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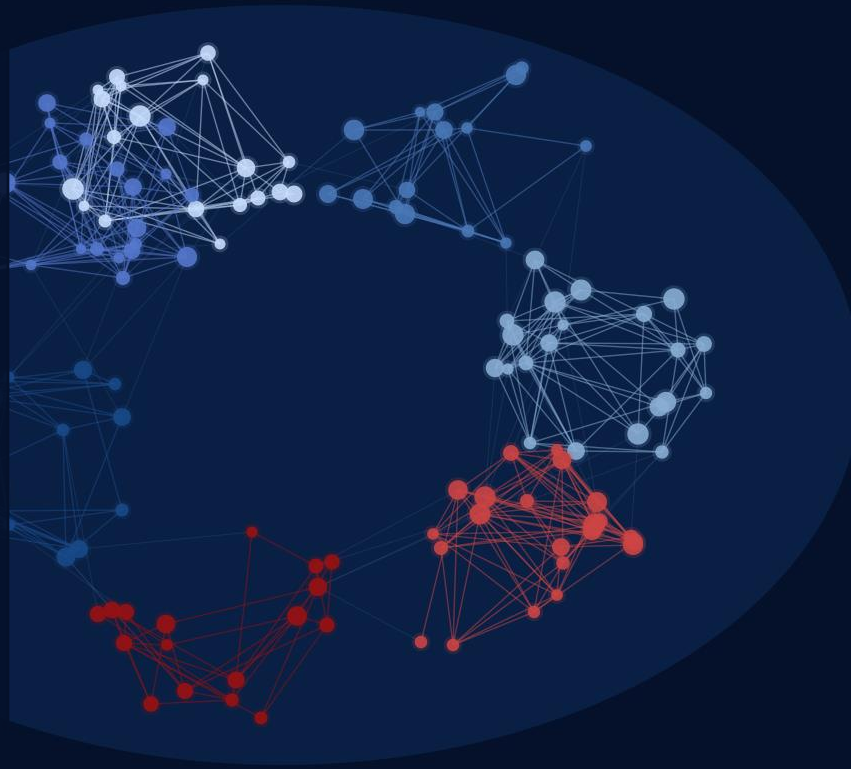
Military Health Research Symposium (MHRS) 2026

Early Functional Network Phenotypes Predict Long-term Cognitive Risk After Mild Traumatic Brain Injury



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Disclosures

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

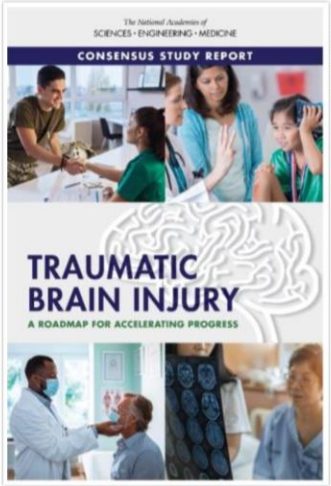
NASEM RECOMMENDATIONS

A POLICY SHIFT TOWARD BIOLOGY-DRIVEN TBI CLASSIFICATION

- Move beyond mild, moderate, severe
- Emphasize objective, measurable domains
- Enable precision diagnosis and prognosis

Recommendation 1:
Create and implement an updated classification system for TBI. The current clinical classification scheme for TBI should be updated to be more accurate and informative for care and research

NASEM REPORT | Traumatic Brain Injury: A Roadmap for Accelerating Progress



Traumatic Brain Injury: A Roadmap for Accelerating Progress, a new consensus study report from the National Academies of Sciences, Engineering, and Medicine's Committee on Accelerating Progress in Traumatic Brain Injury Research and Care, examines how progress can be advanced in TBI care and research and develops a roadmap to help guide the field.

CBI-M: A MULTIDIMENSIONAL FRAMEWORK FOR TBI

ELSEVIER

The Lancet Neurology

Volume 24, Issue 6, June 2025, Pages 512-523

Policy View

A new characterisation of acute traumatic brain injury: the NIH-NINDS TBI Classification and Nomenclature Initiative

