Age at First Exposure to Repetitive Head Impacts Is Associated with Smaller Thalamic Volumes in Former Professional American Football Players

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Abstract

Thalamic atrophy has been associated with exposure to repetitive head impacts (RHI) in professional fighters. The aim of this study is to investigate whether or not age at first exposure (AFE) to RHI is associated with thalamic volume in symptomatic former National Football League (NFL) players at risk for chronic traumatic encephalopathy (CTE). Eighty-six symptomatic former NFL players (mean age = 54.9 ± 7.9 years) were included. T1-weighted data were acquired on a 3T magnetic resonance imager, and thalamic volumes were derived using FreeSurfer. Mood and behavior, psychomotor speed, and visual and verbal memory were assessed. The association between thalamic volume and AFE to playing football and to number of years playing was calculated. Decreased thalamic volume was associated with more years of play (left: $p=0.03$; right: $p=0.03$). Younger AFE was associated with decreased right thalamic volume ($p=0.014$). This association remained significant after adjusting for total years of play. Decreased left thalamic volume was associated with worse visual memory ($p=0.014$), whereas increased right thalamic volume was associated with fewer mood and behavior symptoms ($p=0.003$). In our sample of symptomatic former NFL players at risk for CTE, total years of play and AFE were associated with decreased thalamic volume. The effect of AFE on right thalamic volume was almost twice as strong as the effect of total years of play. Our findings confirm previous reports of an association between thalamic volume and exposure to RHI. They suggest further that younger AFE may result in smaller thalamic volume later in life.

Keywords: age at first exposure; chronic traumatic encephalopathy; repetitive head impacts; sports-related head injury; thalamus

Introduction

AMERICAN FOOTBALL accounts for a high exposure to repetitive head impacts (RHI). During a single game, players may experience as many as 86 head impacts.¹ Chronic traumatic

encephalopathy (CTE) is a neurodegenerative disease that has been associated with exposure to RHI.^{2–5} Moreover, most of the pathologically confirmed cases of CTE have had a history of exposure to RHI, making RHI exposure a likely but not sufficient cause of CTE (for review, see ⁶). Of further note, the clinical presentation of

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CTE is not well understood.⁷⁻⁹ Next-of-kin interviews and medical record reviews of deceased males with neuropathologically confirmed CTE suggest that CTE presents with impaired behavior (e.g., impulsivity, physical and verbal aggression), mood (e.g., depression, apathy, and related symptoms), and cognition (e.g., memory and executive dysfunction, and eventual dementia).⁹ To date, CTE can only be diagnosed post-mortem. Thus, the development of biomarkers to support CTE diagnosis during life and the identification of contributing risk factors for the development of CTE are critical for early disease detection.⁸

In a study of neuropathologically confirmed cases of CTE in former football players, there was a significant association between total years playing and severity of post-mortem tau pathology.¹⁰ In another study of living former National Football League (NFL) players, greater estimated cumulative RHI exposure (based, in part, on the total number of years played) was correlated with higher levels of later-life plasma tau.¹¹ A study of former high school and college football players demonstrated a dose-response relationship between estimated RHI exposure and risk of later-life impairments in mood, behavior, and cognition.¹²

There is evidence that not only exposure to RHI but also younger age at first exposure (AFE) may be an important risk factor for brain alterations in symptomatic former NFL players.^{13,14} Stamm and associates^{13,14} were the first to show the effect of AFE with playing football. Younger AFE (i.e., less than age 12) was associated with pronounced white matter alterations in the corpus callosum¹⁴ as well as increased later-life cognitive impairment.¹³ This vulnerability to RHI in children and adolescents may be linked closely to critical periods of brain development.^{15,16} Despite the growing concern about long-term consequences of early exposure to RHI, however, 4.9 million youth athletes are participating currently in football in the United States.^{17,18}

The thalamus is a central subcortical structure involved in the majority of cortex-controlled processes and pathways (for review see¹⁹). It is considered to be a key structure in cortical communication via nonreciprocal cortico-thalamo-cortical pathways, thereby providing an important hub for a dense flow of information between cortical areas.²⁰⁻²² Its prominent and distinctive position in the center of the brain along with strong connections to all parts of the cortex, as well as to numerous subcortical networks,²⁰ makes it a particularly important structure. Regional brain atrophy has been described in the thalamus and structures of the limbic system in CTE.^{3,7,23} To date, however, only one study has investigated the association between thalamic volume and exposure to RHI.²⁴ In that study, Bernick and colleagues²⁴ examined 224 professional fighters using magnetic resonance imaging (MRI) and neuropsychological testing. Their results showed an association between decreased thalamic volume and two measures of exposure to RHI; total number of professional fights and years of professional fighting. In addition, the study reported an association between slower processing speed and smaller thalamic volumes.²⁴

To what extent these findings are generalizable to athletes exposed to RHI while participating in contact sports other than professional fighting remains to be elucidated. Because the thalamus is a key structure in numerous functional networks,²⁵ whether and to what extent neurocognitive and behavioral function might be associated with thalamic volume warrants further investigation. To date, the relationship between RHI exposure, including the age when exposure begins, and thalamic volume in former professional football players has not been described. The age of first exposure is of particular public health interest given that far more youth athletes participate in football than those age 18 and older.¹⁸ This

study examined thalamic volume and its association with AFE, total years of play, as well as associations with neurobehavioral functioning, in symptomatic former professional football players.

Methods

This study was part of the Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests (DETECT) project, funded by the National Institutes of Health (R01 NS 078337). The main goal of this project is to develop biomarkers for the *in vivo* diagnosis of CTE. Details of this project and its protocol are described elsewhere.^{11,14,26,27} The study and related procedures were approved by the Boston University Medical Center Institutional Review Board and by the Partners Institutional Review Board. Written informed consent was obtained from all participants before enrollment.

