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Aging with Traumatic Brain Injury

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Objectives

The Attendees will be able to:

- List common medical complications after traumatic brain injury (TBI) during rehabilitation phase and life long
- Discuss mortality after TBI
- Explain characteristics of chronic traumatic encephalopathy

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Outline

- Epidemiology of traumatic brain injury
- Brain injury as a disease process
- Medical Complications after TBI
- Chronic traumatic encephalopathy
- Mortality after TBI

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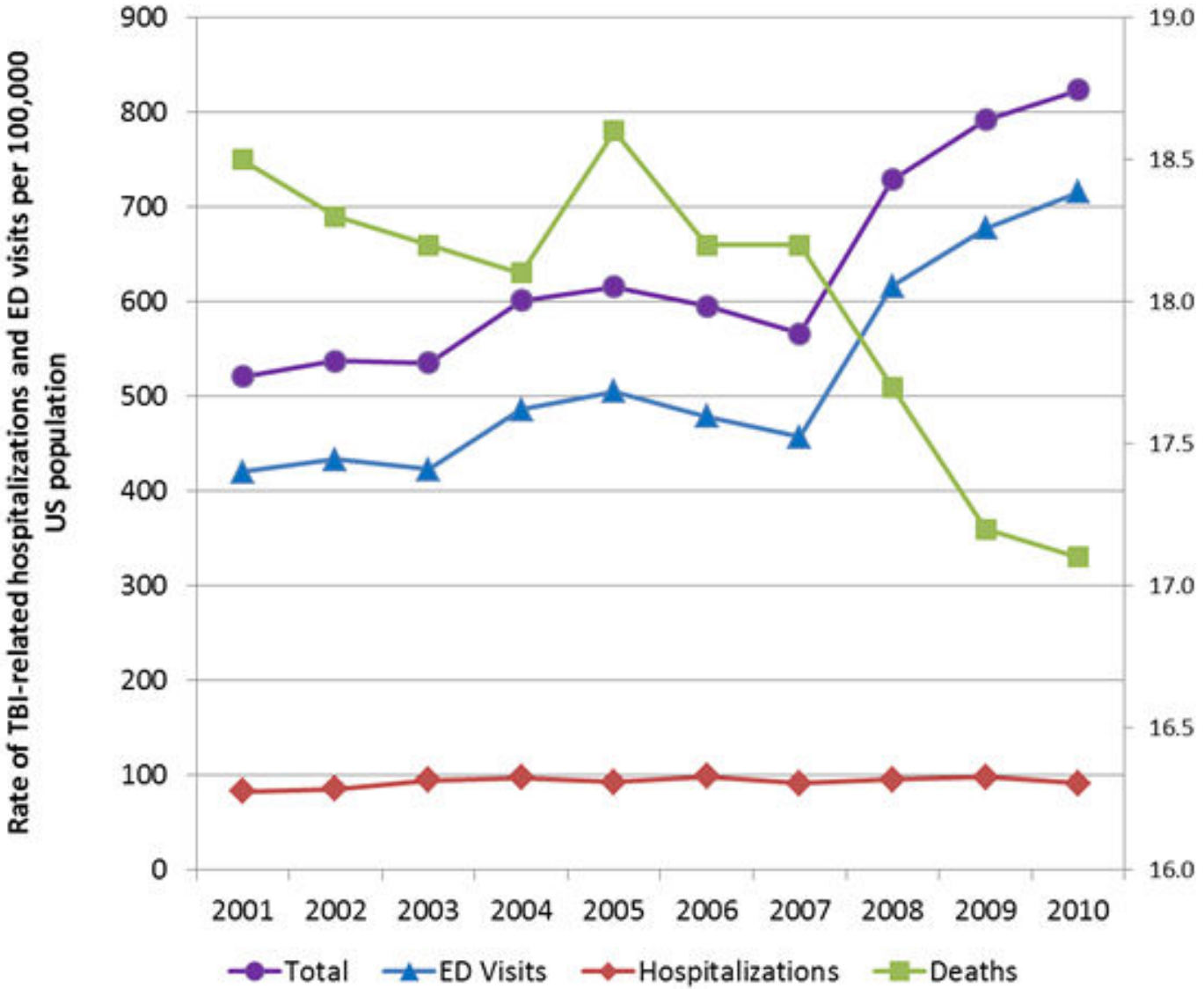
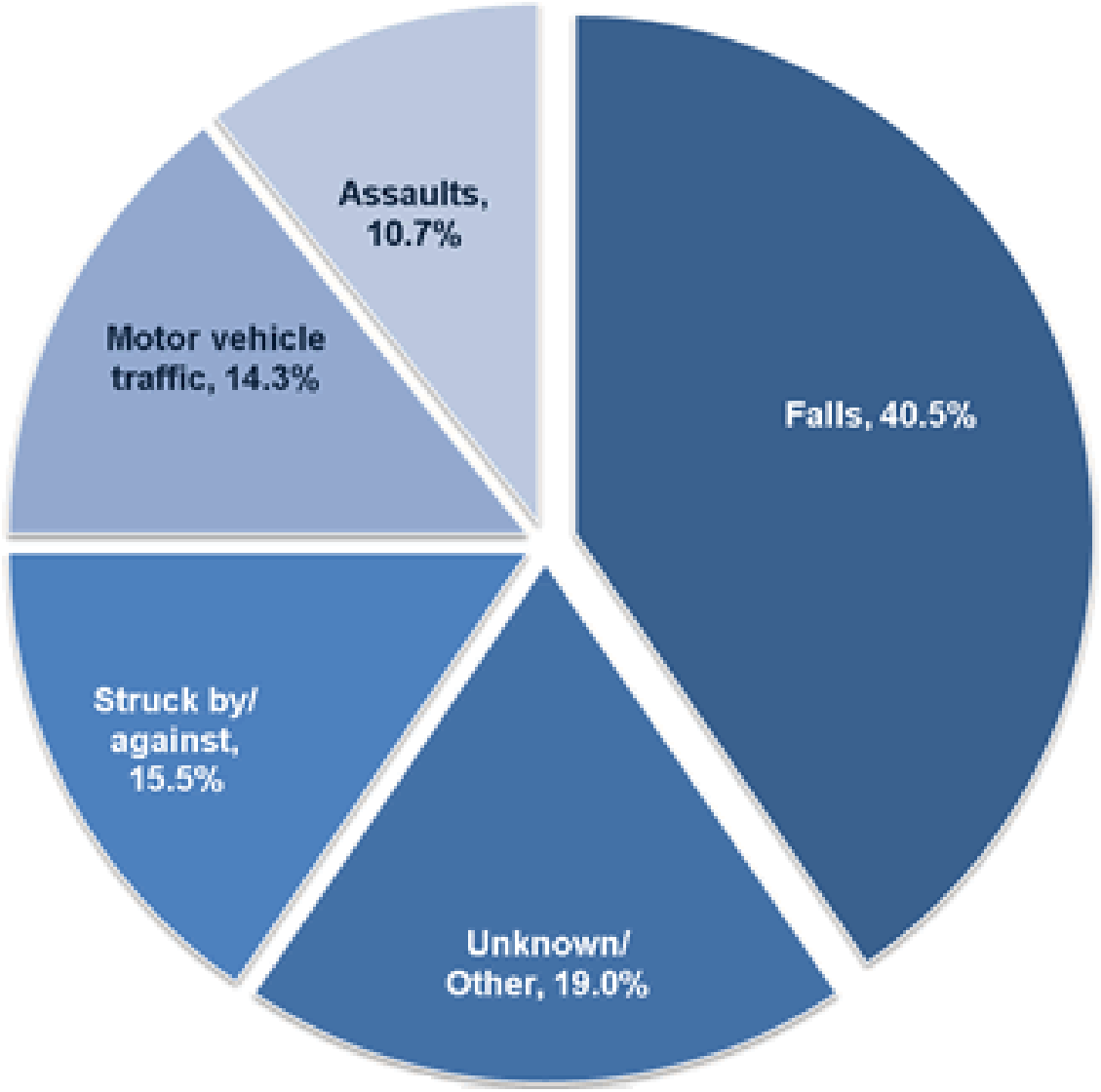
Rates of TBI-related ED Visits, Hospitalizations, and Deaths United States 2001-2010



