

Clinicopathologic Phenotypes of Chronic Traumatic Encephalopathy: Distinct Traumatic Risk-Factors

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Disclosures

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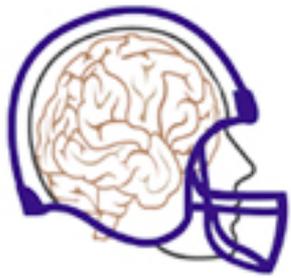
Nothing to disclose

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Co-founder, Medical Director, CLF
Royalties Houghton Mifflin Harcourt
Legal Expert Opinion (NCAA etc)



ROBERT C. CANTU, MD
NEUROLOGICAL SURGERY INC.

More than just a mentor

- Clinical Professor of Neurosurgery & Neurology, BUSM
- Co-Director, CTEC
- Co-Founder, Medical Director Concussion Legacy Foundation (formerly Sports Legacy Institute)
- Co-Director, Neurologic Sports Injury Center

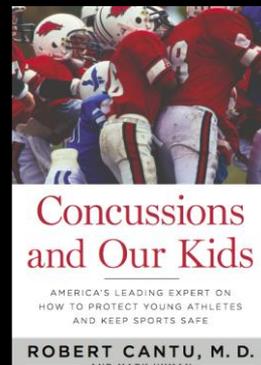
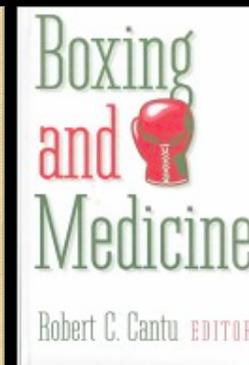
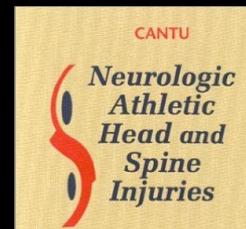


Google

Cantu RC

Scholar

About 22,800 results (0.05 sec)





Robert Stern PhD, Ann McKee MD, Chris Nowinski, Robert Cantu MD

The CTE Center was founded in 2008, at the Boston University School of Medicine

- 1.) Pathological Studies: VA CTEC Brain Bank , UNITE Pathology-UO1 Pathological Studies
- 2.) Clinical Studies: DETECT & LEGEND studies, *New UO1 Clinical Biomarker Studies

Overview

Pathology

Clinical Presentation

Risk-Factors

Chronic Traumatic Encephalopathy

What is it?...

- ① Also “Punch-Drunk” & “Dementia Pugilistica”
- ② A progressive neurodegeneration
- ③ A unique tauopathy with a characteristic pattern
- ④ All reported cases have brain trauma, usually repetitive

Feb 25, 2015

NINDS/NIBIB National Consensus Meeting Pathological Criteria for the Post-mortem Diagnosis of CTE



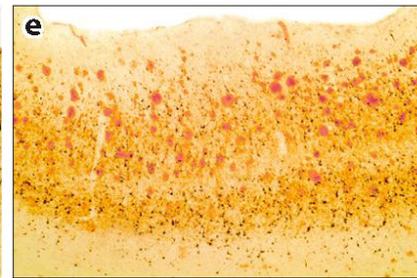
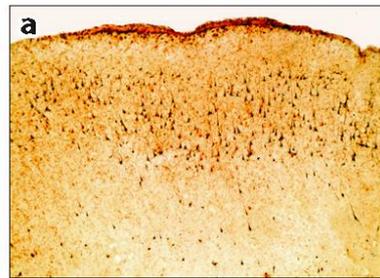
McKee AC, Alvarez V, Bieniek K, Cairns N, Crary J, Dams-O'Connor K, Folkerth R, Keene D, Litvan I, Montine T, **Montenigro PH**, et al. **“Preliminary Results of the NINDS/NIBIB Consensus Conference to Evaluate Pathological Criteria for the Diagnosis of CTE”** 67th AAN Meeting, DC, Neurology 2015.

CTE Pathological Criteria (Mckee et al 2013 Brain)

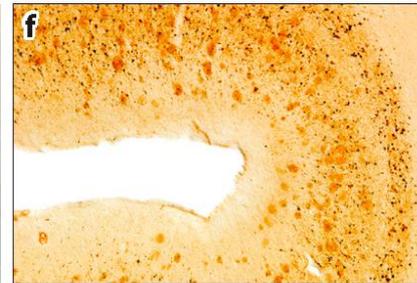
CTE

AD

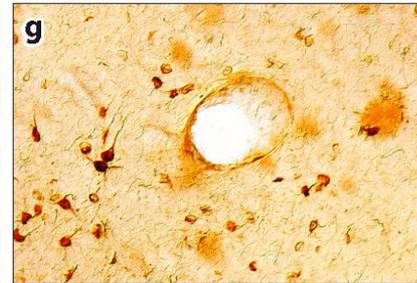
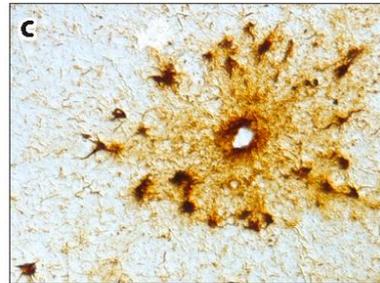
Cortical Layers