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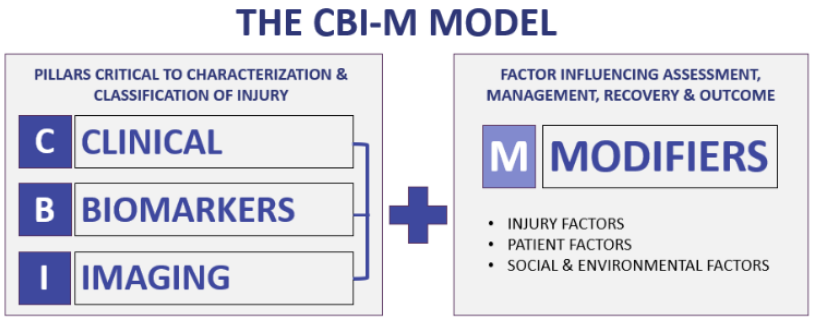
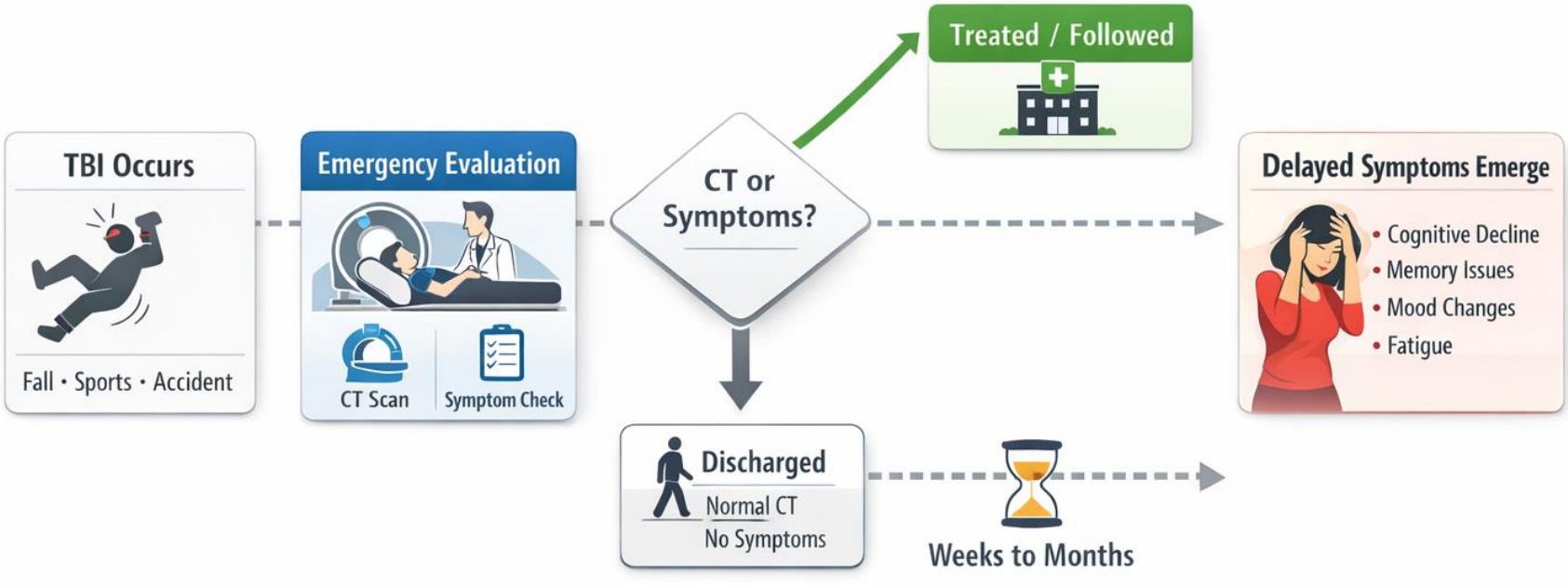
Show more



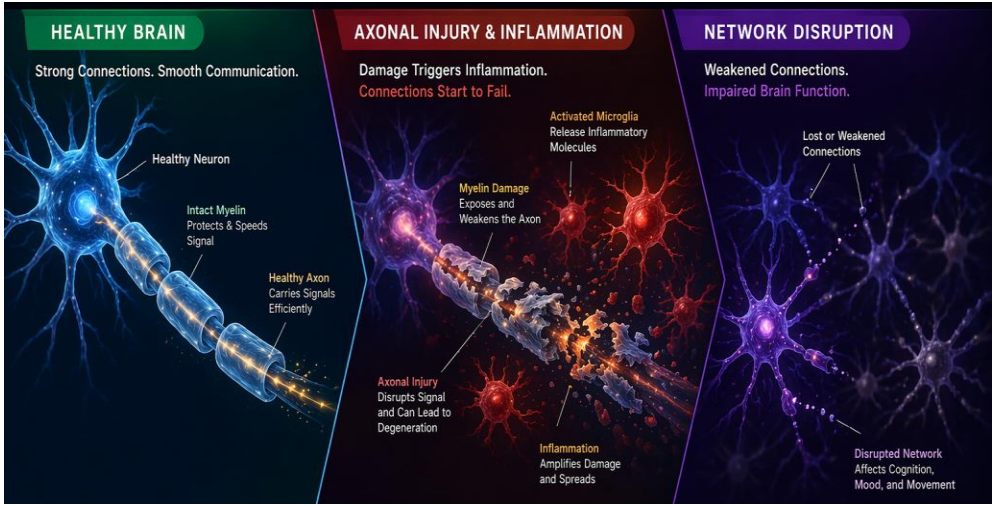
"Imaging is a core pillar - not an optional add-on."

