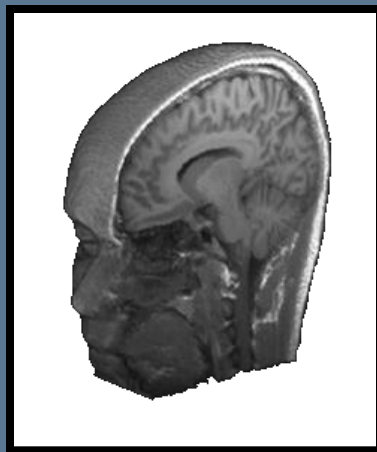


# Biomarkers of increased diffusion anisotropy in semi-acute mild traumatic brain injury: A longitudinal perspective

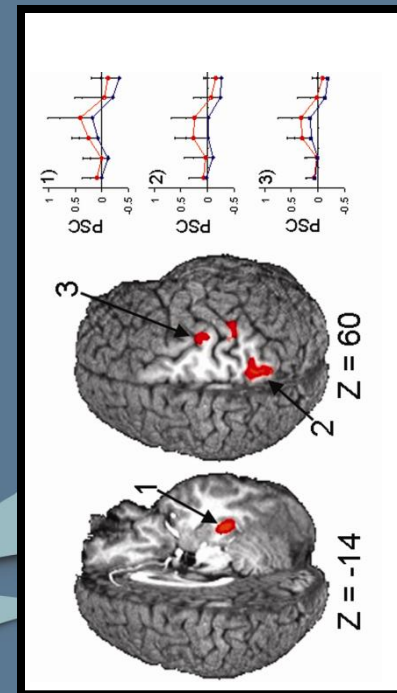
**Andrew Mayer, Ph.D.**

Mind Research Network

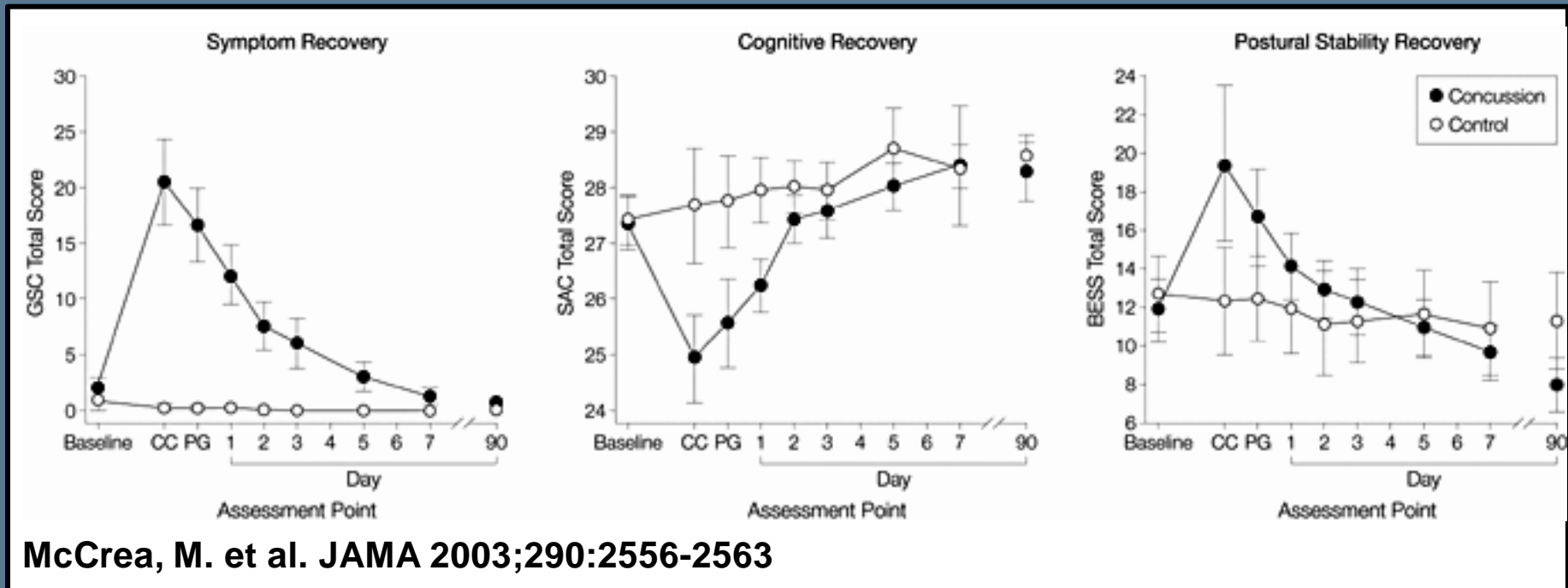
University of New Mexico,  
Departments of Neurology  
And Psychology



