Dementia after Traumatic Brain Injury:
What is the Pathology

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A Case Report

- A 46 year old man, flag military officer
- Graduate of Service Academy
- Master's degree Physics; Business courses Harvard
- 1 prior TBI c brief LOC from boxing in college
- No FH of dementia, TBI, neurologic or psych disease

Kenney et al, *J Neuropath Exp Neurol* 2017

TBI at Age 46

- While sitting in a parked car, broadsided by a truck traveling ~45 mph
- + LOC at scene.
- Examination:
  - Agitated and combative. GCS 12 (4E 5M 3V),
  - Zygomatic fracture, myocardial contusion
- Witnessed generalized tonic clonic seizure in ED,
- Head CT scan:
  - Intracranial Normal- No intracerebral hemorrhage, shift or contusion
  - Multiple facial fractures

Kenney et al, *J Neuropath Exp Neurol* 2017

Hospital Course

- Transferred to ICU and “critical” for 3 days
- Hospitalized for 12 days with surgery for facial fractures and hyperbaric oxygen therapy for eye trauma
- Discharged home for convalescent leave with physical therapy and neurocognitive rehab
- Post-traumatic amnesia 18 days

Kenney et al, *J Neuropath Exp Neurol* 2017

Military Medical Board
1 month after Injury

- Residual L optic neuropathy with APD, L VI palsy
- Decreased short term memory
  - Recall 1/4 objects at 5 minutes, name current president only, unable to define the word “island”, 4 animals in 1 minute
- MRI:
  - 8 mm bifrontal extra-axial fluid collections w/o mass effect;
  - increased signal intensity in the left periventricular white matter (occipital horn)
- Phenytoin changed to phenobarbital
- EEG: no focal or paroxysmal changes
- Placed on limited duty for 6 months

Kenney et al, *J Neuropath Exp Neurol* 2017

Military Medical Board
2 - 16 months after Injury

- Normal mental status exam;
- Subjective memory complaints
- Neuropsychological testing:
  - Mild deficits in digit symbol test, Halstead, reading comprehension (12th %tile)
  - Resolve by 16 months
- Assigned limited duty because of L abducens and single post-traumatic seizure

Kenney et al, *J Neuropath Exp Neurol* 2017

Military Medical Board
21 months after Injury (age 48)

Frank Benson (UCLA Behavioral Neurology Unit):

- Subjective word-finding difficulties; possible irritability
- Normal sleep, appetite and energy; no depression, headache, seizure, vertigo, tinnitus
- Neurological Exam: L VI, mild difficulty copying 3-D figures, Digit span (7 forward, 4 back), normal QMSE

Kenney et al, *J Neuropath Exp Neurol* 2017

Military Medical Board
21 months after Injury (age 48)

Frank Benson (UCLA Behavioral Neurology Unit):

- "Performed excellently on series of tests difficult for individuals with frontal lobe damage."
- "Recovery far better than would be anticipated and can be said to have returned to normal"
- Assessment: "Operating well WNL; greatest problem patient's own concern about his ability to cope in periods of extreme stress"
- Fit for full duty without restrictions

Kenney et al, *J Neuropath Exp Neurol* 2017

Military Medical Board
4.5 years after Injury (age 51)

- Pt contemplating retirement from active duty
- On non-verbal and non-visual learning task, performed worse than on earlier testing; general memory and incidental memory markedly impaired:

	7 mos p TBI	1 year p TBI	4.5 years p TBI
Verbal IQ	115	118	118
Performance IQ	117	111	**108**
Full-scale IQ	116	116	113

Kenney et al, *J Neuropath Exp Neurol* 2017

Military Medical Board
4.5 years after Injury (age 51)

- Neuropsych testing “significant deficits in bilateral fine motor slowing and bilateral sensory motor signs consistent with mild to mildly moderate global cognitive impairment”
- Medically retired with 60% VA service connected disability
  - 30% for nervous condition and memory impairment,
  - 10% for post-traumatic seizure
  - 20% for facial Fx, L abducens palsy and optic neuropathy

Kenney et al, *J Neuropath Exp Neurol* 2017

Follow-up after Retirement

7.5 years p TBI (age 54)

- No complaints, working full time as financial advisor

11.5 years p TBI (age 58)

- c/o occasional short term memory loss (denies forgetting directions, important dates or phone numbers or getting lost)
- MMSE 30/30

12.5 years p TBI (age 59)

- Difficulty with name recall and short term memory (forgets where parked car)
- c/o fatigue
- Retires from civilian employment as financial advisor

Kenney et al, *J Neuropath Exp Neurol* 2017

Follow-up after Retirement

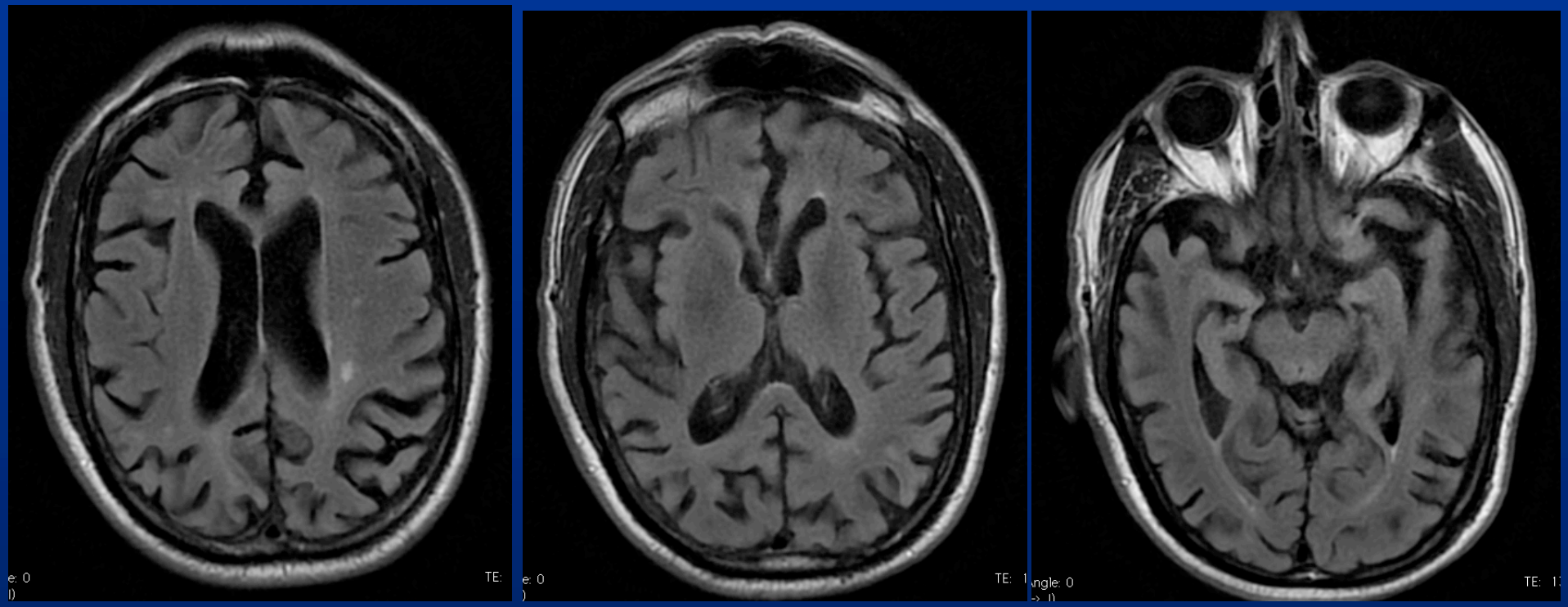
12.5 years p TBI (age 59):

- Neuropsych testing: “Declining performance is not consistent with expected pattern of cognitive recovery and suggests the possibility of an early dementing process”

	7 mos p TBI	1 year p TBI	4.5 years p TBI	12.5 yrs p TBI
Verbal IQ	115	118	118	117
Performance IQ	117	111	**108**	**99**
Full-scale IQ	116	116	113	**108**

Kenney et al, *J Neuropath Exp Neurol* 2017

MRIs (21 years after TBI, age 67)



"Global volume loss. Multiple foci of hyperintense T2 signal in subcortical and periventricular white matter. No significant interval change compared to MRI 2 years prior."

Kenney et al, *J Neuropath Exp Neurol* 2017

Follow-up after Retirement

13 years p TBI (age 60)

- Donepezil begun for cognitive decline,
- Depression likely secondary to cognitive disorder; Sertraline increased

Kenney et al, *J Neuropath Exp Neurol* 2017

Follow-up after Retirement

13.5 years p TBI (age 60)

- c/o increased irritability, sadness, decreased energy, hypersomnolence, guilt, decreased exercise tolerance; stable memory problems, frustration with performance abilities
- Add Effexor XR.

16.5 years p TBI (age 63)

- “Frontotemporal dementia due to TBI”
- Mood disorder due to TBI

Kenney et al, *J Neuropath Exp Neurol* 2017

Follow-up after Retirement

17 years p TBI (age 64)

- Memory 0/3 at 5 minutes, problems with complex 2 step command, trouble copying figures, abnormal clock draw
- MMSE 20/30
- Spells: hyperventilation with spastic arm motion, postictal confusion with return to normal over 1-2 hours; recur every 3-4 months even with AEDs
- Neuropsych testing- deficits in all domains of cognition but particularly memory;
- most c/w cortical dementia (AD), but can't r/o FTD

Kenney et al, *J Neuropath Exp Neurol* 2017

Follow-up after Retirement

20 years p TBI (age 67)

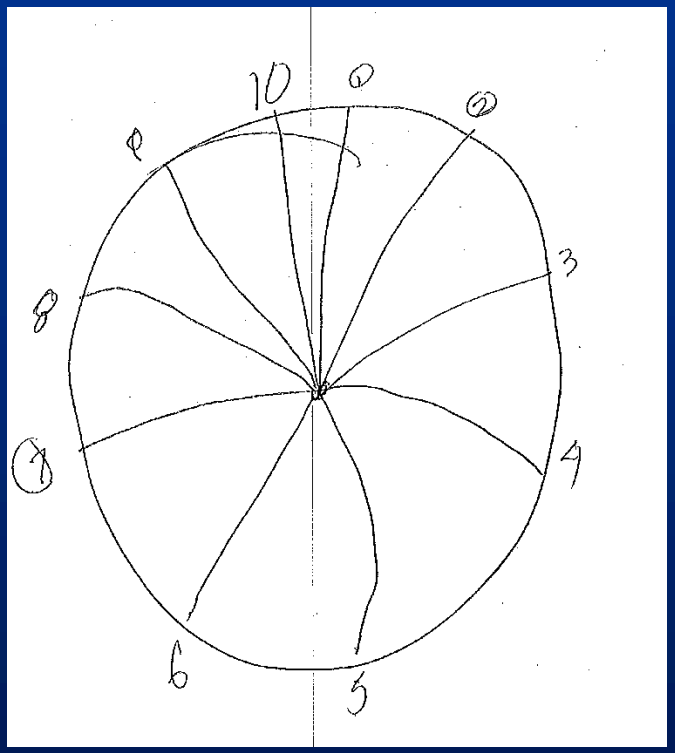
- MMSE 11/30; Second clock draw
- Spells: staring, listlessness; Increased frequency and duration of spells; EEG not epileptiform
- Recent increased agitation; patient has no memory for public behavioral outbursts, including striking companion and police being called
- Citalopram added for behavioral outbursts
- Patient moved and care for in SNF; died at age 72 severely demented 25 years after his TBI

Kenney et al, *J Neuropath Exp Neurol* 2017

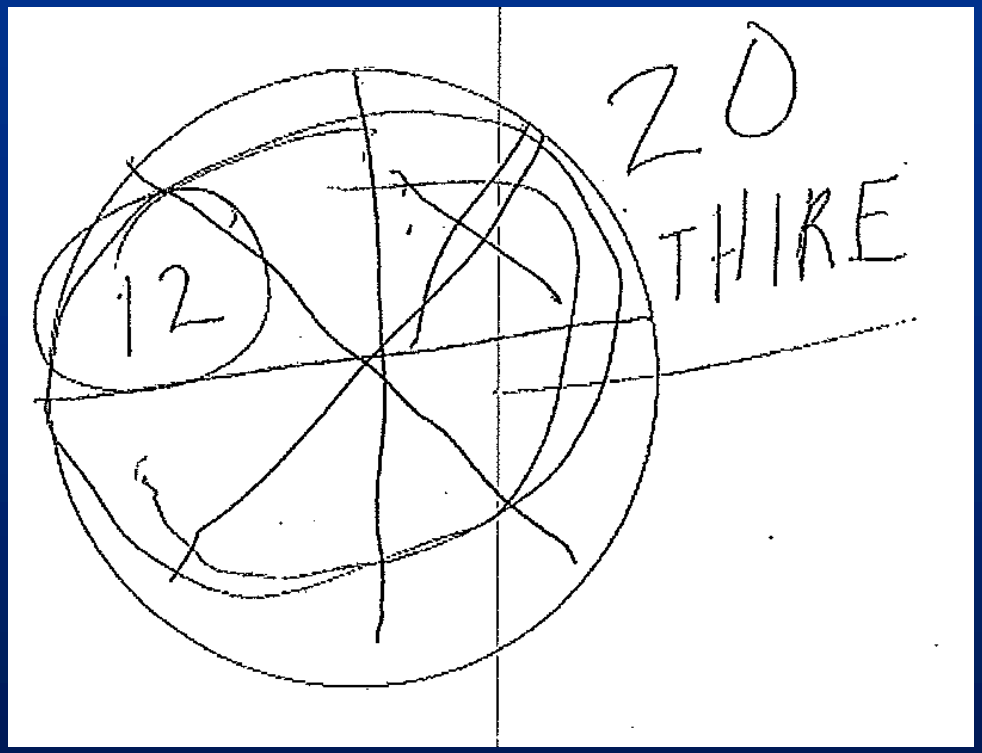
Serial Clock Drawing

Serial clock draws (Age, Years after TBI, MMSE):

64 yo, 17 yrs, 20/30



67, 20 yrs, 11/30



Kenney et al, *J Neuropath Exp Neurol* 2017

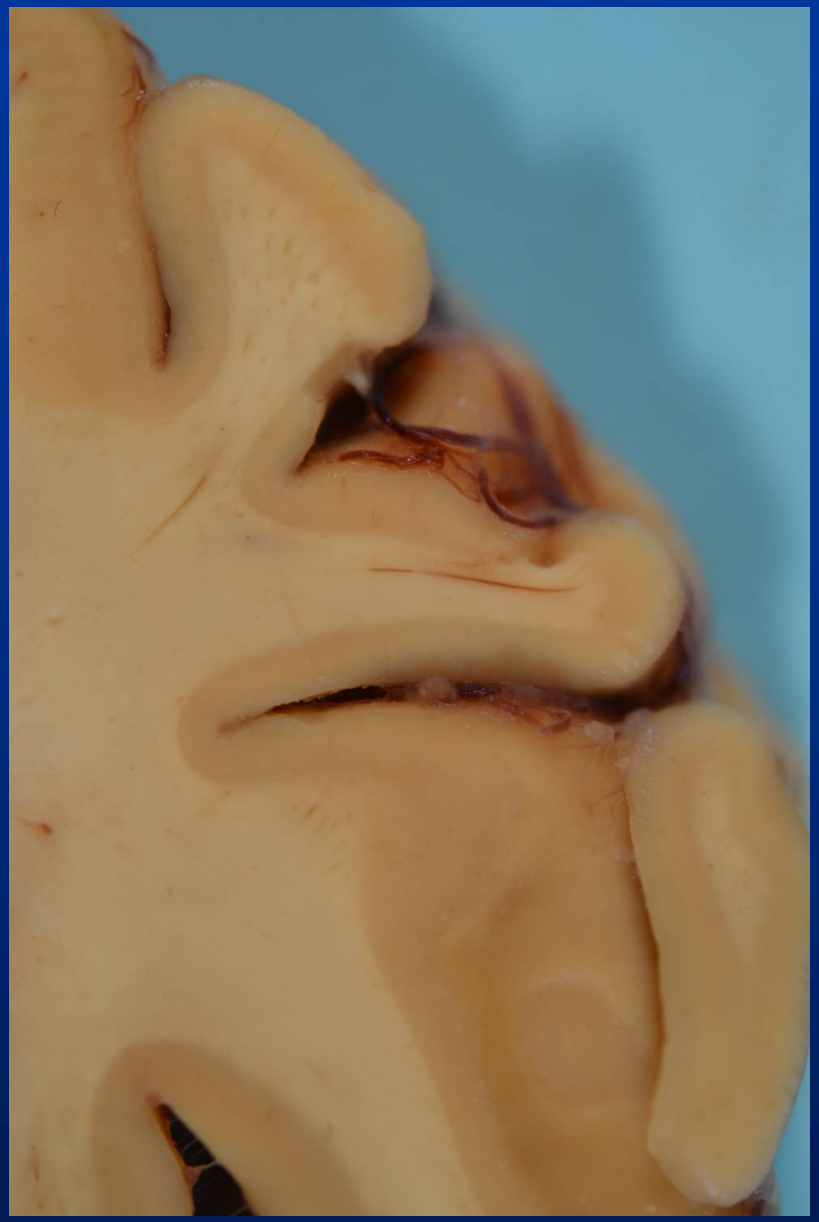
Summary of Case

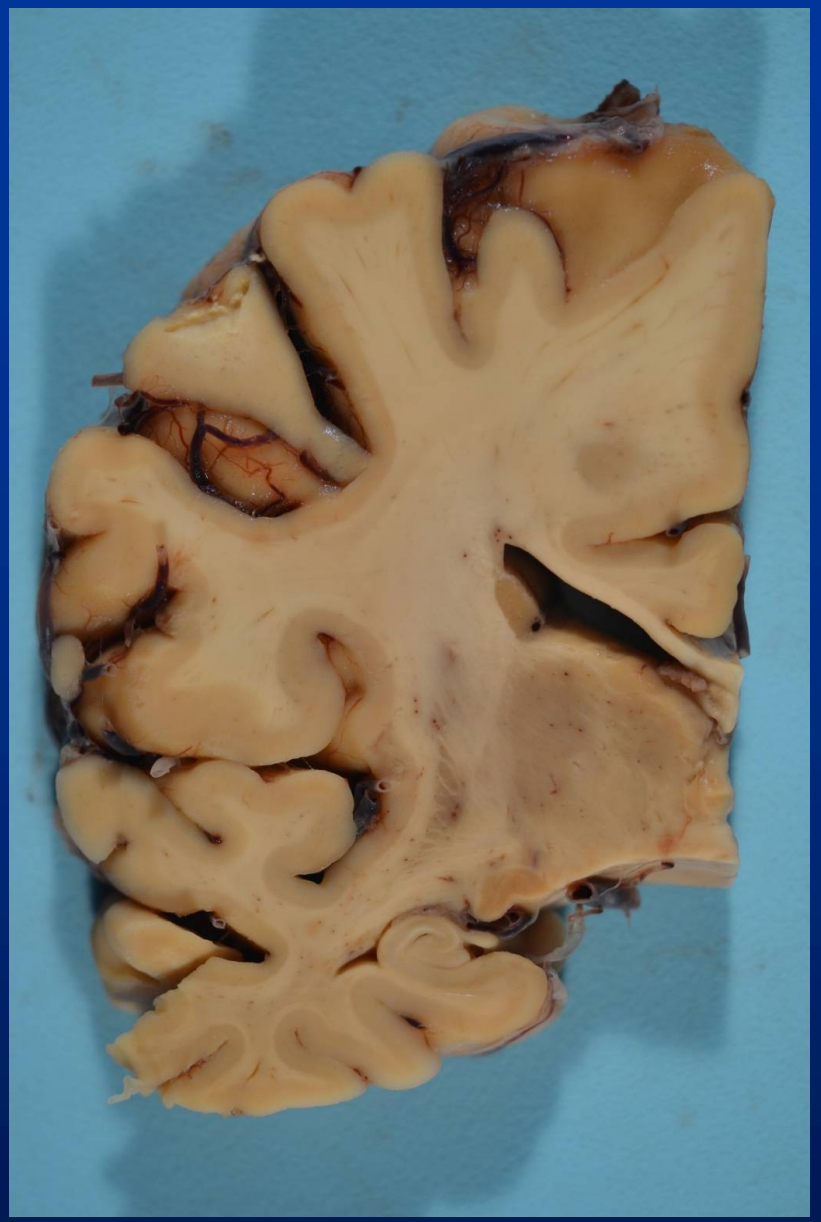
- Moderate TBI in mid-life
- Gratifying (but perhaps incomplete) recovery over subsequent 2 years. Able to return to full duty as Flag Officer
- Progressive decline starting approximately 10 years after TBI
  - Behavioral and affective features prominent
  - Performance IQ declines faster than Verbal IQ
  - Features of Fronto-temporal Dementia
- Death within 12 years of dementia diagnosis (25 years after TBI)

