Neuroimaging Markers of Acute mTBI

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Neurometabolic Changes in the Acute Phase after Sports Concussions Correlate with Symptom Severity

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Abstract

Sports concussion is a major problem that affects thousands of people in North America every year. Despite negative neuroimaging findings, many athletes display neurophysiological alterations and post-concussion symptoms such as headaches and sensitivity to light and noise. It is suspected that neurometabolic changes may underlie these changes. In this study we investigated the effects of sports concussion on brain metabolism using ^{1}H-MR spectroscopy by comparing a group of 12 non-concussed athletes with a group of 12 concussed athletes of the same age (mean 22.5 years) and education (mean 16 years). All athletes were scanned 1-6 days post-concussion in a 3T Siemens MRI, and were administered a symptom scale to evaluate post-concussion symptomatology. Participants also completed a neuropsychological test battery to assess verbal memory, visual memory, information processing speed, and reaction time, and no group differences were detected relative to controls. Concussed athletes showed a higher number of symptoms than non-concussed athletes, and they also showed a significant decrease in glutamate in the primary motor cortex (M1), as well as significant decreases in *N*-acetylaspartate in the prefrontal and primary motor cortices. No changes were observed in the hippocampus. Furthermore, the metabolic changes in M1 correlated with self-reported symptom severity despite equivalent neuropsychological performance. These results confirm cortical neurometabolic changes in the acute post-concussion phase, and demonstrate for the first time a correlation between subjective self-reported symptoms and objective physical changes that may be related to increased vulnerability of the concussed brain.

Diffusion tensor imaging of acute mild traumatic brain injury in adolescents

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ABSTRACT

Background: Despite normal CT imaging and neurologic functioning, many individuals report postconcussion symptoms following mild traumatic brain injury (MTBI). This dissociation has been enigmatic for clinicians and investigators.

Methods: Diffusion tensor imaging tractography of the corpus callosum was performed in 10 adolescents (14 to 19 years of age) with MTBI 1 to 6 days postinjury with Glasgow Coma Scale score of 15 and negative CT, and 10 age- and gender-equivalent uninjured controls. Subjects were administered the Rivermead Post Concussion Symptoms Questionnaire and the Brief Symptom Inventory to assess self-reported cognitive, affective, and somatic symptoms.

Results: The MTBI group demonstrated increased fractional anisotropy and decreased apparent diffusion coefficient and radial diffusivity, and more intense postconcussion symptoms and emotional distress compared to the control group. Increased fractional anisotropy and decreased radial diffusivity were correlated with severity of postconcussion symptoms in the MTBI group, but not in the control group.

Conclusions: In adolescents with mild traumatic brain injury (MTBI) with Glasgow Coma Scale score of 15 and negative CT, diffusion tensor imaging (DTI) performed within 6 days postinjury showed increased fractional anisotropy and decreased diffusivity suggestive of cytotoxic edema. Advanced MRI-based DTI methods may enhance our understanding of the neuropathology of TBI, including MTBI. Additionally, DTI may prove more sensitive than conventional imaging methods in detecting subtle, but clinically meaningful, changes following MTBI and may be critical in refining MTBI diagnosis, prognosis, and management. **Neurology® 2008;70:948-955**

A prospective diffusion tensor imaging study in mild traumatic brain injury

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ABSTRACT

Objectives: Only a handful of studies have investigated the nature, functional significance, and course of white matter abnormalities associated with mild traumatic brain injury (mTBI) during the semi-acute stage of injury. The present study used diffusion tensor imaging (DTI) to investigate white matter integrity and compared the accuracy of traditional anatomic scans, neuropsychological testing, and DTI for objectively classifying mTBI patients from controls.

Methods: Twenty-two patients with semi-acute mTBI (mean = 12 days postinjury), 21 matched healthy controls, and a larger sample (n = 32) of healthy controls were studied with an extensive imaging and clinical battery. A subset of participants was examined longitudinally 3-5 months after their initial visit.

primarily affecting diffusion perpendicular to axons. Diffusion tensor imaging measurement may have utility for objectively classifying mTBI, and may serve as a potential biomarker of recovery. **Neurology® 2010;74:643-650**

DTI findings evident beyond symptoms and demonstrated clinical recovery

- DTI to investigate WM integrity and compare accuracy of conventional scanning, neuropsych testing and DTI to objectively classify MTBI patients from controls
- 22 semi-acute MTBI (M=12 days post); 21 matched healthy controls (non-trauma)
- 16 of 22 MTBI had LOC (AAN Gr 3)
- Neuropsych tests of attn, memory, WM, proc. speed, EF, WTAR, TOMM
- No Diff b/n MTBI & Control on MRI or neuropsych measures; NP effect sizes comparable to literature at T1 (.10-.90 range)
- MTBI showed increased fractional anisotropy (FA) associated with reduced radial diffusivity (RD) in corpus callosum and several left hemisphere WM tracts
- DTI superior to other measures in classifying MTBI from controls
- Longterm follow-up (3-5 months) on 10 MTBI, 15 NC's; largely normalization on DTI, normal clinical measures

Abnormal resting state functional connectivity as a marker for diagnosing and predicting recovery in mild traumatic brain injury (MTBI)

Guangyu Chen[1], Thomas Hammeke[2], Gang Chen[1], Michael McCrea[3], B. Douglas Ward[1], Sarah Miller[4], Shi-Jiang Li[1, 2]

