Depressive symptoms and white matter dysfunction in retired NFL players with concussion history

Jeremy Strain, BS
Nyaz Didehbani, PhD
C. Munro Cullum, PhD
Sethesh Mansinghani, BS
Heather Conover, BS
Michael A. Kraut, MD
John Hart, Jr., MD
Kyle B. Womack, MD

Correspondence to Dr. Hart: jhart@utdallas.edu

ABSTRACT

Objective: To determine whether correlates of white matter integrity can provide general as well as specific insight into the chronic effects of head injury coupled with depression symptom expression in professional football players.

Method: We studied 26 retired National Football League (NFL) athletes who underwent diffusion tensor imaging (DTI) scanning. Depressive symptom severity was measured using the Beck Depression Inventory II (BDI-II) including affective, cognitive, and somatic subfactor scores (Buckley 3-factor model). Fractional anisotropy (FA) maps were processed using tract-based spatial statistics from FSL. Correlations between FA and BDI-II scores were assessed using both voxel-wise and region of interest (ROI) techniques, with ROIs that corresponded to white matter tracts. Tracts demonstrating significant correlations were further evaluated using a receiver operating characteristic curve that utilized the mean FA to distinguish depressed from nondepressed subjects.

Results: Voxel-wise analysis identified widely distributed voxels that negatively correlated with total BDI-II and cognitive and somatic subfactors, with voxels correlating with the affective component ($p < 0.05$ corrected) localized to frontal regions. Four tract ROIs negatively correlated ($p < 0.01$) with total BDI-II: forceps minor, right frontal aslant tract, right uncinate fasciculus, and left superior longitudinal fasciculus. FA of the forceps minor differentiated depressed from nondepressed athletes with 100% sensitivity and 95% specificity.

Conclusion: Depressive symptoms in retired NFL athletes correlate negatively with FA using either an unbiased voxel-wise or an ROI-based, tract-wise approach. DTI is a promising biomarker for depression in this population. ***Neurology*® 2013;81:25–32**

GLOSSARY

BDI-II = Beck Depression Inventory II; **CI** = confidence interval; **CTE** = chronic traumatic encephalopathy; ***DSM-IV-TR*** = *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, text revision; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FLAIR** = fluid-attenuated inversion recovery; **NFL** = National Football League; **ROC** = receiver operating characteristic; **ROI** = region of interest; **TBI** = traumatic brain injury; **TBSS** = tract-based spatial statistics.

Depression after traumatic brain injury (TBI) can manifest days or years after injury,[1] but the mechanisms underlying this association remain unknown. White matter damage has been described independently in both major depression and TBI, but whether such damage is etiologically associated with mood disturbance in either or both conditions has not been established.

Depressive symptoms can be quantified using self-assessment questionnaires that target defining characteristics of depression. A popular self-report instrument is the Beck Depression Inventory II (BDI-II), which consists of 21 questions, each rated on a 1–4 scale based on severity.[2] The BDI-II provides general information regarding depressive symptoms, but can be further partitioned into subfactors that address different constellations of symptoms. One model proposed by Buckley et al.[3] uses the BDI-II to categorize each item into 1 of 3 symptom groupings. The 3 factors are designated as affective (e.g., loss of pleasure, loss of interest), cognitive (e.g., sadness, self-criticalness), and somatic (e.g., loss of energy, irritability) symptoms.

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Supplemental data at www.neurology.org

From the Berman Laboratory for Learning and Memory (J.S., N.D., S.M., H.C., M.A.K., J.H.), Center for Brain Health, Dallas; School of Behavioral and Brain Sciences (C.M.C., K.B.W.), Department of Psychiatry, The University of Texas at Dallas; Department of Neurology and Neurotherapeutics (C.M.C., J.H., K.B.W.), University of Texas Southwestern Medical Center, Dallas; and Department of Radiology (M.A.K.), The Johns Hopkins School of Medicine, Baltimore, MD.

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American-style football players often sustain numerous concussive and subconcussive impacts—head impacts that do not elicit neurologic symptoms that can lead to white matter damage.[4–6] We evaluated a population of retired National Football League (NFL) players in order to study the relationship between white matter integrity and the manifestation of depressive symptoms. Using diffusion tensor imaging (DTI), we assessed white matter integrity with the scalar value, fractional anisotropy (FA),[7] and correlated that measure with overall depression scores as well as each of the 3 subfactors derived from the BDI-II.

