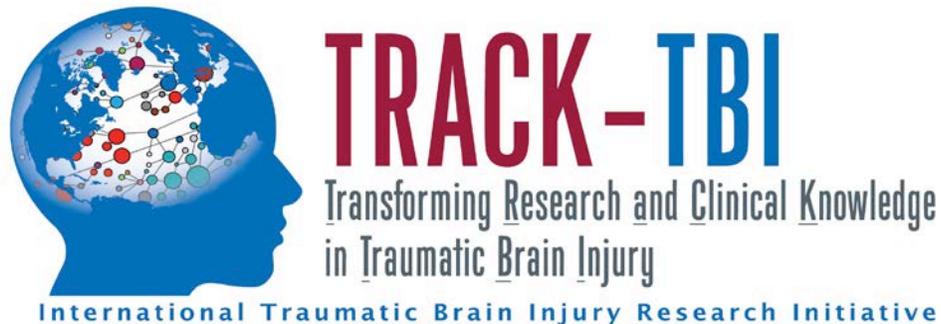


FDA Public Meeting: March 3, 2016

Advancing the Development of Biomarkers in Traumatic Brain Injury

Correlation of Biomarkers with Clinical Outcomes

Harvey Levin, PhD



**TBI
Endpoints
Development**

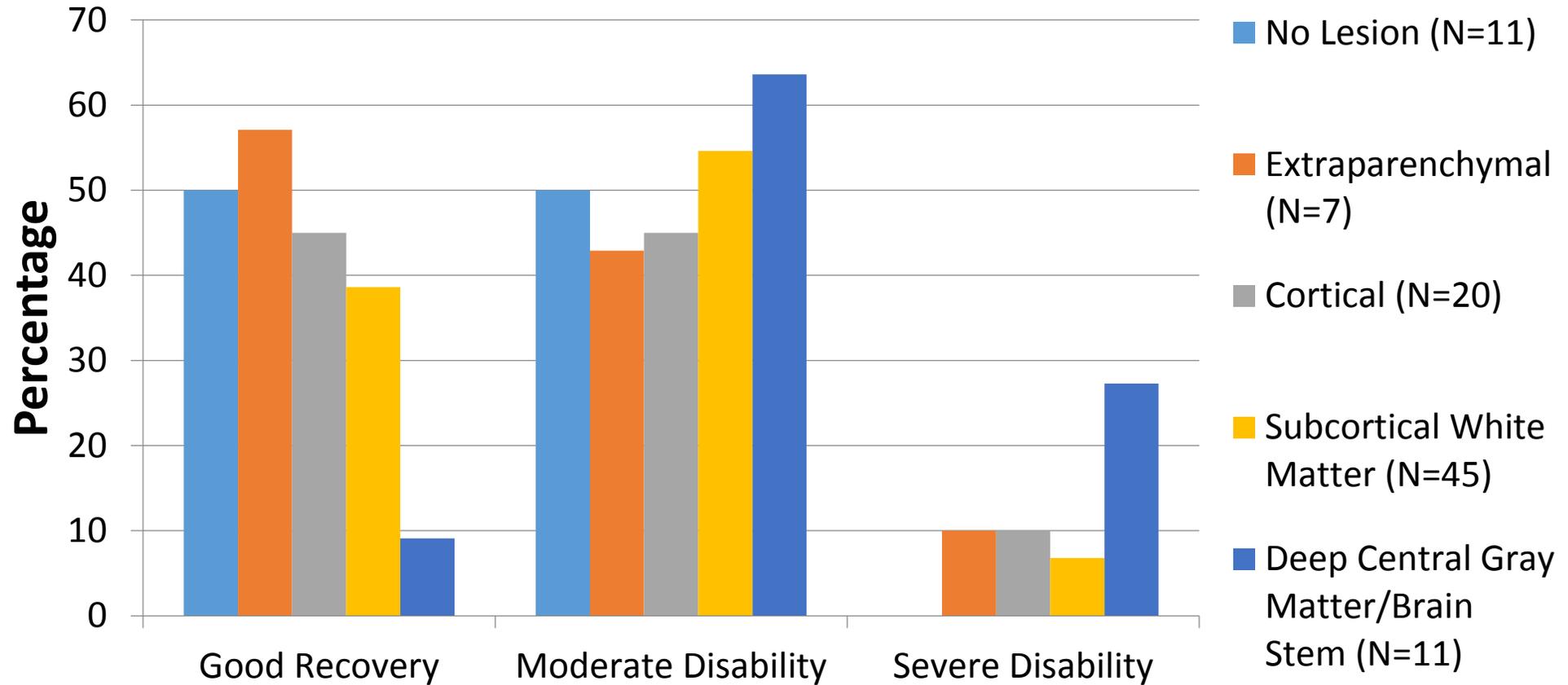
A Collaborative Effort for Advancing Diagnosis and Treatment of TBI