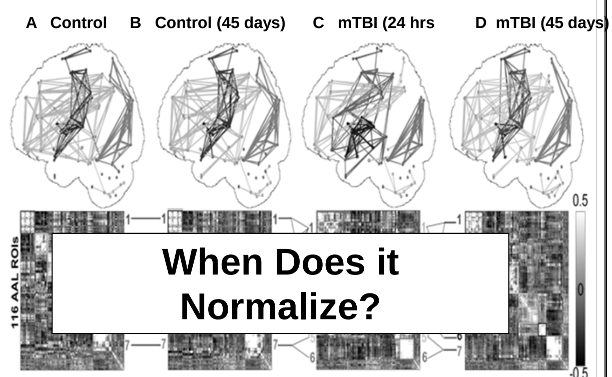

Figure 7. Illustration of modular analysis. As compared with control baseline, prominent reconfiguration of modular networks occurred in 24 hours after SRC, and the pattern was reinstated in recovery 45 days later.

- **Significant abnormalities in functional connectivity between brain regions after acute MTBI**
- 14 areas of significantly different connectivity at 13 hours in MTBI group
- Connectivity findings correlate with clinical results (balance, cognition)
- Findings also indicate recovery in connectivity from 13 hrs to 7 weeks
- **Connectivity abnormalities resolved by 7 weeks**

Persistent Physiological Changes After SRC

J Head Trauma Rehabil
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Acute Effects and Recovery After Sport-related Concussion: A Neurocognitive and Quantitative Brain Electrical Activity Study

Michael McCrea, PhD, ABPP-CN; Leslie Prichep, PhD; Matthew R. Powell, PhD, ABPP; Robert Chabot, PhD; William B. Barr, PhD, ABPP

QEEG as a marker of recovery after sport-related concussion. **Keywords:** *brain injury, concussion, electroencephalography, neuropsychological tests*

Physiological recovery may extend beyond clinical recovery, but normal by D45

- Investigate clinical utility, sensitivity of portable, automatic QEEG device in detecting abnormal brain activity after MTBI
- 28 concussed athletes, 28 matched controls
- Sport concussion research design; baseline QEEG and all clinical measures
- Follow-up DOI, Days 3, 5, 8, 45
- **Recovery in symptoms, cognition, balance over first week** **(c/w literature)**
- **QEEG abnormalities at D8**
- All measures normal at D45

Prognostic Utility of Imaging Biomarkers?

J Head Trauma Rehabil
Vol. 27, No. 3, pp. 188–198

Diffusion Tensor Imaging Findings Are Not Strongly Associated With Postconcussional Disorder 2 Months Following Mild Traumatic Brain Injury

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Objective: To examine the relation between diffusion tensor imaging (DTI) of the corpus callosum and postconcussion symptom reporting following mild traumatic brain injury (MTBI). **Participants:** Sixty patients with MTBI and 34 patients with orthopedic/soft-tissue injuries (Trauma Controls) prospectively enrolled from consecutive admissions to a level 1 trauma center. **Procedure:** Diffusion tensor imaging of the corpus callosum was undertaken using a Phillips 3T scanner at 6 to 8 weeks postinjury. Participants also completed a postconcussion symptom checklist. The MTBI group was divided into 2 subgroups based on the International Classification of Diseases, Tenth Revision symptom criteria for postconcussion disorder (PCD): PCD Present (n = 21), PCD Absent (n = 39). **Main Outcome Measures:** Measures of fractional anisotropy and mean diffusivity for the genu, body, and splenium of the corpus callosum. Participants also completed the British Columbia Post-Concussion Symptom Inventory. **Results:** The MTBI group reported more postconcussion symptoms than the trauma controls. There were no significant differences between MTBI and trauma control groups on all DTI measures. In the MTBI sample, there were no significant differences on all DTI measures between those who did and did not meet the *International Classification of Diseases, Tenth Revision* research criteria for postconcussion disorder. **Conclusions:** These data do not support an association between white matter integrity in the corpus callosum and self-reported postconcussion syndrome 6 to 8 weeks post-MTBI. **Keywords:** *corpus callosum, diffusion tensor imaging, mild traumatic brain injury, postconcussion symptoms*

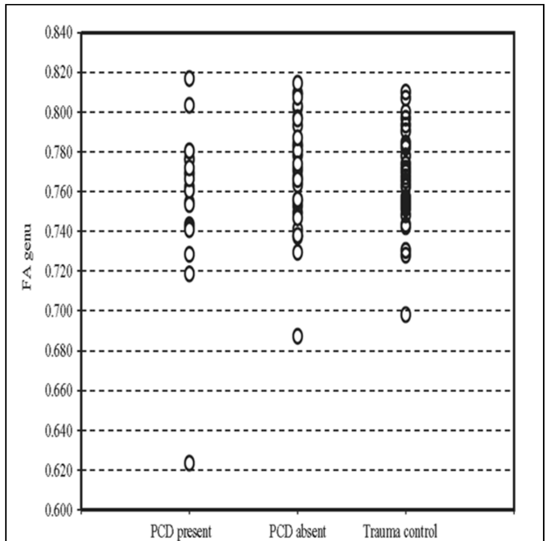

Figure 1. Scatter plot of FA genu by PCD group. N = 90 (PCD present, n = 21; PCD absent, n = 39; Trauma controls, n = 34); FA indicates fractional anisotropy; PCD, *ICD-10* postconcussion disorder.

