2017

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Recommended Citation

Strain, Jeremy F.; Didehbani, Nyaz; Spence, Jeffrey; Conover, Heather; Bartz, Elizabeth K.; Mansinghani, Sethesh; Jeroudi, Myrtle K.; Rao, Neena K.; Fields, Lindy M.; Kraut, Michael A.; Cullum, C. Munro; Hart, John Jr; and Womack, Kyle B., ,"White matter changes and confrontation naming in retired aging national football league athletes." Journal of Neurotrauma.34,2. 372-379. (2017).
https://digitalcommons.wustl.edu/open_access_pubs/5518

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White Matter Changes and Confrontation Naming in Retired Aging National Football League Athletes

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Abstract

Using diffusion tensor imaging (DTI), we assessed the relationship of white matter integrity and performance on the Boston Naming Test (BNT) in a group of retired professional football players and a control group. We examined correlations between fractional anisotropy (FA) and mean diffusivity (MD) with BNT T-scores in an unbiased voxelwise analysis processed with tract-based spatial statistics (TBSS). We also analyzed the DTI data by grouping voxels together as white matter tracts and testing each tract's association with BNT T-scores. Significant voxelwise correlations between FA and BNT performance were only seen in the retired football players ($p < 0.02$). Two tracts had mean FA values that significantly correlated with BNT performance: forceps minor and forceps major. White matter integrity is important for distributed cognitive processes, and disruption correlates with diminished performance in athletes exposed to concussive and subconcussive brain injuries, but not in controls without such exposure.

Keywords: concussion; DTI; naming; National Football League; TBSS; white matter

Introduction

THE BOSTON NAMING TEST (BNT)[1] is a visual confrontation naming test used in neuropsychological assessment of clinical populations, and requires the integrity of multiple, individual cognitive processes for effective task performance.[2] The ability to identify a visual stimulus and verbally supply its name requires white matter-mediated communication between multiple cortical and subcortical structures, leading to the supposition that in addition to dysfunction in gray matter structures, white matter pathology could lead to impaired naming.[3]

Cognitive components engaged in naming and their corresponding brain regions have been identified using lesion and imaging data. Visual object recognition is associated with neural activity in the temporo-occipital ''what pathway''; a polysynaptic projection system involving the striate, prestriate and inferior temporal cortices.[4,5] Semantic processing is associated with neural activity in the left inferior parietal-posterior superior temporal lobe,[6,7] anterior temporal pole,[8,9] lateral temporal cortex,[8] and fusiform gyrus. Semantic to phonological transfer relies on the left posterior inferior temporal lobe,[10] whereas access to the output phonological lexicon is subserved in part by the left inferior parietal lobule[11] and left frontal operculum.[10] Speech is also supported in

part by the left pre-supplementary motor area (pre-SMA).[12,13] These cortical regions in addition to others function as nodes in a network connected by white matter pathways to facilitate naming. Several of these white matter pathways have been defined. The inferior longitudinal fasciculus (ILF) is critical for interconnecting the regions involved in the temporo-occipital pathway, which are situated along its length.[5] The posterior segment of the indirect portion of the arcuate fasciculus connects the posterior superior temporal lobe with the inferior parietal lobe, whereas the anterior segment connects the inferior parietal lobe to frontal regions.[14] The traditionally conceived direct portion of the arcuate fasciculus connects posterior temporal regions with frontal speech areas.[14] Connections from the pre-SMA to the frontal operculum have been termed the frontal aslant tract (FAT).[15] Interruption of white matter connections has been associated with language impairments. For example, surgical resection of the left uncinate fasciculus has resulted in impaired naming and verbal fluency,[16] and isolated damage to the corpus callosum within callosotomy patients can result in a naming impairment.[17]

Studies of traumatic brain injury (TBI) patients have shown that white matter pathways are susceptible to damage from head trauma. Diffuse axonal injury (DAI) occurs when there is shearing or stretching of white matter caused by the torsion forces created by

