New Frontiers in Concussion Management

Biomarkers

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Neurometabolic Cascade Following Cerebral Concussion/MTBI

(Giza & Hovda, 2001)

K+

Calcium

Glutamate

Glucose

Cerebral Blood Flow

% of normal

0 50 100 200 300 400 500

2 6 12 20 30 // 6 24 // 3 6 10

minutes hours days

UCLA Brain Injury Research Center
What is a Biomarker?

“Measureable internal indicators of changes in organisms at the molecular or cellular level that provide information regarding injury mechanisms”

Mondello et al., Expert Rev Mol Diag., 2011

No animals were harmed in the making of this slide

Courtesy of David Hovda, Ph.D., UCLA
Current Biomarkers

Blood Tests

Brain Imaging

Other Methods
Blood Biomarkers

And Sports-Related Concussion
Blood Biomarkers

- No current FDA approved blood test
- Huge area of interest over past 5 years
- Significant funding by DOD
- Promising but years away from clinical use
- Likely to be used as **one component**
  Of concussion evaluation
Blood Biomarkers

- Large body of work in Europe
- S100-B source of research
- Very high sensitivity but low specificity (good at picking up trauma, not good at differentiating brain trauma from other trauma)
- Studies have shown that any kind of trauma can lead to elevations (Romner et al, 2000, Bazarian, 2006)
A Potential Model for Blood Biomarkers

Blood Biomarkers
Current Limitations

• Thousands of potential markers
• How would it be used?
  – Age related differences?
  – Oversensitivity to non-brain trauma?
• What is the correlation with clinical signs and Symptoms?
Functional MRI (fMRI) and Sports-Related Concussion
ADVANTAGES AND DISADVANTAGES OF fMRI

- Sensitive to subtle changes
- Safe and non-invasive
- No exposure to radiation
- Permits serial scanning
- Can be used in children

- Studies take 45 minutes
- Very expensive
- No standardization across centers

Response to Finger Tapping
Functional MRI and Sports Concussion

Lovell, Collins, Eddy, Becker, Pardini, Maroon, Field, Marion, and Boada (2001-2006) RO1 HD 42386-05
Brain Metabolism is Related to Recovery

- Over 200 high school athletes studied using fMRI
  - Tested within 7 days of concussion and at point of clinical recovery
- Hyperactivation predicts CLINICAL recovery time
- Hyperactivation correlates with recovery on NP testing

Lovell et al., Neurosurgery, 2007
Recovery: fMRI Subsample

N = 208

Cumulative Percent Recovery

<table>
<thead>
<tr>
<th>Days</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 days</td>
<td>25%</td>
</tr>
<tr>
<td>26 days</td>
<td>50%</td>
</tr>
<tr>
<td>45 days</td>
<td>75%</td>
</tr>
<tr>
<td>92 Days</td>
<td>90%</td>
</tr>
</tbody>
</table>

Mean Age: 16.2 yrs
Gender: 78% male

Days to Recover

<table>
<thead>
<tr>
<th>Range</th>
<th>4 – 211 days*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>26.2 days</td>
</tr>
</tbody>
</table>

* End of study period

Lovell, Pardini, Collins et al., Neurosurgery 2007
Diffusion Tensor Imaging/Tractography
And Sports-Related Concussion
DTI and Tractography

- Evaluates integrity of white matter tracts by measuring the preferential direction of proton diffusion.
- Organized structure of white matter tracts confers directionality - anisotropy
- Disruption of white matter leads to decreased fractional anisotropy and disruption of fiber tracking
Diffusion Tensor Imaging

Normal Side

Abnormal Side

Lesion
DTI and Tractography

• Advantages:
  – More available than fMRI
  – Shows white matter disruption

• Disadvantages:
  – Time consuming
  – Expensive
MR Spectroscopy

And Sports-Related Concussion
MR Spectroscopy

Evaluates specific chemical markers that can be disrupted by brain injury

• Advantages:
  – More available than fMRI
  – Show white matter disruption

• Disadvantages:
  – Time consuming
  – Expensive
Typical spectrum and regions of interest showing peaks of metabolites of interest (Creatine-CR, myo-inosital-MI, Glutamate-Glu, N-acetylaspartate-NAA. Henry et al., BMC Neurology, 2011
Spectra in dorsolateral pre-frontal cortex. Concussed group differed significantly from control group on all markers. Acute assessment was within 5 days of injury, chronic assessment 6 months after injury.