Biomarker Balancing Act:
Sensitivity vs. Specificity

Neuropsychiatry

RESEARCH PAPER

Diffusion tensor imaging studies of mild traumatic brain injury: a meta-analysis

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► Additional figures and tables are published online only. To view these files please visit the journal online (http://jnnp.bmj.com/content/83/9.toc).

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ABSTRACT
Objectives To assess the possibility that diffusion tensor imaging (DTI) can detect white matter damage in mild traumatic brain injury (mTBI) patients via systematic review and meta-analysis.
Methods DTI studies that compared mTBI patients and controls were searched using MEDLINE, Web of Science, and EMBASE, (1980 through April 2012).
Results A comprehensive literature search identified 28 DTI studies, of which 13 independent DTI studies of mTBI patients were eligible for the meta-analysis. Random effect model demonstrated significant fractional anisotropy (FA) reduction in the corpus callosum (CC) (p=0.023, 95% CIs −0.466 to −0.035, 280 mTBIs and 244 controls) with no publication bias and minimum heterogeneity, and a significant increase in mean diffusivity (MD) (p=0.015, 95% CIs 0.062 to 0.581, 154 mTBIs and 100 controls). Meta-analyses of the subregions of the CC demonstrated in the splenium FA was significantly reduced (p=0.025, 95% CIs −0.689 to −0.046) and MD was significantly increased (p=0.013, 95% CIs 0.113 to 0.950). FA was marginally reduced in the midbody (p=0.099, 95% CIs −0.404 to 0.034), and no significant change in FA (p=0.421, 95% CIs −0.537 to 0.224) and MD (p=0.264, 95% CIs −0.120 to 0.438) in the genu of the CC.
Conclusions Our meta-analysis revealed the posterior part of the CC was more vulnerable to mTBI compared with the anterior part, and suggested the potential utility of DTI to detect white matter damage in the CC of mTBI patients.

and DTI studies demonstrated decreased FA in the CC.[6 7] Further, both linear and angular acceleration may damage callosal fibers, which may lead to microstructural changes that can be identified in neuroimaging studies, particularly DTI.[8] In addition, postmortem studies revealed histological lesions in the CC (reviewed in refs[9 10]).

Although a number of DTI studies with mTBI patients have investigated brain damage, they yielded inconsistent results. While some studies reported an increase or no change in FA following mTBI,[11] other studies reported a significant reduction in FA.[12]

Thus, we hypothesised that the microstructure brain damage in mTBI patients can be detected by DTI; moreover, we hypothesised that also mTBI patients show similar location and direction of microstructure brain damage to that with moderate to severe traumatic brain injury, that is, FA is reduced in the CC and IC in mTBI patients. To investigate the hypotheses, we carried out a systematic review of the literature of DTI studies of mTBI patients and conducted a meta-analysis of DTI studies of mTBI patients, and have located a priori-defined region of interest (ROI). Although we have a hypotheses, we do not confine ROI in the CC and IC, but performed a meta-analysis wherever it was possible, for the entire brain, to examine whether DTI can be a biomarker of mTBI.

METHODS

Meta-Analytic Methods and the Importance of Non-TBI Factors Related to Outcome in Mild Traumatic Brain Injury: Response to Bigler et al. (2013)

Glenn J. Larrabee[1], Laurence M. Binder[2], Martin L. Rohling[3], and Danielle M. Ploetz[3]

Acute DTI differences have been reported in association with mTBI, with evidence of normalization over 3–5 months post trauma (Mayer et al., 2010). Lange, Iverson, Brubacher, Madler, and Heran (2012b) compared patients with mTBI to orthopedic controls on DTI 6–8 weeks post trauma. There were no significant DTI differences between mTBI and trauma controls. Moreover, within the mTBI subjects, there were no DTI differences between those subjects who met versus those who did not meet ICD-10 criteria for postconcussion disorder. In a meta-analysis of 13 studies reporting DTI findings in mTBI, Aoki, Inokuchi, Gunshin, Yahagi, and Suwa (2012) reported significant effect sizes for both the corpus callosum and the splenium of the corpus callosum. Inspection of their Figure 2 shows an overall effect size of –0.25 for fractional anisotropy in the corpus callosum (small and ineffective for purposes of diagnosis due to 82% overlap of mTBI and control distributions, see Cohen, 1988). Only one of the 13 studies employed orthopedic trauma controls, examined subjects 2 months post trauma, and yielded the second smallest effect size, –0.067, p = .756, representing a 95% overlap of controls and mTBI (Lange et al., 2012b). Interestingly, this