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head trauma.[18,19] Following TBI, enhanced glial inflammation has been attributed to both white matter dysfunction and cognitive decline, which may be more evident with aging.[20,21] How patterns of axonal injury relate to the cognitive deficits associated with TBI remains to be clarified. Previous investigations of TBI patients with white matter damage have shown neuropsychological deficits in speed of processing, working memory, and attention, without a clear gross structural correlate for these deficits.[22–25] Cognitive and mood disturbances are also prevalent in patients with chronic traumatic encephalopathy (CTE) through postmortem confirmation and review of past medical records.[26] Examination of anatomical correlates with cognitive function can assist in medical guidance prior to manifestation of symptoms. The potential consequences of repeated subconcussive head impacts on the integrity of white matter are not well understood.

White matter structural integrity may be assessed *in vivo* by measuring changes in water diffusion within white matter using an MRI-based technique called diffusion tensor imaging (DTI).[27,28] The degree of directionality of water diffusion is quantified as a scalar value, fractional anisotropy (FA), that distinguishes between abnormal and healthy white matter based on the cylindrical patterns of the diffusion. White matter pathway disruption as assessed by FA has been correlated with performance on some neuropsychological tasks,[16,29,30] including naming performance.[31]

Professional football players who experienced subconcussive head impacts[32,33] may be susceptible to increased risk for progressive cognitive decline and affective disorders[34,35] with aging.[32,33] A subconcussive impact is defined as any blow to the head that does not result in a concussion. This type of impact is innately entwined with high-risk sports and is often difficult to discern. In a previous study, we found that retired National Football League (NFL) athletes with impaired cognition and/or depression (symptomatic athletes) demonstrated significant white matter disruption compared with either healthy controls or asymptomatic retired athletes, and found some to be impaired on tests of naming (BNT), word finding, and episodic memory.[31] This led to the question of whether the performance on any of these tests would correlate with the degree of white matter damage in an anatomically specific manner. Here we report a relationship between confrontation naming and its correlates with damaged white matter in tracts interconnecting cortical regions known to be involved in semantic processing.

The goal of this study was to determine whether disruption in specific white matter regions or pathways correlated with BNT scores in a population with a history of concussion.[30] We anticipated that these findings would also provide insight into the differential vulnerability of any such regions to the type of injuries typically experienced by these athletes and, therefore, into the specific cognitive subcomponents of naming that may be most affected.

Methods

Subjects

We recruited two cohorts of subjects, described subsequently, for a study of cognition and mood in retired NFL athletes. All subjects gave informed written consent in accordance with the Declaration of Helsinki. The Institutional Review Boards of the University of Texas Southwestern Medical Center and the University of Texas at Dallas approved the study protocols and consent forms.

Thirty-two retired NFL athletes were recruited from a local gathering of retired NFL athletes living in the North Texas region, from meetings of the NFL Athletes Association local chapter,

through local advertising, and by word of mouth. Six athletes had a Beck Depression Inventory II (BDI) score >11, suggesting significant depressive symptoms, and were excluded from analysis. One subject showed signs that clinically suggested Alzheimer's disease and was removed from our study because of possible complications from a different comorbid pathology. The remaining 25 athletes ranged in age from 41 to 79, (mean = 61.1, SD = 12.2), with education that ranged from 15 to 18 years, (mean = 16.3, SD = 0.78) (Table 1). Their NFL experience ranged from 2 to 15 years, (mean = 8.92, SD = 3.61). Eighteen were Caucasian and seven were African American. Concussion history was accumulated from self-reports, and were classified using the American Academy of Neurology (AAN) Practice Parameter guidelines for grading concussion.[32] Concussion severity ranged from brief periods of confusion to loss of consciousness for several hours. Seven of the athletes met clinical criteria for mild cognitive impairment (MCI). All but two of the athletes experienced some degree of concussion while actively participating in the NFL, which ranged from 1 to 12 in any single athlete (mean = 4.04, SD = 3.36). Additional demographic information can be found in Table S1 (see online supplementary material at http://www.liebertpub.com).

