Blast Injury Institute
Concussion and Chronic Traumatic Encephalopathy (CTE)

James P. Kelly, MA, MD
Director
National Intrepid Center of Excellence

Clinical Professor of Neurosurgery
University of Colorado School of Medicine
Primary: Direct exposure to over pressurization wave
IED: Improvised Explosive Device
New Humvee
## Four Categories of Blast Injury

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Possible Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Impact of the shock waves (over pressurization waves)</td>
<td>Trauma to the lungs, inner ear, abdominal organs, eyes, TBI</td>
</tr>
<tr>
<td>Secondary</td>
<td>Flying debris and bomb fragments</td>
<td>Penetrating or blunt trauma from sharp or blunt objects</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Individuals being thrown by the blast</td>
<td>Fractures, penetrating or blunt trauma, TBI</td>
</tr>
<tr>
<td>Quaternary</td>
<td>Anything not directly due to the blast (may even be complication of existing conditions)</td>
<td>Burns; crush injuries; asthma or COPD from dust, smoke, or toxic fumes; heart problems; hypertension</td>
</tr>
</tbody>
</table>

TBI Numbers By Severity

DoD Numbers for Traumatic Brain Injury
’00 – ’12 Totals

- Penetrating - 2%
- Severe - 1%
- Moderate - 8%
- Mild - 82%
- Not Classifiable - 7%

Total 266,810

Source: Armed Forces Health Surveillance Center
# Sport Concussion: Clinician Challenges

<table>
<thead>
<tr>
<th>UNKNOWN</th>
<th>CLINICAL APPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury Biomechanics</td>
<td>How much is enough to cause concussion?</td>
</tr>
<tr>
<td>Diagnosis &amp; Assessment</td>
<td>What are the most effective methods to diagnose and evaluate athletes with SRC?</td>
</tr>
<tr>
<td>Recovery Time</td>
<td>How long does it typically take to recover after SRC?</td>
</tr>
<tr>
<td>Injury Management</td>
<td>When is it safe for an athlete to return to play?</td>
</tr>
<tr>
<td>Long-term Effects</td>
<td>Are there potential long-term risks associated with repetitive concussion?</td>
</tr>
</tbody>
</table>

What Does the Science Tell Us?
What is a Concussion?

After blow to head, disruption of normal brain cellular activity (“Neurometabolic Cascade”) commonly causes rapid onset of neurologic dysfunction:

- **Clinical Symptoms**: headache, dizziness, dazed/confused, poor concentration, feeling in a fog, nausea, etc.
- **Physical Signs/Acute Injury Characteristics**: LOC (<10%), PTA (<25%)
- **Neurobehavioral Changes**: irritability, mood changes, etc.
- **Cognitive Impairment**: memory, attention, reaction time, processing speed
- **Sleep Disturbance**: drowsiness, insomnia, hypersomnia

It Starts at the Beginning: Concussion is about what happened to the athlete at the time of the injury event.
Effects of Routine Head Impact Exposure

Correlating Head Impact Exposure with Clinical Effects & Outcome

Is it About “How Many” or “How Much”?  

HS Impacts: 500-750/season  
(Broglio et al 2011; Schnebel et al 2007)

College Exposure: 500-1400/season  
(Crisco et al 2010; Schnebel et al 2007; Guskiewicz et al 2007)
Higher score indicates more severe symptoms; error bars represent 95% CI.
Lower score indicates more severe cognitive impairment; error bars = 95% CI
McCrea et al., JAMA 2003
Association Between Recovery & Risk

> 80% Achieve Complete Recovery in 7-10 Days

75% of repeat concussions within first 7 days
92% of repeat concussions within first 10 days

McCrea et al., JAMA 2003; 290:2556-2563
Incidence, Clinical Course, and Predictors of Prolonged Recovery Time Following Sport-Related Concussion in High School and College Athletes

Michael McCrea,1 Kevin Guskiewicz,2,3,4 Christopher Randolph,5 William B. Barr,6 Thomas A. Hammeke,7 Stephen W. Marshall,3,4,6 Matthew R. Powell,9 Kwang Woo Ahn,10 Yunfai Wang,11 and James P. Kelly11

