CONCUSSION/MTBI & NEURODEGENERATIVE DISEASE

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Research | Diagnosis | Solutions

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U of T NEUROLOGY

DISCLOSURE

- CIHR, NIH, WESTON BRAIN INSTITUTE, TANENBAUM INSTITUTE FOR SCIENCE IN SPORT
- CLINICAL TRIALS: BIOGEN, ANAVEX, JANSSEN, ELI LILLY, BMS, GSK, ROCHE
- CONSULTANCY: LILLY, EISAI

OBJECTIVES

- Review relationship between brain injury and delayed neurodegeneration
  - Chronic traumatic encephalopathy
  - Alzheimer’s Disease
  - Parkinson's Disease
  - ALS

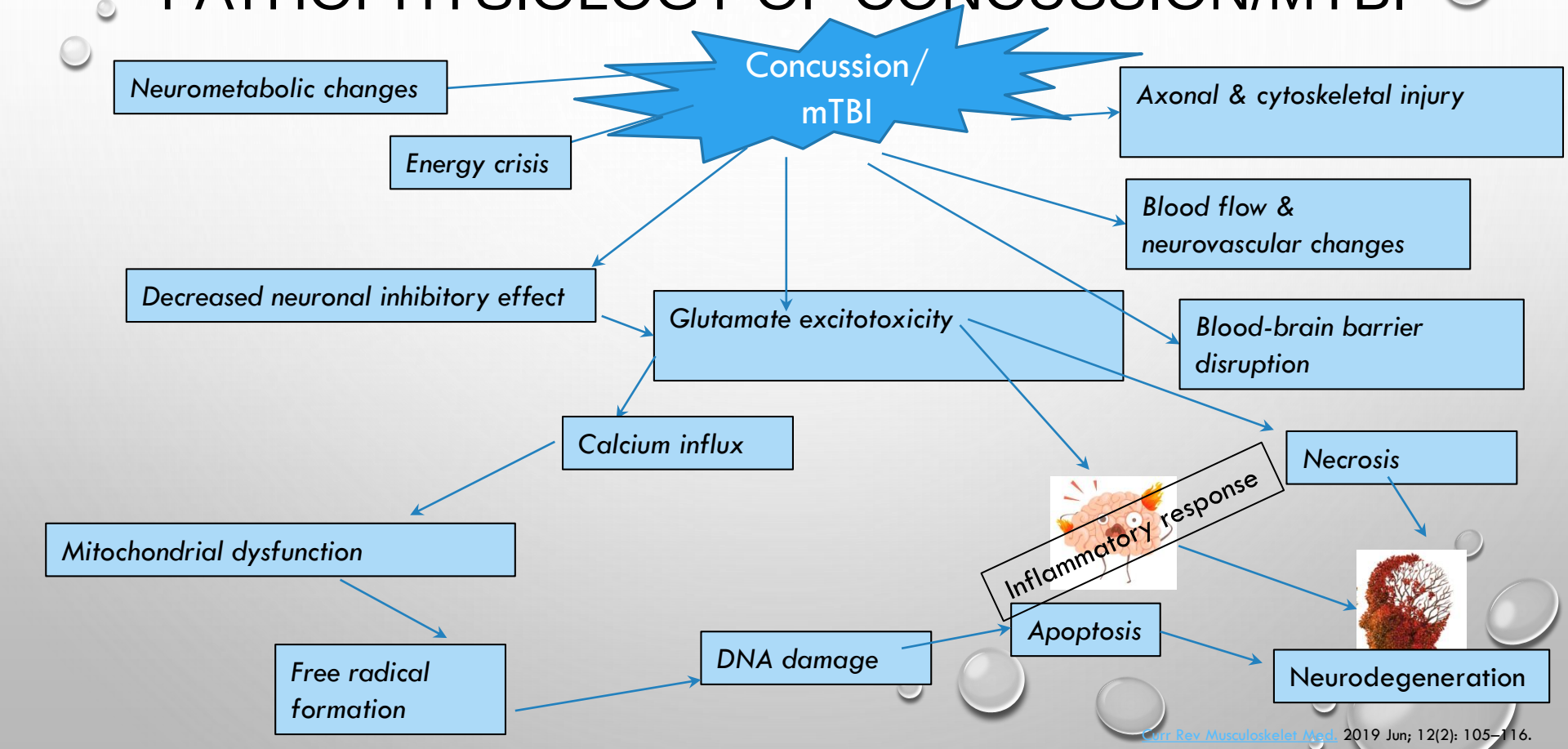
TYPES OF BRAIN INJURIES

- **CONCUSSION/MILD TRAUMATIC BRAIN INJURY (MTBI)**
  - often used interchangeably
    - mTBI Glascow Coma scale 13-15 at 30min post-injury +
      - <30min LOC
      - <24hr post-traumatic amnesia
      - Impaired mental status at time of accident (confusion, disorientation etc)
      - Transient neurological deficit
- Moderate-severe TBI: bruising or contusion, tearing/laceration, bleeding

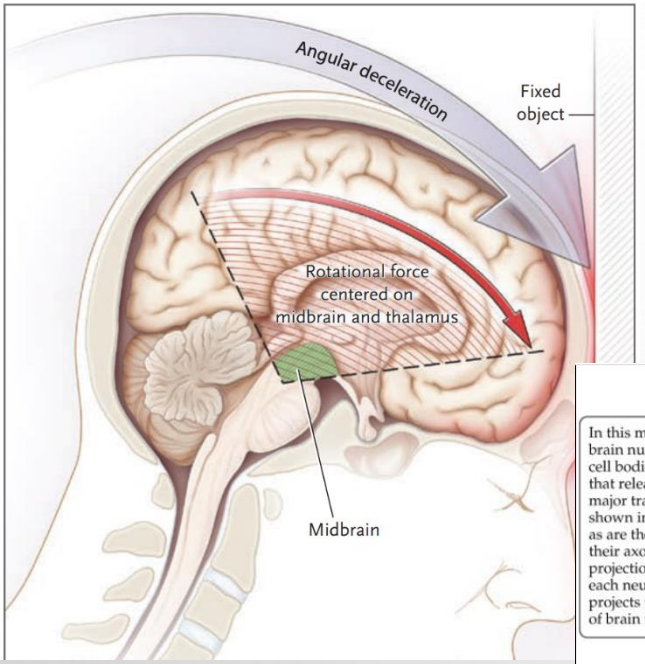
CONCUSSION

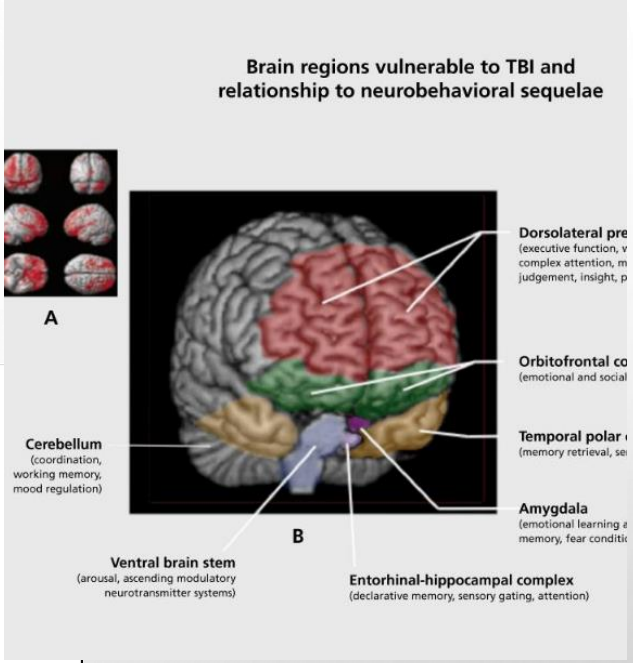
- Acute neurophysiological effect of blunt impact or other mechanical energy applied to the head or other body part such as from sudden acceleration, deceleration or rotational forces.
  - trauma does not have to be directly to head, can be from whiplash effect on the brain or trauma elsewhere on the body
  - immediate and temporary alteration of mental functioning due to trauma

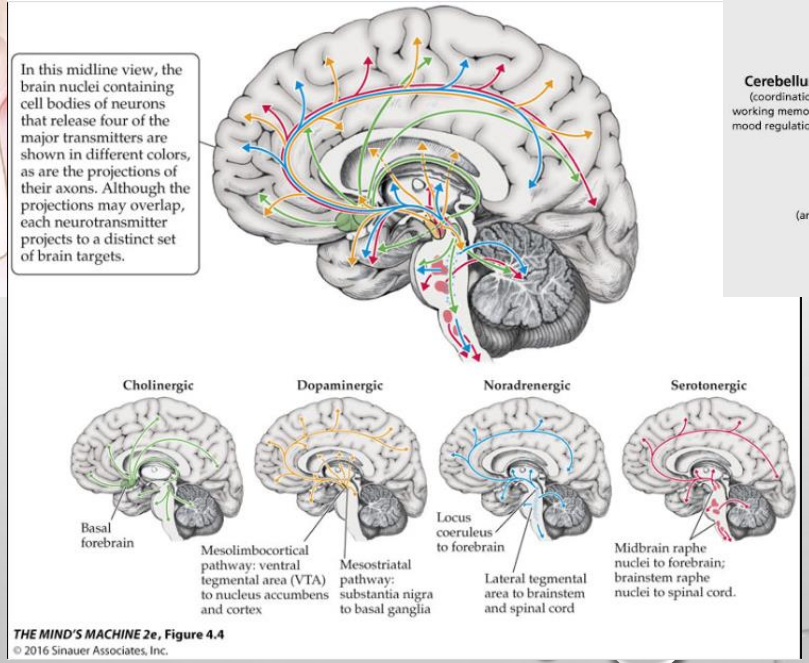
PATHOPHYSIOLOGY OF CONCUSSION/MTBI



Curr Rev Musculoskelet Med. 2019 Jun; 12(2): 105–116.







