Realizing a Neurobiopsychosocial Model of mTBI:

Research and Clinical Applications






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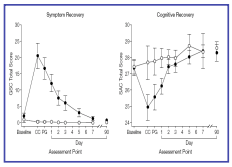
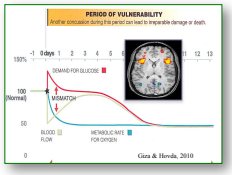
MEDICAL COLLEGE OF WISCONSIN

Advances in TBI Science:

Acute Effects & Recovery

TRUE NATURAL HISTORY OF INJURY & RECOVERY



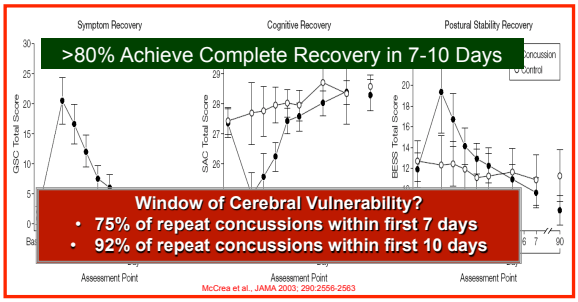


Clinical Recovery:
How long does it take for signs & symptoms to recover?

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

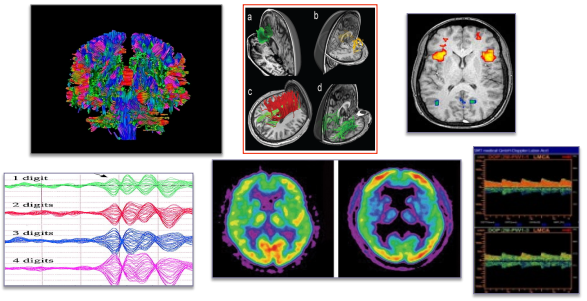
What Factors Predict Recovery and Outcome?

Association Between Recovery and Risk

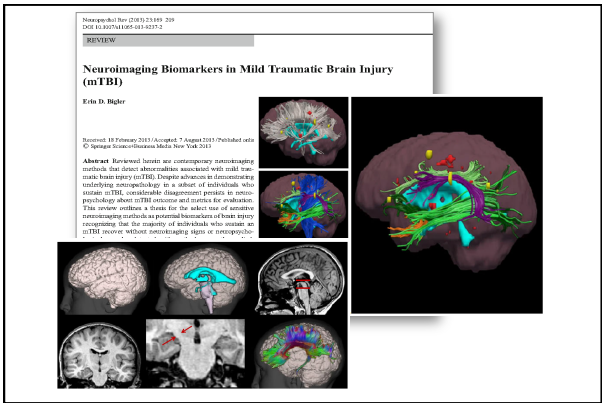


RTP: When is the Brain Ready?

Pursuit of the Perfect "Biomarker"



Diagnostic & Prognostic Value in Clinical Care?



Neuropsychol Rev (2013) 23:169–209
DOI 10.1007/s11065-013-9237-2

REVIEW

Neuroimaging Biomarkers in Mild Traumatic Brain Injury (mTBI)

Erin D. Bigler

Received: 18 February 2013 / Accepted: 7 August 2013 / Published online
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Abstract Reviewed herein are contemporary neuroimaging methods that detect abnormalities associated with mild traumatic brain injury (mTBI). Despite advances in demonstrating underlying neuropathology in a subset of individuals who sustain mTBI, considerable disagreement persists in neuropsychology about mTBI outcome and metrics for evaluation. This review outlines a thanks for the select use of sensitive neuroimaging methods as potential biomarkers of brain injury recognizing that the majority of individuals who sustain an mTBI recover without neuroimaging signs or neuropsycho-

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 MR-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

JOURNAL OF NEUROTRAUMA 27:65–76 (January 2010)
© Mary Ann Liebert, Inc.
DOI: 10.1089/neu.2009.0982

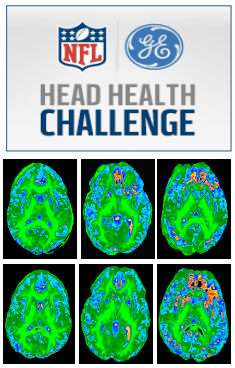
Neurometabolic Changes in the Acute Phase after Sports Concussions Correlate with Symptom Severity

Luke C. Henry,[1] Sébastien Tremblay,[1] Yvan Boulanger,[2] Dave Ellemberg,[3,4] and Maryse Lassonde[1]

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.

