

Prognostic Biomarkers in Mild Traumatic Brain Injury

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Name	Role	Relationship	Company
Durga Roy, MD	Co-Investigator	Head Injury Serum Markers for Assessing Response to Trauma Study Team (HeadSMART)	ImmunArray
Durga Roy, MD	Principal Investigator	Awardee NARSAD Young Investigator Award	Brain Behavior Research Foundation
Jessica Gill, PhD	Principal Investigator	Beacon-Bitol Study	Danaher Pharmaceuticals

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Objectives

- Describe the heterogeneity of neuropsychiatric symptoms in mild traumatic brain injury
- Interpret emerging evidence on clinical, blood biomarker and imaging prognosticators in mild traumatic brain injury
- Apply a clinical framework for assessment and treatment of neuropsychiatric symptoms after mild traumatic brain injury

THE IMPACT OF TRAUMATIC BRAIN INJURY (TBI) IN THE U.S.



**2.6
MILLION**

TBIs in the U.S.
annually



**3.2 TO 5.3
MILLION**

with TBI-related
disability



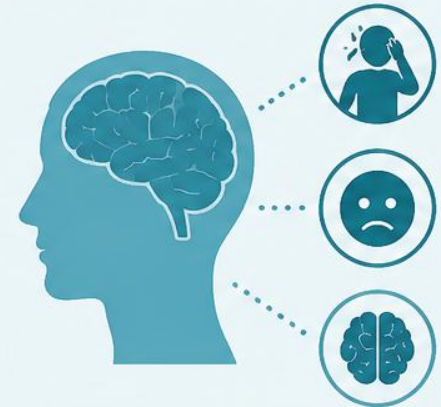
**\$60–221
BILLION**

in annual direct and
indirect medical costs



43%

with functional or
neuropsychiatric
sequelae



TBIs are a major public health challenge—affecting millions of lives and creating a substantial health and economic burden.

Source: Centers for Disease Control
and Prevention (CDC)

Why do psychiatrists need to know about mild TBI (mTBI)?

- The MOST common TBI: constitutes 70-90% of all TBI
- Patients frequently present to psychiatry before neurology
- Psychiatric symptoms a primary reason people seek care
- Great variance in persistence and severity of symptoms
- Devastating outcomes of suicide, cognitive problems, disability



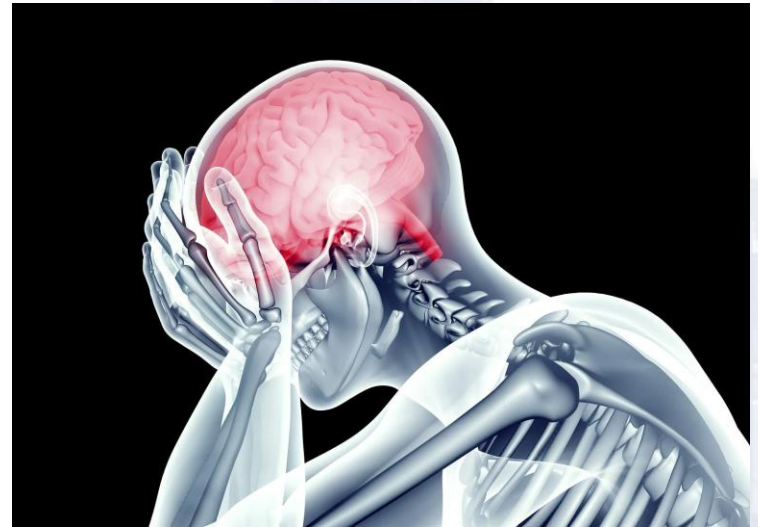
PAST

PRESENT

TBI: A Diagnostic Evolution

Where we were: A Clinical Diagnosis

- Traumatically induced physiological disruption of brain function:
 - loss of consciousness
 - alteration in mental state
 - loss of memory
 - +/- focal neurological deficits or head imaging findings



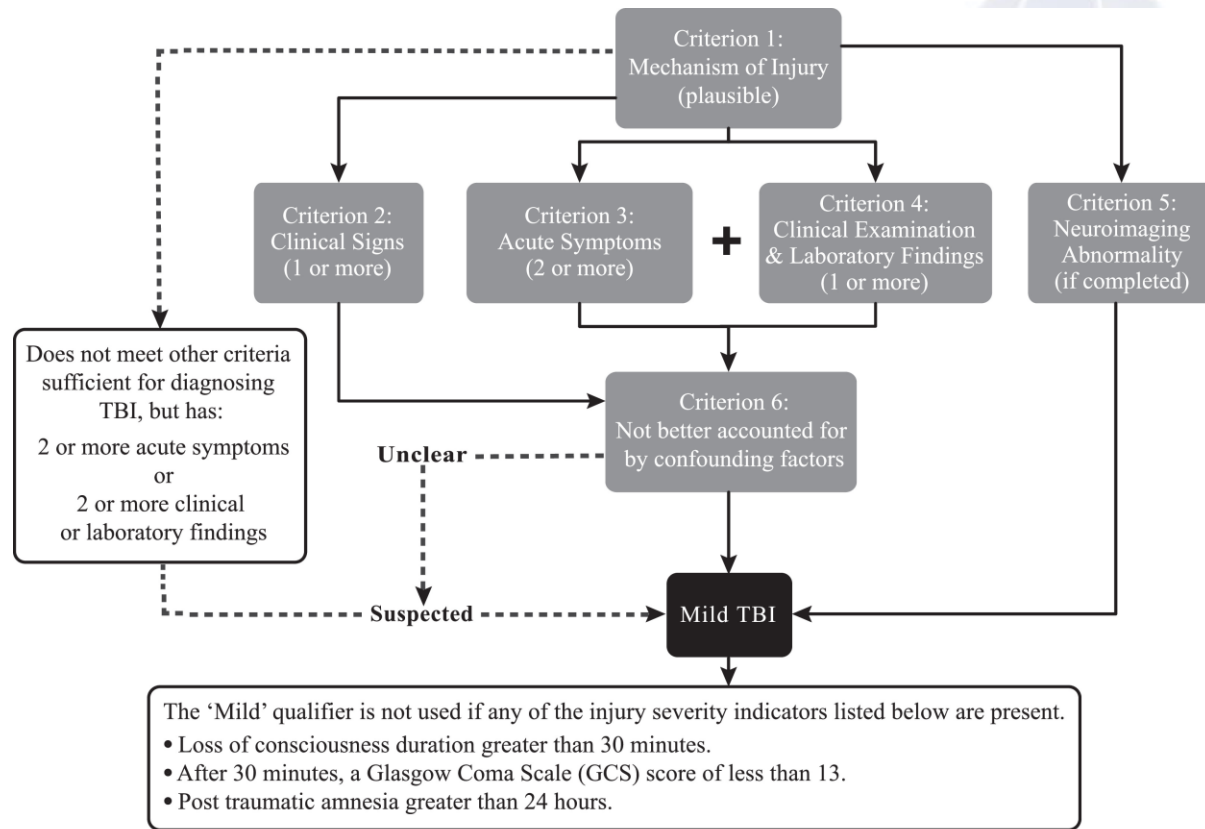
Symptoms are used to diagnose the condition

