Advanced Imaging Methods for Early Microstructural and Metabolic Changes Following Traumatic Brain Injury

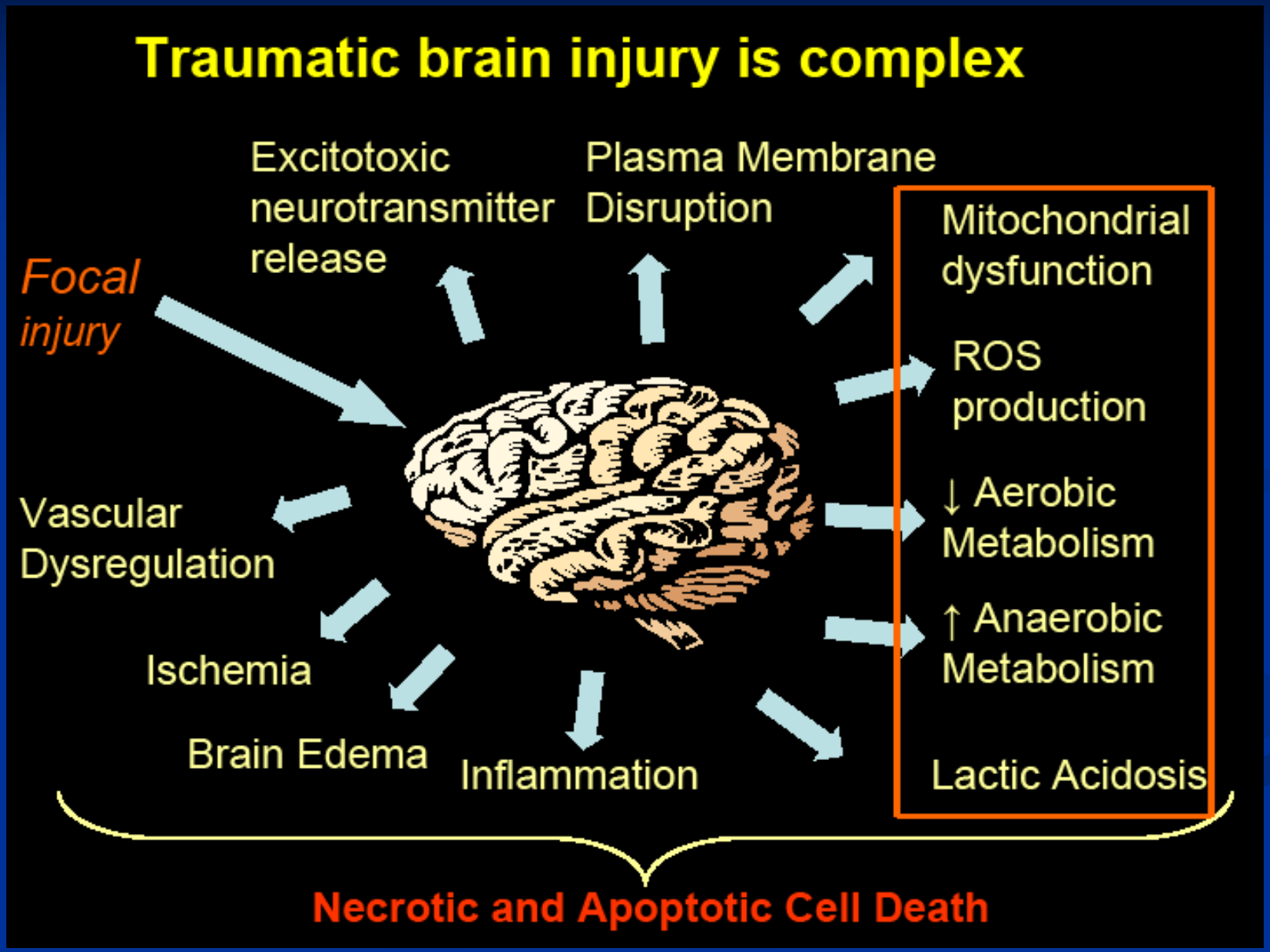
Rao P Gullapalli

Department of Diagnostic Radiology & Nuclear Medicine

University of Maryland School of Medicine

Baltimore, MD 21201

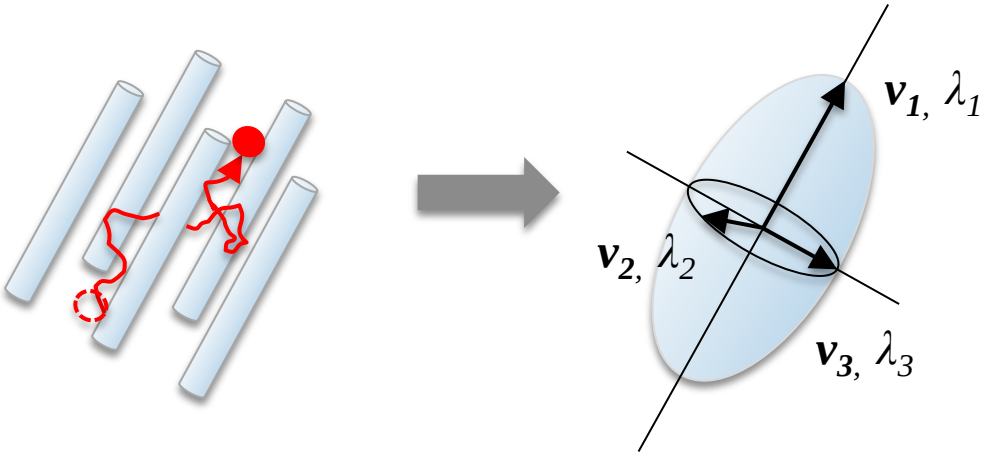
The Problem!


Traumatic brain injury is complex
Excitotoxic neurotransmitter release
Plasma Membrane Disruption
Focal injury
Mitochondrial dysfunction
ROS production
↓ Aerobic Metabolism
↑ Anaerobic Metabolism
Lactic Acidosis
Vascular Dysregulation
Ischemia
Brain Edema
Inflammation
Necrotic and Apoptotic Cell Death

Diffusion Tensor Imaging

- Understanding tissue alterations at an early stage following traumatic brain injury (TBI) is critical for injury management and prevention of more severe secondary damage to the brain.

- Diffusion tensor imaging (DTI) is a powerful tool for studying white mater microstructure change.



- DTI has been used extensively in evaluating axonal damage following TBI.

Magnetic Resonance Spectroscopy

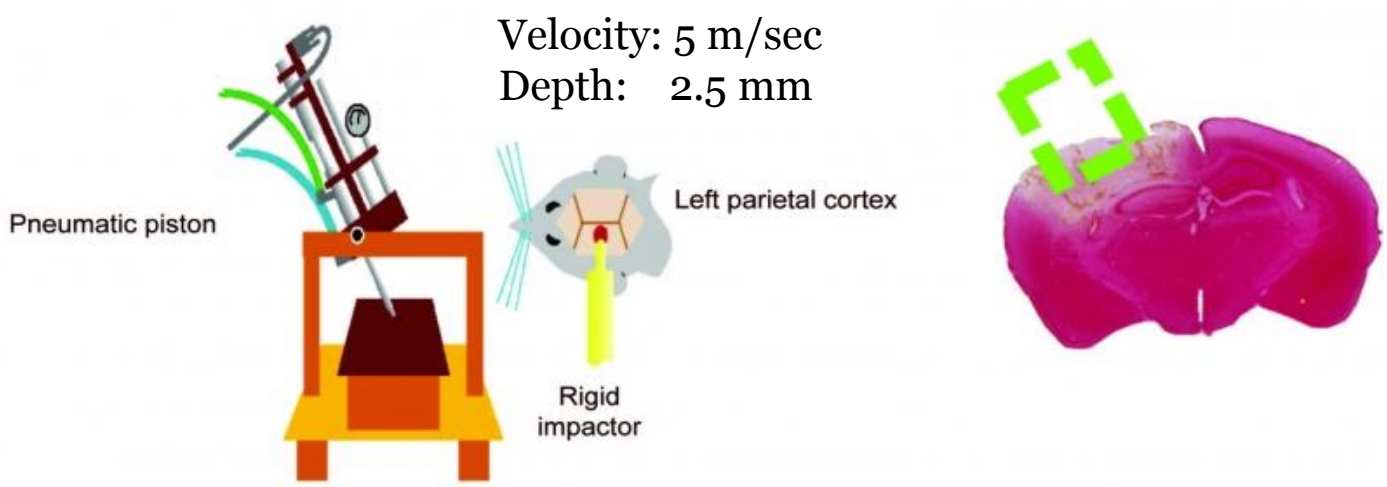
- Provides a non-invasive assessment of tissue metabolites in vivo.
- Sensitive to various metabolites including
  - N-acetylaspartate – neuronal marker
  - Choline – synthesis & breakdown of cell membranes
  - Creatine – related to metabolic energy
  - Lactate – indicator of hypoxic conditions
  - Myo-inositol – sensitive to osmoregulatory changes
  - Glutamate/Glutamine – neuronal transmission

Injury Models

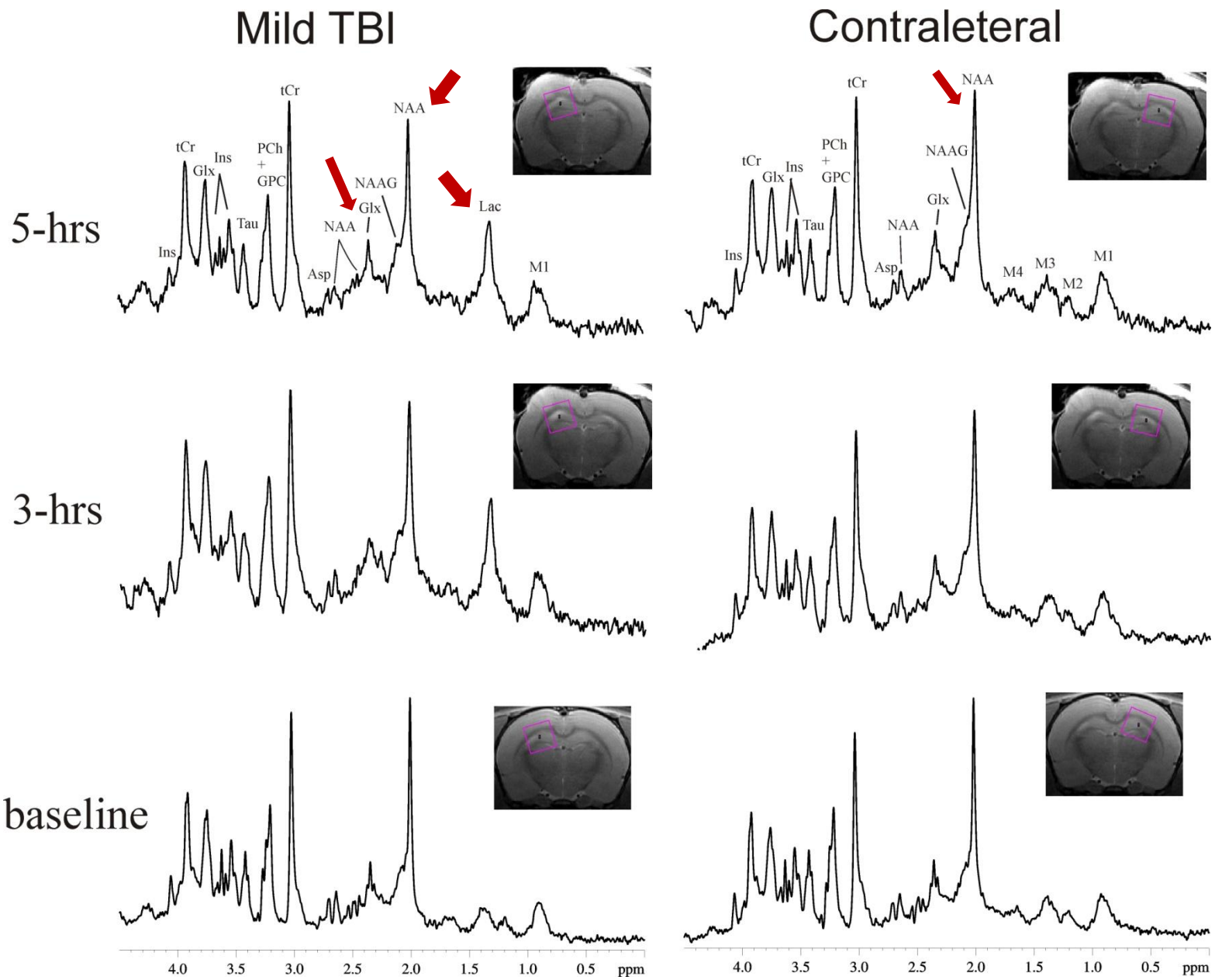
- Controlled Cortical Impact
- Under Belly Blast: Fourney-Fiskum Model
- Blast Overpressure: Simard-Gerzanich Model