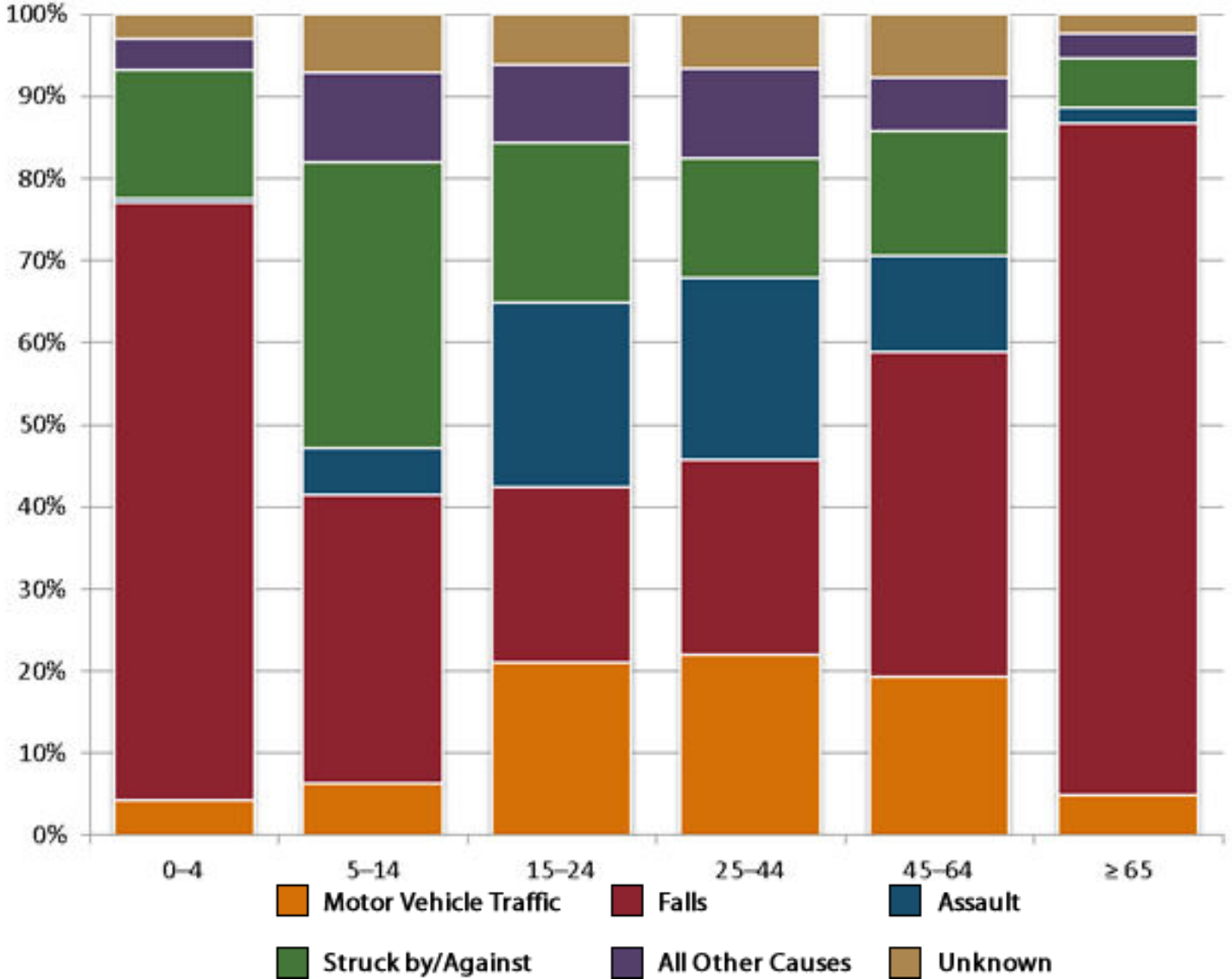
CDC

Leading Causes of TBI – ED Visits, Hospitalization, Death (2006-2010)



- CDC

Percent Distributions of TBI-related ED Visits by Age Group and Injury Mechanism – United States 2006-2010



- CDC

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Classification of TBI

- Pathological/anatomical – focal vs diffuse
  - the injury is localized to one area (focal)
    : Like a blood clot (hematoma)
  - the injury is throughout the entire brain (diffuse)
    : Like a concussion or shear injury

- Pathophysiological
  - primary vs secondary

- Severity
  - Glasgow Coma Scale – GCS scores from 3-15:
    based on eye opening (1-4)
    best motor response (1-6)
    best verbal response (1-5)
  - mild (13-15), moderate (9-12) or severe (3-8)

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Mechanistic Classification

- Impact
  - acceleration/deceleration injury
  - vascular hemorrhage (SDH), axonal injury
- Inertial loading
  - traumatic axonal injury
- Penetrating
  - direct parenchymal damage : local tissue necrosis
- Blast
  - parenchymal injury - brain swelling

  (shock wave from an explosive device)

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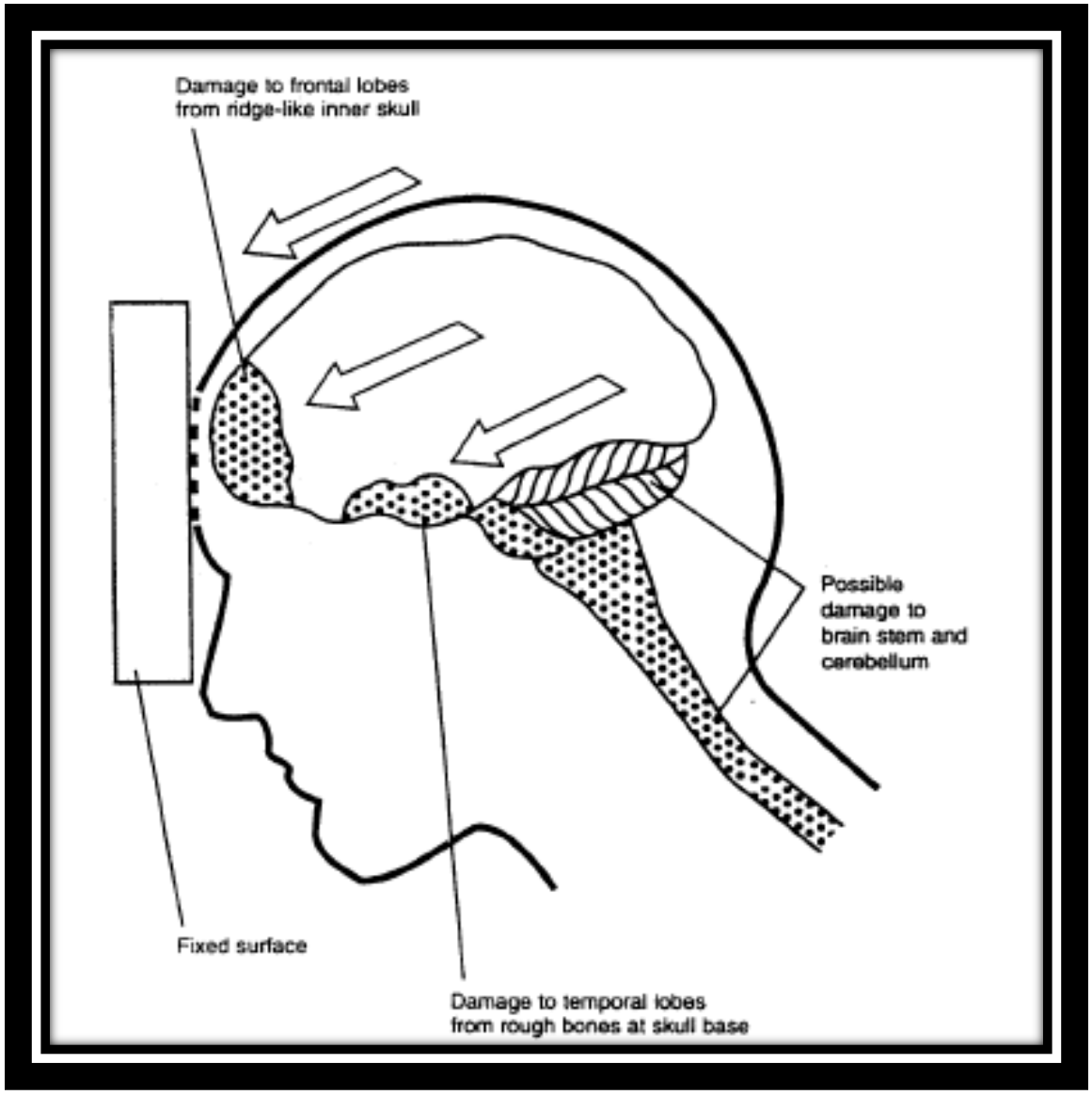
Acceleration/Deceleration Injury



