Icahn School of Medicine at Mount Sinai

The Ronald M. Loeb Center for Alzheimer's Disease

Neuropathology Brain Bank at Mount Sinai

Traumatic Brain Injury

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Disclosures

I have no relevant financial relationships to disclose

Overview

- Acute TBI
- Chronic TBI

Introduction: overview of TBI

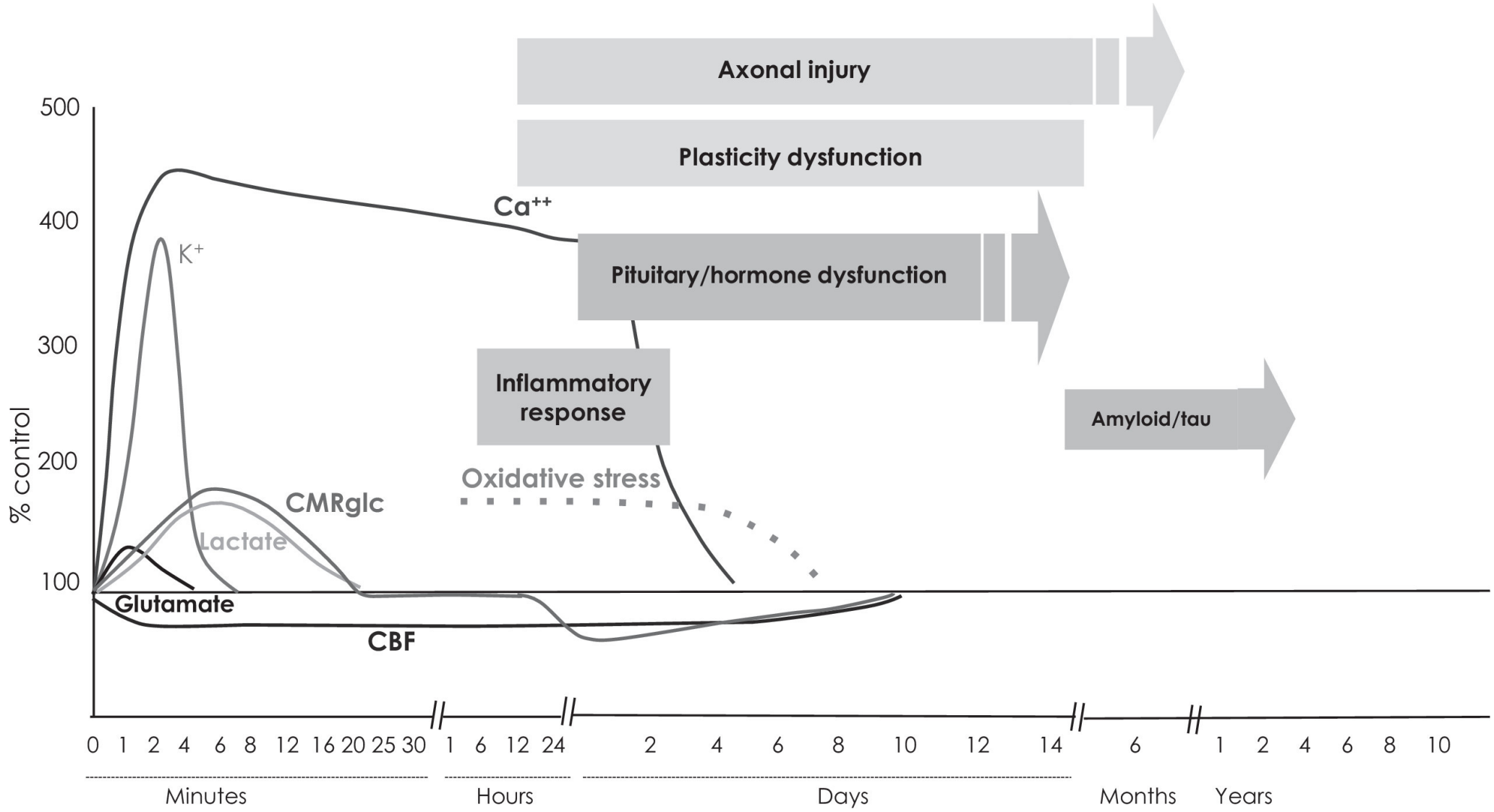
- *Definition*: “an alteration in brain function, or other evidence of brain pathology, caused by an external force”*
- The *causes are numerous* and include penetrating and non-penetrating injuries
- Begins with *mechanical deformation* of the brain parenchyma
- Triggers pathophysiological responses that are among the most complex phenomenon of all organs, with a myriad of dynamic structural/cellular, metabolic, molecular processes that vary with time and severity

* Menon DK, Schwab K, Wright DW, et al: Position statement: definition of traumatic brain injury. Arch Phys Med Rehabil 91(11):1637–1640, 2010 21044706

Introduction: overview of TBI

- Understanding TBI requires a holistic approach:
  - Macroscopic (structural/gross neuroanatomy)
  - Microscopic (cellular/physiological)
  - Molecular
- In considering the pathobiology, it is common to discuss in the context of:
  - Mild through severe
  - Focal and diffuse
  - Acute and chronic

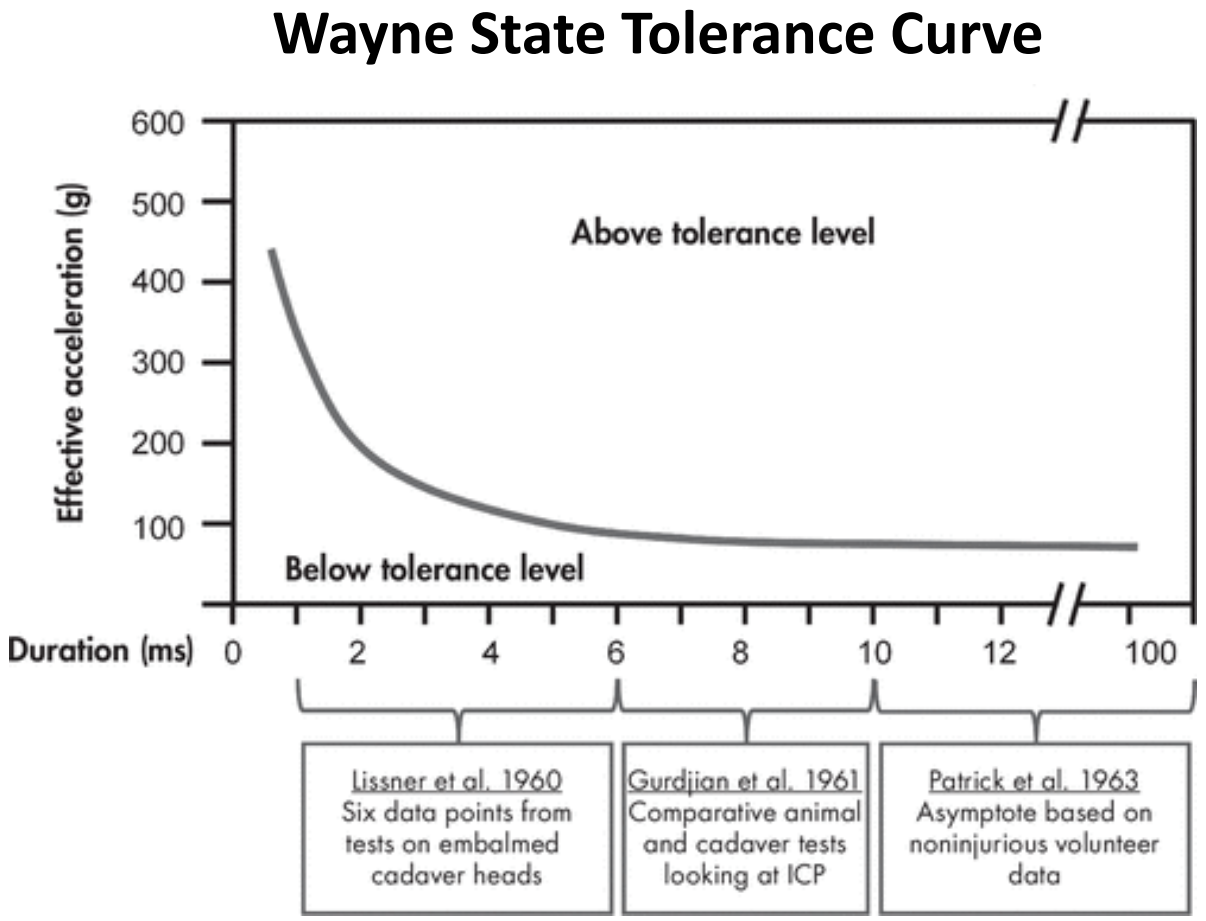
The “metabolic cascade”



Giza CC, Hovda DA. The Neurometabolic Cascade of Concussion. J Athl Train. 2001 Sep;36(3):228-235. PMID: 12937489; PMCID: PMC155411.

Biomechanics of TBI: general concepts

- *Human data is critical* for developing protective equipment and safety standards
- Human data is *difficult to obtain* because functional outcomes are hard to obtain is laboratory settings (e.g., cadaveric research)



Textbook of Traumatic Brain Injury. (2018). United States: American Psychiatric Association Publishing.

Glasgow Coma Scale (GCS) predicts outcomes

- Different degrees of morbidity and mortality
- Assumes that different forms of TBI are comparable
  - But injuries are often mixed, *recent studies focus on pathoanatomical characteristics*

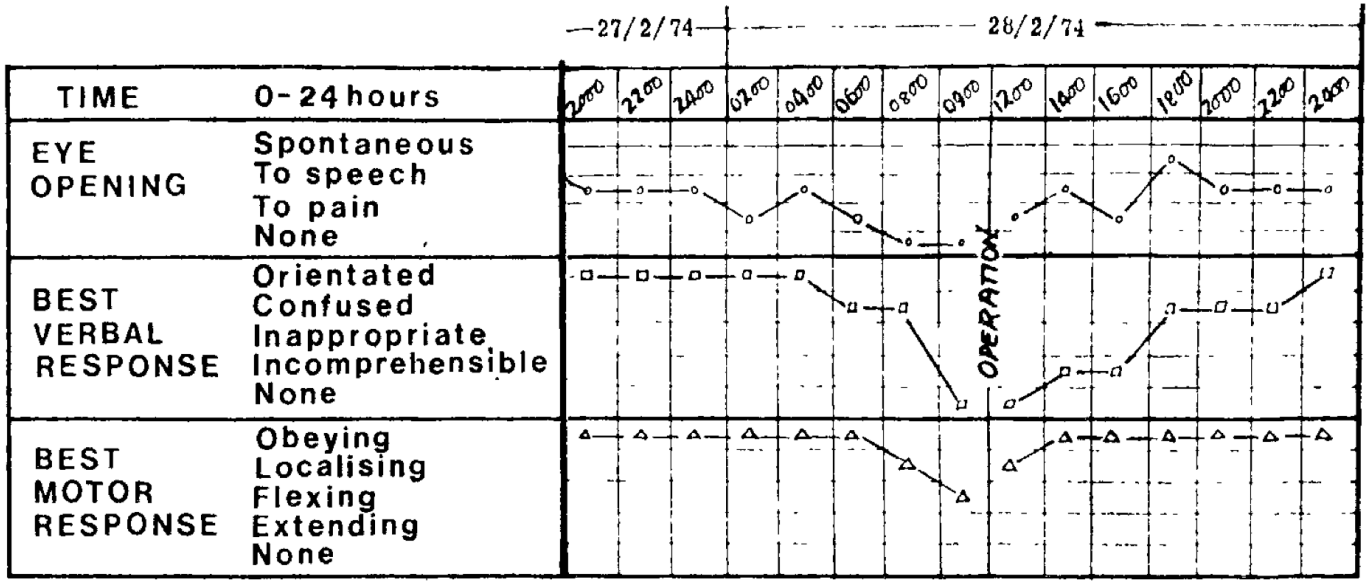
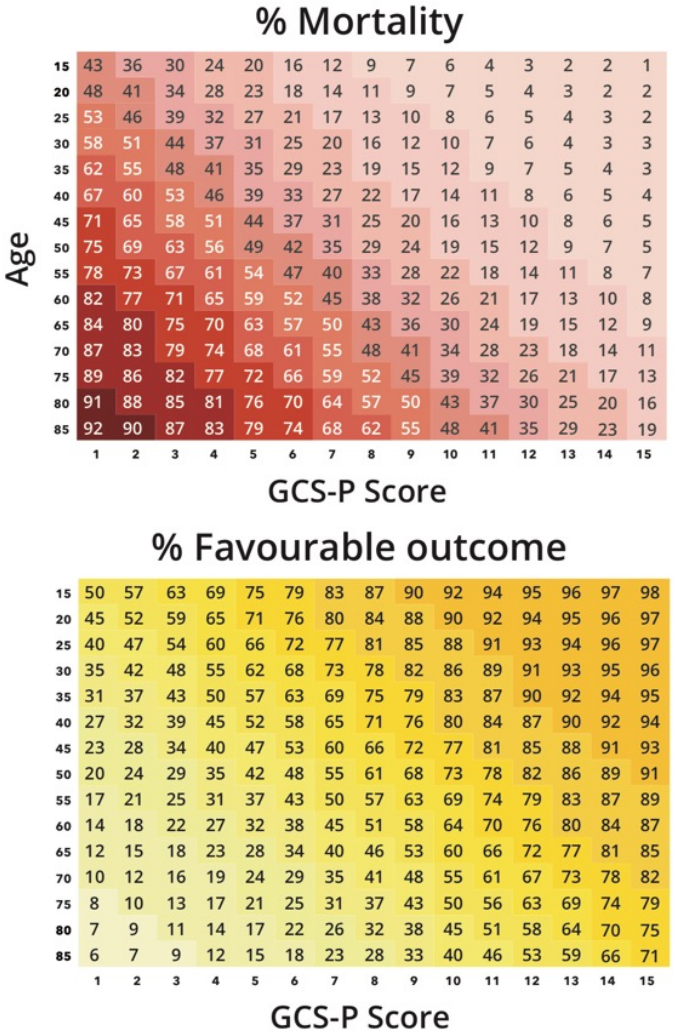


Chart for recording assessment of consciousness.

Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974 Jul 13;2(7872):81-4.



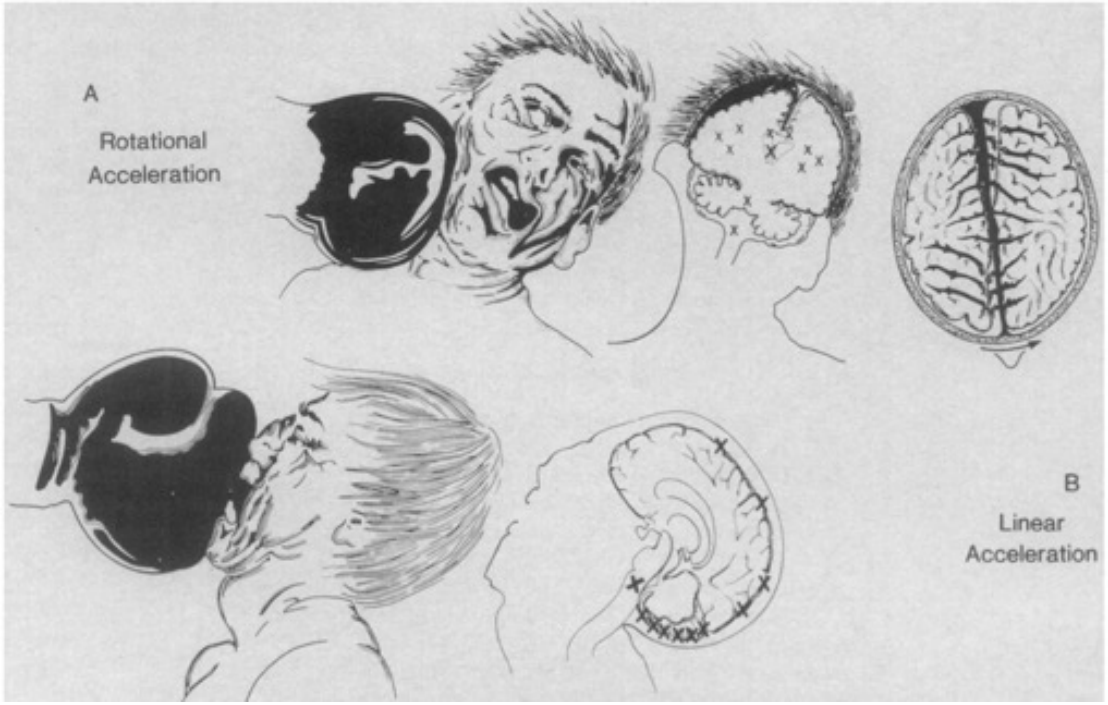
Murray, Brennan, Teasdale. Simplifying the use of prognostic information in traumatic brain injury. Part 2: Graphical presentation of probabilities. J Neurosurgery 2018 128(6):1621-1634

Acute TBI: classification

Criteria	Mild (“concussion”)	Moderate	Severe
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of Consciousness (LOC)	0-30 min	> 30 min and < 24 hr	> 24 hr
Alteration of consciousness/mental state (AOC)	a moment up to 24 hr	> 24 hours. Severity based on other criteria	
Post-traumatic amnesia (PTA)	0-1 day	> 1 and < 7 d	> 7 d
Glasgow Coma Scale (best available score in first 24 hours)	13-15	9-12	< 9

Biomechanics of TBI: kinematics

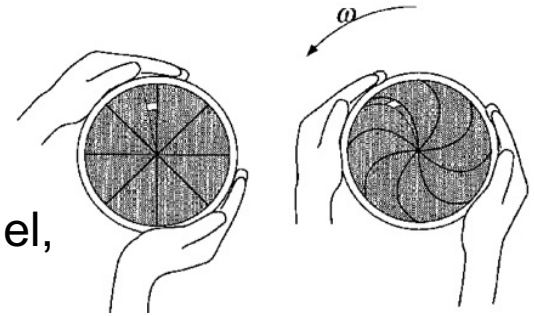
- Kinematics: branch of mechanics concerned with *motion of objects* without reference to forces cause
- Relative contribution of forces/acceleration to TBI determine maximal force location (and force gradient)
- Skull bending, fracture (local injury) and rotation (diffuse injury) are thought to be more important to brain injury



Lampert PW, Hardman JM. Morphological changes in brains of boxers. JAMA 1984;251:2676-9.