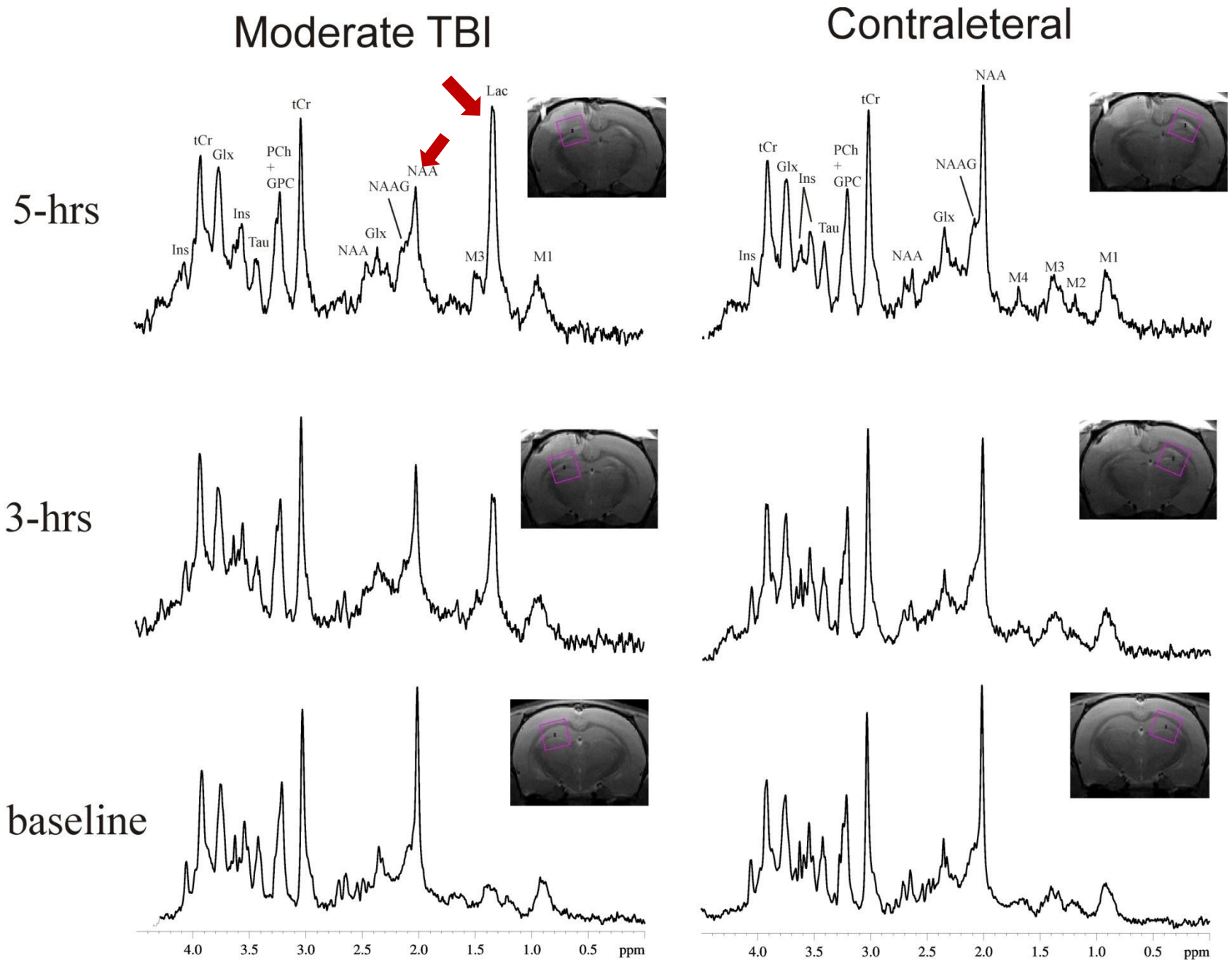
Controlled Cortical Impact

Controlled Cortical Impact (CCI) injury model*

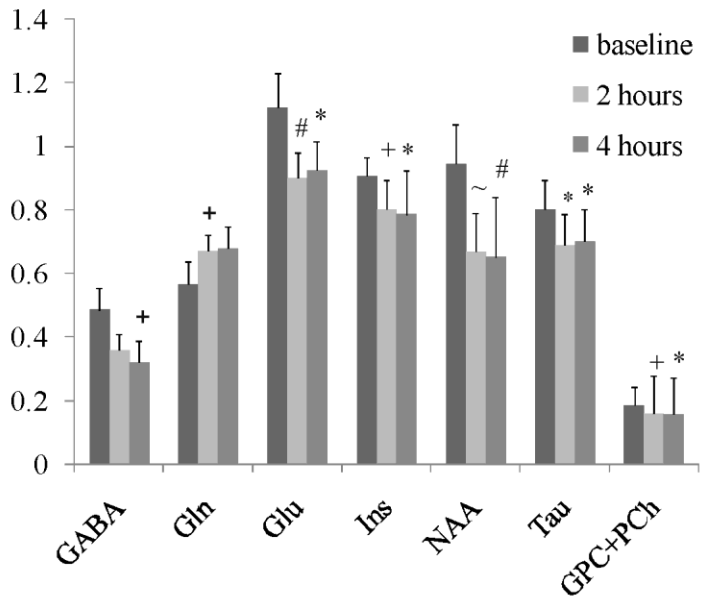


* Dixon et al., J Neurosci Methods. 1991; 39:253-62.

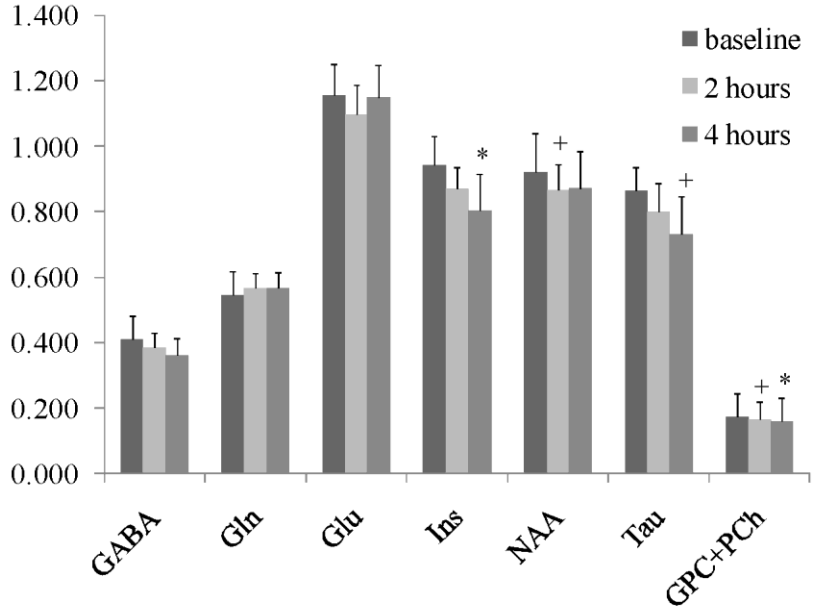

Mild TBI
Contraleteral
5-hrs
3-hrs
baseline
tCr
Glx
Ins
PCh
+
GPC
Tau
NAA
NAAG
Lac
Asp
M1
M2
M3
M4
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Moderate TBI
Contraleteral
5-hrs
3-hrs
baseline
Lac
tCr
Glx
PCh
+
GPC
Ins
Tau
NAAG
NAA
M3
M1
M4
M2
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

