JOURNAL OF NEUROTRAUMA 35:278–285 (January 15, 2018)

DOI: 10.1089/neu.2017.5145

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

Vivian Schultz,[1,2] Robert A. Stern,[3,4] Yorghos Tripodis,[3,5] Julie Stamm,[1,3,6] Pawel Wrobel,[1,2] Christian Lepage,[1,7] Isabelle Weir,[5] Jeffrey P. Guenette,[1,8] Alicia Chua,[5] Michael L. Alosco,[3] Christine M. Baugh,[3,9] Nathan G. Fritts,[3] Brett M. Martin,[10] Christine E. Chaisson,[3,10] Michael J. Coleman,[1] Alexander P. Lin,[1,8,11] Ofer Pasternak,[1,8] Martha E. Shenton,[1,8,12,13,*] and Inga K. Koerte[1,2,13,*]

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

[1]Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.
[2]Department of Child and Adolescent Psychiatry, Psychosomatic, and Psychotherapy, Ludwig-Maximilian-University, Munich, Germany.
[3]BU Alzheimer's Disease and CTE Center, Boston University, Boston, Massachusetts.
[4]Departments of Neurology, Neurosurgery, and Anatomy & Neurobiology, Boston University School of Medicine, Boston, Massachusetts.
[5]Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts.
[6]Department of Kinesiology, University of Wisconsin, Madison, Madison, Wisconsin.
[7]Department of Psychology, University of Ottawa, Ottawa, Ontario, Canada.
[8]Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.
[9]Interfaculty Initiative in Health Policy, Harvard University, Boston, Massachusetts.
[10]Data Coordinating Center, Boston University School of Public Health, Boston, Massachusetts.
[11]Center for Clinical Spectroscopy, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.
[12]VA Boston Healthcare System, Brockton Division, Brockton, Massachusetts.
[13]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.
*Authors contributed equally.

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 callosum[14] 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 see [19]). 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 colleagues[24] 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 = $1 \times 1 \times 1$ mm^3, 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 – R[32]; Wisconsin Card Sorting Test[33]; 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 Functioning - 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 Ideation[47] were administered using a semi-structured interview by either a licensed psychiatrist or clinical psychologist.

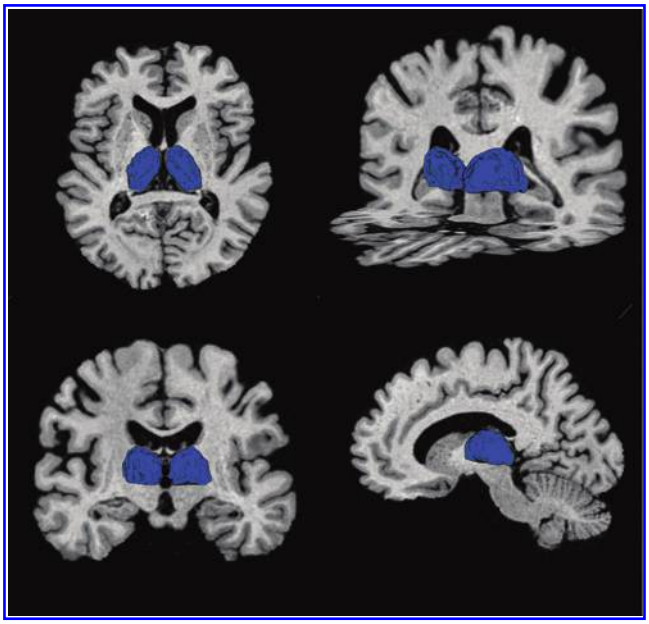

FIG. 1. A three-dimensional reconstruction of the thalamus as region of interest. The model was created from one randomly selected person using the model maker module of Slicer 4.5. Blue = thalamus. The model is shown from four different views on a para-mid axial, sagittal, and coronal slice and is superimposed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

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 coworkers[48] 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 mm^3 and the left thalamus was on average 53.2 mm^3 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

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 mm^3 (**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.

