Translational Neuroscience Imaging

Mild Traumatic Brain Injury

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Introduction

Goals

• Introduce the clinical problem of mild traumatic brain injury (m-TBI)

• Introduce basic concepts of diffusion MRI and its application to m-TBI research

• Inspire students to develop an interest in clinical and translational neuroscience

Outline

• About me

• Diffusion MRI

• Translational research in m-TBI

• Ongoing m-TBI research at the Philadelphia VA
About me

Undergraduate

- Syracuse University
- Physics and mathematics
- Why medical school?

Medical school

- Columbia University College of Physicians and Surgeons
Early research experiences

Voxel-Based Morphometry

Early research experiences

Quantitative Susceptibility Mapping

T2*  QSM

Ware et al. ASNR 2008 Annual meeting
Liu et al. *JMRM* 2014

Chen et al. *Radiology* 2014
“Translational” Research

Translational research Keys

- Perspective
  - Problems worth addressing
  - Problems possible to address
- Breadth of technical knowledge/abilities
- Collaboration
### Traumatic Brain Injury (TBI)

<table>
<thead>
<tr>
<th>Severity Index</th>
<th>Mild TBI/Concussion</th>
<th>Moderate TBI</th>
<th>Severe TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroimaging Findings</td>
<td>Normal structural imaging</td>
<td>Normal or abnormal structural imaging</td>
<td>Normal or abnormal structural imaging</td>
</tr>
<tr>
<td>Initial GCS</td>
<td>13-15</td>
<td>3-12</td>
<td>&lt; 9</td>
</tr>
<tr>
<td>Loss of Consciousness (LOC)</td>
<td>0-30 min</td>
<td>&gt; 30 min and &lt; 24 hours</td>
<td>&gt; 24 hrs</td>
</tr>
<tr>
<td>Length of Alteration of Consciousness (AOC)</td>
<td>a moment up to 24 hours</td>
<td>AOC &gt; 24 hours [use other criteria]</td>
<td></td>
</tr>
<tr>
<td>Length of Posttraumatic Amnesia (PTA)</td>
<td>0 – 1 day</td>
<td>&gt; 1 and &lt; 7 days</td>
<td>&gt; 7 days</td>
</tr>
</tbody>
</table>

80%

Traumatic Brain Injury (TBI)

Moderate/Severe

Mild
“Mild” Traumatic Brain Injury

High prevalence among athletes and Veterans
  - Est. 10-20% prevalence in post-9/11 combat Veterans
  - Blast injuries

• High public health burden
  - Up to 25% may experience *chronic physical, cognitive, and affective symptoms* 

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Complications of m-TBI

Compared to non-head injuries, m-TBI is associated with¹,²:

- Higher risk of chronic physical, somatic, and emotional symptoms
- Poorer neuropsychiatric outcomes
- Higher rates of comorbid psychiatric and substance use disorders
- Lower likelihood of returning to work
- Higher levels of healthcare resource utilization

Complications of m-TBI

Dementia?

- Punch-drunk syndrome (?)
- Dementia Pugilistica (1920s)
- Chronic traumatic encephalopathy (1973)

✓ Progressive neurodegenerative disorder
✓ Repetitive concussions + subconcussive head impacts
✓ Onset months, years, or decades after period of injuries

Chronic Traumatic Encephalopathy: A Potential Late Effect of Sport-Related Concussive and Subconcussive Head Trauma

Brandon E. Gavett, PhD, Robert A. Stern, PhD, Ann C. McKee, MD

Perelman School of Medicine at University of Pennsylvania
Penn Radiology
The spectrum of disease in chronic traumatic encephalopathy

- Accumulation of tau protein
- Disordered axonal varicosities
- Degenerated and disrupted white matter tracts
Control brain

John Grimsley

73 year old boxer

Staining for Tau protein
Complications of m-TBI

*CTE has been pathologically confirmed to occur in:*

- Football players
- Hockey players
- Military Veterans who experienced blast injury
- Professional wrestlers
- Mixed-martial artists
- Rugby players
- Soccer players
- Major league baseball player (???!!)
- Etc.
A report shows that Jovan Belcher, who killed his girlfriend before taking his own life in 2012, probably expanded sports concussion laws may help ensure safety of all teenage athletes.