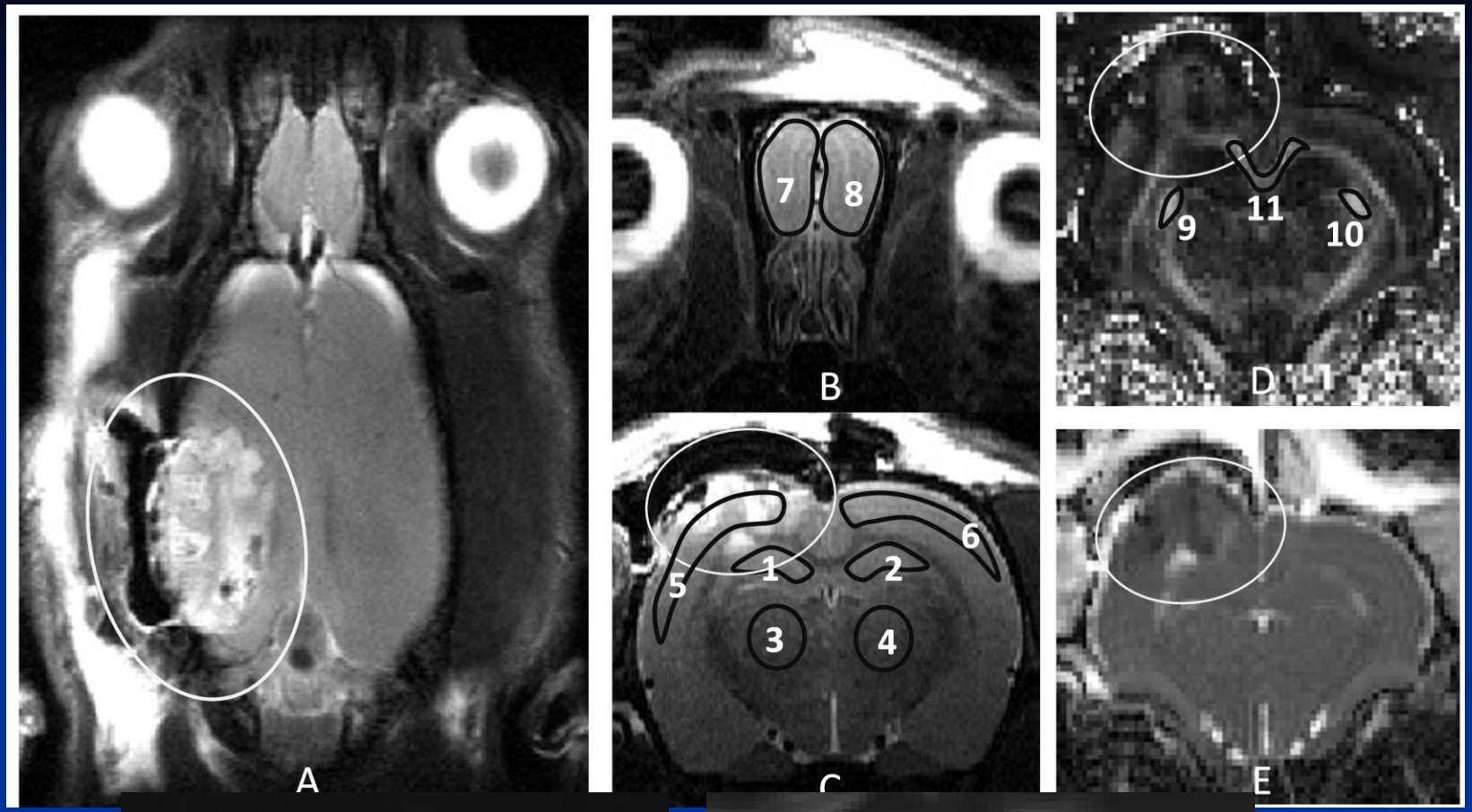
Early Metabolic Changes in Hippocampus

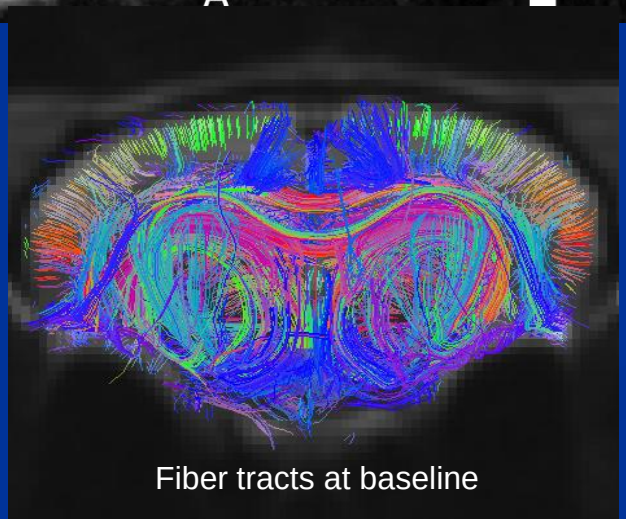


Ipsilateral Hippocampus

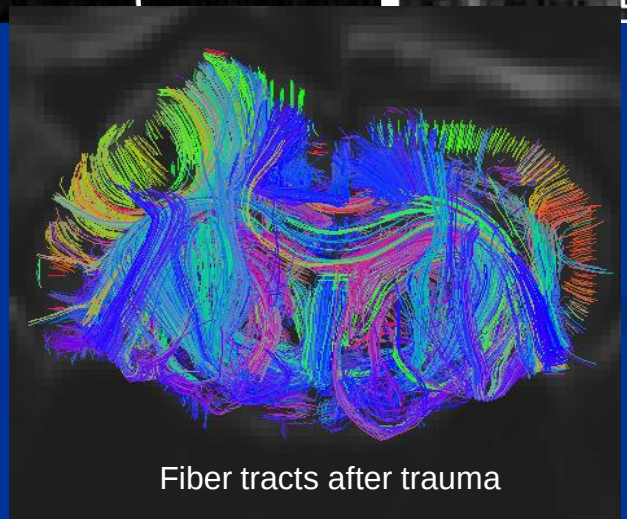


Contralateral Hippocampus



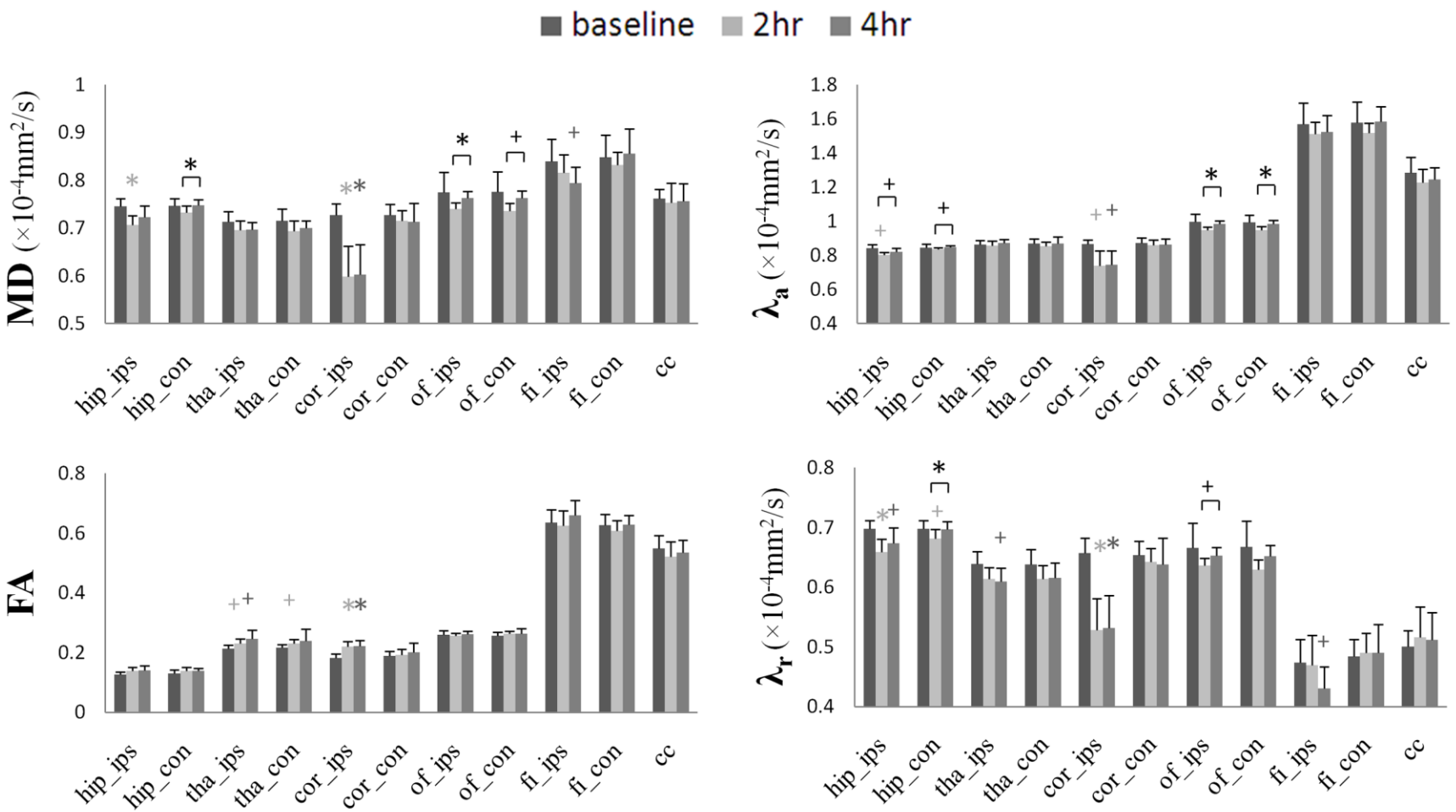


Fiber tracts at baseline

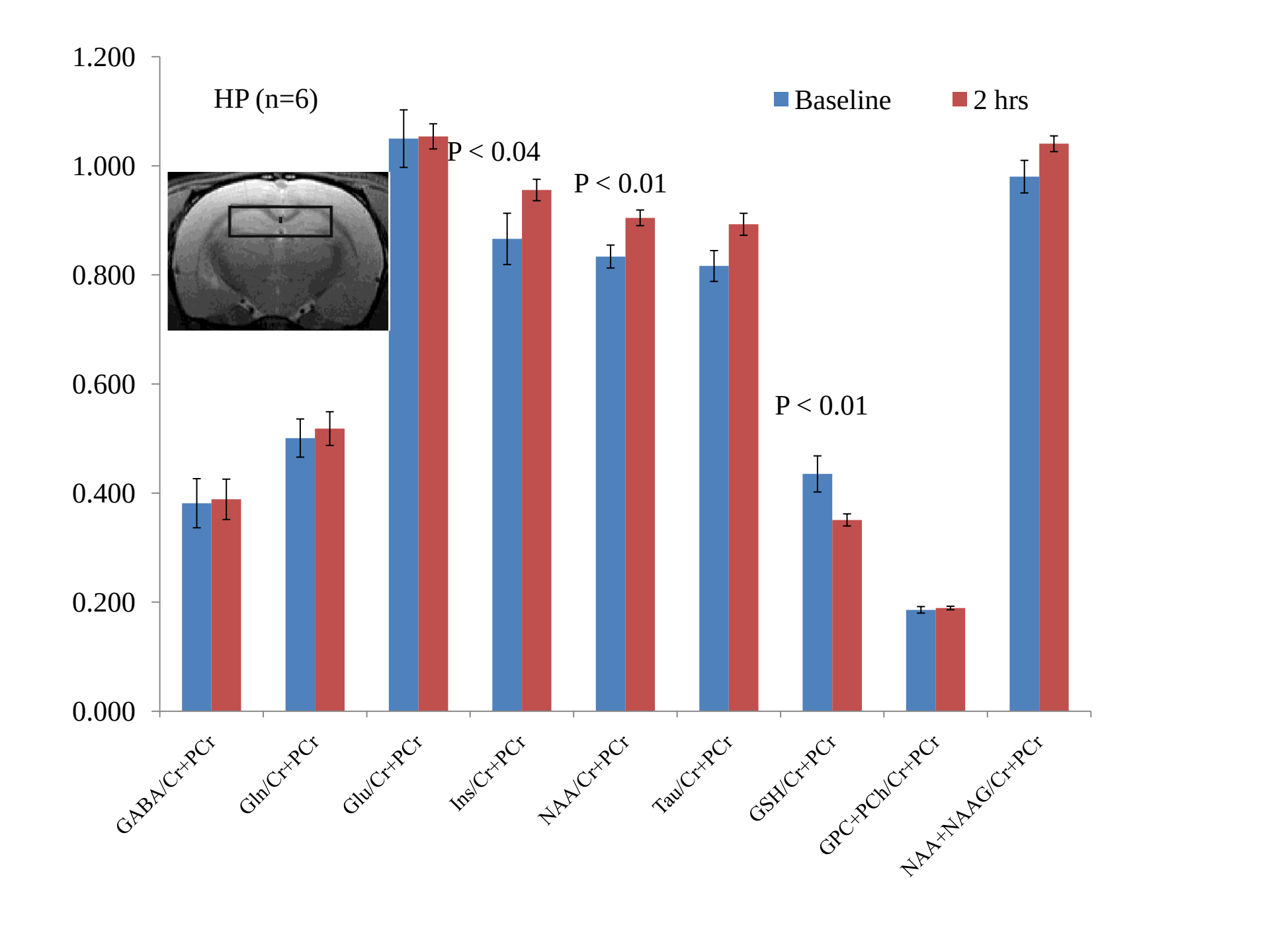


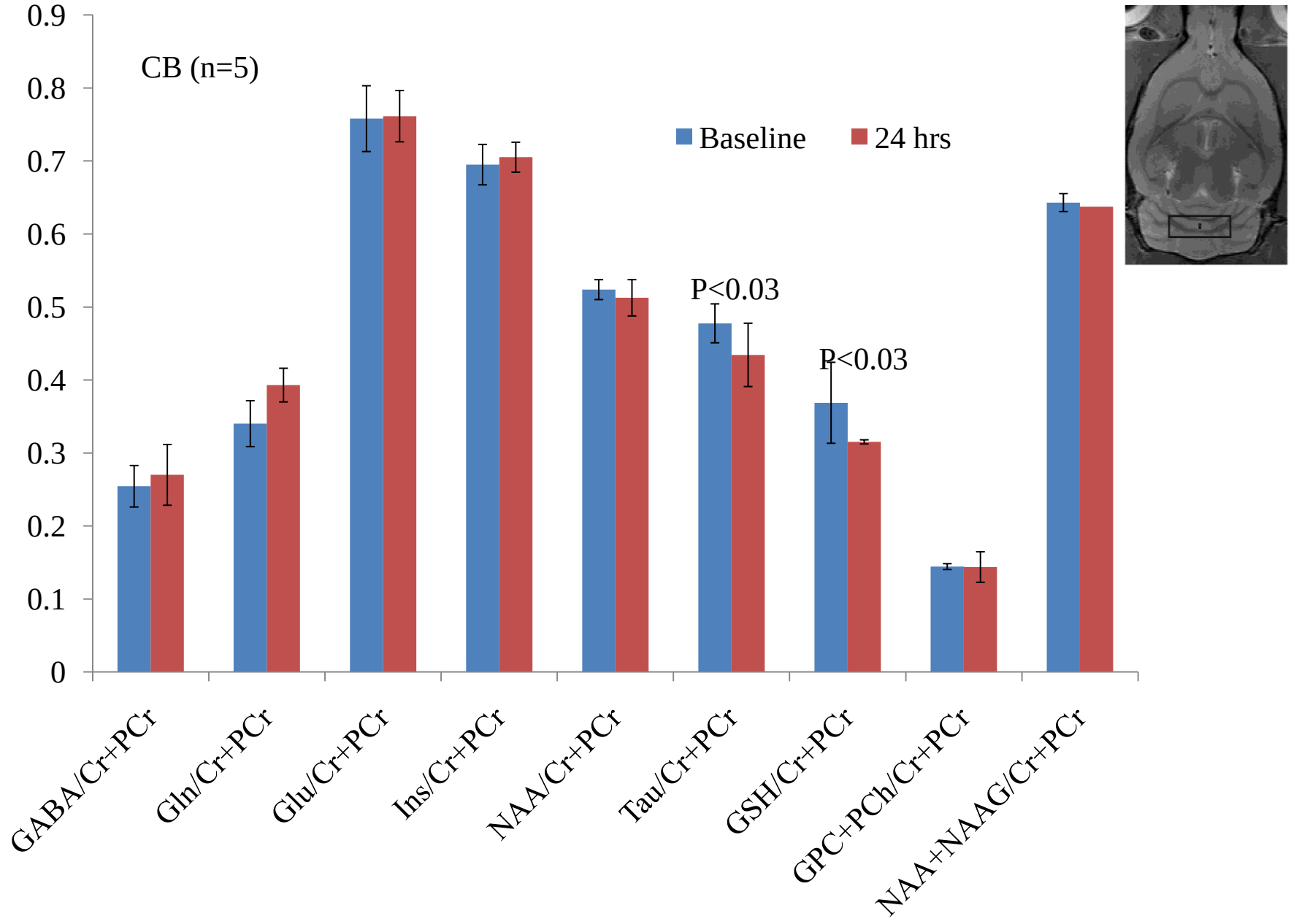
Fiber tracts after trauma

Diffusion Tensor Imaging

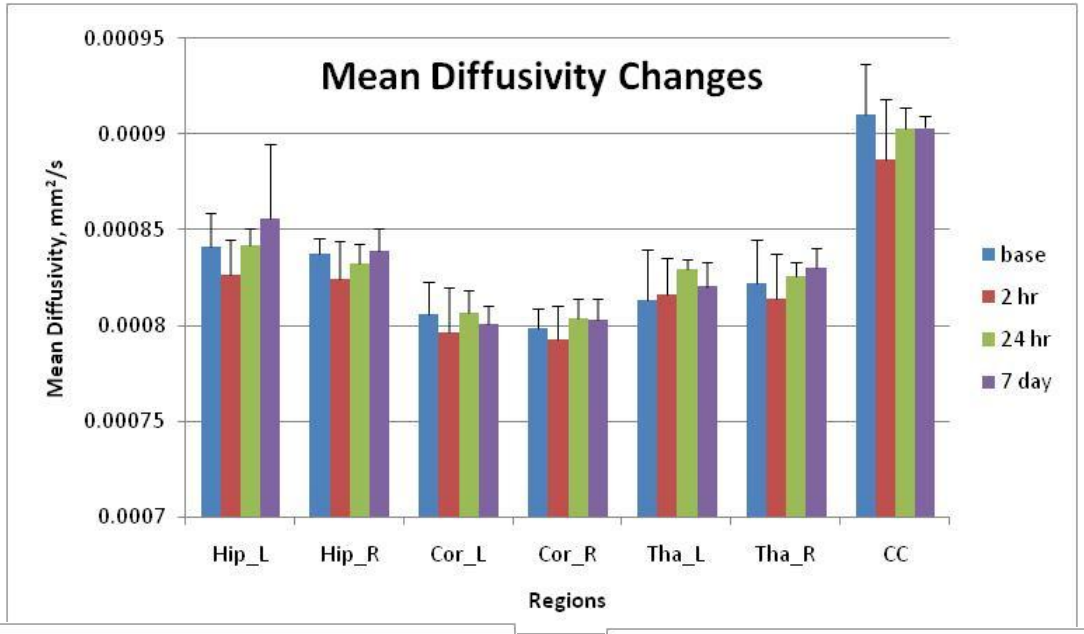


Underbelly Blast
Fourney-Fiskum Model