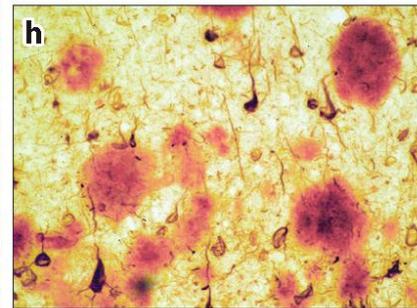
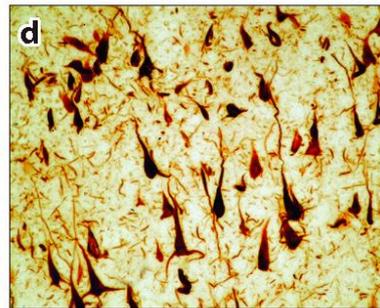
Sulcal Depths



Perivascular



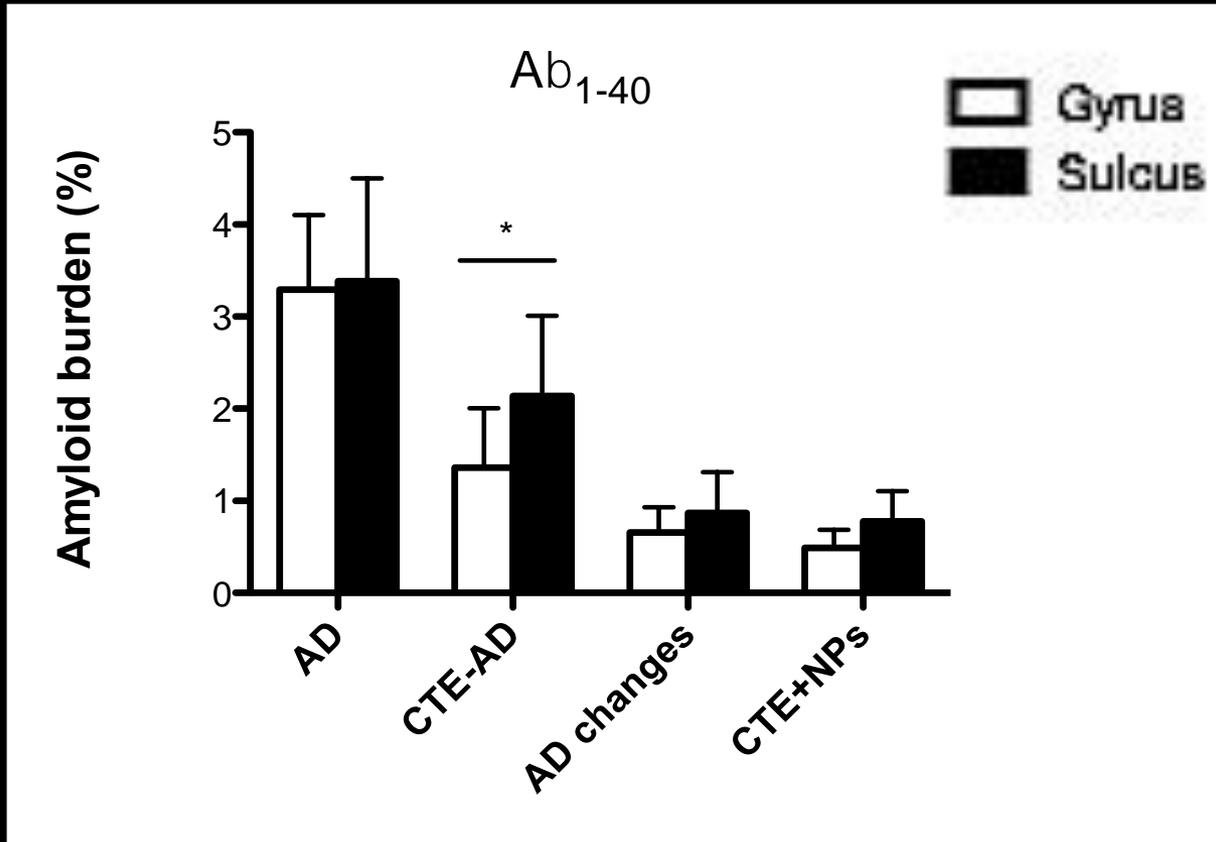
Tauopathy



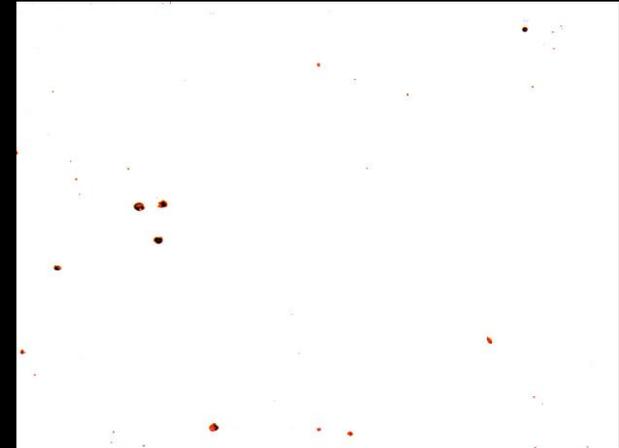
Amyloid-beta in CTE?