The control group consisted of 22 cognitively normal male controls selected from prior aging studies that fulfilled our inclusion criteria. Controls were screened to have no history of known concussion, repetitive exposure to subconcussive brain injuries, participation in college or professional football, mental illness, cognitive complaints, or neurological disorders. Age ranged from 41 to 77 (mean = 59.4, SD = 11.8), with a minimum of 11 years and a maximum of 20 years of education (mean = 16.2, SD = 2.4) (Table 1). Twenty of the controls were Caucasian, and two were African American. Four were retired, and 18 were employed at the time of the study.

Neuropsychological data

Neuropsychological assessment included measures of general cognitive ability, attention, language, memory, visuospatial and executive function, and processing speed[30] prior to neuroimaging. The standard 60 item BNT[1] was used as a measure of visual confrontation naming. Participants were instructed to indicate the name of each picture as quickly and as accurately as possible. A trained neuropsychological technician or neuropsychologist performed all testing. Normalized T-scores were generated from each subject's raw BNT score, which took into account age, education, sex, and ethnicity.[33]

Statistical analysis of neuropsychological data

Although this article focuses on the BNT, three other neuropsychological assessments (California Verbal Learning Test, Rey-Osterrieth Complex Figure Test, Semantic Object Retrieval Test) were markedly different between athletes and controls in a different subset published elsewhere.[35] We used the Bayesian information criterion (BIC) to identify the best set of variables, among the previously mentioned assessments, that would best predict FA at the voxel level across the entire white matter

TABLE 1. DEMOGRAPHIC INFORMATION

	Control	Athletes
Number of subjects	22	25
Age	59.4 (11.8)	61.1 (12.2)
Education	16.2 (2.4)	16.3 (0.78)
Ethnicity (C/AA)	20/2	18/7

C, Caucasian; AA, African American.

skeleton.[34] The residual noise variance was calculated for each variable combination at the voxel level and subjected to the BIC. The BIC is a model selection criterion, which attempts to prevent overfitting by penalizing complexity. It is a common variable selection method in multiple regression to choose a parsimonious model with high predictive ability. Therefore, variables that contribute little to prediction are effectively removed from the model, and those that are retained contribute more to prediction without exceeding the complexity penalty. The variable combination that produces the lowest BIC comprises the final model for prediction of FA. The variable(s) corresponding with the best model were compared between groups using the Levene's test for equality of variances, whereas means were compared using independent T-tests in the Statistical Package for Social Sciences SPSS (SPSS Inc., Chicago, IL).

Imaging data

DTI data were acquired on a 3 T MRI system, with an acquisition matrix of 128×128, field of view of 224×224 mm, slice thickness of 2 mm and interslice gap of 1 mm. Images were acquired using 30 gradient directions (b = 1000 sec/mm^2) along with one b$_0$ image.

Image analysis

Preprocessing included correction for motion and eddy current distortions followed by skull stripping[35] using FSL 4.1.7 (www.fmrib.ox.ac.uk/fsl/).[36] Scans were inspected to validate that head movement was <3 mm for all subjects during data acquisition. Tensors were estimated and FA maps created using the MedINRIA software package (www-sop.inria.fr/asclepios/software/MedINRIA/). Both FA and MD data were analyzed with tract based spatial statistics (TBSS)[37] in FSL, using a mean FA skeleton threshold of 0.2.

Voxelwise correlations of the entire white matter skeleton with BNT T-scores were performed using the ''Randomise'' tool in FSL with threshold-free cluster enhancement and correction for multiple comparisons using family-wise error rate in a Monte Carlo 5000 permutation-based approach.[38] This study focuses on only one cognitive domain; however, other tests of cognition were significant as described by Hart and coworkers,[35] and we adjusted our p value to compensate (Bonferonni correction $p < 0.02$). Age was regressed from the imaging data prior to the execution of Randomise to make the imaging data comparable to the BNT T-scores that were already stratified for age.

