Traumatic Brain Injury: What Do We Know? What Should We Do?

Elaine R. Peskind, MD

Assoc. Director, Alzheimer’s Disease Research Center
Friends of Alzheimer’s Research Professor
Department of Psychiatry & Behavioral Sciences
University of Washington School of Medicine

Co-Director
VISN 20 Mental Illness Research, Education, and Clinical Center (MIRECC)

Staff Psychiatrist, Joint Base Lewis McChord, Tacoma WA
2.4 million Service Members have been deployed to Iraq and Afghanistan; approximately 9-18% return with symptomatic mTBI.
Potential Consequences of Repetitive Mild Head Trauma

NFL Pro-Bowl 1988

There is growing concern that repetitive concussive and subconcussive head injuries can set in motion pathogenic processes that later emerge as neurodegenerative dementing disorders.

McKee et al., *J Neuropathol Exp Neurol* 68:709-735, 2009
Images from CNN
Junior Seau had degenerative brain disease when he committed suicide.
Chronic Traumatic Encephalopathy in Blast-Exposed Military Veterans and a Blast Neurotrauma Mouse Model

Lee E. Goldstein,1,2,3,4* Andrew M. Fisher,1,4 Chad A. Tagge,1,4 Xiao-Lei Zhang,5 Libor Velisek,5 John A. Sullivan,5 Chirag Uperti,5 Jonathan M. Kracht,4 Maria Ericsson,6 Mark W. Wojnarowicz,1 Cezar J. Goletiani,5 Giorgi M. Maglakelidze,5 Noel Casey,1,3 Juliet A. Moncaster,1,3 Olga Minaeva,1,3,4 Robert D. Moir,7 Christopher J. Nowinski,8 Robert A. Stern,2,8 Robert C. Cantu,8,9 James Geiling,10 Jan K. Blusztajn,2 Benjamin L. Wolozin,2 Tsuneya Ikezu,2 Thor D. Stein,2,11 Andrew E. Budson,2,11 Neil W. Kowall,2,11 David Chargin,12 Andre Sharon,4,12 Sudad Saman,13 Garth F. Hall,13 William C. Moss,14 Robin O. Cleveland,15 Rudolph E. Tanzi,7 Patric K. Stanton,5 Ann C. McKee2,8,11*
Tau pathology in the brain of a 27 year old Iraq Veteran

Photomicrographs of tau-immunostained section of the frontal cortex showing frequent neurofibrillary tangles and neuritic threads (Omalu et al, Neurosurg Focus 31:E3, 2011).
FDDNP-PET scan results for five retired NFL players and one control subject.

Scatter plots of FDDNP binding values in players and controls

Repetitive sports concussion is associated with increased risk of the rare mid-life dementing disorder, chronic traumatic encephalopathy (CTE).

Traumatic brain injury (TBI) is currently the best characterized environmental risk factor for developing the common late-life dementing disorder, Alzheimer’s disease.
The Controversy

- Controversy about etiology, course, and treatment of persistent somatic, cognitive, and behavioral symptoms in Iraq and Afghanistan Veterans following mTBI.
- An epidemiological study in military personnel found that symptoms of chronic mTBI (except for headache) more correlated with PTSD and depression.
The Controversy (continued)

- However, many skilled clinicians are convinced that war combatants’ chronic symptoms of mTBI reflect real albeit subtle persistent brain damage.
- Do these chronic symptoms reflect persistent changes in brain structure, function, and/or cerebrospinal fluid biomarkers of neurodegeneration?
Participants

- 34 male Iraq/Afghanistan Veterans with blast-induced mild traumatic brain injury
  - Mean age 31.6 ± 9.2 years
- 16 non blast-exposed Iraq/Afghanistan Veterans
  - Mean age 32.8 ± 7.3 years (15M, 1F)
- 12 civilian community controls – FDG-PET only
  - Mean age 53 ± 2.0 years (7M, 5F)
- 55 male civilian community controls – CSF only
  - Mean age 31.8 ± 6.8 years
Participants

• 17 of the mTBI Veterans also met DSM-IV criteria (via CAPS interview) for combat operations posttraumatic stress disorder (PTSD).

• The mTBI group had higher scores for depression and alcohol use and had poorer sleep.

