DEFENSE CENTERS OF EXCELLENCE

For Psychological Health & Traumatic Brain Injury

Do Head Injuries Cause Chronic Traumatic Encephalopathy?

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DVBIC Defense and Veterans Brain Injury Center

DHCC Deployment Health Clinical Center

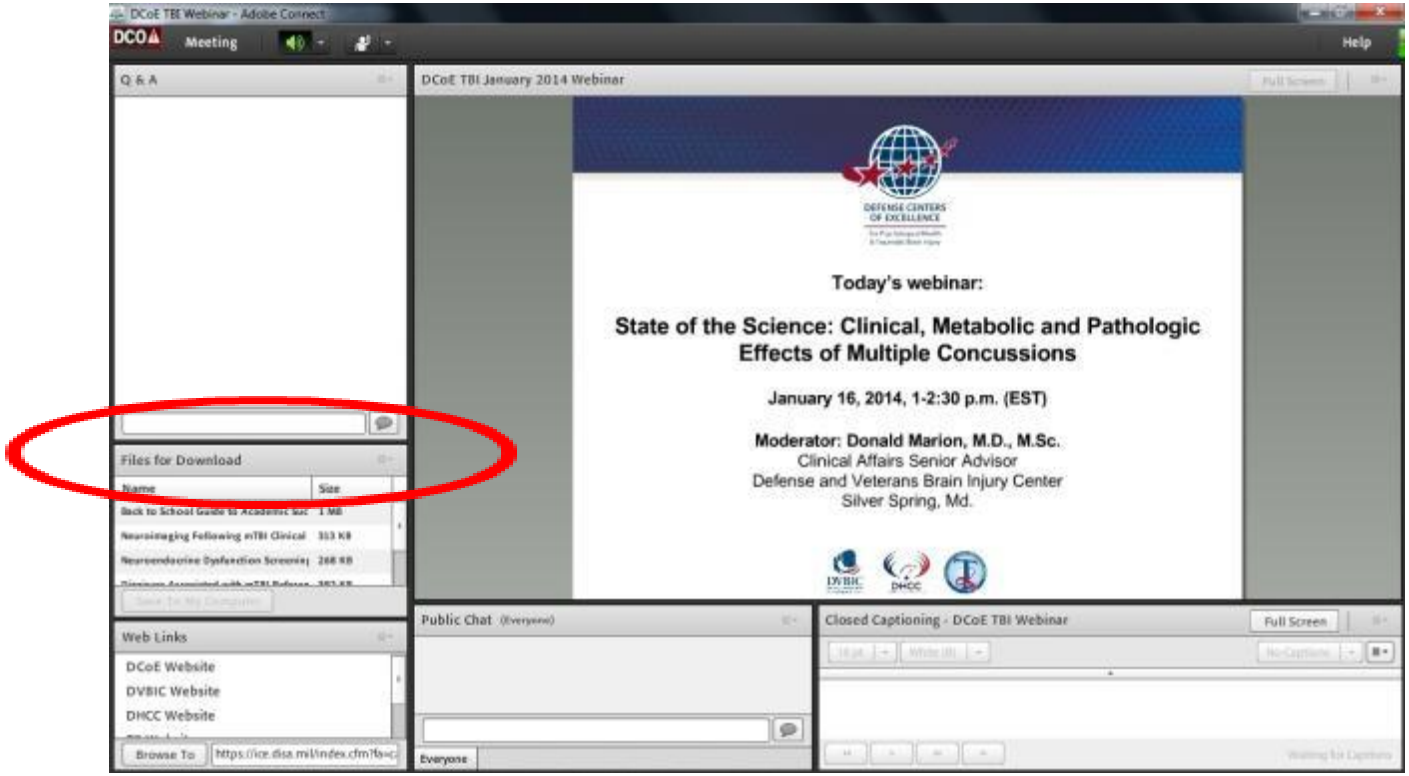
National Center for Telehealth & Technology

Webinar Details

- Live closed captioning is available through Federal Relay Conference Captioning (see the “Closed Captioning” box)
- Webinar audio is **not** provided through Adobe Connect or Defense Connect Online
  - Dial: CONUS **888-455-0936**; International **773-799-3736** Use participant pass code: **1825070**
- Question-and-answer (Q&A) session
  - Submit questions via the Q&A box

Resources Available for Download

Today's presentation and resources are available for download in the "Files" box on the screen, or visit **dvbic.dcoe.mil/online-education**



Continuing Education Details

- DCoE's awarding of continuing education (CE) credit is limited in scope to health care providers who actively provide psychological health and traumatic brain injury care to active-duty U.S. service members, reservists, National Guardsmen, military veterans and/or their families.

- The authority for training of contractors is at the discretion of the chief contracting official.
  - Currently, only those contractors with scope of work or with commensurate contract language are permitted in this training.

Continuing Education Accreditation

- This continuing education activity is provided through collaboration between DCoE and Professional Education Services Group (PESG).

- Credit Designations include:
  - 1.5 AMA PRA Category 1 credits
  - 1.5 ACCME Non Physician CME credits
  - 1.5 ANCC Nursing contact hours
  - 1.5 CRCC
  - 1.5 APA Division 22 contact hours
  - 0.15 ASHA Intermediate level, Professional area
  - 1.5 CCM hours
  - 1.5 AANP contact hours
  - 1.5 AAPA Category 1 CME credit

Continuing Education Accreditation

Physicians
This activity has been planned and implemented in accordance with the essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME). Professional Education Services Group is accredited by the ACCME as a provider of continuing medical education for physicians. This activity has been approved for a maximum of 1.5 hours of *AMA PRA Category 1 Credits* TM. Physicians should only claim credit to the extent of their participation.

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Nurse CE is provided for this program through collaboration between DCOE and Professional Education Services Group (PESG). Professional Education Services Group is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. This activity provides a maximum of 1.5 contact hours of nurse CE credit.

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(ACCME Non Physician CME Credit) For the purpose of recertification, The National Board for Certification in Occupational Therapy (NBCOT) accepts certificates of participation for educational activities certified for AMA PRA Category 1 Credit TM from organizations accredited by ACCME. Occupational Therapists may receive a maximum of 1.5 hours for completing this live program.

Physical Therapists
Physical Therapists will be provided a certificate of participation for educational activities certified for AMA PRA Category 1 Credit TM. Physical Therapists may receive a maximum of 1.5 hours for completing this live program.

Psychologists
This Conference is approved for up to 1.5 hours of continuing education. APA Division 22 (Rehabilitation Psychology) is approved by the American Psychological Association to sponsor continuing education for psychologists. APA Division 22 maintains responsibility for this program and its content.

Continuing Education Accreditation

Rehabilitation Counselors
The Commission on Rehabilitation Counselor Certification (CRCC) has pre-approved this activity for 1.5 clock hours of continuing education credit.

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This program has been pre-approved by The Commission for Case Manager Certification to provide continuing education credit to CCM® board certified case managers. The course is approved for up to 1.5 clock hours. PESG will also make available a General Participation Certificate to all other attendees completing the program evaluation.

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Other Professionals
Other professionals participating in this activity may obtain a General Participation Certificate indicating participation and the number of hours of continuing education credit.

Questions and Chat

- Throughout the webinar, you are welcome to submit technical or content-related questions via the Q&A pod located on the screen. **Please do not submit technical or content-related questions via the chat pod**.
- The Q&A pod is monitored during the webinar; questions will be forwarded to presenters for response during the Q&A session.
- Participants may chat with one another during the webinar using the chat pod.
- The chat function will remain open 10 minutes after the conclusion of the webinar.

Summary and Learning Objectives

Contact sports have long been suspected of causing prolonged or permanent neurologic injury in some athletes; the 2005 findings of unusual brain pathology in a retired NFL football player magnified concern for this association. The brain pathology involved accumulation of the protein tau in masses called tangles or threads. To date, more than 150 cases of chronic traumatic encephalopathy (CTE) have been confirmed by autopsy, with the vast majority being athletes in contact sports. Records show these individuals suffered a range of cognitive, emotional, behavioral, and motor symptoms. In some cases, co-occurring neurological conditions were present that could also account for observed symptoms.

The distribution of accumulated tau masses, the criteria for diagnosis, and the clinical presentation of CTE remain controversial among researchers. At this time, there is no consensus regarding the clinical presentation of CTE that could enable diagnosis in living persons. There is no fluid or neuroimaging biomarker validated for diagnosis, although some imaging approaches show promise in their ability to differentiate different neurological conditions and normal aging. The literature on CTE is also limited by the strong influence of a few individual researchers, whose studies may be influenced by selection bias. This webinar will address the current neuropathological diagnostic criterion for CTE and highlight recent findings that support or refute the association of CTE with multiple concussions.