Stoler & Hill, Coping with concussion and mild traumatic brain injury, 2013

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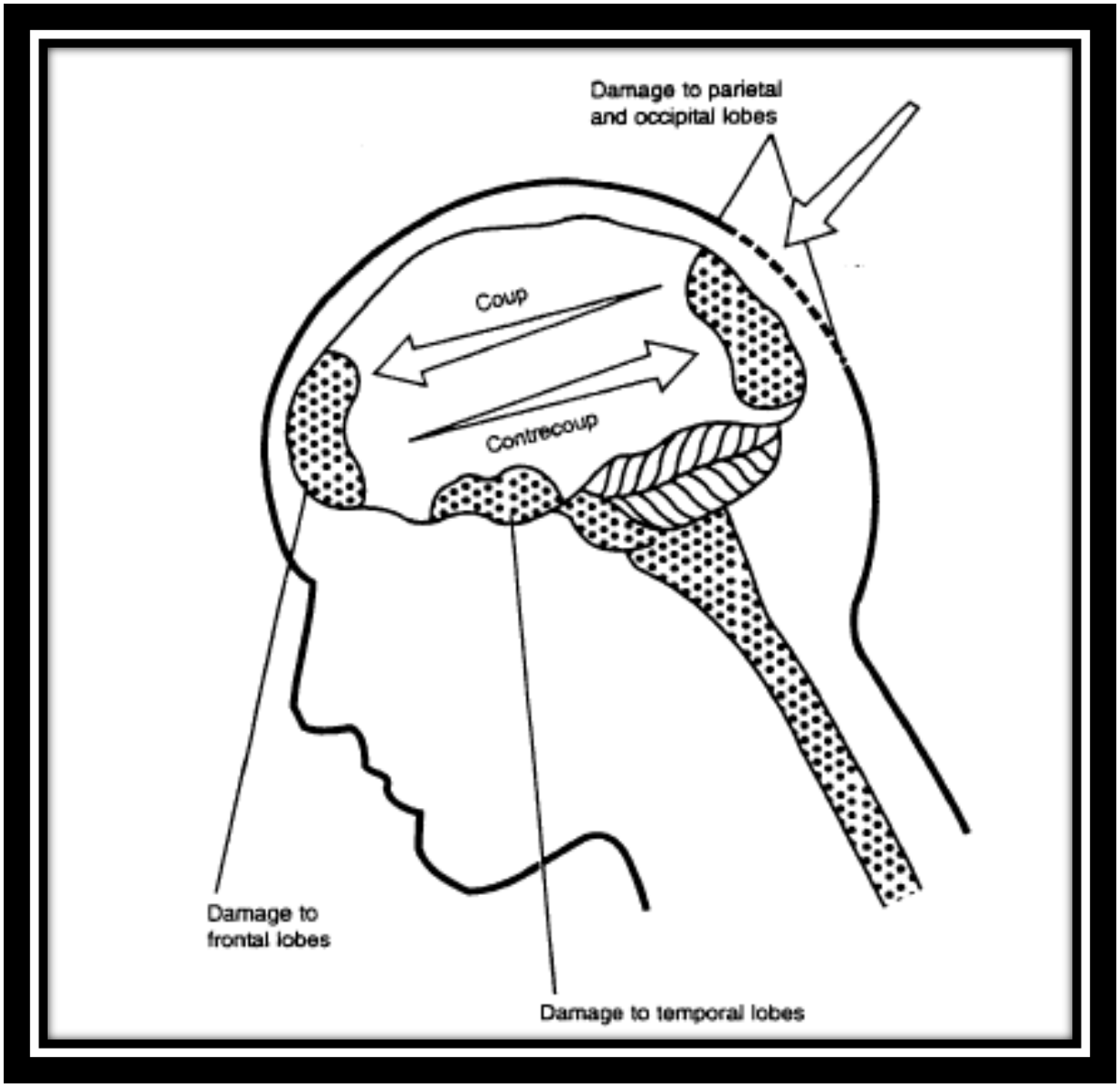
Coup/Countercoup Injury



Stoler & Hill, Coping with concussion and mild traumatic brain injury, 2013

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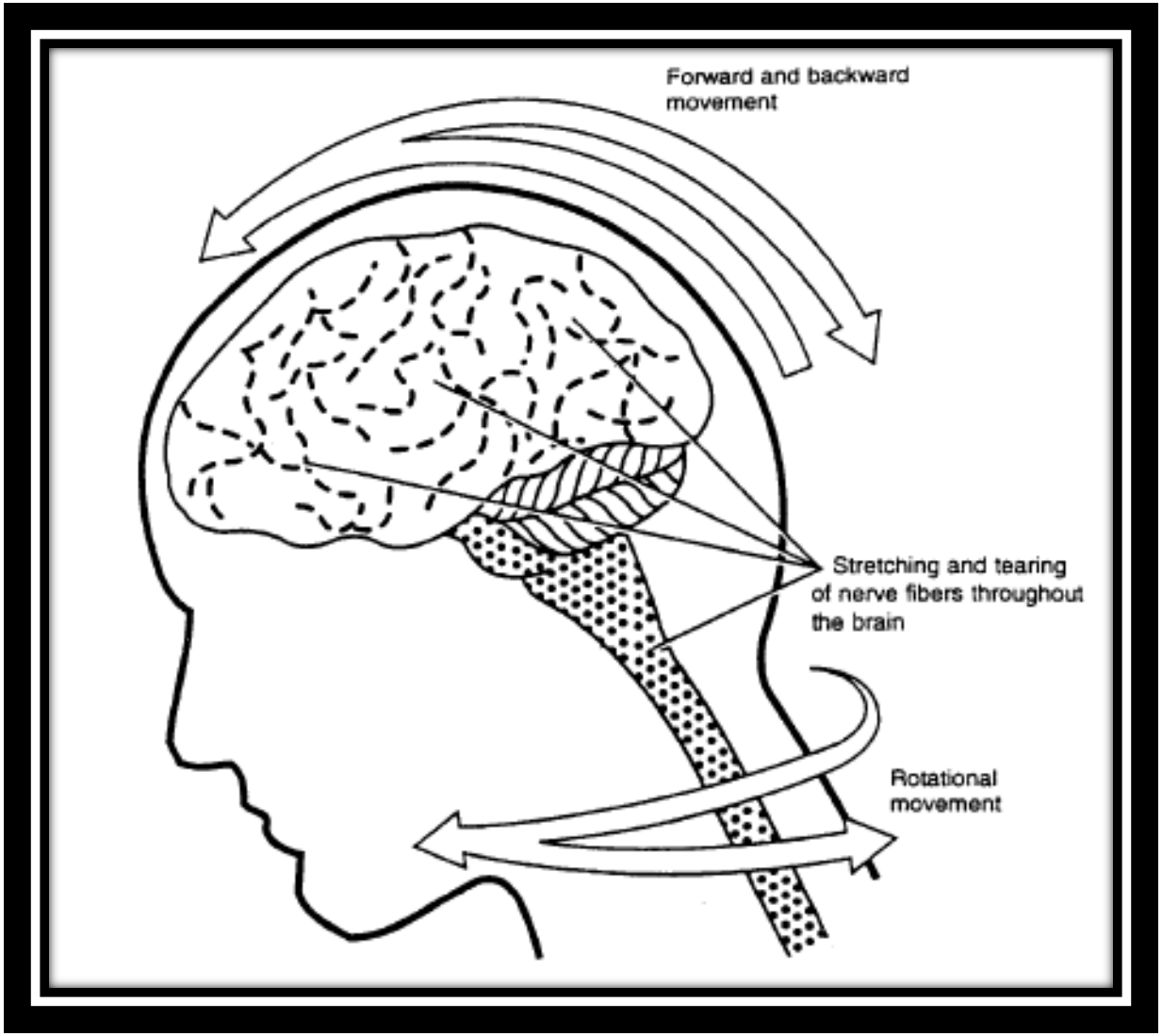
Whiplash Injury



Stoler & Hill, Coping with concussion and mild traumatic brain injury, 2013

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Primary vs Secondary Injury

- Primary injury
  - The damage that occurs to the brain tissue and blood vessels at the moment of impact
  - Could be bleeding or shear injury
  - This cannot be changed

- Secondary injury
  - Is what we treat in the Intensive Care Unit
  - All of the damage as a result of the primary injury
  - Begins moments after impact
  - Includes:
    - Biochemical changes within the brain cell
    - Decreased energy production within the brain cell
    - Changes in cellular electrical function
    - Changes in blood flow within the brain
    - Ability of injured brain cell to use oxygen correctly
    - Changes in brain metabolism
    - Edema (swelling) and increased intracranial pressure

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TBI: Primary Injury

Focal Injury- Contusions

- Most common in the anterior temporal and orbitofrontal regions regardless of site of impact
- Hemorrhage, edema, tissue distortion, scarring
- Often see a coup and contrecoup injury.