Kenney et al, *J Neuropath Exp Neurol* 2017

Kenney et al, *J Neuropath Exp Neurol* 2017

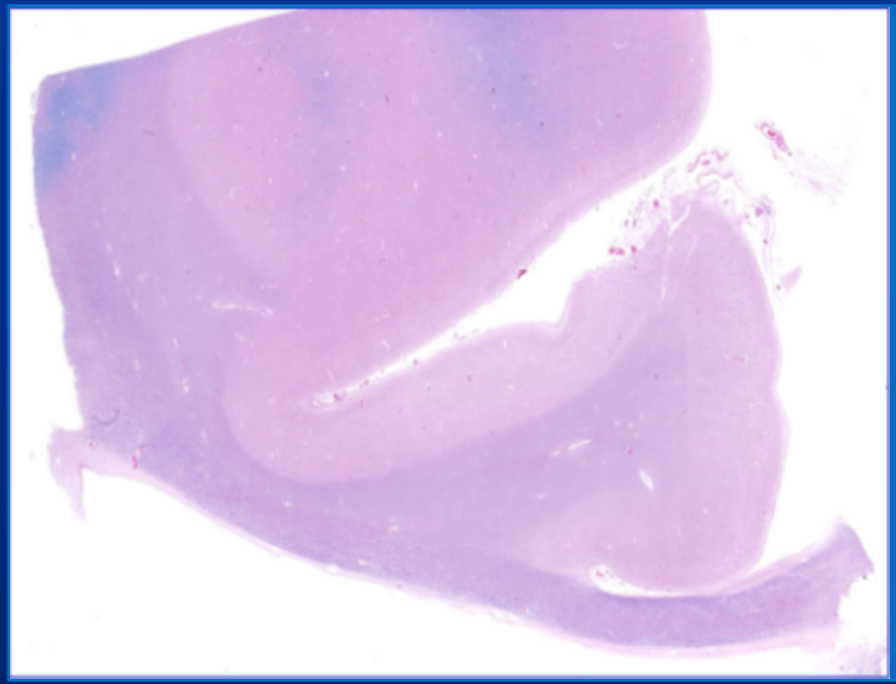
Brain Weight 930 gm.



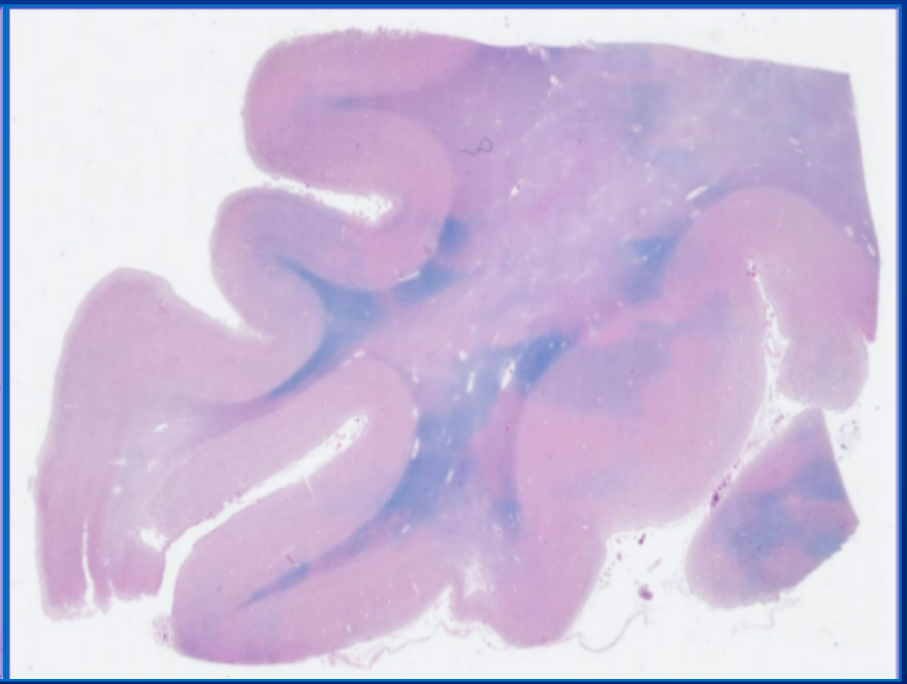


Kenney et al, *J Neuropath Exp Neurol* 2017

Luxol Fast Blue-Hematoxylin Stain



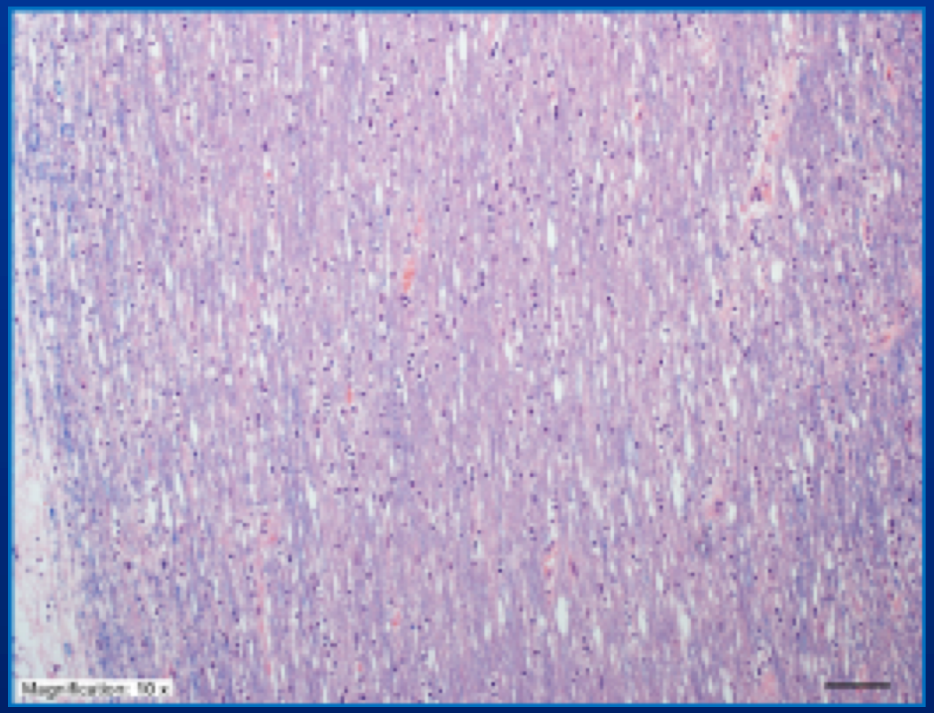
Left Splenium



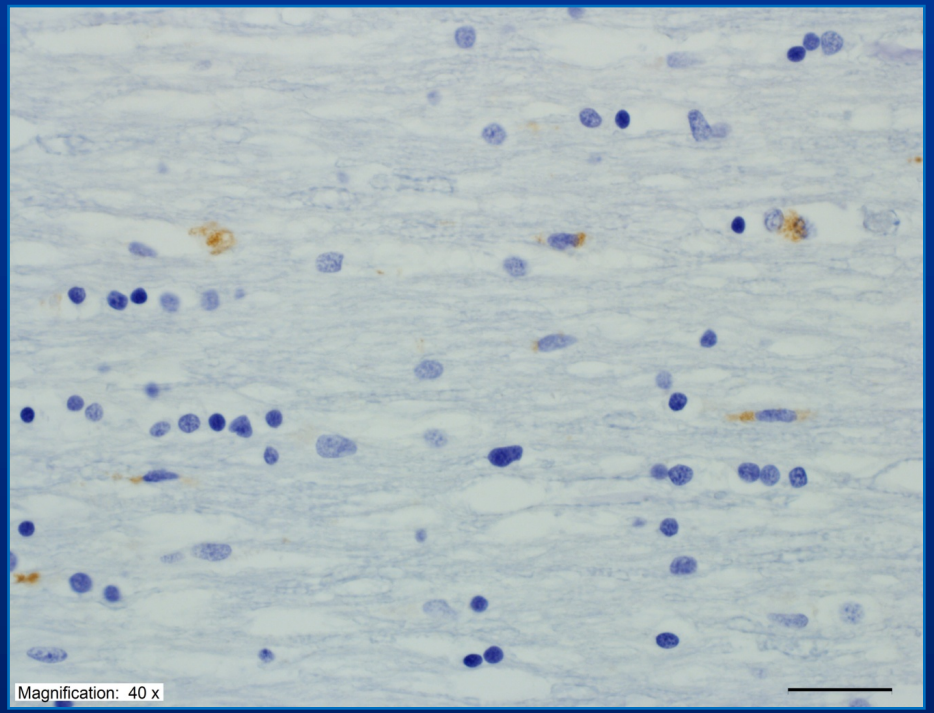
Left Superior Temporal Cortex

Kenney et al, *J Neuropath Exp Neurol* 2017

Posterior Corpus Callosum



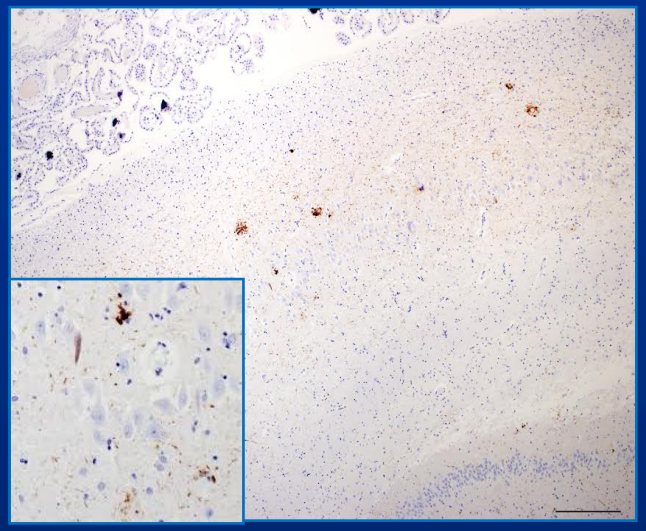
LFB-H Stain



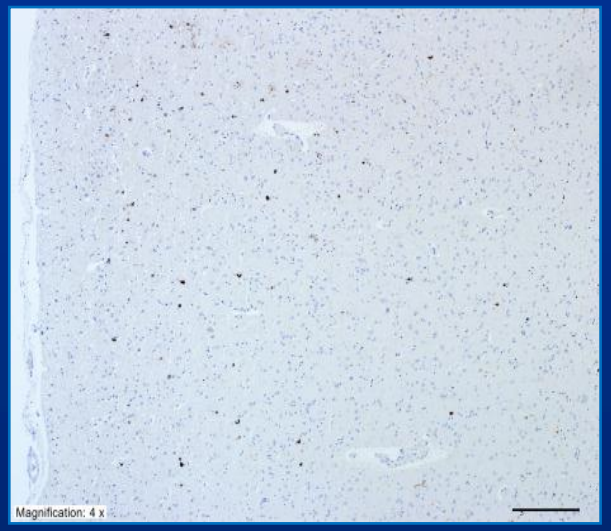
CD 68 IHC (microglia)

Kenney et al, *J Neuropath Exp Neurol* 2017

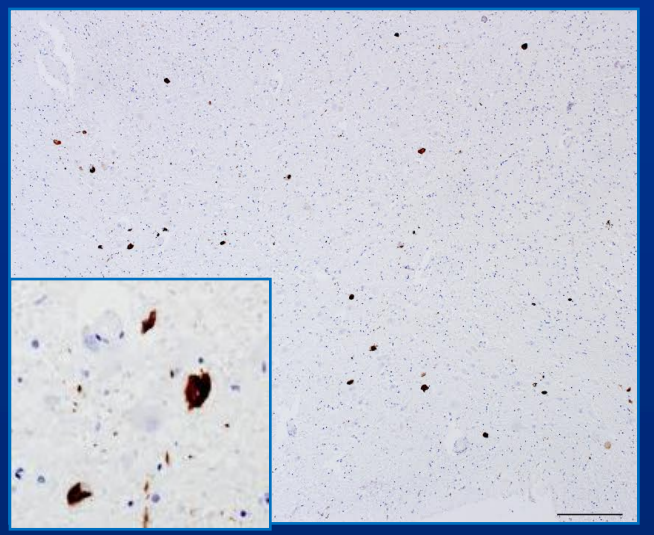
Tau IHC (AT8)



Hippocampus, CA1



Insular Cortex



Mamillary Body

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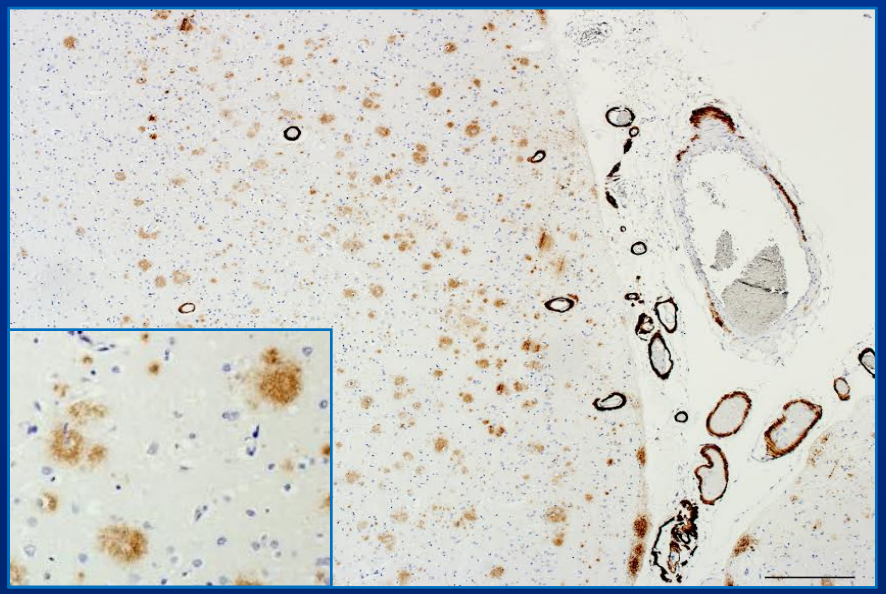
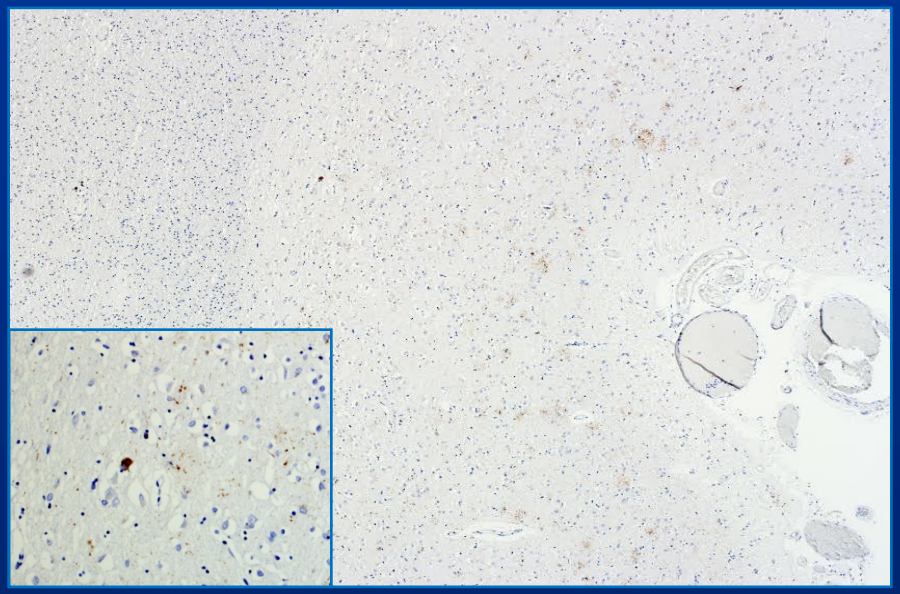
β-amyloid IHC (4G8)



