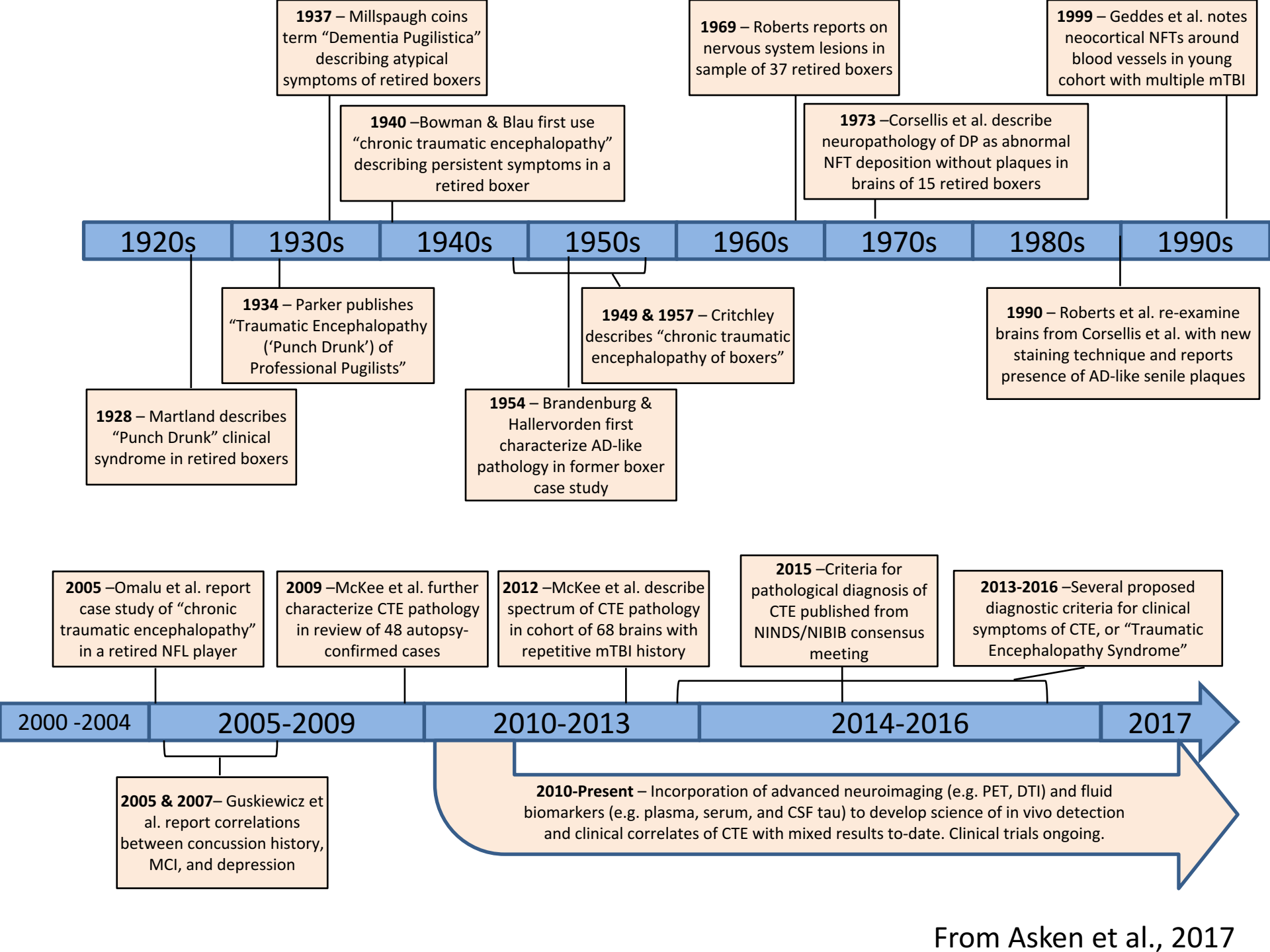
Chronic Traumatic Encephalopathy and Football

State of the Science

Breton Asken, MS, ATC
University of Florida

Overview

- Brief historical perspective
- Distinguishing *PATHOLOGY* from *SYNDROME*
- CTE neuropathology
- CTE clinical syndrome
  - Traumatic encephalopathy syndrome (TES)
- Challenges to the clinical examination
  - Cognitive reserve and “Neuropsychology 101”
- Research Gaps
- Take Home Points



From Asken et al., 2017

"Punch Drunk"

VOLUME 91
NUMBER 15

PUNCH DRUNK *

HARRISON S. MARTLAND, M.D.
NEWARK, N. J.

For some time fight fans and promoters have recognized a peculiar condition occurring among prize fighters which, in ring parlance, they speak of as "punch drunk." Fighters in whom the early symptoms are well recognized are said by the fans to be "cuckoo," "goofy," "cutting paper dolls," or "slug nutty."

1928

"Traumatic Encephalopathy"

1934

TRAUMATIC ENCEPHALOPATHY (' PUNCH DRUNK ') OF PROFESSIONAL PUGILISTS *

By

HARRY L. PARKER, The Mayo Clinic, Rochester, Minnesota

The result, immediate or remote, of repeated injuries to the brain of a professional boxer forms a study all in itself, and contrasts with the more usual sequelæ seen when patients have received only one injury in the course of industrial or other pursuits. The problem, moreover, forms one phase of the extremely complicated and highly controversial subject of head injury and its consequence. For purposes of description, the injuries received by pugilists in activities of their profession may be divided into those received during an actual bout, serious enough to cause death immediately or a few hours later, and those which more by their repetition than by their severity lead to slower development of disability during the fighter's career. It is with this latter group that this paper is concerned.

"Chronic Traumatic Encephalopathy"

1940

CHAPTER 13

PSYCHOTIC STATES FOLLOWING HEAD AND BRAIN INJURY IN ADULTS AND CHILDREN

KARL MURDOCK BOWMAN, A.B., M.D.
ABRAM BLAU, M.Sc., M.D., C.M.

The diagnosis of chronic traumatic encephalopathy of pugilists was made

1949 & 1957

BRITISH MEDICAL JOURNAL

MEDICAL ASPECTS OF BOXING, PARTICULARLY FROM A NEUROLOGICAL STANDPOINT*

BY
MACDONALD CRITCHLEY, M.D., F.R.C.P., F.A.C.P.

Neurologists have visualized this state of chronic traumatic encephalopathy as being based upon multiple minor cerebral contusions, possibly with initial pinpoint haemorrhages later replaced by a gliosis, cortical atrophy, and

American Football

NEUROSURGERY

CHRONIC TRAUMATIC ENCEPHALOPATHY IN A NATIONAL FOOTBALL LEAGUE PLAYER

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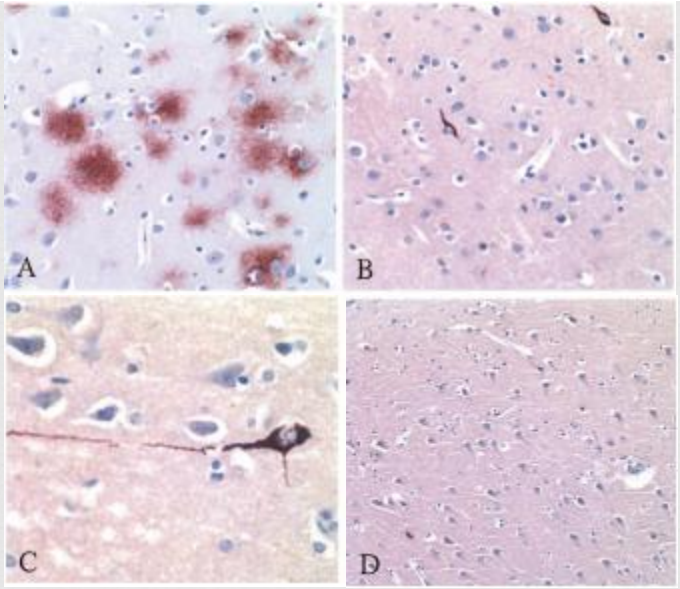


Cause of death: Heart Attack

2005 – the "modern" CTE era

Is CTE the same as "Punch Drunk"?