METHODS

Subjects. Thirty-two retired NFL athletes underwent detailed neurologic, neuropsychologic, and neuroimaging evaluations. Our first subject was enrolled in November 2010 and recruitment is still ongoing. Participants 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 through word of mouth. A comprehensive analysis of our entire athlete cohort at an earlier recruitment stage was performed previously.[8] Therefore, to alleviate complications that could confuse our findings, subjects with a clinical diagnosis of either mild cognitive impairment or Alzheimer disease were excluded, resulting in a sample size of 26.

The athlete cohort ranged in age from 41 to 79 years (mean age 57.8, SD 11.3), with NFL experience ranging from 2 to 15 years (mean 8.62, SD 3.75). Sixteen were Caucasian and 10 were African American. Demographic information is shown in table 1, including former position played classified based on speed, as described in Lehman et al.[9] Concussion history was acquired from self-reports and classified using the American Academy of Neurology practice parameter guidelines for grading concussion (1997). Two subjects reported never having had a concussion, but the remaining 24 athletes reported having from 1 to 11 concussions (mean 3.85, SD 3.02). On average, all athletes were scanned 4 weeks following neuropsychological examination. An expanded profile of our subjects can be found in table e-1 on the *Neurology*® Web site at www.neurology.org.

Twenty-two cognitively normal controls were recruited from prior aging studies. Subjects were excluded if they had prior history of concussion, repetitive exposure to subconcussional head injuries, participation in college or professional football, mental illness, cognitive complaints, or neurologic disorders. Controls ranged in age from 41 to 77 years (mean 59.4, SD 11.8), with education ranging from 11 to 20 years (mean 16.2, SD 2.4). Twenty of the controls were Caucasian, and 2 were African American.

Standard protocol approvals, registrations, and patient consents. All subjects gave written informed consent in accordance with the Declaration of Helsinki and the institutional review boards of the University of Texas Southwestern Medical Center and University of Texas at Dallas approved the study protocols and consent forms.

Beck Depression Inventory II. Depression severity was quantified using the BDI-II.[2] Depressive symptoms were analyzed in 2 formats, with BDI-II total score as well as depressive domains divided into the 3 subcomponents of affective, somatic, and cognitive symptoms based on the 3-factor model.[3] Total BDI-II scores were used to divide the participants into either a nondepressed group with minimal symptoms (1–12) or a depressed group with mild to moderate symptoms of depression (>12).[2] In all cases, a clinical evaluation utilizing the *DSM-IV-TR* diagnostic criteria agreed with the BDI-II–based classification.[10] None of the subjects had a history of depression prior to entering the NFL, and only 2 of the subjects were currently undergoing treatment for depression at the time of our study. Two trained neuropsychologists conducted all neuropsychological testing and were blind to the imaging results at the time of testing.

Statistical analysis of demographic information. Distribution and median differences between our depressed and nondepressed groups were assessed using a Mann-Whitney *U* test and independent-samples median test. Selected variables that were subjected to these analyses were age, number of concussions, white matter lesion burden, years in the NFL, and mean FA for the entire white matter skeleton. All scans were processed and analyzed by the same individual who was not blind to the neuropsychological data.

MRI acquisition and analysis. Scanner specifications and acquisition of our fluid-attenuated inversion recovery (FLAIR) images and DTI scans are explained in e-Methods along with our analytical approach to quantifying white matter hyperintensities.[8,11] Preprocessing of DTI data included correction for motion and eddy current distortions followed by skull stripping[12] using FSL 4.1.7 (www.fmrib.ox.ac.uk/fsl/).[13] Tensors were estimated and FA maps created using the MedINRIA software package (www-sop.inria.fr/asclepios/software/MedINRIA/). The

Table 1 Demographic information of our cohort for athletes with (n = 5) and without (n = 21) depression[a]

	Asymptomatic athletes (n = 21)	Symptomatic athletes (n = 5)
Age, y	41–79, 58.7 (11.9)	43–62, 54.0 (7.78)
Sex, % male	100	100
Caucasian/African American	14/7	2/3
Years in NFL	2–15, 8.86 (3.98)	5–12, 7.6 (2.71)
Beck Depression Inventory II	0–11, 4.29 (3.72)	18–28, 23.6 (4.28)
Number of concussions	0–10, 3.43 (2.87)	3–11, 5.6 (3.29)
Positions (speed/nonspeed)	14/7	5/0

Abbreviation: NFL = National Football League.
[a] Unless otherwise stated, values are range, mean (SD).