LeBron James Explains Why He Won’t Let His Kids Play Football

In 2012, after Kansas City Chiefs linebacker Jovan Belcher shot and killed his girlfriend before fatally shooting himself in the head, LeBron James expressed concerns about the safety of his children in contact sports.
What can be done???

- Clinical evaluation & management of persistent symptoms following m-TBI remains challenging
- Few effective therapies
- High diagnostic overlap, no objective diagnostic tests
- Poor understanding of pathophysiology

Reliable biomarkers are sought to better understand the pathophysiology of m-TBI, improve diagnostic accuracy, and improve outcome prediction
Diffusion MRI

Why?

- Noninvasive
- No ionizing radiation
- Fast

- Provides microstructural information about white matter
  - Axonal integrity

How does it work?
MRI Signal Amplitude (Brightness)
Axons

MRI Signal Amplitude (Brightness)
MRI Signal Amplitude (Brightness)
Axons

Magnetic gradient 1
Magnetic gradient 2

\[ S = S_0 \times e^{-bD} \]
Metrics

Diffusion weighted image (DWI)

Diffusion tensor imaging (DTI)
- Mean diffusivity (MD)/Apparent diffusion coefficient (ADC)
- **Fractional anisotropy (FA)**
- Radial diffusivity (RD)
- Axial diffusivity (AD)

Color FA
NORMAL AXONS

Magnetic gradient 1

Magnetic gradient 2

MRI Signal (Brightness)
Magnetic gradient 1

Magnetic gradient 2

MRI Signal (Brightness)

AXONAL INJURY
Does it work?

Diffusion tractography based on the diffusion tensor model accurately depicts white matter tracts...

Given key assumptions:

✓ No crossing fibers in a voxel
✓ Fibers do not change direction within a voxel
DTI in m-TBI

• Several studies have demonstrated regions of reduced FA in groups of subjects with m-TBI compared to controls

• Reductions in FA in this setting are believed to reflect “axonal injury”

Tremblay et al. *Brain*. 2014

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Detection of Blast-Related Traumatic Brain Injury in U.S. Military Personnel

Christine L. Mac Donald, Ph.D., Ann M. Johnson, Dana Cooper, B.S., Elliot C. Nelson, M.D., Nicole J. Werner, Ph.D., Joshua S. Shimony, M.D., Ph.D., Abraham Z. Snyder, M.D., Ph.D., Marcus E. Raichle, M.D., John R. Witherow, M.D.,* Raymond Fang, M.D., Stephen F. Flaherty, M.D., and David L. Brody, M.D., Ph.D.
Abnormal White Matter Integrity Related to Head Impact Exposure in a Season of High School Varsity Football

Elizabeth M. Davenport,1,3,8 Christopher T. Whitlow,1–3,7 Jillian E. Urban,3,8 Mark A. Espeland,4 Youngkyoo Jung,1–3,8 Daryl A. Rosenbaum,5 Gerard A. Gioia,10 Alexander K. Powers,6,9 Joel D. Stitzel,3,6,8,9 and Joseph A. Maldjian1–3
The distribution of injuries is spatially heterogeneous, and no single distinct pattern has emerged.

Specific locations, however, are more commonly affected:

- **Corpus callosum**
- **Internal capsule**
- **Frontal and temporal lobe white matter pathways**
- **Cingulum bundle**

Our Research

What is the predictive value and ultimately clinical significance of DTI in combat Veterans who have sustained m-TBI?

