ORIGINAL CONTRIBUTION

Neuroimaging of Cognitive Dysfunction and Depression in Aging Retired National Football League Players

A Cross-sectional Study

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Objectives: To assess cognitive impairment and depression in aging former professional football (National Football League [NFL]) players and to identify neuroimaging correlates of these dysfunctions.

Design: We compared former NFL players with cognitive impairment and depression, cognitively normal retired players who were not depressed, and matched healthy control subjects.

Setting: Research center in the North Texas region of the United States.

Patients: Cross-sectional sample of former NFL players with and without a history of concussion recruited from the North Texas region and age-, education-, and IQ-matched controls. Thirty-four retired NFL players (mean age, 61.8 years) underwent neurological and neuropsychological assessment. A subset of 26 players also underwent detailed neuroimaging; imaging data in this subset were compared with imaging data acquired in 26 healthy matched controls.

Main Outcome Measures: Neuropsychological measures, clinical diagnoses of depression, neuroimaging measures of white matter pathology, and a measure of cerebral blood flow.

Results: Of the 34 former NFL players, 20 were cognitively normal. Four were diagnosed as having a fixed cognitive deficit; 8, mild cognitive impairment; 2, dementia; and 8, depression. Of the subgroup in whom neuroimaging data were acquired, cognitively impaired participants showed the greatest deficits on tests of naming, word finding, and visual/verbal episodic memory. We found significant differences in white matter abnormalities in cognitively impaired and depressed retired players compared with their respective controls. Regional blood flow differences in the cognitively impaired group (left temporal pole, inferior parietal lobule, and superior temporal gyrus) corresponded to regions associated with impaired neurocognitive performance (problems with memory, naming, and word finding).

Conclusions: Cognitive deficits and depression appear to be more common in aging former NFL players compared with healthy controls. These deficits are correlated with white matter abnormalities and changes in regional cerebral blood flow.

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CONSIDERABLE INTEREST HAS been expressed in the neurobehavioral changes, in terms of cognition and mood, that occur in some retired National Football League (NFL) players; despite increased media attention, however, little has been done to examine later-life functioning systematically in retired professional athletes. Neurocognitive assessments in athletes and nonathletes in the short term after concussion have demonstrated deficits in working memory, attention, and processing speed.[1-3] Wide variation exists in the persistence of these defects, with most individuals showing good recovery within days, weeks, or months after injury and a small minority showing persistent deficits.[4-7]

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A University of Michigan self-report symptom survey of retired NFL players noted that, among US men aged 30 to 49 years, 0.1% reported memory problems

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compared with 1.9% of retired football players.[8] Among men older than 56 years, these numbers increased to 1.2% in the general population and 6.1% among retired players. Among aging retired NFL players, 11% have reported experiencing depression, with a correlation between history of recurrent concussions and a lifetime history of depression.[9] Traumatic brain injury has been noted as a potential risk factor for neurodegenerative diseases, including Alzheimer disease (AD).[10] An association between repeated concussion and mild cognitive impairment (MCI) and reported memory impairments has also been suggested in retired NFL players, with a 5-fold increase in MCI diagnosis and a 3-fold greater prevalence of reported memory problems compared with retirees without a history of concussion. Furthermore, an earlier onset of AD was found in these players compared with the general population.[11] Unfortunately, the University of Michigan statistics[8] were based on responses to a questionnaire about subjective memory difficulties, without further detail, corresponding examination, or neurocognitive testing to assess for impairments or to establish formal diagnoses. Another syndrome, chronic traumatic encephalopathy (CTE), is emerging as a putative clinical diagnosis and has gained media attention as a result of suicides of some former NFL players. Chronic traumatic encephalopathy is described as occurring in individuals who have experienced previous brain injuries and is behaviorally manifested by changes in personality and/or mood (eg, depression, apathy, and suicidality), cognition, and movement. At this point, CTE remains a pathological diagnosis that is not universally accepted, and clinical diagnostic criteria have yet to be established.[12]

McKee and colleagues[13] and Omalu et al[14] recently reported on their examination of autopsy specimens from retired players who committed suicide and found pathological markers believed to be consistent with CTE. Neuropathologically, CTE is characterized by extensive tau-immunoreactive neurofibrillary tangles and marked accumulation of tau-immunoreactive astrocytes, without the accumulation of β-amyloid that is characteristic of AD. In a subset of cases, further evaluation showed a TAR DNA–binding 43-kDa proteinopathy throughout the frontal and temporal cortical regions and diencephalon. Three of the subjects in the initial sample had also manifested a progressive motoneuron disease (eg, similar to amyotrophic lateral sclerosis) exemplified by progressive weakness and TAR DNA–binding 43-kDa protein inclusions in the spinal cord.[15] These findings suggest that examination for upper and lower motoneuron disease is warranted in these players as they age. With regard to other potential risk factors for dementia, several reports have noted that a history of more severe traumatic brain injury has been linked to the development of AD later in life.[16]

Neuroimaging techniques can help clarify the brain changes that underpin neurobehavioral dysfunction. For example, diffusion tensor imaging (DTI)[17] has shown damage to white matter tracts in boxers with postconcussive injury.[18] Magnetic resonance (MR) spectroscopy, which measures brain metabolite levels, was performed in 40 athletes after concussion and showed alterations of brain metabolite levels.[19] When these data were compared with neuropsychological measures, MR spectroscopy was found to be associated with cognitive impairment.[20] However, the optimal use of neuroimaging in assessing brain status in this setting is in combination with neurocognitive measures, so that the findings from each set of investigative techniques can inform the interpretation of the other.[21,22]

We assessed neurobehavioral, neurological, and neuroimaging markers in a sample of aging former NFL players. To control for the neuroimaging measures used that are sensitive to age (DTI) and history of previous random lesions (arterial spin labeling [ASL]), we recruited a healthy control group (matched for age, educational level, and estimated IQ). We hypothesized that neurobehavioral disorders in former professional (American-style) football players would be present regardless of concussion history and that structural brain abnormalities would be associated with observed neurobehavioral deficits.