1Department of Neurosurgery and Neurology, Medical College of Wisconsin, Milwaukee, Wisconsin
2Department of Exercise and Sport Science, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
3Department of Orthopedics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
4Injury Prevention Research Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
5Department of Neurology, Loyola University Medical School, Maywood, Illinois
6Departments of Neurology and Psychiatry, New York University School of Medicine, New York, New York
7Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin
8Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
9Department of Neuropsychology, Marshfield Clinic–Minocqua Center, Minocqua, Wisconsin
10Division of Biostatistics, Medical College of Wisconsin, Milwaukee, Wisconsin
11U.S. Department of Defense, National Intrepid Center of Excellence, Bethesda, Maryland

(RECEIVED, September, 21, 2011; REVISION FINAL, June 7, 2012; ACCEPTED, June 7, 2012)

Abstract

Sport-related concussion (SRC) is typically followed by clinical recovery within days, but reports of prolonged symptoms are common. We investigated the incidence of prolonged recovery in a large cohort (n = 18,531) of athlete seasons over a 10-year period. A total of 570 athletes with concussion (3.1%) and 166 controls who underwent pre-injury baseline assessments of symptoms, neurocognitive functioning and balance were reassessed immediately, 3 hr, and 1, 2, 3, 5, 7, and 45 or 90 days after concussion. Concussed athletes were stratified into typical (within 7 days) or prolonged (>7 days) recovery groups based on symptom recovery time. Ten percent of athletes (n = 57) had a prolonged symptom recovery, which was also associated with lengthier recovery on neurocognitive testing (p < .001). At 45–90 days post-injury, the prolonged recovery group reported elevated symptoms, without deficits on cognitive or balance testing. Prolonged recovery was associated with unconsciousness (odds ratio [OR], 4.15; 95% confidence interval [CI], 2.12–8.15), posttraumatic amnesia (OR, 1.81; 95% CI, 1.00–3.28), and more severe acute symptoms (p < .0001). These results suggest that a small percentage of athletes may experience symptoms and functional impairments beyond the typical window of recovery after SRC, and that prolonged recovery is associated with acute indicators of more severe injury. (JINS, 2013, 19, 22–33)

- 10% take > 7 days to recover
- Other reports of higher percentages
- < 5% take > 45 days
- Acute severity predicts recovery
Amateur boxing
Hypothesis

• Diffuse Axonal Injury (DAI)
  – Shearing of neurons
• Leakage of proteins in the cerebrospinal fluid (CSF)
  – NFL (neurons)
  – GFAP (astrocytes)
  – Tau (neurons)
• Lumbar puncture to access CSF
Boxing Study

- 14 boxers (3 female), age 22±3.8 yrs
- 10 Controls (0 female), age 30±6.3 yrs
- LP 7-10 days after bout
- New LP 3 months after rest
- Interviews at day 7-10
  - Amount of hits to the head
  - Severity, ie groggneness
Study design:
Amateur boxers, n= 14
CSF taken:
- Week after a bout
- After 3 months of rest from boxing
- Healthy controls, n= 10

Total Tau

P = 0.006
Neurofilament (NFL)

Study design:
Amateur boxers, n= 14

CSF taken:
- Week after a bout
- After 3 months of rest from boxing
- Healthy controls, n= 10

![Bar graph showing NFL levels after different periods](image)

- After a bout
- After rest
- Controls

P= 0.0001
Many (>15) or high impact hits

Few hits

Pathophysiology

- Biomechanical forces cause tissue deformation, shearing and fluid wave propagation through the hemisphere.
- Irritation leads to rapid, chaotic electrical depolarization across the cortex.
Pathophysiology - 2

• Neurotransmitters / neurochemicals are released in excessive (excitotoxic) amounts, driving up cellular metabolism (hyperglycolysis) and lactic acid levels
Pathophysiology - 3

• Na – K pump failure and axonal stretch injury lead to Calcium influx and axonal swelling or disintegration
Pathology

- Rotational injuries lead to diffuse shearing of small vessels
- Diffuse axonal injury is underlying lesion
MRI Findings

CT
Read as Normal

Routine MRI- GRE
Possible Lesion Corpus Callosum

New TBI Study- SWI
Multiple Lesions Detected
Brain Trauma-Related Neurodegeneration: Strategies to Define, Detect and Predict

July 22-23, 2013
Bethesda, Maryland

Sponsors

• National Institutes of Health (NIH)
• Foundation for the NIH (FNIH)
• National Football League (NFL)
Chronic Traumatic Encephalopathy

- Punch-Drunkeness (Martland, 1928)
- Dementia Pugilistica (Millspough, 1937)
- Chronic Progressive Traumatic Encephalopathy of the Boxer (Critchley, 1957)
- Psychopathic Deterioration of Pugilists (Courville, 1962)
Mechanics of Boxing