Impact forces:

1. Linear – easier to understand
2. Rotational – hard to model, likely more important



McLean et al., Biomechanics of closed head injury, Head injury: pathophysiology and management. 2nd edition

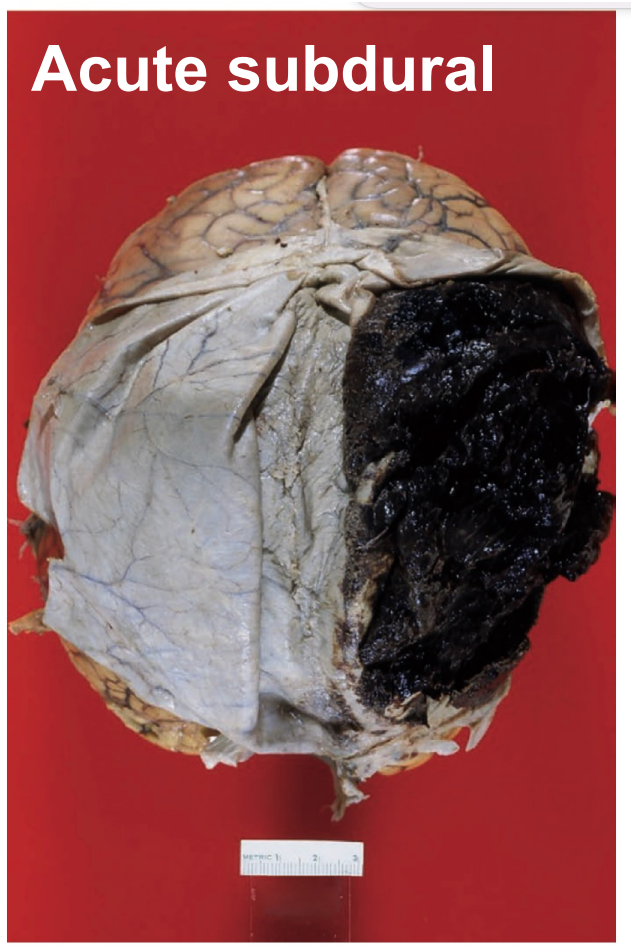
Biomechanics of TBI: stress concentration

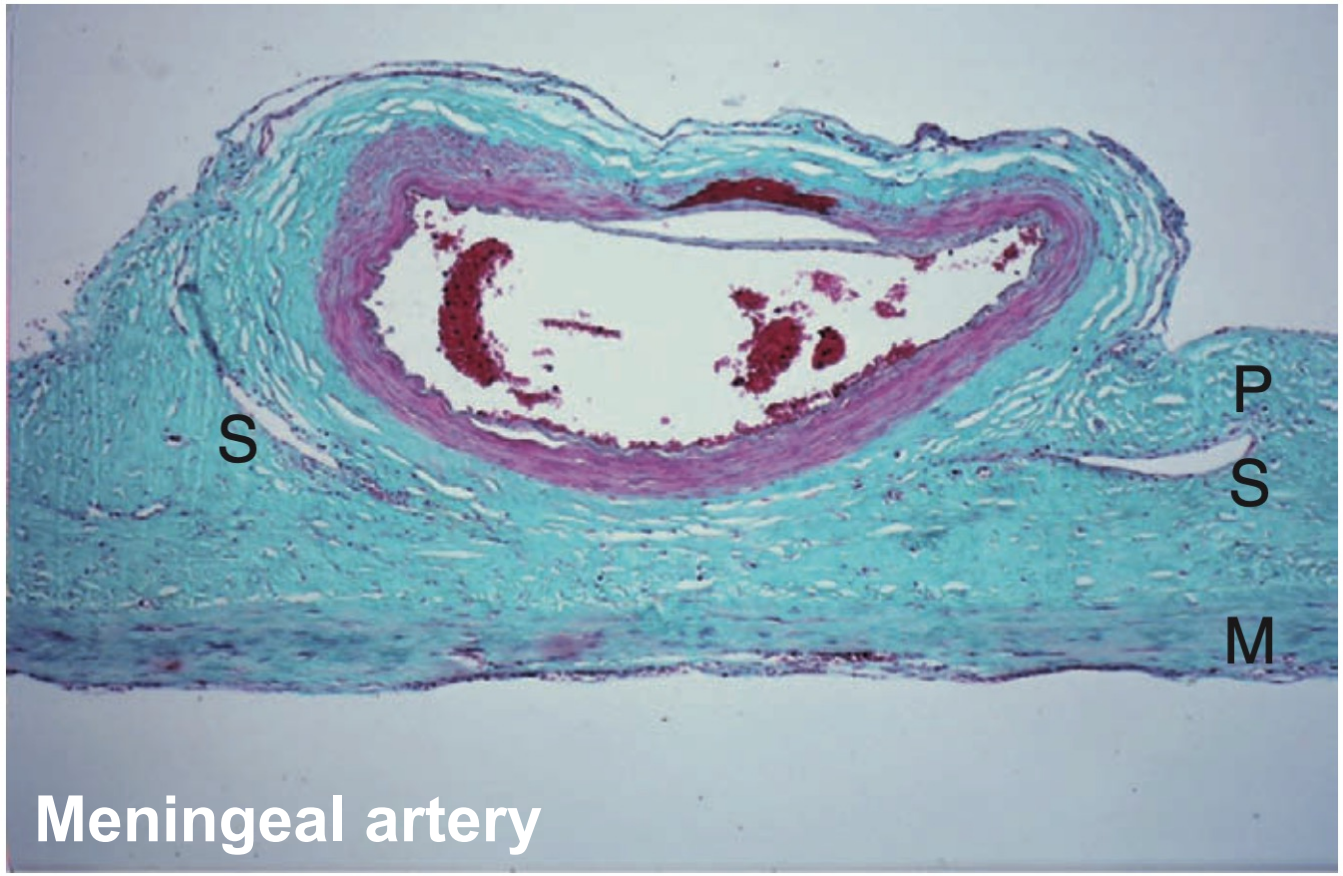
- *Stress concentration:* point where the stress is greater than its surrounding area from irregularities in geometry or the material structure. An object is stronger when force is evenly distributed: a reduction in area results in a localized increase in stress.
- *Strain*: measure of deformation of the material. A material can fail when a concentrated stress exceeds the material's theoretical cohesive strength.

Acute TBI: focal lesions

- Moderate to severe localized to distinct compartments
- *Hematomas*
  - Subdural, epidural, intraparenchymal
  - Local damage, reduced blood flow, ischemia, and edema
- *Contusions*
  - Hemorrhages at sites of impact with bony prominences
  - Common in frontal and temporal lobe, typically crests of gyri (white matter if severe)
  - Coup and countre coup
- Hemorrhage causes *ischemia, edema, and necrosis* with cavitation and gliosis
- Diagnosis: Imaging (CT for blood) and biomarkers (e.g., GFAP)

Epidural hematoma





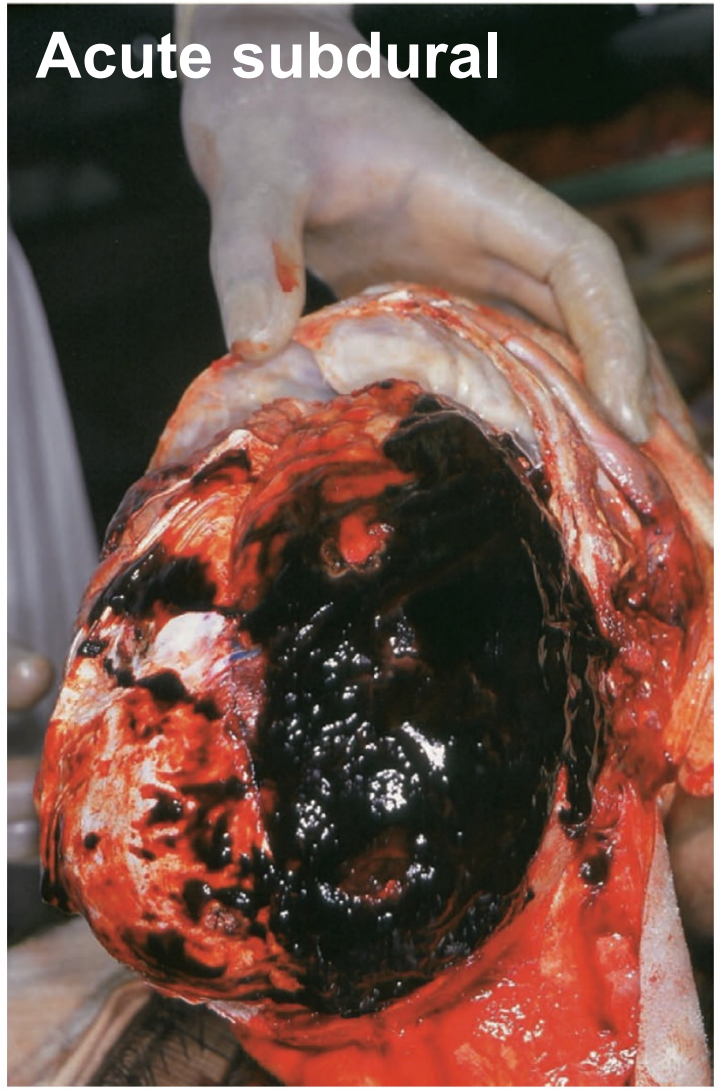
Periosteal layer

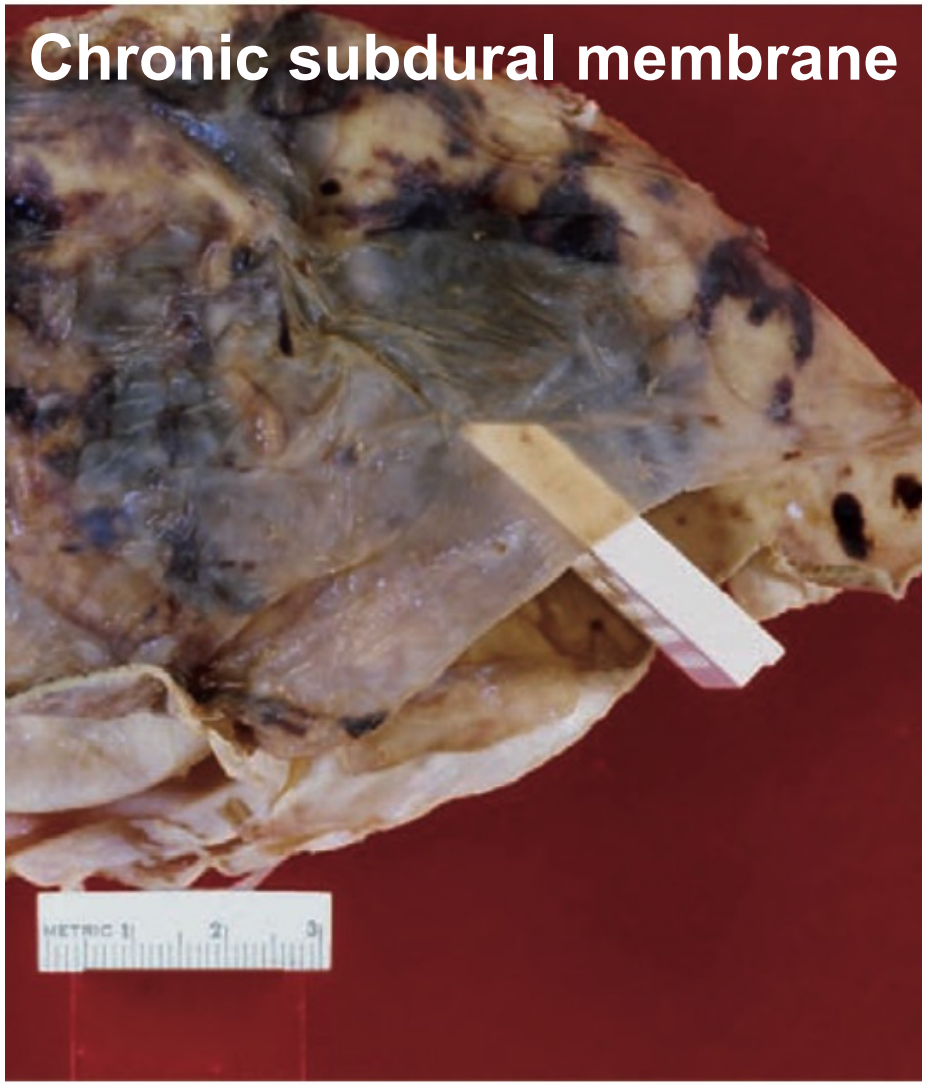
Dural sinus

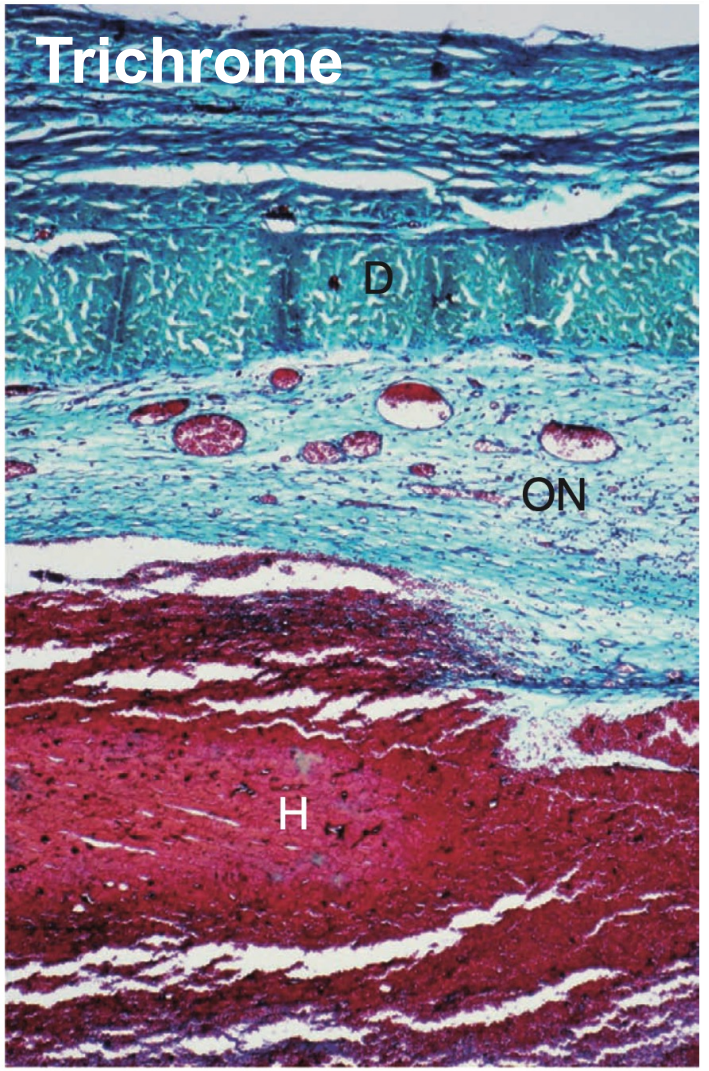
Meningeal layer

Itabashi, et al, Chapter 6 - Blunt force head injury. Forensic Neuropathology, Academic Press, 2007, Pages 167-198,

Subdural hematoma

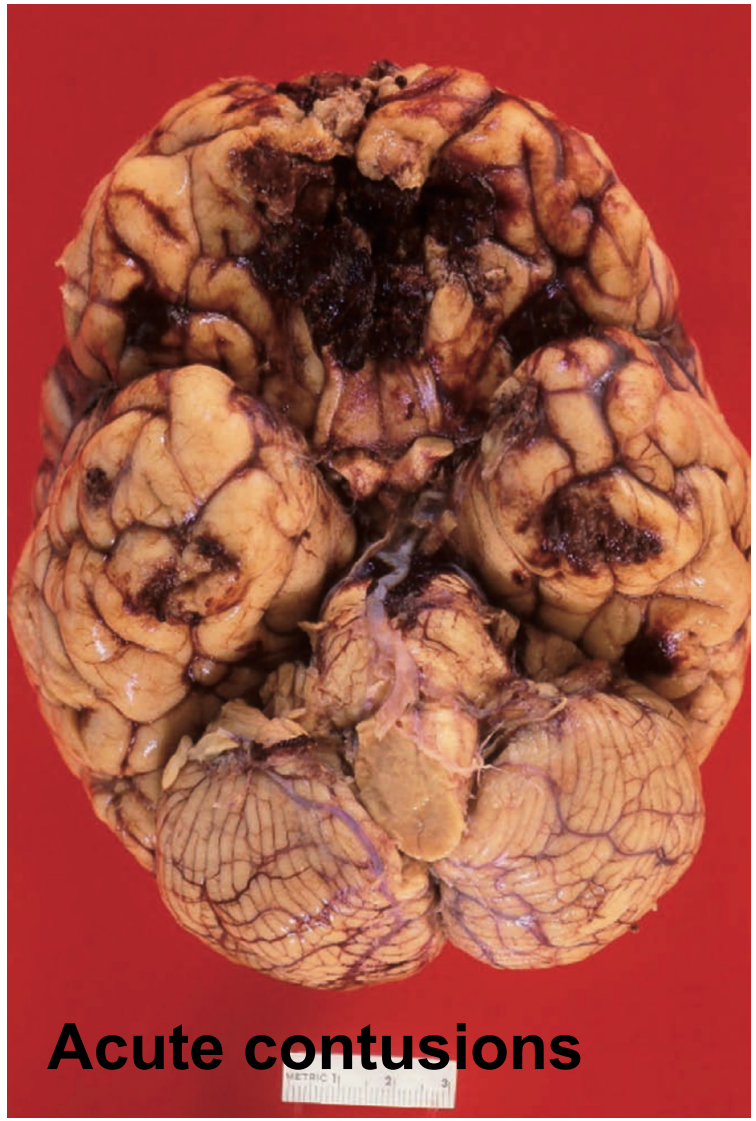


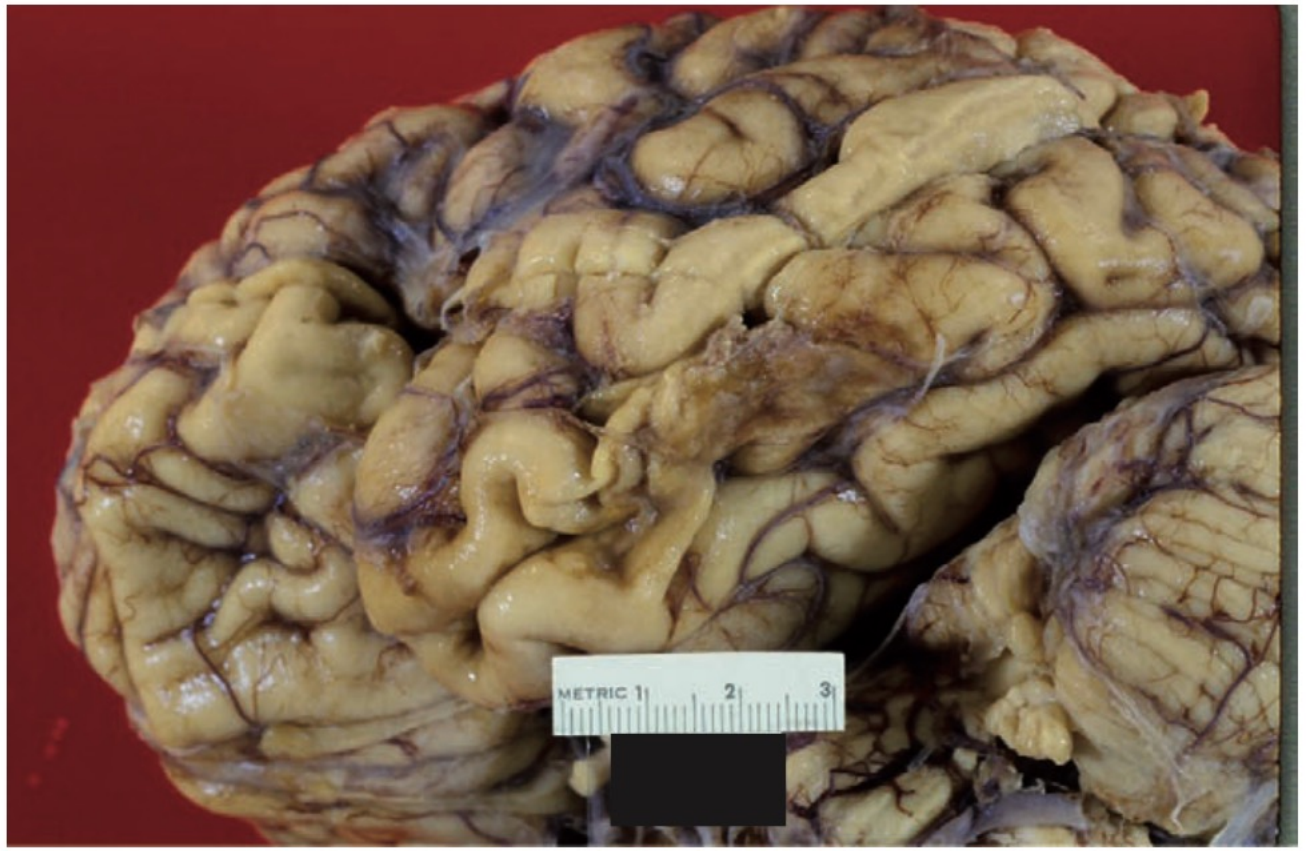




Itabashi, et al, Chapter 6 - Blunt force head injury. Forensic Neuropathology, Academic Press, 2007, Pages 167-198,