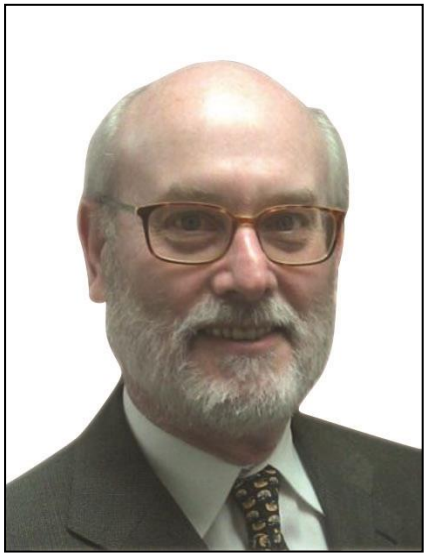
- At the conclusion of this webinar, participants will be able to:
  - Describe the brain pathology observed in CTE
  - Recognize the cognitive, behavioral, and neurological signs attributed to CTE
  - Understand the limitations of the current literature on CTE
  - Articulate what is known or not known regarding the association of multiple concussions and CTE
  - Discuss the potential risks of contact sports, such as football, and later development of CTE

Anne E. Bunner, Ph.D.

Anne E. Bunner, Ph.D.

- Program analyst in the Research Division of the Defense and Veterans Brain Injury Center (DVBIC)
- Previously served as associate director for clinical research at the Physicians Committee for Responsible Medicine
- Authored numerous publications in several laboratory and clinical research areas
- Education:
  - Ph.D., Biology, The Scripps Research Institute

Donald W. Marion, M.D., M.Sc.



Donald W. Marion, M.D.

- Senior clinical consultant in the Clinical Affairs Division of DVBIC
- Academic neurosurgeon who has focused on the clinical pathophysiology and treatment of TBI for more than 25 years
- Previously served as professor and chair of the Department of Neurosurgery, The Boston University School of Medicine; professor and vice-chair, Department of Neurosurgery, The University of Pittsburgh School of Medicine; and director of the Brain Trauma Research Center at the University of Pittsburgh
- Education:
  - M.D., University of California

Disclosures

- The views expressed herein are those of the presenter and do not reflect the official policy of the Department of the Army, Department of Defense, or DVBIC.
- The presenter does not intend to discuss the off-label/investigative (unapproved) use of commercial products or devices.
- The presenter has no relevant financial relationships to disclose.

Polling Question #1

Select the statement that best reflects your current understanding of CTE:

- ❑ I could tell you what “C.T.E.” stands for.
- ❑ I could identify at-risk individuals.
- ❑ I could describe some of the clinical and neuropathological features of CTE.
- ❑ I could give this seminar.
- ❑ I could apply the consensus diagnostic criteria to photomicrographs of autopsy-derived brain tissue.

POINT

Repeated head injuries are the primary causative agent in the development of CTE.

Presentation "Roadmap"

Presentation by Dr. Bunner

- What is CTE? Basics, history, clinical manifestation, pathology
- How is CTE distinct?
- Limitations in the literature, weaknesses of critics' arguments

Presentation by Dr. Marion

- "Discrediting CTE researchers"
- "Series of red herrings"
- Describing the benefits of team sport
- Explaining a longitudinal study for Dr. Bunner's edification

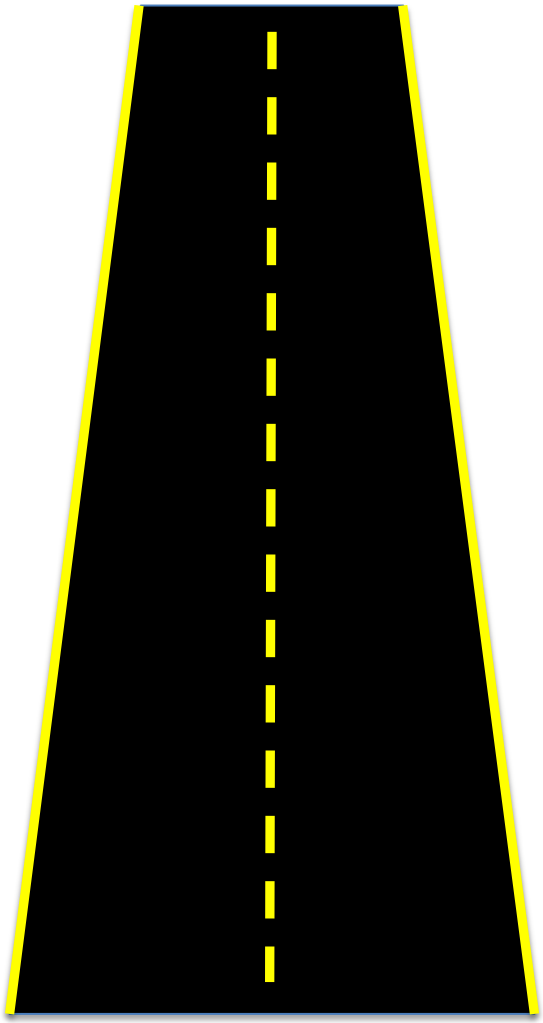


Image credit: Dr. Wesley Cole

"I don't need the British Medical Association to tell me getting hit on the head can't do me any good."

Undefeated World Champion boxer Terry Marsh
Retired in 1987, after epilepsy diagnosis

(Corsellis, 1989)

What is CTE?

- CTE is a progressive neurodegenerative disease associated with repeated head trauma.
- CTE has only been observed in the context of repeated head trauma, predominantly among athletes who play contact sports.
- CTE is diagnosed by post-mortem examination of brain tissue.

Historical Perspective

- Harrison Martland in 1928 reported “punch drunk” syndrome in boxers that involved gait problems, cognitive decline, tremors, and other symptoms.
- Phrase “chronic traumatic encephalopathy” first appeared in literature in 1949
- Neuropathology described as early as 1967
- Bennet Omalu in 2005 reported first case of CTE in former NFL player
- 2015 systematic review counted 153 autopsy-confirmed cases.

(Martland, 1928; Critchley, 1957; Corsellis, 1989; Omalu et al., 2005; Maroon et al., 2015)

Clinical Signs and Symptoms

- Data in confirmed cases is limited to retrospective reports of deceased persons.
- Symptoms include:
  - **Behavioral/emotional:** Mood swings, disinhibition, paranoia, irritability, violent outbursts, impulsiveness
  - **Cognitive:** Confusional episodes; problems with attention, concentration, memory, executive function, language; visuospatial difficulties
  - **Motor function:** Tremor, balance problems, gait problems, spasticity, parkinsonism

(Lehman et al., 2012; Gardner et al., 2015; Lakhan et al., 2012; Mendez, 1995)

Clinical Signs and Symptoms

- Symptoms attributed to CTE are mostly non-specific and could be due to other diseases or conditions.
- Frequent comorbidity: 25 of 68 CTE cases also diagnosed with motor neuron disease, Alzheimer's disease (AD), Lewy body disease, frontotemporal lobar degeneration.
- Three research groups have developed research diagnostic criteria for living persons with probable CTE.

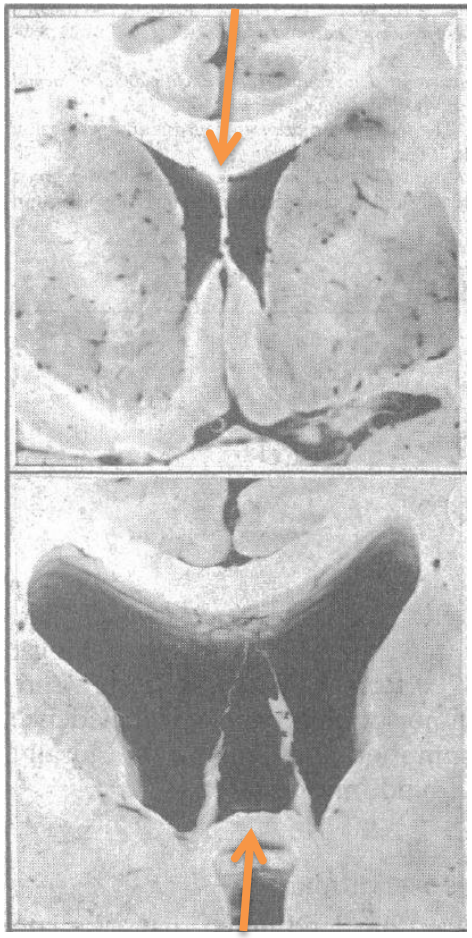
(McKee et al., 2013; Victoroff, 2013; Jordan, 2013; Montenigro et al., 2014)

Gross Pathology in CTE Brains

- The septum pellucidum is a double membrane in the center of the brain.
- Cavum septum pellucidum
  - Describes a split in this membrane
  - Is commonly seen in CTE
  - Also in ~15% of people
- Other gross pathology in CTE
  - Reduced brain weight
  - Enlargement of ventricles
  - Thinning of corpus callosum

(Corsellis, 1989)

Normal septum pellucidum



Cavum septum pellucidum

(Corsellis 1989)

