White Matter Damage and Cognitive Impairment After Mild Traumatic Brain Injury
Toronto Sick Kids 3rd Brain Injury in Children
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Disclosures

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• Conflicts of Interest: none
Axonal injury can be the predominant neuropathological feature in many TBI patients with reduced levels of consciousness and/or impaired cognitive function during life.

Fig. 9—A bundle of the internal capsule of the third case (survival for 24 days). (Holmes silver impregnation × 235).

The large blobs are the retraction balls (arrows to two) which form at the ends of severed nerve fibres. Fragmented and degenerating axons can also be seen.
Traumatic Axonal Injury is Common

**Table 2. Neuropathology**

<table>
<thead>
<tr>
<th>Patient</th>
<th>AI</th>
<th>Hypoxic/ischemic damage</th>
<th>Contusion</th>
<th>Gliding contusion</th>
<th>Hematoma (&gt;3 cm)</th>
<th>ASDH</th>
<th>ICP</th>
<th>Skull fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
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<td>0</td>
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<td>7</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>LASDH craniotomy (low)</td>
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<td>8</td>
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<td>+++</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>ICP monitor</td>
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<tr>
<td>9</td>
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<td>+++</td>
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<td>0</td>
<td>0</td>
<td>Small LASDH</td>
</tr>
<tr>
<td>11</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Small bilateral</td>
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<tr>
<td>12</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>EDH</td>
</tr>
</tbody>
</table>

Blumbergs et al., J Neurotrauma 1995
“Since the amount of DAI was directly proportional to the severity of injury (duration of coma and quality of outcome), we conclude that axonal damage produced by coronal head acceleration is a major cause of prolonged traumatic coma and its sequelae.”
Conventional Imaging Methods do NOT Accurately Reveal Axonal Injury

- CT is sensitive primarily to hemorrhage and skull fracture
- Conventional MRI is sensitive to edema and mass effect
- Diffusion weighted MRI is sensitive to infarction
- T2* and Susceptibility Weighted MRI are sensitive to microhemorrhages.

All of these pathologies can be associated with traumatic axonal injury, but axonal injury can occur without any of them.

Thus, a negative CT or conventional MRI does NOT indicate that there has been no injury to the brain.
Diffusion Tensor Imaging (DTI)

A  Diffusion Tensor Imaging

1. Collect diffusion weighted images in six or more directions
2. Calculate diffusion tensor for each voxel
3. Separate parallel ($\lambda_1$, axial) from perpendicular ($\lambda_2, \lambda_3$, radial) diffusion. Calculate anisotropy.

Brain white matter: organized, myelinated axons

B  Traumatic axonal injury: simplified model

Axonal Disruption: reduced $\lambda_1$ (axial), reduced anisotropy
Myelin Injury: incr. $\lambda_2, \lambda_3$ (radial), reduced anisotropy
Mixed Injury: greatly reduced anisotropy
Correlation with Injury Severity

Change in Relative Anisotropy accurately reflects injury severity.

For the least severe injuries, (1.0 mm) DTI may be more sensitive than immunohistochemistry.

Further investigation of these least severe injuries.
What about concussion?

TBI-TBI

No obvious lesion

Shitaka et al JNEN 2011
Subtle Axonal Injury

- **TBI-TBI**
- **TBI-Sham**
- **Sham-Sham**

**Ipsi. Cortex & ext. capsule**

- **D**
- **E**
- **F**

**Ipsi. Thal.**

- **G**
- **H**
- **I**

**Corpus Callos.**

- **J**
- **K**
- **L**
DTI in rcTBI

Bennett et al Neuroscience Letters 2012
Delayed Reduction in Axial Diffusivity

C: White Matter

D: RA

E: RD

F: AD

G: MD

Sham  rcTBI 24h  rcTBI 7d

0.45  0.50  0.55  0.60  0.65  0.70

0.40  0.45  0.50  0.55  0.60  0.65

0.35  0.40  0.45  0.50  0.55  0.60

0.90  1.00  1.10  1.20  1.30  1.40

0.65  0.70  0.75  0.80  0.85  0.90

**  **  **  **  **  **

*  *  *  *  *  *
Human Studies

Orbitofrontal White Matter – Chronic Blast -TBI

Voxel Size: 0.5 x 0.5 x 0.5 mm
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.
Examples of DTI Abnormalities.
(Note normal Conventional MRI)
Analysis: Hand-drawn, multi-slice Regions-of-Interest
Brain Regions Commonly Injured in Civilian TBI.

