Concussion & the Possible Consequences

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Conflict Statement
• I have no financial conflict of interest
• All views are my own

Roadmap
• What is a concussion
• Incidence/prevalence
• Long-term effects
• Human studies
• Animal studies
• Future directions
Concussions

What is a concussion?
- Diffuse
- Invisible; no biomarker
- Microscopic
- Metabolic
- Axonal
- No biomarker
* Concussion is a transient neurometabolic injury that typically resolves in under 2 weeks

Signs & Symptoms

Acute symptoms vary:
- Time to presentation
- Duration
- Severity
- Type
- By sex, age, etc.

"Once you've seen one concussion... you've seen one concussion."
Signs & Symptoms

- Difficulty thinking clearly
- Feeling slowed down
- Difficulty concentrating
- Difficulty remembering new information
- Headache
- Balance problems
- Loss of memory
- Sensitive to noise or light
- Irritability
- Nausea
- Dizziness
- Difficulty concentrating

Concussion Epidemiology

- 1.6-2.8 million concussions sustained annually in the U.S.
- Figures may be an underestimate as concussions are underreported and underdiagnosed; some studies suggest that >50% go unrecognized.
- In recent years, the number of diagnosed concusion has increased in some populations.

More to come...
Concussion v. repetitive brain trauma

Chronic Traumatic Encephalopathy (CTE)
The latest on CTE

• Neuropathological diagnosis

The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy

• No Tau, no Aß Tau, no Aß and Aß depths of sulcus
CTE is unique neuropathology

- Normal: No Tau, no AD
- CTE: Tau, no AD
- Alzheimer's disease: Tau and AD

Sections double immunostained for Aβ and tau.

Stages of Tau Pathology

- Stage I: mean age: 76.7 ± 13 years
- Stage II: mean age: 64.1 ± 16 years
- Stage III: mean age: 64.7 ± 14 years
- Stage IV: mean age: 74.4 ± 12 years

McKee et al, 2013, Brain
Clinical Presentation of CTE

Clinical presentation of chronic traumatic encephalopathy

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Robert W. McCrohon, Jr.

Abstract

Objectives: The goal of this study was to examine the clinical presentation of chronic traumatic encephalopathy (CTE) in neurologically confirmed cases.

Methods: Thirty-one adult male subjects were selected from all cases of neuropathologically confirmed CTE at the Boston University Center for the Study of Traumatic Encephalopathy brain bank.

Results: Clinical presentation less well understood. Symptoms correlated with CTE fall in 3 domains:
- Cognition (e.g., memory difficulties)
- Mood (e.g., depression, anxiety)
- Behavior (e.g., explosivity)
The latest on CTE

- Football Players Diagnosed with CTE, convenience sample


The latest on CTE

- The punchline:
  - In convenience sample of posthumously examined brains from individuals who played football, there was a high rate of CTE
  - More severe CTE was more frequently found in individuals who played at a higher level and individuals who died at an older age
- The caveats:
  - Referral bias, recall bias, no comparison group, etc.

Gaps in knowledge

- Human studies leave many unanswered questions:
  - True incidence/prevalence of concussion
  - Incidence/prevalence of CTE; no in vivo diagnosis
  - Causal relationship between brain trauma and CTE
  - Causal relationship between football and/or CTE pathology and associated symptoms
  - Definitive claims of progressive nature of pathology or clinical symptoms
Gaps in knowledge

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  • True incidence/prevalence of concussion
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Animal model of TBI & CTE

• Weight dropped (54.3gm bolt) onto head
• Head free to rotate
• Measure loss of consciousness time
• Measure cognitive function

<table>
<thead>
<tr>
<th>Animal Model of TBI &amp; CTE</th>
<th>Challenges</th>
<th>Beyond CTE</th>
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<tbody>
<tr>
<td>Takeaways:</td>
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<tr>
<td>• Repeat brain injury, in short succession, causes CTE-like tau accumulation</td>
<td>• Generalizability of animal model to humans unclear</td>
<td>• Depression</td>
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<tr>
<td>• CTE-like tau accumulation causes some behavioral symptoms in mice</td>
<td>• Similar experiments in humans unethical or infeasible</td>
<td>• Anxiety</td>
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<td>• Antibody induced removal of tau reverses behavioral symptoms to some extent</td>
<td>• Change in game/exposure over time</td>
<td>• Executive Dysfunction</td>
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<td>• Hard to find appropriate “control” group for NFL athletes for purposes of comparison</td>
<td>• Physical Activity</td>
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<td></td>
<td>• …and many more</td>
<td>• Team-building</td>
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<td>• Social Support</td>
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Thank you

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