Pathology of CTE

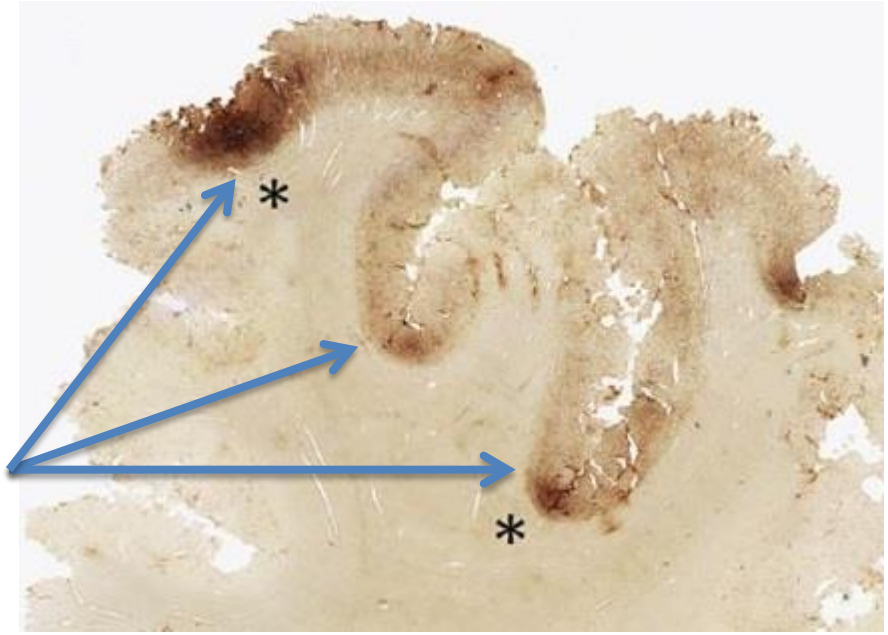
- CTE associated with accumulation of tau protein
  - Neurofibrillary tangles (NFTs): Dense aggregates of toxic protein
  - Neuritic threads (NTs): Elongated threads of protein aggregate
- NFTs and NTs occur in the cerebral cortex
  - Inconsistent data regarding specific locations
- Beta-amyloid plaques occur in about half of cases

(Omalu et al., 2011; McKee et al., 2013)

Where Are the NFTs and NTs?

- Researcher Ann McKee finds tangles and threads at the depths of the cortical sulci (SUL-sy)
  - Sulci are the "valleys" in the folds of brain tissue

Section of frontal cortex from CTE case



sulci

Brown staining indicates tau accumulation

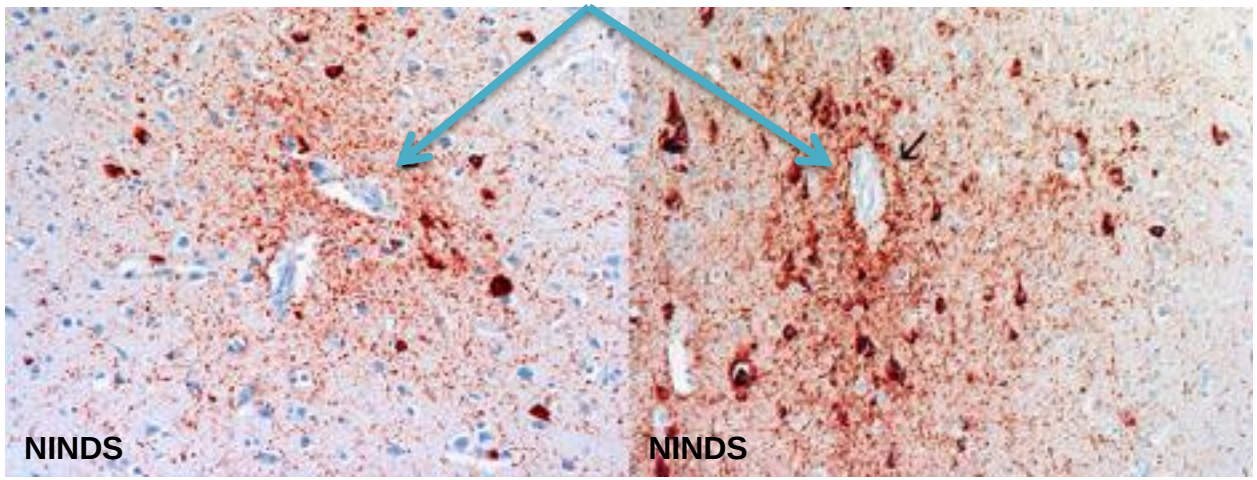
Figure 2A. Whole-mount 50-Km coronal sections of superior frontal cortex from Case A.

(McKee et al., 2009)

Where Are the NFTs and NTs?

- Researcher Ann McKee finds tangles and threads around small blood vessels ("perivascular space")

Blood vessels



Tau aggregates are red

Image credit: National Institute of Neurological Disorders and Stroke

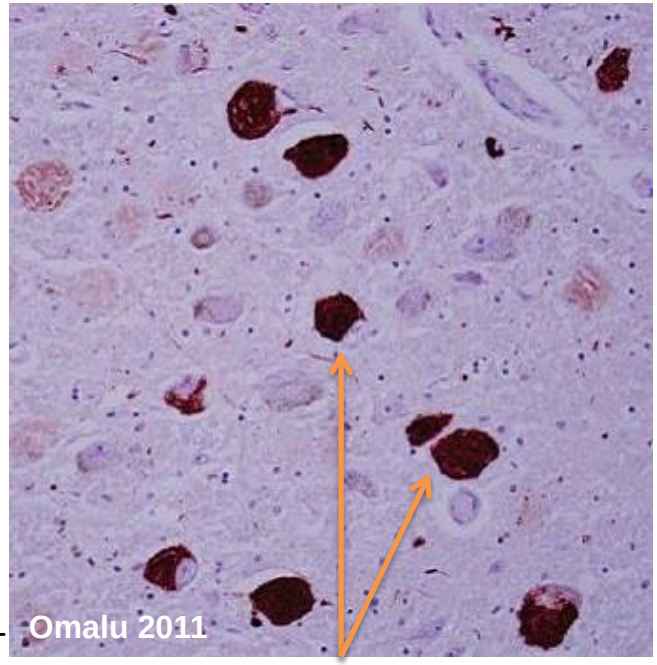
(U.S. Department of Health and Human Services, National Institute of Neurological Disorders (NINDS), 2015)

Where Are the NFTs and NTs?

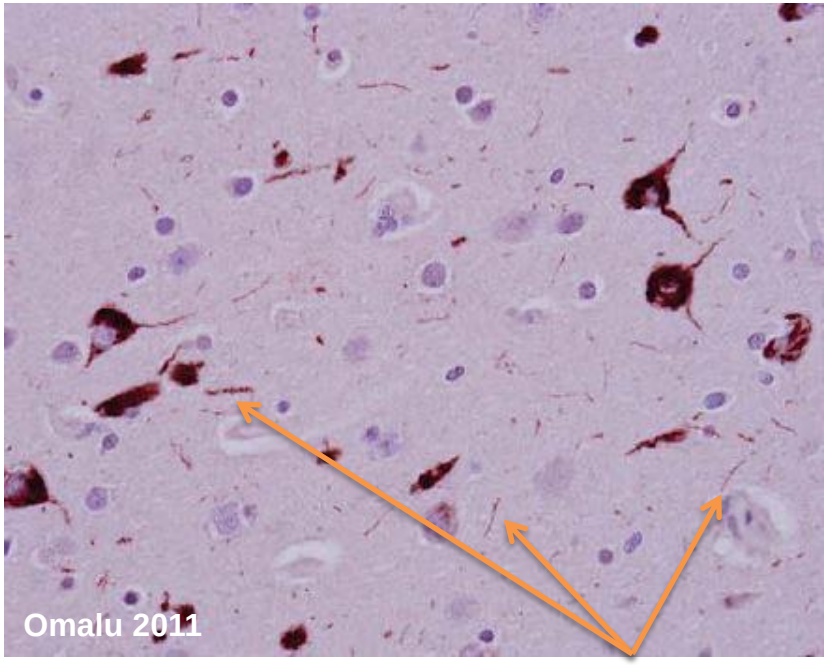
- Researcher Bennet Omalu finds tangles and threads distributed throughout cerebral cortex and sometimes in the brainstem.

Tau aggregates are red

Figure 3. Photomicrographs of sections of the brain from case 14 that was CTE positive.



Neurofibrillary tangles



Neuritic threads

Figure 2. Photomicrographs of sections of the brain from case 3 that was CTE positive.

(Omalu et al., 2011)

Why are NFTs and NTs Bad?

- Ideally, proteins in cells are like toothbrushes: They are made, they serve a function, they wear out, they are recycled.

- When proteins accumulate, it is like a garbage workers' strike: It is hard to move around and do business with all the trash piles.

- NFTs and NTs are resistant to "trash truck" cells called autophages.

Image credit: clipartpanda.com

Image credit: clipartlord.com

Stages of CTE Have Been Proposed

- Stages are based on series of post-mortem examinations.
- Stages are thought to occur in consecutive fashion.
- Red/pink is tau aggregates.