Contusions





Chronic contusion

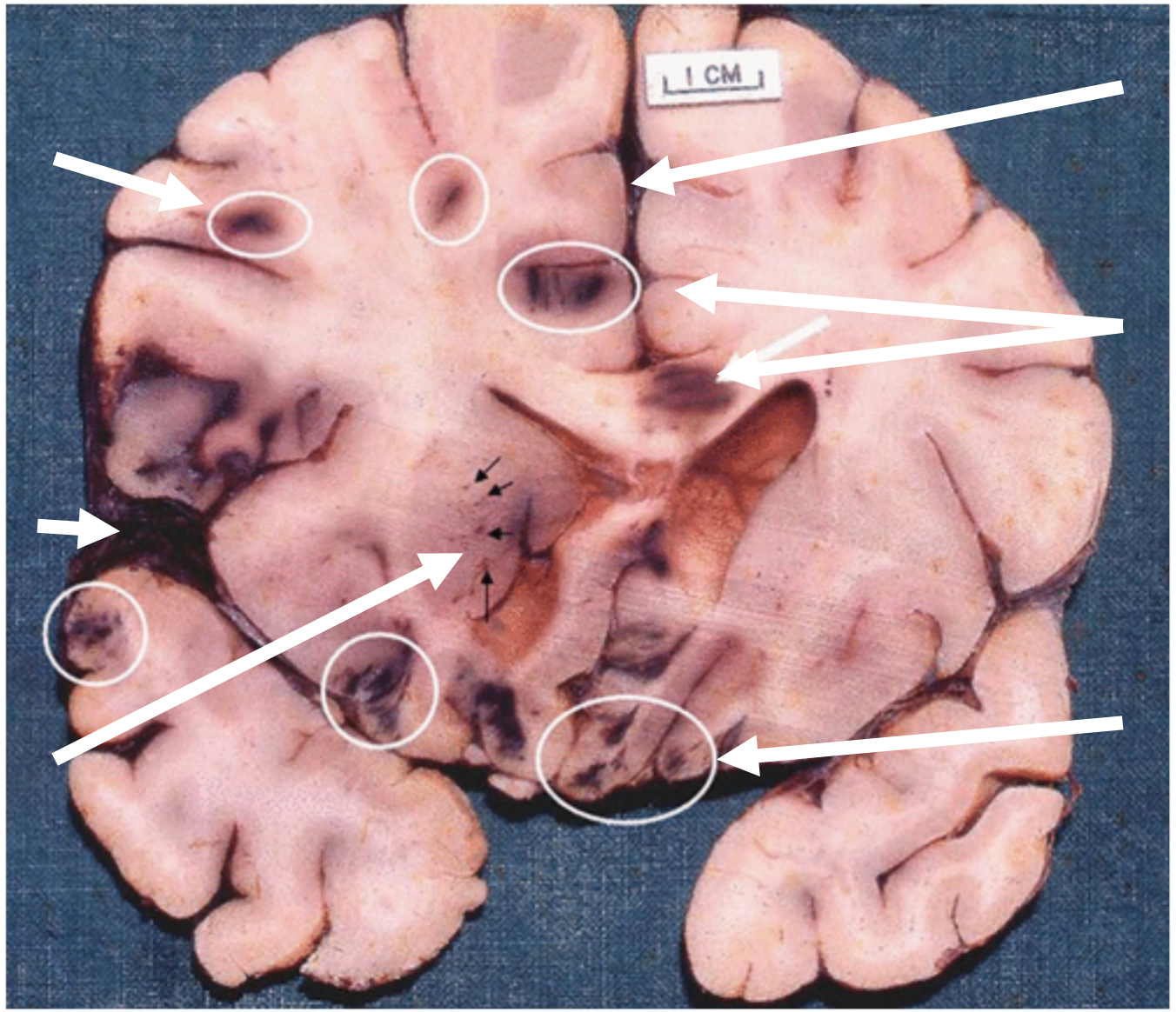
Itabashi, et al, Chapter 6 - Blunt force head injury. Forensic Neuropathology, Academic Press, 2007, Pages 167-198,

Severe TBI

Hemorrhages at gray/white mater junction (rotational)

Subarachnoid hemorrhage

Petechial hemorrhages in the basal ganglia



Swelling and midline shift

Hemorrhagic shear in the corpus callosum and cingulate

Hemorrhages at the surface (skull interface)

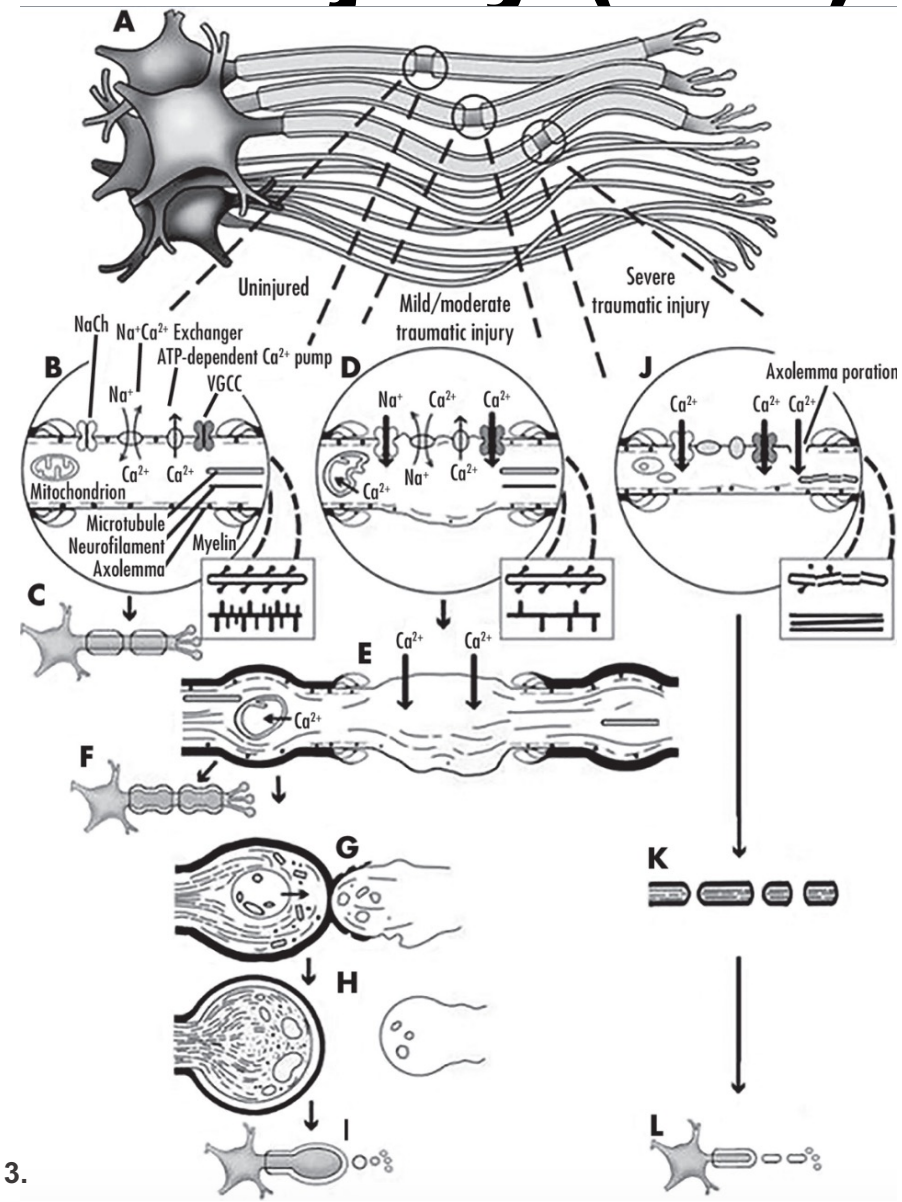
Bigler et al., Neuropathology of Mild Traumatic Brain Injury: Relationship to Neuroimaging Findings. *Brain Imaging and Behavior* 6(2):108–136, 2012.

Acute TBI: diffuse injury

- Mild to severe TBI
- Shows a more widespread distribution
- Animal and human studies have highlighted
  - *Diffuse axonal injury (DAI)*: shear forces disrupt axons, “spheroid” formation, axons degenerate and fragment, then neurons undergo Wallerian degeneration
  - *Diffuse vascular injury (DVI)*: Microvasculature more resistant than axons (seen in severe fatal head injuries), results in multiple small hemorrhages and damage to the BBB

Microscopic: diffuse axonal injury (DAI)

- Axons are the most vulnerable, but DAI also includes the constellation of effects on neurons, glia, blood vessels and neuronal networks
- Stretch deformation of axolemma, microtubules axonal neurofilaments
- Leads to membrane damage
- Physiologic (metabolic and ionic): altered permeability, ionic (Ca2+) dysregulation, impaired axonal transport, evoking sublethal or lethal cellular damage (secondary axotomy)



Smith et al., "Therapy Development for Diffuse Axonal Injury." *Journal of Neurotrauma* 30(5):307–323, 2013.

Acute TBI: cellular mechanisms

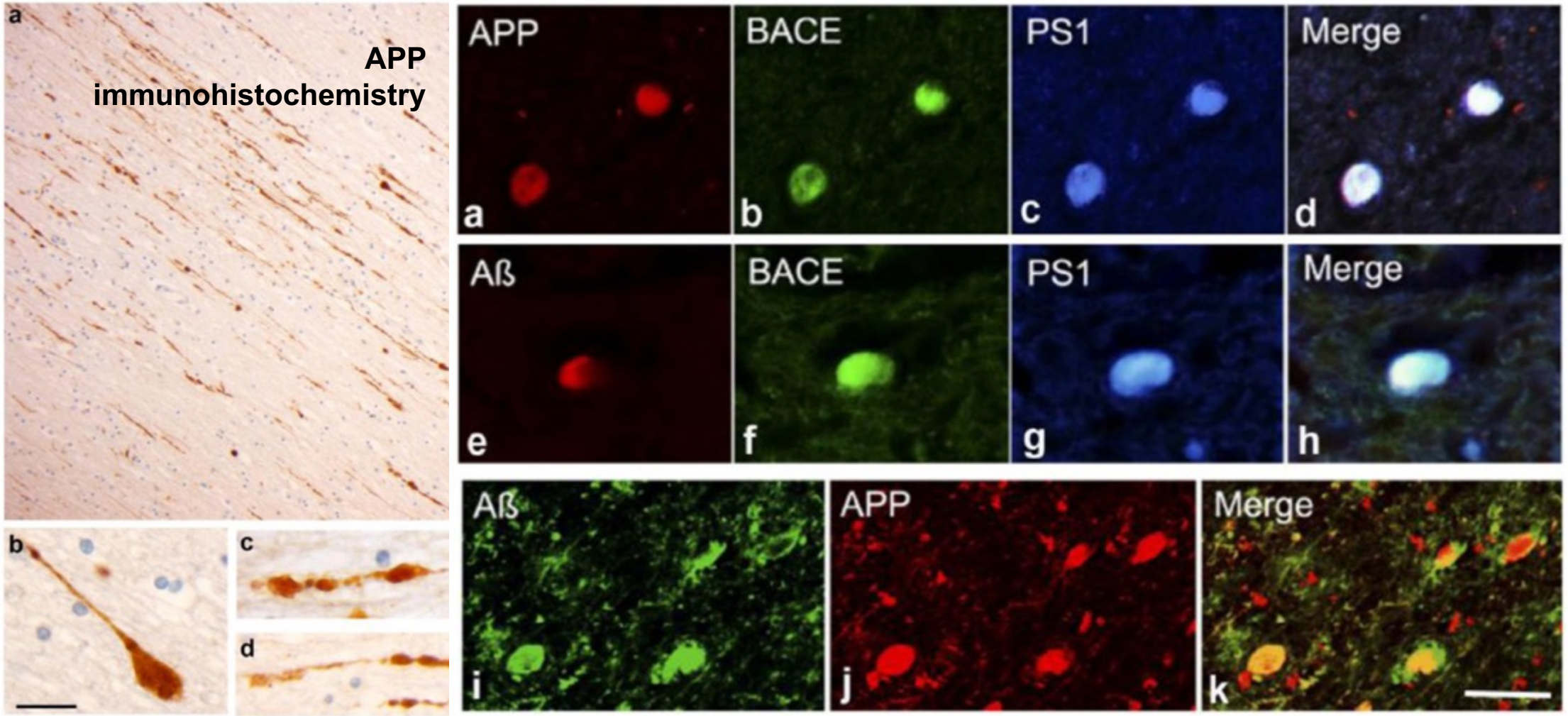
Excitotoxicity

- Glutamate surge: rapid increase in extracellular glutamate from excessive release, leakage, extravasation from disruption of the BBB and reduced astrocyte reuptake
- Causes excessive stimulation, high extracellular K+ and intracellular Na+/Ca2+, release of Ca2+ from intracellular stores
- Triggers a *metabolic crisis* and energy failure following failed restoration of homeostasis via increased ATP-dependent pumps
- High Ca2+ activates Ca2+ dependent proteases (calpains/caspases), generation of reactive oxygen/nitrogen species and mitochondrial impairment triggering *apoptosis*

Wallerian degeneration

- Phenomena unique to CNS when a nerve fiber is severed or crushed
- The axon separated from the neuron cell body degenerates distal to the injury
- Atypical cell death mechanism since neurons undergoing this process remain alive

Acute TBI: diffuse axonal injury



Johnson et al., *Exp Neurol*. 2013 August ; 246: 35–43

Chronic traumatic encephalopathy & tauopathy

Primary (non-amyloid) tauopathies

Clinical: Cognitive, movement, motor neuron, and psychiatric disorders

Neuroanatomical: Neocortex, subcortical, brainstem, spinal cord

Neurohistological: Neurons, astrocytes & oligodendrocytes

Biochemical: Tau isoform ratio, secondary modifications & filament ultrastructure

Genetic: Autosomal dominant mutations (*MAPT*), common risk alleles (17q21.31 haplotypes)

FTDP-17T (rare)

Primary age-related tauopathy (very common)
Age-related tau astrogliopathy (very common)
Progressive supranuclear palsy (20,000)
Corticobasal degeneration (rare)
Argyrophilic grain disease (rare to common)
FTLD with Pick Bodies (rare)
Globular glial tauopathy (rare)

Chronic traumatic encephalopathy (uncommon)

Lytico-Bodig disease (ALS/PDC) of Guam (rare)

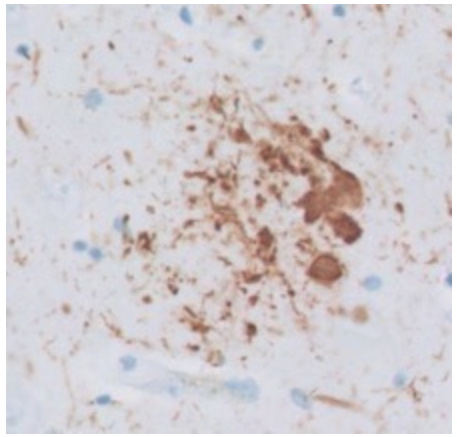
Myotonic dystrophy (20,000)

Subacute sclerosing pan-encephalitis (rare)
Postencephalitic parkinsonism (rare)

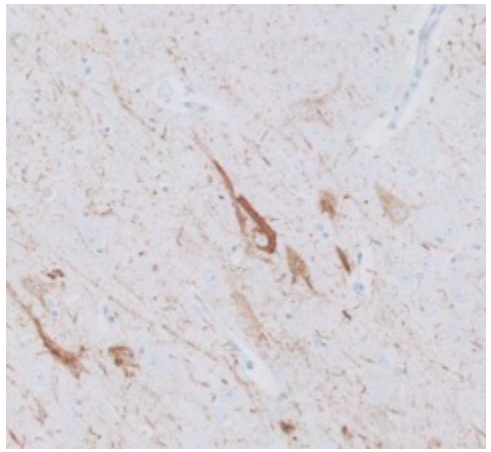
Gangliоglioma (rare)