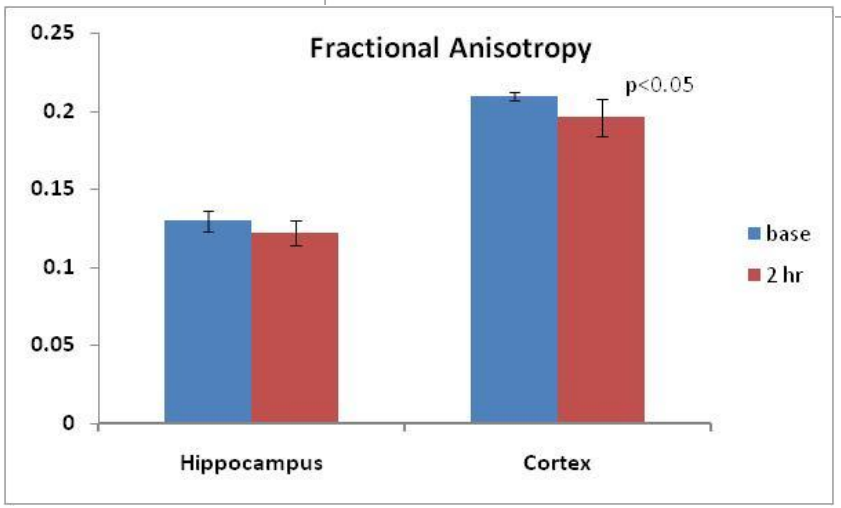

HP (n=6)
Baseline
2 hrs
P < 0.04
P < 0.01
P < 0.01
1.200
1.000
0.800
0.600
0.400
0.200
0.000
GABA/Cr+PCr
Gln/Cr+PCr
Glu/Cr+PCr
Ins/Cr+PCr
NAA/Cr+PCr
Tau/Cr+PCr
GSH/Cr+PCr
GPC+PCh/Cr+PCr
NAA+NAAG/Cr+PCr

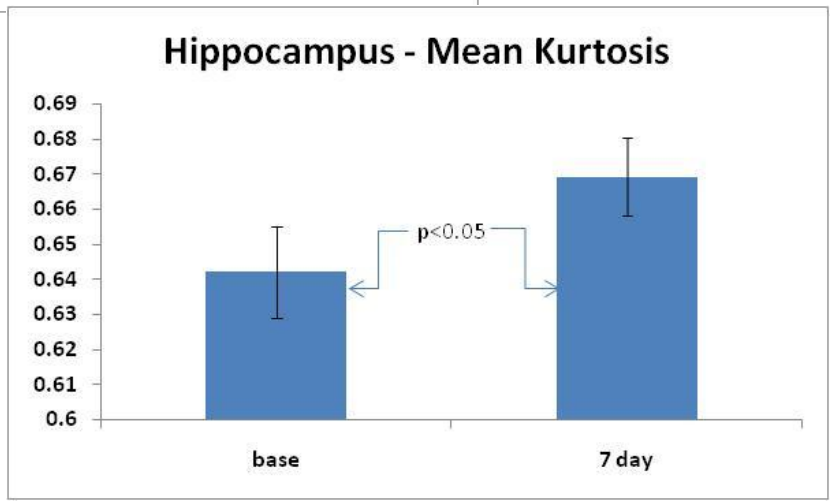

CB (n=5)
Baseline
24 hrs
P<0.03
P<0.03
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
GABA/Cr+PCr
Gln/Cr+PCr
Glu/Cr+PCr
Ins/Cr+PCr
NAA/Cr+PCr
Tau/Cr+PCr
GSH/Cr+PCr
GPC+PCh/Cr+PCr
NAA+NAAG/Cr+PCr

