Bridge to Clinical Translation:

Acute Effects & Natural History of Recovery after Mild Traumatic Brain Injury






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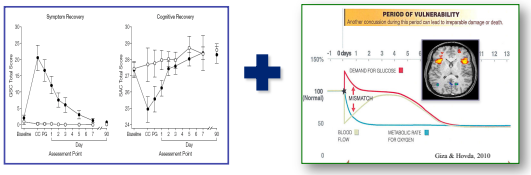
NCAA•DOD Grand Alliance CARE Consortium

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?

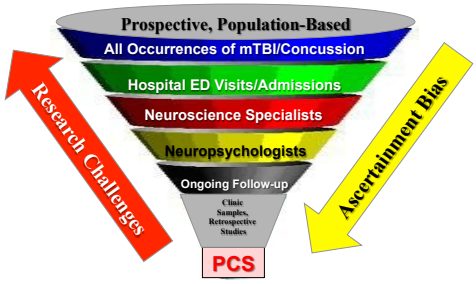
What Factors Predict Recovery and Outcome?

Understanding Acute mTBI:
It Starts at the Beginning

"mTBI is about what happened to the patient at the time of the injury event…and defined by the characteristics and course of clinical signs and symptoms during the acute period"

James P. Kelly, MD
Former Director, National Intrepid Center for TBI

Methods Matter:
Selection Bias & The Denominator Problem



Significant Impact on Epidemiology and Clinical Science of mTBI

Alternative Paradigms for mTBI Research

***Sports Laboratory Assessment Model* (SLAM)**

Evidence-based Injury Assessment, Management and Return to Play

Consensus Statement on Concussion in Sport—the 4th International Conference on Concussion in Sport Held in Zurich, November 2012

Summary of evidence-based guideline update: Evaluation and management of concussion in sports

American Medical Society for Sports Medicine: position statement: concussion in sport

National Athletic Trainers' Association Position Statement: Management of Sport Concussion

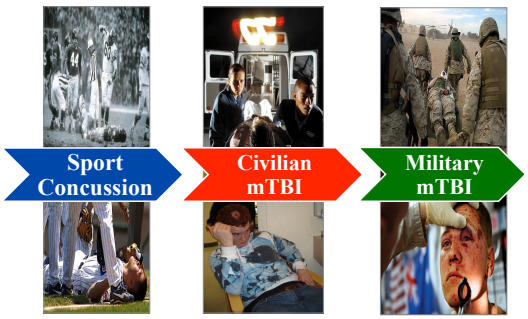
Science Driving Best Practice!

Froedtert & Medical College of Wisconsin

New Frontiers in the Assessment and Management of Sport-Related Concussion

Children's Hospital of Wisconsin

"Translational Research"



Advancing the Science to Benefit all Populations at Risk of mTBI

Sports, Civilian and Military mTBI

Are They Fair Comparisons?

Clinical Translation

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.

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

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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.

New Evidence Base to Drive Best Clinical Practice & Improve Outcome After MTBI

Acute Effects and Recovery Time Following Concussion in Collegiate Football Players

The NCAA Concussion Study

JAMA 2003; 290:2556-2563

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Context Lack of empirical data on recovery time following sport-related concussion hampers clinical decision making about return to play after injury.

Objective To prospectively measure immediate effects and natural recovery course relating to symptoms, cognitive functioning, and postural stability following sport-related concussion.

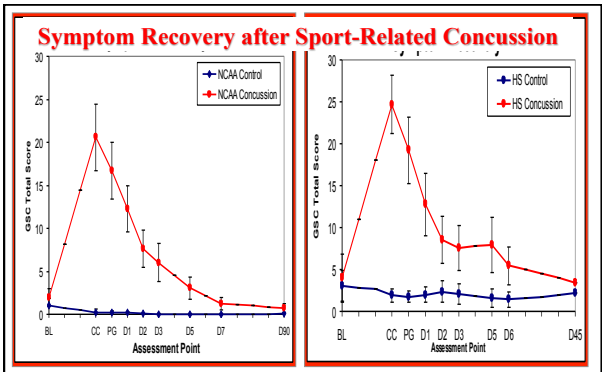
Design, Setting, and Participants Prospective cohort study of 1631 football players from 15 US colleges. All players underwent preseason baseline testing on concussion assessment measures in 1999, 2000, and 2001. Ninety-four players with concussion (based on American Academy of Neurology criteria) and 56 noninjured controls underwent assessment of symptoms, cognitive functioning, and postural stability immediately, 3 hours, and 1, 2, 3, 5, 7, and 90 days after injury.

