Imaging Horizons in Traumatic Brain Injury

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University of Utah
26th Annual Update in Physical Medicine and Rehabilitation
March 16, 2012
Growing Storm

- >1.5 million cases of TBI annually U.S.
  - Civilian trauma
  - U.S. Military trauma
  - Sport-related injury
- Vast majority are mild injuries
- But... many patients with mTBI develop persistent symptoms (5-50%)
- Substantial disability
- At risk group: young healthy individuals
Imaging Traumatic Brain Injury

• CT remains the standard of care in acute head injury
• MRI can be clinically useful in certain circumstances
• Milder forms of TBI, conventional imaging so far limited with respect to correlation w long-term outcome and persistent Sxs
• Newer techniques in MR imaging show promise in showing more subtle areas of brain abnormality and areas that are occult on conventional imaging
73yo M w HA
Horizons in MR imaging of TBI

Mild injury
- Normal conventional CT and MR
- 5-50% suffer from post-concussive syndrome (symptomatic 3 months later)
- why? who?
- Pathophysiology?

Mod/severe
- Spectrum of outcomes
- Can we improve our ability to predict outcome?
- Tailor rehabilitation treatment
- Develop targeted therapy

NYU Langone Medical Center
Classification of Acquired Brain Injury (ABI)

ABI
Brain damage that is not congenital.

Traumatic Brain Injury (TBI)
Physical trauma to the brain.

- Mild
- Moderate
- Severe

Non-Traumatic Brain Injury (NTBI)
Brain injury not involving external mechanical force.

- Stroke
- Meningitis
- Brain Tumors
- Infection
- Poisoning
- Hypoxia
- Ischemia
- Substance Abuse

Civilian Sport-related Blast
Mild Traumatic Brain Injury (MTBI) “Growing Epidemic”

- A significant public health care problem
- 75% of over 1.5 million annual TBI cases
- 50% of soldiers who have TBI during deployment have MTBI
- 20% don’t return to work
- Highest risk: 15 - 24yo M
- ~ $17 billion annually in health care and productivity loss
Questions for neuroimagers

• Where is the lesion? One abnormality precede another?
  – White matter
  – Cortex
  – Gray matter
  – Neuronal connectivity

• What is the pathogenesis of disease?
  – Predisposition / susceptibility to disease
  – Vascular insult
  – BBB disruption
  – Excitotoxicity
  – Inflammation

• Can we improve prediction of outcome?
• Can we improve targeted therapy?
• Is there an imaging biomarker for this injury?
Imaging White Matter in mTBI
White matter - DAI?

- Key feature in moderate to severe TBI
- Diffuse / widespread injury to axons
- Concentration of lesions at gray/white junction
- Rotational, accelerational/decelerational injury
- Pathologically axonal damage
- SWI, DTI, MRS
SWI - susceptibility weighted imaging

Post-processed image based on GRE
• Specifically takes phase information
• Superimposes on magnitude information
• Result is that very sensitive to local susceptibility effects, fewer artifacts

• See some types of intracranial blood better
• See mineralization (iron deposition, calcification) better

Paramagnetism, susceptibility, phase, magnitude
Paramagnetism

\[ B_0 \]
Paramagnetism

\[ \mathbf{B}_0 \]
Uniform field

Field inhomogeneity
Paramagnetic substances:
- Deoxyhemoglobin
- Intracellular methemoglobin
- Hemosiderin
- Iron

Particularly suited for high field
SWI

• 3-6x more sensitive than traditional GRE T2
• Number of lesions on SWI correlated with neuropsychological measures of function
• More sensitive for brainstem lesions, thought to have prognostic implications
Isotropic diffusion

Equal in all directions

FA = 0

Anisotropic diffusion

Restricted in some directions

Maximum FA = 1

DTI - Diffusion Tensor Imaging
DTI Metrics: Mean Diffusivity (MD)

↑↑↑↑ MD

↓ MD

slide courtesy of Amit Saldane
DTI Metrics: Fractional Anisotropy (FA)
Tractography – CST and SLF
In theory: Axonal damage versus edema

**Diffusion:**

- ↓ FA
- ↓ Dax
- ↑ MD

**Diffusion:**

- ↑ MD
- ↓ FA
- ↑ Drad

- Mod/Severe TBI decreased FA in all 13 ROIs
- MTBI decreased FA in SLF, central corona, parietooccipital WM
Voxel-based Analysis FA

- MTBI<Control (p<0.05)
- reduced FA from FSL TBSS analysis in corpus callosum, occipital and frontal regions.