Diffusion Changes

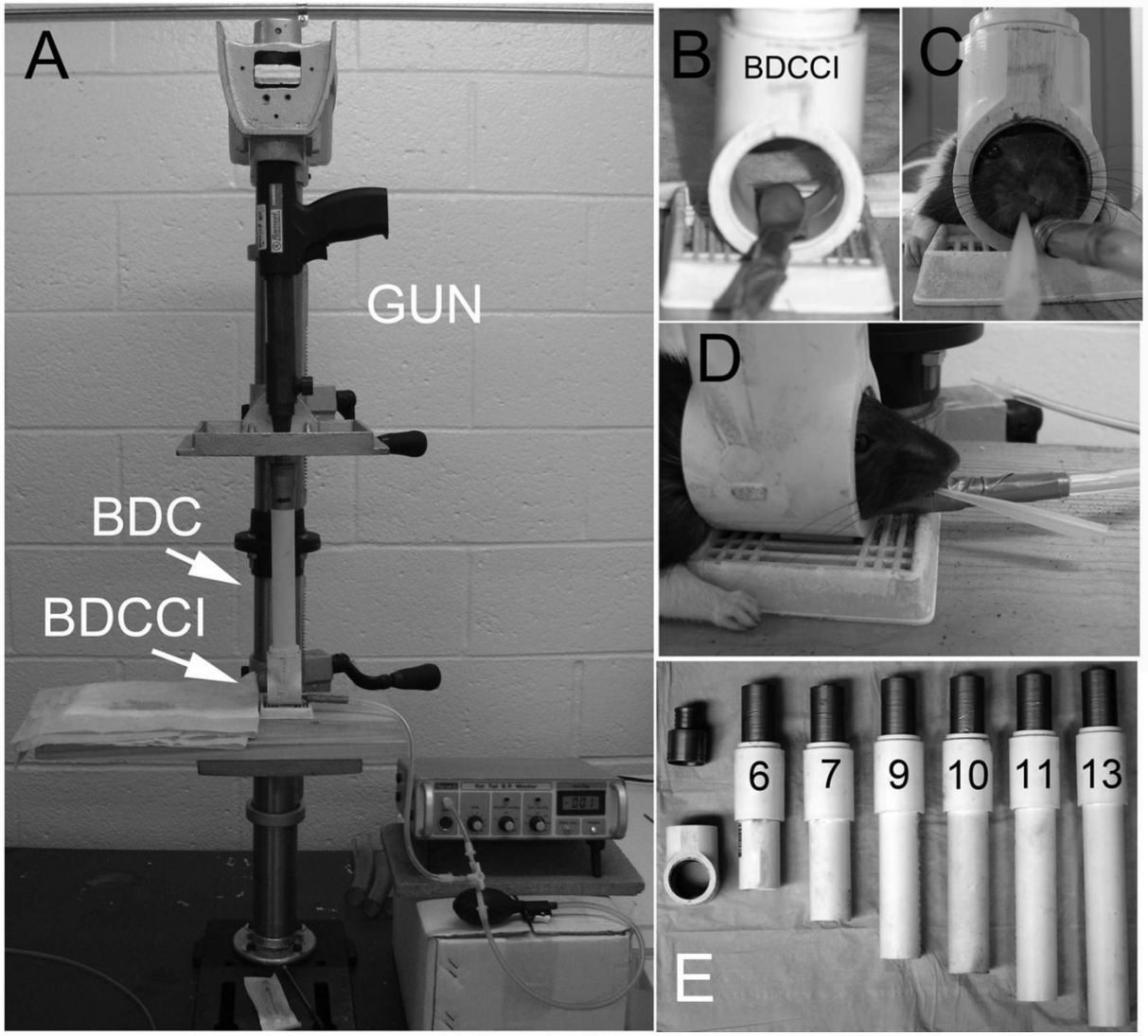


Considerable variability in the data



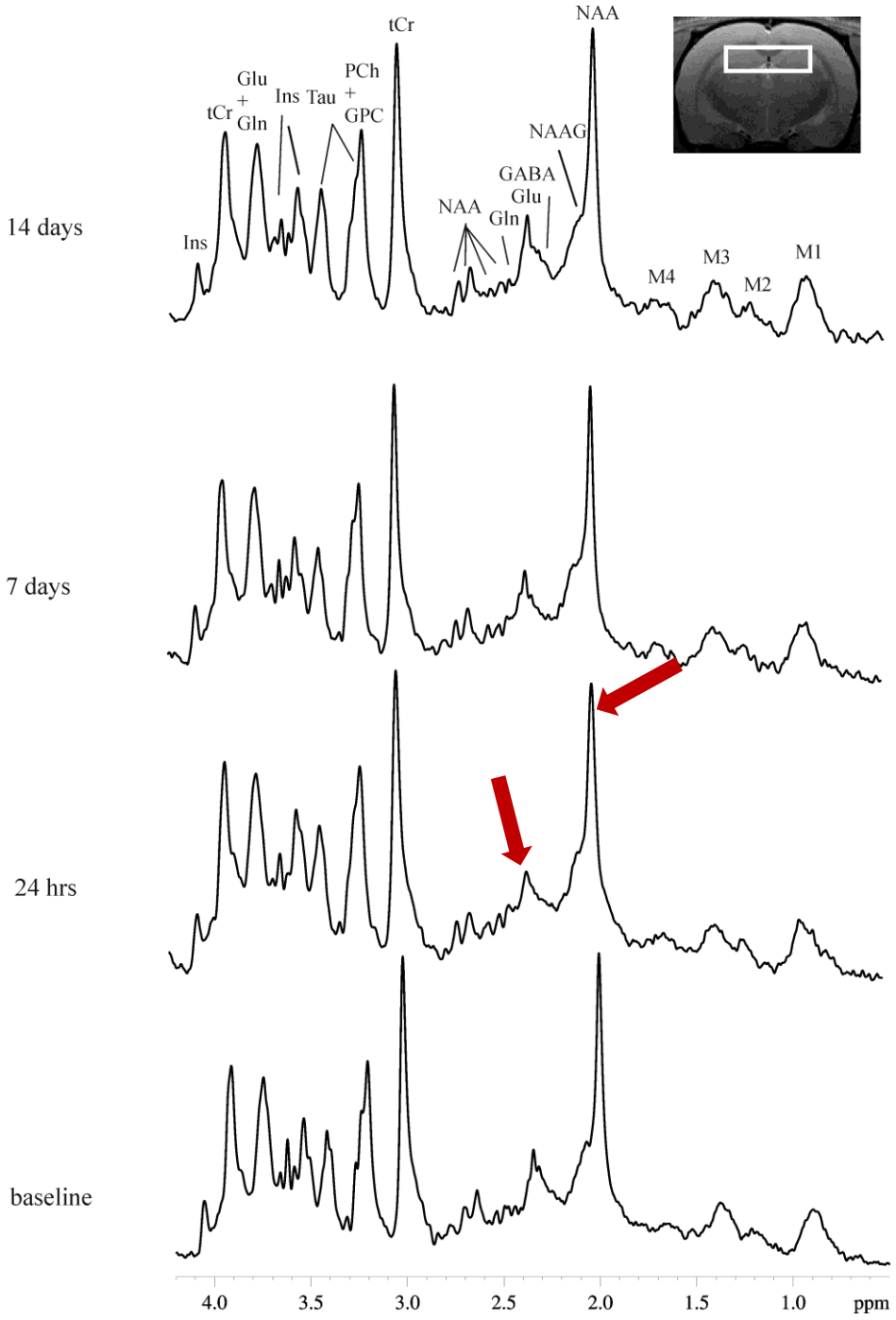


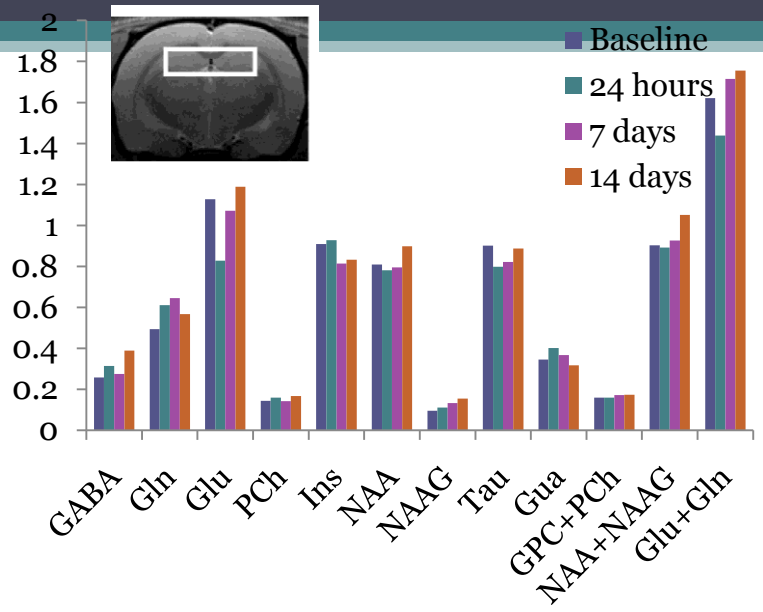
Blast Overpressure
Simard & Gerzanich Model



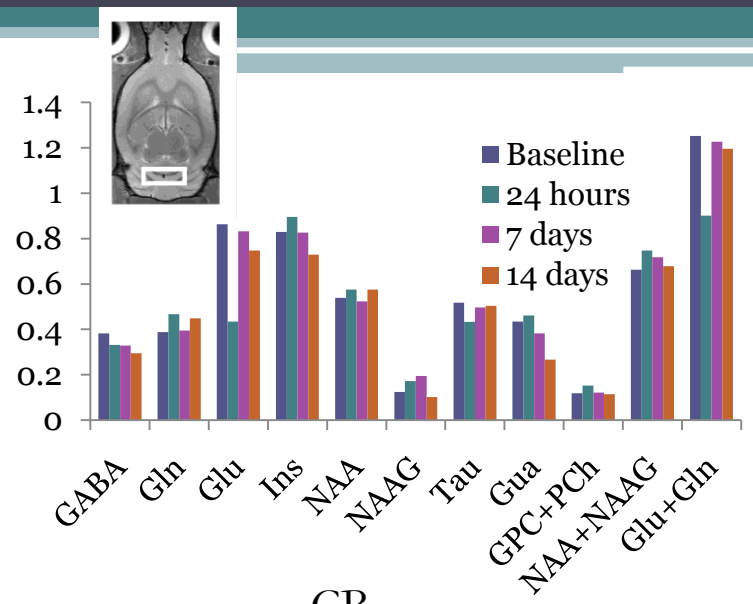
- **Cranium only blast injury apparatus (COBIA).**
- **No thoracic transmission of blast wave.**
- **Generated by detonating 0.22 caliber cartridges of 128 or 179 mg of smokeless powder.**
- **Peak overpressure can reach as high as 1300 kPa**

Spectroscopic changes following Blast overpressure

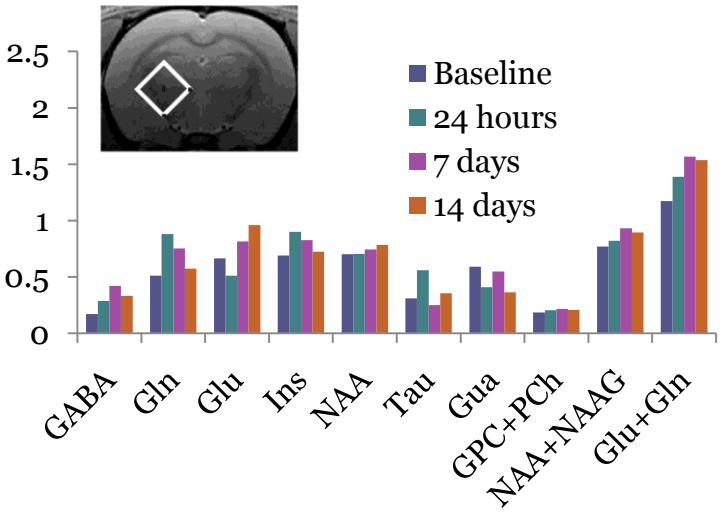




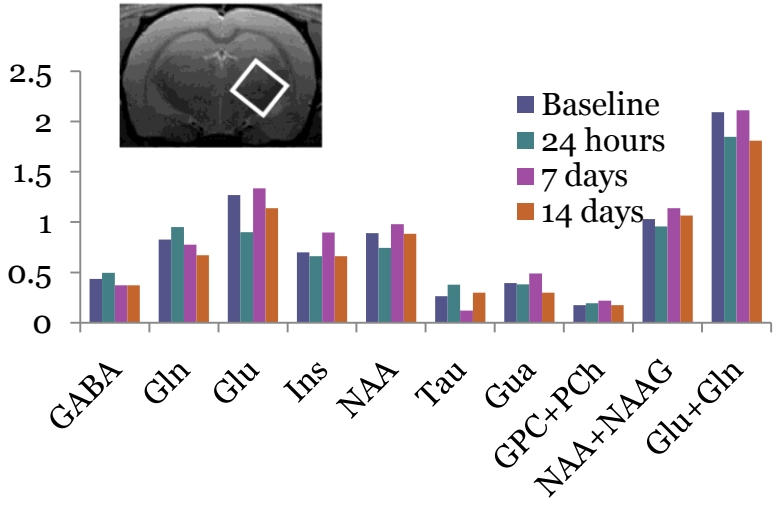
HP



CB



IC left



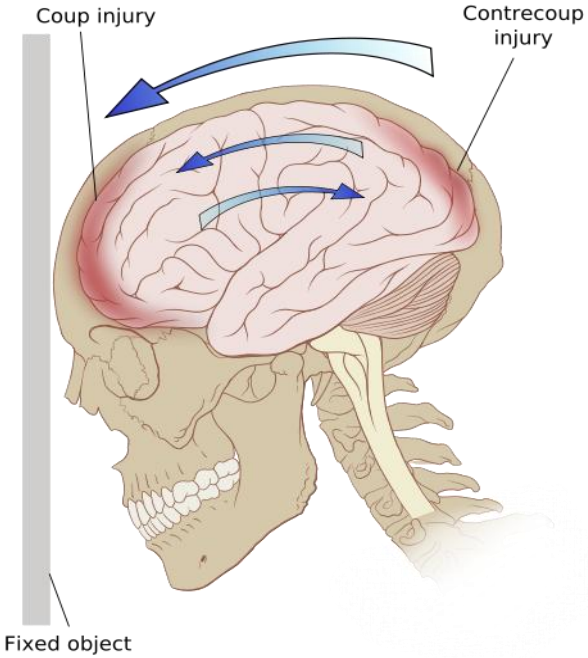
IC right

Summary from Experimental Models

- **Early biochemical changes appear to be dependent on the injury model.**
- **All models show changes in NAA, Taurine and myo-inositol suggesting some neuronal damage and changes in osmolarity probably due to inflammation. Microstructural changes in hippocampus and ipsilateral regions**
- **Underbelly blast: decrease in glutathione (antioxidant) immediately following injury suggesting that the injury mechanism leads to oxidative stress. Mechanism not reported earlier in vivo. Microstructural changes in hippocampus & thalamus.**
- **Blast overpressure – creates an imbalance in excitatory and inhibitory activity via the Glu-Gln cycle.**

Traumatic Brain Injury

Traumatic injuries remain the leading cause of death in children and in adults aged 45 years or younger.