- 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



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GE-NFL HEAD HEALTH CHALLENGE I

A Prospective Study of Advanced MRI Biomarkers to Determine Acute Physiological Effects and Longitudinal Recovery After Sport-Related Concussion

Investigative Team:
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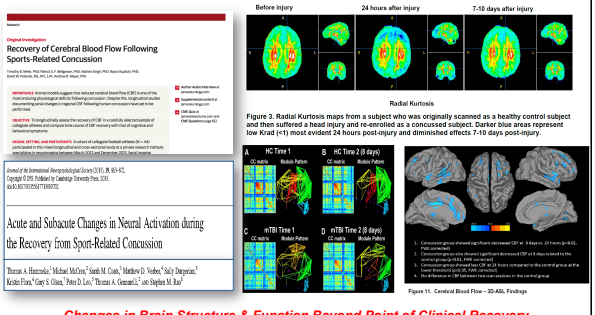
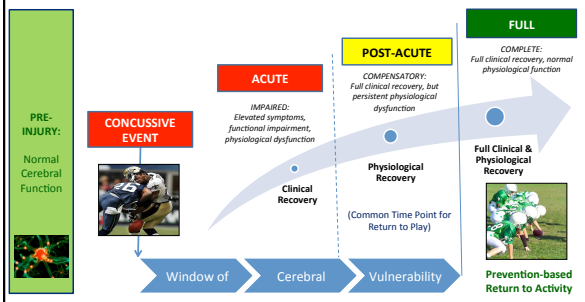
Andrew Nencka, PhD; Kevin Koch, PhD; L. Tugan Muftuler, PhD; Yang Wang, MD; Shi-Jiang Li, PhD; Melissa Lancaster, PhD; Lindsay Nelson, PhD

MRI Markers of Injury & Recovery



Changes in Brain Structure & Function Beyond Point of Clinical Recovery

Integrated mTBI Recovery Model



Evidence-Based Approach to Injury Management

What About Exceptions to the Rule?

What Factors Predict Recovery & Outcome after mTBI?

The Clinical Neuropsychologist, 23: 1368–1390, 2009
http://www.psypress.com/tcn
ISSN: 1385-4046 print/1744-4144 online
DOI: 10.1080/13854040903074652

Psychology Press

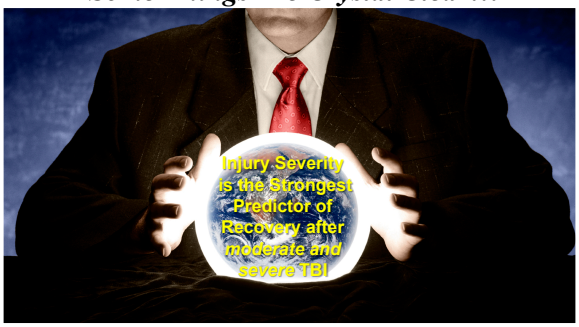
AN INTEGRATED REVIEW OF RECOVERY AFTER MILD TRAUMATIC BRAIN INJURY (MTBI): IMPLICATIONS FOR CLINICAL MANAGEMENT

Michael McCrea[1,2], Grant L. Iverson[3,4], Thomas W. McAllister[5], Thomas A. Hammeke[2], Matthew R. Powell[1], William B. Barr[6], and James P. Kelly[7,8]