TBI Patient Journey: Acute Focus, Chronic Blindspots



NO OBJECTIVE MEASURE OF BRAIN HEALTH → MISSED OPPORTUNITY FOR EARLY DETECTION & INTERVENTION

Imaging the Hidden Injury in TBI?

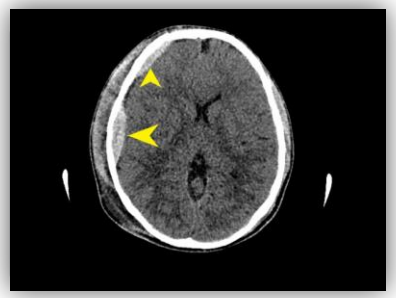


Biological underpinnings of injury

How Do We Image Injury?

Different modalities capture different dimensions of injury

CT Scan

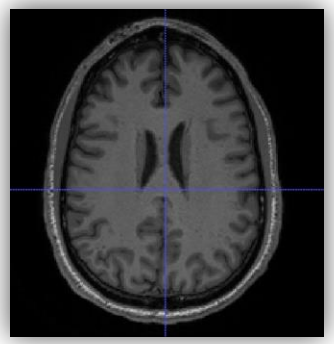


Detects: bleeding, fractures, herniation

Misses: subtle axonal or network-level damage

First-line in ER

Structural MRI

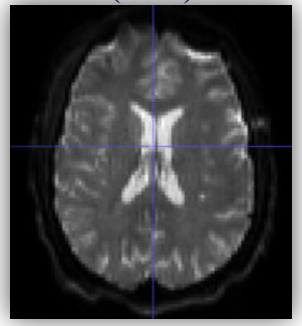


Detects: atrophy, white matter lesions

Misses: functional disruption, network changes

Often normal in mTBI

Diffusion Tensor Imaging (DTI)

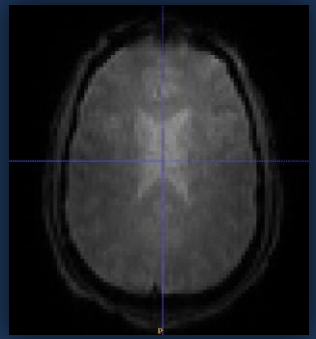


Detects: axonal injury, white matter tract damage

Misses: dynamic connectivity, system-level function

Maps white matter microstructure – captures axonal and vascular injury and is often abnormal

Resting state functional MRI (rs-fMRI)



Captures: spontaneous brain network activity at rest

&

Sensitive to functional disruption corresponding to microstructural injury

Used in this study

Imaging Markers of Network Dysfuntion

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> *"Can early functional network organization identify mTBI patients at risk for long-term cognitive difficulties?"*

