Current Challenges and Opportunities in Concussion

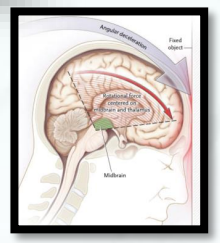
Michael S. Jaffee, MD, FAAN
Chair, Department of Neurology
Director, UF BRAIN Center
Bob Paul Family Professor of Neurology
University of Florida

UF Brain Injury, Rehabilitation, and Neuroresilience Center
UNIVERSITY of FLORIDA

UFHealth
UNIVERSITY OF FLORIDA HEALTH

GAMEPLAN

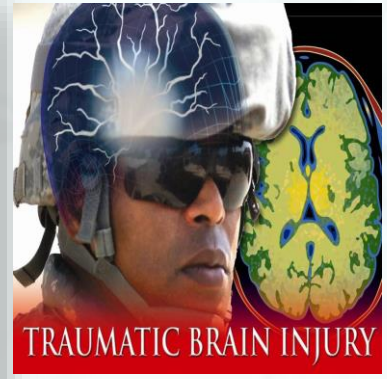
- What Exactly Are We Talking About and Why?
- Evolving Clinical Management
- Facing the Future: Promise and Challenge

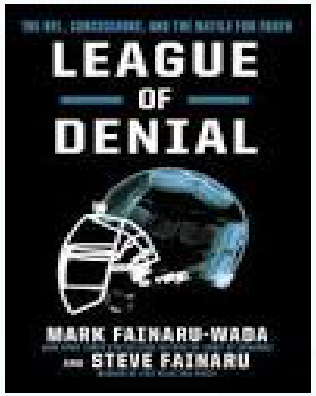


Zackary Lystedt

How Did We Get Here?

- Increased National Attention
  - Issue of Military TBI /concussion fueled by concerns addressed by access and conditions at Walter Reed
  - Increased attention to issue in professional sports (NFL) and catastrophic H.S. Injuries
- Brought More Resources





DoD RESPONSES

npr WUFT news arts & life music programs shop

shots HEALTH NEWS FROM NPR

TREATMENTS

How A Team Of Elite Doctors Changed The Military's Stance On Brain Trauma

8:16

+ Queue

Download

Embed

Transcript

June 10, 2016 · 5:21 PM ET

Heard on All Things Considered

JON HAMILTON

DEFENSE CENTERS OF EXCELLENCE
For Psychological Health & Traumatic Brain Injury

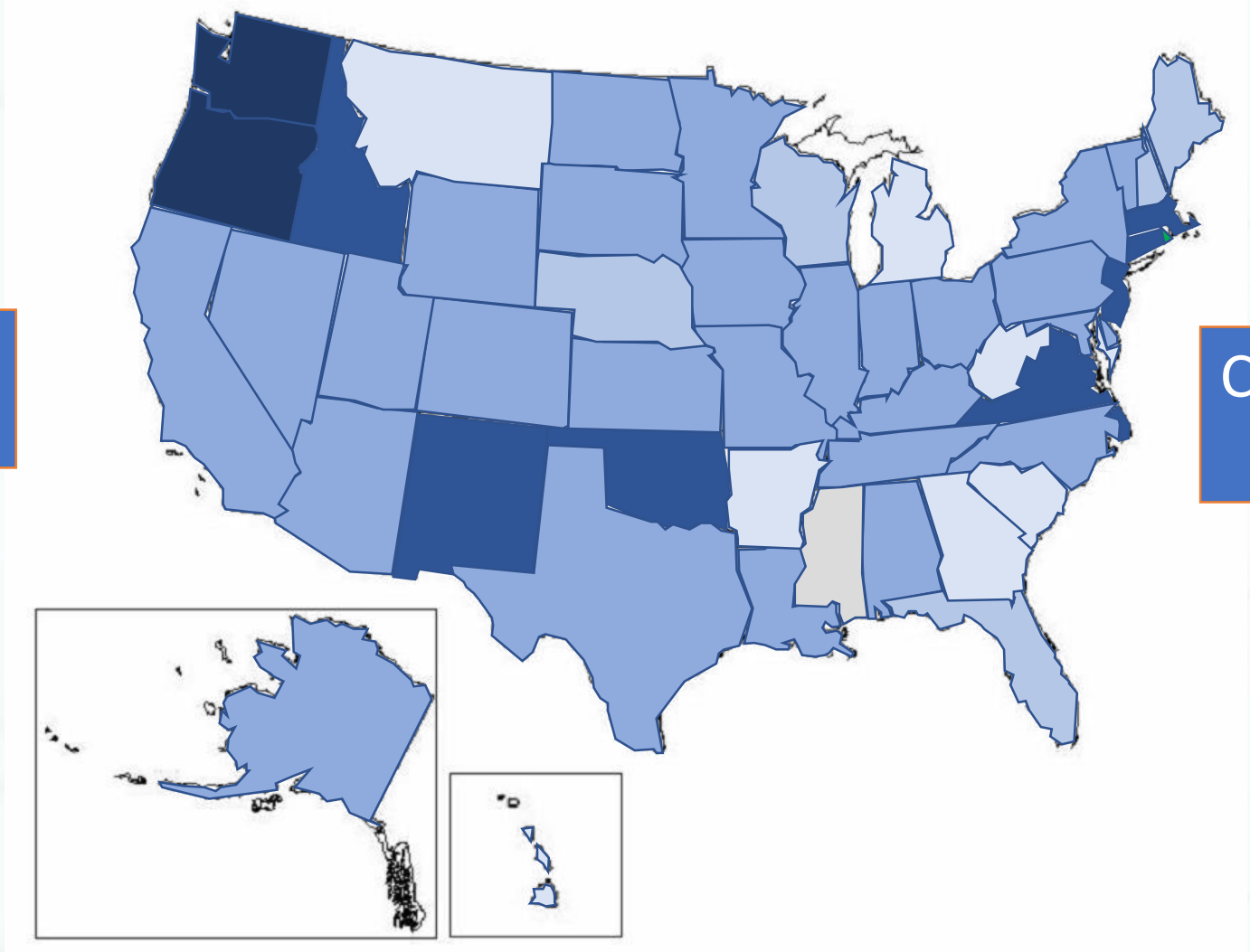
PROPERTY OF U.S. GOVERNMENT

NICoE
National Intrepid Center of Excellence

DVBIC
DEFENSE AND VETERANS BRAIN INJURY CENTER

ATHLETIC POLICY

Response to athletic concussion concerns



Concussion Policy 2009 - 2014

Mild TBI is also known as ***Concussion.***

"Mild" does not refer to symptoms, but rather ***injury severity.***

CLOSED TBI SEVERITY CLASSIFICATION

Mild	Moderate	Severe
Normal imaging	Normal or abnormal imaging	Abnormal imaging
LOC: 0-30 min	LOC > 30 min < 24 hrs	LOC > 24 hrs
AOC: up to 24 hrs	AOC > 24 hrs	
PTA: 0-1 day	PTA > 1 and < 7 days	PTA > 7 days

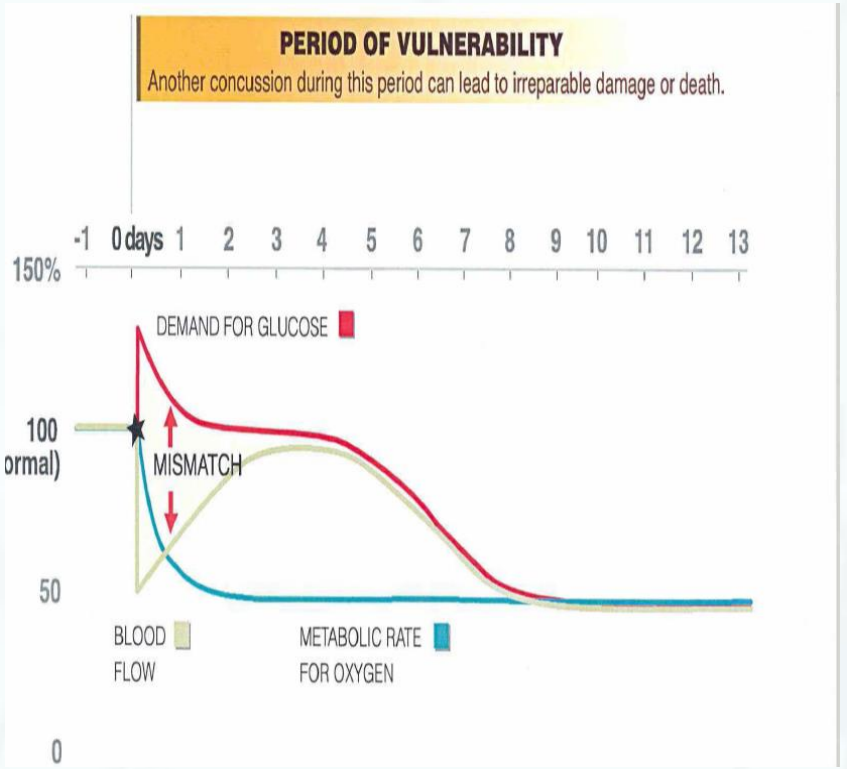
KEY POINTS:

- LOC is **NOT** required for the diagnosis of concussion.
- Symptoms alone (e.g., headache) do **NOT** equate to a concussion diagnosis.

CONCUSSION DIAGNOSTIC SYSTEMS

	GCS	LOC	PTA	Other
ACRM	13-15	<30 min	<24 hours	At least 1 of LOC, PTA, altered mental status, or focal neuro deficit
CDC		<30 min	<24 hours	Altered mental status, amnesia, and symptoms
WHO	13-15	<30 min	<24 hours	At least 1 symptom, rule out other causes
AAN (Retired)	*Grade 1:* Altered mental status, no LOC, symptoms <15 min *Grade 2:* Altered mental status, symptoms >15 min *Grade 3:* LOC of any duration			
Cantu	*Grade 1:* no LOC, PTA <30 min, symptoms <24 hours *Grade 2:* LOC <1 min or PTA >30 min but <24 hours or symptoms >24 hours <7 days *Grade 3:* LOC >1 min or PTA >24 hours or symptoms >7 days			

