



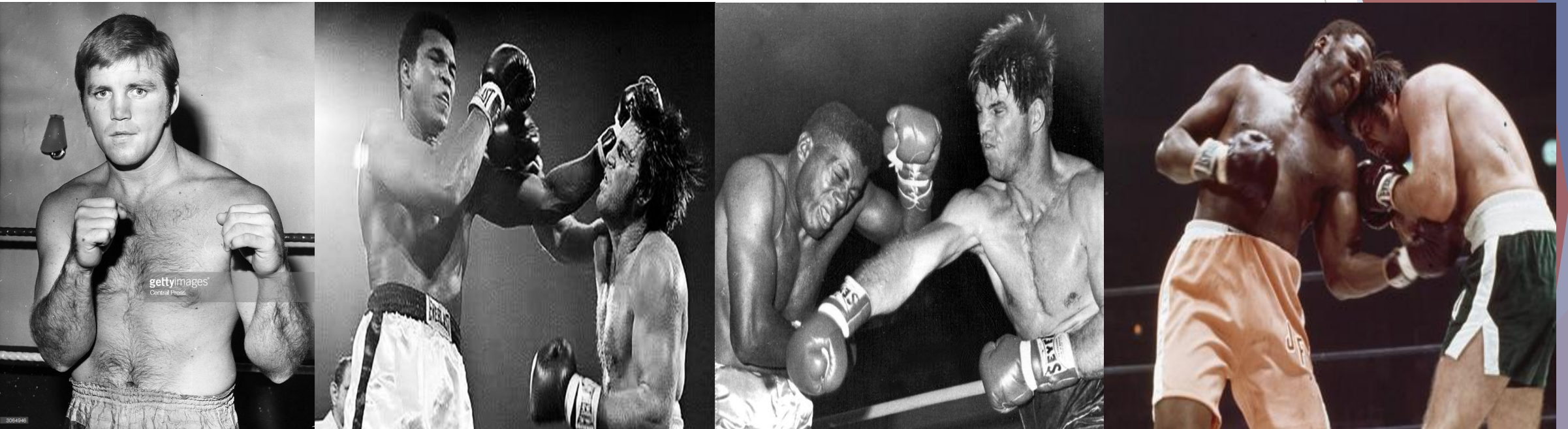
TBI-BH ECHO

Traumatic Brain Injury - Behavioral Health ECHO
UW Medicine | Psychiatry and Behavioral Sciences

TBI & Chronic Traumatic Encephalopathy



Jerry Quarry

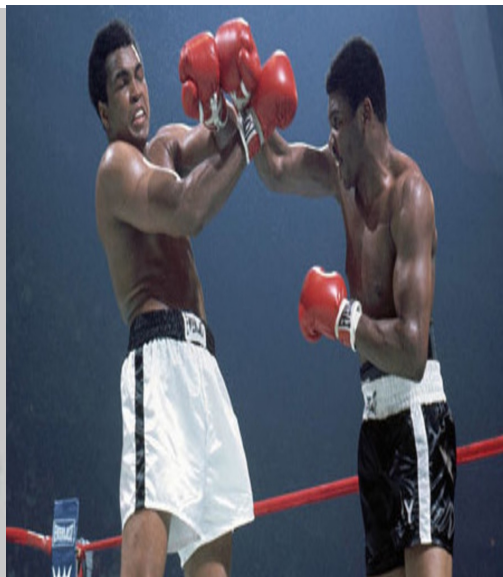


Jerry Quarry

- ▶ Jerry Quarry became a professional boxer in May of 1965 and fought in 14 bouts that year alone, including 3 in the month of June.
- ▶ Quarry ultimately fought in 66 bouts, boxed 419 rounds, and his opponents included Floyd Patterson, Joe Frazier, and Muhammad Ali.
- ▶ Quarry was diagnosed with dementia at age 47 and died at age 53.



Jimmy Young

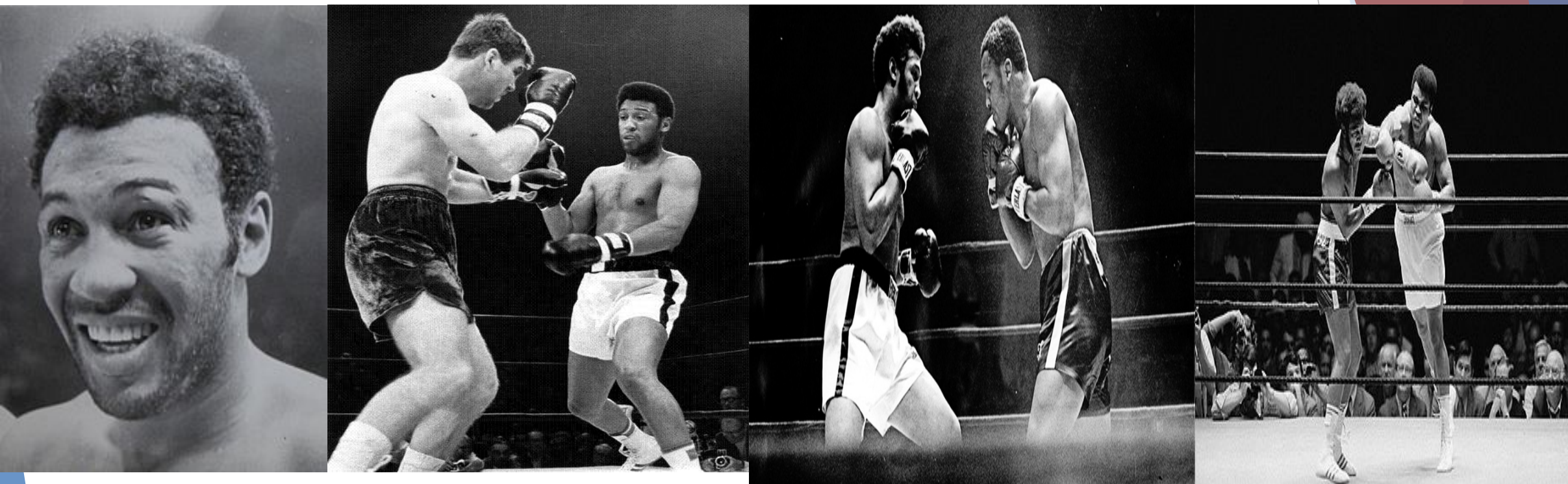


Jimmy Young

- ▶ Jimmy Young fought in 56 bouts, boxed 447 rounds
- ▶ Was a sparring partner for Ali and George Foreman, and fought Ali, Foreman, and Ken Norton
- ▶ Young died at age 56 with dementia.



Jimmy Ellis



Jimmy Ellis

- ▶ Jimmy Ellis fought in 53 bouts, boxed 342 rounds, and fought Quarry, Patterson, Frazier, and Ali.
- ▶ Ellis died at 63 with dementia



“Aaron Hernandez had severe CTE; daughter sues NFL, Pats”



“Dr. Ann McKee, the director of the CTE Center at Boston University, said Hernandez had Stage 3 (out of 4) of the disease, which can cause violent mood swings, depression and other cognitive disorders .”



Objectives

- ▶ By the end of this lecture the attendee will be able to list the various forms of traumatic brain injury including the clinical features, the course and prognosis and pathophysiology and neuropathology.
- ▶ By the conclusion of this lecture the attendee will be able to list the problems involved with the validity of Traumatic Encephalopathy Syndrome (Chronic Traumatic Encephalopathy).



Traumatic Brain Injury

- ▶ Traumatic brain injuries (TBIs) can affect people of all ages:
 - ▶ major cause of death and disability
 - ▶ incidence of ~10 million people worldwide.
- ▶ TBIs can include penetrating injuries and closed-head injuries.
- ▶ TBIs categorized into mild, moderate and severe based on clinical factors, such as
 - ▶ the duration and severity of consciousness (if present)
 - ▶ the presence of amnesia and neurological symptoms
 - ▶ the results of structural brain imaging (such as CT or MRI).
- ▶ Moderate and severe TBI are neurosurgical and intensive care concerns.