METHODS

SUBJECTS AND DIAGNOSTIC CRITERIA

We recruited our cross-sectional sample of participants after presentations of the study at a local gathering of retired NFL players living in the North Texas region, during a meeting of the NFL Players Association local chapter, and through local advertising and word of mouth among retired NFL players. In an attempt to obtain a reasonable cross section of retired athletes, we included all 34 retired NFL athletes who inquired about the study whether or not they reported cognitive symptoms. Each player underwent a complete neurological and neuropsychological evaluation. From this information, we performed clinical assessments of the athletes' cognitive status to identify them as cognitively normal or cognitively impaired and, if impaired, to determine their diagnosis. Participants ranged in age from 41 to 79 (mean age, 61.8; 95% CI, 57.8-65.7) years. Their professional football experience ranged from 2 to 15 (mean duration, 9.7; 95% CI, 8.4-10.9) years. Twenty-eight participants were active businessmen, and 6 were retired; 23 were white, and 11 were African American. Mean educational level was 16.3 (95% CI, 16.0-16.5) years. Three players were left-handed. Eighteen played offense and 16 played defense. Twenty-nine players exercised regularly (≥3 times/wk). Subjects had undergone a mean of 4.5 operations with general anesthesia during their lifespan.

Concussion history was obtained retrospectively from participants and informants and classified using the 1997 American Academy of Neurology practice parameter guidelines for grading concussion.[23] Players reported a lifetime history of concussions ranging from just a few seconds of confusion to loss of consciousness for several hours. All but 2 of the 34 players had sustained at least 1 concussion (range, 1-13 concussions), with a mean of 4.0 concussions during their life span (a mean of 2.0 concussions per participant were grade 1; 0.5, grade 2; and 1.6, grade 3). Twenty-six players completed the neuroimaging studies; 8 were claustrophobic and did not undergo MR imaging (MRI).

In addition, 85 healthy control participants from normal aging studies at the Center for BrainHealth underwent screening. Controls with known concussions were excluded, as were those with a history of playing college or professional football, with reported cognitive complaints, or with a neurological or a psychiatric disorder. Healthy controls were matched for age, educational background, and estimated IQ to the retired NFL players who participated in the neuroimaging studies.

Subjects in the control group ranged in age from 41 to 79 (mean age, 60.1; 95% CI, 54.6-64.1) years and had a mean educational level of 16.2 (16.0-16.7) years. Two controls were left-handed,

Table 1. Scores on All Cognitive Measures by Cognitively Impaired and Intact Retired NFL Players and Control Subjects[a]

	Mean (95% CI)[b]				
	Healthy Controls (n = 26)	Unimpaired NFL Players (n = 12)	CI NFL Players (n = 10)	*F* Value	*P* Value
Age, y	60.1 (55.6-64.6)	55.4 (47.2-63.4)	66.6 (61.6-71.6)	2.86	.07
Educational level, y	16.2 (15.3-17.1)	16.6 (16.0-17.2)	16.1 (15.6-16.6)	0.29	.75
Attention, cognitive flexibility					
Trail Making Test Part A T score	49.0 (45.8-52.1)	50.2 (44.2-56.2)	52.0 (47.8-56.2)	0.55	.58
Trail Making Test Part B T score	54.1 (50.6-57.5)	51.9 (44.9-58.9)	46.8 (40.5-53.1)	2.23	.12
WAIS-IV Digit Span SS	11.0 (9.6-12.3)[c]	9.3 (7.2-11.5)	10.3 (8.4-12.2)	1.08	.35
Processing speed					
WAIS-IV Coding SS	11.1 (10.0-12.0)[d]	10.5 (9.3-11.8)	10.5 (9.2-11.8)	0.41	.67
Language					
Category fluency T score	49.5 (45.5-53.5)[e]	49.5 (42.5-56.5)	42.3 (37.0-47.6)	2.23	.12
COWAT T score	50.2 (46.2-54.1)[e]	48.1 (44.1-52.1)	48.3 (39.7-56.9)	0.26	.77
BNT T score	53.4 (48-57.9)[d]	48.6 (42.3-54.9)	36.2 (29.8-42.6)	10.72	<.001[f]
SORT naming	15.5 (15.3-15.8)	14.6 (13.6-15.5)	12.6 (10.3-14.9)	11.01	<.001[f]
Visuospatial skills					
ROCFT copy T score	50.6 (46.0-55.1)[c]	46.3 (38.9-53.8)	48.7 (42.2-55.1)	0.65	.53
ROCFT delayed recall T score	58.3 (52.3-64.2)[c]	56.6 (48.1-65.0)	35.5 (28.5-42.5)	11.91	<.001[f]
Episodic and semantic memory					
CVLT T score	60.2 (57.2-63.2)	52.1 (46.9-57.3)	39.6 (32.5-46.7)	23.24	<.001[f]
SORT total score	30.2 (29.6-30.8)	29.6 (28.9-30.0)	27.9 (26.6-29.2)	5.55	.007

Abbreviations: BNT, Boston Naming Test; CI, cognitively impaired; COWAT, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; NFL, National Football League; ROCFT, Rey-Osterrieth Complex Figure Test; SORT, Semantic Object Retrieval Test; SS, scaled score; WAIS-IV, Wechsler Adult Intelligence Scale–Fourth Edition.