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Frontal Lobe Injury

- Impulsivity and disinhibition
- Inability to appreciate the effects of one's own behavior or remarks on others
- Impaired communication skills. Uncharacteristic lewdness .
- Blunted affect
- Aggression, outbursts of rage, and violent behavior
- Amotivation and apathy
- Disorganization and executive dysfunction
- Attentional and memory deficits.
- Mood dysregulation

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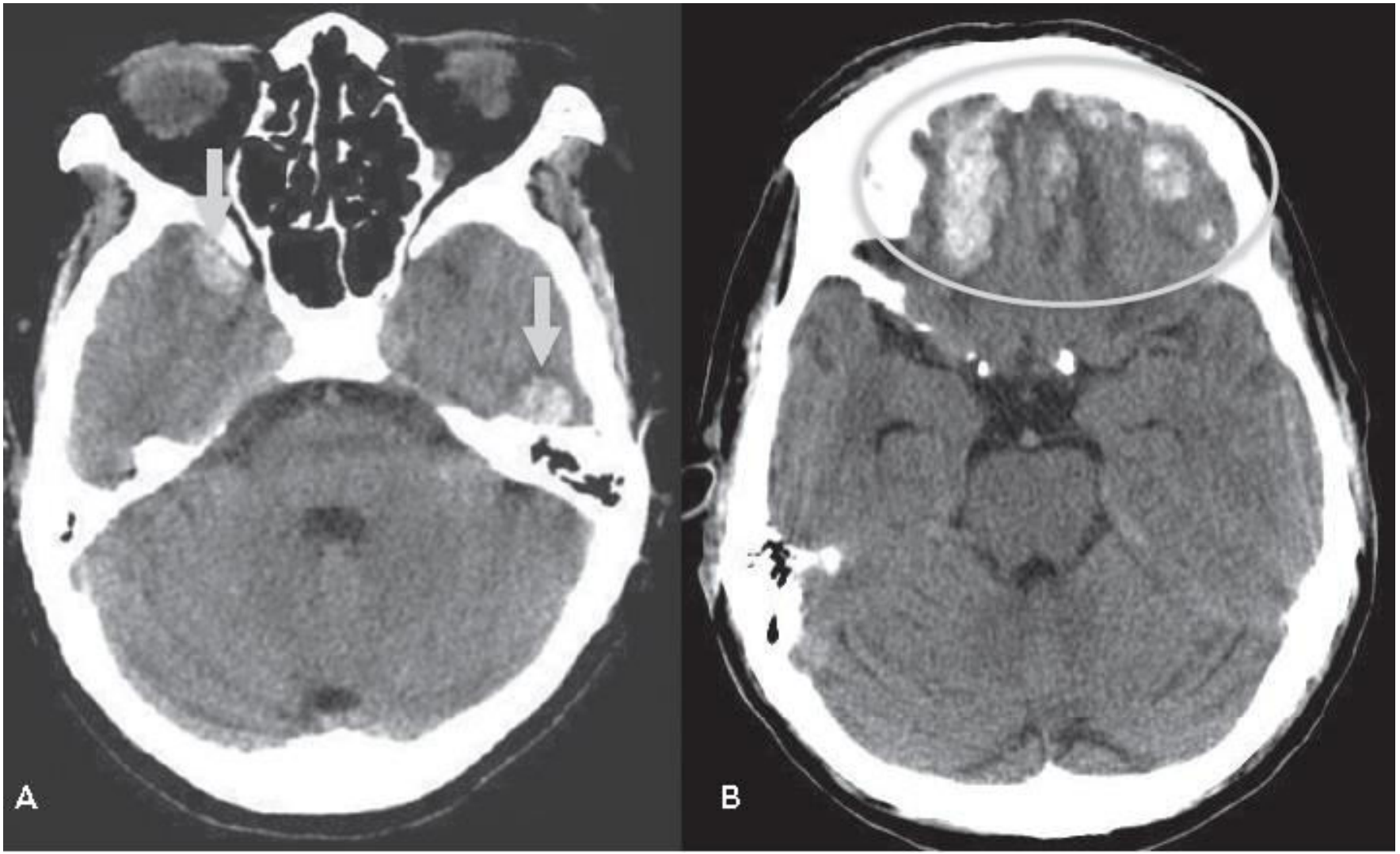
Cerebral Contusion



Zasler, Katz & Zafonte, Brain Injury Medicine, 2013

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Temporal Lobe Injury

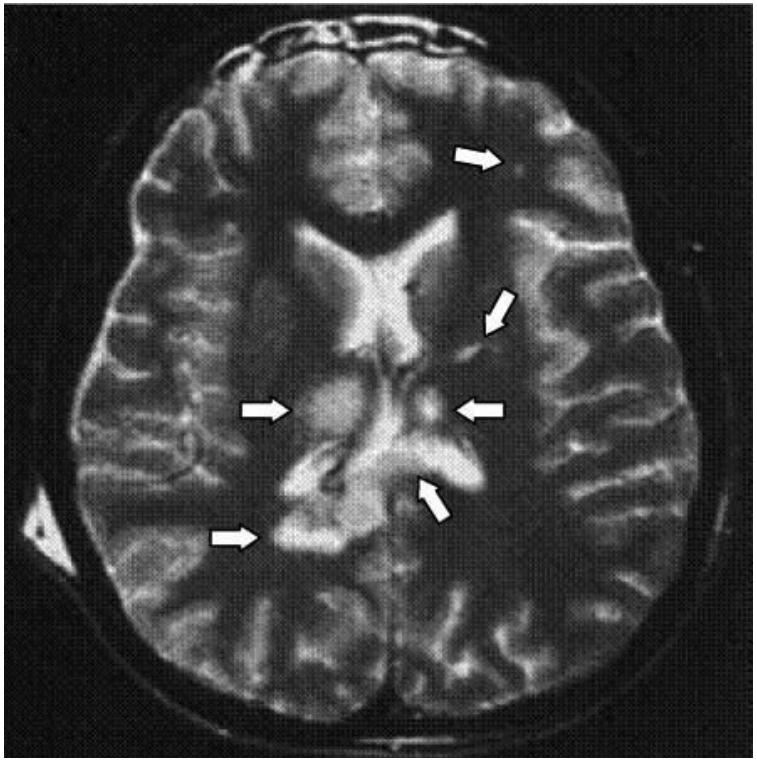
- Behavior changes include episodic hyperirritability, angry or aggressive outbursts, and sudden onset of dysphoric mood states

- Dominant temporal lobe injury causes language disturbances (aphasias) and disorders of sensation or sensory integration

Diffuse axonal injury

- Caused by shear-type forces that result in generalized, widespread disruption of axonal fibers and myelin sheaths

- Usually occurs at the junction between gray and white matter where there are different tissue densities
  - brainstem, corpus callosum, basal ganglia, thalamus and the cerebral hemispheres



Zasler, Katz & Zafonte, Brain Injury Medicine, 2013

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Life after TBI

- TBI is not just an event, similar to a broken bone that will heal over time

- Traumatic brain injury is a chronic disease impacting multiple organ systems
  - permanent
  - caused by non-reversible pathological alternations
  - requires special training of the patient for rehabilitation
  - may require a long period of observation, supervision or care

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Aging with TBI

"…in an adult trauma patient, acute injury is not just a brief physiological setback to a healthy life, but rather signals significant long-term mortality in a large number of patients."