Definition of Traumatic Brain Injury

- Application of external physical forces to the brain, including acceleration/deceleration and/or blast-related forces
- The forces applied produce immediately apparent physiological disruption of brain function and/or structure, usually evidenced by an alteration of mental state and/or sensorimotor impairments
- The alteration of mental state and/or sensorimotor impairments produces at least transient functional disability



Definition and Classification of TBIs

- ▶ Alteration in mental state at the time of the injury:
 - ▶ feeling dazed/confused or uncertain about what is happening
 - ▶ having difficulty in thinking clearly or responding inappropriately to mental status questions
- ▶ Neurological deficits
 - ▶ for example, weakness, loss of balance and/or change in vision that may or may not be transient, and an intracranial lesion



Exclusions

- Perinatal (birth) trauma
- Hypoxia-ischemia (anoxia)
- Inflammatory disorders of the central nervous system
- Toxic insults
- Metabolic insults
- Primary ischemic or hemorrhagic strokes
- Seizure disorders and/or their consequences
- Intracranial surgery
- Electroconvulsive Therapy
- Cerebral neoplasms
- Skull fracture or intracranial hematoma (i.e., epidural, subdural) without cerebral involvement
- Pure psychological trauma



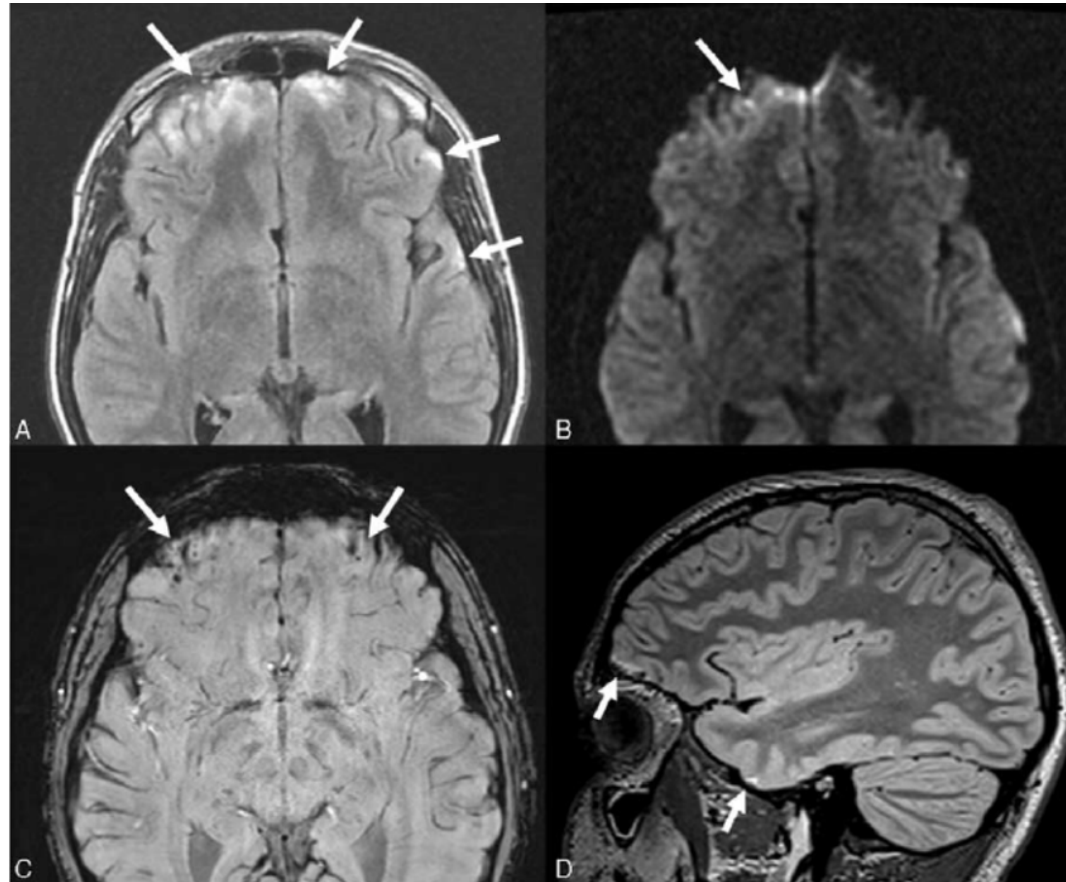
Definition and Classification of TBI

	Mild TBI	Moderate TBI	Severe TBI
Structural Brain Imaging	Normal	Normal or Abnormal	Normal or Abnormal
Loss of Consciousness	0-30 min	30 min to 24H	>24H
Altered Mental State	≤24H	>24H	>24H
Post-traumatic Amnesia	≤1 Day	1-7 Days	>7 Days
Glasgow Coma Scale score	13-15*	9-12*	<9*

*Best score achieved in the first 24H after trauma



Complicated mTBI



GCS

Glasgow Coma Score		
Eye Opening (E)	Verbal Response (V)	Motor Response (M)
4=Spontaneous 3=To voice 2=To pain 1=None	5=Normal conversation 4=Disoriented conversation 3=Words, but not coherent 2=No words.....only sounds 1=None	6=Normal 5=Localizes to pain 4=Withdraws to pain 3=Decorticate posture 2= <u>Decerebrate</u> 1=None
		Total = E+V+M



Conditions Associated with Traumatic Brain Injuries

- ▶ **Subconcussive head trauma**

- ▶ Head traumas that do not result in any subjective or objective symptoms
- ▶ ?To which degree repeated subconcussive head traumas in contact sports add to the risk of developing chronic traumatic encephalopathy (CTE) is currently unknown, but is under active investigation



Conditions Associated with Traumatic Brain Injuries

▶ Repetitive mild TBI

- ▶ Repeated episodes of concussion or mild traumatic brain injury
- ▶ Primarily experienced by contact sports athletes and in military personnel who are exposed to training and/or combat
- ▶ Believed to initiate the CTE pathophysiological process



Conditions Associated with Traumatic Brain Injuries

- ▶ **Post-concussive syndrome (also known as post-concussion disorder)**
 - ▶ Mild TBI that persists beyond the expected recovery period (>3 months)
 - ▶ Nonspecific subjective symptoms, such as headache, fatigue, dizziness, poor concentration, sleep disturbances, anxiety, irritability and depressed mood
 - ▶ The symptoms of PCS are highly variable, which makes determining the prevalence of this disorder difficult to calculate
 - ▶ Estimated at 10-15% of patients with concussion



Conditions Associated with Traumatic Brain Injuries

- ▶ **Traumatic Encephalopathy Syndrome (Chronic Traumatic Encephalopathy)**
 - ▶ Chronic neurodegenerative disorder believed to be initiated by repeated head trauma
 - ▶ The term suggested for the clinical counterpart to CTE, primarily in research settings, is **traumatic encephalopathy syndrome**
 - ▶ First described in retired professional boxers
 - ▶ now also recognized in amateur and professional athletes involved in many different contact sports and in military veterans



Mild TBI

- ▶ Mild TBI and concussion are interchangeable terms for the least severe form of TBIs and represent 80-90% of cases.
- ▶ Mild TBI is typically caused by blunt nonpenetrating head trauma and results in transient symptoms that are detected through clinical observations, patient self-reporting or observations by witnesses (when available).



Mild TBI

- ▶ Symptoms are highly variable and can include:
 - ▶ physical (for example, nausea and vomiting, dizziness and headache),
 - ▶ cognitive (for example, poor concentration and memory problems) and
 - ▶ behavioral (for example, irritability and emotional lability) symptoms as well as
 - ▶ loss of consciousness.
- ▶ According to the American Congress of Rehabilitation Medicine criteria, CT of the brain, as well as a routine neurological examination, might (or might not) be normal.
- ▶ No single test is available to assist making a clinical diagnosis of mild TBI*.