Step 1 – Retrospectively analyze a large DTI data set collected in combat Veterans at the Philadelphia VA
**Study Design**

Post-deployment evaluation at Philadelphia VA 2008-2013

+ **TBI Screen**

TBI evaluation

Brain MRI

+ **TBI Diagnosis**

Neuropsychological testing

**Exclusion criteria** (n)

- Age > 50 (5)
- Abnormal brain MRI (4)
- Medical comorbidity (3)
- >1 year between clinical evaluation and brain MRI (3)
- Noncombat veterans (3)
- Less than 6 months of follow-up data (8)
- Severe non-head injury, e.g. amputation (0)

*Included all Veterans who screened positive on the initial TBI questionnaire and underwent brain MRI*

*After applying exclusion criteria, N = 72*
Polytrauma Evaluation

- All Veterans screening positive for possible m-TBI
- Details of traumatic incident(s) as recalled by each subject
- Neurobehavioral symptom inventory (NSI)

### Neurobehavioral Symptom Inventory

<table>
<thead>
<tr>
<th>Affective</th>
<th>Cognitive</th>
<th>Somatic</th>
<th>Vestibular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Concentration</td>
<td>Headache</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Sleep</td>
<td>Forgetfulness</td>
<td>Nausea</td>
<td>Balance</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Decision-making</td>
<td>Vision</td>
<td>Coordination</td>
</tr>
<tr>
<td>Sadness</td>
<td>Slowed thinking</td>
<td>Light sensitivity</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
<td>Hearing difficulty</td>
<td></td>
</tr>
<tr>
<td>Frustration</td>
<td></td>
<td>Taste/smell changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Appetite changes</td>
<td></td>
</tr>
</tbody>
</table>
Measures

Demographics
✓ Age
✓ Education level

Clinical characteristics
✓ Psychiatric diagnoses
✓ Symptom scores (PCL, BDI, NSI)
✓ Substance use
✓ Neuropsychological test scores
✓ TBI diagnosis

Injury characteristics
✓ Time from injury (at scan)
✓ Mechanism of injury
✓ Loss of consciousness

Outcome measures
✓ Return to employment
✓ Healthcare utilization (total number of healthcare visits/time of follow-up)
Imaging

- 1.5 T MRI
- 30-direction DTI (b=0 s/mm² and b=1000 s/mm²)
- DTI post-processed + analyzed with TBSS¹, part of FSL²

- Motion correction, brain extraction
- Generate DTI metrics
- Align subjects’ data to common space
- Generate “FA skeleton”
- Project each subject's FA data onto the mean FA skeleton

FA Fiber Integration (FAFI)

- Automated tractography performed from each voxel
- Integration of FA along the resultant tracts
- FA sum deposited within the starting voxel
- **FAFI is sensitive to distant changes in FA that occur along tracts which pass through the that voxel**

*Area under the curve (AUC) of FA along a fiber tract*
Statistical Design

Univariate analysis

- Group differences in FA and FAFI
- Regression of FA and FAFI across all subjects

Multivariate analysis

- Controlled for age, education, and time from injury

- Education level
- Psychiatric diagnoses
- Loss of consciousness
- Age
- Mechanism
- Time from injury
- TBI diagnosis
- Symptom scores
- Return to employment
- Healthcare utilization
## Population Characteristics

### (n=72)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>31 (22-46)</td>
</tr>
<tr>
<td>Percent male</td>
<td>93%</td>
</tr>
<tr>
<td>Education level (some college or higher)</td>
<td>43%</td>
</tr>
<tr>
<td>PTSD</td>
<td>82%</td>
</tr>
<tr>
<td>Depression</td>
<td>36%</td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>35%</td>
</tr>
</tbody>
</table>

### DTI correlates of population characteristics

- Substance use disorder (FAFI): $p < .025$
- Depression (FA): $p < .025$
Population Characteristics

- Affective NSI cluster (FAFI – inverse correlation)
  \[ p < .025 \]

- NSI total score (FAFI – inverse correlation)
  \[ p < .025 \]

No statistically significant relationships:
Age, education level, PTSD, PCL score, other NSI clusters
TBI Characteristics