The **Mind**  
RESEARCH NETWORK  
FOR NEURODIAGNOSTIC DISCOVERY



# TBI Classifications



**MILD**

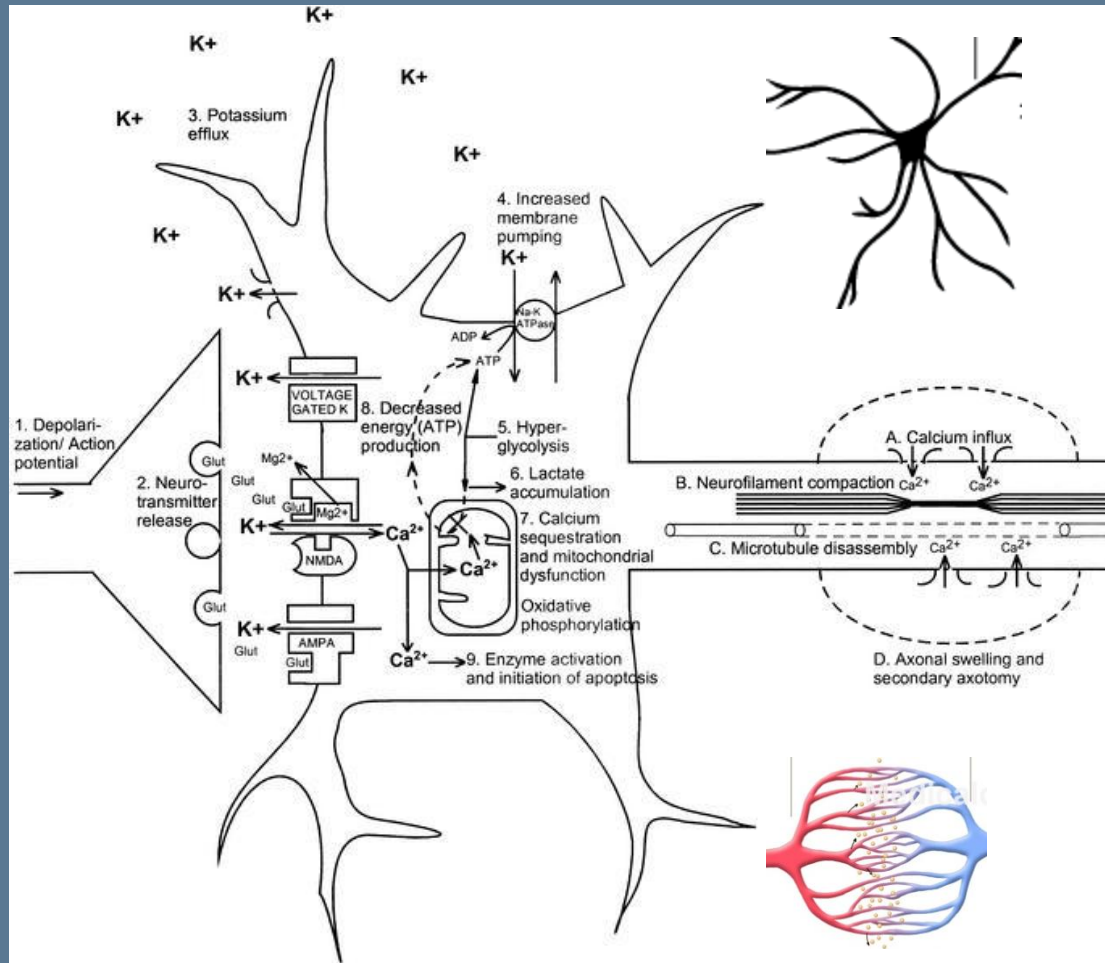
**MODERATE**

**SEVERE**

- mTBI difficult to detect (CT OR MRI) BUT majority (85-90%) of patients recover within 3-6 months
- Can biomarkers map recovery process?

**(Iverson, 2005; Bigler, 2008; Belanger et al., 2005 & 2007)**

# Diffuse Injury Mechanisms



(Barkhoudarian et al. 2011)

- MEG; FMRI (Mayer et al., 2009; 2011; under review; Zhen et al., under review);  $^1H$ -MRS (Gasparovic et al., 2009; Yeo et al., 2011)
- DTI (Mayer et al., 2010; Ling et al., 2011; Ling et al., in press);  $^1H$ -MRS (Gasparovic et al., 2009; Yeo et al., 2011)

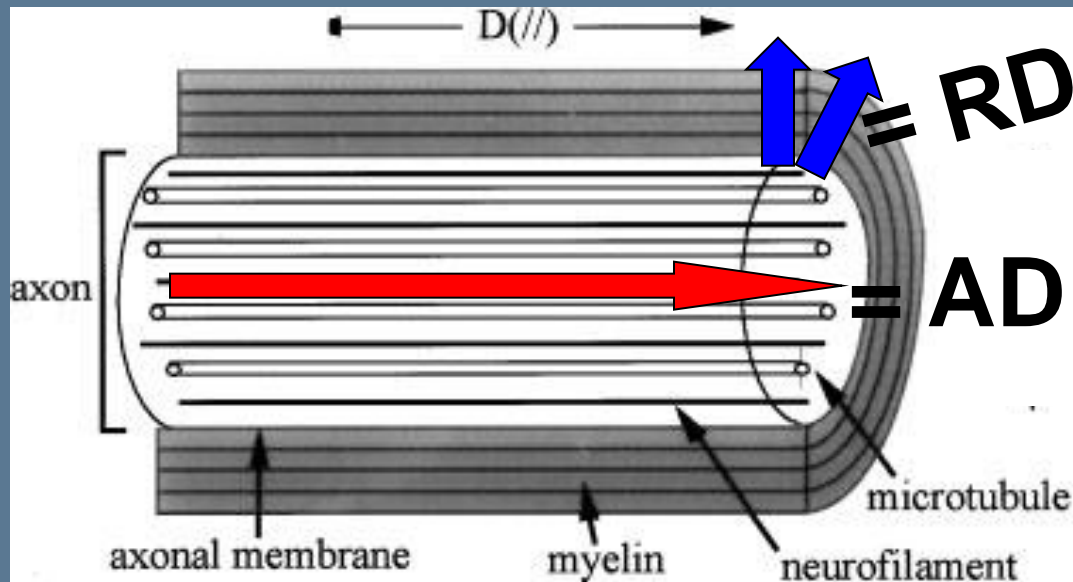
# Diffusion Tensor Imaging



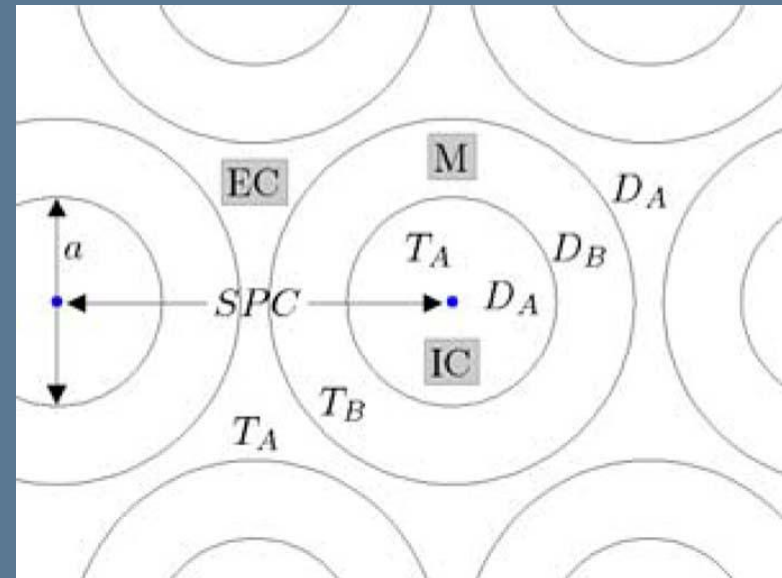
1)  $AD = \lambda_1$

2)  $RD = (\lambda_1 + \lambda_2) / 2$

$$FA = \sqrt{\frac{3}{2}} \cdot \frac{\sqrt{(\lambda_1 - \lambda)^2 + (\lambda_2 - \lambda)^2 + (\lambda_3 - \lambda)^2}}{\sqrt{(\lambda_1)^2 + (\lambda_2)^2 + (\lambda_3)^2}}$$