Dementia Pugilistica

• Neuronal loss, gliosis, senile plaques, hydrocephalus, attenuation of the corpus callosum, diffuse axonal injury, neurofibrillary tangles, cerebellar atrophy

• Jack Dempsey, Joe Louis, Floyd Paterson, Jerry Quarry, Mike Quarry, Emile Griffith, Sugar Ray Robinson and Muhammed Ali (Parkinsonism variant)
CT of 338 Active Pro Boxers

- Abnormal in 25 (7%)

- Atrophy most common finding (the number of bout was correlated with degree of atrophy)

- Focal low density (traumatic encephalopathy) in only 3 boxers

(Jordan, BD et al 1992)
US Olympic Boxing Team

- 1986 USA Boxing asks US Olympic Committee to a formal study
- Johns Hopkins group performs detailed assessment of boxers before and after 1988 Olympic Games (baseline and post-competition neuropsych, EEG, BAEP, balance/coordination)
- Results find no evidence of deficits in boxers in pre-post comparison
- Association between total number of fights before baseline and cognitive deficits (Stewart WF, Gordon B, Seines O et al, 1994)
Boxers at USMA – West Point

• 14 boxers who had sustained concussions (n=6 AAN Grades I, n=8 Grade 2) with full symptom recovery by day 4 post-injury
• All had pre-injury baseline computerized neuropsychological testing
• No cadet had returned to baseline on Simple Reaction Time on day 4 post-injury

(Warden DL et al, 2001)
Boxers at Notre Dame

• 82 collegiate amateur boxers participating in a 7-day single elimination tournament
• 30 non-boxing controls
• Used computerized test battery before and within 2 hours after each bout
• Except for boxers whose bouts were stopped by the referee (n=7), there was no evidence in post-bout cognitive dysfunction

(Moriarty et al, 2004)
Diffusion Tensor MRI

- Regions of increased and decreased apparent diffusion coefficient (ADC), and decreased fractional anisotropy (FA) in boxers compared to controls
- Abnormalities are assumed to reflect chronic, cumulative brain injury resulting from repeated mild TBI in boxers

(Chappell MH et al, 2006)
What about football?

*Football (UK) = Soccer (US)*
Football study

- 23 football players
  - 10 headed the ball >10x
  - 13 headed the ball >20x
- 10 controls
- 30m “corner kick”
- LP 7-10 days after
## Results - Football

<table>
<thead>
<tr>
<th></th>
<th>Soccer players with 10 approved headings (n=10)</th>
<th>Soccer players with 20 approved headings (n=13)</th>
<th>Controls (n=9(^b))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>26 (19-32)</td>
<td>23 (20-28)</td>
<td>24 (22-27)</td>
</tr>
<tr>
<td><strong>Total number of headings</strong></td>
<td>14 (11-20)</td>
<td>23 (20-57)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Albumin ratio</strong></td>
<td>4.1 (2.4-9.3)</td>
<td>3.9 (2.0-8.7)</td>
<td>4.1 (2.5-6.3)</td>
</tr>
<tr>
<td><strong>NF-L (ng/L)</strong></td>
<td>&lt;125</td>
<td>&lt;125</td>
<td>&lt;125</td>
</tr>
<tr>
<td><strong>T-tau (ng/L)</strong></td>
<td>315 (170-400)</td>
<td>250 (190-420)</td>
<td>320 (120-540)</td>
</tr>
<tr>
<td><strong>GFAP (ng/L)</strong></td>
<td>265 (180-510)</td>
<td>260 (190-330)</td>
<td>280 (190-460)</td>
</tr>
<tr>
<td><strong>S-100B in CSF ((\mu)g/L)</strong></td>
<td>0.87 (0.71-1.2)</td>
<td>0.82 (0.48-1.3)</td>
<td>1.1 (0.77-1.2)(^c)</td>
</tr>
<tr>
<td><strong>S-100B in serum ((\mu)g/L)</strong></td>
<td>0.060 (0.030-0.12)</td>
<td>0.040 (0.010-0.07)</td>
<td>0.040 (0.030-0.060)</td>
</tr>
</tbody>
</table>
Conclusion - Football

No neurochemical evidence for neuronal injury caused by heading in soccer
Junior Seau #55
NFL’s Junior Seau had brain disease CTE when he killed himself

By Barry Wilner - Associated Press
Thursday, January 10, 2013

Junior Seau, one of the NFL’s best and fiercest players for two decades, suffered from a degenerative brain disease often associated with repeated blows to the head when he committed suicide last May, the National Institutes of Health said in a study released Thursday.

