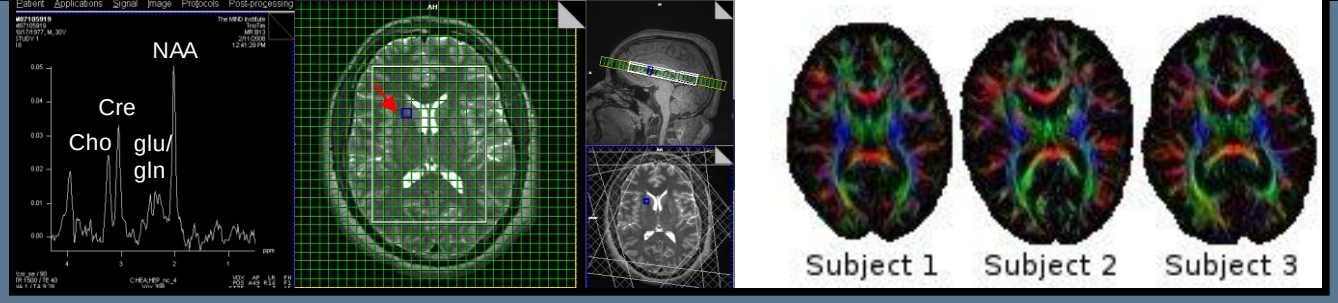


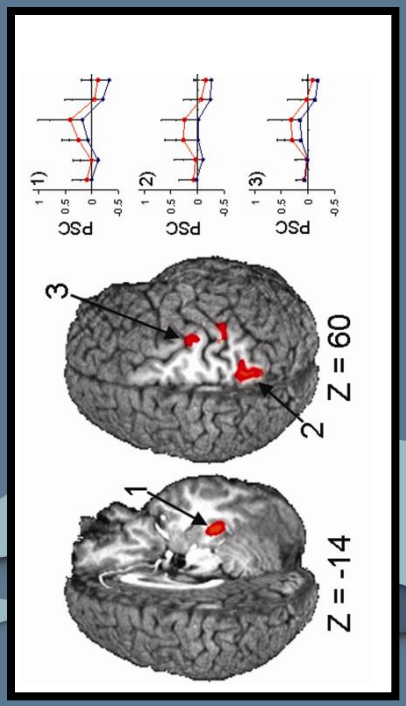
Neuroimaging in Pediatric Mild Traumatic Brain Injury

Andrew Mayer, Ph.D.

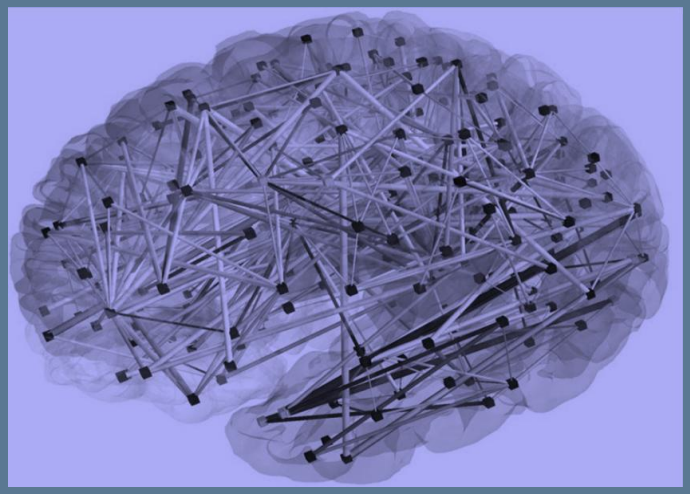
Mind Research Network

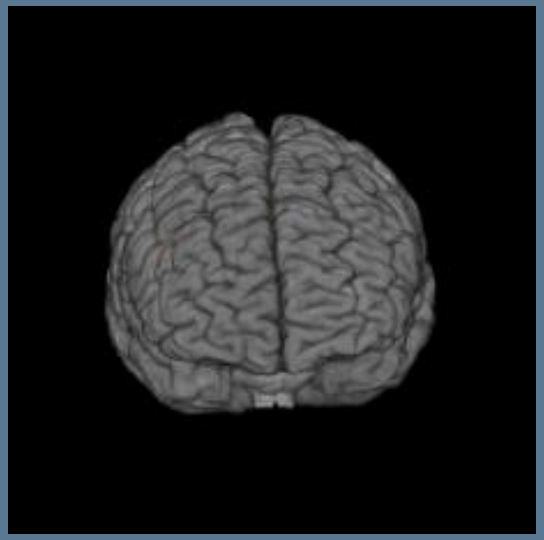
University of New Mexico,
Departments of Neurology
And Psychology

The Mind RESEARCH NETWORK
FOR NEURODIAGNOSTIC DISCOVERY



Problem Statement/Goals of Talk





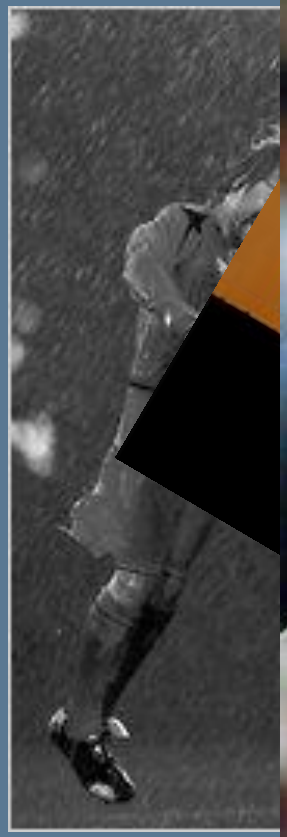
- Overview imaging measures of gray/white matter structural pathology and functional pathology in pmTBI
- Evaluate whether neuroimaging findings are more sensitive than current gold standards in pmTBI
- COI: Funded as investigator and consultant on several NIH/DoD grants

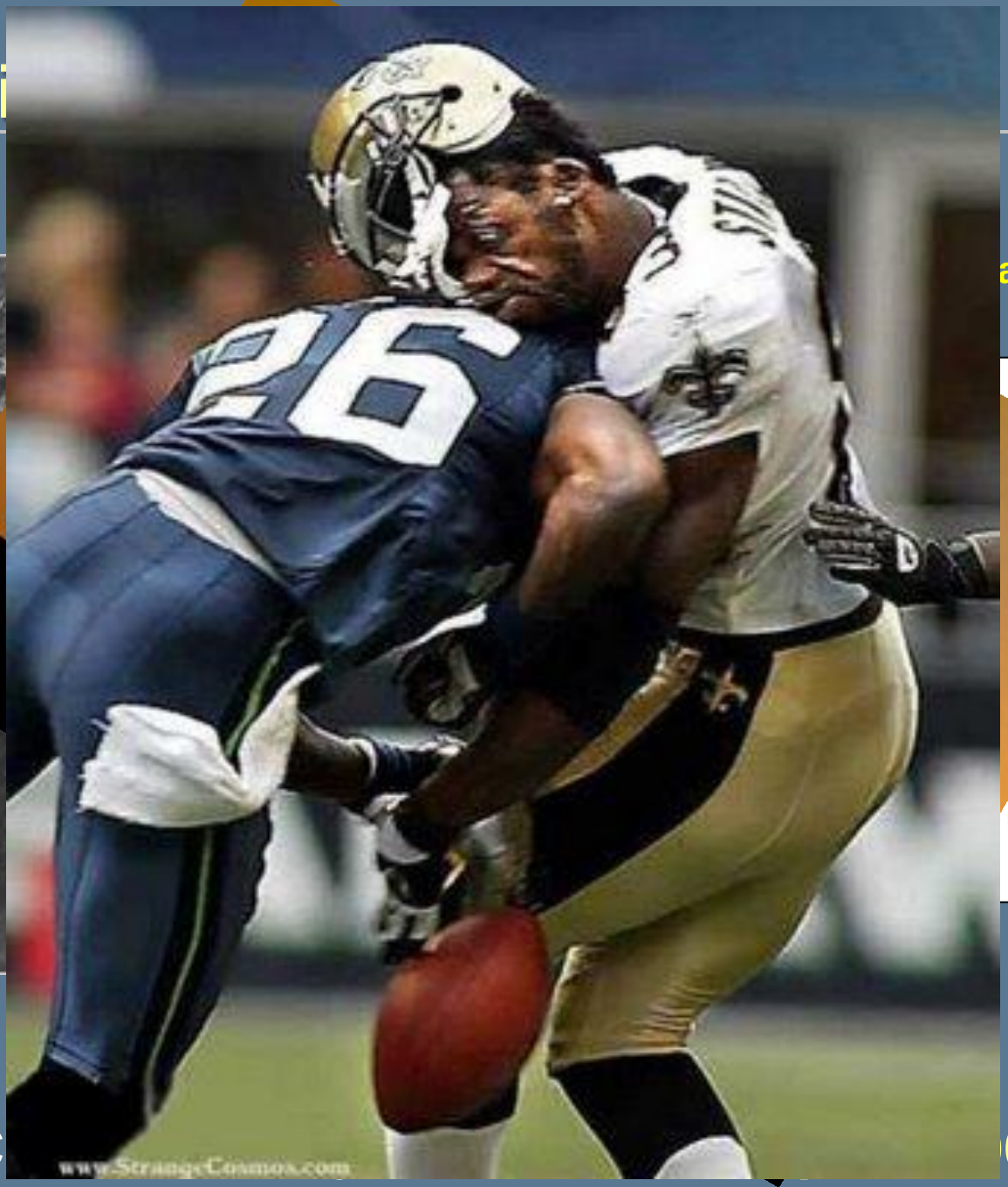
Epidemiology: “The Silent Epidemic”

- TBI contributes to nearly a third of injury-related deaths in US
- Estimated annual cost = $60 billion dollars
- Approximately 1.7 million people experience a TBI per year
  - 52,000 people die from head injury per year
  - 275,000 people are hospitalized for TBI and survive per year
  - 1.4 million head-injured people are treated in hospital emergency rooms per year
  - Untreated?????

(Faul et al., 2010 CDC report)

Epidemi



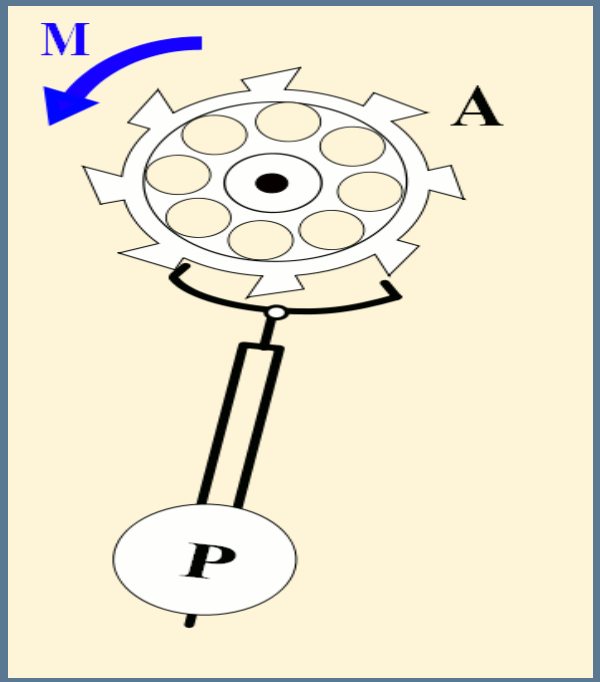


ates

- C 07)