Severity Definition Criteria

Criteria	Mild	Moderate	Severe
Structural Imaging	Normal	Normal or Abnormal	Normal or Abnormal
Loss of Consciousness	0-30 min	>30 min and <24 hours	>24 hours
Alteration of Mental State	≤24 hours	>24 hours	>24 hours
Post- Traumatic Amnesia	≤24 hours	>24 hours and <seven days	>seven days
Glasgow Coma Scale (best available score in the last 24 hours)	Score 13-15	Score 9-12	Score 3-8

Where we are: An Integrated Assessment

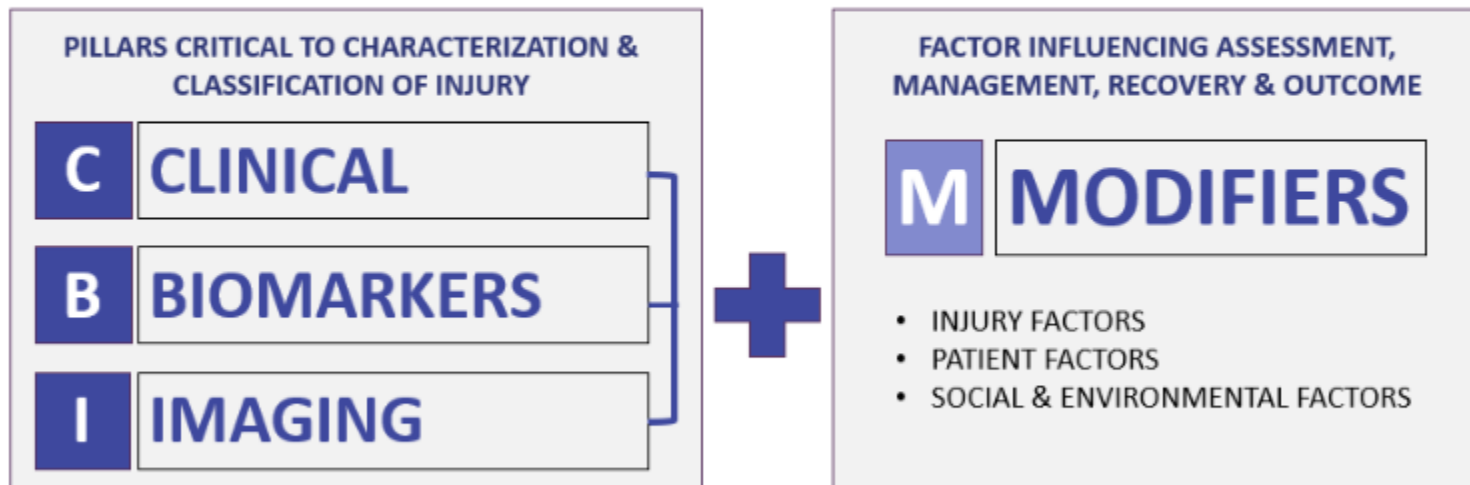
ACRM Consensus Definition of Mild TBI (mTBI)



Symptoms are combined with objective signs

Where we are going: Precise Phenotyping

THE CBI-M MODEL



Symptoms and objective signs are combined with signature biomarkers and contextual factors



Heterogeneity in Mild TBI

Persisting Symptoms after Concussion (PSaC)

Neurologic

- Headaches
- Dizziness
- Tinnitus
- Diplopia
- Photophobia

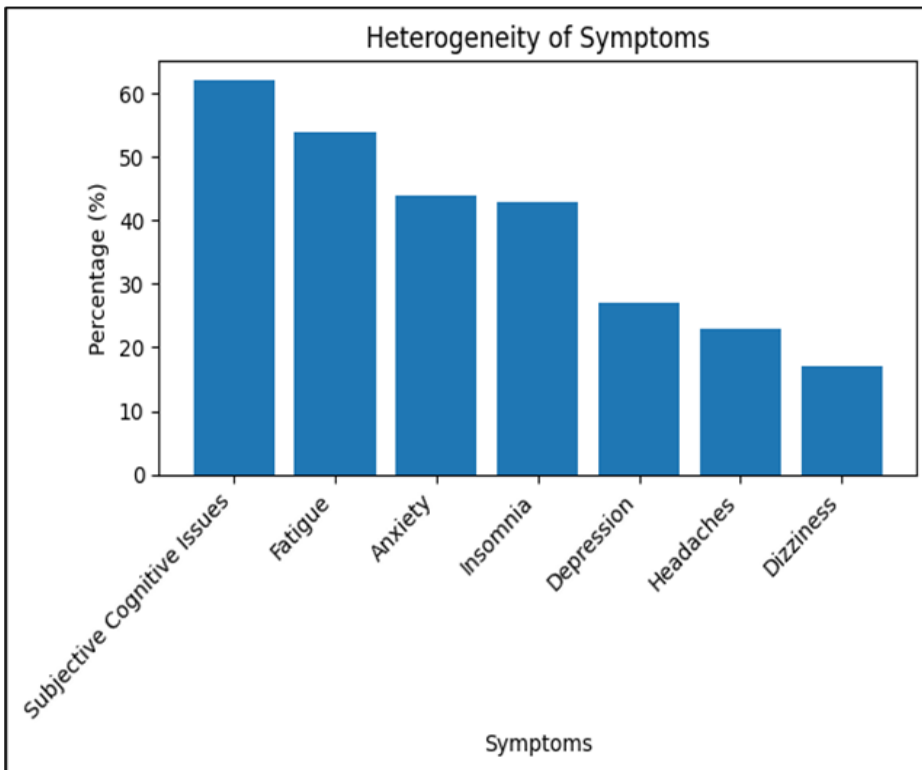


Cognitive/Psychiatric

- Loss of concentration
- Loss of memory
- Fatigue
- Irritability
- Anxiety
- Depressed mood
- Insomnia

Can be monosymptomatic or clustered

“Mild” TBI is a Misleading Label



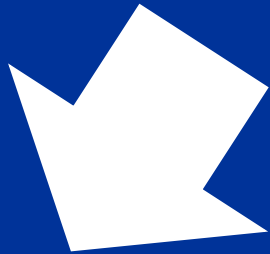
- Often completely resolve after 7–10 days
- 10-15% of cases persist at 3 months
- 38% people have persistent symptoms up to 4 years later