- Most discuss as synonymous
- Vastly different clinical presentations

- Punch Drunk
  - Primarily motor symptoms
  - Symptoms present *DURING* careers
  - Cognitive changes only seen later in minority of cases
- CTE
  - Cognitive and/or behavioral symptoms first
  - Symptoms typically present many years after retirement
  - Motor symptoms rare

Does Impact Mechanism Matter?

Boxers

- Rotational > Linear
  - ↑ Brain stem involvement
- CTE + Motor features
  - 83.3% (5/6)
- CTE + severe cerebellar dentate NFTs
  - 80.0% (4/5)
- "Classic" CTE cases
  - Prior to the year ~2000

American Football

- Linear > Rotational
  - ↑ Cortical/frontal involvement
- CTE + Motor features
  - 18.8% (3/16)
- CTE + severe cerebellar dentate NFTs
  - 16.7% (2/12)
- "Modern" CTE cases
  - 2000 and later

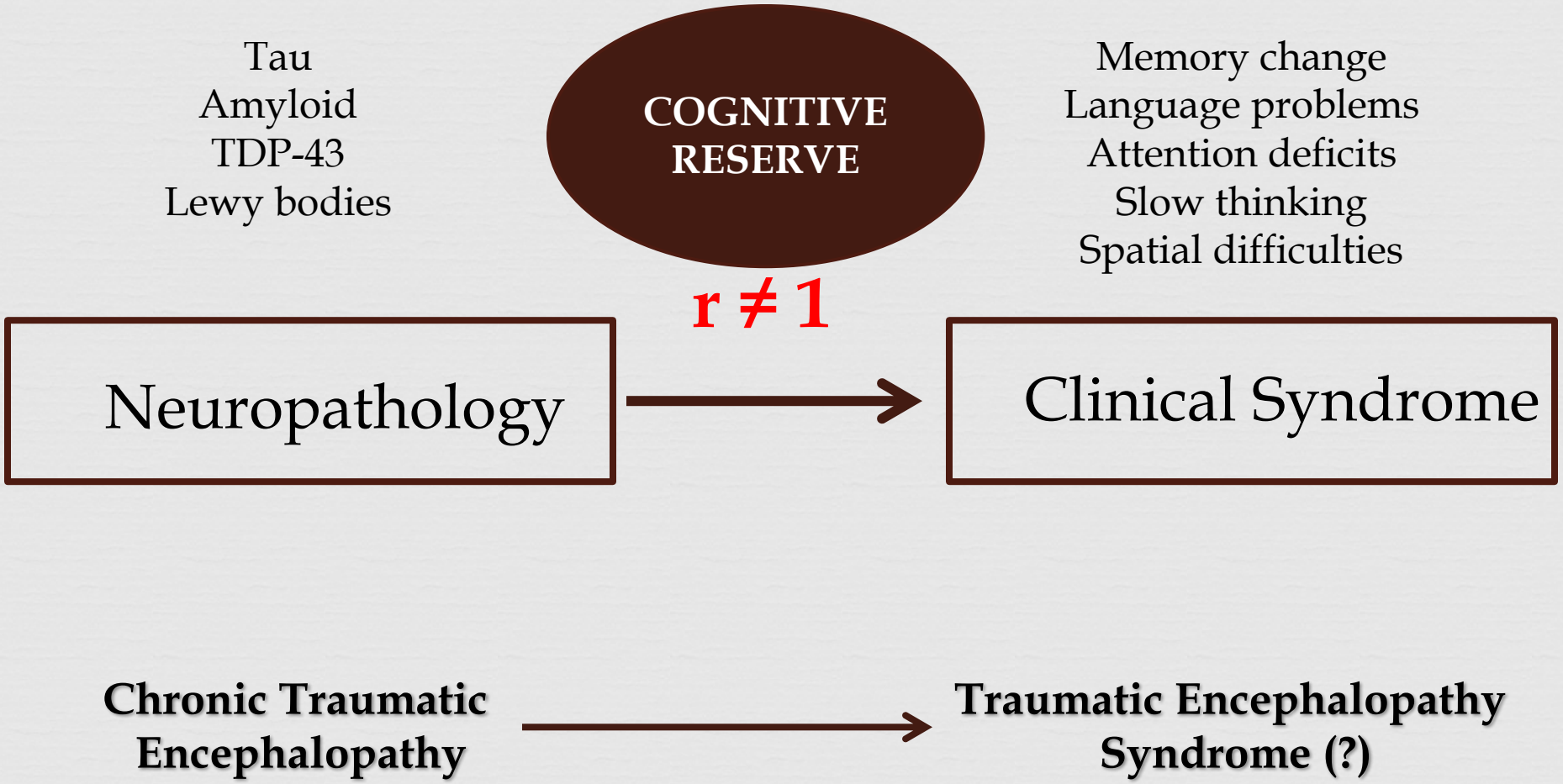
Montenigro et al., 2015

Terminology

Neuropathology vs. Clinical Syndrome

"Does repetitive brain trauma increase risk for *neuropathological changes*?"

"Does repetitive brain trauma increase risk for *dementia*?"


Tau
Amyloid
TDP-43
Lewy bodies
COGNITIVE RESERVE
Memory change
Language problems
Attention deficits
Slow thinking
Spatial difficulties
r ≠ 1
Neuropathology
Clinical Syndrome
Chronic Traumatic Encephalopathy
Traumatic Encephalopathy Syndrome (?)

Factors Influencing Clinical Correlates of Chronic Traumatic Encephalopathy (CTE): a Review

Breton M. Asken[1] · Molly J. Sullan[1] · Aliyah R. Snyder[1] · Zachary M. Houck[1] · Vaughn E. Bryant[1] · Loren P. Hizel[1] · Molly E. McLaren[1] · Duane E. Dede[1] · Michael S. Jaffee[2] · Steven T. DeKosky[2] · Russell M. Bauer[1]

JAMA Neurology

Research Gaps and Controversies in Chronic Traumatic Encephalopathy A Review

Breton M. Asken, MS, ATC; Molly J. Sullan, MS; Steven T. DeKosky, MD; Michael S. Jaffee, MD; Russell M. Bauer, PhD

The Need to Separate Chronic Traumatic Encephalopathy Neuropathology from Clinical Features

Grant L. Iverson[a,*], C. Dirk Keene[b], George Perry[c] and Rudolph J. Castellani[d]

CTE vs. TES

- CTE
  - Neuropathological diagnosis
  - Confirmable only via autopsy
    - Irrespective of presence or absence of any symptoms
- TES
  - Clinical diagnosis
  - Symptom presentation
    - Irrespective of underlying neuropathology
    - Some reach level of "dementia"
- CTE/TES and Dementia
  - Not synonymous
    - Dementia is a very specific term describing a CLINICAL syndrome
    - Requires FUNCTIONAL impairment and change from previous level
      - Inability to independently perform activities of daily living
      - Cooking, managing finances, personal care, etc.
  - Only a small % of identified CTE cases had dementia

CTE Neuropathology

Tau

- Stabilizes neuron microtubules (structural component)
  - Railroad ties
- Concussive forces can phosphorylate tau protein
- Phosphorylation of tau leads to detachment and misfolding
- Misfolded tau not cleared and accumulates
- Axon transport systems become dysfunctional
  - Train can't get down the tracks