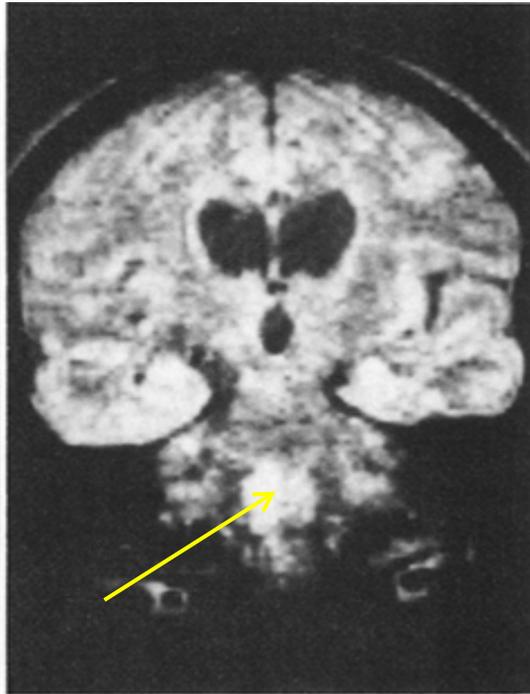
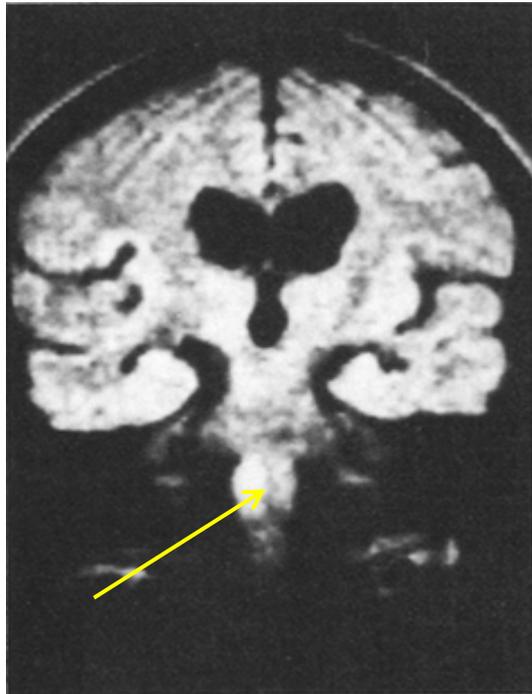
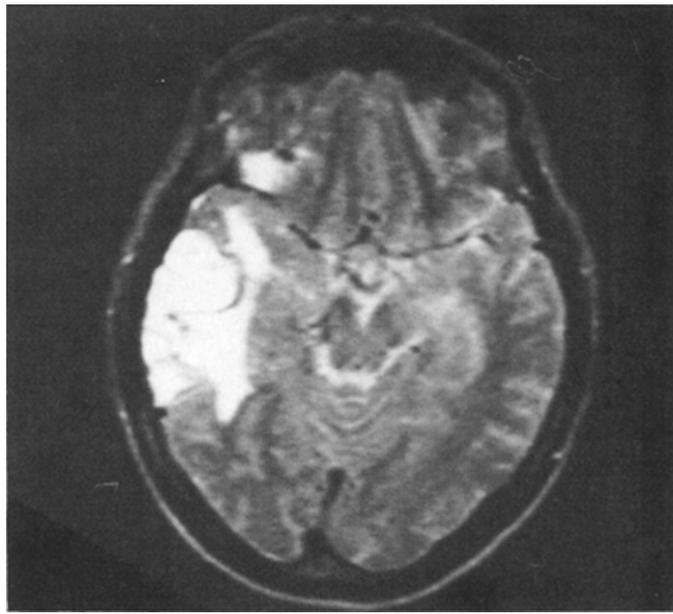
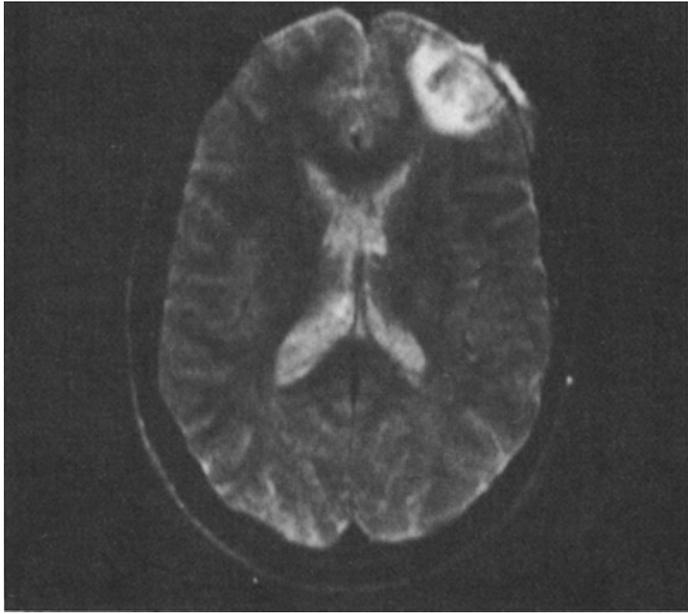
Goals of Presentation