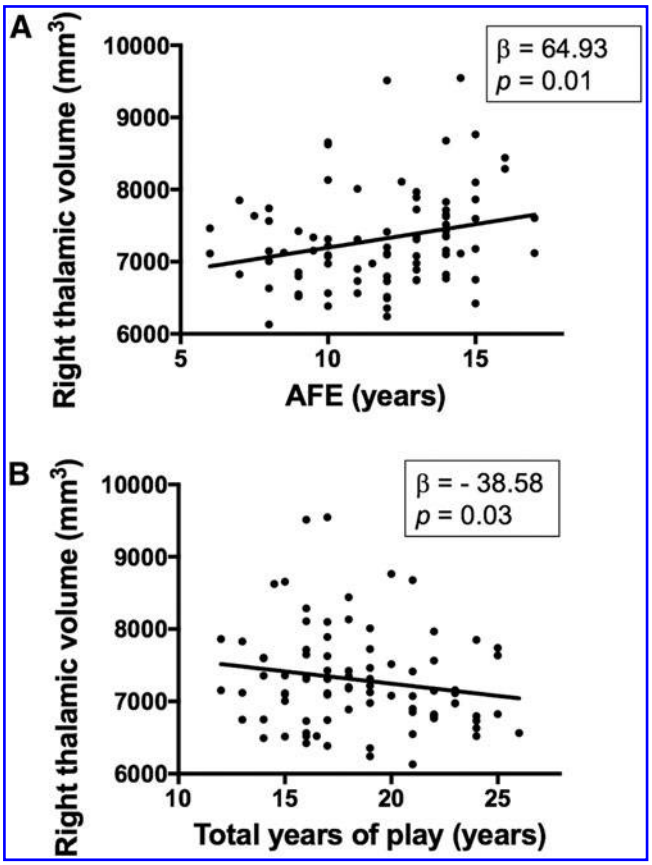

FIG. 2. Displays significant associations between exposure variables and right thalamic volume. (**A**) Association between age at first exposure (AFE) to football adjusted for total years of play and absolute right thalamic volume. (**B**) Relation between total years of play and absolute right thalamic 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 concussion[58] and exposure to RHI.[24] More specifically, the study by Bernick and associates[24] 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 colleagues[59] 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 (60*g*)[60] than those sustained during boxing (71*g*)[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 mm^3 in the left and 38.6 mm^3 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 severe[63] 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, resulting 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 mm^3 for every year athletes had started playing earlier and a decrease of 38.6 mm^3 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 coworkers[71] 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 colleagues[73] 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 patients[75] 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., microgliosis[77]).

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.

Acknowledgments

The authors extend their appreciation to the study participants who make this work possible. This study was supported by the NIH R01 NS 078337 (RAS, YT, CMB, NGF, BMM, CC); F31 NS 081957 (JMS); 1F32NS096803-01 (MLA); P30 AG13846 (RAS, YT, MLA, CMB, BMM, CC); UL1-TR000157 (RAS); P41 EB015902 (OP); T32GM074905 (IW), and participant travel was partially funded by JetBlue Airlines, the National Football League, and the NFL Players Association. The sponsors had no role in the design or conduct of the study, the collection, analysis, or interpretation of the data, in the preparation, review, or approval of the manuscript, or in the decision to submit the study for publication. This study was also partly supported by the Else Kröner-Fresenius Foundation, Germany (IK), by a VA Merit Award (MES, MC), by the Canadian Institutes of Health Research Frederick Banting and Charles Best Doctoral Award (CL), and by the German Academic Exchange Service PROMOS award (VS). Finally, this work was completed in partial fulfillment of VS's dissertation.

Author Disclosure Statement

RAS is a paid consultant to Avanir Pharmaceuticals, Inc. (Aliso Viejo, CA), Biogen (Cambridge, MA), and Eli Lilly (Indianapolis, IN). He receives royalties for published neuropsychological tests (including the NAB and BQSS) from Psychological Assessment Resources, Inc. (Lutz, FL). CMB receives research funding through the Harvard Football Players Health Study, which is funded by the NFL Players' Association. For all other authors, no competing financial interests exist.

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. Montenigro, 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., Giwerc, 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., Wohnoutka, 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. Saalmann, 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. Montenigro, 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., Noback, 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., Giwerc, 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., Isomura, 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 Waeckerle, 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.