Participants

Ninety-six former professional football players were included in the DETECT project. Study participants met the following inclusion criteria based on the DETECT study protocol: male, 40–69 years of age and a minimum of 12 years of organized football experience with at least two years of active participation in the NFL. Moreover, all participants had complaints of cognitive, mood, and behavioral symptoms for at least six months before participation, based on self-report. Potential participants with contraindications for MRI or lumbar puncture, history or diagnosis of any central nervous system disease, and English as a second language were excluded.

As part of DETECT, participants underwent a comprehensive assessment that included neurological as well as psychiatric examination, neuropsychological testing, standardized mood and behavior questionnaires, neuroimaging, a lumbar puncture for cerebrospinal fluid analysis, and genetic testing. The present study examines only imaging data and neuropsychological and mood and behavior measures.

Among the 96 enrolled subjects, 10 participants were excluded because of missing T1-weighted MRI data or poor data quality. Thus, a final sample size of 86 former NFL players was analyzed in this study (mean age: 54.9 ± 7.9 years). For 75 former NFL players, both neurobehavioral and imaging data were available.

Exposure variables

The AFE and total years of play. The age participants started playing organized tackle football and the total number of years they played tackle football were reported. Both were treated as continuous variables.

MRI data acquisition

All neuroimaging data were acquired on a 3-Tesla MRI Scanner (Verio, Siemens Healthcare, Erlangen, Germany) with a 32-channel head array and the Syngo MR-B17 software suite. We acquired neuroimaging data on the 3-Tesla MRI Scanner with a 32-channel head array and the Syngo MR-B17 software suite. T1-weighted images were acquired with a three dimensional magnetization-prepared-rapid-gradient-echo sequence (MPRAGE): repetition time (TR)=1800 msec, echo time (TE)=3.36 msec, voxel size= $1 \times 1 \times 1$ mm³, acquisition matrix=256×256, flip angle=7 degrees.

Image processing

Image data format was converted from DICOM to Nifti and visually inspected for quality. T1-weighted images were aligned and centered. Afterward, the T1-weighted images were automatically segmented using FreeSurfer 5.3 (<http://surfer.nmr.mgh.harvard.edu/>, Athinoula A. Martinos Center for Biomedical

Imaging, Charlestown, MA) resulting in a segmentation of the deep gray matter structures (including the thalamus) as well as a parcellation of the cortex.^{28–30} The quality of the obtained FreeSurfer segmentation and parcellation was then visually assessed. An estimated total intracranial volume was automatically calculated for each participant using FreeSurfer. Finally, bilateral thalamic volume was calculated based on the FreeSurfer label maps of the thalamus in each hemisphere (Fig. 1).

Neurobehavioral outcomes: cognition, mood, and behavior

A set of standardized assessments was administered to examine cognitive function as well as mood and behavior.

Cognitive function. Participants completed the following measures of cognition: Trail Making Test A and B (TMT)³¹; Digit Symbol Coding from the Wechsler Adult Intelligence Scale - Revised (WAIS-R)³²; Digit Span from the WAIS - R³²; Wisconsin Card Sorting Test³³; Animal Naming,³⁰ Controlled Oral Word Association Test (COWAT)³⁴; Color-Word Interference Subtest from the Delis-Kaplan Executive Function System (DKEFS)³⁵; Boston Qualitative Scoring System (BQSS) for the Rey-Osterrieth Complex Figure (ROCF)³⁶; and the Story Learning, List Learning, Map Reading, and Naming Tests from the Neuropsychological Assessment Battery (NAB).³⁷ All tests were administered by a trained research assistant under the supervision of a licensed clinical neuropsychologist. All tests were double-scored by a second trained research assistant.

Mood and behavior. The following self-report measures were used to assess mood and behavior: Apathy Evaluation Scale (AES),³⁸ Barratt Impulsivity Scale (BIS-11),³⁹ Beck Depression

Inventory II (BDI-II),⁴⁰ Beck Hopelessness Scale (BHS),⁴¹ Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A),⁴² Brown-Goodwin Lifetime History of Aggression (LHA),⁴³ Center for Epidemiologic Studies - Depression Scale (CES-D),⁴⁴ and the Buss-Durkee Inventory.⁴⁵ The Hamilton Depression Rating Scale (HDRS)⁴⁶ and the Modified Scale for Suicidal Ideation⁴⁷ were administered using a semi-structured interview by either a licensed psychiatrist or clinical psychologist.

Raw data from the neurobehavioral measures were converted to age-, gender-, and education-corrected standardized scores, when available. Next, on the basis of conceptual and empirical grounds, we generated four factor scores from the outcome measures using principal component analyses. Alosco and coworkers⁴⁸ provide a detailed account of our method for creating these factors. The factors and their constituent measures are as follows: Factor 1—Mood and Behavior: AES, BDI-II, BHS, BIS-11, BRIEF-A Behavioral Regulation Index, CES-D, HDRS, LHA; Factor 2—Attention and Psychomotor Speed: COWAT, DKEFS Color Word Interference (Inhibition/Switching score), TMT A and B, and Digit Symbol; Factor 3—Verbal Memory: NAB Story Learning (Phrase Unit Immediate and Delayed Recall scores) and NAB List Learning (Short and Long Delayed Recall scores); and Factor 4—Visual Memory: BQSS (Immediate Presence and Accuracy, and Delayed Presence and Accuracy scores).

Statistical analyses

We used Statistical Analysis System (SAS version 9.4; SAS Institute Inc., North Carolina) for all statistical analyses. Results of our inferential tests with a *p* value below 0.05 were reported as statistically significant. Both the mixed effects regression analyses exploring the relation between volume and exposure as well as the analyses investigating the association between volume and neurobehavioral factor scores were controlled for age, body mass index (BMI), and estimated total intracranial volume, adjusting for correlation of bilateral regions of interest. Moreover, the analyses exploring the relation between AFE and volume were adjusted for total years of play. Therefore, all presented results account for the positive relationship between AFE and total years of play.