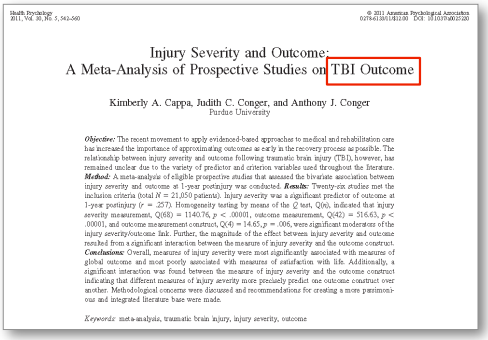
[1]Neuroscience Center, Waukesha Memorial Hospital, WI, [2]Department of Neurology, Medical College of Wisconsin, WI, USA, [3]Department of Psychiatry, University of British Columbia, Vancouver, BC, [4]British Columbia Mental Health & Addiction Services, Vancouver, BC, Canada, [5]Section of Neuropsychiatry, Dartmouth Medical School, Lebanon, NH, [6]Departments of Neurology and Psychiatry, New York University School of Medicine, NY, [7]Departments of Neurosurgery and Physical Medicine and Rehabilitation, University of Colorado Denver School of Medicine, CO, USA, and [8]National Intrepid Center of Excellence, Defense Centers of Excellence for Psychological Health and TBI, U.S. Department of Defense, Bethesda, MD, USA

The diagnosis and treatment of mild traumatic brain injury (MTBI) have historically been hampered by an incomplete base of scientific evidence to guide clinicians. One question has been most elusive to clinicians and researchers alike: What is the true natural history of MTBI? Fortunately, the science of MTBI has advanced more in the last decade than in the previous 50 years, and now reaches a maturity point at which the science can drive an evidence-based approach to clinical management. In particular, technological advances in functional neuroimaging have created a powerful bridge between the clinical and basic science of MTBI in humans. Collectively, findings from clinical, basic science, and functional neuroimaging studies now establish a foundation on which to build integrative theories and testable hypotheses around a comprehensive model of MTBI recovery. We review the current scientific literature on postconcussion symptom recovery, neuropsychological outcome, and neurophysiological healing after MTBI. Special emphasis is placed on how the new evidence base can help guide clinicians in the evaluation and management of military-related MTBI.

TBI Prognosis and Outcome:
Some Things Are Crystal Clear…



Association Between Injury & Outcome



Injury Severity and Outcome:
A Meta-Analysis of Prospective Studies on TBI Outcome

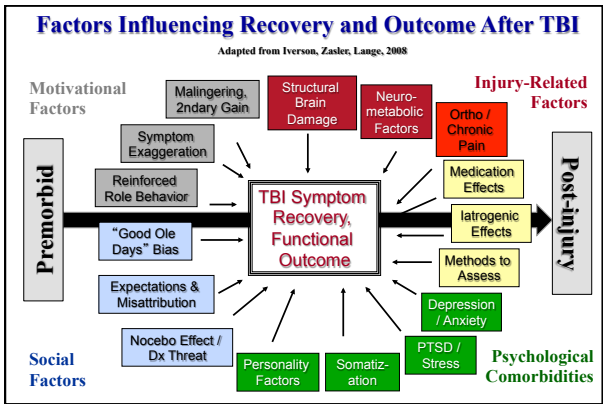
Kimberly A. Cappa, Judith C. Conger, and Anthony J. Conger
Purdue University

Predicting Outcome after mTBI

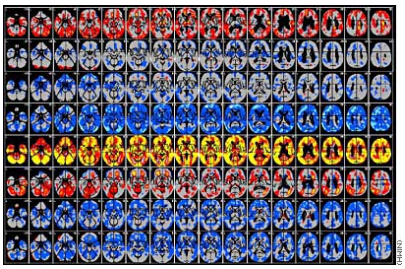
Early Predictor	Productivity	Global Outcome	Quality of Life
LOC	.23	.23	.06
PTA	.27	.43	ns
GCS	.19	.38	.18
LOStay	.35	.14	.14

