



Long-Term Consequences of Repetitive Head Impacts in Former American Football Players

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Disclosures

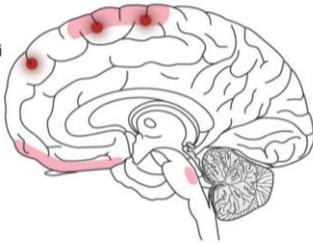
I have the following relevant financial relationships to disclose:

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- **Alzheimer's Association**

Chronic Traumatic Encephalopathy (CTE)

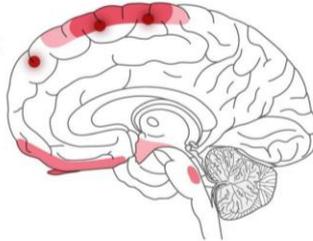
Stage I

Isolated perivascular centers
Predilection for depths of sulci
within superior, dorsolateral,
and inferior frontal cortices
Locus coeruleus



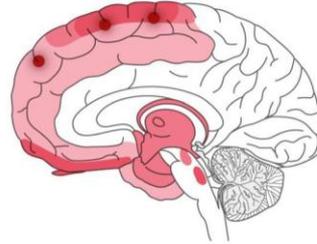
Stage II

Multiple centers in
frontal, temporal, and parietal
neocortices
Diencephalon
Nucleus basalis of Meynert



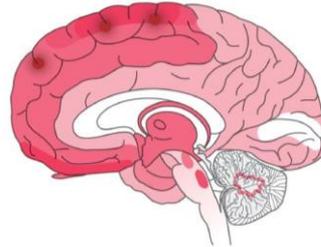
Stage III

Widespread neocortical
involvement
Hippocampus
Amygdala
Basal ganglia

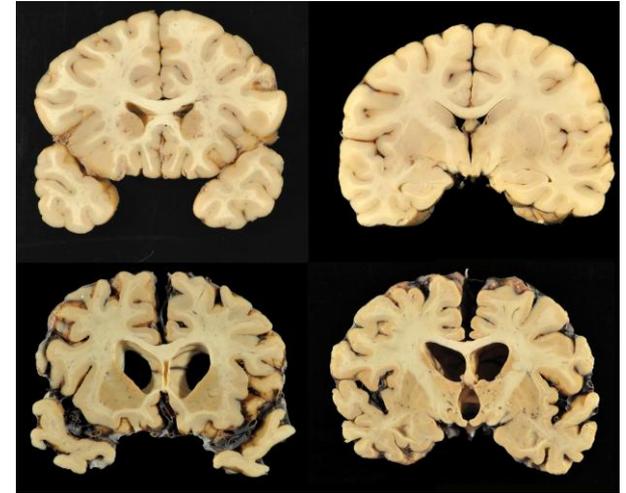


Stage IV

Medulla
Cerebellum
Cervical spinal cord



No CTE



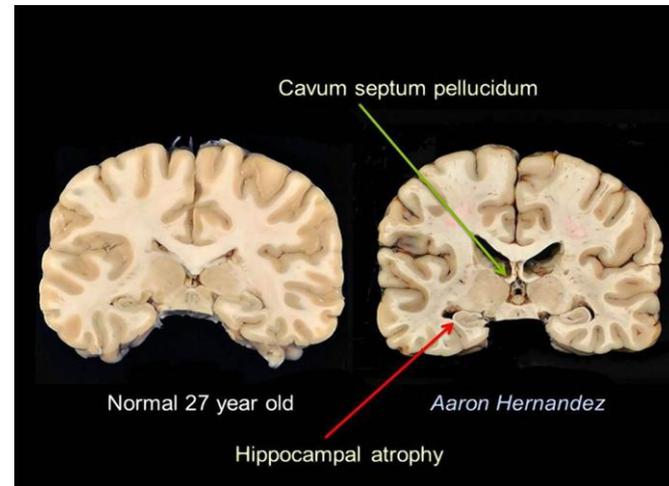
CTE

Neurodegenerative disorder
Diagnosis is only done at postmortem

Exposure to Repetitive Head Impacts



Former New England Patriots Player Aaron Hernandez



Boston University Chobanian & Avedisian School of Medicine

Exposure to repetitive head impacts increases the risk of CTE

Traumatic Encephalopathy Syndrome (TES)

VIEWS & REVIEWS

National Institute of Neurological Disorders and Stroke Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome

Douglas I. Katz, MD, Charles Bernick, MD, David W. Dodick, MD, Jesse Mez, MD, Megan L. Mariani, BS, Charles H. Adler, MD, PhD, Michael L. Alexoo, PhD, Laura J. Baker, MD, Sarah J. Banks, PhD, William B. Barr, PhD, David L. Brody, MD, PhD, Robert C. Cantu, MD, Kristen Cairns-Cooksey, PhD, Yonas E. Gedda, MD, Barry D. Jordan, MD, Thomas W. McAllister, MD, Elaine R. Peskind, MD, Ronald C. Petersen, MD, PhD, Jennifer V. Wehrle, PhD, Ross D. Zafonte, DO, Esmar M. Foley, MS, Debra J. Babcock, MD, PhD, Walter J. Korczyn, MD, Yorgos Tsipogiannis, PhD, Eric C. Melrose, MD, Martha E. Shenton, PhD, Jeffrey L. Cummings, MD, Eric M. Reiman, MD, and Robert A. Stern, PhD

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Abstract

Objective

To develop evidence-informed, expert consensus research diagnostic criteria for traumatic encephalopathy syndrome (TES), the clinical disorder associated with neuropathologically diagnosed chronic traumatic encephalopathy (CTE).

Methods

A panel of 20 expert clinician-scientists in neurology, neuropsychology, psychiatry, neurosurgery, and physical medicine and rehabilitation, from 11 academic institutions, participated in a modified Delphi procedure to achieve consensus, initiated at the First National Institute of Neurological Disorders and Stroke Consensus Workshop to Define the Diagnostic Criteria for TES, April, 2019. Before consensus, panelists reviewed evidence from all published cases of CTE with neuropathologic confirmation, and they examined the predictive validity data on clinical features in relation to CTE pathology from a large clinicopathologic study (n = 298).