- A β deposition in **43% of CTE** subjects.
- A β in CTE occurs at an **earlier age** and an **accelerated** rate (OR=11.1, p=0.025).
- A β plaques associated with increased severity of CTE **tau stage** (β =0.53, p=0.003) and **dementia** (OR=4.50, p=0.007)

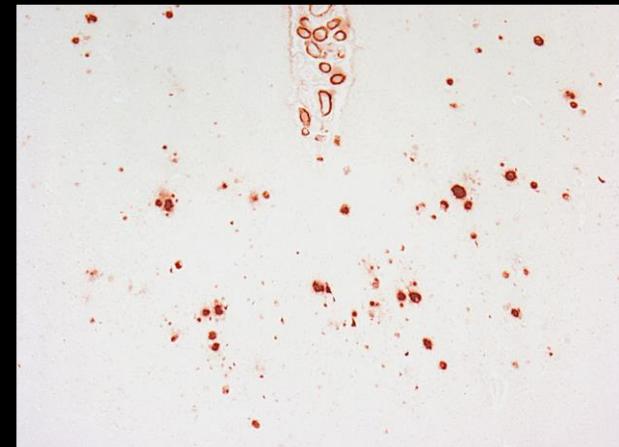
A β 1-40 in the sulcus



Gyrus



Sulcus



To date, CTE is
only diagnosed at *autopsy*

We need validated clinical criteria

- ① Refine risk-factors
- ② Identify preventative measures
- ③ Develop treatments