- Some abnormalities but mostly normal
Simulations predict high shear stresses in specific regions, independent of blast orientation.
Brain Regions Predicted to be Susceptible to Blast: *More Commonly Affected*

- **Bilateral Cingulum**
  - Relative Anisotropy
  - Control: 0.25, 0.30, 0.35, 0.40, 0.45, 0.50
  - TBI: **p=0.0015**

- **Bilat. Mid. Cerebellar Peduncle**
  - Relative Anisotropy
  - Control: 0.25, 0.30, 0.35, 0.40, 0.45
  - TBI: ***p=0.0003***

- **Left Orbitofront White Matter**
  - Relative Anisotropy
  - Control: 0.10, 0.15, 0.20, 0.25, 0.30, 0.35
  - TBI: *p=0.04*

- **Right Orbitofront White Matter**
  - Relative Anisotropy
  - Control: 0.10, 0.15, 0.20, 0.25
  - TBI: *p=0.007*
Assessment of Individual Subjects:

18/63 Definitely Abnormal on DTI
All 63 had normal CTs and normal conventional MRIs including T2*

Bilateral Cingulum
Control TBI
0.25
0.30
0.35
0.40
0.45
0.50 ** p=0.0015
(13)
Relative Anisotropy

Bilat. Mid. Cerebellar Peduncle
Control TBI
0.25
0.30
0.35
0.40
0.45
0.50 *** p=0.0003
(14)
Relative Anisotropy

Left Orbitofront White Matter
Control TBI
0.10
0.15
0.20
0.25
0.30
0.35
p=0.04
(8)
Relative Anisotropy

Right Orbitofront White Matter
Control TBI
0.10
0.15
0.20
0.25
0.30
0.35
*p=0.007
(13)
Relative Anisotropy

Number of Abnormal Regions of Interest
(Relative Anisotropy <2 StDev Below Control)

Number of Subjects
A
B

18/63 Observed, 2/63 Expected, p=0.0001, Chi-Square
DTI-based correlations with clinical outcomes
Clinical Outcomes

• Global: Glasgow Outcome Scale-Extended
• Neuropsychological Testing
• Neurological Evaluation
• Psychiatric Interview for Depression and Post-traumatic stress disorder (PTSD)
Overall Outcome: Glasgow Outcome Scale

- Substantially worse than expected for civilians with “mild” TBI, based on historical samples (10-20% Moderate-Severe Disability at 6-12 months).
- High levels of disability in control group as well.

Mac Donald et al, unpublished data
### Table S2: Neuropsychological Test Performance