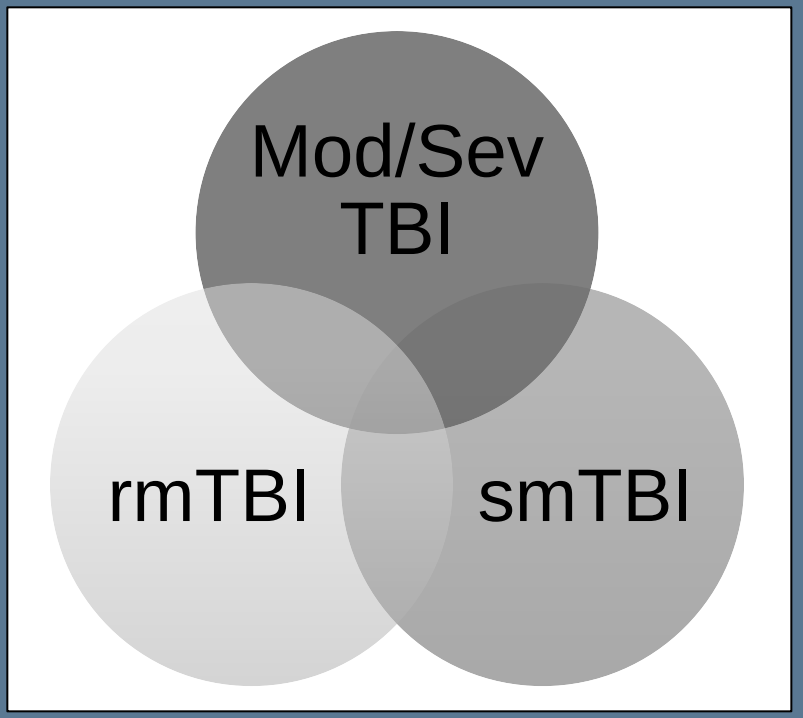
Historical Perspectives on mTBI

- Neurobehavioral symptoms; single versus repetitive mTBI



Permanent neurological damage

Psychiatric entity



Long-Term Consequences

Brain Advance Access published December 2, 2012

doi:10.1093/brain/aws307 Brain 2012: Page 1 of 22 | 1

BRAIN
A JOURNAL OF NEUROLOGY

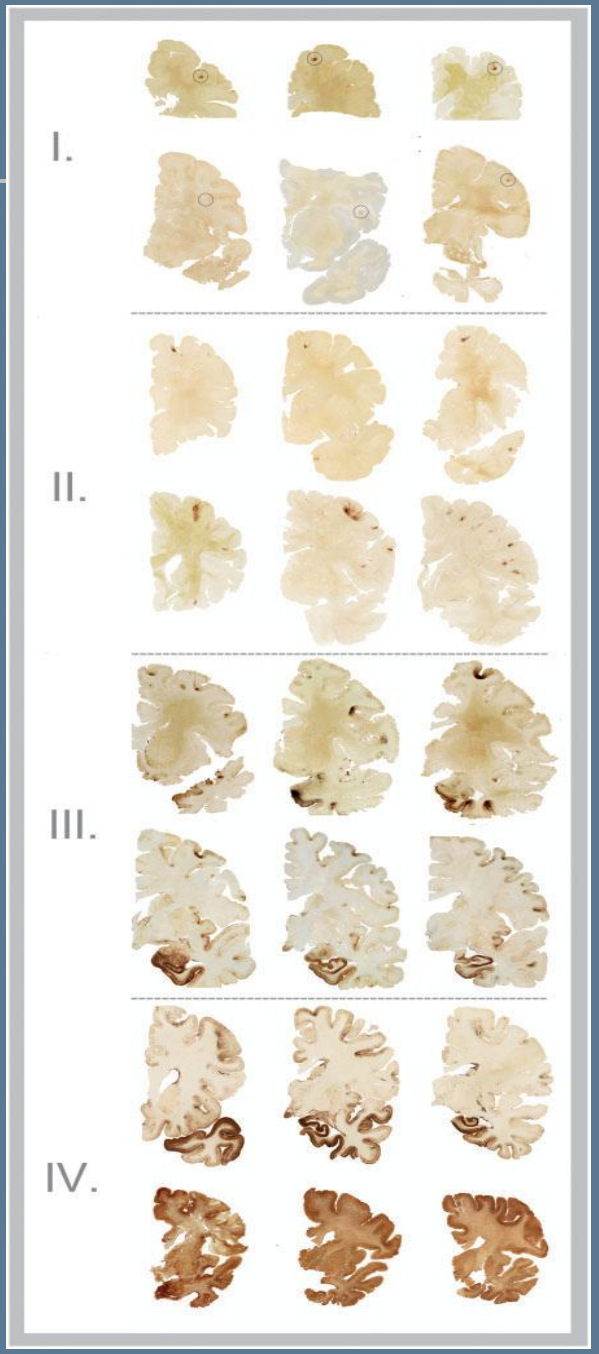
The spectrum of disease in chronic traumatic encephalopathy

Ann C. McKee,[1,2,3,4,5] Thor D. Stein,[1,5] Christopher J. Nowinski,[2,4,6] Robert A. Stern,[2,3,4,7] Daniel H. Daneshvar,[2,4] Victor E. Alvarez,[2,4] Hyo-Soon Lee,[3,4] Garth Hall,[8] Sydney M. Wojtowicz,[1,2] Christine M. Baugh,[2,4] David O. Riley,[2,4] Caroline A. Kubilus,[3,4] Kerry A. Cormier,[1] Matthew A. Jacobs,[2,4] Brett R. Martin,[9] Carmela R. Abraham,[3,10] Tsuneya Ikezu,[3,4,11] Robert Ross Reichard,[12] Benjamin L. Wolozin,[3,4,11] Andrew E. Budson,[1,3,4] Lee E. Goldstein,[3,4,12,13,14,15] Neil W. Kowall[1,3,4,5,*] and Robert C. Cantu[2,6,7,16,*]

DeKosky et al., 2010; McKee et al., 2009

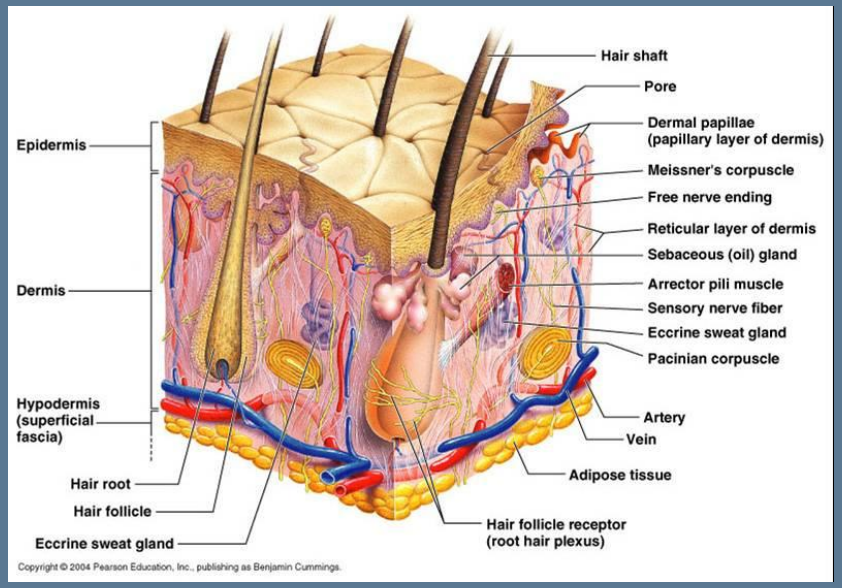
Long-Term Consequences

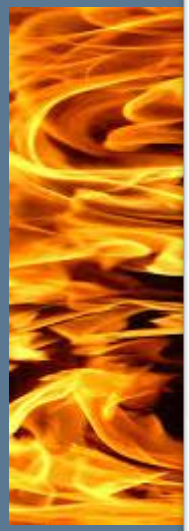
- Chronic Traumatic Encephalopathy (McKee et al., 2012; Chritchley 1949, 1957) A.K.A. dementia pugilistica (Martland, 1928; Millspaugh, 1937)
- Hyper-phosphorylated tau in deep perivascular spaces
- More prominent frontal-temporal involvement, diencephalon
- Prominent neurobehavioral sequelae

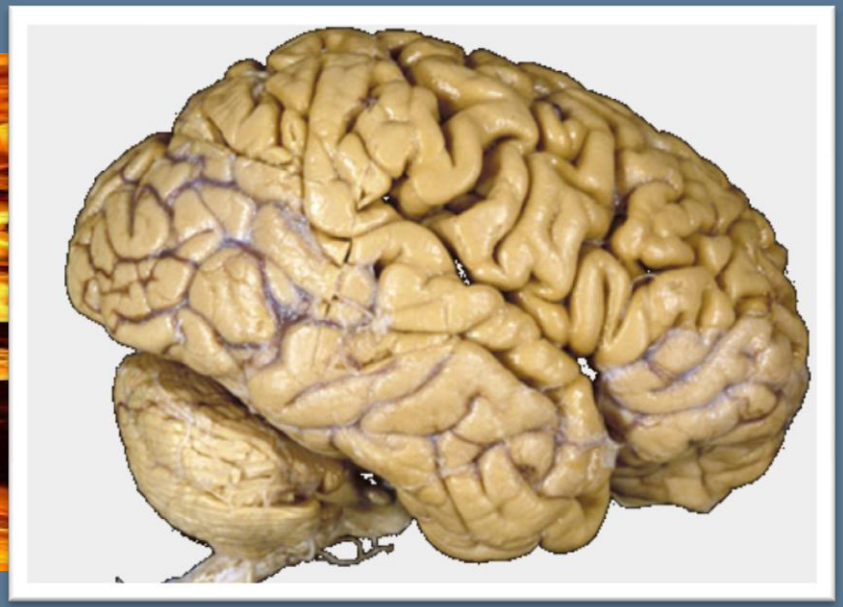


McKee et al., 2012

Clinical Lessons from Dermatology



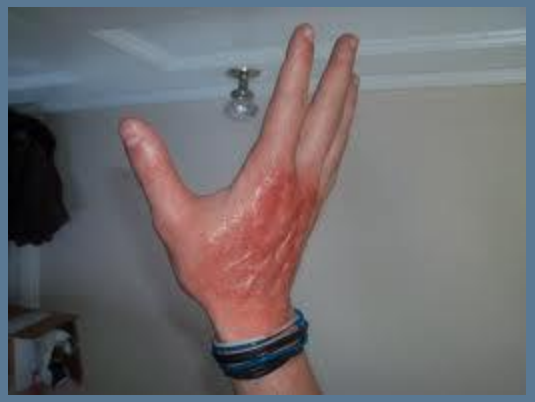


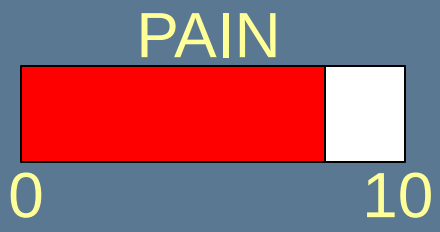


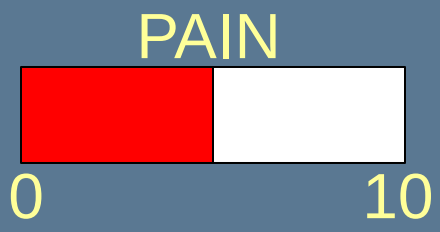
Pearson Education, 2004

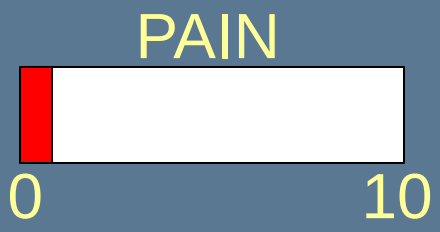
More meaningful statements about injury based on objective classification system using anatomical substrates/other biomarkers

Clinical Lessons from Dermatology





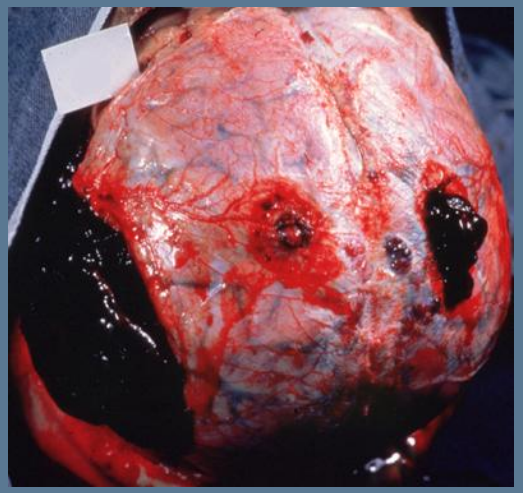


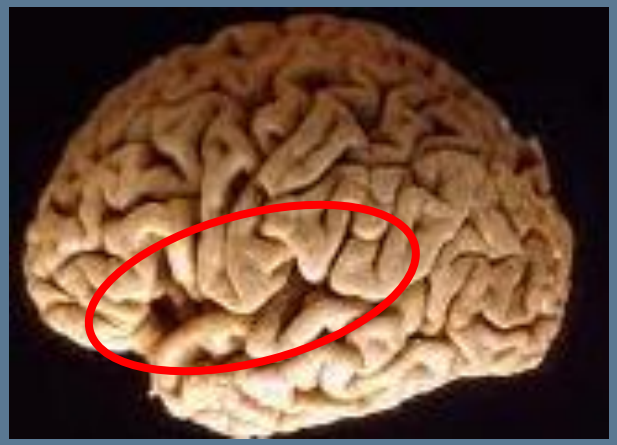


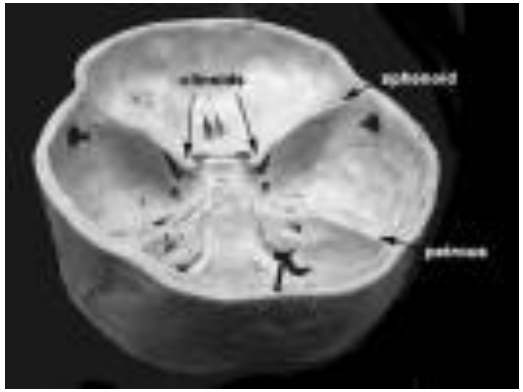
Each injury stage is likely associated with different types of pathophysiology and behavioral (e.g., pain) symptoms