Tauopathy: diverse neuronal & glial inclusions

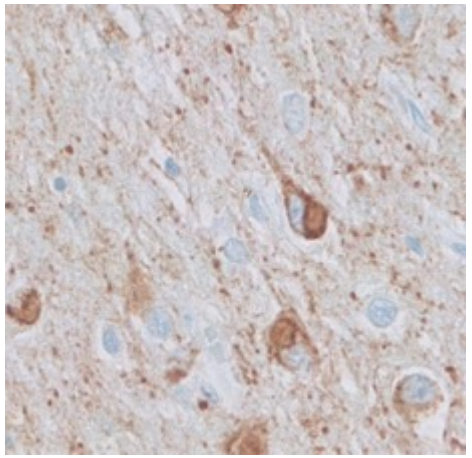
Neurons



Neuritic amyloid plaque

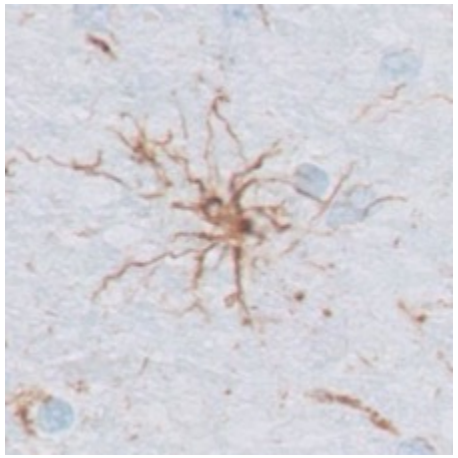


Neurofibrillary tangle

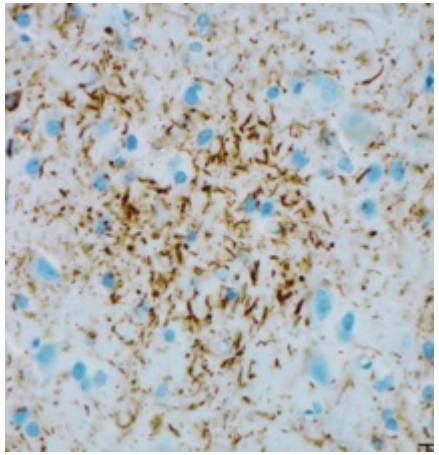


Pick body

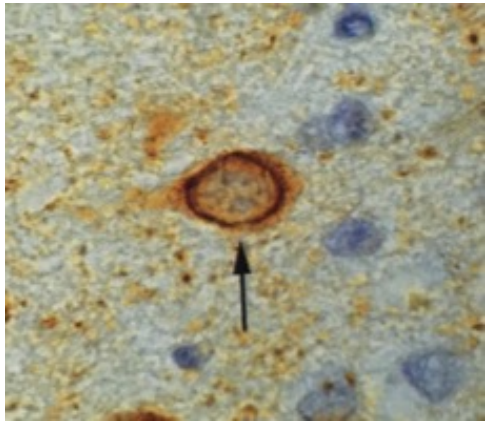
Glia



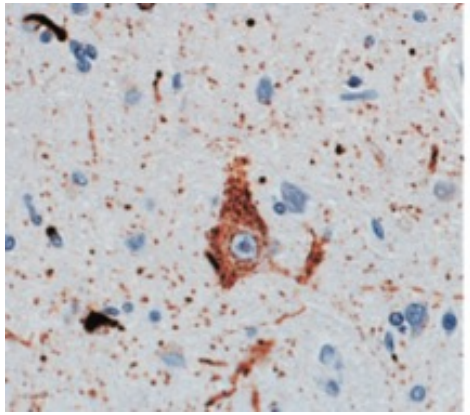
Tufted astrocyte



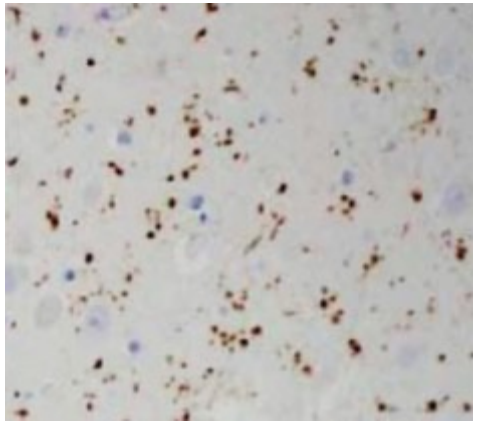
Astrocytic plaque



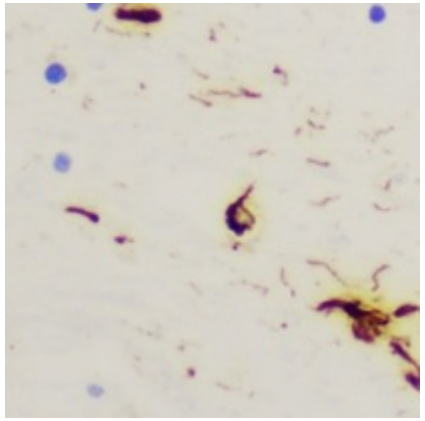
Nuclear ring



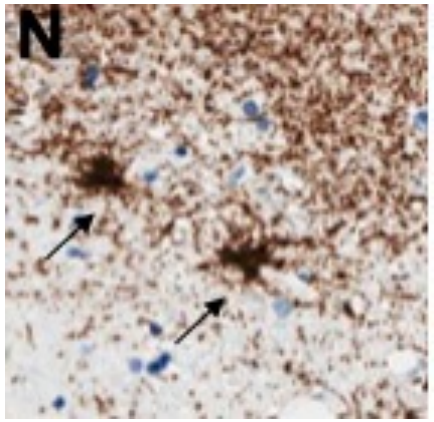
Granular cytoplasmic



Argyrophilic grains



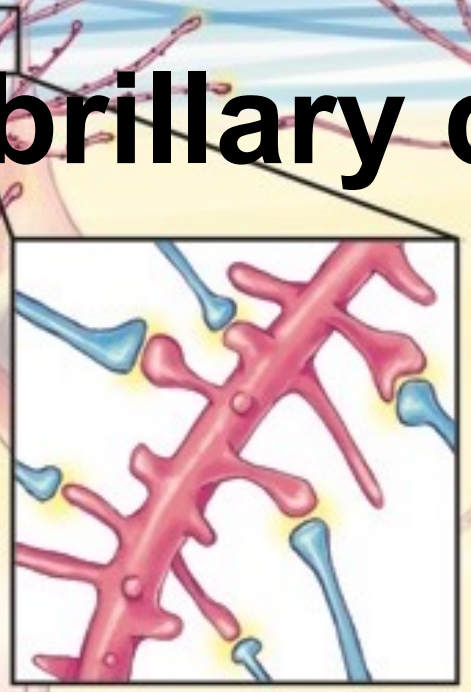
Coiled bodies



Thorn astrocyte

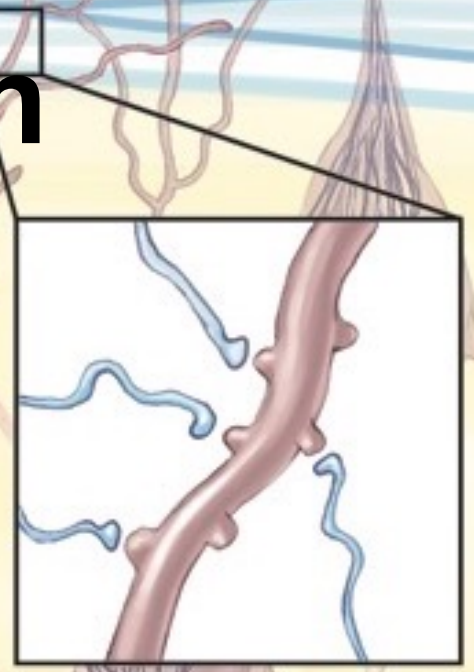
Abnormal hyperphosphorylated tau immunohistochemistry

Neurofibrillary degeneration



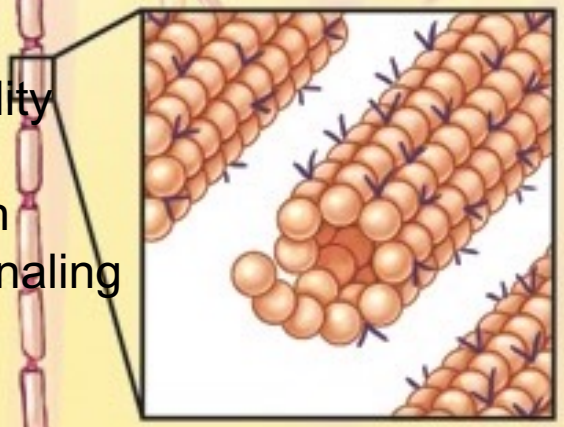
Tau oligomers

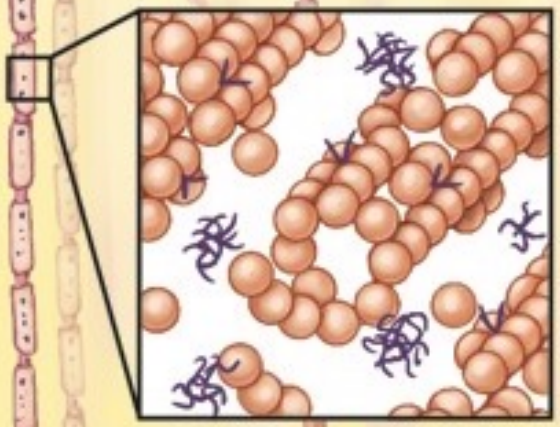
Propagation & aggregation



Cell death

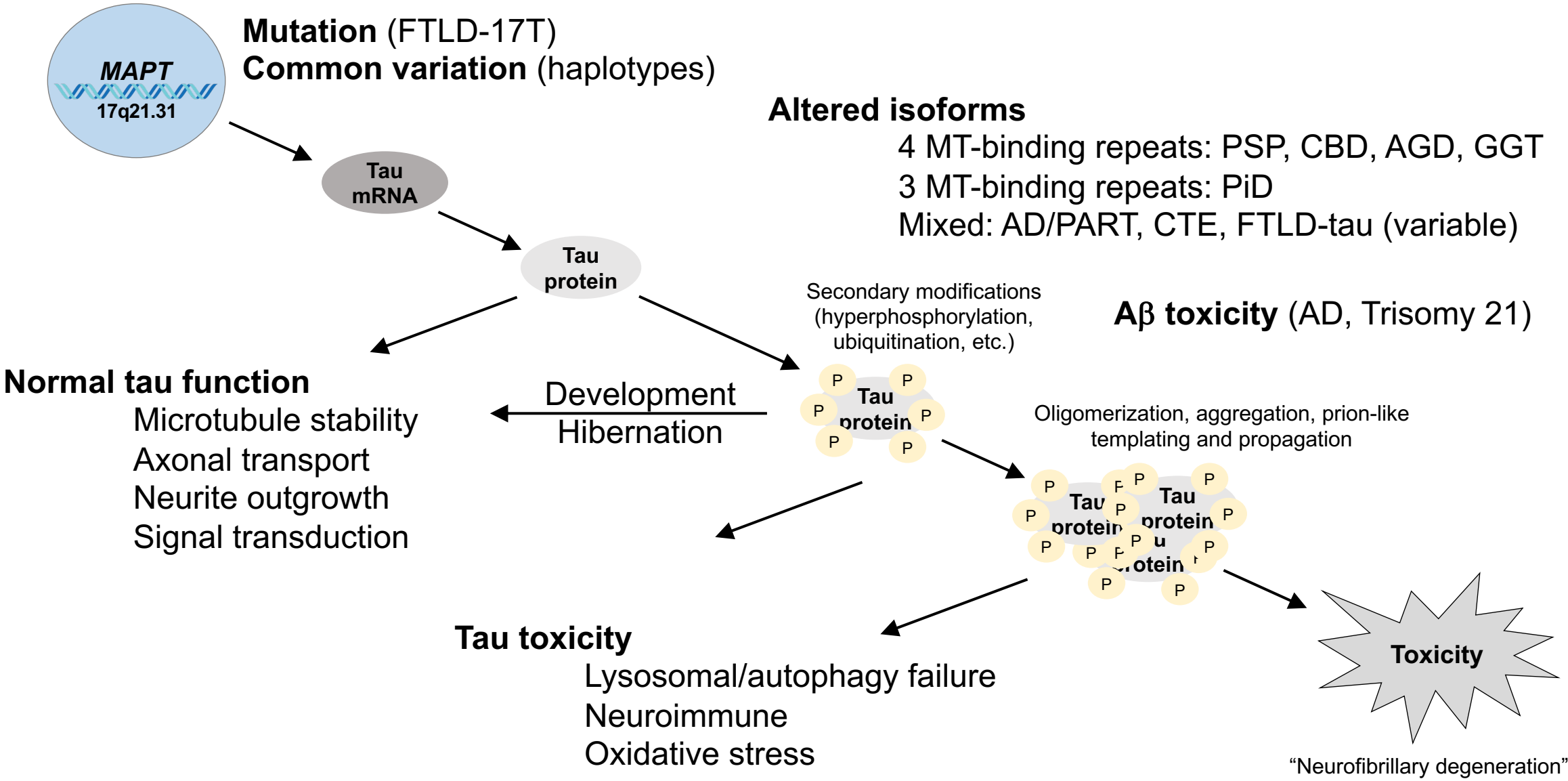
Tau function
- Microtubule stability
- Axonal transport
- Neurite outgrowth
- Growth factor signaling
- Others





Tau toxicity (gain of function)
- Post-translational modifications
- Neuroinflammation
- Oxidative stress
- Lysosomal failure
- Synaptic failure

Tauopathy: molecular & cellular mechanisms



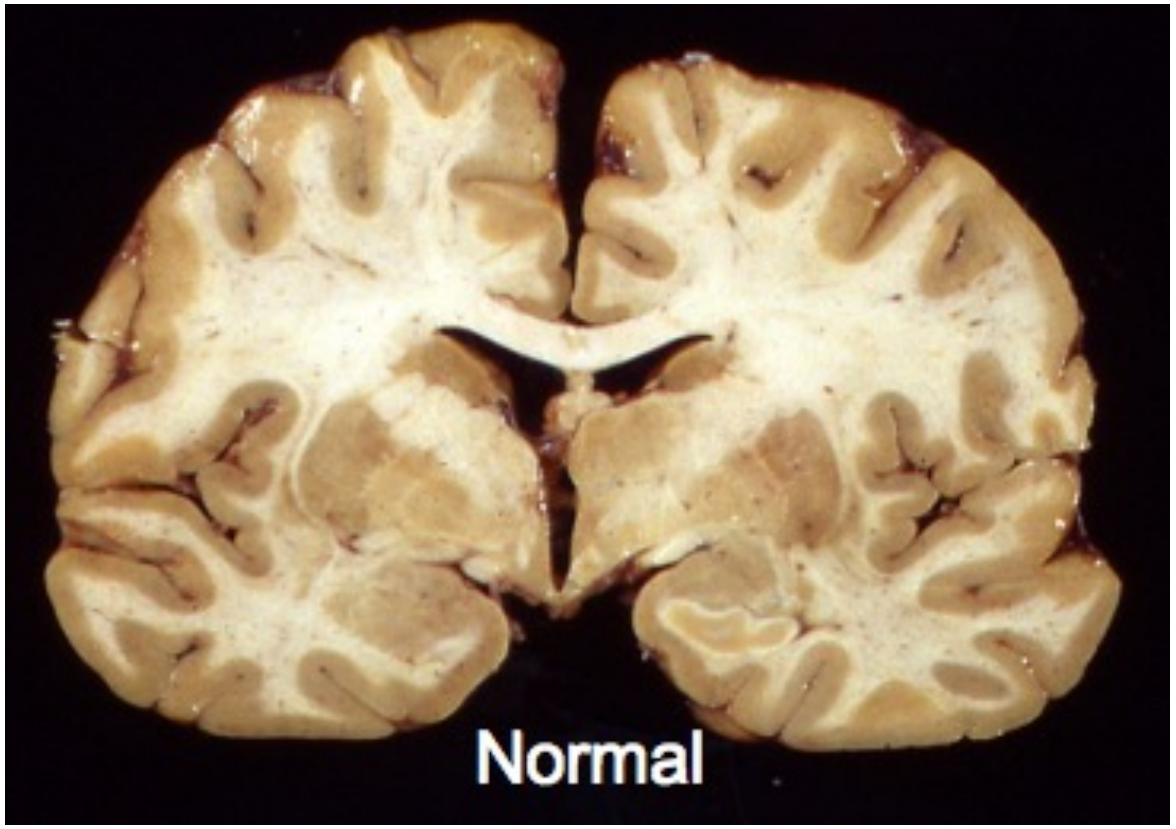
Chronic traumatic encephalopathy (CTE)

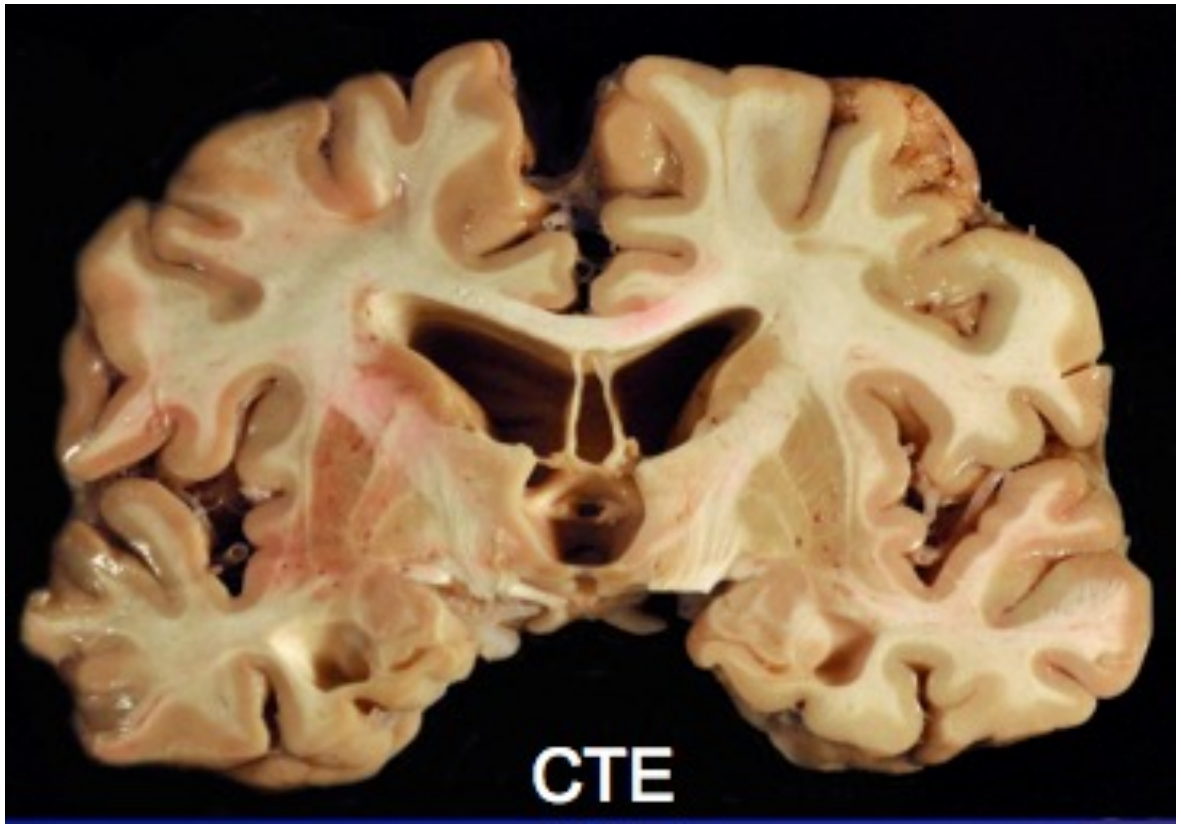
- A distinct progressive neurodegenerative disease, first described in boxers by Martland (1928)
- Later termed *dementia pugilistica*, then *chronic traumatic encephalopathy*; seen in sports, “head banging”, intimate partner violence, blast, etc.
- Caused by mild yet repetitive concussive and subconcussive injuries
- Symptoms:
  - Early memory and cognitive impairment, depression, impulse control problems and behavioral abnormalities
  - Progresses to dementia, movement disorder, motor neuron disease

Harrison S. Martland, MD, ca. 1940

Martland HS: Punch drunk. JAMA 91:1103–1107, 1928

CTE: Gross neuropathology



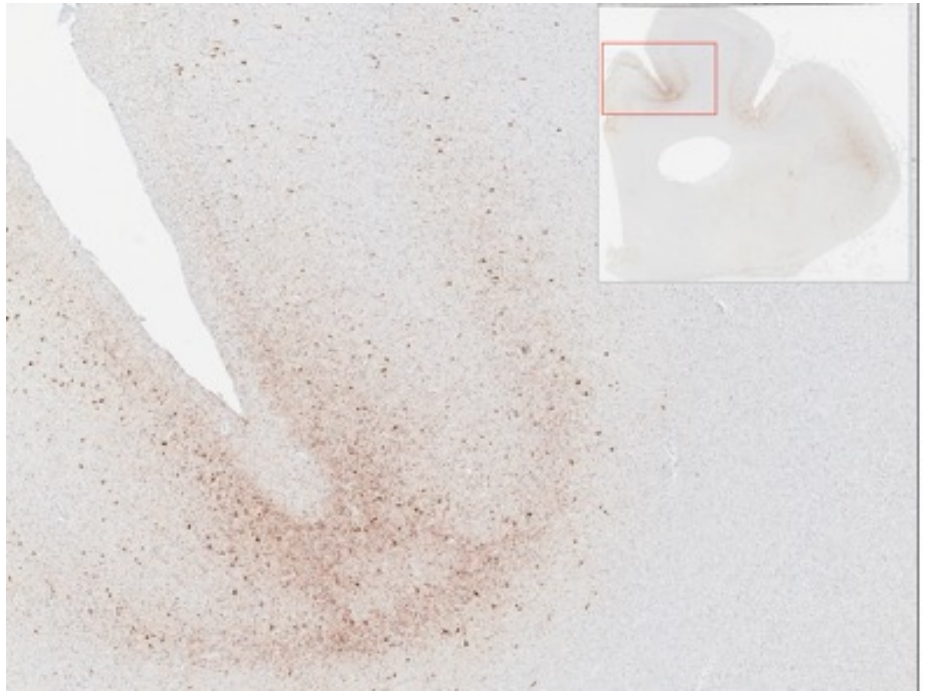


Atrophy & ventricular dilatation, cavum septum pellucidum, destruction of the mammillary bodies, substanta nigra & locus coeruleus pallor, callosal thinning