- 63 subjects, 21 controls within 90 days of injury
Conventional MRI, SWI, DTI

Anatomy

vs.

Proton MR spectroscopy ($^1$H-MRS)

Metabolism

- N-acetyl-aspartate (NAA)
- Choline (Cho)
- Creatine (Cr)
- myo-inositol (mI)

- **Single injury**
  - 13 nonprofessional athletes

- **Double injury**
  - 3 with second injuries
- Signal from all voxels averaged to yield metabolic concentrations for the entire tissue and its WM and GM fractions

1Gonen et al. MRM 1997, 1998; Goelman et al. MRM 2006
NAA concentration distribution
21 14 days from trauma

Whole Brain
GM
WM

Controls n=13
Patients n=26

p=0.039
p=0.026

mM/g wet weight
Axonal pathology

Localization

GM Finding

WM Finding

Suspected pathology

<table>
<thead>
<tr>
<th>Localization</th>
<th>neurons</th>
<th>astrocytes</th>
<th>oligodendrocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA</td>
<td>Cr</td>
<td>ml</td>
<td>Cr</td>
</tr>
<tr>
<td>Cho</td>
<td></td>
<td>Cr</td>
<td>Cho</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WM Finding</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA ↓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suspected pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axonal dysfunction</td>
</tr>
</tbody>
</table>
WM conclusions

- WM is clearly abnormal
- Diffusely abnormal or abnormal in multiple (subcortical?) regions
- Lack of GM changes indicates no clear cell body injury that precedes WM changes in acute injury
- Therefore lower WM NAA levels and FA may represent
  - Early WM injury before neuronal cell body injury
  - Axonal dysfunction and edema rather than true degeneration
Looking at the cortex in mTBI
What about the cortex?

• How can we examine the cortex using neuroimaging?
• Structural imaging -- volumetrics
• Functional imaging -- FDG-PET imaging, fMRI
37yo M remote history of TBI
Cortical function using MRI: BOLD (Blood oxygen level dependent) fMRI

- Indirect measure of neuronal activity
- CMRO (cerebral metabolic rate O2) / CBF
BOLD fMRI

- Activate neurons, increases CBF
- Decreases relative amt of deoxy Hb
- Decreases paramagnetism
- Decreases T2* dephasing
- Increases signal
Example of a simple paradigm - Visual stimulus

- Increased signal corresponding to periods of stimulus = activated areas (red)
- Decreased signal corresponding to periods of stimulus = Deactivated area (blue)
24 patients 2-12 mo after mTBI with persistent Sxs; working memory task

Gosselin et al, J Neurotrauma 2011
Gosselin et al, J Neurotrauma 2011
Cortical conclusions

• Chronically - are there focal areas of cortical atrophy?
• Cortical dysfunction; metabolic imaging
Implicating the Deep Gray
- Thalamus is the central relay station
- Expect injury to result in non-focal symptoms
- Other deep gray nuclei have a role in motor coordination
Morphological shape analysis

- Thalamic shape analysis
  - Thalamic boundaries manually outlined UNC shape software
  - Group-based morphological shape difference between MTBI and control was generated to view the local surface deformation

AP, PA, medial-lateral views of left thalamus
Segments 4 and 6 of thalamus (p < 0.05)

Im M, RSNA 2011
TrueFISP ASL Perfusion MRI provides high-res perfusion imaging: Labeled (A) and control (B) images obtained with TASL. The control image has high signal intensity due to un-inverted blood flow entering tissue space. The difference of the two images (C) is a relative map of cerebral blood flow.
Assessment of thalamic perfusion in patients with mild traumatic brain injury by true FISP arterial spin labelling MR imaging at 3T

The decrease of thalamic CBF was significantly correlated with several neurocognitive measures including processing and response speed, memory/learning, verbal fluency and executive function in patients.

Table I. The mean and standard deviation (SD) of CBF measure in different brain regions among patients with MTBI and healthy controls.