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

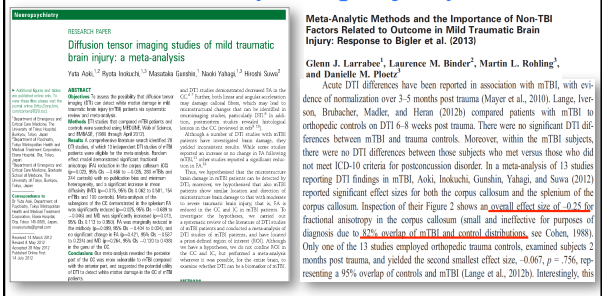
Cappa et al, 2011, Meta-Anal of head injury Outcome, Health Psychol, V3, 542



What is the Single Biomarker of Heterogeneity?



Biomarker Balancing Act: *Sensitivity vs. Specificity*



Neuropsychiatry

RESEARCH PAPER

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

Yuta Aoki,[1,2] Ryosta Inokuchi,[1,3] Masataka Gunshin,[1] Naoki Yahagi,[1,3] Hiroshi Suwa[2]

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[2]

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 Utility at the Individual Patient Level?

Prognostic Utility of Imaging Biomarkers?

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

Roel T. Lange, PhD; Grant L. Iverson, PhD; Jeffrey B. Brubacher, MD; Burkhard Mueller, PhD; Maneuj K. Heran, MD

Objective: To examine the relation between diffusion tensor imaging (DTI) of the corpus callosum and postconcussion symptoms 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 Philips 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 = 22), PCD Absent (n = 38). **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 symptoms 6 to 8 weeks post-MTBI. **Keywords:** *corpus callosum, diffusion tensor imaging, mild traumatic brain injury, postconcussion symptoms*

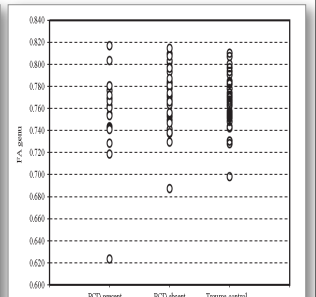


Figure 1. Scatter plot of FA genu for PCD group, $N = 90$ [PCD present, $n = 22$; PCD absent, $n = 39$; Trauma controls, $n = 34$]. FA indicates fractional anisotropy; PCD, *ICD-10* postconcussion disorder.

About Injury & Who Comes to Injury

A Prospective Biopsychosocial Study of the Persistent Post-Concussion Symptoms following Mild Traumatic Brain Injury

Minna Wäljas,[1,2] Grant L. Iverson,[3] Roel T. Lange,[4–6] Ullamari Hakulinen,[1,2] Prasun Dastidar,[2,7] Heini Huhtala,[8] Suvi Limatainen,[1] Kaisa Hartikainen,[1,2] and Juha Öhman[2,7]

Abstract

This study examined multiple biopsychosocial factors relating to post-concussion symptom (PCS) reporting in patients with mild traumatic brain injuries (mTBI), including structural (computed tomography and magnetic resonance imaging [MRI]) and microstructural neuroimaging (diffusion tensor imaging [DTI]). Patients with mTBIs completed several questionnaires and cognitive testing at approximately one month (*n* = 126) and one year (*n* = 103) post-injury. At approximately three weeks post-injury, DTI was undertaken using a Siemens 3T scanner in a subgroup (*n* = 71). Measures of fractional anisotropy were calculated for 16 regions of interest (ROIs) and measures of apparent diffusion coefficient were calculated for 10 ROIs. Patients were compared with healthy control subjects. Using *International Classification of Diseases, Tenth Revision* (ICD-10) PCS criteria and mild or greater symptom reporting, 59% of the mTBI sample met criteria at one month and 38% met criteria at one year. However, 31% of the healthy control sample also met criteria for the syndrome—illustrating a high false-positive rate. Significant predictors of ICD-10 PCS at one month were pre-injury mental health problems and the presence of extra-cranial bodily injuries. Being symptomatic at one month was a significant predictor of being symptomatic at one year, and depression was significantly related to PCS at both one month and one year. Intracranial abnormalities visible on MRI were present in 12.1% of this sample, and multifocal areas of unusual white matter as measured by DTI were present in 50.7% (compared with 12.4% of controls). Structural MRI abnormalities and microstructural white matter findings were not significantly associated with greater post-concussion symptom reporting. The personal experience and reporting of post-concussion symptoms is likely individualized, representing the cumulative effect of multiple variables, such as genetics, mental health history, current life stress, medical problems, chronic pain, depression, personality factors, and other psychosocial and environmental factors. The extent to which damage to the structure of the brain contributes to the persistence of post-concussion symptoms remains unclear.