To minimize variance, we employed a bootstrapping method.⁴⁹ Specifically, we resampled 500 replicates with replacement, each with a size equal to the original sample, and we reran the mixed effect-regression model across all replicates. The resulting confidence intervals were calculated using bias-adjustment correction.⁵⁰ We used the Mahalanobis distance to identify any extreme observations, but no outliers were found. Further, the variance was not found to increase with AFE. Similarly, we explored the associations between volume and the standardized neurobehavioral factor scores using mixed-effects regression models for all 75 participants with complete neurobehavioral and imaging data. We also computed partial correlations, adjusting for age, BMI, estimated total intracranial volume, and years of education.

Results

Table 1 summarizes the demographic and clinical characteristics of the sample. Mean age was 54.9 (standard deviation [SD]=7.9) years. The AFE ranged from six to 17 years (mean: 11.8 years, SD=2.6). The number of total years played ranged from 12 to 26 years (mean: 18.4 years, SD=3.4).

Right and left thalamic volume was negatively correlated with total years of play (left, *p*=0.012; right, *p*=0.03; Table 2). The longer the time athletes actively participated in football, the smaller the thalamus. The right thalamus was on average 38.6 mm³ and the left thalamus was on average 53.2 mm³ smaller for every year of play. Right thalamic volume was associated with AFE after adjusting for total years of play (*p*=0.014). Here, the younger the athlete's age

FIG. 1. A three-dimensional reconstruction of the thalamus as region of interest. The model was created from one randomly selected person using the model maker module of Slicer 4.5. Blue = thalamus. The model is shown from four different views on a para-mid axial, sagittal, and coronal slice and is superimposed on the individual T1-weighted image. The label map as basis for the three-dimensional model was not modified for the image creation.

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

	Former professional football players (n = 86)
	Mean (SD)
Age	54.86 (7.91)
AFE	11.77 (2.60)
Total years of play	18.41 (3.42)
Years of education	16.43 (0.96)
Body mass index	32.91 (4.96)
No. of concussions*	123.10 (580.00)
No. times lost consciousness	4.49 (16.50)

SD, standard deviation; AFE, age at first exposure.

*Based on self-report following being given a modern definition of concussion, as reported previously.^{78,79}

when he started playing tackle football, the smaller his thalamic volume. In fact, AFE had a greater impact on thalamic volumes than did total years of play. That is, for every year a participant started playing earlier, the average decrease in thalamic volume was 64.9 mm³ (Fig. 2). In contrast, there was no significant association between left thalamic volume and AFE ($p = 0.872$).

The relationships between the neurobehavioral factor scores and thalamic volume are presented in Table 3. A significant positive correlation was found between left thalamic volume and visual memory ($r = 0.28$, $p = 0.0143$). The smaller the left thalamus, the worse the individual's visual memory performance. Right thalamic volume was positively associated with mood and behavior—i.e., the worse the mood and behavioral symptoms, the larger the right thalamic volume ($r = 0.34$, $p = 0.0029$).

Discussion

The purpose of this study was to investigate the effect of exposure to repetitive concussive and subconcussive head impacts on thalamic volume, as well as the association between thalamic volume and neurobehavioral function in a group of symptomatic former professional football players, ages 40 to 69. Our results show that the longer an athlete participated in football and the younger he was when he began playing, the smaller the thalamic volume. Of note, the effect of the AFE to tackle football on right thalamic volume was almost twice as strong as the effect of total years of play.

The reasons for this loss in thalamic volume remain uncertain, although they might represent a manifestation of direct traumatic brain injury-associated pathology (including diffuse axonal injury-associated wallerian degeneration) or of neuroinflammatory and/or neurodegenerative pathologies.^{51,52} Future studies are needed to investigate these potential mechanisms further.

FIG. 2. Displays significant associations between exposure variables and right thalamic volume. (A) Association between age at first exposure (AFE) to football adjusted for total years of play and absolute right thalamic volume. (B) Relation between total years of play and absolute right thalamic volume.

Thalamic volume and exposure to RHI

Volume reduction in the thalamus has been reported in a variety of psychiatric and neurological disorders such as depression,⁵³ schizophrenia,⁵⁴ substance use disorder,⁵⁵ and in prodromal and later stages of Alzheimer disease.^{56,57} Decreased thalamic volume has been reported in neuropathologically confirmed cases of CTE, which, in turn, was associated with a history of exposure to RHI.³ Results from this study also confirm the literature on living athletes, where there is an association between decreased thalamic volume and concussion⁵⁸ and exposure to RHI.²⁴ More specifically, the study by Bernick and associates²⁴ of active professional fighters suggests that exposure to more fights is associated with decreased bilateral thalamic volumes. In fighters, thalamic volume decreased

TABLE 2. THALAMIC VOLUMES AND EXPOSURE

Volume	Exposure	Mean	Bias	Lower bound	Upper bound	p value
Left thalamus	Total years of play	-53.2477	1.76261	-105.235	-7.80051	0.012
	AFE adjusted for total years of play	55.4455	0.80439	-62.3679	141.501	0.872
Right thalamus	Total years of play	-38.5831	0.44464	-86.486	-0.2263	0.03
	AFE adjusted for total years of play	64.9266	0.072667	2.2071	118.462	0.014

Bold indicates <0.05 .

AFE, age at first exposure.

