.0 (6.4) years since last concussion. The temporal relationship between increased TSPO expression and sports-related TBI may be best elucidated using a longitudinal design with [^{11}C]DPA-713 PET imaging from the time of measured head impact. It is also important to note that [^{11}C]DPA-713 PET signal is only an indirect measure of microglial activation in the living brain, and DTI outcome measures, such as FA and MD, are only indirectly representative of underlying white matter structure. Our results support further in vitro experiments of activated microglia and white matter tract anatomy directly in carefully selected postmortem tissue from players of all ages.[46]

Conclusions

By demonstrating higher TSPO PET signal and altered DTI indices in several brain regions of young NFL players, we support future use of [^{11}C]DPA-713 PET and DTI to examine these markers associated with brain injury and repair in athletes playing collision sports. Because there is interest in targeting microglial pathways and immune modulation to prevent neurodegeneration,[37,47,48] further human studies using [^{11}C]DPA-713 PET and DTI in individuals with history of sports-related TBI may inform strategies for future translational research and immune-based interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

Is localized brain injury, indicated by higher translocator protein signal and white matter changes, linked to National Football League (NFL) play?

Findings

In this cross-sectional, case-control study of young NFL players compared with control participants, players showed higher translocator protein positron emission tomographic signal in 8 of 12 regions examined. Limited significant white matter changes were also observed in NFL players compared with control participants, although players and control participants did not differ in regional brain volumes or neuropsychological performance.

Meaning

These results suggest that localized brain injury may be associated with NFL play, although further study is needed to test links to onset of neuropsychiatric symptoms.

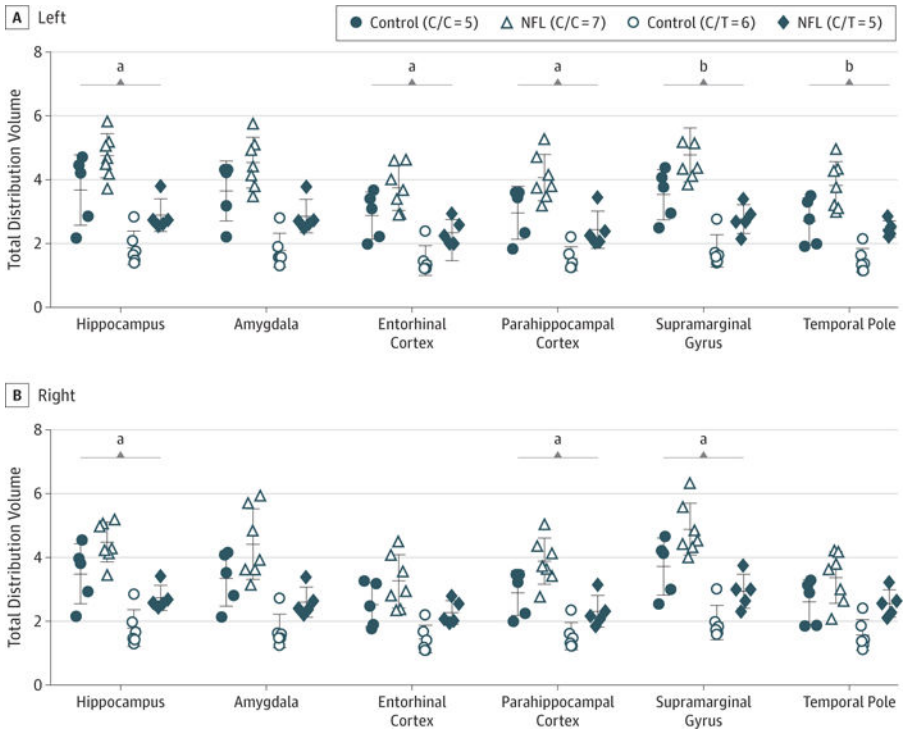

Figure 1. Scatter Plots of Regional Total Distribution Volume Values in Active and Recently Retired National Football League (NFL) Players and Control Individuals Injected With [^{11}C]DPA-713

Individual total distribution volume data from NFL and control cohorts are shown along with mean (SD) values. Using 2-way analysis of variance with genetic group (C/C vs C/T) and cohort (NFL vs control) as independent fixed factors, regional total distribution volume values in 8 of the 6 right and left side regions (12 total regions) were significantly higher than those of control participants. The threshold for significance after accounting for multiple comparisons was $P < .06/12 = .004$.