GFAP (Glial fibrillary acidic protein)& UCH-1 (Ubiquitin carboxy-terminal hydrolase L1)

- ▶ GFAP IS A STRUCTURAL PROTEIN FOUND ALMOST EXCLUSIVELY IN ASTROCYTES
 - ▶ GFAP is a specific marker of astrocyte injury in either white or gray matter that is elevated in patients with traumatic intracranial abnormalities on CT
- ▶ GFAP reliably distinguishes between trauma patients with mTBI and those without head injury
- ▶ GFAP levels are not affected by extracranial trauma or exercise
- ▶ UCH-L1 IS A DEGRADATION ENZYME HIGHLY AND EXCLUSIVELY EXPRESSED IN NEURONS
 - ▶ Blood levels have been demonstrated to distinguish mTBI patients from those without injuries
 - ▶ Wang KK, Yang Z, Zhu T, et al. Rev Mol Diagn. 2018
 - ▶ Papa L, Lewis LM, Silvestri S, Falk JL, 2012



Mild TBI

- ▶ Symptoms of mild TBI resolve within 7-10 days in 80-90% of cases
 - ▶ most patients with post-concussive symptoms will show resolution of their symptoms within 1-12 weeks.
- ▶ The recovery period after sports concussion might be shorter
 - ▶ athletes are typically in better physical condition than patients with non-sports-related mild TBI.



Mild TBI

- ▶ Non-sports-related mild TBI more often associated with
 - ▶ pre-existing behavioral, psychiatric and/or substance abuse problems
 - ▶ increase their susceptibility to injury and might prolong recovery
 - ▶ sports-related TBIs might result from lower mechanical forces than non-sports-related TBIs.



Indications for Neuroimaging after Concussion

- ▶ Abnormal neurologic exam including tests of gait
- ▶ Progressive headaches
- ▶ Recurrent vomiting
- ▶ Loss of consciousness >1 minute
- ▶ Prolonged anterograde amnesia
- ▶ Seizure
- ▶ Skull fx
- ▶ Age >60
- ▶ Etoh/Drug intoxication
- ▶ Coagulopathy
- ▶ Rapid blood tests: ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP)
-- that are released from the brain into blood within 12 hours of head injury with structural damage (?)
- ▶ GCS <12 - 2 hours post-injury



Management of Sports Concussion

- ▶ When a concussion is suspected the athlete must be immediately removed from play for a neurologic examination, including cognitive and balance testing.
- ▶ Standardized sideline tests, such as the **Sports Concussion Assessment Tool 3** and **Balance Error Scoring System**, may be useful, but the reliability, validity, specificity, and sensitivity, without an individual **baseline**, remain undefined.



Management of Sports Concussion

- ▶ If the athlete is diagnosed with a concussion they cannot return to play that day
- ▶ Should be managed by a health care practitioner with demonstrated competence in the treatment of concussion.
- ▶ Athletes should be free of symptoms or back to their baseline before they are cleared to begin the 5-day return to play protocol .

STEP - 24 HOUR	REHABILITATION PROGRESSION
1	Light aerobic exercise
2	Sports specific exercise
3	Non- contact training drills
4	Full Contact practice
5	Return to play



Management of Sports Concussion

- ▶ Metabolic abnormalities following a concussion usually resolve within 7-10 days
 - ▶ although the asymptomatic athlete may begin the protocol they should not be subjected to contact until they are 10 days after injury, at the minimum.
- ▶ Case studies of **catastrophic brain swelling** have been reported in, usually young, athletes who have suffered a **second brain injury while still symptomatic from the first injury**.
 - ▶ Termed second impact syndrome, and although there are no strong scientific data for support.
 - ▶ Should be respected.



Concussion Management

- ▶ Neurocognitive testing, such as the computerized Immediate Post Concussion Assessment and Cognitive Test, can be useful in assessing cognitive function in an athlete who has suffered a concussion.
- ▶ The testing is only helpful when it can be compared with a baseline test completed by the athlete before the injury occurred.



Concussion Management

- ▶ The testing is only another parameter to assist in the clinical management of the injured athlete, and test-retest reliability is variable.
- ▶ A diagnosis and recommendations regarding return to play cannot be made solely according to the results.
- ▶ The American Academy of Neurology recommends that each athlete who has suffered a concussion be assessed and managed individually without relying on a grading system.



Concussion Management

- ▶ The type of sport and the risk of recurrent head injury should factor into the return to play decision.
- ▶ The use of protective equipment **does not reduce** the risk of concussion.
 - ▶ Helmets, headgear, and mouth guards may prevent serious head, face, and oral injury but do not protect against concussion.



Repeated Mild TBI — CTE?

- ▶ Repeated mild TBIs and subconcussive head impacts have been associated with the development of chronic traumatic encephalopathy (CTE), particularly in contact sports athletes and military veterans.
- ▶ Notably, CTE is a neuropathological diagnosis:
 - ▶ requires post-mortem examination
 - ▶ given that no established or validated clinical criteria and
 - ▶ no biomarkers to support the diagnosis ante mortem are available
 - ▶ criteria for the clinical counterpart — traumatic encephalopathy syndrome (TES) — have recently been suggested.



Repeated Mild TBI — CTE?

- ▶ A progressive neurological condition in retired boxers called ‘punch drunk syndrome’, which was believed to be linked to repetitive head blows, was initially described by Harris Martland in 1928, following which the condition was called ‘dementia pugilistica’, before being referred to as CTE in the 1940s.

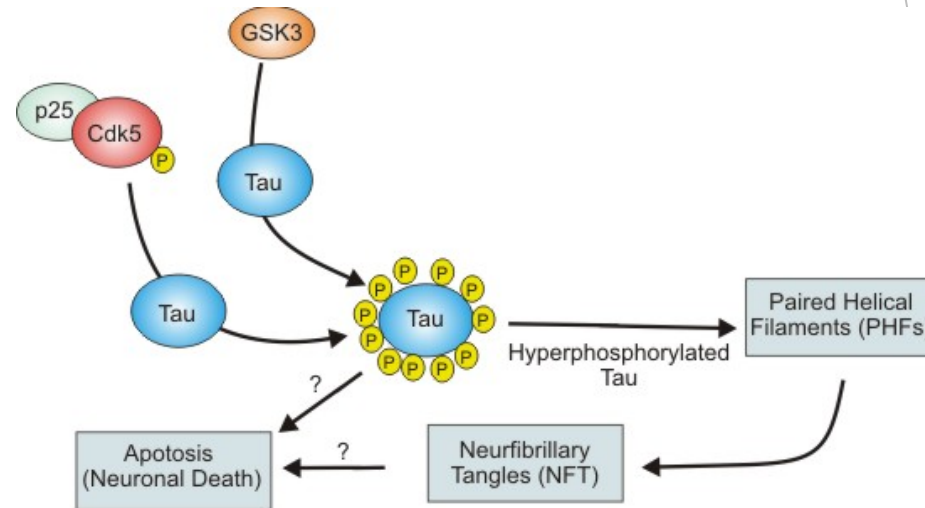
- ▶ Martland HS (1928) Punch drunk. J Am Med Assoc 91:1103-1107.