- Rationale and timeliness of clinical outcome assessments (COAs) for traumatic brain injury (TBI)
- Validation of the Glasgow Outcome Scale (GOS) and Extended version (GOSE) by pathology seen on neuroimaging
- Advantages and limitations of GOS/GOSE as a global outcome measure for clinical trials of drugs/interventions with specific mechanisms and effects
- COAs for specific domains and contexts of use (COU): Need for further validation studies and development of composite measures

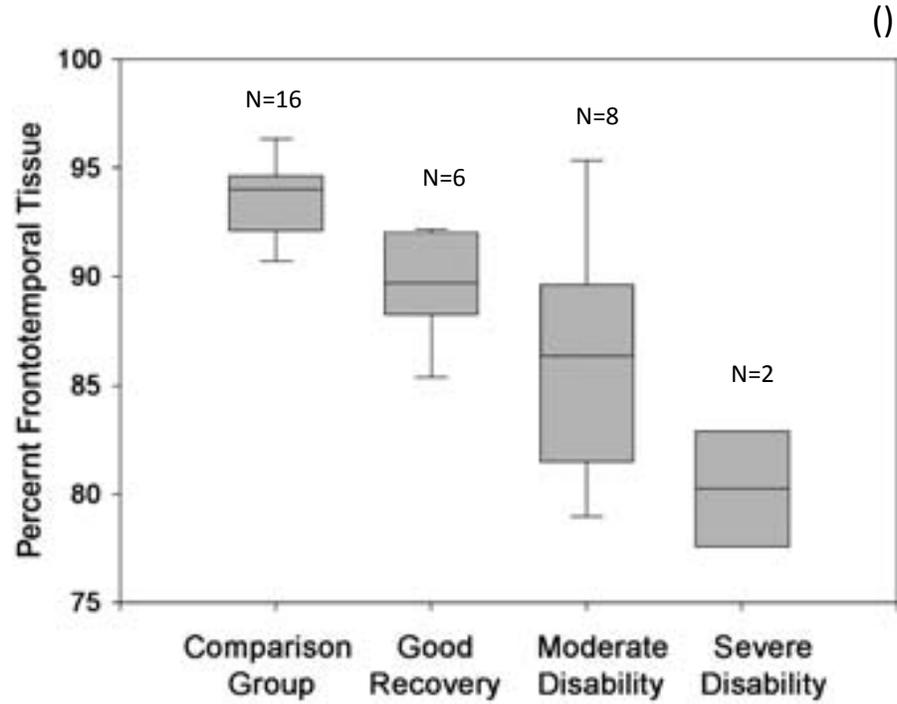
Relation of Depth of Brain Lesion to Outcome (GOS ≥ 6 Months) After Closed TBI

