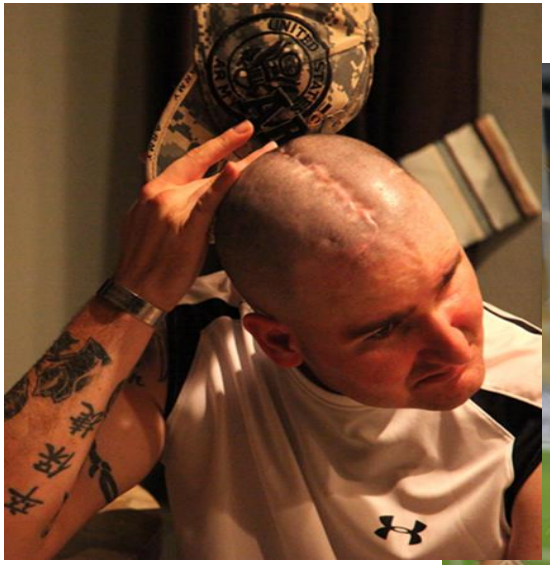
Brain Health 2022: Head Injury



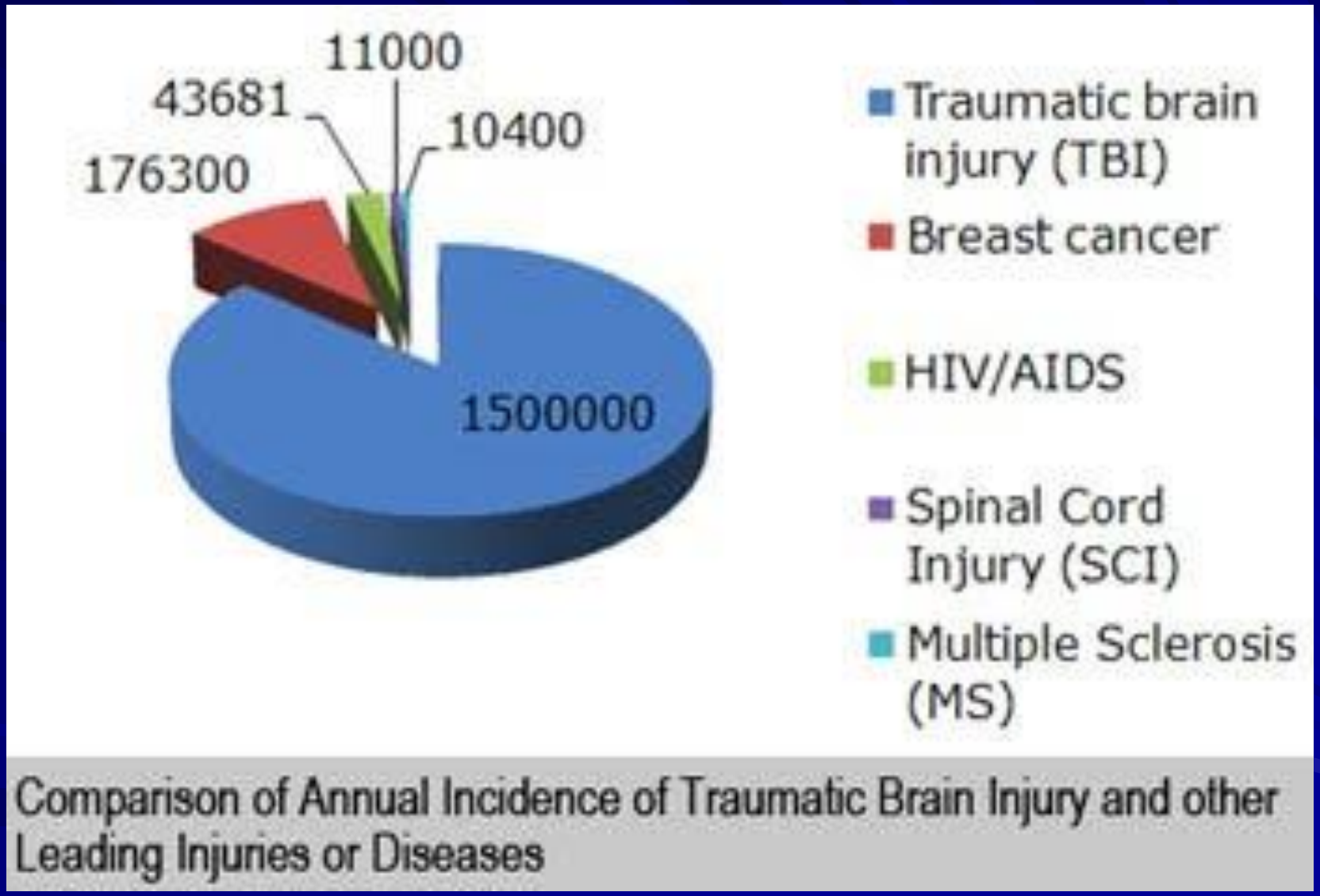
Dr Vanessa Raymont
University of Oxford
vanessa.raymont@psych.ox.ac.uk

- Traumatic Brain Injury (TBI) = ‘silent epidemic’

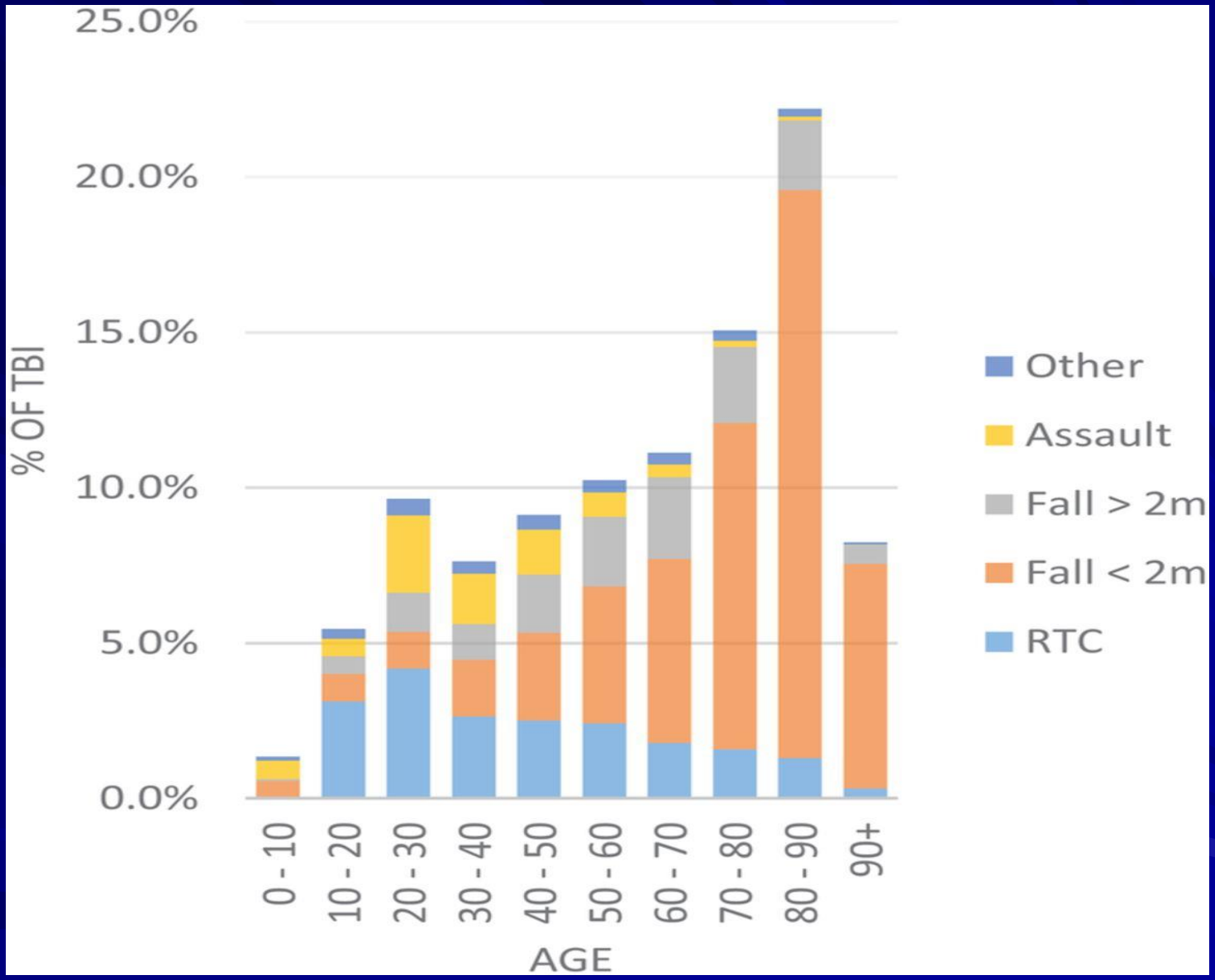
- In UK - TBI every 3 mins; 2% of population (1.4m) attend A&E/year
- Leading cause of death & disability in < 40s
- Many unreported & 75% concussions/mild TBI

- 1.3m living with long term disabilities in UK; 60% of offenders have TBIs
- ↑ > 50% in past decade
- Acute & on-going costs $400b/year (£15b in UK) = 0.5% of annual global output; 10m cases annually

