Olfactory Function and Associated Clinical Correlates in Former National Football League Players

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Abstract

Professional American football players incur thousands of repetitive head impacts (RHIs) throughout their lifetime. The long-term consequences of RHI are not well characterized, but may include olfactory dysfunction. RHI has been associated with changes to brain regions involved in olfaction, and olfactory impairment is common after traumatic brain injury. Olfactory dysfunction is a frequent early sequelae of neurodegenerative diseases (e.g., Alzheimer's disease), and RHI is associated with the neurodegenerative disease, chronic traumatic encephalopathy (CTE). We examined olfaction, and its association with clinical measures, in former National Football League (NFL) players. Ninety-five former NFL players (ages 40–69) and 28 same-age controls completed a neuropsychological and neuropsychiatric evaluation as part of a National Institutes of Health–funded study. The Brief Smell Identification Test (B-SIT) assessed olfaction. Principal component analysis generated a four-factor structure of the clinical measures: behavioral/mood, psychomotor speed/executive function, and verbal and visual memory. Former NFL players had worse B-SIT scores relative to controls ($p=0.0096$). A B-SIT cutoff of 11 had the greatest accuracy (c-statistic=0.61) and specificity (79%) for discriminating former NFL players from controls. In the former NFL players, lower B-SIT scores correlated with greater behavioral/mood impairment ($p=0.0254$) and worse psychomotor speed/executive functioning ($p=0.0464$) after controlling for age and education. Former NFL players exhibited lower olfactory test scores relative to controls, and poorer olfactory test performance was associated with worse neuropsychological and neuropsychiatric functioning. Future work that uses more-comprehensive tests of olfaction and structural and functioning neuroimaging may improve understanding on the association between RHI and olfaction.

Keywords: American football; chronic traumatic encephalopathy; National Football League; olfaction; repetitive head impacts

Introduction

REPETITIVE HEAD IMPACTS (RHIs) refers to the cumulative exposure to concussive and subconcussive injuries, such as the thousands of impacts incurred by professional American football players throughout their athletic careers.^{1–6} RHI has become a societal concern because of its association with later-life neurological conditions, including chronic traumatic encephalopathy (CTE). CTE is a unique neurodegenerative disease that can only currently be diagnosed using recently defined neuropathological criteria⁷ and is caused, in part, by exposure to RHI.^{8,9} Postmortem

next-of-kin interviews describe early-life behavioral/mood and/or later-life cognitive impairment as the core clinical features of CTE.^{10,11} Previous work that examined clinical function in former National Football League (NFL) players has also found mood (i.e., depression) and cognitive deficits in this population.^{12,13} Despite these findings, long-term RHI-related clinical impairments in living subjects in general, and American football players in particular, remain poorly characterized.

Olfactory dysfunction may be one clinical consequence associated with RHI. Impairments in olfaction (e.g., threshold, identification, and discrimination) are a common sequela of traumatic

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brain injury (TBI), including mild TBI (mTBI).^{14–18} Olfactory impairments in TBI are believed to involve tensile and shearing effects to the olfactory nerve at the cribriform plate, and/or direct injury to the olfactory system, including the olfactory bulb in the ventral aspect of the frontal lobe, and the olfactory cortex and processing regions (e.g., frontal lobe base, orbitofrontal cortex [OFC], and medial temporal lobes [MTLs]).^{19–27} Like TBI, RHI has also been shown to impact olfactory function. One study found that active boxers (without nasal cavity pathology) exhibited worse olfactory function relative to controls, including decreased olfactory threshold and odor identification.²⁸ Olfaction impairment, as defined by the Brief Smell Identification Test (B-SIT), was the most common neurological deficit in 126 Operation Iraqi Freedom/Operation Enduring Freedom war veterans that sustained one or more combat-related mTBI with loss of consciousness LOC.²⁹ Other work found no effect for number of concussions on olfactory function in a small sample of 22 active university football players, but those who had a concussion >33 months earlier exhibited worse olfactory test performance relative to ≤33 months earlier.³⁰ Overall, extant evidence supports the negative impact of RHI on olfactory function, at least in the short term.