($F(2,72)=3.19$, $P<0.05$, (Levin H et al, J Neurosurgery, 69:1988))

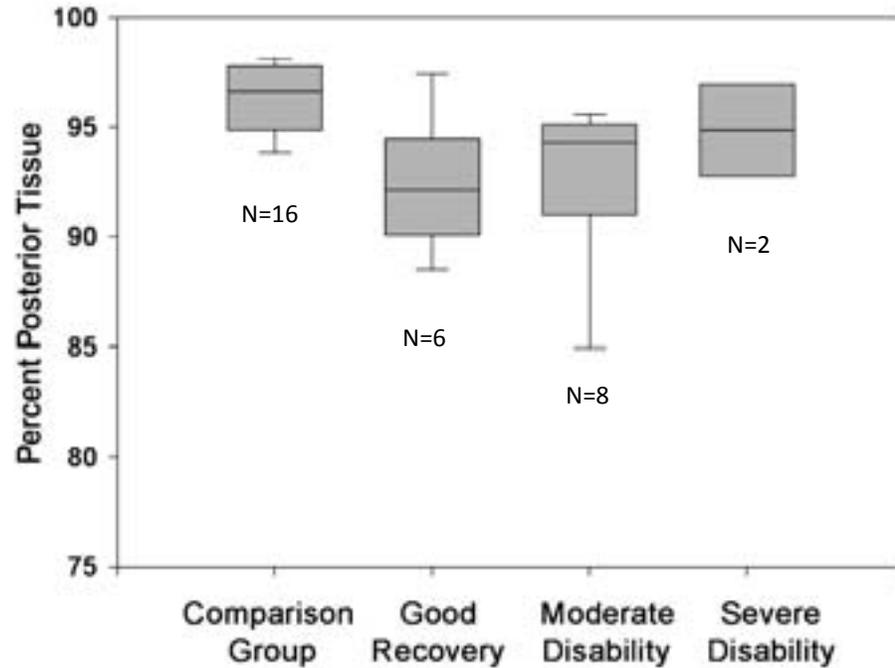




Moderate to Severe TBI in Children: GOS at 1 year in Relation to Percent of Frontotemporal and Posterior Volumes Comprised by White Matter (Wilde EA et al., J Neurotrauma 22: 2005, 33-44)