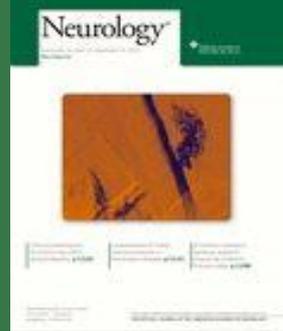
Overview

Pathology

Clinical Presentation

Risk-Factors

Clinical presentation of chronic traumatic encephalopathy



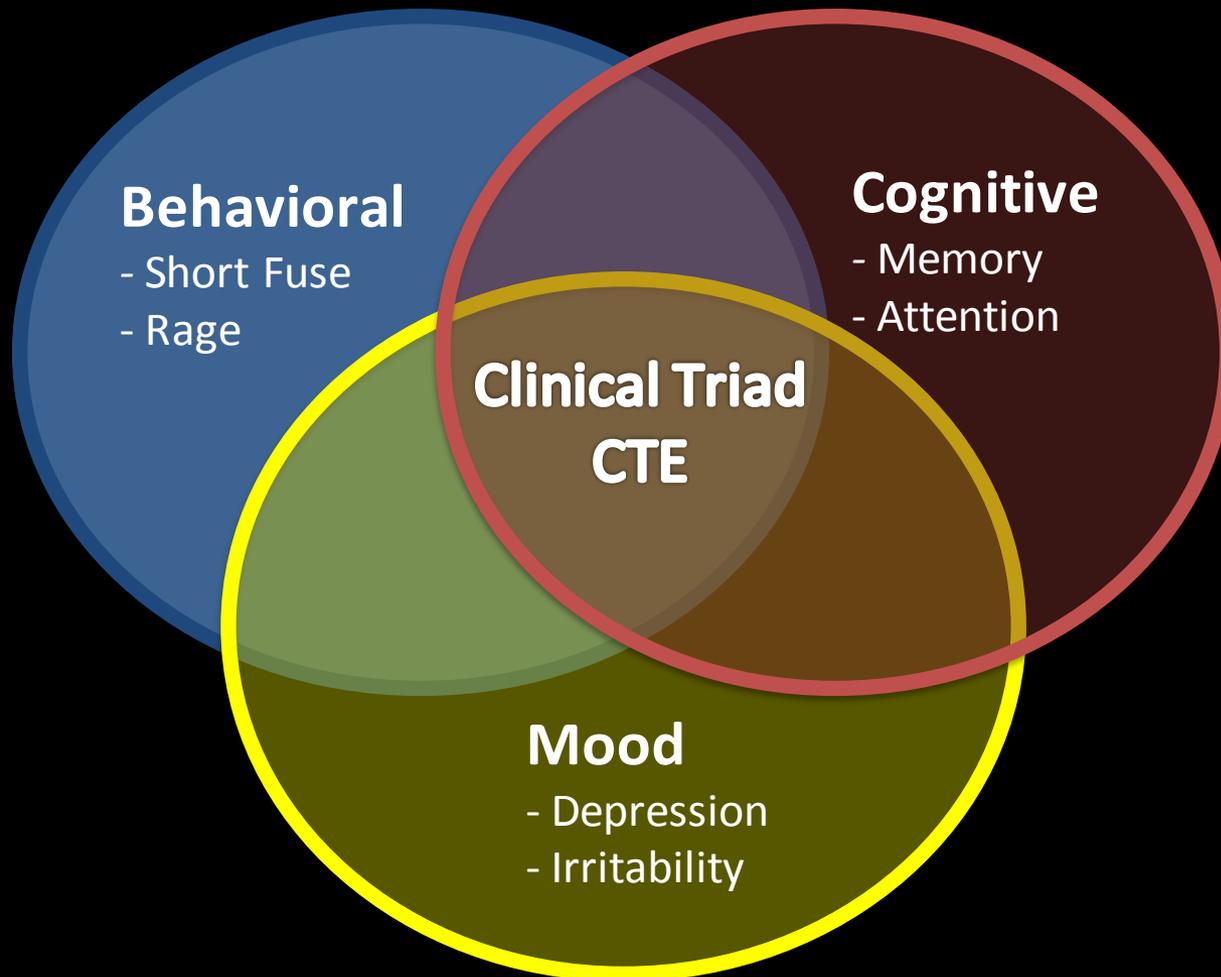
Clinical Presentation

- N=36 CTE pathologically confirmed
- No co-morbid disease
- Detailed psychological autopsies performed
 - Symptom frequencies quantified
 - 2 subtypes discerned