Olfaction deficits associated with RHI exposure may also extend into later life. RHI has been linked with long-term changes of olfactory system structures, such as the OFC and MTL, and functional magnetic resonance imaging (fMRI)-measured frontal lobe activation impairment and hippocampal atrophy have been observed in former living NFL players.^{31–39} RHI is a necessary risk factor for CTE and, in the advanced stages of CTE, phosphorylated tau (p-tau) accumulates in the olfactory bulbs. Tau aggregation and other pathology (e.g., atrophy and axonal dysintegrity) is also common in key olfactory tracts and brain regions in CTE, such as the frontal lobes and MTL.⁸ In Alzheimer's disease (AD), another neurodegenerative tauopathy, p-tau is found in the olfactory system (e.g., hippocampus) upon autopsy and is associated with olfactory deficits during life.^{40–43} Olfactory deficits predict AD progression, occur before dementia-related symptom onset (e.g., preclinical AD), and are correlated with clinical impairment (e.g., memory and executive dysfunction).^{44–53} Because of these findings, olfactory tests have important clinical utility in AD that also appears evident in other neurodegenerative tauopathies (e.g., frontotemporal lobar degeneration disorders, progressive supranuclear palsy, and corticobasal degeneration).^{54,55}

To our knowledge, no study has examined olfactory dysfunction as a possible long-term clinical consequence of exposure to RHI. The aim of this study was to examine olfactory function, using the B-SIT, in former NFL players presumably at high risk for CTE (based on duration of football played, position played, and being symptomatic at the time of study entry) compared to same-age controls. We also investigated the association between the B-SIT and behavioral/mood and neuropsychological tests in the former NFL players.

Methods

Subjects

The sample included 124 subjects (96 former NFL players; 28 same-age controls) from the National Institute of Neurological Diseases and Stroke-funded study, entitled, Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests (DETECT). The primary aim of DETECT is to develop clinical biomarkers for the *in vivo* diagnosis of CTE. Consequently, it was essential that a high risk for CTE cohort was recruited, and thus the targeted sample included former professional American football

players, a population in which CTE neuropathology has been most well documented.⁸ Recruitment and data collection for DETECT began in November 2011 and concluded in October 2015. Former NFL players were recruited through e-mails to and presentations for members of the NFL Players Association and/or NFL Alumni Association, as well as through Boston University Alzheimer's Disease and CTE Center social media postings and word of mouth. Inclusion criteria included: ages 40–69 years and a minimum of 2 years of active playing time in the NFL. To further increase the possibility of having CTE, former NFL players were also required to have 12 or more total years of participation in organized tackle football and to have self-reported complaints of cognitive, behavioral, and mood symptoms for at least 6 months before study entry. Former NFL players must also not have had a history of concussion within 1 year of entry into DETECT.

The control subjects were recruited through social media postings, flyers, and word of mouth. Control subjects were also between ages 40 and 69. In addition, in order to investigate the long-term consequences of RHI exposure in the former NFL players, the control subjects were required to have no history of organized contact sport involvement (e.g., football, hockey, soccer, lacrosse, and wrestling) and no history of TBI. Three of the controls had a history of soccer play and 1 a history of amateur wrestling, but this was not considered meaningful participation given the brief length of play and/or lack of significant exposure to RHI. For all subjects, exclusion criteria included English as a second language, MRI, and/or lumbar puncture contraindications, and history of any other central nervous system diagnosis. Test effort was also assessed through embedded and nonembedded performance validity measures, and evaluation of neuropsychological test scores by two neuropsychologists for any peculiar score profiles. The sample of former NFL players was reduced from 96 to 95 after exclusion of 1 subject because of poor effort, as evidenced by: failure on multiple performance validity tests (embedded and nonembedded measures); several neuropsychological scores at floor; and external evidence that supported intentional poor effort. Table 1 presents sample characteristics.

As part of DETECT, all subjects underwent comprehensive examinations during a single 2- to 3-day visit that included a neurological evaluation, neuropsychological testing, a structured psychiatric interview, extensive self-report measures of mood and behavior, neuroimaging, blood and cerebrospinal fluid collection, and genetic testing. Only neuropsychological and neuropsychiatric (i.e., mood and behavior) data relevant to the current study objectives were examined. At the time of this study, not all neuroimaging and fluid biomarker measures were available for analysis. All protocols were approved by the Boston University Medical Center Institutional Review Board. Subjects provided their written informed consent before participation and were given a copy of all signed consent forms.