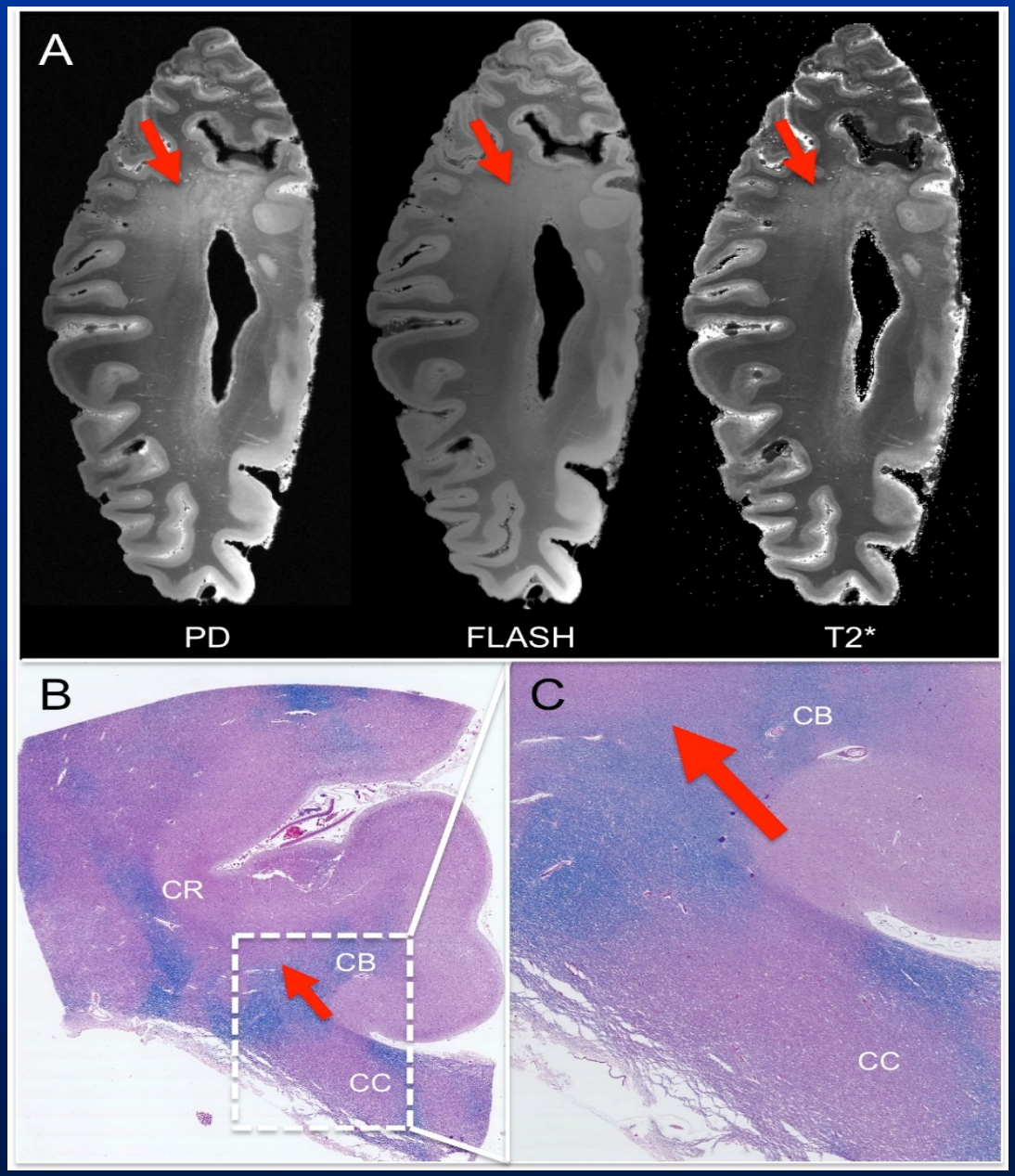
Superior Middle Temporal



Superior Middle Temporal

Kenney et al, *J Neuropath Exp Neurol* 2017

Ex-vivo MRI Histopathological Correlation

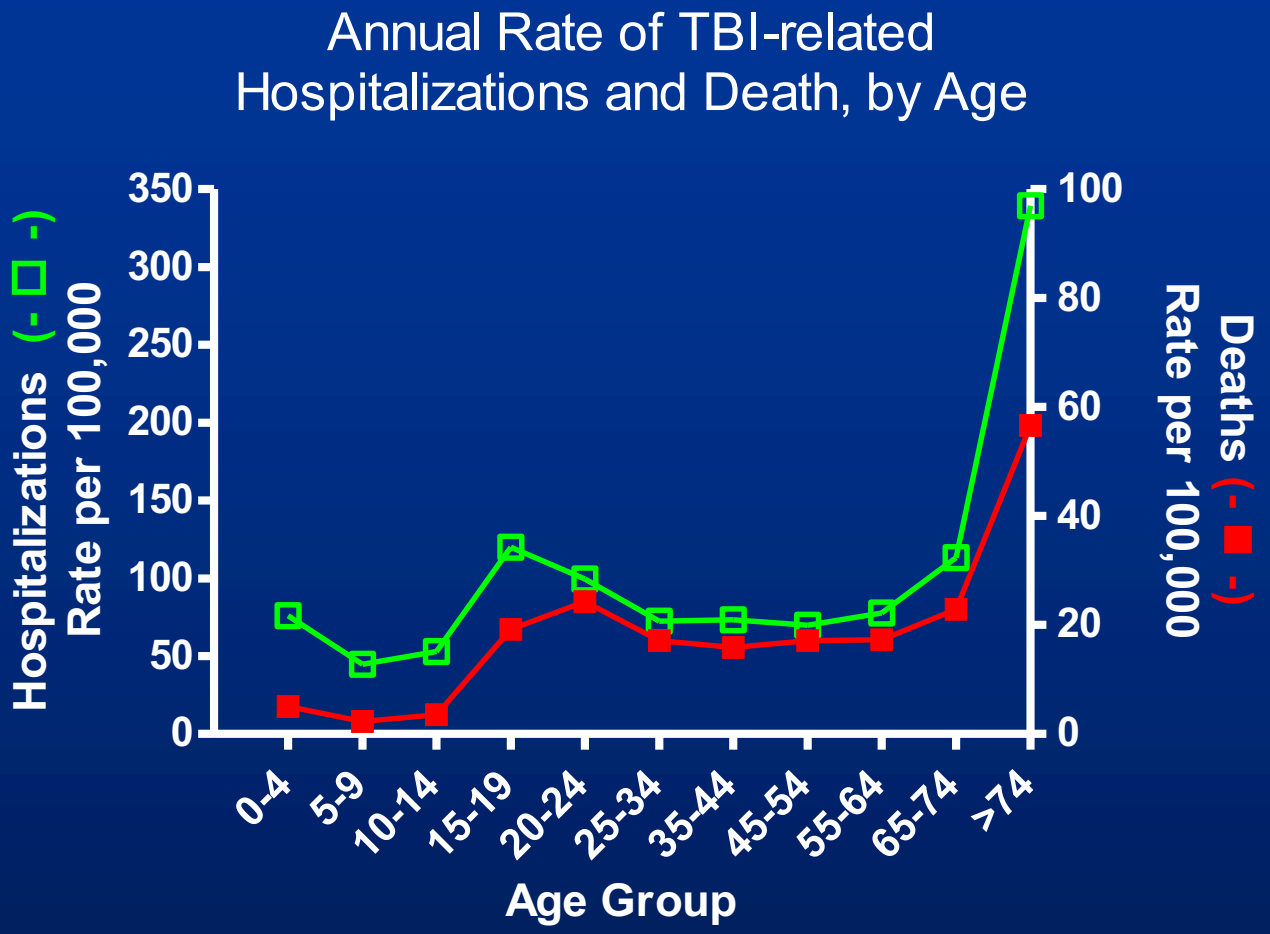


Kenney et al, *J Neuropath Exp Neurol* 2017

Outline of Presentation

- Epidemiology of TBI
  - With emphasis on TBI in the elderly
- Epidemiologic studies on risk of dementia after TBI
- Pathologic studies on post-TBI dementia
  - After multiple repetitive mild TBIs
  - After single moderate to severe TBI
- Analysis of NACC Database
- Military Retirement Homes Study

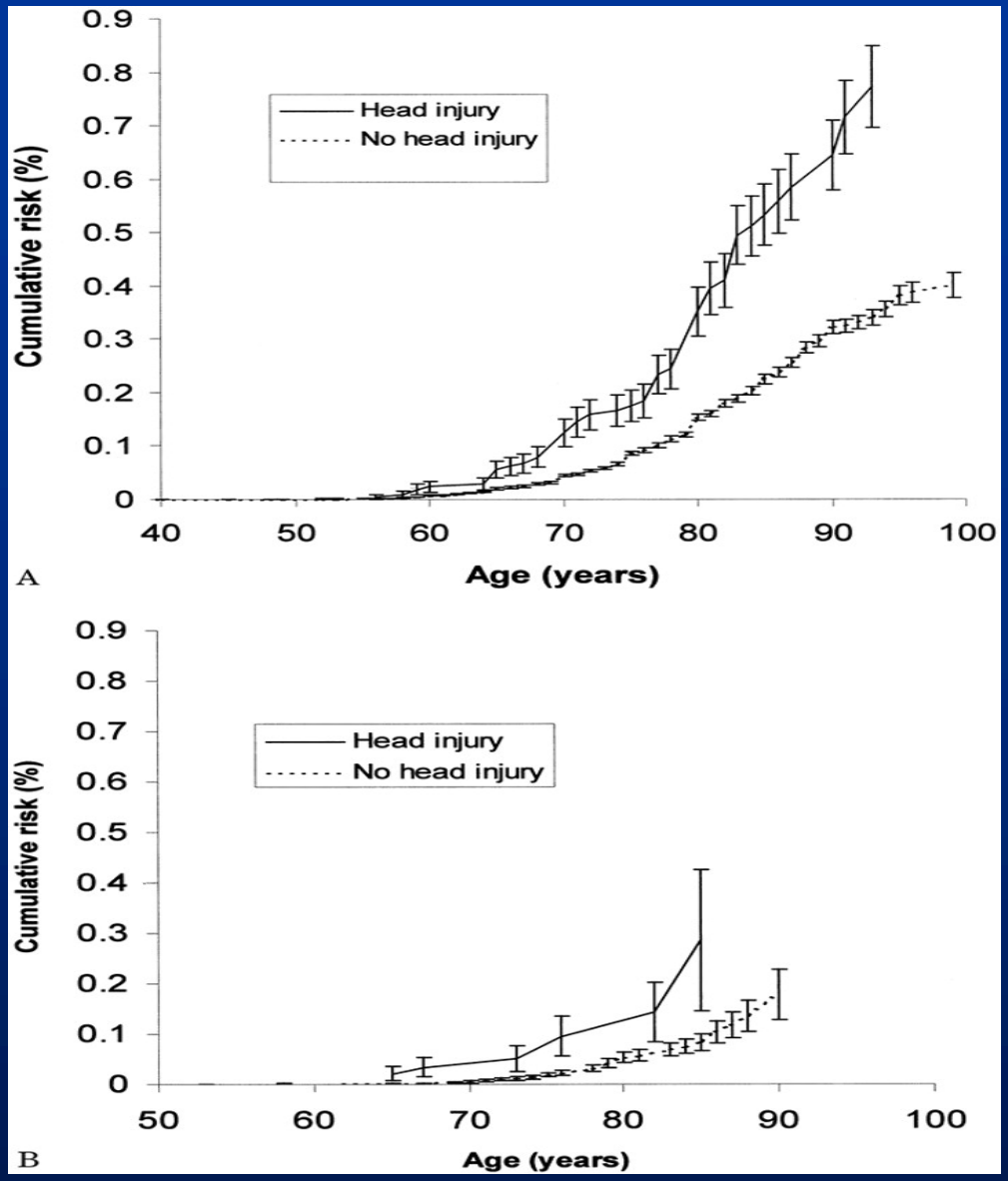
Epidemiology of TBI



Division of Injury Response, National Center for Injury Prevention and Control
Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2010

MIRAGE Study (n=14,668):

The cumulative risk of AD in relation to TBI among parents and siblings of patients with AD



First-degree relatives

OR 4.0 (95% CI 2.9 - 5.5) for TBI w/ LOC
OR 2.0 (95% CI 1.5 – 2.7) for TBI w/o LOC

Spouses

OR 9.9 (95% CI 6.5 - 15.1) for TBI w/ LOC
OR 3.1 (95% CI 2.3 – 4.0) for TBI w/o LOC

Guo, Z. et al. *Neurology* 2000;54:1316-1323

Population-based cohort study (Taiwan)

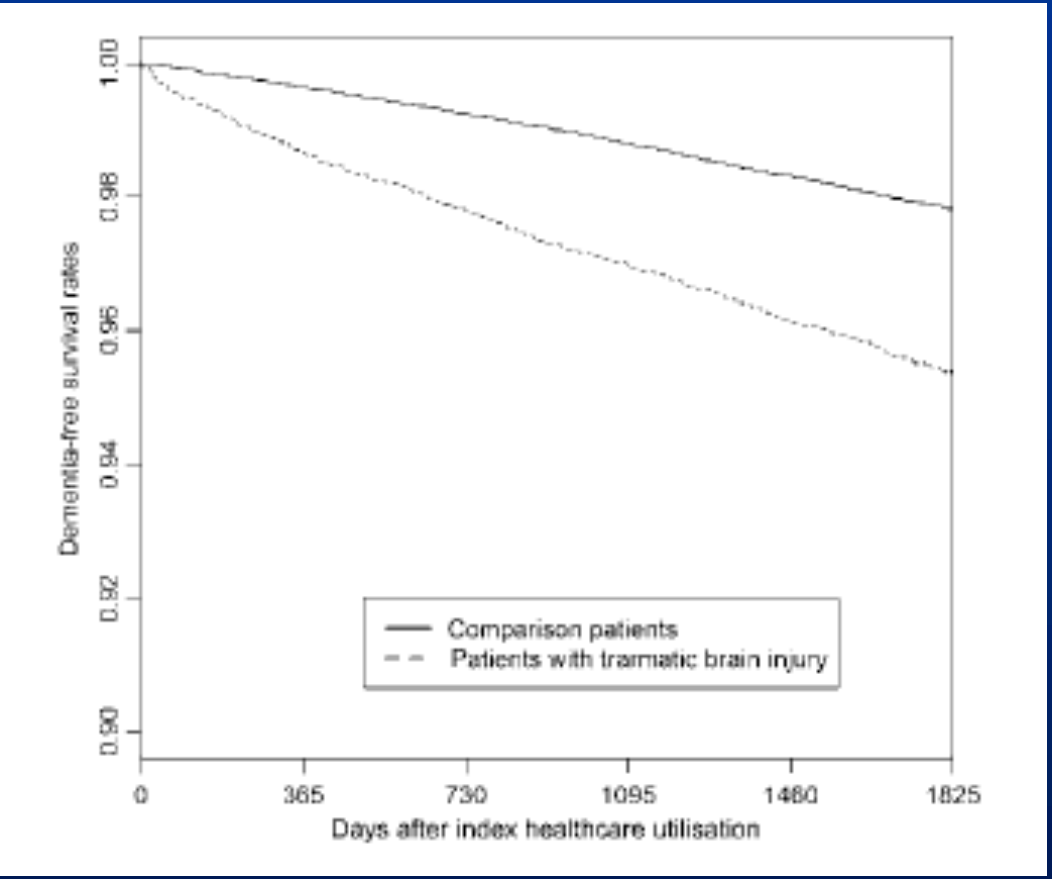
- National Health Insurance Database
  - Detailed longitudinal claims data from 1 million individuals enrolled in Taiwan National Health Insurance Program
  - 44,925 patients receiving ambulatory or inpatient hospital care for TBI between 2000 - 2004
    - Exclude < 15 years of age and ICU admissions
    - Exclude those with diagnosis of dementia
    - 4.5% 4-year incidence
  - 224,625 non-TBI controls (matched for age and gender)
  - Analyze 5 years after index TBI for incident dementia

Wang et al, *JNNP* 2012;83:1180-1185

Population-based cohort study (Taiwan)

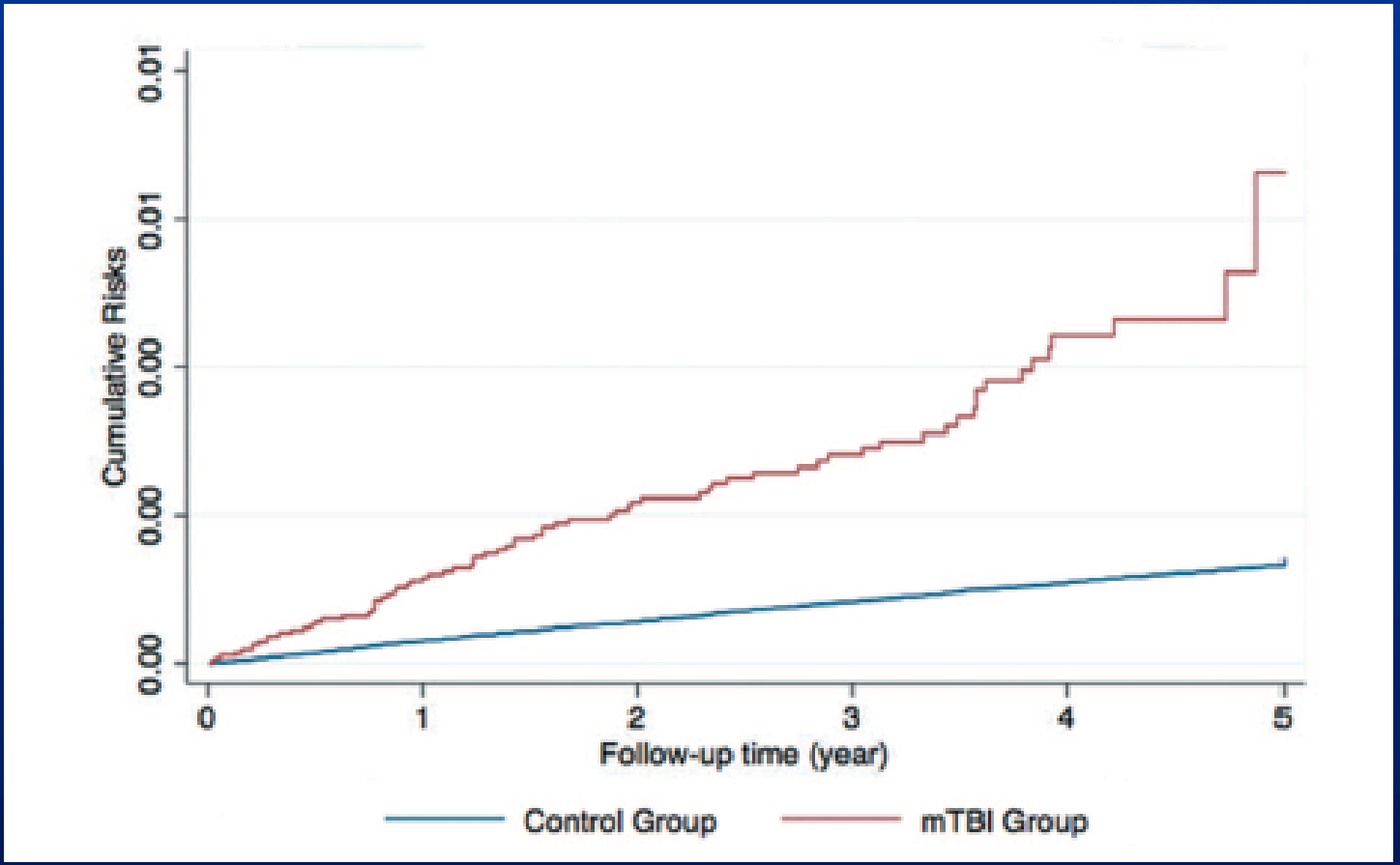
- 1196 (2.6%) TBI patients developed dementia
- vs. 3439 (1.53%) of non-TBI
- Crude HR 2.06 (95% CI 1.93 – 2.20)
- Adjusted* HR 1.68 (95% CI 1.57 – 1.80)

(*Adjusted for stroke, diabetes, hyperlipidemia, hypertension, CAD, heart failure, atrial fibrillation)



Wang et al, *JNNP* 2012;83:1180-1185

Population-based cohort study (Taiwan Study—mTBI only)