Beaulieu, 2001



Peled, 2007

- **AD and RD may measure different pathology (Song et al., 2003; MacDonald et al., 2007)**

# Current State of Affairs

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- Reports of increased FA (Bazarian et al., 2007; Wilde et al., 2008; Mayer et al., 2010; Hartikainen et al., 2010; Chen et al., 2012)
- Reports of decreased FA in civilian (Arfanakis et al., 2002; Inglese et al., 2005; Lipton et al., 2009; Miles et al., 2008; Smits et al., 2010) and in military (MacDonald et al., 2011)
- Reports of similar FA (Zhang et al., 2010; Messe et al., 2010)
- Few longitudinal studies in civilian mTBI (Arfanakis et al., 2002 (n = 2); Mayer et al., (n = 9)), one in military (MacDonald et al., 2011) and relatively few examining AD and RD

# Aims

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**A1: Replication (N =28), clinical correlations (N = 50) and recovery (N = 26)**

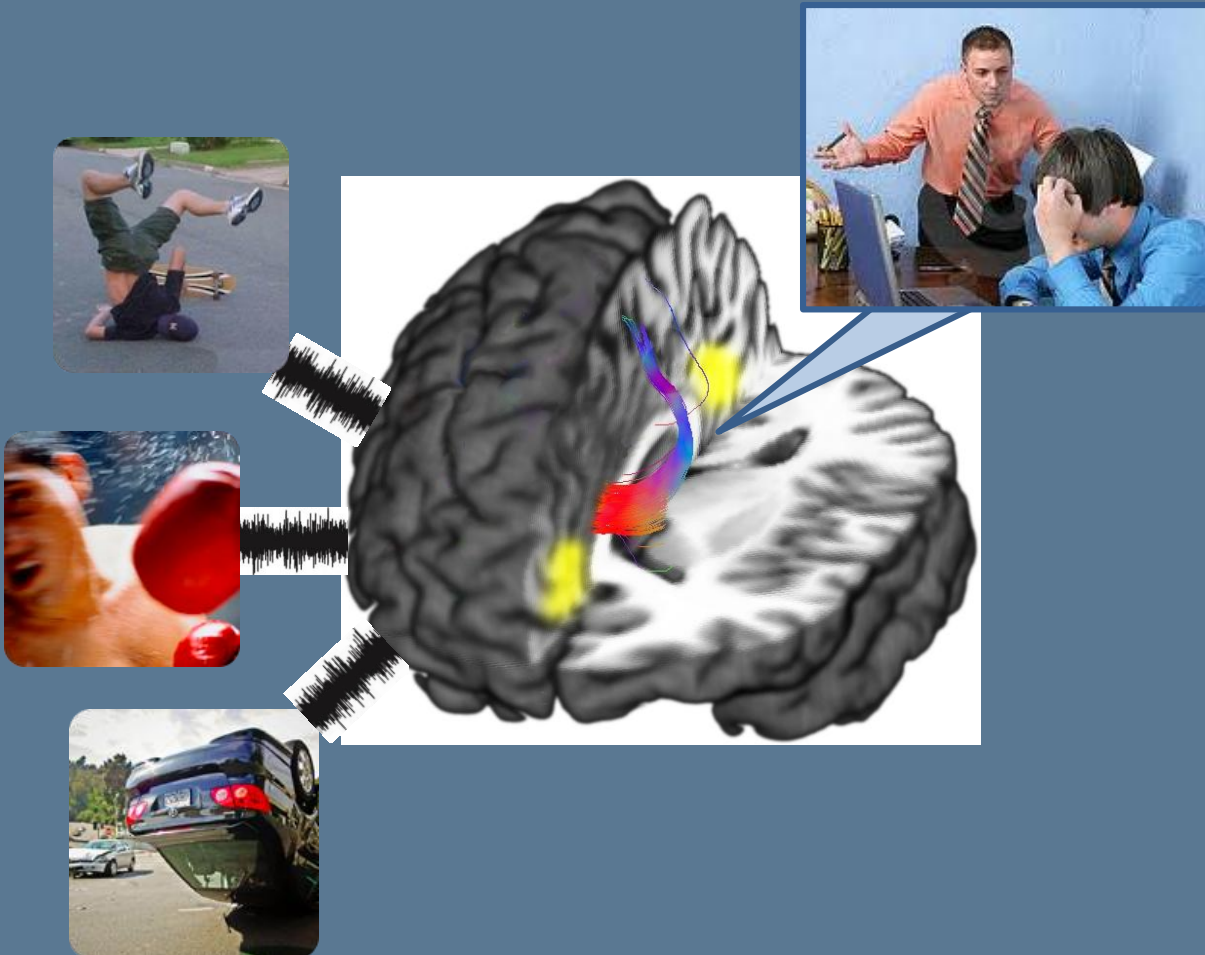
**A2: More sophisticated analytic techniques to better characterize spatially diffuse lesions**

- **mTBI Inclusion Criteria**
  - **Standard (evaluated with 21 days of injury)**
  - **Yoked clinical design**
  - **DTI = 30 directions (TR = 9000 ms; TE = 84 ms; 2 mm<sup>3</sup> voxels; 72 slices; repeated twice)**



