Predictive Modeling of Cognitive Impairments from Head Trauma
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Tom M. Talavage, Larry J. Leverenz, Anne E. Zakrajsek, Meghan E. Robinson, Umit Yoruk, Kent Butz
Consortium of Purdue research entities, established to investigate neurological consequences of repetitive blows to the head

- Purdue MRI Facility (Talavage)
- Human Injury Research & Regenerative Technologies (Nauman)
- Intercollegiate Athletic Department (Leverenz)

Funded (2009-2010) by the Indiana State Department of Health Spinal Cord and Brain Injury Research Fund & General Electric Healthcare

Total support = $170,000
Traumatic Brain Injury

• TBI Case Definition (CDC, 1995):
  – Injury to the head with one or more of
    - Skull fracture.
    - Observed or self-reported decrease/loss of consciousness
    - Amnesia
    - Neurological or neuropsychological abnormality
    - Diagnosed intracranial lesion (hemorrhage, contusion, penetrating wound)
    - Death resulting from head trauma

"Concussion"
What We Did

• 24 high school football players initially recruited for study
  – Study approved by Purdue IRB, parent consent obtained
  – 21 players participated for entire season
• Players’ helmets outfitted with accelerometers to track head impacts throughout season
  – All pre-season and in-season games and practices
• All players underwent baseline ImPACT™ testing and fMRI scans
• 11 players brought in for in-season and post-season follow up testing
Methods: Testing Schedule

• **Pre-Season Assessment**
  - Prior to beginning of contact drills
  - 24 enrollees underwent f/MRI
    - P114 data invalid due to pain-killers (wrist surgery)
  - 23 enrollees took ImPACT™
    - P110 suffered foot injury on last day of non-contact drills; returned to play during week 6 of season
    - P114 data invalid due to pain-killers
  - 22 enrollees began season with team
    - P109 quit; P110 injured
Methods: Testing Schedule

• In-Season Assessment
  – 1-3 players invited per week
    • Criteria for invitation:
      1. Diagnosed with a concussion
      2. Not diagnosed with concussion, but HIT System outlier
         » Multiple 100G or higher events
         » Large number of events
      3. Not diagnosed with concussion or HIT System outlier
    • Criteria 2 & 3 expected to yield Control group
    • Performed w/in 72 hours of game or diagnosis
  – 15 initiated, 14 completed (11 players)
Methods: Testing Schedule

• **Post-Season Assessment**
  – Conducted 1-3 months after end of season
  – 10 of 11 participants undergoing In-Season assessment invited back
    • P107 declined to return for 2nd In-Season assessment (following diagnosis of concussion) due to fear of “too many MRIs”

*(Note: 6 of 11 players participated in Season #2)*
What We Found

<table>
<thead>
<tr>
<th>No Change in Neurological Behavior (FOI-)</th>
<th>Change in Neurological Behavior (FOI+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Season</td>
<td>Pre-Season</td>
</tr>
<tr>
<td>In-Season</td>
<td>In-Season</td>
</tr>
<tr>
<td>No Clinically-Observed Impairment (COI-)</td>
<td>Clinically-Observed Impairment (COI+)</td>
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<tr>
<td></td>
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<tr>
<td>Pre-Season and In-Season fMRI studies show no change</td>
<td>Newly discovered category: Some players with no clinically-observable impairments still show significant alterations during In-Season fMRI</td>
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<tr>
<td></td>
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<tr>
<td>Not Observed</td>
<td>All players with concussion show significant alteration during In-Season fMRI</td>
</tr>
</tbody>
</table>

Adapted from Talavage et al., *J Neurotrauma* (in press)
So Why Do We Care?
So Why Do We Care?