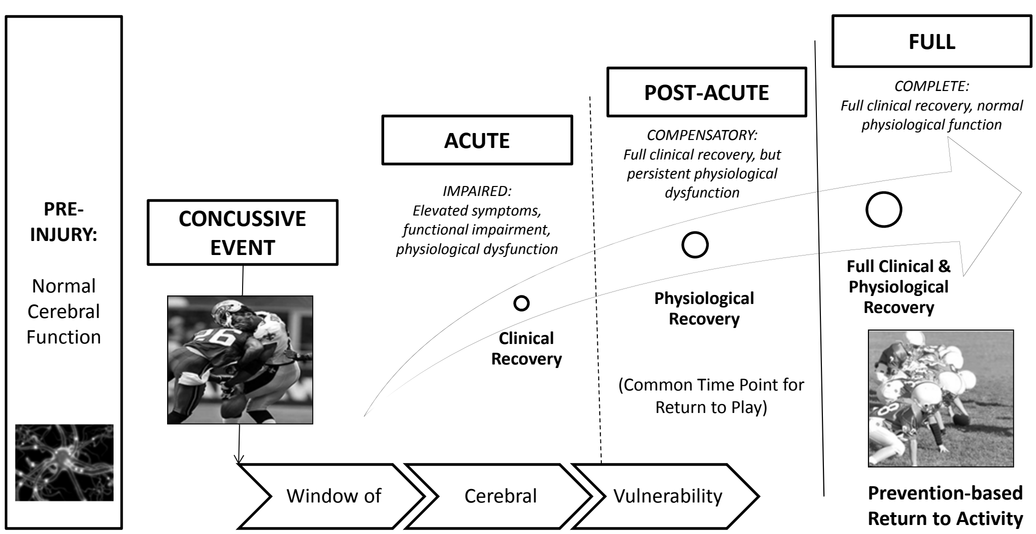
Diagnostic, Prognostic Value at the Individual Patient Level?

Acute Effects and Recovery after mTBI: *State of the Science*

1. Better understanding of biomechanical threshold for mTBI (clinical context)
2. Wealth of clinical studies: Elevated symptoms, cognitive impairment, functional impairments acutely
3. Emerging data on disruption and time course of changes in normal brain physiology and connectivity
4. Rapid/gradual recovery in days in overwhelming majority
5. Consistency in evidence across populations (sports, civilian, military)

Toward an Integrated Model of Recovery

Integrated Recovery Model



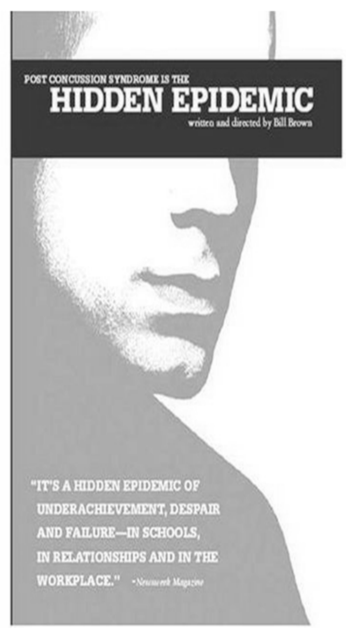
Science Driving Evidence-based Management

Real Life Recovery Model

Postinjury Phase	Evidence on Clinical & Physiological Recovery	Patient Experience
Super Acute (~first 5 day)	Symptoms, cognitive dysfunction can be severe, disrupt daily function Brain in neurometabolic crisis – inability to recruit resources	Symptoms, Cognitive dysfunction render unable to perform normal daily functions, RTW, etc.; Exertion may negatively impact recovery
Acute (~5-30 days)	Gradual improvement in symptoms, cognitive function; full recovery in ~90% of cases Brain on course back to normal metabolic state – compensatory overrecruitment of resources	Gradual return to full function at work/school/home that requires more effort than customary to meet normal demands; fatigue present
Chronic (> 30 day)	Brain returned to normal state Small percentage with persistent symptoms (PCS) PCS Significantly influenced by comorbidities, non-injury factors	Resume all normal activities without complication, restriction or accommodation Complex set of comorbidities affecting recovery

What About the "Miserable Minority"?

" This gripping educational film explores the connection between concussion and suicidal depression - a little known medical condition called Post Concussion Syndrome (PCS). PCS is possibly the most under-diagnosed, yet widespread condition affecting young people today. PCS masks itself by appearing as many other symptoms including the inablilty to learn, abuse of drugs and alcohol and the loss of motivation or joy."



"A Must See for Concussion Victims and Their Families" – William Brown, film-maker

What's the true incidence of "PCS"?

- Epidemiology?
  - Frequent citation of influential Alexander (1995 *Neurology*) review article: **"at one year after injury approximately 15% of [mild TBI] patients still have disabling symptoms"**
  - Articles referenced for this figure are Rutherford et al., 1978; McLean et al., 1983.
    - This figure and these citations echoed in multiple publications, but…..