In addition to the voxelwise analysis of the skeletonized data, we also examined these data in a tractwise manner by isolating the portions of the TBSS-derived skeleton that fell within the boundaries of several white matter tract regions of interest (ROI). All white matter tracts described by Wakana and coworkers[39] excluding the anterior thalamic radiations were included in our study along with the FAT.[40] For a list and graphical depiction of all tracts included in this study see Supplementary Figure 1. We calculated a mean FA value for each tract by averaging the FA from the skeletal voxels identified by each tract ROI.[41,42] The age-corrected mean FA values by tract and each subject's BNT T-score were analyzed with a bivariate Pearson correlation using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL).

ROI creation

The boundaries of each ROI used in the tractwise analysis were determined by performing DTI deterministic tractography with the MedINRIA software package and employing a multiple ROI approach appropriate for each tract of interest.[15,40,42,43] in 28 cognitively normal college students who were recruited from the University of Texas at Dallas for a study of higher order semantic processing. Tractography was performed in native space and the tracts, as defined in each subject, were transformed into Montreal Neurological Institute (MNI) space, combined across subjects and

then limited to only those voxels present in a majority of subjects. Because the brain region sampled by an individual voxel may contain fibers from more than one tract, especially in regions where tracts are closely approximated, the resulting tractograms of neighboring tracts may contain overlapping voxels. To avoid using data from the same voxel for more than one tract, we developed an algorithm for assigning such overlapping voxels to one tract or the other (see Eq. 1). For each pair of tracts with overlapping voxels, two values, one for each tract as reference, were calculated for each overlapping voxel. This value would take into account the probability of tract occupancy adjusted for the relative size of both tracts. The voxel was then assigned to the reference tract with the higher value. This value was calculated by taking the proportion of subjects whose tract occupied each overlapping voxel (a), and multiplying it by the log transform of the ratio of the number of voxels in the alternate tract (x) to the number of voxels in the reference tract (y). The log transform of the ratio of tract size was necessary to preserve representation of small tracts.

$$c = a \ln\left(\frac{x}{y}\right) \qquad \text{[Eq. 1]}$$

We found it necessary to create tract ROIs in the manner described rather than using pre-existing resources such as the Johns Hopkins University (JHU) atlas supplied with FSL for two reasons. First, we found that the ROIs for the anterior cingulum bundle from the JHU atlas aligned poorly with the TBSS skeleton in MNI space, whereas the ROI produced with our method was a much better fit and allowed inclusion of this important tract in our analysis (see online supplementary material at http://www.liebertpub.com). Second, creating our own ROIs allowed for the flexibility to incorporate projections from the pre-SMA that are not represented in the standard atlases, but can be readily demonstrated by tractography.[15]

Results

BIC

The BIC identified four different model combinations with relatively similar predictive value. Three of these models included the BNT, with the highest fit being for the model that only included the BNT. Provided that the BNT was robustly identified as a strong predictor of white matter integrity, the remainder of this article will focus on this specific neuropsychological assessment.

Behavioral results

The mean BNT T-score of the retired athletes was significantly lower than the mean performance of the control group ($p = 0.005$), with the retired football players mean falling in the low average range (mean = 43.2, SD = 11.4), whereas the mean value for controls was average (mean = 52.6, SD = 10.2), with almost one standard deviation separating them. Despite this difference in mean performance, the variance of BNT T-scores was similar between groups as assessed by the Levene's test for equality of variance.