- WHO identified TBI as major public health problem with huge unmet needs



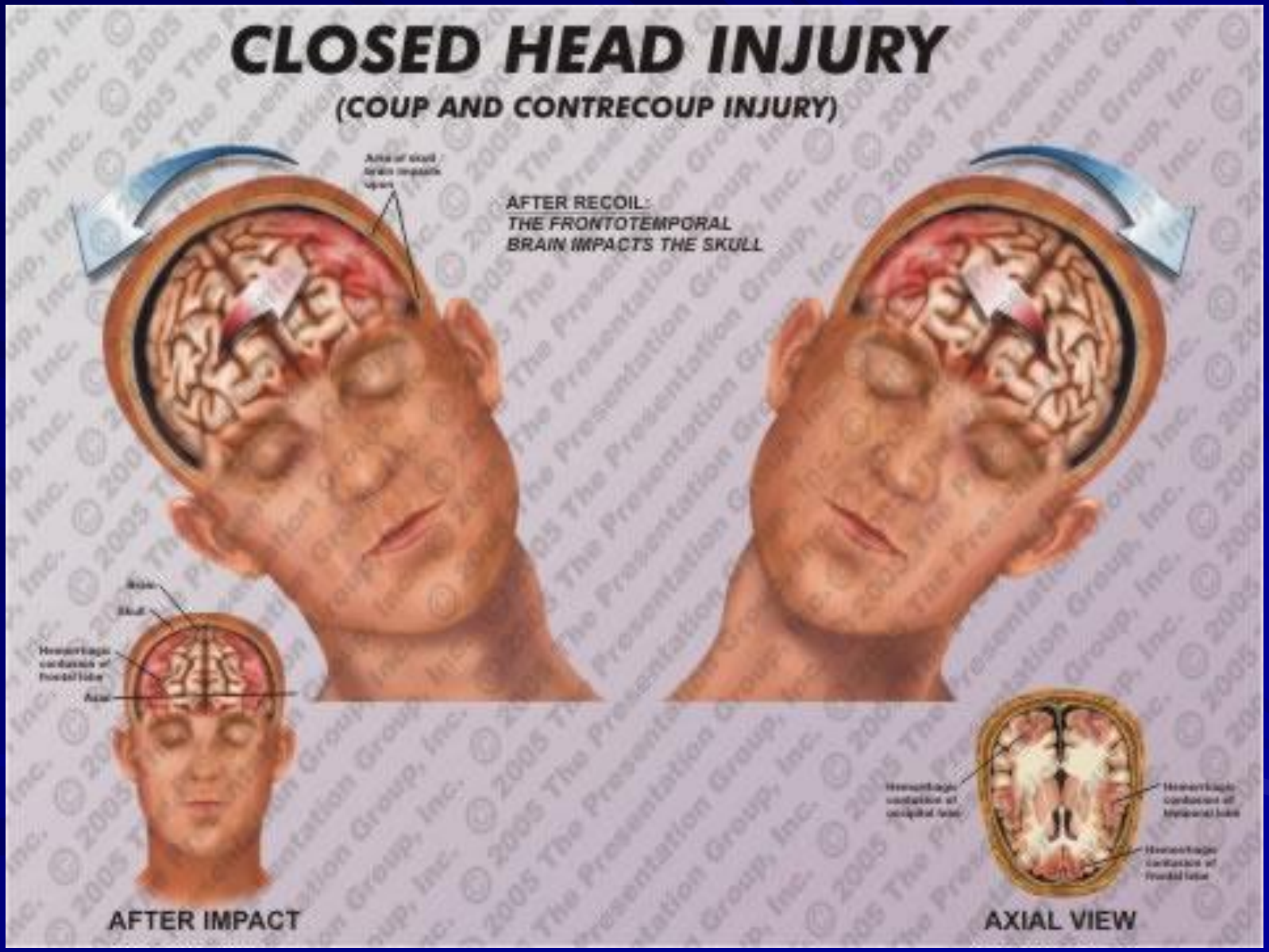
Comparison of Annual Incidence of Traumatic Brain Injury and other Leading Injuries or Diseases



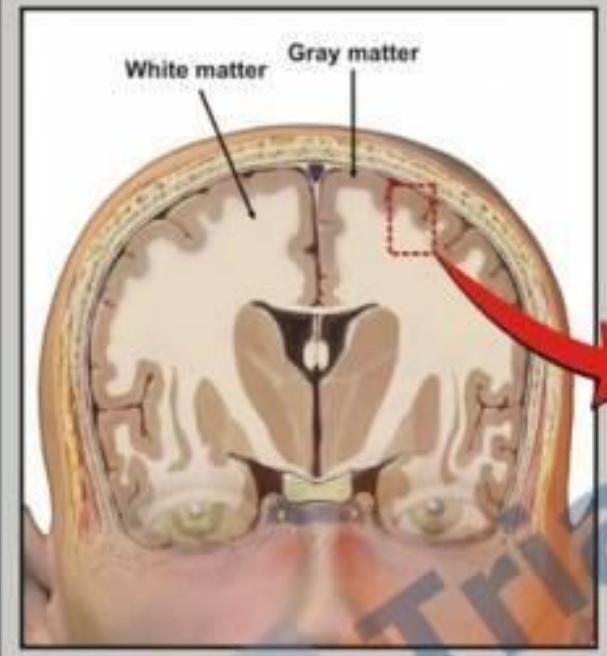
Lawrence T. et al. BMJ Open 2016;6:e012197. doi:10.1136/bmjopen-2016-012197

TBI can be classified on severity (mild, moderate, and severe), mechanism (closed or penetrating), or location (focal or diffuse)

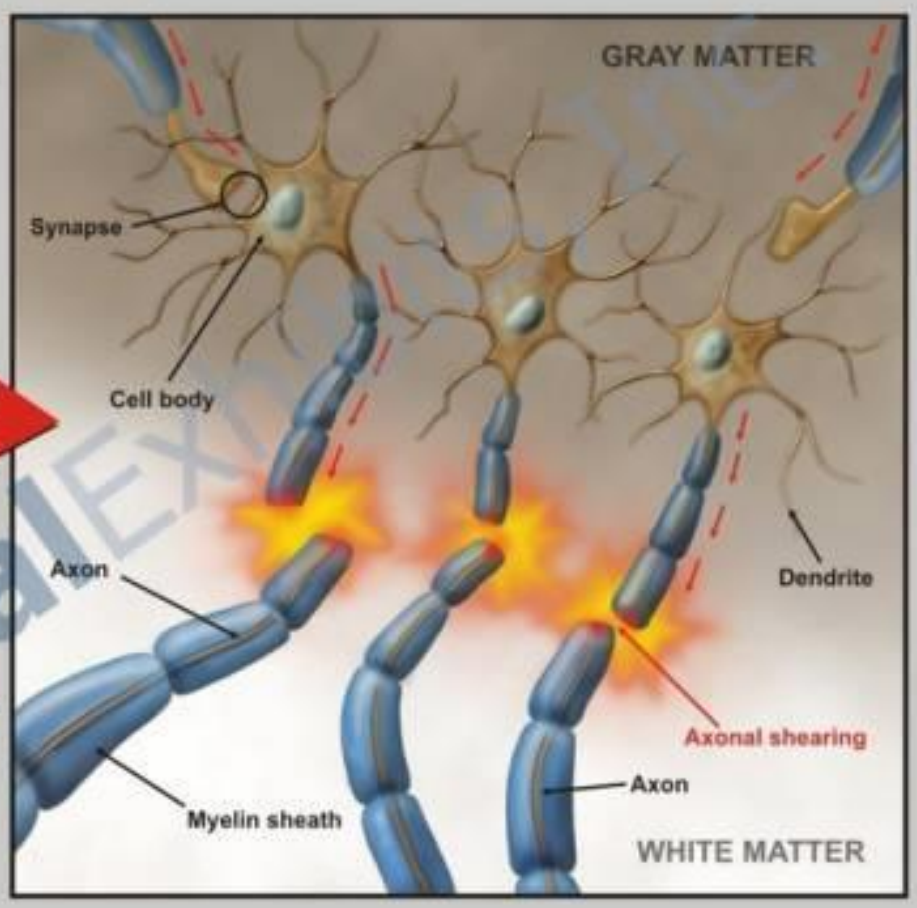
Severity of traumatic brain injury			
	GCS	PTA	LOC
Mild	13–15	<1 day	0–30 min
Moderate	9–12	>1 to <7 days	>30 min to < 24 hours
Severe	3–8	>7 days	>24 hours


CLOSED HEAD INJURY
(COUP AND CONTRECOUP INJURY)
AFTER RECOIL:
THE FRONTOTEMPORAL
BRAIN IMPACTS THE SKULL
AFTER IMPACT
AXIAL VIEW