Measures

Olfactory function. The B-SIT⁵⁶ is a standardized 5- to 10-minute, 12-item odorant test that was used to measure olfactory function. Six items are food related (lemon, banana, pineapple, chocolate, cinnamon, and onion) and six are nonfood related (rose, gasoline, smoke, turpentine, soap, and paint thinner). The scent is microencapsulated then released by scratching the strip with a pencil tip. Subjects then sniff and select one of four possible multiple-choice answers, with scores ranging from 0 to 12 (higher score reflects better performance). Raw scores are converted to age-adjusted percentiles from the administration manual to determine abnormal performance compared to normative data (for a detailed description of the development of normative data for the B-SIT, see Doty⁵⁶). Because abnormal performance is age dependent, the cutoff for determining abnormal olfactory function is different across age groups. Briefly, the normative data for the B-SIT were

TABLE 1. SAMPLE DEMOGRAPHIC, ATHLETIC, AND MEDICAL CHARACTERISTICS

Characteristic	NFL (n = 95)	Control (n = 28)	p value
Age, mean (SD) years	55.29 (7.88)	57.14 (6.94)	0.265
Education, mean (SD) years	16.41 (0.97)	17.46 (2.19)	0.019
African American ^a , n (%) (N = 94 for NFL)	41 (43.6)	1 (3.6)	<0.001
AFE to football ^a , mean (SD) years (N = 94)	11.93 (2.56)	0.0 (0.0)	—
Duration of football play, mean (SD) years	18.22 (3.50)	0.0 (0.0)	—
Duration of play in the NFL, mean (SD) years	8.10 (2.80)	0.0 (0.0)	—
Primary position group, n (%)		—	—
Offensive line	28 (29.5)	—	—
Running back	8 (8.4)	—	—
Tight end	5 (5.3)	—	—
Offensive skill	1 (1.1)	—	—
Defensive line	15 (15.8)	—	—
Linebacker	20 (21.1)	—	—
Defensive back	18 (18.9)	—	—
Body mass index, mean (SD) kg/m ²	33.42 (5.09)	27.84 (3.84)	<0.001
Played other contact sports, n (%)	24 (25.3)	4 (14.3)	0.223
Hypertension ^a , n (%) (N = 92 for NFL and 27 for controls)	47 (51.1)	5 (18.5)	0.003
High cholesterol ^a , n (%) (N = 89 for NFL)	47 (52.8)	7 (25.0)	0.010
Diabetes ^a , n (%) (N = 91 for NFL)	8 (8.8)	1 (3.6)	0.361
Heart disease ^a , n (%) (N = 90 for NFL)	8 (8.9)	0 (0.0)	0.102
Use of excessive alcohol, n (%)	49 (51.6)	8 (28.6)	0.032
Use of illicit drugs, n (%)	60 (63.2)	15 (53.6)	0.361
Use of performance enhancing drugs ^a , n (%) (N = 87)	13 (14.9)	0 (0.0)	0.030

^aSample size reduced because of missing data.

SD, standard deviation; AFE, age of first exposure; NFL, National Football League.

developed to be analogous to the University of Pennsylvania Smell Identification Test (UPSIT), and there is a percentile rank for each 5-year age category that is used to identify abnormal olfactory function. As an example, a 45- to 49-year-old male subject with a B-SIT raw score of 8 has an age percentile rank of 4, which is classified as abnormal. In contrast, a 55- to 59-year-old with a B-SIT score of 6 is deemed to be abnormal (age percentile rank of 3). Table 2 provides the age groups of the current sample and corresponding cut-off scores for determining abnormal olfaction. The B-SIT has adequate test-retest reliability ($r = 0.71$)^{57,58} and strong clinical utility in TBI,¹⁶ aging,⁵¹ and neurodegenerative diseases (e.g., AD).⁴⁰

Neuropsychological measures. All subjects completed a neuropsychological test battery as part of DETECT to assess cognitive function in the major domains, including attention, executive function, psychomotor speed, visual and verbal episodic memory, language, motor, and visuospatial functions. All tests are widely used in clinical research settings. The tests demonstrate excellent psychometric properties, including reliability and validity. Raw scores were converted to standardized scores that account for age,

sex, and/or educational attainment. The tests included: Trail Making Test (TMT) Parts A and B⁵⁹; Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span and Digit Symbol Tests⁶⁰; Wisconsin Card Sorting Test⁶¹; Controlled Oral Word Association Test (COWAT)⁶²; Delis-Kaplan Executive Function System Color-Word Interference Test (DKEFS)⁶³; Boston Qualitative Scoring System for the Rey-Osterrieth Complex Figure (ROCF)⁶⁴; Neuropsychological Assessment Battery (NAB) Story Learning Test, List Learning Test, Map Reading Test, and Naming Test⁶⁵; and Animal Fluency.⁶²