[a] $P < .004$.

[b] $P < .001$.

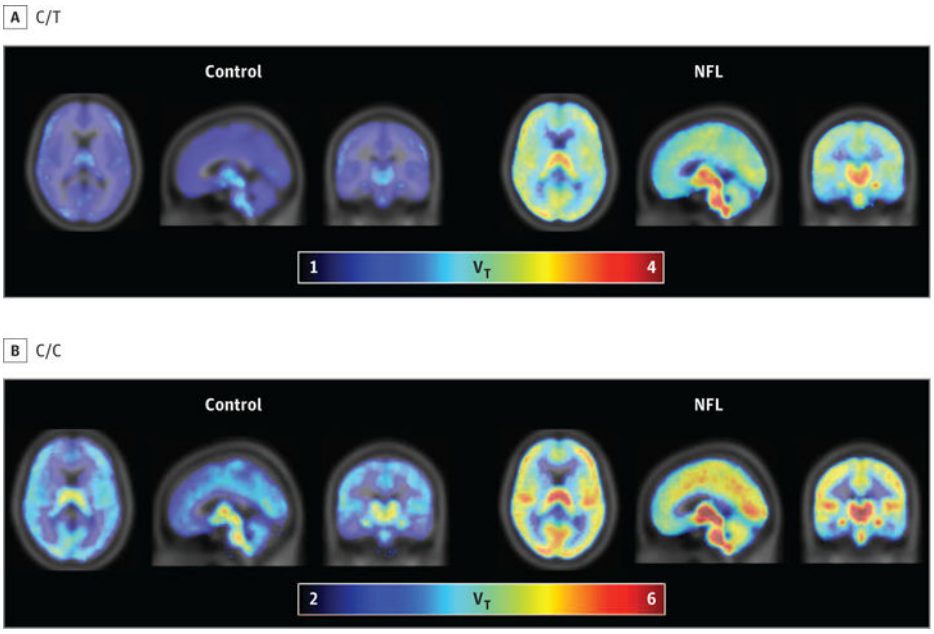

Figure 2. Former National Football League (NFL) Players Demonstrate Higher Binding of [^{11}C]DPA-713 Across Many Brain Regions Compared With the Brains of Age-, Sex-, Education-, and Body Mass Index-Matched Control Individuals

A, Mean parametric [^{11}C]DPA-713 total distribution volume (V_T) images displayed in groups of 3 views (left to right: axial, sagittal, and coronal) from 6 controls (left 3 views) and 5 NFL players (right 3 views) with C/T rs6971 genotype are presented. B, Mean parametric [^{11}C]DPA-713 V_T images from 5 controls (left 3 views) and 7 NFL players (right 3 views) with C/C rs6971 genotype are presented.

Table 1

Clinical and Demographic Characteristics

Characteristic	NFL (n = 14)	Control (n = 16)	*P* Value[a]
Age, mean (SD), y	31.3 (6.1)	27.6 (4.9)	.08
Race, No. (%)			
African American	3 (21)	3 (19)	>.99
White	11 (79)	13 (81)	
BMI, mean (SD)	30.8 (3.3)	28.5 (5.3)	.17
Duration of education, mean (SD), y	16.8 (1.0)	16.9 (2.1)	.80
rs6971 *TSPO* genotype, No. (%)			
C/C	7 (58)	5 (45)	.68
C/T	5 (42)	6 (55)	
Players, No. (%)			
Active	4 (29)	NA	NA
Retired	10 (71)	NA	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); C/C, high affinity binder; C/T, mixed affinity binder; NA, not applicable; NFL, National Football League.