[a] T scores are demographically corrected scores with a mean of 50 (SD, 10). Higher scores reflect better performance, with scores lower than 40 denoting impairment. Scaled scores have a mean of 10 (SD, 3), with higher scores indicating better performance. Four patients with diagnoses of depression were not included.

[b] Data given are scores unless otherwise indicated.

[c] Data were missing for 4 participants.

[d] Data were missing for 5 participants.

[e] Data were missing for 1 participant.

[f] Significance value was set at $P < .004$. Differences were significant between healthy controls and CI retired NFL players and between unimpaired and CI retired NFL players. Four patients with diagnoses of depression were not included.

24 were white, and 2 were African American. Five were retired, and 21 were active businessmen. We gathered full clinical, neuropsychological, and neuroimaging data for all 26 controls. All participants gave written informed consent in accordance with the institutional review board of The University of Texas Southwestern Medical Center and The University of Texas at Dallas.

NEUROCOGNITIVE TESTS

The neuropsychological measures included the following (organized by domain of cognitive function): (1) general intelligence measured by the Wechsler Abbreviated Scale of Intelligence,[24] with estimated IQ calculated from the Vocabulary and Matrix Reasoning Subtests; (2) attention and cognitive flexibility measured by the Trail Making Test Parts A and B[25] and the Digit Span Subtest from the Wechsler Adult Intelligence Scale–Fourth Edition[26]; (3) processing speed measured by the Coding Subtest of the Wechsler Adult Intelligence Scale—Fourth Edition; (4) language, measured by the Category Fluency Subtest of the Boston Diagnostic Aphasia Examination,[27] the Controlled Oral Word Association Test,[28,29] and the Boston Naming Test[30]; (5) visuospatial skills measured by the Rey-Osterrieth Complex Figure Test (copy and memory components)[31]; (6) episodic and semantic memory measured by the California Verbal Learning Test–II[32] and the Semantic Object Retrieval Test,[33] consisting of one score for semantic memory retrieval and another for name production (word finding); and (7) mood measured by the Beck Depression Inventory–II.[34] The domain of executive function was represented in the test battery (eg, Trail Making Test Part B and Controlled Oral Word Association Test) but is not listed separately owing to the overlap of tasks with other domains.

All testing was performed by a trained neuropsychological technician or neuropsychologist (C.M.C. or N.D.). Clinical diagnoses were rendered by the cognitive neurologist (J.H.) after a review of each participant's history and results of the neurobehavioral status and neurological examinations. Next, neuropsychological scores for each subject were interpreted by 2 neuropsychologists (N.D. and C.M.C.) blinded to identity, history, and other data to determine the presence, level, and pattern of impairment. A consensus was reached in terms of the presence and severity of cognitive deficit.

One-way between-participants analyses of variance were conducted to evaluate differences on all cognitive measures among controls and NFL players with and without cognitive impairment. Significant findings were followed by a Tukey Honestly Significant Difference post hoc test. Pearson correlations assessed the relationship between neuropsychological test results with concussion history and years of playing in the NFL. We performed 14 comparisons between cognitive measures (**Table 1**) with the numbers of concussions and years of playing. To protect against inflated type I error and adjust for multiple comparisons, we used Bonferroni correction with the *P* value set at less than .004.

NEUROLOGICAL ASSESSMENT

A detailed neurological history (including a questionnaire for postconcussive symptoms), standardized neurological examination (ie, cranial nerves, motor and sensory functions, coor-

dination, gait, and reflexes), and neurobehavioral examination were performed by a cognitive neurologist (J.H.) for each player. The evaluation also included a clinician-administered survey of cognitive symptoms (ie, attention, language, memory, visuospatial skills, executive/cognitive control functions, and psychomotor speed) and postconcussive symptoms (eAppendix 1; http://www.jamaneuro.com).

The neurobehavioral examination included a detailed history of mental status, including assessment of attitude, behavior, mood/affect, speech, thought process, perceptions, insight, and judgment, which are described in eAppendix 2. Clinical psychiatric diagnoses were made by a behavioral neurologist (J.H.) and psychologist (N.D.) using standard criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) (*DSM-IV-TR*)[35] in conjunction with clinical mental status examination data and a self-report of depressive symptoms (Beck Depression Inventory–II).