01 **Map brain network organization**

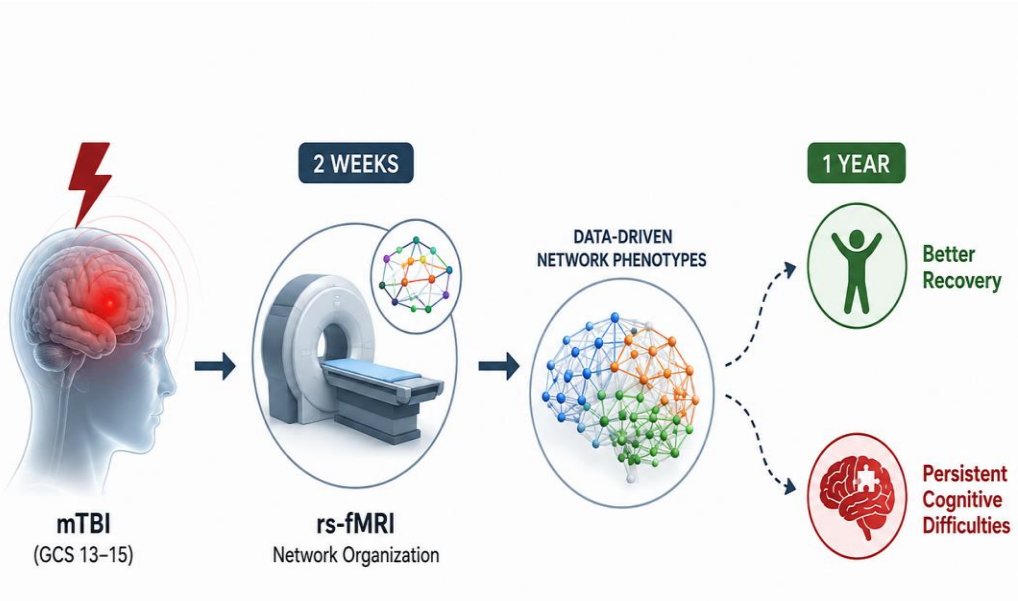
Using rs-fMRI at 2 weeks

02 **Identify distinct patient subgroups**

Data-driven clustering to capture recovery heterogeneity

03 **Predict long-term cognitive outcome**

Do early network patterns predicts cognitive risk of a patient at 1 year?



Data : Cohort & Imaging

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TRACK-TBI

Transforming Research and Clinical Knowledge in Traumatic Brain Injury · Multi-site longitudinal observational study

409

mTBI patients

GCS 13–15

2 weeks

Post-injury imaging

+ 6-month follow-up

rs-fMRI

Resting-state fMRI

Functional connectivity

Multi-site

Data collection

Standardized 3T MRI protocol

Data : Cognitive Measures & Outcome

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Cognitive Measures

Assessed at 2 weeks, 6 months, and 1 year

RAVLT (Rey Auditory Verbal Learning Test)

Verbal learning & memory (total + delayed recall)

TMT A/B (Trail Making Test)

Executive function & cognitive flexibility

WAIS-IV (Wechsler Adult Intelligence Scale)

Processing speed index

5 neuropsychological tests in total

1-Year Outcome Definition[5]

Cognitive Impairment

Score in the impaired range (below the 9th or above the 91st percentile) on at least 2 of the 5 tests.

●●○○○ on ≥ 2 of 5 tests

OR

Cognitive Decline

A reliable drop (≥ 90% Reliable Change Index) on at least 2 of the 5 tests, versus the patient's best earlier score at 2 weeks or 6 months.

●●○○○ on ≥ 2 of 5 tests

Poor 1-year outcome = **Impairment OR Decline**

[5] *Schneider, A. L. C., Yue, J. K., Karr, J. E., Nelson, L. D., Satris, G. G., McCrea, M. A., Yuh, E. L., Manley, G. T., Diaz-Arrastia, R., & TRACK-TBI Investigators. (2022). Cognitive outcome 1 year after mild traumatic brain injury: Results from the TRACK-TBI study. Neurology, 98(12), e1248–e1261. https://doi.org/10.1212/WNL.0000000000201416*

Feature extraction : Resting-state fMRI to graph metrics

Each scan of 2-week timepoint is denoised, reduced to a 156-region connectivity matrix, then summarized with three graph-theory measures.

STEP 1

Preprocessing & denoising

Head motion corrected and each brain normalized to a common template, then noise and physiological confounds removed.

Pipelines used: fMRIPrep XCP-D

STEP 2

Functional connectivity

Mean BOLD signal is taken from a **156-region** cortical atlas; pairwise correlation builds each patient's connectivity matrix.

STEP 3

Graph metrics

Three graph-theory measures are computed for every one of the **156 regions** in the network.

WHAT EACH GRAPH METRIC CAPTURES

Nodal efficiency

How quickly a region exchanges information with the rest of the brain — *integration*.

Local clustering

How tightly neighboring regions interconnect — *specialization*.

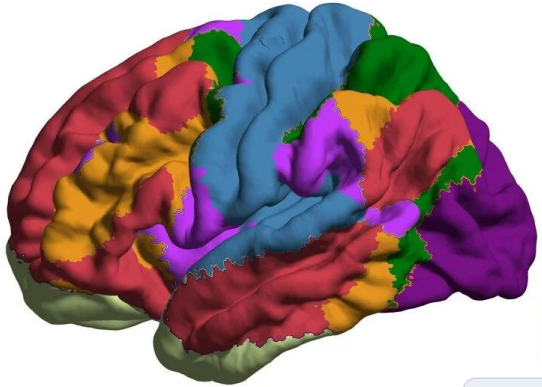
Betweenness centrality

How much a region bridges systems as a hub — *hub role*.