Clinical presentation of chronic traumatic encephalopathy



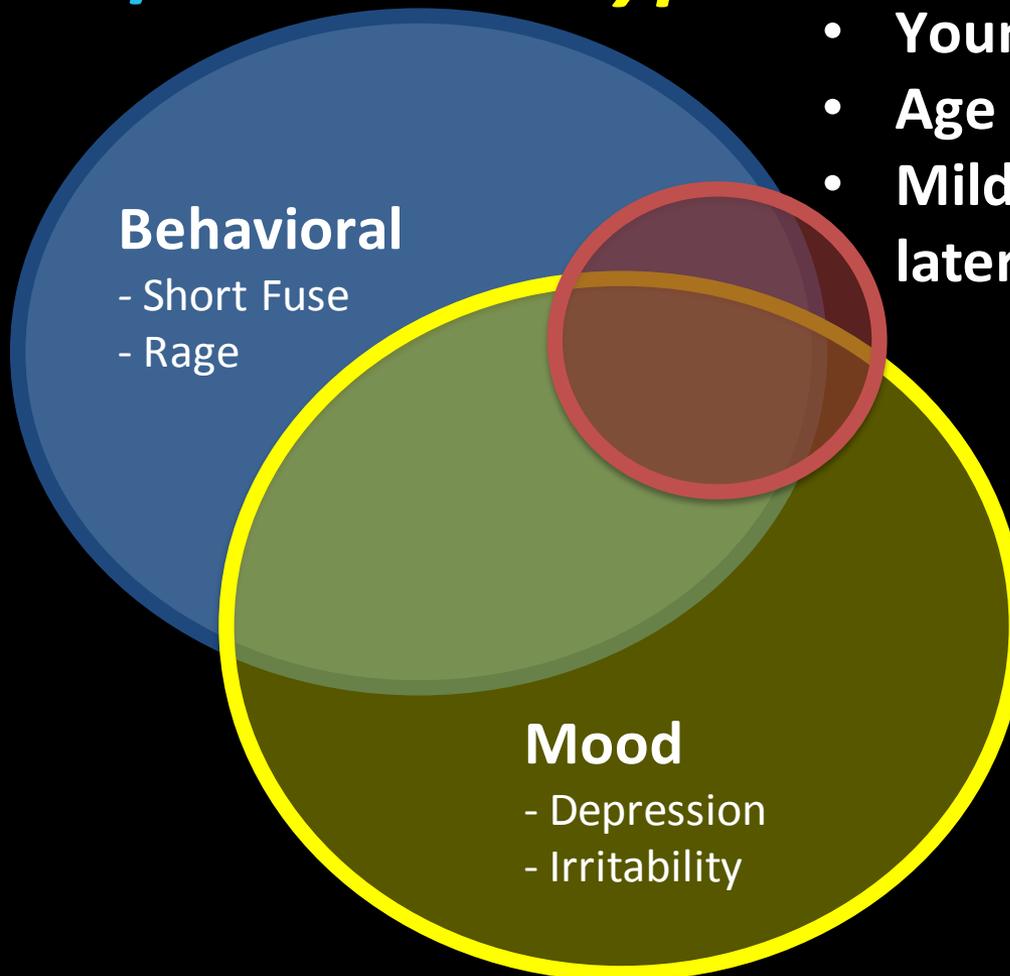
Clinical Triad



Clinical presentation of chronic traumatic encephalopathy



Behavioral/Mood *Subtype*



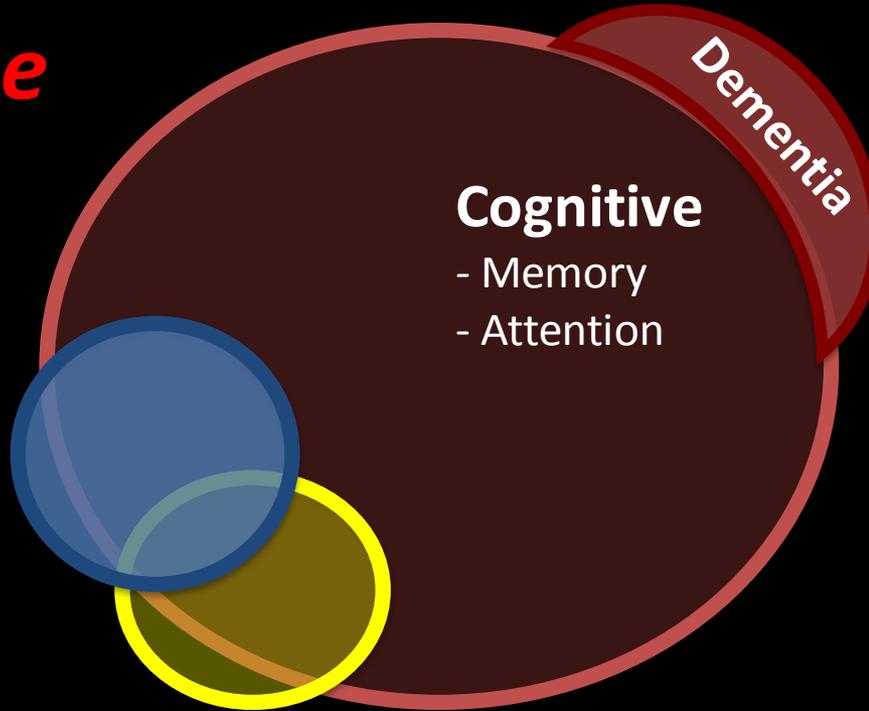
- Younger at onset
- Age = 35
- Mild cognitive symptoms later in life.

Clinical presentation of chronic traumatic encephalopathy



Cognitive Subtype

- Older at onset
- Age= 56
- 46% progressed to have B/M disorders
- 56% progressed to dementia



Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome

Philip H Montenegro¹, Christine M Baugh², Daniel H Daneshvar³, Jesse Mez⁴, Andrew E Budson^{4,5}, Rhoda Au^{2,6}, Douglas I Katz^{2,7}, Robert C Cantu^{8,9} and Robert A Stern^{1,4,2,8*}

Clinical Presentation

- Reviewed N=86 CTE pathologically confirmed
- Confirmed subtypes
- Proposed clinical research criteria

Overview

Pathology

Clinical Presentation

Risk-Factors

Risk-Factors

Severity of CTE Pathology:

- ① Years playing football ($p < 0.0001$)
- ② Years since retirement ($p < 0.0001$)
- ③ Informant reported concussions?
- ④ Steroid use ($p = 0.73$)

Repetitive-TBI

Evidence in the pattern of CTE pathology

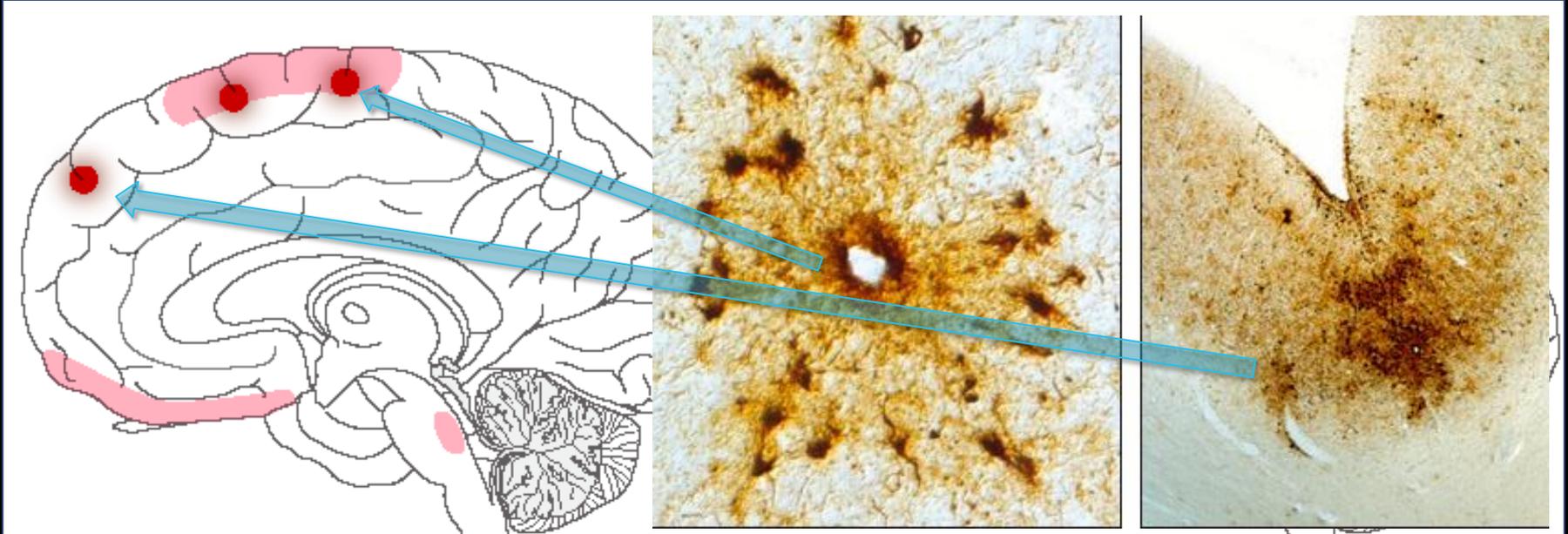
- ① Sulcal depth
- ② Perivascular
- ③ Fronto-limbic progression