Behavioral/mood. Participants completed a range of standardized self-report and semistructured interviews to assess behavior and mood symptoms, including depression, suicidality, hopelessness, apathy, aggression, impulsivity, and hostility. The tests included: Hamilton Depression Rating Scale (HDRS)⁶⁶; Beck Depression Inventory-II (BDI-II)⁶⁷; Center for Epidemiologic Studies Depression Scale (CES-D)⁶⁸; Beck Hopelessness Scale (BHS)⁶⁹; Apathy Evaluation Scale (AES)⁷⁰; Modified Scale for Suicidal Ideation⁷¹; Brown-Goodwin Lifetime History of Aggression⁷²; Buss-Durkee Inventory⁷³; Behavior Rating Inventory of Executive Functioning—Adult Version⁷⁴; and the Barratt Impulsivity Scale (BIS-11).⁷⁵

Statistical analysis

Independent-samples *t*-tests determined differences in B-SIT scores between the former NFL and control groups. Because there was significant difference in the between-group variance, the Satterthwaite approximation was used for the *t*-test group comparison. Receiver operating characteristic (ROC) curves were then conducted to identify the optimal B-SIT cut-off score using the area under the ROC curve and the highest c-statistic value for distinguishing the former NFL group from controls. To examine the association between the B-SIT and behavioral/mood and neuropsychological function in the former NFL players, principal component analysis (PCA) was used to generate factor composite scores using the above-

TABLE 2. B-SIT CUT-OFF SCORES FOR ABNORMAL OLFACTORY FUNCTION BY AGE GROUP (BASED ON DOTY⁵⁶)

Age group ^a	B-SIT raw cutoff score for abnormal function	Age percentile rank
40–44	8	5
45–49	8	4
50–54	8	4
55–59	6	3
60–64	5	3
65–69	4	4

^aOnly age groups relevant to the current sample are presented.

B-SIT, Brief Smell Identification Test.

listed measures—excluding the B-SIT—in order to limit the number of analyses and reduce risk for type 1 error. An iterative method was applied to generate a factor structure that was the most parsimonious and theoretically consistent with *a priori* clinical domains. The following approach was used to determine item retention: 1) Only factors with an eigenvalue >1 were retained; and 2) following a VARIMAX rotation, items with a loading of <0.5 were removed and the PCA was repeated until both criteria were satisfied. Partial correlations adjusting for age and education were performed to investigate the relationship between the B-SIT and each of the factor scores. For all analyses, the significance level was set at an alpha of 0.05.

Results

Brief Smell Identification Test performance and receiver operating curve analyses

Figure 1 shows differences in the mean B-SIT total score between the former NFL players and controls. Independent *t*-tests showed that B-SIT scores were significantly lower in the former NFL players (mean = 10.3; standard deviation [SD] = 1.7) versus the controls (mean = 10.9; SD = 0.9; $t = -2.65$; $p = 0.010$). This effect remained significant after adjusting for age ($p = 0.045$). Of the former NFL players, 6 had B-SIT scores that fell in the clinically abnormal range, whereas no controls had an abnormal B-SIT test score. The ages of the 6 former NFL players with abnormal olfactory function were 40 (B-SIT raw score = 6), 51 (B-SIT raw score = 7), 54 (B-SIT raw score = 5), 54 (B-SIT raw score = 7), 62 (B-SIT raw score = 3), and 67 (B-SIT raw score = 6). They played football for an average of 19.33 (SD = 4.63) years, with an average of 9.33 (SD = 4.27) years in the NFL, and began playing football at the average age of 12.33 (SD = 3.50). Of these 6 subjects, 3 were lineman and 3 were linebackers, and there was a reported median of 87.5 concussions (after being provided with a modern definition of concussion).⁷⁶ The median number of reported concussions in the 89 former NFL players with normal olfactory function was 50

(mean, SD = 645.56, 1999.66). In the overall sample of former NFL players ($N = 95$), all subjects indeed reported a history of recurrent concussions (median = 50). On average, former NFL players reported that 4.63 (SD = 16.45) concussions resulted in LOC of any duration. Among those who reported a history of LOC ($n = 64$), there was an average of 1.70 (SD = 4.01; range, 0–30) concussions that resulted in LOC for greater than 1 min, 0.66 (SD = 1.68; range, 0–10) resulted in LOC for greater than 5 min, and 0.08 (SD = 0.28; range, 0–1) resulted in LOC for greater than 30 min. (Of note, sample size for LOC greater than 1 min was 63, and 62 for LOC greater than 30 min because of missing data.) Bivariate correlations showed that total B-SIT score was not associated with a history of LOC of any duration ($p = 0.988$), LOC for greater than 1 min ($p = 0.655$), or LOC for greater than 5 min ($p = 0.352$). Only 5 subjects reported a history of one concussion that resulted in LOC for greater than 30 min, and independent-sample *t*-test revealed no effect on total B-SIT score ($p = 0.623$). Independent-sample *t*-tests also revealed that there were no significant differences between subjects with normal and abnormal olfactory test performance on number of concussions that resulted in LOC of any duration ($p = 0.528$).