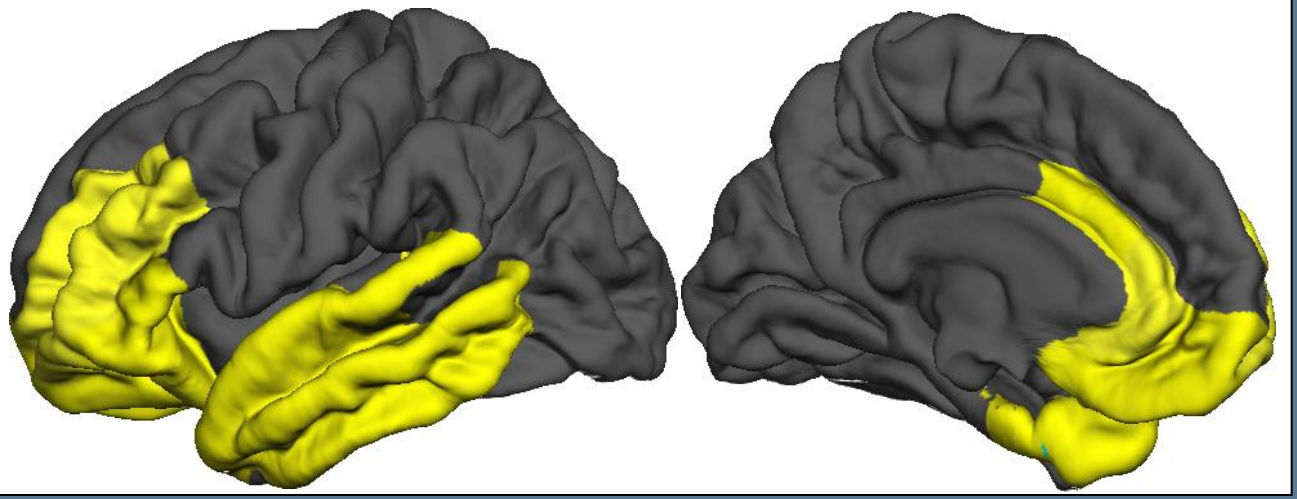
Focal Pathology and Location

- **Atrophy, lesions and cellular alterations**





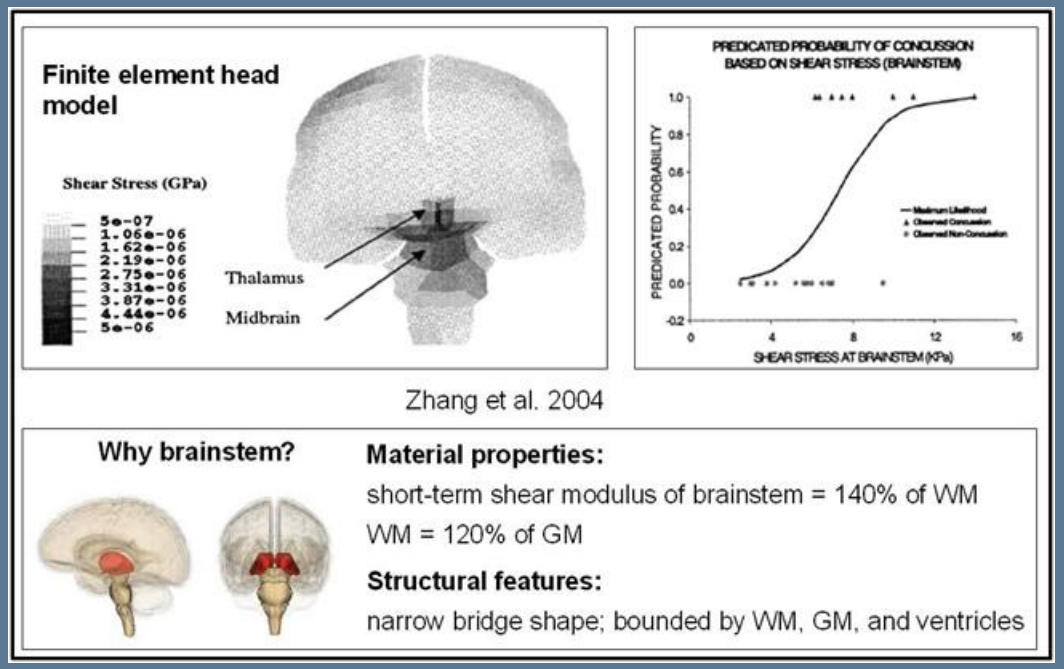


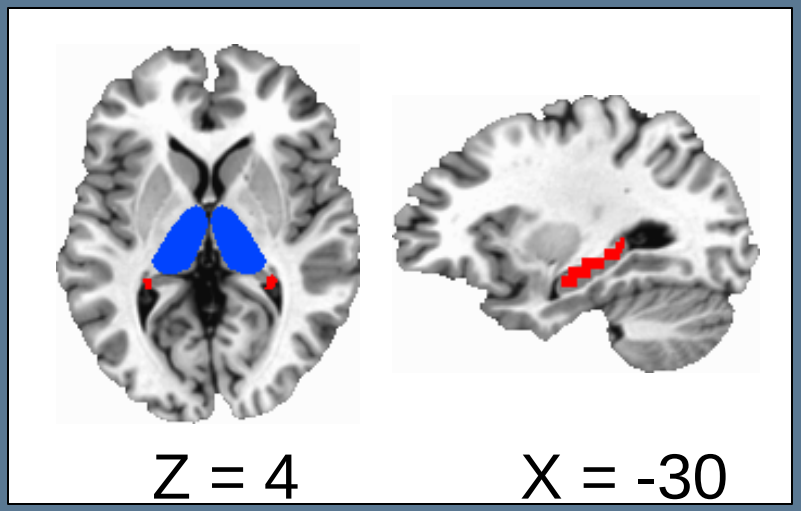


Bigler et al., 2013; McAllister & Stein, 2010

Focal Pathology and Location

- **Morphology of sub-cortical structures**
- **Frequently reported site for diffusion and/or atrophic changes in animal models**
- **Selected ROI**

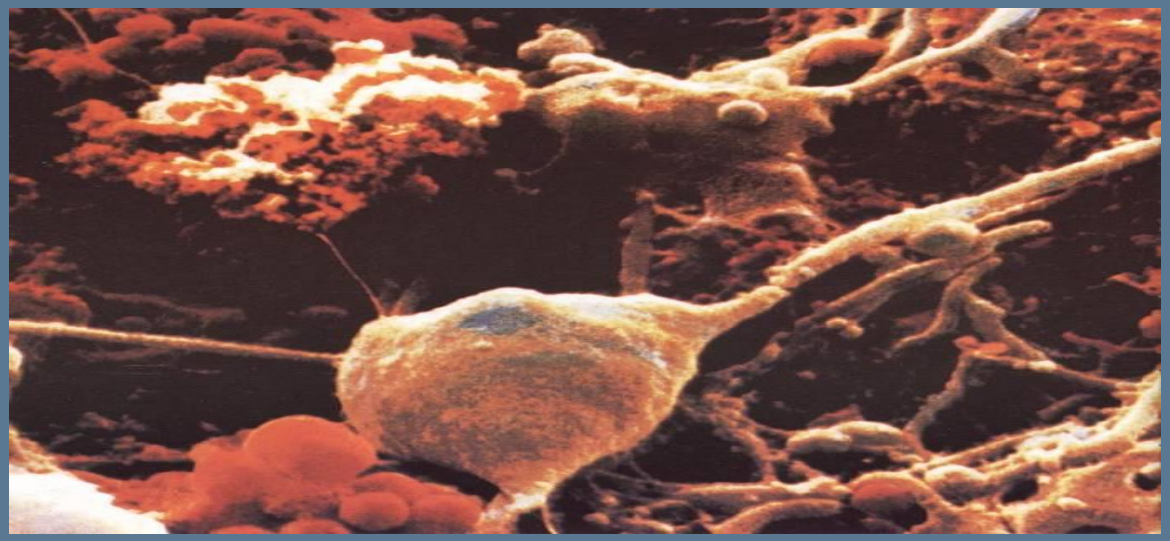




Diffuse Injury Mechanisms

- Stretch -> Mechanoreceptor dysregulation (e.g., Na^+) -> Voltage dependent receptor activation & ionic flux (Ca^{2+}, K^+, Na^+) -> Activation of proteolytic enzymes (e.g., Calpain, Calpase-3) -> Neurofilament sidearms loss and compaction -> Cytoskeletal collapse -> axotomy

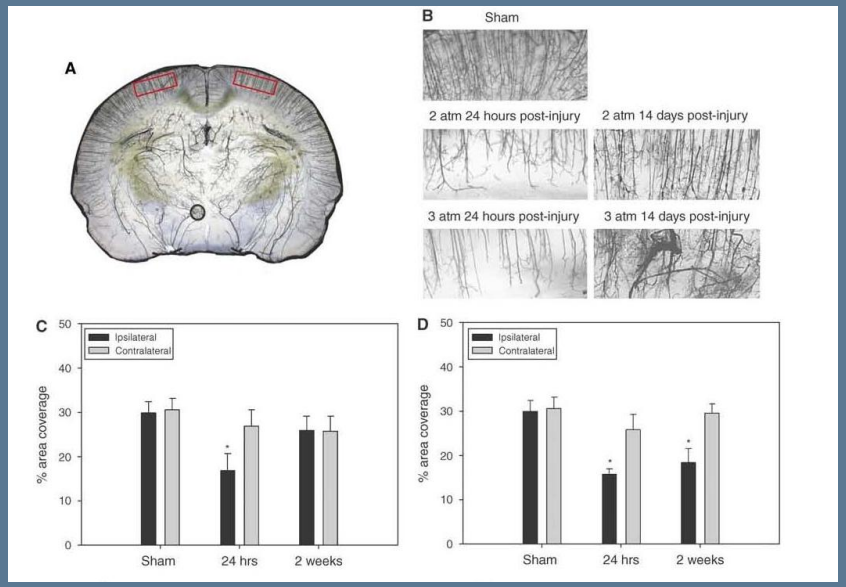
See work of Gennarelli, Povlishock, Wolf



Diffuse, secondary axonal injury may be the most common pathology which occurs over a span of weeks. Less severe version more common in mTBI.

TBI and Vasculature

- **Reduction in CBF (Soustiel & Sviri, 2007)**
- **Decoupling between CBF and oxidative metabolism (Vespa et al., 2005; Soustiel & Sviri, 2007)**
- **Animal work (Parks et al., 2009) suggests large changes in microvasculature**



2 atm 3 atm

(Parks et al., 2009; *J Cer Blood Flow & Metabolism*)

Considerations: Pediatric TBI

- **Neurodevelopment (ongoing myelination and excitatory neurotransmitter system)**
  - Baseline and subsequent recovery trajectory difficult to assess
- **Different injury biomechanics (fall versus motor vehicle accident), tissue mechanics (skull thickness, parenchymal water content), head-body weight ratio and musculo-skeletal**
- **Increased incidence of cerebral edema, diffuse white matter injuries & auto-dysregulation**
- **Recovery from pmTBI one month (Maugans et al., 2012) or 1 year post-injury (Yeates et al. 2012)?**

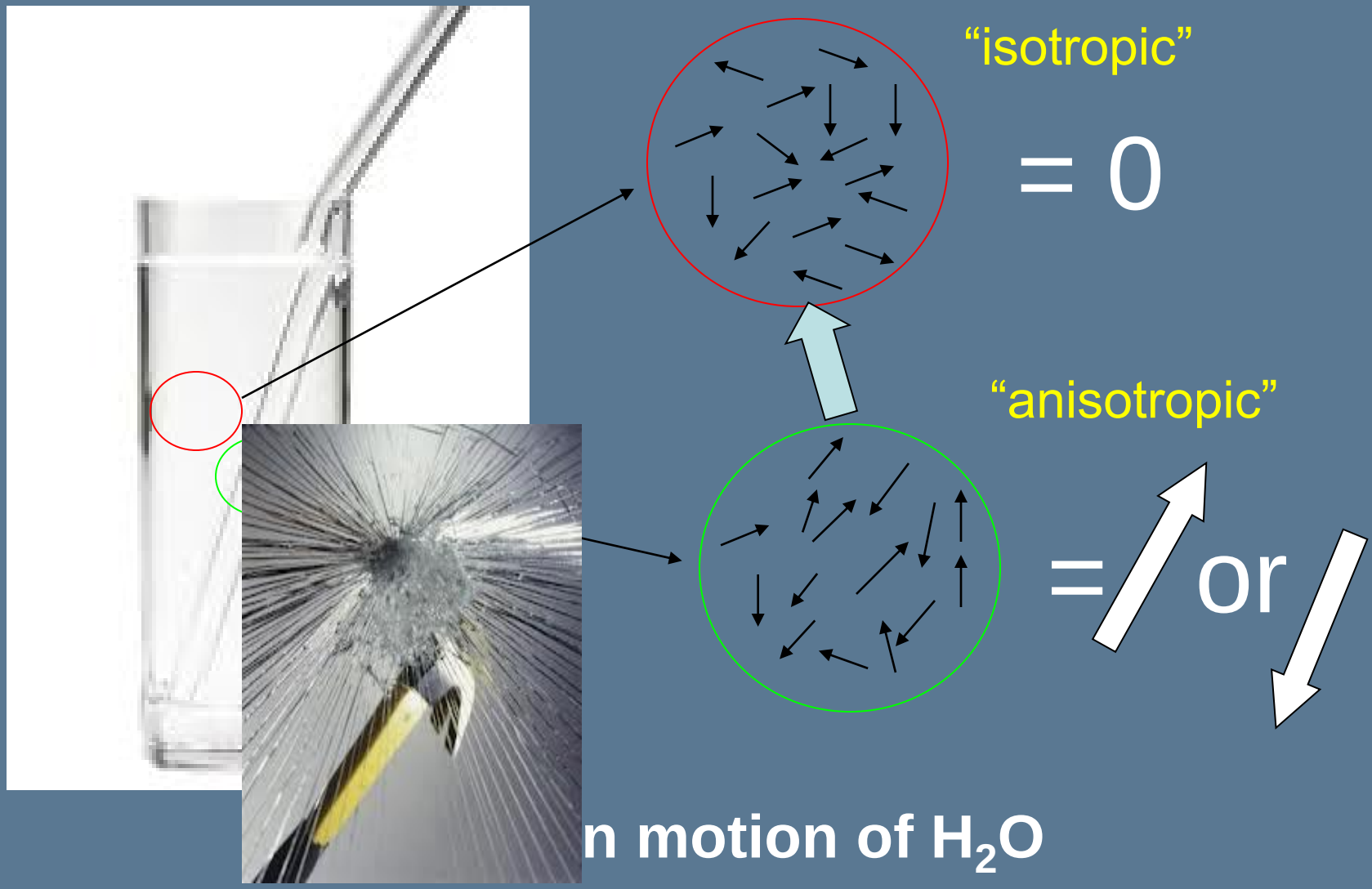
(Adelson and Kochanek, 1998; Giza et al., 2007; Kochanek, 2006)

Other Clinical Considerations

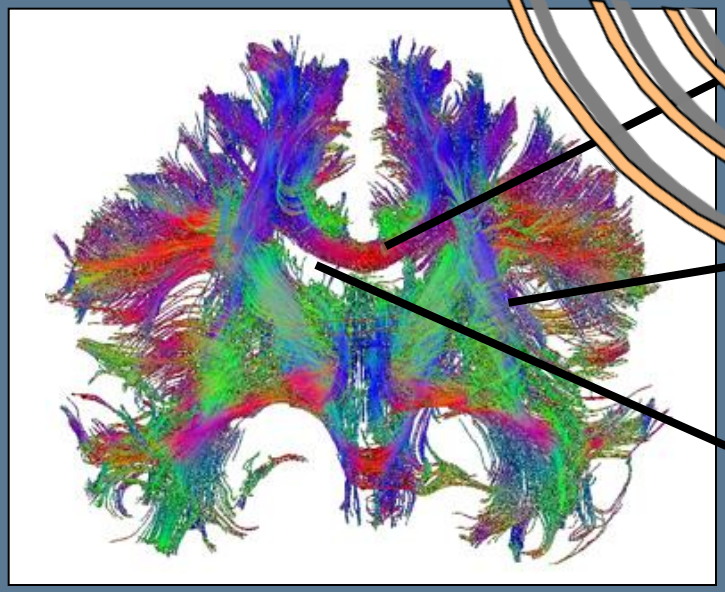
- **Heterogeneous injury in terms of biomechanical forces**
- **Recovery curve (time-post injury)**
  - Patients improve, some deteriorate, all at different rates