CONCUSSION PATHOPHYSIOLOGY



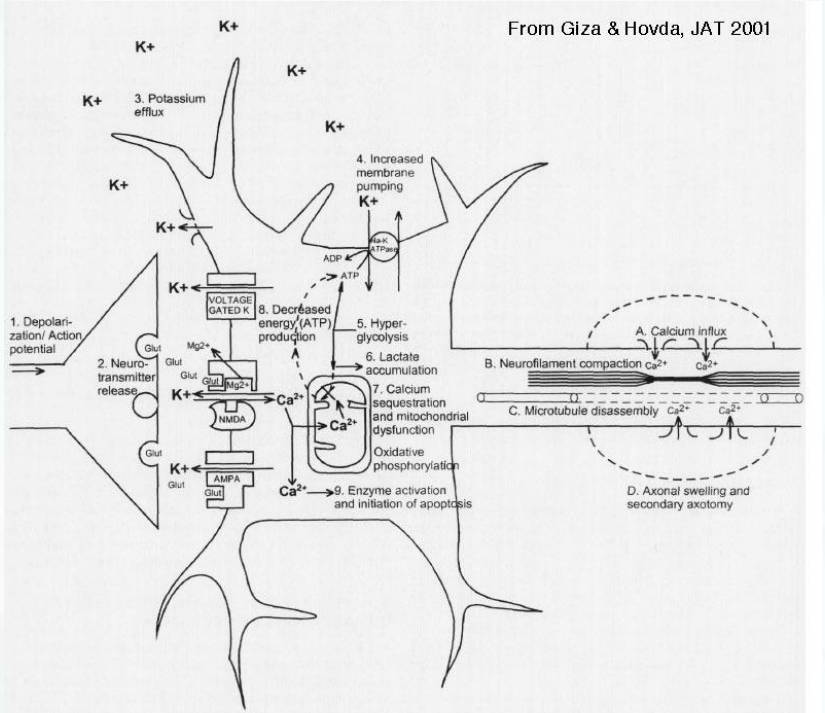


Figure 2. Neurometabolic cascade following traumatic injury. (1) Nonspecific depolarization and initiation of action potentials. (2) Release of excitatory neurotransmitters (EAAs). (3) Massive efflux of potassium. (4) Increased activity of membrane ionic pumps to restore homeostasis. (5) Hyperglycolysis to generate more adenosine triphosphate (ATP). (6) Lactate accumulation. (7) Calcium influx and sequestration in mitochondria leading to impaired oxidative metabolism. (8) Decreased energy (ATP) production. (9) Calpain activation and initiation of apoptosis. A, Axolemmal disruption and calcium influx. B, Neurofilament compaction via phosphorylation or sidearm cleavage. C, Microtubule disassembly and accumulation of axonally transported organelles. D, Axonal swelling and eventual axotomy. K^+, potassium; Na^+, sodium; Glut, glutamate; Mg^{2+}, magnesium; Ca^{2+}, calcium; NMDA, N-methyl-D-aspartate; AMPA, d-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid.

DSM-V → Where is Postconcussive Disorder? Actual Current Preferred Term by Clinicians: *Persistent Symptoms after Concussion (PSaC)*

Mild Neurocognitive Disorder Due to TBI

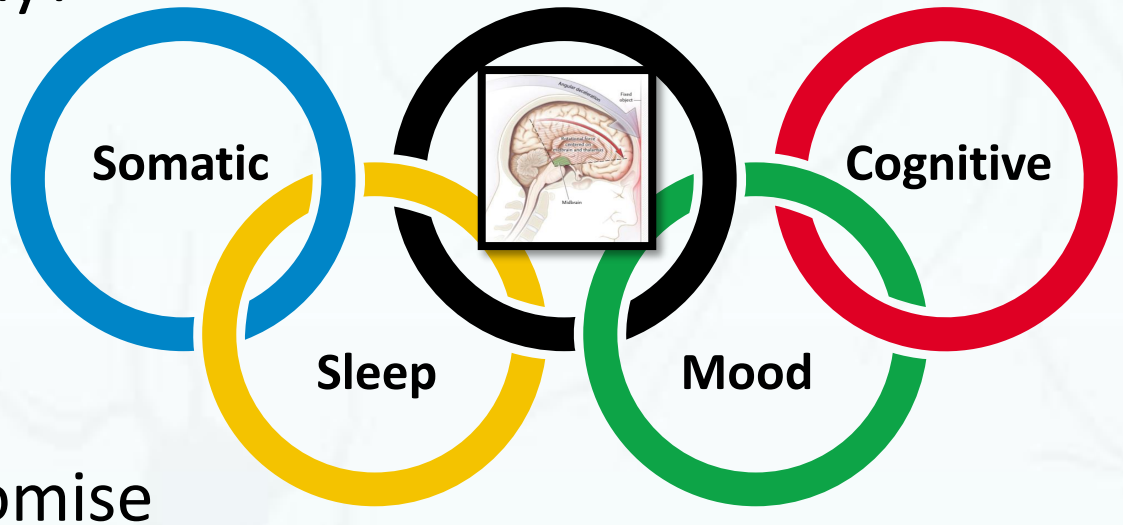
- Criteria:
  - No impairment in complex IADLs but may require greater effort
  - Decline in cognitive domains (e.g., Complex Attention, Executive Function, Learning and Memory, Language, Perceptual-Motor, Social Cognition)
- Evidence of TBI with 1 of the following:
  - LOC
  - Post-traumatic Amnesia
  - Disorientation and Confusion
  - Neurological signs (can be radiological)
  - Presents immediately after TBI (or recovery of consciousness) and persists beyond acute recovery

Major Neurocognitive Disorder Due to TBI

- Criteria:
  - Impairment in IADLs
  - Decline in cognitive domains (e.g., Complex Attention, Executive Function, Learning and Memory, Language, Perceptual-Motor, Social Cognition)
- Evidence of TBI with 1 of the following:
  - LOC
  - Post-traumatic Amnesia
  - Disorientation and Confusion
  - Neurological signs (can be radiological)
  - Presents immediately after TBI (or recovery of consciousness) and persists beyond acute recovery
- Code With or Without Behavioral Disturbance

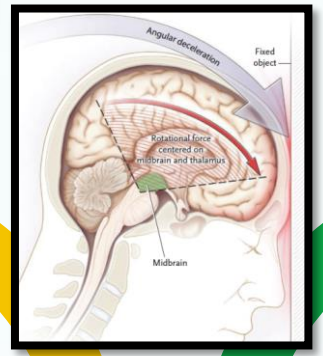
GAMEPLAN

- What Exactly Are We Talking About and Why?
- Evolving Clinical Management
- Facing the Future: Promise and Challenge



CONCUSSION SIGNS & SYMPTOMS

<u>Cognitive Symptoms</u>
"Fogginess"
Cognitive fatigue
Inattention
Memory deficits



<u>Somatic Symptoms</u>
Headaches
Nausea
Dizziness/Poor balance
Light/Sound Sensitivity

<u>Sleep Disturbance</u>
Insomnia
Fragmented sleep
Hypersomnia
Hyposomnia

<u>Mood</u>
Irritability
Lability
↓frustration tolerance
Sadness
Anxiety

ROLE OF EVIDENCE

- General Trends
  - Higher Level of Evidence Closest to Acute Injury
  - As timeline increases, recommendation become more consensus guidelines
- Highest Level of Evidence
- Acute Education regarding Symptom Education and Expectation of Recovery Time

SHORT REPORT

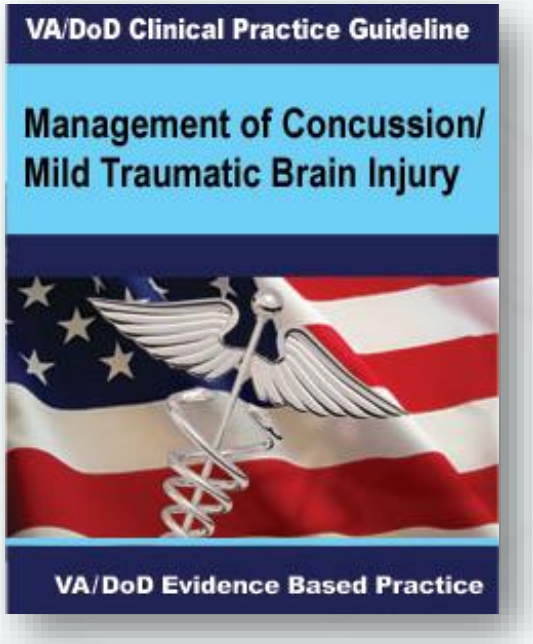
Impact of early intervention on outcome following mild head injury in adults

J Ponsford, C Willmott, A Rothwell, P Cameron, A-M Kelly, R Nelms, C Curran

J Neurol Neurosurg Psychiatry 2002;**73**:330–332

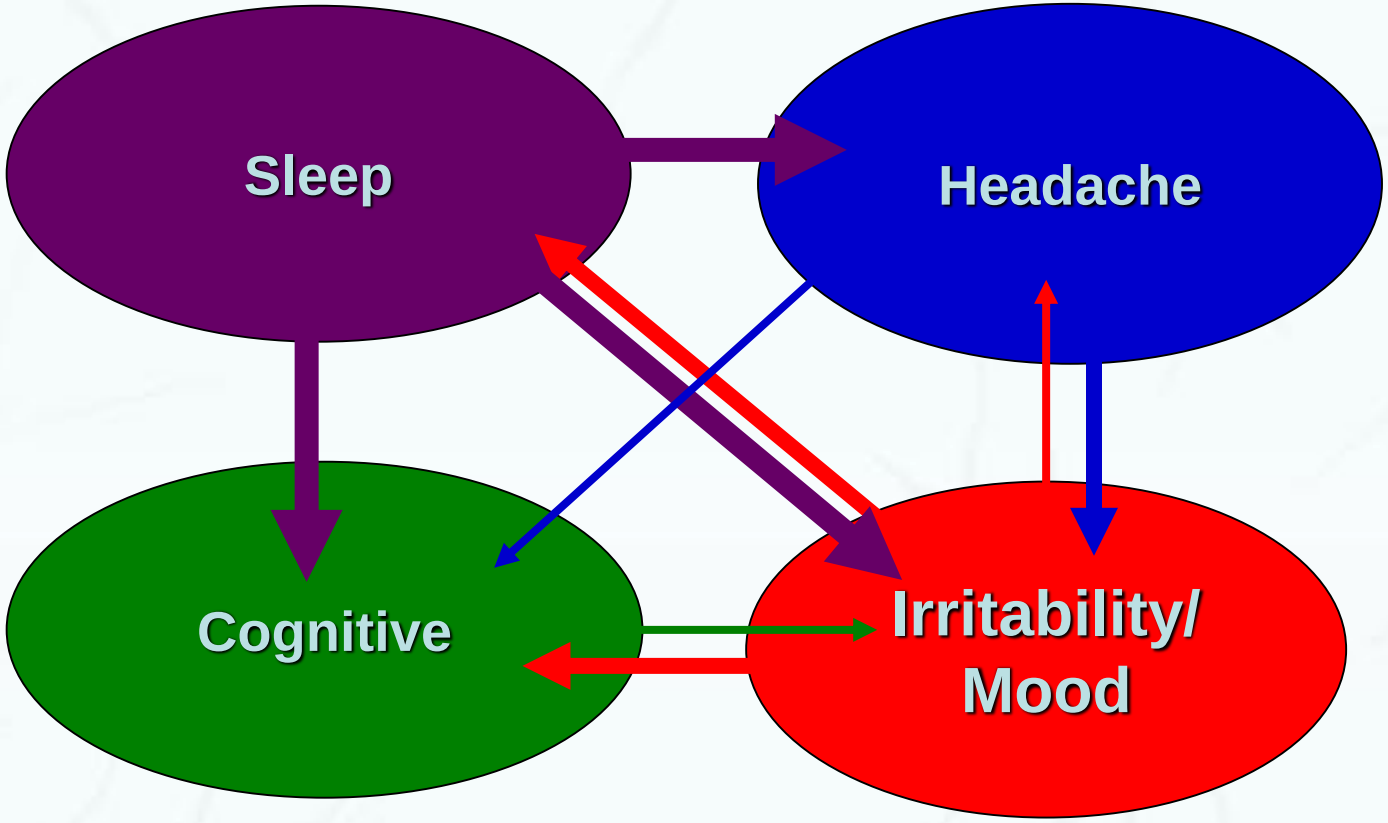
KEY GUIDELINES:
Based on Target Symptom Approach