Results

Consensus was achieved in 4 rounds of the Delphi procedure. Diagnosis of TES requires (1) substantial exposure to repetitive head impacts (RHIs) from contact sports, military service, or other causes; (2) core clinical features of cognitive impairment (in episodic memory and/or executive functioning) and/or neurobehavioral dysregulation; (3) a progressive course; and (4) that the clinical features are not fully accounted for by any other neurologic, psychiatric, or medical conditions. For these meeting criteria for TES, functional dependence is graded on 5

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Editorial
Embracing the Unknown in the Diagnosis of Traumatic Encephalopathy Syndrome
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Podcast
Dr. Alex Menze talks to Dr. Robert Stern about the paper "National Institute of Neurological Disorders and Stroke Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome."
NPub.org/bskmc

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Go to neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of this article.

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Diagnostic Criteria:

- Cognitive Impairment and/or
- Neurobehavioral Dysregulation
- Progressive Course
- Exposure to repetitive head impacts
- Not fully accounted for by other disorders

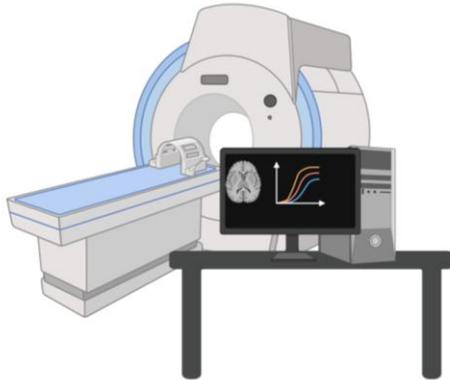
Provisional Levels of Certainty for CTE Pathology:

- Suggestive of CTE
- Possible CTE
- Probable CTE
- Definite CTE with TES

Potential Biomarkers for the Detection of CTE

Neuroimaging Biomarkers

- Magnetic Resonance Imaging (MRI)
 - Structural, Diffusion, Functional
- Magnetic Resonance Spectroscopy (MRS)
- Positron Emission Tomography (PET)



Body Fluid Biomarkers

- Cerebrospinal fluid
- Blood
 - Plasma



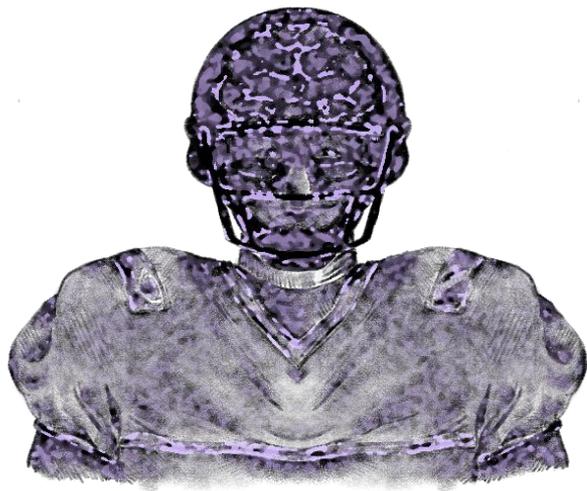
Identifying Possible Biomarkers In Vivo

How can we investigate this?

In living individuals at greater risk for CTE, such as people who participated in contact or collision sports.



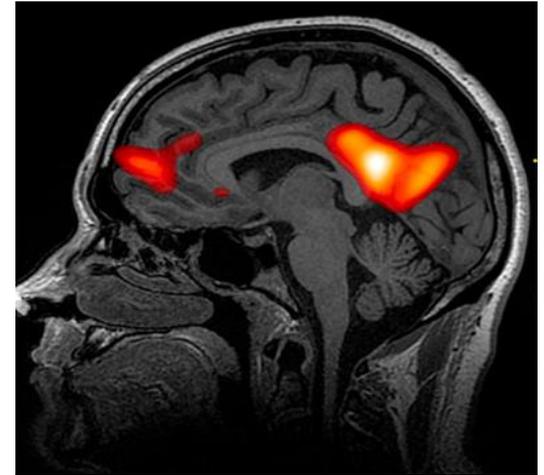
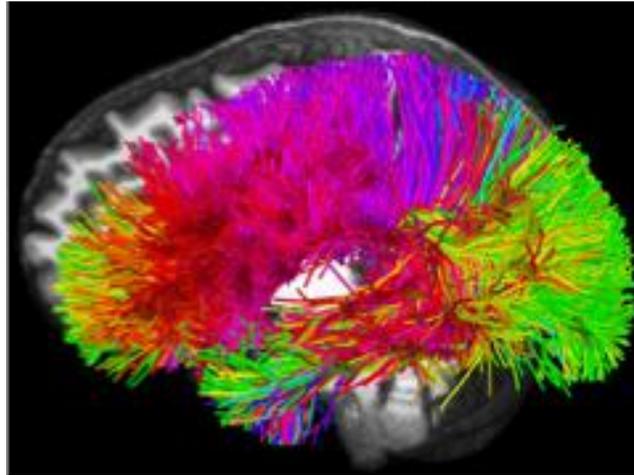
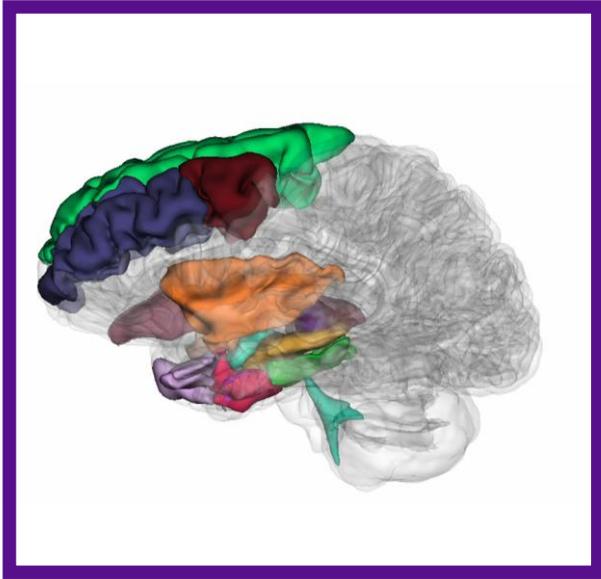
DIAGNOSE CTE Research Project