NEJM, 2011; THE MIND'S MACHINE 2004, ARCINIEGAS 2001

SYMPTOM HETEROGENEITY AMONG PATIENTS

COGNITIVE SYMPTOMS

Difficulty thinking-confusion

Slowed processing

Difficulty remembering

Unable to concentrate

PERSONALITY/MOOD

Irritable

Depression

Anxiety

Lability

Impulsivity

Sleep changes

PHYSICAL

Headache

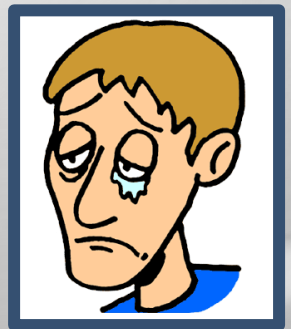
Vision abnormalities

Dizziness/Vertigo

Sensitivity to light or noise

Balance problems

Fatigue



PERSISTENT SYMPTOMS OF CONCUSSION
AKA POST-CONCUSSION SYNDROME

- *Heterogeneous concept with different definitions (**DSM-IV, ICD-10**)*
- ***Berlin consensus statement 2016**: 'PERSISTENT SYMPTOMS' FOLLOWING SPORT RELATED CONCUSSION C SHOULD REFLECT FAILURE OF NORMAL CLINICAL RECOVERY—THAT IS, SYMPTOMS THAT PERSIST BEYOND EXPECTED TIME FRAMES (IE, >10–14 DAYS IN ADULTS AND >4 WEEKS IN CHILDREN).*
- 10% (-58%) of people do not recover from concussion/mTBI within 3 months
- Concussions can lead to serious somatic, affective, & cognitive sequelae
- Persist for months, years or permanently following injury
- Can occur after 1 but more common after repeated concussions

Jotwani et al, Curr Sports Med Report, 2010 Jan-Feb;9(1):21-6

DELAYED EFFECTS OF TBI

DELAYED EFFECTS OF CONCUSSION/MTBI

- TBI (all severities) associated with increased risk of dementia
- Lancet Report: TBI is a modifiable risk factor for dementia
  - Single mTBI increased risk of dementia (OR 1.6, 95% CI 1.6–1.7)
  - Multiple TBIs increased the risk of dementia OR 2.8, 2.5–3.2
  - Study of 178779 veterans with TBI with propensity matched veterans without TBI found dementia risk was associated with TBI severity (**HR 2.4, 95% CI 2.1–2.7 for mild TBI without loss of consciousness; 2.5, 2.3–2.8 for mild TBI with loss of consciousness;** and 3.8, 3.6–3.9 for moderate to severe TBI)
  - A cohort study of 28815 older adults with concussion, found the risk of dementia doubled, with 1 in 6 developing dementia over a mean follow-up of 3.9 years

Tolppanen, 2017 Alz Dem; Barnes JAMA 2019 Neurology; Yaffe 2019 Neurology; Redelmeier 2019 JAMA Neurology; Livingston 2020 Lancet

CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)

- **Progressive**, neurodegenerative process
- Triggered by repetitive mild traumatic brain injury (mTBI) - including concussive & subconcussive blows
- Evolves **slowly** over decades
- Symptoms usually appear **years after injury but can be worsening of PCS**

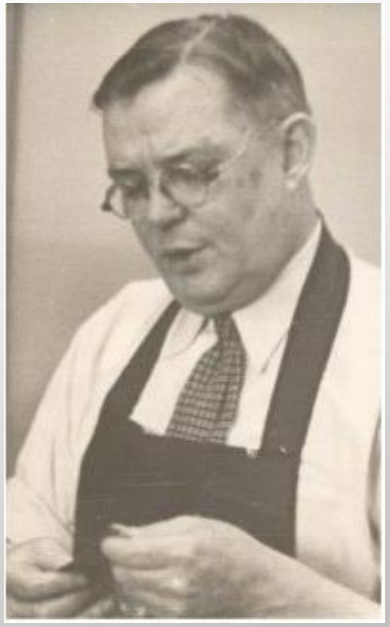
CHRONIC TRAUMATIC ENCEPHALOPATHY

- First described in boxers but now observed in hockey, football and other sports as well as military, motor vehicle accidents, abuse.

DEMENTIA PUGILISTICA

- First reported by Martland 1928 in boxers

- motor, psychiatric, & cognitive symptoms
- progressive, evolving gradually or after a significant bout
- boxers progress to Dementia Pugilistica 7-35 years after initiation of boxing - often many years after last boxing match
- Dementia Pugilistica usually occurs in professional boxers who have had multiple bouts and who are known for "taking a punch”



CHRONIC TRAUMATIC ENCEPHALOPATHY

- described by B. Omalu in 2005, in a NFL player

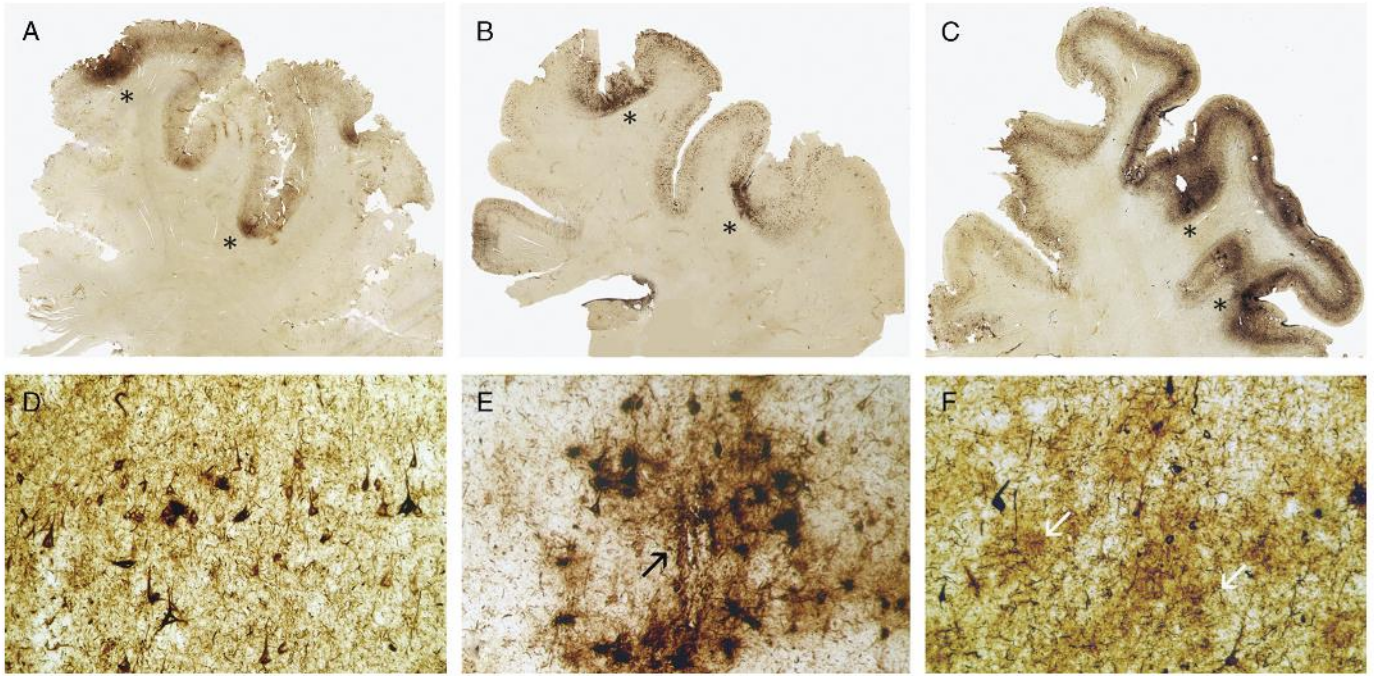


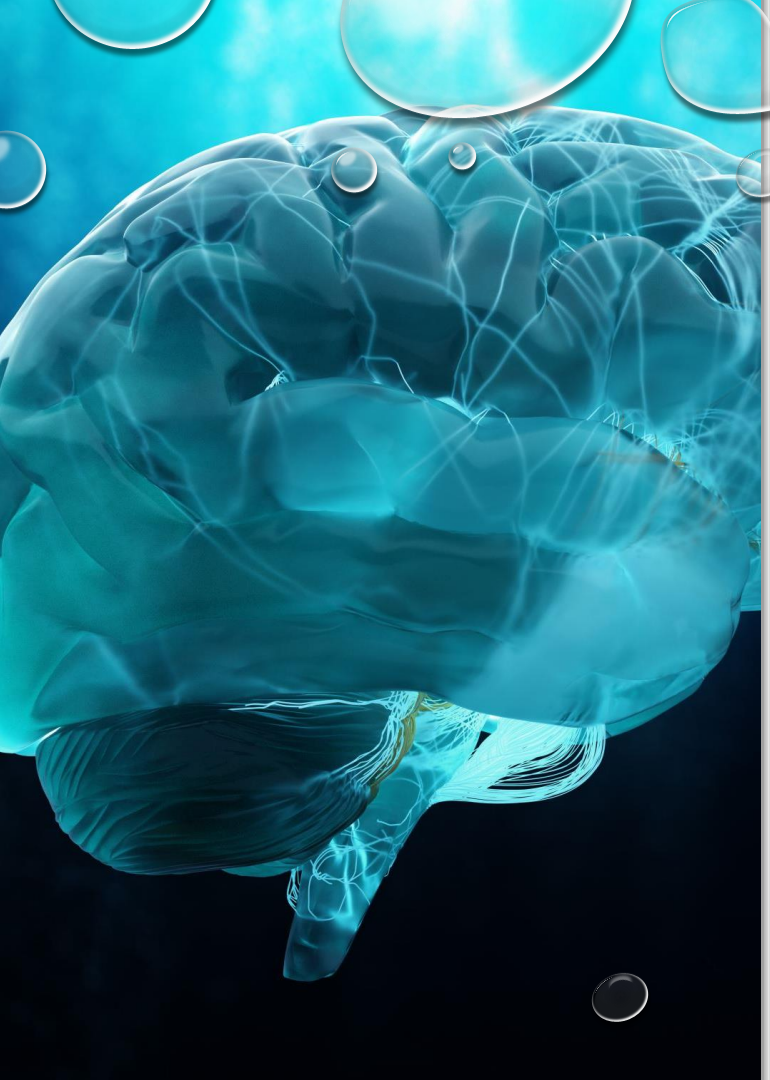
FIGURE 2. (A–C) Whole-mount 50-μm coronal sections of superior frontal cortex from Case A **(A)**, Case B **(B)**, and Case C **(C)**