<table>
<thead>
<tr>
<th>Regions</th>
<th>Side</th>
<th>Controls</th>
<th>MTBI</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>Right</td>
<td>59.1 ± 12.9</td>
<td>46.9 ± 10.4</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>55.2 ± 9.2</td>
<td>45.0 ± 9.7</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>57.1 ± 8.1</td>
<td>45.9 ± 9.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Putamen</td>
<td>Right</td>
<td>51.9 ± 12.9</td>
<td>50.5 ± 8.3</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>48.0 ± 11.3</td>
<td>45.4 ± 7.8</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>48.9 ± 11.6</td>
<td>49.5 ± 8.1</td>
<td>0.86</td>
</tr>
<tr>
<td>Caudate</td>
<td>Right</td>
<td>65.5 ± 15.3</td>
<td>53.7 ± 12.8</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>59.8 ± 10.7</td>
<td>50.1 ± 14.7</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>62.7 ± 9.2</td>
<td>51.9 ± 12.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Frontal GM</td>
<td>Right</td>
<td>66.7 ± 10.6</td>
<td>63.1 ± 4.7</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>64.0 ± 5.8</td>
<td>61.2 ± 5.6</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>65.3 ± 4.8</td>
<td>62.2 ± 4.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Frontal WM</td>
<td>Right</td>
<td>25.3 ± 8.4</td>
<td>23.0 ± 7.4</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>25.6 ± 7.6</td>
<td>22.5 ± 6.0</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>25.5 ± 7.8</td>
<td>23.2 ± 6.7</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*p-values were Bonferroni corrected of multiple comparisons. GM = gray matter, WM = white matter.
Cognitive Deficits Correlate with Reduced Thalamic Perfusion

<table>
<thead>
<tr>
<th>Neuropsych Tests</th>
<th>Right Side</th>
<th>Left Side</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processing Speed</td>
<td>0.60</td>
<td>0.51</td>
<td>0.59</td>
</tr>
<tr>
<td>Response Speed</td>
<td>0.72</td>
<td>0.64</td>
<td>0.72</td>
</tr>
<tr>
<td>Memory</td>
<td>0.47</td>
<td>0.37</td>
<td>0.44</td>
</tr>
<tr>
<td>Cancellation Error</td>
<td>0.46</td>
<td>0.55</td>
<td>0.54</td>
</tr>
<tr>
<td>Verbal Fluency (FAS)</td>
<td>0.67</td>
<td>0.58</td>
<td>0.66</td>
</tr>
<tr>
<td>Stroop</td>
<td>0.32</td>
<td>0.18</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Unpublished data.
Iron imaging - SWI, MFC

- Iron necessary for normal brain function
- Tightly regulated
- Excess can be toxic - ROS
- Abnormal distribution of iron in the brain after mTBI
- SWI
- MFC is sensitive to small field inhomogeneities. Shown to correlate well with non-heme iron content in the brain
Deep Gray Matter Iron Susceptibility Weighted Imaging (SWI)

Control 45 yo male

MTBI 42 yo male
Iron deposition in MTBI - MFC

MTBI

control
# Brain Iron Quantification in Mild Traumatic Brain Injury: A Magnetic Field Correlation Study

**Table 2: Average MFC values \((s^{-2}) \pm SDs\) in healthy controls and patients with mild traumatic brain injury**

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Controls</th>
<th>mTBI Patients</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate</td>
<td>269 ± 146</td>
<td>326 ± 147</td>
<td>.111</td>
</tr>
<tr>
<td>Thalamus</td>
<td>149 ± 59</td>
<td>181 ± 65</td>
<td>.036*</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>689 ± 252</td>
<td>873 ± 327</td>
<td>.002*</td>
</tr>
<tr>
<td>Putamen</td>
<td>430 ± 166</td>
<td>493 ± 234</td>
<td>.331</td>
</tr>
<tr>
<td>Splenium</td>
<td>243 ± 190</td>
<td>210 ± 140</td>
<td>.638</td>
</tr>
<tr>
<td>Frontal lobe white matter</td>
<td>273 ± 176</td>
<td>203 ± 153</td>
<td>.130</td>
</tr>
</tbody>
</table>

**Note:** Asterisk indicates statistically significant comparisons.
MFC component analysis: Macro and Micro

• MFC provides a quantitative measure of magnetic field inhomogeneities (MFIs) created by spatial variations in magnetic susceptibility.
• By removing macroscopic MFIs (i.e. air, cavities, bone) on MFC ($\text{MFC}_{\text{mac}}$), $\text{MFC}_{\text{mic}}$ represents MFIs that are primarily contributed by nonheme iron.