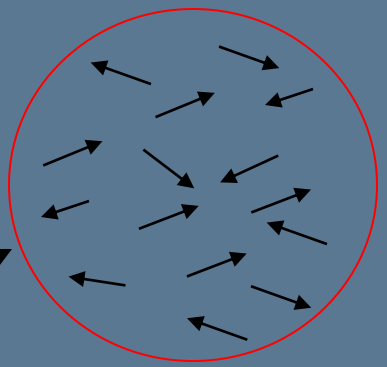
  - Majority of mTBI patients recover BUT majority of publications based on those who do not (i.e., special, non-representative population)
  - Effects of repetitive injuries unknown (from second impact syndrome to chronic traumatic encephalopathy)

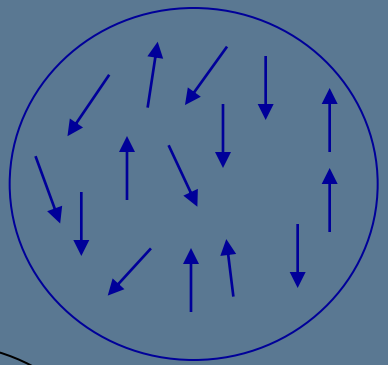
Diffusion Tensor Imaging

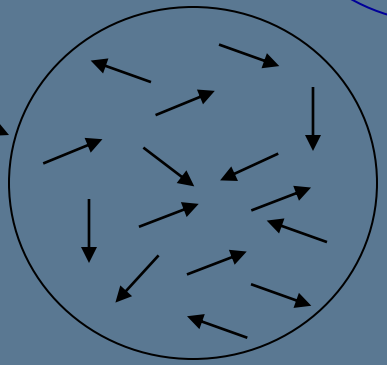


Diffusion Tensor Imaging









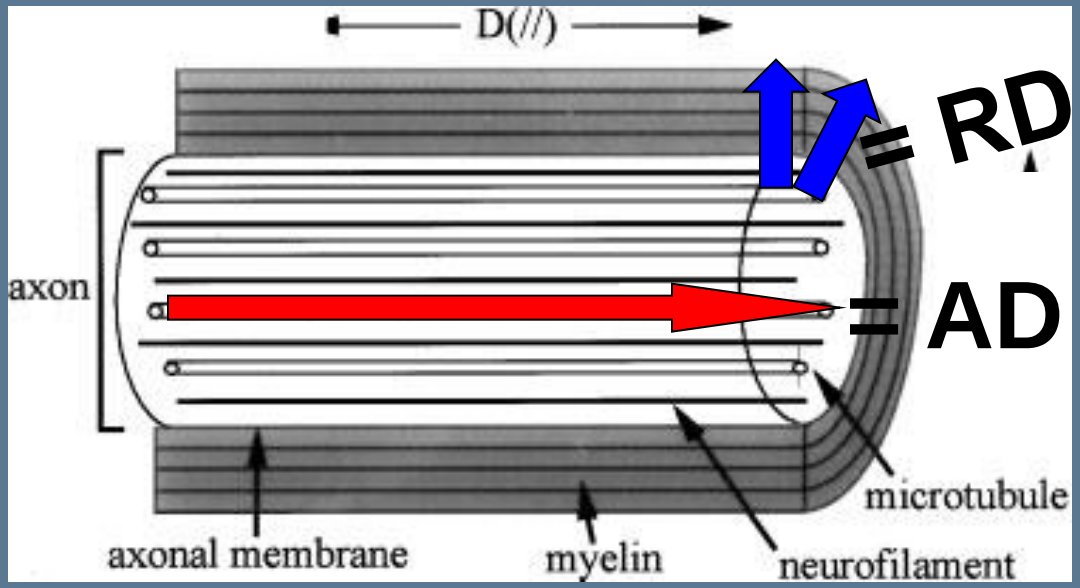
= 0

Diffusion Tensor Imaging: WM

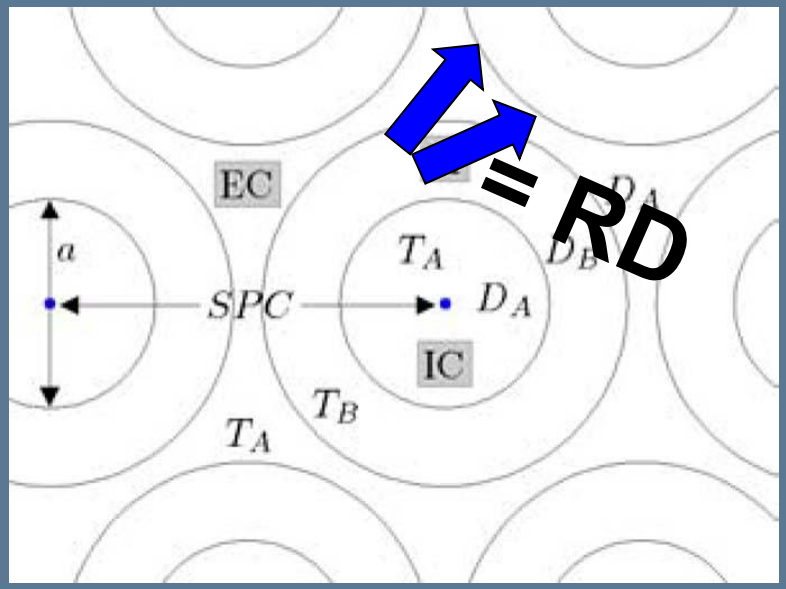
1) AD = λ_1

2) RD = (λ_1 + λ_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

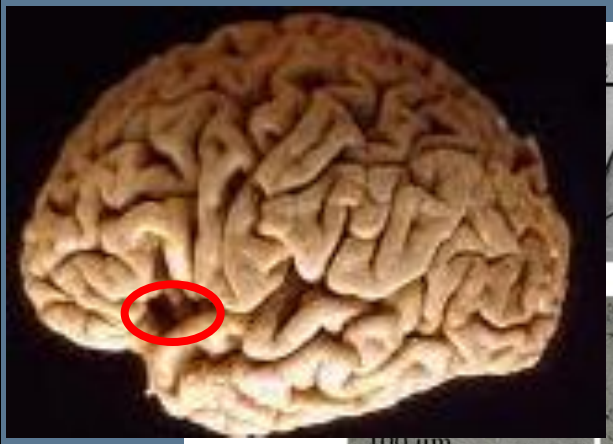


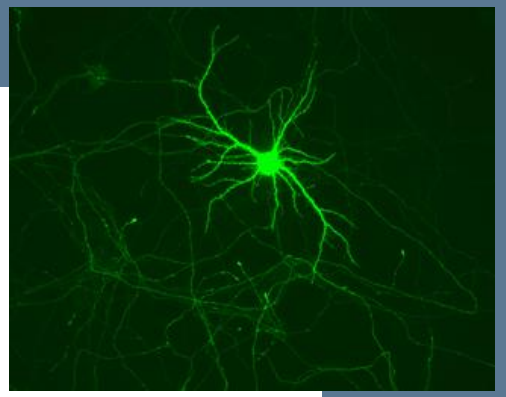
Peled, 2007

- **AD and RD may measure different pathology (Song et al., 2003; MacDonald et al., 2007)**
- **1.0 cubic micrometer = 1 x 10^{-9} microlitre**

Diffusion Tensor Imaging: GM

- **GM DTI (Albensi et al., 2000; Budde et al., 2011; Zhou et al., 2012)**

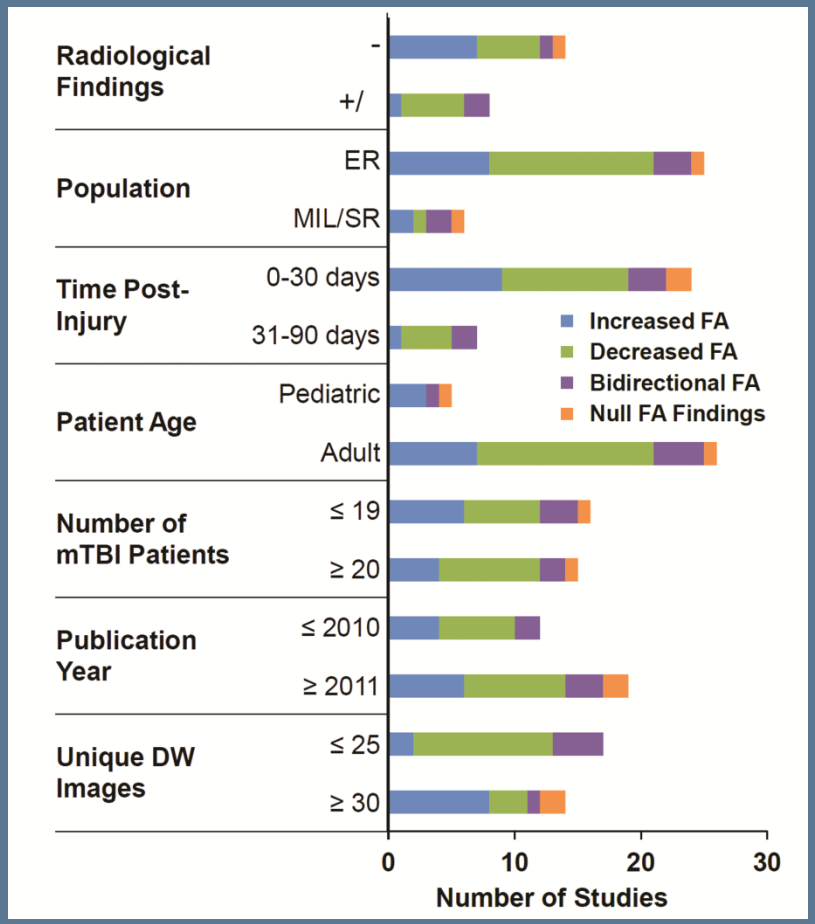




Zhou et al., 2012

pmTBI DTI and Structural Literature

- **Semi-acute WM DTI (Wilde et al., 2008 (3 related); McAllister et al., 2012; Maugans et al. 2012; Borich et al., 2013 (1 related); Murugavel et al., 2014)**

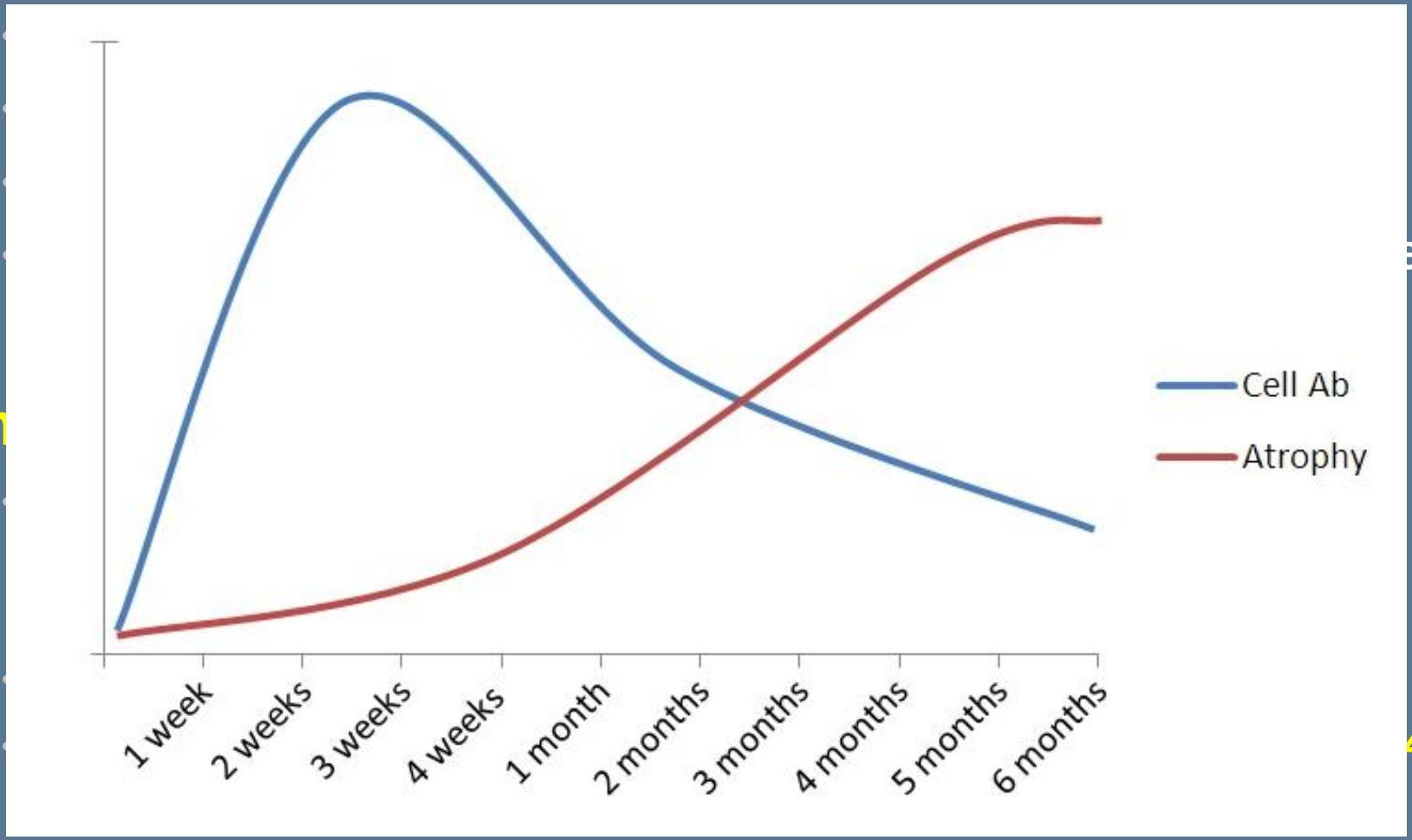


- **No pmTBI studies in semi-acute or chronic GM DTI**
- **No prospective studies of atrophy in semi-acute to chronic pmTBI**
- **Cross-sectional studies of chronic atrophy (Beauchamp et al., 2011 @ 10 years; Bigler et al. 2013 @ 2.7 years)**