Whole brain voxelwise results

In the voxelwise correlation between BNT T-scores and FA, significant clusters were seen only in the athlete group, and these resided primarily along corpus callosal projections. Specifically, we found voxel clusters in the bilateral anterior corona radiata, left posterior corona radiata, and the splenium and body of the corpus callosum. The BIC was implemented to target the specific cognitive measure or measures that best predicted FA; however, if the other cognitive measures had been incorporated as covariates, then
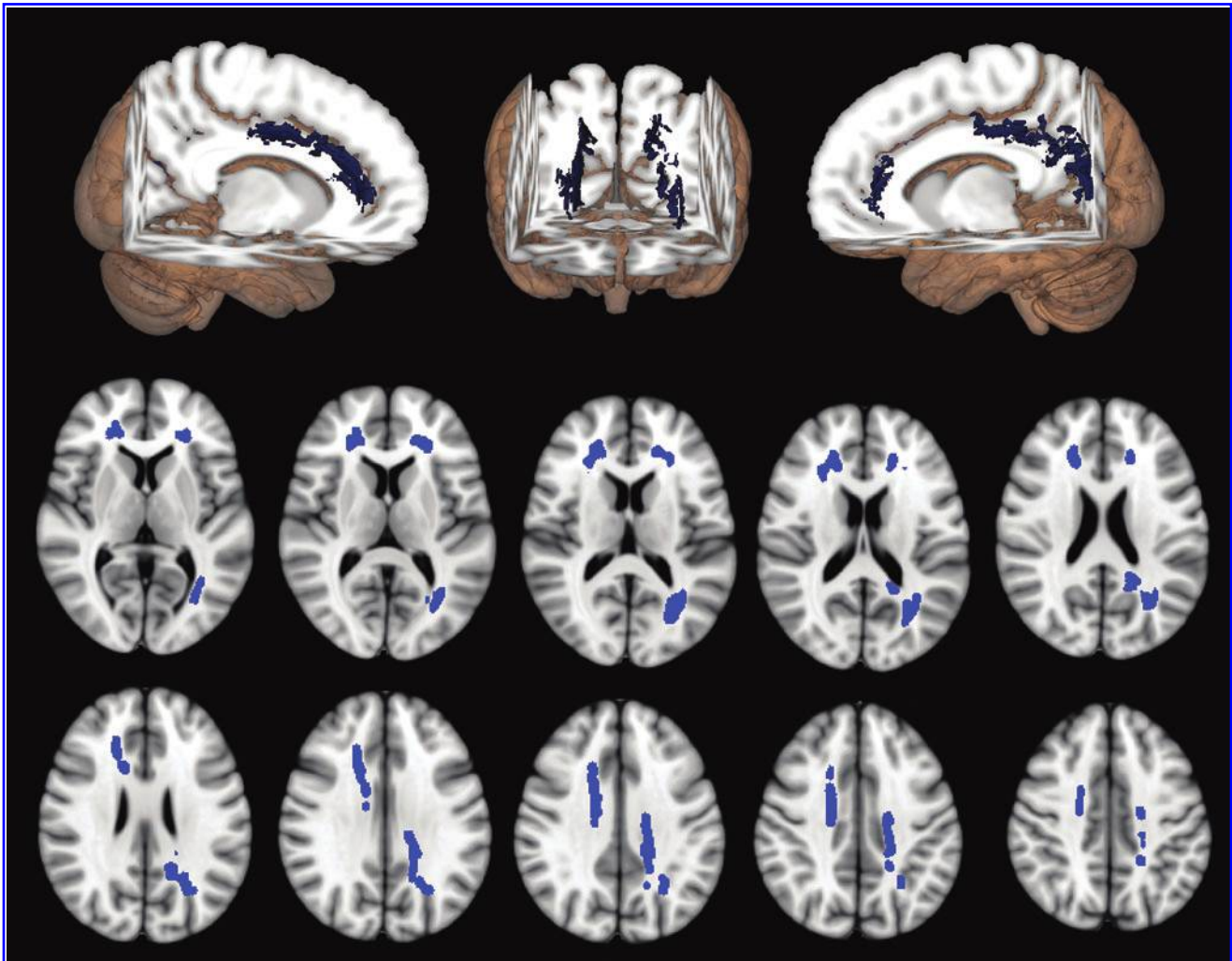
FIG. 1. Voxelwise correlation for retired professional athletes' fractional anisotropy (FA) values and Boston Naming Test (BNT) T-scores. Blue voxels are significant at $p < 0.02$ corrected for multiple comparisons. Axial slices are in radiological orientation with the results thickened for better visibility using the ''tbss_fill'' script.