After blinded review and ratings of the neuropsychological information by a board-certified clinical neuropsychologist (C.M.C.), we evaluated the neuropsychological data and interpretations in conjunction with the neurological evaluation and structural MRI to obtain a consensus clinical diagnosis. Criteria for neurological diagnosis consisted of *DSM-IV-TR* criteria for dementia,[35] the criteria of McKhann et al[36] for AD, and the criteria of Petersen et al[37] for MCI. A diagnosis of fixed cognitive deficit was determined using criteria of reported cognitive symptoms after a neurological event (eg, cerebrovascular accident, traumatic brain injury) that are reported to be static and not progressive (guidelines from *International Statistical Classification of Diseases, 10th Revision*[38]) and having a corresponding deficit on neurocognitive testing. The participants also underwent evaluation for amyotrophic lateral sclerosis because this diagnosis has been noted to be more common among retired players in some reports.[39]

NEUROIMAGING MEASURES

The imaging data were acquired on a 3-T MRI instrument (Philips). Imaging protocols are described in the following paragraphs.

Fluid-Attenuated Inversion Recovery

We acquired fluid-attenuated inversion recovery (FLAIR) images in an oblique axial plane (inversion time/repetition time/echo time, 2800/11000/150 milliseconds) using a field of view of 230 × 230 mm and a reconstructed resolution of 0.45 × 0.45 mm^2. We acquired 24 sections 5 mm thick with a 1-mm intersection gap. Lesions were defined as exhibiting FLAIR signal intensity greater than 2 SDs above the mean. The lesions were then edited manually to remove spurious voxels owing to fat signal, motion, edge effect, or coil sensitivity inhomogeneity. We calculated the total lesion volume, and the lesions were divided manually into deep or periventricular white matter lesions.

Hemosiderin Scan

Hemosiderin scans were used to assess for previous bleeding. Imaging variables included gradient echo, voxel size of 0.44 × 0.44 × 4 mm^3, gap of 1 mm, repetition time of 753 milliseconds, flip angle of 18°, acquisition number of 8, and scan duration of 124 seconds.

Diffusion Tensor Imaging

Diffusion tensor imaging data were acquired with an acquisition matrix of 128 × 128, field of view of 224 × 224 mm, section thickness of 2 mm, and intersection gap of 1 mm. We acquired images from 30 gradient directions (b value, 1000 s/mm^2) along with a single B_0 image. Preprocessing included correction for motion and eddy current distortions followed by skull stripping[40] using the FMRIB Software Library (FSL) (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/http:///).[41] Tensors were estimated and fractional anisotropy (FA) maps were created using MedINRIA (http://www-sop.inria.fr/asclepios/software/MedINRIA/). The FA data were analyzed with tract-based spatial statistics[42] in FSL, using a mean FA skeleton threshold of 0.2. Voxelwise analysis of the skeletonized data was performed using the randomize tool[43] in FSL with threshold-free cluster enhancement[44] and correction for multiple comparisons using the familywise error rate. All the DTI comparisons included age as a covariate.

Arterial Spin Labeling

To estimate cerebral blood flow, we performed pseudocontinuous ASL (pCASL) and phase-contrast MRI.[45] From the phase-contrast data, we calculated the total flux in the 4 feeding arteries (left and right internal carotid arteries and left and right vertebral arteries), providing an estimate of the blood flow to the entire brain. The whole-brain volume was estimated from magnetization-prepared rapid acquisition gradient-echo data, from which the mean blood flow per unit of brain mass was calculated in units of milliliters per 100 g per minute. Next, a brain mask was applied to the pCASL difference images, and we calculated the whole-brain mean pCASL signal (in units of MR signal). By comparing these 2 mean values, the conversion constant between the pCASL MR signal and the physiologic unit was obtained and used to calibrate the pCASL signal for individual voxels, yielding cerebral blood flow maps. Imaging variables for pCASL scan were gradient echo, voxel size of 2.5 × 2.5 × 5 mm^3, repetition time of 4 seconds, labeling duration/delay 1.6/1.5 seconds, 30 averages, labeling radiofrequency interval of 1 millisecond, radiofrequency duration of 0.5 milliseconds, and flip angle of 18°.

RESULTS

NEUROCOGNITIVE STATUS

Diagnoses

Of the 34 participants, 20 (including 5 who were depressed without cognitive impairment) were cognitively normal (59%). Four were diagnosed as having a fixed cognitive deficit (12%); 8, MCI (24%); and 2, dementia (6%). Of those with dementia, one participant had vascular dementia (history of diabetes mellitus and stroke) and the other had regions of cystic change on MRI that had the appearance of lesions remotely associated with traumatic brain injury consistent with the clinical history. No participants demonstrated signs suggestive of amyotrophic lateral sclerosis. For subsequent analyses, those diagnosed as having a fixed deficit, MCI, or dementia were grouped as cognitively impaired to maximize sample sizes for statistical comparisons.

Eight of the 34 participants (24%) were diagnosed as having depression, including 6 without a previous diagnosis of or treatment for depression. Three of the 8 participants with depression had concurrent cognitive deficits that were not believed to be attributable solely to

Table 2. Results From the FLAIR Images

	Retired NFL Players	Control Subjects	*P* Value
Age, mean, y	66.6	65.15	.6
White matter lesion volume, mean, mL			
All	8.13	2.38	.04
Deep	1.01	0.22	.02
Around ventricles	7.13	2.23	.06

Abbreviations: FLAIR, fluid-attenuated inversion recovery; NFL, National Football League.

depression. Thus, these 3 were included in their cognitive diagnostic group (as cognitively impaired) and in the depression analyses.