Heterogeneity lies in severity, persistence in phenotypes

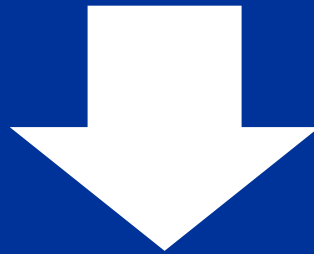


Clinical Prognosticators in Mild TBI

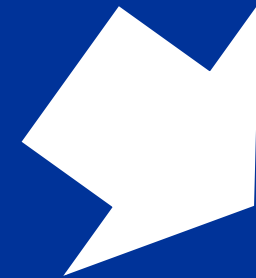
THE UTILITY OF CLINICAL, BLOOD, AND NEUROIMAGING BIOMARKERS



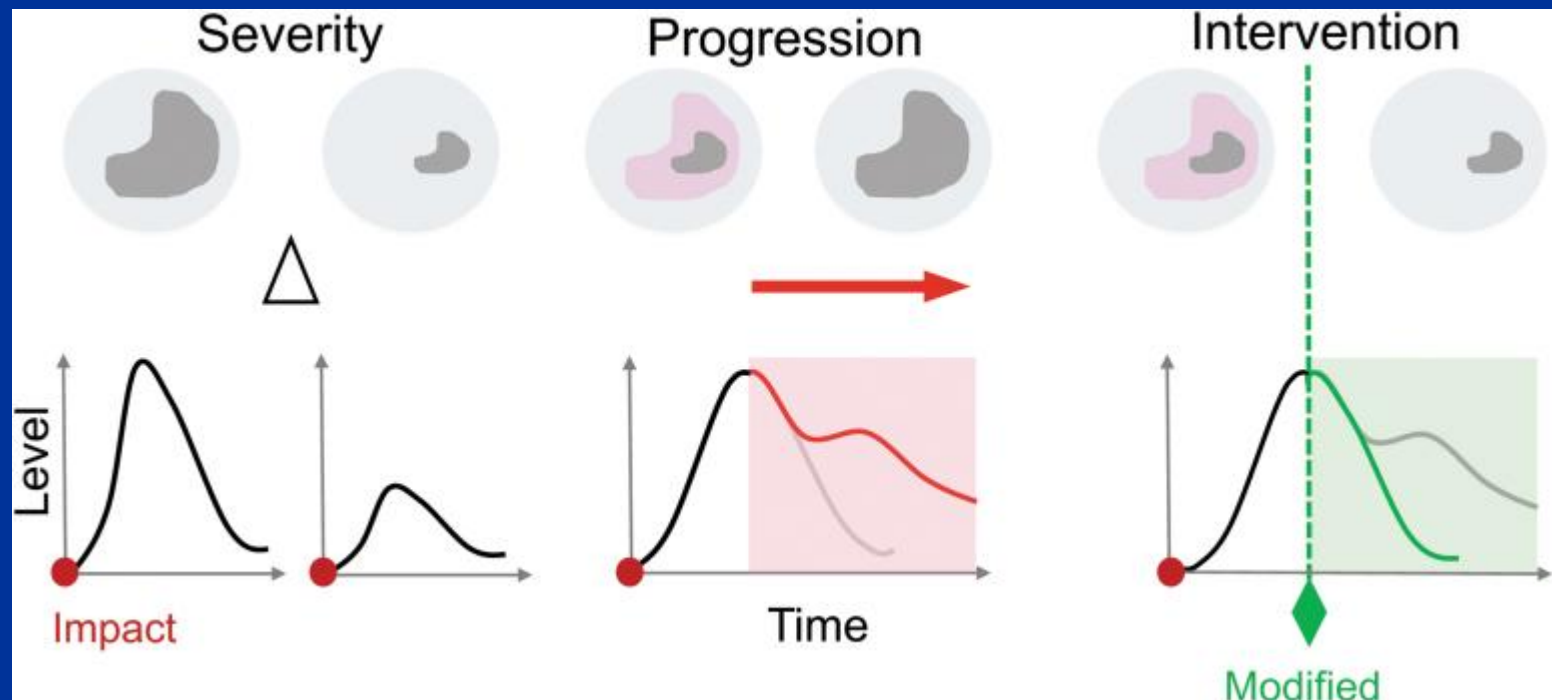
Diagnostic



Prognostic



Predictive

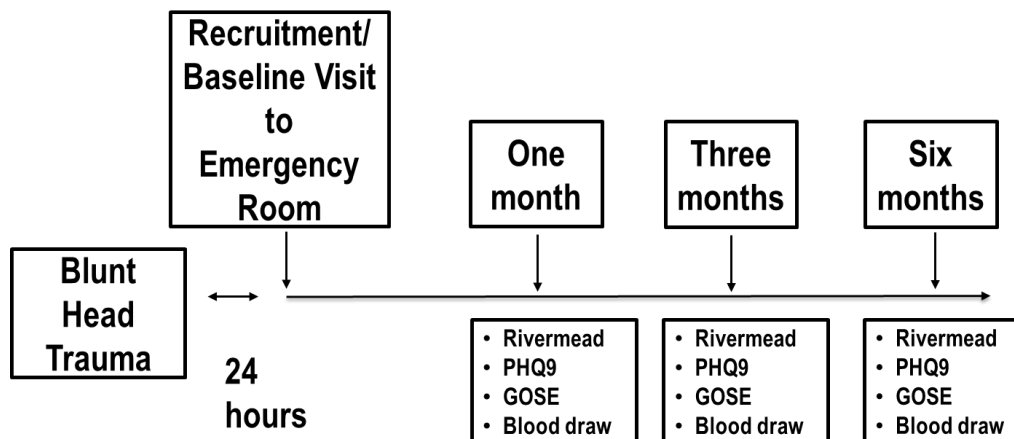
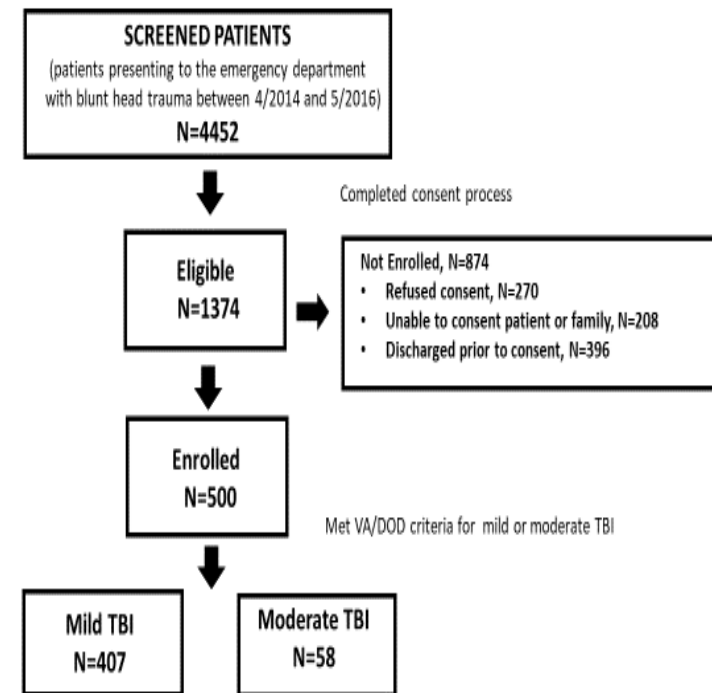