$\chi^2 = 6.69, df = 2, p = 0.035$

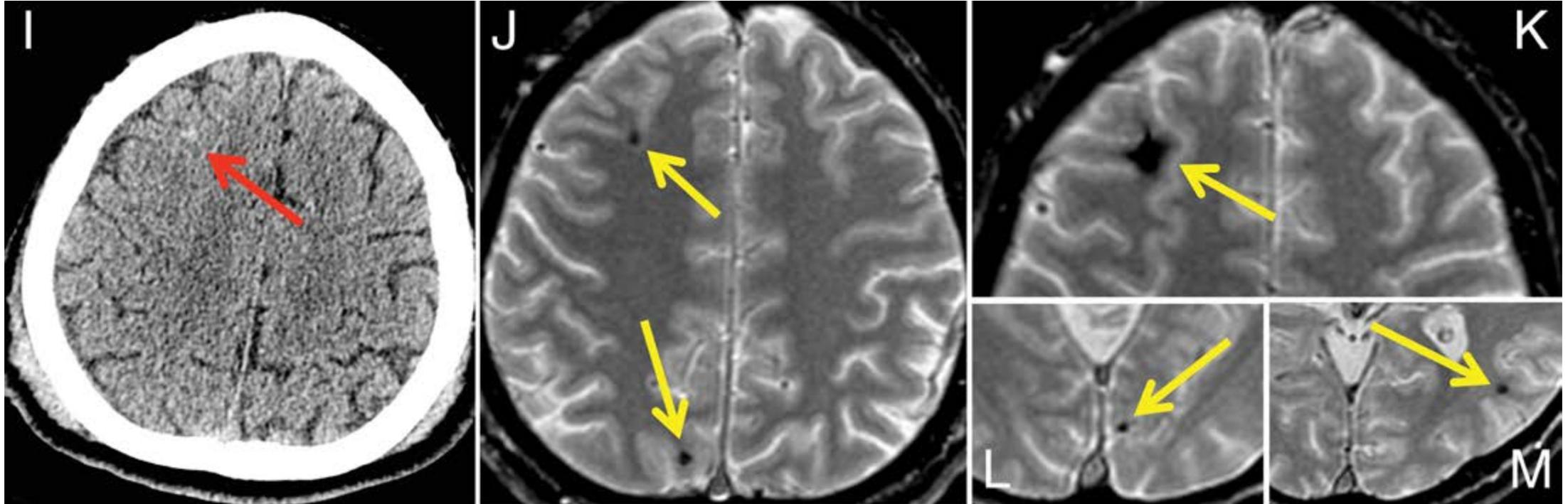


$\chi^2 = 0.706, df = 2, p = 0.703$

MRI Improves 3-Month Outcome Prediction in mTBI

(Yuh et al., Ann Neurol 2013 Feb;73(2):224-35)

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MRI Improves 3-Month Outcome Prediction in MTBI

(Yuh et al, Ann Neurol. 2013, 73(2):224-35)

1. Univariate Ordinal Logistics Regression of 3-Month Dichotomized GOS-E upon MRI Predictors

Predictor	Category (N)	Odds Ratio in GOS-E	P-value
Brain contusion	One or more (21)	3.5	0.004
Axonal injury	≥4 foci [DAI] (14)	3.0	0.03

2. Multivariate Ordinal Logistics Regression with clinical, demographic, SES, CT controlled

Brain contusion	One or more	4.5	0.01
Axonal injury	≥4 foci	3.2	0.03

Disability After Severe Head Injury: Using GOS

(Jennett, Snoek, Bond & Brooks, JNNP, 44:1981 285-293)