Henry et al., BMC Neurology, 2011
Event-Related Potentials (ERPs)
And Sports-Related Concussion
ERP’s

- Electrical signals recorded in response to stimulus (e.g. P300).
- Some studies have showed persistent difficulties, even after patients had clinically returned to normal.

Introducing a novel approach of network oriented analysis of ERPs, demonstrated on adult attention deficit hyperactivity disorder

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Go/No-go
Pattern recognition
Unsupervised clustering

HIGHLIGHTS

• Introducing a novel network-oriented analysis method of event related potential (ERP) activities and evaluating its value in the identification and severity-grading of adult ADHD patients.
• The analysis yielded high specificity and sensitivity and individual scores correlated well with behavioral assessments, suggesting that the proposed approach may have merit as an objective electrophysiological marker and individual subject severity grade in adult ADHD patients.
• This novel approach may provide both diagnostic and drug development tools for use in diverse neurological disorders.

ABSTRACT

Objective: Introducing a network-oriented analysis method (brain network activation [BNA]) of event related potential (ERP) activities and evaluating its value in the identification and severity-grading of adult ADHD patients.

Methods: Spatio-temporal interrelations and synchronicity of multi-sited ERP activity peaks were extracted in a group of 13 ADHD patients and 13 control subjects for the No-go stimulus in a Go/No-go task. Participants were scored by cross-validation against the most discriminative ensuing group patterns and scores were correlated to neuropsychological evaluation scores.

Results: A distinct frontal-central-parietal pattern in the delta frequency range, dominant at the P3 latency, was unraveled in controls, while central activity in the theta and alpha frequency ranges predominated in the ADHD pattern, involving early ERP components (P1–N1–P2–N2). Cross-validation based on this analysis yielded 92% specificity and 84% sensitivity and individual scores correlated well with behavioral assessments.

Conclusions: These results suggest that the ADHD group was more characterized by the process of exerting attention in the early monitoring stages of the No-go signal while the controls were more characterized by the process of inhibiting the response to that signal.

Significance: The BNA method may provide both diagnostic and drug development tools for use in diverse neurological disorders.

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The Challenge:
Capturing the complex interconnections of the brain at work

- Every brain function is based on neural network activation
- Brain disorders are the result of disruptions in those Brain Network Activations (BNA)
- Therapeutic interventions induce changes in BNA

Can we accurately capture BNAs?
Magnetoencephalography (MEG) and Sports-Related Concussion
MEG Unit
MEG

• Advantages:
  - Better temporal resolution than EEG or fMRI
  - More Sensitive?

• Disadvantages
  - Technology is very expensive
  - Few people using it
High Definition Fiber Tracking
Okonkwo et al, 2012
Current Controversies

- What are risk factors for long-term damage? (e.g. exposure, gender, other factors)
- What factors determine who is afflicted and who isn’t?
- What is the real risk to kids?
Chronic Traumatic Encephalopathy (CTE)

Short-term dysfunction vs. long-term damage?

Future risk for dementia in athletes injured during childhood?
TAU PROTEIN
What Does it Mean?

Normal 65   NFL Athlete 45 years old   Pro Boxer

BU Center For Traumatic Encephalopathy
A LIFESPAN MODEL OF UNDERSTANDING MTBI

<table>
<thead>
<tr>
<th>BIRTH</th>
<th>CHILDHOOD/TEENS</th>
<th>COLLEGE/PROS</th>
<th>RETIREMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• APOE-4?</td>
<td>• Genetic Expression</td>
<td>• Bigger…</td>
<td>• Genetics?</td>
</tr>
<tr>
<td>• IQ?</td>
<td>• Brain Development</td>
<td>• Faster…</td>
<td>• Aging?</td>
</tr>
<tr>
<td>• Migraine?</td>
<td>• Contact Sports?</td>
<td>• Stronger…</td>
<td>• TBI?</td>
</tr>
<tr>
<td>• LD/ADD?</td>
<td>• Increased Risk?</td>
<td>• Injury History?</td>
<td>• Diseases</td>
</tr>
<tr>
<td>• Other factors?</td>
<td></td>
<td>• Risk of Injury?</td>
<td>- Alzheimer’s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Natural Selection?</td>
<td>- HBP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Stroke</td>
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SUMMARY

• Explosion of research on biomarkers over last five years
• Will likely play an important role moving forward
• No one technology will become “gold standard”
• Brain injuries will continue to require careful clinical diagnosis