Clinical and Modifying Contributors of Outcomes after mTBI

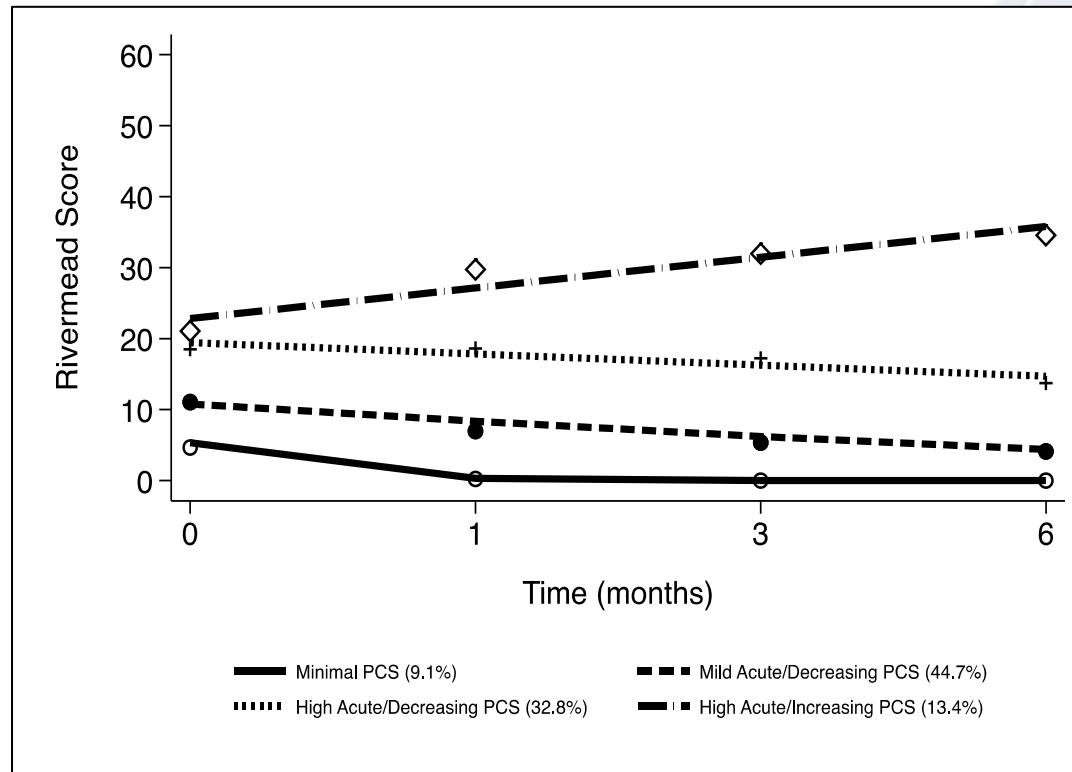
We aimed to :

- Recognize PSaC heterogeneity and trajectories
- Identify specific injury factors that predict poor PSaC outcomes
- Determine clinical signs that predict PSaC
- Quantify clinical signs at injury as prognosticators of outcomes

Collaborative Investigation: HeadSMART Study



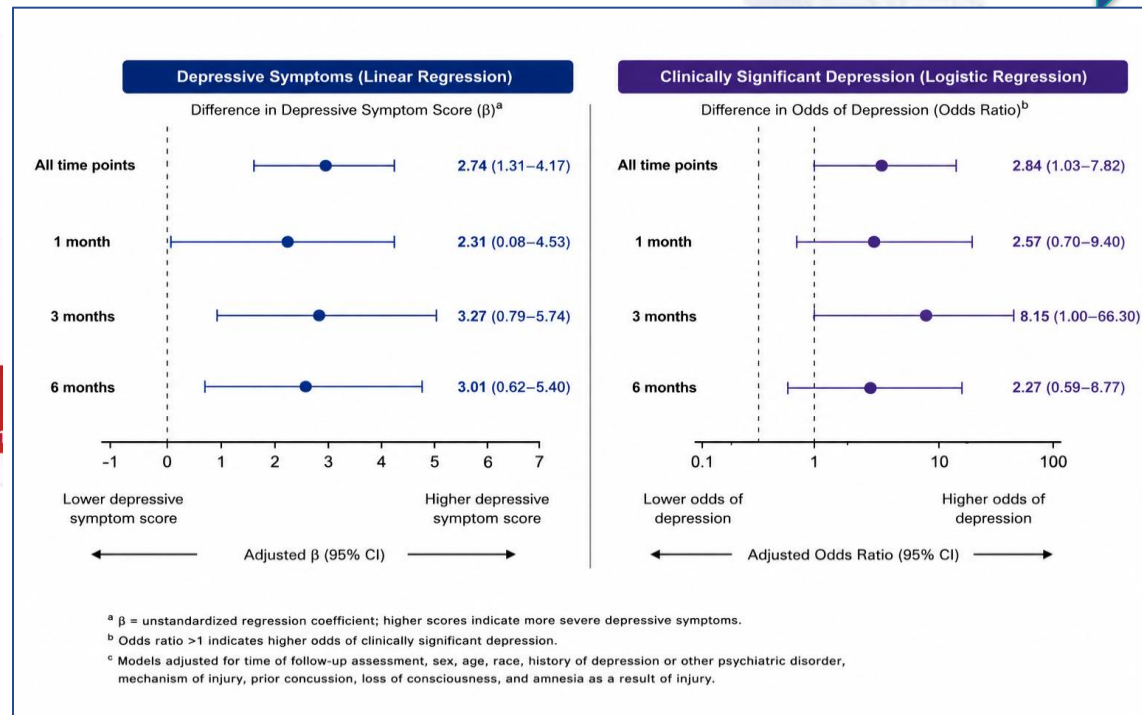
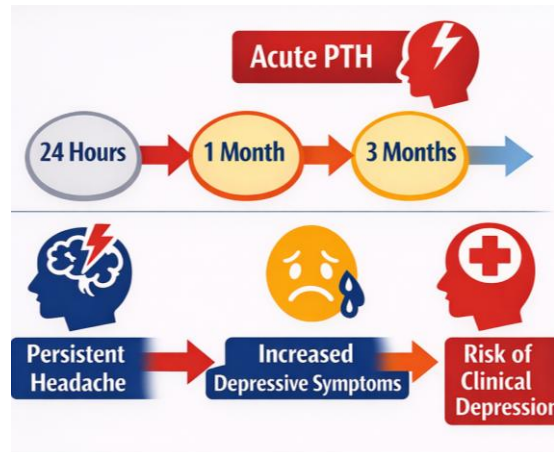
PSaC Heterogeneity and Trajectories