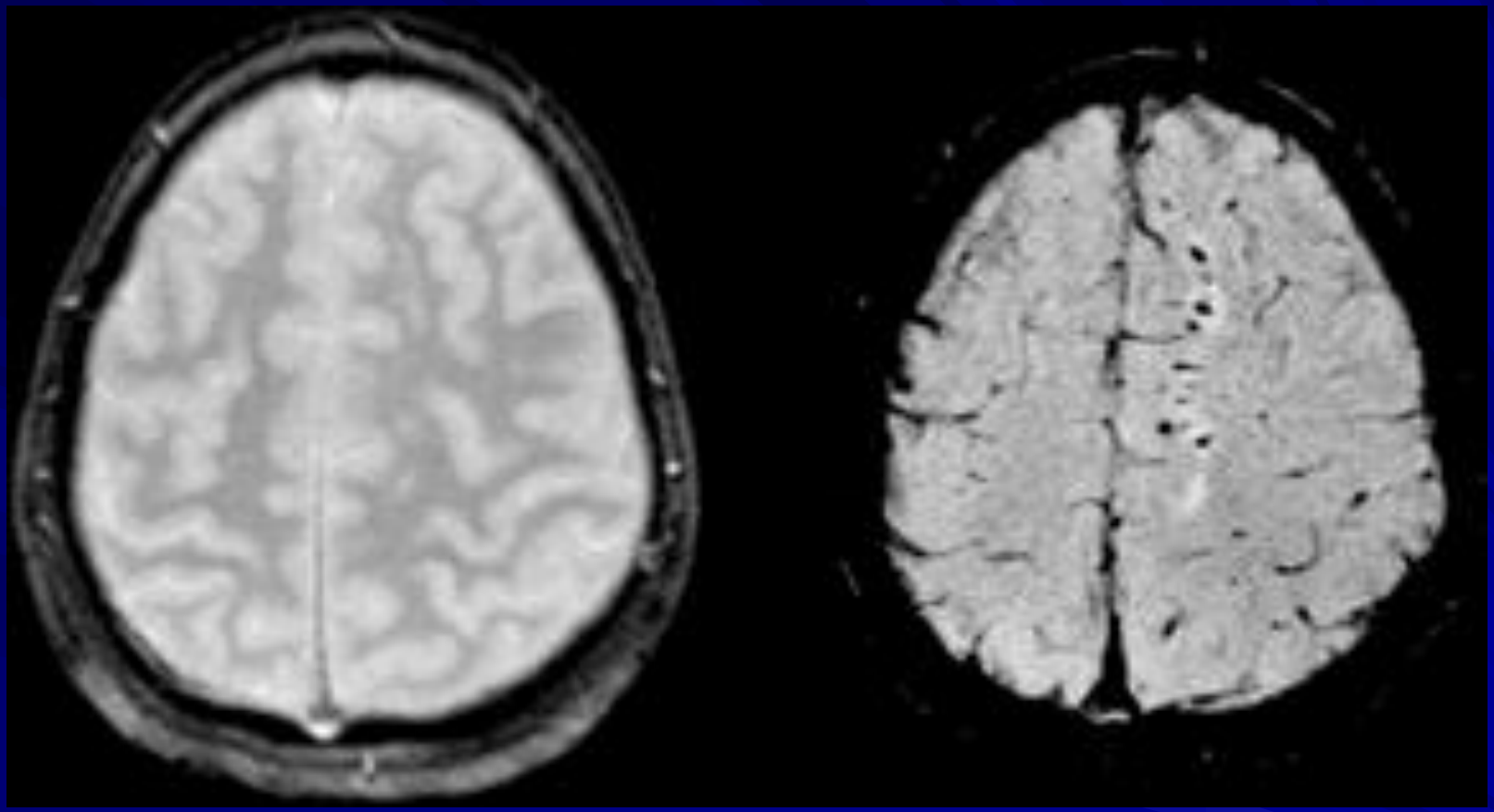
DIFFUSE AXONAL INJURY



Sudden acceleration-deceleration forces cause injury to the brain.



The injury is greatest in where the density difference is greatest.
Most tearing occurs at the gray-white matter junction.

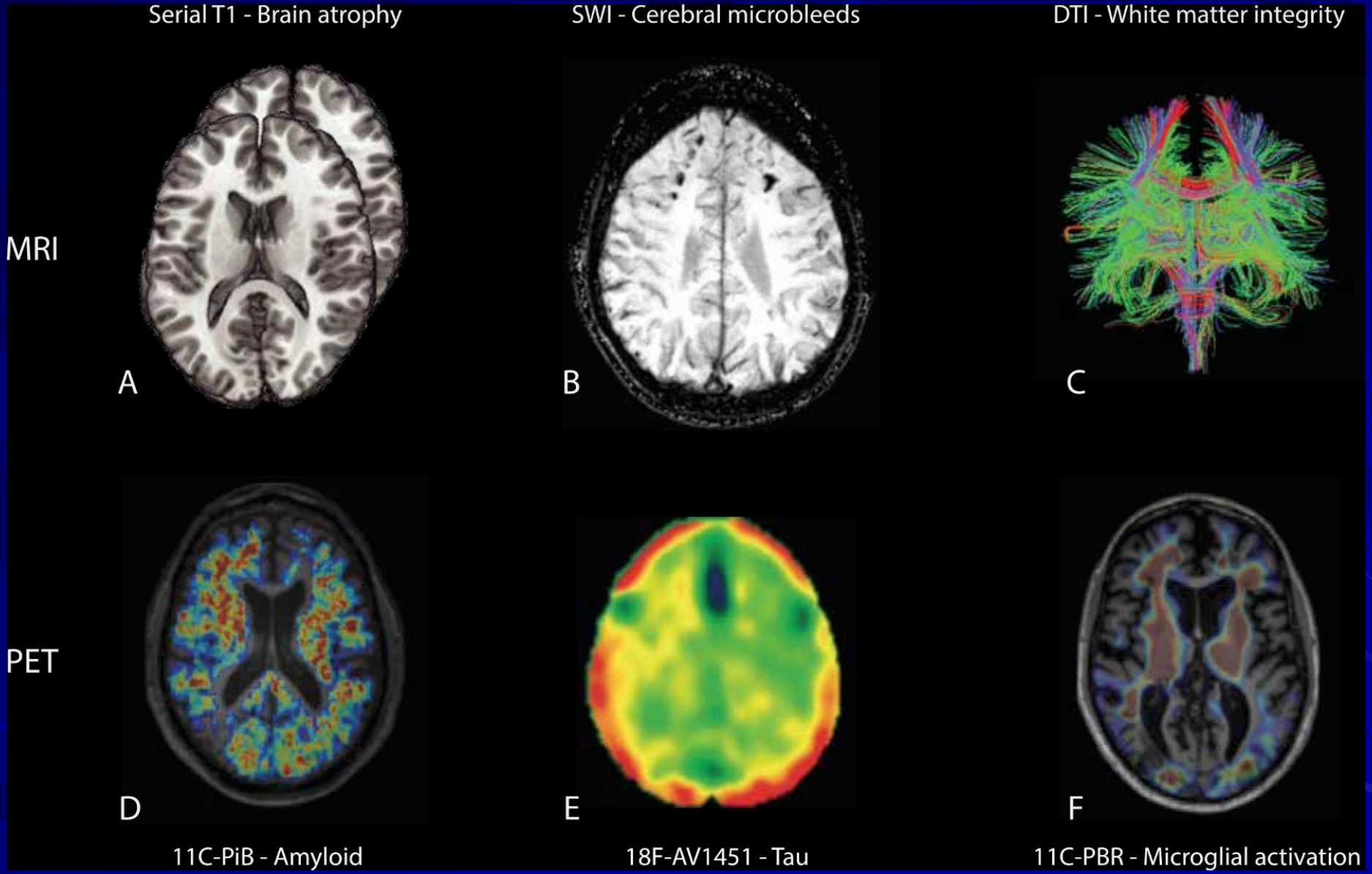


Comparison of diffuse axonal injury imaged with conventional MRI (left) and susceptibility weighted imaging (right)

- TBI = caused by a bump, blow, or jolt to the head, or penetrating head injury (CDC Injury Centre, 2019)
- But…NINDS definition = alteration in brain function, or other evidence of brain pathology, caused by an external force (Menon et al., 2010)
- 'TBI is a biomechanical problem' - subclinical impacts important!
- Some axons in mTBI recover but many eventually rupture; 43-68% of mild TBI have normal CT/MRI

- More sensitive modalities:
- 1) diffusion tensor imaging - shifting diffusion metrics common - ?associated with cognitive/functional prognosis in mTBI
- 2) functional MRI
- 3) magnetic resonance spectroscopy
- 4) FDG PET
- 5) SPECT - hypoperfusion in mTBI
- 6) susceptibility weighted imaging - microhaemorrhages in mTBI

→ **Need better biomarkers to <u>define</u> TBI**



Graham NSN, Sharp DJ. J Neurol Neurosurg Psychiatry 2019;90:1221–1233. doi:10.1136/jnnp-2017-317557

Primary injury cannot explain subsequent changes…

- → acute effects e.g. Diffuse Axonal Injury (DAI)
- → disruption of metabolic & cerebral blood flow during the acute phase of TBI - in ALL severity levels

- → neurotransmitter & free radical release, calcium & sodium influx, mitochondrial dysfunction, inflammatory factor release, ↓ connectivity, damaged blood-brain barrier, aggregation of amyloid & tau, cerebral atrophy