TABLE 3. THALAMIC VOLUMES AND NEUROBEHAVIORAL FACTOR SCORES

	Left			Right		
	Partial correlation	t value	p value	Partial correlation	t value	p value
Factor 1: mood and behavior	0.14	1.23	0.2208	0.34	3.08	0.0029
Factor 2: attention/psychomotor speed	-0.03	-0.22	0.8245	-0.04	-0.34	0.7321
Factor 3: verbal memory	-0.19	-1.71	0.0912	-0.05	-0.4	0.6888
Factor 4: visual memory	0.28	2.51	0.0143	0.16	1.36	0.1777

Bold indicates <0.05.

by 0.4% (right) and 0.3% (left) with each fight.²⁴ In a more recent study from the same group, Banks and colleagues⁵⁹ continued to find a statistically significant relationship between greater exposure and smaller thalamic volume. Moreover, apolipoprotein E genotype status did not impact this relationship.

Although linear head accelerations sustained during professional football are lower (60g)⁶⁰ than those sustained during boxing (71g)⁶¹ and although exposure to RHI may vary between player positions in football,¹ our results are consistent with the aforementioned study in that exposure to RHI is associated with reduced thalamic volume. More specifically, total years of playing football were associated with a decrease in volume of 53.2 mm³ in the left and 38.6 mm³ in the right thalamus, per year of RHI exposure.

Thalamic volume and AFE

This is the first study showing that AFE to RHI in tackle football has an impact on subcortical gray matter volume. We found that younger AFE to playing tackle football was associated with a smaller right thalamic volume. In a previous study of the DETECT sample, younger AFE was associated with structural alterations in the corpus callosum.¹⁴ In another study, younger AFE was associated with increased later-life cognitive impairment.¹³ These results suggest that RHI may have a greater impact on the developing brain than on the mature brain.

Another study investigating AFE did not find significant results between RHI and brain structural changes. This study, however, examined brain structures that were not specific to developmental trajectories, and half of the sample did not play any youth football or played only one year of youth football.⁶² Previous studies have also shown that age has a major influence on recovery from concussion, with adolescents experiencing more severe⁶³ and prolonged post-concussive deficits in visual and verbal memory^{63–65} compared with adults.

This vulnerability to brain injury may be linked closely to a critical period of brain development and maturation during puberty. In fact, adolescence is considered a key period for brain maturation.¹⁶ Important processes for proper brain development occurring during puberty are possibly selective and involve competitive elimination processes.^{66,67} These processes include the downsizing of synapses, gray matter volume, glucose use, and neurotransmitter receptor densities.⁶⁸ The exact functional significance of these elimination patterns is unknown. They likely play a role in cortical plasticity necessary for accommodating to environmental needs that are crucial for brain maturation, however.^{66,67} Moreover, these developmental processes do not occur uniformly.^{68,69} In fact, maturation of the cerebral cortex seems to follow a hetero-chronic pattern that shows regional variation.^{16,68–70} This means that age of onset for these processes likely vary between brain structures, re-

sulting in a period of several years during adolescence in which the brain may be particularly vulnerable to external insults.⁷¹

Earlier age for starting to play football could be linked possibly to more years of play and thus have driven the results. It is therefore noteworthy that the association between thalamic volume and AFE remained significant when adjusting for total years of play. In fact, the effect of AFE on right thalamic volume was almost double the effect of total years of play with a decrease of 64.9 mm³ for every year athletes had started playing earlier and a decrease of 38.6 mm³ for every year athletes had played longer. The significant association between AFE and thalamic volume emphasizes that every year of difference in AFE accounts for reduced thalamic volume later in life.

Previous studies^{13,14} report AFE below age 12 to be significantly associated with increased impairment and structural brain alterations. The linear relationship found here, however, does not contradict a threshold at a certain age as found in previous studies.^{13,14} This difference with previous results may be explained by the high between-subject variability in thalamic volume, which decreases power to detect significant thresholds at a certain age. It could also be because of differing neurodevelopmental trajectories in the investigated brain regions. For example, Brown and coworkers⁷¹ showed that the thalamus increases in volume until the age of 17.8 years with a plateau reached at around age 20, whereas another subcortical gray matter structure, the hippocampus, already peaked by 14.2 years and decreased in volume thereafter.⁷¹ These examples demonstrate the importance of taking into account the developmental trajectory of the structure and/or function being studied with regard to AFE.

Importantly, only the right thalamus seemed to be affected by AFE. A possible explanation here is the difference in development between the two hemispheres. The left hemisphere has a peak developmental time approximately between age three and six, whereas the right hemisphere has a growth spurt between age eight and 10.⁷² The latter is much more likely to reflect interference in neurodevelopmental processes as children begin playing football closer in age to this growth spurt than to that of the left hemisphere (mean AFE was 11.8 years in our study cohort).

Thalamic volume and neurobehavioral functioning

This study also revealed a significant association between decreased left thalamic volume and worse visual memory performance. This observation is consistent with a previous report by Konstantinou and colleagues⁷³ who examined 17 male patients after an average of 8.36 years of moderate to severe traumatic brain injury. They used neuroimaging as well as a neuropsychological testing battery to investigate the relation between structural brain alterations and neurocognitive outcome measures. Smaller thalamic volumes correlated with lower scores in visual memory, as assessed

with the ROCF (the same test used in our study), as well as with all other neurocognitive measures. Thalamic pathology has also been implicated in early memory loss in neurodegenerative disorders, including Alzheimer's disease.⁷⁴ It is not clear, however, why there was only a relationship between thalamic volume and visual but not verbal memory.

Mood and behavior were positively correlated with right thalamic volume, meaning that the larger the thalamic volume, the worse the reported mood and behavioral symptoms. It is noteworthy that larger right thalamic volume has been found in medication-naïve depressive patients⁷⁵ and that a decrease in thalamic volumes has been associated with successful antidepressant treatment.⁷⁶ Thus, our finding of an association between right thalamic volume and worse mood and behavioral symptoms may reflect the previously described relationship between thalamic volume and depressive symptoms. Future studies are nonetheless needed to further investigate this association.