Address correspondence to:
Inga K. Koerte, MD
Psychiatry Neuroimaging Laboratory
1249 Boylston Street
Boston, MA 02215

E-mail: ikoerte@bwh.harvard.edu

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2. Benjamin L. Brett, Amy M. Nader, Zachary Y. Kerr, Avinash Chandran, Samuel R. Walton, J. D. DeFreese, Kevin M. Guskiewicz, Michael McCrea. 2022. Disparate Associations of Years of Football Participation and a Metric of Head Impact Exposure with Neurobehavioral Outcomes in Former Collegiate Football Players. *Journal of the International Neuropsychological Society* **28**:1, 22-34. [Crossref]
3. Breton M. Asken, Gil D. Rabinovici. 2021. Identifying degenerative effects of repetitive head trauma with neuroimaging: a clinically-oriented review. *Acta Neuropathologica Communications* **9**:1. . [Crossref]
4. Michael L. Alosco, Megan L. Mariani, Charles H. Adler, Laura J. Balcer, Charles Bernick, Rhoda Au, Sarah J. Banks, William B. Barr, Sylvain Bouix, Robert C. Cantu, Michael J. Coleman, David W. Dodick, Lindsay A. Farrer, Yonas E. Geda, Douglas I. Katz, Inga K. Koerte, Neil W. Kowall, Alexander P. Lin, Daniel S. Marcus, Kenneth L. Marek, Michael D. McClean, Ann C. McKee, Jesse Mez, Joseph N. Palmisano, Elaine R. Peskind, Yorghos Tripodis, Robert W. Turner, Jennifer V. Wethe, Jeffrey L. Cummings, Eric M. Reiman, Martha E. Shenton, Robert A. Stern, Charles H. Adler, Michael L. Alosco, Rhoda Au, Laura Balcer, Sarah Banks, William Barr, Charles Bernick, Sylvain Bouix, Robert C. Cantu, Kewei Chen, Michael J. Coleman, Jeffrey L. Cummings, David W. Dodick, Lindsay Farrer, Jennifer Fitzsimmons, Yonas Geda, Judith Goldberg, Robert Helm, Keith A. Johnson, Douglas I. Katz, Ivan Kirov, Inga K. Koerte, Neil Kowall, Alexander P. Lin, Yvonne Lui, Daniel S. Marcus, Kenneth L. Marek, Megan Mariani, Charles Marmar, Michael McClean, Ann C. McKee, Jesse Mez, Jason Miller, Joseph N. Palmisano, Ofer Pasternak, Elaine R. Peskind, Hillary Protas, Eric Reiman, Aaron Ritter, Martha E. Shenton, Robert A. Stern, Yi Su, Yorghos Tripodis, Robert W. Turner, Jason Weller, Jennifer V. Wethe. 2021. Developing methods to detect and diagnose chronic traumatic encephalopathy during life: rationale, design, and methodology for the DIAGNOSE CTE Research Project. *Alzheimer's Research & Therapy* **13**:1. . [Crossref]
5. Joshua Sandry, Ekaterina Dobryakova. 2021. Global hippocampal and selective thalamic nuclei atrophy differentiate chronic TBI from Non-TBI. *Cortex* **145**, 37-56. [Crossref]
6. J. Cournoyer, C. Karton, D. Koncan, M.D. Gilchrist, R.C. Cantu, T.B. Hoshizaki. 2021. Brain trauma exposure for American tackle football players 5 to 9 and 9 to 14 years of age. *Journal of Biomechanics* **127**, 110689. [Crossref]
7. Jaclyn Caccese, Julianne Schmidt, Jena Moody, Steven Broglio, Thomas McAllister, Michael McCrea, Paul Pasquina, Thomas Buckley, CARE Consortium Investigators. 2021. Association between sports participation history and age of first exposure to high-risk sports with concussion history. *Research in Sports Medicine* **7**, 1-13. [Crossref]
8. Sean C. Rose, Keith Owen Yeates, Joseph T. Nguyen, Patrick M. Ercole, Natalie M. Pizzimenti, Matthew T. McCarthy. 2021. Subconcussive Head Impacts and Neurocognitive Function Over 3 Seasons of Youth Football. *Journal of Child Neurology* **36**:9, 768-775. [Crossref]
9. David Kaufmann, Nico Sollmann, Elisabeth Kaufmann, Rosanna Veggeberg, Yorghos Tripodis, Pawel P Wrobel, Janna Kochsiek, Brett M Martin, Alexander P Lin, Michael J Coleman, Michael L Alosco, Ofer Pasternak, Sylvain Bouix, Robert A Stern, Martha E Shenton, Inga K Koerte. 2021. Age at First Exposure to Tackle Football is Associated with Cortical Thickness in Former Professional American Football Players. *Cerebral Cortex* **28**. . [Crossref]
10. Joel Castellanos, Cheng Perng Phoo, James T. Eckner, Lea Franco, Steven P. Broglio, Mike McCrea, Thomas McAllister, Jenna Wiens. 2021. Predicting Risk of Sport-Related Concussion in Collegiate Athletes and Military Cadets: A Machine Learning Approach Using Baseline Data from the CARE Consortium Study. *Sports Medicine* **51**:3, 567-579. [Crossref]
11. Grant L. Iverson, Douglas P. Terry, Jaclyn B. Caccese, Fionn Büttner, Zachary C. Merz. 2021. Age of First Exposure to Football Is Not Associated with Midlife Brain Health Problems. *Journal of Neurotrauma* **38**:5, 538-545. [Abstract] [Full Text] [PDF] [PDF Plus]
12. Robert C. Cantu, Madeline Uretsky. Consequences of Ignorance and Arrogance for Mismanagement of Sports-Related Concussions: Short- and Long-Term Complications 3-17. [Crossref]
13. Jeffrey S. Brooks, Kody R. Campbell, Wayne Allison, Andrew M. Johnson, James P. Dickey. 2021. Career Head Impact Exposure Profile of Canadian University Football Players. *Journal of Applied Biomechanics* 1-11. [Crossref]
14. Radhika Balagopal, Michelle Won, Saumil S. Patel, Alice Z. Chuang, Anne B. Sereno. 2020. Heading-Related Slowing by Twenty-Four Hours in Youth Athletes. *Journal of Neurotrauma* **37**:24, 2664-2673. [Abstract] [Full Text] [PDF] [PDF Plus]