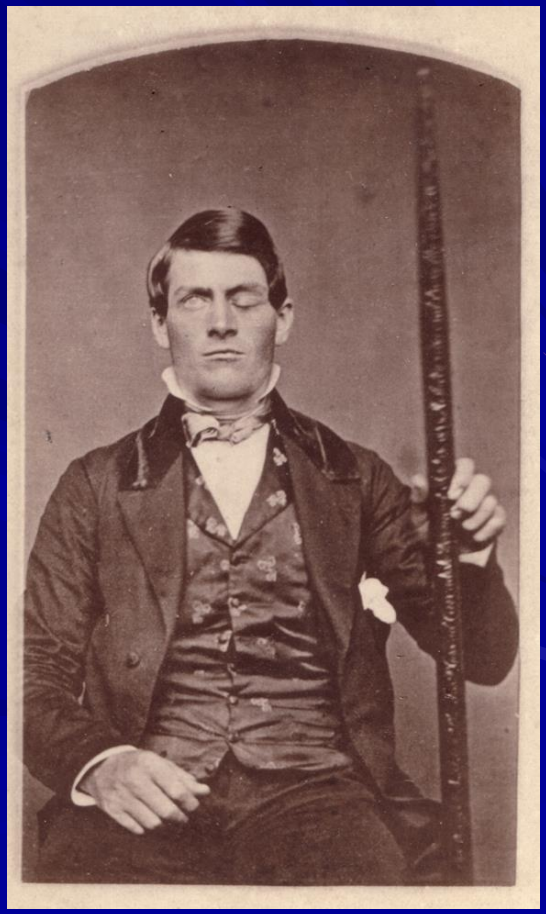
Secondary injury may continue for years → (often missed) symptoms & neurodegeneration later

NB - mild TBI - ?predominately neurometabolic & reversible

Neurobehavioural outcomes

- **Delirium** - affects up to 70%
- **Post-concussion syndrome** - headaches, dizziness, ↓ concentration; course unclear - 7-33% persist
- **MAY PROGRESS TO…**

- **Behavioural disturbances** - restlessness, agitation, disinhibition, aggression, apathy, lability, anhedonia, withdrawal, functional v organic?
- **Psychological issues** - psychological adjustment, change in relationships/roles, vocational issues, community reintegration, high carer burden
- **Psychiatric disorders -** psychosis (2-3x ↑), anxiety disorders (up to 70%), depression (up to 77%)
- **Personality change & neuropsychiatric disorders**

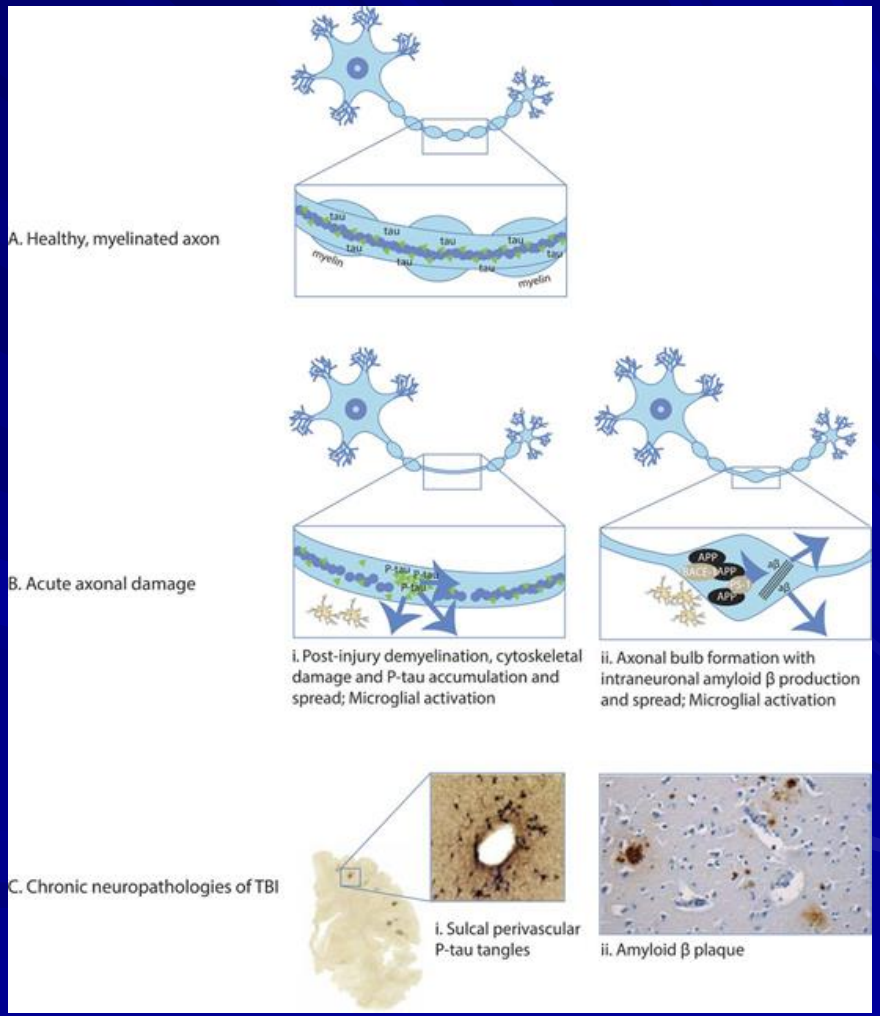


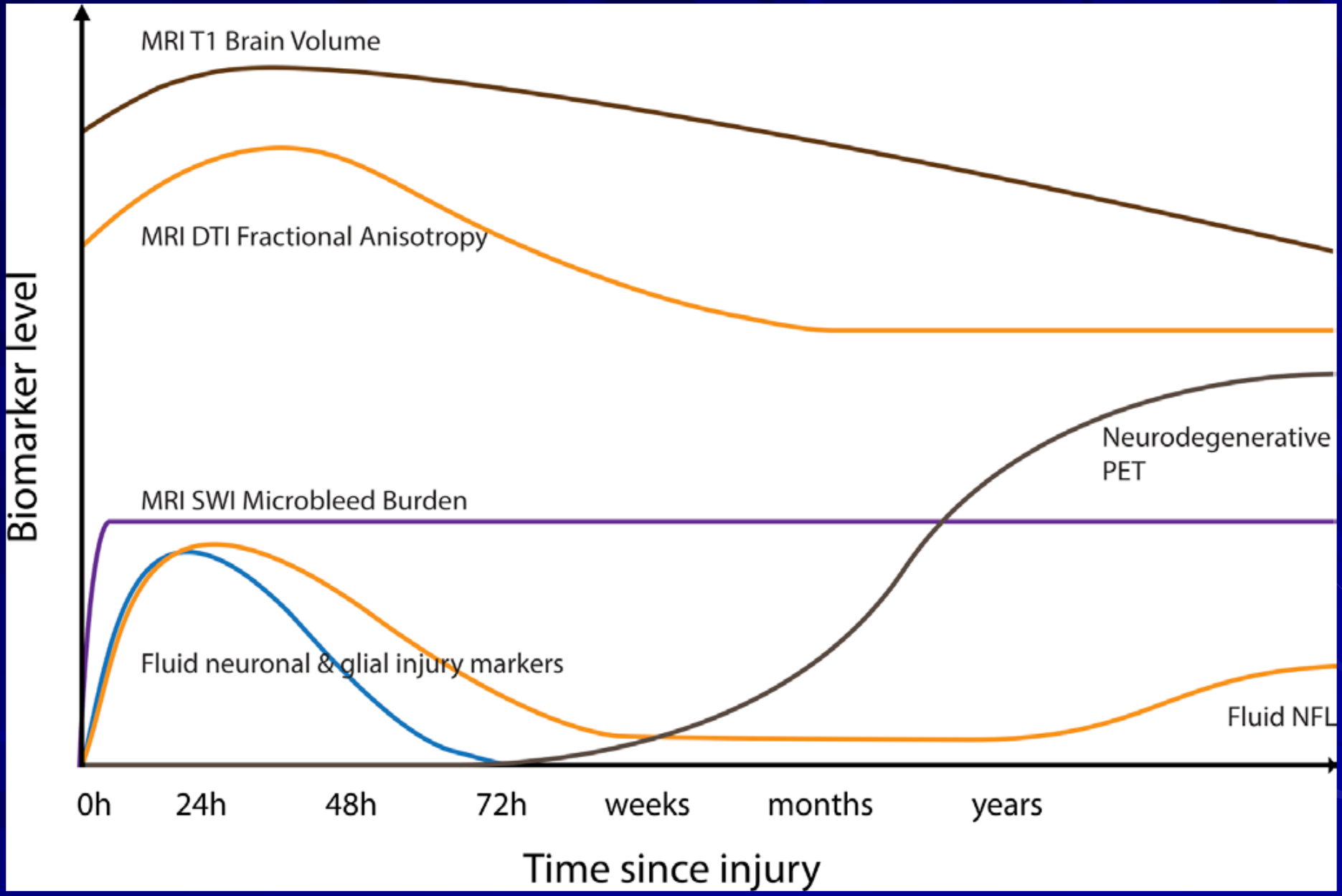
TBI and the elderly (age of impact important)

- Falls - most common cause of TBI & leading cause of TBI related death among > 75
- Elderly - greater long-term effects, poorer prognosis, higher mortality, worse cognitive, mood, social, functional outcome, despite less severe injuries
- ↑ vulnerability of the ageing brain to TBI - ?reduced brain reserve, medical comorbidities, neuropsychiatric disturbance, existing cognitive impairment

Fixed steps or accelerating mechanisms?