Feature extraction : From regions to brain systems

Each metric is averaged within seven canonical networks, giving a compact, biologically meaningful set of 21 features per patient.

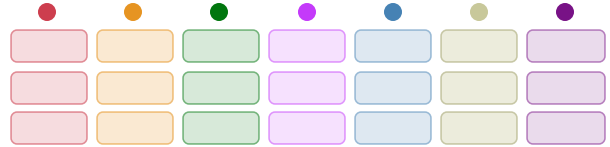
SEVEN CANONICAL NETWORKS · YEO ATLAS[6]



- **DMN** Default mode
- **FPN** Frontoparietal
- **DAN** Dorsal attention
- **SN** Salience / ventral attn.
- **SMN** Somatomotor
- **LIM** Limbic
- **VIS** Visual

BUILDING THE FEATURE SET

Each metric is averaged across the regions inside a network, so every network is described by **three values**.



3 metrics across **7 networks** = **21** **features per patient**

Why summarize into networks?

- mTBI disrupts communication across brain systems, not isolated regions
- Network averages capture coordinated dysfunction across distributed regions.
- Reduces dimensionality (468 → 21 features).
- Retains biologically meaningful, interpretable brain organization.

[6]Yeo, B. T. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. Journal of Neurophysiology, 106(3), 1125–1165. https://doi.org/10.1152/jn.00338.2011

Analysis : From network features to cognitive risk

The 21 network measures were used to identify data-driven patient phenotypes and to test their risk of poor long-term cognitive outcome.

21 network measures > **Data-driven clustering** > **Patient phenotypes** > **Cognitive outcome**

Identify phenotypes

Hierarchical clustering of the 21 network measures identified phenotypes among patients with mTBI at 2 weeks post-injury, with stability confirmed by bootstrap consensus.

WHAT DRIVES PHENOTYPE DIFFERENCES

- **Efficiency across the seven functional networks**
- **Hub organization across the seven functional networks**
- **Local clustering across the seven functional networks**

Phenotypic variation was driven primarily by efficiency and hub organization across the seven functional networks.

Test cognitive risk

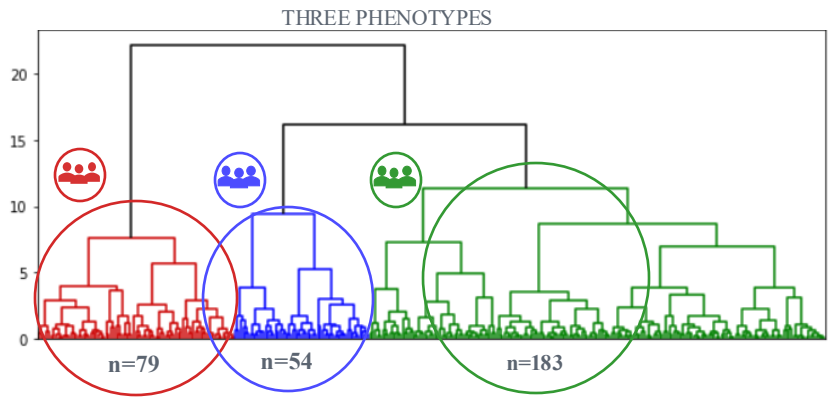
AGE- AND SEX-ADJUSTED MODELS

- **Linear regression** for cognitive performance (RAVLT, TMT-A/B, WAIS-PSI) at 2 weeks and 6 months.
- **Logistic regression** for poor 1-year cognitive outcome (impairment or decline).
- All p-values FDR-corrected.

Recovery heterogeneity: Three distinct brain-network phenotypes

Clustering the 21 measures sorted patients into **three subgroups** , each sharing a characteristic pattern of brain-network organization. The phenotypes differed mainly in **network efficiency** and **hub organization**.

HOW THE GROUPS EMERGED



Hierarchical clustering in PCA space (patients only). Three stable phenotypes, confirmed by **bootstrap consensus**.

THE THREE PHENOTYPES

Most disrupted

Efficiency ↓ | Hub ↑ | Clustering ↓

Broadly reduced efficiency with elevated hub burden across systems.

Intermediate

Efficiency ≈ | Hub ≈ | Clustering ↑

Organization close to the overall patient average.