Limitations

The cross-sectional study design precluded a more definitive link between RHI and thalamic volume as well as the establishment of causality between AFE and thalamic atrophy. Future studies should include a longitudinal design to understand better RHI-related brain changes as well as neurobehavioral changes. Moreover, future studies should investigate anatomical subsegments of the thalamus separately. Another limitation of this study is the lack of a comparison group of asymptomatic former professional football players. Based on the study design that only symptomatic former professional football players were included in DETECT, the results presented here are not generalizable to asymptomatic former professional football players or football players who did not compete at a professional level.

A further limitation of our study is that our findings are not generalizable to football players who did not compete at a professional level. The results may also not generalize to other groups frequently exposed to RHI. Future studies should include asymptomatic former professional football players as well as male and female athletes participating in different levels of intensity and in different contact sports. Finally, without post-mortem analysis, it is not possible to determine whether or not our findings are specifically related to the tauopathy of CTE or to other long-term consequences of RHI—e.g., among the reasons for a smaller thalamic volume may be exposure to RHI (i.e., microgliosis⁷⁷).

Conclusion

Younger AFE and duration of exposure to RHI are associated with smaller thalamic volume in symptomatic former professional football players, a population at increased risk for the development of CTE. Smaller thalamic volume is also associated with worse performance in visual memory tasks. Longitudinal studies are needed to confirm these findings as well as to examine the association between neurodevelopmental processes and exposure to RHI.

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References

1. Crisco, J.J., Fiore, R., Beckwith, J.G., Chu, J.J., Brolinson, P.G., Duma, S., McAllister, T.W., Duhaime, A.C., and Greenwald, R.M. (2010). Frequency and location of head impact exposures in individual collegiate football players. *J. Athl. Train.* 45, 549–559.
2. Lenihan, M.W., and Jordan, B.D. (2015). The clinical presentation of chronic traumatic encephalopathy. *Curr. Neurol. Neurosci. Rep.* 15, 23.
3. McKee, A.C., Cantu, R.C., Nowinski, C.J., Hedley-Whyte, E.T., Gavett, B.E., Budson, A.E., Santini, V.E., Lee, H.S., Kubilus, C.A., and Stern, R.A. (2009). Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J. Neuropathol. Exp. Neurol.* 68, 709–735.
4. Mez, J., Stern, R.A., and McKee, A.C. (2013). Chronic traumatic encephalopathy: where are we and where are we going? *Curr. Neurol. Neurosci. Rep.* 13, 407.
5. Ling, H., Morris, H.R., Neal, J.W., Lees, A.J., Hardy, J., Holton, J.L., Revesz, T., and Williams, D.D. (2017). Mixed pathologies including chronic traumatic encephalopathy account for dementia in retired association football (soccer) players. *Acta Neuropathol.* 133, 337–352.
6. Baugh, C.M., Stamm, J.M., Riley, D.O., Gavett, B.E., Shenton, M.E., Lin, A., Nowinski, C.J., Cantu, R.C., McKee, A.C., and Stern, R.A. (2012). Chronic traumatic encephalopathy: neurodegeneration following repetitive concussive and subconcussive brain trauma. *Brain Imaging Behav.* 6, 244–254.
7. McKee, A.C., Stern, R.A., Nowinski, C.J., Stein, T.D., Alvarez, V.E., Daneshvar, D.H., Lee, H.S., Wojtowicz, S.M., Hall, G., Baugh, C.M., Riley, D.O., Kubilus, C.A., Cormier, K.A., Jacobs, M.A., Martin, B.R., Abraham, C.R., Ikezu, T., Reichard, R.R., Wolozin, B.L., Budson, A.E., Goldstein, L.E., Kowall, N.W., and Cantu, R.C. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain* 136, 43–64.
8. Montenigro, P.H., Baugh, C.M., Daneshvar, D.H., Mez, J., Budson, A.E., Au, R., Katz, D.I., Cantu, R.C., and Stern, R.A. (2014). Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. *Alzheimers Res. Ther.* 6, 68.
9. Stern, R.A., Daneshvar, D.H., Baugh, C.M., Seichepine, D.R., Montenigro, P.H., Riley, D.O., Fritts, N.G., Stamm, J.M., Robbins, C.A., McHale, L., Simkin, I., Stein, T.D., Alvarez, V.E., Goldstein, L.E., Budson, A.E., Kowall, N.W., Nowinski, C.J., Cantu, R.C., and McKee, A.C. (2013). Clinical presentation of chronic traumatic encephalopathy. *Neurology* 81, 1122–1129.
10. Cherry, J.D., Tripodis, Y., Alvarez, V.E., Huber, B., Kiernan, P.T., Daneshvar, D.H., Mez, J., Montenigro, P.H., Solomon, T.M., Alosco, M.L., Stern, R.A., McKee, A.C., and Stein, T.D. (2016). Microglial neuroinflammation contributes to tau accumulation in chronic traumatic encephalopathy. *Acta Neuropathol. Commun.* 4, 112.