Lee et al, *PLoS One 2013* 8(5):e62422

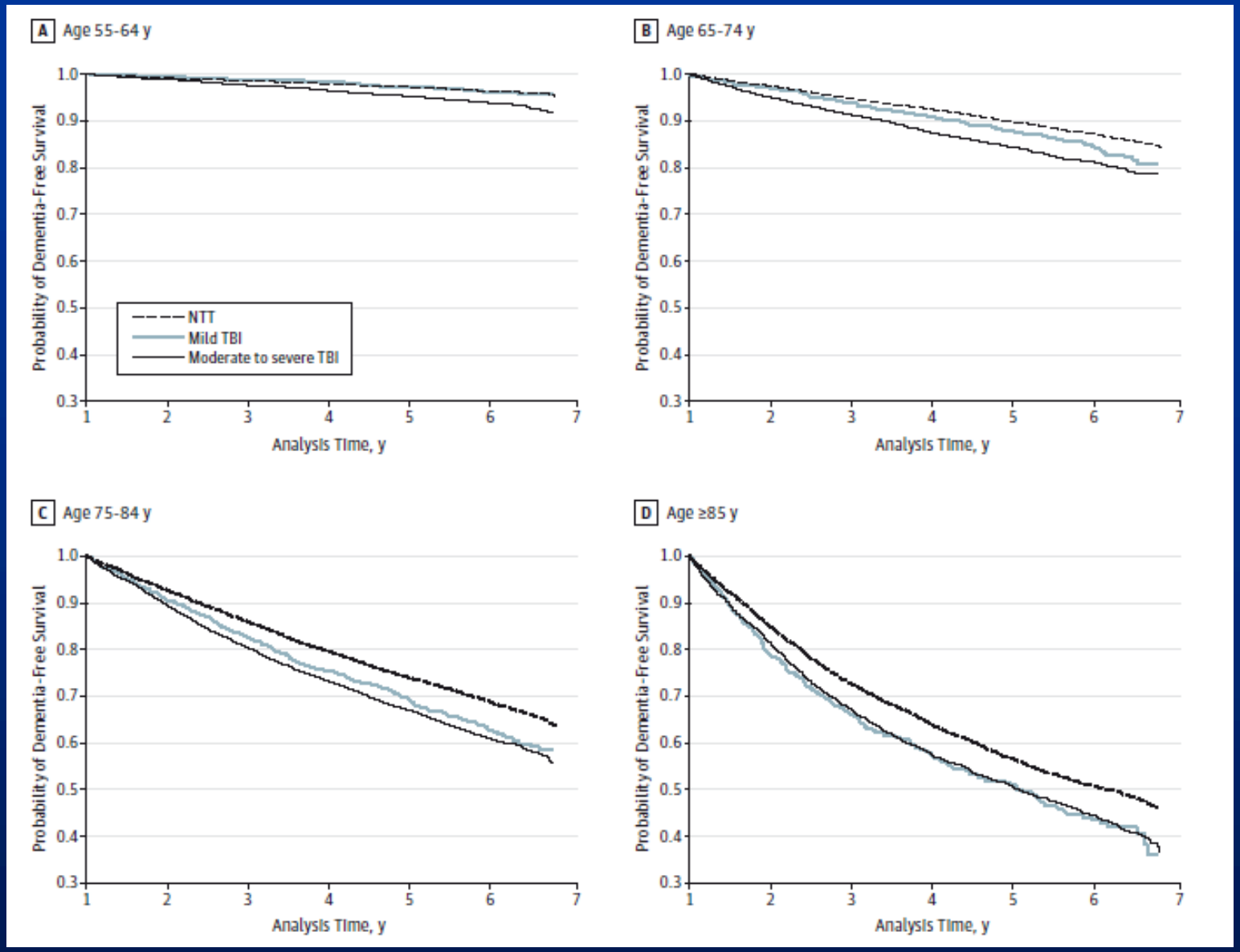
Dementia Risk after TBI vs. Non-Brain Trauma

Table 2. Association Between TBI and Risk of Dementia Stratified by Age and TBI Severity[a]

Patient Group	No. of Patients	HR (95% CI)	*P* Value
Aged 55-64 y (reference NTT)	40 444		
Mild TBI	4670	1.11 (0.80-1.53)	.55
Moderate to severe TBI	10 027	1.72 (1.40-2.10)	<.001
Aged 65-74 y (reference NTT)	27 991		
Mild TBI	2810	1.25 (1.04-1.51)	.02
Moderate to severe TBI	8808	1.46 (1.30-1.64)	<.001
Aged 75-84 y (reference NTT)	29 113		
Mild TBI	2800	1.21 (1.08-1.36)	<.005
Moderate to severe TBI	12 803	1.27 (1.19-1.36)	<.001
Aged ≥85 y (reference NTT)	15 314		
Mild TBI	1443	1.25 (1.09-1.44)	<.005
Moderate to severe TBI	8438	1.14 (1.06-1.24)	<.005

Gardner et al, *JAMA Neurol* 2014;71:1490-1497

Dementia Risk after TBI vs. Non-Brain Trauma



Gardner et al, *JAMA Neurol* 2014;71:1490-1497

Population-based cohort study (Sweden)

- Swedish men conscripted for military service, 1969 – 1986 (n = 811,622)
  - All underwent medical and cognitive evaluations at conscription (age 18.4 ± 0.8 years)
- Linked to Swedish national patient register (launched in 1964)
  - Medical encounters for TBI identified via ICD codes
  - ICD codes for AD, VaD, EtOHlic dementia, dementia of unspecified type
  - Follow-up for 40 years to identify Young Onset Dementia

Nordstrom et al, *Ann Neurol* 2014;75:374-381

Swedish Military Conscripts Study

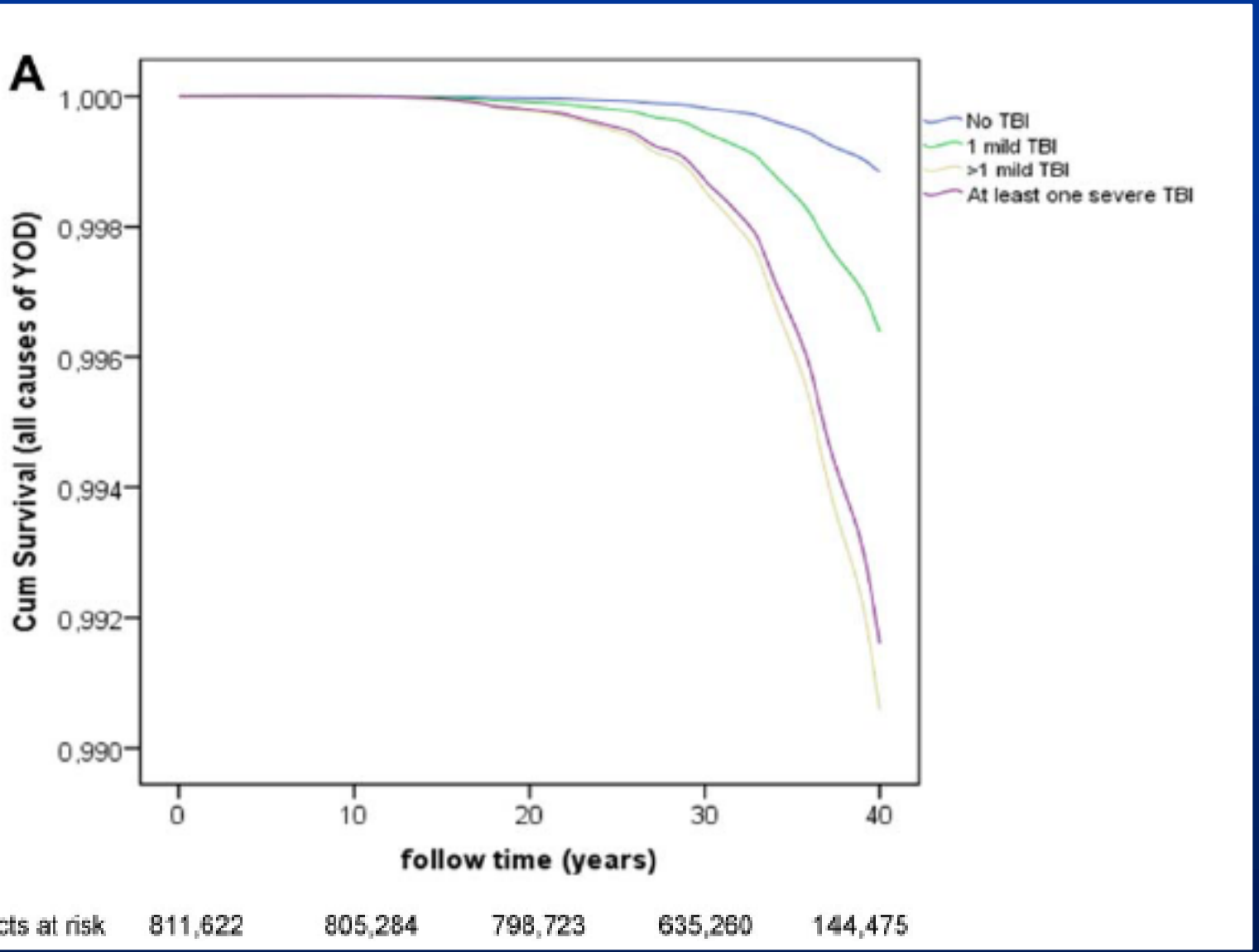
TABLE 2. Associations between TBIs and the Outcome of Dementia

TBI Type	All Cases of Dementia, n = 566			Alzheimer Dementia, n = 177			Other Forms of Dementia,[a] n = 389		
	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI
1 mild TBI, n = 34,698									
Age-adjusted model[b]	63	3.0	2.3–4.0	10	1.5	0.8–2.8	53	3.8	2.8–5.2
Minimally adjusted model[c]	62	1.6	1.2–2.2	10	1.3	0.7–2.5	53	1.7	1.3–2.3
Model adjusted for all confounders[d]	59	1.5	1.1–2.0	8	1.0	0.5–2.0	51	1.7	1.2–2.3
Case–control study[e]	59	1.8	1.2–2.8	8	1.5	0.5–4.1	51	2.1	1.3–3.1
>1 mild TBI, n = 4,569									
Age-adjusted model[b]	20	8.3	5.3–13.1	3	3.9	1.3–12.3	17	10.4	6.3–17.2
Minimally adjusted model[c]	19	2.1	1.3–3.4	3	2.8	0.9–9.1	17	2.0	1.2–3.4
Model adjusted for all confounders[d]	18	1.8	1.1–3.0	3	2.5	0.8–8.1	15	1.7	1.0–2.9
Case–control study[e]	18	2.4	1.4–4.1	3	—		15	2.1	1.2–3.8
1 severe TBI, n = 5,982									
Age-adjusted model[b]	25	7.9	5.2–11.9	1	1.0	0.1–7.1	24	11.4	7.4–17.5
Minimally adjusted model[c]	25	2.9	1.9–4.5	1	0.8	0.1–5.6	24	3.4	2.2–5.3
Model adjusted for all confounders[d]	25	2.3	1.5–3.6	1	0.7	0.1–5.2	24	2.6	1.6–4.1
Case–control study[e]	25	2.9	1.8–4.6	1	—		24	3.0	1.6–5.3

[a]Vascular dementia, alcohol dementia, dementia of unspecified type.
[b]Adjusted for the influence of age, and place and year of conscription.
[c]Adjusted for the variables listed above and overall cognitive function and alcohol intoxication.
[d]Adjusted for the variables listed above and weight, height, knee extension strength, TBI in parents, dementia in parents, income, educational level, systolic blood pressure, drug intoxication, depression, and cerebrovascular disease.
[e]For the case–control study, controls were selected using propensity scores based on all confounders listed above. Every subject with 1 mild TBI was matched with 1 control, and every subject with at least 2 mild TBIs or 1 severe TBI was matched with 9 controls. Hazard ratios are adjusted for propensity scores. No case–control study was performed for Alzheimer dementia in subjects with at least 2 mild TBIs or 1 severe TBI, because the cohort included few such cases.
CI = confidence interval; HR = hazard ratio; TBI = traumatic brain injury.

Nordstrom et al, *Ann Neurol* 2014;75:374-381

Swedish Military Conscripts Study



Nordstrom et al, *Ann Neurol* 2014;75:374-381

Estimate of Population Attributable Risk of Dementia Due to TBI

- Christchurch (New Zealand) Health and Development Study
  - Birth cohort study of 1265 children born in Christchurch in mid-1977
  - Data gathered through regular parental interviews, subject self-report, teacher questionnaires, review of medical and hospital records
  - 1003 completed FU by age 25 (78.3% FU rate)
  - 458 TBI events by age 25
    - 32% prevalence
    - 12% admitted to hospital at least overnight

McKinlay et al, Brain Inj 2008

- Random dialing survey of 2701 residents of Colorado
  - 24% reported one or more TBI with loss of consciousness
  - Of those, reported treatment for most severe TBI:
    - 24% (5.7% of total) were admitted to the hospital at least overnight
    - 38% (8.9% of total) were treated in ED and released
    - 12% (2.9% of total) were seen in doctor's office and released
    - 25% (6% of total) did not seek medical attention

Whiteneck et al, JHTR 2015

Estimate of Population Attributable Risk of Dementia Due to TBI

PAR = p (RR-1) / 1+p(RR-1)

		Relative Risk			
		1.5	**2.0**	**2.5**	**3.0**
p(TBI)	**5%**	2.44%	4.76%	6.98%	9.09%
	10%	4.76%	9.09%	13.04%	16.67%
	15%	6.98%	13.04%	18.37%	23.08%
	20%	9.09%	16.67%	23.08%	28.57%
	30%	13.04%	23.08%	31.03%	37.50%

Dementia after repetitive mild TBI

- Studies of athletes offers several advantages
  - High frequency of concussion
  - Ability to do pre-injury testing in large sample
  - Injuries are usually witnessed
  - Systematic followup feasible
  - Lower frequency of confounders
- Disadvantage
  - Mechanical forces generally lower than in motor vehicle or combat settings

Risk of Dementia after Repeated mild TBI

- Dementia Pugilistica (Martland 1928)
  - "Punch drunk syndrome"
  - Current term: Chronic Traumatic Encephalopathy
- Prevalence of CTE in boxers approximately 20%
  - No Class I studies
- Higher risk in professional boxers, compared to amateur

Football: The Moral Equivalent of War

- American Football
  - Derived from British prep school game of Rugby
  - Started in 1870s in the Ivy League
  - Faculty and administrators (all Civil War veterans) wanted to provide students the moral formation that combat provides
  - "Moral Equivalent of War"

- 1870's - 1905
  - Collegiate football spread rapidly to Midwest, and specially the defeated South
  - Evolved into a very brutal game, with frequent injuries and deaths
    - 18 collegiate football players died in 1905 alone
  - Banned at Columbia, NYU, Northwestern, California, Stanford by 1906
  - Rules committee named at the request of President Theodore Roosevelt
    - Legalized forward pass; outlawed flying wedge formation
    - Committee grew into the National Collegiate Athletic Association

2001 Health Survey of Retired NFL Players

History of concussion from participating in professional football: *61% of all respondents*

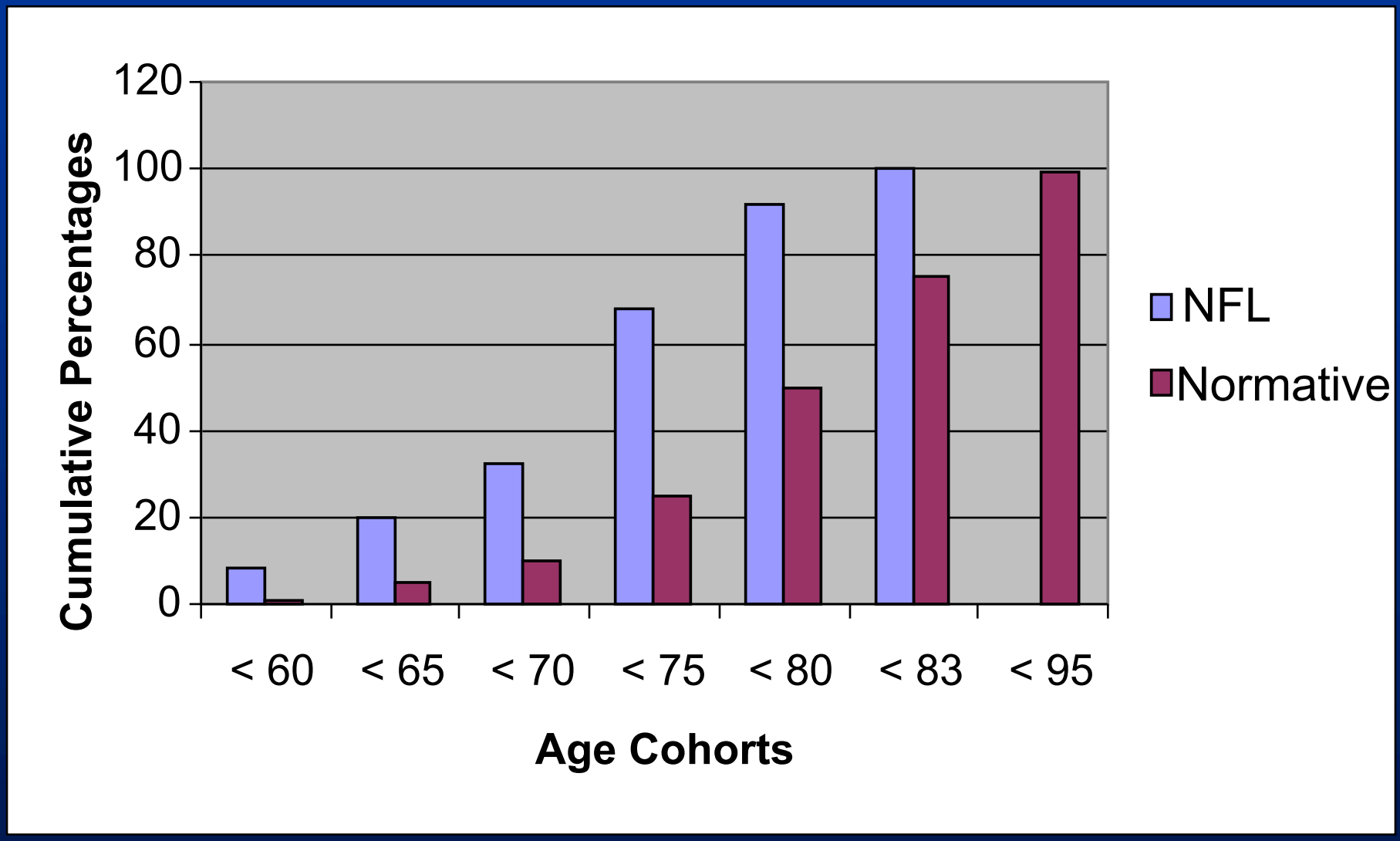
- Ave no. concussions during pro football career: 2.1
- 24% of respondents sustained 3 or more concussions
- 12% of respondents sustained 5 or more concussions
- 71% reported having returned to play on the same day as their concussion (18% reported this occurrence 3+ times)

16% reported that concussions have a permanent effect on thinking/ memory skills as they get older

MA McCrea, *Mild TBI and Postconcussion Syndrome*, Oxford Univ. Press, 2008

Recurrent Concussion as Risk for Dementia

NFL vs. Normative PAD Age Distribution



MA McCrea, *Mild TBI and Postconcussion Syndrome*, Oxford Univ. Press, 2008

CDC/NIOSH Study or Retired NFL Players

- 3,439 retired NFL players
  - At least 5 credited playing seasons 1959 – 1988
  - Vital status from pension fund records, IRS, SSA, and National Death Index (NDI)
  - Cause of Death from NDI and State Death Certificates
  - Standardized Mortality Ratio (SMR) adjusted for age, race, and calendar year of death
- Players stratified as to “speed” and “non-speed” positions
  - Speed: Quarterbacks, running back, halfback, fullback, wide receiver, tight end, defensive back, linebacker
  - Non-speed: All defensive and offensive linemen

Lehman, EJ et al, *Neurology* 2012:79:1970-4

CDC/NIOSH Study or Retired NFL Players

Cause of Death	Underlying		Contributing	
	n	SMR (95% CI)	n	SMR (95% CI)
All deaths	334	0.53 (0.48 – 0.59)	782	0.54 (0.51 – 0.58)
All cancers	85	0.58 (0.46 – 0.72)	122	0.63 (0.53 – 0.76)
All cardiovascular causes	126	0.68 (0.56 – 0.81)	340	0.71 (0.64 – 0.79)
All neurodegenerative	10	2.83 (1.36 – 5.21)	17	3.26 (1.90 – 5.22)
Dementia/Alzheimer disease	2	1.80 (0.22 – 6.50)	7	3.86 (1.55 – 7.95)
Amyotrophic Lateral Sclerosis	6	4.04 (1.48 – 8.79)	7	4.31 (1.73 – 8.87)
Parkinson disease	2	2.14 (0.26 – 7.75)	3	1.69 (0.35 – 4.94)
All Injuries	41	0.63 (0.45 – 0.86)	57	0.69 (0.52 – 0.89)
Violence	13	0.27 (0.14 – 0.46)	13	0.26 (0.14 – 0.45)
All other causes	59	0.34 (0.26 – 0.43)	233	0.37 (0.33 – 0.42)