# Analytic Assumptions

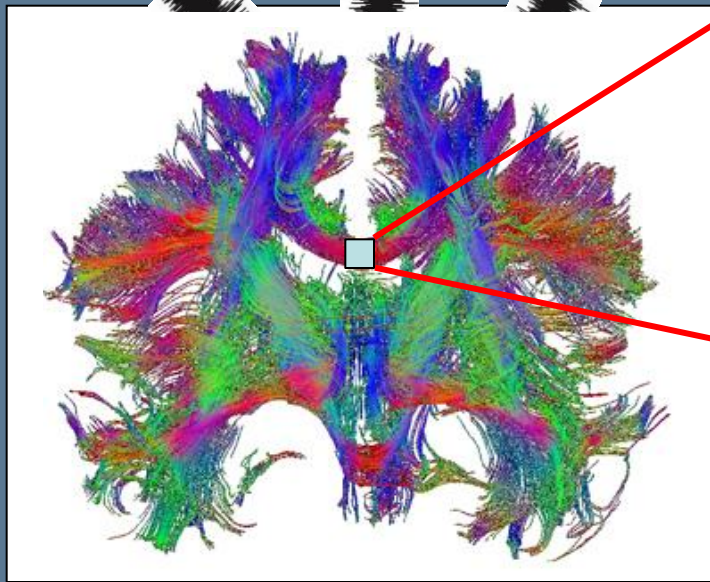
- Heterogeneous conditions produce spatially homogeneous injuries



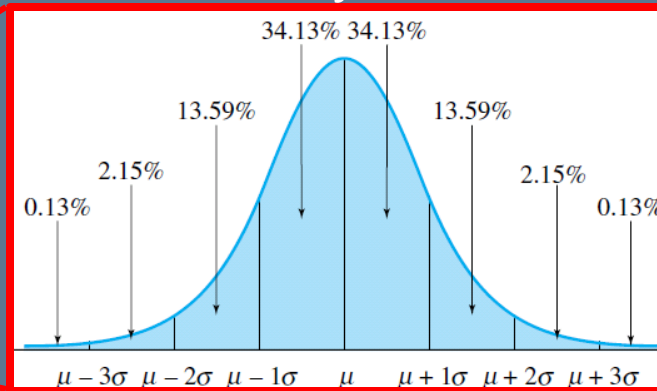
# Revised Analytic Strategies



HC Only =  $\bar{X}, s$



White et al., 2009



mTBI & HC

$$z = \frac{(X - \bar{X})}{s}$$



$z \geq 2$  or  $z \leq -2$   
& min(128  $\mu$ l)



# Clinical Characteristics/Findings

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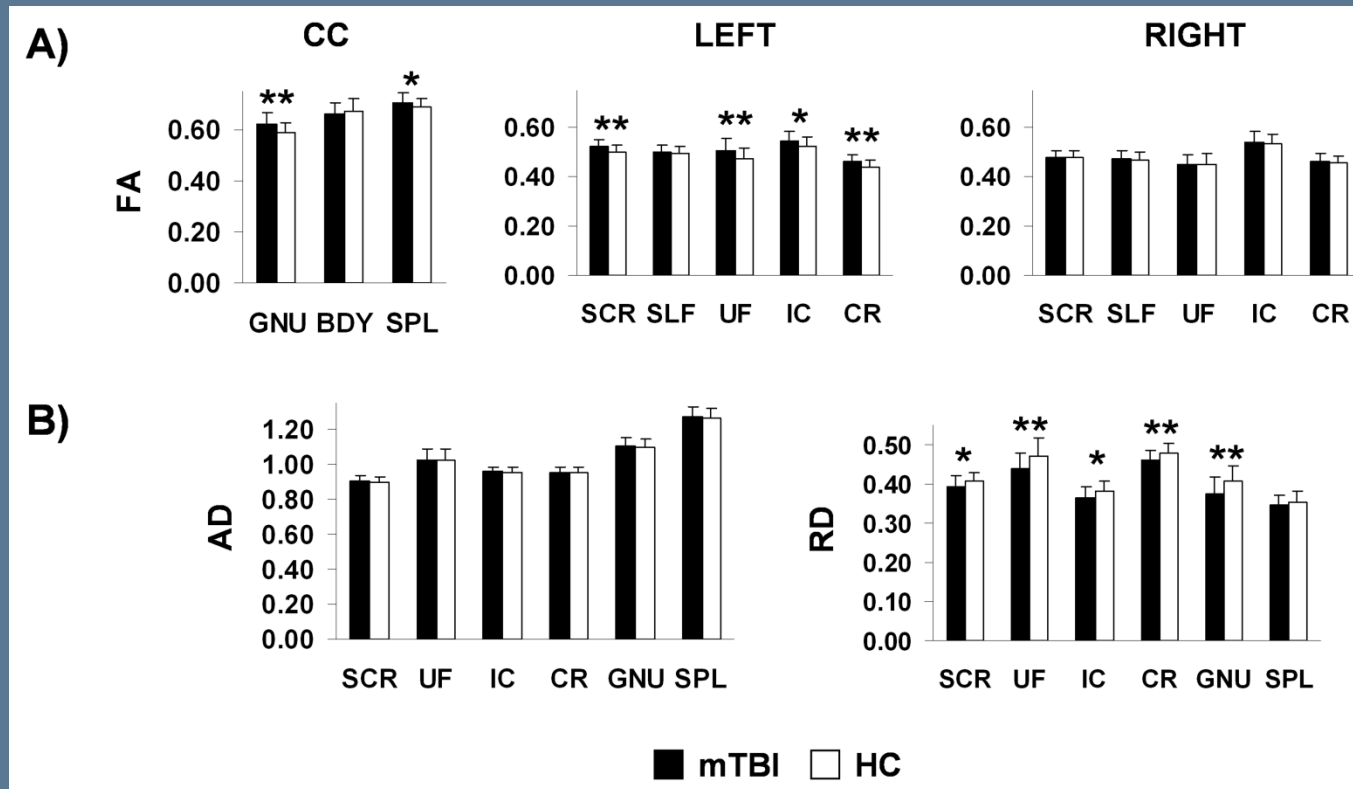