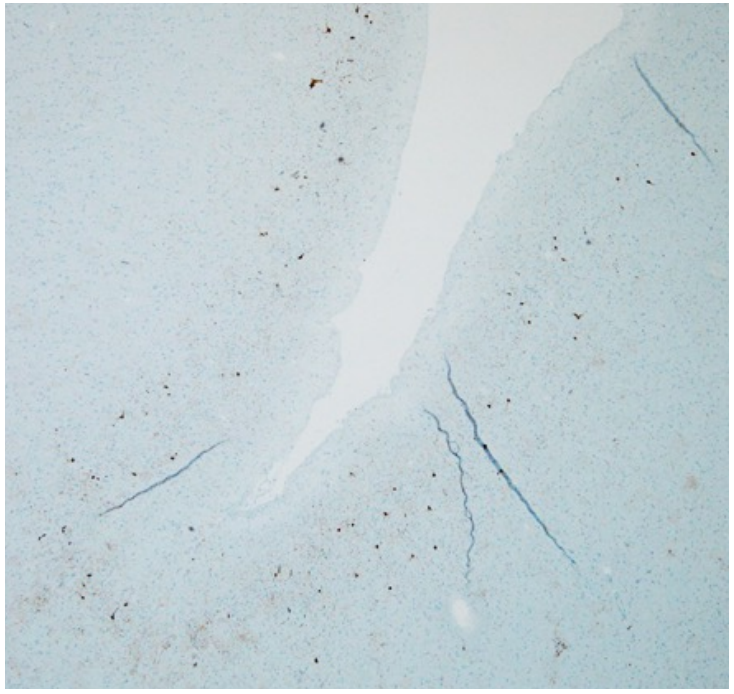
Stern RA, Riley DO, Daneshvar DH, Nowinski CJ, Cantu RC, McKee AC (2011) Long-term consequences of repetitive brain trauma: chronic traumatic encephalopathy. PM R 3:S460–S467. doi:10.1016/j.pmrj.2011.08.008

CTE: Microscopic neuropathology

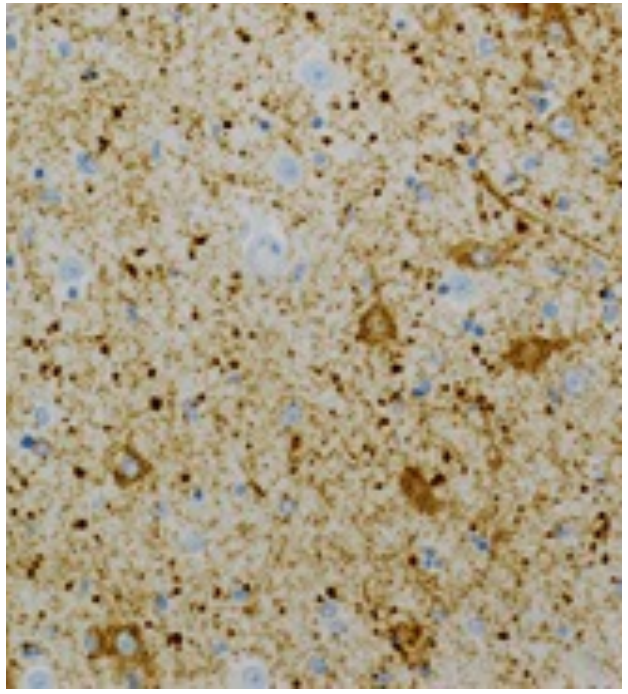
P-tau immunohistochemistry (AT8)



Sulcal predominance



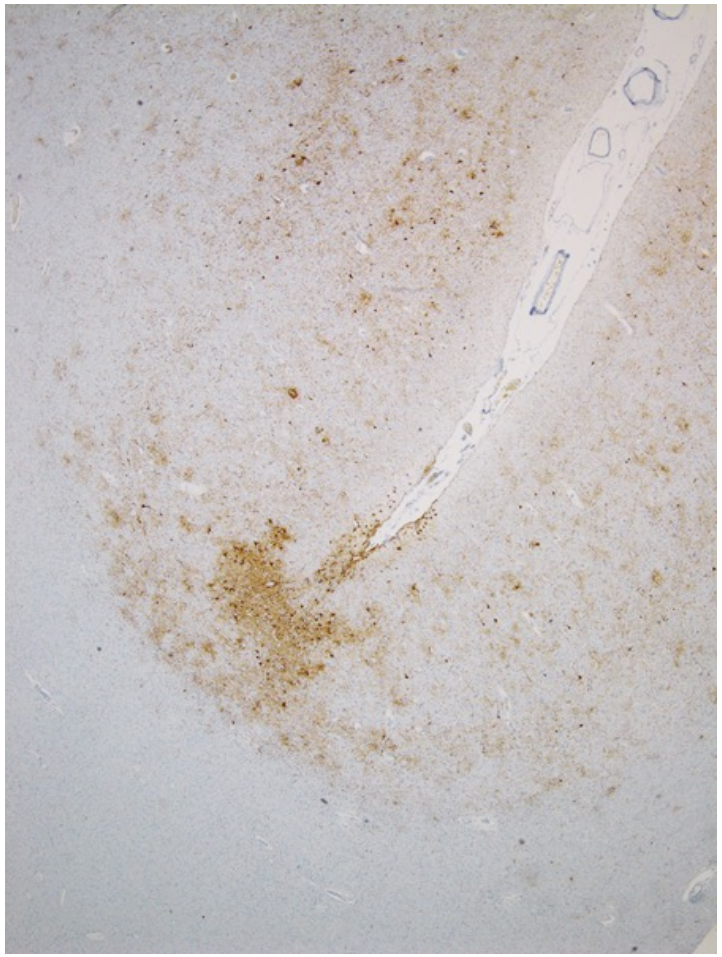
Superficial tangles (temporal)

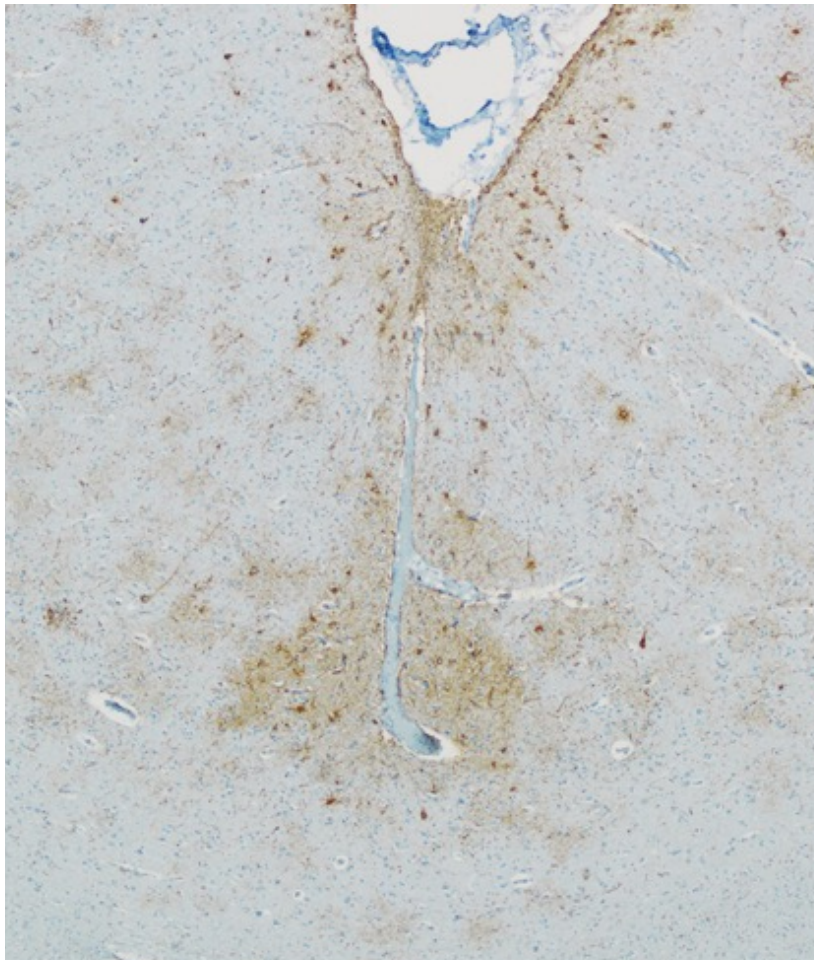


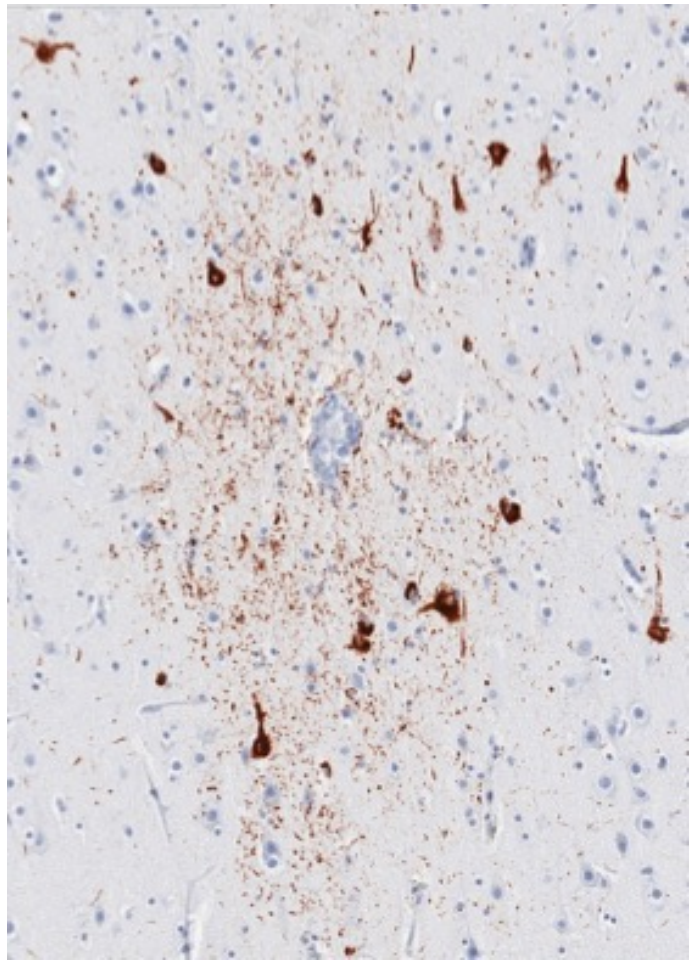
Grains (amygdala)

CTE: Microscopic neuropathology

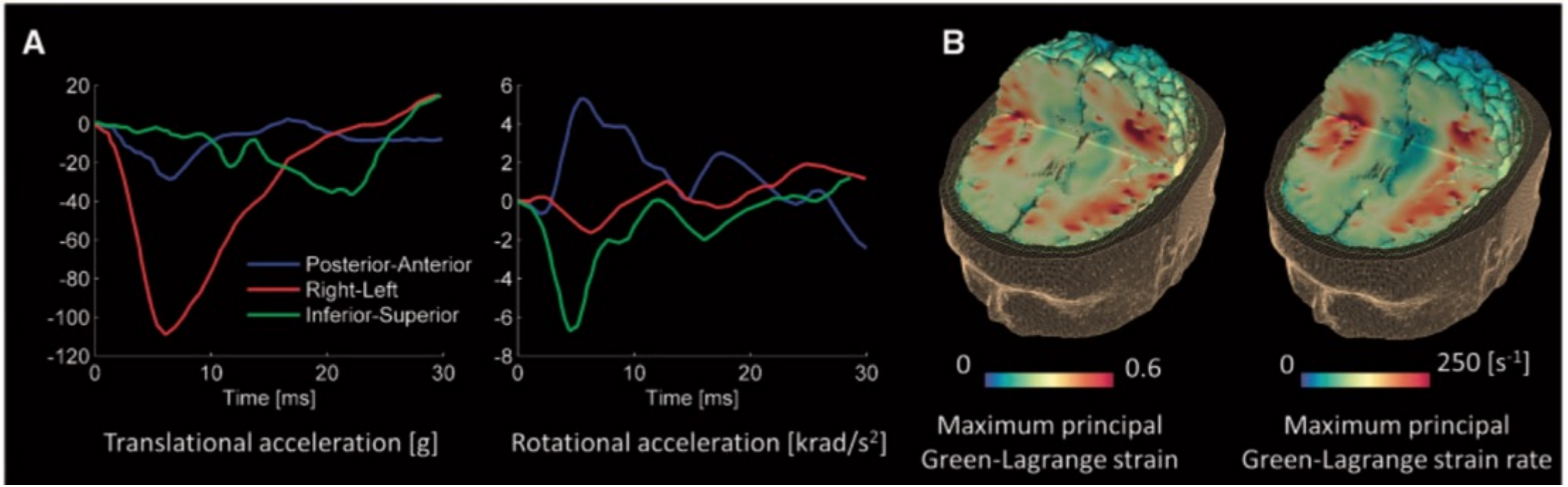
Pathognomonic lesion examples (p-tau IHC)







CTE: biomechanics

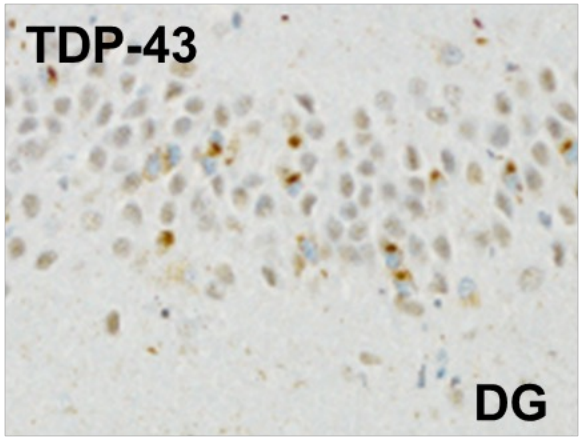


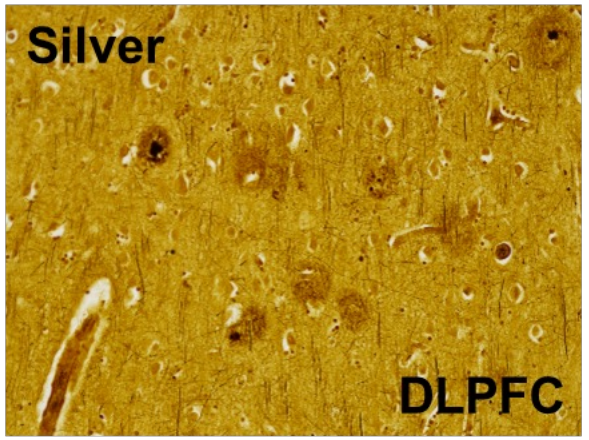
- The computational models predict large strain at the depths of sulci
- The volume of sulcal regions exceeding brain injury thresholds significantly larger than gyral regions

Ghajari, M., P. J. Hellyer and D. J. Sharp (2017). "Computational modelling of traumatic brain injury predicts the location of chronic traumatic encephalopathy pathology." Brain **140**(2): 333-343.

Mixed pathology in CTE

- *Polyproteinopathy*: common
- *TDP-43*
  - Hippocampal sclerosis/LATE
- *Aβ plaques* (diffuse or neuritic) in 52%
- *Synucleinopathy*





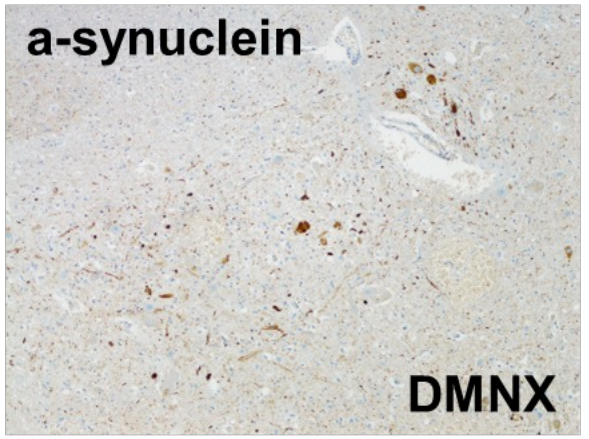


TABLE 1. Descriptive Characteristics of Brain Donors (n = 571)

Variable	Mean (SD) or n (%)
Age at death, yr, median [IQR] [range]	65.0 [46.0–76.0] [18–97]
Education level	
Some high school or high school diploma/GED	38 (6.7)
Some college or college degree	383 (67.1)
More than college or graduate degree	150 (26.3)
Male sex	565 (98.9)
Race	
White	466 (81.6)
Black/African American	87 (15.2)
Other race	18 (3.2)
Contact sports	
Neurodegenerative pathology	
CTE, stages III–IV	246 (43.1)
TDP-43 inclusions	137 (24.0)
Alzheimer disease	107 (18.7)
Hippocampal sclerosis	96 (16.8)
Neocortical Lewy bodies	34 (6.0)
FTLD-TDP	24 (4.2)
FTLD-tau	24 (4.2)
Cerebrovascular pathology	
Arteriolosclerosis [mod-sev]	292 (51.1)
CAA [mod-sev]	123 (21.5)
Microinfarcts	110 (19.3)
Atherosclerosis [mod-sev]	108 (18.9)
Gross infarcts	77 (13.5)
White matter rarefaction [mod-sev]	251 (44.0)

Stein, T. D., P. H. (2015). "Beta-amyloid deposition in chronic traumatic encephalopathy." Acta Neuropathol.