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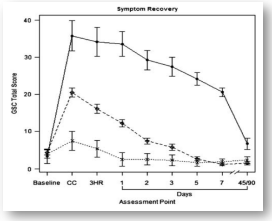
Predicting Risk & Recovery After SRC

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

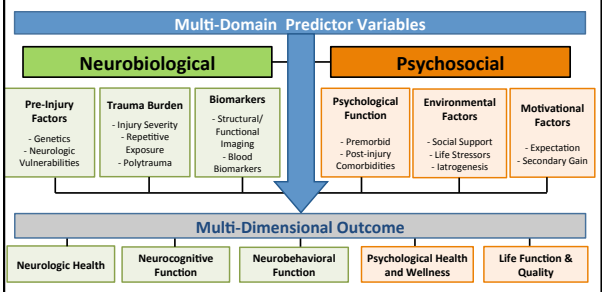
Michael McCrea,[1] Kevin Guskiewicz,[2,3,4] Christopher Randolph,[5] William B. Barr,[6] Thomas A. Hammeke,[7] Stephen W. Marshall,[3,4] Matthew R. Powell,[8] Kwang Woo Ahn,[9] Yanzhi Wang,[10] and James P. Kelly[11]



- 10% take > 7 days to recover
- **Acute severity predicts subacute recovery (LOC, PTA, 24 hr GSC)**
- 2.5% symptomatic > 45 days
- No impairment on objective measures at Day 45 relative to BL

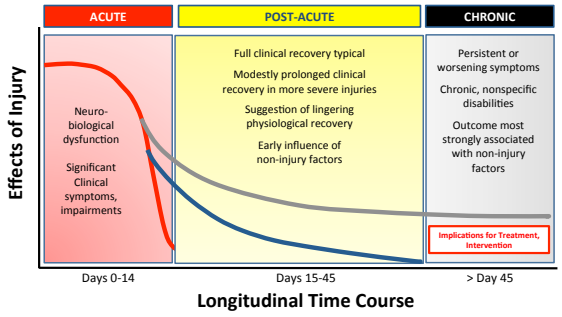
Neurobiopsychosocial Model of mTBI:

Multidimensional Prediction of Recovery, Outcome & Risk



McCrea & McAllister, 2013

mTBI Recovery, Outcome & Risk Model



Role of Assessment as Intervention & Prevention

ARTICLES

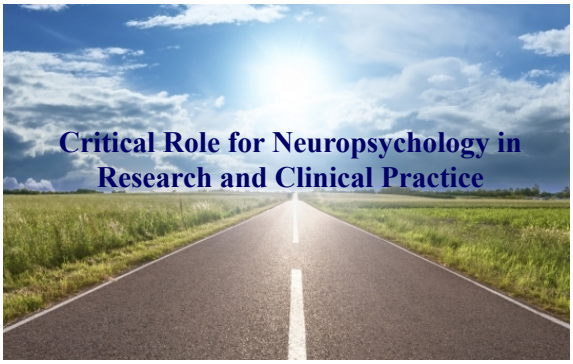
Brief Cognitive Behavioral Interventions in Mild Traumatic Brain Injury

SHORT REPORT

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

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

Never Underestimate the Value of the Neuropsychologist!