Omalu, Neurosurgery, 2005, McKee, JNEN, 2009

SYMPTOMS OF CHRONIC TRAUMATIC ENCEPHALOPATHY

Behavioral/ Psychiatric	Cognitive	Motor
• Emotional lability • Explosivity • Impulse control • Inappropriate/disinhibited • Morbid jealousy • Paranoia • Aggression/violent • Mood disturbance (depression, anxiety, mania, suicidality, hopelessness, apathy) • Disinhibition • Psychosis	• Memory • Attention • Concentration • Executive function • Language • Visuospatial • Dementia	• Parkinsonism • Progressive incoordination & difficulty ambulating • Few developed ALS-like • Dysarthria • Gait ataxia

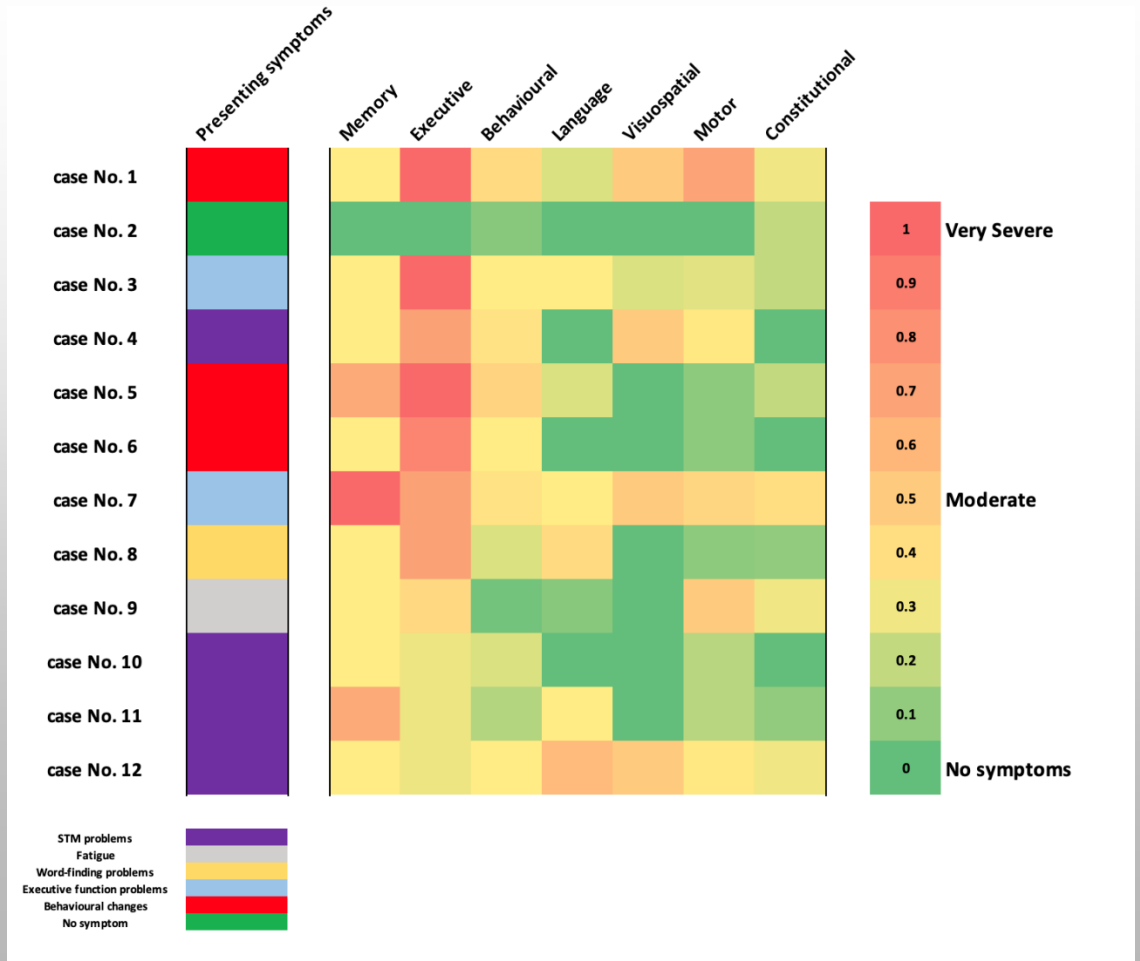
Critchley 1957; Roberts 1969; Ryan 1998; Morrison 1986; Guterman and Smith 1987; Mendez 1995; Erlanger et al 1999; Jordan 2000; Blennow et al 2005; Toth et al 2005, Stern 2013



OUR BRAIN DONATION COHORT

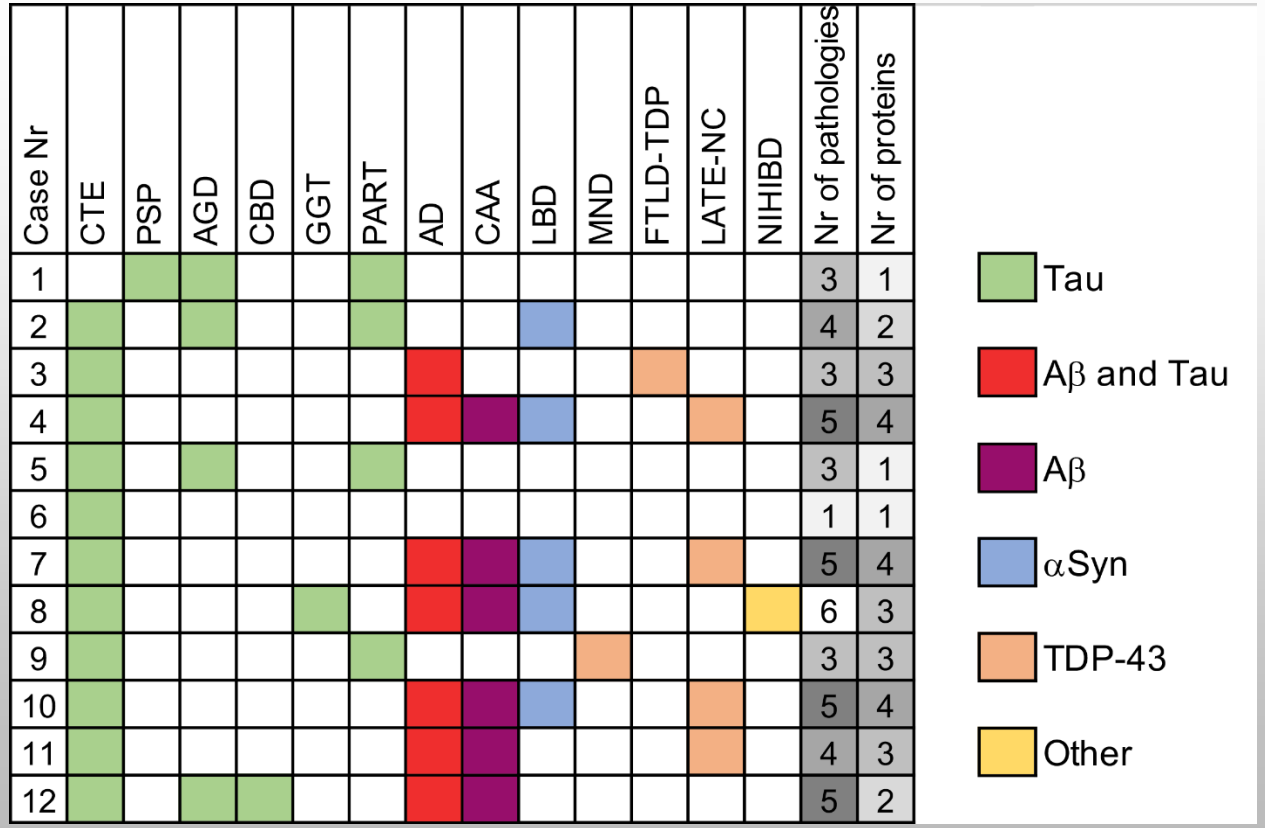
11/12 HAVE CTE IN BRAIN

SUMMARY OF 12 CASES FOLLOWED BY CCC



Taghdiri, under review

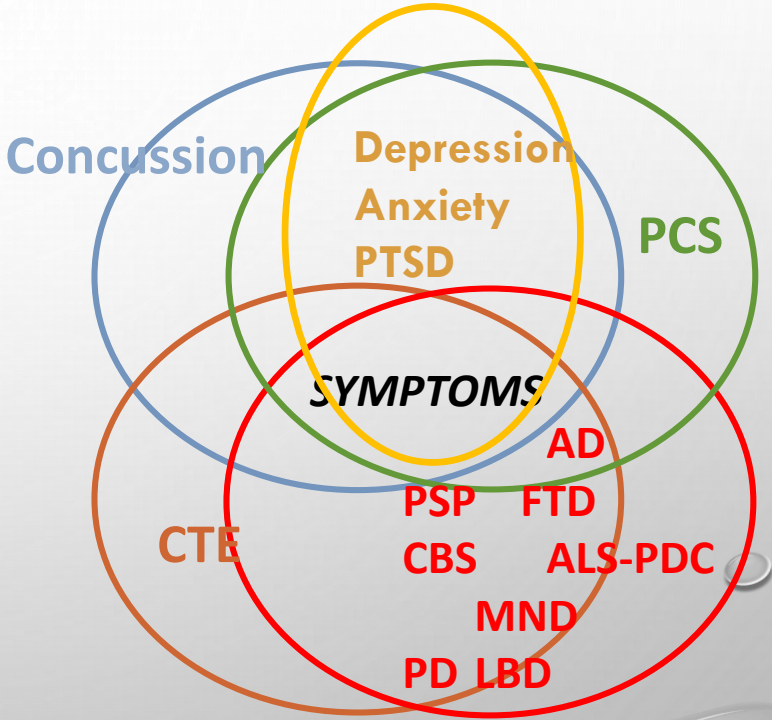
SUMMARY



Courtesy of Dr. Gabor Kovacs

THE CHALLENGE OF DETECTING PCS & (CTE) *IN VIVO*

Multitude of symptoms:
Anxiety; Depression; Irritability/aggression/violent outbursts; Poor insight/ judgment; Apathy; Memory loss; Concentration deficits; Dysarthria; Parkinsonism;