• Nearly all the mTBI Veterans had persistent postconcussive symptoms.
<table>
<thead>
<tr>
<th>Symptom</th>
<th>TBI (N=33)</th>
<th>Control (N=15)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forgetfulness</td>
<td>67 %</td>
<td>20 %</td>
<td>.001</td>
</tr>
<tr>
<td>Feeling anxious or tense</td>
<td>67 %</td>
<td>13 %</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Difficulty falling or staying asleep</td>
<td>64 %</td>
<td>13 %</td>
<td>.002</td>
</tr>
<tr>
<td>Ringing in ears</td>
<td>64 %</td>
<td>0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Irritability</td>
<td>61 %</td>
<td>13 %</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Headaches</td>
<td>61 %</td>
<td>7 %</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sensitivity to noise</td>
<td>58 %</td>
<td>0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Poor concentration/attention</td>
<td>52 %</td>
<td>13 %</td>
<td>.001</td>
</tr>
<tr>
<td>Hearing difficulty</td>
<td>52 %</td>
<td>0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Slowed thinking</td>
<td>52 %</td>
<td>13 %</td>
<td>.001</td>
</tr>
</tbody>
</table>
Blast Exposure History

• Average time since last blast exposure was 4 years
• The average number of blast exposures resulting in loss of consciousness was 1.
• Majority had repetitive mTBI. Average number of blast exposures in Iraq or Afghanistan in the mTBI group was 14.
  – single blast-mTBI  9%
  – 2-5 blast mTBIs  29.4%
  – 6-10 blast mTBIs  20.6%
  – 11-15 blast mTBIs  6%
  – 16-20 blast mTBIs  14.7%
  – 21-50 blast mTBIs  9%
  – 51-100 blast mTBIs  11.8%
Multimodal Neuroimaging

- Structural Neuroimaging
  - Diffusion Tensor Imaging
  - Macromolecular Proton Fraction (MPF) Mapping

- Functional Neuroimaging:
  - $[^{18}\text{F}]$-Fluorodeoxyglucose Positron Emission Tomography ($[^{18}\text{F}]$-FDG-PET)
Isotropic diffusion within a single voxel
Cellular elements that contribute to diffusion anisotropy

Hagmann, P. et al. Radiographics 2006;26:S205-S223
Anisotropic diffusion within a single voxel
Neuroimaging of Blast-Trauma TBI: State-of-the-Art

- Magnetic Resonance (MR) Diffusion Tensor Imaging
  - Levin et al., *NeuroImage*, 2010
  - Davenport et al., *Neuroimage*, 2012
  - Morey et al., *Human Brain Mapping*, 2012
  - Bazarian et al., *J Head Trauma Rehabil*, 2012
  - Jorge et al., *Am J Psychiatry*, 2012
**RESULTS:**

- Decreased fractional anisotropy in genu of corpus callosum in mTBI Veterans compared to Nonblast Veterans (p <0.05)
- Within mTBI group, no differences between Veterans with and without PTSD
Diffusion Tensor Imaging: Conclusions

• Preliminary results from our laboratory show decreased FA in corpus callosum an average of 4 years following last blast exposure in Iraq and Afghanistan Veterans with mTBI vs. deployed control Veterans without TBI, consistent with diffuse axonal injury.

• These results could not be attributed to PTSD.

• DTI studies in Iraq/Afghanistan Veterans vary among labs – both in Methods and Results

• Are there other structural MRI techniques which may be more sensitive to chronic changes following blast concussion mTBI?
Macromolecular Proton Fraction (MPF) Mapping

- MPF is a magnetization transfer structural imaging technique which provides an index of macromolecular composition.
- MPF correlates with indices of central myelin integrity in humans and in animal models of multiple sclerosis and spinal cord injury.
Macromolecular Proton Fraction (f) Histogram Parameters for blast-exposed (N=27) vs. non-blast exposed Iraq/Afghanistan Veterans (n=16)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>mTBI</th>
<th>Controls</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM</td>
<td>$f_1$ (%)</td>
<td>5.56±0.35</td>
<td>5.86±0.22</td>
</tr>
<tr>
<td>WM</td>
<td>$f_2$ (%)</td>
<td>11.17±0.66</td>
<td>11.87±0.3</td>
</tr>
<tr>
<td>Mixed</td>
<td>$f_3$ (%)</td>
<td>8.36±0.60</td>
<td>9.01±0.30</td>
</tr>
</tbody>
</table>