<table>
<thead>
<tr>
<th>Test</th>
<th>TBI (n=47)</th>
<th>Control (n=18)</th>
<th>TBI GOSE &lt;7 (n=41)</th>
<th>TBI GOSE 7-8 (n=6)</th>
<th>TBI+ PTSD (n=29)</th>
<th>TBI No PTSD (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>25-Foot Walk (seconds)</strong> (Motor Strength, Balance, Coordination)</td>
<td></td>
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<tr>
<td></td>
<td>4.7±1.0</td>
<td>5.2±2.1</td>
<td>4.8±1.0</td>
<td>4.2±1.2</td>
<td>4.7±1.0</td>
<td>4.6±0.9</td>
<td>0.41 (T)</td>
</tr>
<tr>
<td><strong>Conners’ Continuous Performance Test II</strong></td>
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</tr>
<tr>
<td>Omission Errors: (Attention Lapses)</td>
<td>-0.14±1.3</td>
<td>-0.45±2.1</td>
<td>0.47 (U)</td>
<td>-0.21±1.3</td>
<td>0.36±0.4</td>
<td>0.15 (T)</td>
<td>0.04 (U)</td>
</tr>
<tr>
<td>Commission Errors: (Impulsivity)</td>
<td>-0.17±1.0</td>
<td>-0.1±1.1</td>
<td>0.38 (T)</td>
<td>-0.19±1.0</td>
<td>-0.09±1.0</td>
<td>0.41 (T)</td>
<td>0.06 (T)</td>
</tr>
<tr>
<td>Hit Rate: (Reaction Time)</td>
<td>0.23±0.9</td>
<td>0.06±1.1</td>
<td>0.26 (T)</td>
<td>0.25±0.8</td>
<td>0.10±1.4</td>
<td>0.36 (T)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hit Rate Block Change: (Sustained Vigilance)</td>
<td>-0.22±1.1</td>
<td>-0.26±1.0</td>
<td>0.33 (U)</td>
<td>-0.26±1.1</td>
<td>0.06±0.5</td>
<td>0.34 (U)</td>
<td>0.20 (U)</td>
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<tr>
<td><strong>Wisconsin Card Sorting Test:</strong> Total Errors (Concept Formation, Mental Flexibility)</td>
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<tr>
<td></td>
<td>0.66±0.9</td>
<td>0.58±0.8</td>
<td>0.38 (T)</td>
<td>0.66±1.0</td>
<td>0.62±0.6</td>
<td>0.46 (T)</td>
<td>0.43 (T)</td>
</tr>
<tr>
<td><strong>Rey-Osterrieth Complex Figure Test:</strong> Delayed Recall (Visual Memory)</td>
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<tr>
<td></td>
<td>-0.55±1.7</td>
<td>0.03±1.3</td>
<td>0.10 (T)</td>
<td>-0.58±1.7</td>
<td>-0.32±1.5</td>
<td>0.36 (T)</td>
<td>-0.84±2.0</td>
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<tr>
<td><strong>Wechsler Test of Adult Reading</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(Estimate of Pre-injury Verbal Intelligence)</td>
<td>-0.18±1.2</td>
<td>-0.24±1.3</td>
<td>0.40 (U)</td>
<td>-0.22±1.1</td>
<td>0.07±1.4</td>
<td>0.27 (T)</td>
<td>0.36 (T)</td>
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<tr>
<td><strong>California Verbal Learning Test II</strong></td>
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<tr>
<td>Long-Delay Free Recall (Verbal Memory)</td>
<td>-0.13±0.9</td>
<td>0.0±0.9</td>
<td>0.35 (U)</td>
<td>-0.05±0.9</td>
<td>-0.7±1.0</td>
<td>0.13 (U)</td>
<td>0.46 (T)</td>
</tr>
<tr>
<td>Total Intrusions (Falsely Recalled Items)</td>
<td>-0.15±1.0</td>
<td>-0.44±1.5</td>
<td>0.31 (U)</td>
<td>-0.11±1.1</td>
<td>-0.42±0.5</td>
<td>0.15 (U)</td>
<td>0.32 (U)</td>
</tr>
<tr>
<td>List B vs. Trial 1 List A (Proactive Memory Interference)</td>
<td>-0.34±1.1</td>
<td>0.11±1.1</td>
<td>0.07 (T)</td>
<td>-0.39±1.1</td>
<td>-0.08±0.9</td>
<td>0.26 (T)</td>
<td>0.46 (T)</td>
</tr>
<tr>
<td><strong>Grooved Pegboard</strong> (Motor Speed &amp; Coordination)</td>
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<tr>
<td>Dominant Hand Time</td>
<td>-1.1±0.8</td>
<td>-1.4±0.6</td>
<td>0.10 (T)</td>
<td>-1.06±0.9</td>
<td>-1.35±0.5</td>
<td>0.22 (T)</td>
<td>0.13 (U)</td>
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<tr>
<td>Non-Dominant Hand Time</td>
<td>-1.0±0.8</td>
<td>-1.3±0.8</td>
<td>0.16 (T)</td>
<td>-1.07±0.8</td>
<td>-0.68±0.6</td>
<td>0.15 (T)</td>
<td>0.26 (T)</td>
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<td><strong>Trail Making Test</strong></td>
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<tr>
<td>Trails A time (Visual Scanning, Coordination)</td>
<td>-0.29±1.1</td>
<td>-0.09±0.9</td>
<td>0.25 (T)</td>
<td>-0.33±1.0</td>
<td>-0.02±1.3</td>
<td>0.25 (T)</td>
<td>0.08 (T)</td>
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<tr>
<td>Trails B time (Trails A + Mental Flexibility)</td>
<td>-0.23±1.1</td>
<td>0.02±0.9</td>
<td>0.20 (T)</td>
<td>-0.26±1.1</td>
<td>-0.02±0.9</td>
<td>0.30 (T)</td>
<td>0.12 (T)</td>
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<td><strong>Symbol Digit Modalities Test</strong></td>
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<tr>
<td>(Working Memory)</td>
<td>-0.22±0.8</td>
<td>0.14±1.0</td>
<td>0.04 (U)</td>
<td>-0.27±0.8</td>
<td>0.08±0.5</td>
<td>0.24 (U)</td>
<td>0.46 (U)</td>
</tr>
<tr>
<td><strong>Controlled Oral Word Association</strong></td>
<td></td>
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<tr>
<td>Total Score: (Verbal Fluency)</td>
<td>-0.80±0.9</td>
<td>-1.08±0.7</td>
<td>0.12 (T)</td>
<td>-0.81±0.9</td>
<td>-0.75±1.0</td>
<td>0.44 (T)</td>
<td>0.42 (T)</td>
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</table>
## Neurobehavioral Rating Scale