Cohort Demographics

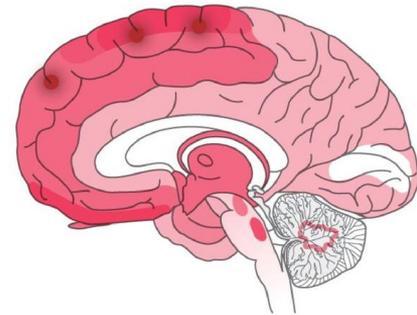
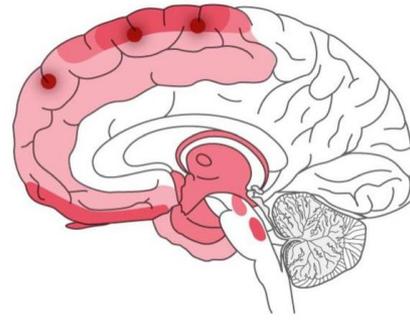
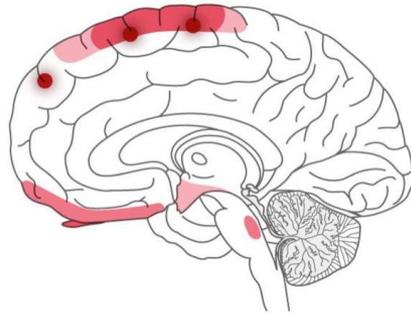
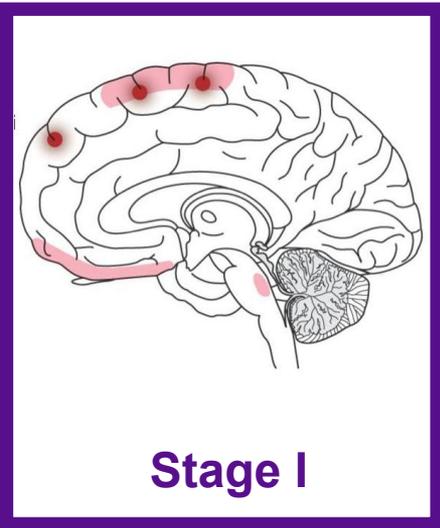
	Unexposed Asymptomatic Controls n=54	Former American Football Players n=170
Age	59.4 (8.5) years	57.2 (8.2) years
Years of Education	17.1 (3.4) years	16.7 (1.5) years
Body Mass Index	31 (4.6)	32.7 (4.7)
e4 Carrier (n=218)	10 (18.5%)	47 (28%)
Race	19 Black or African American, 34 White, 1 Native Hawaiian or Pacific Islander	58 Black or African American, 108 White, 3 Multiple Races
TES Diagnosis	0 (0%)	108 (63%)

Neuroimaging Data



Overarching Research Question

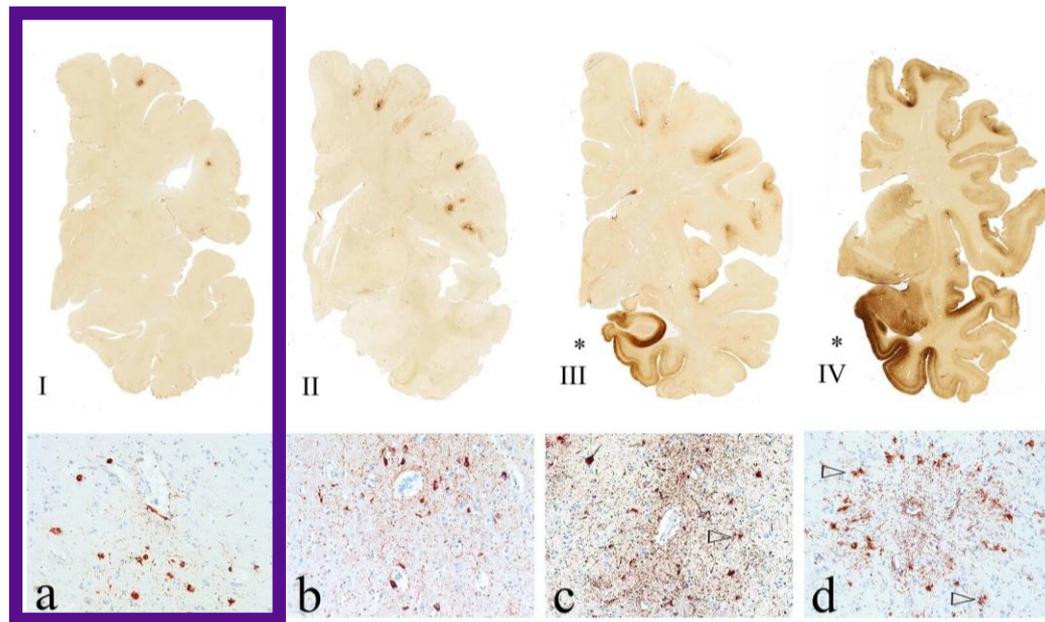
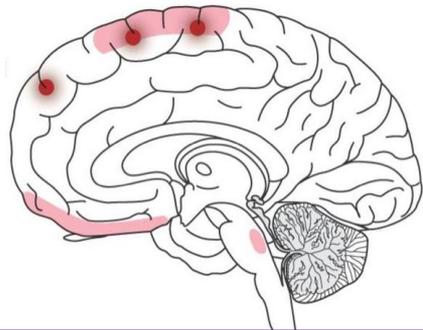
Are there identifiable neuroimaging signatures indicative of CTE, and how do these align with the clinical diagnosis of TES and the established levels of certainty for CTE pathology?



