Mild Traumatic Brain Injury & Postconcussion Syndrome:

New Evidence Base for Evaluation and Management

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Director of Brain Injury Research

mTBI: What’s all the Fuss About?

Hospitalizations Due to Head Injury

- 2.5-3.8 million mTBI estimated annually in U.S.
- True incidence unclear: 30-50% never receive medical attention
- Far fewer see a neurosurgeon, neurologist or neuropsychologist
- Subset with persistent symptoms and disability (“PCS”)
- Costly public health issue in the billions of $
- Hot Buttons: Sports, Military

mTBI Disconnect:
Lowest Mortality, Major Clinical Challenge, Least Science
Clinical Challenges in mTBI

- Was the accident sufficient to cause the patient to sustain a traumatic brain injury?
- What are the effects of this injury on brain function?
- How long should it take for the patient to recover?
- Is the cause of their persistent symptoms “organic” or “mental”?

*Historically, all hampered by lack of science*

Challenges in mTBI Research: *One Reason It’s So Hard*

Comorbidities in mTBI Patients Presenting to Level I Trauma Center

<table>
<thead>
<tr>
<th>Mechanism of Injury (n=1,566)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>MVC</td>
<td>55.4%</td>
</tr>
<tr>
<td>Fall</td>
<td>19.1%</td>
</tr>
<tr>
<td>Assault</td>
<td>11.8%</td>
</tr>
<tr>
<td>Trauma</td>
<td>10.0%</td>
</tr>
<tr>
<td>MCC</td>
<td>3.8%</td>
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</tbody>
</table>

- Pre-Admission Narcotics: 10%
- DSM Axis I Diagnosis: 15%
- Alcohol on Admission: 15%
- Psychotropic Medication: 18%
- Narcotics Given in ED: 44%

L. Nelson et al., TCN 2013
Research Challenges in mTBI: 
*The Denominator Problem*

Prospective, Population-Based 
- Occurrences of mTBI/Concussion
- Hospital ED Visits/Admissions
- Neuroscience Specialists
- Neuropsychologists
- Ongoing Follow-up

Retrospective, Clinic Samples

Significant Impact on Epidemiology and Clinical Science of mTBI

Do As I Say…

“Dad, I want to be a scientist”

“That’s great, honey. Just stay out of the weeds and pick something other than mTBI to study.”
Alternative Paradigms for mTBI Research

Sports Laboratory Assessment Model (SLAM)

Sports Concussion: mTBI Laboratory

(Barth, 2001)

- Large sample at risk
- Defined Exposure Period
- Preinjury Baseline Measures
- Eye Witness Account: AIC’s
- Immediate Assessment
- Serial Testing/Continuity
- Normal Controls
- Repetitive Concussion
- Chronic Exposure
- Longterm follow-up

How Can We Inform the Broader Science of mTBI?
Lessons Learned

1. Wealth of data on acute clinical effects and recovery after SRC & mTBI.

2. Emerging research on acute physiological effects and recovery after SRC & mTBI.

3. Movement toward an integrated, evidence-based neurobiopsychosocial model of mTBI recovery.

New Understanding of mTBI
Rethinking Postconcussion Syndrome

Scientific Advances in mTBI:
Acute Effects & Recovery

MECHANISM

TRUE NATURAL HISTORY

Minimum Threshold:
How much is enough to cause brain injury?

Clinical Recovery:
How long does it take for sign & symptoms to recover?

Physiological Recovery:
How long does the brain take to recover?

Driving Evidence Based Diagnosis, Assessment and Management
Biomechanics of TBI

The Tried & True

Ommaya & Gennarelli, Brain, 1974

Long Road of Clinical Translation

mTBI Laboratory!
Biomechanics of mTBI in Humans: How Much is Enough to Cause Brain Injury?

Measure and record blows to the head:
- Impact location
- Impact magnitude
- Impact duration
- Linear and angular acceleration components
- Exact times of impacts
- Sync w/ video

HITS Studies: Concussion Threshold?

MORE THAN A “DING”
- > 250K impacts in 100 players
- 19 concussion with HITS
- Ave. impact of concussive events: 103g (33) (<1% of NC impacts > 95g)
- Controlling for rotational acceleration, location of impact on the head, concussion:
  - 17x more likely if PLA >100g
  - 15x more likely if PRA > 5000r/sec2

Guskiewicz et al, UNC

Pellman et al: peak acceleration-concussion 98 g (+/- 28), non-concuss 60 g (+/- 24)
Zhang (2004): Probability of MTBI – 25% at 66g, 50% at 82g, 80% at 106 g
Brolinson (2006): Average peak acceleration 103.3 g (range 56-118 g)
What Does That Mean in Real Life?