### Table S3: Neurobehavioral Rating Scale Results

<table>
<thead>
<tr>
<th>Rating</th>
<th>TBI (n=47)</th>
<th>Control (n=18)</th>
<th>P</th>
<th>TBI GOSE &lt;7 (n=41)</th>
<th>TBI GOSE 7-8 (n=6)</th>
<th>P</th>
<th>TBI+ PTSD (n=29)</th>
<th>TBI No PTSD (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Score</strong> (Max 87, Higher Scores Worse)</td>
<td>11.6±7.3</td>
<td>7.9±6.8</td>
<td>0.03</td>
<td>12.0±7.5</td>
<td>8.7±5.5</td>
<td>0.18</td>
<td>13.9±7.8</td>
<td>7.8±4.3</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Executive/Cognitive Dysfunction</strong> (Max 24)</td>
<td>3.8±2.8</td>
<td>3.1±2.6</td>
<td>0.23</td>
<td>4.0±2.9</td>
<td>2.5±1.8</td>
<td>0.11</td>
<td>4.3±3.2</td>
<td>3.1±1.9</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Positive Symptoms</strong> (Max 21)</td>
<td>1.4±1.6</td>
<td>1.1±1.8</td>
<td>0.11</td>
<td>1.5±1.7</td>
<td>0.8±0.4</td>
<td>0.31</td>
<td>2.0±1.8</td>
<td>0.6±0.7</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Negative Symptoms</strong> (Max 12)</td>
<td>1.1±1.3</td>
<td>0.8±1.0</td>
<td>0.23</td>
<td>1.1±1.2</td>
<td>1.3±1.6</td>
<td>0.43</td>
<td>1.4±1.4</td>
<td>0.8±0.9</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Mood/Affect Abnormalities</strong> (Max 15)</td>
<td>3.4±2.6</td>
<td>2.1±2.2</td>
<td>0.03</td>
<td>3.5±2.7</td>
<td>3.2±1.9</td>
<td>0.46</td>
<td>4.1±2.9</td>
<td>2.3±1.7</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Oral/Motor Dysfunction</strong> (Max 12)</td>
<td>0.7±1.0</td>
<td>0.1±0.3</td>
<td>0.02</td>
<td>0.7±1.0</td>
<td>0.5±0.5</td>
<td>0.50</td>
<td>0.8±1.1</td>
<td>0.4±0.6</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Worst Single Domain Score</strong> (Max 3)</td>
<td>1.8±0.6</td>
<td>1.4±0.8</td>
<td>0.04</td>
<td>1.9±0.6</td>
<td>1.7±0.5</td>
<td>0.25</td>
<td>1.9±0.7</td>
<td>1.7±0.5</td>
<td>0.18</td>
</tr>
</tbody>
</table>
PSTD

**A**

% of Subjects Meeting All Criteria for PTSD

- Control: 5/18
- TBI: 29/47

* p=0.014

**B**

PTSD Severity: CAPS Total Score

- Control
- TBI

** p=0.004

*** p=0.0003

% of Subjects with Moderate-Severe Disability

- All Criteria for PTSD: 31/34
- Not all Criteria for PTSD: 19/31
PSTD - Subscales

A. Reexperiencing: CAPS B Score

B. Avoidance & Numbing: CAPS C Score

C. Increased Arousal: CAPS D Score

** p=0.003

* p=0.04

** p=0.007
Depression

* p=0.05

Depression Severity: MADRS Total Score

Control  TBI
Clinical Predictors of PTSD Severity

**E**

$r = -0.29, p=0.02$

**F**

$\star p=0.03$

PTSD Severity:
CAPS Total Score

Education (years)

(Military Acute Concussion Evaluation)
Hypothetical Model

Baseline

Stressor (Combat etc.)