11. Alosco, M.L., Tripodis, Y., Jarnagin, J., Baugh, C.M., Martin, B., Chaisson, C.E., Estochen, N., Song, L., Cantu, R.C., Jeromin, A., and Stern, R.A. (2017). Repetitive head impact exposure and later-life plasma total tau in former National Football League players. *Alzheimers Dement. (Amst)* 7, 33–40.
12. Montenegro, P.H., Alosco, M.L., Martin, B.M., Daneshvar, D.H., Mez, J., Chaisson, C.E., Nowinski, C.J., Au, R., McKee, A.C., Cantu, R.C., McClean, M.D., Stern, R.A., and Tripodis, Y. (2017). Cumulative head impact exposure predicts later-life depression, apathy, executive dysfunction, and cognitive impairment in former high school and college football players. *J. Neurotrauma* 34, 328–340.
13. Stamm, J.M., Bourlas, A.P., Baugh, C.M., Fritts, N.G., Daneshvar, D.H., Martin, B.M., McClean, M.D., Tripodis, Y., and Stern, R.A. (2015). Age of first exposure to football and later-life cognitive impairment in former NFL players. *Neurology* 84, 1114–1120.
14. Stamm, J.M., Koerte, I.K., Muehlmann, M., Pasternak, O., Bourlas, A.P., Baugh, C.M., Giverc, M.Y., Zhu, A., Coleman, M.J., Bouix, S., Fritts, N.G., Martin, B.M., Chaisson, C., McClean, M.D., Lin, A.P., Cantu, R.C., Tripodis, Y., Stern, R.A., and Shenton, M.E. (2015). Age at first exposure to football is associated with altered corpus callosum white matter microstructure in former professional football players. *J. Neurotrauma* 32, 1768–1776.
15. Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., Paus, T., Evans, A.C., and Rapoport, J.L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nat. Neurosci.* 2, 861–863.
16. Lebel, C., Walker, L., Leemans, A., Phillips, L., and Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *Neuroimage* 40, 1044–1055.
17. Powell, J.W., and Barber-Foss, K.D. (1999). Traumatic brain injury in high school athletes. *JAMA* 282, 958–963.
18. Daniel, R.W., Rowson, S., and Duma, S.M. (2012). Head impact exposure in youth football. *Ann. Biomed. Eng.* 40, 976–981.
19. Bell, P.T., and Shine, J.M. (2016). Subcortical contributions to large-scale network communication. *Neurosci. Biobehav. Rev.* 71, 313–322.
20. Oh, S.W., Harris, J.A., Ng, L., Winslow, B., Cain, N., Mihalas, S., Wang, Q., Lau, C., Kuan, L., Henry, A.M., Mortrud, M.T., Ouellette, B., Nguyen, T.N., Sorensen, S.A., Slaughterbeck, C.R., Wakeman, W., Li, Y., Feng, D., Ho, A., Nicholas, E., Hirokawa, K.E., Bohn, P., Joines, K.M., Peng, H., Hawrylycz, M.J., Phillips, J.W., Hohmann, J.G., Wahnoutka, P., Gerfen, C.R., Koch, C., Bernard, A., Dang, C., Jones, A.R., and Zeng, H. (2014). A mesoscale connectome of the mouse brain. *Nature* 508, 207–214.
21. Saalman, Y.B., Pinsk, M.A., Wang, L., Li, X., and Kastner, S. (2012). The pulvinar regulates information transmission between cortical areas based on attention demands. *Science* 337, 753–756.
22. Sherman, S.M. (2007). The thalamus is more than just a relay. *Curr. Opin. Neurobiol.* 17, 417–422.
23. Montenegro, P.H., Corp, D.T., Stein, T.D., Cantu, R.C., and Stern, R.A. (2015). Chronic traumatic encephalopathy: historical origins and current perspective. *Annu. Rev. Clin. Psychol.* 11, 309–330.
24. Bernick, C., Banks, S.J., Shin, W., Obuchowski, N., Butler, S., No-back, M., Phillips, M., Lowe, M., Jones, S., and Modic, M. (2015). Repeated head trauma is associated with smaller thalamic volumes and slower processing speed: the Professional Fighters' Brain Health Study. *Br. J. Sports Med.* 49, 1007–1011.
25. Herrero, M.T., Barcia, C., and Navarro, J.M. (2002). Functional anatomy of thalamus and basal ganglia. *Childs Nerv. Syst.* 18, 386–404.
26. Koerte, I.K., Hufschmidt, J., Muehlmann, M., Tripodis, Y., Stamm, J.M., Pasternak, O., Giverc, M.Y., Coleman, M.J., Baugh, C.M., Fritts, N.G., Heinen, F., Lin, A., Stern, R.A., and Shenton, M.E. (2016). Cavum septi pellucidi in symptomatic former professional football players. *J. Neurotrauma* 33, 346–353.
27. Stern, R.A., Tripodis, Y., Baugh, C.M., Fritts, N.G., Martin, B.M., Chaisson, C., Cantu, R.C., Joyce, J.A., Shah, S., Ikezu, T., Zhang, J., Gercel-Taylor, C., and Taylor, D.D. (2016). Preliminary study of plasma exosomal tau as a potential biomarker for chronic traumatic encephalopathy. *J. Alzheimers Dis.* 51, 1099–1109.
28. Desikan, R.S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., and Killiany, R.J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 31, 968–980.