CTE Neuropathology

National Institute of Neurological Disorders and Stroke

Report from the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy

9 pathologists shown 19 brain regions from 25 brains with progressive

[redacted] In general, there was excellent agreement among the pathologists with regard to distinguishing CTE from the other tauopathies [redacted]

- Independent review blinded to age, sex, and clinical history

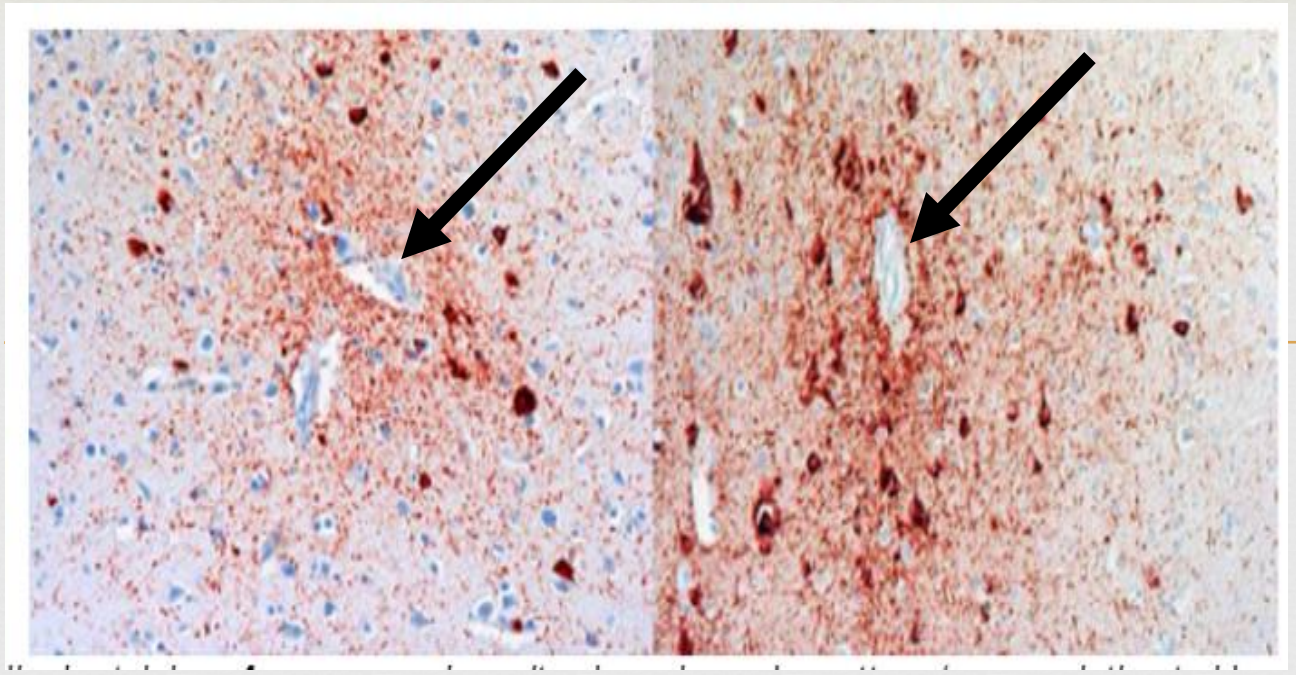
Nigel J. Cairns - Washington University, St. Louis
Dennis W. Dickson - Mayo Clinic, Jacksonville
Rebecca Folkerth – Brigham and Women's Hospital, Boston
C. Dirk Keene - University of Washington, Seattle
Ann McKee - Boston University (Principal Investigator of one of the NIH CTE grants)
Daniel Perl - Uniformed Services University of the Health Sciences, Bethesda
Thor Stein - Boston University
Willie Stewart - University of Glasgow, Scotland
Jean Paul Vonsattel - Columbia University, New York

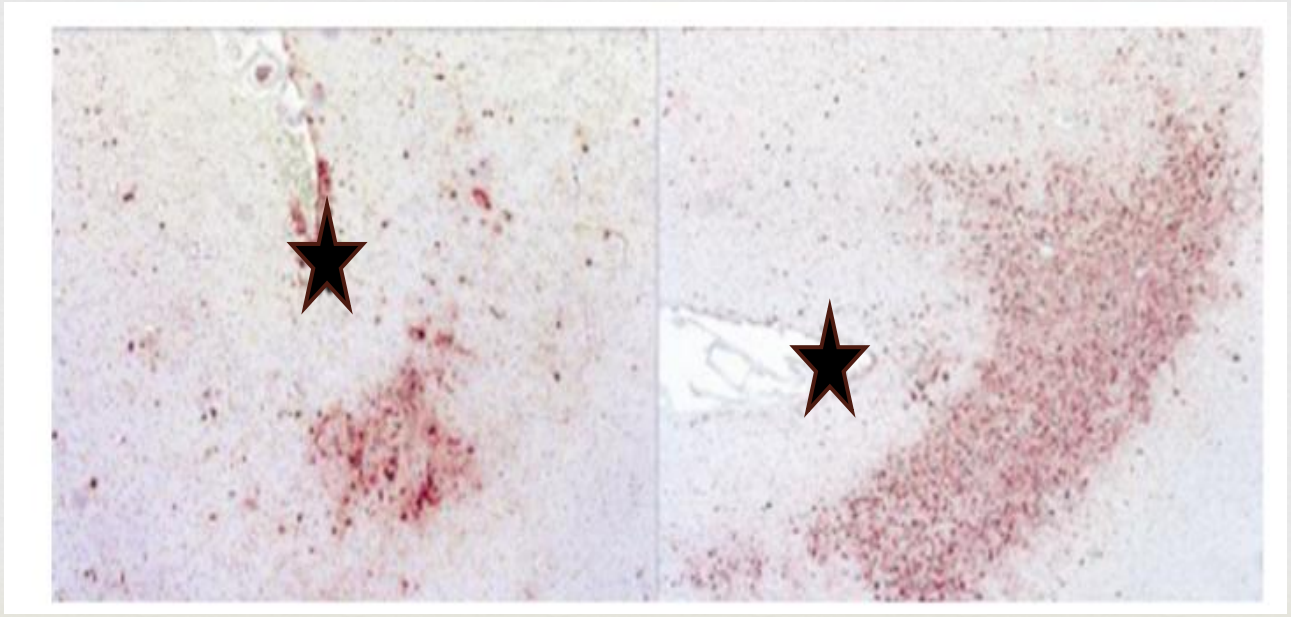
McKee et al., 2016

CTE Neuropathology

- REQUIRED
  - "In CTE, the tau lesion considered pathognomonic **was an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci"**

McKee et al., 2016





Is CTE Progressive?