Over 25,000 Athlete Seasons, 2,500+ Concussions Studied

Symptom Recovery After mTBI

Not tonight, honey, I have a concussion.

Symptom Recovery after Sport-Related Concussion



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

McCrea et al., JAMA 2003

How Long Does it Take to Recover?

Rate of Postinjury Recovery in HS and College Athletes (n=790)	Total (%)	Cumulative Total (%)
Rapid (< 1 day)	21.1	21.1
Gradual (> 1 day, < 7 days)	64.3	85.4
Prolonged (1 week – 1 month)	11.9	97.3
Persistent (> 1 month)	2.7	100.0

Rapid, Uncomplicated Recovery is the Norm

views & reviews NEUROLOGY 1995;45:1253-1260

Mild traumatic brain injury:
Pathophysiology, natural history, and clinical management

Michael P. Alexander, MD

Mild traumatic brain injury (TBI) is one of the most common neurologic disorders, with only migraine and herpes zoster having higher incidences and only migraine having a higher prevalence.[1] Most patients with mild TBI recover within weeks to months without specific intervention, but at 1 year after injury approximately 15% of patients still have disabling symptoms.[2] The incidence of mild TBI patients who will be persistently symptomatic is approximately 25/100,000, estimated as 15% of 180/100,000 mild TBI incidence.[3] This is equal to the annual incidence of Parkinson's disease (20/100,000), multiple sclerosis (3/100,000), Guillain-Barré syndrome (2/100,000), motor neuron disease (2/100,000), and myasthenia gravis (0.4/100,000) combined[4] (27.4/100,000). The modal persistently symptomatic patient is a man in

one article[5] on mild TBI, and that article described the effect of mild TBI on the natural history of Parkinson's disease.

The clinical phenomenology of mild TBI follows coherently from the neuropathology. The clinical deficits caused by the neurologic injury can be understood as manifestations of impaired attention. The natural course of recovery can be anticipated. The associated injuries that contribute symptoms to the clinical picture have reasonably specific treatments. The risk factors for developing persistent symptoms can be recognized. Recognition and appropriate management of the risk factors may block development of chronic disability. This review will provide a framework for clinical management of the patient with mild TBI.

15% of mTBI patients still have disabling symptoms 1 year after injury

2. Rutherford WH, Merrett JD, McDonald JR. Symptoms at one year following concussion from minor head injuries. Injury 1978;10:225-230.
3. McLean A, Temkin NR, Dikmen S, et al. The behavioral sequelae of head injury. J Clin Neuropsychol 1983;5:361-376.

Rutherford et al., 1979
- 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
- No controls (e.g., ortho injuries)

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***.