29. Fischl, B., Salat, D.H., van der Kouwe, A.J., Makris, N., Segonne, F., Quinn, B.T., and Dale, A.M. (2004). Sequence-independent segmentation of magnetic resonance images. *Neuroimage* 23, Suppl 1, S69–S84.
30. Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., and Dale, A.M. (2004). Automatically parcellating the human cerebral cortex. *Cereb. Cortex* 14, 11–22.
31. Reitan, R.M. (1992). *Trail Making Test: Manual for Administration and Scoring*. Reitan Neuropsychology Laboratory: Tucson, AZ.
32. Wechsler, D. (1997). *Manual for the Wechsler Adult Intelligence Scale-III*. Psychological Corporation: San Antonio, TX.
33. Heaton, R.K., Chelune, G.J., Talley, J., Kay, G.G., and Curtiss, G. (1993). *Wisconsin Card Sorting Test manual: Revised and Expanded*. Psychological Assessment Resources Inc: Odessa, FL.
34. Lezak, M.D., Howieson, D.B., Bigler, E.D., and Tranel, D. (2012). *Neuropsychological Assessment*, 5th ed. Oxford University Press: Oxford, UK.
35. Delis, D.C., Kaplan, E., and Kramer, J.H. (2001). *Delis-Kaplan Executive Function System (D-KEFS)*. Psychological Corporation: San Antonio, TX.
36. Stern, R.A., Javorsky, D.J., Singer, E.A., Singer, N.G., Duke, L.M., Somerville, J.A., Thompson, J.A., and Kaplan, E. (1999). *Boston Qualitative Scoring System (BQSS) for the Rey-Osterrieth Complex Figure*. Psychological Assessment Resources (PAR): Odessa, FL.
37. Stern, R., and White, T. (2003). *The Neuropsychological Assessment Battery (NAB)*. Psychological Assessment Resources: Lutz, Florida.
38. Marin, R.S., Biedrzycki, R.C., and Firinciogullari, S. (1991). Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res.* 38, 143–162.
39. Barratt, E.S. (1965). Factor analysis of some psychometric measures of impulsiveness and anxiety. *Psychol. Rep.* 16, 547–554.
40. Beck, A., Steer, R., and Brown, G. (1996). *Manual for the BDI-II*. Psychological Corporation: San Antonio, TX.
41. Beck, A., and Steer, R. (1988). *Manual for the Beck Hopelessness Scale*. Psychological Corporation: San Antonio, TX.
42. Roth, R.M., Isquith, P.K., and Gioia, G.A. (2005). *BRIEF-A: Behavior Rating Inventory of Executive Function—adult version: professional manual*. Psychological Assessment Resources: Lutz, Florida.
43. Brown, G.L., Goodwin, F.K., Ballenger, J.C., Goyer, P.F., and Major, L.F. (1979). Aggression in humans correlates with cerebrospinal fluid amine metabolites. *Psychiatry Res.* 1, 131–139.
44. Radloff, L.S. (1977). The CES-D Scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement* 1, 385–401.
45. Buss, A.H., and Durkee, A. (1957). An inventory for assessing different kinds of hostility. *J. Consult. Psychol.* 21, 343–349.
46. Hamilton, M. (1960). A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 23, 56–62.
47. Miller, I.W., Norman, W.H., Bishop, S.B., and Dow, M.G. (1986). The Modified Scale for Suicidal Ideation: reliability and validity. *J. Consult. Clin. Psychol.* 54, 724–725.
48. Alosco, M.L., Jarnagin, J., Tripodis, Y., Platt, M., Martin, B., Chaisson, C.E., Baugh, C.M., Fritts, N.G., Cantu, R.C., and Stern, R.A. (2017). Olfactory function and associated clinical correlates in former National Football League players. *J. Neurotrauma* 34, 772–780.
49. Efron, B., and Tibshirani, R. J. (1994). *An Introduction to the Bootstrap*. Chapman & Hall/CRC Press: Boca Raton, FL.
50. Efron, B. (1987). Better bootstrap confidence intervals. *J. Am. Stat. Assoc.* 82, 171–185.
51. Johnson, V.E., Stewart, W., and Smith, D.H. (2013). Axonal pathology in traumatic brain injury. *Exp. Neurol.* 246, 35–43.
52. Koerte, I.K., Lin, A.P., Muehlmann, M., Merugumala, S., Liao, H., Starr, T., Kaufmann, D., Mayinger, M., Steffinger, D., Fisch, B., Karch, S., Heinen, F., Ertl-Wagner, B., Reiser, M., Stern, R.A., Zafonte, R., and Shenton, M.E. (2015). Altered neurochemistry in former professional soccer players without a history of concussion. *J. Neurotrauma* 32, 1287–1293.
53. Webb, C.A., Weber, M., Mundy, E.A., and Killgore, W.D. (2014). Reduced gray matter volume in the anterior cingulate, orbitofrontal cortex and thalamus as a function of mild depressive symptoms: a voxel-based morphometric analysis. *Psychol. Med.* 44, 2833–2843.
54. Okada, N., Fukunaga, M., Yamashita, F., Koshiyama, D., Yamamori, H., Ohi, K., Yasuda, Y., Fujimoto, M., Watanabe, Y., Yahata, N.,