The NIH, based in Bethesda, Md., said Seau’s brain revealed abnormalities consistent with chronic traumatic encephalopathy or CTE. It said that the study included unidentified brains, one of which was Seau’s, and that the findings on Seau were similar to autopsies of people “with exposure to repetitive head injuries.”

Seau’s family requested the analysis of his brain.

The star linebacker played for 20 NFL seasons with San Diego, Miami and New England before retiring in 2009. He died of a self-inflicted shotgun wound.

He joins a list of several dozen football players who were found to have CTE. Boston University’s center for study of the disease reported last month that 34 former pro players and nine who played only college football suffered from CTE.

“I was not surprised after learning a little about CTE that he had it,” Seau’s 23-year-old son Tyler said. “He did play so many years at that level. I was more just kind of angry I didn’t do something more and have the awareness to help him more, and now it is too late.”

Any of us were aware of the side affects that could be going...
The atrophied brain of chronic traumatic encephalopathy -- the result of cumulative concussions. (Courtesy Ann McKee)
Top row: Brain sections showing dense tau protein deposition in multiple areas of frontal cortex (boxes). Bottom row: Microscopic images showing large numbers of tau-containing neurofibrillary tangles (dark brown spots) in the areas of damage.
Three brain sections from Mr. Creekmur showing dense tau deposits (brown) in the insula (1), temporal (2) and frontal (3) cortices, amygdala (4) and hippocampus (5) in the absence of beta amyloid plaques. A normal control brain would not show any brown discoloration.
Chronic Traumatic Encephalopathy #4

Photographs by Ann C. McKee, Boston University/Bedford Veterans Hospital
Cerebral Cortex / Bielschowski silver stain
Parkinson-Dementia Complex of Guam  (Daniel Perl, MD)
Magnified View of Neurofibrillary Tangles in Hippocampus
Parkinson-Dementia Complex of Guam  (Daniel Perl, MD)
PET Scanning of Brain Tau in Retired National Football League Players: Preliminary Findings

- 5 retired NFL players ages 45-73
- FDDNP-PET signals (tau & amyloid) were higher in players in all subcortical regions and the amygdala

Small, GW et al. Geriatric Psychiatry 2013;21:138-144
Traumatic Brain Injury and Chronic Traumatic Encephalopathy: A Forensic Neuropsychiatric Perspective

- There are no uniform diagnostic criteria for mTBI and CTE
- The evidence for a relationship between TBI and CTE is mixed and post-mortem only

Wortzel HS, Brenner LA, Arciniegas, DB. Behavioral Sciences and the Law. 2013
THE NATIONAL INTREPID CENTER OF EXCELLENCE

an instrument of hope, healing, discovery and learning
NICoE Satellites (Artist’s Rendering)
Extensive microhemorrhage - DAI

76 scattered T2 hyper-intensities

Small focus of encephalomalacia and gliosis inferior Left frontal Lobe
Radiology Findings: Structural

Structural Imaging Findings
N = 542
Results: Group Analysis

- Group Results for TBI patients:

1. **DTI**: shows commonly damaged areas in the internal capsule, corpus callosum, and cingulum

2. **Perfusion**: shows damage in the cingulum and cerebellum

3. **fMRI**: reveals abnormalities in the cerebellum with memory tasks

4. **Resting state fMRI**: show unique activity in the cerebellum and hyperactivity in the cingulum
NICoE has seen 508 cohort patients through August 2013