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FA data were then processed using tract-based spatial statistics (TBSS)[14] in FSL, a technical white matter processing program that is used for group DTI analysis to a common template. The TBSS method aligns all subjects to Montreal Neurological Institute space by creating and applying a nonlinear matrix, using FSL's nonlinear registration tool. TBSS creates a study-specific "group mean FA skeleton" that contains the core central regions of white matter shared in common by the subjects. After thresholding the mean FA map at the standard value 0.2, FA values are projected onto the group skeleton from each subject for the "local center" of each tract.

We used the resultant skeletonized FA data in a series of voxel-wise correlations of depression severity (as measured by BDI-II total score) with FA, looking first at the composite BDI-II score and subsequently at the Buckley 3-factor scores. The voxel-wise correlations were performed using the Randomize tool in FSL utilizing a permutation-based Monte Carlo analysis with 5,000 permutations, threshold-free cluster enhancement, and correction for multiple comparisons using a family-wise error rate of $p < 0.05$. Age was treated as a covariate and extracted from each design matrix prior to the analysis. We assessed for FA differences between nondepressed athletes and cognitively normal controls by performing a voxel-wise group comparison using age as a covariate and identical parameters as described in the previous correlation.

Tract level analysis. In addition to the voxel-wise analysis, we examined these data in a tract-wise manner by isolating portions of the TBSS-derived skeleton that fell within the boundaries of several regions of interest (ROI) representing specific white matter tracts. We recruited 9 cognitively normal college students in order to delineate the best representation of each tract from a normal population. To construct the white matter tracts we listed in table 2, we performed a multiple ROI approach in the deterministic tractography program called MedINRIA (www-sop.inria.fr/asclepios/software/MedINRIA/). All white matter tracts were warped into common space using the same warp matrices derived from that corresponding subject's FA map applied with FLIRT from FSL. In common space all 9 representations of the same tract were superimposed, and the tract ROIs we defined reflect the voxels that were present in a majority of the subjects. All voxels were inspected and edited to ensure that they were uniquely represented in only one tract.

The mean FA value was calculated for each tract by averaging skeletal voxels that resided within each tract ROI.[15] Correlations were performed between tract-derived FA values and either total BDI-II score or subfactors of BDI-II. The age-corrected mean FA values by tract were exported and analyzed with a bivariate Pearson correlation using the SPSS statistical program. A more stringent threshold was applied to our data to compensate for the numerous correlations performed, with $\alpha = 0.01$.

For those ROIs that were significantly correlated with the total BDI-II score, we plotted a receiver operating characteristic (ROC) curve to test the ability of the mean FA of these tracts to distinguish the depressed from the nondepressed athletes.

Table 2 Association between fractional anisotropy and depression within white matter tracts[a]

	BDI total	Cognitive	Affective	Somatic
CC_A	−0.284	−0.292	−0.239	−0.227
CC_P	−0.053	−0.089	−0.079	−0.018
Cing left	−0.456	−0.443	−0.414	−0.376
Cing right	−0.431	−0.474	−0.368	−0.311
CS left	−0.318	−0.279	−0.249	−0.319
CS right	−0.280	−0.215	−0.136	−0.136
DC left	−0.167	−0.046	−0.217	−0.220
DC right	−0.425	−0.314	−0.437	−0.422
FMajor	−0.411	−0.371	−0.383	−0.361
FMinor	−0.550[b]	−0.508[b]	−0.474	−0.496[b]
FAT left	−0.321	−0.193	−0.266	−0.408
FAT right	−0.535[b]	−0.412	−0.474	−0.563[b]
FOF left	−0.420	−0.330	−0.414	−0.409
FOF right	−0.352	−0.325	−0.317	−0.309
ILF left	−0.429	−0.346	−0.363	−0.445
ILF right	−0.406	−0.318	−0.369	−0.414
SLF left	−0.521[b]	−0.520[b]	−0.388	−0.469
SLF right	−0.438	−0.486	−0.291	−0.365
UF left	−0.466	−0.369	−0.434	−0.466
UF right	−0.505[b]	−0.435	−0.464	−0.471

Abbreviations: BDI = Beck Depression Inventory; CC_A = anterior corpus callosum; CC_P = posterior corpus callosum; Cing = cingulum; CS = corticospinal tract; DC = descending cingulum; FAT = frontal aslant tract; FMajor = forceps major; FMinor = forceps minor; FOF = fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; SLF = superior longitudinal fasciculus; UF = uncinate fasciculus.
[a] Data are displayed as *R* values.
[b] $p < 0.01$.