15. Z. V. Salii. 2020. ХРОНІЧНА ПОСТТРАВМАТИЧНА ЕНЦЕФАЛОПАТІЯ. ПОГЛЯД НА ПРОБЛЕМУ. *Вісник медичних і біологічних досліджень* :3, 167-174. [Crossref]
16. Anthony K. Savino, Lihong Huang, Jingzhen Yang, Natalie M. Pizzimenti, Matthew T. McCarthy, Sean C. Rose. 2020. Head Impact Burden Differs Between Seasons in Youth and High School US Football Players. *Annals of Biomedical Engineering* **48**:12, 2763-2771. [Crossref]
17. Jaclyn B. Caccese, Zac Houck, Thomas W. Kaminski, James R. Clugston, Grant L. Iverson, Kelsey N. Bryk, Jessie R. Oldham, Paul F. Pasquina, Steven P. Broglio, Thomas W. McAllister, Michael McCrea, April Marie (Reed) Hoy, Joseph B. Hazzard, Louise A. Kelly, Justus D. Ortega, Nicholas Port, Margot Putukian, T. Dianne Langford, Christopher C. Giza, Joshua T. Goldman, Holly J. Benjamin, Julianne D. Schmidt, Luis A. Feigenbaum, James T. Eckner, Jason P. Mihalik, Jessica Dysart Miles, Scott Anderson, Christina L. Master, Micky W. Collins, Anthony P. Kontos, Sara P.D. Chrisman, Alison Brooks, Jonathan C. Jackson, Gerald McGinty, Kenneth L. Cameron, Adam Susmarski, Patrick G. O'Donnell, Stefan Duma, Steve Rowson, Christopher M. Miles, Christopher T. Bullers, Brian H. Dykhuizen, Laura Lintner, Thomas A. Buckley. 2020. Estimated age of first exposure to American football and outcome from concussion. *Neurology* **95**:21, e2935-e2944. [Crossref]
18. Robert C. Lynall, Kevin M. Barrett. 2020. Recovery after football-related concussion. *Neurology* **95**:21, 945-946. [Crossref]
19. Lauren L. Bennett, Steve J. Stephen, Charles Bernick, Guogen Shan, Sarah J. Banks. 2020. Sex Moderates the Relationship That Number of Professional Fights Has With Cognition and Brain Volumes. *Frontiers in Neurology* **11**. . [Crossref]
20. Samuel A Bobholz, Benjamin L Brett, Lezlie Y España, Daniel L Huber, Andrew R Mayer, Jaroslaw Harezlak, Steven P Broglio, Thomas McAllister, Michael A McCrea, Timothy B Meier. 2020. Prospective study of the association between sport-related concussion and brain morphometry (3T-MRI) in collegiate athletes: study from the NCAA-DoD CARE Consortium. *British Journal of Sports Medicine* **7**, bjsports-2020-102002. [Crossref]
21. Michael L. Alosco, Alyssa Phelps, Robert A. Stern. Chronic Traumatic Encephalopathy 227-236. [Crossref]
22. Orit H. Lesman-Segev, Lauren Edwards, Gil D. Rabinovici. 2020. Chronic Traumatic Encephalopathy: A Comparison with Alzheimer's Disease and Frontotemporal Dementia. *Seminars in Neurology* **40**:04, 394-410. [Crossref]
23. Alyssa Phelps, Jesse Mez, Robert A. Stern, Michael L. Alosco. 2020. Risk Factors for Chronic Traumatic Encephalopathy: A Proposed Framework. *Seminars in Neurology* **40**:04, 439-449. [Crossref]