Civilian Symptom Recovery

Predictors of Postconcussive Symptoms 3 Months After Mild Traumatic Brain Injury

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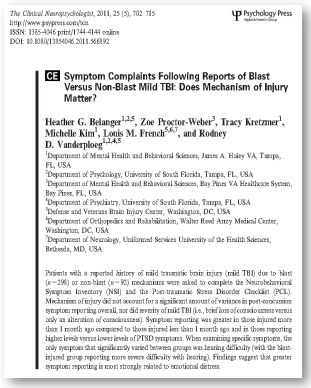
Objective: There is continuing controversy regarding predictors of poor outcome following mild traumatic brain injury (mTBI). This study aimed to prospectively examine the influence of preinjury factors, injury-related factors, and postinjury factors on outcome following mTBI. *Method:* Participants were 123 patients with mTBI and 100 trauma patient controls recruited and assessed in the emergency department and followed up 1 week and 3 months postinjury. Outcome was measured in terms of reported postconcussional symptoms. Measures included the ImPACT Post-Concussional Symptom Scale and cognitive concussion battery, including Attention, Verbal and Visual memory, Processing Speed and Reaction Time modules, pre- and postinjury SF-36 and MINI Psychiatric status ratings, VAS Pain Inventory, Hospital Anxiety and Depression Scale, PTSD Checklist–Specific, and Revised Social Readjustment Scale. *Results:* Presence of mTBI predicted postconcussional symptoms 1 week postinjury, along with being female and premorbid psychiatric history, with elevated HADS anxiety a concurrent indicator. However, at 3 months, preinjury physical or psychiatric problems but not mTBI most strongly predicted continuing symptoms, with concurrent indicators including HADS anxiety, PTSD symptoms, other life stressors and pain. HADS anxiety and age predicted 3-month PCS in the mTBI group, whereas PTSD symptoms and other life stressors were most significant for the controls. Cognitive measures were not predictive of PCS at 1 week or 3 months. *Conclusions:* Given the evident influence of both premorbid and concurrent psychiatric problems, especially anxiety, on postinjury symptoms, managing the anxiety response in vulnerable individuals with mTBI may be important to minimize ongoing sequelae.

- 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



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Psychology Press

CE Symptom Complaints Following Reports of Blast Versus Non-Blast Mild TBI: Does Mechanism of Injury Matter?

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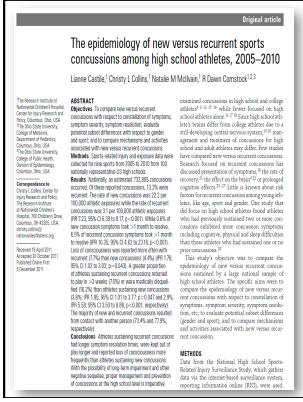
Patients with a reported history of mild traumatic brain injury (mild TBI) due to blast (*n* = 296) or non-blast (*n* = 92) mechanisms were asked to complete the Neurobehavioral Symptom Inventory (NSI) and the Post-traumatic Stress Disorder Checklist (PCL). Mechanism of injury did not account for a significant amount of variance in post-concussion symptom reporting overall, nor did severity of mild TBI (i.e., brief loss of consciousness versus only an alteration of consciousness). Symptom reporting was greater in those injured more than 1 month ago compared to those injured less than 1 month ago and in those reporting higher levels versus lower levels of PTSD symptoms. When examining specific symptoms, the only symptom that significantly varied between groups was hearing difficulty (with the blast-injured group reporting more severe difficulty with hearing). Findings suggest that greater symptom reporting in most strongly related to emotional distress.

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



Original article

The epidemiology of new versus recurrent sports concussions among high school athletes, 2005–2010

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ABSTRACT

Objectives To compare new versus recurrent concussions with respect to constellation of symptoms, symptom severity, symptom resolution; evaluate potential subset differences with respect to gender and sport; and to compare mechanisms and activities associated with new versus recurrent concussions.

Methods Sports-related injury and exposure data were collected for nine sports from 2005 to 2010 from 100 nationally representative US high schools.

Results Nationally, an estimated 732,805 concussions occurred. Of these reported concussions, 13.2% were recurrent. The rate of new concussions was 22.2 per 100,000 athletic exposures while the rate of recurrent concussions was 3.1 per 100,000 athletic exposures (IRR 7.22, 95% CI 6.39 to 8.17, p<0.001). Within 0.6% of new concussion symptoms took >1 month to resolve, 6.5% of recurrent concussion symptoms took >1 month to resolve (IRR 10.35, 95% CI 4.52 to 23.69, p<0.001). Loss of consciousness was reported more often with recurrent (7.7%) than new concussions (4.4%) (IRR 1.78, 95% CI 1.32 to 3.02, p=0.043). A greater proportion of athletes sustaining recurrent concussions returned to play in >2 weeks (7.5%) or were medically disqualified (16.2%) than athletes sustaining new concussions (3.9%; IRR 1.95; 95% CI 1.01 to 3.77, p=0.047 and 2.9%; IRR 5.58; 95% CI 3.50 to 8.89, p<0.001, respectively). The majority of new and recurrent concussions resulted from contact with another person (73.4% and 77.9%, respectively).