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The flow chart (figure 1) demonstrates the details of the design. Sensitivity, specificity, odds ratio, and positive and negative predictive values with their respective 95% confidence intervals (CI) were calculated along with a positive likelihood ratio for the best-performing cut point identified by the ROC analysis.

Voxel-based morphometry. Volumetric processing was conducted using FSL-VBM within FSL.[16] We isolated only prefrontal gray matter using the ROI available from the Harvard Center for Morphometric Analysis to quantify a metric of prefrontal atrophy for each subject in our study. These volumes were then implemented as a covariate into our voxel-wise and tract-wise designs in subsequent analyses.

RESULTS Five athletes were identified as depressed (mean BDI-II 23.6, SD 4.28), while 21 athletes were not (mean BDI-II 4.29, 3.72). Depressed and nondepressed athletes did not differ in age, experience in the NFL, number of concussions, or volume of T2-weighted white matter hyperintensities on FLAIR MRI scans. FLAIR scans for depressed subjects are displayed in figure e-1. All depressed athletes reported at least 3 concussions (table 1). Four of the 5 depressed athletes reported symptom onset to have occurred following retirement from the NFL and one reported depression symptoms immediately following a concussion that ended his career.

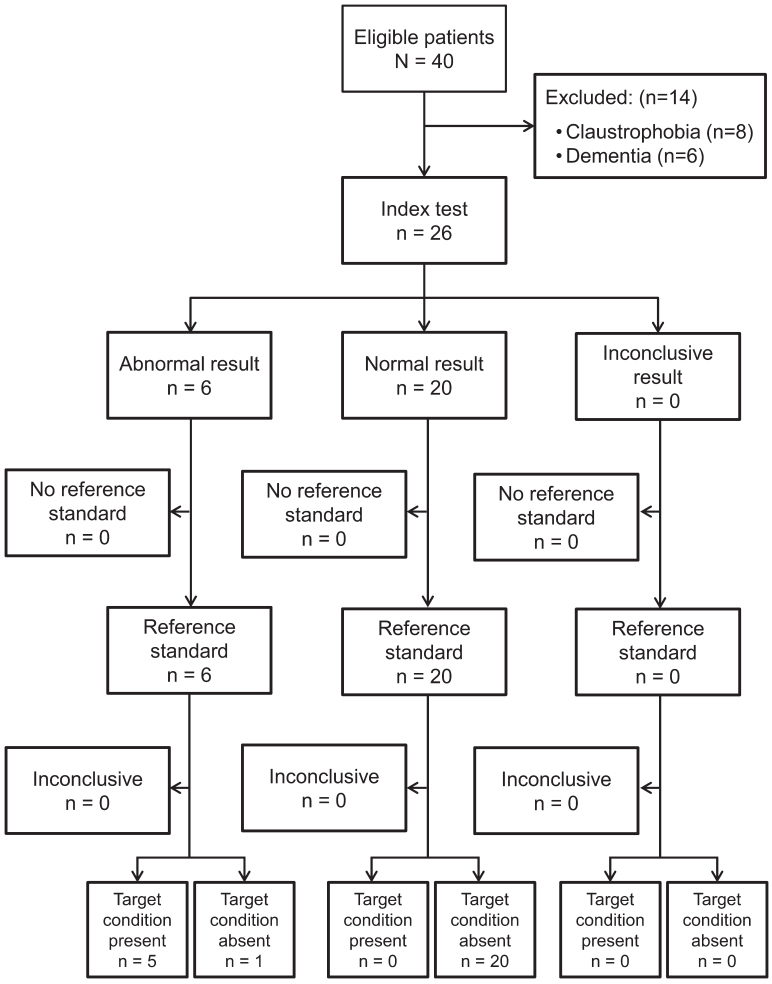
Voxel-wise correlations for all athletes revealed negatively correlated voxels dispersed throughout the white matter skeleton for FA and BDI-II total score ($p < 0.05$ corrected) (figure 2A). Similar distributions were found for the cognitive and somatic Buckley factors (figure 2, C and D), but the affective component was more localized to bilateral frontal and right posterior regions ($p < 0.05$ corrected) (figure 2B). There were no significant differences in FA between healthy controls and nondepressed retired athletes ($p > 0.05$). Our results remained essentially unaffected after incorporating prefrontal atrophy as an additional covariate into the voxel-wise analysis.