Table 7 *Frequency of deficits in each outcome category*

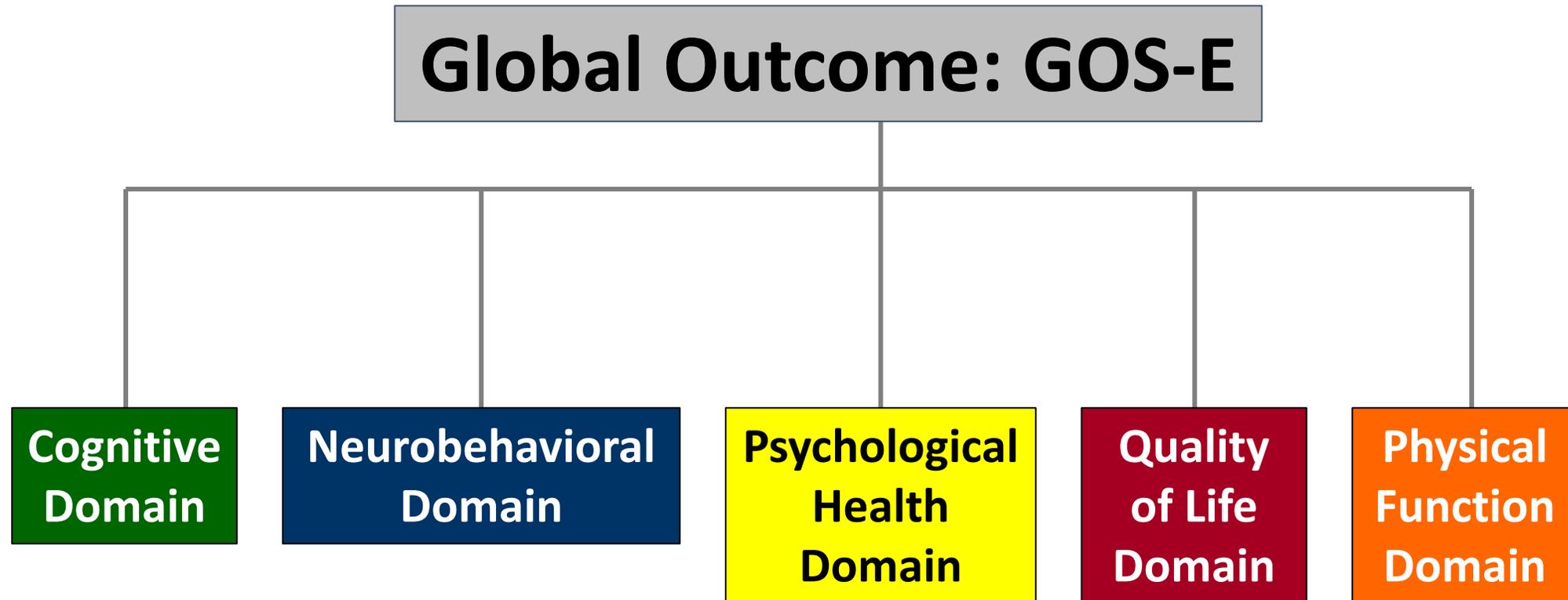
		<i>Good recovery</i> 29	<i>Moderate disability</i> 23	<i>Severe disability</i> 9
Physical (as a whole)	Mild	29	23	6
	Severe	0	0	2
Personality	Mild	12	15	1
	Severe	0	3	7
Cognitive (as a whole)	Mild	29	21	2
	Severe	0	2	7
Verbal IQ	Mild	3	9	2
	Severe	0	0	4
Performance IQ	Mild	13	13	1
	Severe	0	1	8
Verbal memory	Mild	11	12	1
	Severe	1	5	8
Non-verbal memory	Mild	16	11	2
	Severe	0	5	7

Table 8 *Contribution of mental and physical features to overall disability in each outcome category*

<i>Balance of disability</i>	<i>Good recovery</i> 55	<i>Moderate disability</i> 60	<i>Severe disability</i> 30	<i>Total</i> 145
Mental worse	56%	48%	63%	54%
Physical worse	27%	30%	23%	28%
Equal	17%	22%	13%	18%

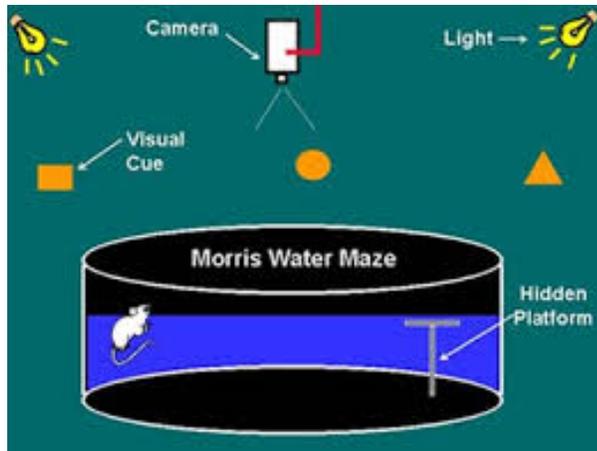
Multi-Dimensional Assessment of TBI Outcome