- Different severities described
  - 4 stages proposed in 2013 based on degree and distribution of pTau (and other proteins)
- Cannot identify *in vivo* with neuroimaging
- Current evidence all cross-sectional
- **"it remains unclear whether all cases progress, progress at the same rate, or whether some instances of CTE persist indefinitely as early-stage disease."**

(Stein et al. 2014)

NINDS Conclusions on CTE

- "…thus far, this pathology has only been found in individuals exposed to brain trauma, typically multiple episodes."
- Areas that need further study:
  - Specific pathological stages of the disorder – progressive?
  - Further characterization of amyloid and TDP-43 pathologies
- **"It is especially important for the community to understand that it is not yet possible to correlate clinical symptoms or future brain health with the signature pathologic feature of CTE."**

McKee et al., 2016

CTE Pathology Resources

Journal of Neuropathology & Experimental Neurology

Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury FREE

Ann C. McKee, MD ✉, Robert C. Cantu, MD, Christopher J. Nowinski, AB,

The Neuropathology of Chronic Traumatic Encephalopathy

Ann C. McKee ✉, Thor D. Stein, Patrick T. Kiernan, Victor E. Alvarez

Alzheimer's Research & Therapy

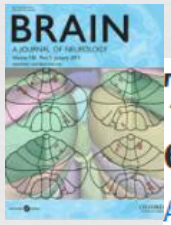
Chronic traumatic encephalopathy: a spectrum of neuropathological changes following repetitive brain trauma in athletes and military personnel

Thor D Stein, Victor E Alvarez and Ann C McKee ✉

Journal of Neuropathology & Experimental Neurology

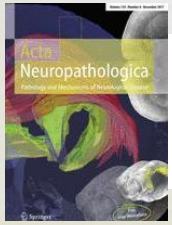
TDP-43 Proteinopathy and Motor Neuron Disease in Chronic Traumatic Encephalopathy FREE

Ann C. McKee, MD ✉, Brandon E. Gavett, PhD, Robert A. Stern, PhD,



The spectrum of disease in chronic traumatic encephalopathy FREE

Ann C. McKee ✉, Thor D. Stein, Christopher J. Nowinski, Robert A. Stern,



Beta-amyloid deposition in chronic traumatic encephalopathy

Thor D. Stein[1,2,3,4] · Philip H. Montenigro[3,5] · Victor E. Alvarez[3,6] · Weiming Xia[2] ·

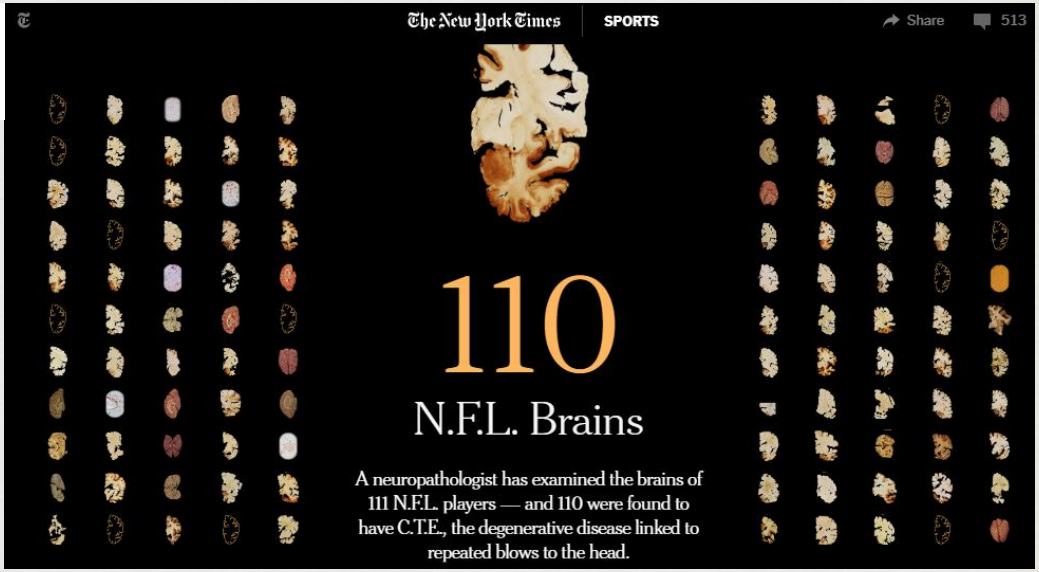
Prevalence and Risk

Recent Data and Limitations

CNN

CTE found in 99% of studied brains from deceased NFL players

The New York Times



USA TODAY

Study: CTE diagnosed in 99% of former NFL players studied by researchers

JAMA | Original Investigation

Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football

Views 162,850 | Cited by 47

- 177 of 202 (87.6%) of deceased former football players with CTE pathology
  - 110 of 111 (99%) former NFL
  - 7 of 8 (88%) of former CFL players
  - 9 of 14 (64%) of semi-pro football players
  - 48 of 53 (91%) of collegiate football players
  - 3 of 14 (21%) of high school football players
  - 0 of 2 (0%) pre-high school
- Variable severities
- NOT new cases – many previously reported in earlier studies
  - Not all cases carried forward…….
- ALL reported clinical symptomatology (selected/biased series)

What does that mean?

- 202 brains were collected from a *convenience sample*
  - Specialized recruitment
    - 1) individuals who played football AND
    - 2) complained of neurological problems before death
  - **Prevalence estimates (% values) are not informative**
- Equivalent to determining prevalence of chronic ankle instability from sample of athletes with prior ankle injury now complaining of ankle problems
- NEED inclusion of participants across entire health spectrum, with and without repetitive trauma exposure

Best Guesses So Far

- Bieniek et al. (2015) – Mayo Clinic Brain Bank
  - 66 brains from participants with collision sport exposure
    - 21 (32%) had CTE pathology
  - 0 brains without collision sport exposure had CTE
- LIMITATION
  - Determination of collision sport history
    - Obituaries, medical records, yearbooks
  - Very high likelihood that many individuals without *documented* exposure actually played those sports

Asymptomatic CTE

- Difficult to determine based on current study methods
- Common finding in Alzheimer Disease literature
  - After age 70, high prevalence of asymptomatic AD
  - No reported symptoms during life – AD found postmortem
- Earlier CTE study of 68 confirmed cases
  - 11% were asymptomatic
    - Some with relatively severe pathology (i.e. Stage III or higher)
- Essential group to study
  - Susceptibility, protective factors, preserving function, etc.

Concussion vs. "Subconcussion"

- Often weak or nonexistent correlation between number of self-reported concussions and CTE severity
- Total participation years possibly better predictor
  - Implication for subclinical impact exposure
  - Still inconsistent among studies
- Vast majority of cases – extensive history of both
- Coaches' and clinicians' role
  - Limit impacts where possible
  - Practice setting – "friendly fire" impacts

It's not concussions that cause CTE. It's repeated hits, a study finds

"Now we have both the scientific proof, the pathologies to support it, and all the evidence to show that concussion is not linked to long-term neurological disease,"

"CTE develops early, soon after injury. It doesn't take years, or decades. It starts early. It persists. And all of our evidence to date shows it's progressive."

To try and understand the source of the changes, Goldstein and his colleagues mimicked the experiences of the human brains in mouse models, by exposing mice to repeated head trauma, like that in football, and single blast head trauma,

BRAIN
A JOURNAL OF NEUROLOGY

Concussion, microvascular injury, and early tauopathy in young athletes after impact head injury and an impact concussion mouse model

were not restrained during experimental exposure. The single-repeat design incorporated two impacts separated by 15 min to mimic a minimal repeat head injury as commonly occurs during a single session of contact sport play or practice (Crisco *et al.*,

Population-Specific Considerations

- Repetitive brain trauma appears necessary
  - Proximity of exposure?
- Clinically diagnosed injury vs. subclinical trauma vs. both
  - "necessary but not sufficient"
    - Presence is required, but by itself will not produce outcome
  - "sufficient but not necessary"
    - Will produce outcome by itself, but so will other factors
- Civilian risk
  - Single/isolated brain injury event(s)
    - MVA, fall, assault
- Military and athlete risk
  - Repeated event
    - Multiple impact, blast exposure

End-goal of rehab

↓

Return to exposure

Generational Considerations

- Playing styles, practice regulations, concussion recognition/treatment have changed drastically
- Formalized protocols allow for rest/rehabilitation after *diagnosed* injuries
- Many participation levels now limiting contact practices
- Evidence for "window of vulnerability" after a concussion
  - Reducing incidence of playing through injuries
  - Eliminate sustaining more impacts when brain is vulnerable
  - Immediate recognition and removal improving, but still problematic currently
  - Ex) Boxers from old studies – NEVER stopped

Conclusions

- Unknown prevalence
- Unknown incidence
- Unknown risk factors beyond repetitive trauma
- Cannot be diagnosed prior to death