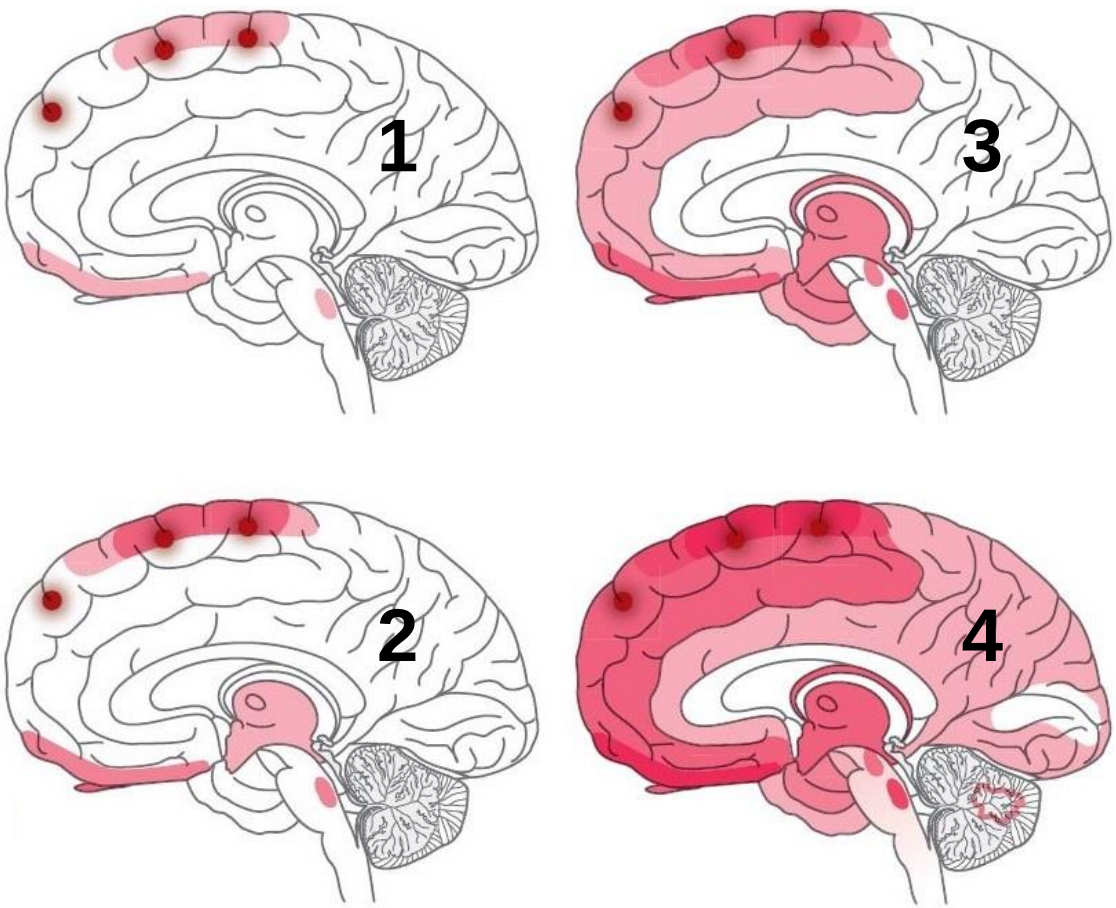


Image credit: Montenigro, 2015. Figure 3. Comparison of hyperphosphorylated tau progression

(Montenigro et al., 2015; McKee et al., 2013)

CTE and AD

- Tau accumulates in both CTE and AD.
- Tau deposits are found in different patterns in the two diseases.

CTE is Distinct from AD

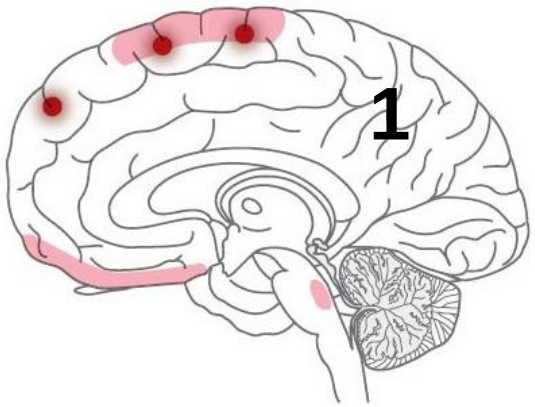
CTE

Stage I

Isolated perivascular centers

Predilection for depths of sulci within superior, dorsolateral, and inferior frontal cortices

Locus coeruleus

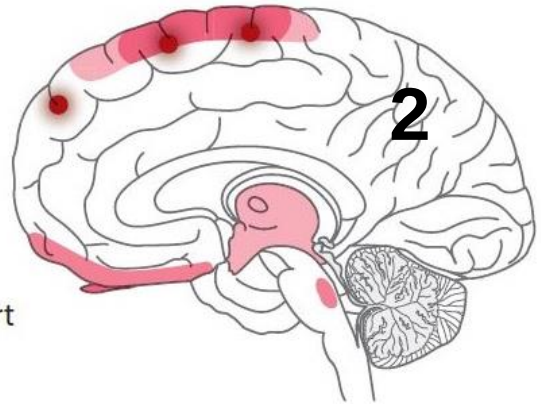


Stage II

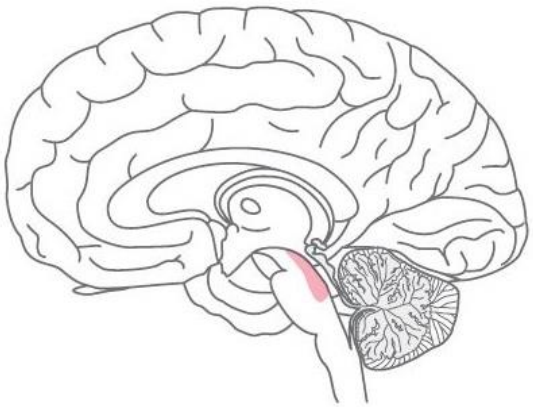
Multiple centers in frontal, temporal, and parietal neocortices

Diencephalon

Nucleus basalis of Meynert



AD

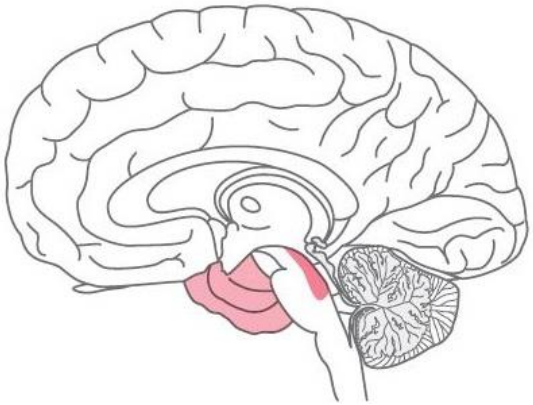


Stages a–c

Locus coeruleus

Upper raphe nuclei

Magnocellular nuclei



Stages 1a, I–II

Transentorhinal cortex

Entorhinal cortex

(Montenigro et al., 2015)