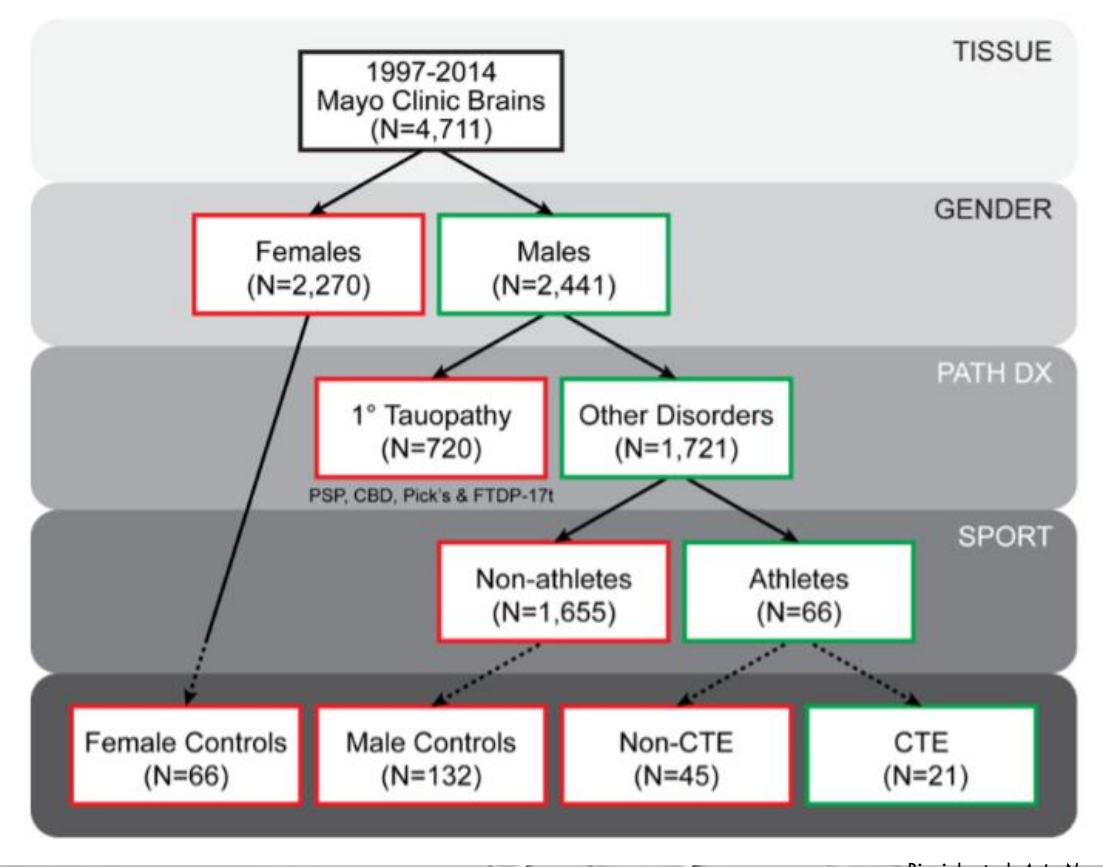


Front in Neuroscience, 2013

CTE OUTSIDE OF ATHLETES: 0 - 2.2%

- ADAMS ET AL: 1 OF 164 BRAIN DONORS FHS STUDY (0.6%)
- FORREST ET AL: 0 OF 310 VIENNA TRANS-DANUBE AGEING STUDY
- POSTNUPTA ET AL: 3 OF 532 DONORS IN SEATTLE ACT STUDY (0.6%)
- SUTER ET AL, 2022: 4 OF 180 DONORS ROYAL PRINCE ALFRED HOSPITAL
- IN SYDNEY, AUSTRALIA (2.2%)
- MCCANN ET AL, 2022: 5 OF 636 SYDNEY BRAIN BANK (0.8%)

CTE IN NON-PROFESSIONAL ATHLETES



Bieniek et al, *Acta Neuropathol*. 2015 December ; 130(6): 877–889.

MTBI/CONCUSSION & DEMENTIA

- Increasing evidence that mTBI can increase risk of Dementia
  - retrospective population-based case-controlled 25 yr retrospective study using province-wide (Man) medical health data collected 1 Apr-31 Mar 1990–1991 to 2014–2015
  - 28021M (mean age ±sd, 25±18yrs) & 19462W (30±21 years) in concussion group; 81871M (25±18 years) & 57159W (30±21yrs) in the matched control group
  - Outcomes: Dementia, ADHD, PD, Mood disorder

Table 4 Hazard ratios for risk of dementia diagnosis

Age of diagnosis			
	Mean±SD		
Control	73.8±19.3		
Concussion	71.0±19.6	Corrected for SEF and CMI	
Model 1a		**Model 1b**	
HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
1.75 (1.63 to 1.87)	<0.001	1.72 (1.61 to 1.84)	<0.001
Model 2a Sex interaction		**Model 2b**	
0.95 (0.83 to 1.09)	0.49	0.93 (0.82 to 1.07)	0.33
Model 3a Multiple concussion		**Model 3b**	
1.70 (1.59 to 1.82)	<.001*	1.67 (1.56 to 1.79)	<.001*
1.63 (1.26 to 2.11)	<0.001†	1.62 (1.25 to 2.10)	<0.001†
1.19 (0.62 to 2.28)	0.60‡	1.20 (0.63 to 2.30)	0.60‡
Model 4a Controlling for other conditions of interest		**Model 4b**	
1.55 (1.45 to 1.67)	<0.001	1.54 (1.43 to 1.65)	<0.001
Model 5a Proportionality model		**Model 5b**	
0.97 (0.97 to 0.98)	<0.001	0.97 (0.97 to 0.98)	<0.001

Morissette MP, et al. Fam Med Com Health 2020;8:e000390.

MTBI/CONCUSSION & PARKINSON'S DISEASE

Table 5 Hazard ratios for risk of Parkinson's disease diagnosis

Age of diagnosis			
	Mean±SD		
Control	62.0±17.5		
Concussion	59.6±17.3	Corrected for SEF and CMI	
Model 1a		**Model 1b**	
HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
1.61 (1.45 to 1.80)	<0.001	1.57 (1.41 to 1.75)	<0.001
Model 2a Sex interaction		**Model 2b**	
0.94 (0.76 to 1.16)	0.56	0.94 (0.76 to 1.16)	0.55
Model 3a Multiple concussion		**Model 3b**	
1.58 (1.42 to 1.76)	<.001*	1.54 (1.38 to 1.72)	<.001*
1.11 (0.70 to 1.76)	0.67†	1.11 (0.70 to 1.76)	0.67†
2.91 (1.28 to 6.65)	0.01‡	2.96 (1.29 to 6.77)	0.01‡
Model 4a Controlling for other conditions of interest		**Model 4b**	
1.31 (1.17 to1.46)	<0.001	1.28 (1.15 to 1.44)	<0.001
Model 5a Proportionality model		**Model 5b**	
0.98 (0.98 to 1.02)	0.81	0.98 (0.98 to 1.02)	0.88

Morissette MP, et al. Fam Med Com Health 2020;**8**:e000390.

MTBI/CONCUSSION

Regardless of age, sex, socioeconomic status and residence, having suffered a single concussion in one's lifetime increased the likelihood of later being diagnosed with:

Parkinson's disease by 57%
Dementia by 72%
ADHD (Attention-Deficit Hyperactivity Disorder) by 39%
Mood and Anxiety Disorders (MADs) by 72%
Sustaining multiple concussions further increased the risk for developing both PD and dementia.

Morissette MP, et al. Fam Med Com Health 2020;**8**:e000390.

- Older participants without known dementia enrolled in 1 of 3 longitudinal, community-based cohort studies of aging and cognition: THE RELIGIOUS ORDERS STUDY, THE RUSH MEMORY AND AGING PROJECT, OR THE MINORITY AGING RESEARCH STUDY

Table 1. Demographic, Clinical, and Neuropathologic Characteristics of the Study Participants[a]

Characteristic	All participants (N = 1689)	No TBI (n = 1024)	TBI with LOC (n = 161)	TBI without LOC (n = 504)	*P* value
Demographic characteristics					
Age at death, mean (SD), y	89.2 (6.7)	89.0 (6.7)	89.5 (7.7)	89.6 (6.4)	.26
Sex					
Female	1138 (67)	681 (66)	97 (60)	360 (71)	.02
Male	551 (33)	343 (33)	64 (40)	144 (29)	
Race					
Black	80 (5)	54 (5)	2 (1)	24 (5)	.08
White	1601 (95)	968 (95)	157 (99)	476 (95)	
Ethnicity					
Latino	46 (3)	26 (3)	7 (4)	13 (3)	.41
Non-Latino	1639 (97)	996 (97)	154 (96)	489 (97)	
Educational level, mean (SD), y	16.2 (3.6)	16.0 (3.5)	16.6 (3.7)	16.6 (3.8)	.004

Agrawal, JAMA Network Open. 2022;5(4):e229311.