Conclusions Athletes sustaining recurrent concussions had longer concussion resolution times, were kept out of play longer and reported less of consciousness more frequently than athletes sustaining new concussions. With the possibility of long-term impairment and other negative sequelae, proper management and prevention of concussions at the high school level is imperative.

examined concussions in high school and college athletes[4–6 8–9] while fewer focused on high school athletes alone.[6 7 10] Since high school athlete's brains differ from college athletes due to a still-developing central nervous system,[11,12] management and treatment of concussions for high school and adult athletes may differ. Few studies have compared new versus recurrent concussions. Research focused on recurrent concussions has discussed presentation of symptoms,[8] the rate of recovery,[5] the effect on the brain[12] or prolonged cognitive effects.[13–17] Little is known about risk factors for recurrent concussion among young athletes, like age, sport and gender. One study that did focus on high school athletes found athletes who had previously sustained two or more concussions exhibited more concussion symptoms including cognitive, physical and sleep difficulties than those athletes who had sustained one or no prior concussions.[8]

This study's objective was to compare the epidemiology of new versus recurrent concussions sustained by a large national sample of high school athletes. The specific aims were to compare the epidemiology of new versus recurrent concussions with respect to constellation of symptoms, symptom severity, symptom resolution, etc; to evaluate potential subset differences (gender and sport); and to compare mechanisms and activities associated with new versus recurrent concussion.

METHODS

Data from the National High School Sports-Related Injury Surveillance Study, which gathers data via the internet-based surveillance system, reporting information online (RIO), were used

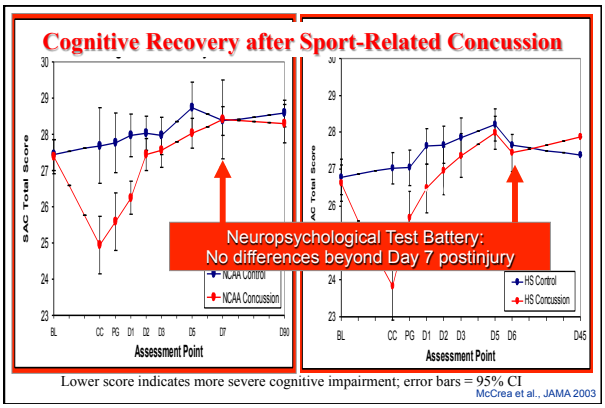
Population-Based Studies

- Nationally, estimated 732,805 concussions
- 0.6% of new concussions took > 1 month for symptoms to resolve (99.4% full recovery)
- 6.5% of recurrent concussions took > 1 month to resolve (93.% full recovery)

Is Symptom Recovery Really Recovery?