- **2009 VA-DoD CPGs**
- Highest-rated mTBI CPG in a 2011 research study published in *Brain Injury*



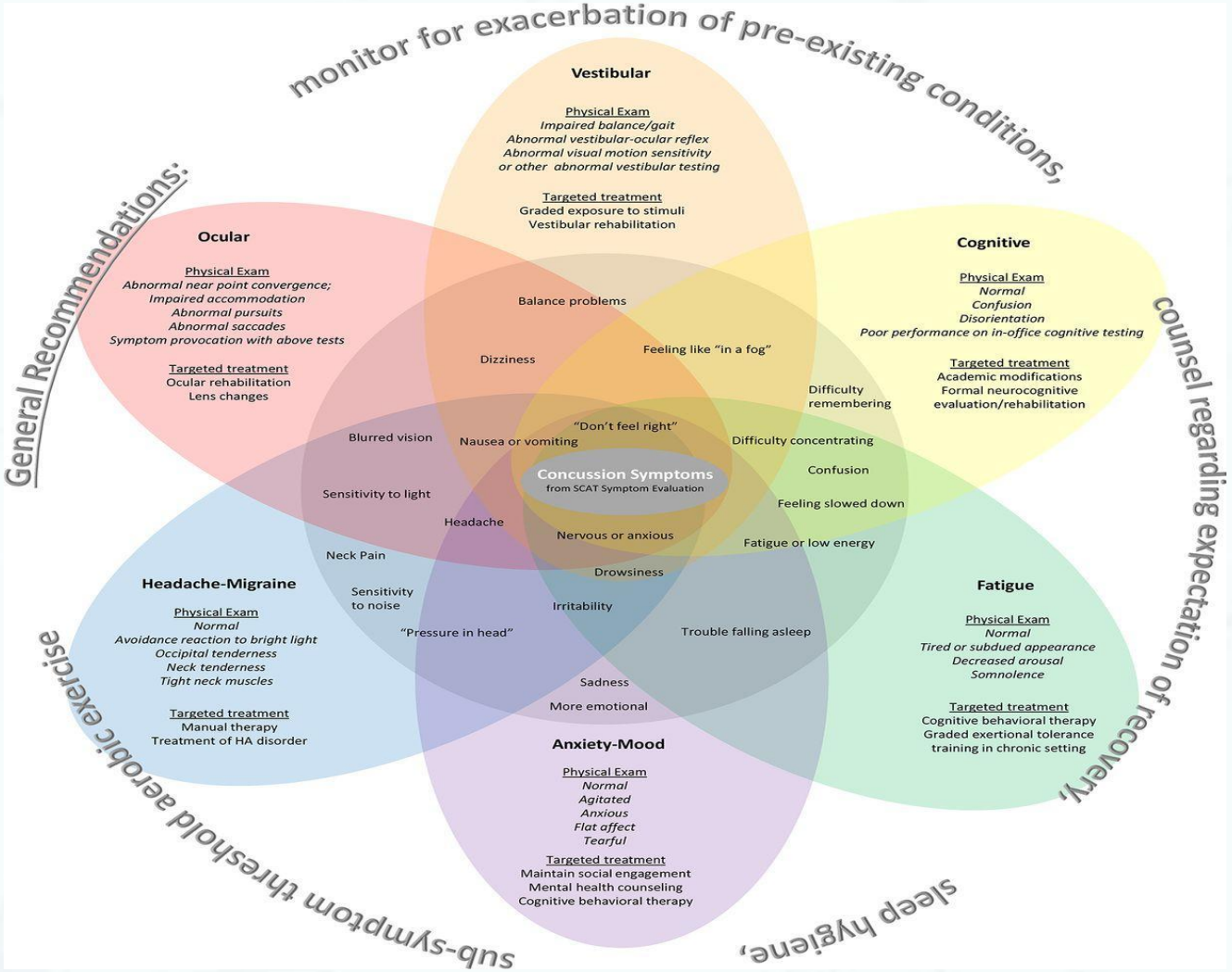
Ontario Neurotrauma Foundation
Fondation ontarienne de neurotraumatologie

mTBI SYMPTOM INTERACTION

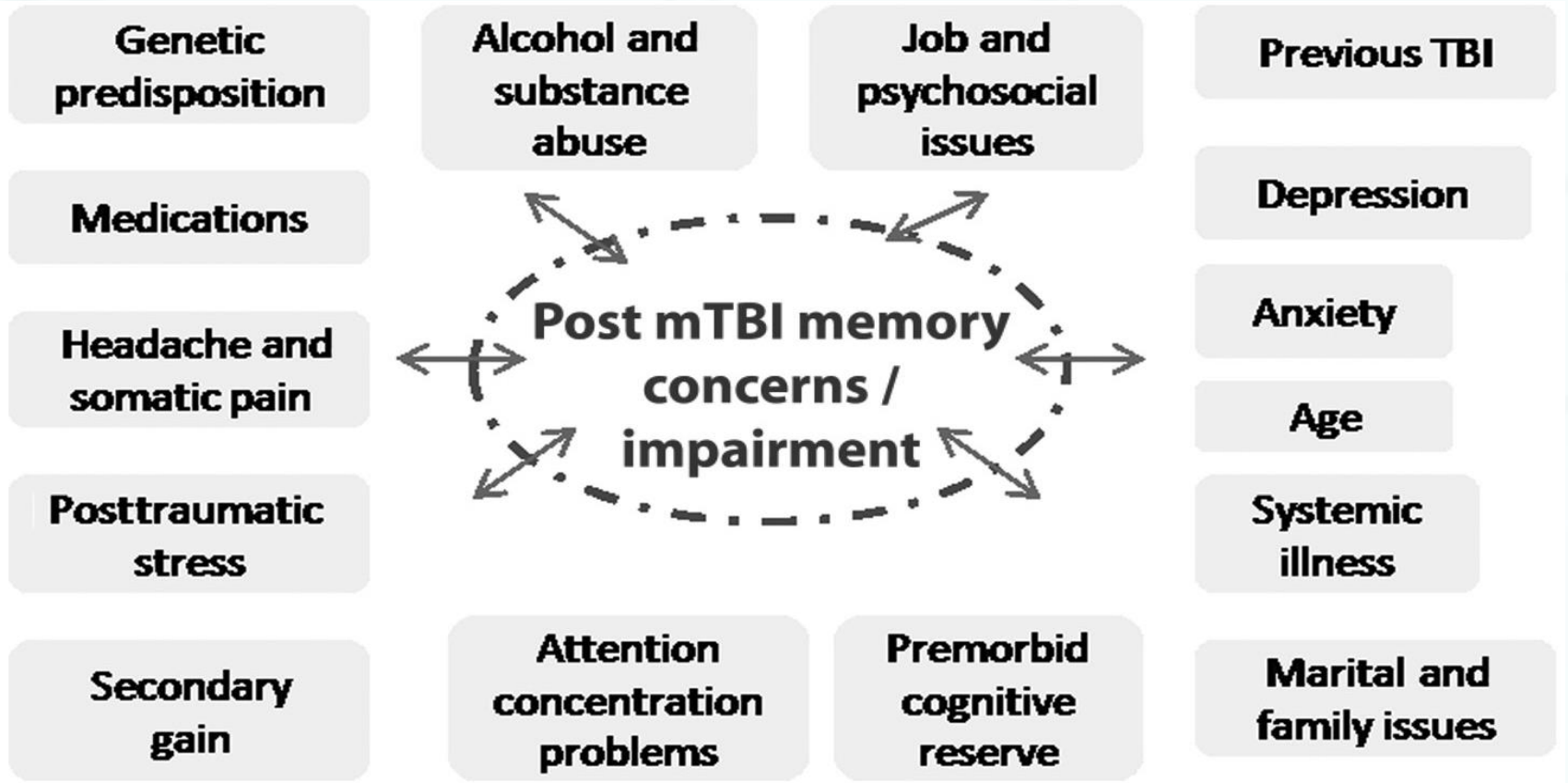


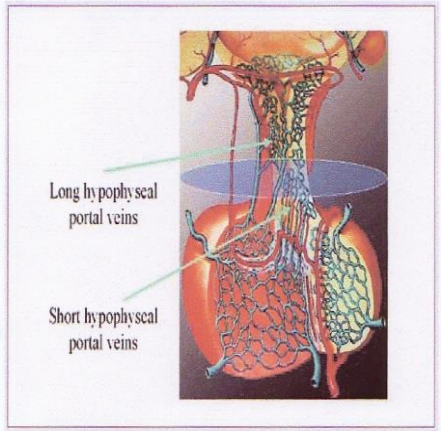
Overlapping clinical profiles: an emerging concept to facilitate individualised management after sport-related concussion.

Harmon KG, Clugston JR, Dec K, *et al.* American Medical Society for Sports Medicine position statement on concussion in sport. *Br J Sports Med* 2019;**53:**213-225.