CTE Clinical Syndrome

Traumatic Encephalopathy Syndrome (TES)

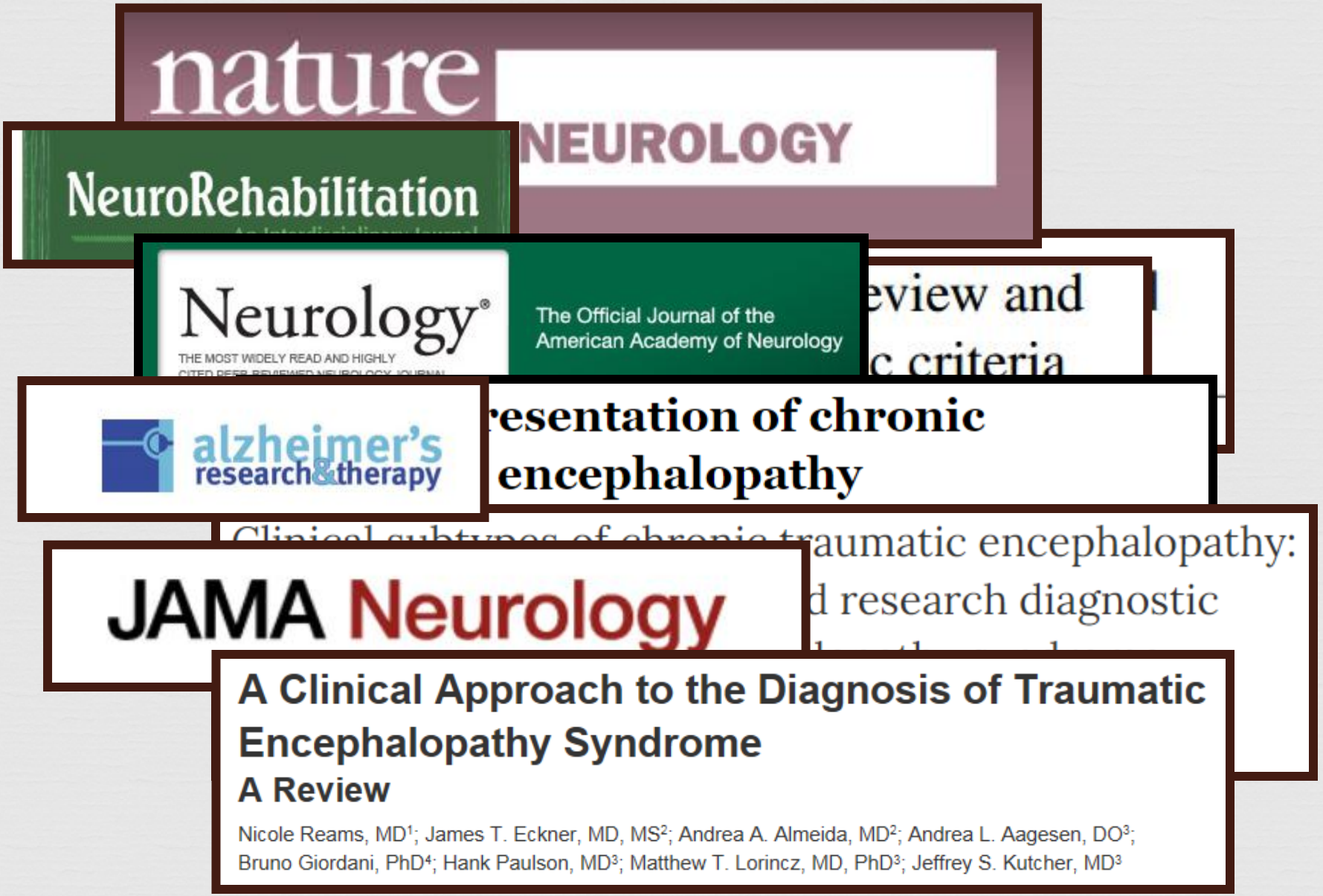
Clinical Presentation

Table 2 Summary of clinical features of chronic traumatic encephalopathy found in the literature

Behavioral features	Mood features	Cognitive features	Motor features
Explosivity	Depression	Dementia	Ataxia
Loss of control	Hopelessness	Memory impairment	Dysarthria
Short fuse	Suicidality	Executive dysfunction	Parkinsonism
Impulsivity	Anxiety	Lack of insight	Gait Disturbance
Aggression	Fearfulness	Perseveration	Tremor
Rage	Irritability	Impaired attention and	Masked facies
Physical violence	Labile emotions	concentration	Rigidity
Verbal violence	Apathy	Language difficulties	Muscle weakness
Inappropriate speech	Loss of interest	Dysgraphia	Spasticity
Boastfulness	Fatigue	Alogia	Clonus
Childish behavior	Flat affect	Visuospatial	
Social inappropriateness	Insomnia	difficulties	
Disinhibited speech	Mania	General cognitive impairment	
Disinhibited behavior	Euphoria	Reduced intelligence	
Paranoid delusions	Mood swings		
Personality changes	Prolix		
Psychosis			
Social isolation			

BEHAVIOR MOOD COGNITIVE MOTOR (?)

Proposed Clinical Symptoms



Broad Perspective

Montenigro et al. (2014)

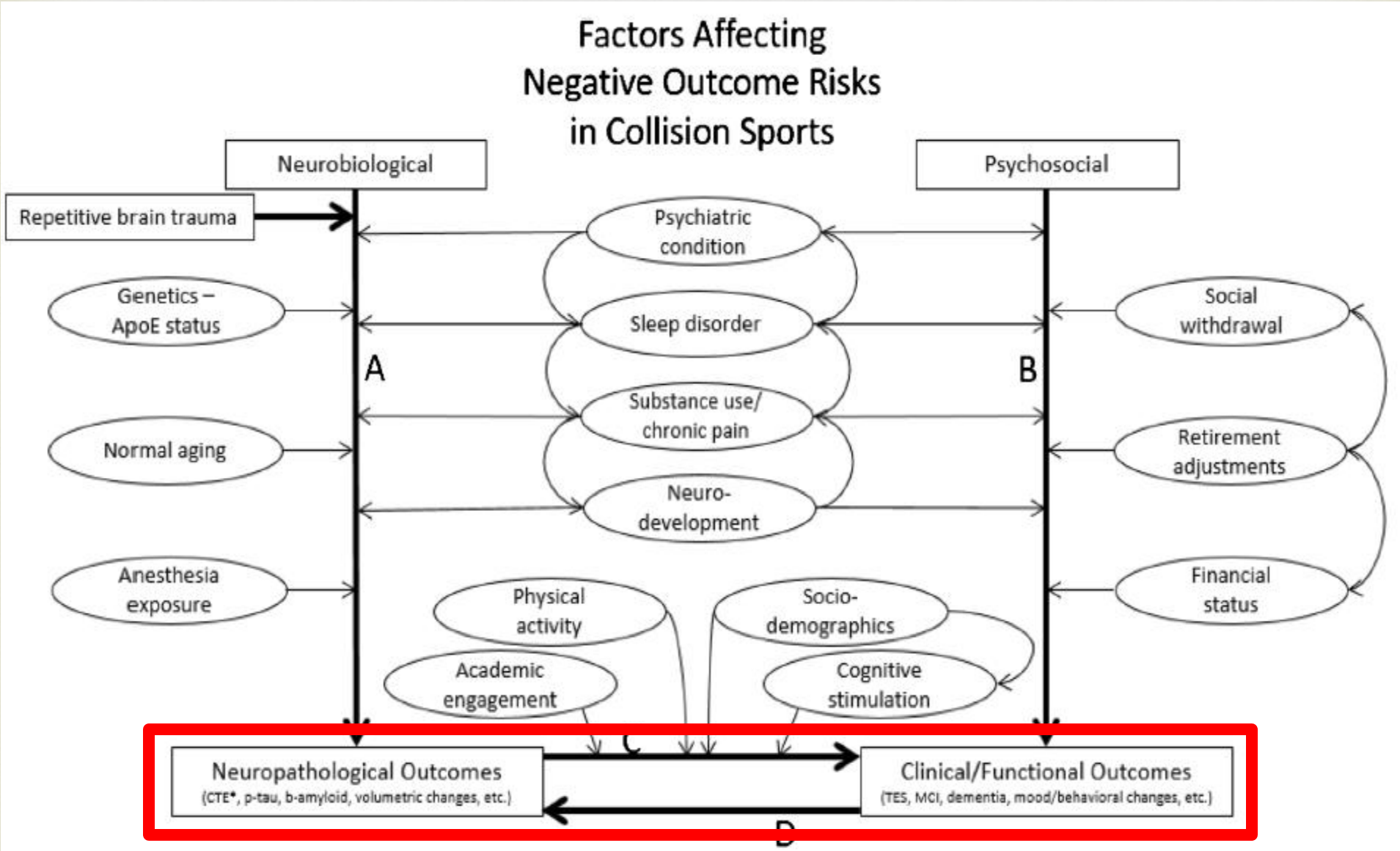
- Lit Review – 202 cases
  - 70% boxers, 48% pre-1970
- Sensitivity over specificity
  - Research application
- Modeled off NIA-AA process for AD
  - Biomarkers for informing diagnostic certainty
- Mood/behavior can define syndrome
- Not meant to predict specific underlying pathology