Primary injury:

Structural changes due to mechanical forces

Secondary injury:

Widespread degeneration of neurons, gial cells, axons

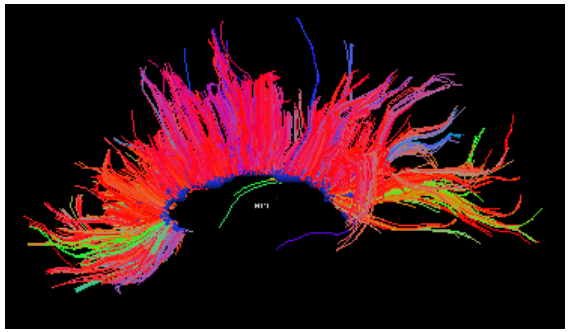
Patient outcome is hard to predict!

The major focus of TBI management:

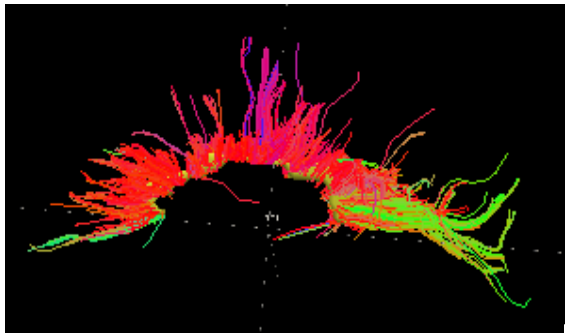
Prevention of secondary injuries

Diffusion Tensor Imaging in Evaluating TBI

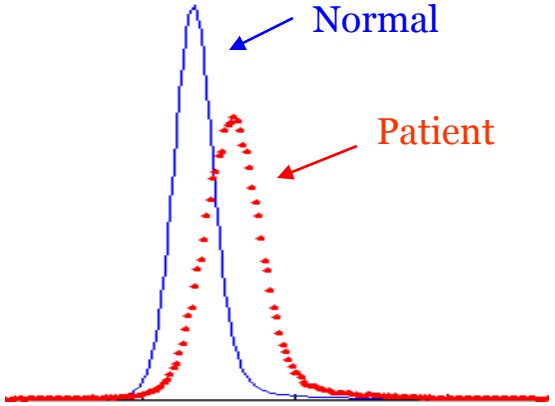
Normal



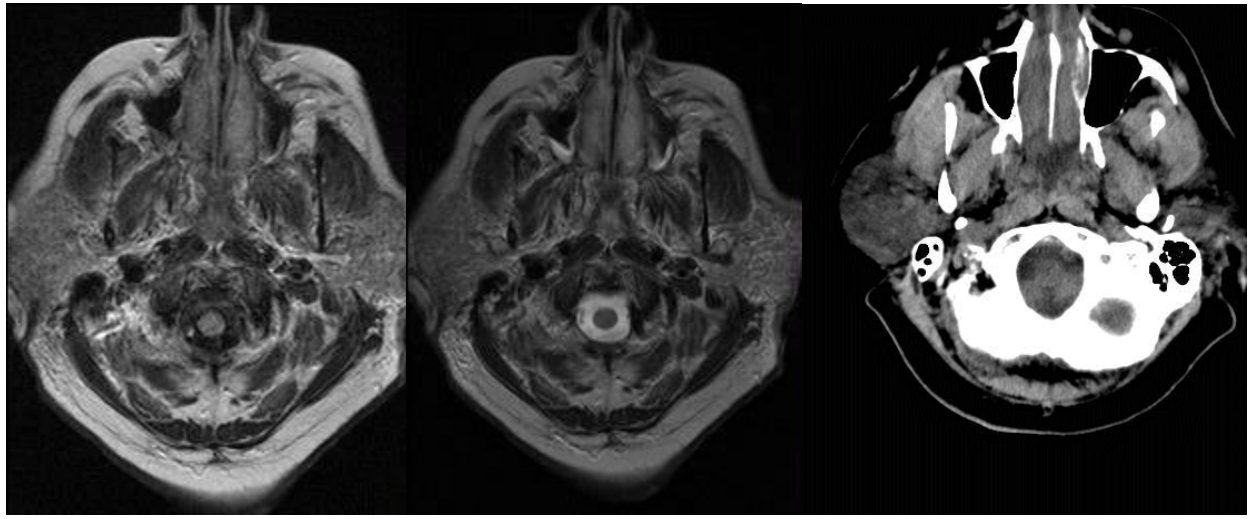
Patient



Whole brain ADC histogram



Abnormal DTI
despite negative conventional MRI and CT findings!



Does normal DTI mean no injury?

- Acutely post injury:
  - Increased *FA*
  - Reduced *MD*

  Possible cause: cytotoxic edema, reduced extracellular space, etc.
- Chronic stage:
  - Reduced *FA*
  - Increased *MD*

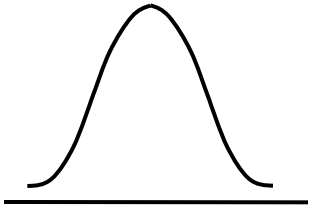
  Possible cause: edema, cellular destruction, axonal degeneration, etc.
- At sub-acute stage, DTI parameters may undergo pseudo-normalization[1,2].
- Does this mean there is no injury?

[1]MacDonald et al., 2007. [2]Mayer et al, 2010

Beyond DTI: Diffusion Kurtosis

– the Non-Gaussian property of water diffusion

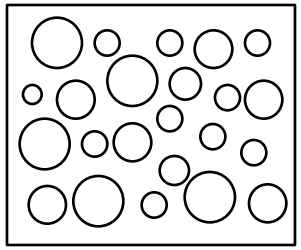
Uniform water diffusion



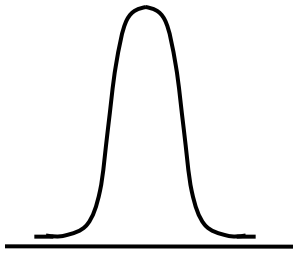
K=0

Gaussian (**DTI**)

$$\ln\frac{S(b)}{S(0)} = -bD$$



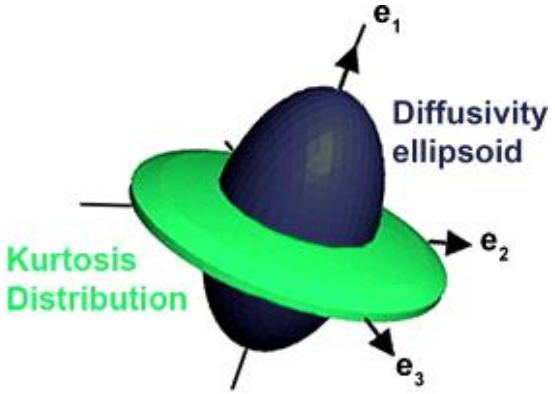
Non-uniform water diffusion



K>0

Non-Gaussian (**DKI***)

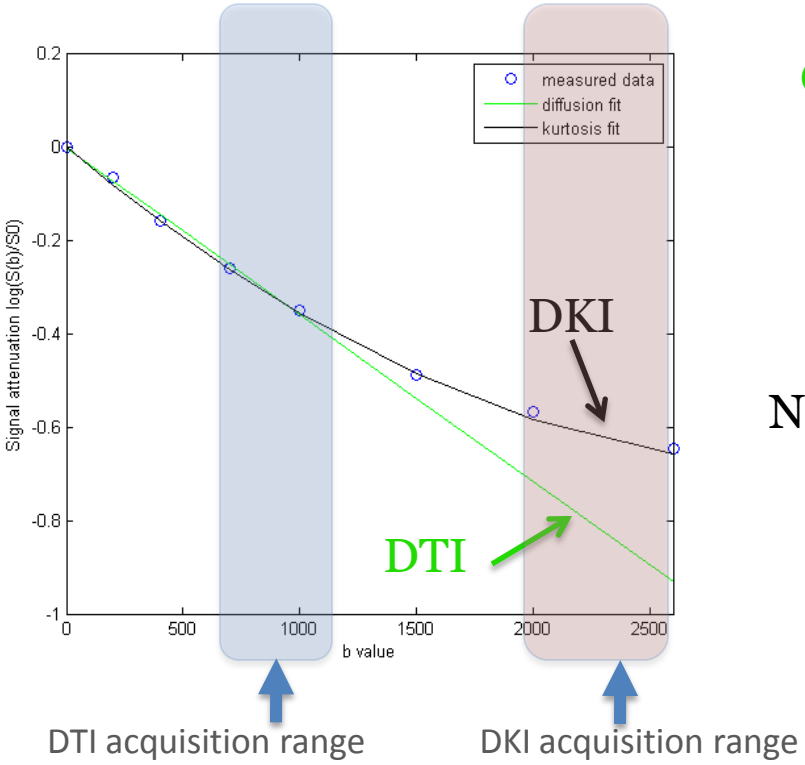
$$\ln\frac{S(b)}{S(0)} = -bD + \frac{1}{6}b^2D^2K$$



* Jensen JH, et al. Magn Reson Med. 2005; 53:1432-40.

Diffusion Kurtosis

– the Non-Gaussian property of water diffusion



Gaussian (**DTI**)

$$\ln\frac{S(b)}{S(0)} = -bD$$

Non-Gaussian (**DKI***)

$$\ln\frac{S(b)}{S(0)} = -bD + \frac{1}{6}b^2D^2K$$

Diffusion kurtosis

- tissue complexity (heterogeneity)[1]
- higher sensitivity in characterizing tissue microstructure[2,3]

[1] Jensen JH, Helpern JA, 2010. [2] Falangola MF et al, 2008. [3] Hui ES et al., 2008.