significant voxels would have only survived at $p < 0.05$ (Fig. S3). The same correlation in the control group yielded no significant clusters, even after relaxing our statistical threshold to $p < 0.05$, corrected. All significant voxels in this analysis were positively correlated between FA and BNT performance (Fig. 1). No significant correlation was found for MD and behavioral performance.

Tractwise results

With tract-based analysis, we identified which white matter tracts exhibited the most robust correlation with BNT performance. The mean FA values for each tract were used as proxy indicators for the integrity of the entire tract.[41,44,45] Significant tracts were only found within the athlete group. The results for each tract ROI are shown in Table 2. Two tracts were shown to be significant: forceps minor and forceps major. The Pearson correlation coefficients are displayed with the graphs for each tract having a p value <0.02 in Figure 2. No white matter tracts revealed a significant finding with MD.

Discussion

The goals of this study were to examine the relationship of white matter integrity in retired professional football players to their

performance on the BNT, and to observe whether similar relationships can be identified in normal populations. These athletes have been exposed to head impacts ranging from unquantifiable subconcussive events[29] to specifically remembered or documented concussions. Whereas both groups had similar variance in BNT T-scores, the retired football players performed worse, and only their variance was explained by white matter integrity. This suggests that different factors drive the variance in confrontation naming in the two groups. Although we cannot assume causality, white matter damage is well described in brain injuries,[13,39] and we have previously shown that retired symptomatic NFL athletes with cognitive impairment, depression, or both have compromised white matter integrity compared with either controls or asymptomatic retired NFL players.[30]

In our voxelwise analysis, significant clusters within the athlete group were localized around the corpus callosum and its extending projections. The corpus callosum is a dense white matter structure that is structurally vulnerable to jarring or torsional forces that occur in head impacts. Damage to this structure can result in a variety of deficits, including impaired naming.[17]

In our cohort of aging professional athletes, the tracts with FA values that significantly correlated with BNT T-scores were the

TABLE 2. WHITE MATTER TRACT CORRELATIONS WITH BOSTON NAMING TEST SCORES

Fractional anisotropy correlation with Boston Naming Test scores

| A								
Left hemisphere tracts	ILF	FAT	SLF	UF	CS	PP	Cing	FOF
R values	0.39	0.29	0.30	0.08	0.41	0.05	0.41	0.39
B								
Right hemisphere tracts	ILF	FAT	SLF	UF	CS	PP	Cing	FOF
R values	0.37	0.13	0.36	0.22	0.23	−0.07	0.45	0.44
C								
Corpus callosum region	Forceps minor	Anterior CC	Posterior CC	Forceps major				
R values	0.51*	0.11	−0.13	0.58*				

*p value < 0.02.

ILF, inferior longitudinal fasciculus; FAT, frontal aslant tract; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus; CS, corticospinal tract; PP, perforant pathway; Cing, cingulum. FOF, fronto-occipital fasciculus; CC, cingulate cortex.

forceps minor and forceps major. The specific tracts detected in this study with lower FA correlated with poorer BNT T-scores, and these tracts conduct signals to gray matter regions that subserve cognitive operations or representations engaged by the visual confrontational naming task. One prior study looked at the interaction between white matter and naming performance, which yielded diffuse findings, including the forceps major.[28] The forceps major, which encompasses axons that travel through the splenium of the corpus callosum, has been suggested as an important region for cross-hemispheric transfer of picture information.[46] Damage to fibers that pass across the splenium has been shown in several studies to produce alexia,[47,48] and in some cases naming deficits,[49] indicating the importance of the splenium in language function.