Closed-Head Impacts (repetitive)

Biomechanics of injury and accumulation

Montenigro P, Bernick C, Cantu RC. Brain Pathology. 2015

Evidence in the pattern of CTE pathology



Closed-Head Impacts (repetitive)

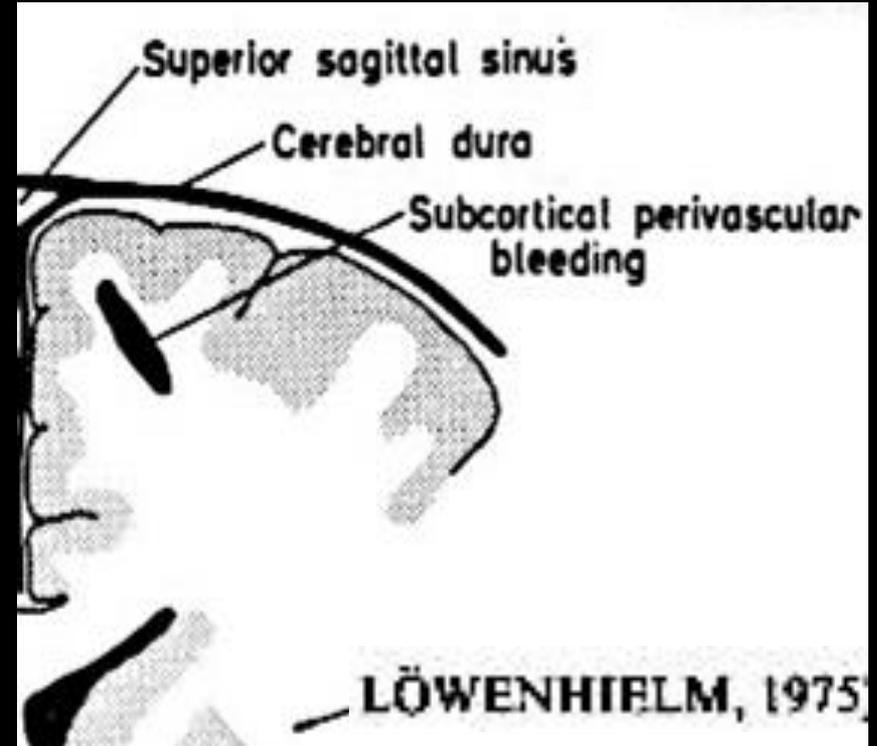
Biomechanics of injury and accumulation

Closed-Head Impact Biomechanics?

Closed Head Impacts



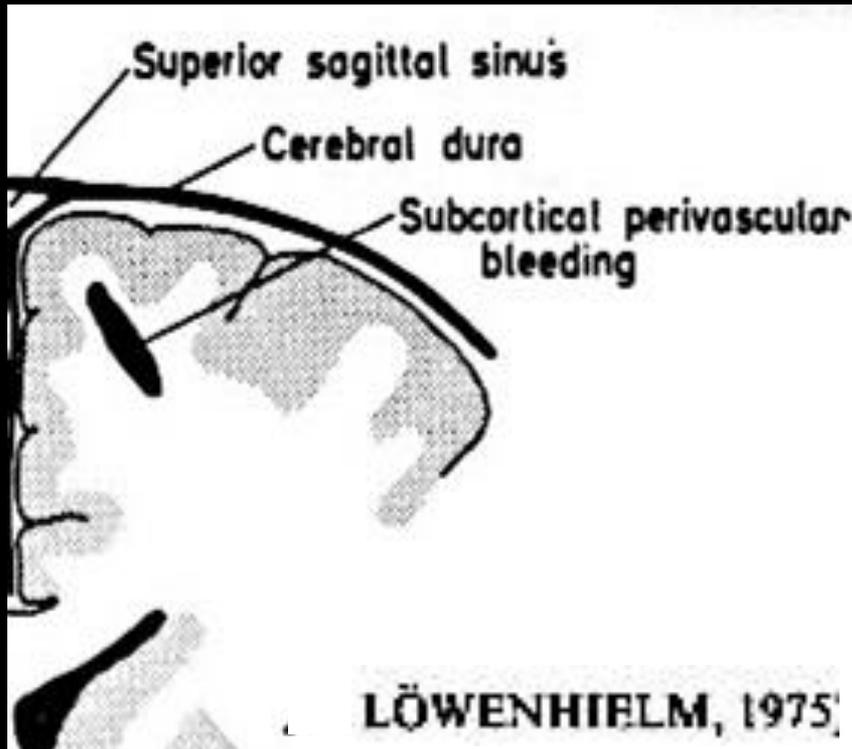
Gliding Contusion



- Frontal parasagittal
- Perivascular
- Sulcal depth

Closed-Head Impact Biomechanics?