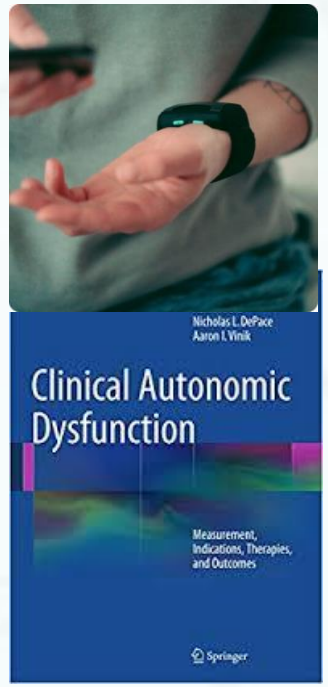


MANY REASONS FOR PERSISTENT SYMPTOMS

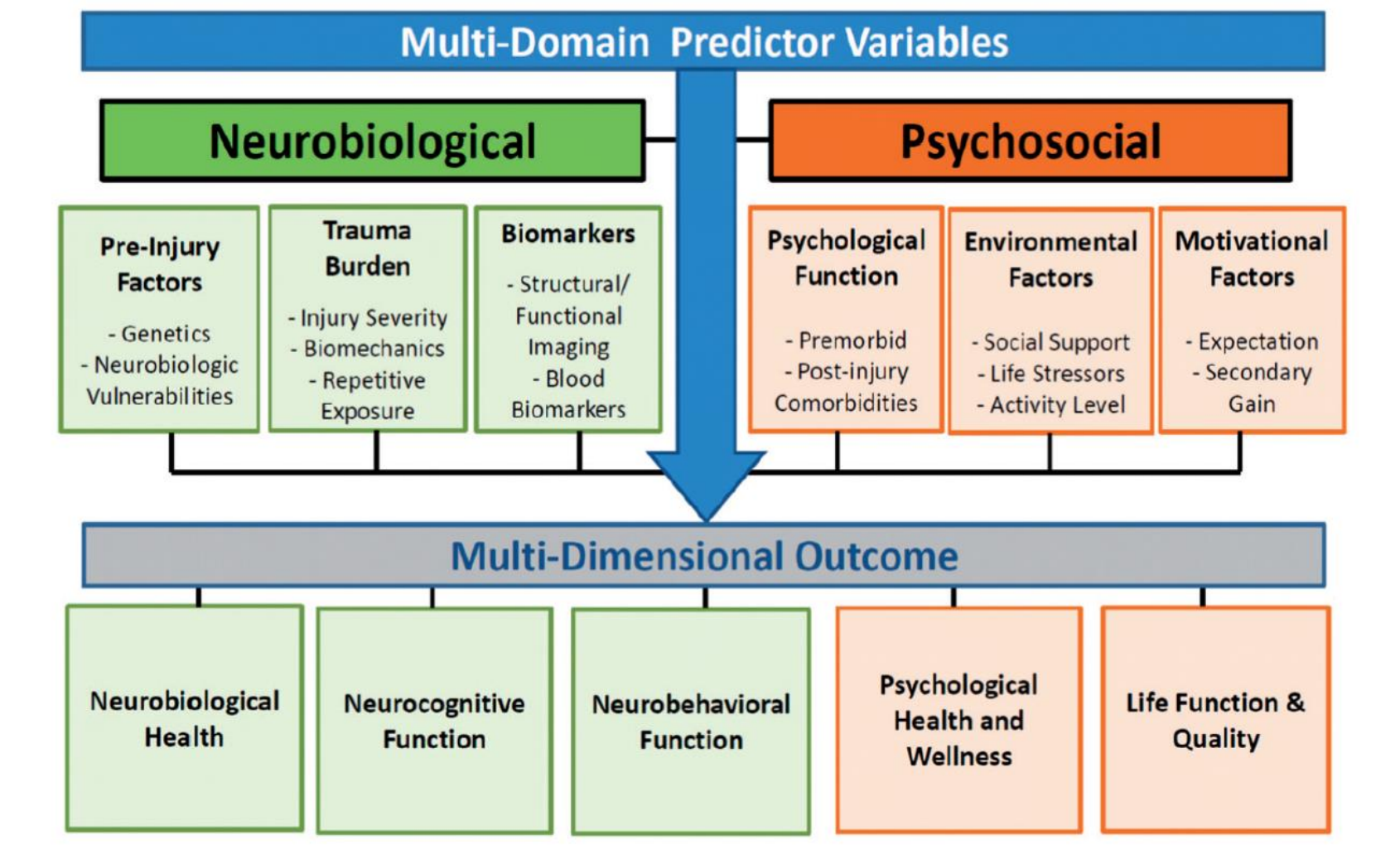




Continuum Lifelong Learning Neurol 2010;16(6)

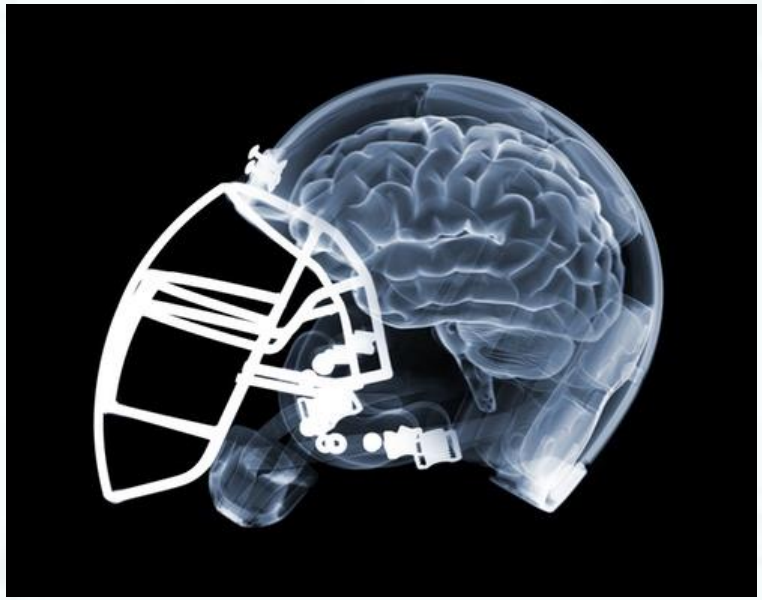


TRANSDISCIPLINARY MODEL: *NeuroBioPsychoSocial Approach*



GAMEPLAN

- What Exactly Are We Talking About and Why?
- Evolving Clinical Management
- Facing the Future: Promise and Challenge



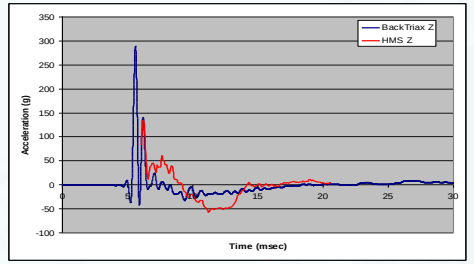
ASPIRATIONAL GOALS

- Portable Rapid Noninvasive Objective Assessment
  - Accurate diagnosis
  - Determine recovery
- How Do We Get There?
  - The promise of technology

ROUGH ORGANIZATION SCHEME FOR CONCUSSION TECHNOLOGY

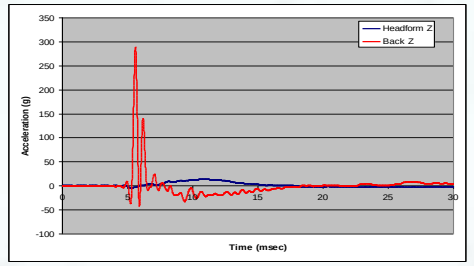
- Event Detection
  - Helmet Sensors
  - Non-Helmet Sensors (Mastoid, EarBuds, Mouthguard, Retainer)
- Clinical Diagnostic Assessment
  - Vestibular/Balance
  - Neurocognitive – multiple products for computer-based cognitive
  - Vision and Eye Movements
- Prevention
- Symptom Treatment

Internal Mount Sensor



Lab vs. Theater

External Mount Sensor

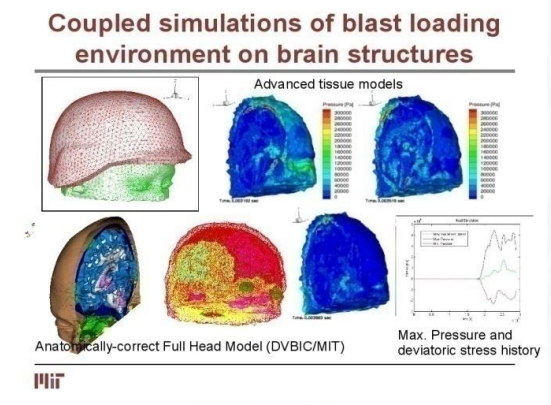


Sensor vs. Headform

NFL HEAD HEALTH CHALLENGE

BIOMARKERS STUDIED IN CURRENT DETECTION ADVANCES AND INVESTIGATIONS

- Serum / CSF Biomarkers
  - LDH, GFAP, NSE, S-100B
  - UCH-L1, MAP-2, Tau, Spectrin Products
  - Proteomics
- Advanced Neuroimaging Techniques
  - DTI, fMRI, MRS
  - SPECT, PET
- Neurophysiology: Advanced EEG, Evoked Potentials, Heart Rate Variability, more
- Computer Models
- Others: Vestibular Measurements, Nystagmus, more…
- Challenges
  - Specificity
  - Utility
  - Clinical Correlation with Symptoms
  - Context Matters – Acute vs Chronic …

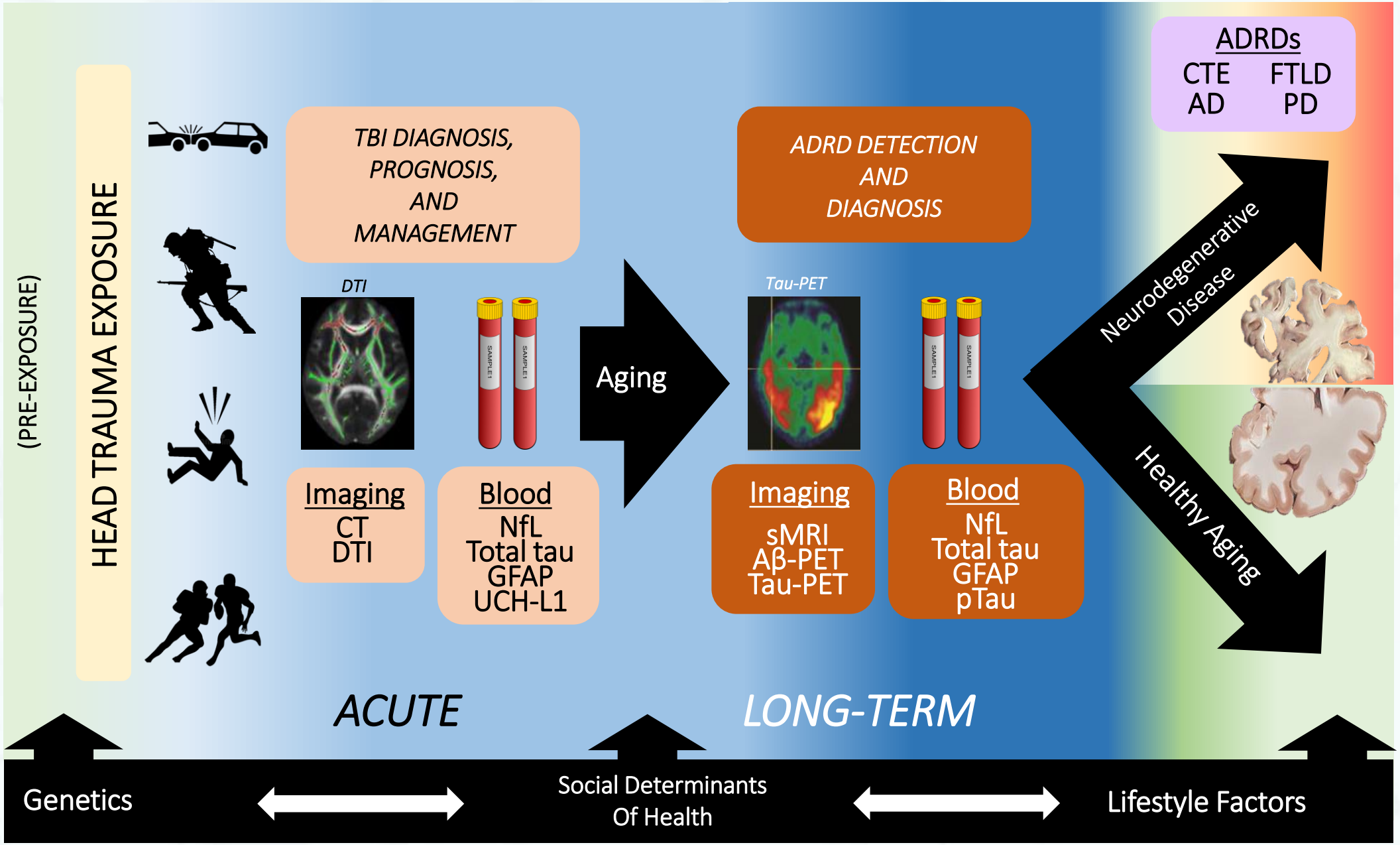


2018 Banyan Assay

2020 Abbott Device

"Concussion" Blood Test UCHL1 and GFAP – actually correlates with CT abnormality

BIOMARKER CONTEXTS OF USE



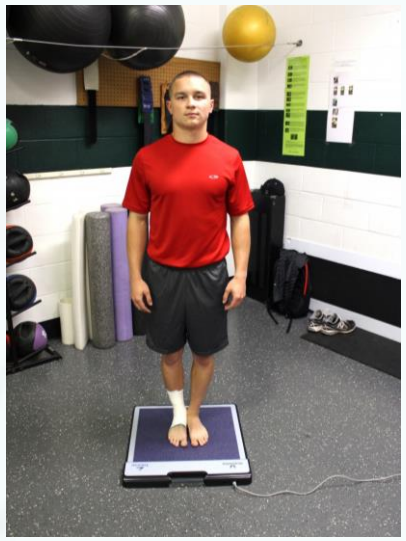
CONCUSSION TECHNOLOGY: *Detection & Diagnosis*

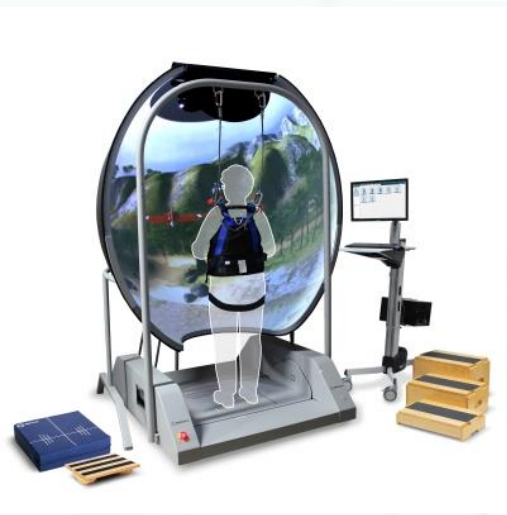
These are example to illustrate landscape.
This talk is ***not*** endorsing any specific product.