Jensen JH et al MRM 2009
Diffusion Imaging of Gray Matter: Non-Gaussian DWI

• DWI, DTI assumes Gaussian distribution of diffusion
• Kurtosis is a measure of deviation from Gaussian
Specifically useful in GM?
More specific index of tissue microstructural complexity than conventional DWI, DTI? -- cellular components and barriers of diffusion

Thalamic DTI and DKI
26 patients with MTBI vs 18 controls

<table>
<thead>
<tr>
<th>Measures</th>
<th>Controls</th>
<th>MTBI</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>0.84 ± 0.02</td>
<td>0.86 ± 0.05</td>
<td>0.10</td>
</tr>
<tr>
<td>FA</td>
<td>0.31 ± 0.02</td>
<td>0.31 ± 0.03</td>
<td>0.20</td>
</tr>
<tr>
<td>MK</td>
<td>1.28 ± 0.04</td>
<td>1.23 ± 0.08</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Ge Y. Proc ISMRM 2006
In Group 2 MK in the thalamus was significantly correlated to neuropsychological z-scores for attention, concentration, and processing speed.
Thalamic function and connectivity: rsfMRI

- Spontaneous brain activity
- Low-frequency fluctuations in BOLD signal
- Coherent areas form networks
- Normal brain is organized into a small-world with significant modularity and highly connected hub regions

Wang, J et al Frontiers in systems neuroscience June 2010
Van den Heuvel MP, Euro Neuropsycho 2010

Event-related BOLD fMRI

Resting-state BOLD fMRI

Spontaneous low-freq fluctuations (<0.1Hz)
Normal brain is organized into a small-world with significant modularity and highly connected hub regions.
Thalamic Resting-State Functional Networks: Disruption in Patients with Mild Traumatic Brain Injury

©2011 by Radiological Society of North America

Default mode network (DMN): strongly active at rest; collection & evaluation of information; medial temporal lobe, medial prefrontal cortex, PCC, medial, lateral, and inferior parietal cortex.

Van den Heuvel MP, Euro Neuropsycho 2010
Default Mode Network Disruption in Mild Traumatic Brain Injury

• Default mode network (DMN) is of particular interest. DMN is a well-established network which is active at rest and suppressed during tasks requiring attention and decision making.

• There was significantly reduced fcMRI in PCC and parietal regions and increased frontal fcMRI around MPFC in patients with MTBI (P<0.01)

Zhou Y et. al. submit to Arch Neurol

NYU Langone Medical Center
Thalamic Conclusions

• Thalamus isn’t normal
• Focal nuclei may be injured
• Reduced MK may be related to decreased diffusion barriers (e.g., cell membranes) and decrease # of compartments (e.g., extra- and intra-cellular)
• Thalamic injury occurs early on in the disease
• Abnormal “hyper” connectivity in the resting state
What next?
Challenge

• Link separate hypotheses (white matter, gray matter, excitotoxicity, inflammation, genetic factors ApoE4, amyloid precursor protein, tau, iron)