Saltiel et al. Relative Contributions of Mixed Pathologies to Cognitive and Functional Symptoms in Brain Donors Exposed to Repetitive Head Impacts. Ann Neurol. 2023 Nov 3

CTE: Diagnostic consensus criteria

Required (pathognomonic lesion)

- ✓p-tau+ aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci

Supportive features (p-tau)

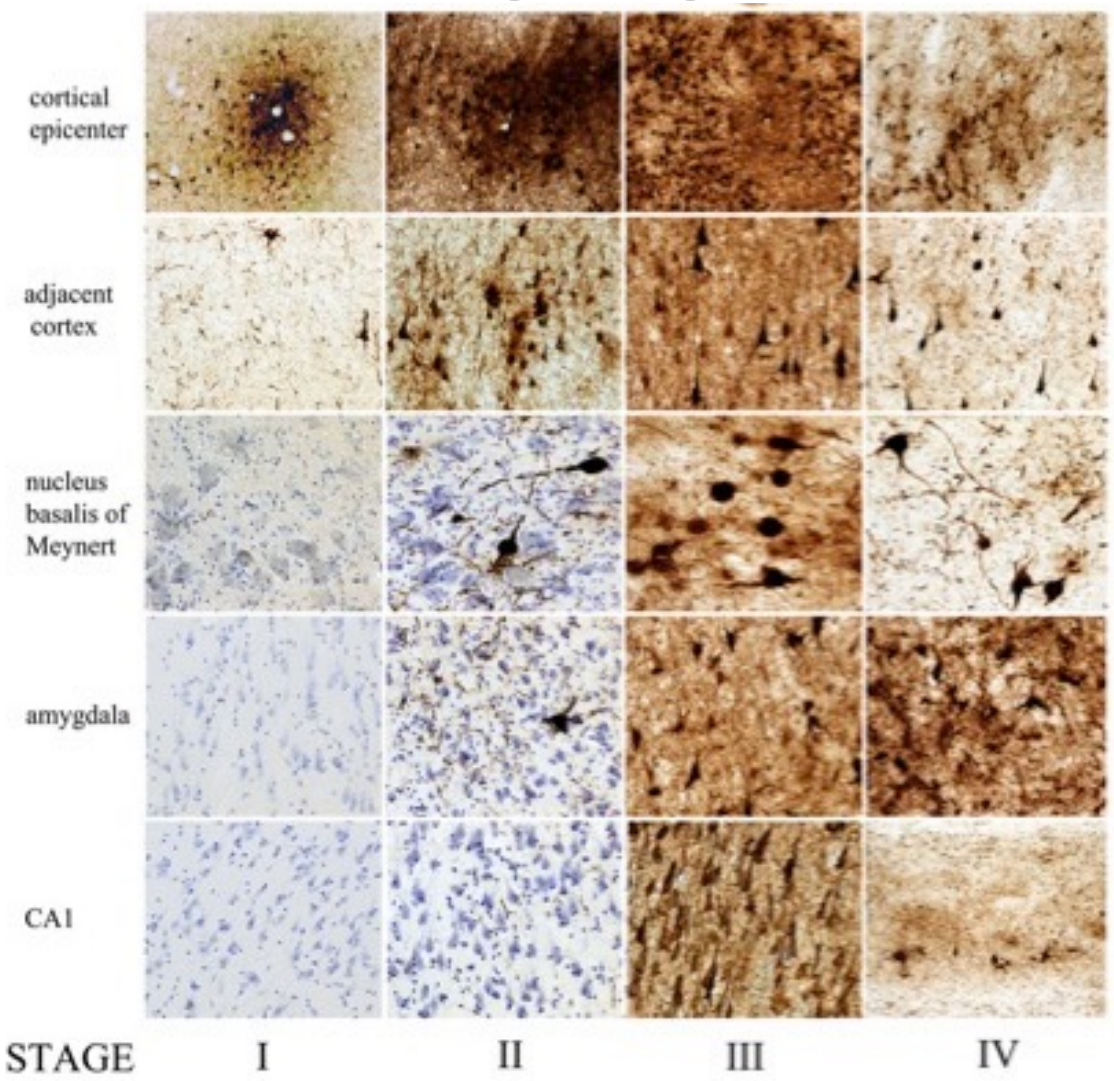
- ✓ NFTs affecting superficial layers (layers II–III)
- ✓ NFTs in CA2 and prominent proximal dendritic swellings in CA4
- ✓ p-tau+ aggregates in subcortical nuclei
- ✓ p-tau+ thorny astrocytes at the glial limitans (subpial and periventricular)
- ✓ p-tau+ large grain-like and dot-like structures

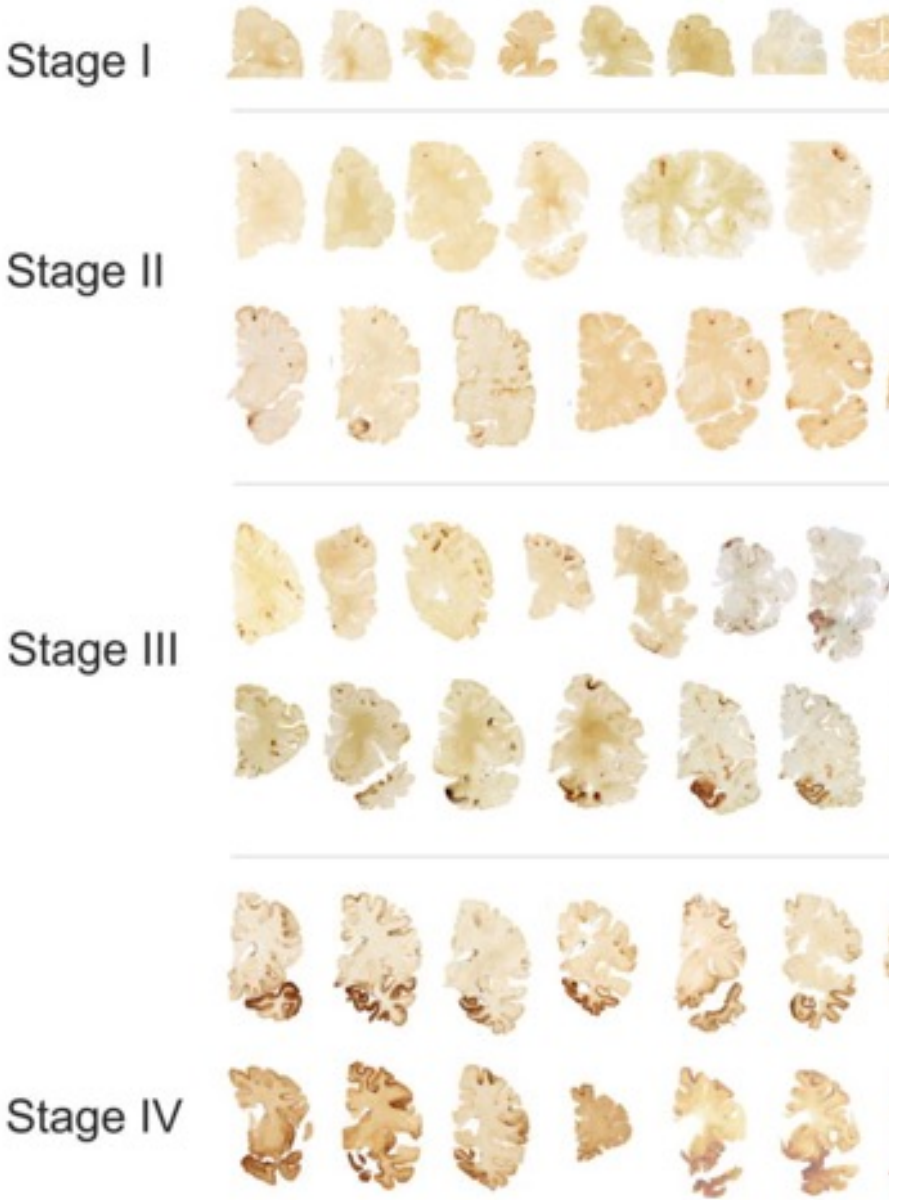
Other pathologies (non-p-tau)

- ✓Disproportionate 3rd ventricle dilatation, septal changes, mammillary body atrophy, contusions, other signs of TBI
- ✓TDP-43+ inclusions

McKee et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. Acta Neuropathol. 2016 Jan;131(1):75-86.

CTE: staging





p-tau IHC

McKee, et al (2013). "The spectrum of disease in chronic traumatic encephalopathy." Brain **136**(Pt 1): 43-64.

CTE: Controversy?

COMMENTARY

Does CTE call for an end to youth tackle football?

Despite press about a recent study, a link between hits to the head and CTE isn't clear-cut. More data and a risk-benefit analysis are needed.

By Jason Chung , Peter Cummings and Uzma Samadani | FEBRUARY 10, 2018 — 8:37AM

StarTribune

NOAH MUSSER • KANSAS CITY STAR/TNS

*"CTE pathology in the brain has been shown by British pathologists to be **present in approximately 12 percent of normal healthy aged people** who died at an average age of 81 years (Ling et al. Acta Neuropathologica). The presence of CTE pathology in the brain on autopsy has not been shown to correlate with neurologic symptoms before death. To be clear, CTE pathology could be present in a normal person."*

*"The scientific evidence linking youth casual sports play to brain injury, brain injury to CTE, and CTE to dementia is **not strong**."*

*"The pathology and link between head impacts and long-term neurological conditions such as CTE is still unclear, with **questions of causation yet to be settled**."*

CTE: Controversy?

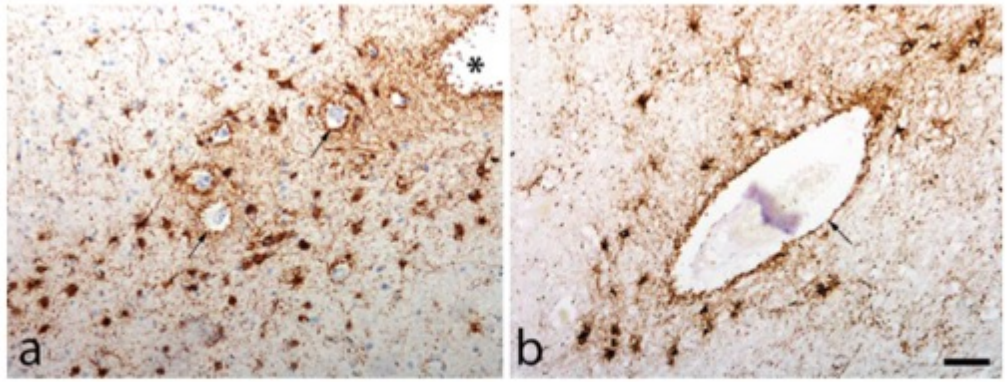
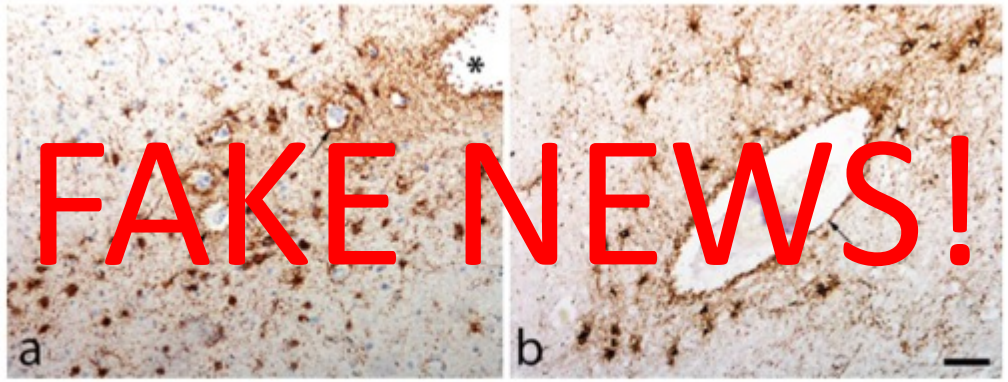


Fig. 1 Characteristic histological features of chronic traumatic encephalopathy (CTE). Abnormal perivascular accumulation of tau-immunoreactive lesions in neurons, astrocytes and neurites in an irregular pattern at the depth of the sulcus in the frontal cortex [*arrows* pointing to blood vessels, *asterisks* locating at bottom of sulcus; **a**, **b** tau immunohistochemistry (AT8); *bar* in **a** 25 μm, in **b** 25 μm]

13% of normal individuals have CTE pathology?

Ling, H., J. L. Holton, K. Shaw, K. Davey, T. Lashley and T. Revesz (2015). "Histological evidence of chronic traumatic encephalopathy in a large series of neurodegenerative diseases." *Acta Neuropathol* **130**(6): 891-893.

CTE: Controversy?



FAKE NEWS!

Fig. 1 Characteristic histological features of chronic traumatic encephalopathy (CTE). Abnormal perivascular accumulation of tau-immunoreactive lesions in neurons, astrocytes and neurites in an irregular pattern at the depth of the sulcus in the frontal cortex [*arrows* pointing to blood vessels, *asterisks* locating at bottom of sulcus; **a**, **b** tau immunohistochemistry (AT8); *bar* in **a** 25 μm, in **b** 25 μm]

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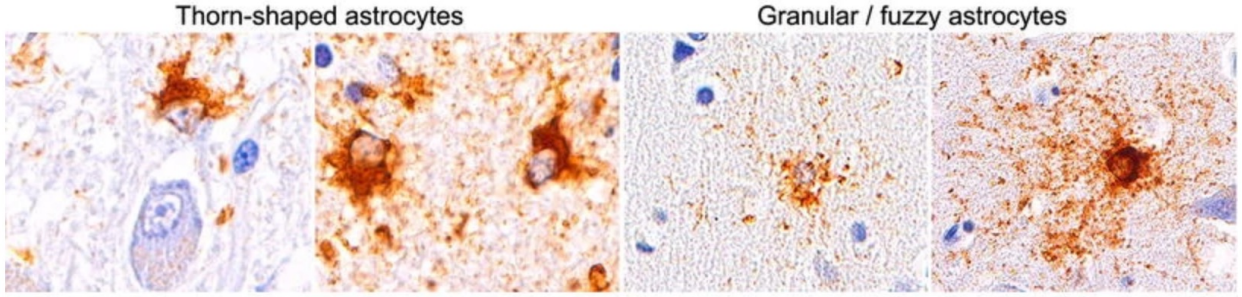
Acta Neuropathol (2016) 131:87–102
DOI 10.1007/s00401-015-1509-x

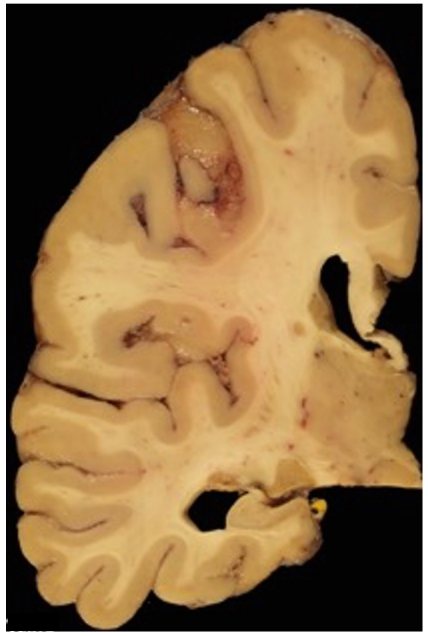
CONSENSUS PAPER

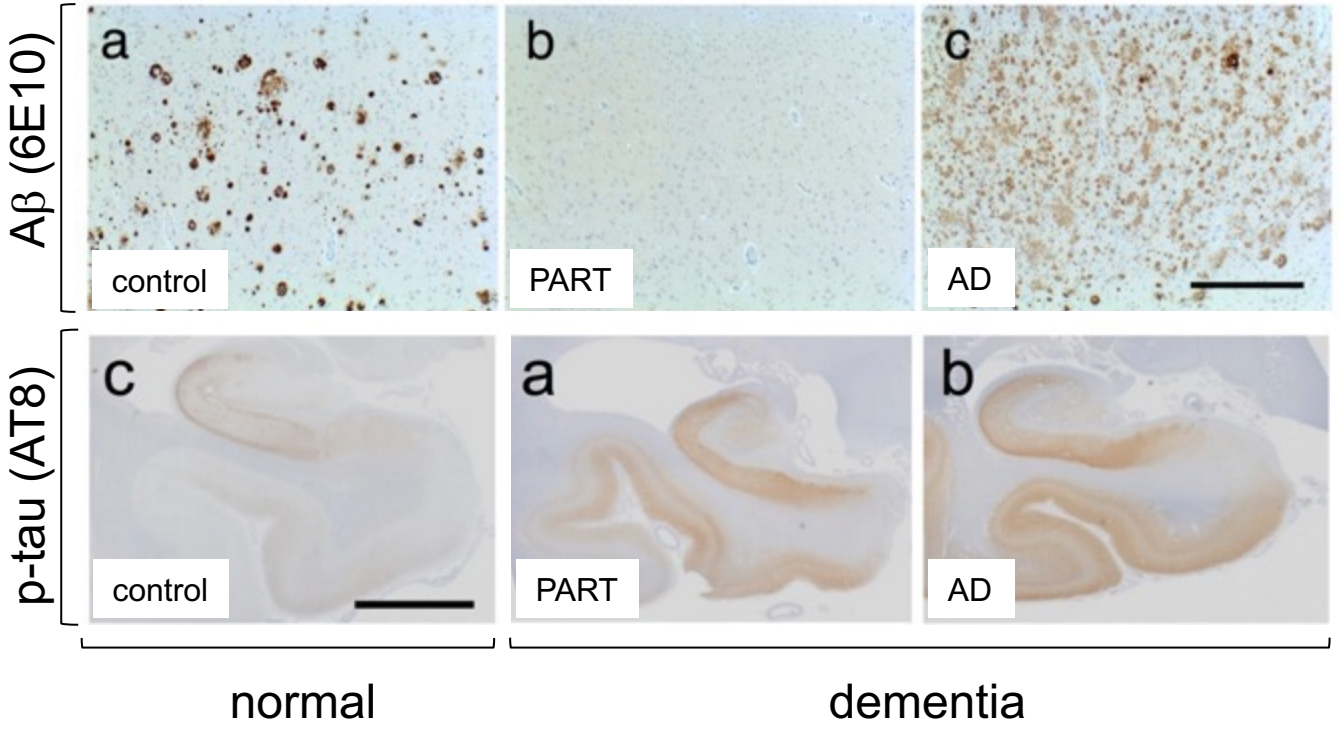
Aging-related tau astrogliopathy (ARTAG): harmonized evaluation strategy

Gabor G. Kovacs[1] · Isidro Ferrer[2] · Lea T. Grinberg[3,4] · Irina Alafuzoff[5] · Johannes Attems[6] · Herbert Budka[7] · Nigel J. Cairns[8] · John F. Crary[9,33] · Charles Duyckaerts[10] · Bernardino Ghetti[11] · Glenda M. Halliday[12] · James W. Ironside[13] · Seth Love[14] · Ian R. Mackenzie[15] · David G. Munoz[16] · Melissa E. Murray[17] · Peter T. Nelson[18] · Hitoshi Takahashi[19] · John Q. Trojanowski[20] · Olaf Ansorge[21] · Thomas Arzberger[22] · Atik Baborie[23] · Thomas G. Beach[24] · Kevin F. Bieniek[17] · Eileen H. Bigio[25] · Istvan Bodi[26] · Brittany N. Dugger[24,27] · Mel Feany[28] · Ellen Gelpi[29] · Stephen M. Gentleman[30] · Giorgio Giaccone[31] · Kimmo J. Hatanpaa[32] · Richard Heale[6] · Patrick R. Hof[33] · Monika Hofer[21] · Tibor Hortobágyi[34] · Kurt Jellinger[35] · Gregory A. Jicha[36] · Paul Ince[37] · Julia Kofler[38] · Enikö Kövari[39] · Jillian J. Kril[40] · David M. Mann[41] · Radoslav Matej[42] · Ann C. McKee[43] · Catriona McLean[44] · Ivan Milenkovic[1,45] · Thomas J. Montine[46] · Shigeo Murayama[47] · Edward B. Lee[20] · Jasmin Rahimi[1] · Roberta D. Rodriguez[48] · Annemieke Rozemüller[49] · Julie A. Schneider[50,51] · Christian Schultz[52] · William Seeley[3] · Danielle Seilhean[10] · Colin Smith[13] · Fabrizio Tagliavini[31] · Masaki Takao[53] · Dietmar Rudolf Thal[54,55] · Jon B. Toledo[20] · Markus Tolnay[56] · Juan C. Troncoso[57] · Harry V. Vinters[58,59] · Serge Weis[60] · Stephen B. Wharton[37] · Charles L. White III[32] · Thomas Wisniewski[61,62,63] · John M. Woulfe[64] · Masahito Yamada[65] · Dennis W. Dickson[17]



CTE: Controversy?