BALANCE TECHNOLOGY*:
High & Low Tech Examples

These are example to illustrate landscape.
This talk is ***not*** endorsing any specific product.

**Specific clinical domain.*





ROUGH ORGANIZATION OF PREVENTION AND TREATMENT TECHNOLOGIES

- Prevention
  - Technique & Training (e.g., Reduction in contact during practice)
  - Rule Changes
  - Equipment (e.g., Cervical Collar, Turf Technology, Concussion Tether)
  - Helmet Research Continues
  - "Nutritional Armor"
    - Omega 3, Ketone Bodies, More …

- Symptom Treatment
  - Target-Symptom (Rehab Approach)
  - Generalized Treatment

TECHNOLOGY APPLIED TO TREATMENT:
Mixed Evidence

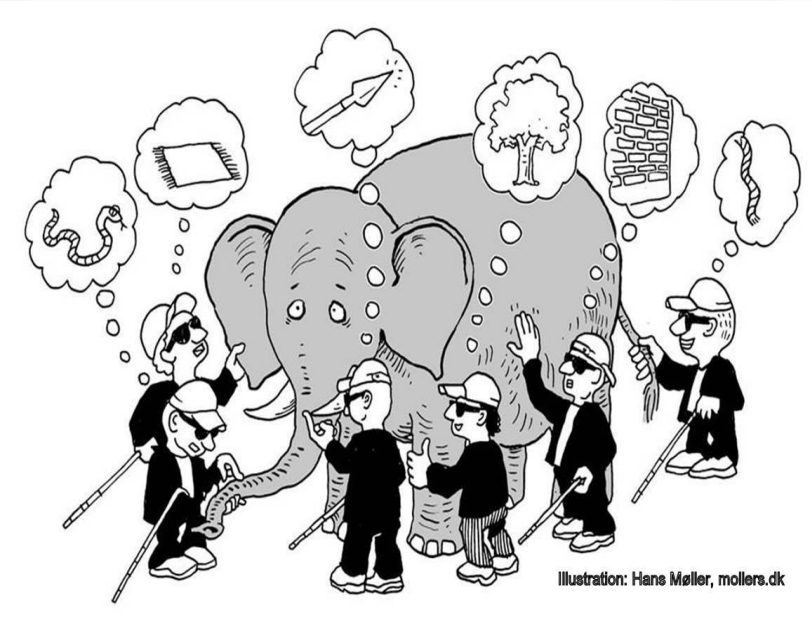
These are example to illustrate landscape.
This talk is ***not*** endorsing any specific product.

TECHNOLOGY:
Opportunities with New Challenges in Near-term

- Beware Idea that technology will provide us 100% accurate, objective answers – “Perfection is the Enemy of Good”
  - Goal: Perfect rapid mechanical detectors, biomarker detectors, etc.
  - Challenge with serum markers
    - Functional disruption not involving cell lysis or destruction seen in moderate/severe TBI
- Beware of “WOG” syndrome
- Understanding clinical correlation
- Second-order questions lead to new management challenges
  - Management of full resolution of clinical symptoms with exertion but remaining biomarker?
    - Seen with neurophysiology markers (e.g., qEEG, functional networks)

RESEARCH CHALLENGES

- Clinical Correlation
  - Roles of Placebo, Nocebo, Lessebo
  - Emerging Concepts
- Translation
- Blind Men and the Elephant
- Attachment to Old Assumptions



TRANSLATION CHALLENGES

- Translation of Preclinical Animal Trials to Human Trials
  - Similar Challenges in Stroke (vascular acquired brain injury)
  - Possible Issues with lack of Gyrencephalic Models
    - Difficult genetic models
- Translation of case series to RCTs
  - Possible Challenges with:
    - Appropriate selection
    - Role of Comorbidities

BLAST INJURY:
Blind Men & the Elephant Case

Preclinical Data

- Differences in DTI between blast and impact TBI
- Event-related potentials in blast and non-blast exposures
- Differences in fMRI between breacher instructors and students
- Inflammatory markers in animal studies
- Physiological, histological, and/or behavioral differences between blast and non-blast in shock tubes with rodents
- Low-level axonal, neuronal, and/or glial damage/reactivity in porcine models

Clinical Data

- Clinical studies varied by domain
- No difference in neuropsychological testing patterns
  - Belanger, 2009
- Difference in vestibular testing patterns between blast and non-blast
  - Hoffer, 2010
- DTI data in literature is varied

- Statistically significant findings from MRMC Blast Conference
- 75 experts representing DoD, DOT, DVA, academia, and industry
- 5 countries represented

REEVALUATING ASSUMPTIONS & CONVENTIONAL WISDOM

PM R 8 (2016) S91-S100

www.pmrjournal.org

Advanced Sports Medicine Concepts and Controversies

The Role of Controlled Exercise in Concussion Management

John Leddy, MD, Andrea Hinds, PhD, Dan Sirica, BS, Barry Willer, PhD

REEVALUATING ASSUMPTIONS EXAMPLE

Ali most famous example of *Dementia Pugilistica.*

Review of Data:

- Parkinson's started on one side of his body.
- Began in his 30s and 40s.
- Responded to dopamine as a treatment.
- Slowly progressive.

NEW CHALLENGES:
Chronic Traumatic Encephalopathy

REVIEW ARTICLE

Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury

Ann C. McKee, MD, Robert C. Cantu, MD, Christopher J. Nowinski, AB, E. Tessa Hedley-Whyte, MD, Brandon E. Gavett, PhD, Andrew E. Budson, MD, Veronica E. Santini, MD, Hyo-Soon Lee, MD, Caroline A. Kubilus, and Robert A. Stern, PhD

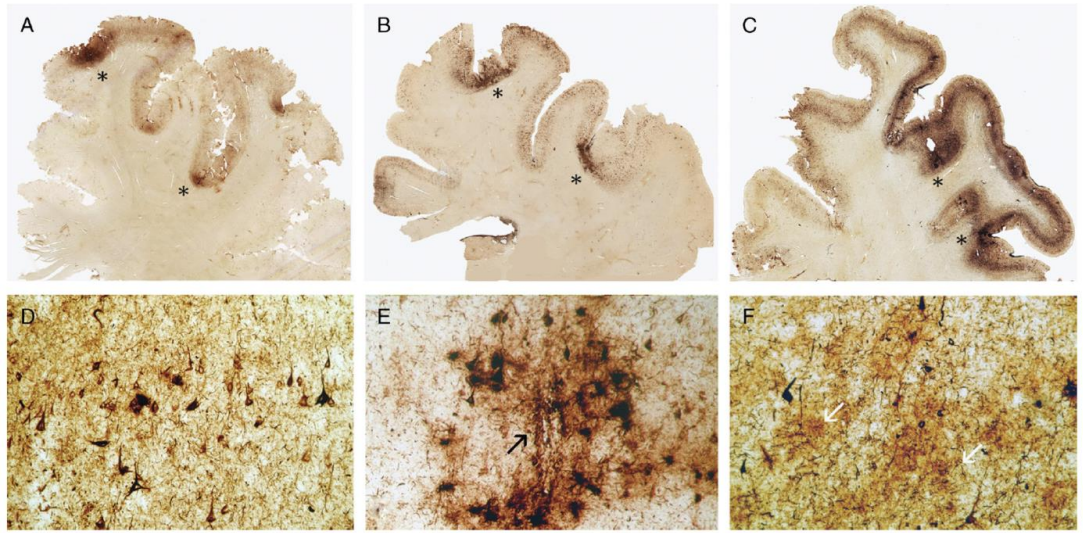


FIGURE 2. (A–C) Whole-mount 50-μm coronal sections of superior frontal cortex from Case A **(A)**, Case B **(B)**, and Case C **(C)** immunostained for tau with monoclonal antibody CP-13 showing extensive immunoreactivity that is greatest at sulcal depths (asterisks) and is associated with contraction of the cortical ribbon. **(D–F)** Microscopically, there are dense tau-immunoreactive neurofibrillary tangles (NFTs) and neuropil neurites throughout the cortex, Case A **(D)**, Case B **(E)**, and Case C **(F)**. There are focal nests of NFTs and astrocytic tangles around small blood vessels **(E**, arrow**)** and plaquelike clusters of tau-immunoreactive astrocytic processes distributed throughout the cortical layers **(F**, arrows**)**.

- Ongoing objective scientific research to better understand triggers and pathways.
- Can there be antemortem diagnosis?
- Need for longitudinal understanding.