Demographic Variables

We performed independent 2-tailed *t* tests to compare demographic variables between 26 retired NFL players undergoing neuroimaging and their 26 matched controls. No significant differences between the NFL players and controls were found in terms of age ($t_{50} = 0.21$; $P = .84$), educational level ($t_{50} = -0.41$; $P = .68$), or estimated full-scale IQ ($t_{50} = 0.49$; $P = .63$). One-way between-participants analyses of variance (2-tailed) were conducted to evaluate differences in demographic variables among controls (n = 26), retired NFL players without cognitive impairment or depression (n = 12), and retired NFL players with cognitive impairment (n = 10). No significant differences were detected across groups for educational level ($F_{2,45} = 0.29$; $P = .75$), estimated full-scale IQ ($F_{2,45} = 0.13$; $P = .88$), or age ($F_{2,45} = 2.86$; $P = .07$). In examining differences between cognitively impaired vs nonimpaired players, we found no significant difference in the number of concussions ($t_{34} = -0.86$; $P = .39$) or the number of years played in the NFL ($t_{34} = -1.93$; $P = .06$).

We found no differences between the impaired vs nonimpaired NFL players' groups for vascular risk factors (eg, hypertension, diabetes mellitus, high cholesterol levels) or alcohol use. None of the players reported corticosteroid use while playing, and no current abuse of other drugs was found in either group. Seven of the NFL players complained of headaches and 1 complained of dizziness; however, we found no significant differences between impaired vs nonimpaired players on these symptoms.

Neuropsychological Measures

Using age-adjusted scores, results of 1-way analyses of variance revealed significant differences on tests of naming (Boston Naming Test), word finding (Semantic Object Retrieval Test, Naming Subtest), and visual (Rey-Osterrieth Complex Figure Test, Delayed Recall Subtest) and verbal (California Verbal Learning Test) episodic memory (Table 1). We found no significant correlations between neuropsychological measures and concussions or the number of years played in the NFL.

NEUROIMAGING

FLAIR Images

Total and deep white matter lesion volumes were significantly different between NFL players with cognitive deficits (n = 10) and age-matched controls (n = 20). The periventricular white matter lesion volume alone was not significantly different between the 2 groups (**Table 2**). No difference was found in white matter lesion volumes between cognitively impaired and unimpaired players or between symptomatic (cognitive impairment and/or depression) and unimpaired players ($P > .05$).

Hemosiderin Scan

Of all the subjects, only 3 healthy controls and 3 retired NFL players (2 with no impairments and 1 with MCI and depression) had small foci of hemosiderin deposition. The NFL player with MCI and mild depression demonstrated a focus of hemosiderin deposition in the pons that had an appearance most compatible with a cavernous angioma. None of the foci of likely hemosiderin deposition in any of the participants were colocated with foci of an elevated FLAIR signal that would suggest gliosis, and no encephalomalacia was found in the vicinity of any of these foci. The subject with the most numerous foci (4 foci; 2 on each side) demonstrated no cognitive abnormalities.

DTI Analysis

The primary DTI analysis compared FA between the retired athletes with impairments of cognition and/or mood (symptomatic athletes [n = 14]) and their age-, education-, and IQ-matched controls (n = 14). This comparison demonstrated widely distributed reductions of FA in frontal and parietal regions bilaterally as well as along the corpus callosum and in the left temporal lobe (**Figure 1**). The reverse contrast between these same groups yielded no significant voxels where the FA was higher in the symptomatic athletes than in their matched controls. The comparison of the asymptomatic retired athletes who had no cognitive impairment or depression (n = 12) with their matched controls likewise showed no voxels in which FA differed. (We performed a secondary analysis to see whether the finding of reduced FA in the symptomatic athletes persisted if this group was compared with the asymptomatic athletes [eFigure] instead of their matched controls. This comparison had similar results to the one between symptomatic athletes and their matched healthy controls.)

In additional analyses, cognitive impairment and depression were considered separately. **Figure 2**A shows the comparison of FA between the retired athletes with cognitive impairment (n = 10) and their matched controls (n = 10), whereas Figure 2B shows the same comparison for those with depression (n = 6) and their matched controls (n = 6). Both comparisons again show widely distributed voxels with lower FA in the athlete groups; however, the changes for those with cognitive impairment are more constricted in topographic extent than were seen in the entire symptomatic athlete group.