• Consider American Football...
  – More than 1.1 million youth (almost exclusively male) play high school football each year
  – 67,000 are diagnosed with concussion (mild TBI) each year [Broglio et al., 2009; Gregory et al., 2010]
  – *Probable that a like number go unreported* [McCrea et al., 2004]

• Concerns:
  – Players who continue to play with TBI are at greater risk for future injury [Guskiewicz et al., 2003]
  – Biomechanics suggest that injury can accumulate over time [Ommaya et al., 1994]
    • Supported by post-mortem evaluation of professional athletes [Omalu et al., 2005, 2006]
  – *Players who experience sub-concussive impacts may also accumulate neural injury!* [McKee et al., 2009]
ImPACT™

• Computerized neurocognitive test
• Six Modules measure
  – Verbal recognition memory
  – Spatial recognition memory
  – Visual working memory
  – Cognitive speed
  – Visual-motor speed
  – Verbal working memory and cognitive speed
• Gives immediate test results and flags scores that deviate from the individual’s baseline score or population normative data.
ImPACT™

• Because ImPACT™ gave us the first clue that something different was going on, could it be used to identify FOI-/COI+ individuals?

• ImPACT™ was able to identify concussed subjects (COI+) but not functionally impaired (FOI+) subjects.

• There was some moderate correlation between the verbal composite score or worst score and signal changes in the frontal and temporal lobes.

• What is the Worst Score?
  – A unique way to interpret ImPACT™ scores.
  – The score with the greatest change from baseline, positive or negative, in either verbal or visual composite.
Regression analysis of regional fMRI activity as a function of ImPACT scores in COI- athletes for in-season and post-season assessments (p-values indicate significant relationships).

<table>
<thead>
<tr>
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<th>Δ Visual</th>
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# ImPACT™

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<th>In-Season</th>
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<th>Post-Season</th>
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<td>76*</td>
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<td></td>
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<td>100</td>
<td>73*</td>
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<tr>
<td>121</td>
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<td>79</td>
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<td>70*</td>
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* = flagged by ImPACT
Concussion Biomechanics

• Focal Injury
  – Coup/contrecoup phenomenon
  – Primary axotomy & hematoma

• Diffuse injury
  – Result of whole-brain shearing
  – Linked to Wallerian degeneration

• Rotational acceleration
  – Tied to focal & diffuse injury
  – Rotational strains may penetrate to brainstem to induce motor/consciousness deficits
  – Not reflected in any head injury criteria

P.V. Bayly, et al.
Concussion Biomechanics

• Not a contact phenomenon
  – Brain does not hit cranial vault in mild TBI

• Rotational shear and pressure gradients
  – Whiplash induces concussions (Ommaya 1968)
  – Concussions without head motion (Gurdjian 1976)
  – Frontal lobe (anterior fossa) a critical injury ROI in biomechanics and in CTE (Ommaya 1974; McKee 2009)

Football Helmet Telemetry

- Helmet Impact Telemetry (HIT™) System (Simbex; Lebanon, NH)
- Measures six linear accelerations
  - Approximates linear acceleration at head CG
  - Approximates impact location

Image from Chicago Tribune, 6 October 2010
What is a G-force?

- G-force is a misnomer
- Acceleration, not force
  - $F = ma \rightarrow a = \frac{F}{m}$
  - Acceleration due to gravity is 9.81 m/s$^2$
- G-force is a multiple of acceleration due to gravity

\[ a = \frac{\text{weight}}{\text{mass}} \rightarrow 1G \]

\[ a = \frac{(\text{velocity})^2}{\text{radius}} \rightarrow 1G \]
Head Collision Summary

- Using our categories we find statistically significant differences in total number and location of head collision events
  - COI-/FOI+ experienced \textit{more total} events at all levels
  - COI-/FOI+ experienced \textit{more top front} events at all levels
  - COI+/FOI+ experienced \textit{“more” high-G side} events
    - Consistent with previous expectations

Talavage et al., \textit{J Neurotrauma} (in press)
Why Use MRI/fMRI?

- Traditional neuroimaging does not reveal structural changes due to mTBI
- Functional MRI (fMRI) images changes in neurometabolism that have been correlated to mTBI
- DTI and SWI reveal nerve bundle disruption and microbleeds

The dataset is courtesy of Gordon Kindlmann at the Scientific Computing and Imaging Institute, University of Utah, and Andrew Alexander, W.M. Keck Laboratory for Functional Brain Imaging and Behaviour, University of Wisconsin, Madison
What Does fMRI *Really* Show?