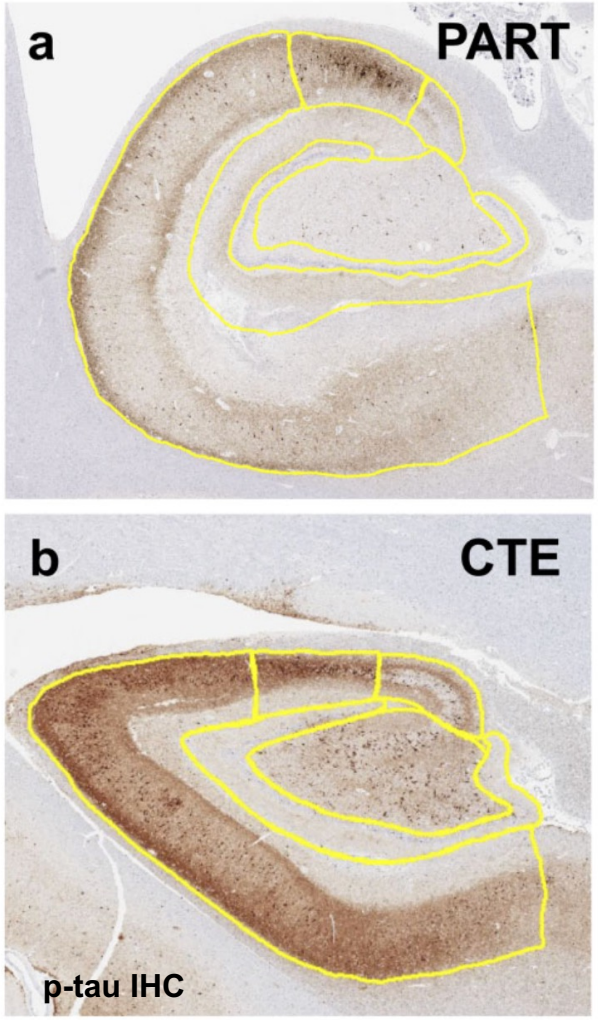


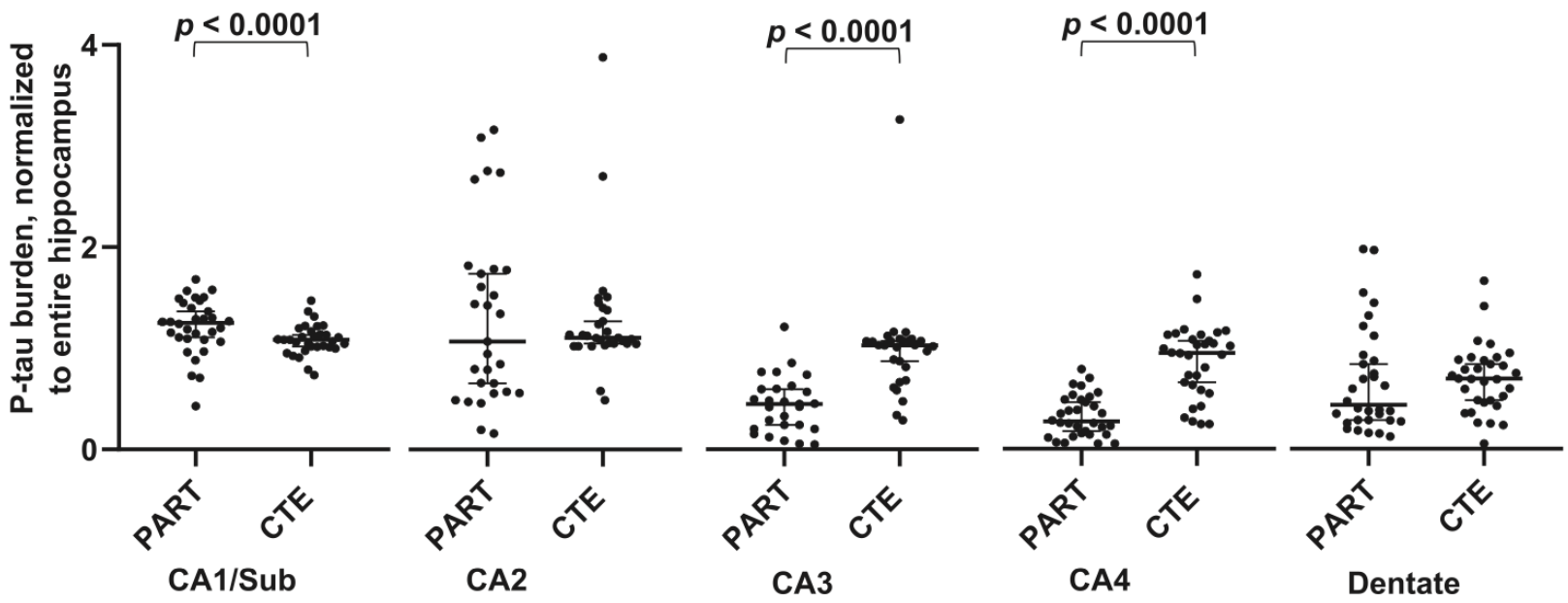


Primary age-related tauopathy vs. “classical” AD

1. Crary, J. F., J. Q. Trojanowski, J. A. Schneider, J. et al., (2014). "Primary age-related tauopathy (PART): a common pathology associated with human aging." Acta Neuropathol 128(6): 755-766.
2. Santa-Maria, I., Haggiagi, A., Liu, X.M., Wasserscheid, J., Nelson, P.T., Dewar, K., Clark, L.N., and Crary, J.F. 2012. The MAPT H1 haplotype is associated with tangle-predominant dementia. Acta Neuropathologica 124:693-704

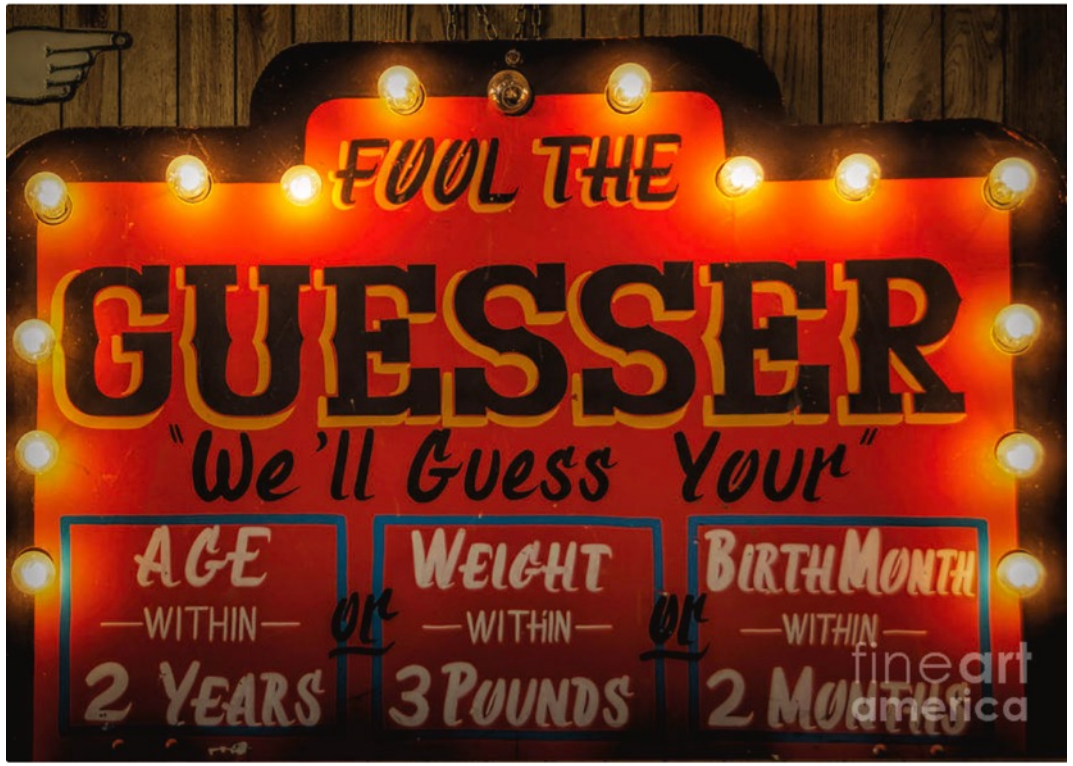
CTE: Selective vulnerability in CTE





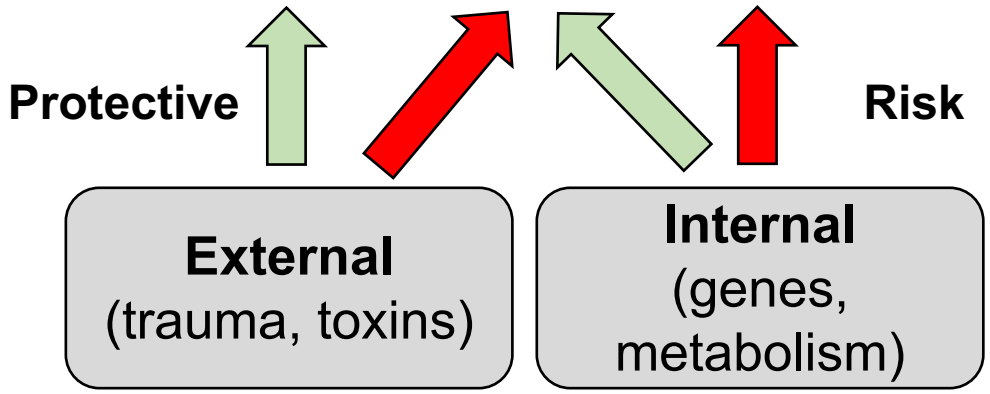
Farrell et al. Differential Vulnerability of Hippocampal Subfields in Primary Age-Related Tauopathy and Chronic Traumatic Encephalopathy. J Neuropathol Exp Neurol. 2022 Sep 19;81(10):781-789

Age prediction model

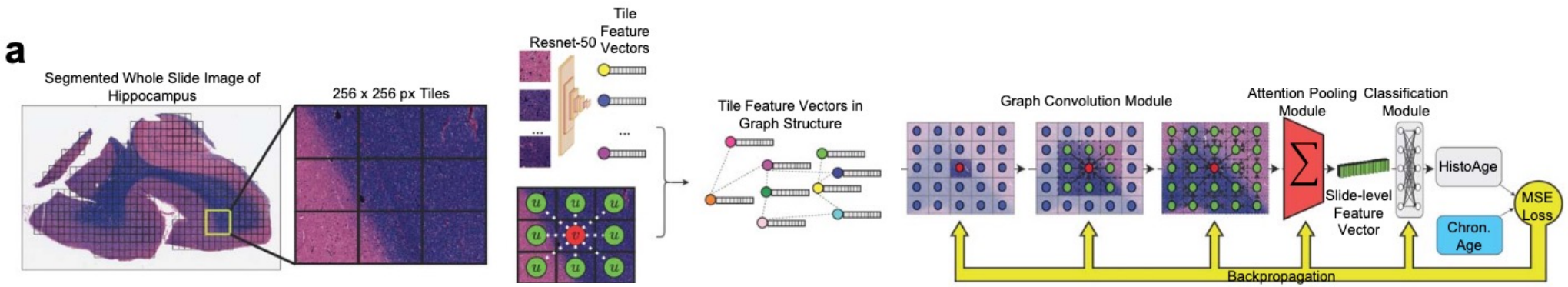


- **Discordance between *chronological* and *biological* age = age acceleration**
- **Rates differ by organ, population, species**
- **Factors can be *protective* or *accelerate* aging**
- **Aging can be *normal, pathologic,* or *successful***

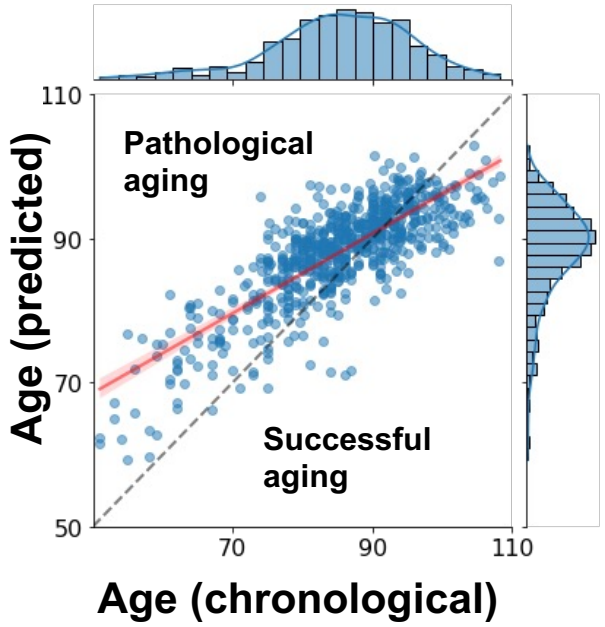
Paul Rudd **Wilford Brimley**

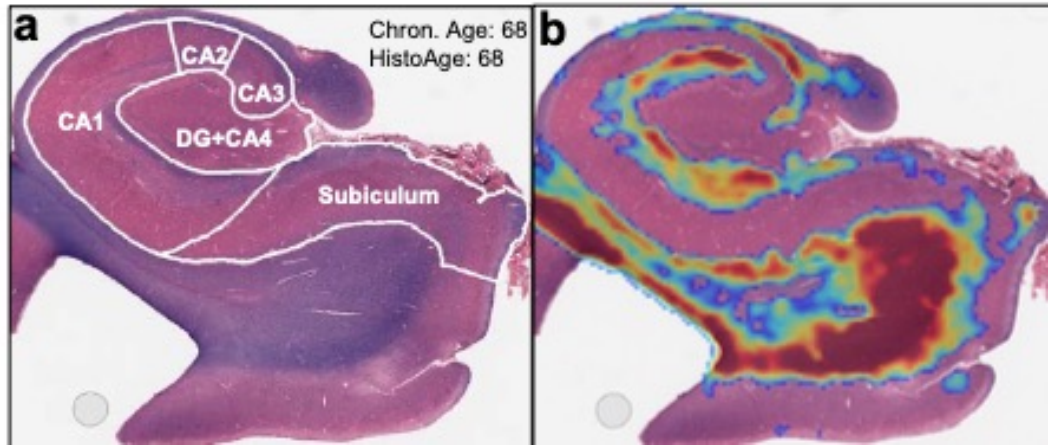


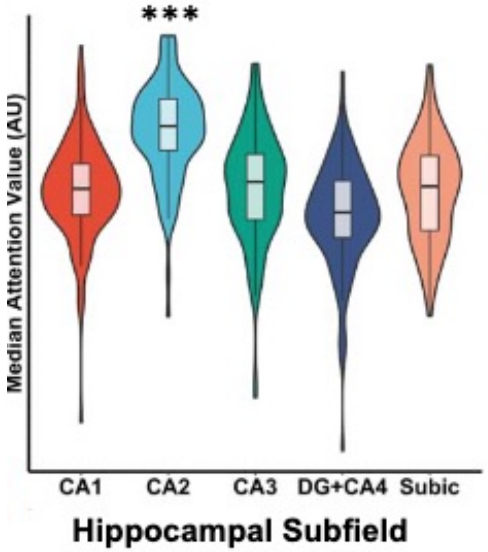
HistoAge brain age-acceleration model



Gabe Marx MD



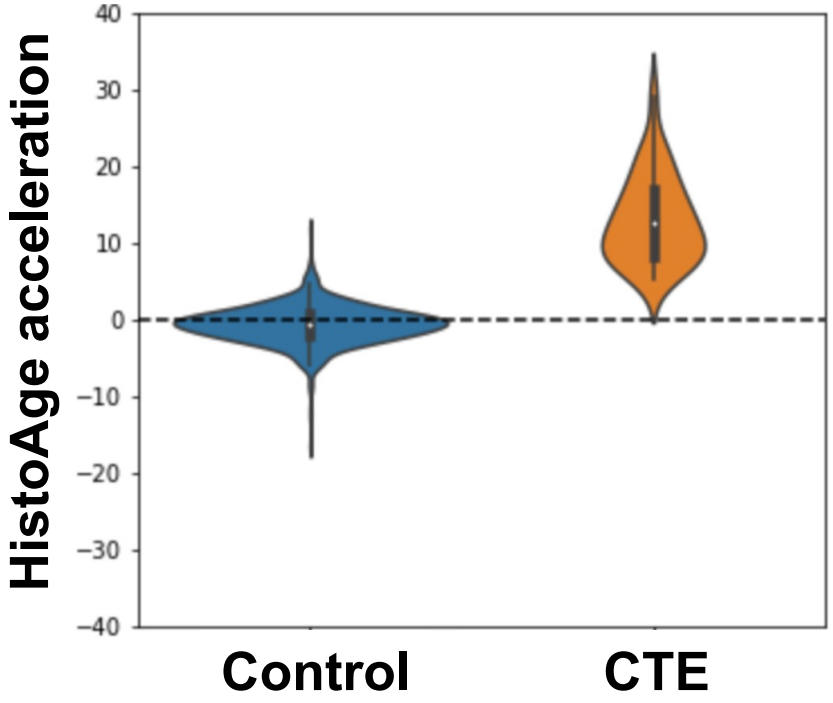


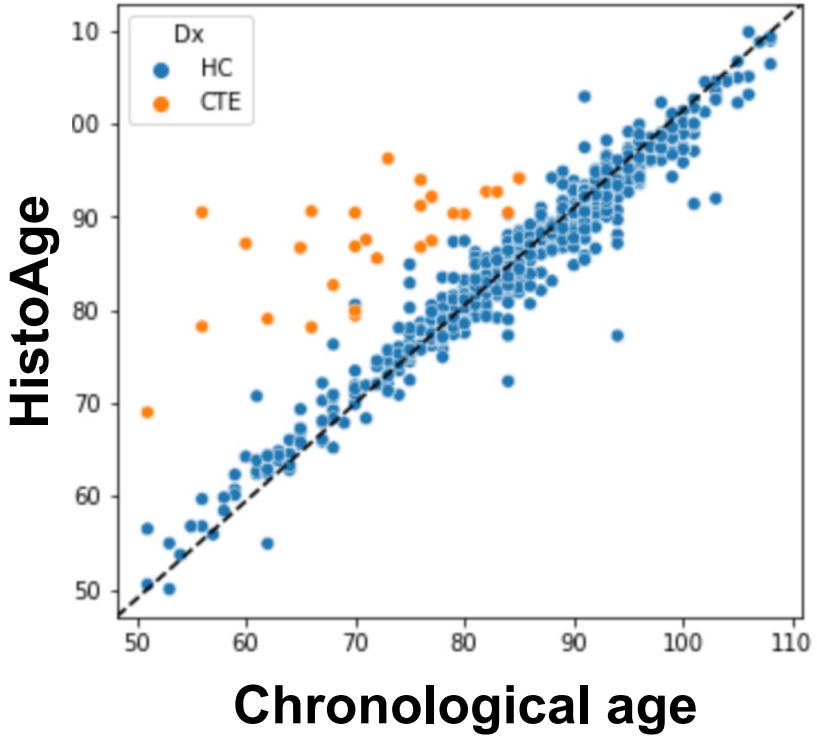


Marx et al., Histopathologic brain age estimation via multiple instance learning. Acta Neuropath. 2023 Oct 10. PMID: 37815677.

HistoAge brain age-acceleration in CTE

Gabe Marx MD





Unpublished

CTE: Controversy?

- Mez, J et al (2017). "Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football." JAMA 318(4): 360-370
  - Of 202 deceased players of American football from a brain donation program, CTE was neuropathologically diagnosed in 177 players across all levels of play (87%)
- Bieniek, KF (2015). "Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank." Acta Neuropathol **130**(6): 877-889.
  - >1,700 brains, CTE in 21/66 contact sport athletes (32%)
  - 0/165 with CTE in controls without brain trauma or contact sports
  - 0/33 brains with CTE with a single TBI

Level of play	CTE positive	(Percent)
Professional	110 of 111	99%
College football	48 of 53	91%
High school football	3 of 14	21%

Exposure	CTE Present	CTE Absent	Total
Contact Sports	21	45	66
No Contact Sports	0	198	198
Total	21	243	264

Strong evidence linking contact sports to CTE!