24. Madeline Uretsky, Christopher J. Nowinski. 2020. Chronic Traumatic Encephalopathy: Advocacy and Communicating with the Public. *Seminars in Neurology* **40**:04, 461-468. [Crossref]
25. Benjamin L. Brett, Samuel A. Bobholz, Lezlie Y. España, Daniel L. Huber, Andrew R. Mayer, Jaroslaw Harezlak, Steven P. Broglio, Thomas W. McAllister, Michael A. McCrea, Timothy B. Meier. 2020. Cumulative Effects of Prior Concussion and Primary Sport Participation on Brain Morphometry in Collegiate Athletes: A Study From the NCAA–DoD CARE Consortium. *Frontiers in Neurology* **11**. . [Crossref]
26. Jaclyn B. Caccese, Barry A. Bodt, Grant L. Iverson, Thomas W. Kaminski, Kelsey Bryk, Jessie Oldham, Steven P. Broglio, Michael McCrea, Thomas McAllister, Thomas A. Buckley. 2020. Estimated Age of First Exposure to Contact Sports and Neurocognitive, Psychological, and Physical Outcomes in Healthy NCAA Collegiate Athletes: A Cohort Study. *Sports Medicine* **50**:7, 1377-1392. [Crossref]
27. Jaclyn B. Caccese, Fernando V. Santos, Felipe Yamaguchi, John J. Jeka. 2020. Age of First Exposure to Soccer Heading and Sensory Reweighting for Upright Stance. *International Journal of Sports Medicine* . [Crossref]
28. Brittany L. Kmush, Madeline Mackowski, Justin Ehrlich, Bhavneet Walia, Arthur Owora, Shane Sanders. 2020. Association of Professional Football Cumulative Head Impact Index Scores With All-Cause Mortality Among National Football League Players. *JAMA Network Open* **3**:5, e204442. [Crossref]
29. Steve J. Stephen, Guogen Shan, Sarah J. Banks, Charles Bernick, Lauren L. Bennett. 2020. The Relationship Between Fighting Style, Cognition, and Regional Brain Volume in Professional Combatants: A Preliminary Examination Using Brief Neurocognitive Measures. *Journal of Head Trauma Rehabilitation* **35**:3, E280-E287. [Crossref]
30. GRACE H. LO, TIMOTHY E. MCALINDON, ANDREA M. KRISKA, LORI LYN PRICE, BONNY J. ROCKETTE-WAGNER, LISA A. MANDL, CHARLES B. EATON, MARC C. HOCHBERG, REBECCA D. JACKSON, C. KENT KWOH, MICHAEL C. NEVITT, JEFFREY B. DRIBAN. 2020. Football Increases Future Risk of Symptomatic Radiographic Knee Osteoarthritis. *Medicine & Science in Sports & Exercise* **52**:4, 795-800. [Crossref]
31. Diana O. Svaldi, Chetas Joshi, Emily C. McCuen, Jacob P. Music, Robert Hannemann, Larry J. Leverenz, Eric A. Nauman, Thomas M. Talavage. 2020. Accumulation of high magnitude acceleration events predicts cerebrovascular reactivity changes in female high school soccer athletes. *Brain Imaging and Behavior* **14**:1, 164-174. [Crossref]
32. Jaclyn B. Caccese, Grant L. Iverson, Kenneth L. Cameron, Megan N. Houston, Gerald T. McGinty, Jonathan C. Jackson, Patrick O'Donnell, Paul F. Pasquina, Steven P. Broglio, Michael McCrea, Thomas McAllister, Thomas A. Buckley. 2020. Estimated Age