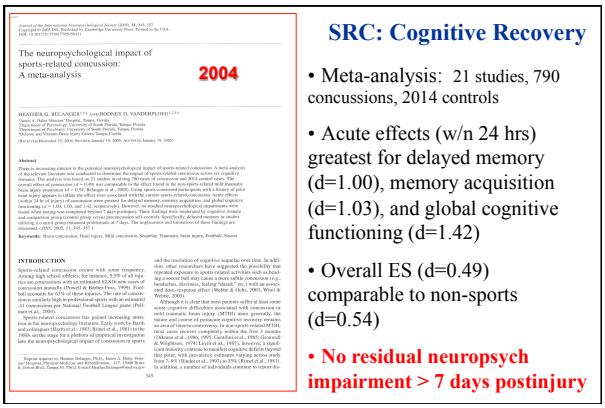
Performance-Based mTBI Assessment

Hot Pursuit of Better Signal Detection



Lower score indicates more severe cognitive impairment; error bars = 95% CI

McCrea et al., JAMA 2003



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

2004

SRC: Cognitive Recovery

- 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**

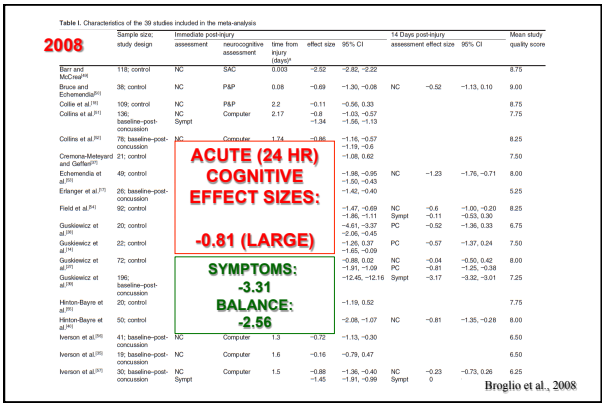


Table I. Characteristics of the 39 studies included in the meta-analysis

2008

ACUTE (24 HR) COGNITIVE EFFECT SIZES:

-0.81 (LARGE)

SYMPTOMS: -3.31

BALANCE: -2.56

	Sample size; study design	Immediate post-injury assessment	neurocognitive assessment	time from injury (days)[a]	effect size	95% CI	14 Days post-injury assessment	effect size	95% CI	Mean study quality score
Barr and McCrea[44]	118; control	NC	SAC	0.003	−2.52	−2.82, −2.22				8.75
Bruce and Echemendia[55]	38; control	NC	P&P	0.08	−0.69	−1.30, −0.08	NC	−0.52	−1.13, 0.10	9.00
Collie et al.[16]	109; control	NC	P&P	2.2	−0.11	−0.56, 0.33				8.75
Collins et al.[51]	136; baseline–post-concussion	NC Sympt	Computer	2.17	−0.8 −1.34	−1.03, −0.57 −1.56, −1.13				7.75
Collins et al.[52]	78; baseline–post-concussion	NC	Computer	1.74	−0.86	−1.16, −0.57 −1.19, −0.6				8.25
Cremona-Meteyard and Geffen[53]	21; control					−1.08, 0.62				7.50
Echemendia et al.[54]	49; control					−1.98, −0.95 −1.50, −0.43	NC	−1.23	−1.76, −0.71	8.00
Erlanger et al.[17]	26; baseline–post-concussion					−1.42, −0.40				5.25
Field et al.[54]	92; control					−1.47, −0.69 −1.86, −1.11	NC Sympt	−0.6 −0.11	−1.00, −0.20 −0.53, 0.30	8.25
Guskiewicz et al.[56]	20; control					−4.61, −3.37 −2.06, −0.45	PC	−0.52	−1.36, 0.33	6.75
Guskiewicz et al.[18]	22; control					−1.26, 0.37 −1.85, −0.09	PC	−0.57	−1.37, 0.24	7.50
Guskiewicz et al.[57]	72; control					−0.88, 0.02 −1.91, −1.09	NC PC	−0.04 −0.81	−0.50, 0.42 −1.25, −0.38	8.00
Guskiewicz et al.[58]	196; baseline–post-concussion					−12.45, −12.16	Sympt	−3.17	−3.32, −3.01	7.25
Hinton-Bayre et al.[59]	20; control					−1.19, 0.52				7.75
Hinton-Bayre et al.[45]	50; control					−2.08, −1.07	NC	−0.81	−1.35, −0.28	8.00
Iverson et al.[36]	41; baseline–post-concussion	NC	Computer	1.3	−0.72	−1.13, −0.30				6.50
Iverson et al.[35]	19; baseline–post-concussion	NC	Computer	1.6	−0.16	−0.79, 0.47				6.50
Iverson et al.[37]	30; baseline–post-concussion	NC Sympt	Computer	1.5	−0.88 −1.45	−1.36, −0.40 −1.91, −0.99	NC Sympt	−0.23 0	−0.73, 0.26	6.25