B-SIT scores ranged from 3 to 12 for the former NFL players, and there was minimal variability in the controls (range, 8–12). ROC curve analyses showed a B-SIT cut-off score of 11 maximized accuracy for distinguishing the former NFL players from controls (c-statistic = 0.61; sensitivity = 43%; specificity = 79%). Of note, body mass index (BMI)⁷⁷ and race⁷⁸ have previously been shown to affect olfactory function, but the *t*-test revealed that B-SIT scores were not associated with race (white vs. nonwhite; $p = 0.218$), and bivariate correlations did not show a relationship between the B-SIT and BMI ($p = 0.119$) or years of education ($p = 0.481$) in this sample.

Principal component analysis results

The iterative model selection for PCA revealed a four-factor structure to be the most parsimonious and conceptually consistent with *a priori* and empirically based clinical domains. Table 3 presents the factor domains and the loadings of each neuropsychological input measure. The four factors included: 1) behavioral/mood (HDRS, BHS, CES-D, BDI-II, BIS-11, Brown-Goodwin Lifetime History of Aggression, AES, and the BRIEF—A Behavioral Regulation Index subscale); 2) psychomotor speed/executive function (TMT Parts A and B, WAIS-R Digit Symbol, DKEFS Color Word Inhibition/Switching, and COWAT); 3) verbal memory (NAB Story Learning Phrase Unit—Immediate Recall and Delayed Recall, NAB List Learning—Short and Long Delayed Recall); and 4) visual memory (ROCF Immediate Copy, Presence, & Accuracy, and Delayed Presence & Accuracy). The NFL group had significantly more impaired factor scores than the control group in the behavioral/mood ($t_{(98.82)} = 9.85$; $p < 0.001$) and psychomotor speed/executive function ($t_{(57.125)} = -2.61$; $p = 0.012$) domains, but not the verbal ($p = 0.209$) or visual ($p = 0.102$) memory domains. However, when the tests that make up the factor scores were examined individually, the former NFL players exhibited significantly worse performance, relative to controls, across most of the cognitive and behavioral/mood measures, after controlling for age and education (see Table 4). There was a particularly large difference between groups on TMT Part B, and, in fact, sensitivity analyses showed that when the entire sample was restricted to those who scored below 1 SD on TMT Part B (i.e., T-score <40 ; n for former NFL players = 36 and n for controls = 6), the magnitude in the mean difference on B-SIT scores between former NFL players and controls was much greater (mean difference = 1.75; $p < 0.001$).

FIG. 1. Mean differences in B-SIT total score between the former NFL players and same-age controls. y-axis are B-SIT raw total scores and higher scores reflect better performance. x-axis included the former NFL players ($N = 95$) and same-age controls ($N = 28$). The difference between the former NFL players and age-matched controls is statistically significant ($p = 0.0096$). B-SIT, Brief Smell Identification Test; NFL, National Football League.