- **BOLD Signal**
  - Blood Oxygenation Level Dependent Signal
  - fMRI intensity shows $\text{HbO} : \text{HbR}$

- **Neural activity results in increased demand for metabolites**
  - Not a function of excitation vs. inhibition
  - More an effect of neural input than neural output
fMRI Results Summary

• *Concussed* players exhibited varying degrees of altered activation (2-back vs. 1-back), with deviation from Pre-Season corresponding to apparent severity.

• “Controls” *without* ImPACT™ deviation exhibited consistent activity across assessments.

• “Controls” *with* ImPACT™ deviation exhibited appreciably deviant activity during season.
## fMRI Results Summary

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Adapted from Talavage et al., *J Neurotrauma* (in press)
fMRI Region of Interest Analysis

- 116 anatomically-based regions of interest (ROIs) obtained from MarsBaR

- Average $t$-statistic computed for each ROI and player

- Group mean and standard deviation computed for each ROI

- 99.9% Confidence Interval defined to identify ROIs that are “abnormal” in re-test situations

- ROI identified as “abnormal” for a classified group only if within confidence interval at Pre-Season
Players with *no* observed impairments or concussions (COI-/FOI-) exhibit consistent fMRI activity from Pre-Season to Post-Season.
COI-/FOI-

- In-Season fMRI consistently “normal”
  - 3/116 ROIs exhibit abnormal group mean
  - 0/116 ROIs abnormal in majority of players

- Post-Season fMRI less “consistent”
  - 8/116 ROIs exhibit abnormal group mean
  - 10/116 ROIs abnormal in majority of players
Players with functionally-observed impairment in the absence of a diagnosed concussion (COI-/FOI+) exhibit significant reductions of fMRI activity in the frontal lobe.

GROUP (Pre-Season)

Player 120
COI-/FOI+

- In-Season fMRI consistently “abnormal”
  - \(~\frac{46}{116}\) ROIs exhibit abnormal group mean
  - \(~\frac{29.5}{116}\) ROIs abnormal in majority of players
- Post-Season fMRI much more “normal”
  - \(\frac{13}{116}\) ROIs exhibit abnormal group mean
  - \(\frac{4}{116}\) ROIs abnormal in majority of players

- Altered ROIs of particular interest
  - Bilateral MFG, SFG [7/7 assessments]
  - Bilateral Superior Parietal Lobule; R Culmen [6/7]
fMRI ROI Analysis: L DLPFC

Region of Interest Analysis: L MFG/L SFG

Pre-Season Group
(Random Effects, N=23)

Favoring 2-back
Display threshold: $p_{FDR} < 0.05$

Favoring 1-back

---

COI-/FOI-

**Player 105**
**Player 107**
**Player 112**
**Player 122**

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COI-/FOI+

**Player 102**
**Player 115**
**Player 120**
**Player 121**

---

**In-Season #1**

**In-Season #2**

**Post-Season**

**COI-/FOI+ average t-statistic in anatomical region of interest outside Pre-Season Group 99.9% confidence interval**
COI+/FOI+

• In-Season fMRI generally “normal”
  – 13/116 ROIs exhibit abnormal group mean
  – 12/116 ROIs abnormal in majority of players
• Post-Season fMRI comparable to In-Season
  – 16/116 ROIs exhibit abnormal group mean
  – 14/116 ROIs abnormal in majority of players

• Altered ROIs of particular interest
  – L Middle Temporal Gyrus, L middle Occipital Gyrus,
    L Superior Temporal Gyrus, Cerebellum
fMRI ROI Analysis: L M/STG
Talavage et al., *J Neurotrauma* (in press)

Region of Interest Analysis: L MTG/L STG

Favoring 2-back
Display threshold: $p_{FDR} < 0.05$
Favoring 1-back

Pre-Season Group
(Random Effects, N=23)

**COI+/FOI+**

Table: Players and sessions:

<table>
<thead>
<tr>
<th>Player</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Pre-Season</td>
</tr>
<tr>
<td>103</td>
<td>In-Season #1</td>
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<tr>
<td>118</td>
<td>Post-Season</td>
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**L MTG**
**L STG**

**COI-/FOI-**

**COI+/FOI+ average t-statistic in anatomical region of interest outside Pre-Season Group 99.9% confidence interval**

Display threshold: $p_{FDR} < 0.05$
fMRI Region of Interest Summary

• **Pre-Season:** groups consistent with one another

• **In-Season:** stark differences observed
  – COI-/FOI- look like Pre-Season
  – COI+/FOI+ exhibit some localized changes, but generally consistent with Pre-Season
  – COI-/FOI+ exhibit **substantial** differences in brain activation

• **Post-Season:** more comparable across population
  – COI-/FOI- and COI-/FOI+ become comparable
  – COI+/FOI+ improved, but regions of differences similar to In-Season
Yes, HITS correlates with fMRI!

- More collision events = greater deviation of frontal lobe fMRI

Talavage et al., *J Neurotrauma* (in press)
Thoughts...COI+/FOI+

- COI+/FOI+ group was small and notably heterogeneous in probable source events...yet still exhibited group-wise consistency
  - Measured deficits were related to **verbal** function
  - The few consistent fMRI alterations were in **L MTG** and **L STG** ... language-related areas
  - Had at least one large (>80 G) hit to the *side* of the helmet, but unclear if this was causal relative to the concussion
Thoughts...COI-/FOI+

• COI-/FOI+ group was notably homogeneous
  – Interestingly, 3 of 4 were *linemen*
  – Position is consistent with observation of large number of collision events AND prominence of top front collision events
  – Consistently exhibited fMRI changes in **DLPFC**
  – fMRI changes suggest alteration in ability to *restructure inputs* [Cheng 1985]
    • No longer able to use “normal” strategy for 2-back
On “Concussions”

• Classical definition of concussion is inaccurate ... too narrow

• Both COI+/FOI+ and COI-/FOI+ groups should be considered “concussed”
  – Almost certainly represent ends of a continuum
  – Question: Single-event vs. accrued damage?

• Reports that COI+/FOI+ may not correlate with long-term impairment likely because this form of injury is *detected* and *treated*
Possible Implications?

- Does “short-term” impairment correspond to accrual of damage per chronic traumatic encephalopathy (CTE)?
  - Season #2 returnees *did* exhibit 2nd Pre-Season fMRI and ImPACT™ measures comparable to 1st Pre-Season
  - But is this 100% recovery...?

- Difficulty *restructuring* inputs for categorical classification suggests a more *diffuse* injury...
  - If players continue to participate with *diffuse* injury, they may advance to secondary axotomy!

- Difficulty restructuring inputs for categorical classification suggests a more *diffuse* injury...
  - If players continue to participate with *diffuse* injury, they may advance to secondary axotomy!
Is This The End of Football?

Cover of Sports Illustrated, 1 November 2010

Ideas for Future Examination

• If we can detect COI-/FOI+ on-site, similar treatment (removal from play) may result in lesser effect and better prognosis...**BUT HOW?**

• Alternately, can we **prevent** these injuries?
  – Correlation with collision events suggests that altered (better, in this case) technique might lead to lesser impairment....
  – Hit counts?
  – Regardless...**can we change the culture of using one’s head?**

http://dailysentinel.com/gallery/collection_079ba6dc-afda-11df-8516-001cc4c002e0.html
Partners in PANIC
(http://spin.ecn.purdue.edu/panic)

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  Dr. Henry Feuer (IUSM)        Prof. Alex Francis (PU-SLHS)
  Dr. Mark Lovell (UPMC)        Dr. Micky Collins (UPMC)
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  Prof. Wayne Chen (PU-ME)      Prof. Doug Adams (PU-ME)
  Prof. Jeff Gilger (PU-ES)     Prof. Riyi Shi (PU-BME)

• Our dedicated graduate students
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  Kent Butz (ME)                

• Assisting undergraduate students
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  Kyle O’Keefe (ME)            