Neuroimaging in Pediatric Mild Traumatic Brain Injury

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Mind Research Network

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Problem Statement/Goals of Talk

- Overview imaging measures of gray/white matter structural pathology and functional pathology in pmTBI
- Evaluate whether neuroimaging findings are more sensitive than current gold standards in pmTBI
- COI: Funded as investigator and consultant on several NIH/DoD grants
Epidemiology: “The Silent Epidemic”

- TBI contributes to nearly a third of injury-related deaths in US
- Estimated annual cost = $60 billion dollars
- Approximately 1.7 million people experience a TBI per year
  - 52,000 people die from head injury per year
  - 275,000 people are hospitalized for TBI and survive per year
  - 1.4 million head-injured people are treated in hospital emergency rooms per year
- Untreated????

(Faul et al., 2010 CDC report)
Epidemiology: “The Silent Epidemic”

- Much higher incidence for children

Children “not just little adults” (Giza 2007)

Estimated Average Annual Rates

United States, 2002-2006
Historical Perspectives on mTBI

• Neurobehavioral symptoms; single versus repetitive mTBI

Permanent neurological damage

Psychiatric entity

Mod/Sev TBI

rmTBI

smTBI
The spectrum of disease in chronic traumatic encephalopathy


DeKosky et al., 2010; McKee et al., 2009
Long-Term Consequences

- **Chronic Traumatic Encephalopathy** (McKee et al., 2012; Chritchley 1949, 1957) A.K.A. dementia pugilistica (Martland, 1928; Millspaugh, 1937)

- Hyper-phosphorylated tau in deep perivascular spaces

- More prominent frontal-temporal involvement, diencephalon

- Prominent neurobehavioral sequelae
More meaningful statements about injury based on objective classification system using anatomical substrates/other biomarkers
Clinical Lessons from Dermatology

Each injury stage is likely associated with different types of pathophysiology and behavioral (e.g., pain) symptoms.
Focal Pathology and Location

- Atrophy, lesions and cellular alterations

Bigler et al., 2013; McAllister & Stein, 2010
Focal Pathology and Location

- Morphology of sub-cortical structures
- Frequently reported site for diffusion and/or atrophic changes in animal models
- Selected ROI
Diffuse Injury Mechanisms

- Stretch $\rightarrow$ Mechanoreceptor dysregulation (e.g., $\text{Na}^+$) $\rightarrow$
  
  - Voltage dependent receptor activation & ionic flux ($\text{Ca}^{2+}$, $\text{K}^+$, $\text{Na}^+$) $\rightarrow$
  
  - Activation of proteolytic enzymes (e.g., Calpain, Calpase-3) $\rightarrow$
  
  - Neurofilament sidearms loss and compaction $\rightarrow$
  
  - Cytoskeletal collapse $\rightarrow$ axotomy

See work of Gennarelli, Povlishock, Wolf

Diffuse, secondary axonal injury may be the most common pathology which occurs over a span of weeks. Less severe version more common in mTBI.
TBI and Vasculature

- Reduction in CBF (Soustiel & Sviri, 2007)
- Decoupling between CBF and oxidative metabolism (Vespa et al., 2005; Soustiel & Sviri, 2007)
- Animal work (Parks et al., 2009) suggests large changes in microvasculature

(Parks et al., 2009; J Cer Blood Flow & Metabolism)
Considerations: Pediatric TBI

• Neurodevelopment (ongoing myelination and excitatory neurotransmitter system)
  - Baseline and subsequent recovery trajectory difficult to assess

• Different injury biomechanics (fall versus motor vehicle accident), tissue mechanics (skull thickness, parenchymal water content), head-body weight ratio and musculo-skeletal

• Increased incidence of cerebral edema, diffuse white matter injuries & auto-dysregulation

• Recovery from pmTBI one month (Maugans et al., 2012) or 1 year post-injury (Yeates et al. 2012)?