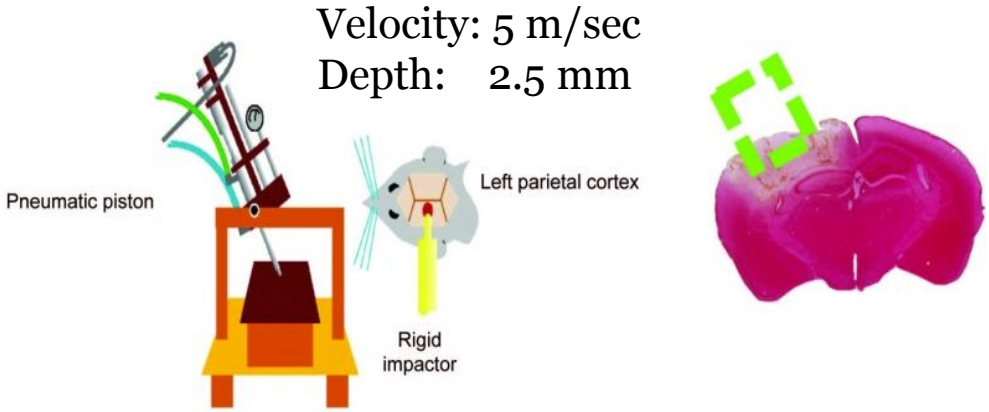
Our Goal

- To investigate whether diffusion kurtosis parameters provide information over and beyond that available from DTI parameters regarding tissue damage following TBI

- Whether DKI is sensitive to microstructure changes in grey matter

Animal Preparation

Controlled Cortical Impact (CCI) injury model*



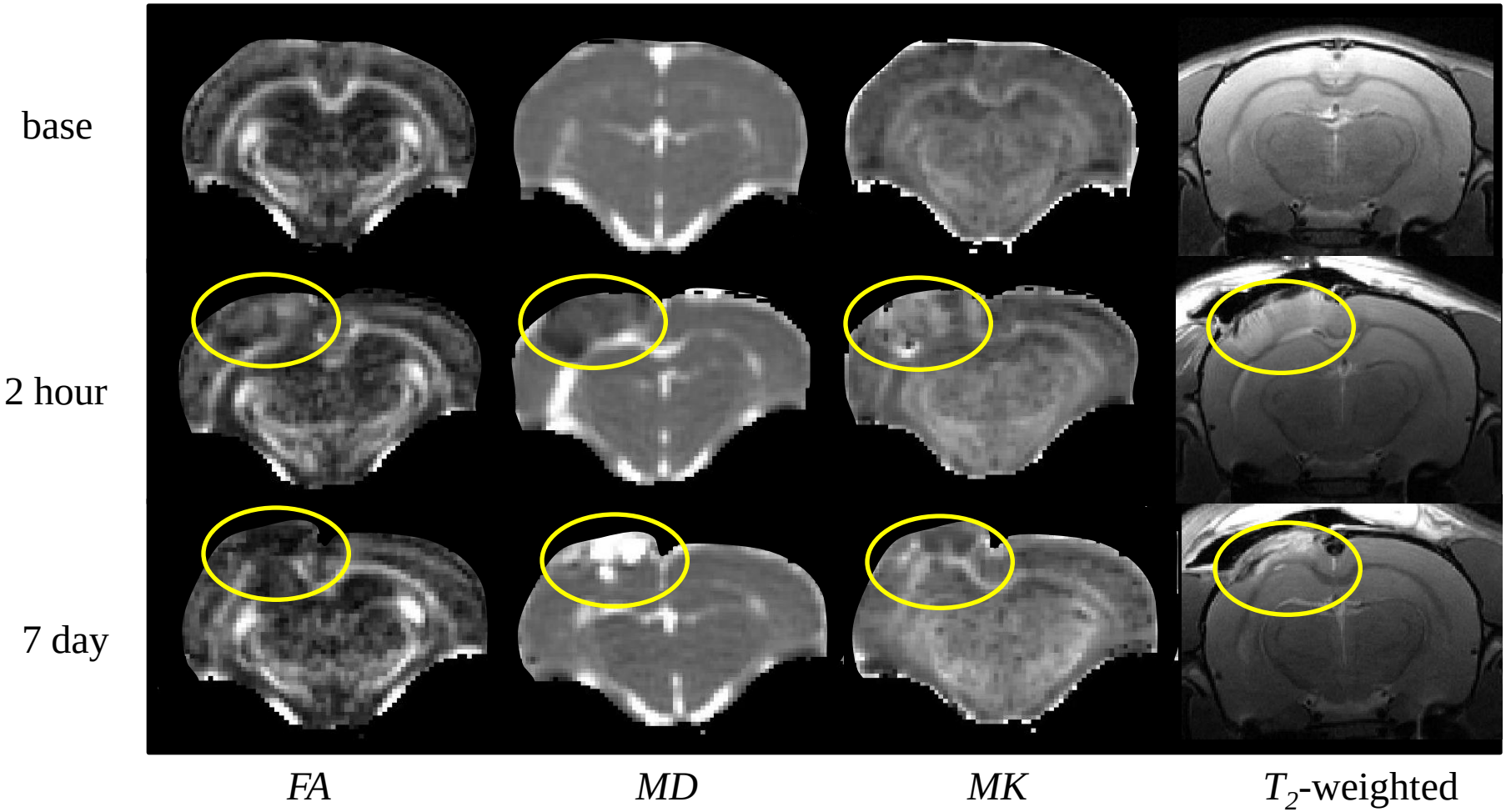
DKI protocol:

- 30 directions
- 2 b-values (b=1000 and 2000 s/mm²)
- 2 averages
- TR/TE = 6000/50 ms

- Rats (Adult male Sprague-Dawley): n = 12
- Imaging (Bruker 7T): baseline (1 day before injury)
  acute stage (2 hours post injury)
  sub-acute stage (7 days post injury, n = 7)
- Histology: 7 days post injury after imaging

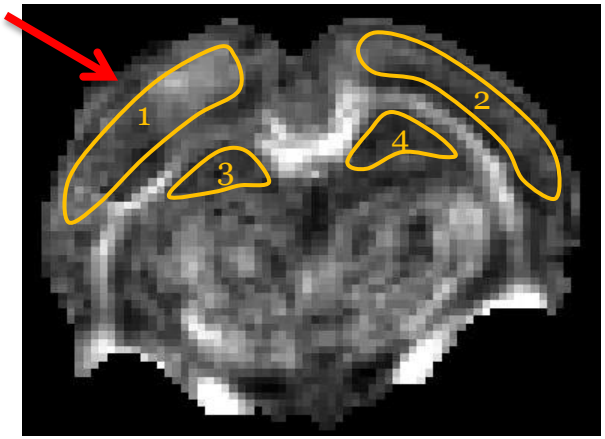
* Dixon et al., J Neurosci Methods. 1991; 39:253-62.