Injury to Medial Frontal Circuits

Acute Stress Response

(Injury to Amygdala Circuits)

Compensation & Recovery

Fear Extinction Learning & Habituation

Fear Reinforcement & Consolidation

PTSD
DTI Predictors of PTSD Severity

A

DTI: Relative Anisotropy
Left Posterior Limb of the Internal Capsule

B

DTI: Relative Anisotropy
Right Posterior Limb of the Internal Capsule

C

DTI: Relative Anisotropy
Right Orbitorfrontal White Matter

D

DTI: Relative Anisotropy
Right Cingulum Bundle

\[ r = -0.29, p=0.02 \]

\[ r = -0.28, p=0.03 \]

\[ r = -0.27, p=0.03 \]

\[ r = -0.22, p=0.07 \]
DTI Predictors of PTSD Severity

• Initial DTI predictors were modest.
• Importantly, these predictors FAILED TO REPLICATE in an independent cohort of 40 acute-blast related TBI patients enrolled at LRMC from 2010-2011.
• Similar DTI abnormalities were present in the replication set, but there was no relationship with PTSD severity
Future Directions

• Advanced multivariate analysis methods for clinical-radiological correlations

• Higher spatial and angular resolution DTI (the new Siemens Human Connectome Project Skyra scanner is now capable of 1.25 mm isotropic spatial resolution DTI, which will now allow resolution of voxels at the gray-white junction
High Spatial Resolution DTI

2 mm ‘standard’ DTI  1.25 mm ‘high res.’ DTI

Van Essen et al, Diffusion MRI 2nd Ed, 2013 in press)
Open Questions

• What are the precise pathophysiological determinants of DTI abnormalities in humans?
• Will DTI and/or other new imaging methods be useful clinically, outside of research studies?
• Can these advanced MRI techniques be performed and analyzed quickly in the acute brain injured patients?
• Can these techniques and their interpretation be standardized across multiple centers?
• Can these techniques be used to predict which patients will benefit from therapeutics targeting axonal injury?
Conclusions

- Non-invasive imaging of axonal injury may allow alignment of basic and clinical outcome measures in TBI.
- Most previous preclinical therapeutic trials have not focused on axonal injury
  - AND ALL HAVE FAILED IN HUMAN TRIALS.
- We propose that preclinical efficacy assessments use axonal protection as a primary outcome measure.
- Behavioral test in animal models with greater relevance including tests of social cognition and emotional regulation may also be important (though this is a topic for another talk).
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Funded by the US Department of Defense:
Congressionally Directed Medical Research Program
- Diffusion Tensor Imaging (Relative Anisotropy) Distinguished Injured from Control at both Acute and Subacute Time Points in Mice.
- Mean Diffusivity Distinguished Acute from Subacute Injury in Mice. *If similar in humans, this could have forensic implications...*
Varying Injury Severity

Bregma -1.22 mm

<table>
<thead>
<tr>
<th>Control</th>
<th>2x Magnification</th>
<th>60x Magnification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mm TBI</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>1.5 mm TBI</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>2.5 mm TBI</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
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</tbody>
</table>
DTI abnormalities in the corpus callosum vs. processing speed

**FIG. 3.** Scatterplot with regression lines illustrating the relation of mean FA in the fiber system emanating from the splenium of the corpus callosum to flanker task baseline reaction time in both groups. Regression lines demonstrated remarkable similarity for the two groups.

Chronic 9-16 year old moderate to severe TBI patients.  
*Correlation p=.043*

Wilde et al., J Neurotrauma 2006  
*and see also Levin et al, J Head Trauma Rehab 2008.*
Neuropsychological domain scores as a function of the number of ROIs with Fractional Anisotropy < 1 Std Dev from the control mean.