- 100 g PLA equivalent to 25 mph MVA into brick wall, striking head against dash (unhelmeted)
- Significant rotational acceleration component
- Highlights significance of head impacts in SRC (not so mild)
- Provides context for interpretation of injury mechanisms

Progress in mTBI Research: 

*Acute Effects & Recovery*

<table>
<thead>
<tr>
<th>INJURY MECHANISMS</th>
<th>TRUE NATURAL HISTORY OF RECOVERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold/Dynamics: How much is enough to cause brain injury?</td>
<td>Clinical Recovery: How long does it take for signs &amp; symptoms to recover?</td>
</tr>
<tr>
<td></td>
<td>Physiological Recovery: How long does it take for the brain to recover?</td>
</tr>
</tbody>
</table>

New Evidence Base to Guide Diagnosis, Assessment and Management
Over 25,000 Athlete Seasons, 1,500 Concussions Studied

Can we measure the acute effects of...

...What does early recovery look like?
Symptom Recovery After mTBI

Higher score indicates more severe symptoms; error bars represent 95% CI

McCrea et al., JAMA 2003
How Long Does it Take to Recover?

<table>
<thead>
<tr>
<th>Rate of Postinjury Recovery in HS and College Athletes (n=790)</th>
<th>Total (%)</th>
<th>Cumulative Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid (&lt; 1 day)</td>
<td>21.1</td>
<td>21.1</td>
</tr>
<tr>
<td>Gradual (&gt; 1 day, &lt; 7 days)</td>
<td>64.3</td>
<td>85.4</td>
</tr>
<tr>
<td>Prolonged (1 week – 1 month)</td>
<td>11.9</td>
<td>97.3</td>
</tr>
<tr>
<td>Persistent (&gt; 1 month)</td>
<td>2.7</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**2013 (n=94):** Mean Symptom Recovery **5.75 Days (4.48)**
90% Recover in 10 Days or Less, 2% > 30 days

Incidence, Clinical Course, and Predictors of Prolonged Recovery Time Following Sport-Related Concussion in High School and College Athletes

- 10% take > 7 days to recover
- Acute severity predicts recovery
- 2.5% symptomatic > 45 days
- No impairment on objective measures at Day 45 relative to BL
Translational Research?

How Do the Findings Apply to Other Populations at Risk of mTBI?

Civilian Symptom Recovery

- Prospective study of 123 mTBI patients, 100 TC's
- Evaluated in ED, follow-up at 7 days, 3 mos
- PCS scale and cognitive testing, SF-36, MINI Psychiatric screening, HADS, PTSD CL
- Elevated PCS scores in mTBI group at Day 7, not different from TCs at 3 mos
- PCS at 3 mos predicted by preinjury physical problems and concurrent psychosocial factors, not by mTBI
- Cognitive measures not predictive of PCS at 7 days or 3 mos
Symptoms after Military mTBI

- 298 blast, 92 non-blast mTBI patients
- NSI and PCL administered
- Symptoms higher in mTBI < 1 mo ago vs. > 1 mo ago, and with higher PTSD sx’s
- PCS not predicted by mechanism or acute characteristics of mTBI
- Symptom reporting most strongly associated with emotional distress

Is Symptom Recovery Really Recovery: Performance-Based mTBI Assessment

What is an isosceles triangle? In what year was the Great Wall of China built? Who invented dental floss?

It must be a concussion. He didn’t get even 1 question right.

Hot Pursuit of Better Signal Detection
Cognitive Recovery after Sport-Related Concussion

The neuropsychological impact of sport-related concussion: A meta-analysis

INTRODUCTION
Sports-related concussion occurs with some frequency among high school athletes, for example, 5% or all high school athletes. The prevalence is not known, as most studies are conducted in high-level teams with limited access to professional sports with additional costs. As a result, the diagnosis is usually made in high-level teams with limited access to professional sports with additional costs. As a result, the diagnosis is usually made in high-level teams with limited access to professional sports with additional costs. As a result, the diagnosis is usually made in high-level teams with limited access to professional sports with additional costs.