Those with higher early PCS symptoms continued to worsen
Those with mild early PCS got better

Clinical Factors as Contributors

Injury (Acute Post-traumatic Headache (aPTH) <24h) → 1 Month → 3 Months → 6 Months



Those with incident aPTH had greater odds of clinically significant depressive symptoms across time points

Injury Factors as Contributors

PARTICIPANTS WITH MILD TBI

Distribution into groups based on LOC and AMS

LOC and AMS
N=127

LOC only
N=83

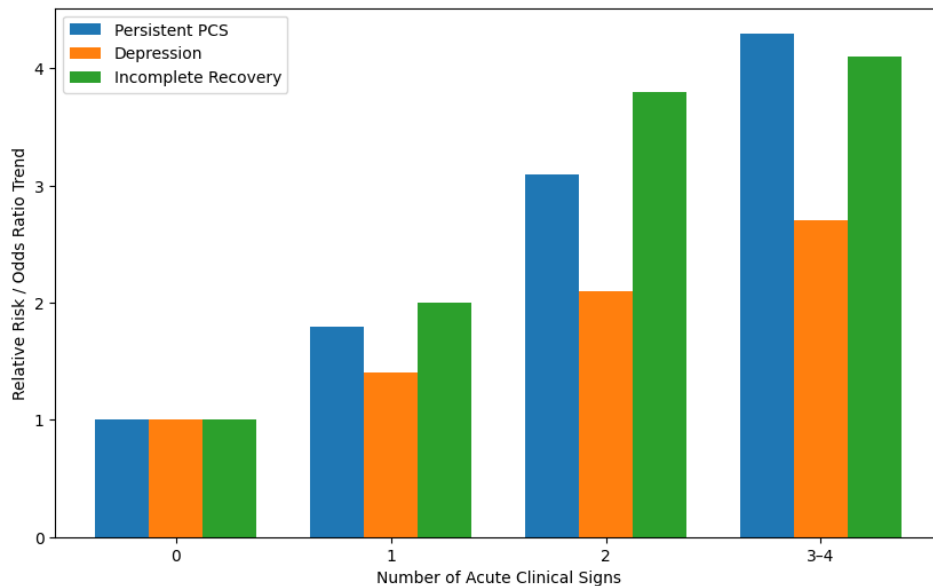
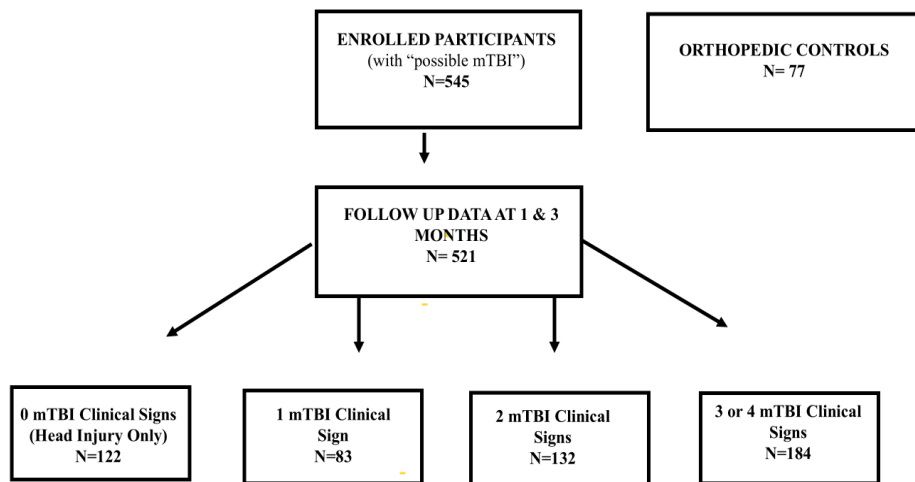
AMS only
N=64

Neither
N=133

- Highest rates of **depressive (44%)** and **post-concussive symptoms (54%)** across time points
- Highest odds of **incomplete functional recovery** out of all 4 groups at each time point (OR 0.70, 0.60, 0.57)

Predicted **depressive symptoms** at one OR=1.59; SE=.35; p= .038 **and** six months OR= 1.60; SE= .40; p= .060, showing its utility as a prognosticator in the **acute and chronic phases**

Quantification of Signs to Stratify Risk



The greater number of clinical signs is associated with higher post-concussive and depressive symptom severity

Key Takeaways of Clinical and Modifying Contributors of Outcomes after mTBI



- Those with severe concussive symptoms early do worse later
- Acute headaches may predict depressive symptom outcomes
- The presence of both LOC and AMS portend the poor prognosis
- More clinically defining signs at injury means worse prognosis