- Nemoto, K., Hibar, D.P., van Erp, T.G., Fujino, H., Isobe, M., Isumura, S., Natsubori, T., Narita, H., Hashimoto, N., Miyata, J., Koike, S., Takahashi, T., Yamasue, H., Matsuo, K., Onitsuka, T., Iidaka, T., Kawasaki, Y., Yoshimura, R., Watanabe, Y., Suzuki, M., Turner, J.A., Takeda, M., Thompson, P.M., Ozaki, N., Kasai, K., and Hashimoto, R. (2016). Abnormal asymmetries in subcortical brain volume in schizophrenia. *Mol. Psychiatry* 21, 1460–1466.
55. Grodin, E.N., and Momenan, R. (2016). Decreased subcortical volumes in alcohol dependent individuals: effect of polysubstance use disorder. *Addict. Biol.* 22, 1426–1437.
56. Eustache, P., Nemmi, F., Saint-Aubert, L., Pariente, J., and Péran, P. (2016). Multimodal magnetic resonance imaging in Alzheimer's disease patients at prodromal stage. *Addict. Biol.* 50, 1035–1050.
57. Zarei, M., Patenaude, B., Damoiseaux, J., Morgese, C., Smith, S., Matthews, P.M., Barkhof, F., Rombouts, S.A., Sanz-Arigita, E., and Jenkinson, M. (2010). Combining shape and connectivity analysis: an MRI study of thalamic degeneration in Alzheimer's disease. *Neuroimage* 49, 1–8.
58. Zagorchev, L., Meyer, C., Stehle, T., Wenzel, F., Young, S., Peters, J., Weese, J., Paulsen, K., Garlinghouse, M., Ford, J., Roth, R., Flashman, L., and McAllister, T. (2016). Differences in regional brain volumes two months and one year after mild traumatic brain injury. *J. Neurotrauma* 33, 29–34.
59. Banks, S.J., Miller, J.B., Rissman, R.A., and Bernick, C.B. (2017). Lack of influence of apolipoprotein e status on cognition or brain structure in professional fighters. *J. Neurotrauma* 34, 380–384.
60. Pellman, E.J., Viano, D.C., Tucker, A.M., Casson, I.R., and Waeckel, J.F. (2003). Concussion in professional football: reconstruction of game impacts and injuries. *Neurosurgery* 53, 799–812.
61. Viano, D.C., Casson, I.R., Pellman, E.J., Bir, C.A., Zhang, L., Sherman, D.C., and Boitano, M.A. (2005). Concussion in professional football: comparison with boxing head impacts—part 10. *Neurosurgery* 57, 1154–1172.
62. Solomon, G.S., Kuhn, A.W., Zuckerman, S.L., Casson, I.R., Viano, D.C., Lovell, M.R., and Sills, A.K. (2016). Participation in pre-high school football and neurological, neuroradiological, and neuropsychological findings in later life: a study of 45 retired National Football League players. *Am. J. Sports Med.* 44, 1106–1115.
63. Covassin, T., Elbin, R.J., Harris, W., Parker, T., and Kontos, A. (2012). The role of age and sex in symptoms, neurocognitive performance, and postural stability in athletes after concussion. *Am. J. Sports Med.* 40, 1303–1312.
64. Field, M., Collins, M.W., Lovell, M.R., and Maroon, J. (2003). Does age play a role in recovery from sports-related concussion? A comparison of high school and collegiate athletes. *J. Pediatr.* 142, 546–553.
65. Zuckerman, S.L., Lee, Y.M., Odom, M.J., Solomon, G.S., Forbes, J.A., and Sills, A.K. (2012). Recovery from sports-related concussion: days to return to neurocognitive baseline in adolescents versus young adults. *Surg. Neurol. Int.* 3, 130.
66. Spear, L.P. (2000). The adolescent brain and age-related behavioral manifestations. *Neurosci. Biobehav. Rev.* 24, 417–463.
67. Bourgeois, J.P., Jastreboff, P.J., and Rakic, P. (1989). Synaptogenesis in visual cortex of normal and preterm monkeys: evidence for intrinsic regulation of synaptic overproduction. *Proc. Natl. Acad. Sci. U. S. A.* 86, 4297–4301.
68. Giedd, J.N. (2008). The teen brain: insights from neuroimaging. *J. Adolesc. Health* 42, 335–343.
69. Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., Nugent, T.F., 3rd, Herman, D.H., Clasen, L.S., Toga, A.W., Rapoport, J.L., and Thompson, P.M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proc. Natl. Acad. Sci. U. S. A.* 101, 8174–8179.
70. Whitford, T.J., Rennie, C.J., Grieve, S.M., Clark, C.R., Gordon, E., and Williams, L.M. (2007). Brain maturation in adolescence: concurrent changes in neuroanatomy and neurophysiology. *Hum. Brain Mapp.* 28, 228–237.
71. Brown, T.T., Kuperman, J.M., Chung, Y., Erhart, M., McCabe, C., Hagler, D.J., Jr., Venkatraman, V.K., Akshoomoff, N., Amaral, D.G., Bloss, C.S., Casey, B.J., Chang, L., Ernst, T.M., Frazier, J.A., Gruen, J.R., Kaufmann, W.E., Kenet, T., Kennedy, D.N., Murray, S.S., Sowell, E.R., Jernigan, T.L., and Dale, A.M. (2012). Neuroanatomical assessment of biological maturity. *Curr. Biol.* 22, 1693–1698.
72. Thatcher, R.W., Walker, R.A., and Giudice, S. (1987). Human cerebral hemispheres develop at different rates and ages. *Science* 236, 1110–1113.
73. Konstantinou, N., Pettemeridou, E., Seimenis, I., Eracleous, E., Papacostas, S.S., Papanicolaou, A.C., and Constantinidou, F. (2016). Assessing the relationship between neurocognitive performance and brain volume in chronic moderate-severe traumatic brain injury. *Front. Neurol.* 7, 29.
74. Aggleton, J.P., Pralus, A., Nelson, A.J., and Hornberger, M. (2016). Thalamic pathology and memory loss in early Alzheimer's disease: moving the focus from the medial temporal lobe to Papez circuit. *Brain* 139, 1877–1890.
75. Zhao, Y.J., Du, M.Y., Huang, X.Q., Lui, S., Chen, Z.Q., Liu, J., Luo, Y., Wang, X.L., Kemp, G.J., and Gong, Q.Y. (2014). Brain grey matter abnormalities in medication-free patients with major depressive disorder: a meta-analysis. *Psychol. Med.* 44, 2927–2937.
76. Young, K.A., Bonkale, W.L., Holcomb, L.A., Hicks, P.B., and German, D.C. (2008). Major depression, 5HTTLPR genotype, suicide and antidepressant influences on thalamic volume. *Br. J. Psychiatry* 192, 285–289.
77. Robinson, S., Berglass, J.B., Denson, J.L., Berkner, J., Anstine, C.V., Winer, J.L., Maxwell, J.R., Qiu, J., Yang, Y., Sillerud, L.O., Meehan, W.P., 3rd, Mannix, R., and Jantzie, L.L. (2017). Microstructural and microglial changes after repetitive mild traumatic brain injury in mice. *J. Neurosci. Res.* 95, 1025–1035.
78. Robbins, C.A., Daneshvar, D.H., Picano, J.D., Gavett, B.E., Baugh, C.M., Riley, D.O., Nowinski, C.J., McKee, A.C., Cantu, R.C., and Stern, R.A. (2014). Self-reported concussion history: impact of providing a definition of concussion. *Open Access J. Sports Med.* 5, 99–103.
79. Alosco, M.L., Jarnagin, J., Tripodis, Y., Martin, B., Chaisson, C., Baugh, C.M., Torres, A., Nowinski, C.J., Cantu, R.C., and Stern, R.A. (2017). Utility of providing a concussion definition in the assessment of concussion history in former NFL players. *Brain Inj.* 31, 1116–1123.

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