Table 2 shows all of the tracts that were included in the analysis along with the corresponding Pearson coefficients. Four white matter tracts had mean FA values that were significantly correlated with the total BDI-II score ($p < 0.01$). These tracts included the forceps minor (figure 3A), right uncinate fasciculus (figure 3B), right frontal aslant tract (figure e-2A), and left superior longitudinal fasciculus (figure e-2B). No tracts uniquely correlated with any of the subfactors that did not also correlate with the total BDI-II score. A second correlation was performed for the forceps minor after removing the impact of prefrontal atrophy but the correlation remained significant ($p < 0.01$, $R = -0.523$).

ROC curve analysis of the 4 tracts with significant associations between mean FA and total BDI-II score revealed that the mean FA of the forceps minor best distinguished the depressed from the nondepressed athletes with an area under the curve of 0.9712 (figure 3C). A mean FA cut point of 0.3896 misclassified only one subject and yielded a sensitivity of 100% (95% CI 47.8–100), a specificity of 95.2% (95% CI 76.2–99.9), an odds ratio of 150.3 (95% CI 5.3–4,229), a positive predictive value of 83.3% (95% CI 35.8–99.6), a negative predictive value of 100% (95% CI 83.2–100), and a positive likelihood ratio of 21.

DISCUSSION Our data from this relatively small cohort demonstrated a significant association between white matter integrity, as measured by DTI FA, and the presence as well as severity of depressive symptoms, as measured by the BDI-II, in retired NFL athletes with a history of concussive or subconcussive impacts. The data show that constellations of depressive symptoms are associated with general, as well as local, white matter disruption, depending on the Buckley 3-factor score used as a correlate. Using the overall BDI-II score threshold associated with clinical depression, the FA

Figure 1 Standards for the reporting of diagnostic accuracy studies



Flow chart of the study to assess the diagnostic accuracy of forceps minor fractional anisotropy (index test) in detecting depression within professional athletes validated with the Beck Depression Inventory II as the reference standard.

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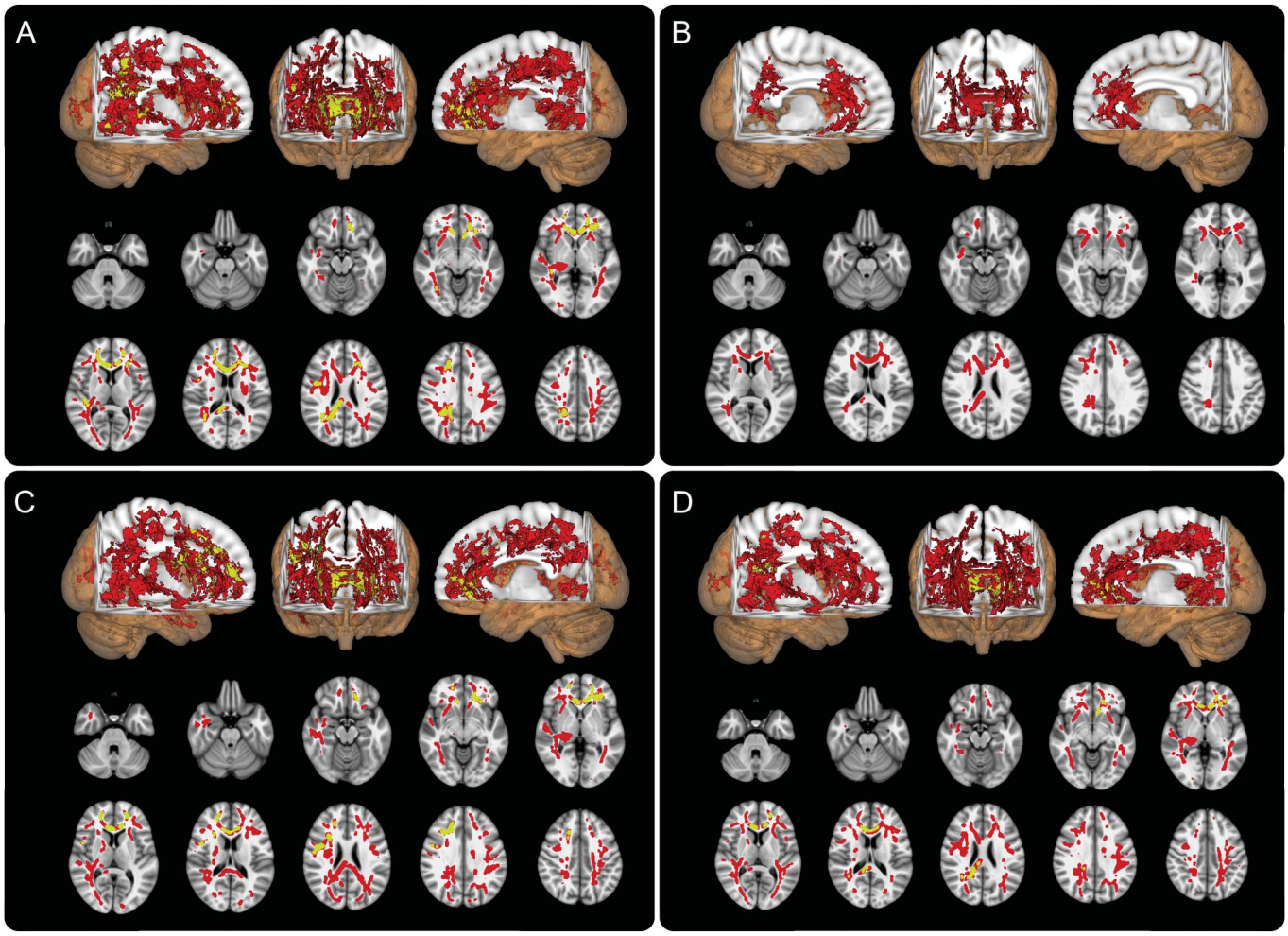
Figure 2 Voxel-wise correlation between white matter and depression in National Football League athletes