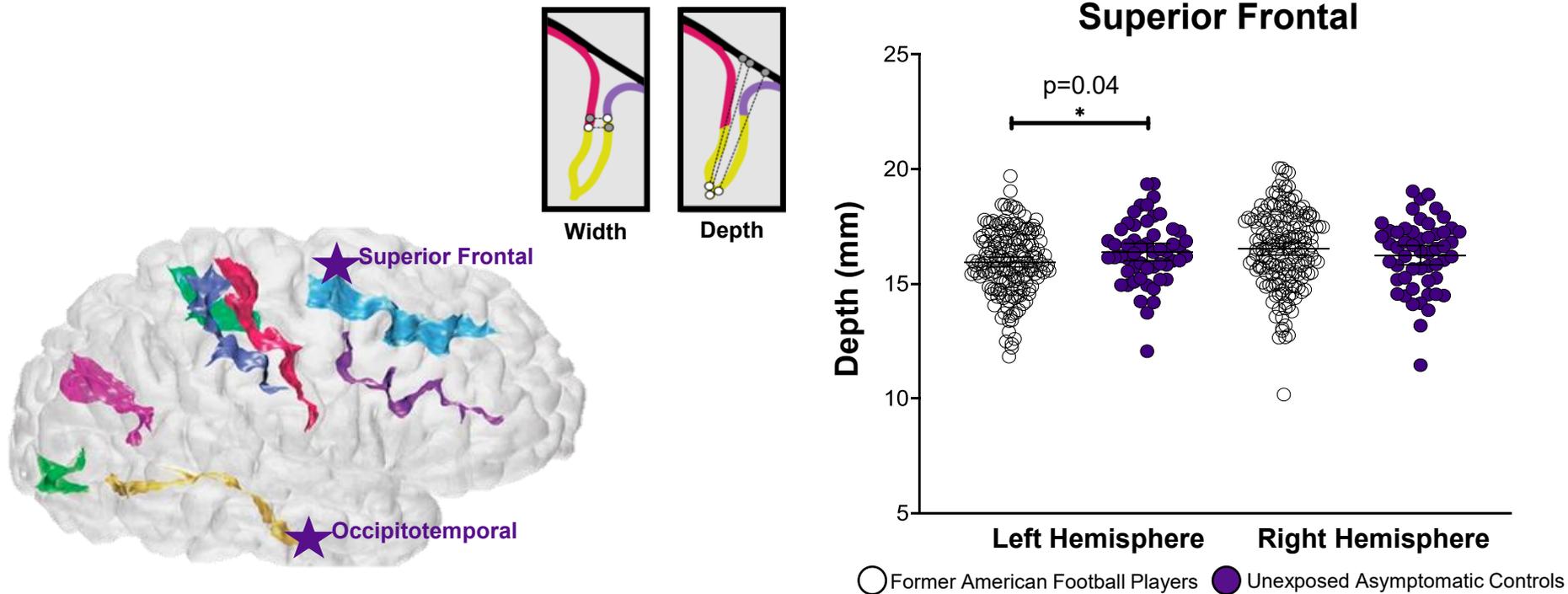
Spotting the Earliest Signs: Biomarkers and Brain Changes in Stage I CTE

CTE Stage I

- Isolated perivascular centers
- Predilection for depths of sulci within superior, dorsolateral, and inferior frontal cortices
- Locus coeruleus

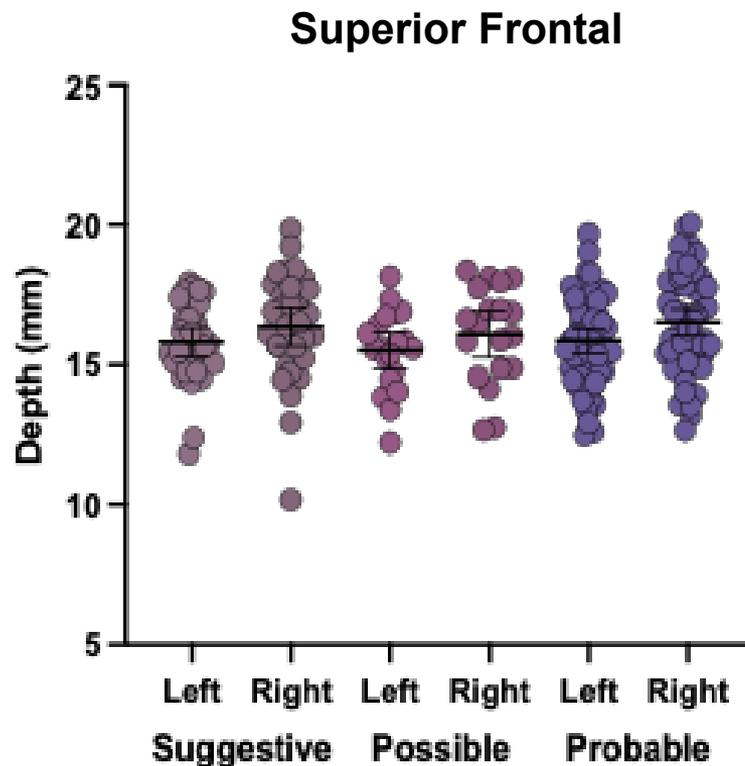
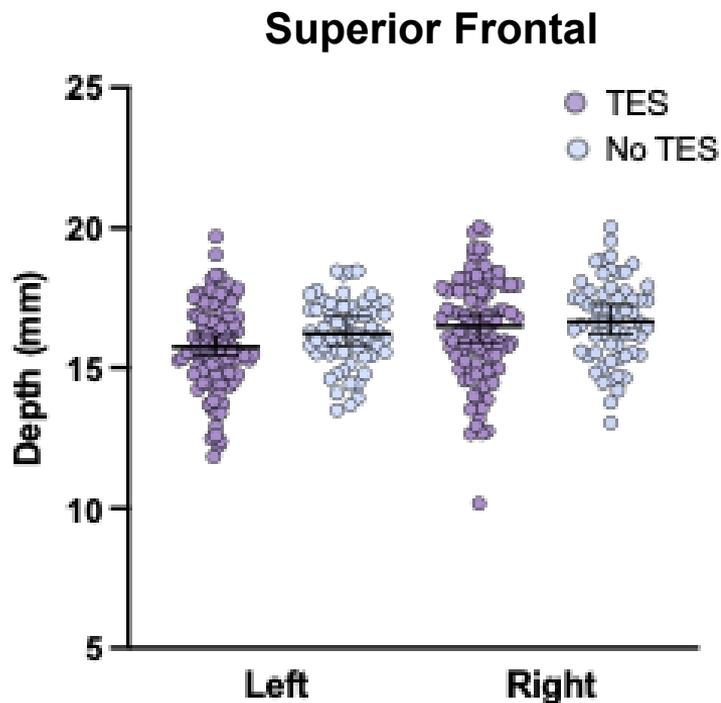


Can we detect sulcal morphological changes in former American football players in brain regions impacted by CTE pathology?