- Mean evaluation = 13 days post /4 months post
- Approximately 70% have LOC/PTA
- Significant differences in subjective complaints; none on objective measures
- pre-morbid IQ lower in both cohorts
- Original = Replication
  - 3.5 days later for replication versus original cohort

# DTI Results (Original Cohort)



- FA, AD and RD (Time 1; mTBI = 22; HC = 21)

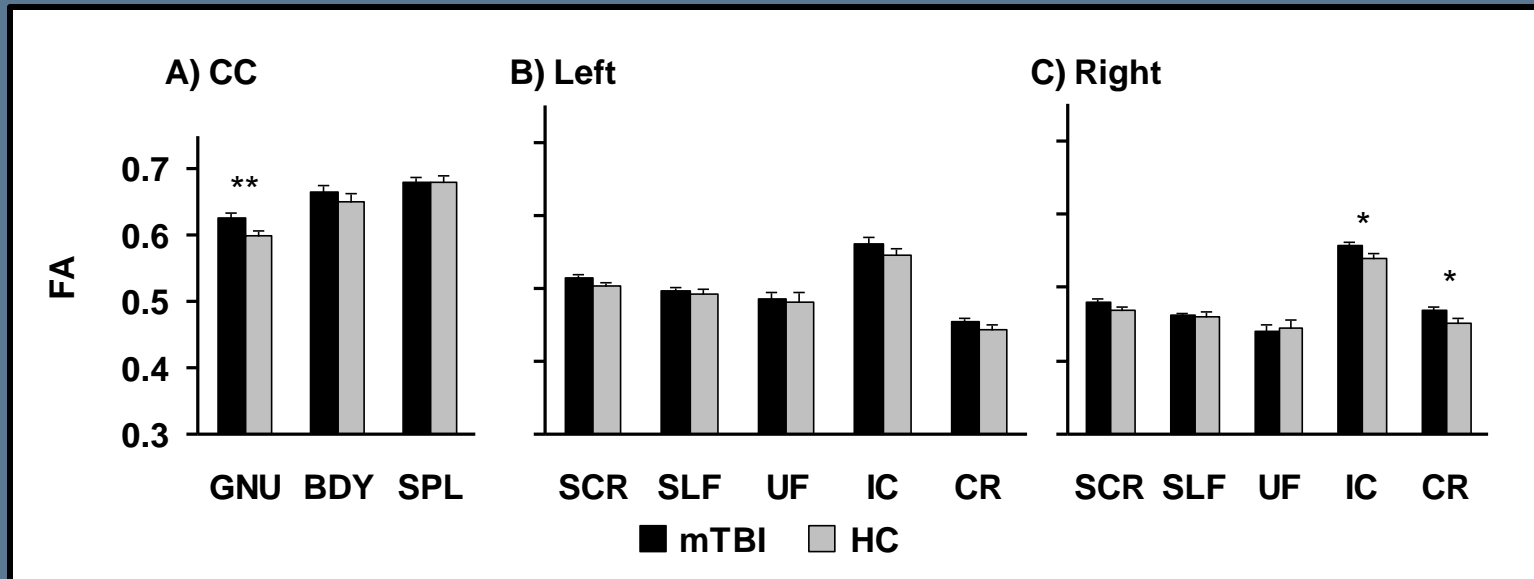


- FA discriminates mTBI from HC (HC = 70%; mTBI = 81%)

# DTI Results (Replication Cohort)



- FA Replication (Time 1; mTBI = 28; HC = 28)