Gliding Contusion



- Frontal parasagittal
- Perivascular
- Sulcal depth

CTE Initiation Site



- Frontal parasagittal
- Perivascular
- Sulcal depth

Closed-Head Impacts

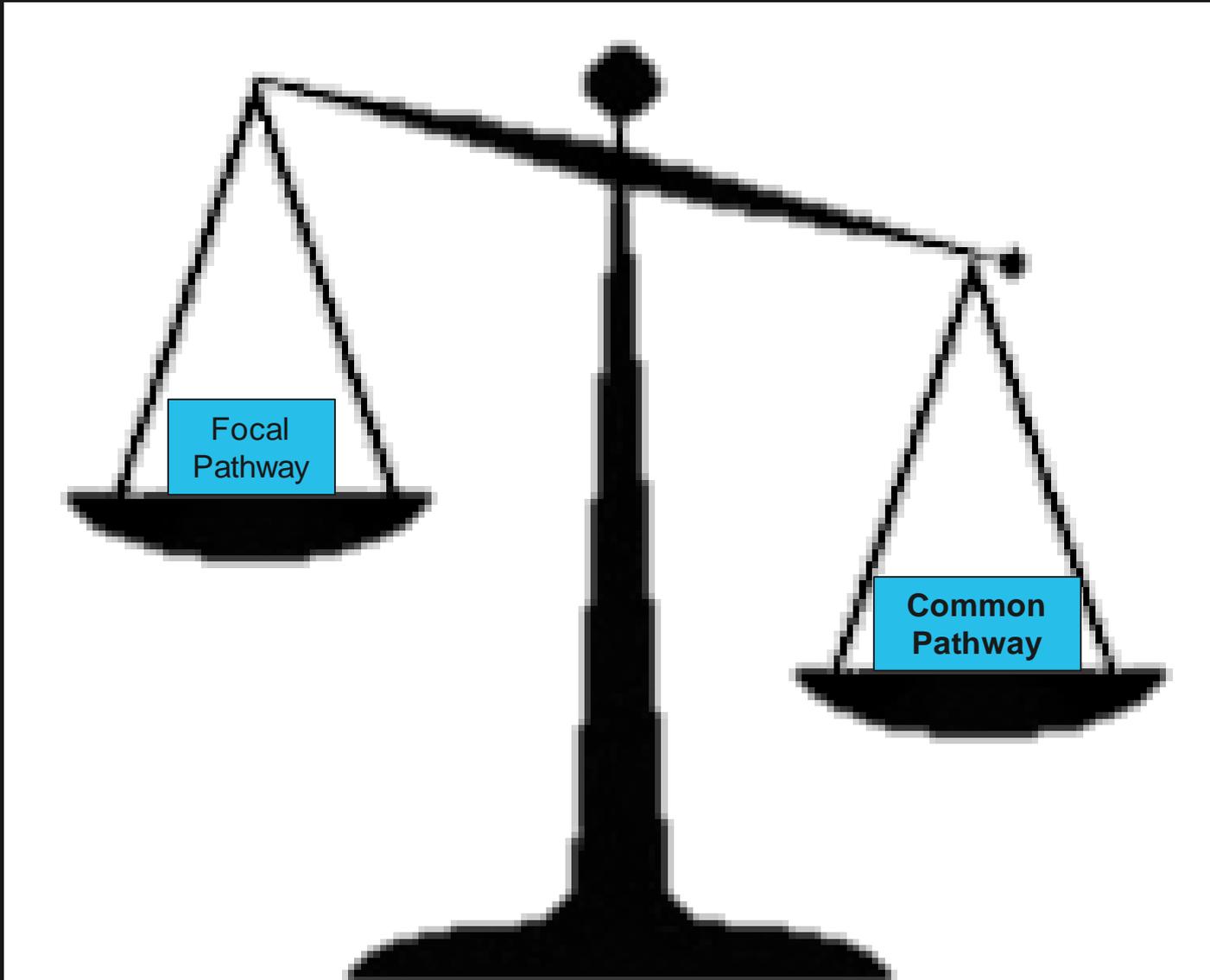
1. Common (vulnerable) pathway

- Gliding *Contusion
- Homogenous

2. Focal (local) Pathway

- Not specific, multiple injuries
- Heterogeneous

Cumulative **Closed-Head Impacts**



Cumulative Closed-Head Impact

When might there be an exception?

Certain sports/situations where local effects of impacts are consistent enough...?

Our hypothesis:

In these situations the local effects may contribute to and alter the cumulative effects.

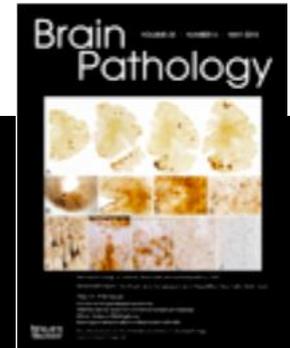
Risk-Factors

Specific CTE Subtypes

- ① Not known...

Clinical Features of Repetitive Traumatic Brain Injury and Chronic Traumatic Encephalopathy

Philip H. Montenegro^{1,2}; Charles Bernick³; Robert C. Cantu^{1,4,5,6}



- Detailed case reports
 - Professional football player
 - Professional boxer
- Secondary analysis comparing clinicopathological features of CTE in boxers vs football players
- Special focus on cerebellum.