of First Exposure to Contact Sports Is Not Associated with Greater Symptoms or Worse Cognitive Functioning in Male U.S. Service Academy Athletes. *Journal of Neurotrauma* **37**:2, 334-339. [Abstract] [Full Text] [PDF] [PDF Plus]

33. Michael L. Alosco, Yorghos Tripodis, Inga K. Koerte, Jonathan D. Jackson, Alicia S. Chua, Megan Mariani, Olivia Haller, Éimear M. Foley, Brett M. Martin, Joseph Palmisano, Bhupinder Singh, Katie Green, Christian Lepage, Marc Muehlmann, Nikos Makris, Robert C. Cantu, Alexander P. Lin, Michael Coleman, Ofer Pasternak, Jesse Mez, Sylvain Bouix, Martha E. Shenton, Robert A. Stern. 2019. Interactive Effects of Racial Identity and Repetitive Head Impacts on Cognitive Function, Structural MRI-Derived Volumetric Measures, and Cerebrospinal Fluid Tau and Aβ. *Frontiers in Human Neuroscience* **13**. . [Crossref]
34. Christy M. Kelley, Sylvia E. Perez, Elliott J. Mufson. 2019. Tau pathology in the medial temporal lobe of athletes with chronic traumatic encephalopathy: a chronic effects of neurotrauma consortium study. *Acta Neuropathologica Communications* **7**:1. . [Crossref]
35. Limin Wu, Joon Y Chung, Shivani Saith, Lorenzo Tozzi, Erin M Buckley, Bharat Sanders, Maria A Franceschini, Sevda Lule, Saef Izzy, Josephine Lok, William J Edmiston, Lauren M McAllister, Sloane Mebane, Gina Jin, Jiaxi Lu, John S Sherwood, Sarah Willwerth, Suzanne Hickman, Joseph El Khoury, Eng H Lo, David Kaplan, Michael J Whalen. 2019. Repetitive head injury in adolescent mice: A role for vascular inflammation. *Journal of Cerebral Blood Flow & Metabolism* **39**:11, 2196-2209. [Crossref]
36. Bern Lee, Lauren L. Bennett, Charles Bernick, Guogen Shan, Sarah J. Banks. 2019. The Relations Among Depression, Cognition, and Brain Volume in Professional Boxers: A Preliminary Examination Using Brief Clinical Measures. *Journal of Head Trauma Rehabilitation* **34**:6, E29-E39. [Crossref]
37. Andrea L. Roberts, Alvaro Pascual-Leone, Frank E. Speizer, Ross D. Zafonte, Aaron L. Baggish, Herman Taylor, Lee M. Nadler, Theodore K. Courtney, Ann Connor, Rachel Grashow, Alexandra M. Stillman, Dean A. Marengi, Marc G. Weisskopf. 2019. Exposure to American Football and Neuropsychiatric Health in Former National Football League Players: Findings From the Football Players Health Study. *The American Journal of Sports Medicine* **47**:12, 2871-2880. [Crossref]
38. Schneider Andrea L.C., Selvin Elizabeth, Liang Menglu, Latour Lawrence, Turtzo L. Christine, Koton Silvia, Coresh Josef, Mosley Thomas, Whitlow Christopher T., Zhou Yun, Wong Dean F., Ling Geoffrey, Gottesman Rebecca F.. 2019. Association of Head Injury with Brain Amyloid Deposition: The ARIC-PET Study. *Journal of Neurotrauma* **36**:17, 2549-2557. [Abstract] [Full Text] [PDF] [PDF Plus] [Supplementary Material]
39. Janet C. Rucker, Jean A. Buettner-Ennever, Dominik Straumann, Bernard Cohen. 2019. Case Studies in Neuroscience: Instability of the visual near triad in traumatic brain injury—evidence for a putative convergence integrator. *Journal of Neurophysiology* **122**:3, 1254-1263. [Crossref]
40. Michael L. Alosco, Robert A. Stern. 2019. Youth Exposure to Repetitive Head Impacts From Tackle Football and Long-term Neurologic Outcomes: A Review of the Literature, Knowledge Gaps and Future Directions, and Societal and Clinical Implications. *Seminars in Pediatric Neurology* **30**, 107-116. [Crossref]
41. Benjamin L. Brett, Daniel L. Huber, Alexa Wild, Lindsay D. Nelson, Michael A. McCrea. 2019. Age of First Exposure to American Football and Behavioral, Cognitive, Psychological, and Physical Outcomes in High School and Collegiate Football Players. *Sports Health: A Multidisciplinary Approach* **11**:4, 332-342. [Crossref]
42. Klein Andrew P., Tetzlaff Julie E., Bonis Joshua M., Nelson Lindsay D., Mayer Andrew R., Huber Daniel L., Harezlak Jaroslaw, Mathews Vincent P., Ulmer John L., Sinson Grant P., Nencka Andrew S., Koch Kevin M., Wu Yu-Chien, Saykin Andrew J., DiFiori John P., Giza Christopher C., Goldman Joshua, Guskiewicz Kevin M., Mihalik Jason P., Duma Stefan M., Rowson Steven, Brooks Alison, Broglio Steven P., McAllister Thomas, McCrea Michael A., Meier Timothy B.. 2019. Prevalence of Potentially Clinically Significant Magnetic Resonance Imaging Findings in Athletes with and without Sport-Related Concussion. *Journal of Neurotrauma* **36**:11, 1776-1785. [Abstract] [Full Text] [PDF] [PDF Plus] [Supplementary Material]
43. Christian Lepage, Marc Muehlmann, Yorghos Tripodis, Jakob Hufschmidt, Julie Stamm, Katie Green, Pawel Wrobel, Vivian Schultz, Isabelle Weir, Michael L. Alosco, Christine M. Baugh, Nathan G. Fritts, Brett M. Martin, Christine Chaisson, Michael J. Coleman, Alexander P. Lin, Ofer Pasternak, Nikos Makris, Robert A. Stern, Martha E. Shenton, Inga K. Koerte. 2019. Limbic system structure volumes and associated neurocognitive functioning in former NFL players. *Brain Imaging and Behavior* **13**:3, 725-734. [Crossref]
44. Jaclyn B. Caccese, Ryan M. DeWolf, Thomas W. Kaminski, Steven P. Broglio, Thomas W. McAllister, Michael McCrea, Thomas A. Buckley. 2019. Estimated Age of First Exposure to American Football and Neurocognitive Performance Amongst NCAA Male Student-Athletes: A Cohort Study. *Sports Medicine* **49**:3, 477-487. [Crossref]
45. Tharmegan Tharmaratnam, Mina A. Iskandar, Tyler C. Tabobondung, Iqdam Tobbia, Prasaanthan Gopee-Ramanan, Taylor A. Tabobondung. 2018. Chronic Traumatic Encephalopathy in Professional American Football Players: Where Are We Now?. *Frontiers in Neurology* **9**. . [Crossref]