TABLE 3. PRINCIPAL COMPONENT ANALYSIS: ROTATED FACTOR STRUCTURE OF NEUROPSYCHOLOGICAL MEASURES

	<i>Behavioral/ mood</i>	<i>Psychomotor speed/executive function</i>	<i>Verbal memory</i>	<i>Visual memory</i>
Trail Making Test Part A Time: T-score	-0.06966	0.68896	0.11117	0.17947
WAIS-R Digit Symbol test: scaled score	-0.19174	0.61329	0.07544	0.07448
Trail Making Test Part B Time: T-score	-0.11986	0.71428	0.10121	0.12156
DKEFS Color-Word Interference Test completion time: scaled score	-0.16786	0.54984	0.22445	-0.00426
Controlled Oral Word Association Test: T-score	0.06384	0.50511	0.18716	0.08994
Boston Qualitative Scoring System for the Rey-Osterrieth Complex Figure Immediate Copy, Presence, & Accuracy: T-score	-0.05440	0.13148	0.18369	0.81557
ROCF Delayed Presence & Accuracy: T-score	-0.09505	0.20317	0.15640	0.82373
NAB Story Learning Immediate Recall: T-score	-0.04022	0.22362	0.81254	0.13459
NAB Story Learning Delayed Recall: T-score	-0.17464	0.28745	0.82580	0.16671
NAB List Learning Short Delay: T-score	-0.00389	0.45680	0.50926	0.40640
NAB List Learning Long Delay: T-score	-0.07493	0.44121	0.53329	0.43803
Hamilton Depression Rating Scale	0.77952	-0.13233	0.08431	-0.05777
Beck Hopelessness Scale	0.75819	-0.12572	0.07391	-0.14549
Barratt Impulsivity Scale	0.78601	-0.07815	-0.13695	0.06050
Beck Depression Inventory-II	0.73543	-0.06734	-0.10622	0.00306
BRIEF Behavioral Regulation Index (BRI): T-score	0.83208	-0.11069	-0.14404	-0.06280
Center for Epidemiologic Studies Depression Scale total score	0.87562	-0.15315	-0.00522	-0.06993
Apathy Evaluation Scale total score	0.81220	-0.15148	-0.08018	-0.13687
Brown-Goodwin Lifetime History of Aggression	0.54647	0.07722	-0.05311	0.04513

Bolded values denote factor loadings >0.5 and define that particular factor.

WAIS-R, Wechsler Adult Intelligence Scale-Revised; DKEFS, Delis Kaplan Executive Function System; ROCF, Rey Osterrieth Complex Figure; NAB, Neuropsychological Assessment Battery; BRIEF, Behavior Rating Inventory of Executive Functioning.

Brief Smell Identification Test and neuropsychological test performance

Partial correlations adjusting for age and education revealed the B-SIT significantly correlated with the behavioral/mood ($r=-0.25$; $p=0.0254$) and psychomotor speed/executive function ($r=0.22$; $p=0.0464$) factor scores in the former NFL players. In each case,

lower B-SIT scores correlated with greater behavioral/mood symptoms and worse psychomotor speed/executive function. Within the behavioral/mood domain, follow-up partial correlations found specific associations between the B-SIT and BHS ($p=0.019$), CES-D ($p=0.054$, marginal significance), and the HDRS ($p=0.017$). Regarding psychomotor speed/executive function, there were significant associations for TMT Part B ($p=0.013$) and Digit Symbol Coding

TABLE 4. NEUROPSYCHOLOGICAL TEST PERFORMANCE IN FORMER NFL PLAYERS AND CONTROLS

	<i>Control Mean (SD)</i>	<i>NFL Mean (SD)</i>	<i>p value</i>
Trails A Time: T-score ^a	54.18 (10.37)	49.01 (11.72)	0.030
Digit Symbol: scaled score ^a	11.71 (2.05)	10.15 (2.03)	0.003
Trails B Time: T-score ^s	52.75 (15.38)	43.77 (15.86)	0.005
DKEFS Inhibition/Switching completion time: scaled score ^c	12.00 (2.68)	10.60 (2.92)	0.078
COWAT: T-score	52.21 (9.80)	48.96 (11.38)	0.197
ROCF Immediate Copy, Presence & Accuracy: T-score	53.39 (7.69)	47.91 (9.93)	0.021
ROCF Delayed Presence & Accuracy: T-score	55.00 (7.88)	48.43 (11.01)	0.006
NAB Phrase Unit (1 & 2) Immediate Recall: T-score	43.00 (10.82)	39.19 (8.45)	0.045
NAB Phrase Unit Delayed Recall: T-score	46.79 (10.12)	41.75 (7.77)	0.006
NAB List A Short Delay: T-score	51.96 (11.99)	44.55 (13.03)	0.014
NAB List A Long Delay: T-score	49.75 (12.88)	41.55 (13.77)	0.010
Hamilton Depression Rating Scale	2.07 (3.04)	9.87 (8.14)	<0.001
Beck Hopelessness Scale ^b	1.32 (2.02)	4.84 (5.67)	0.002
Barratt Impulsivity Scale	49.46 (9.62)	65.38 (15.03)	<0.001
Beck Depression Inventory-II total score ^a	1.93 (3.02)	16.64 (12.14)	<0.001
BRIEF Behavioral Regulation Index (BRI): T-score ^a	46.89 (9.19)	63.45 (13.23)	<0.001
Center for Epidemiologic Studies Depression Scale total score ^a	3.75 (4.20)	21.73 (13.27)	<0.001
Apathy Evaluation Scale total score ^a	24.07 (4.79)	35.87 (10.22)	<0.001
Brown-Goodwin Max Aggression Sum ^a	14.32 (3.29)	18.62 (4.90)	<0.001

Between-group comparisons controlled for age and education.