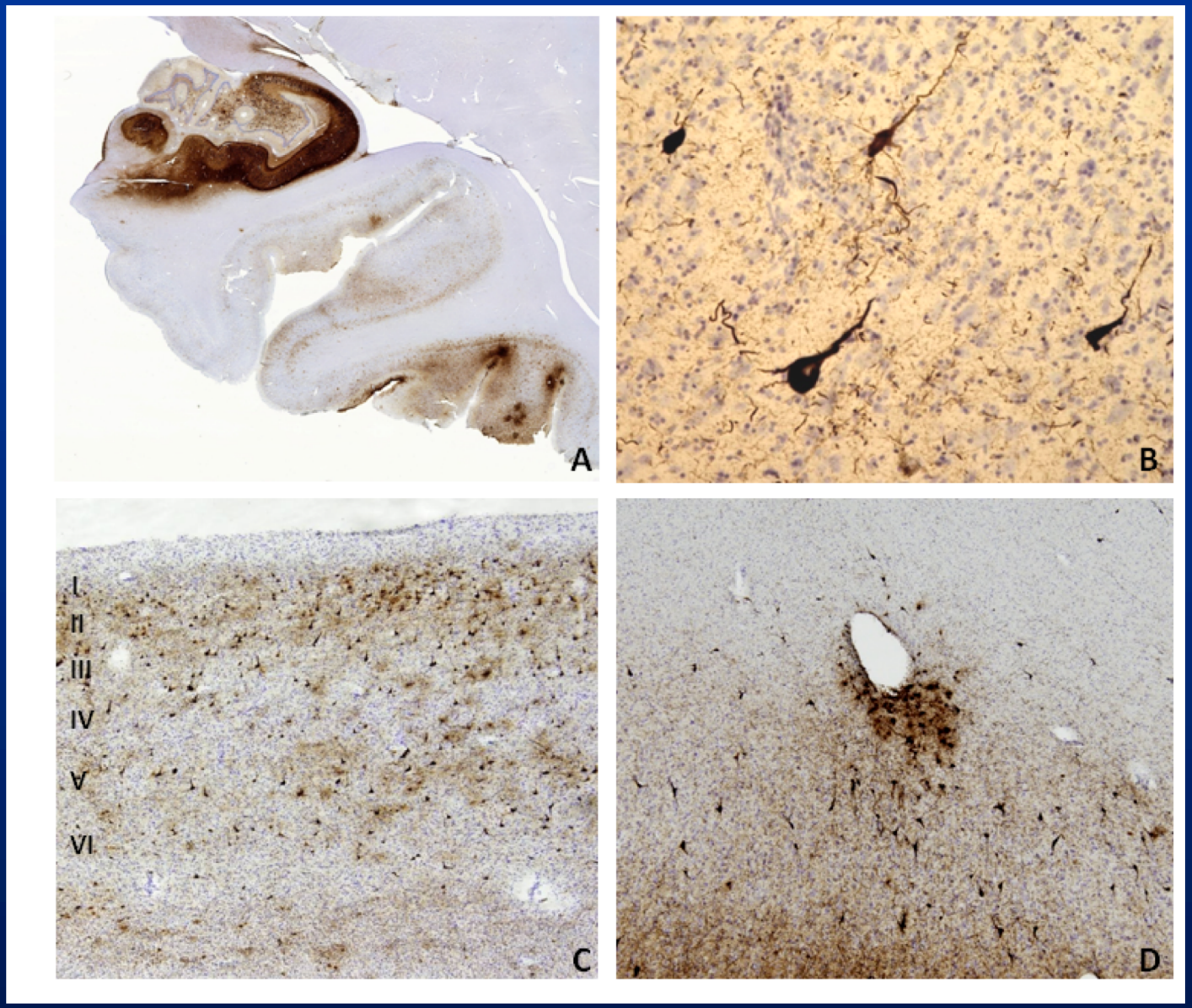
Lehman, EJ et al, *Neurology* 2012:79:1970-4

CDC/NIOSH Study or Retired NFL Players

Cause of Death	Non-speed		Speed	
	n	SMR (95% CI)	n	SMR (95% CI)
All neurodegenerative	3	1.58 (0.33 – 4.61)	14	4.74 (2.59 – 7.95)
Dementia/Alzheimer disease	1	1.51 (0.04 – 8.41)	6	6.02 (2.21 – 13.1)
Amyotrophic Lateral Sclerosis	1	1.71 (0.04 – 9.50)	6	6.24 (2.29 – 13.6)
Parkinson disease	1	1.53 (0.04 – 8.53)	2	2.01 (0.24 – 7.25)

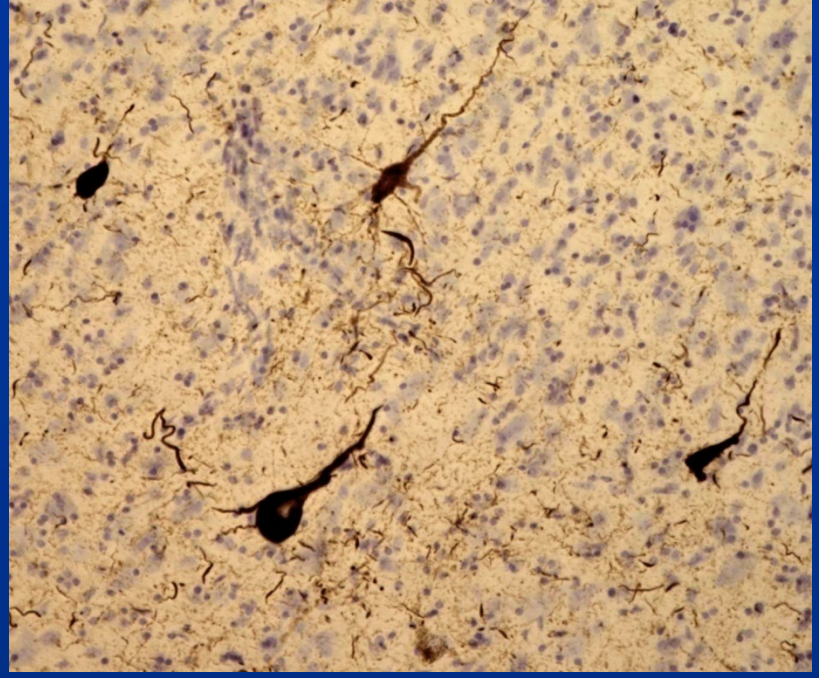
Lehman, EJ et al, *Neurology* 2012:79:1970-4

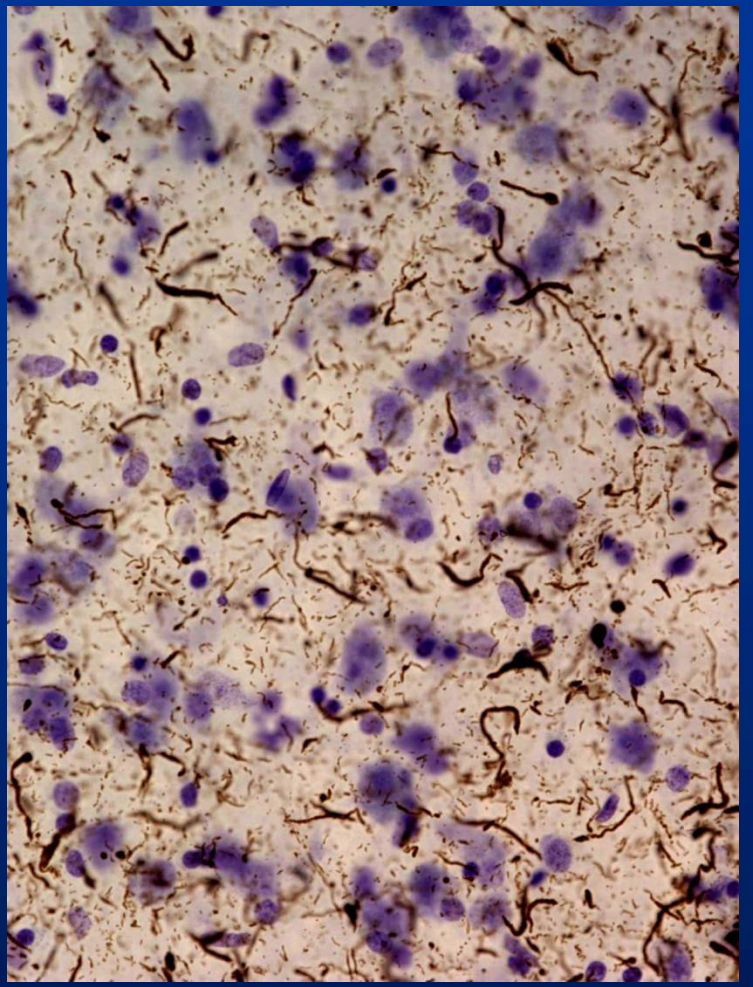
Pathology of CTE

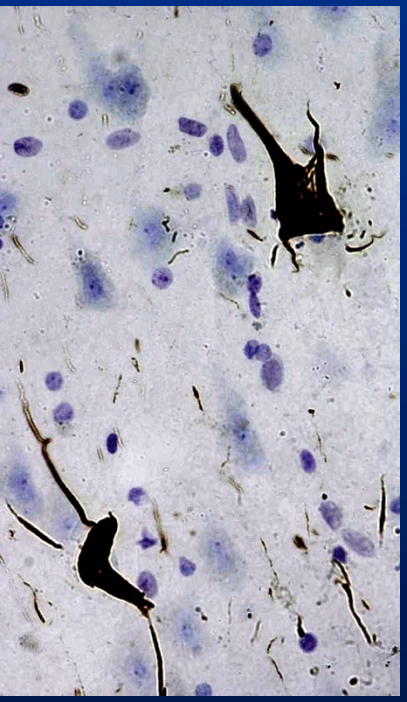


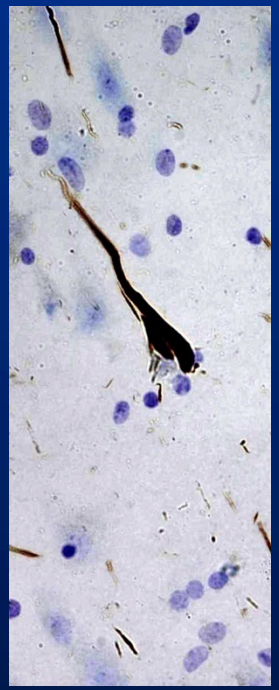
Shively et al, *Arch Neurol* 2012;69:1245-51

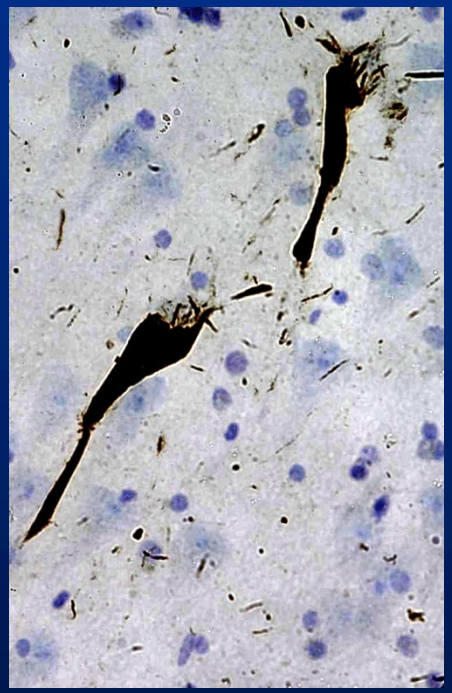
Pathology of CTE











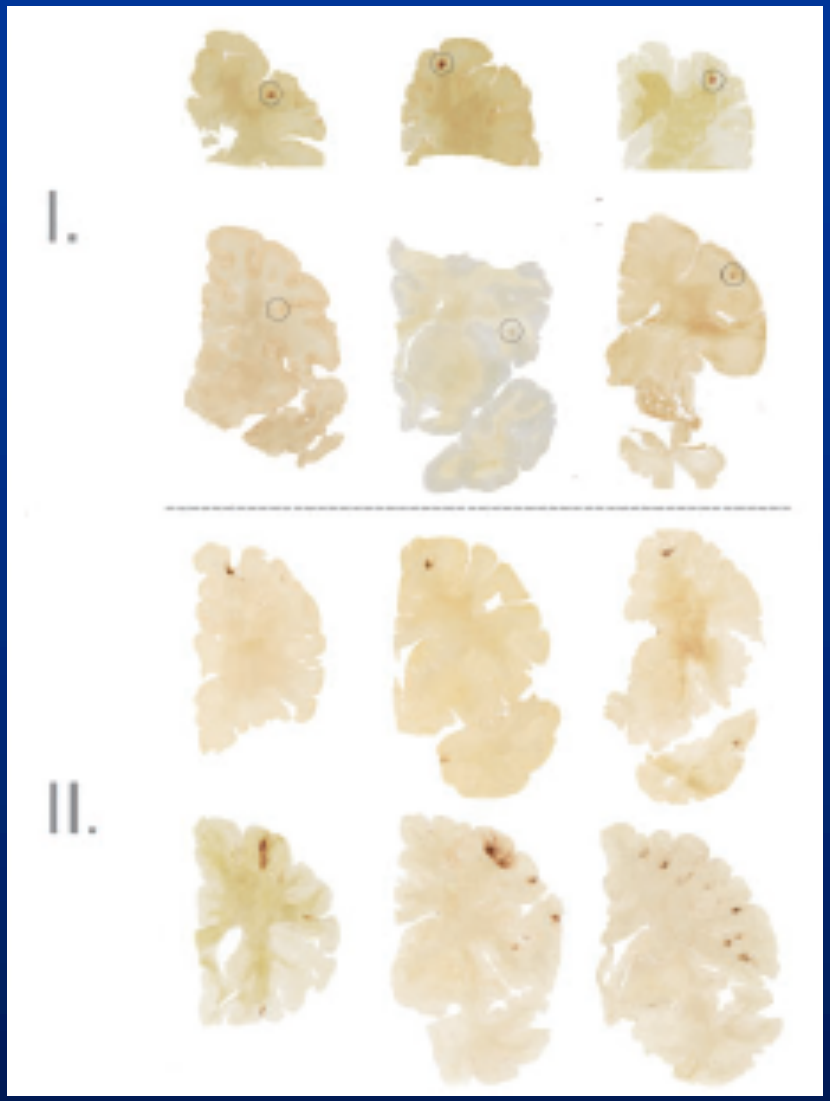
Courtesy of A McKee, D Perl

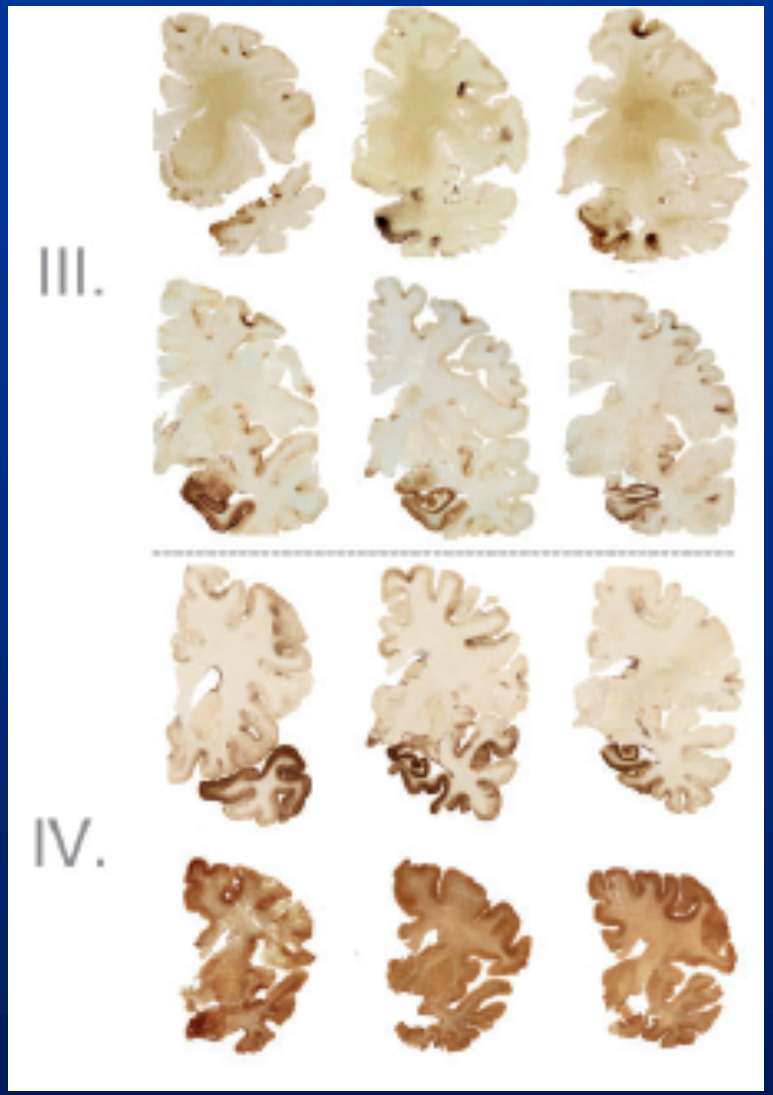
Clinical and Pathologic Features Discriminating between AD and CTE

Clinical	CTE	AD
Short term memory deficits early in the course	+	+++
Depression early in the course	+++	+
Abrupt mood swings, explosive rage	++	+/-
Substance abuse	++	-
Parkinsonism late in the course	+++	+/-
Suicidal behaviors	++	-
Pathologic		
Global cerebral atrophy	+/-	++
Fenestrated cavum septum pellucidum	+	-
Neuritic plaques, amyloid-β deposits	+/-	+++
Neurofibrillary tangles in neocortex	+++ Predominant Layers II, III	+++ Predominant Layers V, VI
Neurofibrillary tangles in hippocampus and parahippocampal gyrus	+++ All of Ammon's Horn	+++ Predominantly in CA1
Neurofibrillary tangles in substantia nigra, locus ceruleus	++	+/-
Neurofibrillary tangles surrounding small blood vessels	+++	-