Repeated Mild TBI — CTE

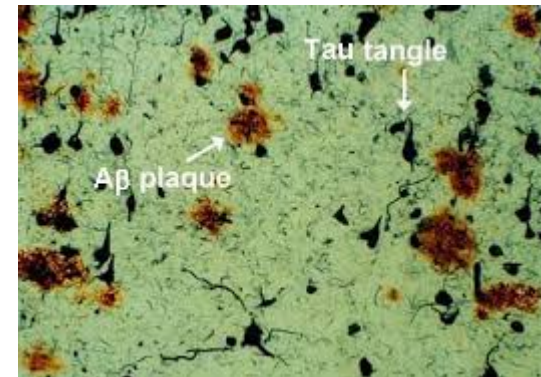
- ▶ In 1973, a neuropathological study (Corsellis, Bruton, & Freeman-Browne, 1973) showed that dementia pugilistica was associated with widespread neurofibrillary tangles (NFTs) in the brain, which were later known to be composed of aggregates of paired helical filament (PHF)-tau.
- ▶ The first case report of CTE in a former American football player was described in 2005, following which CTE pathology was identified in other contact sports athletes, such as ice hockey, soccer and rugby players and wrestlers.

- ▶ Omalu, B. I., DeKosky, S. T., Minster, R. L., Kambou, M. I., Hamilton, R. L., & Wecht, C. H. (2005). Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery*, 57(1), 128-134; discussion 128-134



Repeated Mild TBI — CTE

- ▶ CTE pathology has also been documented in soldiers exposed to explosive blasts, although the number of cases is limited.
- ▶ Amyloid- β (A β) plaques have been found in ~50% of CTE cases and are significantly associated with age and the inheritance of the *APOE* (which encodes apolipoprotein E) $\epsilon 4$ allele.



Clinical Features: From Concussion to CTE

- ▶ The clinical features of CTE are thought to be separated in time from PCS symptoms with a delay period of many years, though this distinction is not always easily made.
- ▶ This remote CTE symptomatology can involve cognitive, behavioral, and motor domains.



Clinical Features: From Concussion to CTE

- ▶ These categories also encompass the range of individual neurological and psychiatric syndromes that have been linked to TBI, including:
 - ▶ AD, FTD, mood and psychotic disorders, PD, and ALS.
- ▶ It is currently unclear whether TBI can predispose to each of these syndromes individually, and if so,
 - ▶ Whether they are caused by their typical molecular pathologies, or
 - ▶ If there are instead multiple distinct syndromes caused by CTE molecular pathologies that are misdiagnosed as AD or PD because of their shared features.



Cognitive Symptoms

- ▶ Cognitive symptoms develop at some point in life in over 90% of patients with confirmed CTE,
 - ▶ Only 30% have been diagnosed with dementia by the time of death.
- ▶ Memory loss and impaired attention and executive function are the most frequently described areas of cognitive impairment,
 - ▶ Language and visuospatial deficits have also been described and may be late features.
- ▶ These are largely based on retrospective determinations of symptoms, rather than being based on formal assessment with standardized neuropsychological testing.



Behavioral Signs/Symptoms

- ▶ Mood changes, including depression, are often reported.
- ▶ Suicidal thinking and completed suicide are common.
- ▶ Impulsivity, aggression, and violence are other common behavioral features.
- ▶ Persecutory delusions and an increased rate of substance abuse may occur.
- ▶ Despite some overlap with the impulsive and dysexecutive symptoms of FTD, frankly inappropriate or disinhibited behavior is rare, at least early in the course of the illness.



Motor Features

- ▶ Parkinsonism, including rigidity, bradykinesia, and tremor, may frequently be present during the disease course.
 - ▶ In the early literature on boxers, parkinsonism was emphasized as a common and frequently presenting feature.
- ▶ In modern descriptions of CTE, parkinsonism is not typically the initial symptom.
 - ▶ The reason for discrepancies between old and new descriptions of CTE is unclear, though it has been proposed that since the older literature mainly dealt with **boxers**, and the current literature with **American football players**, there may be different vulnerabilities in brain regions due to differing mechanisms of trauma.
- ▶ Motor neuron disease (MND), including weakness, spasticity, fasciculations, dysphagia, and dysarthria, has less commonly been described.
- ▶ Ataxia has also been described as a less common feature.



Progression

- ▶ A sequential progression of symptoms associated with corresponding pathological spread has been proposed.
 - ▶ Those with the mildest pathology (Stage I) present with headaches and inattention;
 - ▶ Those with Stage II pathology have mood changes, explosivity, and begin to have memory impairment.
 - ▶ In Stage III there is more cognitive impairment, particularly involving executive functions.
 - ▶ Patients with Stage IV pathology were more likely to have a diagnosis of dementia, exhibit aggression, and have word-finding difficulty.
- ▶ There are also patients in Stages I- III pathology who exhibited no clinical symptoms.



Progression

- ▶ Alternatively, the existing cases also suggest that there may be two possible CTE presentations.
 - ▶ One presents in younger individuals, primarily with behavior, particularly mood, changes.
 - ▶ The other affects older individuals and involves early cognitive impairment with a syndrome similar to AD.
- ▶ Progression tends to be slower than in other neurodegenerative illnesses.
- ▶ These symptom progressions were determined retrospectively by postmortem interviews with next of kin.



Primary Diagnostic Criteria for TES:

- ▶ Substantial Exposure to Repetitive Head Impacts
 - ▶ History of substantial exposure to repetitive impacts to the head is required.
 - ▶ These impacts may or may not have been associated with clinical symptoms or signs of concussion or traumatic brain injury (TBI).
 - ▶ Individuals should be screened for multiple possible sources of exposure over a lifetime.
- ▶ Examples of sources of substantial exposure to repetitive head impacts include:
 - ▶ Involvement in ‘high exposure’ contact or collision sports
 - ▶ Military service
 - ▶ Other



Primary Diagnostic Criteria for TES:

▶ Core Clinical Features

- ▶ Cognitive Impairment or Neurobehavioral Dysregulation, or both, is required to meet TES criteria.
- ▶ A Progressive Course is also required to meet TES criteria
 - ▶ As reported by self or informant, or by clinician's report.
 - ▶ Representing a significant decline from baseline functioning.
 - ▶ With deficits in episodic memory and/or executive functioning
 - ▶ Substantiated by impaired performance on formal neuropsychological testing (if available), as defined by performance at a level of at least 1.5 standard deviations below appropriate norms.



Primary Diagnostic Criteria for TES:

▶ Neurobehavioral Dysregulation

- ▶ As reported by self or informant, or by clinician's report.
- ▶ Representing a significant change from baseline functioning.
- ▶ The determination of "baseline" level of functioning may require clinical judgment in cases where change may have begun during the period of repetitive head impact exposure.
- ▶ With symptoms and/or observed behaviors representing poor regulation or control of emotions and/or behavior, including (but not limited to) explosiveness, impulsivity, rage, violent outbursts, having a "short fuse" (exceeding what might be described as periodic episodes of minor irritability), or emotional lability (often reported as "mood swings"), preferably substantiated by standardized measures that demonstrate clinical impairment in these domains.



Primary Diagnostic Criteria for TES:

- ▶ Not Fully Accounted for by Other Disorders
- ▶ Level of Functional Dependence/Dementia



Risk

- ▶ An accurate understanding of the risk conferred by TBI has been difficult to obtain.
 - ▶ Because CTE is currently a pathological diagnosis, and autopsy series have inherent acquisition bias, there is no current way to define the prevalence in the population.
- ▶ Even within a limited group of athletes it is not possible to determine the prevalence of CTE or risk to an individual.



Risk

- ▶ A large, recent autopsy series that included 34 American football players found that
 - ▶ Pathological stage of disease correlated with length of playing career
 - ▶ An indirect measure for quantifying cumulative head injury.
- ▶ Questionnaires given to retired NFL players have found that the frequency of clinically diagnosed mild cognitive impairment, memory problems, and depression is elevated, particularly for those who reported three or more concussions compared to those who did not report a concussion history.



Risk

- ▶ A study of death certificates among retired NFL players found a **three-fold elevated rate** of dying from neurodegenerative causes compared to the typical population frequency, with **AD and ALS** particularly over-represented.
- ▶ On the other hand, a study of those who played high school American football in Rochester, Minnesota between 1946 and 1956 found no increased rate of later developing dementia, PD, or ALS.