Least disrupted

Efficiency ↑ | Hub ↓

More integrated communication with lower hub burden.

Early network phenotypes identify patients at long-term cognitive risk

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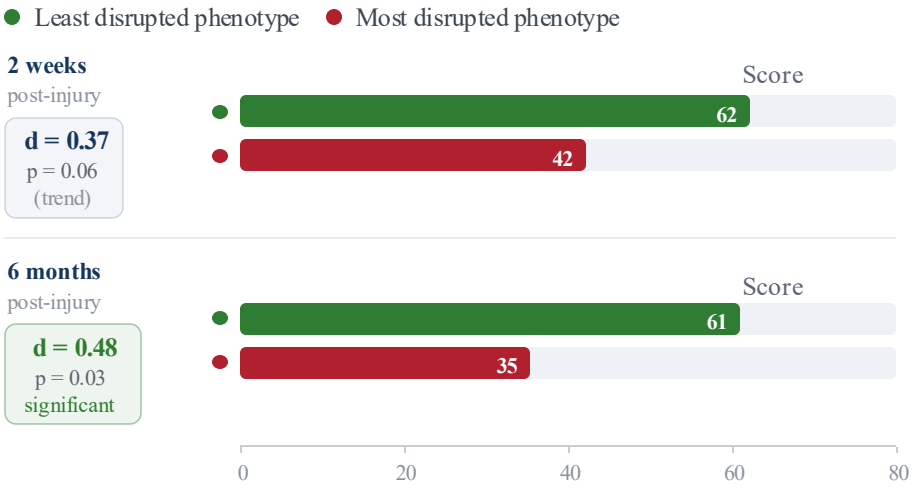
Compared with the **least disrupted** phenotype, the **most disrupted** phenotype remembered fewer words early after injury and was far more likely to have poor cognition one year later.

EARLY MEMORY

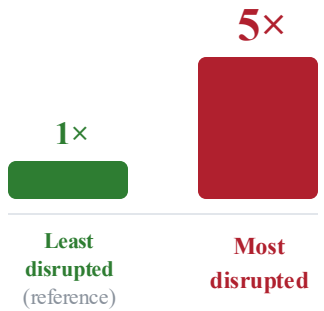
RAVLT verbal memory test. Score = words recalled, so **higher is better**.



Mean RAVLT total recall score. **d** = size of the gap between groups; larger d means a bigger difference.

ONE-YEAR OUTCOME

Odds of a **poor cognitive outcome** at one year.



OR = 5.0 95% CI 1.67 to 14.9 p = 0.035

OR (odds ratio) = how many times higher the odds are versus the reference group. OR of 5.0 means about **5 times the odds** .

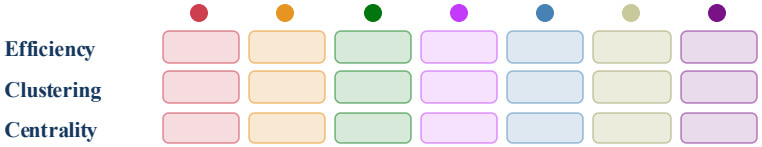
Conclusions: Stratification Biomarkers

Early system-level brain network dysfunction identifies mTBI patients at increased risk of cognitive decline

- **DMN** Default mode
- **FPN** Frontoparietal
- **DAN** Dorsal attention
- **SN** Salience / ventral attn.
- **SMN** Somatomotor
- **LIM** Limbic
- **VIS** Visual

NETWORK FEATURES

Each metric is averaged across the regions inside a network, so every network is described by **three values**.



3 metrics across **7 networks** = **21 features per patient**

1 DETECTABLE EARLY

Just two weeks after injury, resting-state brain network organization identifies three reproducible patient phenotypes.

2 PREDICTS COGNITIVE

The most disrupted phenotype showed poorer early memory and about five times the odds of a poor cognitive outcome at one year.

3 CLINICALLY SCALABLE

Network phenotyping offers a scalable imaging marker for early risk stratification, aligned with NASEM priorities for objective TBI biomarkers.

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LEARNING OBJECTIVES

By the end of this presentation, you will be able to:

01 The "I" in CBI-M classification of TBI

Describe why objective imaging biomarkers are needed to advance TBI classification beyond conventional severity scales.

02 Functional Network Based Imaging Markers

Explain how resting-state functional network organization can identify distinct biological phenotypes in TBI patients

03 Clinical Relevance of Imaging Markers

Discuss how these early network phenotypes can improve prediction of long-term cognitive outcomes and support precision approaches to TBI care.