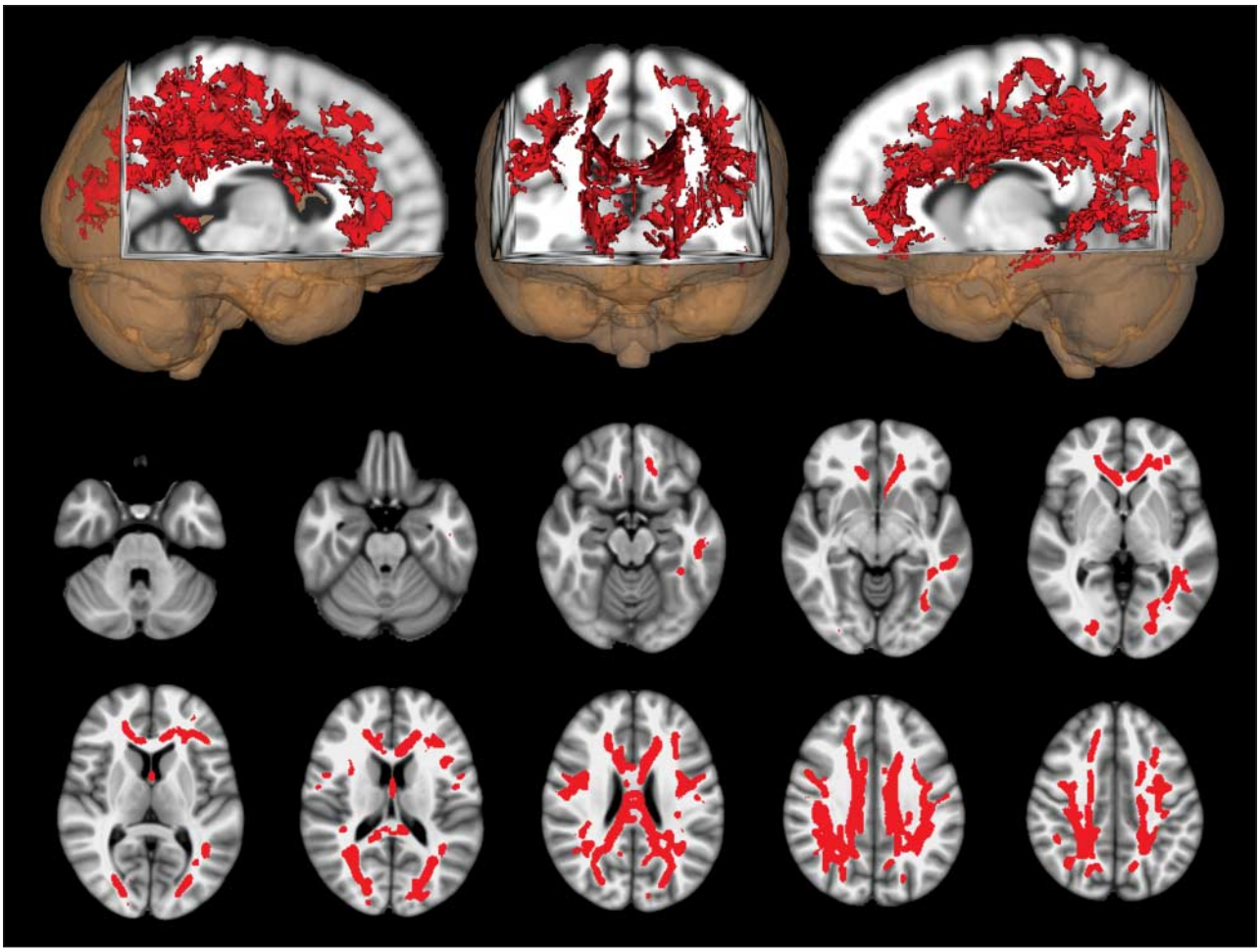

Figure 1. Voxelwise comparison of fractional anisotropy (FA) differences between symptomatic retired professional football players with cognitive impairment and/or depression (n = 14) and their matched control subjects (n = 14) on diffusion tensor imaging. Red indicates voxels in which FA is lower in the symptomatic retired players than in controls ($P < .05$, corrected). Axial images are in radiologic orientation with the results thickened for better visibility using the tract-based spatial statistics "fill" script.

Arterial Spin Labeling

We found regions in the left inferior parietal lobe, posterior superior temporal gyrus, bilateral midcingulate gyri, and right middle frontal gyrus that demonstrated significant ($P < .001$) increases in regional blood flow for impaired players compared with all matched controls (**Figure 3**A). The impaired players also had significantly less blood flow compared with controls in the left temporal pole and right occipital region (Figure 3B). Four of the 10 impaired NFL players and 6 controls were not used because of more than 4 mm of motion misalignment.

COMMENT

In the group of 34 retired NFL players who participated in our study, 14 (41%) demonstrated cognitive deficits, including 4 with fixed cognitive deficits (12%), 8 with MCI (24%), and 2 with dementia (6%). When we compared players with cognitive deficits with players without cognitive deficits and healthy controls, the neuropsychological tests that distinguished the groups were measures of naming, word finding, and visual and verbal episodic memory.

In our sample, the number of individuals with dementia was not different than expected in the general population at this age. Previous studies[8] have noted a higher incidence of dementia in retired players as they aged. The lower incidence in the present study could be the result of a small, motivated volunteer sample (although bias is typically toward more, not fewer, with impairment) or the higher mean IQ of participants. The number of participants with MCI is slightly higher than that expected in the general population,[46,47] and these individuals will be observed to determine whether their clinical progression approximates that of amnestic MCI with a presumed degenerative cause or whether MCI in individuals with significant concussion history exhibits a different course. No neurological abnormalities suggestive of amyotrophic lateral sclerosis were detected in any individuals; however, we acknowledge that the sample size of the study is small. Furthermore, none of the retired players fit the reported clinical profile for CTE at the time of examination.