Reams et al. (2016)

- Modification of existing criteria
- Specificity over sensitivity
  - Clinical application
- Reliance on clinical features
- Cognition a central component
  - Mood/behavior supportive only
- Not meant to predict specific underlying pathology

Limitations of Clinical Diagnostic Criteria

- Non-validated definition of what constitutes "repetitive" or sufficient head trauma exposure
- Yet to identify a "typical" clinical profile
  - Highly variable clinical presentations
  - Low (if any) predictability for underlying pathology
- Difficult to ascertain timing of symptom onset
  - Multiple confounding factors that *DISPROPORTIONATELY AFFECT ATHLETES*



From Asken et al., 2016

CTE and Suicide

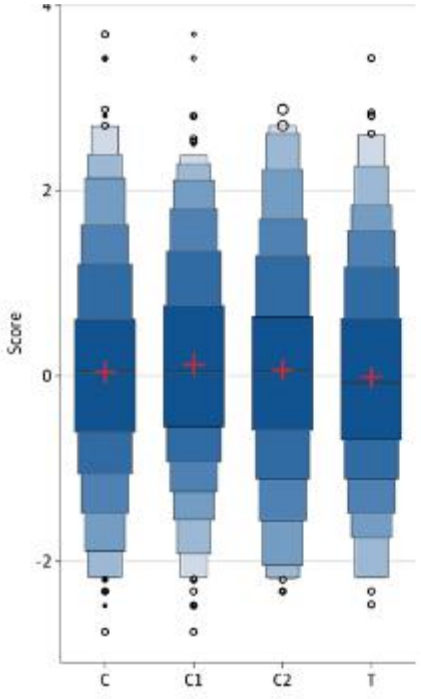
- No established causal link
- Associations are weak and anecdotal, at best
- Retired NFL athletes statistically less likely to die by suicide compared to general population (Baron et al., 2012; Lehman et al., 2016)
- Suicide only recently linked to CTE (Iverson, 2014; 2016)
  - Not listed as "cause of death" in any CTE case prior to 2002 (Maroon et al., 2015)
- Review of retired NFL athlete deaths (1920-2015)
  - 26 of 26,000+ since 1920 died by suicide
  - 21/26 with other documented risk factors (i.e. substantial life stressors)
  - 11/26 occurred between 2009-2015 (Webner & Iverson, 2016)

JAMA Neurology | Original Investigation

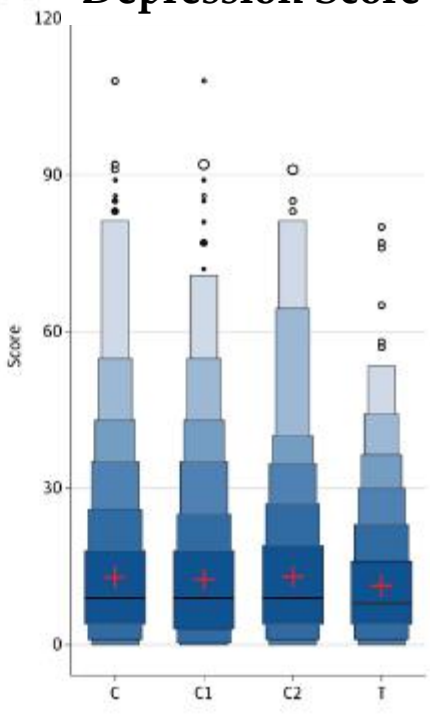
Association of Playing High School Football With Cognition and Mental Health Later in Life

Sameer K. Deshpande, BS; Raiden B. Hasegawa, BA; Amanda R. Rabinowitz, PhD; John Whyte, MD, PhD; Carol L. Roan, PhD; Andrew Tabatabaei; Michael Baiocchi, PhD; Jason H. Karlawish, MD; Christina L. Master, MD, CAQSM; Dylan S. Small, PhD

Composite Cognition



Depression Score



Results Among the 3904 men (mean [SD] age, 64.4 [0.8] years at time of primary outcome measurement) in the study, compared with each control condition, there was no statistically significant harmful association of playing football with a reduced composite cognition score (−0.04 reduction in cognition vs all controls; 97.5% CI, −0.14 to 0.05) or an increased modified Center for Epidemiological Studies' Depression Scale depression score

Conclusions and Relevance Cognitive and depression outcomes later in life were found to be similar for high school football players and their nonplaying counterparts from mid-1950s in Wisconsin.

Sports Health: A Multidisciplinary Approach

Is There Chronic Brain Damage in Retired NFL Players? Neuroradiology, Neuropsychology, and Neurology Examinations of 45 Retired Players

Ira R. Casson, MD,[†‡] David C. Viano, Dr Med, PhD,[*§‖] E. Mark Haacke, PhD,[¶] Zhifeng Kou, PhD,[¶] and Danielle G. LeStrange, RN, MSN, ACNS-BC[#]

Results: The retired players' ages averaged 45.6 ± 8.9 years (range, 30-60 years), and they had 6.8 ± 3.2 years (maximum, 14 years) of NFL play. They reported 6.9 ± 6.2 concussions (maximum, 25) in the NFL. The majority of retired players had normal clinical mental status and central nervous system (CNS) neurological examinations. Four players (9%) had microbleeds in brain parenchyma identified in SWI, and 3 (7%) had a large cavum septum pellucidum with brain atrophy. The number of concussions/dings was associated with abnormal results in SWI and DTI. Neuropsychological testing revealed isolated impairments in 11 players (24%), but none had dementia. Nine players (20%) endorsed symptoms of moderate or severe depression on the BDI and/or met criteria for depression on PHQ; however, none had dementia, dysarthria, parkinsonism, or cerebellar dysfunction. The number of football-related concussions was associated with isolated abnormalities on the clinical neurological examination, suggesting CNS dysfunction. The APOE4 allele was present in 38% of the players, a larger number than would be expected in the general male population (23%-26%).