46. Thomas J. McColl, Rhys D. Brady, Sandy R. Shultz, Lauren Lovick, Kyria M. Webster, Mujun Sun, Stuart J. McDonald, Terence J. O'Brien, Bridgette D. Semple. 2018. Mild Traumatic Brain Injury in Adolescent Mice Alters Skull Bone Properties to Influence a Subsequent Brain Impact at Adulthood: A Pilot Study. *Frontiers in Neurology* **9**. . [Crossref]

47. Michael L. Alosco, Jesse Mez, Yorghos Tripodis, Patrick T. Kiernan, Bobak Abdolmohammadi, Lauren Murphy, Neil W. Kowall, Thor D. Stein, Bertrand Russell Huber, Lee E. Goldstein, Robert C. Cantu, Douglas I. Katz, Christine E. Chaisson, Brett Martin, Todd M. Solomon, Michael D. McClean, Daniel H. Daneshvar, Christopher J. Nowinski, Robert A. Stern, Ann C. McKee. 2018. Age of first exposure to tackle football and chronic traumatic encephalopathy. *Annals of Neurology* **83**:5, 886-901. [Crossref]

48. Eric A. Nauman, Thomas M. Talavage. Subconcussive trauma 245-255. [Crossref]

49. Steven D'Ascanio, Michael L. Alosco, Robert A. Stern. Chronic traumatic encephalopathy: clinical presentation and in vivo diagnosis 281-296. [Crossref]

50. Alexander Lin, Molly Charney, Martha E. Shenton, Inga Katharina Koerte. Chronic traumatic encephalopathy: neuroimaging biomarkers 309-322. [Crossref]