Original citations for the "15%" at 1 year

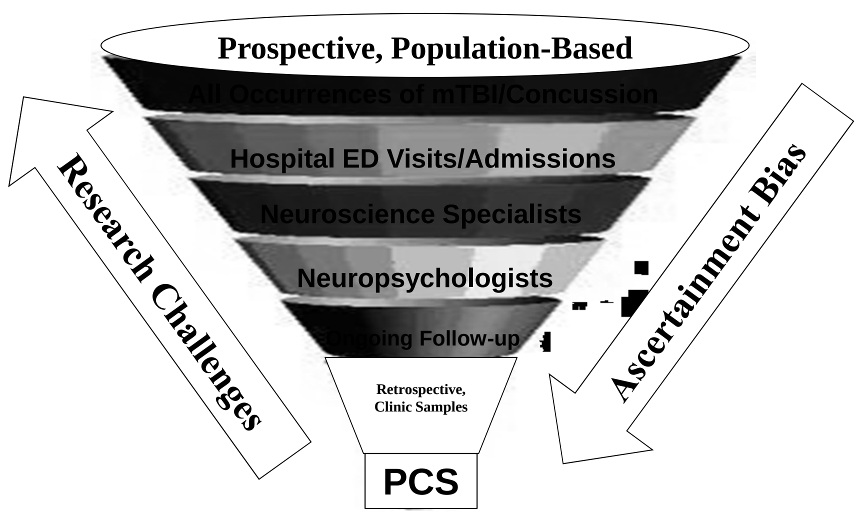
- Rutherford et al., 1979 (actually mis-cited in the Alexander article)
  - 145 consecutive mild TBI cases admitted to hospital in Belfast.
  - 131 followed up at one year, 19 still reporting symptoms (14.5%)
  - 8/19 involved in lawsuits, 6/19 suspected of malingering at 6 weeks post-injury (overlap of 5)
  - 10/19 pts reporting at least one new symptom not endorsed 6 weeks post-injury
  - Age not related to duration of symptoms, but gender was (women more likely to be symptomatic)
  - No controls (e.g., ortho injuries)

Original citations for the "15%"at 1 year

- McLean et al., 1983
  - – 11 pts with mild TBI (GCS 13-15)
  - – 8 pts with mod TBI (GCS 9-12)
  - – 1 pt with severe TBI (GCS=8)
- Controls N=52, friends of pts (non-injured)
- Groups compared on neurocognitive scores and symptom checklist at 3 days & ***1 month*** post-injury.
- No difference in neurocognitive scores, but more symptoms in pt group at ***1 month***.

The moral of the story: Check original sources!

Research Challenges in mTBI:
The Denominator Problem



Significant Impact on Epidemiology and Clinical Science of mTBI

mTBI Outcome

- Neurophysiological basis for sx's & dysfunction *acutely* after MTBI
- Maximal sx's first 72 hrs, rapid improvement over 1st week
- Lower true incidence of PCS
- Persistent symptoms (e.g., PCS) often largely related to comorbidities or non-injury factors
- PCS symptoms highly **nonspecific**
- Multi-factorial model of PCS

Outcome from mild traumatic brain injury
Grant L. Iverson

Purpose of review
The focus of this review is outcome from mild traumatic brain injury. Recent literature relating to pathophysiology, neuropsychological outcome, and the persistent postconcussion syndrome will be integrated into the existing literature.
Recent findings
The MTBI literature is enormous, complex, methodologically flawed, and controversial. There have been dozens of studies relating to pathophysiology, neuropsychological outcome, and the postconcussion syndrome during the past year. Two major reviews have been published. Some of the most interesting prospective research has been done with athletes.
Summary
pain, depression, substance abuse, life stress, unemployment, and protracted litigation).

Keywords
concussion, memory, mild traumatic brain injury, outcome, pathophysiology

Curr Opin Psychiatry 18:301–317 © 2005 Lippincott Williams & Wilkins.

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Current Opinion in Psychiatry 2005, 18:301–317

Abbreviations
fMRI functional magnetic resonance imaging
GCS Glasgow Coma Scale
MTBI mild traumatic brain injury
PTSD posttraumatic stress disorder
SPECT single photon emission computed tomography

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0951-7367

Introduction
The purpose of this review is to integrate the recent literature on mild traumatic brain injury with the existing literature. This literature is enormous, complex, methodologically flawed, and controversial. The literature published from November 2003 through 2004 is emphasized

appreciate that MTBIs can be characterized by damage to the structure and certainly the function of the brain. Approximately 7–20% of consecutive patients presenting to the emergency room with an MTBI have bleeding, bruising, or swelling on day-of-injury computed tomography [4–9,10*]. (Note that at least 25% of people with MTBIs seek no medical attention and 14% are seen at their doctor's office or in clinics [11]. A significant percentage of athletes with minor concussions do not even report the injury to their coaches or trainers [12*]. Therefore, the true frequency of structural lesions in people with MTBIs is far lower than these estimates.) In a recent comprehensive review of the literature, the estimated prevalence of computed tomographic abnormalities of patients seen in the hospital was 5% for those with Glasgow Coma Scale (GCS) scores of 15 and 30% or more for those with GCS scores of 13 [10*]. Moreover,

"Clearly, the estimate of 10-20% of patients with MTBIs not recoverying by 6-12 months is much too high"

What is "PCS"?

- DSM-IV- proposed new category:
  - A. History of a head trauma that has caused significant concussion (loc, pta, sz)
  - B. Evidence from neuropsychological testing of impaired attention or memory
  - C. Three or more occur shortly post-injury and persist for at least 3 months:
    - Headache
    - Dizziness
    - Irritability
    - Fatigue
    - Anxiety, depression, or emotional lability
    - Sleep disturbance
    - Personality change
    - Apathy