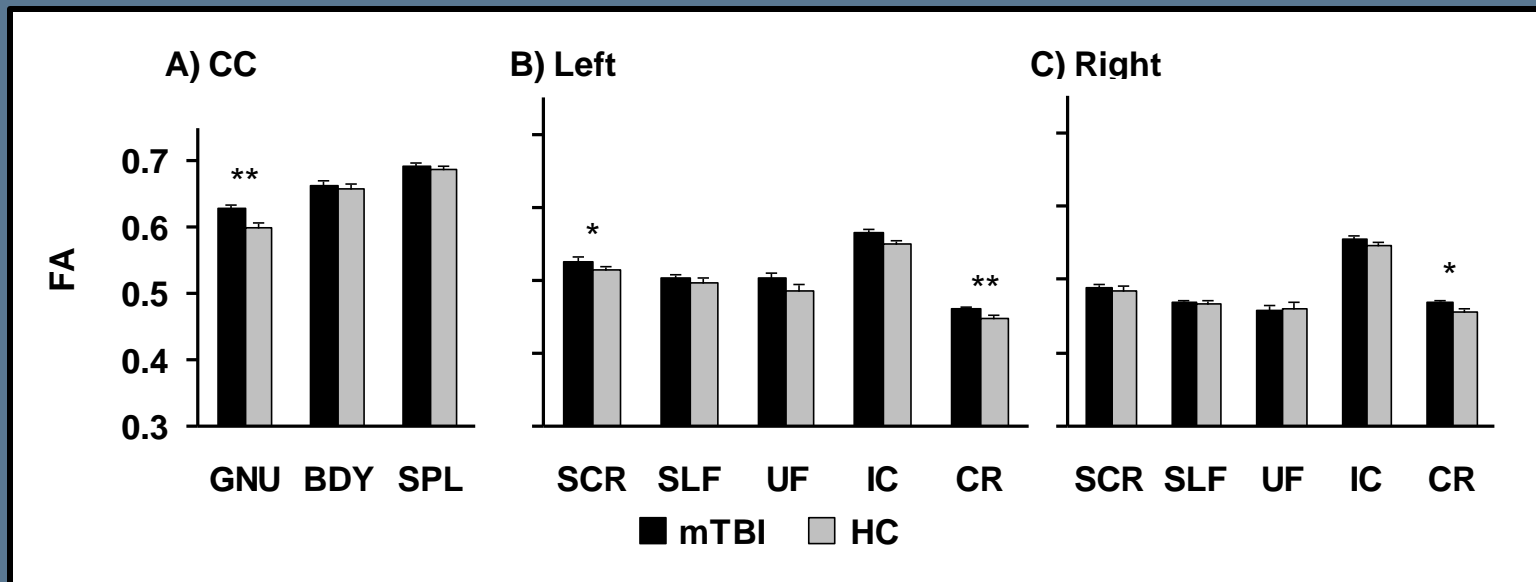


- No differences in voxel-wise analyses

# DTI Results (Pooled Sample)

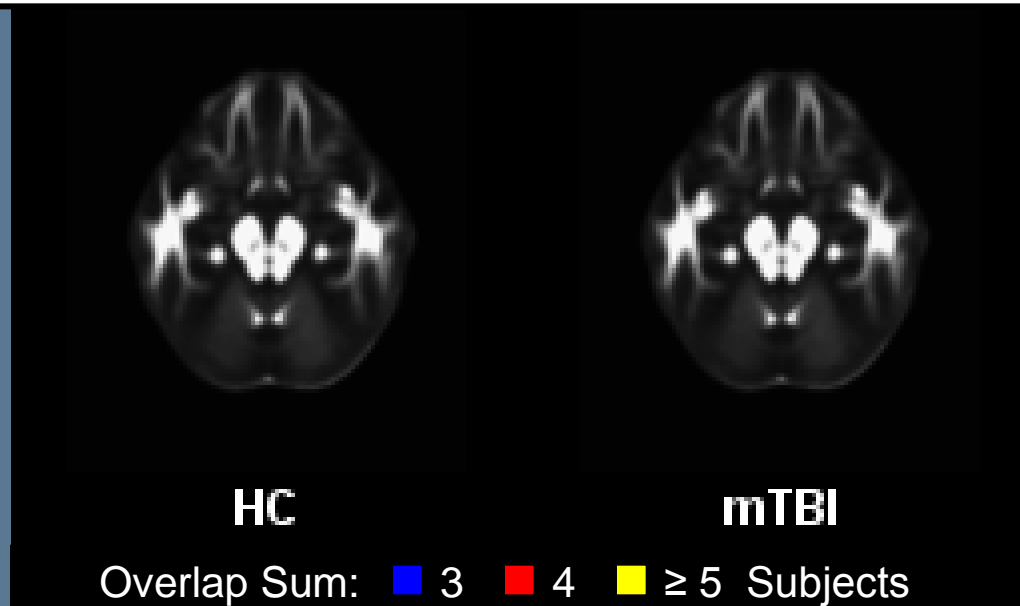
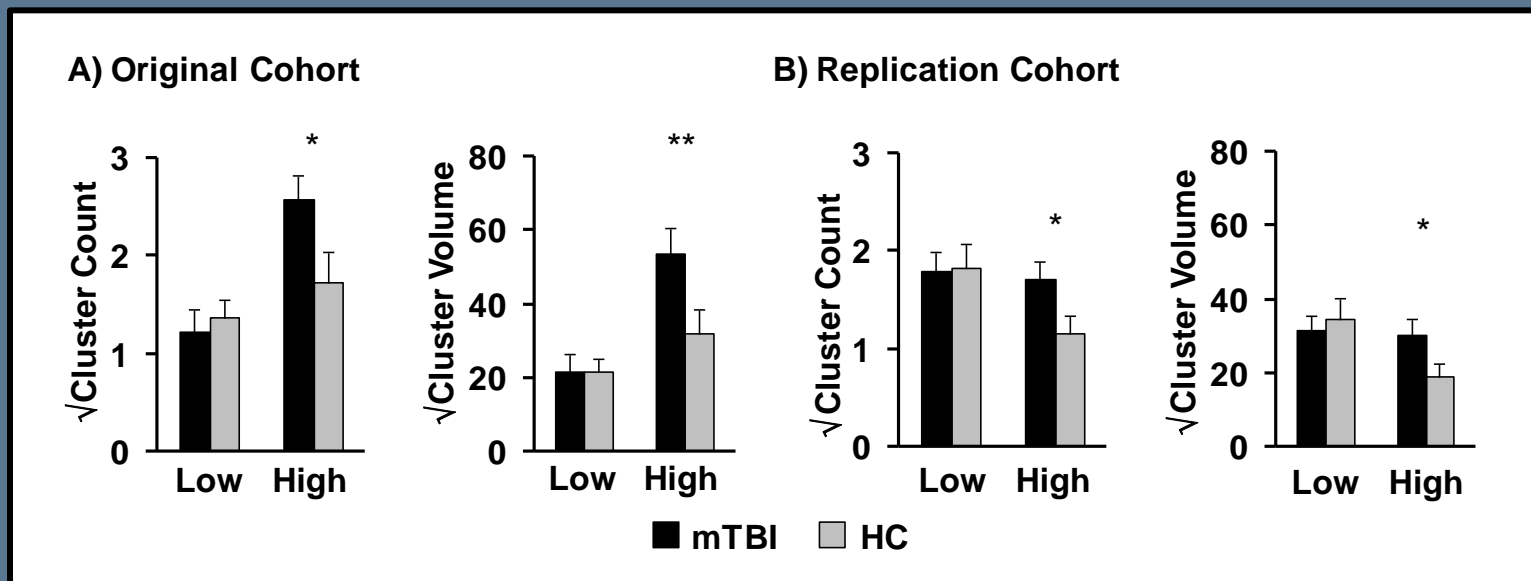


- Time 1; mTBI = 50; HC = 50



- 43/48 show increased FA ( $p < .000$ ); 7 significant and 4 at trend level
- No associations between time-post injury, injury severity (AAN rating) and injury mechanisms. Objective classification with genu significant but modest (71%)