Dodd et al., 2014; Journal of Neurotrauma

Study Inclusion Criteria

- **Participants**



Pediatric Clinical Sample

Age	Gender	Mechanism of Injury	AAN Rating	Days post-injury MRI	Days post-injury NP
12	male	SR	IIIb	20	20
14	male	Fall	III	20	19
12	male	Fall	IIIa	8	8
15	male	SR	IIIa	14	14
14	male	Fall	IIIa	19	19
14	male	MVA	IIIa	11	12
16	male	MVA	IIIb	19	20
17	male	SR	II	15	15
12	male	Fall	IIIa	17	17
12	male	Fall	IIIb	21	21
10	male	SR	IIIa	18	18
10	female	SR	II	7	7
14	male	SR	II	18	14
14	male	SR	IIIa	9	9
17	female	SR	II	20	17
13	male	SR	II	21	19

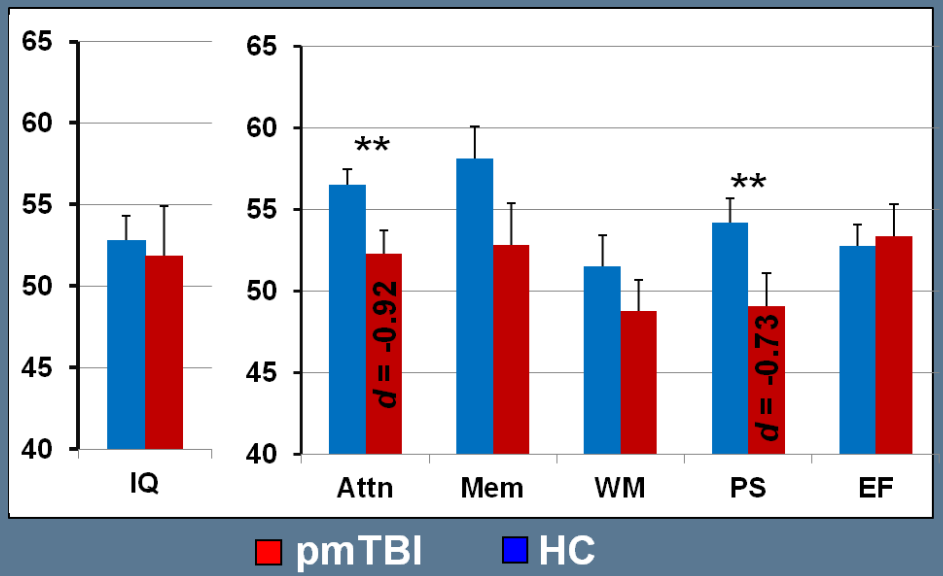
Note: MVA = motor vehicle accident; SR = sports/a AN
Academy of Neurology; and NP = neuropsychological testing

16.06 ± 4.82

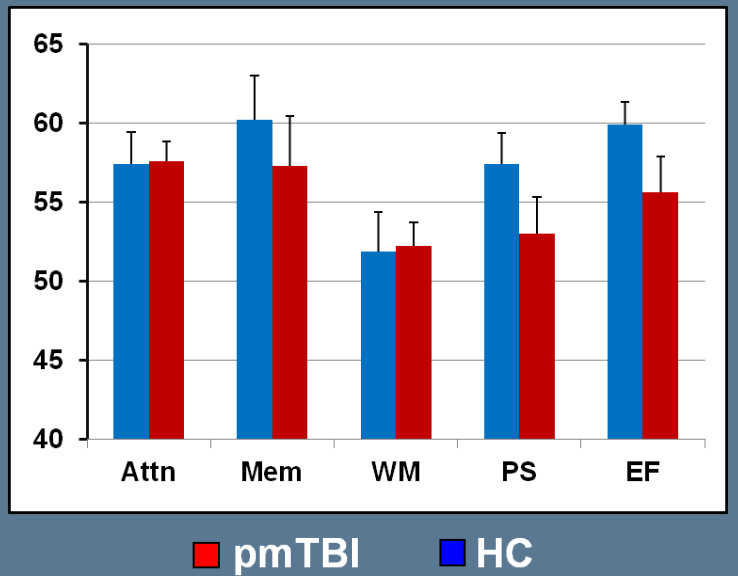
15.56 ± 4.52

Pediatric Clinical Results

- Visit 1 (pmTBI = 15; HC = 15)



V2 (pmTBI = 10; HC = 10)

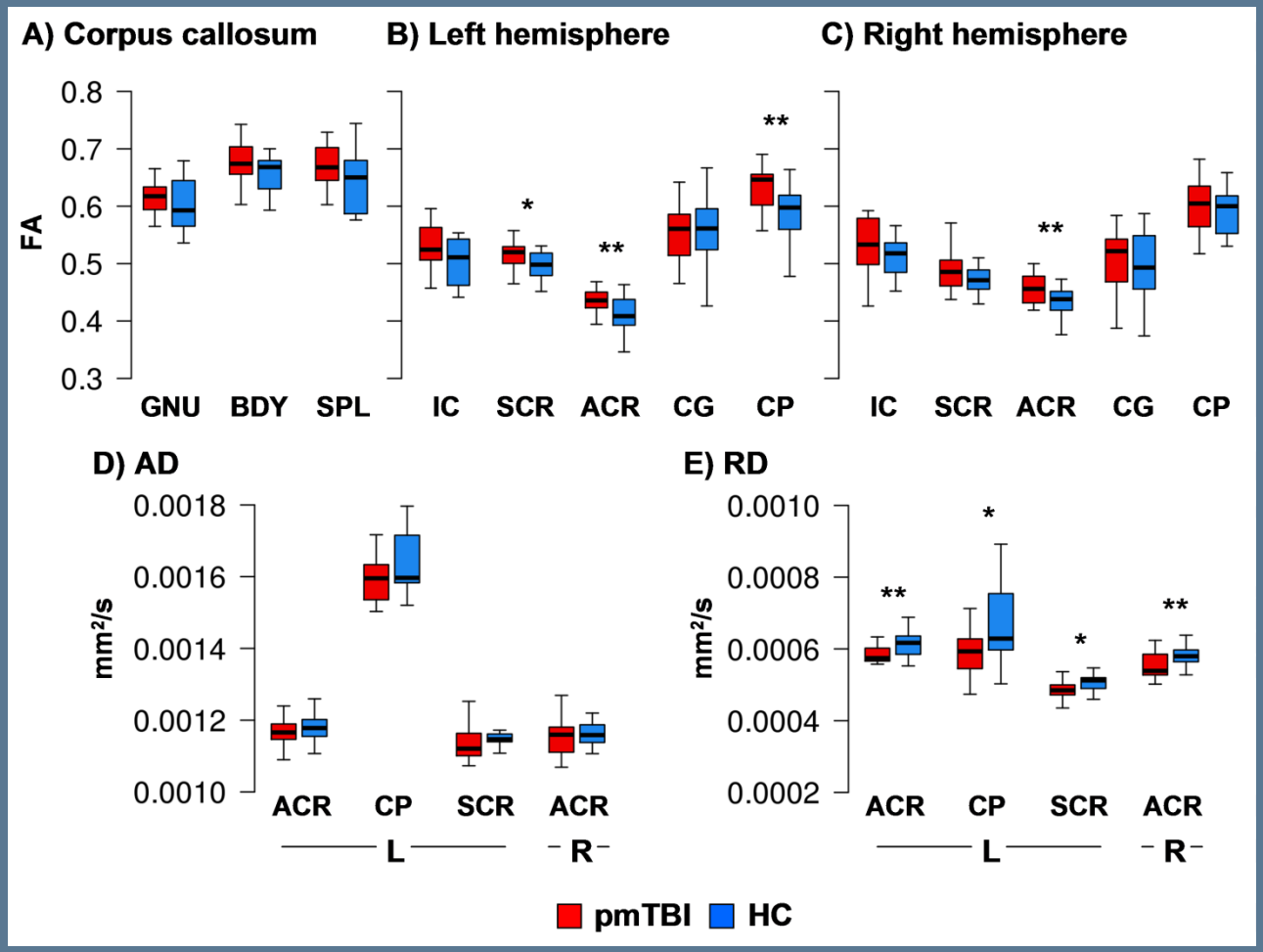


- **Hx of previous pmTBI, IQ & Demographic factors = N.S.**
- **Child/parent report = N.S.**
- **Neurocognitive Testing = $p < 0.05$ at V1 and N.S. at V2 (Attn d = 0.03; PS d = -0.64)**
- **0% positive findings on CT or MRI (T_1/T_2/SWI)**

Mayer et al., 2012; *Journal of Neuroscience*

WM DTI Results

- FA and RD Results (pmTBI = 15; HC = 15)

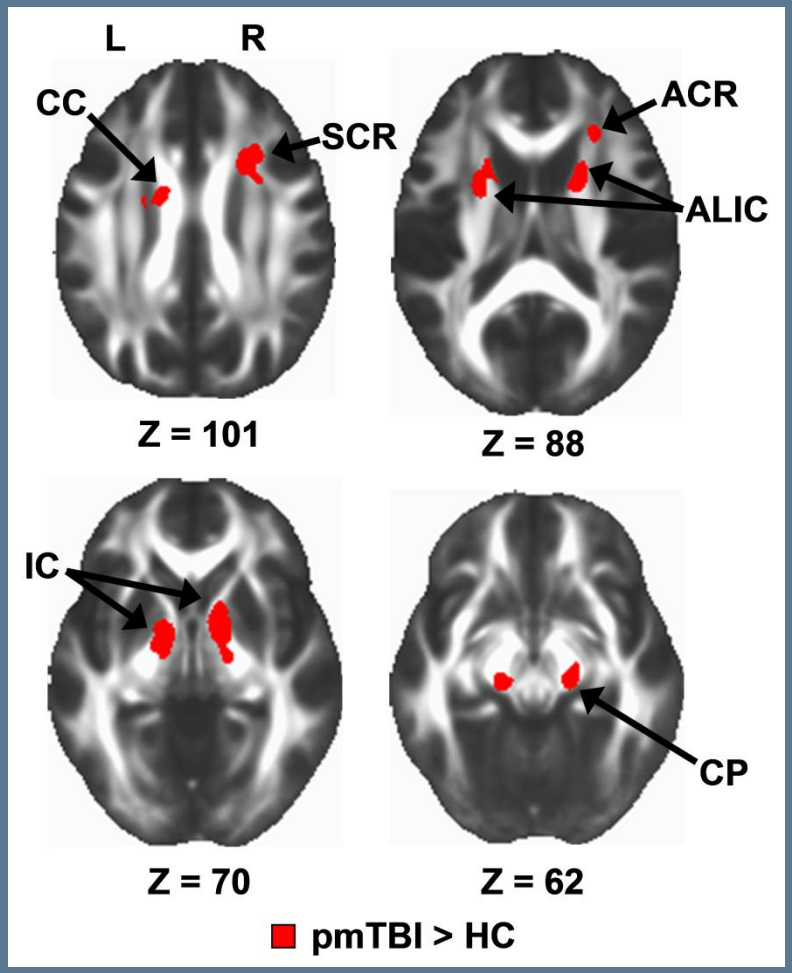


- Increased FA & decreased RD in ROI analyses
- Classify 13/15 pmTBI patients and 14/15 HC*
- Increased FA also present in voxel-wise analyses

Mayer et al., 2012; *Journal of Neuroscience*

WM DTI Results

- FA and RD Results (pmTBI = 15; HC = 15)

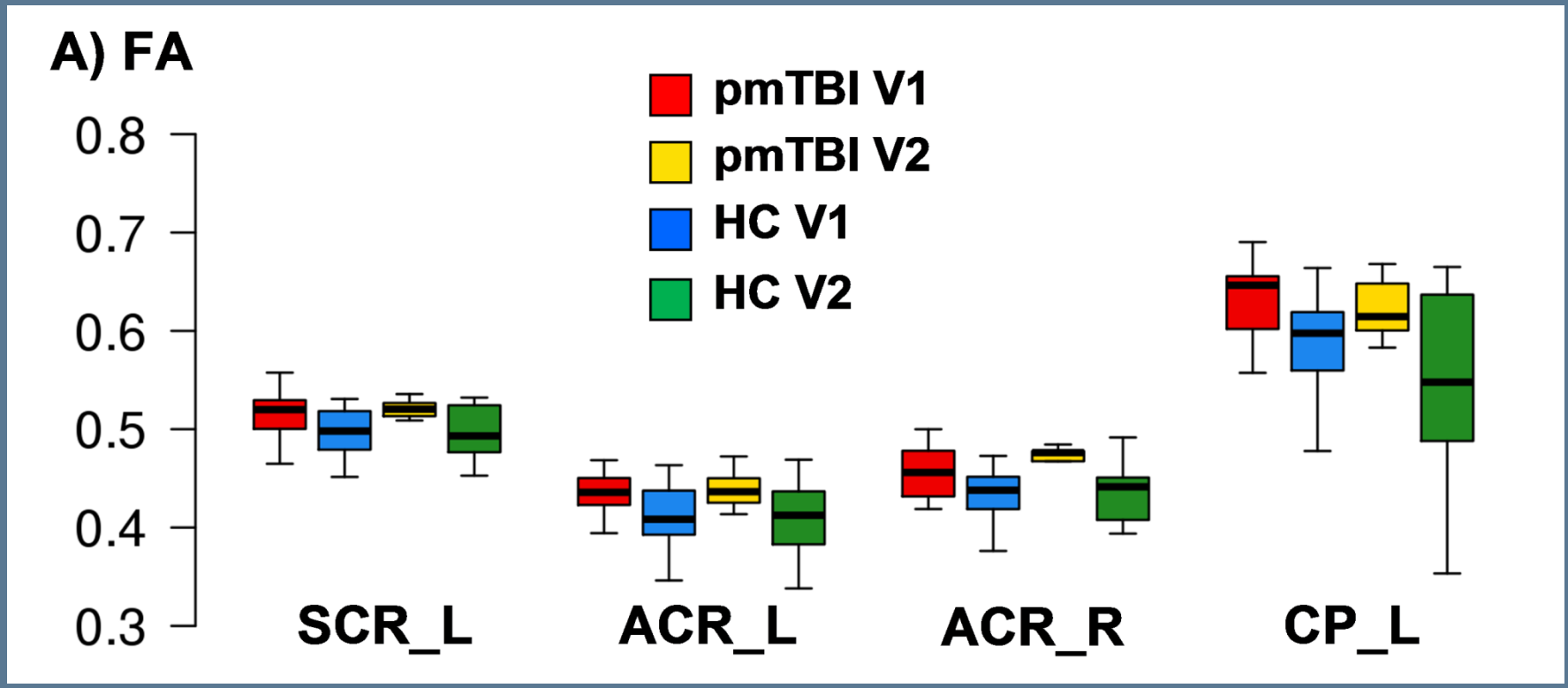


- Increased FA & decreased RD in ROI analyses
- ROI data classify 13/15 pmTBI patients and 14/15 HC
- Increased FA also present in voxel-wise analyses