Shively et al, *Arch Neurol* 2012;69:1245-51

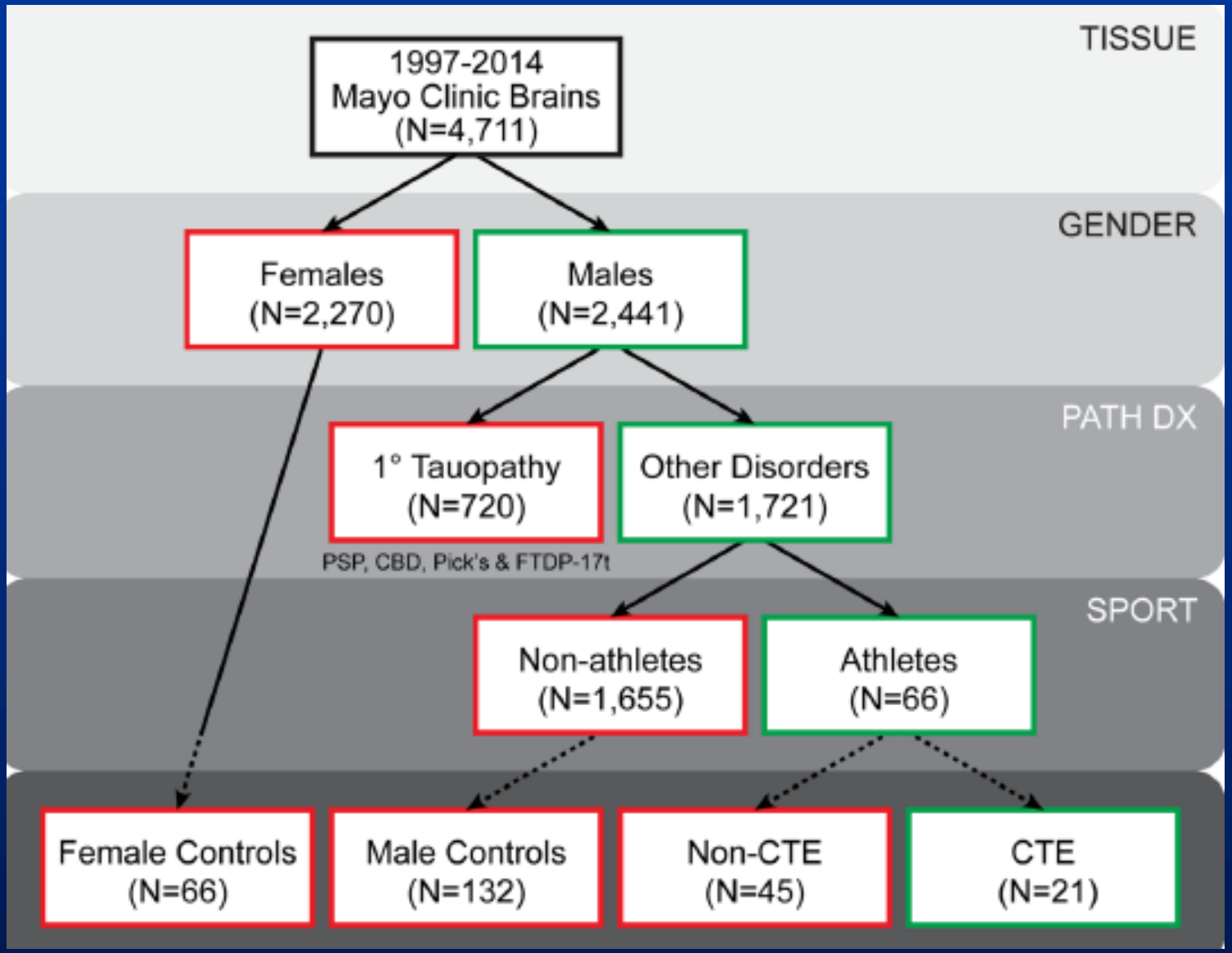
CTE Stages





McKee et al, *Brain* 2012

CTE in a Neuropathology Brain Bank



Bieniek et al, *Acta Neuropath 2015*;130:877-8891

CTE in a Neuropathology Brain Bank

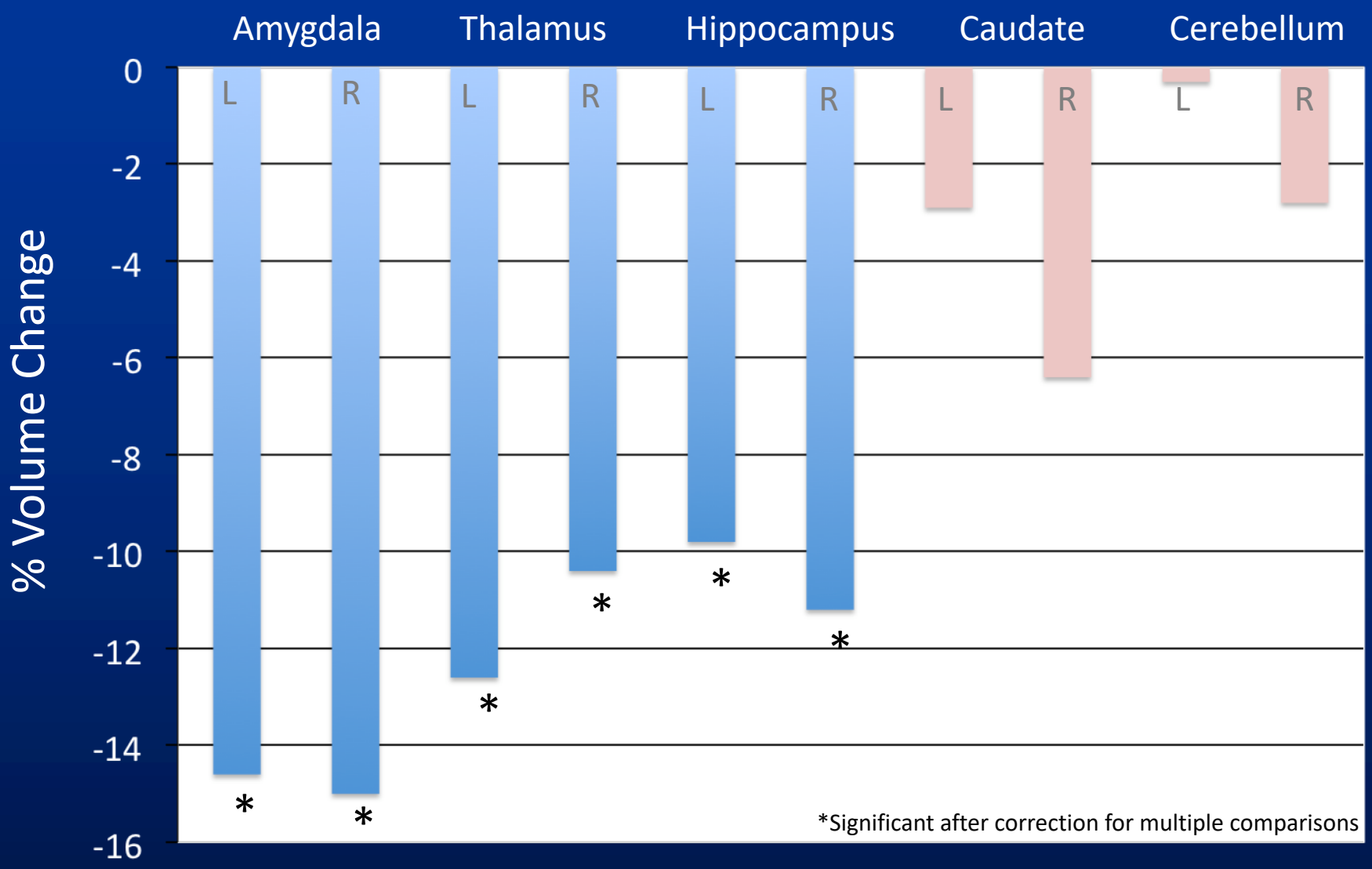
Case #	CTE	Sport	Sport level	Veteran	Education	FHx	Clinical Dx	Path Dx	Onset
1	I	Bk	HS	−	?	−	ALS	ALS	45
2	I	F	HS	−	18	+	FTD	FTLD-FUS	37
3	I	F	HS	+	?	+	ALS	ALS	45
4	I	F	HS	+	16	−	PDD	AD + LBD	65
5	I	F	HS, Co	−	16	−	DLB	LBD	66
6	I	F/Bk/Bb	HS, Co[Bb], sPro[Bb]	+	16	−	MSA	AD + LBD	63
7	I	F/W	HS, Co, Pro[W]	+	16	+	FTD/CVA	AD	?
8	II	?	?	+	16	+	AD	AD	83
9	II	F	?	−	?	−	ALS	ALS	30
10	II	Bb	sPro	+	12	−	NCI	AD	NA
11	II	Bo	Am	−	5	+	AD	AD	75
12	II	F	HS, Co	−	18	−	NCI	AD	NA
13	II	F	HS, Co	−	16	+	NCI	Normal	NA
14	II	F	HS, Co	+	15	−	PSP	LBD	73
15	III	F	HS	−	17	+	AD/PD	AD + LBD	53
16	III	F	HS	+	14	+	DLB	AD + LBD	70
17	III	F	HS, Co, Pro	+	16	+	VaD	FTLD-tau	67
18	III	F/Ru	?	+	16	+	PDD	LBD	65
19	III	F/Bb	Co	−	16	−	AD	FTLD-tau	75
20	IV	Bo	Pro	+	5	−	AD v DLB	AD	77
21	IV	F/Bk/Bb	HS, Co, sPro[Bb]	+	16	+	PSP	FTLD-tau	60

Bieniek et al, *Acta Neuropath 2015*;130:877-8891

What are long-term consequences of single moderate to severe TBI?

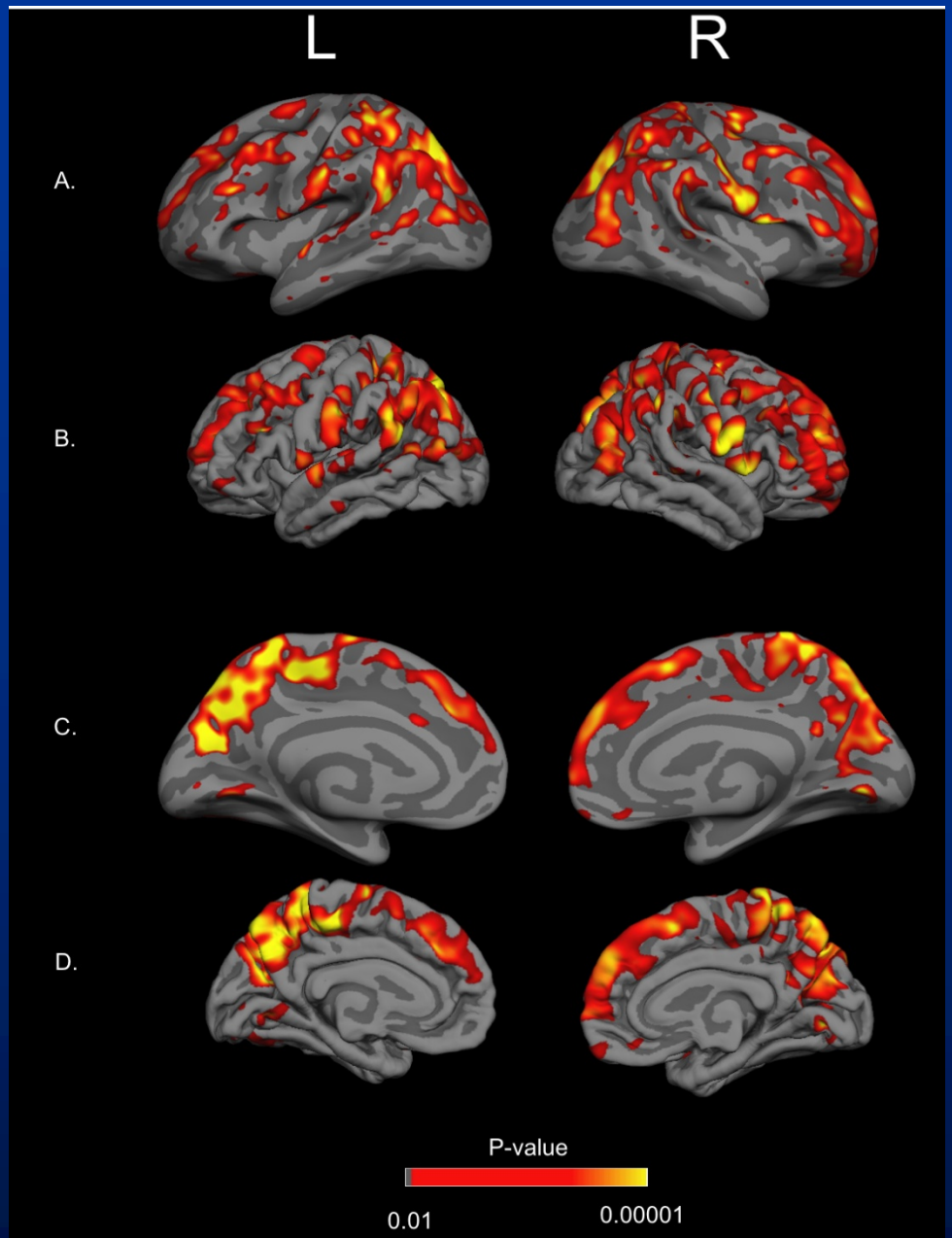
- Regional cerebral atrophy
- Amyloid pathology
- Tau pathology
- Chronic neuroinflammation
- Is TBI associated dementia accelerated AD, CTE-like pathology, or another pathology?

Subcortical atrophy after single TBI



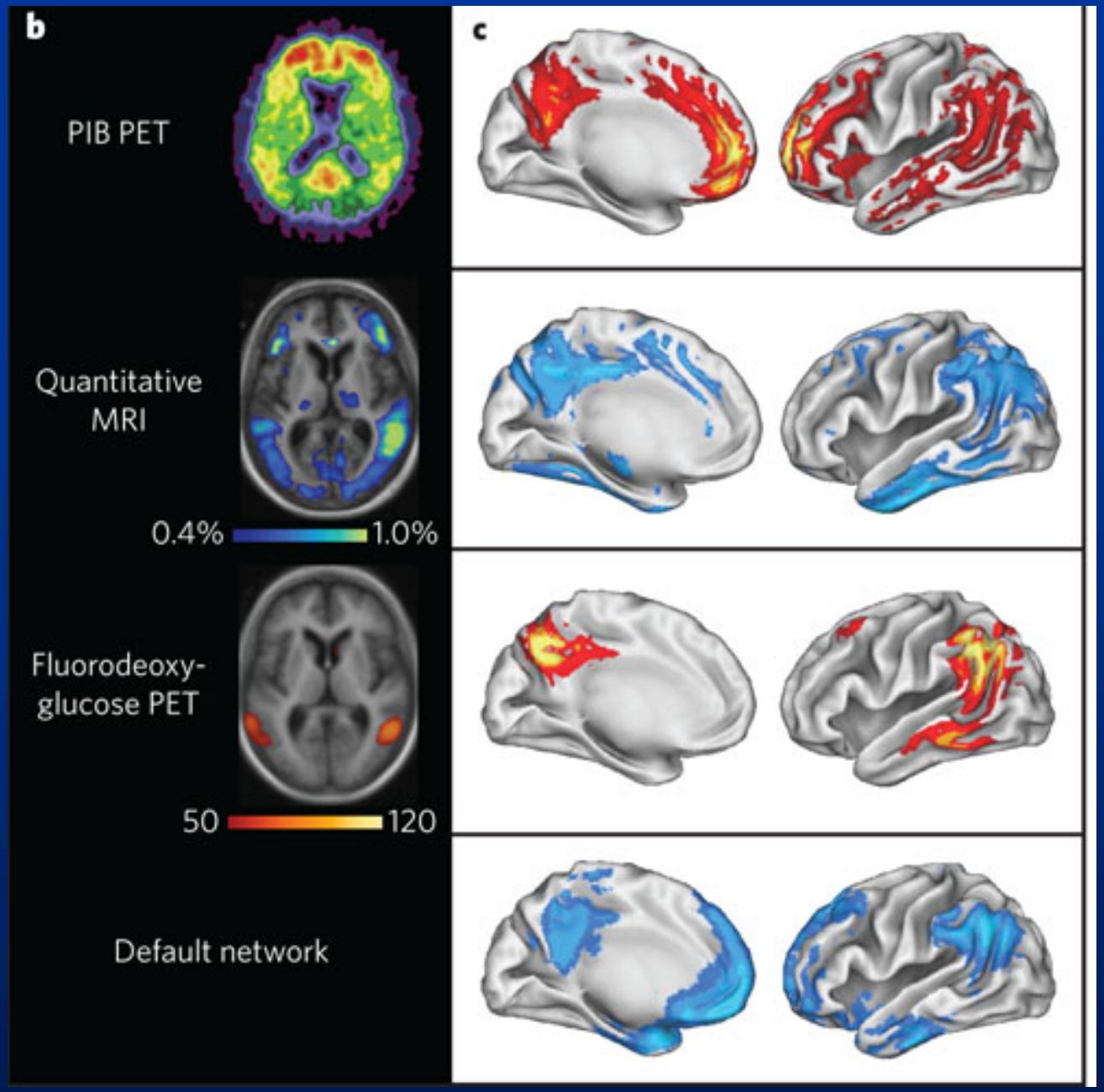
Warner et al, *Arch Neurol* 2010

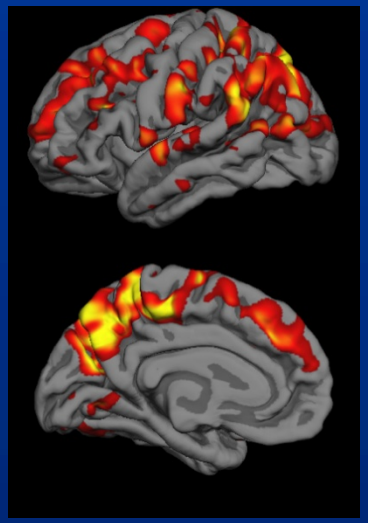
Cortical atrophy after single TBI



- Cortical atrophy regionally selective
- Greatest atrophy seen in:
  - Precuneus
  - Posterior Cingulate
  - Superior Parietal Cortex
  - Superior Frontal Cortex