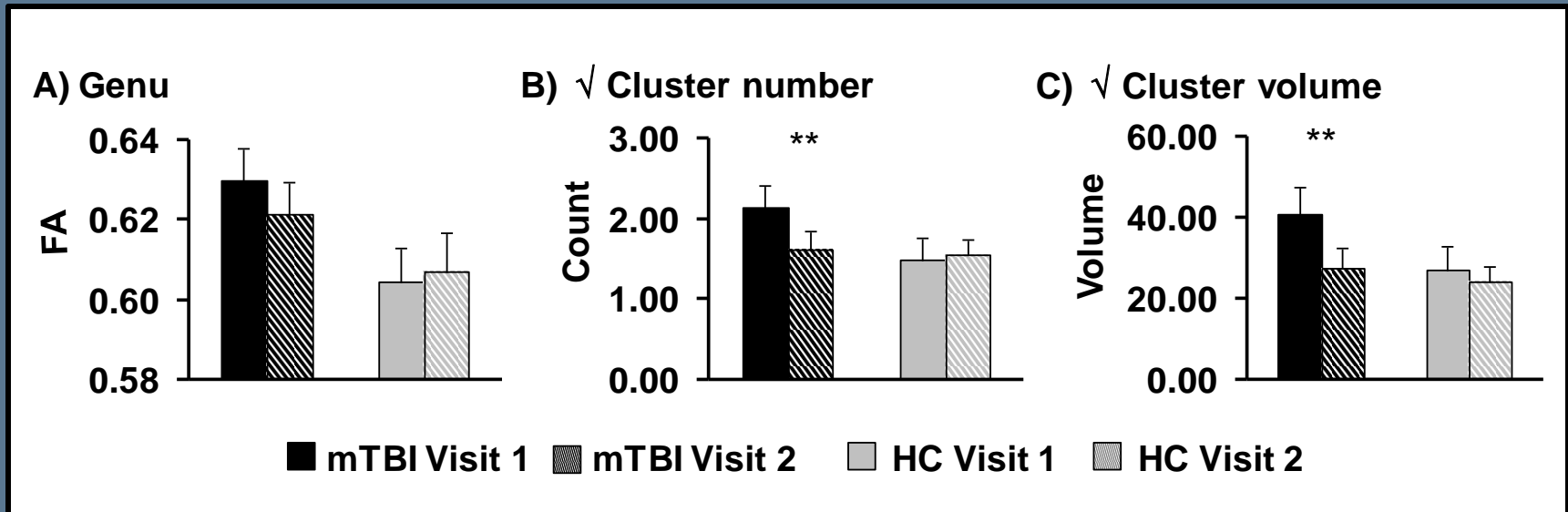
# DTI Results (Cluster Analyses)



# DTI Results (Longitudinal Findings)



- Time 2; mTBI = 26; HC = 26



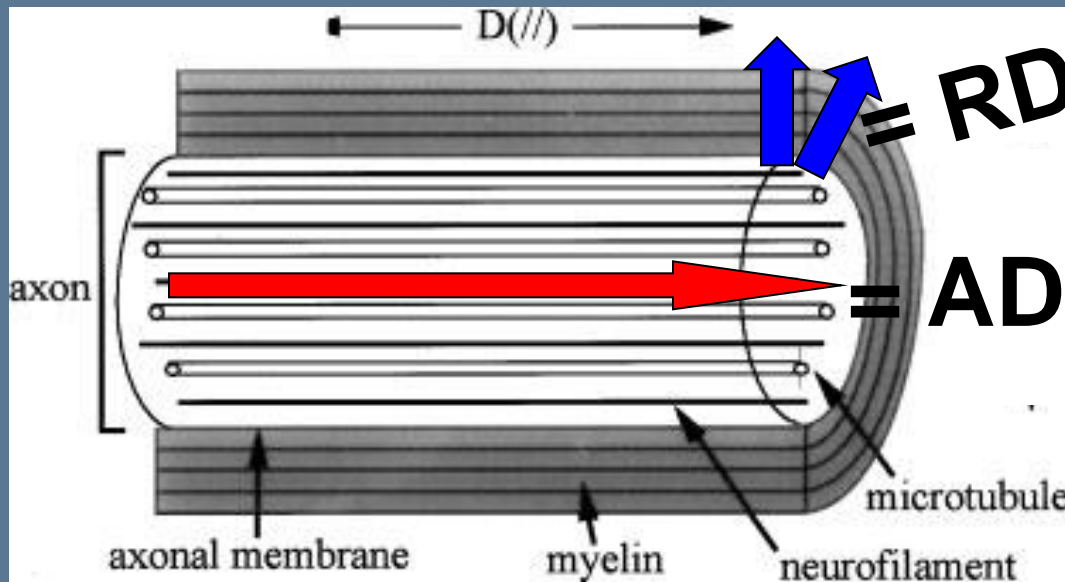
- Reductions weakly associated with decrease in subjective complaints at visit 2



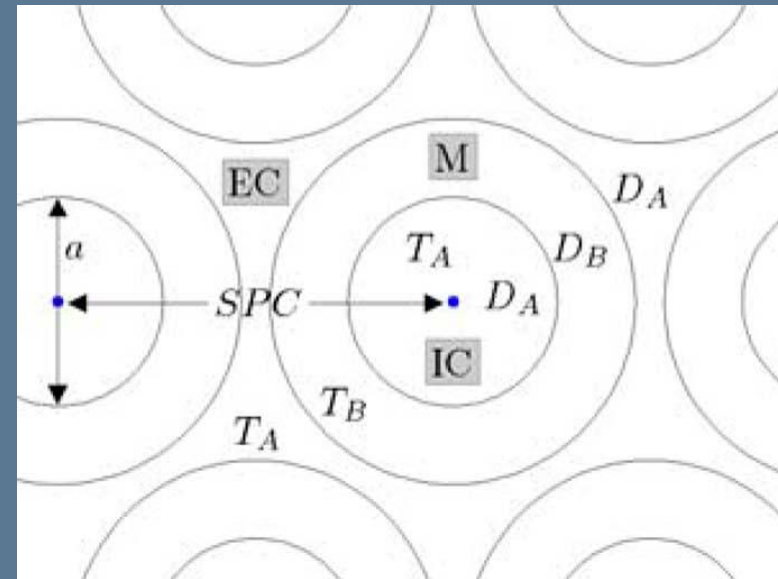
# DTI Summary



- Findings now replicated in third cohort (n = 15)