(Adelson and Kochanek, 1998; Giza et al., 2007; Kochanek, 2006)
Other Clinical Considerations

• Heterogeneous injury in terms of biomechanical forces
• Recovery curve (time-post injury)
  • Patients improve, some deteriorate, all at different rates

• Majority of mTBI patients recover BUT majority of publications based on those who do not (i.e., special, non-representative population)
• Effects of repetitive injuries unknown (from second impact syndrome to chronic traumatic encephalopathy)
Diffusion Tensor Imaging

Diffusion in motion of H$_2$O

"isotropic" = 0

"anisotropic" = or
Diffusion Tensor Imaging
Diffusion Tensor Imaging: WM

1) AD = \( \lambda_1 \)

2) RD = (\( \lambda_1 + \lambda_2 \))/2

\[
FA = \frac{3}{2} \cdot \sqrt{\frac{(\lambda_1 - \lambda)^2 + (\lambda_2 - \lambda)^2 + (\lambda_3 - \lambda)^2}{(\lambda_1)^2 + (\lambda_2)^2 + (\lambda_3)^2}}
\]

• AD and RD may measure different pathology (Song et al., 2003; MacDonald et al., 2007)

• 1.0 cubic micrometer = 1 x 10^{-9} microlitre
Diffusion Tensor Imaging: GM

- GM DTI (Albensi et al., 2000; Budde et al., 2011; Zhou et al., 2012)

Zhou et al., 2012
pmTBI DTI and Structural Literature

- **Semi-acute WM DTI** (Wilde et al., 2008 (3 related); McAllister et al., 2012; Maugans et al. 2012; Borich et al., 2013 (1 related); Murugavel et al., 2014)

  - No pmTBI studies in semi-acute or chronic GM DTI

  - No prospective studies of atrophy in semi-acute to chronic pmTBI

- Cross-sectional studies of chronic atrophy (Beauchamp et al., 2011 @ 10 years; Bigler et al. 2013 @ 2.7 years)

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Dodd et al., 2014; Journal of Neurotrauma
Study Inclusion Criteria

- **Participants**
  - 16 pediatric (10-17 y.o.) mTBI patients
  - HC matched on gender, age and education (+/- 2 years)
  - Patients seen semi-acutely (≈2 weeks)
  - Subset of participants seen approximately 4 months after first visit (≈ 70% for children)

- **mTBI Inclusion Criteria**
  - Medically and psychologically healthy (No history of Axis 1 disorders, neurological disorders, ADHD/Learning disorders, vascular disease, hx previous TBIs w/ > 5 minute LOC)
  - Emergency room admittance (GCS 13-15)
  - LOC (less than 30 minutes) OR altered mental status (PTA < 24 hours)
# Pediatric Clinical Sample

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Mechanism of Injury</th>
<th>AAN Rating</th>
<th>Days post-injury MRI</th>
<th>Days post-injury NP</th>
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Note: MVA = motor vehicle accident; SR = sports/activity related; AAN = American Academy of Neurology; and NP = neuropsychological testing.
Pediatric Clinical Results

- Visit 1 (pmTBI = 15; HC = 15)
- V2 (pmTBI = 10; HC = 10)

- Hx of previous pmTBI, IQ & Demographic factors = N.S.
- Child/parent report = N.S.
- Neurocognitive Testing = p < 0.05 at V1 and N.S. at V2 (Attn d = 0.03; PS d = -0.64)
- 0% positive findings on CT or MRI (T₁/T₂/SWI)

Mayer et al., 2012; Journal of Neuroscience
WM DTI Results

- FA and RD Results (pmTBI = 15; HC = 15)

Mayer et al., 2012; *Journal of Neuroscience*

- Increased FA & decreased RD in ROI analyses
- Classify 13/15 pmTBI patients and 14/15 HC*
- Increased FA also present in voxel-wise analyses

Mayer et al., 2012; *Journal of Neuroscience*
WM DTI Results

- FA and RD Results (pmTBI = 15; HC = 15)

  - Increased FA & decreased RD in ROI analyses
  - ROI data classify 13/15 pmTBI patients and 14/15 HC
  - Increased FA also present in voxel-wise analyses

Mayer et al., 2012; Journal of Neuroscience
WM DTI Results

- FA Visit 2 Results (pmTBI = 10; HC = 10)

- Non-significant changes in FA across 4 month window

Mayer et al., 2012; *Journal of Neuroscience*
DTI Summary: WM

- FA & RD = cytotoxic edema and/or myelin (Wilde et al., 2008; Bazarian et al., 2007)
- Inflammatory processes could also contribute
- Animal models of mTBI suggest extensive axonal/little myelin involvement (Spain et al., 2010)
Image Methods: GM