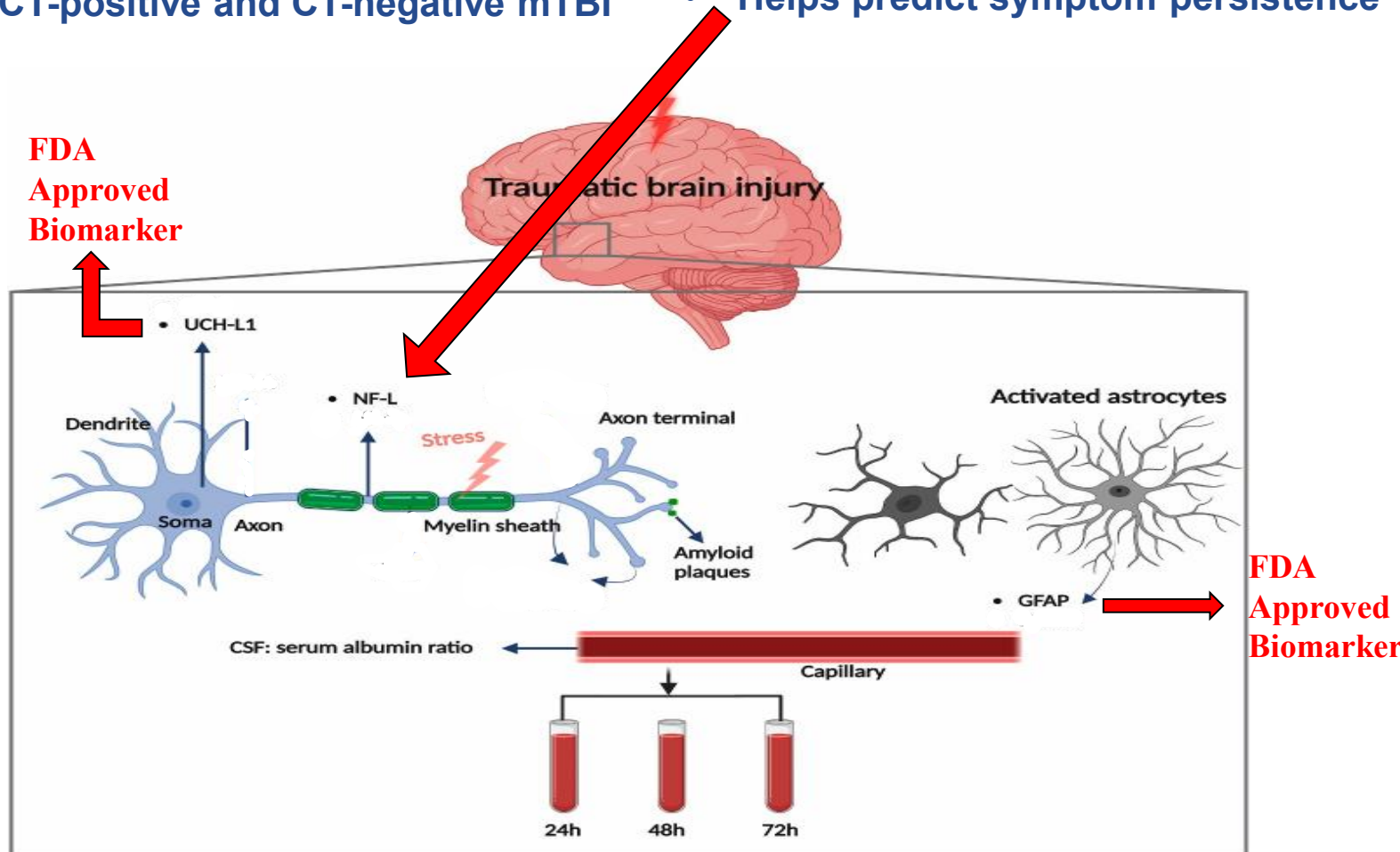
Blood Based Markers of Injury

GFAP and UCH-L1

- Most reliable, rapid elevation acutely
- Most specific to brain tissue
- Differentiate CT-positive and CT-negative mTBI

NfL

- Remains elevated the longest
- Reflects axonal injury
- Helps predict symptom persistence



Blood Biomarker Study Flow Diagram

PARTICIPANT ELIGIBILITY & ENROLLMENT

- Patients ≥ 18 years old
- Presenting to 3 Johns Hopkins EDs in Maryland
 - Suspected mTBI within 72 hours of injury
- Diagnosis based on ACRM criteria (Silverberg et al., 2023)

BASELINE ASSESSMENT (WITHIN 72 HOURS OF INJURY)

- Informed consent
- Demographics & clinical information
- Blood sample collection for biomarker analysis
- Collection of symptom and outcome measures

BIOMARKER ANALYSIS (WITHIN 72 HOURS)

Blood samples analyzed using Simoa Quanterix HD-X provided by Abbott

3-PLEX BIOMARKERS

- NfL
- GFAP
- UCH-L1

ED / BASELINE (≤ 72 HOURS)

- Symptom & outcome measures collected

30-DAY FOLLOW-UP (± 7 DAYS)

- Symptom & outcome measures collected

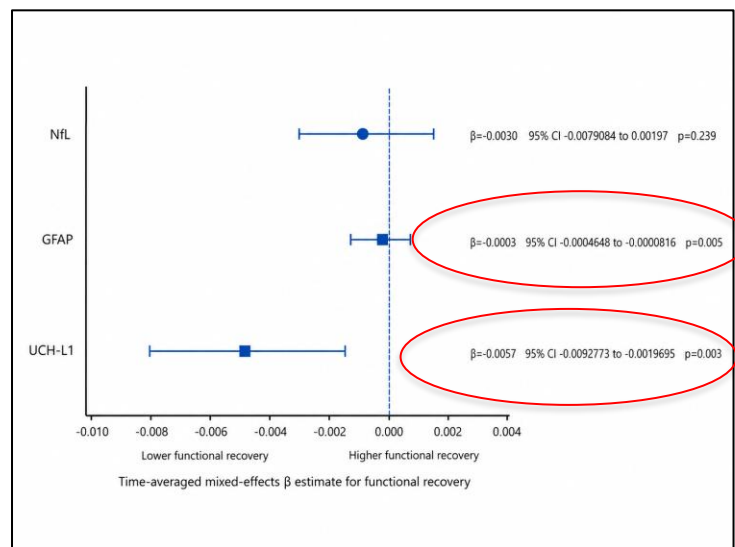
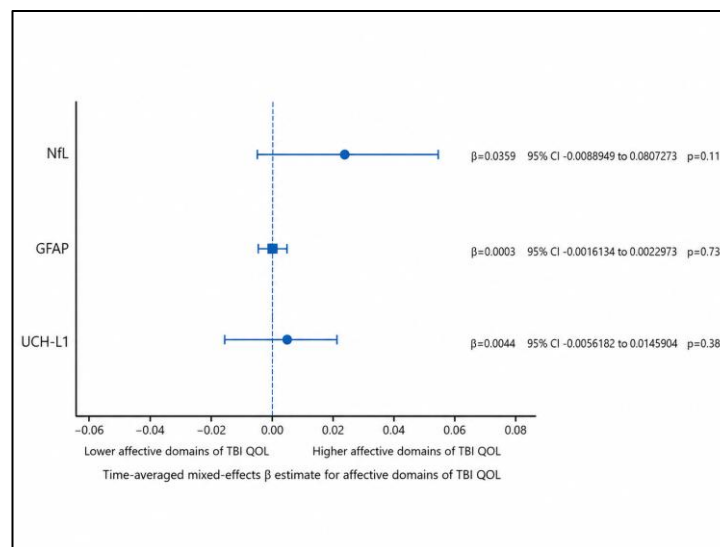
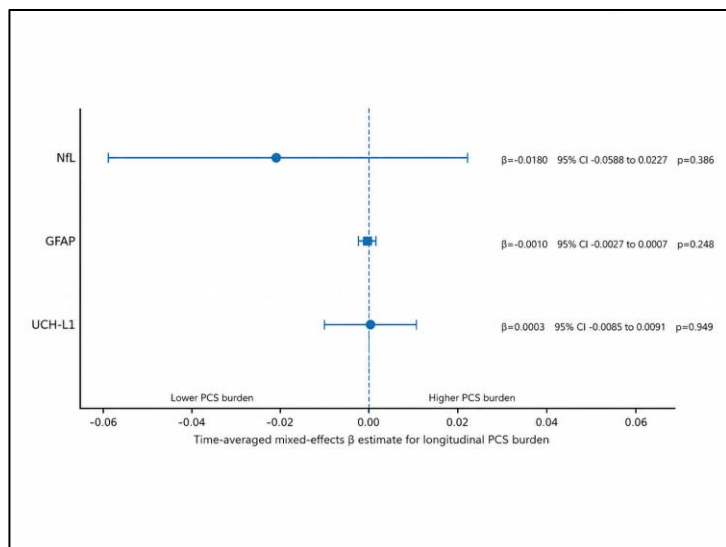
90-DAY FOLLOW-UP (± 14 DAYS)