- ?mechanisms: DAI → tau deposition, AD-related neurodegeneration, chronic inflammation, CV disruption, BBB permeability, oxidative stress, cellular dysfunction - may interact with…
- Confounding factors - age at TBI, co-morbidities, education (≈ ↓ cognitive reserve), APOE, gender
- But while acute TBI → relatively fixed cognitive deficit over time, no consistently predictable, subsequent, more rapid cognitive decline





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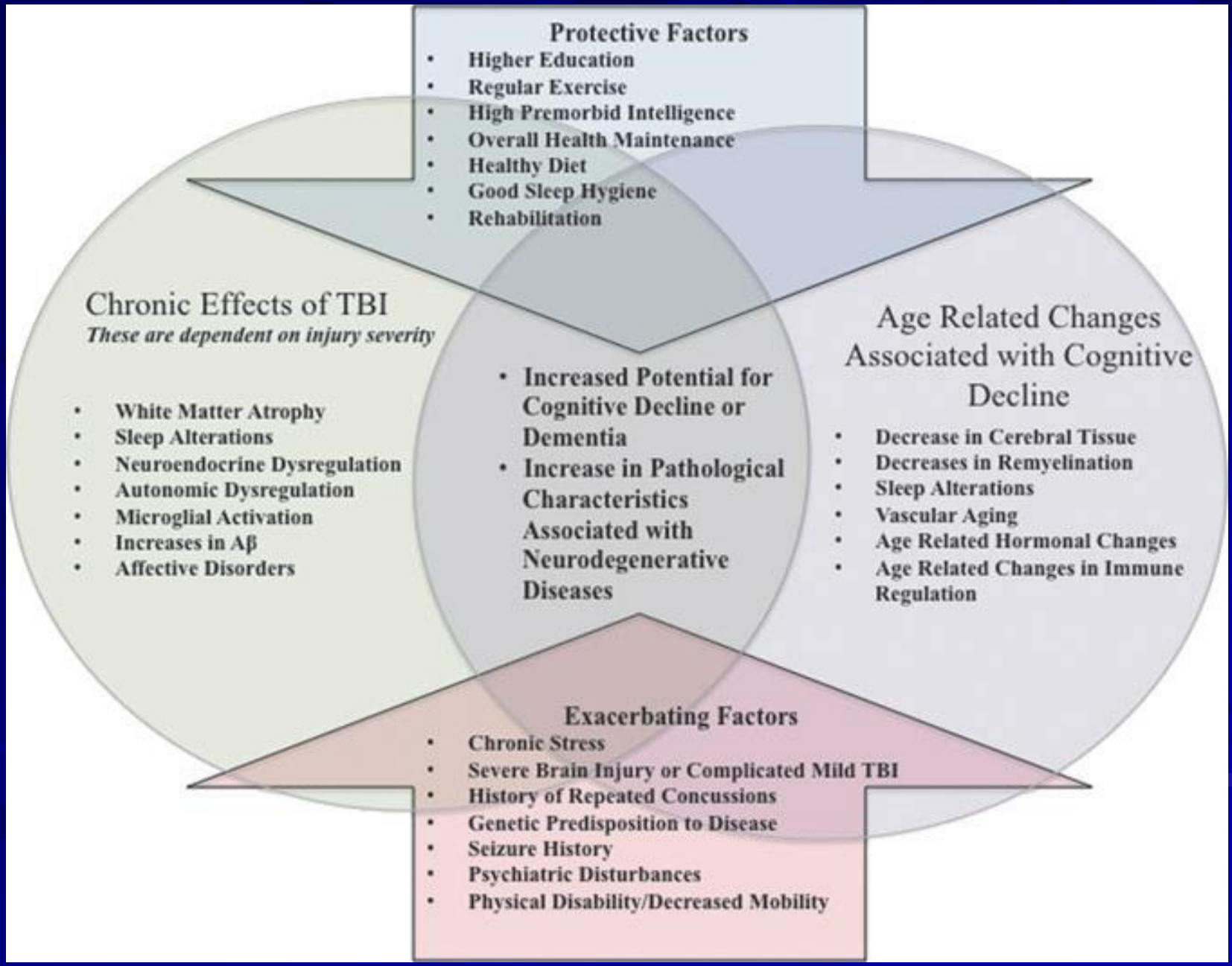
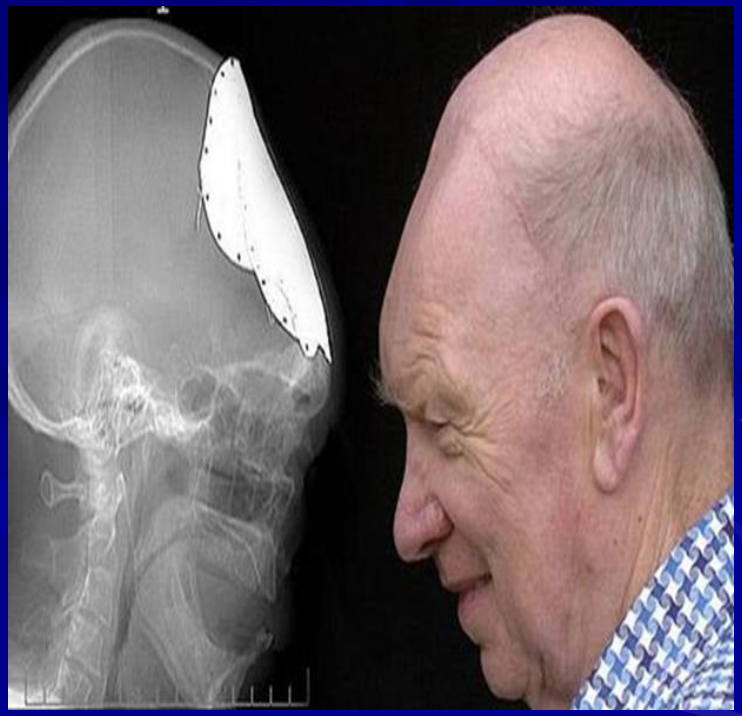

Protective Factors
Higher Education
Regular Exercise
High Premorbid Intelligence
Overall Health Maintenance
Healthy Diet
Good Sleep Hygiene
Rehabilitation
Chronic Effects of TBI
These are dependent on injury severity
White Matter Atrophy
Sleep Alterations
Neuroendocrine Dysregulation
Autonomic Dysregulation
Microglial Activation
Increases in Aβ
Affective Disorders
Increased Potential for Cognitive Decline or Dementia
Increase in Pathological Characteristics Associated with Neurodegenerative Diseases
Age Related Changes Associated with Cognitive Decline
Decrease in Cerebral Tissue
Decreases in Remyelination
Sleep Alterations
Vascular Aging
Age Related Hormonal Changes
Age Related Changes in Immune Regulation
Exacerbating Factors
Chronic Stress
Severe Brain Injury or Complicated Mild TBI
History of Repeated Concussions
Genetic Predisposition to Disease
Seizure History
Psychiatric Disturbances
Physical Disability/Decreased Mobility

TBI & dementia

- 65% (moderate/severe) report long-term cognitive problems (Whiteneck 2004)
- Recent meta-analysis of > 2 million = 1.6x ↑ risk ≈ 5% of all dementia cases (Li 2017)
- The Finnish Care Register = dose–response relationship (Raj 2017)
- Overall - estimated ↑ risk of dementia by 1.5-3x, TBI contributes 5-15% of dementia burden



History of AD link

- Mortimer (1991) meta-analysis = TBI → 1.82 relative risk for developing AD
- Many studies ranked TBI only after age, family history, APOE genotype as risk factor
- In entire literature (i.e., studies published before & after Mortimer meta-analysis) there is ~1.5 ↑ risk for AD associated with TBI - men > women
- Crane 2016 - 3 large community-based cohort studies - 7,130 participants, 1,589 underwent post-mortem from 1994 to 2014. History of TBI with loss of consciousness not associated with AD dementia or the neuropathologic features of AD; was associated with Lewy body disease, PD & progression of parkinsonism
- Weiner 2017 - used VA medical records/ANDI; showed no effects of TBI history on cognition or AD biomarkers

APOE

- APOE4 allele associated with worse outcomes after both moderate/severe TBI (Ariza et al., 2006) & mild TBI (Crawford 2002; Sundstrom 2004)
- >= one APOE4 allele associated with early mortality, worse functional outcome, ↑ risk of AD (Mayeux 1995) after TBI
- BUT - one large study found no overall effect of APOE, but younger APOE4 carriers had worse outcomes (Teasdale 2005), ?age-dependent effect. Other studies have failed to replicate
- APOE4 status in non-Caucasian carriers not well studied - small study finding no statistically significant differences in outcome after TBI in an African cohort (Nathoo 2003)
- Association of APOE with repetitive TBIs not well characterized - several studies suggest APOE4 associated with worse outcome (McKee 2009), BUT – others have failed to find association (Omalu 2011)
- No firm data for other genetic links