Risk

- ▶ This latter study, however, must be interpreted in the context of dramatic changes in protective gear and body habitus of American football players, even at the high school level, over the past 60 years that may influence the biomechanical features of impacts.
- ▶ Prospective, longitudinal studies will be needed to better gauge the risk among American football players.
- ▶ Studies estimating the prevalence among other athletes have also been problematic.



Risk

- ▶ A 1969 study of retired boxers (including many who had fought bareknuckle, less regulated fights) found that 17% had neurologic deficits that could be attributed to boxing.
- ▶ Current longitudinal studies of boxers are underway.



Risk

- ▶ Outside of athletics the effect of TBI on rates of neurologic and psychiatric illness has been the subject of many studies, but limitations in these have led to a lack of confidence in their findings.
 - ▶ Meta-analyses have shown an increased risk associated with history of TBI for the development of:
 - ▶ AD, PD, and ALS
 - ▶ The results and methodologies have varied widely among studies.
- ▶ TBI has been shown to be a risk factor for FTD.
- ▶ Psychiatric symptoms, particularly mood disorders, are common following TBI, but the risk of developing protracted psychiatric illness is less clear.



Risk

- ▶ Many of these studies involved retrospective determination of the TBI
 - ▶ recall bias and incomplete information about its timing and severity.
- ▶ Longitudinal cohort studies eliminate this recall bias, but often determine the presence of TBI by review of medical records or diagnostic codes
 - ▶ Likely missing milder or repeated injuries, which the study of American football players suggests may be highly relevant.



Risk

- ▶ The timing of injury relative to the neurologic diagnosis is also critical, and often poorly assessed in prior studies.
 - ▶ For example, an individual with PD may report a head injury that actually occurred due to the very early stages of the disease, rather than being causative, a phenomenon known to epidemiologists as “reverse causality.”
 - ▶ In one study that stratified the interval between injury and diagnosis, the risk of TBI on PD was no longer present when looking at injuries that occurred more than 10 years before diagnosis.



Other Risk Factors

- ▶ **Apolipoprotein E (APOE) ϵ 4 allele**, the strongest susceptibility gene for AD, is associated with increased risk for many neurodegenerative diseases following TBI.
 - ▶ This association, however, has recently been called into question with respect to CTE.
- ▶ Exciting work in mouse models, however, suggests that APOE ϵ 4 may impair the brain's overall ability to recover following injury.
- ▶ Similarly, alterations in **progranulin** metabolism have been proposed to underlie increased risk of FTD after TBI.
- ▶ Specific mutations in genes encoding **α -synuclein** have been associated with increased risk of PD after TBI and this risk is augmented in a more than additive manner with exposure to paraquat-containing pesticides.



Other Risk Factors

- ▶ It is currently unknown to what degree, if any
 - ▶ recreational drug or steroid use
 - ▶ alcohol abuse
 - ▶ chronic psychiatric illness
 - ▶ cardiovascular risk factors have on modifying risk of CTE
- ▶ There is some evidence that TBI in children or adolescents may be particularly morbid
 - ▶ There may be “critical periods” during which TBI may be more likely to result in a progressive neurodegenerative cascade.
- ▶ **Gender effects** are also **understudied** as the vast majority of cases of CTE have been in **males**, presumably due to **referral bias**.



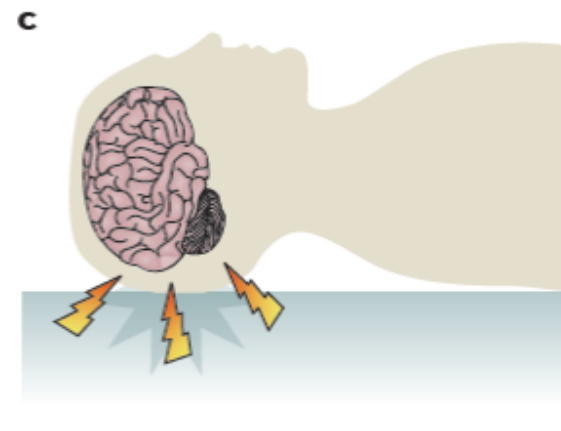
Mechanisms/Pathophysiology



Linear



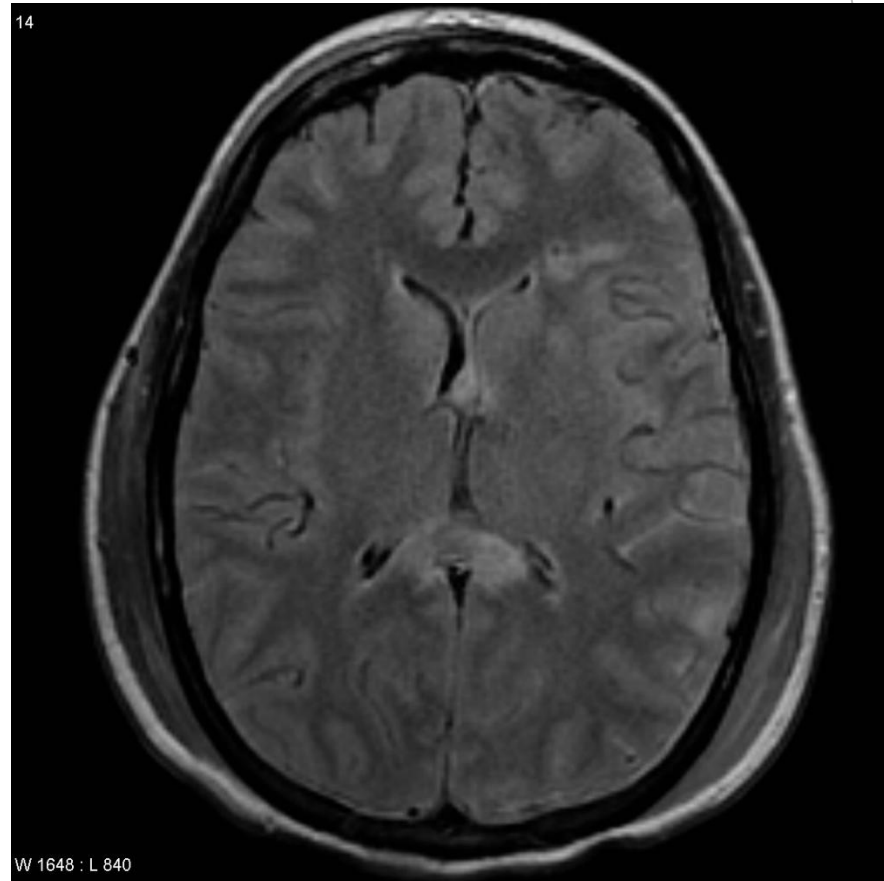
Rotational



Impact
Deceleration

Mechanisms/Pathophysiology: Biochemical

- ▶ These forces generate intracranial pressure gradients through the inertia of the brain that lags behind the skull during the rapid movement.
- ▶ These pressure gradients generate shearing and strain forces that stretch and damage axons, leading to axonal injury, which, when multifocal, is called diffuse axonal injury (DAI).
- ▶ Whether different types of acceleration and deceleration forces cause axonal damage by different mechanisms is unclear;
 - ▶ either focal strains or strains due to differences in densities between different parts of the brain might be at play.
- ▶ Indeed, biomechanical studies have shown that higher stress and strain forces can be observed in the bottom of the sulci in the frontal, parietal and temporal cortices, which also matches the location of tau pathology in CTE.