Image credit: Figure 3. Comparison of hyperphosphorylated tau progression

CTE and AD

CTE | **AD**

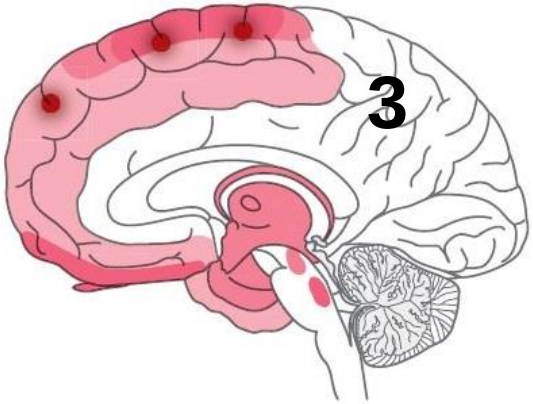
Stage III

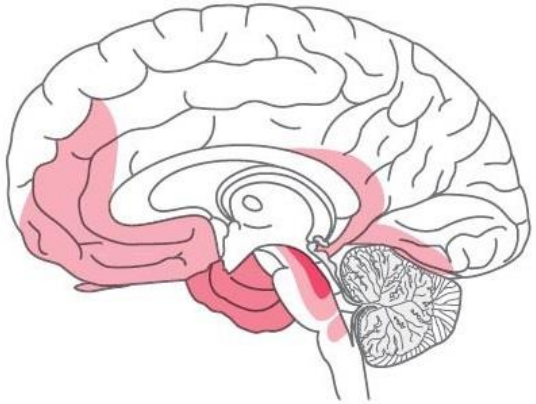
Widespread neocortical involvement

Hippocampus

Amygdala

Basal ganglia





Stages III–IV

Hippocampus

Amygdala

Basal temporal cortex

Insular cortex

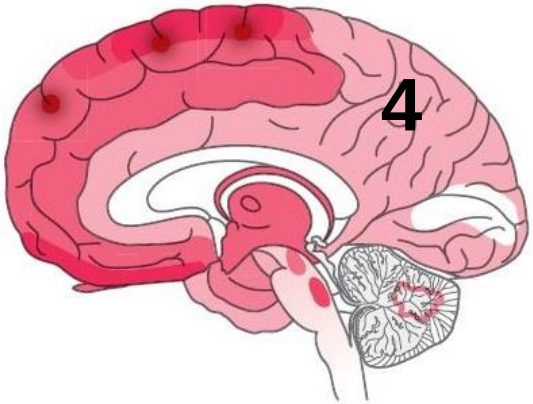
Basal frontal cortex

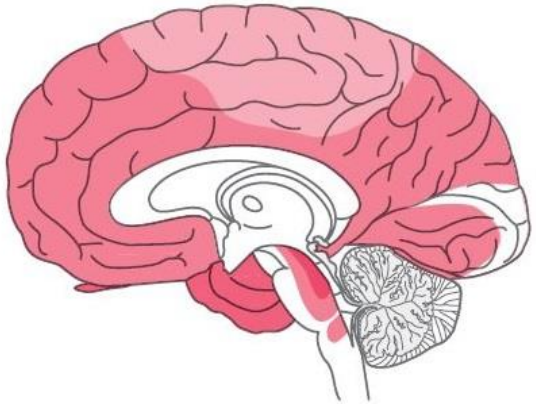
Stage IV

Medulla

Cerebellum

Cervical spinal cord





Stages V–VI

Widespread neocortical involvement

Sparing of cerebellum

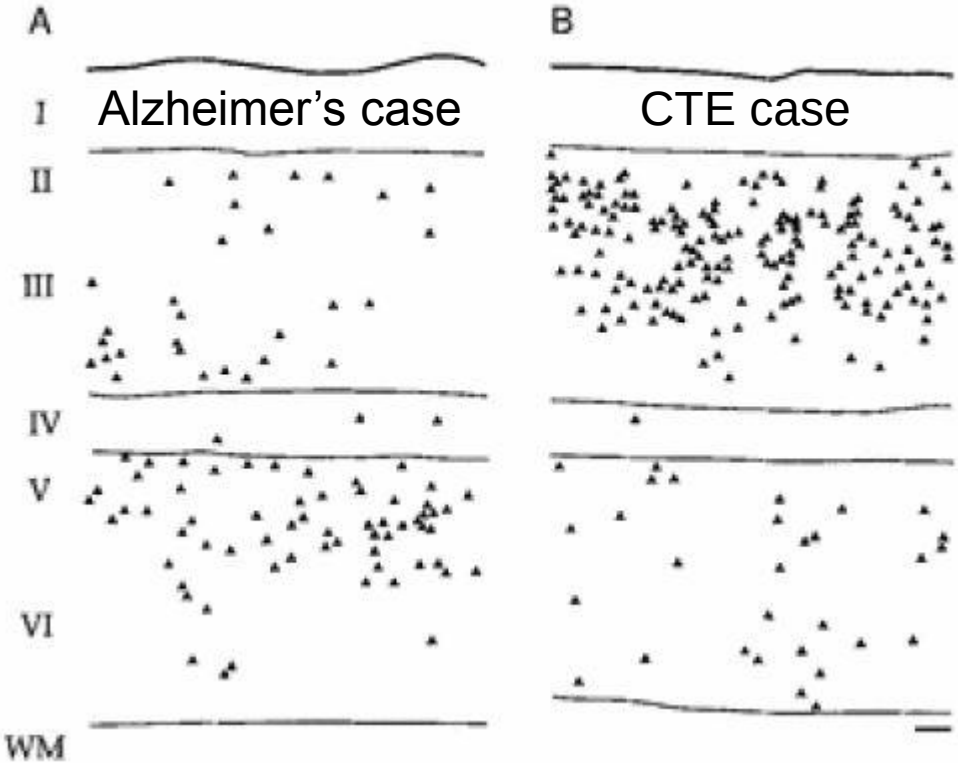
(Montenigro et al., 2015)

Image credit: Figure 3. Comparison of hyperphosphorylated tau progression

CTE and AD

- In CTE, tau is closer to surface of cortex.

Surface of cortex (grey matter)



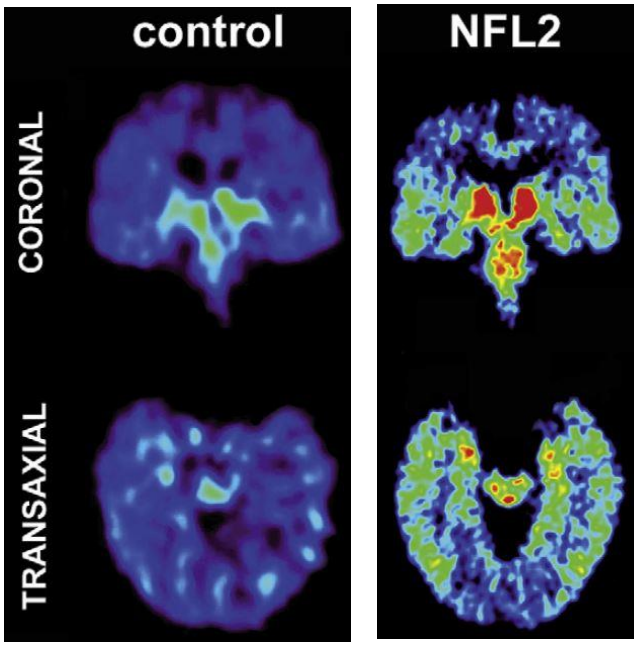
Bottom of grey matter, surface of white matter

Image credit: Figure 1. Computer-generated maps of neurofibrillary tangle (NFT) distribution in inferior temporal cortex of an AD and CTE case

(Hof et al., 1992)

Neuroimaging Offers Promise

- Positron emission tomography (PET) detects radioactive tracers a.k.a. radioligands.
- CTE researchers have used radioligands that bind tau to visualize tau aggregation in living persons.



PET brain images using FDDNP ligand.

Less tau — More tau

Image credit: Small et al., 2013. Figure 1. FDDNP-PET scan results for NFL players and a control

PET Shows CTE-like Pathology in Former NFL Players

- Imaging study of former NFL players with mood and cognitive symptoms, controls, and AD patients
- Tau distribution was distinct in the three groups.
- Neuropathology in the former NFL players was consistent with pathology seen in confirmed CTE cases.

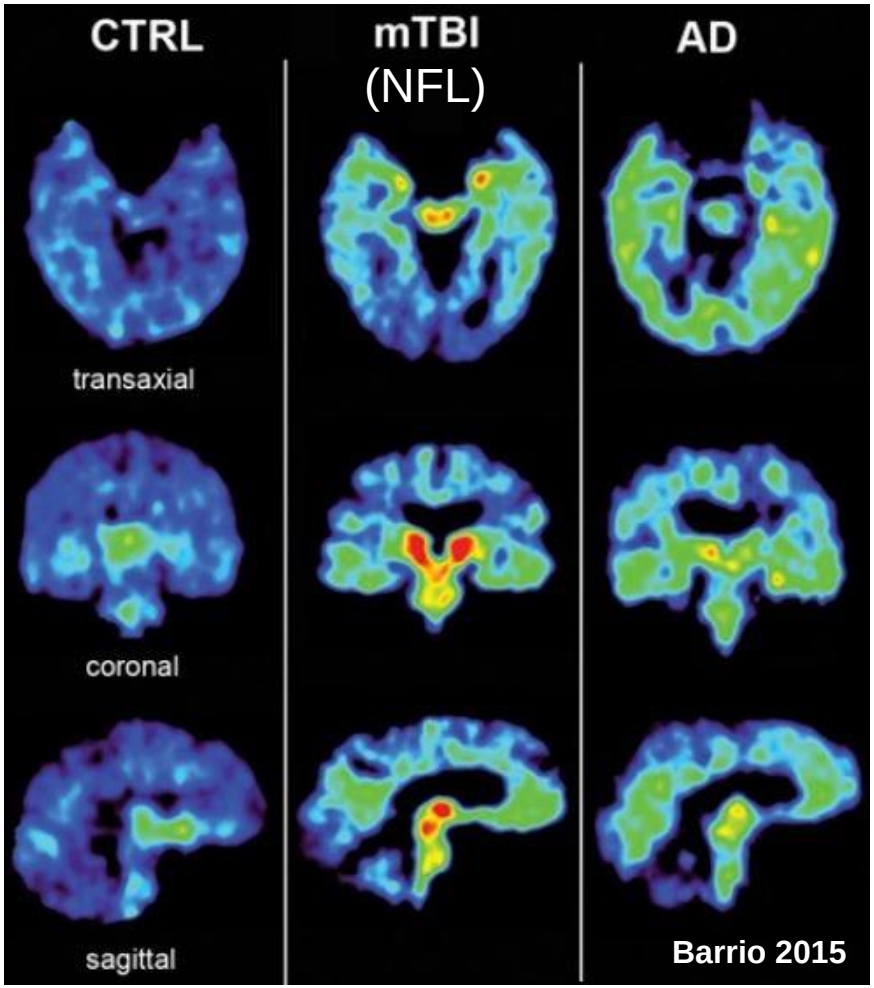


Figure. 1. [F-18]FDDNP distribution volume ratios (DVR) parametric images showing patterns T1 to T4 of increased [F-18] FDDNP signal observed in the mTBI group compared with cognitive control subjects

Less tau — More tau

(Barrio et al., 2015)

Polling Question #2

Signs of CTE do not include:

- ❑ Endocrine dysfunction
- ❑ Behavioral and emotional symptoms
- ❑ Cognitive impairment
- ❑ Motor function problems

Polling Question #3

The neuropathology of CTE is distinct from AD because:

- ❑ Beta-amyloid plaques, which are characteristic of AD, have not been observed in CTE cases.
- ❑ CTE is not distinct from AD.
- ❑ Tau deposition occurs in distinct patterns in the two conditions.