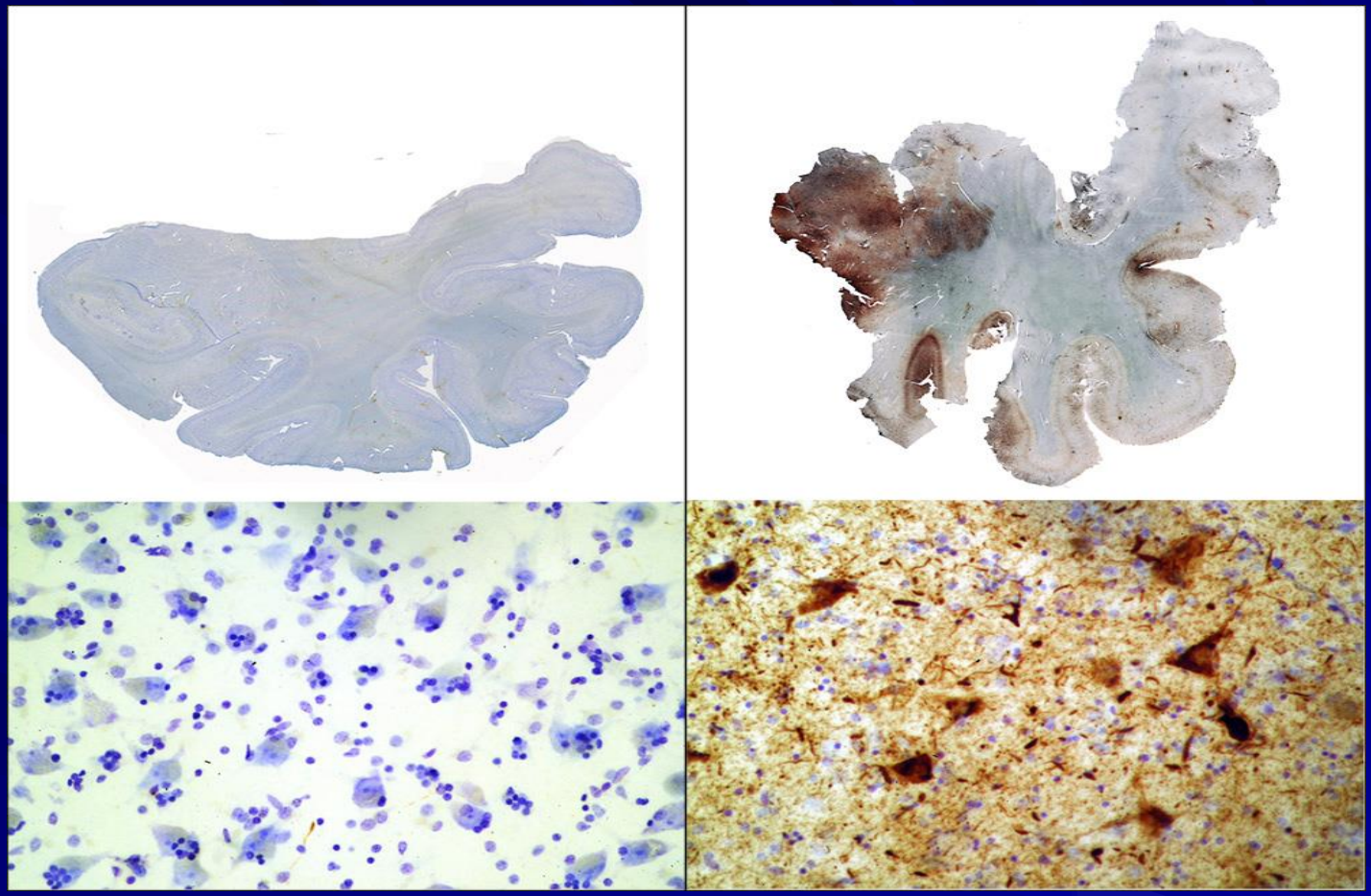
Dementia with Lewy Bodies & Frontal Temporal Dementia

- DLB - unclear link
- Boot 2013 - TBI history not associated for ↑ DLB
- Crane 2016 - Lewy bodies acutely in mTBI, but not with earlier TBI
- Nguyen 2018 - history of TBI with LOC associated with earlier onset of DLB

- Some evidence of ↑ risk with TBI with earlier onset FTD (LoBue 2016), especially behavioural type (Rosso 2003), but not MCI (Deutsch 2015)
- ? TBI lowers the threshold for later impairment by reducing cognitive reserve &/or accelerating the development of pathological processes
- There is no good evidence of a relationship between mild or repeated mild TBI & FTD

Chronic traumatic encephalopathy (CTE)

- “Punch drunk syndrome” - 1928 case report (Martland) - “Dementia pugilistica” - dysarthria, ataxia, pyramidal & extrapyramidal signs, memory impairment, personality changes, ~30% dementia
- 1973 - Corsellis - widespread neurofibrillary tangles
- High overlap of Sx with other conditions i.e. speech, movement, memory changes historically, alterations in personality/cognitive decline more recently
- NIH consensus on pathology 2013, but highly debated - ?mild TBI activates neurodegeneration → CTE OR ?accelerates the expression of other neurodegenerative conditions OR ?progresses over time to involve more brain areas
- McKee 2019 - 61 athletes with repetitive mild TBI - 25% had clinical Sx & “pure” CTE pathology, but 25% had clinical Sx without CTE pathology, 25% had CTE pathology without clinical Sx



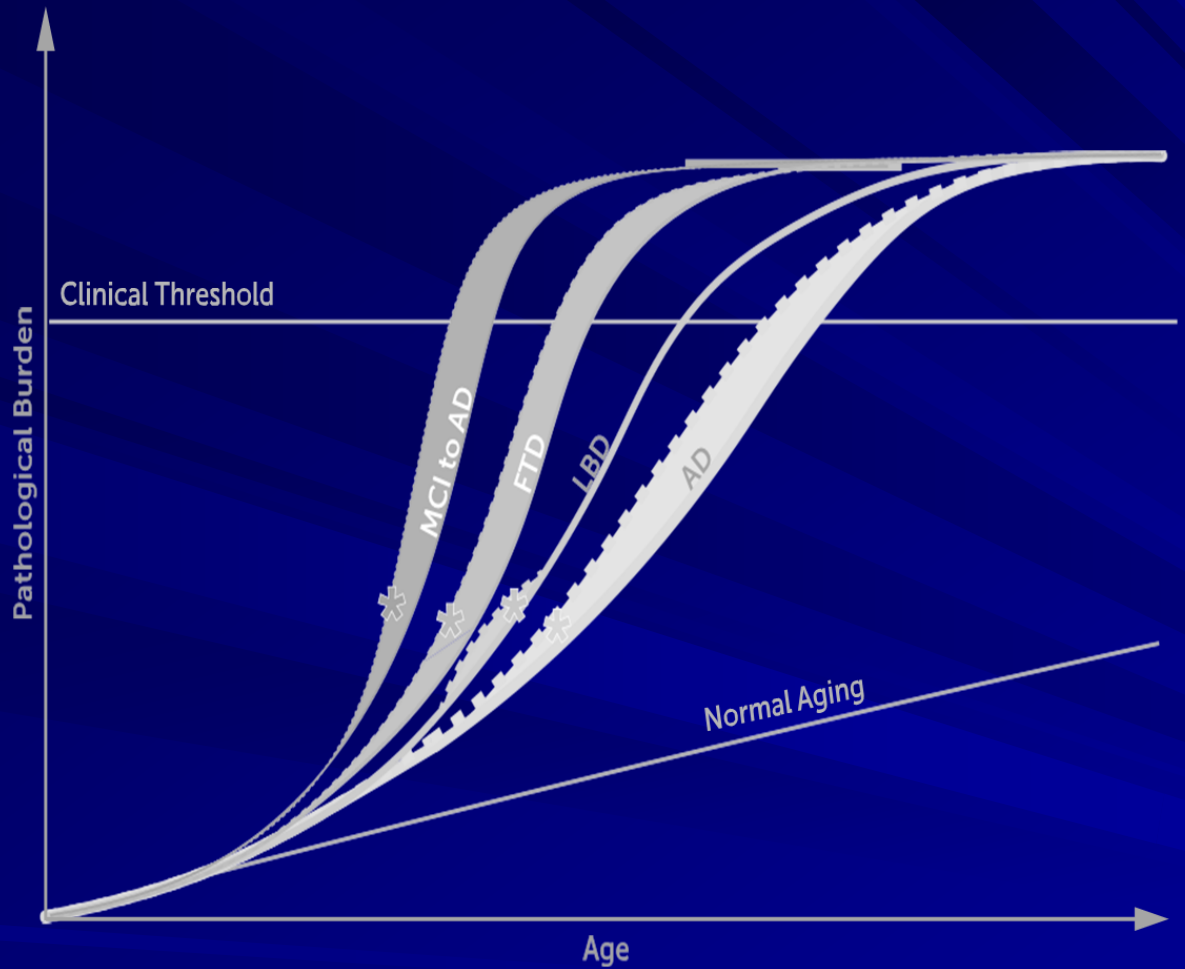
Chronic traumatic encephalopathy is marked by concentrations of tau protein, shown here as brown spots. More tau equals more damage. Left: a normal, 65-year-old brain. Right: former NFL linebacker John Grimsley, who died of a gunshot at age 45 after nine concussions.

Key differences between AD and CTE

	CTE	AD
Neurofibrillary tangles	Layers II and III of cortex, Ammon's Horn of Hippocampus, and Pulvinar	Layers V and VI of cortex and CA_1 of Hippocampus
Clinical Features	Mood disturbances and Parkinson's like features with tangles in substantia nigra and locus ceruleus and few or no Aβ plaques	Cognitive impairment with extracellular amyloid pathology in middle frontal, superior and middle temporal, and inferior parietal lobule
Anatomy	Perivascular distribution of pathology	Severe cerebral atrophy

Mild TBI (mTBI)

- ~100-300 per 100 000
- 8% of mTBI with normal CT have lesions on MRI within 2 weeks - contusions and/or multiple foci of haemorrhagic axonal injury - associated with worse outcome
- Recent population-based studies =1.2 - 3.3 ↑ dementia risk even after adjusting for demographics, medical & psychiatric comorbidities
- Outcome is likely multifactorial e.g. pre-existing personality, stress (role change, litigation), psychiatric conditions e.g. depression/PTSD, substance abuse, chronic pain, Sx expectation & misattribution



[a] Asterisk indicates sustaining a history of TBI. AD=Alzheimer's disease; FTD=frontotemporal dementia; LBD=Lewy body dementia; MCI to AD=developing mild cognitive impairment and progressing to Alzheimer's disease.