Age of First Exposure

Neurology®

Age of first exposure to football and later-life cognitive impairment in former NFL players

Table 1 Demographics

	AFE <12 y (n = 21)	AFE ≥12 y (n = 21)
Age, y, mean (SE)	51.95 (1.33)	52.33 (1.33)
Education, y, mean (SE)	16.62 (0.23)	16.38 (0.20)
Diagnosis of learning disabilities, n (%)	3 (15.79)	0 (0.00)
African American, n (%)	6 (28.57)	12 (57.74)
AFE to football, y, mean (SE)	9.00 (0.28)	14.07 (0.30)
Duration of football play, y, mean (SE)	19.95 (0.74)	17.52 (0.75)
Duration of play in the NFL, y, mean (SE)	7.02 (0.55)	8.67 (0.67)
Total no. of concussions,[c] mean (SE)	392.00 (145.40)	370.30 (234.90)

Neurology®

Age of first exposure to football and later-life cognitive impairment in former NFL players

Interpretation

1. Starting football before age 12 is associated with significantly worse cognition during middle-age (~50s) than those who started playing after age 12

WCST % perseverative responses *T* score	37.58 (1.75)	45.16 (2.08)	−2.79	0.009
WCST % perseverative errors *T* score			−2.90	0.006
WCST % nonperseverative errors *T* score			−1.77	0.085
WCST % conceptual level responses *T* score			−2.12	0.041
NAB-LL immediate recall *T* score			−2.68	0.011*
NAB-LL short delay *T* score			−1.09	0.283
NAB-LL long delay *T* score			−0.54	0.592

Neuropsychology 101

Understanding cognitive reserve and normative reference groups

Normative Comparisons

- Rarely have "healthy" baseline comparison for neuropsychological referral
- Need a large, non-clinical sample to establish performance variability on a given test
  - Determine patient's function relative to ***expected*** performance
    - Orthopedic analogy – compare ROM or MMT to uninjured side
- Each test will have its own normative reference group
  - Establishes standardized scores for the test
    - Percentiles, impairment cutoff criteria, etc.
  - Some "norms" better than others – often patient-specific

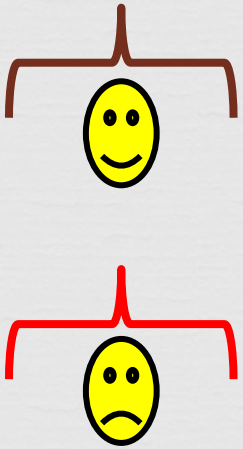
Defining Impairment

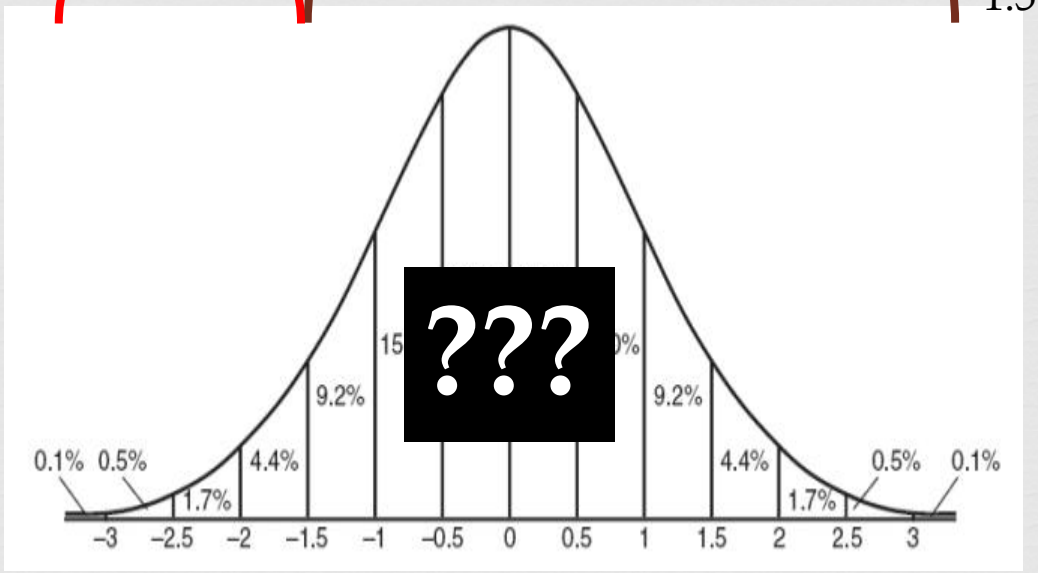
- 1.5 – 2.0 SD below average normative performance
- One test within a cognitive domain vs. composite performance within domain?

2.0 SD below mean = 2nd %ile

1.7 SD below mean = 5th %ile

1.5 SD below mean = ~7th %ile





Normative Reference Factors

- Age – normal development/decline over time
- Sex – biological differences
- Education – exposure to cognitive stimulation/strategies
  - **Self report (years of education) vs. Achievement based (grade-equivalent reading)?**
- Race/Ethnicity – often a proxy for SES (imperfect)
- These factors are known to *significantly* influence *TEST SCORES*
  - Test scores indirectly measure true cognitive function
  - Imperfect…but the standard for defining clinical impairment

"Crystallized" vs. "Fluid" Intelligence

- Crystallized
  - Cognitive abilities largely maintained despite neurological insults
    - Brain injury, *most* mild/moderate severity dementias
  - Ex) Vocabulary, reading, general knowledge
    - Once obtained, they're maintained
    - Excellent measures of premorbid intellectual functioning
      - Inform "expected" abilities on other tests
- Fluid
  - Cognitive abilities broadly susceptible to neurological insults
  - Ex) memory, reasoning, problem solving, attention, aspects of language

Cognitive Reserve and Norms

- Importance of premorbid intelligence estimates and patient history

Understanding the role of cognitive reserve

Preservation of FUNCTION *despite* STRUCTURAL changes due to neurobiological effects of aging, degeneration, neuron loss, etc.

EDUCATION | **OCCUPATIONAL ATTAINMENT** | **SOCIAL ENGAGEMENT** | **GENETICS**

Higher education predicts better crystallized and fluid intelligence
By extension…expected to perform better on cognitive tests

Age of First Exposure

Neurology®

Age of first exposure to football and later-life cognitive impairment in former NFL players

Table 1 Demographics

	AFE <12 y (n = 21)	AFE ≥12 y (n = 21)
Age, y, mean (SE)	51.95 (1.33)	52.33 (1.33)
Education, y, mean (SE)	16.62 (0.23)	16.38 (0.20)
Diagnosis of learning disabilities, n (%)	3 (15.79)	0 (0.00)
African American, n (%)	6 (28.57)	12 (57.74)
AFE to football, y, mean (SE)	9.00 (0.28)	14.07 (0.30)
Duration of football play, y, mean (SE)	19.95 (0.74)	17.52 (0.75)
Duration of play in the NFL, y, mean (SE)	7.02 (0.55)	8.67 (0.67)
Total no. of concussions,[c] mean (SE)	392.00 (145.40)	370.30 (234.90)