Shallower Sulcal Depth in Former American Football Players

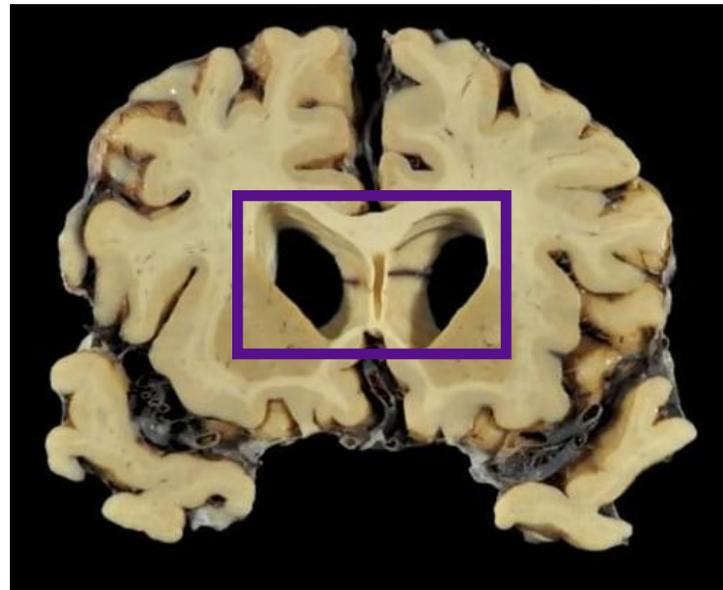
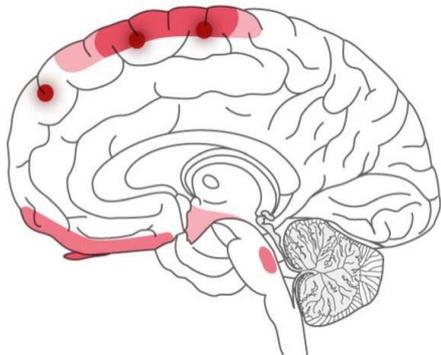
Can sulcal morphology differentiate TES status and/or levels of certainty for CTE pathology in former football players?



Exploring Biomarkers: Stage II CTE

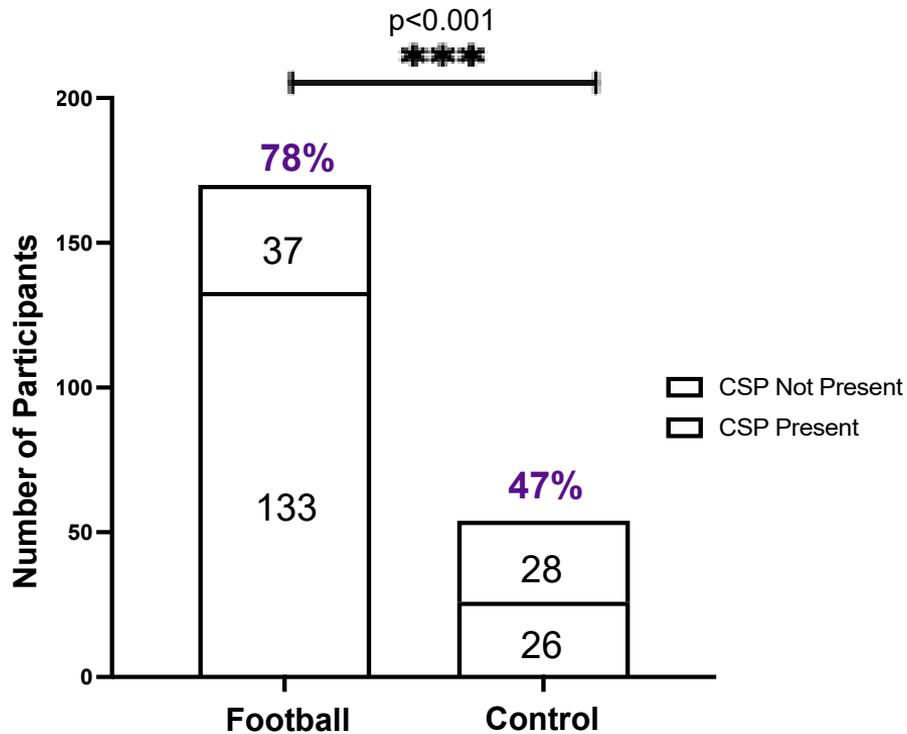
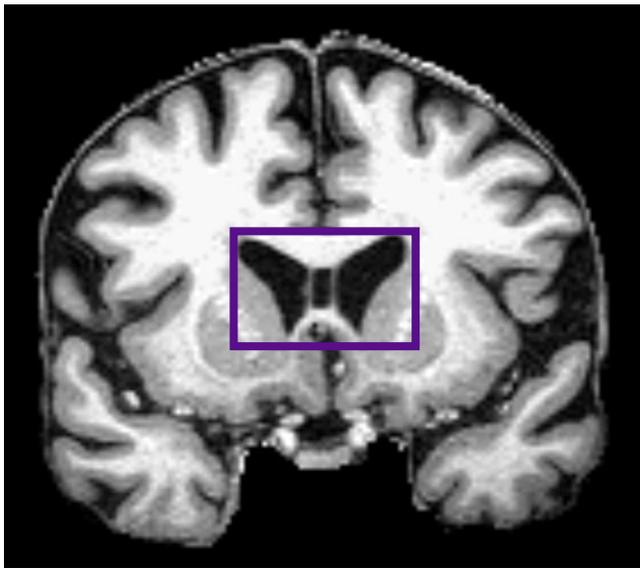
CTE Stage II

- Multiple centers in frontal, temporal, and parietal neocortices
- Diencephalon
- Nucleus basalis of Meynert
- Cavum septum pellucidum