- TBI *contributes* to development of several overlapping neurodegenerative processes
- Progression may plateau after dementia onset
- ?Static reduction of cognitive reserve

LoBue et al, J Neuropsychiatry Clin Neurosci. 2018 ; 30(1): 7–13.

Difficulties

1) neurodegenerative dementias have an insidious onset & may already be present
2) rely on retrospective information
3) lack of universal standard for classifying TBI & most not mTBI
4) most population studies - yet most not recorded in medical notes
5) not controlling for important confounding factors e.g. psychiatric disorders
6) poor matching of cases & controls
7) lack of gold standard dementia criteria
8) short follow-up periods & lack of death data

Key questions - Does mTBI create vulnerability to ND, alter trajectory or accelerate existing changes in mid life & at what dose & at what age(s)?

Cohorts with TBI data

Lifetime mTBI and cognitive deficits in late life

- n=15,752, >50s, assessed annually for 4 years, lifetime TBI data via the Brain Injury Screening Questionnaire
- Significant cognitive impairments associated with TBI at baseline but no worsening in cognitive trajectory over the study duration
- Those with at least one moderate-severe TBI had significantly poorer attention (B=-0.163, p<0.001), executive scores (B=-0.151, p=0.004) and processing speed (B=-0.075, p=0.033)
- Those with at least a single mTBI also demonstrated significantly poorer attention scores (B=-0.052, p=0.001)
- 3 mTBI → poorer executive function (B=-0.149, p=0.025) and attention scores (B=-0.085, p=0.015)
- >= 4 mTBIs → poorer attention (B=-0.135, p<0.001), processing speed (B=-0.072, p=0.009) and working memory (B=-0.052, p=0.036)

PREVENT Dementia Project

- Age range 40-59
- 1:1 balance of family history +/-
- Five centers in UK and Ireland
- N=701 baseline assessments completed

prevent dementia

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The University of Dublin
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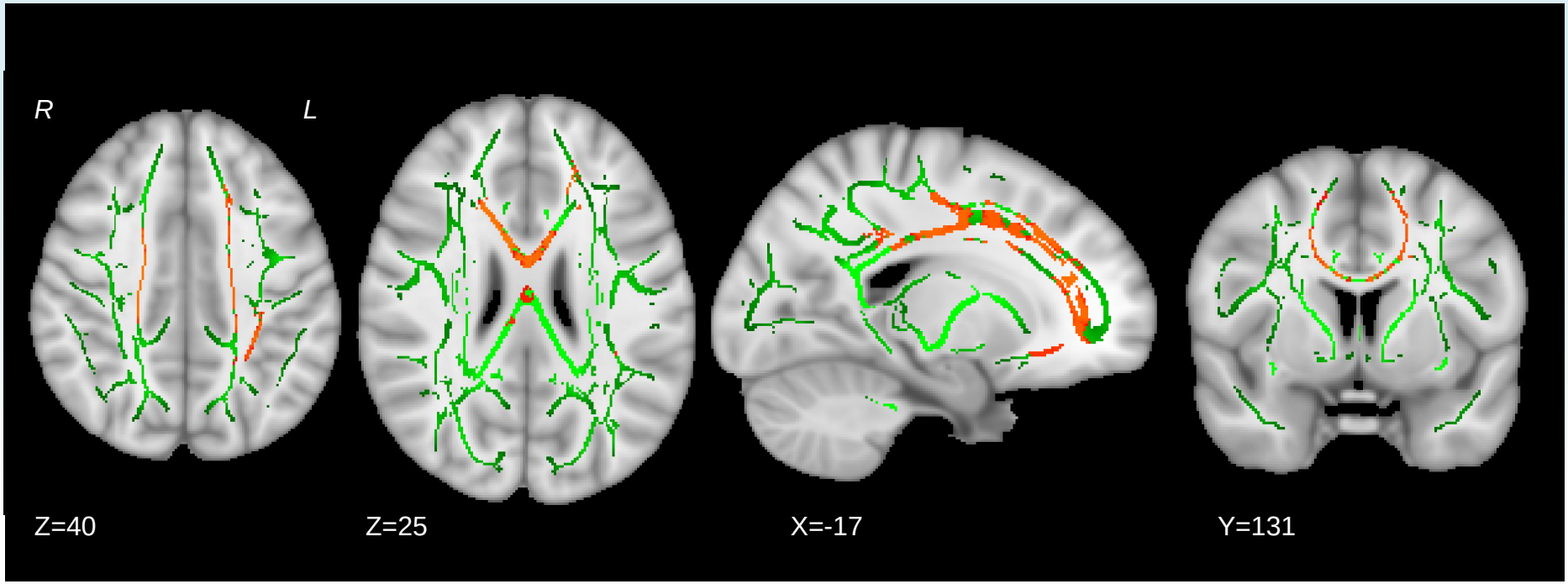
Aetiology of TBI	No of blows	Males v Females	Percentage of PREVENT sample
Falls	370	104 v 178 (37% v 63%)	40.0%
Hit/Bump	217	67 v 110 (37.9% v 62.1%)	26.1%
Sporting Activity	509	144 v 185 (43.8% v 56.2%)	46.9%
RTC	115	39 v 66 (37.1% v 62.9%)	15.0%
Assault	68	36 v 31 (53.7% v 46.3%)	9.5%
Abuse	46	16 v 30 (34.8% v 65.2%)	6.6%
Other	9	5 v 4 (55.6% v 44.4%)	1.3%
Not specified	2	2 v 0 (100% v 0%)	0.3%