National Institute of Neurological Disorders and Stroke Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome

Douglas I. Katz, MD, Charles Bernick, MD, David W. Dodick, MD, Jesse Mez, MD, Megan L. Mariani, BS, Charles H. Adler, MD, PhD, Michael L. Alosco, PhD, Laura J. Balcer, MD, Sarah J. Banks, PhD, William B. Barr, PhD, David L. Brody, MD, PhD, Robert C. Cantu, MD, Kristen Dams-O'Connor, PhD, Yonas E. Geda, MD, Barry D. Jordan, MD, Thomas W. McAllister, MD, Elaine R. Peskind, MD, Ronald C. Petersen, MD, PhD, Jennifer V. Wethe, PhD, Ross D. Zafonte, DO, Éimear M. Foley, MS, Debra J. Babcock, MD, PhD, Walter J. Koroshetz, MD, Yorghos Tripodis, PhD, Ann C. McKee, MD, Martha E. Shenton, PhD, Jeffrey L. Cummings, MD, Eric M. Reiman, MD, and Robert A. Stern, PhD

Correspondence
Dr. Stern
bobstern@bu.edu

Neurology® 2021;96:848-863. doi:10.1212/WNL.0000000000011850

Figure 1 Stepwise Process for Using the NINDS Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome

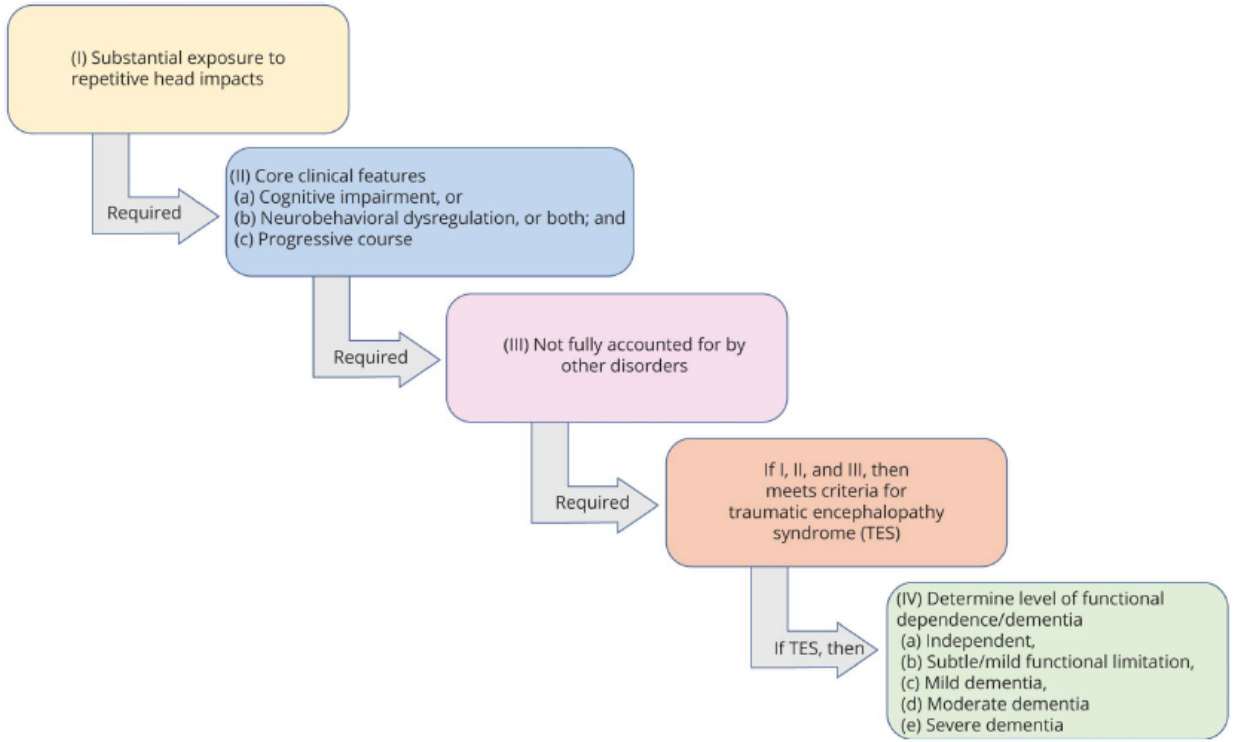


Table 5 Supportive Features Used in Determining Provisional Levels of Certainty for CTE Pathology

The following 3 supportive features are used in determining the provisional levels of certainty for chronic traumatic encephalopathy (CTE) pathology (table 6). These features are frequently present in individuals with underlying CTE pathology, but have insufficient predictive value to qualify as core clinical features.

Delayed onset
Core clinical features begin following a clearly established period of stable functioning after the RHI exposure ends. (A minimum time period of stability before onset and progression of symptoms has not been established but should be substantial [i.e., years] to suggest a history consistent with a degenerative disorder rather than problems associated with TBI or other preexisting conditions.)
Motor signs
Parkinsonism: bradykinesia, rigidity, rest tremor, and parkinsonian gait disorder; these motor signs should not be more consistent with the clinical features of nonparkinsonian neurologic conditions or primary orthopedic problems.
Other motor signs: dysarthria, ataxia, and imbalance; these motor signs should not be more consistent with the clinical features of other neurologic conditions or primary orthopedic problems.
Motor neuron disease: Weakness, dysphagia, other lower motor neuron signs (fasciculations and muscle atrophy), and other upper motor neuron signs (spasticity, hyperreflexia, extensor plantar response, and spastic dysarthria); a diagnosis of amyotrophic lateral sclerosis (ALS) would meet this criterion but is not necessary.
Psychiatric features
These supportive psychiatric features have not been accounted for by neurobehavioral dysregulation described in the core clinical features. They may occur individually or in combination, should represent a clear change from baseline, and should be persistent (i.e., months to years) or progressive. These features can be based on self- or informant report, a history of treatment, or clinician's report. The supportive psychiatric features include the following:
Anxiety: pervasive worries, excessive fears, agitation, or obsessive or compulsive behavior (or both); a formal diagnosis of anxiety disorder would meet this criterion but is not necessary. If available, scores on an established, validated anxiety scale should indicate a moderate level of anxiety or higher.
Apathy: loss of interest in usual activities and loss of motivation or drive. If available, scores on an established, validated apathy scale should indicate a moderate level of apathy or higher.
Depression: feeling overly sad, dysphoric, or hopeless, with or without a history of suicidal thoughts or attempts; a formal diagnosis of major depressive disorder or persistent depressive disorder would meet this criterion but is not necessary. These symptoms should not be a time-limited reaction to an event (e.g., death of family member, illness, and trauma). If available, scores on an established, validated depression scale should indicate a moderate level of depression or higher.
Paranoia: delusional beliefs of suspicion, persecution, or unwarranted jealousy; a formal diagnosis of a psychotic disorder would meet this criterion but is not necessary. If available, scores on an established, validated paranoia scale should indicate a moderate level of paranoia or higher.

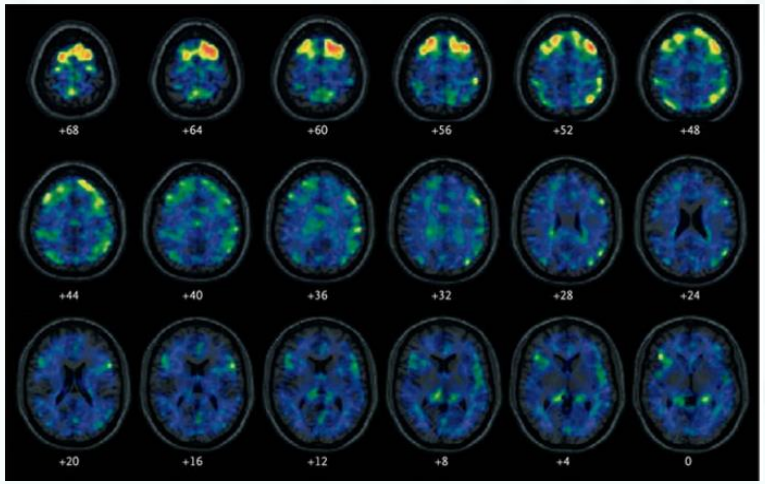
Need for Objective Biomarker for CTE Pathology

TAUVID APPROVAL

FDA Approves First Drug to Image Tau Pathology in Patients Being Evaluated for Alzheimer's Disease

Approval Marks Significant Advance Towards a More Definitive Assessment of Alzheimer's Based on Brain Imaging

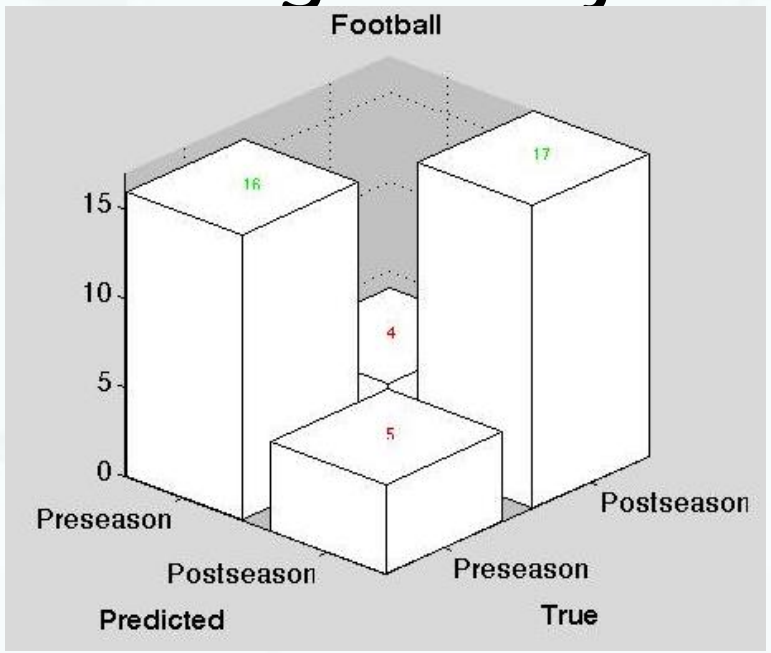
- Indications: "…estimate density and distribution of aggregated tau NFTs in adult patients with cognitive impairment being evaluated for AD"
- AD Misdiagnosis Risks
  - TAUVID does not target β-amyloid
  - NFTs present at moderate levels ("B2")
    - TAUVID (+) likely reflects Braak V-VI
  - Off-target binding in medial temporal regions
    - Only contiguous uptake in neocortex used to support (+) scan

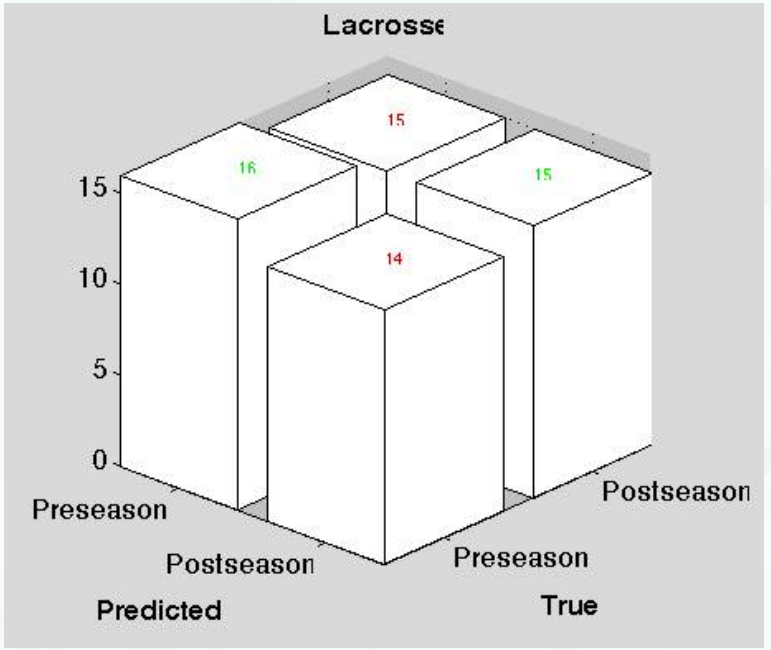


USE LIMITATIONS

TAUVID is not indicated for use in the evaluation of patients for CTE.