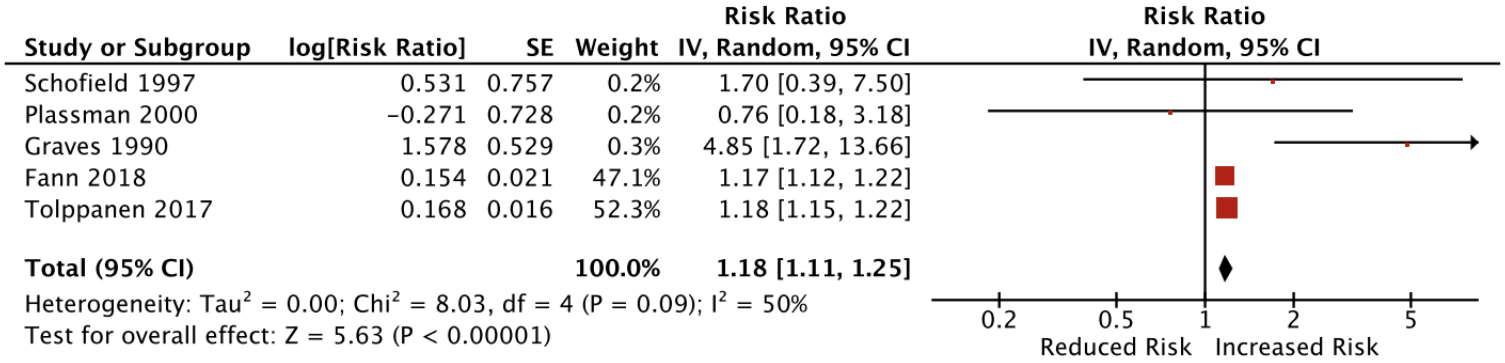
Table 1. Demographic, Clinical, and Neuropathologic Characteristics of the Study Participants[a]

Characteristic	All participants (N = 1689)	No TBI (n = 1024)	TBI with LOC (n = 161)	TBI without LOC (n = 504)	*P* value
Demographic characteristics					
Apolipoprotein E ε4[b]	428 (26)	270 (27)	43 (27)	115 (24)	.40
Burden of vascular risk factors at last evaluation, mean (SD)[c]	1.07 (0.85)	1.06 (0.85)	1.20 (0.87)	1.05 (0.82)	.12
Hypertension	1127 (67)	662 (65)	119 (74)	346 (69)	.03
Diabetes	363 (21)	214 (21)	37 (23)	112 (22)	.74
Smoking history	532 (32)	321 (31)	59 (37)	152 (30)	.29
Burden of vascular disease at last evaluation, mean (SD)[c]	0.69 (0.78)	0.65 (0.76)	0.76 (0.79)	0.76 (0.82)	.01
History of stroke	354 (21)	203 (20)	35 (22)	116 (23)	.35
History of myocardial infarction	352 (21)	198 (19)	38 (24)	116 (23)	.16
History of claudication in lower limbs	465 (28)	262 (26)	50 (31)	153 (31)	.08
Neuropathologic characteristics					
Square root of amyloid-β load, mean (SD)	1.54 (1.12)	1.5 (1.13)	1.74 (1.15)	1.58 (1.08)	.03
Square root of τ-tangles burden, mean (SD)	1.62 (1.36)	1.62 (1.36)	1.47 (1.30)	1.67 (1.37)	.25
AD pathologic diagnosis	1081 (64)	644 (63)	105 (65)	332 (66)	.49
PD pathologic diagnosis[d]	139 (8)	81 (8)	13 (8)	45 (9)	.83
Neocortical LBs[e]	224 (13)	120 (12)	27 (17)	77 (15)	.06
LATE-NC stage[f]					
0	759 (48)	449 (48)	82 (53)	228 (47)	.72
1	293 (19)	177 (19)	23 (15)	93 (19)	
2	156 (10)	97 (10)	16 (10)	43 (9)	
3	368 (23)	215 (23)	33 (21)	120 (25)	
Hippocampal sclerosis[g]	160 (9)	89 (9)	56 (11)	15 (9)	.32
Gross infarcts					
No infarct	1090 (64)	680 (66)	93 (58)	317 (63)	.08
1 Infarct	312 (18)	176 (17)	31 (19)	105 (21)	
Multiple infarcts	287 (17)	168 (16)	37 (23)	82 (16)	
Microinfarcts					
No infarct	1178 (70)	738 (72)	97 (60)	343 (68)	.01
1 Infarct	304 (18)	179 (17)	36 (22)	89 (18)	
Multiple infarcts	207 (12)	107 (10)	28 (17)	72 (14)	

Mild Traumatic Brain Injuries and Future Risk of Developing Alzheimer's Disease: Systematic Review and Meta-Analysis

Table 1
Study characteristics, baseline demographics, factors adjusted for, follow up duration and relative risks

	Study Design	Sample Size	Head Injury Measure	AD Measure	Follow-up (y)	Age (y), Mean (SD)*	Female *n* (%)	RR (95% CI)**	Adjustment
Graves et al. (1990) USA [36]	Case-control	260	Structured Interview	DSM-III-R, NINCDS-ADRDA	10–30	64.9 (NR)	60 (46)	4.85 (1.72, 13.66)	Age, family history of AD
Schofield et al. (1997) USA [35]	Cohort	271	Structured Interview	NINCDS-ADRDA	>30	75.3 (7.3)	197 (73)	1.70 (0.39, 7.50)	Age, sex, education
Plassman et al. (2000) USA [34]	Cohort	1776	Medical Records	DSM-III-R, NINCDS-ADRDA	51–53	72.9 (NR)	0	0.76 (0.18, 3.18)	Education, age, *APOE* ε4
Tolppanen et al. (2017) Finland [37]	Case-control	352,581	National Register	NINCDS-ADRDA, DSM-IV	>5	80.1 (7.1)	230,580 (65)	1.18 (1.15, 1.22)	Socioeconomic position, physical health, drug use
Fann et al. (2018) Denmark [33]	Cohort	2,794,852	National Register	ICD-9	4–18	80.7 (8.7)	NR	1.17 (1.12, 1.22)	Sociodemographic, substance abuse, stroke, cardiovascular diseases, diabetes, hip fracture, asthma or chronic obstructive pulmonary diseases, use of antipsychotics, antidepressants, antiepileptics, benzodiazepines and related drugs



Graham, Journal of Alzheimer's Disease 87 (2022) 969–979

Failure to detect an association between self-reported traumatic brain injury and Alzheimer's disease neuropathology and dementia

Introduction: Recent research with neuropathologic or biomarker evidence of Alzheimer's disease (AD) casts doubt on traumatic brain injury (TBI) as a risk factor for AD. We leveraged the National Alzheimer's Coordinating Center to examine the association between self-reported TBI with loss of consciousness and AD neuropathologic changes, and with baseline and longitudinal clinical status.

Methods: The sample included 4761 autopsy participants (453 with remote TBI with loss of consciousness; 2822 with AD neuropathologic changes) from National Alzheimer's Coordinating Center.

Results: Self-reported TBI did not predict AD neuropathologic changes ($P > .10$). Reported TBI was not associated with baseline or change in dementia severity or cognitive function in participants with or without autopsy-confirmed AD.

Discussion: Self-reported TBI with loss of consciousness may not be an independent risk factor for clinical or pathological AD. Research that evaluates number and severity of TBIs is needed to

M.A. Sugarman et al. / Alzheimer's & Dementia 15 (2019) 686-698

TBI & LEWY BODY DISEASE PATHOLOGY

- In prospective cohort studies (Religious Orders Study and the Memory and Aging Project (ROS and MAP) and Adult Changes in Thought (ACT)
  - 7130 adults and 1,589 autopsy. Exposure—self reported TBI (free of dementia)
  - TBI with LOC < or > 1hr
  - 865 participants reported TBI with LOC
  - In >45,000 person-years of follow-up,: 1,537 dementia and 117 incident PD
    - No association between TBI with LOC and incident dementia or Alzheimer's disease
    - There were associations between TBI with LOC and incident Parkinson's disease and progression of parkinsonian signs
    - Association between TBI with LOC and Lewy bodies

JAMA Neurol. 2016 September 01; 73(9): 1062–1069

TBI & PARKINSON'S DISEASE

JAFARI ET AL.

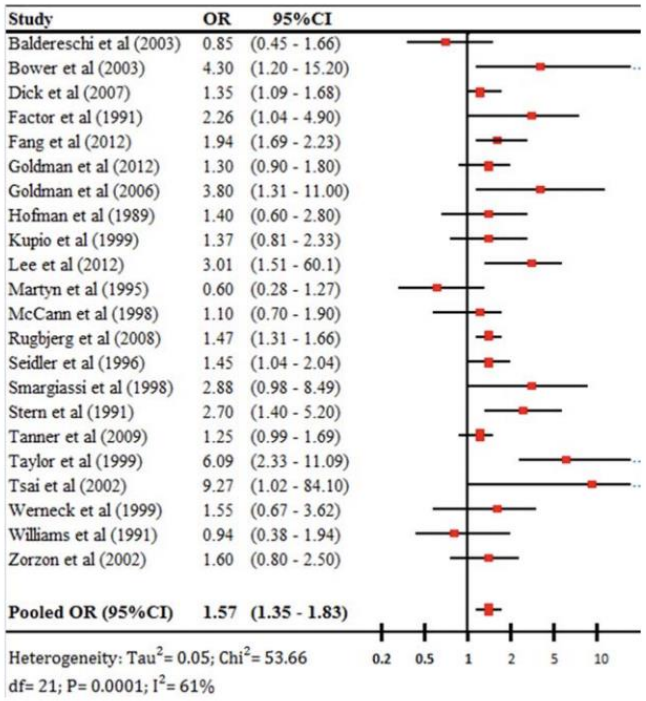


FIG. 2. This forest plot illustrates the odds ratios (ORs) and corresponding confidence intervals (CIs) from studies of Parkinson's Disease and head trauma. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

META_ANALYSIS
TBI & PD

18,344 cases and 79,028 controls were included in the analysis. pooled OR for the association of PD and head trauma was 1.57 (95% CI, 1.35–1.83; I2 statistic, 61%)

Cannot differentiate b/w mild TBI and mod-severe TBI

Movement Disorders, Vol. 28, No. 9, 2013

TBI + CTE + LEWY BODY DISEASE

TABLE 2. Clinical and Exposure Measures Between CTE Pathology Groups

TABLE 3. Contact Sports Play as a Predictor of Neocortical Lewy Body Disease in the FHS, UNITE, and Combined Brain Banks

	FHS (n = 149)		UNITE (n = 204)		Combined (n = 353)	
Predictors	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
Years of contact sports play	1.30 (1.06–1.60)	0.012	1.15 (1.03–1.28)	0.013	1.07 (1.01–1.13)	0.014
Contact sports play >8 years	40.0 (1.75–912)	0.028	1.71 (0.20–14.9)	0.627	6.24 (1.53–25.4)	0.011

FHS: Framingham Heart Study; UNITE: Understanding Neurologic Injury and Traumatic Encephalopathy; participants limited to those with *APOE* genotype data. Cohort-specific and pooled analyses adjusting for age, sex, and APOE ε4.