Our analysis likely does not reveal all tracts that have sustained damage, but only those that when damaged are associated with reduced performance on naming tasks. Even more specifically, our results identify white matter pathways involved in naming that are also vulnerable to brain injury. For example, the forceps major is both important for this process and vulnerable to the type of head impacts common in contact sports.[50] Additionally, in our pursuit of preventing a type I error, we used a very stringent p value, which may have caused us to overlook other potentially important white matter pathways that could have been contributing to the overall variance.

The nature of the linear relationship between FA and BNT performance has several implications for FA in white matter integrity *vis-à-vis* naming circuits. Partial disruption of white matter
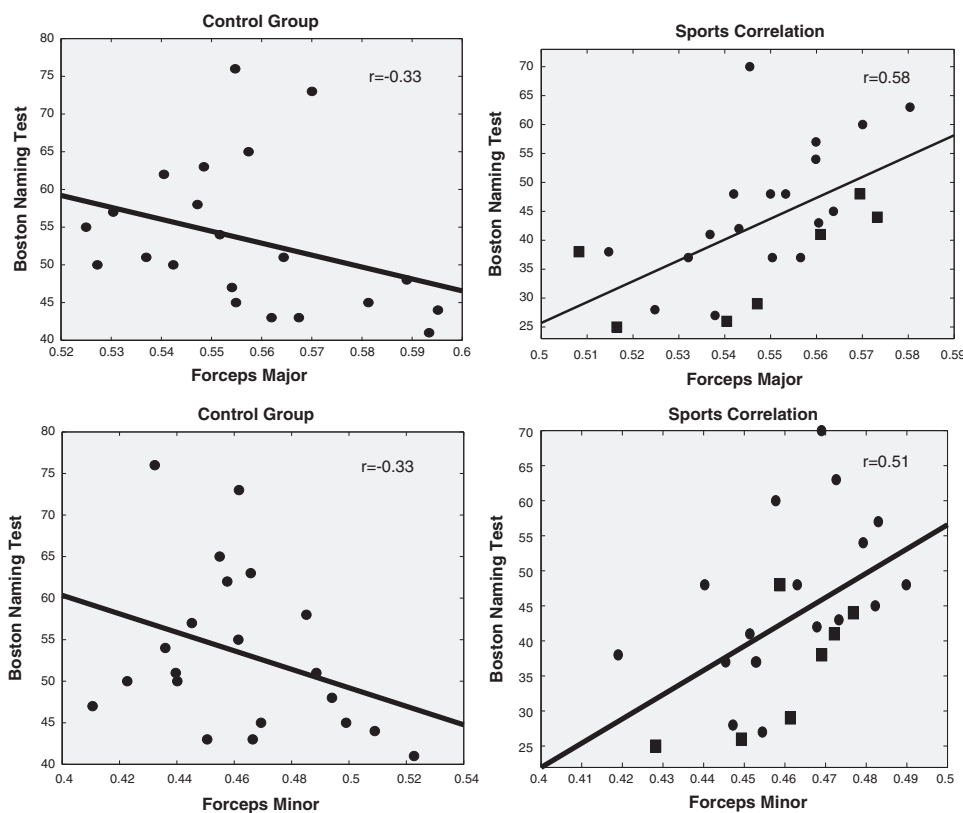
FIG. 2. Tractwise correlation between fractional anisotropy (FA) and fractional anisotropy (BNT) T-scores in both controls and retired profession athletes. Each circle represents a cognitively normal control or athlete depending on the panel. The squares represent athletes with MCI. Pearson correlations are displayed in each quadrant in the top right corner.