- FreeSurfer (v 5.1) with longitudinal pipeline
- ROI (cortical and sub-cortical) and surface-based (cortical) analyses (10 mm FWHM)
- 30 DWI; b = 800

*Mayer et al., in press; Journal Neurotrauma*
FA Findings

- **V1**: Increased FA \((mTBI > HC)\) in right thalamus, L MTG
- FA associated with attention but not PS across both groups
- No change as function of time at V2 \((mTBI > HC)\)

C) Left Temporal Gyrus Cluster

D) Longitudinal \((N = 10)\)

Mayer et al., in press; *Journal of Neurotrauma*
• No thickness differences at V1 (p > 0.10)
• Increased rate of change (normalized V2 – V1) for HC relative to pmTBI
• No subcortical volume differences (p > 0.10)

Mayer et al., in press; Journal of Neurotrauma
Summary: GM Findings in mTBI

- Gray matter FA in adults (Bouix et al., 2013; Ling et al., 2013) and animal studies (Albensi et al., 2000; Budde et al., 2011; Zhou et al., 2012)
- Reports of decreased thalamic FA in chronic/mixed injury populations (Little et al., 2010; Grossman et al., 2011)

Increased FA secondary to cytotoxic edema or potentially a reactive gliosis (Budde et al., 2011; Zhou et al., 2012)

First prospective study of atrophy in pmTBI (Bigler et al., 2013 null)
Temporal Dynamics

Giza and Hovda

Mondello et al., 2011

McCrea, M. et al. JAMA 2003;290:2556-2563
Evoked Functional MRI (fMRI)

- BOLD = indirect (hemodynamic) measure of neuronal activity
- Increased metabolic demands (NA⁺/K⁺ pump), excitatory transmission and/or Glu v. Gln shuttling
- Vasculature response (CBF, CBV, deoxyHb (CMRO₂))
- Alters dephasing of protons (basis for BOLD signal)
- Traditionally used with cognitive task, now used at rest
● Rapid event-related design (N = 14)
● Group (mTBI & HC) x Validity (Valid & invalid) x SOA (200, 400, & 700ms) mixed ANOVA
● Exogenous orienting: 50% valid & 50% invalid trails

Yang et al., 2012; Journal of Neurotrauma
fMRI: Behavioral Data

- Validity Effect score (invalid – valid RT)
- 700 ms SOA effect size = 0.62
- HC exhibit IOR but not mTBI.

Yang et al., 2012; Journal of Neurotrauma
fMRI: Behavioral Data

- HC: $r = -0.63$, $p = 0.02$
- mTBI: $p > 0.10$

A potential disruption of the relationship between basic orienting function and everyday cognitive function in pmTBI

Yang et al., 2012; Journal of Neurotrauma
Evoked fMRI: Results and Replication

- **SOA (200, 400, or 700 ms)**
- **Response**
  - **Cue** (2000 Hz)
  - **Target** (1000 Hz)

**Replication** in adult (Mayer et al., 2009; N = 16) and pediatric (Yang et al., 2012; N = 14) and mTBI samples.
Overall Conclusions

• Neuropsychological results and traditional MRI not very sensitive (for detecting injury??) or recovery occurs on a different time-scale

• Neuroimaging biomarkers have different sensitivity/specificity that may be time-varying (different recovery curves)

• Heterogeneous injury profiles following pmTBI require more clever analytic techniques

• Caveats: Small N with multiple tests, limited anatomical battery, macroscopic measures of microscopic processes
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Does not account for all long-term effects of pmTBI
## Collaborators

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<tr>
<th>Mind Research Network</th>
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<td>Ron Yeo, PhD</td>
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<td>Faith Hanlon, Ph.D.</td>
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Not the first ......

**Sumerian medicine** (~1700 BC)
- Trepanning instruments

**Egyptian period**
- Medical subspecialization.
- One papyrus describes neurologic injury
  - Case descriptions, one of temporal injury and aphasia

**Greece**
- TBI described in fifth book of *Epidemics* *(Hippocrates)*
  - 11 yo boy kicked in forehead by horse. Explore skull with metal probe, determine fracture. Any question, coat skull with barley plaster and scrape away to expose fracture lines. No further treatment if skull fracture present. If no skull fracture, trephinning to release accumulated “humors or to slacken the tightness of the skull.”

**Roman medicine**