Dementia	61.4%	91.4%	100%	<0.001*,†,‡
Parkinsonism	19.5%	60.0%	30.8%	<0.001*,†
APOE ε4 presence ± (%)	28/53 (34.6%)	15/19 (44.1%)	7/8 (46.7%)	0.495*

Numbers are presented as mean (SEM); subjects <50 years-old excluded.
*χ^2 test for proportions.
†$p < 0.05$ for comparison between CTE and CTE-LBD.
‡$p < 0.05$ for comparison between CTE and CTE-AD-LBD.
§$p < 0.05$ for comparison between CTE-LBD and CTE-AD-LBD.

TBI & ALZHEIMER'S DISEASE/PARKINSON'S DISEASE ETIOLOGY

- biologically plausible:
  - Head injury involves microglia activation, inflammation, and release of oxygen radicals
  - Head injury may disrupt blood-brain barrier and thus directly expose the brain to neurotoxins or inflammatory agents
  - Altered axonal transport in TBI could contribute to the initiation and spread of a-beta, tau, alpha-syn pathology - animal models of TBI shows transient increases in a-beta deposition, abnormally modified alpha-syn in cortex and striatum; CSF alpha-syn levels increase following acute TBI, PET amyloid has shown uptake

TBI & FRONTOTEMPORAL DEMENTIA

- Deutsch et al, Dement Geriatr Cog Disord 2015; 39(0):143-153
- Wang et al, Neuroscience, Volume 300, 2015, 94-103
- Jawaid A, Neurodegener Dis. 2009;6(5-6):219-20.
- Daneshvar, D JAMA Network Open Vol. 4,12 e2138801. 1 Dec. 2021

HOW ABOUT HEAD TRAUMA & MND/ALS

COMMENTARY

Soccer, neurotrauma and amyotrophic lateral sclerosis: is there a connection?

Ornella Piazza[1,2], Anna-Leena Sirén[1] and Hannelore Ehrenreich[1]

CURRENT MEDICAL RESEARCH AND OPINION VOL. 20, NO. 4, 2004, 505–508

Table 1. *Overview of the available literature associating neurotrauma and ALS*

Reference	Country	Number of individuals	Study type	Remarks
Jelliffe SE[18] J Nerv Ment Dis 1935;82:415-35	USA	92 ALS patients	Retrospective	10 head and/or neck trauma
Kondo K and Tsubaki T[19] Arch Neurol 1981;38:220-6	Japan	Study A: 712 patients with motor neuron disease (511 with ALS), 637 controls Study B: 158 ALS patients and 158 matched controls	Retrospective, questionnaire, case control study Retrospective, questionnaire, case control study	Previous head injury in 42 patients with motor neuron disease and in 7 controls, mechanical injury (unspecified location) in 48 ALS patients and 27 controls
Gawel M, *et al.*[20] J Neurol Neurosurg Psych 1983;46:1041-3	UK	63 ALS patients and 61 controls	Retrospective, questionnaire, case control study	Head injury and fractures in 32 patients and 42 controls in the previous 5 years
Gallagher JP, *et al.*[21] Acta Neurol Scand 1987;75:145-50	USA	135 ALS patients and 85 multiple sclerosis controls	Retrospective, questionnaire, case control study	Head/neck trauma in 31 ALS patients and in 13 multiple sclerosis ≥ 1 year before onset of disease
Williams DB, *et al.*[15] Neurology 1991;41:1554-7	USA	821 head injured patients	Retrospective, cohort study	1 ALS case
Strickland D, *et al.*[16] Acta Neurol Scand 1996;94:45-50	USA	25 ALS and 25 other neuro-muscular disease patients	Retrospective, questionnaire, case control study	Severe head, neck, back trauma in 15 ALS patients and in 8 controls
Mandrioli J, *et al.*[4] Neurology 2003;60:683-9	Italy	143 ALS patients	Retrospective, cohort study	9 patients suffered head injury not more than 30 years before disease onset

Eur J Epidemiol. 2005;20(3):237-42. doi: 10.1007/s10654-004-6879-7.

Proportionate mortality of Italian soccer players: is amyotrophic lateral sclerosis an occupational disease?

Stefano Belli [1], Nicola Vanacore

Younger age of onset for ALS

Ann Ist Super Sanita. 2018 Oct-Dec;54(4):364-369. doi: 10.4415/ANN_18_04_14.

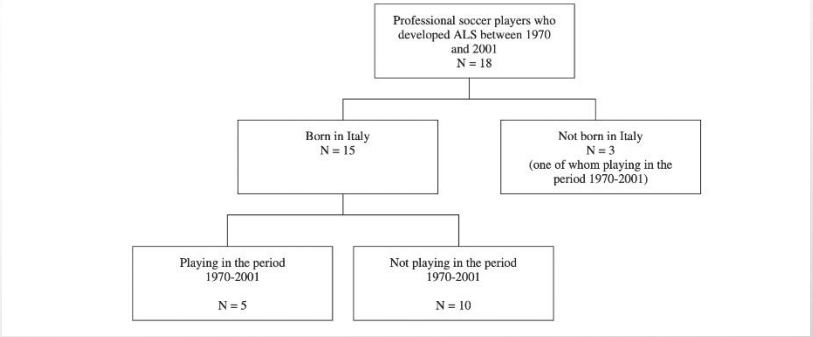
Amyotrophic Lateral Sclerosis and soccer: an internet survey of 29 Italian players

Nicola Vanacore [1], Pierfrancesco Barbariol [1], Bruno Caffari [2], Eleonora Lacorte [1], Ilaria Bacigalupo [1], Stefania Spila Alegiani [2]

doi:10.1093/brain/awh373 *Brain* (2005), **128**, 472–476

Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players

Adriano Chiò,[3] Gianmartino Benzi,[1] Maurizia Dossena,[1] Roberto Mutani[3] and Gabriele Mora[2]



- cohort of 7325 male professional football players
- 1970-2001
- Dose-response relationship: length of activity and ALS dx
- Decreased mean age of onset 51 (>10 yrs lower than expected)

Association of ALS with head injury in a case-control study conducted in New England, USA, (1993–1996)

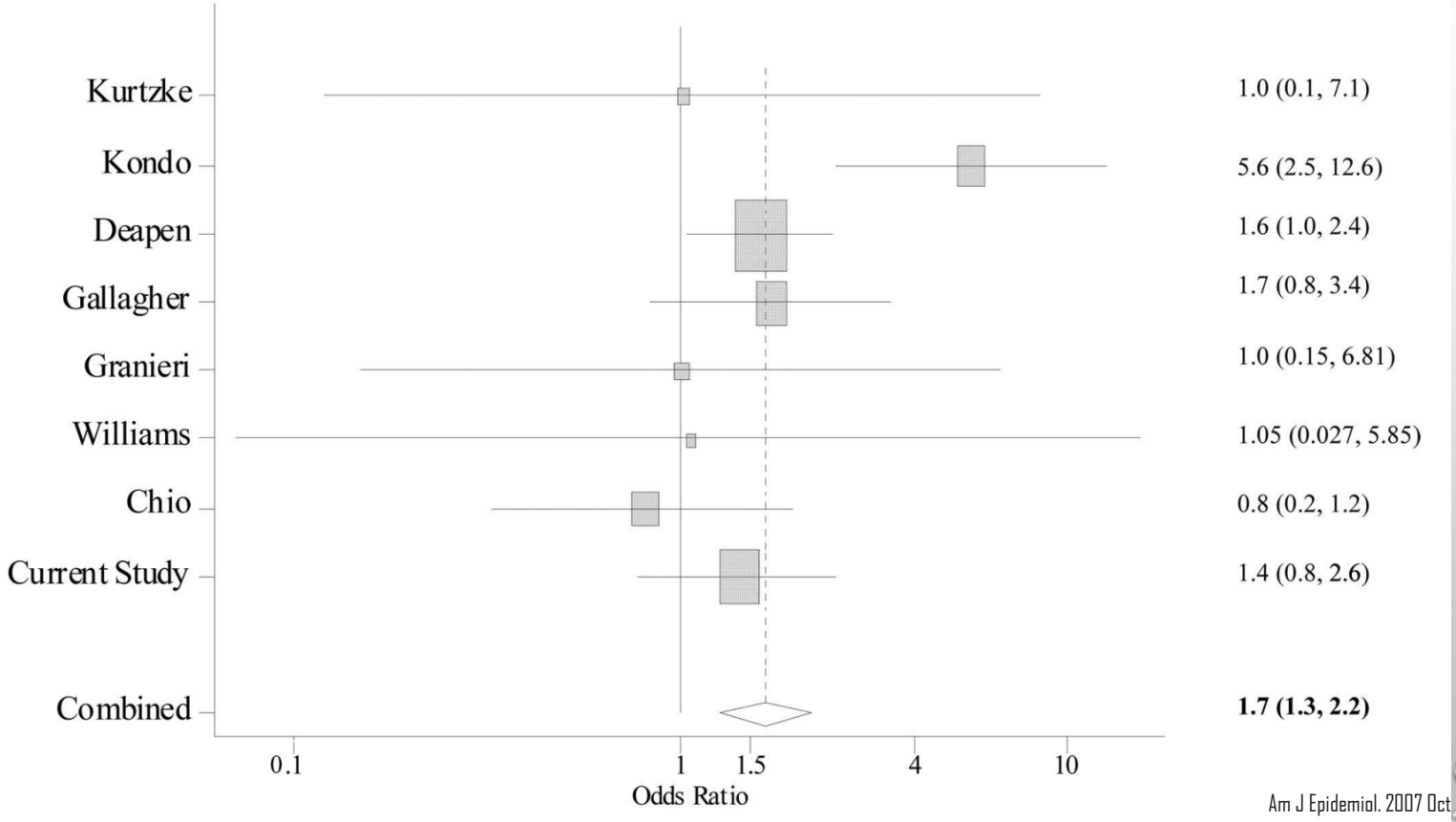
	Cases (%)	Controls (%)	OR (95% CI)	
	n=109	n=255	Model 1*	Model 2†
Number of head injuries				
Never injured	78.0	83.5	1.0	1.0
1 injury	11.9	12.5	1.1 (0.5, 2.2)	0.9 (0.4, 2.0)
>1 injuries	10.1	3.9	2.9 (1.1, 7.6)	3.1 (1.2, 8.1)
Years since last injury				
Never injured	78.0	83.5	1.0	1.0
>30 years	4.6	5.9	0.9 (0.3, 2.7)	0.9 (0.3, 2.7)
10, 30 years	10.1	8.2	1.4 (0.6, 3.1)	1.2 (0.5, 2.9)
≤10 years	7.3	2.4	3.2 (1.0, 9.8)	3.2 (1.0, 10.2)