Limitations of CTE Literature

- No longitudinal or epidemiological studies that could distinguish CTE from other neurological conditions
- Unclear pathological mechanism
- Causative link between repeated TBI and CTE has not been unequivocally established.
- Selection bias (Dr. Marion will explain more)
- Replication of cases in literature

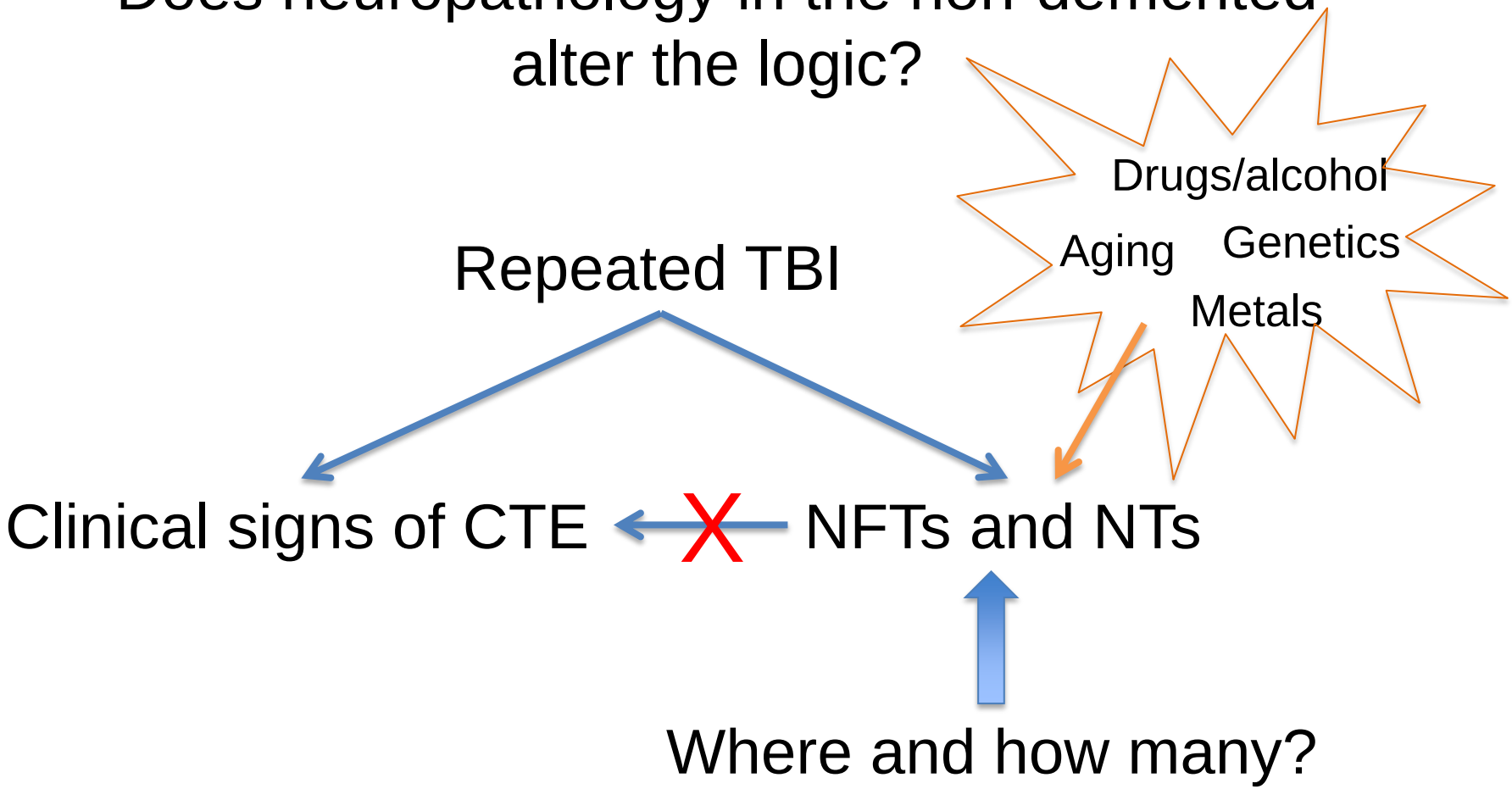
Critics of CTE Researchers

- Dr. Marion will argue that the presence of NFTs in cognitively normal deceased elderly persons (e.g., in the Honolulu-Asian Aging Study) is evidence that NFTs are not caused by TBI and that CTE is not a distinct disease.

(Gelber et al., 2012; White, 2009)

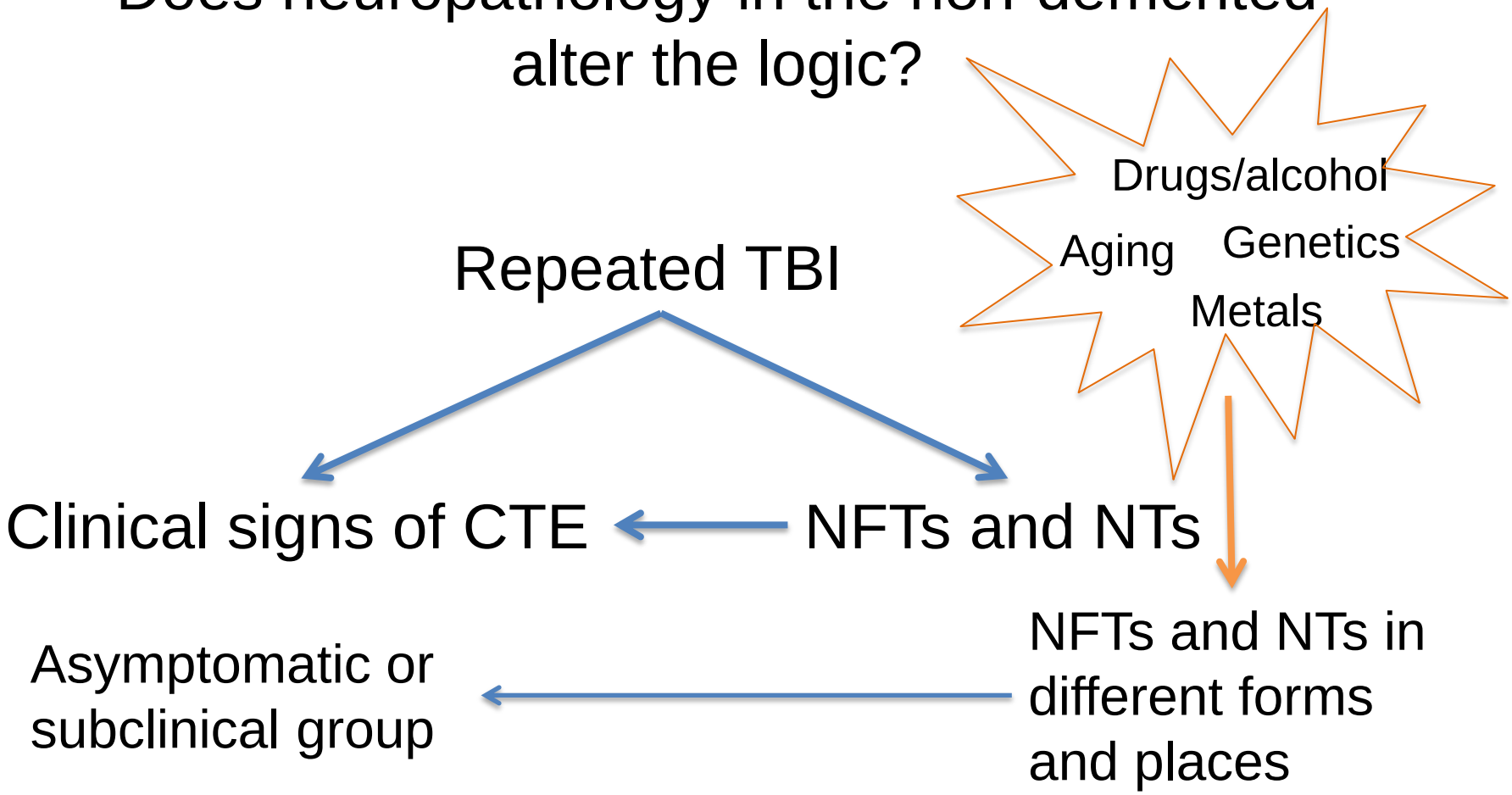
CTE Paradigm

Does neuropathology in the non-demented alter the logic?



CTE Paradigm

Does neuropathology in the non-demented alter the logic?



Critics of CTE Researchers

- Dr. Marion will tell you about one small longitudinal study that showed high school football does not increase long-term risk of neurological diseases.
- However, a recent meta-analysis showed TBI increases risk of:
  - AD by 40%
  - Parkinson's disease by 45%
  - Amytrophic lateral sclerosis by 107%
  - Mild cognitive impairment by 160%
  - Any neurological diagnosis by 55%

(Savica et al., 2012; Perry et al., 2015)

Editorial: Causative Agent?