<sup>a</sup>Independent one-tailed t-test

Plot of group mean whole-brain MPF (f) histograms for Iraq/Afghanistan mTBI (n=27) vs. Iraq/Afghanistan non blast-exposed (n=16) Veterans
Magnetization Transfer Molecular Proton Bound Fraction (MPF): Z-score subtraction maps of MPF values in Blast-mTBI Veterans (N=27) compared to Nonblast Veterans (N=16)

RESULTS:
Reduced MPF in numerous subgyral, cortical-subcortical, and longitudinal white matter (WM) tracts (Zs>4.0, all p’s <0.05)
• Within mTBI group, no differences between Veterans with and without PTSD
• Findings consistent with the mechanism of diffuse axonal injury and suggest alterations of myelin structure in white matter tracts known to be vulnerable to damage in diffuse axonal injury.
• Potential as prospective quantitative biomarker of blast-induced mTBI
### Macromolecular Proton Bound Fraction (f): Voxelwise Subtraction Analysis Results

<table>
<thead>
<tr>
<th>Structure*</th>
<th>Tissue Component</th>
<th>Coordinates (mm)¶</th>
<th>Z score</th>
<th>Reduction (%)@</th>
</tr>
</thead>
<tbody>
<tr>
<td>R External Capsule</td>
<td>WM</td>
<td>(-30, -1, 0)</td>
<td>4.4</td>
<td>10.5 ‡</td>
</tr>
<tr>
<td>R Internal Capsule, Anterior Limb</td>
<td>WM</td>
<td>(-17, 17, 9)</td>
<td>4.0</td>
<td>12.3 §</td>
</tr>
<tr>
<td>R Superior Longitudinal Fasciculus</td>
<td>WM</td>
<td>(-44, -6, 27)</td>
<td>4.1</td>
<td>16.3 ‡</td>
</tr>
<tr>
<td>R Superior Frontal Gyrus</td>
<td>GM, WM</td>
<td>(-24, 59, 22)</td>
<td>4.6</td>
<td>35.8 §</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>(-17, -13, 45)</td>
<td>4.4</td>
<td>7.2 §</td>
</tr>
<tr>
<td></td>
<td>GM/WM Border</td>
<td>(-17, 8, 58)</td>
<td>4.0</td>
<td>27.0 §</td>
</tr>
<tr>
<td></td>
<td>GM/WM Border</td>
<td>(-6, 32, 27)</td>
<td>4.0</td>
<td>17.6 ‡</td>
</tr>
<tr>
<td></td>
<td>GM</td>
<td>(-24, 66, 7)</td>
<td>4.0</td>
<td>36.4 §</td>
</tr>
<tr>
<td>R Middle Frontal Gyrus</td>
<td>WM</td>
<td>(-39, 1, 47)</td>
<td>4.4</td>
<td>19.6 ‡</td>
</tr>
<tr>
<td></td>
<td>GM</td>
<td>(-46, 50, -2)</td>
<td>4.1</td>
<td>28.1 †</td>
</tr>
<tr>
<td></td>
<td>GM/WM Border</td>
<td>(-37, 48, -4)</td>
<td>4.3</td>
<td>16.7 ‡</td>
</tr>
<tr>
<td>L Inferior Frontal Gyrus</td>
<td>GM, WM</td>
<td>(42, 5, 20)</td>
<td>4.3</td>
<td>24.3 §</td>
</tr>
<tr>
<td>R Medial Orbital Gyrus</td>
<td>GM</td>
<td>(-26, 37, -16)</td>
<td>4.2</td>
<td>30.5 ‡</td>
</tr>
<tr>
<td></td>
<td>GM</td>
<td>(-21, 5, -11)</td>
<td>4.1</td>
<td>18.4 §</td>
</tr>
<tr>
<td>R Precentral Gyrus</td>
<td>WM</td>
<td>(-19, -17, 45)</td>
<td>4.4</td>
<td>8.1 §</td>
</tr>
<tr>
<td></td>
<td>GM</td>
<td>(-46, -13, 43)</td>
<td>4.1</td>
<td>19.6 ‡</td>
</tr>
<tr>
<td>R Anterior Cingulate Gyrus</td>
<td>GM</td>
<td>(-3, 41, 18)</td>
<td>4.5</td>
<td>23.6 §</td>
</tr>
<tr>
<td>L Subcallosal Gyrus</td>
<td>GM</td>
<td>(15, 3, -14)</td>
<td>4.3</td>
<td>32.5 §</td>
</tr>
<tr>
<td>L Superior Parietal Lobule</td>
<td>WM</td>
<td>(15, -62, 32)</td>
<td>4.0</td>
<td>15.6 §</td>
</tr>
<tr>
<td>R Precuneus</td>
<td>WM</td>
<td>(-21, -58, 38)</td>
<td>4.2</td>
<td>16.8 §</td>
</tr>
<tr>
<td>L Lingual Gyrus</td>
<td>GM</td>
<td>(12, -91, -11)</td>
<td>4.2</td>
<td>20.2 §</td>
</tr>
</tbody>
</table>