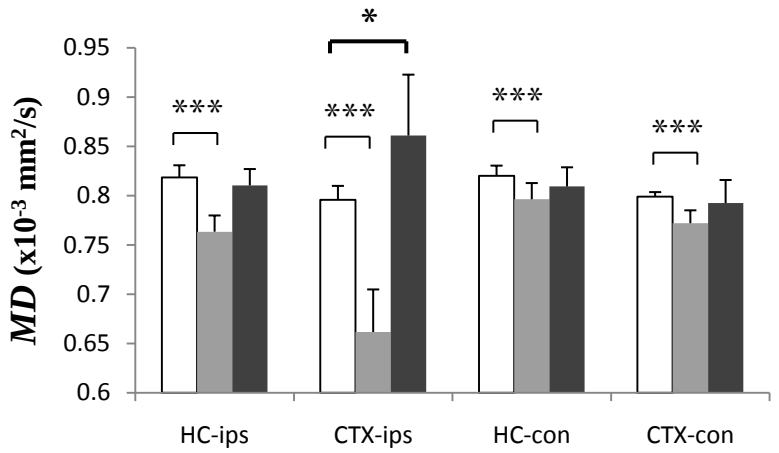
Parametric maps of a representative rat

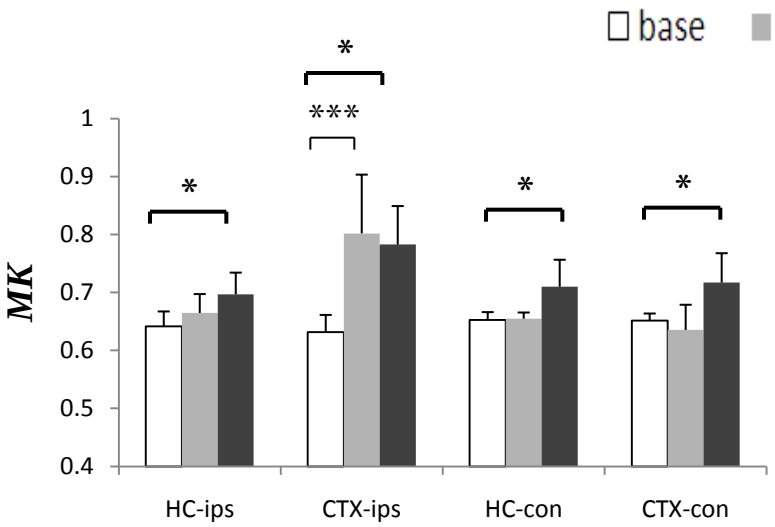


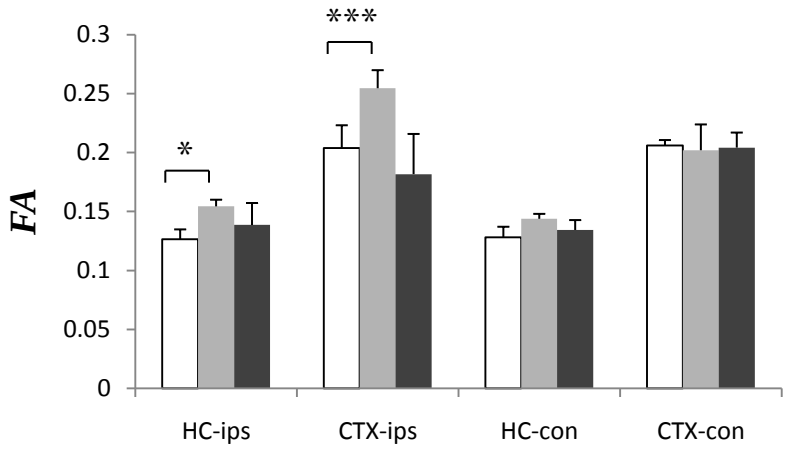
Regional evolution of DKI parameters

Injured site



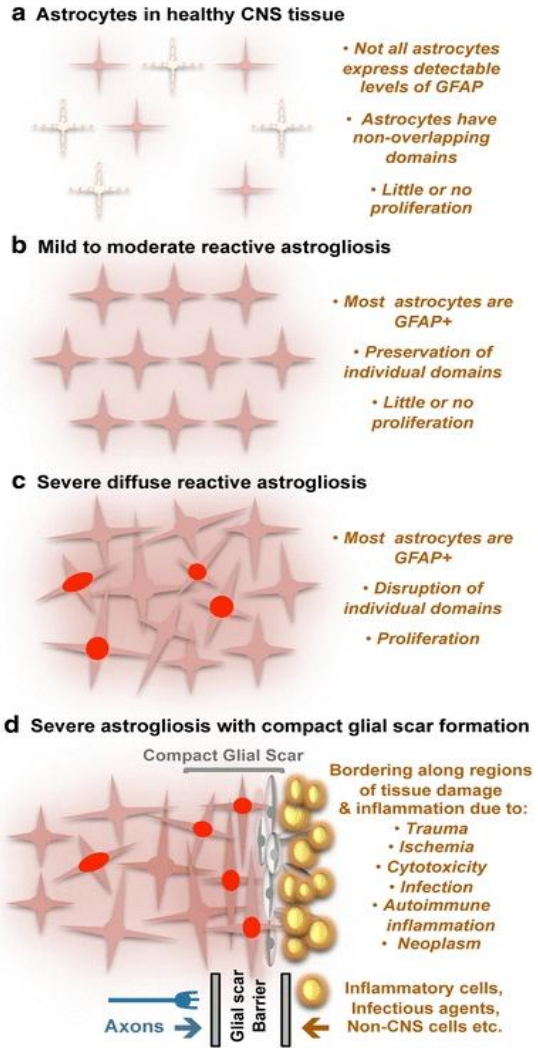


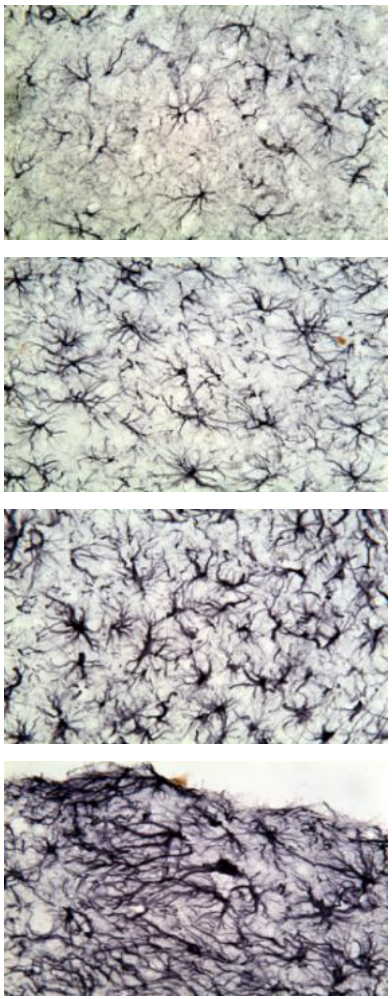




* : $p < 0.05$ *** : $p < 0.0005$

Tissue microstructure & kurtosis





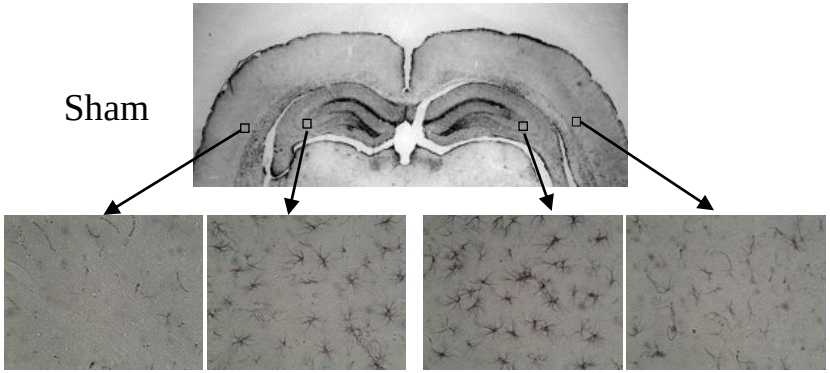
Increased severity of injury

MK ↑

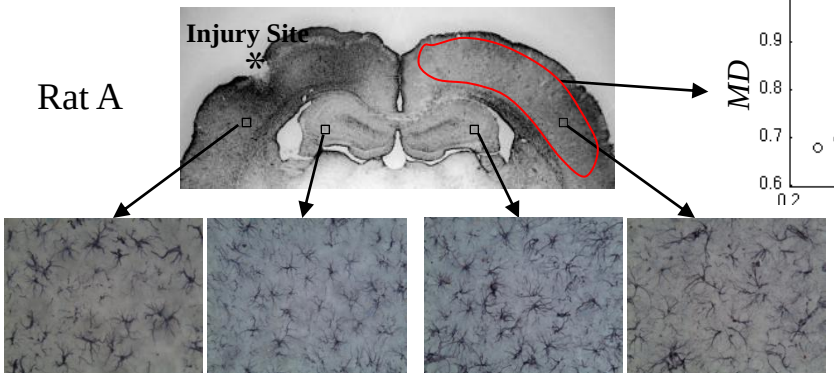
Sofroniew & Vinters, Acta Neuropathol 2010

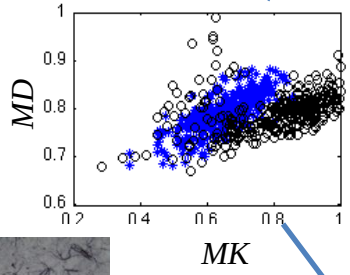
Diffusion Kurtosis – Imaging Marker for Astrogliosis?

Sham

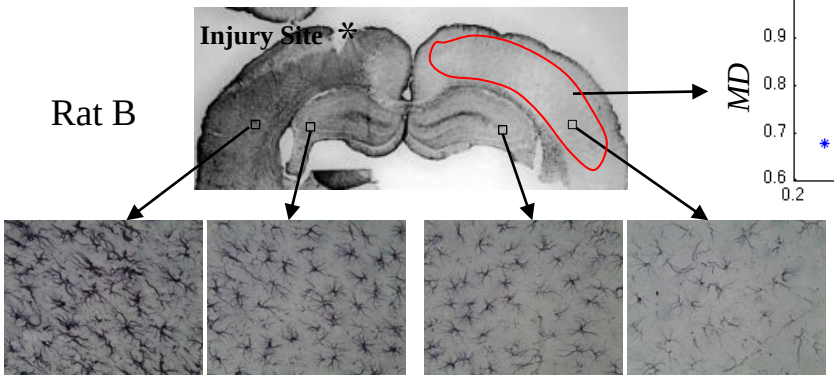


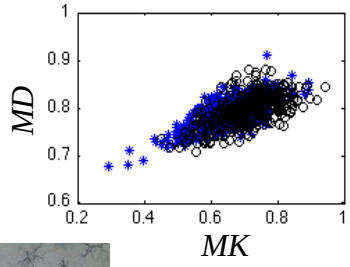
Rat A





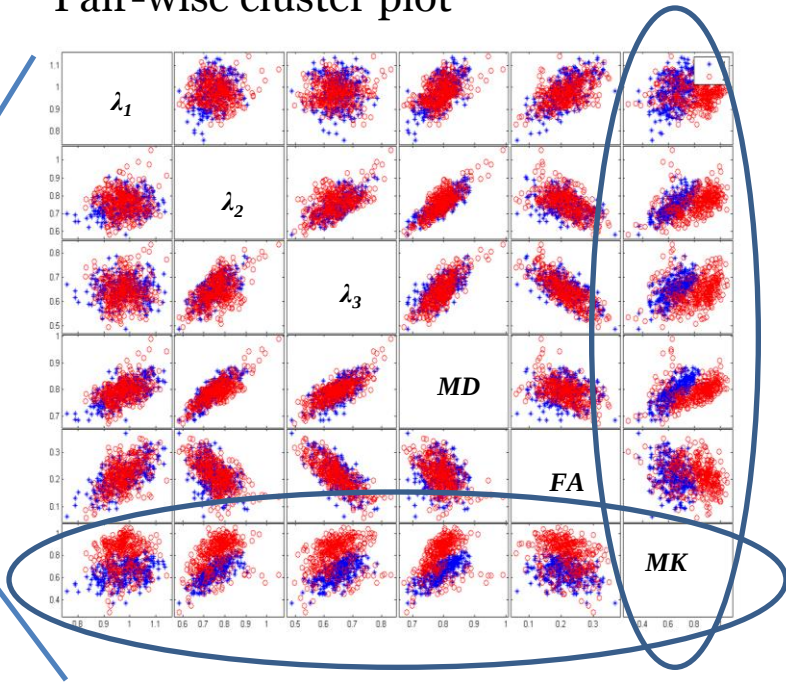
Rat B





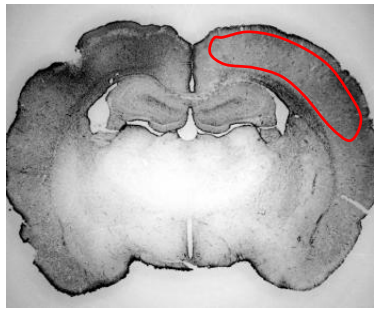
Baseline
7 day post injury

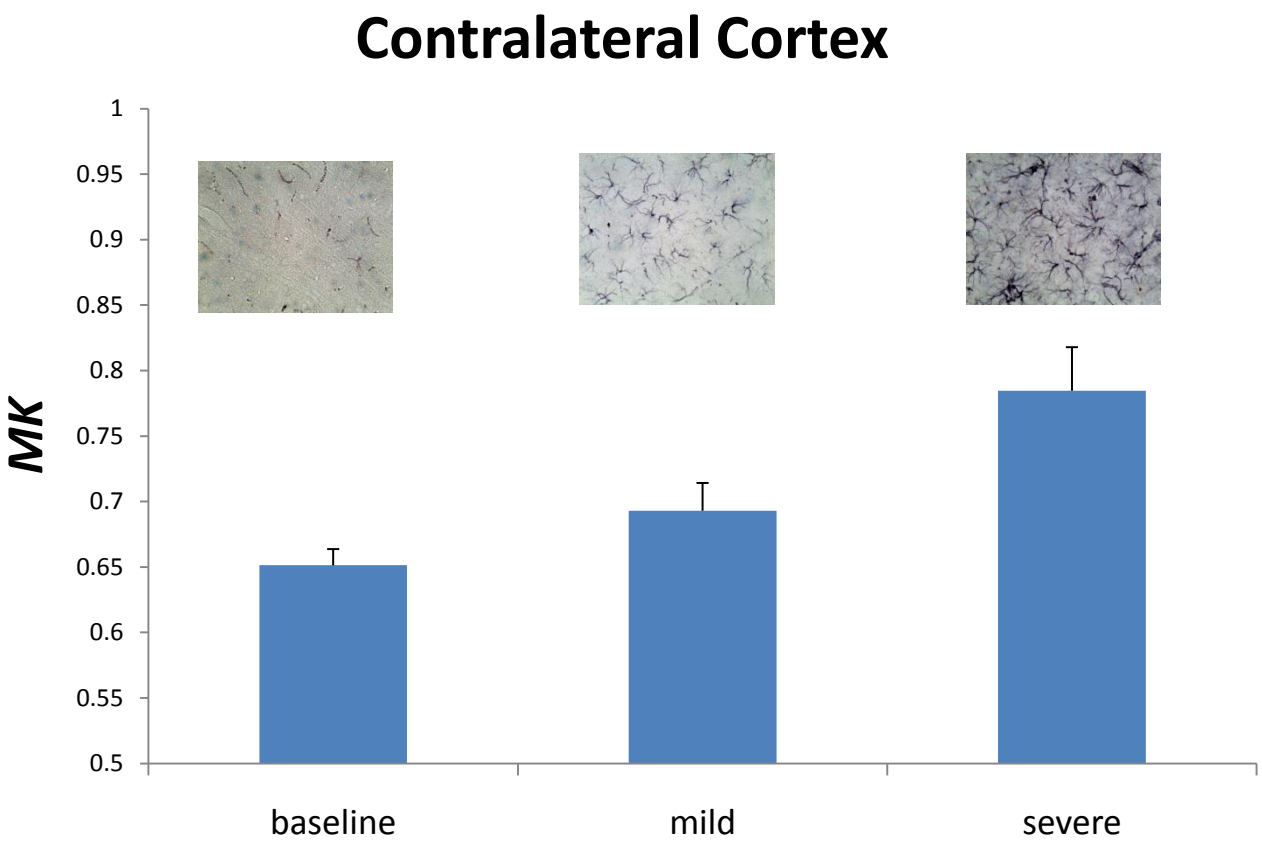
Pair-wise cluster plot



Blue: base line Red: 7 day post injury

Correlation between histology & MK





Conclusion

- We observe a clear association of mean kurtosis with increased GFAP immunoreactivity.
- Mean Kurtosis is increased despite the fact that DTI parameters such as *MD* and *FA* were normal.
- Mean Kurtosis appears to be a sensitive marker for mild inflammatory responses, even in grey matter regions and may help in the management of secondary injury.
- Other biological factors (processes associated with neuro-degeneration, microglia, etc.) can also affect mean kurtosis.
- Future studies will focus on understanding how these factors affect diffusion and kurtosis parameters.

Acknowledgements

Gary Fiskum, Ph.D
Julie Hazelton MS
Department of Anesthesiology

Marc Simard, M.D., Ph.D.
Vladimir Gerzanich, Ph.D.
Department of Neurosurgery

Support from DOD, ONR

Core for Translational Research in Imaging @ Maryland (C-TRIM)

Thank You!