PCS: Largely a Symptom-based Diagnosis

Challenge: Non-specificity of PCS symptoms

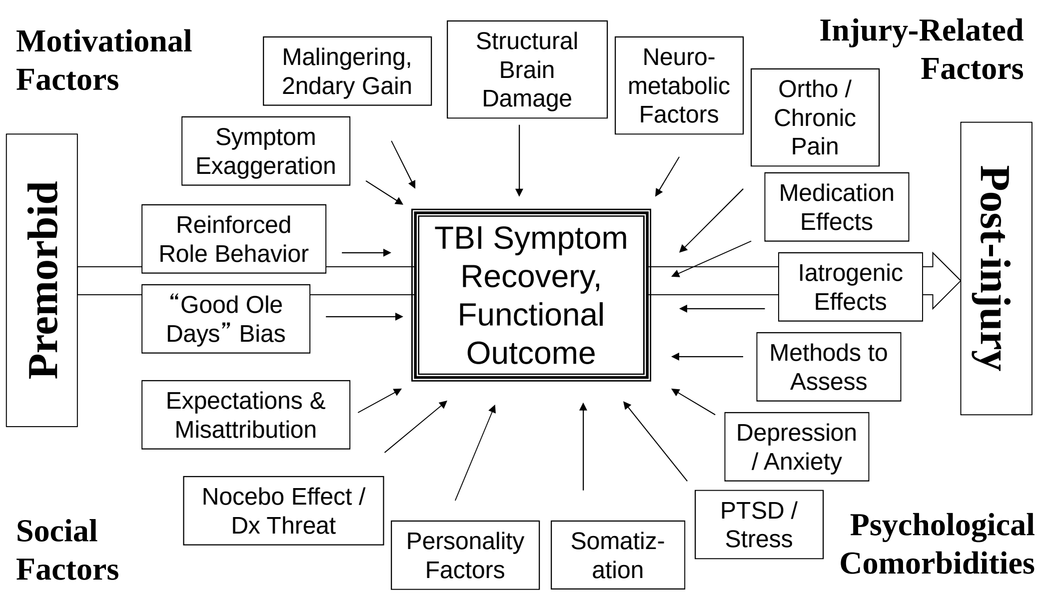
	Headache	Dizziness	Irritability	Memory problems	Conc. problems
College students[1]	36%	18%	36%	17%	42%
Chronic pain[2]	80%	67%	49%	33%	63%
Depressed[3]	37%	20%	52%	25%	54%
PI claimants (non tbi)[4]	77%	41%	63%	46%	71%
mTBI[5]	42%	26%	28%	36%	25%

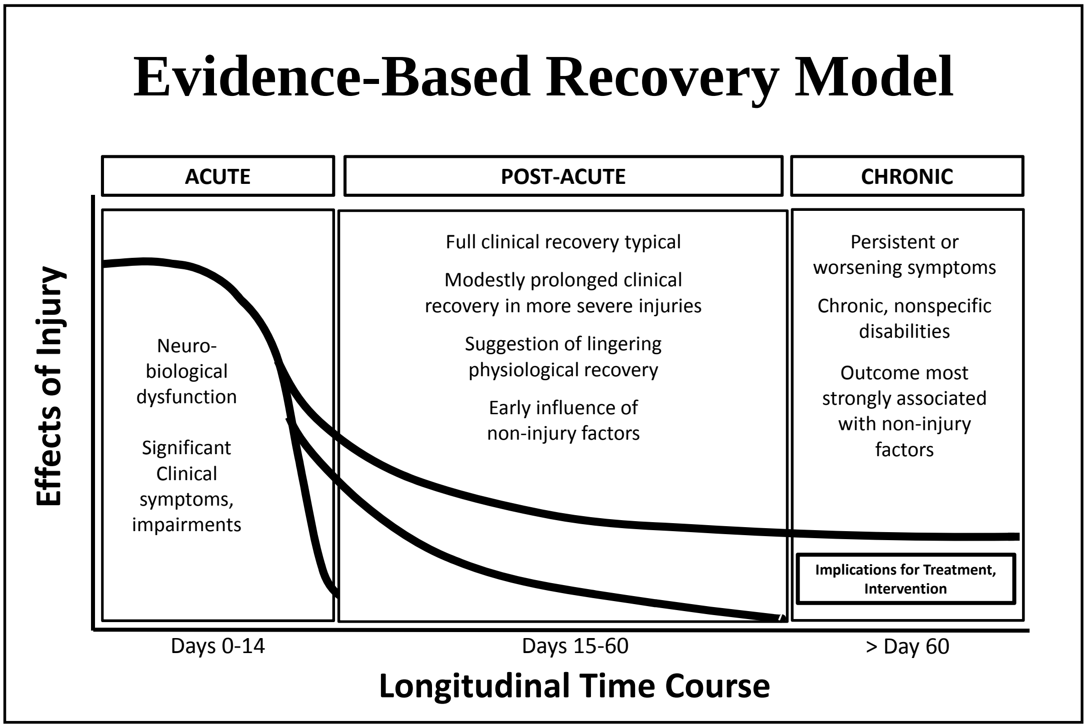
PCS Criteria are Neither Diagnostic nor Prognostic