Davidson GH et al. Long-term survival of adult trauma patients. JAMA 2011;305:1001-1007

- Aging with TBI sustained earlier in life

  - Survival
  - Health care issues
  - Cognitive decline/Risk of dementia
  - Quality of life

What is Going to Happen to Me in the Future – 10, 20 years from now?

- Will I get better?
- Will I get worse?
- What will happen to me when I get old?
- Am I more likely to get Alzheimer's?
  Other dementias?
- Am I likely to age "faster"?

The Answer Is

We are just beginning to understand

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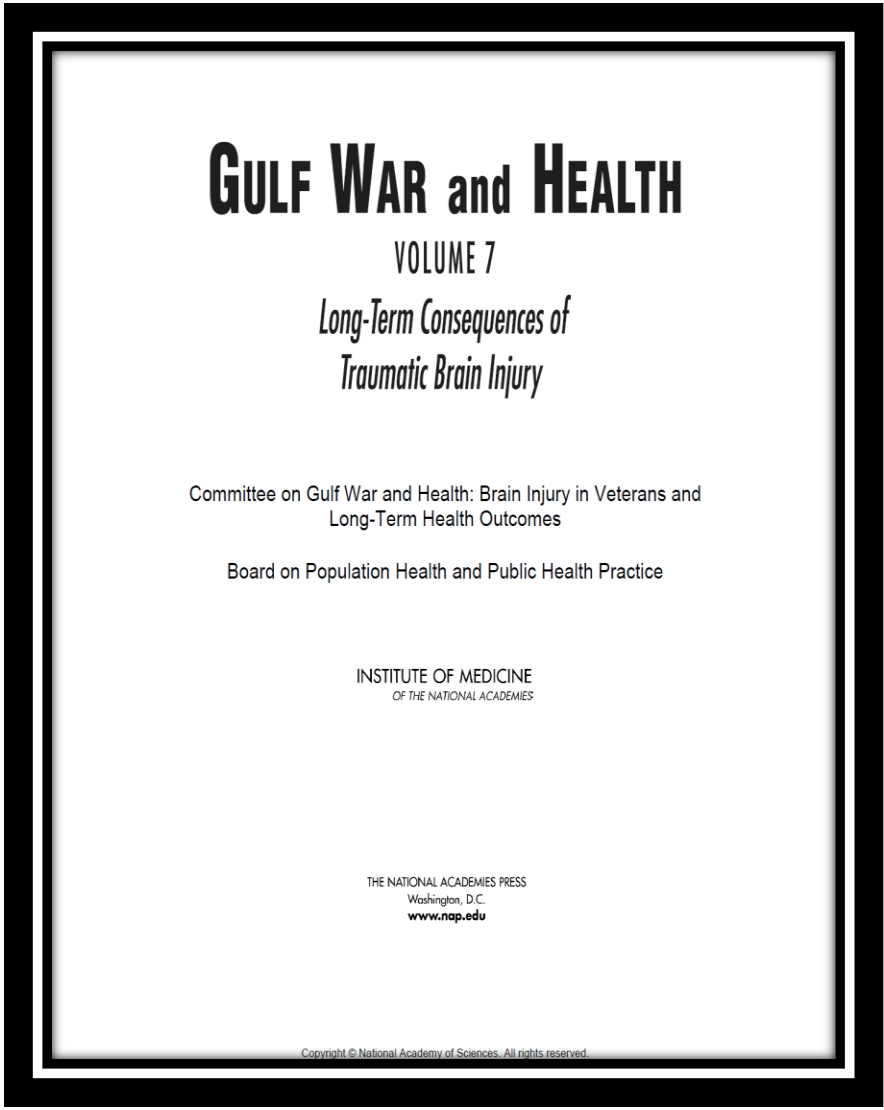
Institute of Medicine 2009

- IOM Report:
  Long-term consequences of TBI
  - Mortality
  - Neurocognitive
  - Neurologic
  - Psychiatric
  - Social



GULF WAR and HEALTH

VOLUME 7

Long-Term Consequences of Traumatic Brain Injury

Committee on Gulf War and Health: Brain Injury in Veterans and Long-Term Health Outcomes

Board on Population Health and Public Health Practice

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

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Institute of Medicine 2009

- This report was initially studied to understand the long-term consequences of traumatic brain injury as related to the Gulf War, but given that most literature relates to traumatic brain injuries in civilians, the conclusions reflect that civilian population.

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Neurocognitive Impairments

- Attention
- Memory – working memory/episodic memory
- Information processing speed
- Executive functions
  - planning, initiating and directing, monitoring, problem-solving, inhibitory control
- Language processing
- Visuospatial constructional skills
- Sensory integrity
- Motor speed and coordination

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Neurocognitive Outcome

The committee concludes, on the basis of its evaluation, that

- There is sufficient evidence of an association between severe TBI and neurocognitive deficits.
- There is limited/suggestive evidence of an association between moderate TBI and neurocognitive deficits.
- There is inadequate/insufficient evidence to determine whether an association exists between mild TBI and neurocognitive deficits.

Neurologic Outcomes from TBI

Seizures
Pituitary Dysfunction
Risk of Neurodegenerative Diseases

Seizures

- TBI causes 20% of symptomatic seizures observed in the general population
- 5-10% with mild to moderate TBI
- 25-30% with severe TBI
- 30%-50% of patients with penetrating head injury

Yablon SA. Arch Phys Med Rehabil, 1993

Post Traumatic Seizures

- 1/2 to 2/3 with experience their first seizure in the 12 months after injury
- 75% by 2 years
- Almost all at 5 years.

Yablon SA. Arch Phys Med Rehabil, 1993

Post Traumatic Seizures (PTS)

- Immediate (IPTS)- first 24 hours
- Early- (EPTS) first 7 days
- Late- (LPTS) after first 7 days

Risk factors for Late PTS

- History of chronic alcoholism
- Family history of seizures
- EPTS 20-30%
- Age: children
  - increased IPTS decreased LPTS vs adults
- APOEε4 allele

Yablon SA. Arch Phys Med Rehabil, 1993

Diaz- Arrastia R, Arch Neurol, 2003

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Posttraumatic Seizure

The committee concludes, on the basis of its evaluation, that

- There is sufficient evidence of a causal relationship between sustaining a penetrating TBI and the development of unprovoked seizures.

- There is sufficient evidence of a causal relationship between sustaining a moderate/severe TBI and the development of unprovoked seizures.

- There is limited/suggestive evidence of an association between sustaining a mild TBI resulting in loss of consciousness or amnesia and the development of unprovoked seizures.

Clinical Presentation of Hypopituitarism

- Temperature lability
- Appetite disturbance
- Disorders of fluid regulation/hypertension
- Fatigue and/or sleep disturbance
- Decreased muscle mass, increased fat mass
- Reduced exercise tolerance and muscle strength
- Amenorrhea, decreased libido, erectile dysfunction
- Decreased cognitive function, concentration, memory
- Mood disturbances, depression, irritability
- Social isolation, decreased quality of life

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Pituitary Dysfunction

Study	Sample	Years Post Injury	Assessment Method	Outcome
Bushnik 2007	64 with varying TBI severity	10 years	Serum determination and glucagon stimulation for growth hormone (GH)	Severe GHD: 39% Moderate GHD: 27% Central Hypothyroidism: 19%
Bondanelli 2004	50 with Mild-severe TBI	12-64 months (22% > 5 years post TBI)	Pituitary screen including growth hormone response to stimulation tests	54% developed pituitary dysfunction within 5 years post-injury Hypogonadism:14% Central Hypothyroidism: 8% Prolactin abnormality: 16% Partial GHD: 20%

Pituitary Dysfunction

- Literature suggests
  - Common
  - Older individuals at increased risk
  - Can occur at various times post-injury
- May contribute to post-TBI morbidity
- Suggested guidelines for screening

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Pituitary Dysfunction

- The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between moderate or severe TBI and endocrine dysfunction, particularly hypopituitarism.

- The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between moderate or severe TBI and growth hormone insufficiency.

Neurodegenerative Diseases and TBI: Is there an association?