Mayer et al., 2012; *Journal of Neuroscience*

WM DTI Results

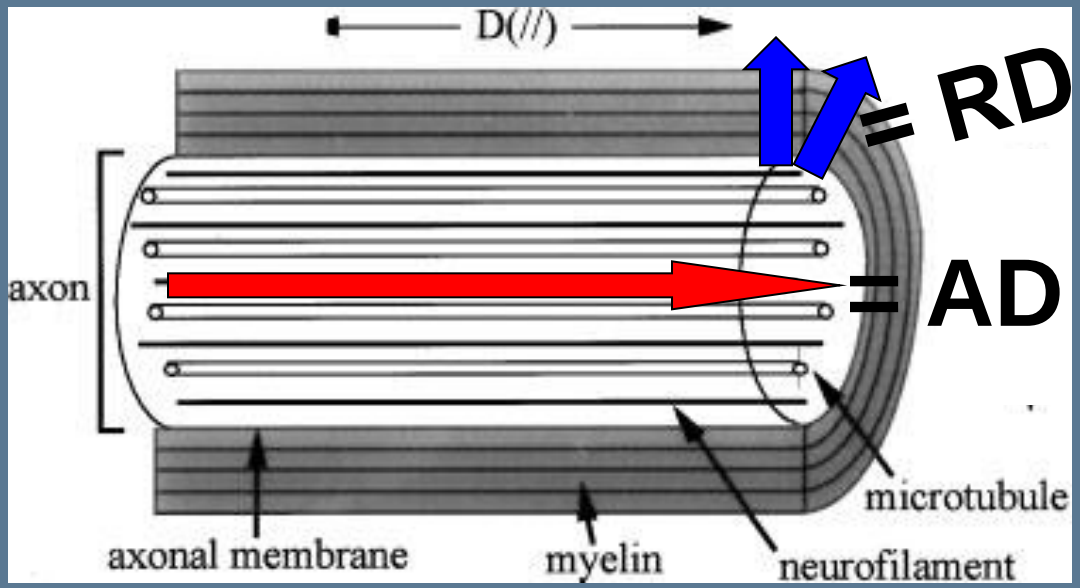
- FA Visit 2 Results (pmTBI = 10; HC = 10)



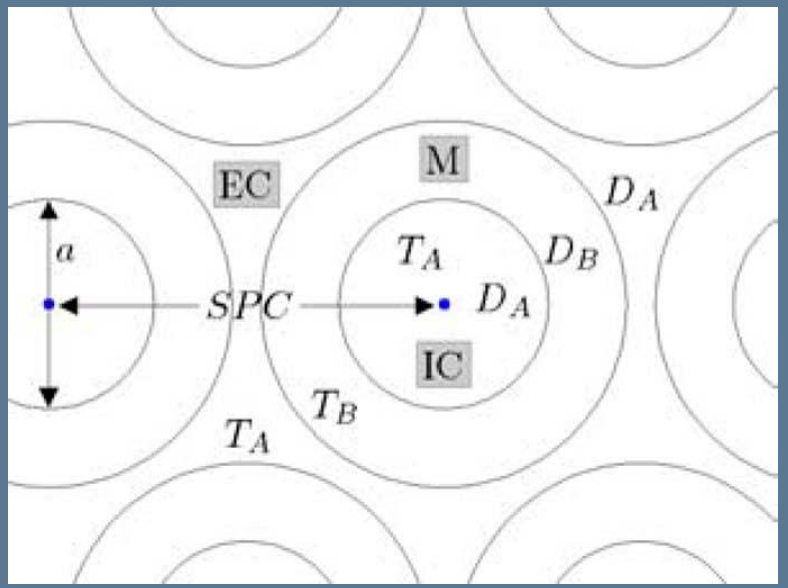
- Non-significant changes in FA across 4 month window

Mayer et al., 2012; *Journal of Neuroscience*

DTI Summary: WM



Beaulieu, 2001

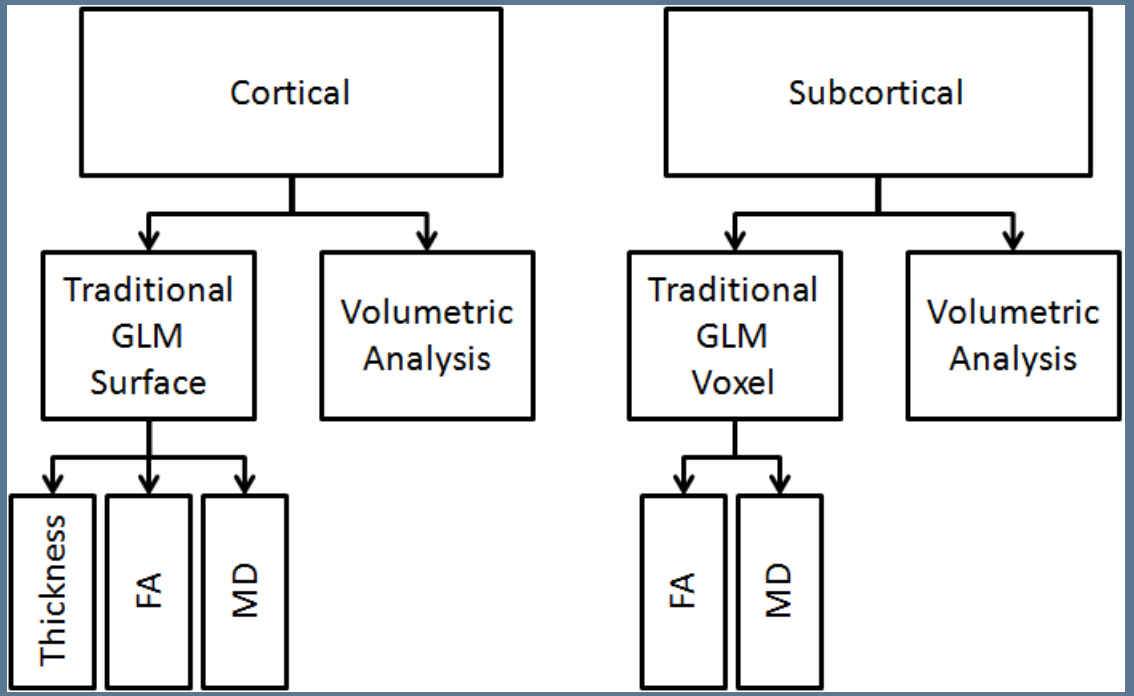


Peled, 2007

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

Image Methods: GM

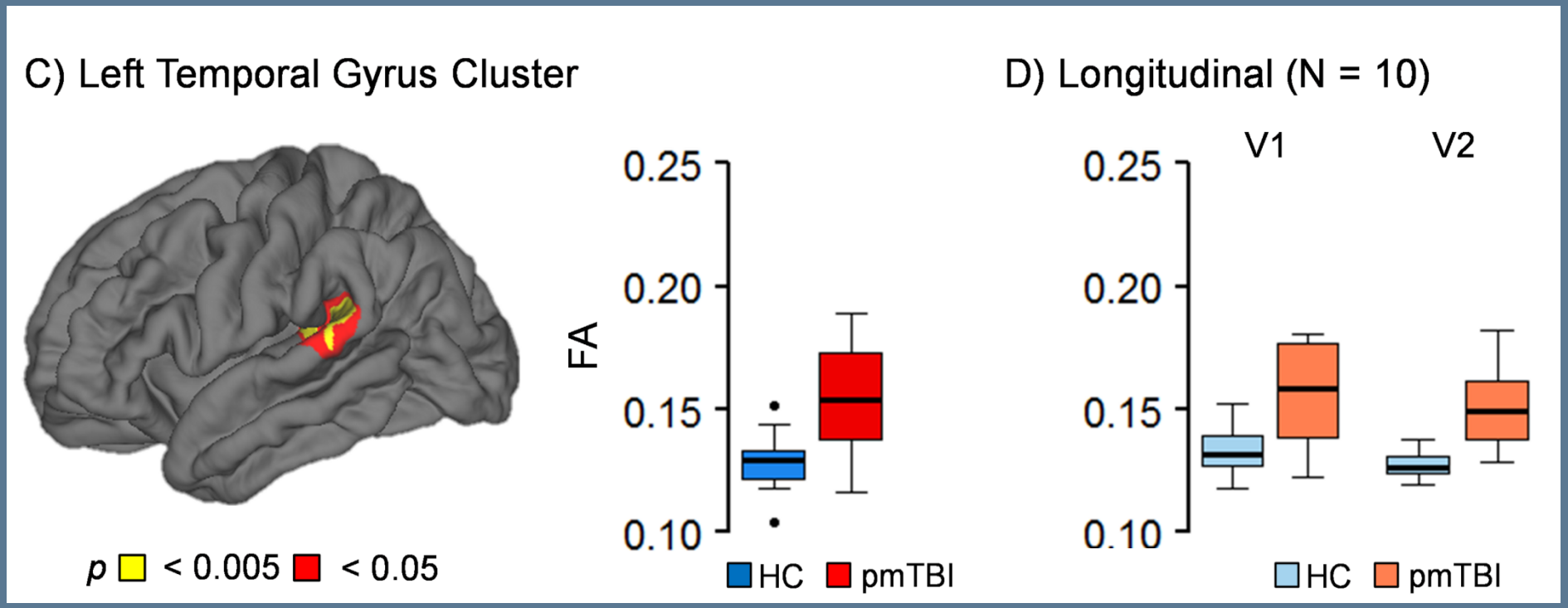
- FreeSurfer (v 5.1) with longitudinal pipeline
- ROI (cortical and sub-cortical) and surface-based (cortical) analyses (10 mm FWHM)
- 30 DWI; b = 800



Mayer et al., in press; *Journal Neurotrauma*

FA Findings

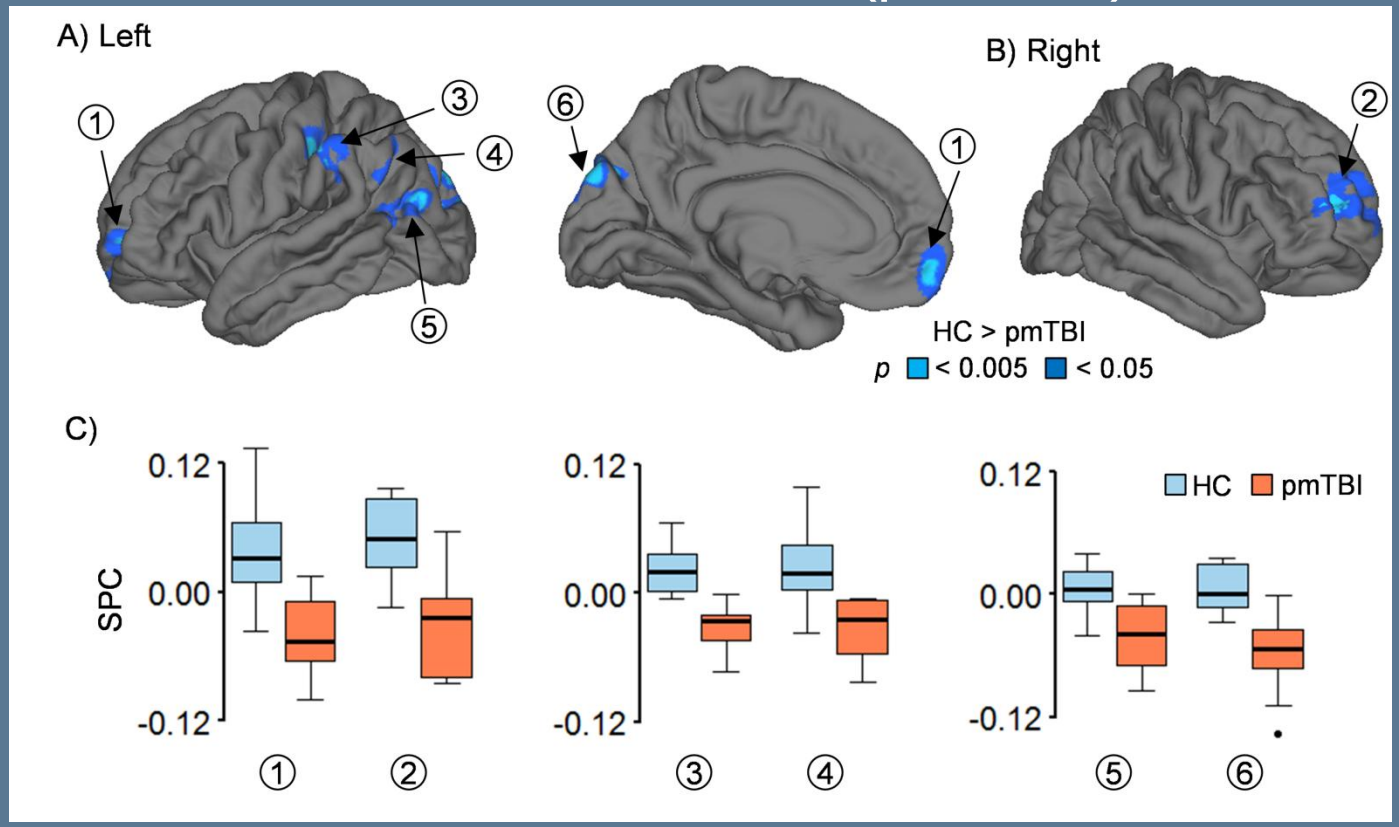
- V1: Increased FA (mTBI > HC) in right thalamus, L MTG
- FA associated with attention but not PS across both groups
- No change as function of time at V2 (mTBI > HC)