Each panel shows negative correlations between fractional anisotropy values and Beck Depression Inventory total score (A) and affective (B), somatic (C), and cognitive (D) subfactors. Red voxels represent significant voxels at $p < 0.05$ corrected for multiple comparisons and yellow voxels represent voxels that survive $p < 0.02$ corrected for multiple comparisons. Axial slices are in radiologic orientation with the results thickened for better visibility using the "tbss_fill" script.

value of one specific tract, the forceps minor, resulted in 100% sensitivity and 95% specificity for identifying individuals with depression. The factor common to all of these individuals that is associated with white matter dysfunction is their remote history of concussions that occurred prior to the detection of the subjects' symptoms.

The BDI-II is commonly used in clinical and research settings and reliably quantifies depressive symptoms.[17] Depression can be manifested by a variety of symptoms that span from emotional to physical as described in Buckley's 3-factor model—affective, cognitive, and somatic. Our findings showed that depressive symptom factors in this cohort correlated differentially with FA: the affective component was associated with focal white matter regions (bilateral frontal and right posterior), and the cognitive and somatic factors were associated with widespread white matter abnormality. Widespread white matter disruption has been reported to correspond with a prior history of depression.[18,19] Interestingly, voxels that survived a more stringent threshold of $p < 0.02$ for the BDI-II total score and cognitive and somatic factors were seen in frontal regions, including the forceps minor, as well as additional posterior regions for the BDI-II total score (figure 2).

DTI measures of FA and other markers of white matter integrity are commonly used for analyses of group data, although the strong correlations obtained in this study were robust to the point that the present analyses could be applied at the single subject level. The 5 individuals who reported significant depressive symptoms, both as a group and individually, could be differentiated from nondepressed subjects using just their low FA values. This implies that irrespective of cause, compromised white matter integrity in the frontal lobes is strongly correlated with depressive symptom severity. Additionally, the significant association of