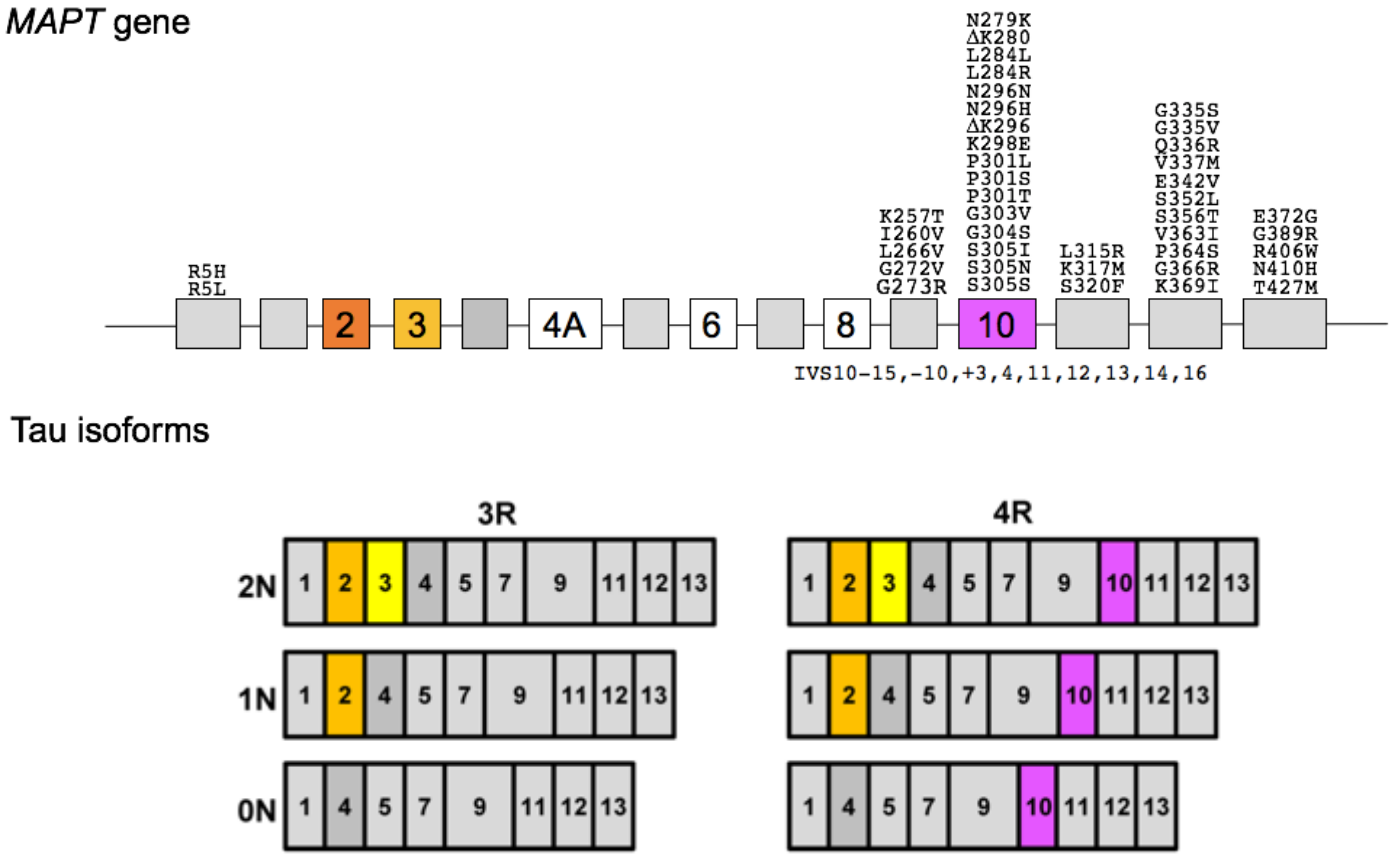
$p = 1.44 \times 10^{-14}$

Bradford Hill criteria for causation

- ✓**Strength:** The larger the association, the more likely it is causal
- ✓**Consistency**: Reproducibility in different persons/places/samples strengthens the likelihood of an effect
- ✓**Specificity**: Causation likely if there is a very specific population and no other likely explanation. The more specific, the more likely
- ✓**Temporality**: The cause must occur before the effect
- ✓**Biological gradient**: Greater exposure leads to greater incidence of the effect
- ✓**Plausibility**: A plausible mechanism between cause and effect is helpful
- ✓**Coherence**: Coherence between epidemiological and laboratory findings increases the likelihood of an effect
- ✓**Experiment**: Occasionally it is possible to appeal to experimental evidence
- ✓**Analogy**: The effect of similar factors may be considered

Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med. 1965;58:295-300
Nowinski et al., Applying the Bradford Hill Criteria for Causation to Repetitive Head Impacts and Chronic Traumatic Encephalopathy. Front Neurol. 2022 Jul 22;13:938163

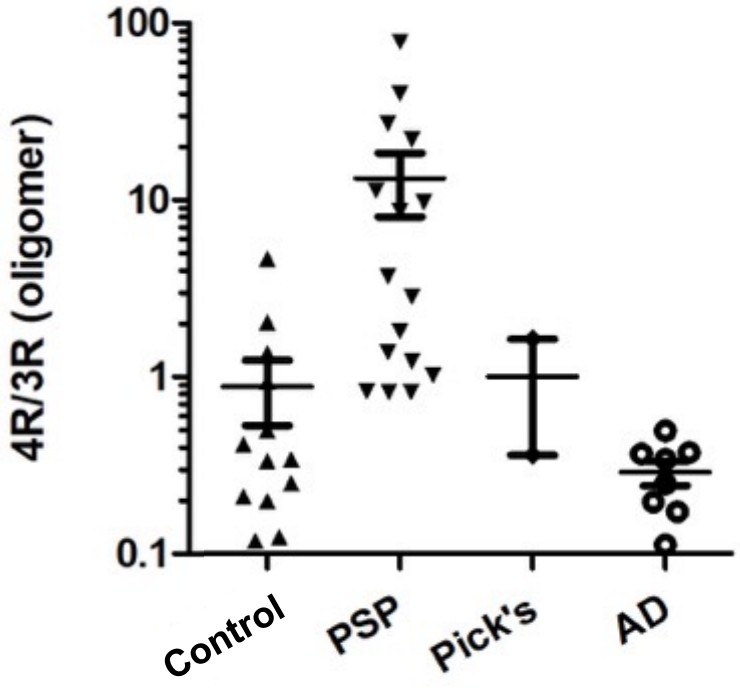
CTE: tau isoforms

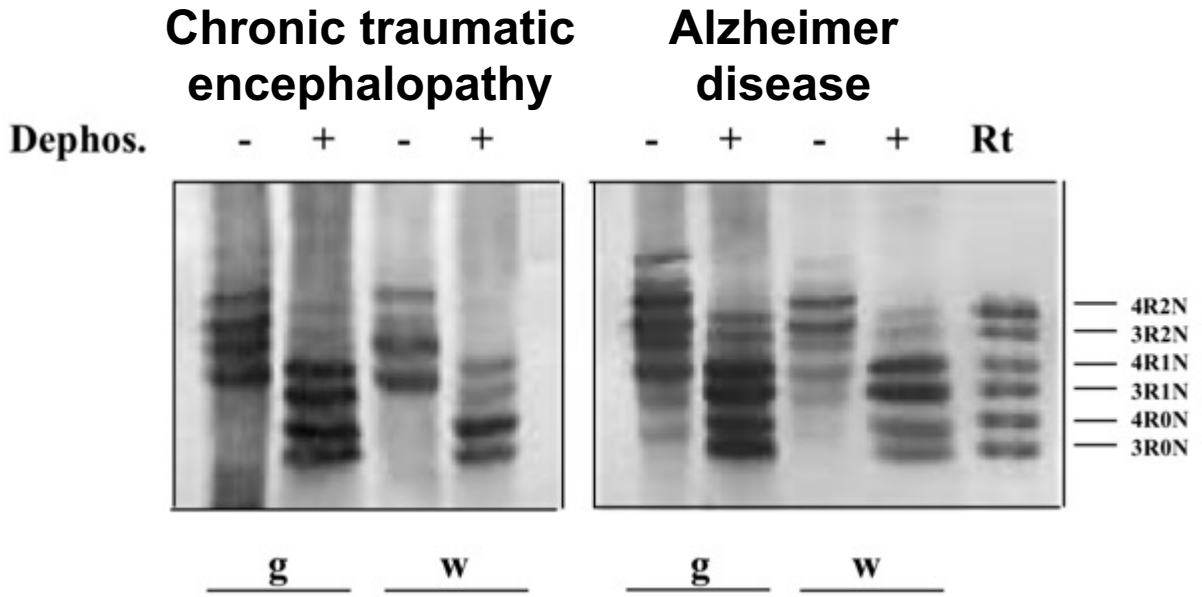


- *MAPT* mutation causes frontotemporal lobar degeneration
- Coding region mutations influence microtubule binding and aggregation
- Mutation near exon 10 influence alternative splicing and tau isoform ratio

Hutton et al. 1998. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* 393:702-705.

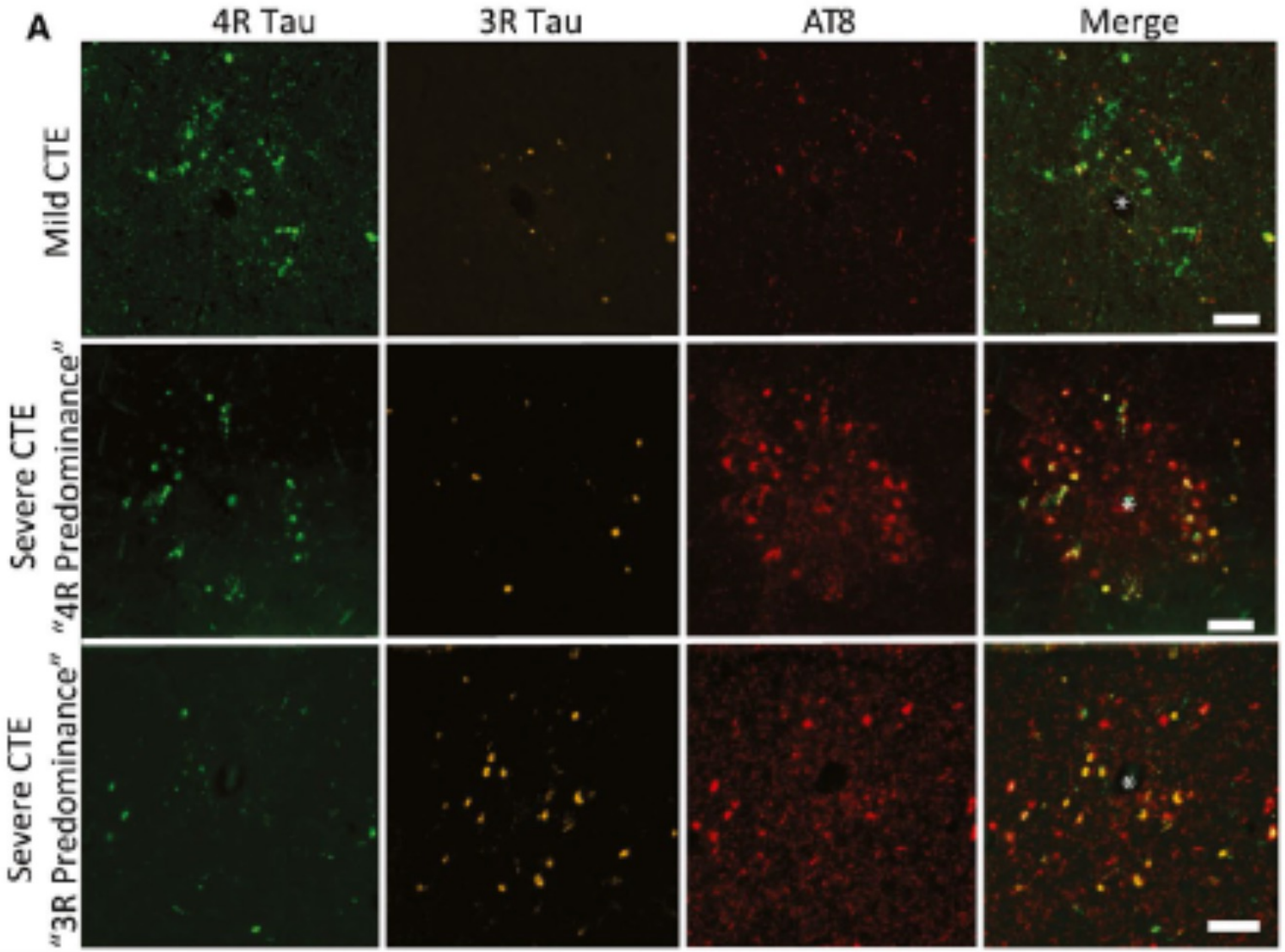
CTE: tau isoforms

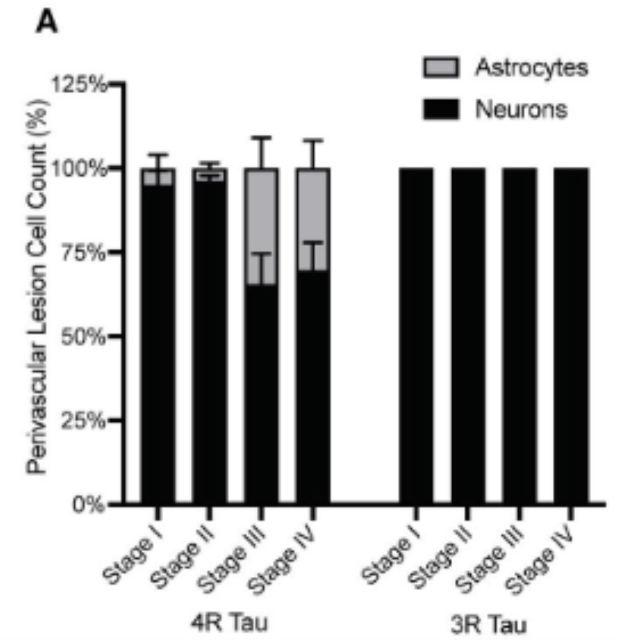


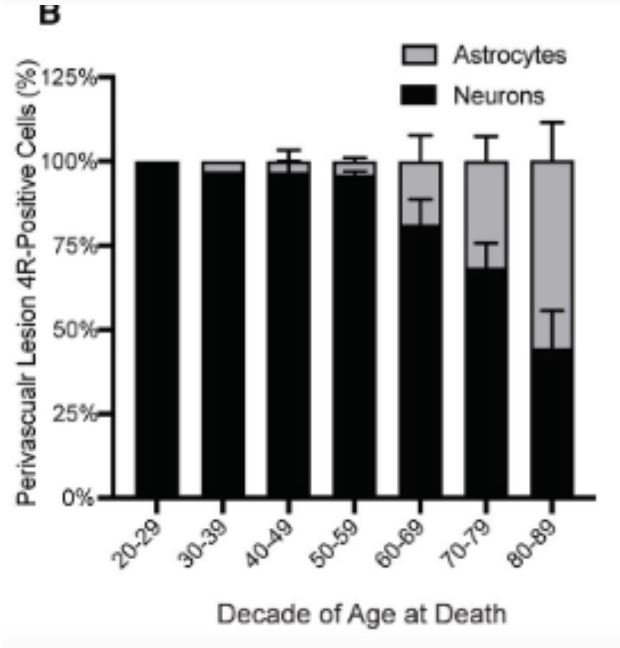


Schmidt, M. L., V. Zhukareva, K. L. Newell, V. M. Lee and J. Q. Trojanowski (2001). "Tau isoform profile and phosphorylation state in dementia pugilistica recapitulate Alzheimer's disease." Acta Neuropathologica **101**(5): 518-524.

CTE: tau isoforms

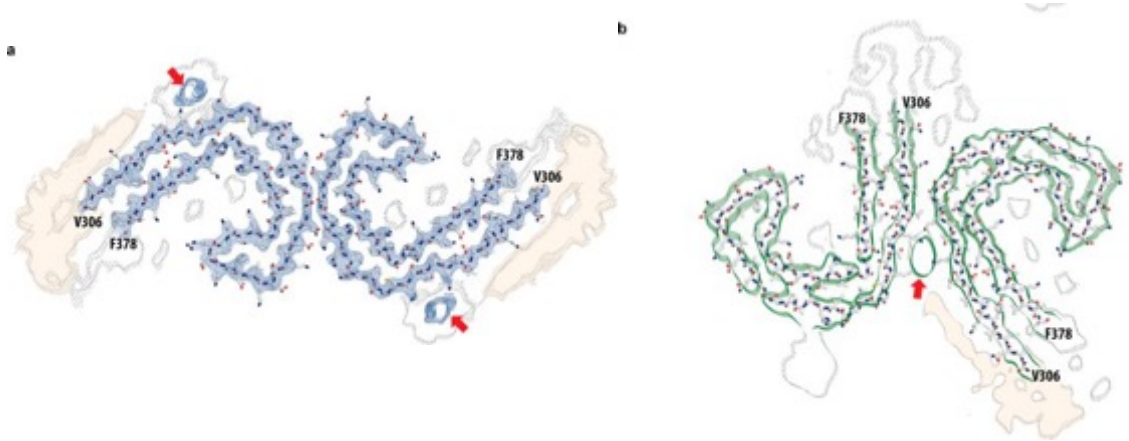




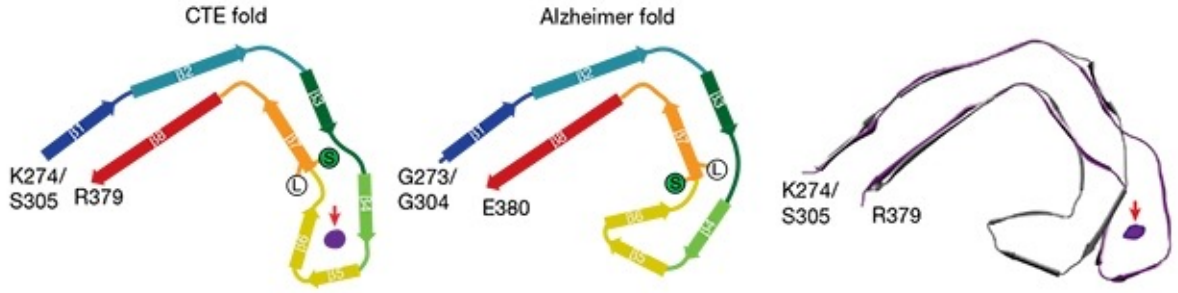


Cherry et al. Evolution of neuronal and glial tau isoforms in chronic traumatic encephalopathy. Brain Pathol. 2020 Sep;30(5):913-925

CTE: tau ultrastructure



Fitzpatrick, A. W. P., B. Falcon, S. He, A. G. Murzin, G. Murshudov, H. J. Garringer, R. A. Crowther, B. Ghetti, M. Goedert and S. H. W. Scheres (2017). "Cryo-EM structures of tau filaments from Alzheimer's disease." Nature **547**(7662): 185-190.



Falcon, B., J. Zivanov, W. Zhang, A. G. Murzin, H. J. Garringer, R. Vidal, R. A. Crowther, K. L. Newell, B. Ghetti, M. Goedert and S. H. W. Scheres (2019). "Novel tau filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules." Nature.

THANKS!