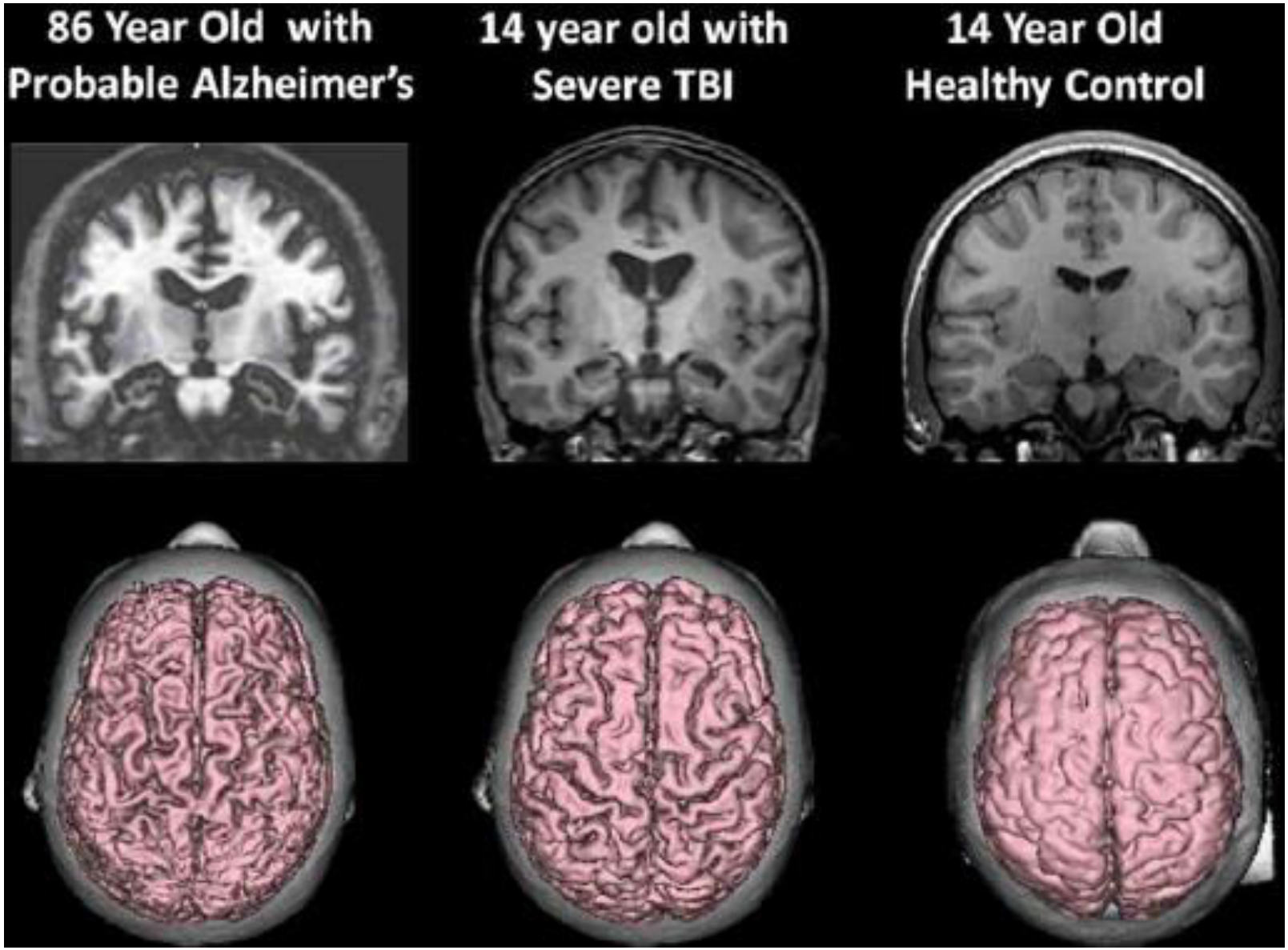
- Dementia of the Alzheimer Type
- Parkinson's Disease
- Multiple Sclerosis
- ALS

Neurodegenerative Diseases and TBI: Is there an association?

- Dementia of the Alzheimer Type
- Parkinson's Disease

- Multiple Sclerosis
- ALS

IOM concludes insufficient evidence



Zasler, Katz & Zafonte, Brain Injury Medicine, 2013

Dementia of the Alzheimer Type

- Significant association
  - Plassman 2000*
  - Schofield 1997**
  - French 1985
  - Broe 1990*
  - Heyman*
  - Guo 2000***
- Increased odds (but not reaching significance)
  - Amaducci 1986
  - Broe 1990
- No significance
  - Guskiewicz 2005

*Moderate to Severe TBI **LOC > 5 minutes ***+LOC

TBI and Risk of Dementia of the Alzheimer Type

The committee concludes, on the basis of its evaluation, that

- There is sufficient evidence of an association between moderate or severe TBI and dementia of the Alzheimer type.

- There is limited/suggestive evidence of an association between mild TBI (with LOC) and dementia of the Alzheimer type.

- There is inadequate/insufficient evidence to determine whether an association exists between mild TBI (without LOC) and dementia of the Alzheimer type.

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IOM Report
TBI and risk of Parkinson's Disease

- The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between moderate or severe TBI and parkinsonism.

- The committee concludes, on the basis of its evaluation, that there is limited/suggestive evidence of an association between mild TBI (with LOC) and parkinsonism.

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Psychiatric Outcomes

- Mood disorder
- Suicide
- Anxiety disorder
- Aggressive behaviors
- Drug and alcohol disorders
- Psychotic disorders

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Mood disorders

The committee concludes, on the basis of its evaluation, that

- There is sufficient evidence of an association between TBI and depression.
- There is inadequate/insufficient evidence to determine whether an association exists between TBI and mania or bipolar disorder.

Suicide

The committee concludes, on the basis of its evaluation, that

- There is limited/ suggestive evidence of an association between TBI and completed suicide.

- There is inadequate/insufficient evidence to determine whether an association exists between TBI and attempted suicide.

Anxiety Disorder

The committee concludes, on the basis of its evaluation, that

- There is limited/suggestive evidence of an association between mild TBI and PTSD in Gulf War military populations.

- There is inadequate/insufficient evidence to determine whether an association exists between mild TBI and PTSD in civilian populations

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Other Psychiatric Outcomes

- Aggressive Behaviors

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between TBI and subsequent development of aggressive behaviors.

Additional evidence that aggression is associated with TBI primarily when frontal cortical lesions are sustained is consistent with a large literature associating frontal lobe damage with loss of behavioral control.

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Other Psychiatric Outcomes

- Alcohol and Drug Abuse

The committee concludes, on the basis of its evaluation, that there is limited/suggestive evidence of an association between TBI and decreased drug and alcohol use, as compared with pre-injury levels, in the 1–3 year period following the TBI.

- Psychosis

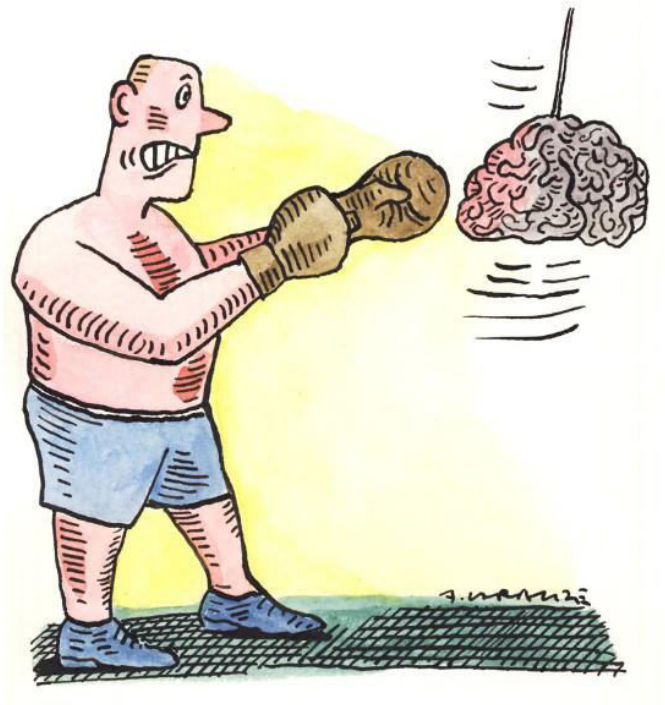
The committee concludes, on the basis of its evaluation, that there is limited/suggestive evidence of an association between moderate or severe TBI and psychosis.

However, even if the TBI is severe, the psychosis does not appear during the first post-TBI year, but rather, becomes apparent in the second and third post-TBI years.