^aN=94, ^bN=93, and ^cN=91 for former NFL players because of missing data.

NFL, National Football League; DKEFS, Delis Kaplan Executive Function System; ROCF, Rey Osterrieth Complex Figure (administered and scores with the Boston Qualitative Scoring System); NAB, Neuropsychological Assessment Battery; BRIEF, Behavior Rating Inventory of Executive Functioning.

($p=0.017$). The B-SIT was not associated with the verbal ($p=0.7419$) or visual memory ($p=0.1978$) factor composites. B-SIT scores were not associated with any of the factor scores in the controls.

Discussion

Former NFL players are believed to be at risk for long-term clinical impairment attributed to exposure to RHI.^{11–13} The current study is the first to show reduced olfactory function in a sample of former NFL players. It is important to note that a majority of the former NFL players (all but 6) fell within the normal range on the B-SIT, and our findings only show that olfactory test scores in former NFL players are lower compared to controls and not necessarily more impaired. We operationalized olfactory function using the total score from the B-SIT and found that a cut-off score of 11 had the highest overall accuracy and specificity for discriminating the former NFL players from age-matched controls. The B-SIT total score also correlated with reported mood symptoms and neuropsychological performance on measures of psychomotor speed/executive function in the former NFL players.

Recurrent blows to the head have been previously associated with acute olfactory deficits in a sample of active boxers,²⁸ and our findings raise the possibility that RHI may lead to long-term changes in olfaction. Helmet accelerometer research suggests that college football players can average >1000 subconcussive events per season.^{1–4} A single mTBI is associated with impaired olfaction that may involve contortion of the olfactory nerve and/or direct injury to the olfactory system (e.g., olfactory bulb in the ventral part of the frontal lobe or olfactory cortex structures, such as the frontal lobe base or MTL).^{17,19–23,26,27,29,79,80} In particular, in TBI (including mild), traumatic lesions in the frontal lobe in general, and the basal frontal lobe in particular, result in lower odor identification test scores relative to lesions anywhere else in the brain.^{21,79–81} The longitudinal effects of a single mTBI/concussion on olfaction are unclear because of the lack of prospective studies. However, it is noted that most head impacts in football occur at the front of the head⁸² and RHI can lead to long-term structural and functional brain changes to olfactory structures, including the OFC, anterior corpus callosum, and MTL, and former NFL players have been shown to exhibit fMRI activation impairment of the frontal lobe, as well as hippocampal atrophy.^{31–37} Future work that examines neuroimaging correlates (e.g., olfactory bulb volume) of olfactory test performance in former NFL players is needed to clarify the neurological underpinnings of our findings. Prospective studies that correlate *in vivo*, comprehensive olfactory testing with post-mortem neuropathological examination of olfaction structures will also be informative.

Lower olfactory test scores were associated with greater reported depressive symptoms, as well as reduced neuropsychological test performance on measures of psychomotor speed/executive function, in this sample of former NFL players. The frontal lobe and subcortical structures (e.g., MTL) play a key role in the modulation of olfaction, and this neural circuitry mediates executive and mood functions (e.g., depression).^{83,84} Diffuse injury to axons projecting to and from frontal and temporal lobe brain regions is common in the setting of TBI (see Chong and colleagues for a review⁸⁵). Research in former NFL players that has used functional and structural MRI shows that activation impairment and microstructural dysintegrity in aspects of the frontal lobe correlates with executive dysfunction and depressive symptoms, respectively.^{39,86} These findings are noteworthy in the context of

recent work that provided class III evidence for the B-SIT in predicting frontal lobe injury with 100% specificity.⁸⁰ Given the 79% specificity for the B-SIT cutoff of 11 and the association between the B-SIT and clinical measures in this sample, the B-SIT may be a brief, inexpensive tool to facilitate detection of short- and long-term neurological impairment associated with RHI exposure.