The prevalence of depression among our retired players (24%) was slightly higher than that expected for this age group (approximately 15%).[48] These findings underscore the need for screening for depression and cognitive dysfunction in retired athletes.[9,48] With regard to the

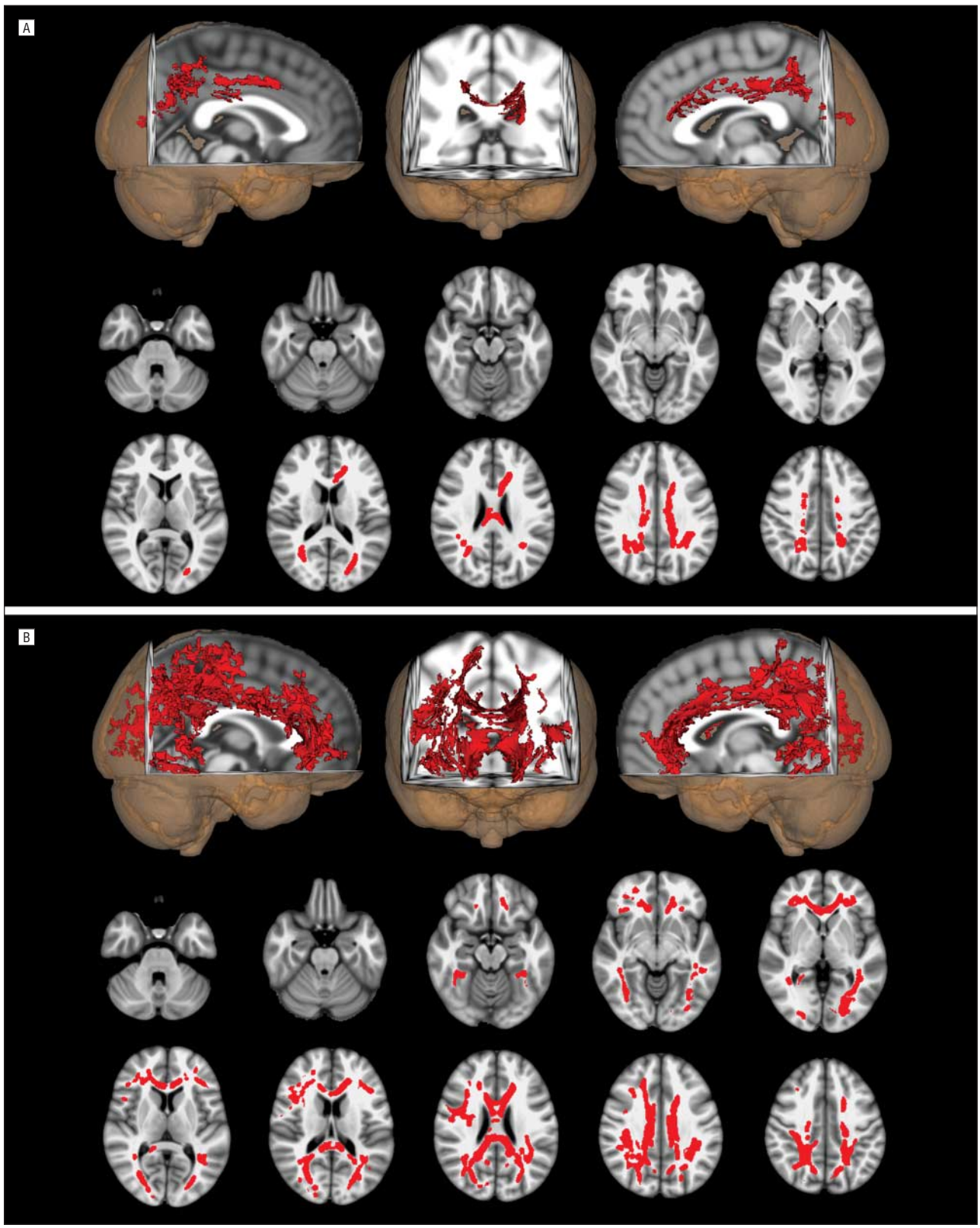

Figure 2. Voxelwise comparison of fractional anisotropy (FA) differences between groups on diffusion tensor imaging. A, Comparison of cognitively impaired retired professional football players (n = 10) and matched control subjects (n = 10). Red indicates voxels in which FA is lower in the cognitively impaired athletes than in controls ($P < .05$, corrected). B, Comparison of retired professional football players with depression (n = 6) and matched controls (n = 6). Red indicates voxels in which FA is lower in the retired players with depression than in controls ($P < .05$, corrected). Axial images are in radiologic orientation with the results thickened for better visibility using the tract-based spatial statistics "fill" script.

possibility of CTE, all reports of CTE in more recently retired athletes have been in individuals who committed suicide.[13,49] Those studies did not examine the relationship between neurobehavioral status or clinical course of symptoms during life; thus, the clinical presentation of depression was not well documented, and little is known about possible neuropsychological correlates. Undetected depression can occur because of the presence of vegetative symptoms of depression (eg, disturbance of sleep, appetite, and volition) without predominant mood indicators (eg, expressed feelings of hopelessness, crying) as seen in the former players in this study, potentially resulting in a failure to report overt symptoms of sadness or depression per se. The field needs prospective investigations into neuropsychiatric symptoms and changes in retired professional athletes, including more detailed assessment of symptoms reportedly associated with CTE.