function, as measured by FA, does not result in a gross impairment of naming performance, which would have graphically appeared as a steep drop in BNT at a specific FA value in Figure 2. Irrespective of the gray matter region subserved, each pathway revealed that the greater the FA value, the higher the naming score. This FA–naming correlation suggests that the associated gray matter regions respond normally to the inputs they receive, and that differences in performance arises from how well information is conducted between these regions. It is unknown whether the white matter alterations seen in our athletes are compensatory, but the identified white matter tracts are susceptible to TBI. We do not suggest that the corpus callosum is the only region to cause a deficit in confrontation naming, but it may be involved in the decreased performance seen in this population. Further studies are required to better separate, if possible, the roles of intrinsic cortical damage and white matter damage in mediating impaired performance on cognitive tests in people who have sustained a TBI.

The relationship between subconcussive injuries and the presence and severity of the white matter abnormalities detected many years later remains unclear. It is possible that the white matter damage occurred with the subclinical trauma, but did not manifest itself symptomatically at that time, only to become apparent after loss of reserve capacity caused by aging and other chronic health issues. The cumulative effect of countless subconcussive deceleration-acceleration head movements during the course of a professional football career (typically preceded by 4–8 years of play in high school and college) may also explain how asymptomatic events lead to later problems. Other possibilities include that even minor damage from these events may interfere with recovery from actual concussions or may predispose the athlete to develop a neurodegenerative disorder[51] that could result in secondary white matter degeneration years later.

One limitation of our study involves our control group. Age-matched cognitively normal controls address the aging component but fail to reflect the same physical activity and lifestyle factors present in former professional football players. An optimal control group would consist of former professional athletes from a different sport with similar levels and types of training, but without exposure to head contact or acceleration/deceleration injuries. Unfortunately it is difficult to identify and recruit such a group. Football players without an overt history of concussion would not be acceptable, because they are still exposed to multiple subconcussional events that are characteristic of American football,[29] and may contribute to future disability. We optimized our control group by matching for several factors that influence cognition and brain structure such as age, education, and intelligence quotient (IQ). We also stringently screened for the presence of concussions or participation in contact sports. The defining characteristic of our control population is the lack of head trauma or participation in football, which we believe is an invaluable attribute in studies such as this one. Although we acknowledge these issues with our control group, it should not distract from the main focus of our article, which is the within-group correlations for the athletes. The primary purpose of the control group was to see if white matter integrity also partially explained their variance in BNT performance, which it did not.

It also remains unclear to what degree other superimposed factors that deleteriously affect white matter (e.g., aging, history of hypertension, diabetes, hypercholesterolemia, stroke, myocardial infarction) might have independently contributed to the BNT performance found in this cohort, although examination of subjects' medical histories did not reveal systematic differences between groups at the time of evaluation. Future longitudinal studies of neuropsychological function and DTI are indicated, and would be most valuable if initial testing was performed early in an athlete's career, with follow-up close to the time of injuries and at regular intervals thereafter, including at, as well as following, retirement.

Conclusion

In summary, our data demonstrate anatomically relevant, significant associations between FA (a measure of white matter integrity) and performance on a standardized confrontation naming task in former NFL athletes, but not in matched controls. The majority of degraded white matter was located along the corpus callosum and affected tracts connecting cortical regions that have previously been implicated in mediating cognitive subcomponents essential for naming. Within the groups we analyzed, only the athletes revealed significant correlations between neuroanatomic and behavioral measures. Although the athletes' median performance on the BNT was worse than that of controls, both groups had equal variance in this performance. White matter damage was able to explain part of the variance only within our athlete group, suggesting that different mechanisms account for the variance in the two groups. Although these results are correlational in nature, the findings show that white matter pathology is associated with naming performance in these aging NFL players, and is distinct from normal aging in controls without exposure to head trauma.

Acknowledgments

Author Disclosure Statement

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