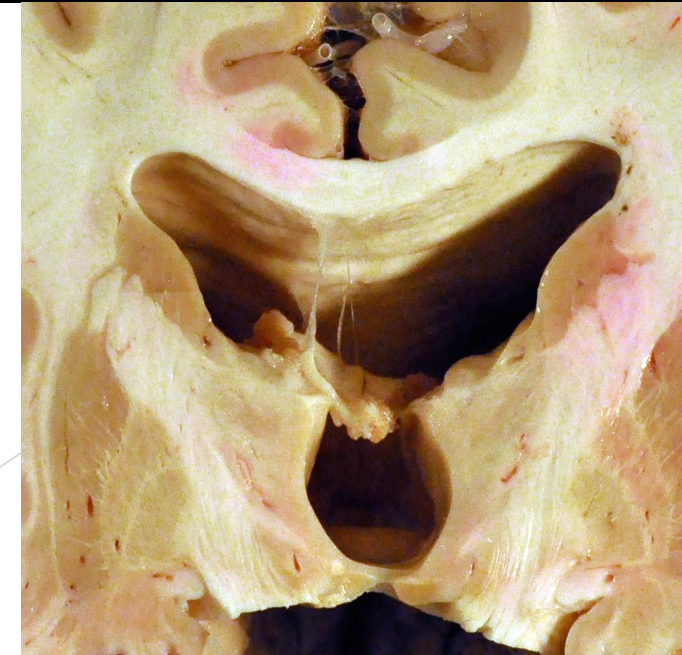
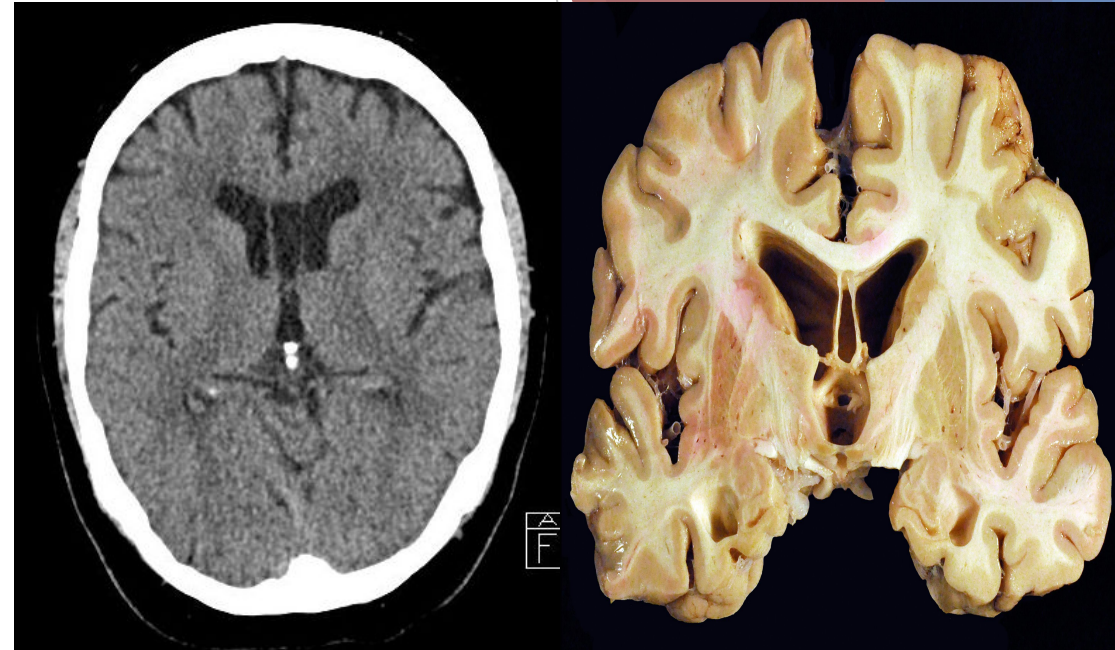
Neuropathology

- ▶ Neuropathological changes found after concussion (mild TBI) include mild multifocal axonal injury together with activation of microglia (the resident innate immune cells of the central nervous system) and microhemorrhages.
- ▶ The multifocal axonal injury typically involves the
 - ▶ fornices, corpus callosum, subcortical white matter and cerebellum.
- ▶ Less-consistent findings include TAR DNA-binding protein 43 (TDP43)-immunopositive neurites and small focal accumulations of PHF-tau, either as NFTs or neuropil threads.



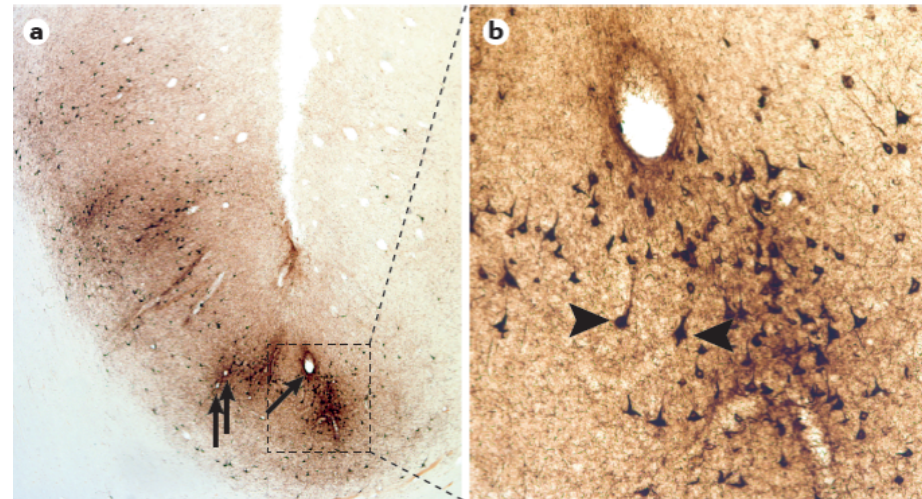
Gross Neuropathology

- ▶ The neuropathology of CTE involves both gross morphological and microscopic changes.
- ▶ For example, gross alterations, such as cavum septum pellucidum (a space between the layers of the septum pellucidum) or septal pellucidum fenestrations, are common pathological findings in CTE
 - ▶ thought to represent traumatic damage to the septum from CSF wave shifts that occur with linear and rotational acceleration.



Neuropathology

- ▶ In the recent US National Institute of Neurological Disorders and Stroke consensus criteria on CTE neuropathology
 - ▶ The pathognomonic lesion of CTE was defined as irregular, perivascular accumulation of phosphorylated tau (P-tau) aggregates in neurons and astrocytes that clustered at the depths of cortical sulci.
- ▶ This hallmark tau lesion distinguishes CTE from other neurodegenerative tauopathies, including Alzheimer disease, progressive supranuclear palsy and argyrophilic grain disease.
 - ▶ Tau abnormalities in CTE often involve the superficial cortical layers of the frontal, temporal and parietal cortices.
- ▶ TDP43 accumulation, A β accumulation and dot-like and spindle-shaped neurites can also be observed.