Although RHI is a necessary (but not sufficient) feature of CTE,^{7–9} CTE cannot currently be diagnosed during life and it is unknown whether any of the subjects from this study have CTE. CTE is well documented in former NFL players who agreed to brain donation,⁷ and the current sample is presumably at high risk for CTE. As such, there is reason to speculate that olfactory loss in the present sample could be related to CTE. CTE is pathologically characterized by an irregular deposition of perivascular p-tau at the sulcal depths.^{7,8} Tau aggregation and other pathology (e.g., atrophy and axonopathy) is common in olfactory tracts and brain regions, including the MTL and frontal lobes in CTE, and in the advanced stages, there is tau accumulation in the olfactory bulbs.^{7,8} Olfactory loss is typical and an early pathological sign of other tauopathies, such as AD, that may involve tau deposition in the olfactory system, including the hippocampus.^{40–43} *In vivo* evidence links worse olfaction with decreased hippocampal volume, and thinner entorhinal cortex in pre-clinical AD,⁴⁵ and white matter dysintegrity in olfactory tracts and decreased metabolic activity in olfactory cortex structures in mild cognitive impairment.⁸⁷ Olfactory tests predict AD clinical progression and have thus been suggested to be useful in the early detection of AD.^{47,88} A similar phenomenon may be evident in CTE, as is supported by the current association between the B-SIT and depressive symptoms and reduced executive function—core clinical features of CTE that may involve frontal and MTL pathological changes.^{7–10} Moreover, the magnitude in the difference on the B-SIT between former NFL players and controls became much larger when the sample was restricted to those with reduced executive function (i.e., TMT Part B T-score <40). Given that a majority of the B-SIT olfactory scores in the former NFL group fell within the normal range, it is plausible that olfactory function may be an early marker of CTE-related neurodegeneration, analogous to AD.⁴⁵ Much more research is needed to empirically test the relationship between olfaction and CTE, including: 1) future studies that examine the association between olfaction tests and proposed clinical research criteria for CTE (i.e., traumatic encephalopathy syndrome¹⁰) and 2) clinicopathological correlation research in autopsy confirmed CTE cases.

The current findings are limited in several ways. We only examined former professional football players, reducing generalizability to individuals who only played football through high school or college, or to former athletes who played other contact sports. The cross-sectional nature of this study limits any causal inferences, and prospective studies that administer serial tests of olfaction before and after RHI exposure will improve understanding on the relationship between RHI exposure and olfaction. The former NFL players reported numerous recurrent concussions throughout their lifetime, as would be expected in this high exposure to RHI population, and prospective studies would allow for determination of a possible threshold of head impacts necessary to disturb olfactory function. Notably, if the lower olfactory test scores in the former NFL players are related to CTE, it is also possible that this may be a reflection of disease progression and not necessarily associated with RHI; that is, RHI is necessary for CTE risk, but its role in the pathological progression of the disease is unclear. The magnitude of mean difference in B-SIT scores between former NFL players and controls was modest; however, the former NFL players had

significantly more variability in scores with a subset demonstrating severe olfactory dysfunction (which was not observed in controls). Moreover, the magnitude increased when restricting the sample to those with reduced cognitive status. In addition, the B-SIT is a brief, 12-item crude measure of olfactory function and may have lacked overall sensitivity to olfactory impairment in this sample. Overall, the clinical significance of the current findings remains to be determined by future work with larger sample sizes that uses more-comprehensive and -sensitive tests of olfaction, such as the 40-item UPSIT, that have been shown to have robust clinical utility in AD⁸⁹ and TBI.⁹⁰ History of sinonasal disease (e.g., allergic rhinitis) was unknown in this sample and therefore presenting as a possible confound of the current results. We did not examine specific olfactory functions (e.g., discrimination or threshold), and this needs to be the target of future work given that specific olfactory impairments could be associated with distinct neurological deficits.⁹¹

Finally, the recruitment methodology of former NFL players and controls in the current study was intended to isolate RHI exposure and identify a sample of subjects at high risk for CTE. In particular, the former NFL players were required to have reported cognitive, behavioral, and mood symptoms for 6 months preceding the time of study entry, and this was not part of the inclusion criteria for the controls. It is plausible that other neurological conditions may account for the current study findings. Of note, it is unlikely to be AD because of the relatively young age of the sample. Once biomarkers for CTE are identified and validated, it will be critical for future work to replicate the current study, and also compare olfactory test performance in subjects with “probable CTE” and other neurodegenerative diseases (e.g., AD and frontotemporal dementia), as well as larger cognitively healthy control groups.

Conclusions

Former NFL players exhibited lower scores on the B-SIT relative to same-age controls, and worse olfaction was correlated with depressive symptoms and psychomotor speed/executive function. Longitudinal studies, including *in vivo* neuroimaging, and possibly post-mortem neuropathological examination, that use more-comprehensive tests of olfactory function are needed to better understand the relationship between RHI exposure, olfaction, and pathology, as well as determine whether odor identification tests can facilitate early detection of long-term neurological impairment associated with RHI exposure.

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