Acute effects (w/n 24 hrs) greatest for delayed memory (d=1.00), memory acquisition (d=1.03), and global cognitive functioning (d=1.42)

Overall ES (d=0.49) comparable to non-sports (d=0.54)

No residual neuropsych impairment > 7 days postinjury

Cognitive Recovery: SRC

- Meta-analysis: 21 studies, 790 concussions, 2014 controls
- Acute effects (w/n 24 hrs) greatest for delayed memory (d=1.00), memory acquisition (d=1.03), and global cognitive functioning (d=1.42)
- Overall ES (d=0.49) comparable to non-sports (d=0.54)
- No residual neuropsych impairment > 7 days postinjury
Cognitive Effects of SRC

Table 1. Characteristics of the 36 studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Immediate post-injury assessment</th>
<th>Neurocognitive assessment</th>
<th>Time from injury (days)</th>
<th>Effect size</th>
<th>95% CI</th>
<th>Assessment effect size</th>
<th>95% CI</th>
<th>Quality score</th>
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<tbody>
<tr>
<td>Bert and McCrea(18)</td>
<td>116, control</td>
<td>NA</td>
<td>NA</td>
<td>24</td>
<td>-0.81</td>
<td>-1.30, -0.29</td>
<td>-1.30, -0.29</td>
<td>0.75</td>
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<tr>
<td>Braze and Enchemendia(19)</td>
<td>56, control</td>
<td>NA</td>
<td>NA</td>
<td>24</td>
<td>-0.56</td>
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<td>Collin et al.(20)</td>
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<td>NA</td>
<td>NA</td>
<td>21</td>
<td>-1.09</td>
<td>-1.59, -0.59</td>
<td>-1.59, -0.59</td>
<td>0.65</td>
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<tr>
<td>Golin et al.(21)</td>
<td>136, control</td>
<td>NA</td>
<td>NA</td>
<td>7</td>
<td>-1.16</td>
<td>-1.65, -0.67</td>
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<td>0.65</td>
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<td>O’Connor et al.(22)</td>
<td>49, control</td>
<td>NA</td>
<td>NA</td>
<td>7</td>
<td>-1.16</td>
<td>-1.65, -0.67</td>
<td>-1.65, -0.67</td>
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<td>Field et al.(23)</td>
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<td>Guskiewicz et al.(24)</td>
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<td>Guskiewicz et al.(25)</td>
<td>22, control</td>
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<tr>
<td>Guskiewicz et al.(26)</td>
<td>72, control</td>
<td>NA</td>
<td>NA</td>
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<td>0.65</td>
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<tr>
<td>Guskiewicz et al.(27)</td>
<td>196, control</td>
<td>NA</td>
<td>NA</td>
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<td>-1.59, -0.59</td>
<td>-1.59, -0.59</td>
<td>0.65</td>
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<tr>
<td>Horton-Byrne et al.(28)</td>
<td>56, control</td>
<td>NA</td>
<td>NA</td>
<td>21</td>
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<td>0.65</td>
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<tr>
<td>Iwamoto et al.(29)</td>
<td>41, control</td>
<td>NA</td>
<td>NA</td>
<td>7</td>
<td>-1.09</td>
<td>-1.59, -0.59</td>
<td>-1.59, -0.59</td>
<td>0.65</td>
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<tr>
<td>Iwamoto et al.(30)</td>
<td>8, control</td>
<td>NA</td>
<td>NA</td>
<td>7</td>
<td>-1.09</td>
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<td>Johnson et al.(31)</td>
<td>36, control</td>
<td>NA</td>
<td>NA</td>
<td>21</td>
<td>-1.09</td>
<td>-1.59, -0.59</td>
<td>-1.59, -0.59</td>
<td>0.65</td>
<td></td>
</tr>
</tbody>
</table>

ACUTE (24 HR) COGNITIVE EFFECT SIZES: -0.81 (LARGE)

SYMPTOMS: -3.31
BALANCE: -2.56

SUBACUTE (14 DAYS) COGNITIVE EFFECT SIZES: -0.26 (SMALL)

SYMPTOMS: -1.09
BALANCE: -1.16

Acute Sports vs. Civilian vs. Military mTBI:
Cognitive Test Performance on Day of Injury

Acute Sports vs. Civilian vs. Military mTBI: Cognitive Test Performance on Day of Injury

Acute Sports vs. Civilian vs. Military mTBI: Cognitive Test Performance on Day of Injury

Acute Sports vs. Civilian vs. Military mTBI: Cognitive Test Performance on Day of Injury
Military mTBI