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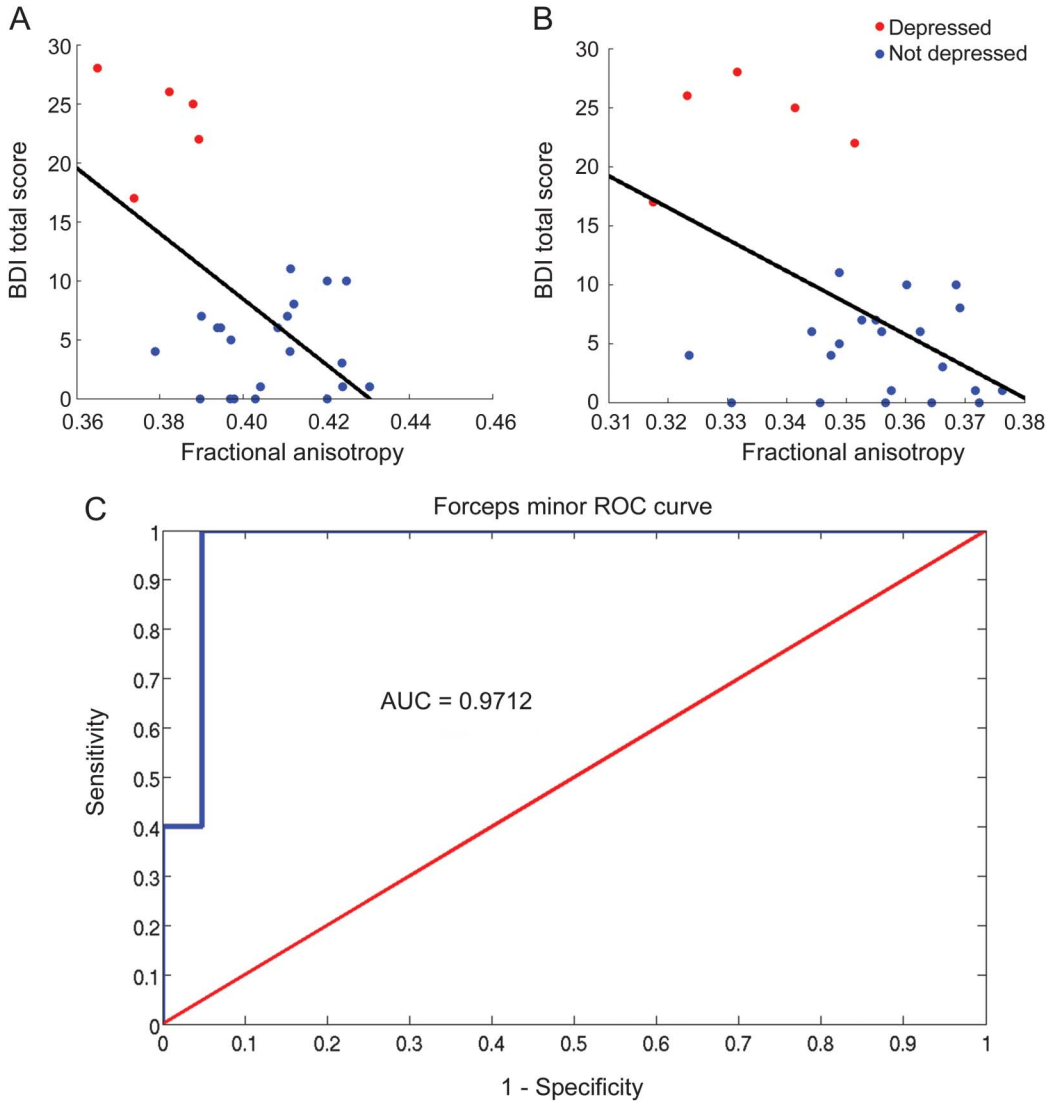
Figure 3 Tract-wise correlations between fractional anisotropy and the Beck Depression Inventory total score



Both forceps minor (A) and right uncinate fasciculus (B) survived a statistical threshold of $p < 0.01$. Subjects with depression are identified in red and nondepressed athletes are designated in blue. (C) Receiver operating characteristic (ROC) curve for fractional anisotropy-derived values from the forceps minor as a classifier for depression. The blue line is the actual classifier data plateauing at 100% sensitivity with 95% specificity. AUC = area under the curve; BDI = Beck Depression Inventory.