Beaulieu, 2001



Peled, 2007

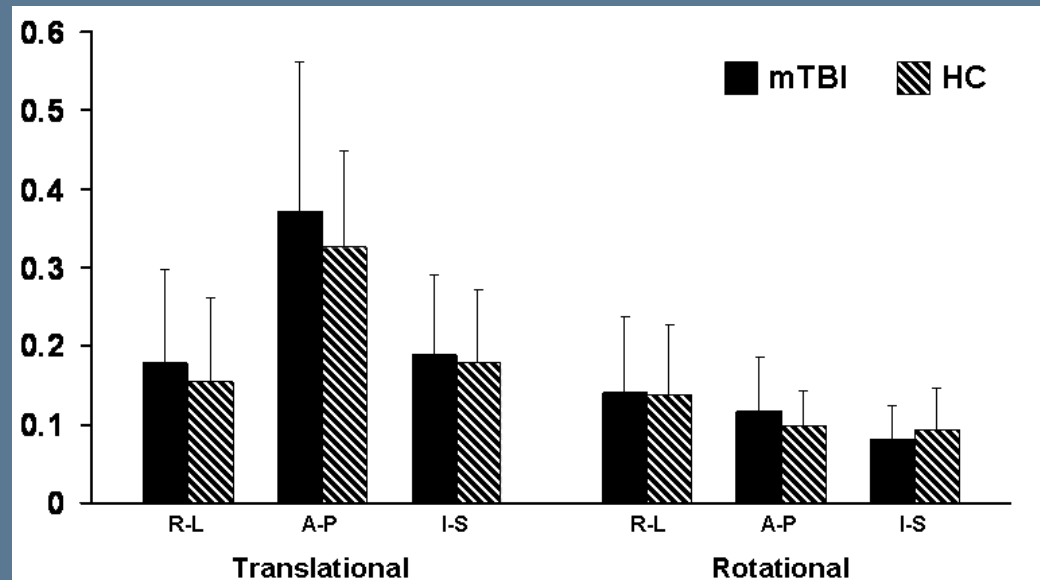
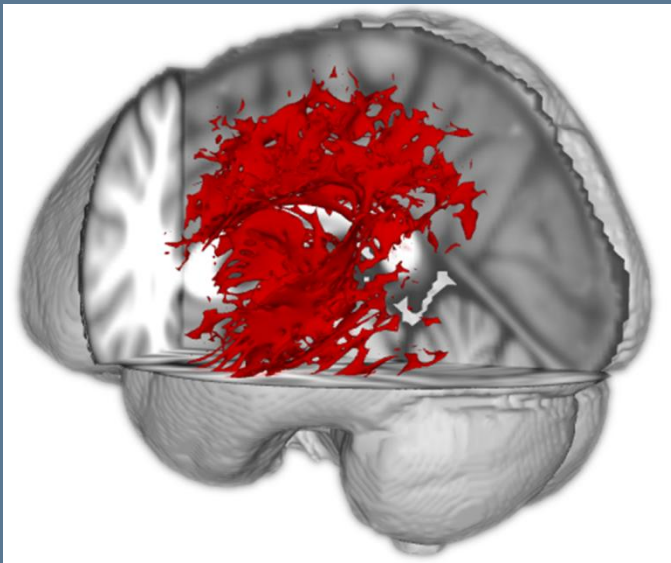
- ↗ FA and variability & ↘ RD = cytotoxic edema and/or myelin (Wilde et al., 2008; Bazarian et al., 2007)??
- Animal models of mTBI suggest extensive axonal/little myelin involvement (Spain et al., 2010)

# DTI Summary: Macroscopic Confounds



## Head Injury or Head Motion? Assessment and Quantification of Motion Artifacts in Diffusion Tensor Imaging Studies

Josef Ling,<sup>1</sup> Flannery Merideth,<sup>1</sup> Arvind Caprihan,<sup>1</sup> Amanda Pena,<sup>1</sup>  
Terri Teshiba,<sup>1</sup> and Andrew R. Mayer<sup>1,2\*</sup>



- MD and FA positively associated with head motion in 49 HC
- No significance ( $p > .10$ ) on measures of motion between groups

# Conclusions

- **Genu may be particularly sensitive as a result of long unmyelinated fibers and initial loading forces**
- **A spatially heterogeneous pattern of increased FA exists in various other white matter tracts, and these “lesions” appear to diminish with recovery.**
- **Relatively modest correlations with neurobehavioral symptoms and patient classification**

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# Collaborators



## Mind Research Network

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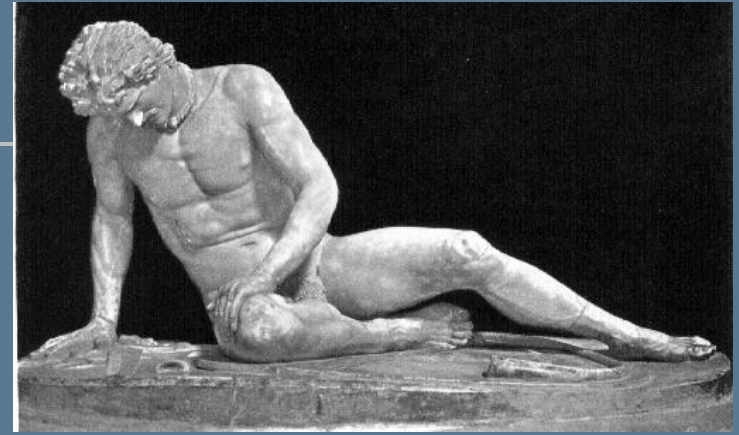
# Not the first .....

## Sumerian medicine (~1700 BC)

- Trepanning instruments

## Egyptian period

- Medical subspecialization.
- One papyrus describes neurologic injury
  - Case descriptions, one of temporal injury and aphasia



## Greece

- TBI described in fifth book of *Epidemics* (Hippocrates)
  - 11 yo boy kicked in forehead by horse. Explore skull with metal probe, determine fracture. Any question, coat skull with barley plaster and scrape away to expose fracture lines. No further treatment if skull fracture present. If no skull fracture, trephining to release accumulated “humors or to slacken the tightness of the skull.”

## Roman medicine

- Galen of Pergamon (129 – 216 AD). Surgeon to gladiatorial games. Associated dizziness with head injury.

# Volume threshold