Executive: $r=-.41$, $p=.0002$,  
Attention: $r=-.26$, $p=.058$  
Memory: $r=-.40$, $p=.000$

Controls: white dots 
Mild adult chronic TBI: gray dots 
Moderate-severe adult chronic TBI: black dots
Specific cognitive deficits related to specific anatomical DTI signal abnormalities

Chronic adult mild TBI patients.

California Verbal Learning Test.

Attention Network Task.


Bilateral Uncinate Fasciculus

Left Anterior Corona Radiata
Single slice, manually placed regions of interest

Fig. 1 Region of interest placement for DTI analysis. Shown are corresponding ROIs for the right hemisphere. The solid ellipse within yellow outline indicates the location and size of the ROI. (A) UF, (B) ILF, (C) genu of corpus callosum, (D) ACR, (E) CB and (F) SLF.

Niogi* Mukherjee* et al, Brain 2008
Many DTI-neuropsychological correlations

Kumar et al., J Neurotrauma 2009.
Dorsolateral prefrontal lobe white matter and executive functions

Acute adult mild TBI

Lipton et al., Radiology 2009 & see also Lipton et al., J Neurotrauma 2008 and Lo et al., JCAT 2009
Acute diffusion tensor tractography vs. 6 month outcome

Wang et al., Archives of Neurology 2008
Acute DTI predictors of 1-year outcome

Perlbarg et al., Human Brain Mapping 2009
Voxel-based analysis and Tract-based spatial statistics
White Matter Edema in Severe Axonal Injury

Gean, NeuroImaging Clinics of North America, 2010
Subtle Hemorrhages Associated with Axonal Injury

Gean, NeurolImaging Clinics of North America, 2010
Subtle Hemorrhages and Edema Associated with Axonal Injury

Gean, NeuroImaging Clinics of North America, 2010
A New Method, Diffusion Tensor Imaging, Shows Abnormalities in TBI Patients Not Seen With Conventional MRI...

... but Whether These Changes Are Due to Axonal Injury is Not Known.

Arfanakis et al. AJNR 2002
Amyloid-precursor protein staining of axonal injury after concussion
Controlled Cortical Impact TBI in Mice

Please see Brody et al., J Neurotrauma 2007 for details.
A Mouse Model of Traumatic Axonal Injury

- Tissue was stained with an antibody for Amyloid-β precursor protein (APP)
  - Under normal conditions, APP traverses the length of axons
  - When axons are injured, axonal transport is impaired
  - APP accumulates in regions of impaired axonal transport
- ROI were chosen for each slice and used only areas of positively stained injured axons which included the entire gradient of staining
The rostral to caudal extent of the corpus callosum containing APP stained injured axons was defined using anatomical landmarks visible on both histology and MR images that encompassed the region of axonal injury.
The complete ROI was sketched over 8-10 slices for both the pre-injury and post-injury images. ROI were defined identically across imaging modalities.
Diffusion Tensor Imaging Reveals Abnormalities that Conventional MRI Does Not in Areas of Traumatic Axonal Injury

Mac Donald et al., Experimental Neurology 2007
Diffusion Tensor Imaging Consistently Distinguished Injured from Uninjured White Matter in Mice, where Conventional MRI Does Not.
There is a Strong, Quantitative Correlation Between DTI Signal Change (Relative Anisotropy) and the Severity of Axonal Injury

![Diagram showing correlation between APP stained axons/mm³ and normalized relative anisotropy](image)

- **A**: Microscopic image with highlighted regions.
- **B**: Graph showing regression line with $r^2 = 0.7895$, $p = 0.0014$. Axes labeled as APP Stained Axons/mm³ on the x-axis and Normalized Relative Anisotropy on the y-axis.
DTI-based Prediction of Axonal Injury in the Hippocampal Commissure...

... Confirmed using APP Immunohistochemistry
Varying time from injury to imaging

Acute time points studied: 4-6 hours, 24 hours, 4 days

Subacute time points studied: 7 days, 30 days

Chronic time point: 6 months (not shown)

Mac Donald et al., J Neurosci 2007
Subacute White Matter Injury (1 week to 1 month) Characterized by edema and demyelination