A Collaborative Effort of TRACK-TBI and TED



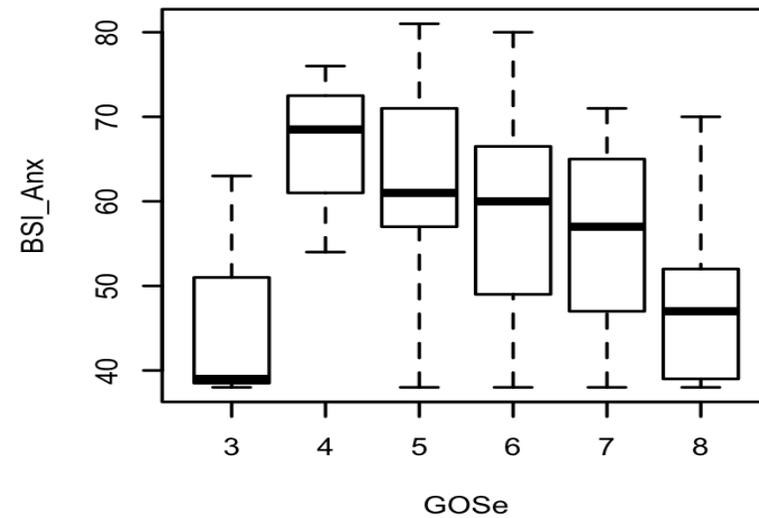
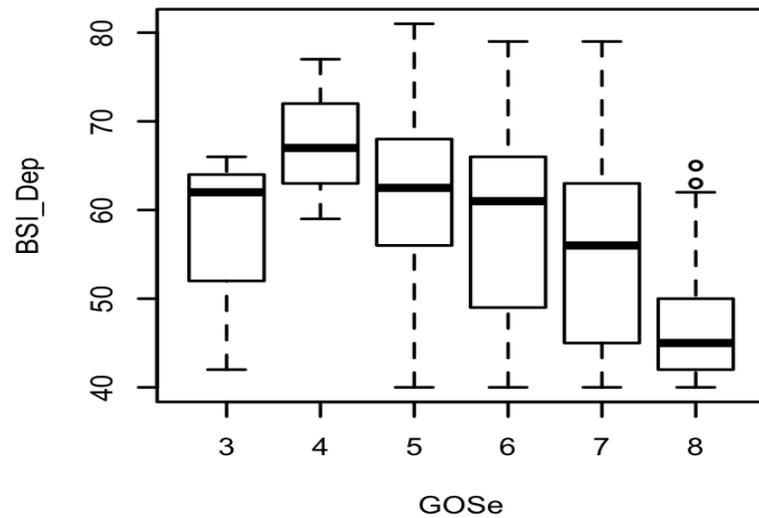
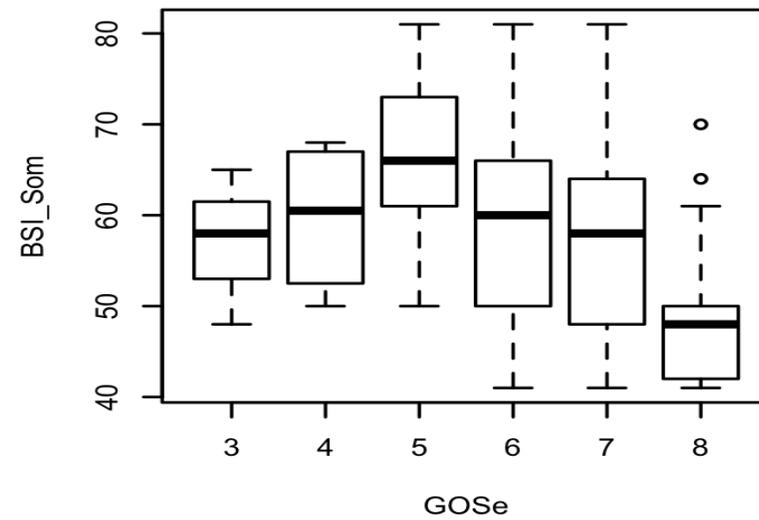
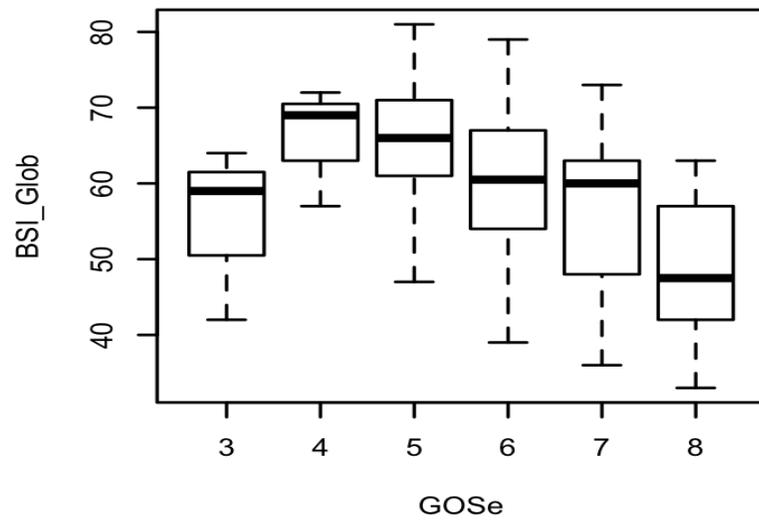
Lost in Translation: Measures of memory used in Phase 1 Trials do not Translate to Global Outcome