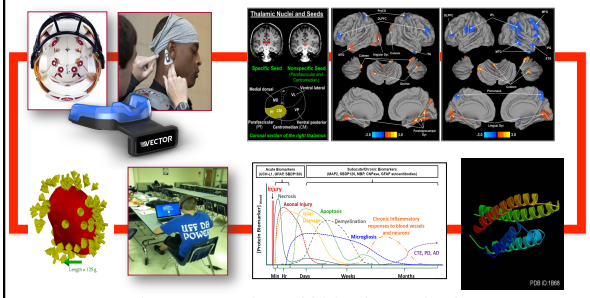


Implications for Translational Research

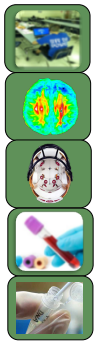
In A Single Study Design?

Future Research Directions:

Comprehensive Study of Injury & Recovery



Understanding the Natural History of Clinical & Neurobiological Recovery



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PROJECT HEAD TO HEAD II

Comprehensive Study of Acute Effects and Recovery After Concussion:

An Integrated Investigation of Head Impact Sensor Technology, Blood Biomarkers, Advanced Neuroimaging, Genetic Testing, and Clinical Outcome Measures

Funded by U.S. Dept. of Defense Combat Casualty Care Research Program

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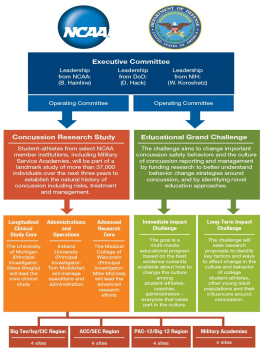
NCAA-DOD GRAND ALLIANCE
A Concussion Research and Education Initiative



Sponsored by United States Department of Defense (DoD) & National Collegiate Athletic Association (NCAA)

3 Years, $28M

Principal Investigators:
S. Broglio, PhD
Thomas McAllister, MD
Michael McCrea, PhD

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ARC Overview: Specific Aim

Utilize the framework of the CSC (Aim 2) to conduct advanced scientific studies which **integrate biomechanical, clinical, neuroimaging, neurobiological and genetic markers** of injury to advance our understanding of neurophysiological effects and recovery after SRC in college athletes.

NCAA•DOD Grand Alliance CARE Consortium

ARC Assessments

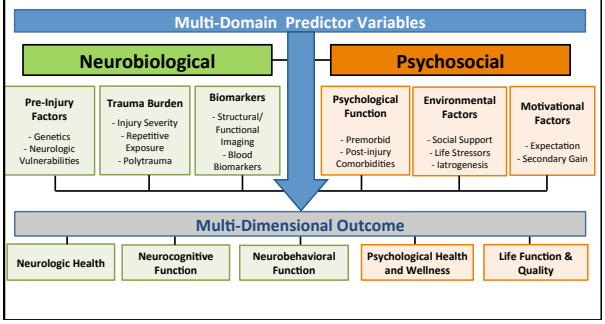
	Pre-Season	Acute Concussion		Sub-Acute Recovery			Chronic/ Remote
	Baseline	<6hrs Post-Injury	24-48hrs Post-Injury	Asymptomatic / Cleared for Return to Play Progression	Unrestricted Return to Play	7 days following Return to Play	6 Months Post-Injury
Neurocognitive and Psychological Health Testing	X	X	X	X	X	X	X
Blood Biomarker & DNA Collection*	X	X	X	X		X	X
Multi-modal MRI Studies	O		X	X		X	X

Exposure: All Athletes Instrumented with head impact sensors (Helmeted, Non-helmeted)

NCAA-DOD Grand Alliance CARE Consortium

Neurobiopsychosocial Model of mTBI:

Multidimensional Prediction of Recovery, Outcome & Risk



Thank You

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