EMERGING CONCEPT:
Subconcussion Preseason vs. Postseason Changes in Resting State fMRI of Student Athletes





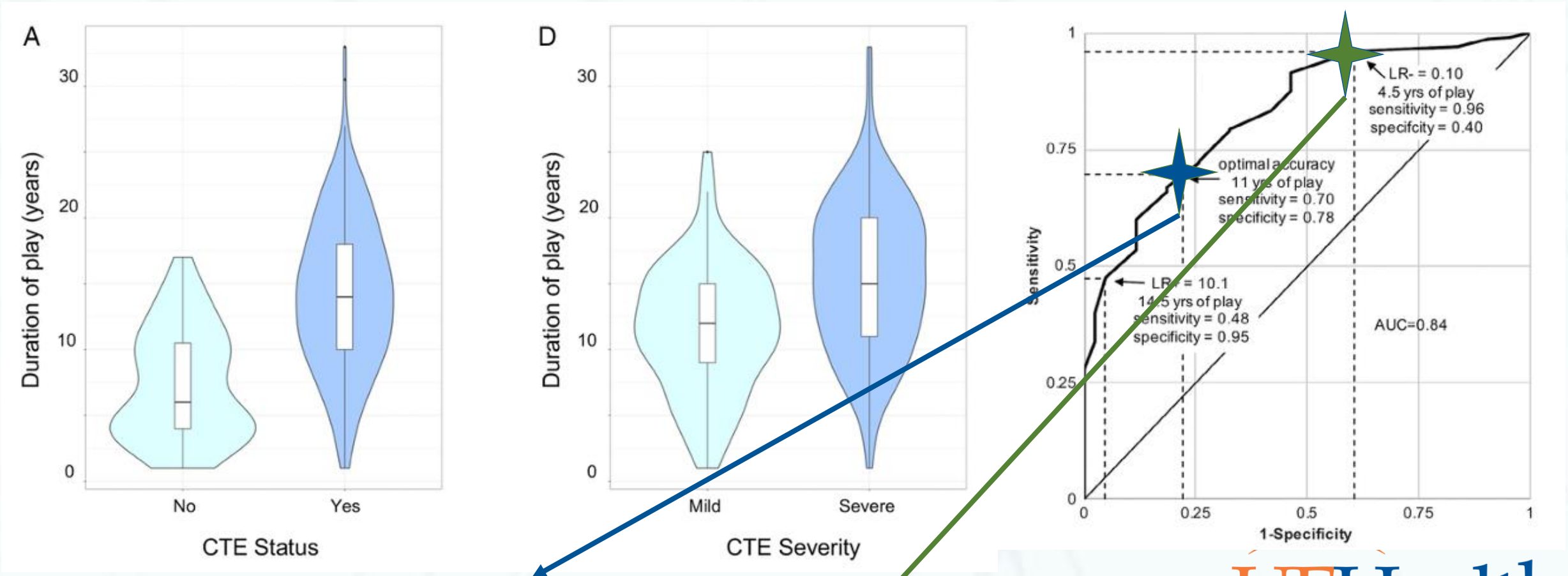
These players do not have concussion. The lacrosse players were studied in the fall practice season and serve as a control.

Druzgal, et al.

Shifting the Clinical Paradigm

TBI with LOC → TBI with PTA → "Concussion" → RHI/Collision Sports/Military

Duration of American Football and CTE Risk

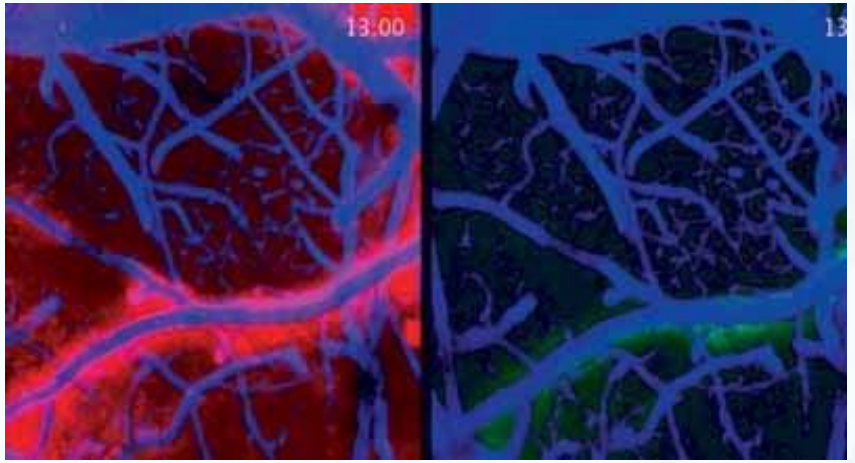


≥ 11 years = optimal sensitivity/specificity balance for underlying CTE

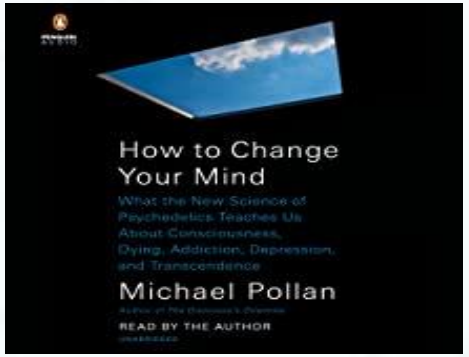
>5 years = maximizes sensitivity (low specificity) to underlying CTE

Mez et al. 2019, *Ann Neurol*

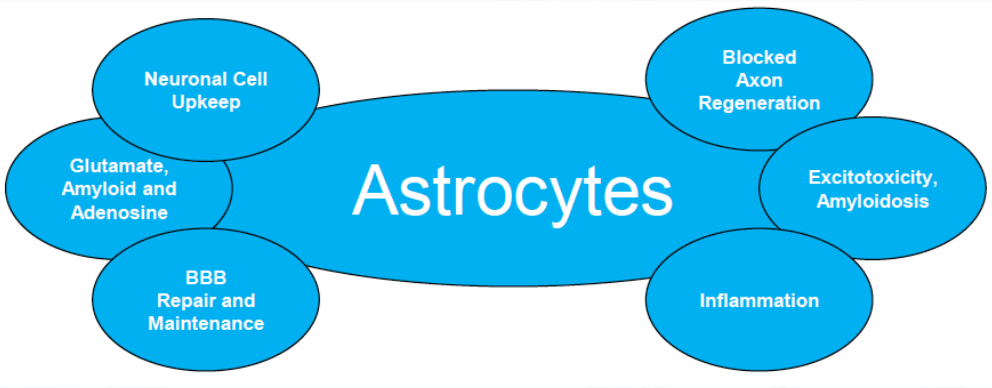
EMERGING TBI LANDSCAPE



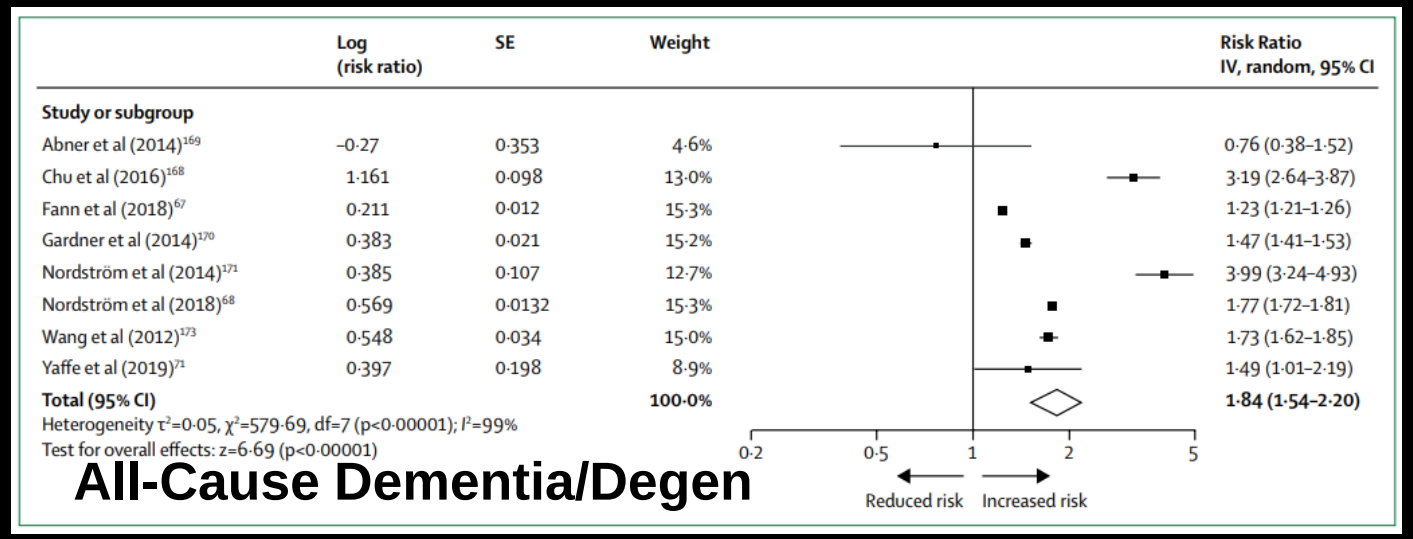
Glymphatics:
Changing Sleep Paradigm



Next Gen Pharmacology



Modifiable Risk Factor



Study or subgroup	Log (risk ratio)	SE	Weight	Risk Ratio IV, random, 95% CI
Abner et al (2014)[169]	−0·27	0·353	4·6%	0·76 (0·38–1·52)
Chu et al (2016)[168]	1·161	0·098	13·0%	3·19 (2·64–3·87)
Fann et al (2018)[67]	0·211	0·012	15·3%	1·23 (1·21–1·26)
Gardner et al (2014)[170]	0·383	0·021	15·2%	1·47 (1·41–1·53)
Nordström et al (2014)[171]	0·385	0·107	12·7%	3·99 (3·24–4·93)
Nordström et al (2018)[68]	0·569	0·0132	15·3%	1·77 (1·72–1·81)
Wang et al (2012)[173]	0·548	0·034	15·0%	1·73 (1·62–1·85)
Yaffe et al (2019)[71]	0·397	0·198	8·9%	1·49 (1·01–2·19)
Total (95% CI)			**100·0%**	**1·84 (1·54–2·20)**

Heterogeneity τ^2=0·05, χ^2=579·69, df=7 (p<0·00001); I^2=99%
Test for overall effects: z=6·69 (p<0·00001)