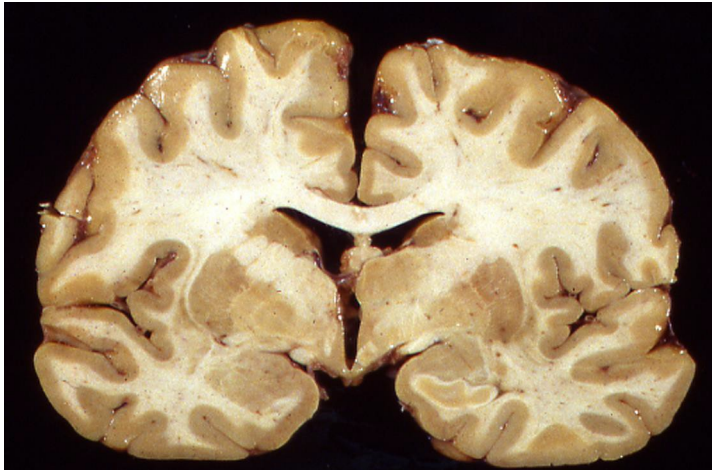


Pathology of CTE

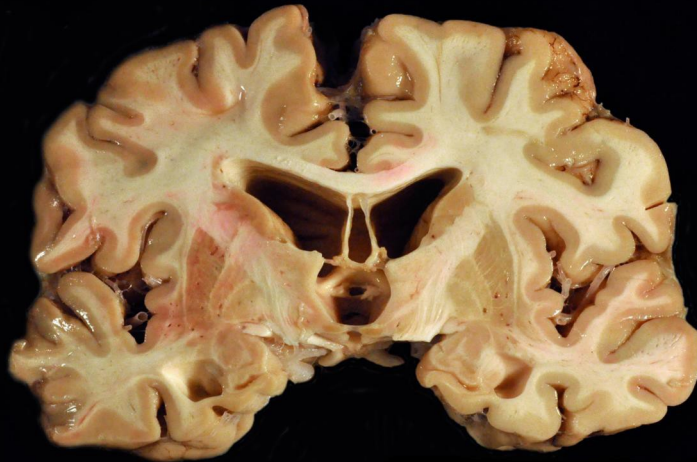
Brain Atrophy

P- Tau

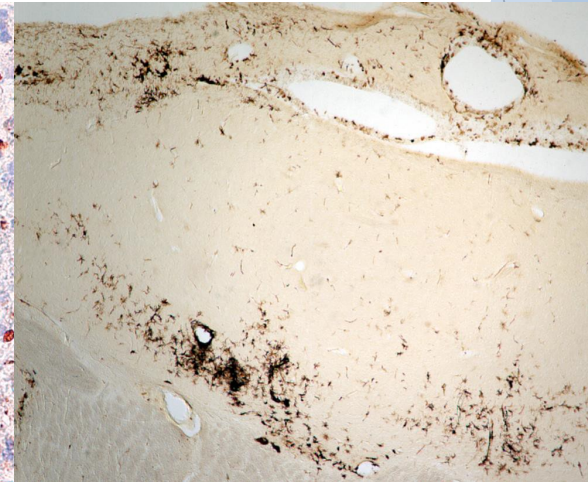
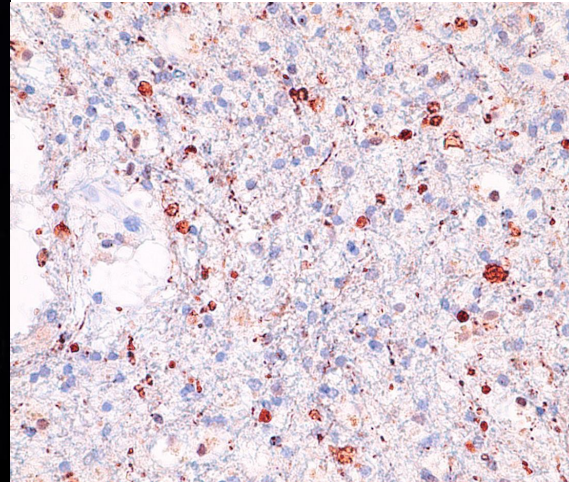
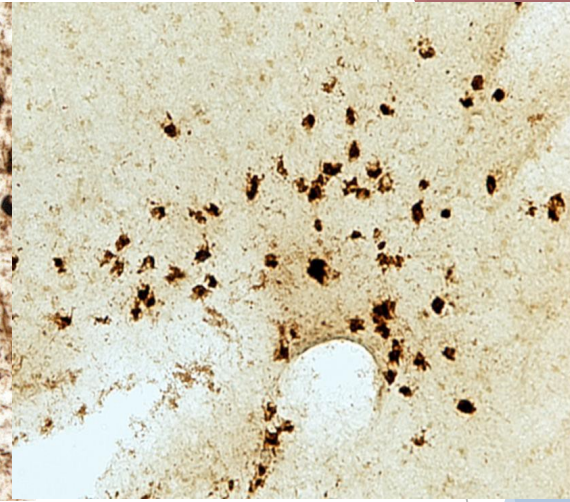
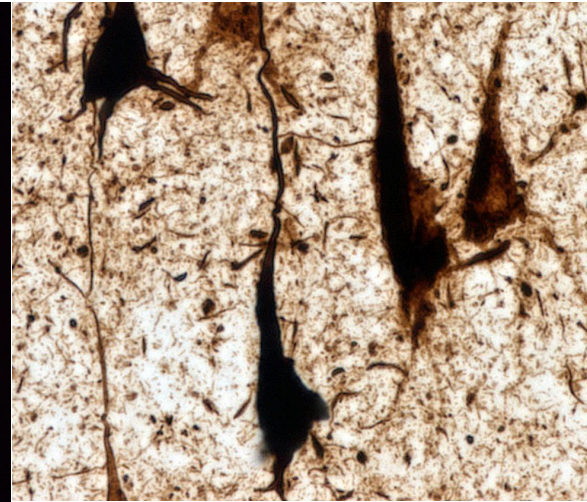
P-TDP-43



Normal



CTE



Stages of CTE by Symptoms and Neuropathology

CTE Stages	Symptoms	Primary brain regions showing tau pathology	Gross structural pathological changes
Stage I	Headache; attention/concentration deficits; depression; suicidality	Depths of frontal cortical sulci; locus coeruleus. Gliosis and axonal loss in white matter tracts	None
Stage II	Depression; suicidality; behavioral changes; memory loss; explosivity; aggression	Cortex; minimal in hippocampus, amygdala, and substantia nigra	Some mild ventricular enlargement; occasional cavum septum pellucidum
Stage III	Cognitive/executive dysfunction; depression; explosivity; aggression; dementia; suicidality	Hippocampus; amygdala; entorhinal cortex; substantia nigra; temporal and parietal cortices	Mild cerebral atrophy and ventricular dilation; some depigmentation of substantia nigra and locus coeruleus; diencephalic and mammillary body atrophy; corpus callosal thinning
Stage IV	Dementia; memory impairment; aggression; paranoia; explosivity; motor symptoms; depression; suicidality	Throughout cortex, temporal lobe	Reduced overall brain weight; ventricular enlargement; cavum/absent septum pellucidum; depigmentation of substantia nigra and locus coeruleus



Primary Brain Areas Associated with Depression and Suicide in CTE

Brain region affected in CTE	Psychiatric phenotype	Relevant articles
Amygdala	Depression, suicide	Maheu et al., 2013; Guilloux et al., 2012
Basal ganglia	Depression	Husain et al., 1991
Diencephalon	Depression, suicide	Mahar et al., 2014; Turecki 2014
Frontal cortex	Depression, suicide	Turecki 2014; Johnston-Wilson et al., 2000
Hippocampus	Depression, suicide	Turecki 2014; Mahar et al., 2014
Locus coeruleus	Depression	Bernard et al., 2011
White matter structures	Depression	Choi et al., 2015

Neuropathology

- ▶ A recent review of >1,700 brains from a neurodegenerative disease brain bank found CTE pathology in one-third of the brains of contact sports athletes, but no CTE-type changes were found in 162 controls or in 33 individuals with a history of a single TBI.
- ▶ Other pathological abnormalities include:
 - ▶ phosphorylated TDP43, which have been observed in 80% of cases, especially in later stages of CTE, and occasionally colocalizes with PHF-tau, axonal injury and neuroinflammation.
 - ▶ ~50% of CTE cases have deposition of AB as either diffuse or neuritic plaques (also known as senile plaques) and ~14% of CTE cases are comorbid for Alzheimer disease.