- Symptom & outcome measures collected

OUTCOME MEASURES COLLECTED AT EACH TIMEPOINT

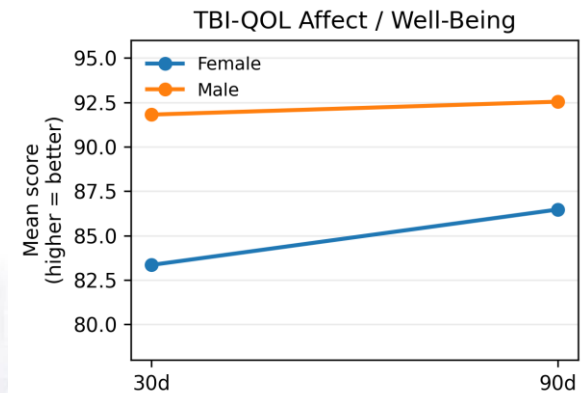
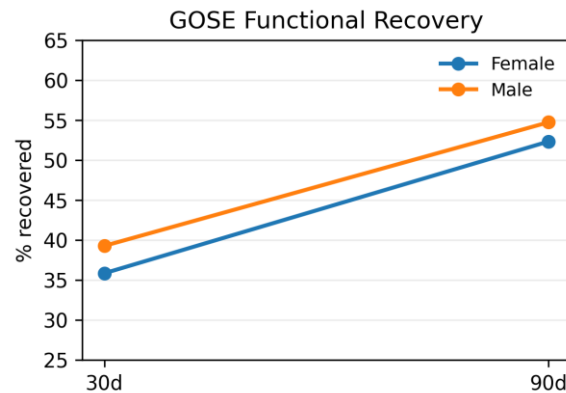
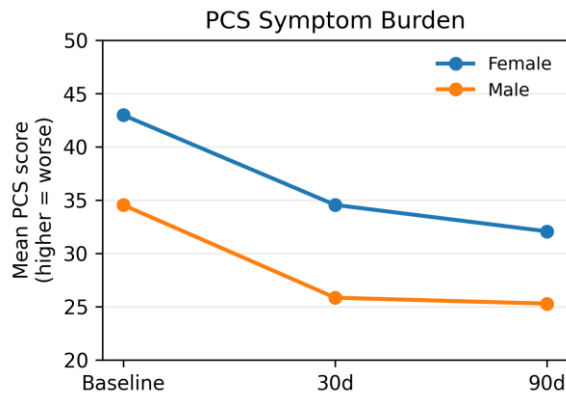
- Post Concussive Symptom Checklist (PCS)
- Positive Affect–Wellbeing Domain of the TBI-QoL
- Extended Glasgow Outcome Scale (GOSE)

Blood Based Markers as a Function of TBI Outcomes



Higher baseline concentrations of GFAP and UCH-L1 were associated with poorer functional recovery across time

Sex Differences Across TBI Outcomes



- Females showed higher PCS symptom burden at baseline across time points
- Functional recovery similar by sex at both 30 and 90 days
- Females showed lower TBI-QOL affect/well-being scores at 30 and 90 days
- Adjusted models showed male sex associated with better affective well-being

Sex differences most pronounced for subjective PCS symptom burden and affective well-being, while functional recovery is comparable between females and males

Key Takeaways on Blood Biomarkers



- Female sex more strongly associated with PCS burden trajectories
- Male sex associated with better emotional well-being outcome
- GFAP and UCH-L1 associated with poorer longitudinal functional recovery
- NfL showed limited prognostic value across all three TBI outcomes



Imaging Prognosticators in Mild TBI

Imaging Markers in mTBI

- Goal is to detect traumatic axonal and/or microvascular injury
- Diffuse axonal injury and microstructural injury not visible on CT
- Advanced imaging includes diffusion MRI, functional MRI
- Identifies distinct injury patterns, affected circuits and networks
- Allows for stratification into biological subtypes
- Offers opportunities for targeted treatment



Establishing the link between post-concussive symptoms and brain network dysfunction: A systematic scoping review of neuroimaging evidence[☆]

Caerwen S. Ellery^{a,b,c}, André N. Avila^{a,b,c}, Melissa G. Papini^{a,b,c}, Melinda Fitzgerald^{a,c}, Sarah C. Hellewell^{a,b,d,*}