Neurology®

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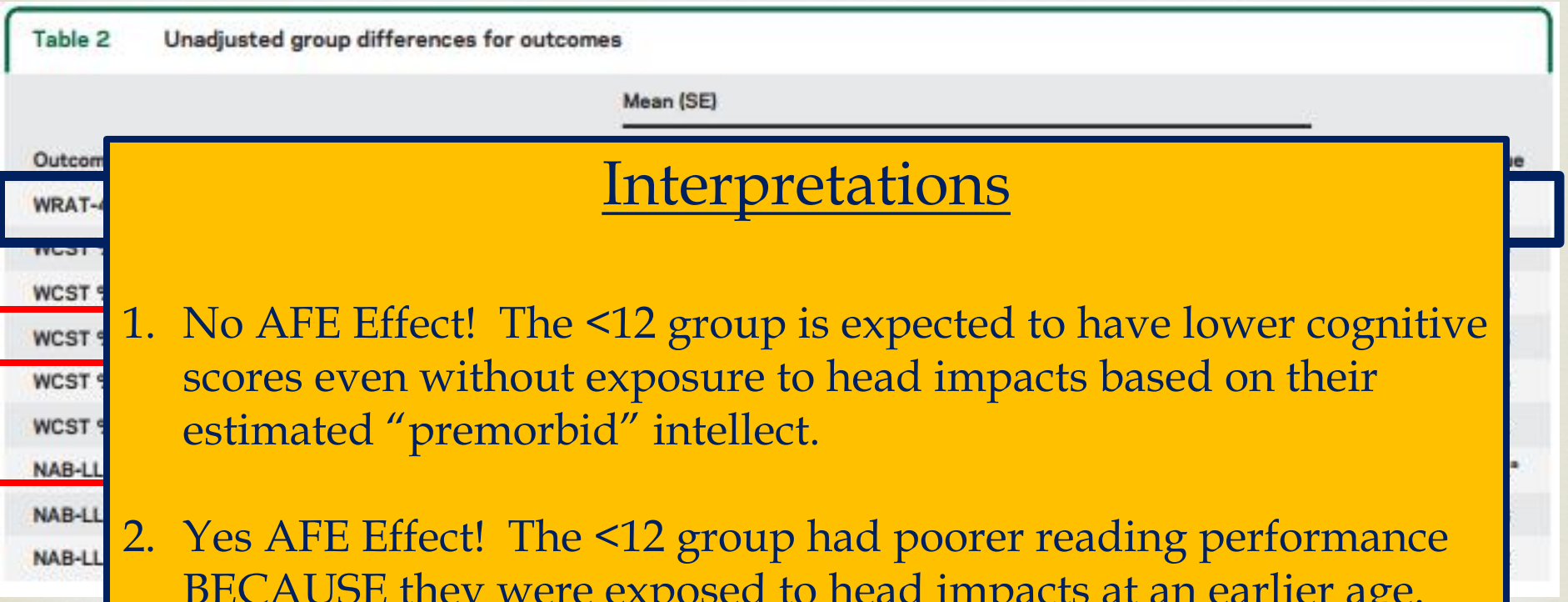

Interpretations

1. No AFE Effect! The <12 group is expected to have lower cognitive scores even without exposure to head impacts based on their estimated "premorbid" intellect.

2. Yes AFE Effect! The <12 group had poorer reading performance BECAUSE they were exposed to head impacts at an earlier age.

Translational Psychiatry

Age of first exposure to American football and long-term neuropsychiatric and cognitive outcomes

ML Alosco[1,2], AB Kasimis[1], JM Stamm[1,3], AS Chua[4], CM Baugh[1,2,5], DH Daneshvar[1], CA Robbins[1,6], M Mariani[1], J Hayden[1], S Conneely[1], R Au[2,7,8,9], A Torres[10,11], MD McClean[12], AC McKee[1,2,13,14,15], RC Cantu[1,2,6,16,17], J Mez[1,2], CJ Nowinski[1,6], BM Martin[1,18], CE Chaisson[1,18], Y Tripodis[1,4,19] and RA Stern[1,2,9,16,19]

	Total sample (N = 214)	*AFE < 12 (n = 101)*	*AFE ⩾ 12 (n = 113)*
Age, mean (s.d.) years	50.68 (13.33)	48.22 (10.87)	52.87 (14.91)
Race, *n* (%) white	192 (89.7)	92 (91.1)	100 (88.5)
Education, mean (s.d.) years	17.07 (2.27)	17.09 (2.38)	17.04 (2.19)
Learning disability (*N* = 206 due to missing data), *n* (%) yes	19 (9.2)	10 (10.6)	9 (8.0)
Reported psychotropic medication, *n* (%) yes	77 (36.0)	39 (38.6)	38 (33.6)
Reported psychiatric diagnosis, *n* (%) yes (*N* = 167 due to missing data)[a]	100 (59.9)	52 (65.8)	48 (54.5)
Seasons of football play, median (IQR)	12.25 (9)	14.00 (10)	10.00 (8)
AFE to football, mean (s.d.)	11.12 (2.47)	8.98 (1.65)	13.04 (1.14)
Total number of concussions (*N* = 210 due to missing data), median (IQR)[b]	17.75 (37)	25.00 (88)	15.00 (23)
Total number of concussions outside of sport/military (*N* = 208 due to	1.00 (2)	1.00 (2)	1.00 (2)

Test	*Total sample (N = 214)*		*AFE < 12 (n = 101)*		*AFE ⩾ 12 (n = 113)*	
	Mean (s.d.)	n *(%), Impaired*	*Mean (s.d.)*	n *(%), Impaired*	*Mean (s.d.)*	n *(%), Impaired*
BRIEF-A BRI[a]	64.11 (15.16)	94 (44.1)	67.01 (14.79)	51 (50.5)	61.50 (15.07)	43 (38.4)
BRIEF-A MI	64.71 (15.54)	103 (48.1)	66.66 (14.73)	55 (54.5)	62.97 (16.09)	48 (42.5)
BTACT[a]	−0.20 (0.90)	15 (7.0)	−0.31 (0.87)	8 (7.9)	−0.11 (0.92)	7 (6.3)
AES	34.15 (11.05)	97 (45.3)	36.42 (10.85)	56 (55.4)	32.12 (10.88)	41 (36.3)
CES-D	20.24 (14.48)	117 (54.7)	23.25 (13.85)	67 (66.3)	17.55 (14.57)	50 (44.2)

- **No difference in cognitive test scores (BTACT)**
- **Mood/behavior scales differed with small to medium effect sizes**

UF Clinic Examples

Patient	Age	Years of Education	Grade-Equivalent Reading Level
1	51	16	6.9 !!!
2	44	15	9.8
3	59	16	1.9 !!!
4	35	16	4.7 !!!
5	51	16	4.4 !!!
6	51	16	9.2
7	42	16	12.5

Years of Education = 16

Grade-Equivalent Reading Level = 4.4*

	Race + Age + Education *Quantity*				Race + Age + Education *Quality*			
Test	**Raw**	**T**	**%ile**	**Descriptor**	**Raw**	**T**	**%ile**	**Descriptor**
Boston Naming Test	36	25	<1	Impaired	36	42	21	Low Avg.
Verbal Fluency – FAS	40	48	42	Average	40	60	84	High Avg.
Category Fluency - Animals	15	41	18	Low Avg.	15	51	53	Average
Trail Making Part A	47″	38	12	Below Avg.	47″	46	34	Average
Trail Making Part B	59″	56	73	Average	59″	70	97	Superior
Booklet Category Test	105	22	<1	Impaired	105	37	9	Below Avg.

Research Gaps

- Prevalence and incidence rates (pathologically or clinically)
  - Biased case series to date
  - 4 subgroups within this population to identify
    - + CTE / + TES
    - + CTE / - TES
    - - CTE / + TES
    - - CTE / - TES
    - Risk factors, protective factors
- Clinical correlates to pathology
  - Absence of patients with neuropsychological eval prior to death
    - All retrospective informant report – major limitations

Take Home Points

- Terminology matters – Neuropathology ≠ Clinical Syndrome
  - Important to clarify risk for incident **pathology** vs. **dementia**
    - **COGNITIVE RESERVE moderates the link**
- Repetitive brain trauma greatest known risk factor for CTE pathology
  - Amount and severity of trauma unknown
  - Clarify nature of "progression"
- The unique pathology of CTE – according to most, but not everyone
  - Pathognomonic sign: **abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci**
    - However…many CTE cases have comorbid neuropathology
- Current clinical research limited by variably appropriate control group comparison
- Read the science!
- Be critical of the science!

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Thank You

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