	Cases (%)	Controls (%)	OR (95% CI)	
	n=109	n=255	Model 1*	Model 2†
Combination of number of head injuries and years since last injury				
Never injured	78.0	83.5	1.0	1.0
1 injury	11.9	12.5	1.1 (0.5, 2.2)	0.9 (0.4, 1.9)
>1 injuries 10 years ago	6.4	3.5	2.2 (0.7, 6.4)	2.2 (0.7, 6.5)
>1 injuries within 10 years	3.7	0.4	9.2 (0.9, 88.3)	11.3 (1.1, 114.3)

Chen et al, Am J Epidemiol. 2007 Oct 1; 166(7): 810–816.

CONCUSSION/MTBI & MOTOR NEURON DISEASE/ALS

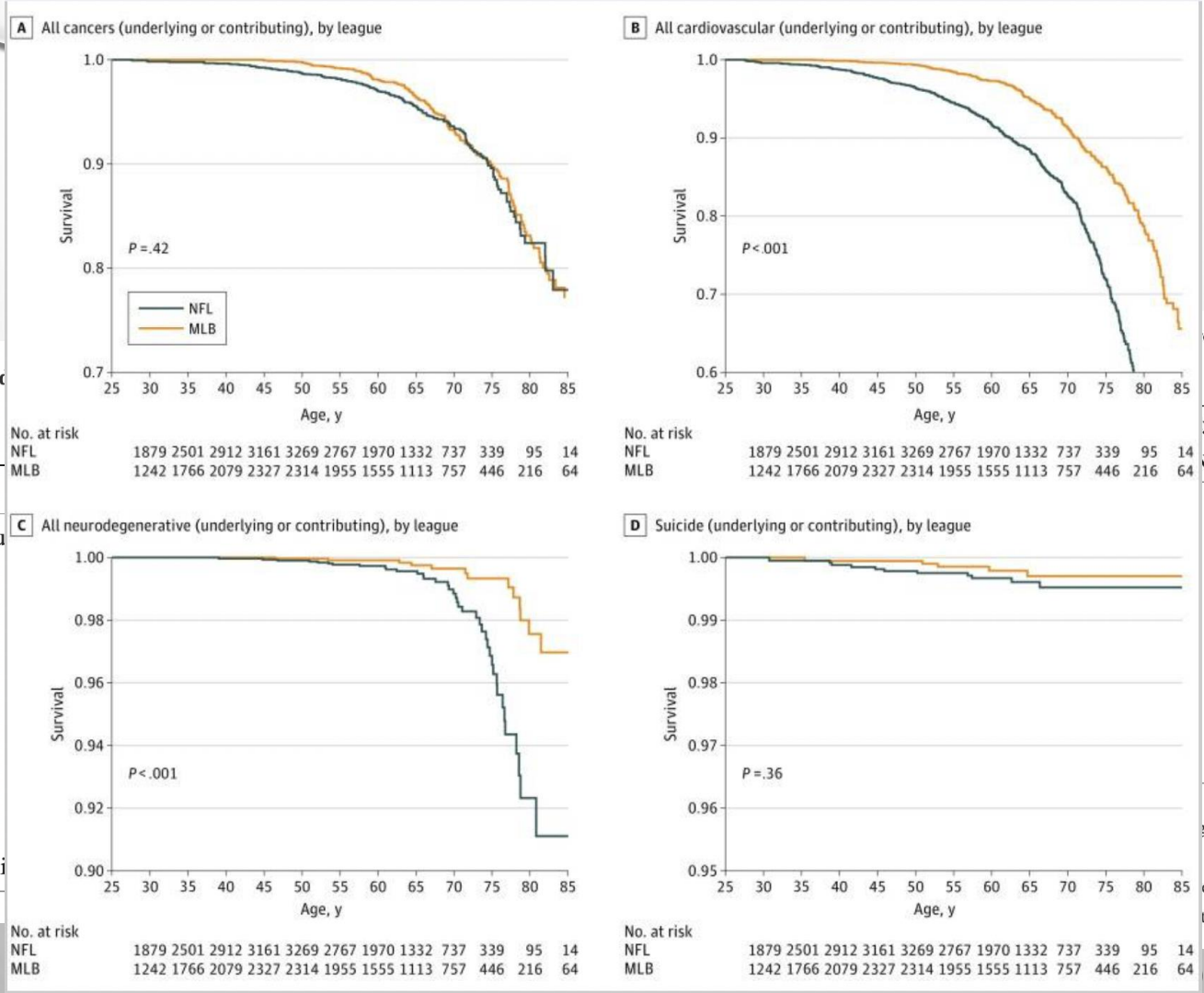
Risk of ALS 1.7 times (95 % CI: 1.3, 2.2, $p < 0.001$) higher among individuals with head injuries



Am J Epidemiol. 2007 Oct 1; 166(7): 810–816.

Characteristics of NFL and

Characteristic
Person-years of follow-u
No. of deaths
White race, No. (%)
Age, mean (SD), y
At debut in league
At start of follow-up
At death
At last date observed, ali



ers[a]

ying or Contributing Cause[b]

No.	MLB, No.	HR (95% CI)
	431	1.26 (1.10-1.44)
	156	1.11 (0.88-1.39)
	225	2.40 (2.03-2.84)
	16	2.99 (1.64-5.45)
	10	2.26 (0.99-5.17)
	3	3.10 (0.84-11.38)
	5	3.45 (1.21-9.83)
	5	1.59 (0.54-4.69)

gue.

e and decade of birth.

t category indicated at least once.

Figure. Study Inclusion and Exclusion Criteria for National Football League (NFL) Cohort and Nested Case-Control Analyses

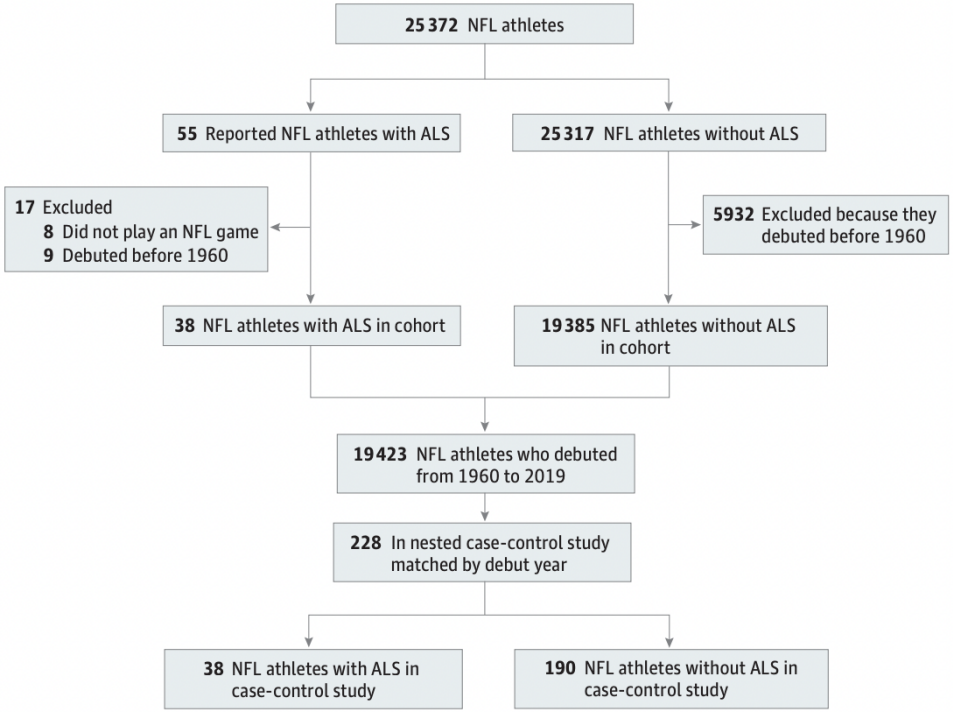


Table 3. Differences Between NFL Athletes With ALS and Matched NFL Athletes Without ALS

Characteristic	Athletes with ALS (n = 38)	Matched athletes without ALS (n = 190)	Odds ratio (95% CI)[a]
Potential ALS risk factors			
Years of NFL play, mean (SD)	7.0 (3.9)	4.5 (3.6)	1.2 (1.1 to 1.3)[b]
BMI at debut, mean (SD)	29.3 (3.2)	29.0 (3.4)	1.0 (0.9 to 1.1)
Black race, No. (%)	14 (36.8)	103 (54.2)	2.0 (1.0 to 4.2)
Markers of fame			
Ever in an NFL Pro Bowl, No. (%)	5 (13.2)	18 (9.5)	1.5 (0.5 to 4.2)
NFL Pro Bowl appearances, mean (SD)	0.18 (0.51)	0.14 (0.49)	1.2 (0.6 to 2.3)
NFL Hall of Fame, No. (%)	0	3 (1.6)	Not applicable
Position, No. (%)[c]			
Nonspeed vs speed	12 (31.6)	53 (27.9)	0.33 (−0.80 to 1.46)