Breakdown of Patients Admitted by Service, October 2010 – August 2013

<table>
<thead>
<tr>
<th>136 Marine</th>
<th>214 Army</th>
<th>123 Navy</th>
<th>35 Air Force</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camp Lejeune, NC</td>
<td>CBWTU-AR</td>
<td>Andrews Air Force Base</td>
<td></td>
</tr>
<tr>
<td>Camp Pendleton</td>
<td>CBWTU-MA</td>
<td>Camp Lejeune, NC</td>
<td></td>
</tr>
<tr>
<td>CBIRF/Indianhead, MD</td>
<td>CBWTU-Rock Island, IL</td>
<td>Camp Pendleton, CA</td>
<td></td>
</tr>
<tr>
<td>Cherry Point, NC</td>
<td>CBWTU-VA</td>
<td>Fort Belvoir, VA</td>
<td></td>
</tr>
<tr>
<td>Dover AFB, DE</td>
<td>Fort Bliss, TX</td>
<td>Great Lakes, IL</td>
<td></td>
</tr>
<tr>
<td>JT Boone BHC I, VA</td>
<td>Fort Bragg, NC</td>
<td>Guantanamo Bay</td>
<td></td>
</tr>
<tr>
<td>Little Creek NAB, VA</td>
<td>Fort Campbell, KY</td>
<td>Little Creek NAB, VA</td>
<td></td>
</tr>
<tr>
<td>NBHC</td>
<td>Fort Carson, CO</td>
<td>Naples, Italy</td>
<td></td>
</tr>
<tr>
<td>New River Air Station, VA</td>
<td>Fort Detrick, MD</td>
<td>Navy Special Warfare</td>
<td></td>
</tr>
<tr>
<td>NHCL</td>
<td>Fort Drum, NY</td>
<td>NNMC</td>
<td></td>
</tr>
<tr>
<td>NH Okinawa</td>
<td>Fort Eustis, VA</td>
<td>Patuxent River, MD</td>
<td></td>
</tr>
<tr>
<td>NNMC</td>
<td>Fort Hood, TX</td>
<td>Quantico, VA</td>
<td></td>
</tr>
<tr>
<td>USMC Base Quantico</td>
<td>Fort Huachua, AZ</td>
<td>NMC Portsmouth, VA</td>
<td></td>
</tr>
<tr>
<td>USMC HQ in Arlington, VA</td>
<td>Fort Knox, TN</td>
<td>NMC San Diego, CA</td>
<td></td>
</tr>
<tr>
<td>WRAMC</td>
<td>Fort Meade, MD</td>
<td>Sigonella, Italy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fort Riley, KS</td>
<td>SOCOM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pentagon</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schofield Barracks, HI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>West Point</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WRAMC</td>
<td>Virginia Beach</td>
<td></td>
</tr>
</tbody>
</table>

Referral Sources by Service

| Camp Lejeune, NC | CBWTU-AR   | Andrews Air Force Base |
| Camp Pendleton   | CBWTU-MA   | Camp Lejeune, NC  |
| CBIRF/Indianhead, MD | CBWTU-Rock Island, IL | Camp Pendleton, CA |
| Cherry Point, NC | CBWTU-VA   | Fort Belvoir, VA  |
| Dover AFB, DE   | Fort Bliss, TX | Great Lakes, IL |
| JT Boone BHC I, VA | Fort Bragg, NC | Guantanamo Bay |
| Little Creek NAB, VA | Fort Campbell, KY | Little Creek NAB, VA |
| NBHC            | Fort Carson, CO | Naples, Italy |
| New River Air Station, VA | Fort Detrick, MD | Navy Special Warfare |
| NHCL            | Fort Drum, NY | NNMC         |
| NH Okinawa      | Fort Eustis, VA | Patuxent River, MD |
| NNMC            | Fort Hood, TX | Quantico, VA  |
| USMC Base Quantico | Fort Huachua, AZ | NMC Portsmouth, VA |
| USMC HQ in Arlington, VA | Fort Knox, TN | NMC San Diego, CA |
| WRAMC           | Fort Meade, MD | Sigonella, Italy |
|                 | Fort Riley, KS | SOCOM       |
|                 | Pentagon     |             |
|                 | Schofield Barracks, HI |             |
|                 | West Point   |             |
|                 | WRAMC        | Virginia Beach |
Results: Single Subject Analysis

- No two TBI injuries are the same - heterogeneous in location and severity
- Individual and personalize analysis are needed
- Sample DTI findings in pt with a normal structural MRI scan:
  - Right Sided Blast TBI subject presents 70+% less tracks in the injured area
Medical Imperative: Challenging Co-morbidity

PTSD
- Flashbacks
- Avoidance
- Hypervigilance
- Nightmares
- Re-Experiencing

TBI
- Cognitive Deficits
- Irritability
- Insomnia
- Depression
- Fatigue
- Anxiety

Polypharmacy

Pain/Suffering

- Headache
- Sensitivity to Light or Noise
- Nausea & Vomiting
- Vision Problems
- Dizziness

Experiencing Pain/Suffering
Interdisciplinary Patient-Centered Evaluation and Treatment
Major Diagnostic and Rehabilitation Equipment

- Magneto Encephalography (MEG) Scanner
- Positron Emission Tomography with Computed Tomography (PET/CT)
- MRI (3-T) / Functional MRI
- Diffusion Tensor Imaging (DTI)
- CAREN (Computer Assisted Rehabilitation Environment) system
- Trans-Cranial Doppler Ultrasound