[a] *P* values for *t* test or Fisher exact test as appropriate. Threshold for significance, $P < .05$.

Table 2

Neuropsychological Performance in NFL Players and Control Participants

Test	Mean (SD) [Range]		*P* Value[b]
	NFL Players (n = 13)[a]	Controls (n = 13)[a]	
Wechsler Test of Adult Reading	110.4 (14.4) [75–128]	117.3 (5.2) [105–122]	.12
Mini-Mental State Examination	27.2 (1.7) [24–29]	28.7 (1.3) [26–30]	.02
Trail Making Test, s			
Part A	19.3 (4.2) [13–25]	21.9 (6.9) [15–38]	.25
Part B	49.0 (19.4) [26–93]	41.2 (9.8) [24–56]	.21
Wechsler Adult Intelligence Scale-IV Coding, raw score	69.2 (14.3) [45–97]	82.6 (13.9) [62–104]	.03
Phonemic fluency, No. of words in 2 min	33.8 (11.3) [22–58]	36.9 (8.4) [27–54]	.43
CVLT-2			
Trials 1–5, raw score (of 80 possible)	60.2 (9.7) [46–76]	68.3 (7.9) [48–78]	.03
Delayed free recall, raw score (of 16 possible)	14.2 (1.6) [12–16]	15.0 (1.7) [10–16]	.21

Abbreviations: CVLT, California Verbal Learning Test-2; NFL, National Football League.

[a] Data from 1 NFL player with moderate depressive symptoms (Hamilton Depression Scale score = 14) was not included in this comparison of neuropsychological performance between cohorts because of a low score on the initial test of effort (Word Memory Test). Three of the 16 control participants in the study did not complete the neuropsychological assessment.

[b] *P* values from *t* tests, with threshold for significance defined as $P < .05/8 = .006$ accounting for multiple tests.

Table 3

Comparison of FA and MD Values From Diffusion Tensor Imaging of NFL Players and Control Participants

	Mean (SD)					
	FA			MD		
ROI	Controls (n = 15)[a]	NFL Players (n = 13)[a]	*P* Value[b]	Controls (n = 15)[a]	NFL Players (n = 13)[a]	*P* Value[b]
PTR						
Left	0.513 (0.017)	0.493 (0.020)	.01	0.0025 (0.0002)	0.0025 (0.0001)	.24
Right	0.503 (0.017)	0.482 (0.018)	.005[c]	0.0026 (0.0001)	0.0026 (0.0001)	.26
ACR						
Left	0.404 (0.018)	0.390 (0.017)	.052	0.0024 (0.0000)	0.0025 (0.0000)	.003[c]
Right	0.411 (0.020)	0.404 (0.022)	.40	0.0025 (0.0001)	0.0026 (0.0000)	.02
SCR						
Left	0.440 (0.020)	0.419 (0.019)	.01	0.0022 (0.0001)	0.0022 (0.0001)	.31
Right	0.440 (0.018)	0.419 (0.021)	.03	0.0022 (0.0001)	0.0023 (0.0001)	.049
PCR						
Left	0.433 (0.026)	0.410 (0.022)	.01	0.0023 (0.0002)	0.0023 (0.0002)	.90
Right	0.434 (0.030)	0.415 (0.028)	.10	0.0024 (0.0002)	0.0025 (0.0001)	.19

Abbreviations: ACR, anterior corona radiata; FA, fractional anisotrophy; MD, mean diffusivity; NFL, National Football League; PCR, posterior corona radiata; PTR, posterior thalamic radiation; ROI, region of interest; SCR, superior corona radiata.

[a]FA and MD values reported for the NFL players and control participants for whom there are diffusion tensor imaging data after excluding data from 1 player and 1 control participant owing to severe motion artifacts and

claustrophobia limiting scan time. Most of these participants also have [^{11}C]DPA-713 positron emission tomographic data.

[b]*P* values for t tests across the 8 selected ROIs.

[c]Accounting for the 8 selected ROIs, the threshold for significance was $P < .05/8 = .006$.