Hook-Punch Biomechanics: *Net Rotational Acceleration*



Montenigro PH, Bernick C, Cantu RC. Clinical Features of Repetitive Traumatic Brain Injury and Chronic Traumatic Encephalopathy. Brain Pathology. 2015

Hook-Punch Biomechanics: *Rotational Acceleration*



Common pathway
+
Local effect

Front-Top Helmet to Helmet: *Net Linear Acceleration*



Montenigro PH, Bernick C, Cantu RC. Clinical Features of Repetitive Traumatic Brain Injury and Chronic Traumatic Encephalopathy. Brain Pathology. 2015

Front-Top Helmet to Helmet: *Linear Acceleration*



Common pathway
+
Local effect

Study Hypothesis

1. Cumulative RTBI = CTE tauopathy
2. Distinct impact exposures = *altered phenotype & progression*

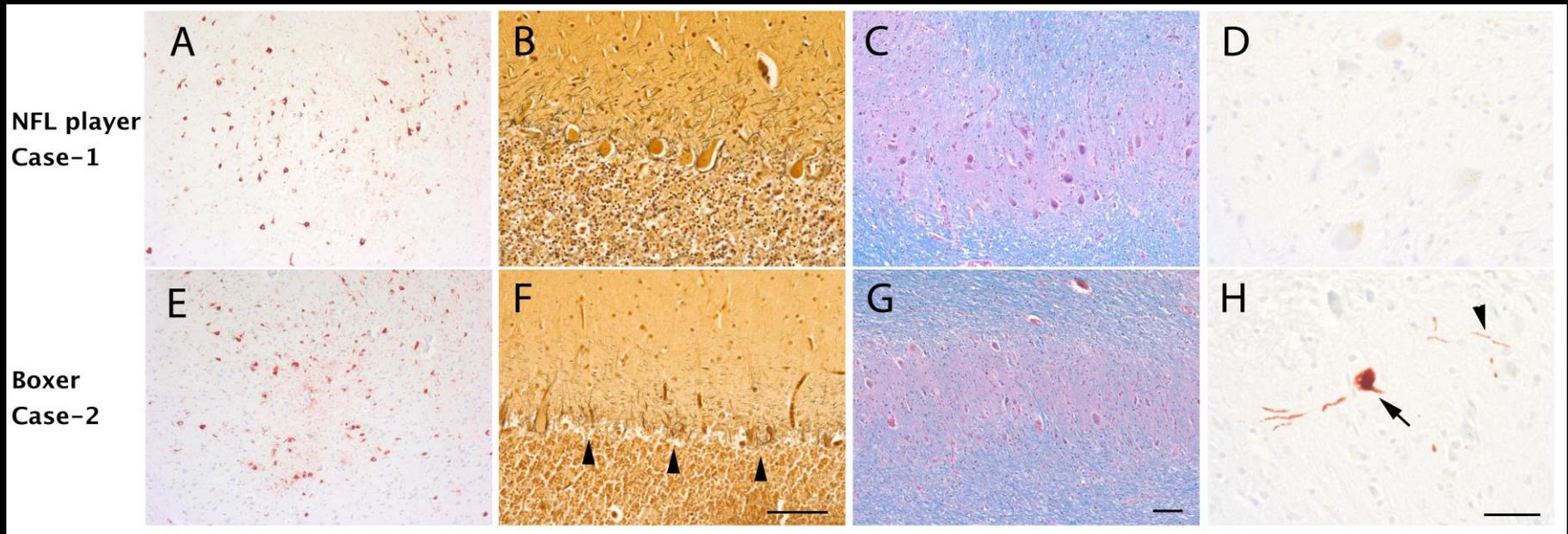


VS



Confirmed-CTE Case Comparison

NFL Player versus *Pro-Boxer*



Cumulative Closed-Head Impacts

Table 7. Comparison of chronic traumatic encephalopathy (CTE) clinicopathological features in boxers vs. football players.

Novel new (secondary) analysis of previously reported cases in McKee <i>et al</i> (52)	Pro Football	Pro Boxing
Late stage CTE (III-IV)	25	7
Mean decade age at symptom onset	50-60	50-60
Mean decade age at time of death	70-80	80-90
[†] Late stage CTE "with motor features"	18.8% (3/16) [‡]	83% (5/6) [‡]
Late stage CTE with cerebellar dentate neurofibrillary tangles	57% (12/21)	71% (5/7)
Late stage CTE with severe (++/+++) dentate neurofibrillary tangles	17% (2/12) [‡]	80% (4/5) [‡]

CTE in the Military: what do we know?

Definition of exposure: *combat-related TBI?*

- Diagnosis: *clinical signs...*

- Source: *Heterogeneous...*

Blast? or Non-Blast?... Breach? or Other?...

Military Boxing? or Football?

Exposure, injury, and outcome?

CTE in the Military: what do we know?

- Of 110 CTE cases pathologically diagnosed at the BU Brain Bank:
 - 23 veterans (21%)
 - 5 of 23 had early-stage CTE
 - 4 out 5 diagnosed with PTSD
 - *Exposures highly heterogeneous*

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- Victor Alvarez
- Andrew Budson
- Douglass Katz

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- Dan Daneshvar
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- And all the athletes, veterans, and families who participate in our research



THANK YOU

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concussionfoundation.org