<table>
<thead>
<tr>
<th>TBI Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=72)</td>
<td></td>
</tr>
<tr>
<td>Blast mechanism</td>
<td>81%</td>
</tr>
<tr>
<td>Loss of consciousness (LOC)</td>
<td>49%</td>
</tr>
<tr>
<td>TBI diagnosis</td>
<td>78%</td>
</tr>
<tr>
<td>Time from injury (range)</td>
<td>3.9 years (1-10)</td>
</tr>
</tbody>
</table>

No statistically significant differences or correlations with imaging metrics:

- Injury mechanism, LOC, TBI diagnosis

DTI correlates of TBI characteristics

Length of time between TBI and MRI (FAFI)
Neuropsychological Testing

*DTI correlates of neuropsychological test performance*

Forward digit span test
(Direct correlation with FA)

\[ p < .025 \]

Forward digit span test
(Direct correlation with FAFI)

\[ p < .025 \]
Neuropsychological Testing

Trails test part B
(Direct correlation with FA)

$p < .025$

No significant correlations with logical memory tests (I&II), trails test part A, or FSIQ
# Outcome

<table>
<thead>
<tr>
<th></th>
<th>Population (n=72)</th>
<th>Employed at follow-up (n = 43)</th>
<th>Unemployed at follow-up (n=29)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>31</td>
<td>31.9</td>
<td>29.1</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Length of follow-up</strong></td>
<td>1.5 (0.5-3.5)</td>
<td>1.5</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td><strong>Time since injury (years)</strong></td>
<td>3.9</td>
<td>3.7</td>
<td>4.2</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Some college education (or higher)</strong></td>
<td>29 (40%)</td>
<td>18 (42%)</td>
<td>11 (38%)</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>PTSD</strong></td>
<td>58 (81%)</td>
<td>32 (74%)</td>
<td>26 (90%)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>25 (35%)</td>
<td>13 (30%)</td>
<td>12 (40%)</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Substance use disorder</strong></td>
<td>32 (44%)</td>
<td>17 (40%)</td>
<td>15 (52%)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Close blast</strong></td>
<td>45 (63%)</td>
<td>30 (70%)</td>
<td>15 (52%)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Loss of consciousness</strong></td>
<td>35 (49%)</td>
<td>25 (60%)</td>
<td>10 (30%)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>TBI diagnosis</strong></td>
<td>56 (78%)</td>
<td>34 (79%)</td>
<td>22 (76%)</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>TBI symptoms</strong></td>
<td>36 (50%)</td>
<td>20 (47%)</td>
<td>16 (55%)</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>NSI (total)</strong></td>
<td>41.4</td>
<td>41</td>
<td>42.1</td>
<td>0.75</td>
</tr>
</tbody>
</table>
Outcome

Return to employment (FA)  Healthcare resource utilization (FAFI)

$p < .025$
Baseline mean left external capsule FA and employment status at follow-up

Unemployed at follow-up

Employed at follow-up

$\textit{p} < .001$
Outcome

Multivariate analysis

Return to employment (FA)
Controlled for age, education level, and time from injury

$p < .025$
Key findings

• Direct correlation between white matter anisotropy and time from injury
  ✓ Repair?
  ✓ Awareness?

• Anisotropy measurements help identify the neural correlates of neuropsychological function and symptomatology

• Differences in white matter microstructure, largely unrelated to other baseline characteristics, may account for observed variance in functional outcomes

• *DTI has the potential to identify subjects with m-TBI who are at high risk of poor functional outcome*
Limitations and future directions

- Technical improvements – towards individual applicability
  - Spatial heterogeneity
  - Standardization?
  - Normative database?
  - Beyond the tensor model – HARDI, Q-ball, diffusion spectrum imaging (DSI)

- Additional modalities
  - Tau imaging

The potential of diffusion-based MRI techniques to improve detection, understanding, and clinical management of m-TBI remains largely untapped
Thank you!

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