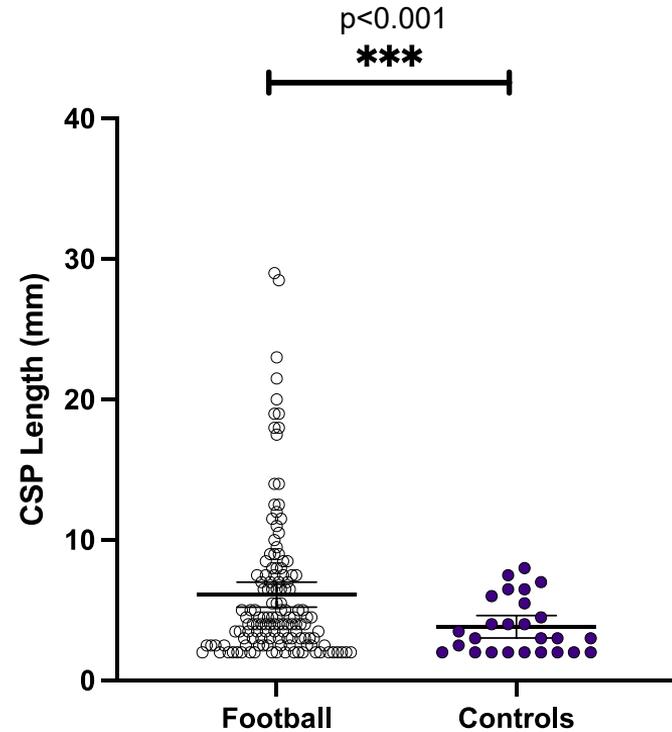
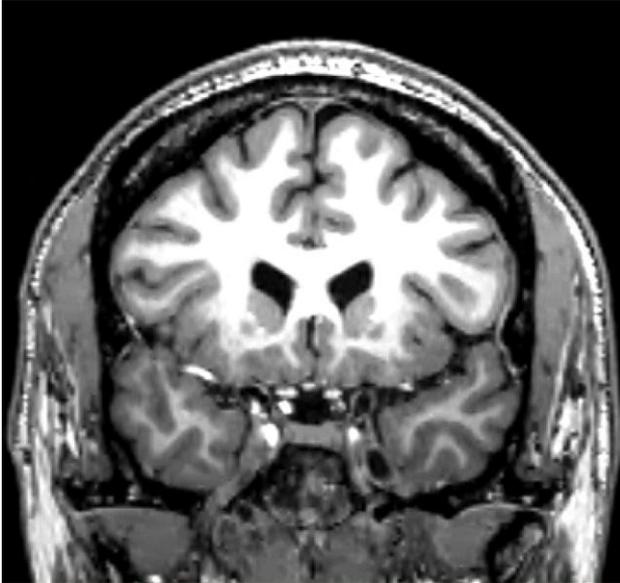
Cavum Septum Pellucidum (CSP)

Do former American football players exhibit a greater prevalence of CSP than unexposed asymptomatic individuals?



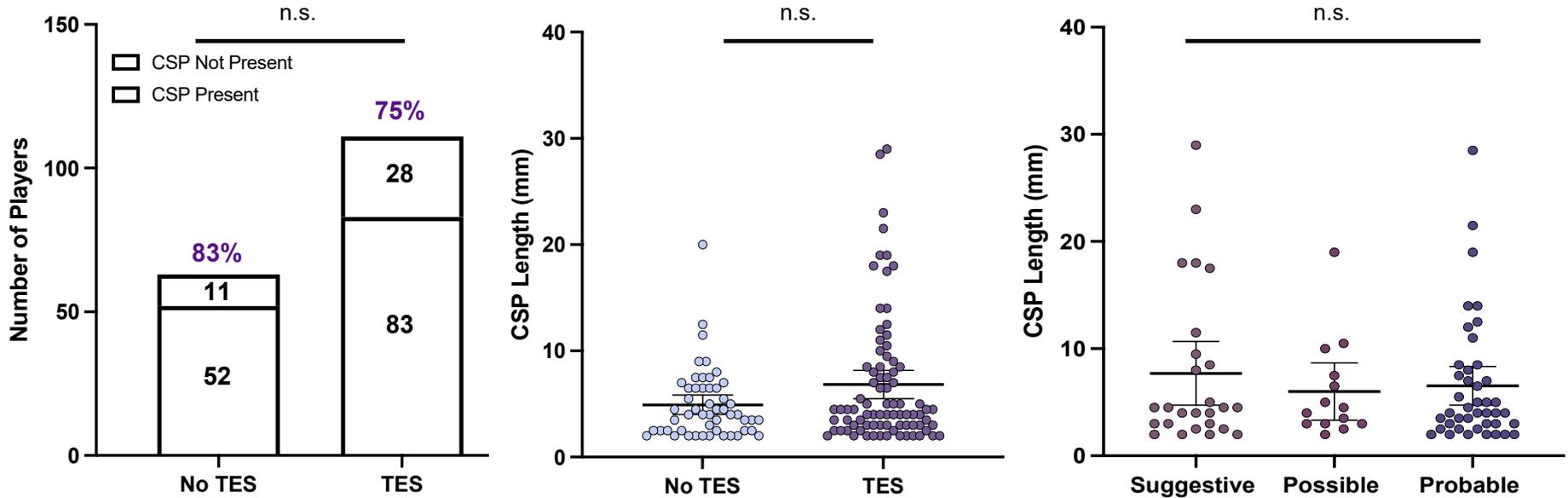
CSP has a higher prevalence in former American football players

Do former American football players exhibit increased CSP length and/or CSP ratio relative to unexposed asymptomatic controls?



CSP length and ratio are greater in former American football players

Can CSP length differentiate TES status and/or levels of certainty for CTE pathology in former football players?

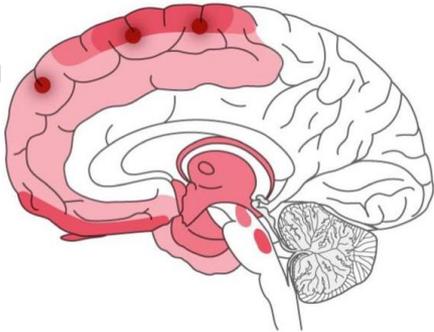


No significant differences in CSP length were observed based on TES diagnosis or levels of certainty for CTE pathology.

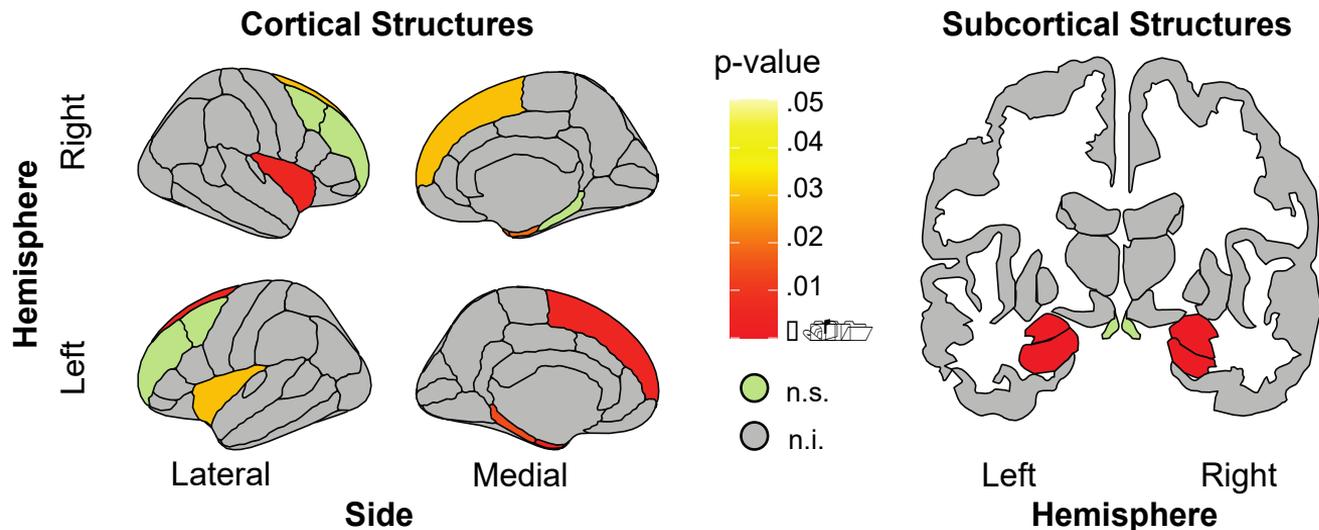
Identifying Key Differences in Stage III CTE