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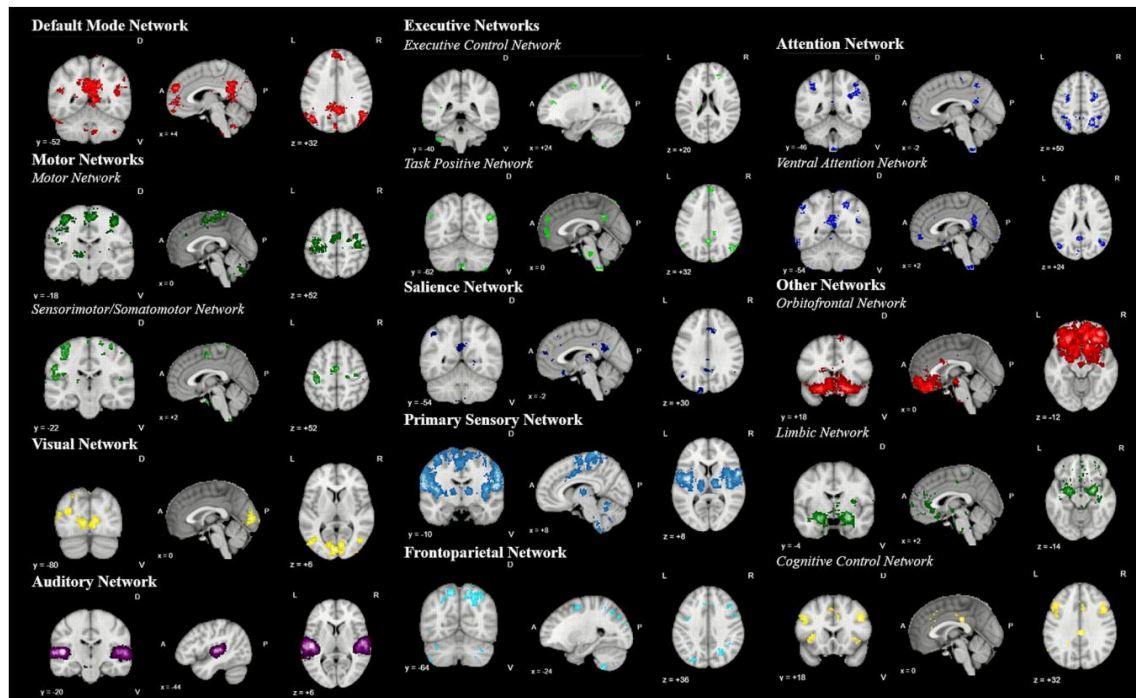
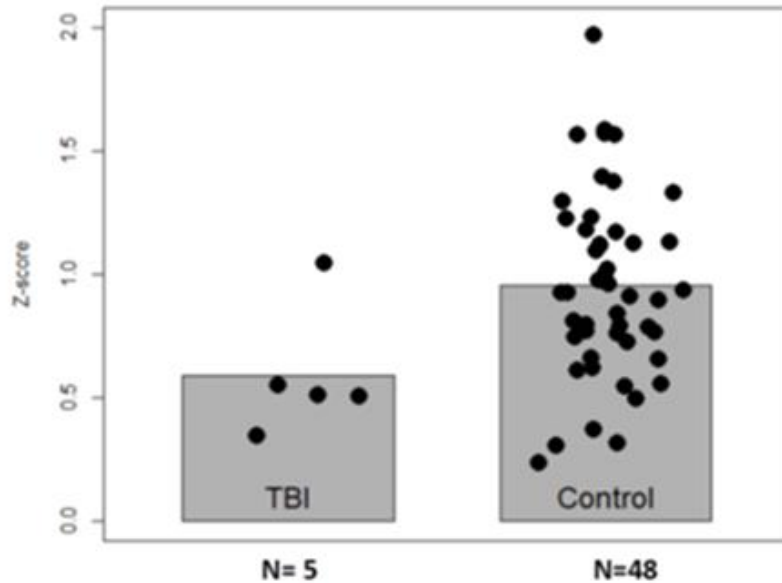


Fig. 1. Coronal, sagittal and axial views of resting-state functional brain networks using Neurosynth (Kent et al., 2026), a meta-analysis functional brain mapping tool which highlights seed regions related to keyword/s from over 14,000 articles.

PCS reflects disrupted integration among default mode, salience, and executive control networks, producing interconnected cognitive, emotional, and physical symptoms

Comparison of within-network DMN functional connectivity in mTBI



The TBI group showed lower within-DMN network connectivity (Z-score $.95 \pm .37$) compared to the control group ($.59 \pm .27$).

Key Takeaways on Imaging

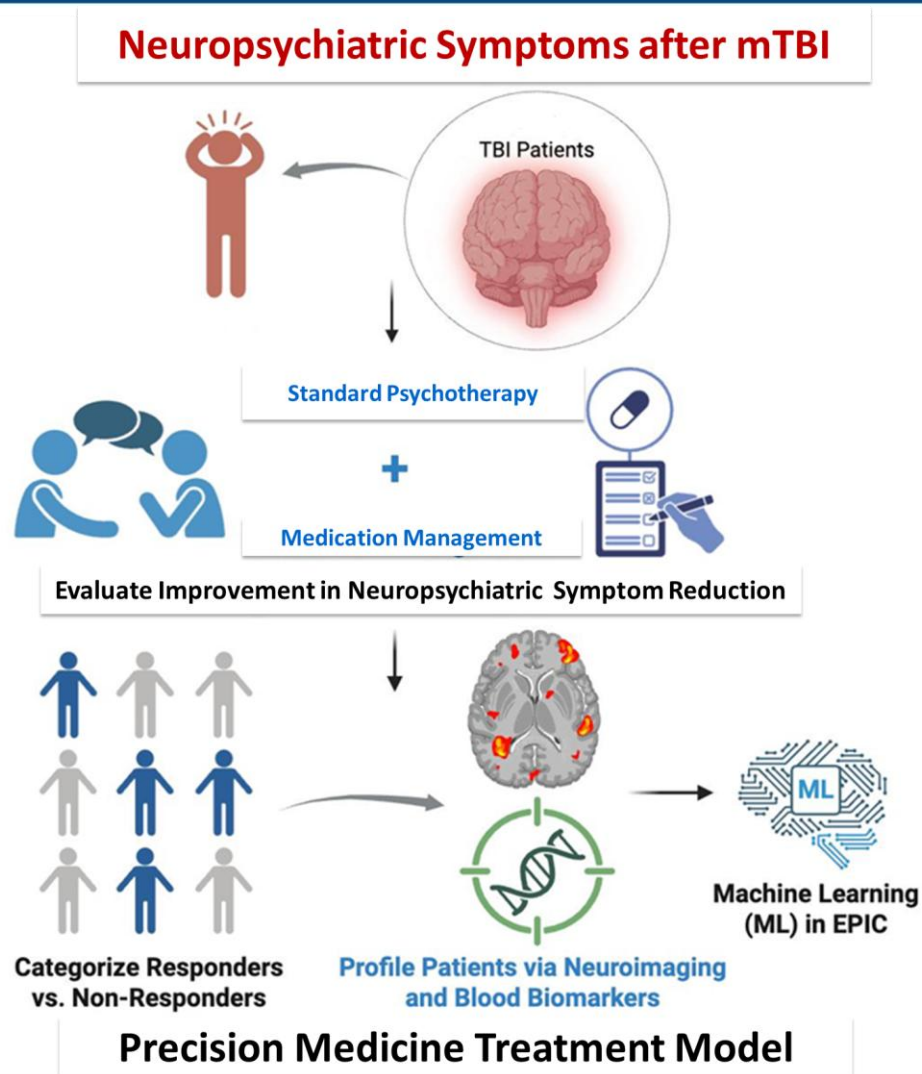


- Of the neuroimaging modalities, network connectivity most promising
- mTBI is increasingly understood as a network disorder
- Imaging abnormalities correlate with outcomes
- Neuroimaging may enable biologic phenotyping
- Specific networks may be targets for neuromodulation

Summary

- Heterogeneity in mTBI exists in severity, persistence, phenotype
- Nosology doesn't fit the DSM
- It's more about the brain that was injured than the brain injury
- Risk stratification still relies on presence/number of clinical signs
- Biomarkers in TBI are not yet at full precision
- Precision medicine in mTBI will need multi-layer modalities

Multi-modal Integration is Key to Precision



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