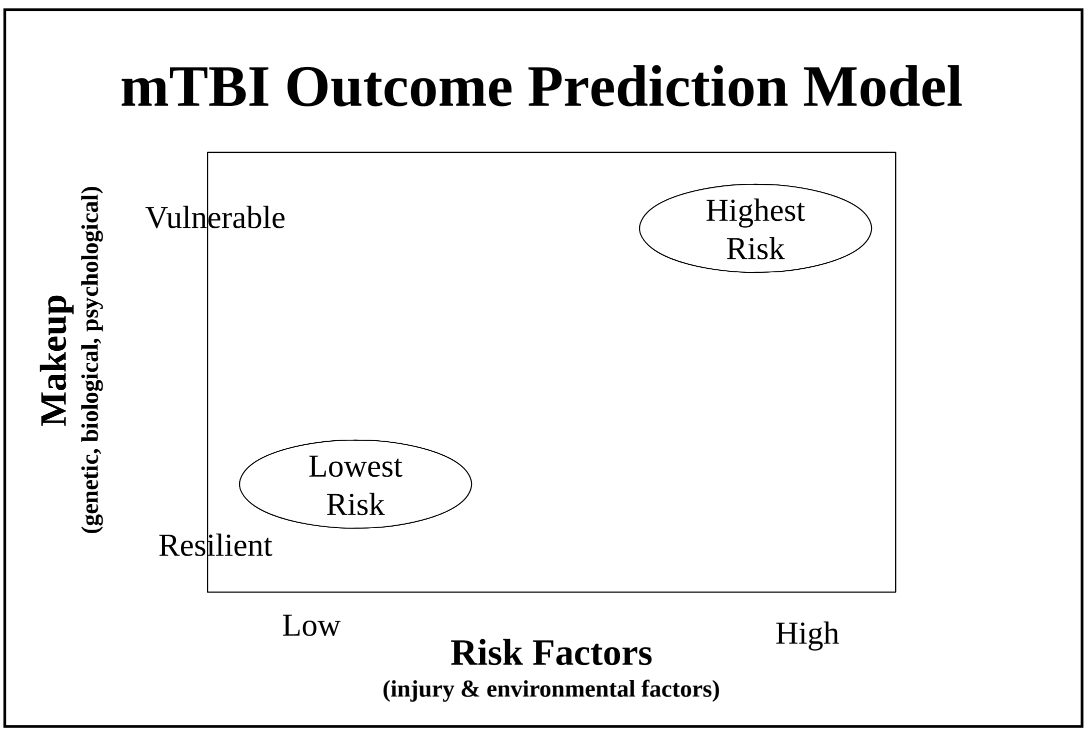
1. Sawchyn et al., 2000; 2. Radanov et al., 1992; 3.Trahan et al., 2001; 4. Dunn et al., 1995; 5. Ingebrigtsen et al., 1998

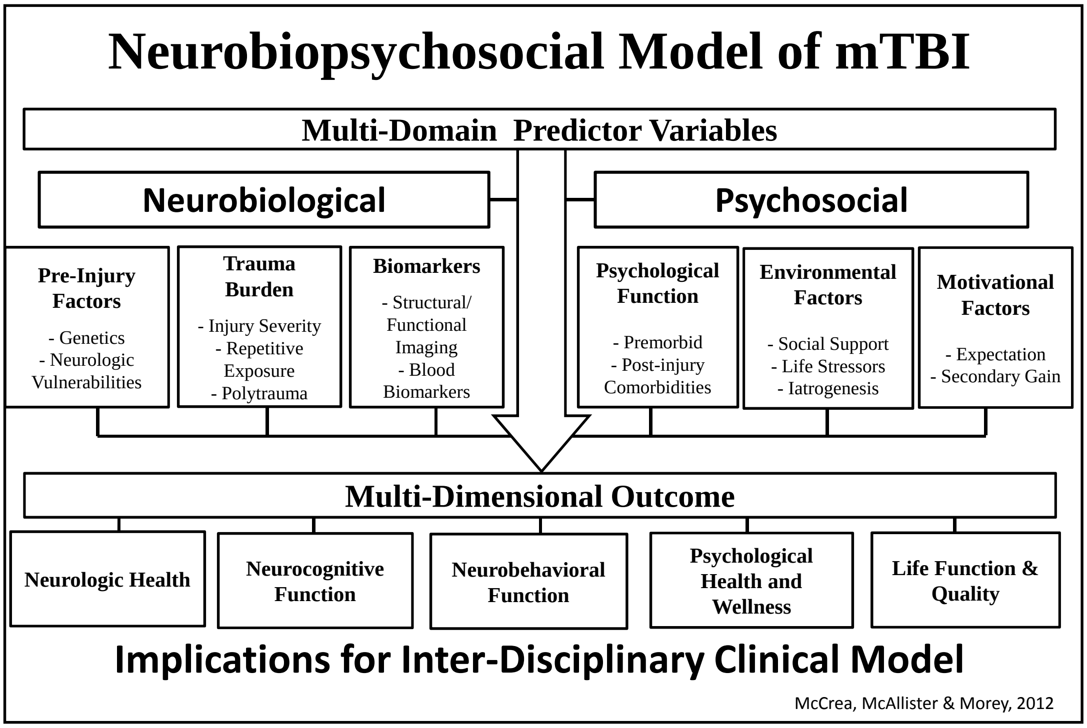
Factors Influencing Recovery and Outcome After TBI

Adapted from Iverson, Zasler, Lange, 2008




Evidence-Based Recovery Model
ACUTE
POST-ACUTE
CHRONIC
Effects of Injury
Neuro-
biological
dysfunction
Significant
Clinical
symptoms,
impairments
Full clinical recovery typical
Modestly prolonged clinical
recovery in more severe injuries
Suggestion of lingering
physiological recovery
Early influence of
non-injury factors
Persistent or
worsening symptoms
Chronic, nonspecific
disabilities
Outcome most
strongly associated
with non-injury
factors
Implications for Treatment,
Intervention
Days 0-14
Days 15-60
> Day 60
Longitudinal Time Course


mTBI Outcome Prediction Model
Makeup
(genetic, biological, psychological)
Vulnerable
Highest
Risk
Lowest
Risk
Resilient
Low
High
Risk Factors
(injury & environmental factors)