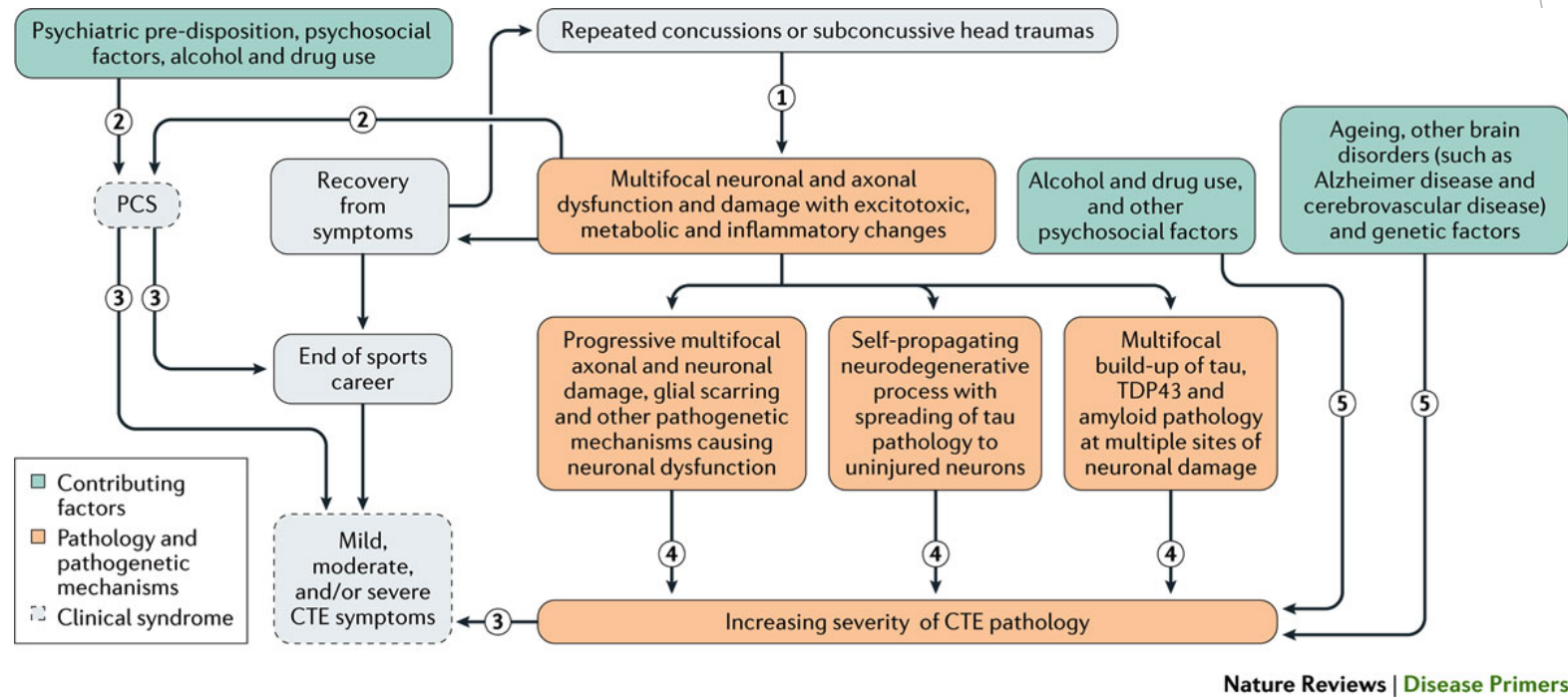


Neuropathology

- ▶ Brains from individuals with CTE have been shown to be fourfold more likely to have A β plaques and to develop plaques 10-15 years earlier than those from a community-based autopsy cohort.
- ▶ Moreover, the presence of A β plaques has been shown to be significantly associated with more-severe PHF-tau and poor clinical status before death, independent of the age of the patient.



Unknowns in the clinical and pathological pathways of chronic traumatic encephalopathy



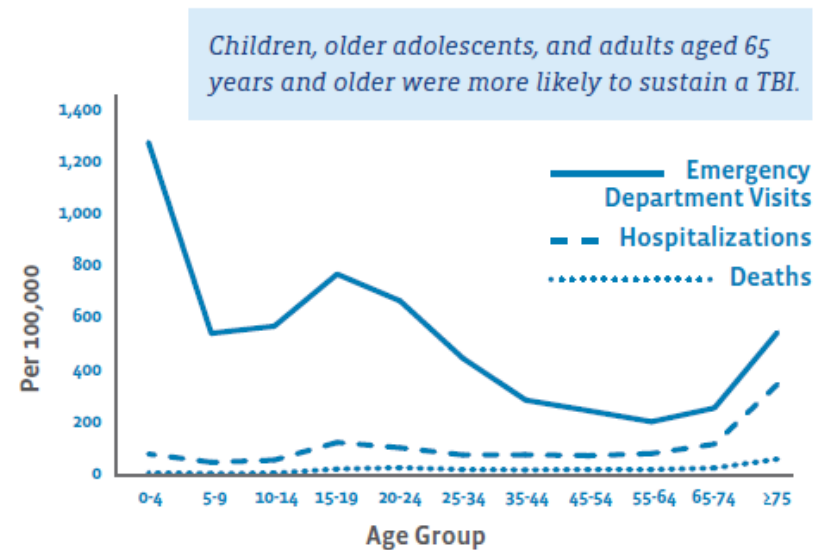
Prevention and Treatment

- ▶ Unlike most other neurodegenerative conditions, CTE has a clear environmental trigger: TBI.
 - ▶ While TBI does not produce CTE in all exposed individuals
 - ▶ It appears to be a necessary trigger in all cases of CTE that have been described to date.
- ▶ There is mounting evidence that TBI also increases risk of a number of other neurodegenerative diseases.
- ▶ Thus, if TBI could be avoided, this would be expected to eradicate CTE entirely and may also reduce incidence of many other neurodegenerative diseases.



Prevention and Treatment

- ▶ Many TBIs sustained in the USA and globally, however, would be difficult to prevent given their accidental uncontrolled nature.
- ▶ TBI in the USA peaks in early childhood, adolescence, and again in later life with falls and motor vehicle accidents being the first and second leading causes, respectively.
- ▶ Thus, clinicians treating these patient populations are uniquely situated to intervene with primary preventative strategies to example, to prevent falls in the elderly or prevent unrestrained motor vehicle accident injuries in children and adolescents.
 - ▶ Beer's List



Prevention and Treatment

- ▶ Currently, there are no disease-modifying treatments for CTE.
- ▶ Agents targeting tau are under development and may have a role in treating incipient or established cases of CTE.
- ▶ Individuals suspected of having TBI-related neurological or psychiatric illness may benefit from treatments targeting their mood, headache, or other symptoms.



Conclusion

- ▶ TBI is widely recognized as a risk factor for several neurodegenerative diseases including AD, FTD, PD, and ALS.
- ▶ Repeated mTBI or subconcussive injuries has also been associated with a unique tauopathy termed CTE that has, in postmortem analyses, been associated with cognitive, behavioral, and motor symptoms.



Conclusion

- ▶ Patients exposed to repeated mTBI or subconcussive injuries, such as athletes, show measurable changes on neuroimaging including structural MRI, functional MRI, and DTI that may be helpful for diagnosis, prognosis, and disease monitoring.
 - ▶ CSF and serum biomarkers indicative of TBI or neurodegeneration may additionally be helpful.
- ▶ Neuropathologically, CTE is defined by neurofibrillary cytoplasmic tangles of hyperphosphorylated tau as well as frequent aggregates of TDP-43 and, occasionally, AB diffuse plaques.



Conclusion

- ▶ Animal and human studies support the triggering of a neurodegenerative cascade involving multiple abnormal proteins following TBI.
- ▶ Longitudinal studies including detailed
 - ▶ Clinical
 - ▶ Neuroimaging
 - ▶ Biomarker assessments
 - ▶ Autopsy
- ▶ ... are needed to further define prevalence, clinical features, and natural history of CTE and other TBI-related neurodegenerative diseases and to pave the way for disease modifying treatment.