- There is insufficient evidence to definitively conclude that repeated TBI causes CTE.
- The evidence was enough for Federal Judge Anita Brody to rule in favor of retired players in a lawsuit.
- Genetics, chemicals, aging, comorbidities, etc. cannot explain the totality of CTE cases.
- Other plausible risk factors are not as highly correlated as repeated TBI.

(Belson, 2015)

Denialists Use Similar Rhetoric

- Denialist response to unwelcome information:
  - "[Insert controversy] is not real."
    - Climate change, CTE, origin of species
- When faced with further evidence:
  - Ok, it's real, but…
    - "Climate change not caused by human activity."
    - "CTE not caused by TBI."
    - "Evolution only causes minor changes in species."

Denialists

- Listening to Dr. Marion's presentation, look for common characteristics of pseudoscience and science denial:
  - Cherry picking of favorable evidence
  - Using weak evidence and testimonials
  - Emphasis on irrelevant findings
  - Using inconsistent and invalid logic
  - Personal attacks
  - Moving the goalpost

"The good thing about science is that it's true whether you believe it or not." – Neil DeGrasse Tyson, astrophysicist

www.youtube.com/watch?v=yRxx8pen6JY

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COUNTERPOINT

There is insufficient evidence to establish causation between sports concussion and CTE.

Disclosures

- The views expressed herein are those of the presenter and do not reflect the official policy of the Department of the Army, Department of Defense, or DVBIC.
- The presenter does not intend to discuss the off-label/investigative (unapproved) use of commercial products or devices.
- The presenter has no relevant financial relationships to disclose.

Polling Question #4

The clinical signs of CTE:

- ❑ Are distinct from those of other neurological and psychological conditions
- ❑ Are non-specific, and can be caused by numerous medical and psychiatric conditions
- ❑ Are used to diagnose CTE in living persons
- ❑ Always include motor signs

Key Questions

- What is CTE?
- Is CTE different than AD?
- If you are a boxer, will you get CTE?
- If you play football, will you get CTE?
- If you are a cheerleader, will you get CTE?

Who is More at Risk for a Concussion?

OR

Image credits: http://classroomclipart.com/clipart-view/Clipart/Cheerleading/cheerleader-jumps-up-holding-pom-poms-clipart-59717_jpg.htm and http://www.bing.com/images/search?q=boxing+clipart+free&view=detailv2&&id=2426D529E621078ADAAA06BD47563D7B9EC3B5EF&selectedIndex=30&ccid=6wojr2wx&simid=608008018078731235&thid=OIP.Meb0a23af6c31f4387eddf962e5aee22bH0&ajaxhist=0

National Institutes of Health (NIH) Consensus Conference – Boston, March 2015

- First consensus conference to evaluate the neuropathological criteria for the diagnosis of CTE
- Conference conceived, organized and hosted by Ann McKee, M.D., Boston University, Principal Investigator (PI) of one of the NIH CTE grants. Four of 11 invited participants were either from Boston or on grants for which Dr. McKee is PI.

(NINDS, 2015)

NIH Consensus Conference

- Attendees
  - 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
  - Daniel Perl - Uniformed Services University of the Health Sciences, Bethesda
  - Thor Stein - Boston University, Boston
  - Willie Stewart - University of Glasgow, Scotland
  - Jean Paul Vonsattel - Columbia University, New York
  - Irene Litvan - University of California San Diego
  - Wayne Gordon - Mount Sinai Hospital, New York

(NINDS, 2015)

NIH Consensus Conference

- Not invited
  - John Povlishock, Virginia Commonwealth University
  - Harvey Levin, Baylor College of Medicine
  - Bennet Omalu, University of California, Davis
  - Joseph Maroon, University of Pittsburgh Medical Center
  - David Brody, Washington University, St. Louis
  - Grant Iverson, Harvard University
  - Paul McCrory, The Florey Institute of Neuroscience and Mental Health, Melbourne

Histopathology

- NIH National Institute of Neurological Disorders and Stroke (NINDS) “Consensus Conference”:
  - Gross: Macroscopic abnormalities of the septum pellucidum, dilation of the 3rd vent are “supportive criteria.”
  - Perivascular accumulation of tau proteins in neurons, astrocytes, and cell processes in an irregular pattern at the depths of cortical sulci is “pathognomonic.”

(NINDS, 2015)

Tau Hyperphosphorylation in Normal Aging

- In a study of 2,332 nonselected autopsy cases ranging in age from one to 100 years, abnormally phosphorylated tau protein within the brain in 2,322 (99.5%) cases, including 90% of those over 10 years of age, and in 100% of cases over 30 years of age.
  - In the same autopsy series, extracellular amyloid beta (Ab) deposits were identified in 44.2%of all brains, with the appearance of Ab occurring later (in older individuals) than occurs with hyperphosphorylated tau.

(Braak , Thal, Ghebremedhin, & Del Tredici, 2011)

Tau Hyperphosphorylation

- Matsuo et al. (1994) identified phosphorylated tau in biopsy-derived brain samples at almost all of the sites tested, although in smaller quantities than found in disease.

- Trojanowski, Newman, Hill, & Lee (1991) identified phosphorylated tau in dystrophic neurites in olfactory epithelium in six out of eight normal control adults.

Tau Hyperphosphorylation and Substance Abuse

- The Edinburgh group performed autopsy studies in 39 HIV-negative opiate abusers and found significant deposition of hyperphosphorylated tau in multiple brain regions of those with a history of opioid abuse compared with 37 age-matched controls.
  - Related both to microglial activation and to breakdown of the blood-brain barrier
  - No correlation with deposition of amyloid beta

(Anthony et al., 2010; Ramage et al., 2005)

Beta-amyloid Plaques

- Role with CTE controversial
  - Plaques not normally associated with CTE (Stein, Alvarez, & McKee, 2014)
  - Beta-amyloid plaques are typical findings (Omalu et al., 2011)

Tau and Amyloid Beta Are Not Even Closely Linked to Clinical AD

- In the Honolulu-Asian Aging Study, Japanese-American men born between 1900 and 1919 were assessed every 2-3 years until death in the period from 1991 until the study finished in 2012.
  - Assessment on each review included clinical and cognitive examination.
  - A total of 593 out of the 3,508 subjects have proceeded to autopsy.
  - At the time of death, 32% were clinically demented at last review (within two years of death), 25.2% demonstrated some cognitive decline, and 42.8% were cognitively normal.

(Gelber, Launer, & White, 2012; White, 2009)

Tau and Amyloid Beta

- At autopsy, 54% of men who were cognitively normal at last examination demonstrated neuropathological lesions including amyloid beta and neurofibrillary tangles.
- This study as well as those of Driscoll, and a separate study by Brayne, document that while these lesions are associated with the clinical syndrome in life in many individuals, in others there are no clinical manifestations, and the pathological abnormalities may represent normal aging.

(Gelber et al., Launer, & White, 2012; White, 2009 ; Driscoll et al., 2006; Brayne et al., 2009)

Causality: Boxing

- Former U.S. Surgeon General C. Everett Koop, M.D.: “Boxing should be eliminated from the Olympics.”
- The American Medical Association and American Academy of Neurology: “Boxing is so inherently injurious to the brain that it should be banned.”

(Rosenthal, 1990)

Causality: Boxing

- But what is boxing?
  - Practicing and employing the *art of self defense*
  - An art form and unique physical self-expression
  - With all of its dynamics, mechanics and nuances, the beauty is in the skill it takes to perform masterfully under extreme competitive conditions.
  - It is using the human form to its greatest capacity in pursuit of athletic excellence.
  - Unless you test your limits, you may never really know your capabilities.

Observations of Dr. Donald Marion, former team neurosurgeon for the Pittsburgh Panthers

Causality: Boxing

- National Safety Council (37 sports)
  - Boxing ranked 26% among sports that required treatment in hospital emergency departments.
  - Most dangerous sports are bicycle riding, basketball and football
  - Cheerleading, golf and fishing have more injuries.
  - Boxing is, however, more dangerous than horseshoe pitching and billiards.

(National Safety Council, 2015)

Causality: Boxing

- Does it effect long term cognitive function/behavior?
  - Boxing is a requirement at the U.S. Military Academy at West Point.
    - Thoralf M. Sundt, Jr.: Famous Chair of Mayo Neurosurgery, pioneer in cerebrovascular procedures, editor of the Journal of Neurosurgery (died at age 62 of bone marrow cancer)
    - Robert McDonald: Secretary of Veterans Affairs, former Chief Executive Officer of Procter & Gamble (age 63)
    - COL Sidney Hinds: National Director, DVBIC

Is Football Safe?

- “The Chicago Tribune reported that in 1904 alone, there were 18 football deaths and 159 serious injuries, mostly among prep school players.”
- The annual Harvard-Yale football series was canceled for two years following the violent 1894 clash that was deemed “the bloodbath at Hampden Park.”

(Klein, 2012)

Football

- The Intercollegiate Athletic Association of the United States (IAAUS), now known as the National Collegiate Athletic Association (NCAA), was formally established on March 31, 1906 to reform the rules and regulations of college sports.

(Miller, 2011)

Teddy Roosevelt

- “In life, as in a football game, the principle to follow is: Hit the line hard; don’t foul and don’t shirk, but hit the line hard!”
- “I believe in rough games and in rough, manly sports. I do not feel any particular sympathy for the person who gets battered about a good deal so long as it is not fatal.”