• Elucidate pathophysiology

• Imaging biomarkers

• Directed development of therapy
Factors Influencing Recovery Rate

Adapted from Michael Selzer MD PhD, Temple University

NYU Langone Medical Center
<table>
<thead>
<tr>
<th>Source</th>
<th>Etiology</th>
<th>Loss of consciousness</th>
<th>Alteration of consciousness</th>
<th>Memory</th>
<th>Neurological symptoms/signs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Congress of Rehabilitation Medicine (Kay et al. 1993)</td>
<td>A traumatically induced physiological disruption of brain function</td>
<td>Any loss of consciousness</td>
<td>Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused)</td>
<td>Any loss of memory for events immediately before or after the accident</td>
<td>Focal neurological deficit(s) that may or may not be transient</td>
<td>After 30 minutes, an initial Glasgow Coma Scale score of 13–15, posttraumatic amnesia not greater than 24 hours</td>
</tr>
<tr>
<td>Centers for Disease Control and Prevention (2003)</td>
<td>Injury to the head resulting from blunt trauma or acceleration or deceleration forces</td>
<td>Observed or self-reported loss of consciousness lasting 30 minutes or less</td>
<td>Observed or self-reported transient confusion, disorientation, or impaired consciousness</td>
<td>Observed or self-reported dysfunction of memory (amnesia) around the time of injury</td>
<td>Observed signs of other neurological or neuropsychological dysfunction, such as seizures acutely following head injury; among infants/very young children: irritability, lethargy, or vomiting</td>
<td></td>
</tr>
<tr>
<td>World Health Organization (Carroll et al. 2004)</td>
<td>An acute brain injury resulting from mechanical energy to the head from external physical forces</td>
<td>Loss of consciousness for 30 minutes or less</td>
<td>Confusion or disorientation</td>
<td>Posttraumatic amnesia for less than 24 hours</td>
<td>Transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery</td>
<td>Glasgow Coma Scale score of 13–15 after 30 minutes must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries</td>
</tr>
</tbody>
</table>
### Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Motor</th>
<th>6</th>
<th>Obeys verbal commands</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>Localizes to noxious stimuli</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Normal flexion to noxious stimuli</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Abnormal flexion to normal stimuli (decorticate posturing)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Extension to noxious stimuli (decerebrate posturing)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>No response to noxious stimuli</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Verbal</th>
<th>5</th>
<th>Fully oriented and converses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>Disoriented and converses</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Voices appropriate words</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Makes incomprehensible sounds</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>No vocalization</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye Opening</th>
<th>4</th>
<th>Opens eyes spontaneously</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>Opens eyes to verbal commands</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Opens eyes to noxious stimuli</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>No eye opening</td>
</tr>
</tbody>
</table>

### TBI Classification

<table>
<thead>
<tr>
<th>TBI Severity</th>
<th>GCS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>13 - 15</td>
</tr>
<tr>
<td>Moderate</td>
<td>8 - 12</td>
</tr>
<tr>
<td>Severe</td>
<td>3 - 9</td>
</tr>
</tbody>
</table>

Motor Score
Verbal Score
+ Eye Opening Score
≈TBI Severity Classification

Teasdale et al., 1974.
Table 15-3. Criteria for postconcuessional syndromes and disorders

**ICD-criteria for postconcussion syndrome**

- A history of TBI and the presence of three or more of the following eight symptoms:
  - Headache
  - Dizziness
  - Fatigue
  - Irritability
  - Insomnia
  - Poor concentration
  - Memory difficulty
  - Intolerance of stress, emotion, or alcohol

**DSM-IV criteria for postconcussional disorder**

- A. History of TBI causing "significant cerebral concussion"
- B. Cognitive deficit in attention and/or memory
- C. Presence of at least three of the following eight symptoms that appear after injury and persist for 3 months:
  - Fatigue
  - Sleep disturbance
  - Headache
  - Dizziness
  - Irritability
  - Affective disturbance
  - Personality change
  - Apathy
- D. Symptoms that begin or worsen after injury
- E. Symptoms of sufficient severity to interfere with social role functioning
- F. Symptoms not better explained by dementia due to head trauma and another disorder

Multi-feature classification

- Improved accuracy (TN+TP) from 79% to 88%
Thank you Team TBI

- Oded Gonen, PhD
- Yulin Ge, PhD
- Elan Grossman, BS
- Michael Im, MD
- Jens Jensen, PhD
- Matilde Inglese, PhD
- Yong-Xia Zong, PhD
- James Babb, PhD
- Joseph Reaume, BA
- Steven Flanagan, MD
- Robert I Grossman, MD
- Xin (Cynthia) Wu, MD
- Leonid Drohznin, MD
- Jennifer Vaughn, MD
- Damon Kenul, BS
- Andrea (Siobhan) Kierans, MD

Funding:
- NIH
- R01 NS039135
- R01NS051623
- CTSI 1 UL1RR029893