Any vs. no blow to head

↑ FA: any blow > no blow

Regions affected - corpus callosum & superior corona radiata



No differences in MD between groups

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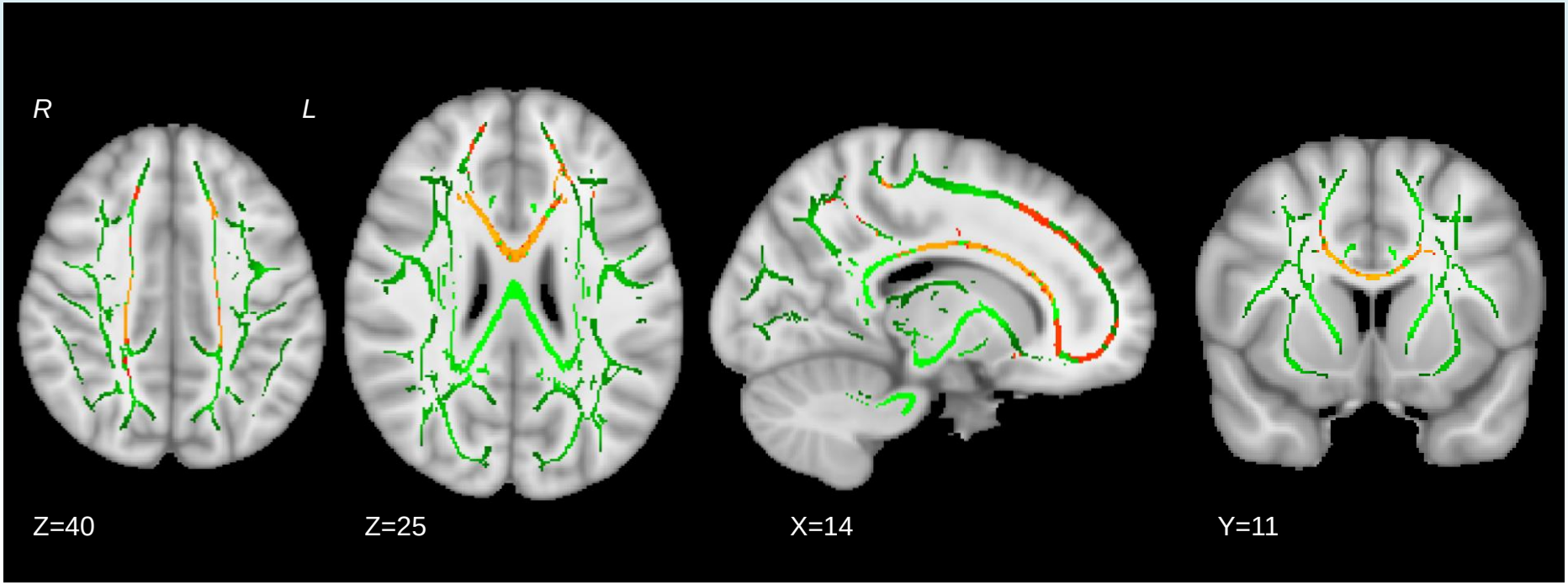
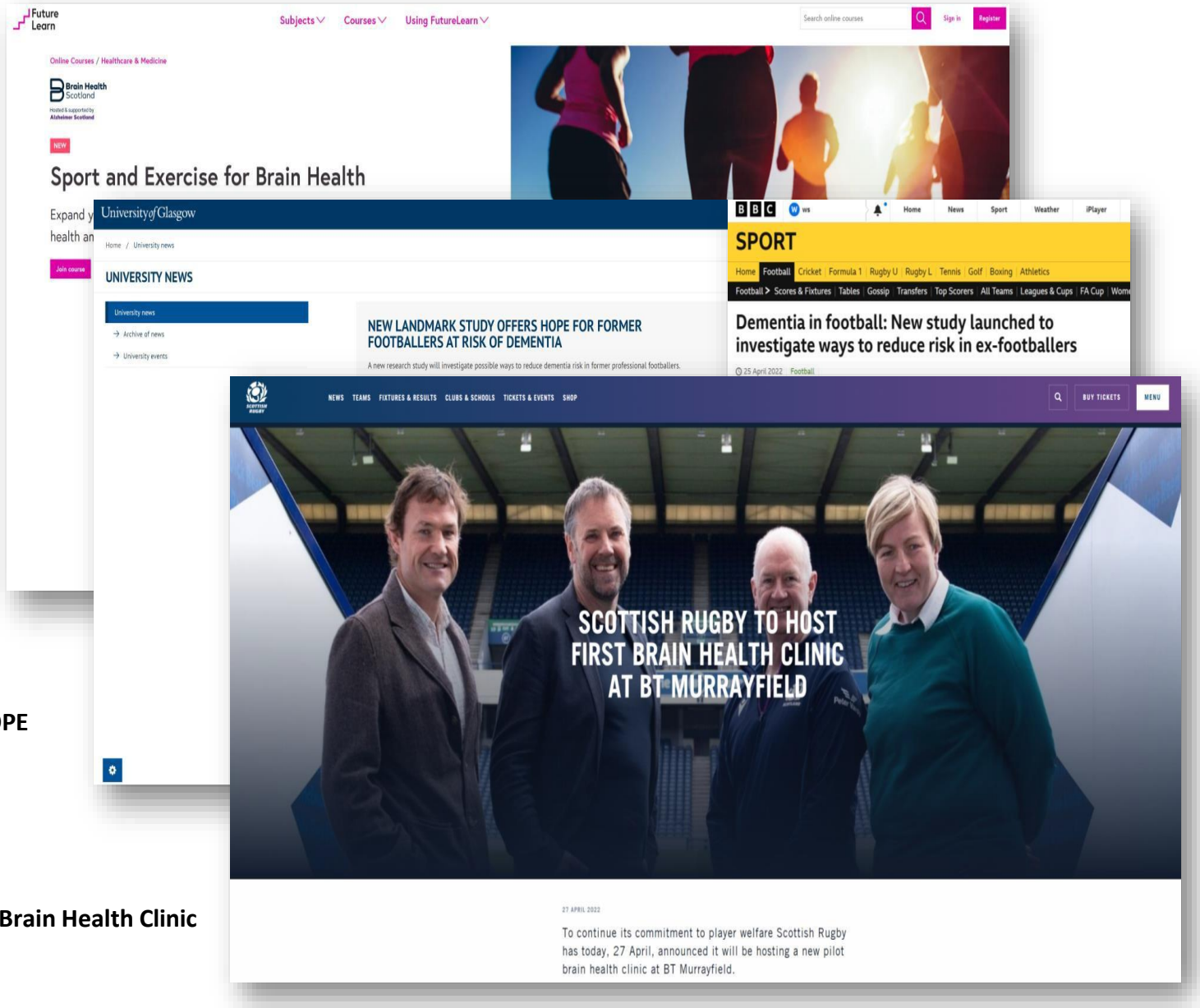
Severity of blow – continuous

Significant positive association with FA



University of Glasgow



MOOC

BrainHOPE

Brain Health Clinic

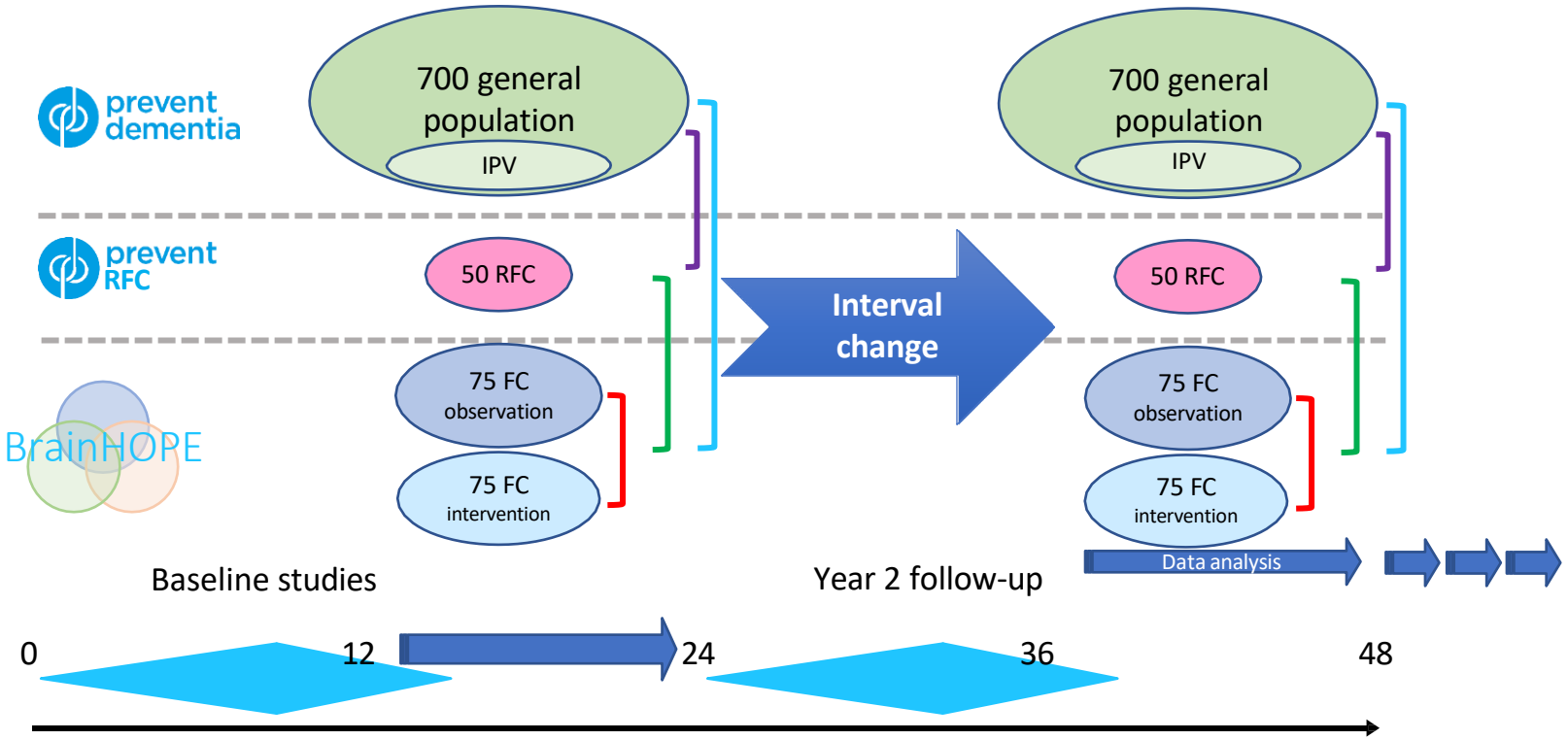
NHS Greater Glasgow and Clyde

University of Glasgow

May '22

- **BrainHope**
- 7 participants in Edinburgh
- 30 booked (16 ICL/12 Edinburgh)
- **Prevent RFC**
- 15 participants in Edinburgh
- 18 booked

PREVENT: "Sports" sub-studies



What do we know?

- TBI has a relationship with neurodegeneration and psychiatric sequelae in SOME - likely multifactorial & related to severity
- Likely no link between TBI & progressive ageing or rate of decline of dementia

- What's unclear:

  - mechanism(s) and if changes stabilise or not

  - if mTBI causes persistent neurodegeneration

  - effect of psychiatric Sx

  - gender differences - more females getting mTBIs - ?neck girth, metabolism, hormonal differences

- We need:

  - better research methods and clinical RWD - but Sx overlap, ?head-impact devices

  - betters biomarkers - atrophy, PET (amyloid, tau, inflammation), vascular, for identification and tracking

  - treatments! - symptomatic, plus devices/augmentation/cognitive rehab etc.

Questions?


RFU
DON'T BE A
HEADCASE
STOP! CHECK FOR CONCUSSION
Check out the RFU's guide to concussion: Information, advice and resources for everyone involved in rugby!
The RFU takes the welfare of its players very seriously. Concussion is important to recognise and manage appropriately, so look below for information relevant to your role, and don't be a HEADCASE!


FUTURE
What is BBC Future?
Best of...
Future Planet
Made on Earth
Why women are more at risk from concussion
MOSAIC@FUTURE
HEALTH
By David Robson
31st January 2020
Women athletes are twice as likely as men to get concussed and the effects are more severe, but with research focusing mainly on men, is concussion in women being overlooked?


© EPA
+7
The Infrascanner 2000 has the ability to spot deadly brain bleeds just moments after the injury happening with up to 90 per cent accuracy. Australian boxing trainer Noel Thornberry (right) is