- incidence ratio, 3.59 (2.58-4.93)
- mortality ratio, 3.94; (2.62-5.69)
- among NFL athletes, significantly longer careers (7.0+/-3.9 years) in ALS c/o to others (4.5+/-3.6 years)
- OR 1.2 (1.1-1.3)
- No differences in ALS status based on proxies of NFL fame, BMI, position played, birth location, or race

Daneshvar, D JAMA Network Open Vol. 4,12 e2138801. 1 Dec. 2021

Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football

Neuropathological Findings in 177 American Football Players, Stratified by Severity of Phosphorylated Tau Pathology (CTE Stage)[a]

CTE Stage	No. of Brain Donors	Age at Death, Median (IQR), y	Neuropathological Features, No. (%)						Other Neuropathological Diagnoses, No. (%)					Pure CTE, No. (%)
			Aß	DP	NP	AA	TDP-43	αs	AD	LBD	FTLD TDP-43	FTLD-Tau	MND	
1	11	36 (25-56)	2 (18)	2 (18)	1 (9)	1 (9)	2 (18)	1 (9)	0	1 (9)	1 (9)	0	0	8 (73)
2	33	49 (29-65)	8 (24)	8 (24)	5 (15)	7 (21)	10 (30)	3 (9)	1 (3)	2 (6)	1 (3)	1 (3)	4 (12)	21 (64)
3	76	67 (57-78)	45 (59)	41 (54)	25 (33)	29 (38)	26 (34)	16 (21)	4 (5)	15 (20)	1 (1)	3 (4)	6 (8)	42 (55)
4	57	76 (69-82)	52 (91)	52 (91)	42 (74)	32 (56)	47 (83)	23 (40)	18 (32)	16 (28)	5 (9)	2 (4)	1 (2)	27 (47)
Total	177	67 (53-78)	107 (61)	103 (58)	73 (41)	69 (39)	85 (48)	43 (24)	23 (13)	34 (19)	8 (5)	6 (3)	11 (6)	98 (55)

JAMA. 2017 Jul 25; 318(4): 360–370.

TBI & PROGRESSION OF SYMPTOMS IN PD

- Patients with PD + mild-moderate TBI showed greater decline in cognitive functioning c/w those without a history of TBI

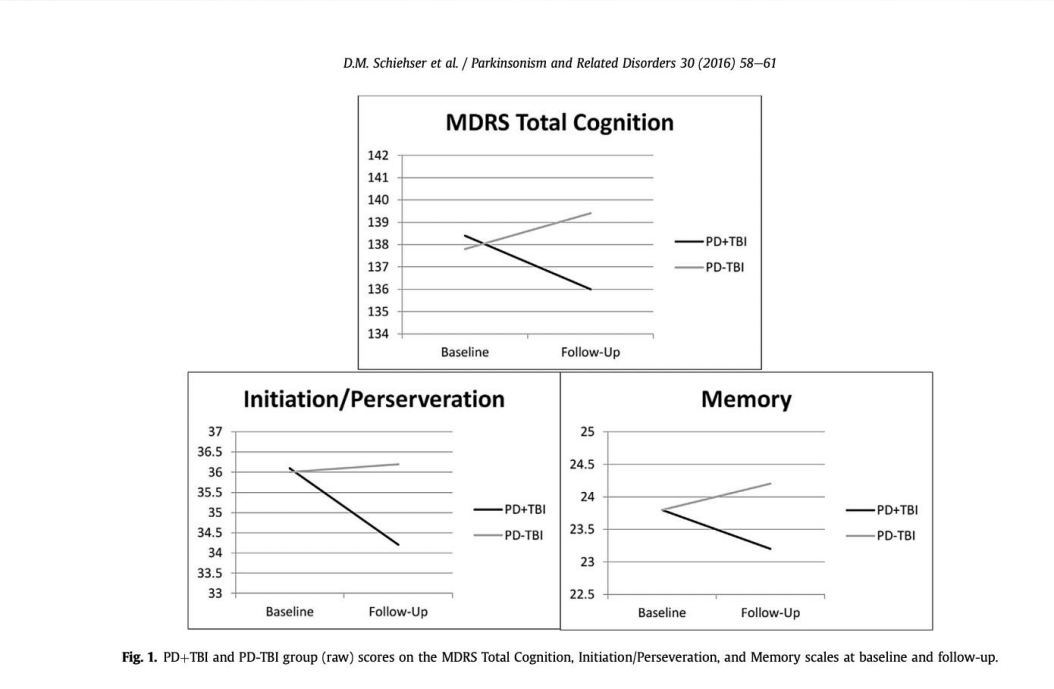


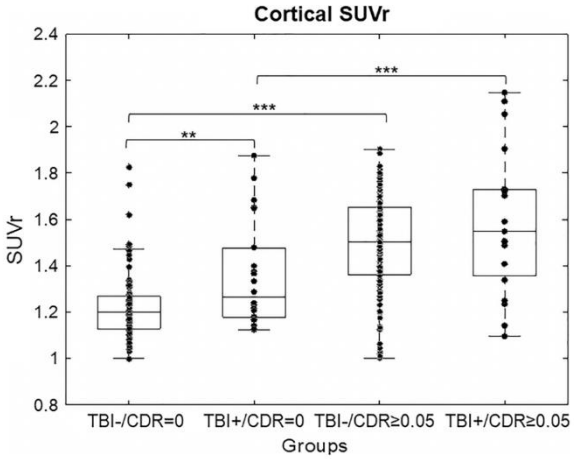
Fig. 1. PD+TBI and PD-TBI group (raw) scores on the MDRS Total Cognition, Initiation/Perseveration, and Memory scales at baseline and follow-up.

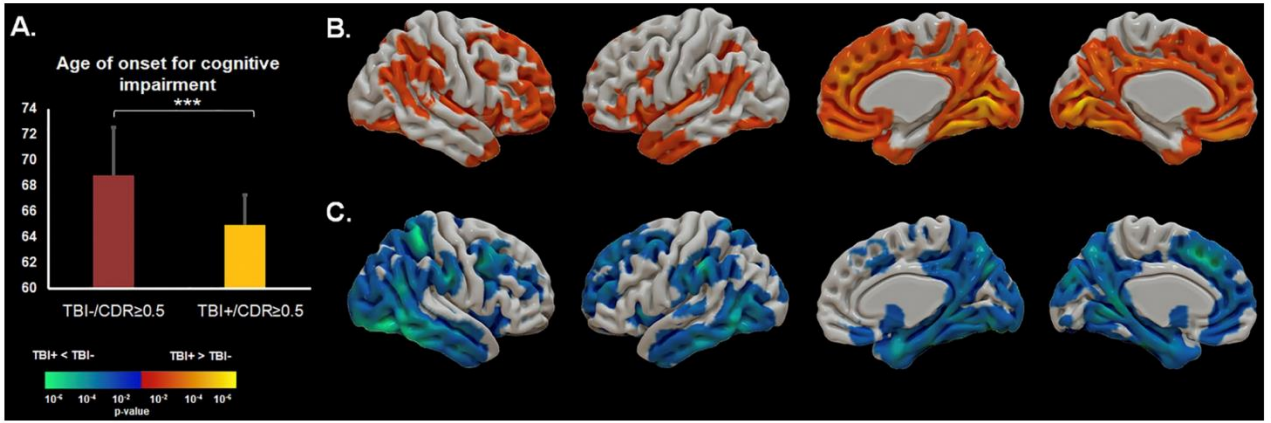
No effect on
Motor function

D.M. Schiehser et al. / Parkinsonism and Related Disorders 30 (2016) 58e61

Table 1 Demographics of the participants in the four different groups

	TBI −/CDR ≥ 0.5	TBI −/CDR = 0	TBI +/CDR ≥ 0.5	TBI +/CDR = 0	*p* overall
Number of participants	*n* = 100	*n* = 100	*n* = 19	*n* = 22	
Age (SD) in years	73.6 (7.8)	70.9 (5.8)	73.5 (8.9)	74.1 (8.1)	0.035
Gender: female/male	48/52	50/50	5/14	9/13	0.265
Handedness: right/left	91/9	89/11	18/1	21/1	0.846
Education (SD) in years	15.8 (2.7)	16.7 (2.4)	15.9 (2.5)	17.6 (2.4)	0.004
APOE-ε4 status (−/+)	64/36	31/69	11/8	9/13	< 0.001
Aβ positivity					< 0.001
Aβ negative	14 (14%)	61 (61%)	2 (11%)	9 (41%)	
Aβ positive	86 (86%)	39 (39%)	17 (90%)	13 (59%)	





Front Neurol. 2021; 12: 573401.
Published online 2021 May 12. doi: 10.3389/fneur.2021.573401
PMCID: PMC8153372
PMID: 34054681

Traumatic Brain Injury Exposure Lowers Age of Cognitive Decline in AD and Non-AD Conditions

Diego Iacono,[1,2,3,4,5,6,*] Sorana Raiciulescu,[7] Cara Olsen,[7] and Daniel P. Perl[1,3]

Front Neu

- 609 NACC SUBJECTS WITH DOCUMENTATION ON TBI
- 361 TBI+ VS 248 TBI-
- TBI+ AND TBI– subjects with a clinical diagnosis of MCI, AD, DLB, PSP, CBD, FTD, vascular dementia, non-ad impairment, and PD.
- RESULTS: Mean age of TBI+ subjects was lower than TBI– subjects at the time of their first cognitive decline assessment (71.6 ± 11.2 vs. 74.8 ± 9.5 year; $p < 0.001$); earlier onset of cognitive decline in TBI+ vs. TBI– subjects was independent of sex, race, attained education, APOE genotype, and clinical diagnoses
- NPS were much more frequent in TBI+ vs. TBI– subjects, including AD and NON-AD neurodegenerative conditions such as PD

SUMMARY

- Concussions/mTBI are implicated in delayed neurodegenerative disease including AD, PD, FTD/ALS but not always
- Concussions/mTBI can alter progression or accelerate symptoms of neurodegenerative disease
- Repeated concussions are the only known risk factor for CTE but very rare in non-professional contact sports

THANK YOU FOR YOUR ATTENTION

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