0·2 0·5 1 2 5
Reduced risk Increased risk

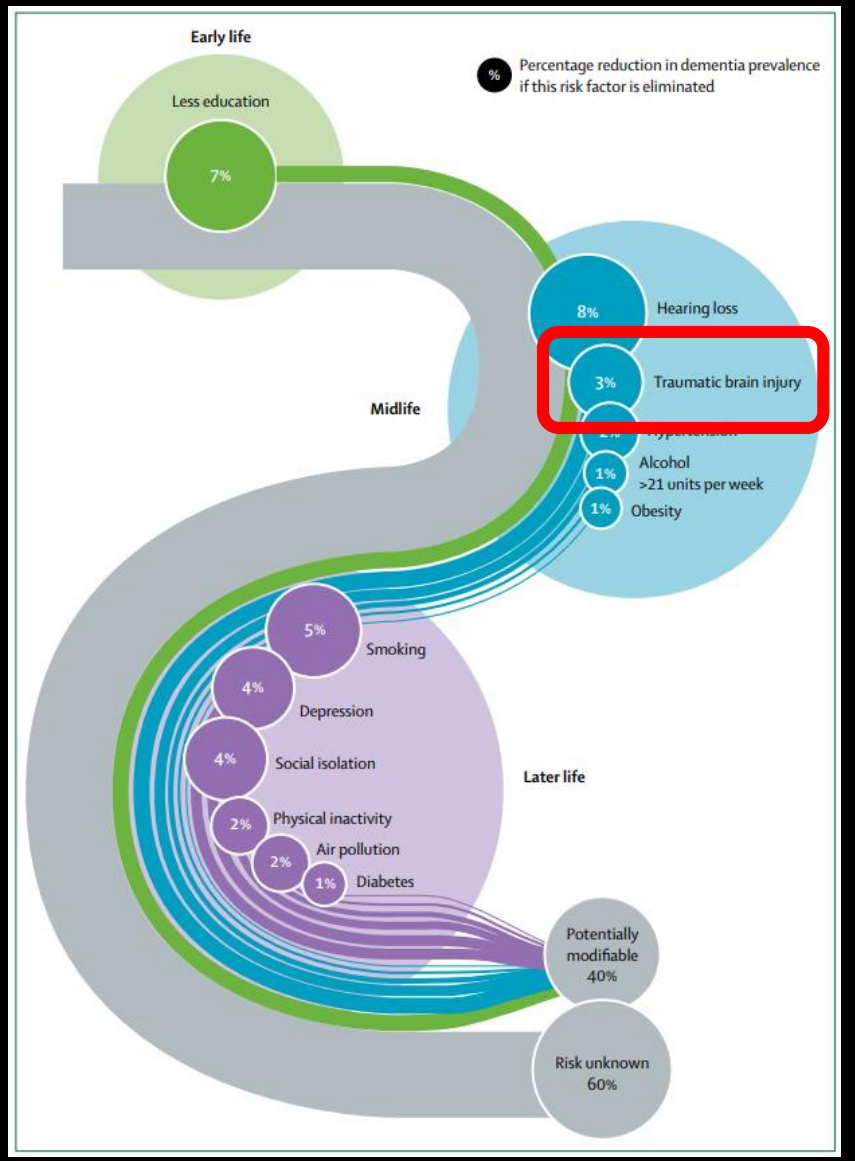
All-Cause Dementia/Degen

Alzheimer's Disease

Lewy Body /Parkinson's

ALS/MND

CTE



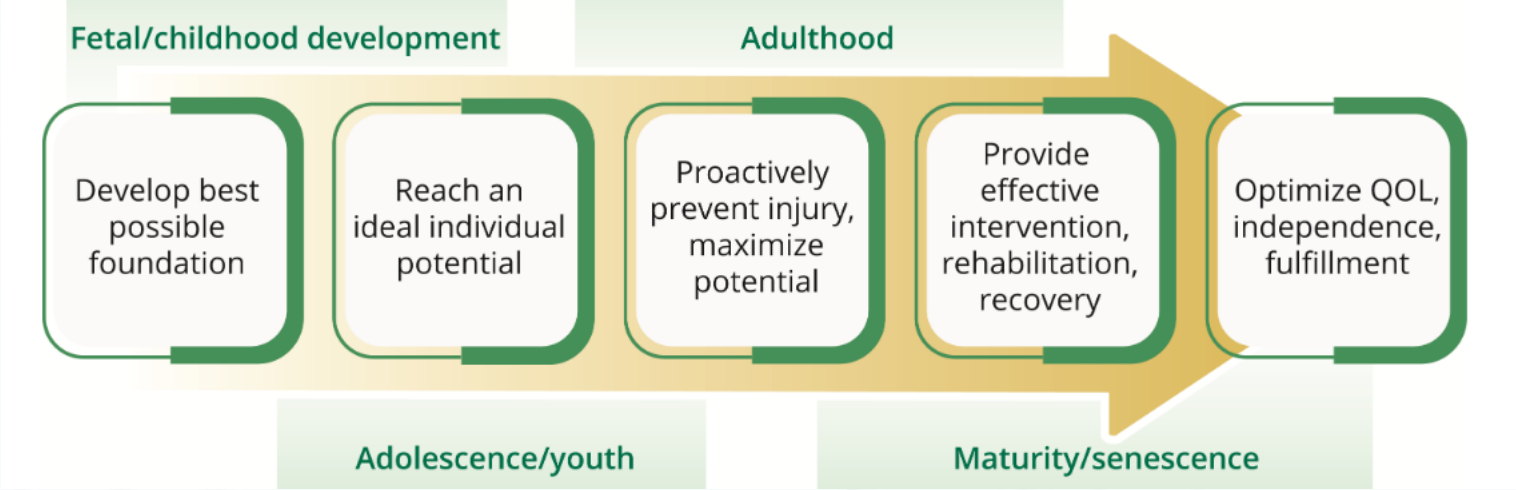
Livingston et al., *Lancet, 2020*

Neurology®

Neurologists Have a Plan for Lifelong Brain Health

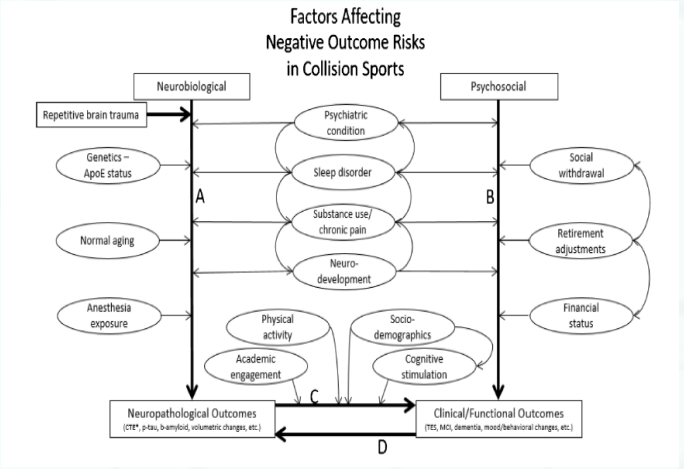
Orly Avitzur, Natalia S Rost and David A Evans

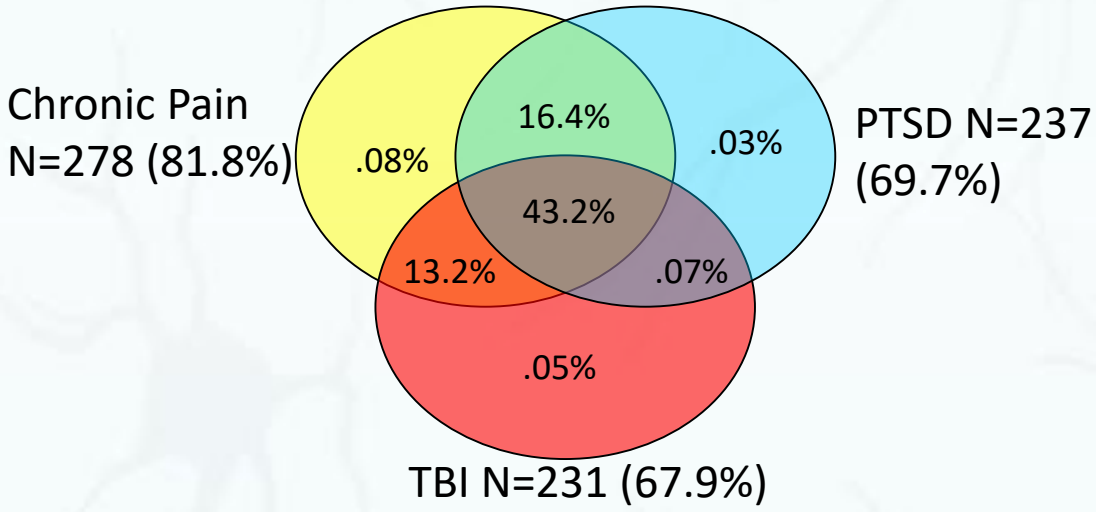
Neurology published online September 14, 2022
DOI 10.1212/WNL.0000000000201339



BEWARE OF PASSIONATE DEBATES

- Beware strong passions
  - May decrease scientific objectivity
  - May miss new observations that allow us to question assumptions
- What is the best tool or device or technology?
  - Computerized neurocognitive tests – original debate
  - As tools for additional domains expand, debate has expanded
- Beware underlying assumption
  - Assumption: Single tool or treatment can help every injured individual
- Context
  - Focus on domains and not specific tool or instrument
  - May need suite assessing multiple domains





Asken et al.
Neuropsychology Review, 26(4), 2016

Relative distribution of the "Polytrauma Triad" in a sample of 340 OEF/OIF veterans evaluated at the VA Boston Polytrauma Network Site.

TOUGH QUESTIONS IN THE FUTURE

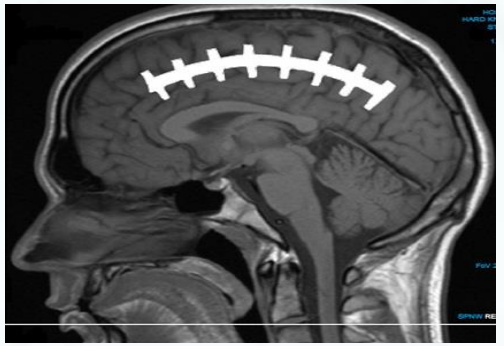
- Possible ethical challenges from technology
  - Abnormal biomarker without known clinical correlation
    - Most Likely: Neurophysiology Measures - qEEG and Networks
    - Analogous example: Echocardiography at NFL Combine
- Goal of Precision Medicine → Individualized Rx but …
- Genetic testing to determine predilection and inform decision vs. free choice
- How far should we transition beyond injury/symptom management and healing to performance enhancement?
  - Evolving trends in sports medicine focusing on performance
    - Low Tech Example: Sleep Extension

WE ARE REBUILDING THE AIRPLANE IN FLIGHT ….

While Waiting for the Rocket Ship!!

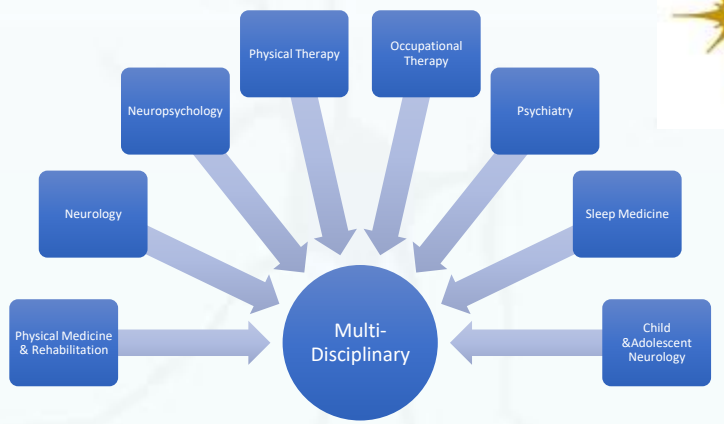
TAKE HOME MESSAGES

- We need an ***organized framework*** to face emerging challenges and understand context.
- ***Emerging technology*** will be an important tool, but no single technology will provide all the answers.
- We need to ***reevaluate and challenge old assumptions.***
- We can advance both the field and patient care by working in ***collaborative interdisciplinary teams***.
- Let's **face the future** together!



- Sports as a Laboratory Model (SLAM)
- University of Virginia
- First study: Baseline cognitive studies and post-injury evaluations revealed cognitive deficits in sports concussion with either LOC or AOC
- Research utilized in development of initial RTP Guidelines

MY THANKS!



CEU Information

- **Breakout Session K:**
- **Overview of Traumatic Brain Injuries**
- **1.0 CEU**