BDI scores with FA was independent of prefrontal cortical atrophy, even for the forceps minor, making it unlikely that secondary axonal degeneration from neuronal loss rather than an intrinsic white matter process fully accounts for the findings. Frontal projections (forceps minor in particular) are not only susceptible to disruption with head injury due to anatomical location but this dysfunction has been linked physiologically to a reduction in hemispheric synchrony.[20]

White matter dysfunction has been reported in concussion with diffuse axonal injury detected both pathologically[21] and in DTI studies.[22] Most subjects in this study have histories of multiple concussions. One previous investigation has demonstrated a general association between DTI white matter abnormalities and depression severity.[18] However, that study did not assess the correlations between severity of depression and abnormalities in individual white matter tracts or in focused ROI. White matter disruption in the hippocampal and prefrontal regions has been implicated in treatment-resistant depression[23,24] and early-onset depression,[25,26] particularly in the frontal lobes.[24] In TBI patients, connectivity within frontal networks was found to be more susceptible to damage and resulted in decreased connectivity.[27] If white matter disruption is the underlying cause of impairment in TBI, it is conceivable that the decreased connectivity is secondary to primary white matter degeneration.

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Considering that intact frontal circuits may be important in mood stability and these circuits' vulnerability to head injury, our findings involving the forceps minor are consistent with the literature as a plausible biomarker for depression severity in a population with a history of concussion.

It is not apparent whether the deficits described in this article could be a result of chronic traumatic encephalopathy (CTE), since this diagnosis at present is a pathologic one.[28–30] The goal of this study was to address the implications of white matter impairment and depression symptom expression during the subjects' natural lifespan; therefore, any connection to CTE would be speculative. We can neither confirm nor deny CTE in any of our patients but this does not invalidate DTI as a possible tool for early detection of CTE in the future.

A limitation of our study involves the lack of a direct temporal association between concussions and depression. Concussion characterization in these studies is based on symptom recollections years or even decades after the episode. This can lead to inaccuracies in reported number or severity of concussions. Four of the depressed subjects reported depressive complaints that did not manifest until after retirement from the NFL, whereas one subject experienced symptom onset immediately following a concussion. Head injury alone might elicit these symptoms, or such injury might interact with other factors to contribute to a delayed response that can manifest with aging. Both of these clinical profiles could be explained by white matter disruption, and the severity or location of the injury might influence the timing of symptom onset. Our data do not address the issue of subconcussive injury,[5,6] which is not possible to accurately quantify retrospectively. Previous studies of white matter disease and aging in depression focused on elderly adults with microvascular changes on T2-weighted FLAIR images.[31] Since there was a presumed etiology for those characteristic lesions, the increased risk of depression appeared to be secondary to white matter damage related to vascular disease. With variable associations between concussion and depression in retired players, factors such as presence and duration of postconcussive symptoms[32] or genetic profile (presence of an *APOE* ε4 allele) may contribute to a concussion leading to significant white matter dysfunction. To further determine whether the present associations imply causation, future longitudinal, prospective studies are indicated.

Our main findings were supported by both our voxel- and tract-wise analyses, implicating the importance of the forceps minor in association with depressive symptoms, a region that mediates interhemispheric connections between the frontal lobes. Prior studies have alluded to the importance for cross-communication between the frontal lobes in relation to the development of depressive symptoms.[33,34] Decreased FA represents white matter disruption, and subjects with the most profound depressive symptoms also had the lowest FA values in this same region. While the number of subjects we studied is small, white matter integrity changes seen in these subjects with depression lead to new insights of possible markers of behavior disturbances in chronic effects of head trauma.

AUTHOR CONTRIBUTIONS

Jeremy Strain: primary author of the manuscript, processed, analyzed, and contributed to interpretation of the data. Nyaz Didehbani: assisted in the conception and design of the study, acquired neuropsychological data, interpretation of the data, and provided insightful revisions of the manuscript. C. Munro Cullum: major role in the conception and design of the study and offered critical revisions of the manuscript, supervised and constructed the neuropsychological battery that was administered to our subjects. Sethesh Mansinghani: responsible for acquisition of the neuroimaging data and assisted with manuscript revisions, contributed to the processing of FLAIR scans and quantification of white matter lesion burden. Heather Conover: primary recruiter for this study, assisted in acquiring demographic information on the subjects. Michael A. Kraut: provided expertise during the conception and design portion of the study and critically reviewed drafts of the manuscript, supervised the initial creation of the neuroimaging battery for the study. John Hart, Jr.: primary advisor behind the conception and design of the study, performed clinical evaluations on subjects who met criteria for depression, provided revisions and assistance in manuscript preparation, contributed to interpretation of the data, contributed to the administrative duties, and obtained funding for the study. Kyle B. Womack: primary interpreter of the data and head of the neuroimaging portion for this study, performed data analysis and reviewed multiple drafts of the manuscript, supervision of the project, and assistance in administrative duties.

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DISCLOSURE

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