Mayer et al., in press; *Journal of Neurotrauma*

Atrophy Findings

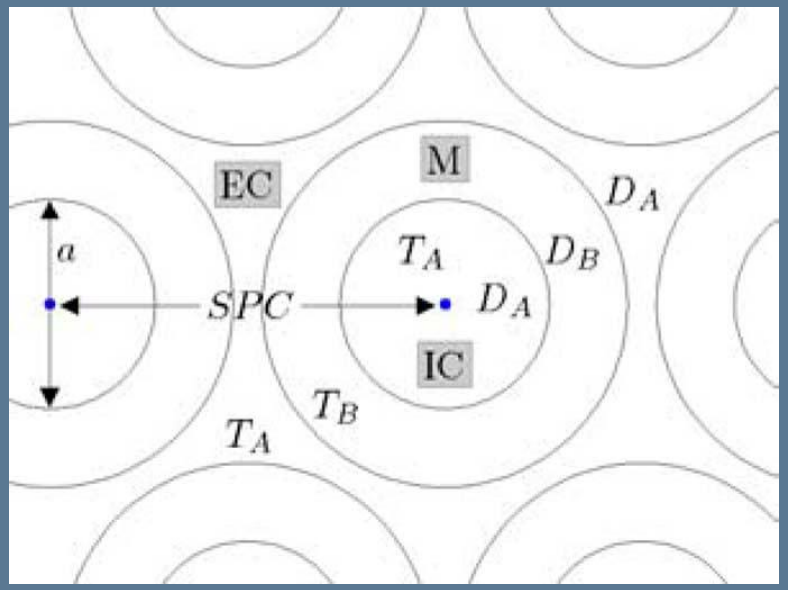
- No thickness differences at V1 (p > 0.10)
- Increased rate of change (normalized V2 – V1) for HC relative to pmTBI
- No subcortical volume differences (p > 0.10)



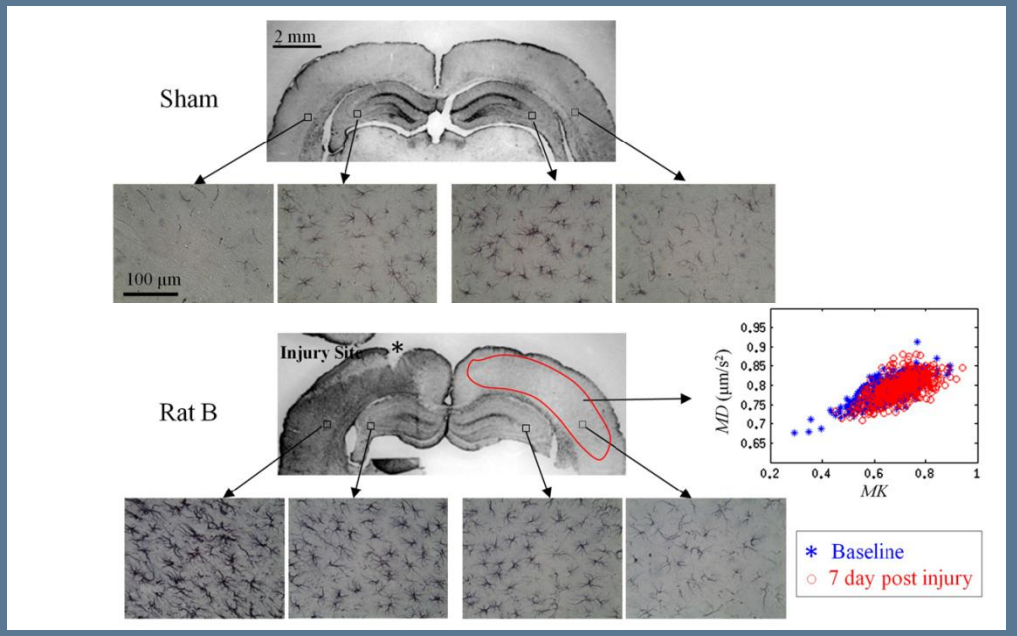
Mayer et al., in press; *Journal of Neurotrauma*

Summary: GM Findings in mTBI

- ↗ gray matter FA in adults (Bouix et al., 2013; Ling et al., 2013) and animal studies (Albensi et al., 2000; Budde et al., 2011; Zhou et al., 2012)
- Reports of decreased thalamic FA in chronic/mixed injury populations (Little et al., 2010; Grossman et al., 2011)



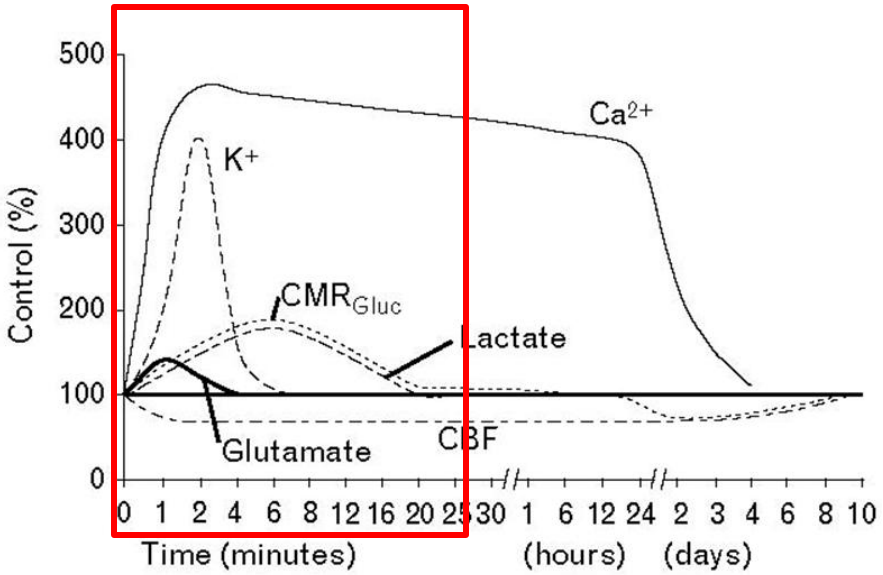
Peled, 2007



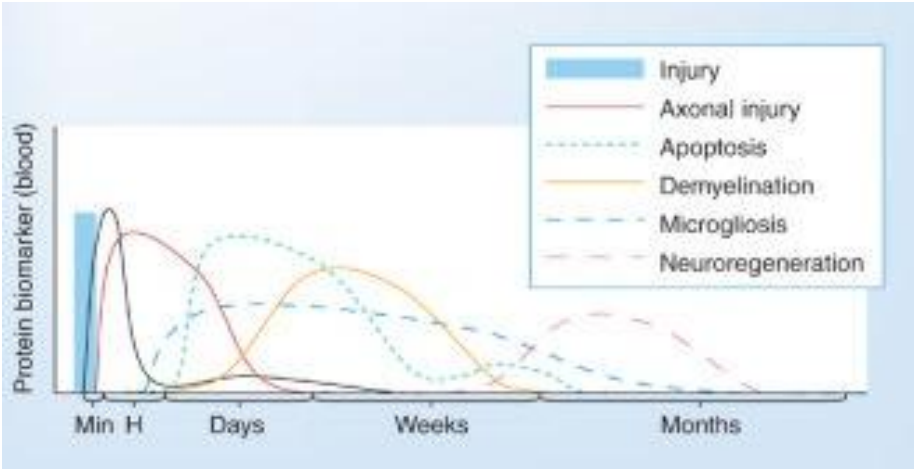
Zhou et al., 2012

- Increased FA secondary to cytotoxic edema or potentially a reactive gliosis (Budde et al., 2011; Zhou et al., 2012)
- First prospective study of atrophy in pmTBI (Bigler et al., 2013 null)

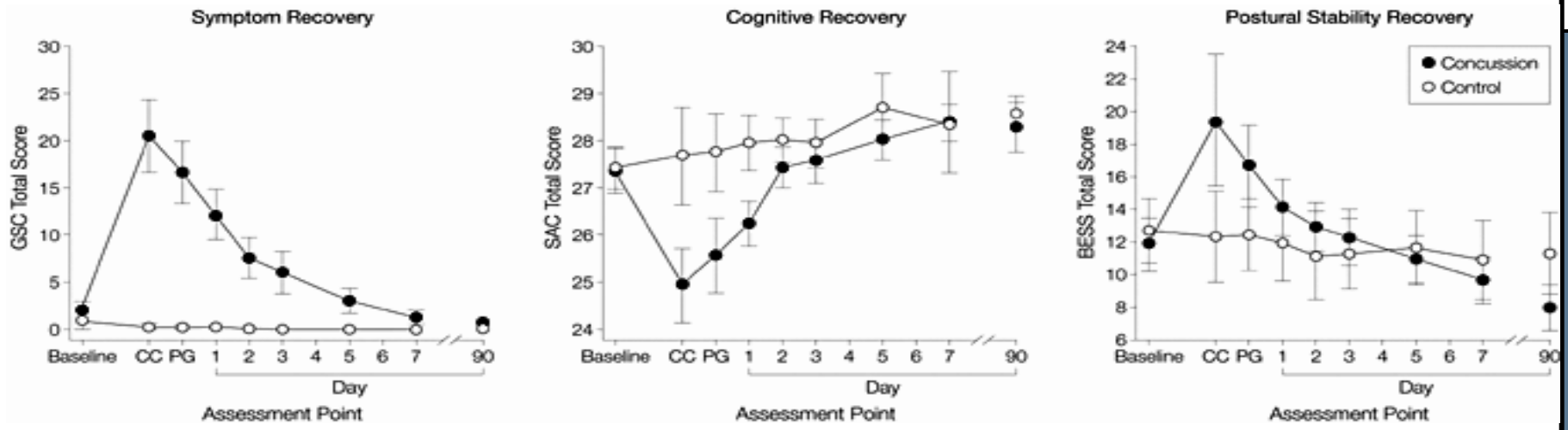
Temporal Dynamics



Giza and Hovda



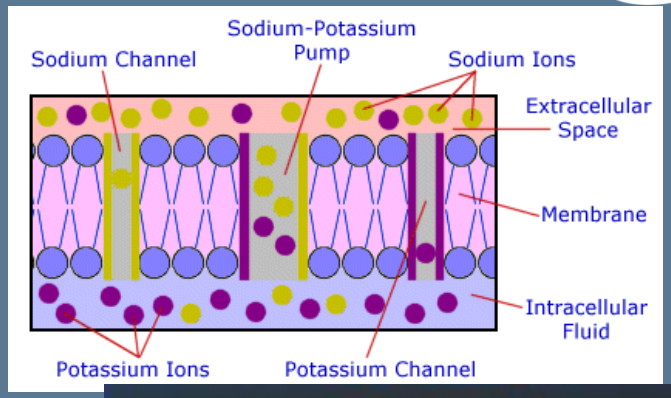
Mondello et al., 2011

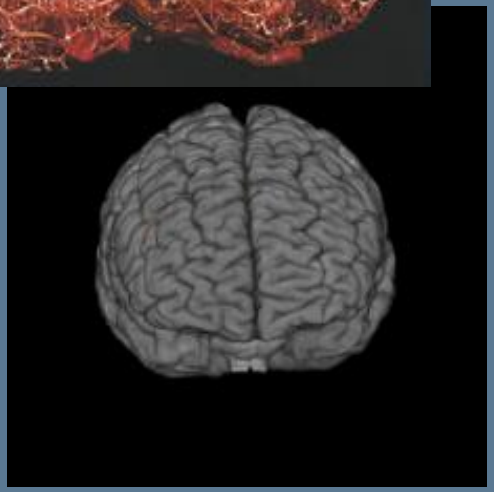


McCrea, M. et al. JAMA 2003;290:2556-2563

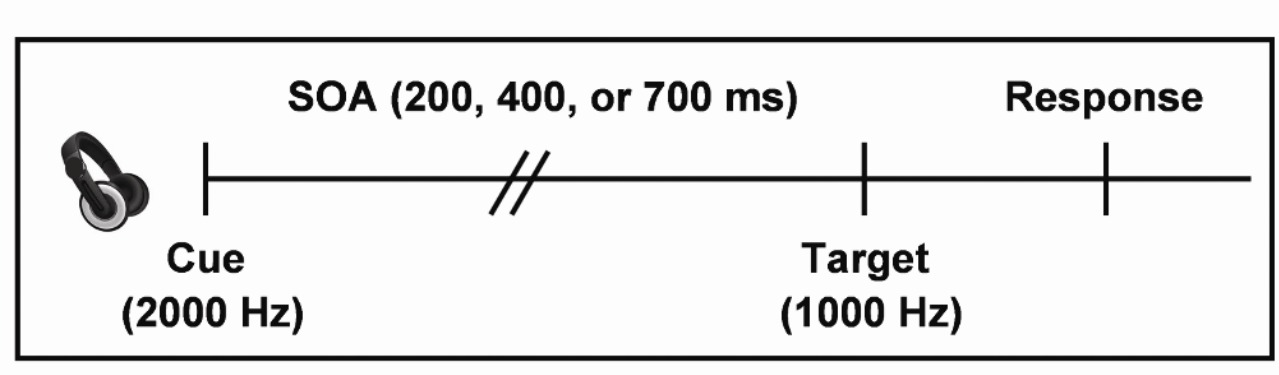
Evoked Functional MRI (fMRI)