Warner et al, *Arch Neurol* 2010

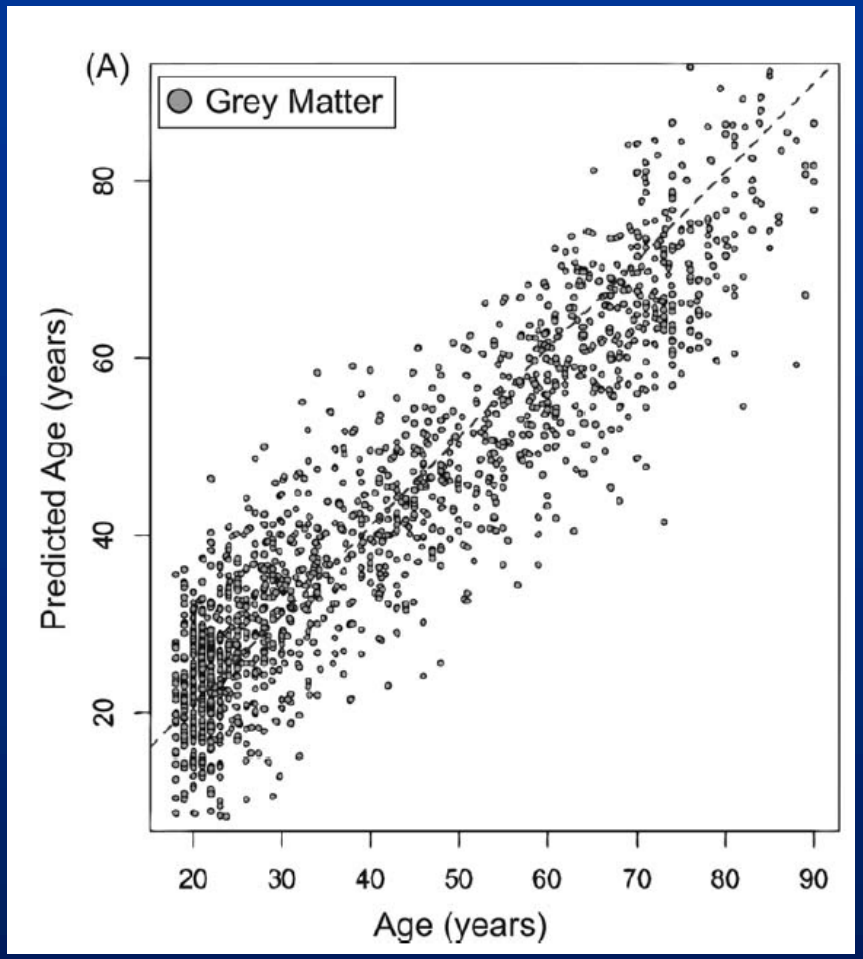


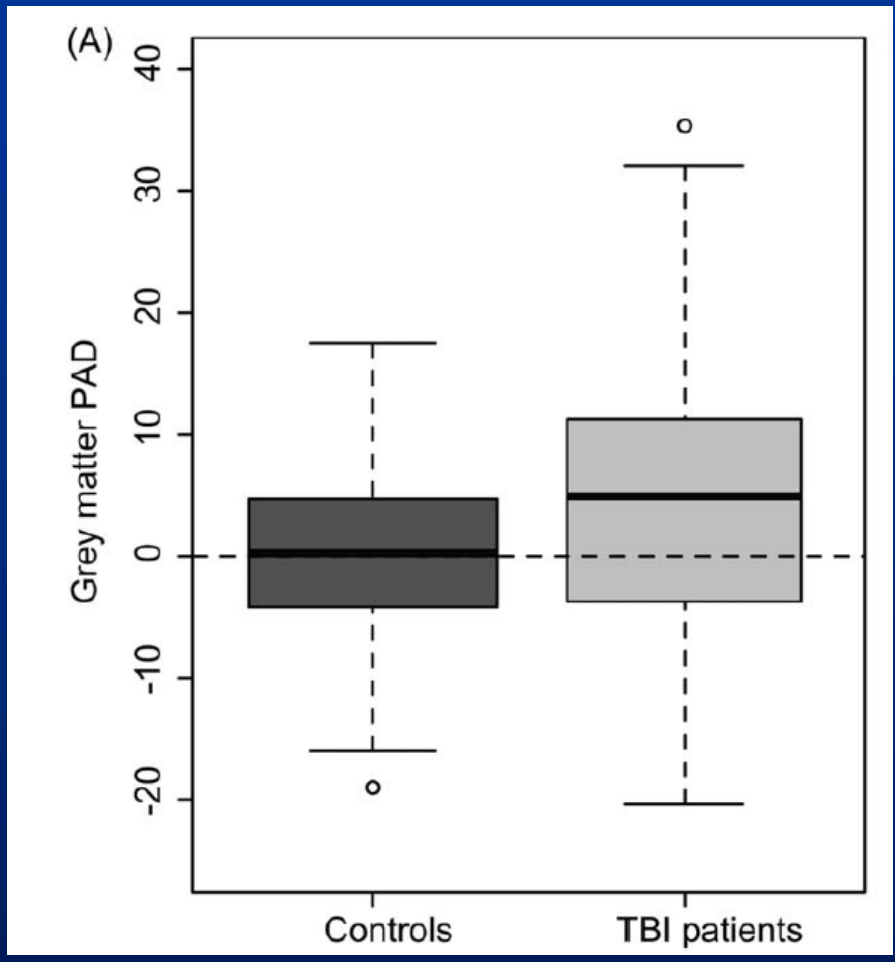


Perrin, Fagan, Holtzman, *Nature* 461:916-922, 2009

Warner et al, *Arch Neurol* 2010

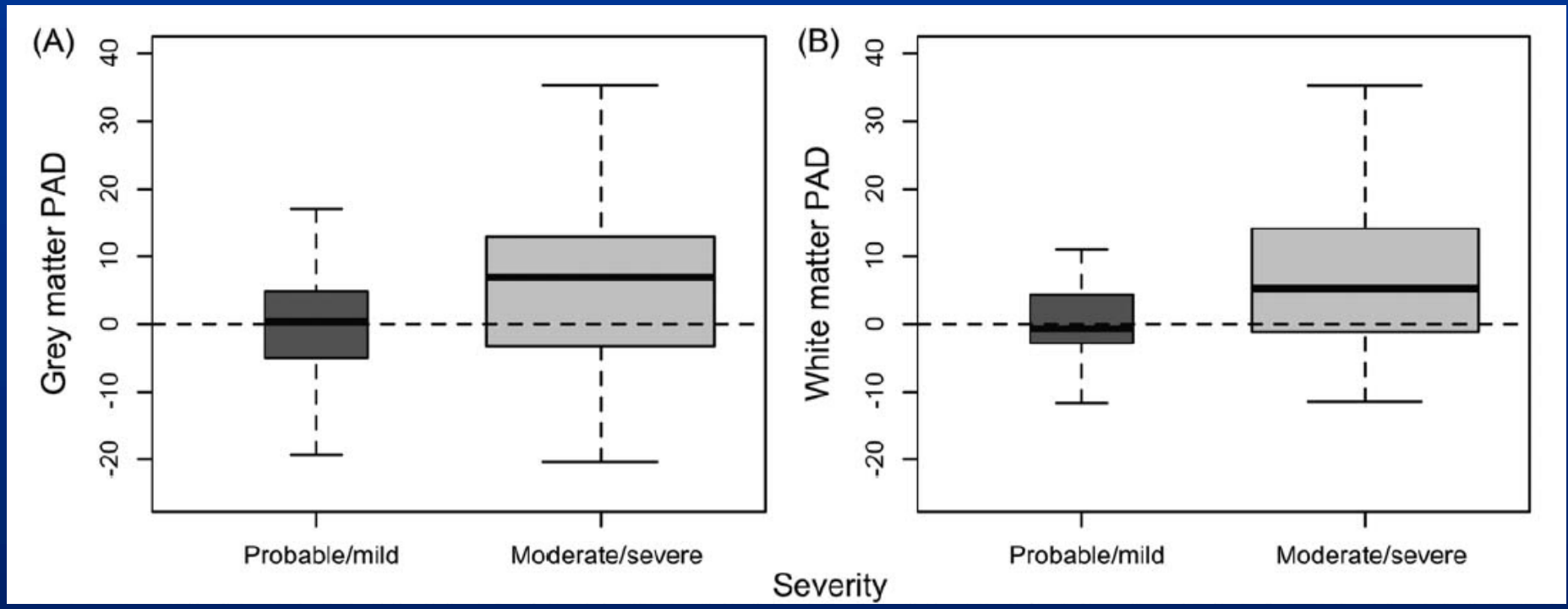
TBI Results in Accelerated Brain Aging Volumetric MRI Study





Cole et al, *Annals Neurology* 2015

TBI Results in Accelerated Brain Aging Volumetric MRI Study



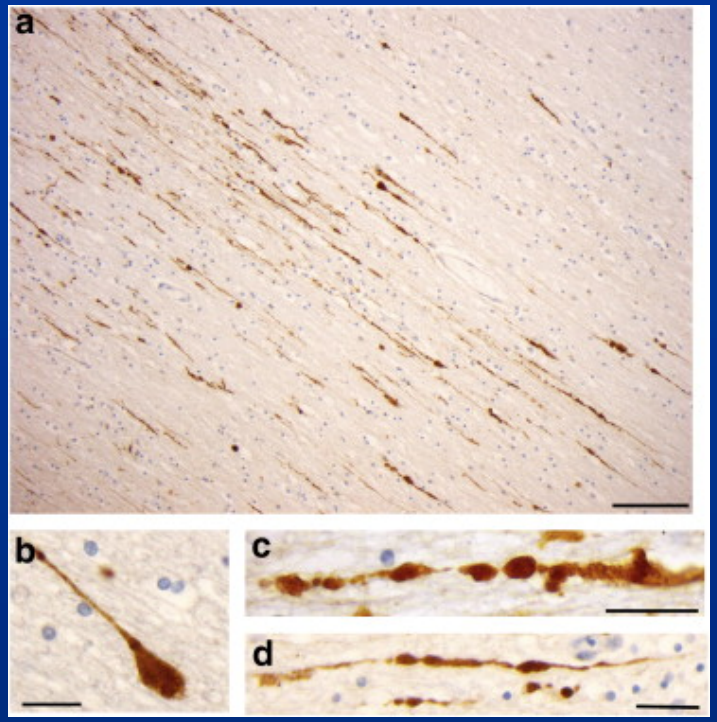
Cole et al, *Annals Neurology* 2015

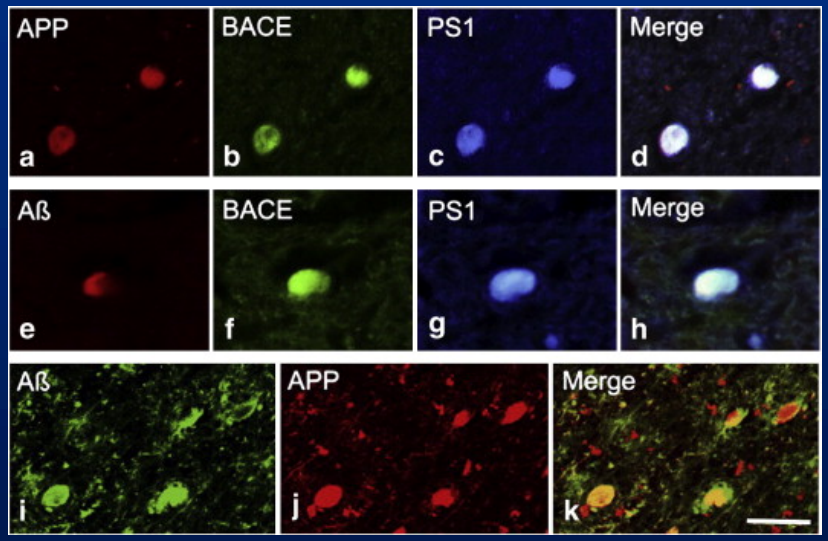
AD-like Pathology after Acute TBI

- Aβ plaques are found in 30% of patients who die acutely following TBI
- Aβ plaques are found in peri-contusional tissue surgically excised within hours of TBI
- Typically diffuse plaques
- Found in grey matter and white matter
- Not known whether these plaques persist or mature into denser neuritic plaques

VE Johnson, W Stewart, DH Smith, *Nature Rev Neurosci* 2010;11:361-370

AD-Like Pathology After TBI





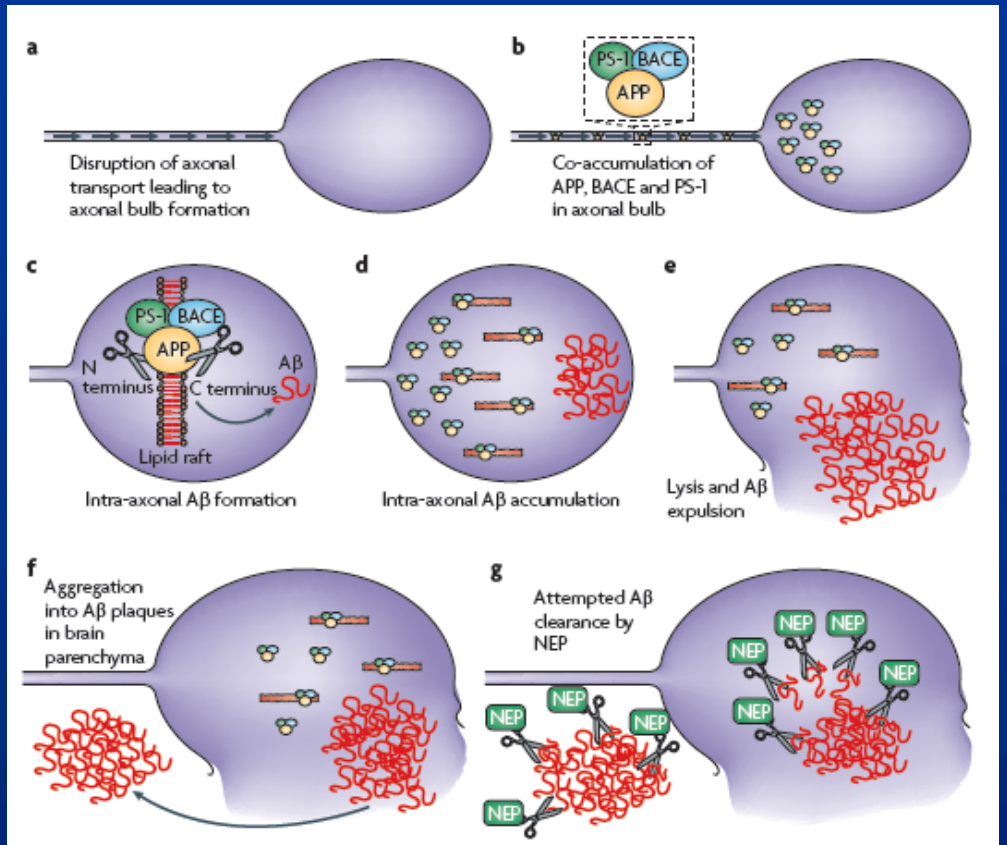
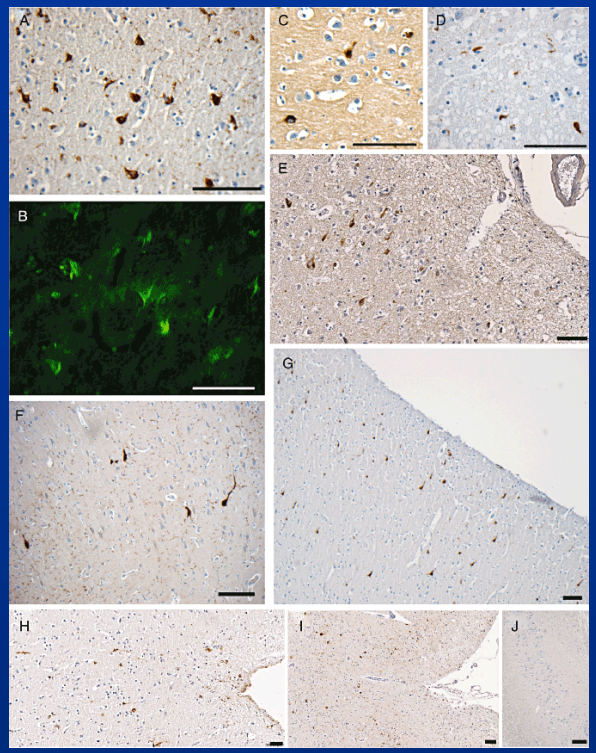
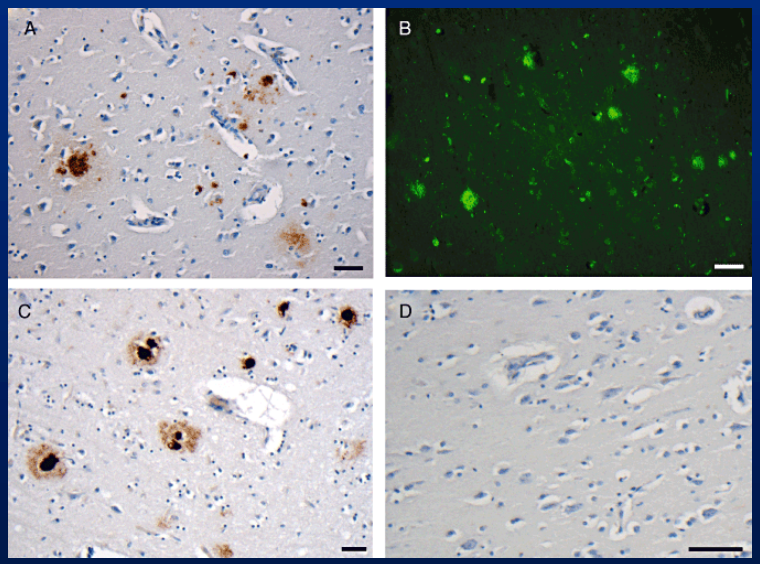


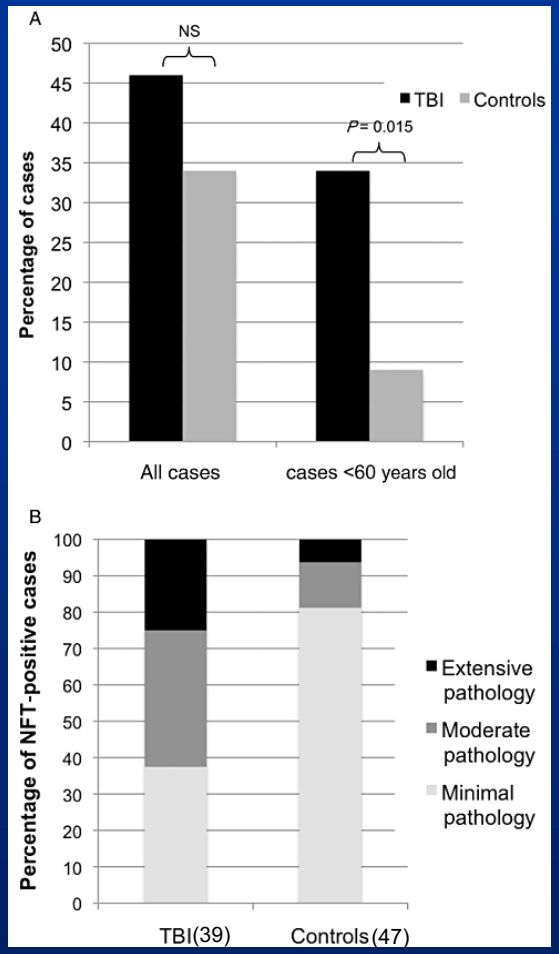
Figure 2 | **Potential mechanisms of post-traumatic amyloid-β formation and clearance.** **a** | The mechanical forces that axons are subjected to during a traumatic event can damage axons by directly altering their structure or by initiating detrimental secondary cascades. Failure of axonal transport in these injured axons results in accumulation of multiple proteins that form swellings at their disconnected terminals known as axon bulbs. **b** | Such protein accumulation has been demonstrated to include the enzymes necessary for the cleavage of amyloid precursor protein (APP) to amyloid-β (Aβ), including presenilin-1 (PS-1) and β-site APP-cleaving enzyme (BACE). **c–d** | Although the precise intracellular mechanism of Aβ genesis remains unclear, lipid rafts have been suggested to be important in allowing APP processing and thus Aβ accumulation within the axonal compartment. **e–f** | Injured axons that go on to degenerate and lyse will expel the accumulated Aβ into the brain parenchyma where it is at risk of aggregating into plaques. **g** | The enzyme that clears Aβ, neprilsyin (NEP), also accumulates in damaged axons and probably mitigates the effects of enhanced Aβ production. The balance of genesis versus catabolism will ultimately determine Aβ build-up. NEP may potentially act to clear Aβ within the axonal compartment or in the extracellular space.