CTE Stage III

- Widespread neocortical involvement
- Hippocampus
- Amygdala
- Basal ganglia



Do former American football players have decreased volume in brain regions known to be impacted by CTE pathology?



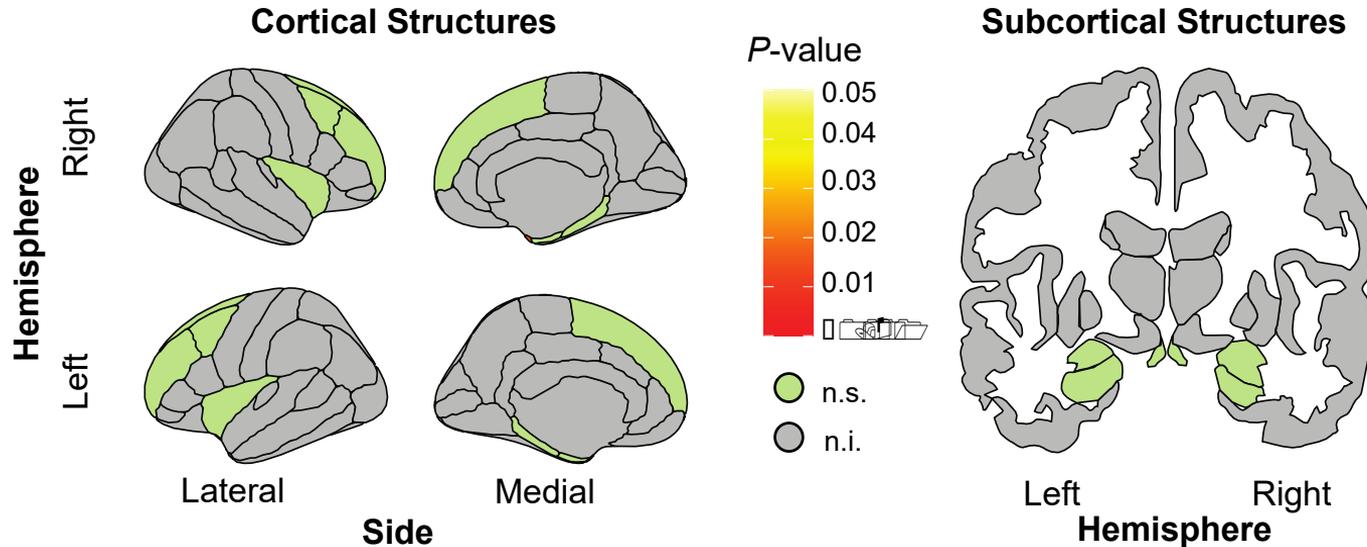
Generalized Least Square Results

ROI	Left Hemisphere p value	Right Hemisphere p value
Superior Frontal	<.01	.03
Caudal Middle Frontal	.067	.6
Rostral Middle Frontal	.5	.5
Entorhinal	<.01	.02
Parahippocampal	.01	.07
Insula	.03	<.01
Temporal Pole	.1	.02
Amygdala	<.01	<.01
Hippocampus	<.01	<.01
Hypothalamus	.5	.87

All p-values are FDR corrected

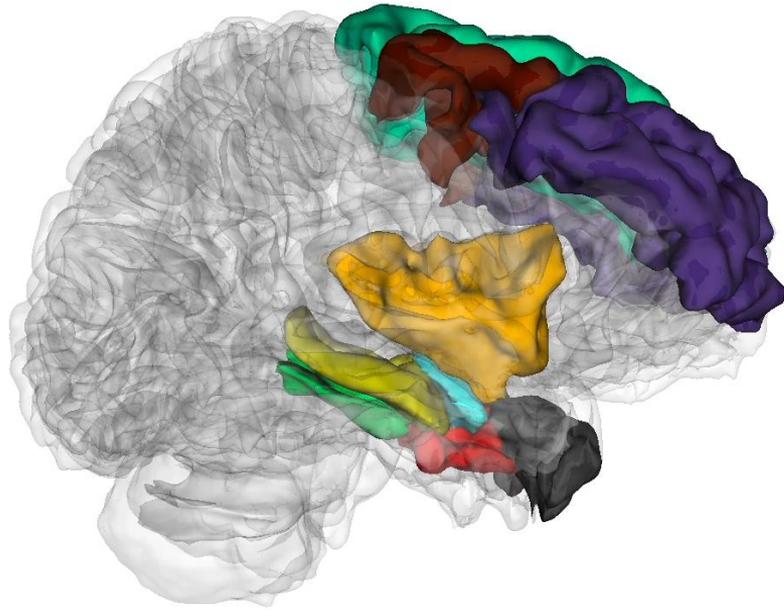
Former American Football Players < Unexposed Asymptomatic Controls

Does brain volume differ between football players with and without a diagnosis of TES?



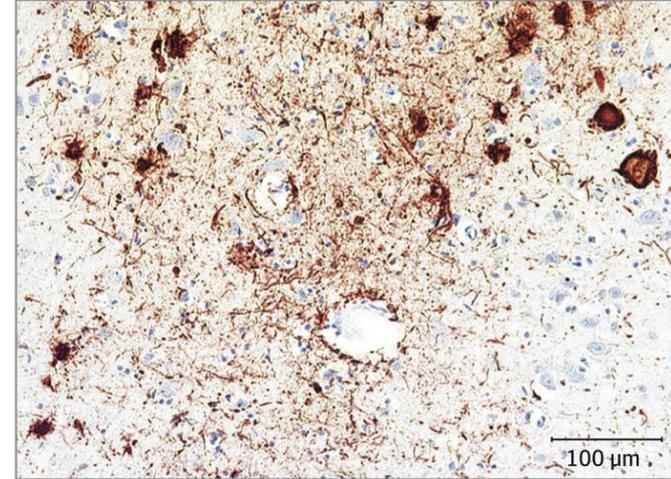
No differences in brain volume and TES status

Precision Neuroscience



Hemisphere

Arciniega et al., 2024, *Brain*.