- 56 MSM w/ mTBI in OEF/OIF
  - 21 non-blast, 35 blast+blunt
- Neurocognitive battery and PAI 4.4 (4.1) months post-injury
- PAI: no group differences on any scales; medium ES for Dep (.49), Stress (.47) (Blast+ > NB)
- No group differences on any cognitive measures after controlling for Dep, Stress
- Little evidence to suggest that blast+blunt results in worse cognitive or psych recovery than blunt

Cognitive Recovery: Civilian mTBI

A quantitative review of the effects of traumatic brain injury on cognitive functioning
DAVID J. SCHROETLEIN & ANNE M. HIMPSHO
Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, USA

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability in young adults. The impact of traumatic brain injury (TBI) can be devastating and recovery can be highly variable. Although there is much information on the effects of TBI on cognitive function, a comprehensive review of the literature is needed to understand the full scope of the problem. This review aims to summarize the current state of knowledge regarding the effects of TBI on cognitive function and to identify areas for future research.

Methods

A systematic review of the literature was conducted. The search included articles published in English from 1990 to 2016. The search strategy included the use of specific keywords related to TBI and cognitive function. The results of the search were analyzed and synthesized to identify the effects of TBI on cognitive function.

Results

The results of the review showed that TBI can have a significant impact on cognitive function. The effects of TBI on cognitive function vary depending on the severity and location of the injury. In general, individuals with mild TBI (mTBI) have more cognitive impairments than those with severe TBI (sTBI). The effects of TBI on cognitive function can persist for months to years after the injury.

Conclusion

The results of this review suggest that TBI has a significant impact on cognitive function. Future research should focus on the identification of factors that moderate the effects of TBI on cognitive function and the development of interventions to improve cognitive function in individuals with TBI.
**Neurocognitive Effects of mTBI**

Effect Sizes: 0.2 Small, 0.5 Medium, 0.8 Large

< 0.3 Difficult to Detect in Individual Patients; large overlap b/n patients and control group

Adapted from Iverson, 2011

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**Non-specificity of Neurocognitive Performance**

Effect Sizes: 0.2 Small, 0.5 Medium, 0.8 Large

< 0.3 Difficult to Detect in Individual Patients; large overlap b/n patients and control group

Adapted from Iverson, 2005
mTBI Clinical Recovery & Outcome

World Health Organization (2004):
- 120 “best evidence” studies on mTBI prognosis
- Symptoms temporary after MTBI, with full recovery in days to weeks in overwhelming majority of kids and adults
- Sound evidence for favorable prognosis
- Little evidence of residual cognitive, behavioral or academic deficits
- Persistent symptoms (i.e., PCS) may be attributable to non-injury factors (demographic, psychosocial, medical, situational factors)

(Carrol et al., 2004)

Progress in mTBI Research:
Acute Effects & Recovery

TRUE NATURAL HISTORY OF RECOVERY

Threshold/Dynamics:
How much is enough to cause brain injury?

Clinical Recovery:
How long does it take for signs & symptoms to recover?

Physiological Recovery:
How long does it take for the brain to recover?

New Evidence Base to Guide Diagnosis, Assessment and Management
Pursuit of the Perfect “Biomarker”

When is the brain fully recovered from mTBI?

fMRI: Brain Activation Changes after mTBI

Figure 2. The location of major cortical activation foci are displayed on a surface-rendered projection. The gyral location of activations (bilateral dorsolateral prefrontal and superior parietal) were similar in both groups from the 0-back to 1-back condition. Major differences, as described in the text, were observed in the 1-back to 2-back comparison. Note the more extensive activation of primarily right superior parietal and dorsolateral prefrontal cortex in patients with mild traumatic brain injury (MTBI).

FUNCTIONAL MRI: ACUTE SRC

**DESIGN & PROTOCOL:**
- 12 FB concussed FB players, 12 matched controls studied 13 hr, 45 d PI
- Clinical testing, event-related fMRI (load dependent WM task)

**CLINICAL EFFECTS/RECOVERY:**
- Acute symptoms and cognitive impairments (RT, WM) at 13 hours
- No impairments at 45 days

**fMRI ACTIVATION STUDIES:**
- 13 HR: Decreased activation of RH attentional networks in SRC group
- Correlate with cog deficits, symptoms
- 45 D: Reversed pattern (SRC>NC) (compensatory increase=recovery)