Broglio et al., 2008

Table I. Contd

2008	Sample size; study design	Immediate post-injury assessment	neurocognitive assessment	time from injury (days)[a]	effect size	95% CI	14 Days post-injury assessment	effect size	95% CI	Mean study quality score
Lovell and Collins[261]	14; control	NC	P&P	1	−0.45	−1.59, 0.68				5.75
Lovell et al.[260]	88; control	NC	Computer	1.5	−1.04	−1.48, −0.60	NC	−0.49	−0.95, −0.03	7.25
		Sympt			−1.52	−1.95, −1.09	Sympt	−0.2	−0.66, 0.27	
Lovell et al.[256]	43; baseline–post-concussion	NC	Computer	1.4	−0.24	−0.66, 0.17	NC	0.4	−0.03, 0.83	6.75
Masciocchi et al.[201]	231; control	NC	P&P	1	−0.13	−0.45, 0.18	NC	0	−0.31, 0.32	8.75
Maddocks et al.[98]	56; control	NC	P&P	0.007	−0.95	−1.44, −0.46				7.50
Maddocks and Saling[91]	20; control	NC	P&P	5	−0.85	−1.68, −0.02				
McClincy et al.[83]	104; baseline–post-concussion	NC	Computer	2.42	−0.86	−1.12, −0.61				
		Sympt			−1.4	−1.64, −1.15				
McCrea et al.[93]	6; baseline–post-concussion	NC	SAC	0.003	−1.15	−1.95, −0.34				
McCrea et al.[94]	601; control	NC	SAC	0.003	−1.1	−1.44, −0.75				
McCrea[95]	118; control	NC	SAC	0.003	−1.65	−1.98, −1.33				
McCrea et al.[96]	91; baseline–post-concussion	NC	SAC	0.003	−1.02	−1.29, −0.75				
McCrea et al.[91]	150; control	NC	SAC	0.003	−1.35	−1.65, −1.05				
		Sympt			−0.95	−1.26, −0.64				
		PC			−0.96	−1.26, −0.64				
Moser and Schatz[277]	35; control	NC	P&P	7	−0.7	−1.35, −0.05				
Moser et al.[206]	122; control	NC	P&P	3.5	−0.45	−0.81, −0.09				
Pellman et al.[103]	95; baseline–post-concussion	NC	P&P	1.5	0.13	−0.15, 0.40				7.00
Pellman et al.[70]	48; baseline–post-concussion	NC	Computer	1.48	−0.42	−0.81, −0.03				
		Sympt			−0.97	−1.35, −0.60				
Peterson et al.[218]	42; control	Sympt	P&P	1	−14.39	−14.92, −13.86				
		PC			−8.83	−9.01, −8.65				
Piland et al.[229]	33; control	Sympt		1	−3.58	−4.09, −3.07				
Riemann and Guskiewicz[81]	32; control	PC		1	−1.92	−2.53, −1.31				
Schatz et al.[184]	138; control	NC	Computer	2	−0.88	−1.20, −0.57				
		Sympt			−1.09	−1.40, −0.78				
Warden et al.[121]	14; baseline–post-concussion	NC	Computer	4	−0.33	−1.06, 0.39				7.00

a When time from injury to initial assessment was <24 hours, the number of minutes were divided by the number of minutes in a day.
Computer = computer-based neurocognitive assessment; **NA** = data not available; **NC** = neurocognitive; **P&P** = pencil and paper neuro control; **SAC** = standardized assessment of concussion; **Sympt** = self-report concussion-related symptoms.