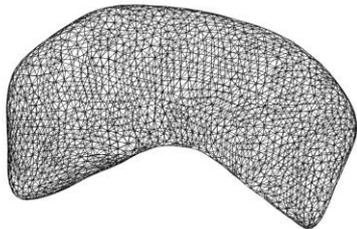
Stage III CTE Pathology

Advanced Neuroimaging Methods

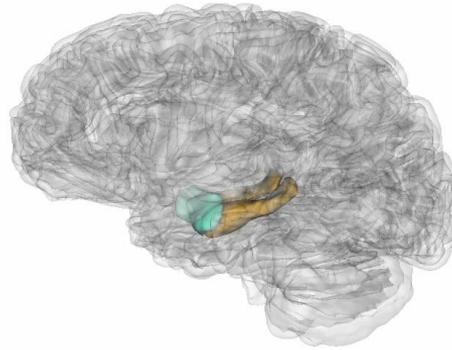
ENIGMA SHAPE ANALYSIS PIPELINE



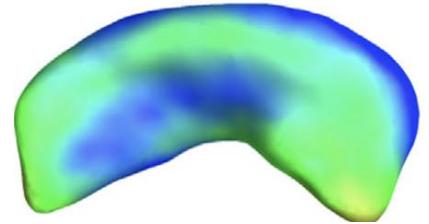
1. QC of Freesurfer subcortical volumes. Input is then used for the shape-processing pipeline.



2. Shape mesh is then created for regions of interest.



3. Mesh is registered to ENIGMA subcortical shape template.

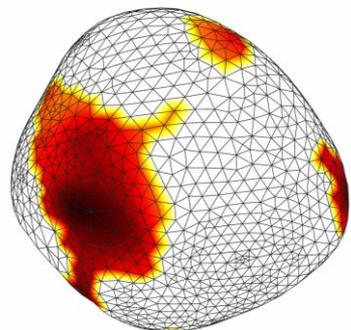


Larger  Smaller

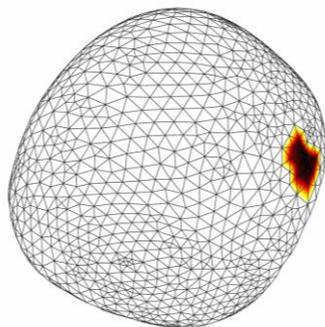
4. Compute Jacobian determinant (surface dilation ratio) metrics across thousands of homologous points for all subjects

Do structural morphological changes of the amygdala and hippocampus mimic the neuropathology of CTE at postmortem?

Amygdala

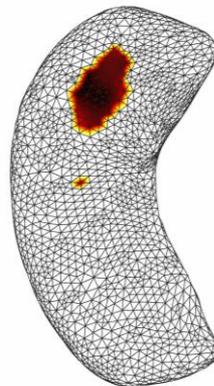


Left

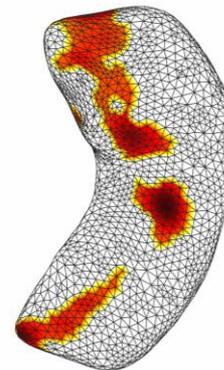


Right

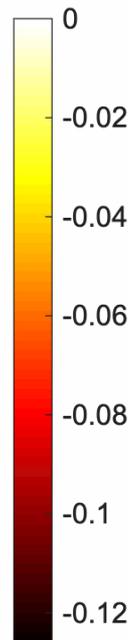
Hippocampus



Left



Right

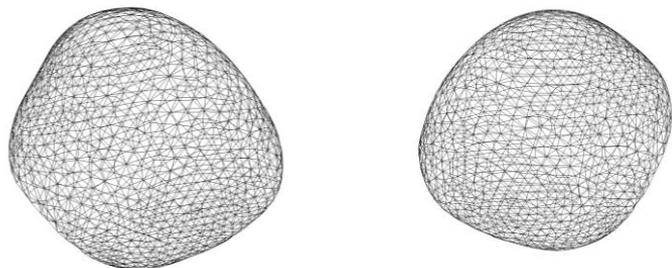


Cohen's d

Surface area contractions in former American football players

Do amygdala and hippocampus morphological changes differ by TES status?

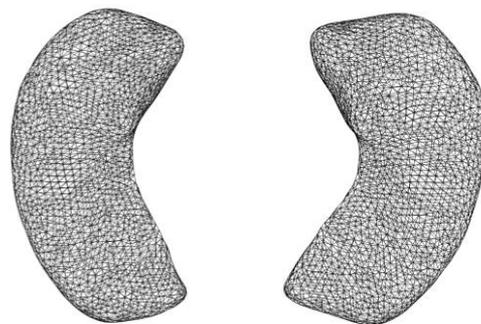
Amygdala



Left

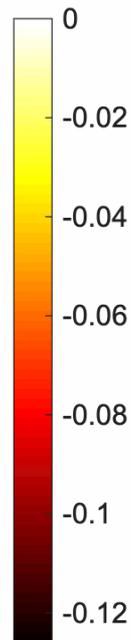
Right

Hippocampus



Left

Right



Cohen's d

No differences in former American football players with and without TES

Conclusion

- There are currently **no** validated *in vivo* biomarkers for CTE.
- TES provides a symptom-based clinical framework, but lacks biological specificity and objective imaging markers.
- Using structural MRI, we identified significant anatomical alterations in former football players in regions known to be vulnerable to CTE, including the sulci, septum pellucidum, hippocampus, and amygdala.
- Importantly, these structural alterations were present independent of TES diagnosis, highlighting a disconnect between clinical classification and underlying brain biology.
- **So, where are we now?**
 - Structural MRI can detect biologically meaningful brain changes associated with repetitive head impacts during life.
 - These findings represent an important step toward biologically grounded imaging biomarkers for in vivo detection and tracking of CTE-related neurodegeneration.

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Q&A