J Rehabil Med 2004; Suppl. 43: 84–105

PROGNOSIS FOR MILD TRAUMATIC BRAIN INJURY: RESULTS OF THE WHO COLLABORATING CENTRE TASK FORCE ON MILD TRAUMATIC BRAIN INJURY

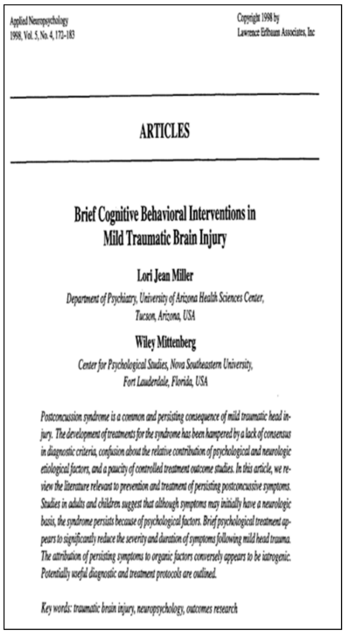
Linda J Carroll,[1] J. David Cassidy,[1,2,3] Paul M. Peloso,[4] Jörgen Borg,[5] Hans von Holst,[6] Lena Holm,[3] Chris Paniak[7] and Michel Pépin[8]

WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury

- Results of survey of non-surgical interventions and cost for mTBI (J Rehabil Med 2004)
- Recommendations for intervention based on the evidence
  - "Evidence that early intervention can reduce long-term complaints, and that this intervention need not be intensive."

…and never underestimate the value of a good Neuropsychologist

Efficacy of Neuropsychological Intervention



Applied Neuropsychology
1998, Vol. 5, No. 4, 172–183

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ARTICLES

Brief Cognitive Behavioral Interventions in Mild Traumatic Brain Injury

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Wiley Mittenberg
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Postconcussion syndrome is a common and persisting consequence of mild traumatic head injury. The development of treatments for the syndrome has been hampered by a lack of consensus in diagnostic criteria, confusion about the relative contribution of psychological and neurologic etiological factors, and a paucity of controlled treatment outcome studies. In this article, we review the literature relevant to prevention and treatment of persisting postconcussive symptoms. Studies in adults and children suggest that although symptoms may initially have a neurologic basis, the syndrome persists because of psychological factors. Brief psychological treatment appears to significantly reduce the severity and duration of symptoms following mild head trauma. The attribution of persisting symptoms to organic factors conversely appears to be iatrogenic. Potentially useful diagnostic and treatment protocols are outlined.

Key words: traumatic brain injury, neuropsychology, outcomes research

SHORT REPORT

Impact of early intervention on outcome following mild head injury in adults

J Ponsford, C Willmott, A Rothwell, P Cameron, A-M Kelly, R Nelms, C Curran

J Neurol Neurosurg Psychiatry 2002;73:330–332

Archives of Clinical Neuropsychology
19 (2004) 805–816

A longitudinal, controlled study of patient complaints following treated mild traumatic brain injury

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Accepted 30 September 2003

MTBI Management to Reduce Disability

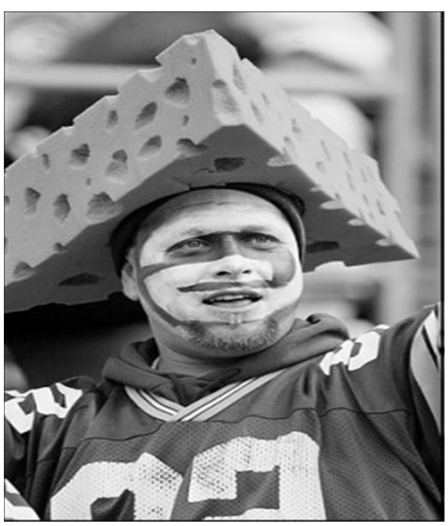
- **Research the Injury Event**: Acute injury characteristics tell the tale, symptoms alone lack specificity for retrospective diagnosis
- **Sooner the Better** (literally): Early psycho-educational intervention (first week) significantly reduces the risk of PCS and longterm disability
- **Biopsychosocial Model**: Functional recovery will depend more on relationship management, stress reduction, and supportive treatment and education than initial injury severity
- **Avoid Either/Or**: Where injury leaves off, other factors often join or take over; somatization does not always equal *malingering*
- **Get 'Em Goin'**: Design a graduated plan of activity and exertion starting as low as tolerable and ramping up to full activity; provide assurance that not harmful

Fueled by the Power of Interdisciplinary Care

Evidence-based mTBI Care

- Early intervention at point of entry (ED)
- Patients with acute/subacute TBI or concussion
  - Before point of contamination
- Inter-disciplinary
  - PM&R, Sports Medicine
  - Neuropsychology
  - Nurse Practitioner
- Systematic Follow-up
- Focus on restoring function, maximizing outcome

Thank You



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