(Klein, 2012)

Football Athletes

- 2012-2013 High School football: 1,086,627
- 2013 NCAA football: 70,147
- 2011, NFL: 1,696

(Hilton, 2014)

Virginia Tech Helmet Sensor Studies

- The incidence of hits to the head during football was investigated by mounting helmet sensors inside football helmets.
  - In one study, 19 boys ages **7 and 8** were found to have absorbed 3,061 hits to the head during the 2011 and 2012 seasons.
    - 60% of those hits were during practice (an average of 9 hits per practice).
    - There were an average of 11 hits per game.
    - None of the boys received a diagnosed concussion.
      - However, they absorbed 11 hits of 80g of force, or greater, a level that represents a higher risk of concussion.

(Young et al., 2014)

Sensor Studies

- Three teams of football players from ages **9 to 12** were tracked for one season.
  - Nearly 12,000 hits were recorded, or an average of 240 per player.
  - Players absorbed more hits during practice and at higher acceleration rates than the younger players.

(Cobb et al., 2013)

NCAA Football

- The median number of head impacts for individual players per practice and per game ranges from 4.8 to 7.5 and 12.1 to 16.3, respectively.
  - Offensive linemen have a higher percentage of impacts to the front than to the back of the helmet.
  - Quarterbacks have a higher percentage to the back than to the front of the helmet.
  - Linebackers and running backs have the greatest peak linear and peak rotational accelerations for impacts to the front of the helmet.
  - Running backs also have the greatest peak linear acceleration for side impacts.

(Crisco et al., 2010)

Longitudinal Cohort vs. Case Studies

- Longitudinal cohort studies track the same people over time.
  - Advantages: Best way to examine long-term risks
  - Disadvantages: Long wait for results
- Case studies examine individuals at a single time point.
  - Advantages: Best for very rare conditions
  - Disadvantages: Prone to selection bias (due to selection of cases not representative of the population)

High School Football Players – 50 Years Later

- **Cohort**
  - All male students who played football from 1946 to 1956 in Rochester, Minnesota high schools, plus a non-football-playing referent group of male students in the band, glee club, or choir
  - Records-linkage system of the Rochester Epidemiology Project
  - From October 31, 2010, to March 30, 2011 all available medical records to assess later development of dementia, Parkinson's disease (PD), or amyotrophic lateral sclerosis (ALS) and the frequency of dementia, PD, or ALS with incidence data from the general population of Olmsted County, Minnesota

(Savica, Parisi, Wold, Josephs, & Ahlskog, 2012)

50 Years Later

- **Results**
  - No increased risk of dementia, PD, or ALS among the 438 football players compared with the 140 non-football-playing male classmates.
  - PD and ALS were slightly less frequent in the football group, whereas dementia was slightly more frequent, but not significantly so.
  - When we compared these results with the expected incidence rates in the general population, only PD was significantly increased; however, this was true for both groups, with a larger risk ratio in the non-football group.

(Savica et al., 2012)

50 Years Later

- **Conclusion**
  - High school students who played American football from 1946 to 1956 did not have an increased risk of later developing dementia, PD, or ALS compared with non-football-playing high school males, despite poorer equipment and less regard for concussions compared with today and no rules prohibiting head-first tackling (spearing).

(Savica et al., 2012)

Team-Based Sports Are Associated with Improved Health

- *A meta-analysis from 1990 through June 2012, a total of 3,668 publications were initially identified, of which 11 met the selection criteria.*
  - Club-based or team-based sport associated with well being and reduced distress and stress, improved self-esteem, social interaction, and fewer depressive symptoms.
  - In general, positive associations with sport participation and psychological, psychosocial and social health domains

(Eime et al., 2013)

Benefits of Team Sport May Be Even More Pronounced for School Students

- *The study sample includes 50,168 ninth grade public school students who completed an anonymous, voluntary statewide survey in 2001.*
  - Students were classified into four groups based on their participation in sports and other activities (e.g., clubs, volunteer work, band, choir, or music lessons): neither, both, other activities only, and sports only.
  - Students involved in sports, alone or in combination with other activities, had significantly higher odds than the other two groups for exercise, milk consumption, and healthy self-image, and significantly lower odds for emotional distress, suicidal behavior, family substance abuse, and physical and sexual abuse victimization.
  - Odds ratios for the group involved in both types of activities were significantly higher than those for all the other groups for all healthy behaviors and measures of connectedness, and significantly lower for all but one of the unhealthy behaviors.

(Harrison et al., 2003)

Coaches' Perspectives

- Participants included 109 youth sport coaches who completed a survey packet consisting of a demographic information questionnaire and the Ohio Sport Satisfaction Index.

- Coaches ranked the variables of having fun, learning life skills, being part of a team, developing confidence, and the excitement of competition as the most important outcomes for the youth they coach.

(Lesyk et al., 2000)

Parent-reported Health-related Quality of Life (HRQOL) in Children Who Play Sports

- Cohort study that used data drawn from the Longitudinal Study of Australian Children in waves 3 (2008) and 4 (2010). Participants were a nationally representative sample of 4,042 Australian children ages 8.25 (SD = 0.44) years at baseline and followed up 24 months later.
  - Children who continued to participate in sports between the ages of 8 and 10 years had greater parent-reported HRQOL at age 10 compared with children who did not participate in sports, children who commenced participation after 8 years of age, and children who dropped out of sports before reaching 10 years of age.
  - Children who participated in both team and individual sports or team sports alone had greater HRQOL compared with children who participated in individual sports alone.
  - **The benefits of sports participation were strongest for girls!**

(Vella et al., 2000)

What Can We Conclude?

- Data reporting is inconsistent across case studies.
- In a recent comprehensive review of all CTE reports, 43% of the cases were re-reported across multiple publications (Maroon et al., 2015)
- There is a significant likelihood of selection, or ascertainment, bias.
- Premortem symptom data is often derived from interviews with family members, is not objective, and is subject to recall biases. (McCrory et al., 2013)

What Can We Conclude?

- In the Boston University case series, 30 (44%) of the CTE subjects overall, and 27% of the pure CTE subjects, showed diffuse, neuritic, or vascular amyloid.
- Of these, seven subjects had sufficient amyloid beta (Ab) and tau pathology to carry the additional diagnosis of AD by 2012 National Institutes on Aging Alzheimer Association criteria.
- Taken together, these findings also raise the issue of Ab plaque pathology and the role Ab metabolism in the putative disease process.

(McKee et al., 2013)

4th Zurich Conference on Concussion in Sport

"It was agreed that Chronic traumatic encephalopathy (CTE) represents a distinct tauopathy with an unknown incidence in athletic populations." (McCrory, et al., Feb.8, 2013, p.8)

"It is further agreed a cause and effect relationship has not as yet been demonstrated between CTE and concussions or exposure to contact sports." (McCrory, et al., Feb.8, 2013, p.8)

"At present, the interpretation of causation in the modern CTE case studies should proceed cautiously." (McCrory, et al., Feb.8, 2013, p.5)

"It was also recognised that it is important to address the fears of parents/athletes from media pressure related to the possibility of CTE." (McCrory, et al., Feb.8, 2013, p.8)

Summary

- While many of these athletes have a history of exposure to head impacts as a part of contact sport, there is insufficient evidence to establish causation between sports concussion and CTE.
- It is likely that many of the cases with neuropathological findings represent the normal aging process, the effects of opiate abuse, or a variant of frontotemporal lobar degeneration.
- Whether particular genetic causes may place athletes at greater risk of neurodegenerative disease is yet to be determined.

Polling Question #5

"Selection bias" is a bias in a scientific investigation:

- ❑ Caused by a sample that is not representative of the population
- ❑ When the investigator's assumptions influence the outcome
- ❑ Caused by a small number of observations
- ❑ Caused by incorrect interpretation of statistics

Questions?

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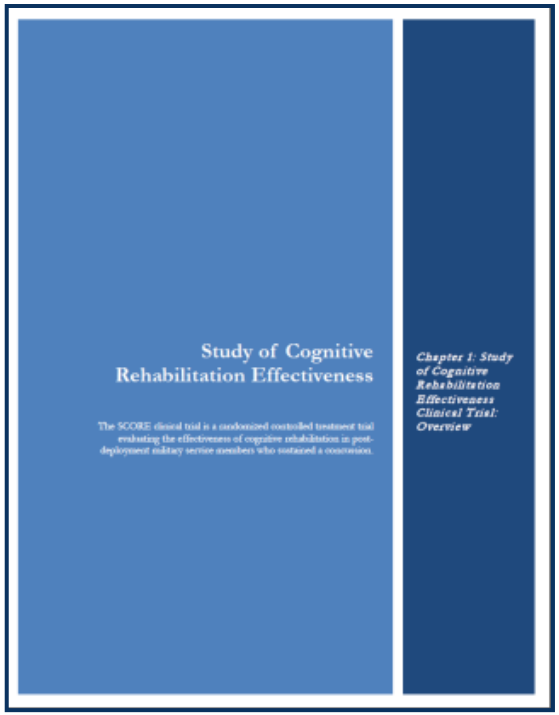
The Study of Cognitive Rehabilitation Effectiveness (SCORE)



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