Overall Conclusions

- Moderate to Severe TBI associated with:
  - Neuroendocrine dysfunction
  - Neurocognitive impairment – Severe TBI
  - Increased risk of seizure
  - Increased risk of
    - Dementia
    - Parkinsonism
- Association with Mild TBI less certain
- Association with TBI and depression/aggressive behavior

Chronic Traumatic Encephalopathy



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Historical Overview

- Punch drunk – Boxers
  - Martland, 1928

- Neuropsychiatric syndrome

(later called traumatic encephalopathy)

  - Parker, 1934

- Dementia Pugilistica
  - Millspaugh, 1937
  - Motor deficits and mental confusion

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Historical Overview

- Chronic traumatic encephalopathy
  - Critchley, 1949

- Corsellis et al. in 1973
  - described the gross and microscopic neuropathology of dementia pugilistica in 15 boxers
  - neuropathologically distinct disorder

- Omalu et al. 2005, 2006
  - reported the first case of CTE in a retired NFL player
  - reported the second case of CTE in a former NFL player

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Historical Overview

- McKee et al. 2009 and Gardner et al. 2014
  - Identified 48 / 158 cases of CTE in the world literature
  - Documented their clinical and neuropathological characteristics

- Montenigro et al. 2014
  - Traumatic Encephalopathy Syndrome – newly proposed
  - Extraordinarily broad in scope
    (people with mild depression and those with late-stage dementia)

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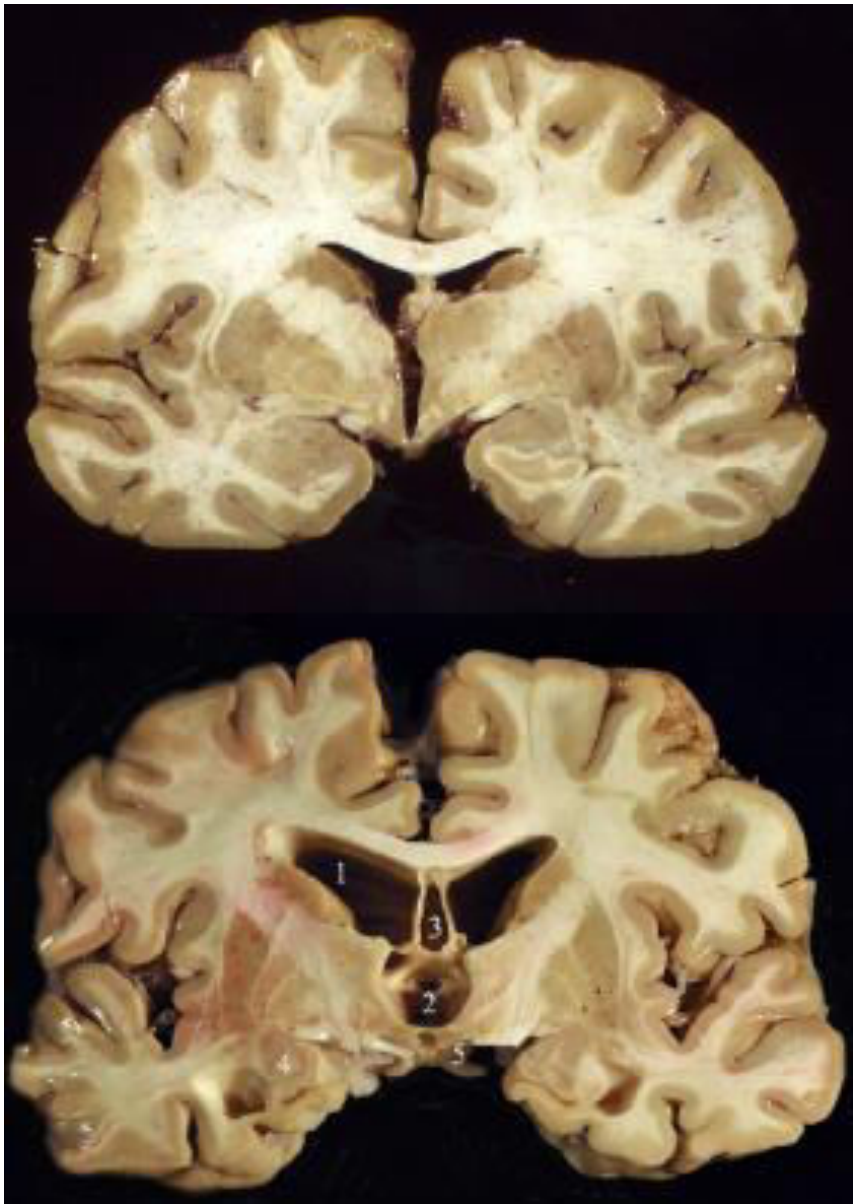
Historical Overview

- Unique neuropathology associated CTE caused by neurotrauma (single or repetitive)

- Increased risk for aging-related cognitive and behavioral changes in some people that contribute to known disease process
  - repetitive neurotrauma might be associated with reductions in cerebral reserve or cognitive reserve

  - more vulnerable to an earlier expression of late-life neurodegenerative disorders.