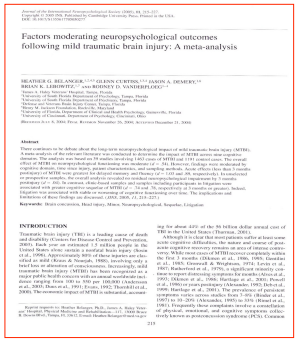
SUBACUTE (14 DAYS) COGNITIVE EFFECT SIZES:

-0.26 (SMALL)

SYMPTOMS: -1.09
BALANCE: -1.16

Broglio et al., 2008

Cognitive Recovery After mTBI



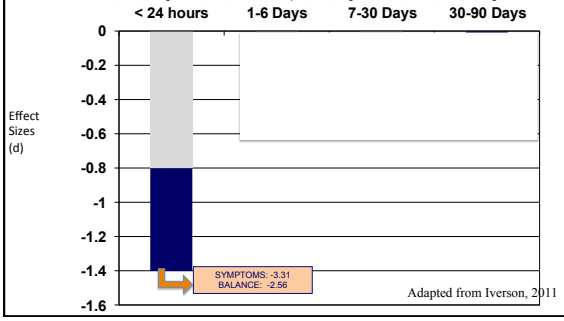
Factors moderating neuropsychological outcomes following mild traumatic brain injury: A meta-analysis

- Meta-analysis: 39 studies, 1463 MTBI cases, 1191 controls
- Overall effect of MTBI on neuropsychological functioning moderate (d=.54)
- Acute: greatest affect on memory (d=1.03), fluency (d =.89)
- Unselected or prospective samples: No residual NP effects by 3 mos. (d=.04)
- Clinic samples (.74) & litigants (. 78) at 3 mos.
- •Litigation associated with stable *or worsening* cognition

Neurocognitive Effects of mTBI

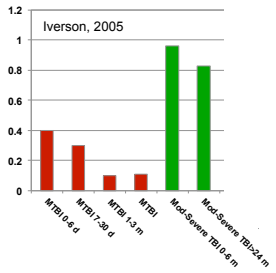
Meta-Analytic Studies and Reviews:

Frencham, 2004; Belanger et al., 2005; Schretlin & Shapiro, 2005; Broglio et al 2008; Iverson, 2011; Rohling et al 2011



Adapted from Iverson, 2011

Non-specificity of Neurocognitive Performance



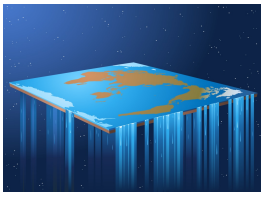
Effect Sizes: 0.2 Small, 0.5 Medium, 0.8 Large

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

Truisms in Neurocognitive Recovery after mTBI?

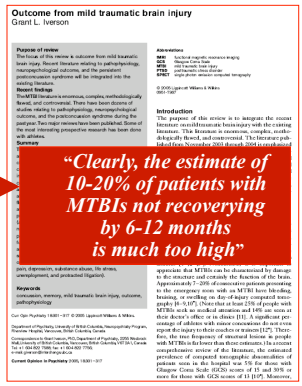
Need to Build Better Mouse Traps?

Trust the Science on Recovery?



mTBI Outcome

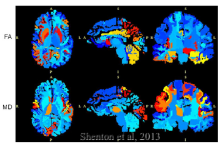
- Neurophysiological basis for sx's & dysfunction *acutely* after MTBI
- Maximal sx's first 72 hrs, rapid improvement over 1st week
- Lower true incidence of PCS
- Persistent symptoms (e.g., PCS) often largely related to comorbidities or non-injury factors
- PCS symptoms highly **nonspecific**
- Multi-factorial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



Outcome from mild traumatic brain injury
Grant L. Iverson

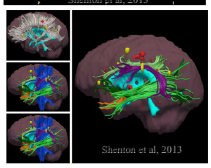
"Clearly, the estimate of 10-20% of patients with MTBIs not recovering by 6-12 months is much too high"

New Frontiers in Brain Injury Science



Acute and Subacute Changes in Neural Activation during the Recovery from Sport-Related Concussion

HEAD HEALTH CHALLENGE



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

MEDICAL COLLEGE OF WISCONSIN

How Long Does it Take for the *Brain* to Recover?

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)

More overlap than discrepancy in evidence on acute effects and recovery after SRC, Civilian and Military mTBI

(Carrol et al., 2004)