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
- Mitochondrial dysfunction
- ROS production
- ↓ Aerobic Metabolism
- ↑ Anaerobic Metabolism
- Lactic Acidosis

Focal injury

- 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*

Velocity: 5 m/sec
Depth: 2.5 mm

Moderate TBI

5-hrs

3-hrs

baseline

Contra lateral
Early Metabolic Changes in Hippocampus

Ipsilateral Hippocampus

Contralateral Hippocampus

[Bar charts showing metabolic changes over time for GABA, Glu, Gln, Ins, NAA, Tau, GPC-PCh in both ipsilateral and contralateral hippocampi.]
Fiber tracts after trauma

Fiber tracts at baseline
Diffusion Tensor Imaging

![Graphs showing MD, λ2, FA, and λ1](image-url)
Underbelly Blast
Fourney-Fiskum Model
CB (n=5)

- Baseline
- 24 hrs

Significant differences indicated by P<0.03.
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
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

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

Non-uniform water diffusion

Gaussian (DTI) \[ \ln \frac{S(b)}{S(0)} = -bD \]

Non-Gaussian (DKI*) \[ \ln \frac{S(b)}{S(0)} = -bD + \frac{1}{6} b^2 D^2 K \]

Diffusion Kurtosis

→ the Non-Gaussian property of water diffusion

Gaussian (DTI)

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

Non-Gaussian (DKI*)

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

Diffusion kurtosis

- tissue complexity (heterogeneity)\(^1\)
- higher sensitivity in characterizing tissue microstructure\(^2,3\)

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*

- 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

DKI protocol:
- 30 directions
- 2 b-values  
  $(b=1000 \text{ and } 2000 \text{ s/mm}^2)$
- 2 averages
- TR/TE = 6000/50 ms

Parametric maps of a representative rat

- **base**
- **2 hour**
- **7 day**

- **FA**
- **MD**
- **MK**
- **$T_2$-weighted**
Regional evolution of DKI parameters

Injured site

**Graphs and Data**

- **MD (x10^{-3} mm^2/s)**
  - HC-ips vs. CTX-ips vs. HC-con vs. CTX-con
  - Significance levels: *: p < 0.05, ***: p < 0.0005

- **MK**
  - HC-ips vs. CTX-ips vs. HC-con vs. CTX-con
  - Significance levels: *: p < 0.05, ***: p < 0.0005

- **FA**
  - HC-ips vs. CTX-ips vs. HC-con vs. CTX-con
  - Significance levels: *: p < 0.05, ***: p < 0.0005
Tissue microstructure & kurtosis

Increased severity of injury

Sofroniew & Vinters, Acta Neuropathol 2010
Diffusion Kurtosis – Imaging Marker for Astrogliosis?

Sham

Rat A

Injury Site

Rat B

Pair-wise cluster plot

Blue: baseline  Red: 7 day post injury

* Baseline

• 7 day post injury

λ₁

λ₂

λ₃

MD

FA

MK

MD

MK
Correlation between histology & MK

Contralateral Cortex

MK

- baseline
- mild
- severe
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!