VE Johnson, W Stewart, DH Smith, *Nature Rev Neurosci* 2010;11:361-370

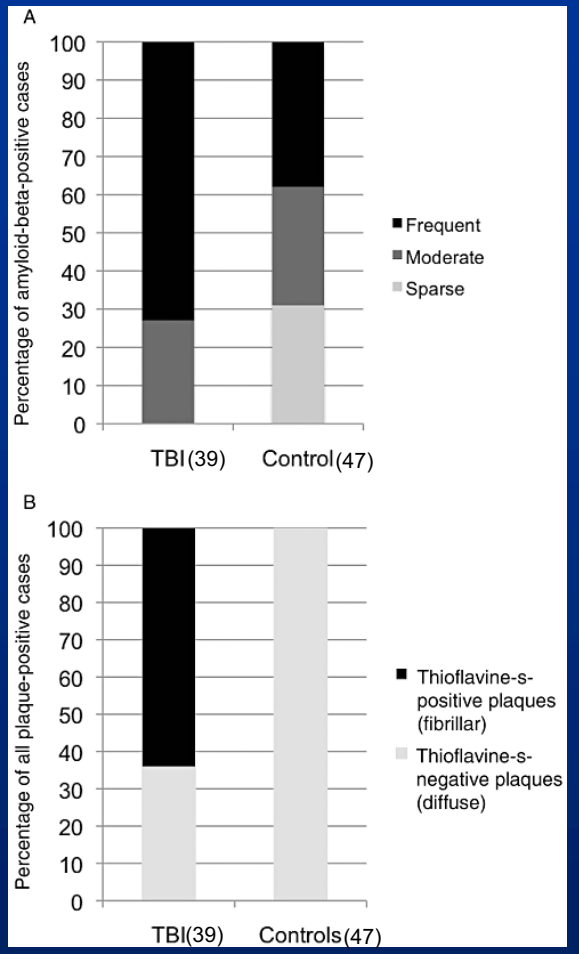
Tau and Amyloid-Beta Pathology Many Years After a Single Traumatic Brain Injury in Humans







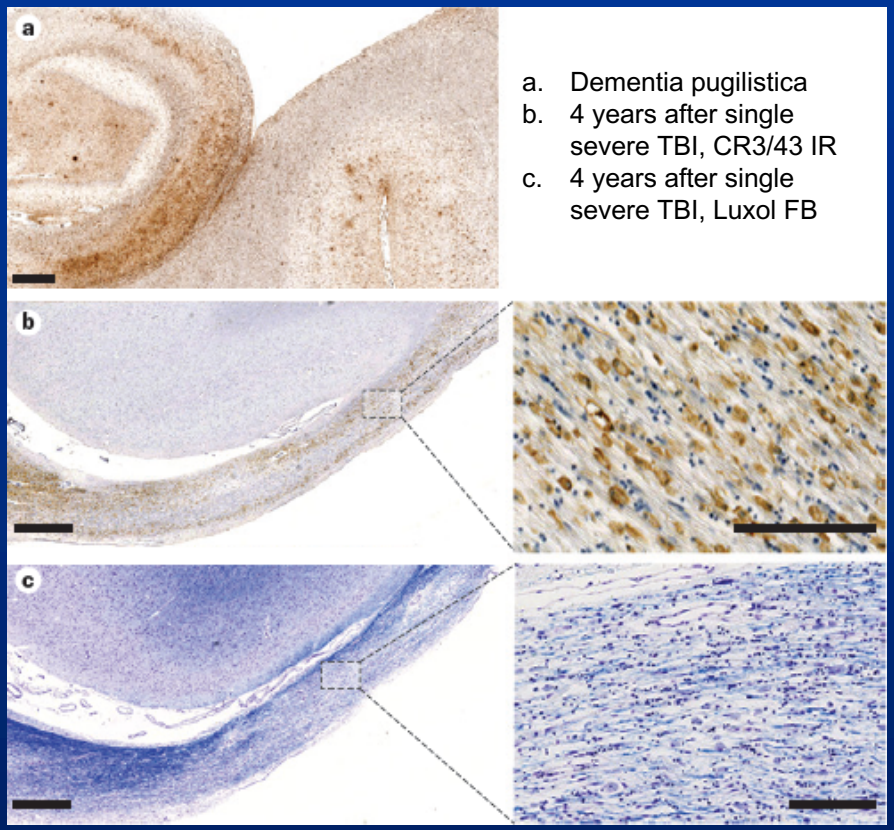
Tangles



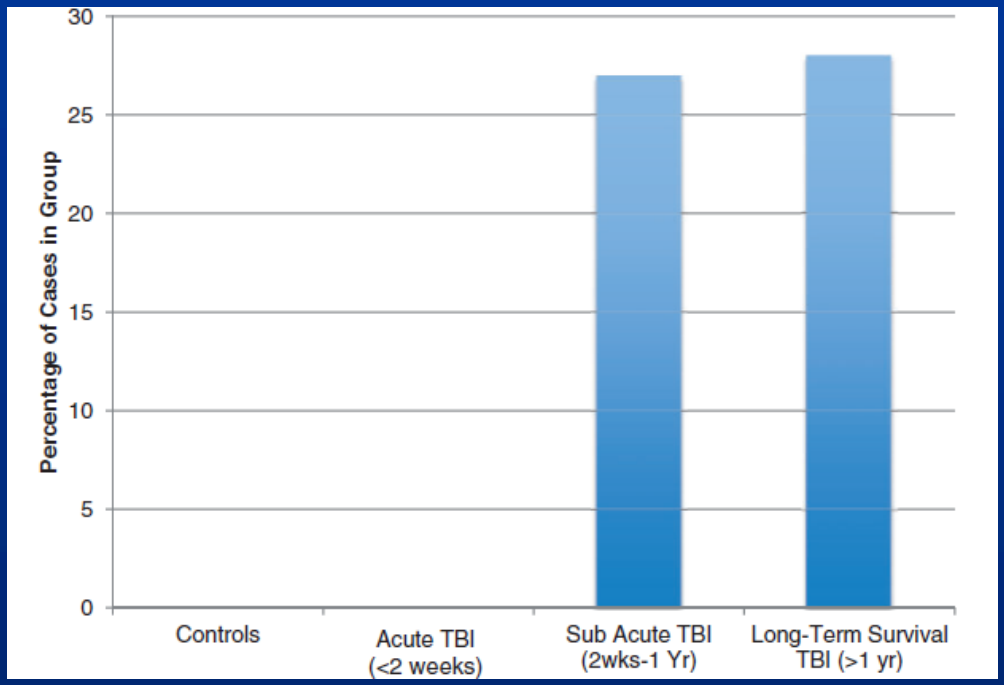
Plaques

Johnson et al (2012) *Brain Pathol* 22:142-149

Chronic neuroinflammation in long-term survivors from TBI



a. Dementia pugilistica
b. 4 years after single severe TBI, CR3/43 IR
c. 4 years after single severe TBI, Luxol FB



Percentage of cases displaying ameboid (Cr3/43 and CD68 immunoreactive cells following TBI survival time versus control subjects

Smith et al (2013) *Nat Rev Neurol 9*:211-221

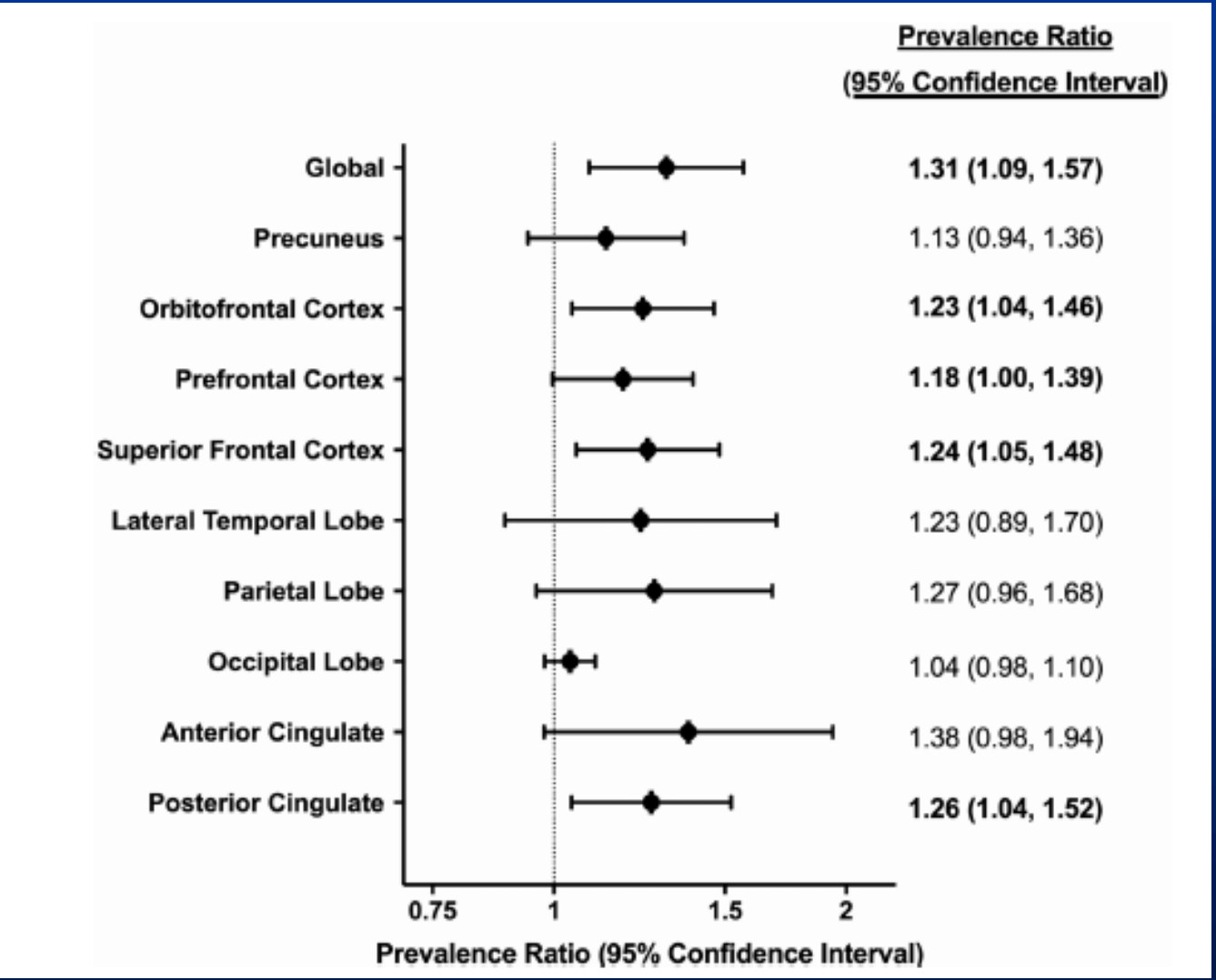
Johnson et al (2013) *Brain* 136:28-42

History of TBI is Associted with increased ^{18}F-Florbetapir binding

ARIC Study

n = 329 (81 with with prior TBI)

Age 75.9 (5.4) years



Schneider et *al,* J. Neurotrauma 2019

Analysis of NACC Database

NACC UDS Data	Risk of AD after TBI		
	O.R. for AD	*95% CI*	*p*
A5, Item 4b1--TBI with Brief LOC	0.998	0.883 - 1.1128	0.9963
A5, Item 4b2--TBI with Extended LOC	1.078	0.896 – 1.298	0.4524
A5, Item 4b3--TBI with chronic deficit or dysfunction	3.060	1.828 – 5.121	<0.0001

Sayed et al, *J. Neurotrauma* 2013;30:1117-1122

Analysis of NACC Database

	TBI (n = 62)	*No TBI (n = 122)*	
	(Mean ± SD)	**(Mean ± SD)**	***p***
Age	66.9 ± 12.5	64.4 ± 11.0	NS
Clinical Judgment of Symptoms [Cognitive]	**Odds Ratio**	**95% C.I.**	***p***
Memory	*0.051*	*0.003 – 0.933*	*0.007*
Judgment	0.834	0.253 – 2.754	0.765
Language	1.067	0.564 – 2.019	0.872
Visuospatial Function	0.889	0.469 – 1.687	0.746
Attention	1.510	0.785 – 2.905	0.251
Fluctuating Cognition	11.52	0.556 – 238.5	0.066
Clinical Judgment of Symptoms [Motor]	**Odds Ratio**	**95% C.I.**	***p***
Gait Disorder	*4.594*	*2.198 – 9.600*	*<0.0001*
Falls	*6.886*	*2.694 – 17.60*	*<0.0001*
Tremor	*2.909*	*1.247 – 6.787*	*0.0160*
Slowness	*3.962*	*1.988 – 7.899*	*0.0001*
Other Neurologic Conditions	**Odds Ratio**	**95% C.I.**	***p***
Seizures	*45.19*	*2.580 – 791.6*	*<0.0001*

Sayed et al, *J. Neurotrauma* 2013;30:1117-1122

Analysis of NACC Database

	TBI (n = 62)	*No TBI (n = 122)*	
	(Mean ± SD)	(Mean ± SD)	*p*
Clinical Judgment of Symptoms [Behavior]	**Odds Ratio**	**95% C.I.**	***p***
Apathy	1.107	0.583 – 2.102	0.870
Depression	*2.039*	*1.057 – 3.931*	*0.044*
Psychosis	*2.038*	*1.162 – 3.574*	*0.015*
Disinhibition	*2.637*	*1.150 – 6.048*	*0.031*
Irritability	*2.106*	*1.096 – 4.049*	*0.031*
Agitation	2.100	0.967 – 4.560	0.070
Personality Change	*3.505*	*1.624 – 7.566*	*0.002*
REM Sleep Behavior Disorder	3.200	0.266 – 38.45	0.556

Sayed et al, *J. Neurotrauma* 2013;30:1117-1122

Analysis of NACC Database

	TBI (n = 62)	*No TBI (n = 122)*	
	(Mean ± SD)	**(Mean ± SD)**	***p***
Behavioral Assessment	**Odds Ratio**	**95% C.I.**	***p***
Delusions	1.439	0.696 – 2.977	0.346
Hallucinations	1.254	0.489 – 3.216	0.631
Agitation	*2.073*	*1.095 – 3.925*	*0.033*
Depression	*2.229*	*1.185 – 4.194*	*0.016*
Anxiety	1.429	0.765 – 2.667	0.270
Elation	2.533	0.740 -- 8.671	0.185
Apathy	1.826	0.962 – 3.466	0.080
Disinhibition	2.043	1.000 – 4.174	0.060
Irritability	*1.934*	*1.032 – 3.627*	*0.041*
Motor Disturbances	1.217	0.612 – 2.420	0.597
Nighttime Behaviors	*2.400*	*1.263 – 4.559*	*0.009*
Appetite	1.159	0.591 – 2.273	0.730

Sayed et al, *J. Neurotrauma* 2013;30:1117-1122

NACC Pathologic Diagnosis

For 20 deaths with NACC pathology data

Pathologic Findings comparing the TBI with Chronic Deficit or Dysfunction and No TBI Group			
Ordinal Measures	X^2	df	p
CERAD Neuritic Plaque Score	8.99	3	0.029
Braak and Braak Stage	2.85	6	0.826
NIA-Reagan Likelihood of Dementia due to AD	3.85	2	0.146
DLB Clinical Syndrome due to DLB Pathology	3.14	2	0.209
Dichotomized Measures	O.R.	95% C.I.	p
Amyloid Angiopathy Dichotomized	0.13	0.026 – 0.674	0.026
Braak and Braak Dichotomized	0.73	0.591 – 3.380	1.000

Sayed et al, *J. Neurotrauma* 2013

TBI in Population Based Dementia Brain Banks

Table 3. Separate Adjusted Associations Between TBI With LOC and Neuropathologic Findings in ACT and in ROS and MAP[a]

	ACT (N = 525)				ROS and MAP (N = 1064)			
	TBI With LOC ≤1 h (n = 80)		TBI With LOC >1 h (n = 14)		TBI With LOC ≤1 h (n = 96)		TBI With LOC >1 h (n = 23)	
Outcome	RR (95% CI)[a]	*P* Value	RR (95% CI)[b]	*P* Value	RR (95% CI)[b]	*P* Value	RR (95% CI)[b]	*P* Value
Braak stage V or VI	1.22 (0.86-1.73)	.26	1.11 (0.61-2.00)	.74	0.87 (0.55-1.37)	.54	0.85 (0.35-2.06)	.71
CERAD intermediate or frequent	1.01 (0.79-1.29)	.92	0.67 (0.36-1.25)	.21	1.01 (0.78-1.31)	.93	1.16 (0.73-1.85)	.54
Amyloid angiopathy	1.08 (0.73-1.59)	.71	1.02 (0.47-2.20)	.96	1.10 (0.88-1.39)	.41	1.11 (0.72-1.71)	.63
Cystic infarcts	0.83 (0.56-1.24)	.37	1.05 (0.52-2.12)	.88	0.95 (0.68-1.33)	.77	1.24 (0.71-2.15)	.45
Hippocampal sclerosis	0.93 (0.41-2.10)	.86	2.34 (1.02-5.30)	.04	0.84 (0.37-1.93)	.68	0.49 (0.07-3.52)	.48
Cerebral microinfarcts								
Any	0.87 (0.64-1.19)	.39	1.23 (0.73-2.09)	.44	1.03 (0.72-1.46)	.88	1.18 (0.63-2.21)	.61
Any cortical	0.92 (0.65-1.31)	.64	1.12 (0.57-2.18)	.74	0.89 (0.53-1.48)	.66	2.12 (1.12-4.01)	.02
Any deep	0.89 (0.60-1.33)	.58	1.67 (0.95-2.93)	.08	1.16 (0.77-1.76)	.48	1.07 (0.47-2.40)	.88
Lewy bodies								
Any	0.93 (0.55-1.59)	.80	2.64 (1.40-4.99)	.003	1.04 (0.67-1.62)	.85	0.95 (0.39-2.31)	.91
Substantia nigra and/or locus ceruleus	0.96 (0.51-1.80)	.89	3.30 (1.71-6.38)	<.001	1.09 (0.69-1.71)	.82	0.82 (0.31-2.22)	.70
Frontal or temporal cortex	1.49 (0.61-3.64)	.38	5.73 (2.18-15.0)	<.001	1.64 (1.00-2.70)	.051	0.74 (0.18-3.00)	.67
Amygdala and/or limbic[c]	1.30 (0.75-2.24)	.35	1.89 (0.69-5.19)	.22	1.16 (0.73-1.84)	.91	0.91 (0.34-2.44)	.85

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Table 5. Adjusted Associations Between TBI With LOC at Younger Than 25 Years and Neuropathologic Findings From Joint Analysis of Data From All 3 Studies[a]

	TBI With LOC <1 h (n = 67)		TBI With LOC ≥1 h (n = 19)	
Outcome[b]	RR (95% CI)[c]	*P* Value	RR (95% CI)[c]	*P* Value
Braak stage V or VI	1.00 (0.66-1.52)	.99	1.03 (0.50-2.14)	.94
CERAD criteria intermediate or frequent	1.09 (0.89-1.32)	.41	0.91 (0.62-1.35)	.65
Amyloid angiopathy	1.07 (0.89-1.29)	.44	0.86 (0.62-1.20)	.38
Cystic infarcts	0.83 (0.58-1.21)	.33	0.84 (0.45-1.60)	.60
Hippocampal sclerosis	1.42 (0.68-2.97)	.35	1.33 (0.37-4.76)	.66
Cerebral microinfarcts				
Any	1.04 (0.78-1.40)	.77	1.66 (1.19-2.32)	.003
Any cortical	1.10 (0.77-1.57)	.60	1.29 (0.71-2.35)	.41
Any deep	1.06 (0.72-1.58)	.76	1.24 (0.64-2.40)	.53
Lewy bodies				
Any	0.95 (0.56-1.62)	.86	1.86 (1.03-3.35)	.04
Substantia nigra or locus ceruleus	1.03 (0.59-1.80)	.91	1.84 (0.94-3.60)	.08
Frontal or temporal cortex	1.53 (0.77-3.03)	.23	2.53 (1.02-6.24)	.045
Amygdala and/or limbic[d]	1.09 (0.60-1.98)	.78	1.77 (0.86-3.64)	.12

Crane et al, *JAMA Neurology* 2016

Conclusions

- TB is a risk factor for late-life dementia
- Unclear whether TBI accelerates AD neuropathology or whether it results in a distinct neuropathology
  - Indications that TBI is associated with increased rate of psychiatric, behavioral, and motor clinical endophenotypes
  - Pathology may be a distinct
- Whether similar pathology occurs after repetitive mTBI or single moderate to severe TBI remains to be determined

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