Gross Neuropathology

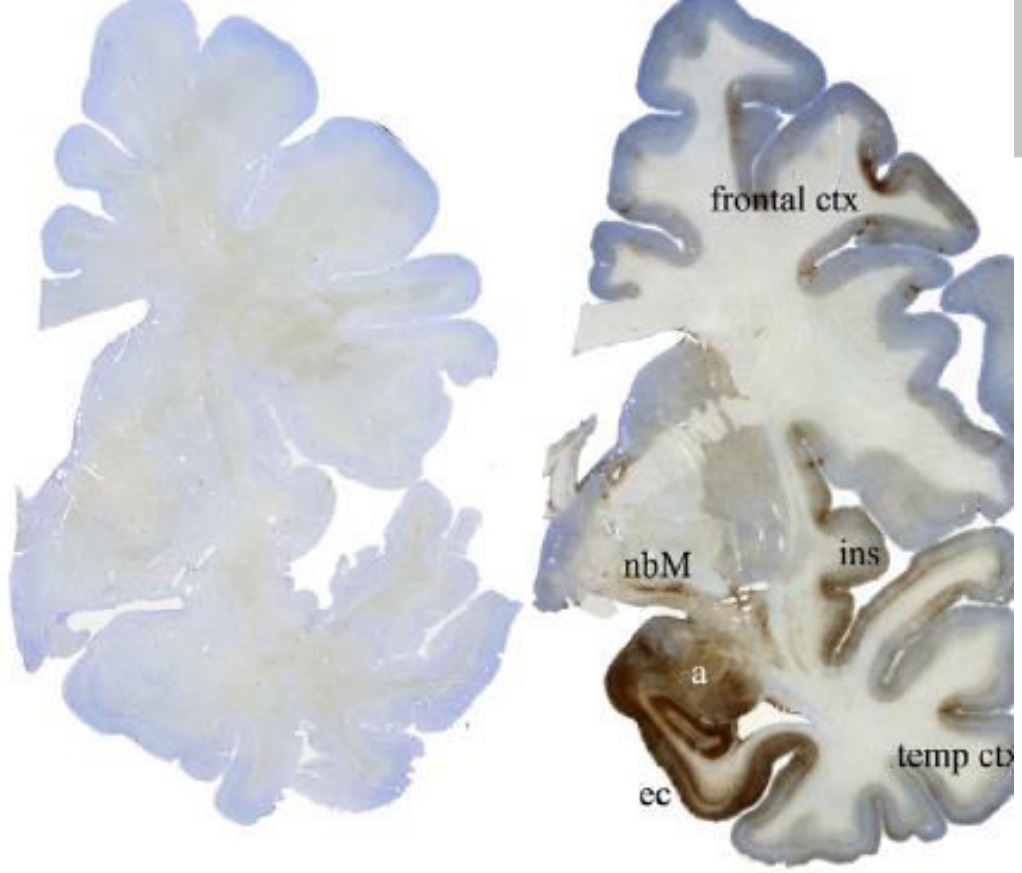


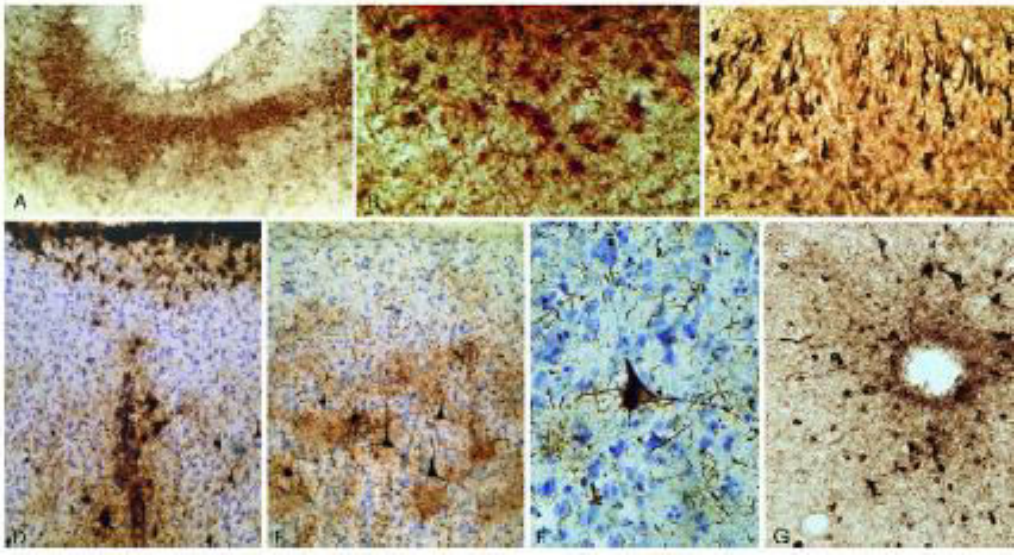
- Overall
  - Decrease in brain mass
  - Cavum septum pellucidum
  - Septal fenestrations
- Ventricles
  - Enlarged lateral/3rd ventricles
- Atrophy
  - Generalized atrophy, particularly of the frontal and temporal lobes
  - The medial temporal lobes
  - Mammillary body
  - Thalamus
- Pallor
  - Locus ceruleus
  - Sustantia nigra

Microscopic Neuropathology

- Neurofibrillary tangle
- Amyloid beta plaques (Aβ plaques)
- Phosphorylated tau

- Perivascular foci of p-tau immunoreactive astrocytic tangles and neurofibrillary tangles
- Irregular cortical distribution with a predilection for the depth of cerebral sulci
- Clusters of subpial and periventricular astrocytic tangles in the cerebral cortex, diencephalon, basal ganglia, and brainstem
- Neurofibrillary tangles in the cerebral cortex located preferentially in the superficial layers





Stern et al. PM R, 2011

Unique/ Characteristic Sites of NFT Formation in CTE:

- CA4 (Endplate) of the Hippocampus (Memory)
- Insular Cortex (provides emotionally relevant context- anger, disgust, anxiety, fear, happiness, sadness; addictive behaviors)
- Mamillary bodies (Memory)
- Hypothalamic nuclei (sleep/wake, circadian rhythms, neuroendocrine, homeostasis)
- Thalamus (relay for most sensory info, consciousness, awareness)
- Amygdala (fear conditioning, memory consolidation, emotional content of memories)

Early Clinical Presentation

- Short-term memory problems
- Executive dysfunction (eg, planning, organization, multitasking)
- Depression and/or apathy
- Emotional instability
- Impulse control problems (eg, disinhibition, having a “short fuse”)
- Suicidal behavior

Late Clinical Presentation

- Worsening memory impairment
- Worsening executive dysfunction
- Language difficulties

- Aggressive and irritable behavior
- Apathy

- Motor disturbance, including parkinsonism

- Dementia (ie, memory and cognitive impairment severe enough to impair social and/or occupational functioning)

Potentional Risk Factors

- Genetics : APOE 4; MAPT; GRN; TARDP
- Family history : First- and/or second-degree relatives with history of dementia
- Type of brain trauma exposure
  - Symptomatic concussions
  - asymptomatic subconcussive blows
  - blast wave; minimum gravitational force
  - degree of axonal injury and/or microhemorrhages

Potentional Risk Factors

- Age and duration of brain trauma exposure
  - : Susceptibility period during youth; years of overall exposure
- Frequency of brain trauma exposure
  - : Minimum number of injuries (eg, can one moderate-severe TBI lead to CTE, without any additional repetitive concussions or subconcussive exposure history?); amount of “rest” (and overall time interval) between injuries
- Chronic inflammation
  - : Obesity, hypertension, diabetes, and heart disease may exacerbate neurodegeneration and NFT formation

Potentional Risk Factors

- Cognitive reserve
  : Greater cognitive reserve (or brain reserve capacity) may be less likely to display the clinical symptoms associated with the neurodegeneration or exhibit them later in the neuropathologic process

- Gender
  : Are women at greater risk if they had the same exposure as men?

- Race : Are there racial differences in risk?

Mild Cognitive Impairment

- A condition where individuals have cognitive and memory impairment, due to diverse and often multifactorial causes, that does not substantially interfere with their daily activities

- In any given person, the extent to which a history of neurotrauma, or the presence of tau in specific brain regions, contributes to subjective or objective cognitive impairment can be extremely difficult to determine.

Alzheimer's Disease and Dementia

- Increased risk for AD in association with moderate to severe TBI in men

- Mild TBIs sustained at age 65 or older, and moderate-severe TBIs sustained at 55 or older might increase a risk for developing dementia

- Absolute increase in risk for dementia following TBI is small (8.4% of those with TBI in middle age or older adulthood vs 5.9% of control subjects)

Causes of Dementia

- Alzheimer's disease
- Frontotemporal dementia
- Vascular dementia
- Lewy body dementia
- Prion diseases
- Huntington's disease
- Infectious diseases (neurosyphillis, HIV-AIDS)
- Hydrocephalus
- Nutritional deficiencies
- Toxic and metabolic disorders

Traumatic Encephalopathy Syndrome

- Montenigro et al. identified 202 published cases of CTE over the past 100 years.

(141 boxers, 54 American football players, 5 ice hockey players and 2 professional wrestlers)

- Research criteria for TES (4 subtypes)

1. TES behavioral/mood variant
2. TES cognitive variant
3. TES mixed variant
4. TES dementia

- Duration of symptoms : a minimum of 12 months.

Exposure Criteria for TES

- Primary source : repetitive hits to the head in sports such as boxing, American football, ice hockey, lacrosse, rugby, wrestling, and soccer

- The person must have played the sport for a minimum of six years, with two years at the college level or higher

Or

- A history of four documented mild TBIs or concussion, or

Two moderate/severe TBIs is necessary

Or

- Military service members exposed to multiple blasts
- Police officers who have hit their heads multiple times during door breaches

9 Supportive Features for TES

1. Impulsivity
2. Anxiety
3. Apathy
4. Paranoia
5. Suicidality
6. Significant Headache
7. Motor signs
8. Documented decline
9. Delayed onset

Minimum of 2 out of 9

Conclusions

- The description of CTE has been expanded to include post-mortem case studies of young athletes, retired athletes, military service members and veterans in addition to boxers.

- At present, the science underlying the neuropathology, clinical features, and causal relationship between the neuropathology and clinical features in CTE is very limited.

- There are no nationally or internationally agreed upon neuropathological or clinical diagnostic criteria for CTE.

Long-term Mortality: Hospitalized Sample

- Mortality 2-3x general population
- Injury severity predominantly moderate to severe with some mild
- Recent evidence suggest 7 year reduction in life expectancy

Harrison-Felix et al.

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Increased Long-term Mortality: Hospitalized Sample

(*Applicable to Mild TBI)

Risk Factors

- Advanced age at time of injury
- Seizures
- Employment status
- Substance abuse
- Physical impairments
- Psychiatric disorder

Cause of Death

- Seizure
- Pneumonia
- Sepsis
- Suicide*
- Accidental Death*
- Substance abuse related*

Institute of Medicine Conclusions

The committee concludes, on the basis of its evaluation, that

- There is sufficient evidence of a causal relationship between penetrating TBI and premature mortality in survivors of the acute injury.

- There is sufficient evidence of an association between moderate or severe TBI and premature mortality in the subset of patients who are admitted into or discharged from rehabilitation centers or receive disability services.

- There is inadequate/insufficient evidence to determine whether an association exists between surviving 6 months or more after sustaining a mild, moderate, or severe TBI and premature mortality.

Thank You!!

Questions or Comments ?