† p<0.05, ‡ p<0.01, § p<0.001 (Independent groups t-test, one-tailed)
Conclusions - MPF

- Observed reduction of bound pool fraction in white matter on whole brain analysis is consistent with the mechanism of diffuse axonal injury.
- Voxelwise analysis of MPF images suggests alterations of myelin structure in white matter tracts known to be vulnerable to damage in diffuse axonal injury.
- Altered MPF parameters have potential as prospective quantitative biomarkers of blast-induced mTBI.
Uptake of FDG. FDG is a glucose analog that is taken up by metabolically active cells by means of facilitated transport via glucose transporters (Glut) in the cell membrane. In the cell cytoplasm, FDG undergoes phosphorylation to form FDG-6-phosphate (6P), which, unlike glucose, cannot undergo further metabolism and becomes trapped within the cell. N = nucleus.
FDG-PET Spatial Normalization and Transformation to Standard Stereotactic Coordinate Space

Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET): Composite Z-score subtraction maps of regional brain glucose metabolism in Blast-mTBI Veterans (N=33) vs. Nonblast Veterans (N=16)

RESULTS:

• Regional glucose hypometabolism in parietal lobes bilaterally, left sensorimotor cortex and right visual cortex in mTBI Veterans (all p’s < 0.05)
• Within mTBI group, no differences between Veterans with and without PTSD
FDG-PET: Composite Z-score subtraction maps of regional brain glucose metabolism in Blast-mTBI Veterans vs. civilian controls (N=12) and Nonblast Veterans vs. civilian controls

RESULTS:
• Compared to civilian community controls, both Blast-mTBI and Nonblast Veterans have glucose hypometabolism in the cerebellum, pons, thalamus and medial temporal lobes bilaterally (all p’s < 0.05).
Summary and Conclusions

• Caution needed!
  – neuropsychological test performance deficits only with difficult executive tasks
  – no differences in CSF biomarkers between blast exposed OIF Veterans and non blast-exposed OIF Veterans
  – more data, analysis, and replication needed
  – must be careful about selection of control groups – need multiple control groups to determine what is specifically blast-related
  – longitudinal follow-up essential!
What Should We Do?

• Much more research needed:
  • DoD ADNI
  • DoD/VA TBI Consortium

• Reducing your own risk
  • Avoid head trauma: wear seatbelt, helmet

• Are contact sports safe?
  • Youth sports, collegiate and professional sports
Collaborators

• VA MIRECC
  – Eric Petrie, MD
  – Murray Raskind, MD
  – Kathleen Pagulayan, PhD
  – Jim Leverenz, MD
  – Cynthia Mayer, DO
  – Kim Hart, PA-C
  – David Hoff, PA-C
  – Jane Shofer, MS

• University of Washington
  – Donna Cross, PhD
  – Satoshi Minoshima, MD, PhD
  – Vasily Yarnykh, PhD
  – Natalia Kleinhans, PhD
  – Todd Richards, PhD
  – Raimondo D’Ambrosio, PhD
  – Tom Montine, MD, PhD
  – Jing Zhang, MD, PhD

• VA GRECC
  – David Cook, PhD
  – Charles Wilkinson, PhD
  – Chang-En Yu, PhD

Ray Bennett, PhD, Baker Risk, San Antonio, TX

Supported by the Department of Veterans Affairs
Collaborators

• Special Thanks to:
  – Command Sgt Maj (ret) Thomas Adams
  – Command Sgt Maj Robert Prosser
  – First Sgt (ret) Creed McCaslin

First Stryker Brigade (Lancers), 25th Infantry Division, Mosul, Iraq, 2004-2005

Supported by the Department of Veterans Affairs