Our findings support a previous study of the relationship of remote concussion and cognitive impairment (ie, MCI and AD) by Guskiewicz et al,[11] who found an association between recurrent concussion (≥3) and MCI but not AD. Tremblay et al[50] compared quantitative voxel-based morphometry, MR spectroscopy, neuropsychological testing, and apolipoprotein E status in 15 former athletes who sustained their last sports concussion more than 3 decades before testing with 15 subjects with no history of traumatic brain injury. Those with concussions showed focal brain volume loss, abnormal findings on MR spectroscopy in the medial temporal lobe and prefrontal cortex, and episodic memory and verbal fluency decrements, indicating structural, neurochemical, and behavioral lesions in these otherwise healthy former athletes. In another study by De Beaumont et al,[51] 19 healthy former athletes with a history of concussion and 21 without concussion underwent neuropsychological testing, an event-related potentials task, and transcranial magnetic stimulation for motor measures. The athletes with a history of concussion demonstrated decreased episodic memory and response inhibition performance, which correlated with delayed event-related potentials and slowed motor speed. These concussion-linked findings in reportedly healthy athletes suggest that remote concussion may result in brain abnormalities and that these findings may be precursors to those reported herein. Unfortunately, none of these studies included neurological and neuropsychological assessment of the clinical diagnostic (eg, dementia, MCI) status of the subjects.

In our cohort of retired players, we found generally mild difficulties in naming and word finding and in episodic memory (verbal and visual). The memory impairment we observed is consistent with previous findings of persistent memory impairments after concussion in some cases.[51,52] We also detected word-finding difficulties that have not been previously reported in aging cohorts of retired players. Future neurocognitive studies of aging athletes should include similar assessments to explore the potential significance of this finding further in terms of cognitive outcomes. A more extensive neuropsychological examination, with additional emphasis on executive function and more detailed analysis of episodic memory and language performances, may be useful.

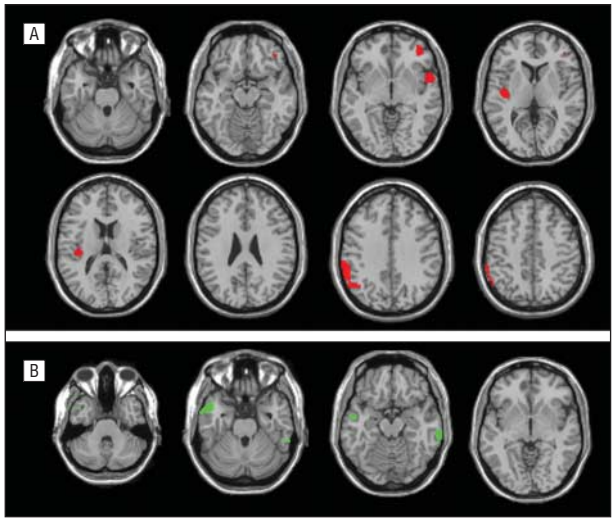

Figure 3. Estimated regional cerebral blood flow (CBF) in retired professional football players with cognitive impairment compared with matched control subjects. A, Estimated regional CBF is increased in impaired retired players in the left inferior parietal lobe, posterior superior temporal gyrus, bilateral midcingulate gyri, and right middle frontal gyrus ($P < .001$). B, Estimated regional CBF is decreased in the left temporal pole and right occipital region of impaired retired players ($P < .001$).

The cognitive dysfunction and depression in the cognitively impaired members of our cohort were associated with disrupted white matter integrity on DTI and with deep white matter lesions on FLAIR. Because these differences were not evident in comparable healthy retired NFL players or in matched controls, disrupted white matter integrity appears to represent a potentially important biomarker for neurobehavioral impairment. These findings differ from a previous study of postconcussional athletes with depression in whom quantitative MRI and functional MRI demonstrated reduced functional MRI signal changes without prominent white matter pathology.[53] The use of a matched control group without concussions is essential to detect these key differences. Further correlation between white matter pathology and cognitive impairments or depression over time may be of prognostic value among those at risk for future neurobehavioral difficulties.

Altered cerebral blood flow patterns in retired NFL players are concordant with brain regions associated with abnormal findings of neuropsychological testing. The left inferior parietal lobule and the superior temporal gyrus are thought to play important roles in naming and word finding,[54] and the increase in blood flow in the impaired players may reflect compensatory responses to impaired function in other regions. The left temporal pole is also associated with naming and verbal memory,[55] and the decreased flow in this region suggests less metabolic activity and associated dysfunction. Our findings suggest that a dynamic process underlies dysfunction in these players as they age and that their deficits do not simply reflect the static effects of previous damage. In a longitudinal study of white matter hyperintensities in aging individuals, advancing white matter abnormalities were associated with different patterns of cortical blood flow increase and decrease compared with what was evident in a subpopulation with static white matter findings. The regions of longitudinally developing cortical blood flow

increase were posited to reflect at least transient cortical compensatory efforts to overcome reduced efficacy of interregional neural communications due to white matter deterioration. The decreased blood flow was exhibited in regions that were posited to have reduced function as a consequence of longer-term disconnection.[56] Similar mechanisms likely underlie the regional increases and decreases in cerebral blood flow that we have observed in our subjects with cognitive abnormalities.

In summary, this comprehensive, multimodal investigation suggests that retired NFL players may be more likely to develop cognitive impairments (problems with memory, naming, and word finding) or depression as they age compared with the general population. These cognitive impairments correlated with changes in blood flow to specific brain regions (left temporal pole, inferior parietal lobule, and superior temporal gyrus) and with white matter abnormalities. Retired NFL players without cognitive impairment or depression did not demonstrate white matter abnormalities compared with controls. Future investigations with larger samples, including these types of detailed histories and multimodal neurobehavioral and neuroimaging studies of this population, are needed.

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