- As a global measure of disability, the GOSE may be insensitive to drugs or other interventions **focused on a specific mechanism** such as preserving hippocampal function to enhance memory
 - The Morris Water Maze (MWM), a pre-clinical outcome measure, tests episodic memory, whereas the GOS/GOSE grades global outcome, taps multiple domains and is a poor analog of the MWM.



Cognitive/Physical/Psych
Health/Neurobeh/HRQOL

GOS-E VS BSI-18



COAs for Cognitive Domains Frequently Impaired by TBI: Episodic Memory, Attention/Processing Speed, Executive Function

Rationale:

- These cognitive domains are frequently impaired after TBI and load on separate components of principal components analysis
- Measures are available for each domain which are Common Data Elements
- The cognitive measures have good psychometric features, are brief to administer, and could potentially form one or more composites.
- COUs include ≤ 3 month outcome for mTBI, 3 and 6 month outcome for moderate TBI, and 3, 6, and 12 month outcome for severe TBI

COAs for Behavioral and Symptom Outcomes

- Post-Concussion symptoms (e.g., headache, dizziness) for the COUs of mTBI (sports concussion) ≤ 10 days, mTBI (all types) ≤ 3 months
- Mood disorder (e.g., depression) for the COU of mild to moderate TBI at ≤ 3 months and 6 months, and severe TBI at 6 and 12 months
- Behavioral disturbance for the COU of severe TBI at 6 and 12 months

Summary and Directions

- Validity of GOS/GOSE is supported by pathology seen on brain imaging across a wide spectrum of TBI severity.
- GOS/GOSE measures global disability, but the mechanism of a drug or other intervention tested in Phase 1 trials that affects a specific domain (e.g., cognition) cannot be extrapolated to global outcome.
- COAs that measure specific domains (e.g., memory) for a specific context of use (COU) may be more sensitive to change and specific to the mechanism of action of the drug or intervention.
- For the COU of 3 month outcome of mTBI without CDE lesions, COAs for symptoms (patient reported outcome) may be most sensitive.