- **BOLD = indirect (hemodynamic) measure of neuronal activity**
- **Increased metabolic demands (NA^+/K^+ pump), excitatory trans-mission and/or Glu v. Gln shuttling**
- **Vasculature response (CBF, CBV, deoxyHb ($CMRO_2$))**
- **Alters dephasing of protons (basis for BOLD signal)**
- **Traditionally used with cognitive task, now used at rest**





fMRI: Auditory Orienting Task

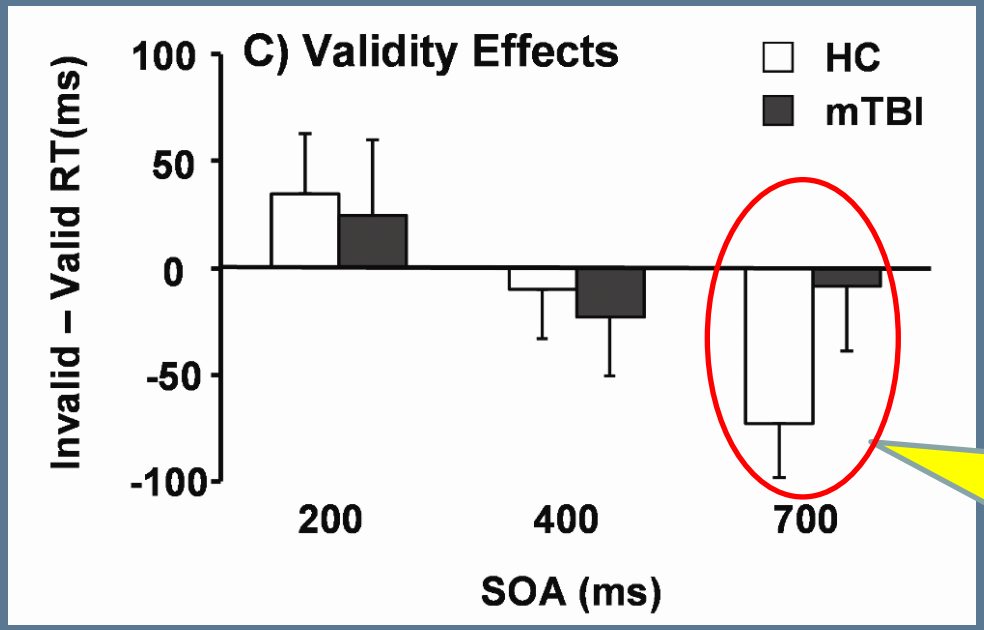


- Rapid event-related design (N = 14)
- Group (mTBI & HC) x Validity (Valid & invalid) x SOA (200,400, &700ms) mixed ANOVA
- Exogenous orienting: 50% valid & 50% invalid trails

Yang et al., 2012; *Journal of Neurotrauma*

fMRI: Behavioral Data

- **Validity Effect score (invalid – valid RT)**
- 700 ms SOA effect size = 0.62
- HC exhibit IOR but not mTBI.

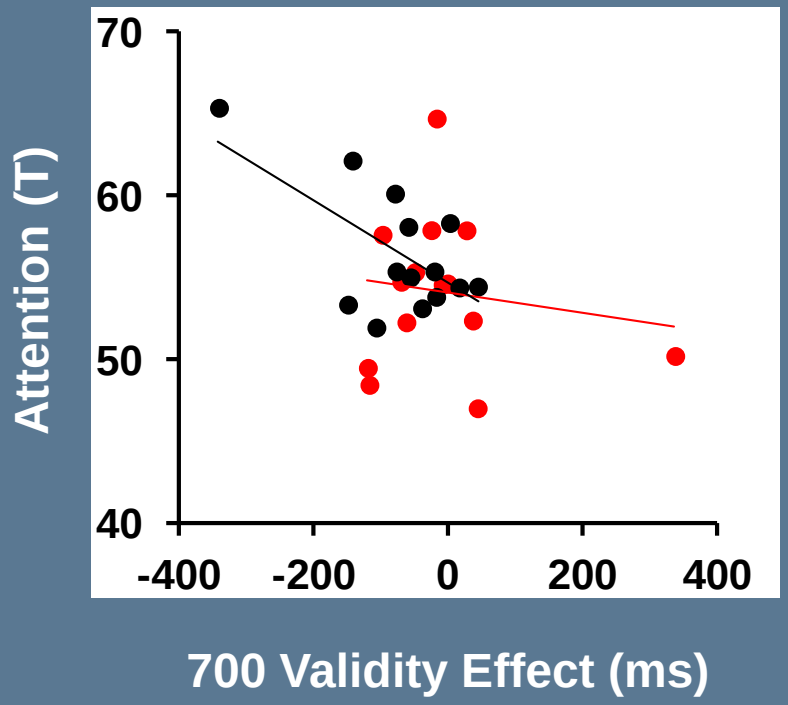


Trend deficits in IOR

Yang et al., 2012; *Journal of Neurotrauma*

fMRI: Behavioral Data

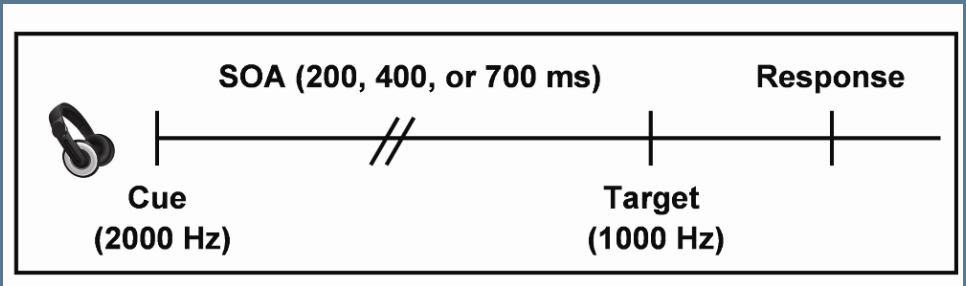
- **HC: r = -0.63 p = 0.02**
  - **mTBI: p > 0.10**

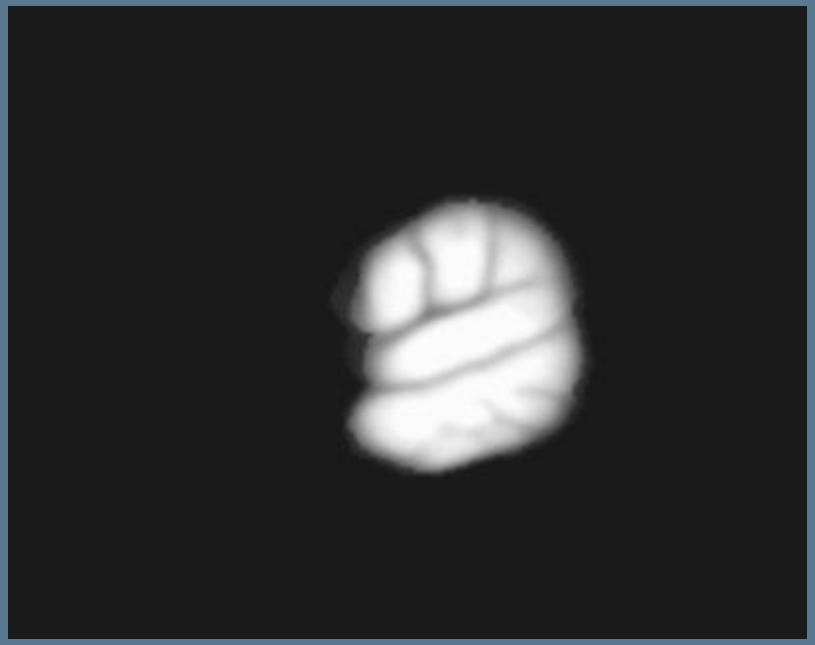


A potential disruption of the relationship between basic orienting function and everyday cognitive function in pmTBI

Yang et al., 2012; *Journal of Neurotrauma*

Evoked fMRI: Results and Replication

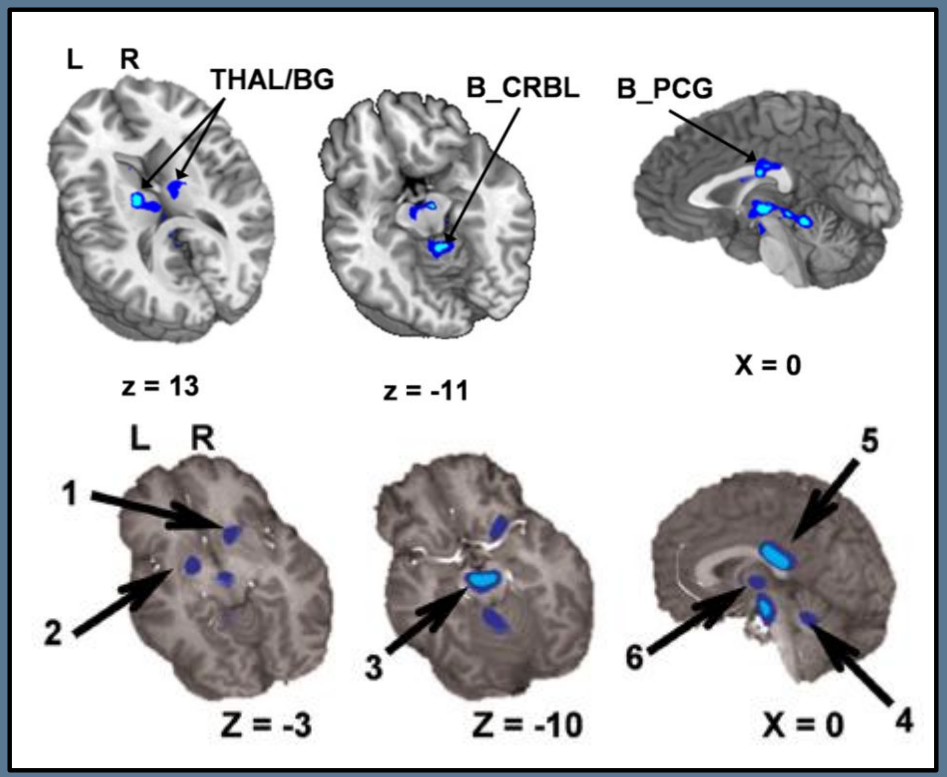




Teshiba et al., 2012

pmTBI

mTBI



Replication in adult (Mayer et al., 2009; N = 16) and pediatric (Yang et al., 2012; N = 14) and mTBI samples

Overall Conclusions

- **Neuropsychological results and traditional MRI not very sensitive (for detecting injury??) or recovery occurs on a different time-scale**
- **Neuroimaging biomarkers have different sensitivity/specificity that may be time-varying (different recovery curves)**
- **Heterogeneous injury profiles following pmTBI require more clever analytic techniques**
- **Caveats: Small N with multiple tests, limited anatomical battery, macroscopic measures of microscopic processes**

Overall Conclusions

- **Neuropsychological results and traditional MRI not very sensitive (for detecting injury??) or recovery occurs on a different time-scale**
- **Neuroimaging biomarkers have different sensitivity/specificity that may be time-varying (different recovery curves)**
- **Heterogeneous injury profiles following pmTBI require more clever analytic techniques**
- **Caveats: Small N with multiple tests, limited anatomical battery, macroscopic measures of microscopic processes**

Overall Conclusions

- **Neuropsychological results and traditional MRI not very sensitive (for detecting injury??) or recovery occurs on a different time-scale**
- **Neuroimaging biomarkers have different sensitivity/specificity that may be time-varying (different recovery curves)**
- **Heterogeneous injury profiles following pmTBI require more clever analytic techniques**
- **Caveats: Small N with multiple tests, limited anatomical battery, macroscopic measures of microscopic processes**

Overall Conclusions

- **Neuropsychological results and traditional MRI not very sensitive (for detecting injury??) or recovery occurs on a different time-scale**
- **Neuroimaging biomarkers have different sensitivity/specificity that may be time-varying (different recovery curves)**
- **Heterogeneous injury profiles following pmTBI require more clever analytic techniques**
- **Caveats: Small N with multiple tests, limited anatomical battery, macroscopic measures of microscopic processes**

“Expectation as an Etiology”-Mittenberg

- Does not account for all long-term effects of pmTBI

Collaborators

Mind Research Network

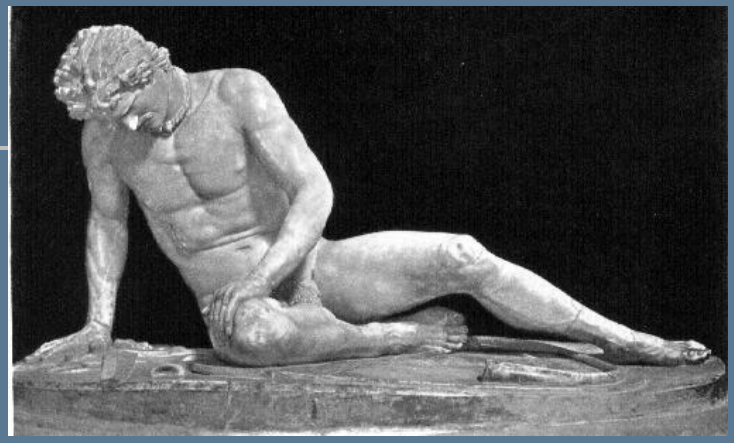
Josef Ling
Terri Teshiba
Stefan Klimaj
Andrew Dodd, M.S.
Zhen Yang, PhD
Arvind Caprihan, PhD
Faith Hanlon, Ph.D.

University of New Mexico

Charles Gasparovic, PhD
John Phillips, MD
Silas Bussman
David Doezema, MD
Ross Reichard, MD
Ron Yeo, PhD

Acknowledgements. Supported by the following grants to AM: The Mind Research Network DOE Grant DE-FG02-99ER62764, NIH/AEN R24-HD050836, NIH R21-NS064464-01A1, and NIH 3R21NS064464-01A1S1

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, trephinning 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.