Mild Traumatic Brain Injury
Lessons from the Civilian Experience

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Traumatic Brain Injury
A Historical Note

- Traumatic brain injuries are among the earliest described illnesses in human history.
  - South African australopithecine ~3 million year old skull with evidence of cranial fractures caused by assault with an antelope humerus.
  - The *Edwin Smith Surgical Papyrus*, ~26th century B.C.E., provides a written description of impaired coordination, contralateral motor deficits, and impaired consciousness following war-time head injuries.

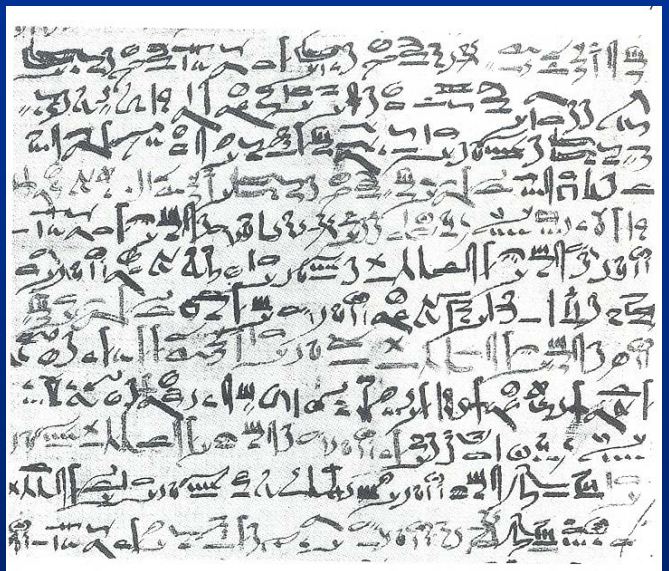


Figure 1.6. A section of the Edwin Smith Surgical Papyrus showing the script and use of two different types of ink. (Courtesy of the University of Chicago Press.)

Figure 1.9. Mummified head of King Seqenenre (c. 1580 B.C.) showing the head wounds that killed him. (Courtesy of the Cairo Museum, Egypt).

S. Finger Origins of Neuroscience 1994, p. 3-17

Traumatic Brain Injury

A major selective factor in early humans

Frequency of Healed Cranial Trauma in Prehistoric Populations			
Site	*Males*	*Females*	*Total*
Peru	40%	25%	31%
Conchopata	25%	31%	26%
Beringa	50%	31%	33%
La Real	41%	19%	31%
Chile	10%	15%	12%
Early Intermediate (200 BC – 600 AD	1.7%	10.3%	5.1%
Middle Horizon (AD 600 – 950)	12.2%	9.3%	10.9%
Late Intermediate (AD 950 – 1400)	26.0%	38.9%	29.2%
Terminal Late Intermediate	14.3%	0%	7.0%
Late Horizon (AD 1400 – 1532)	3.5%	3.2%	3.4%

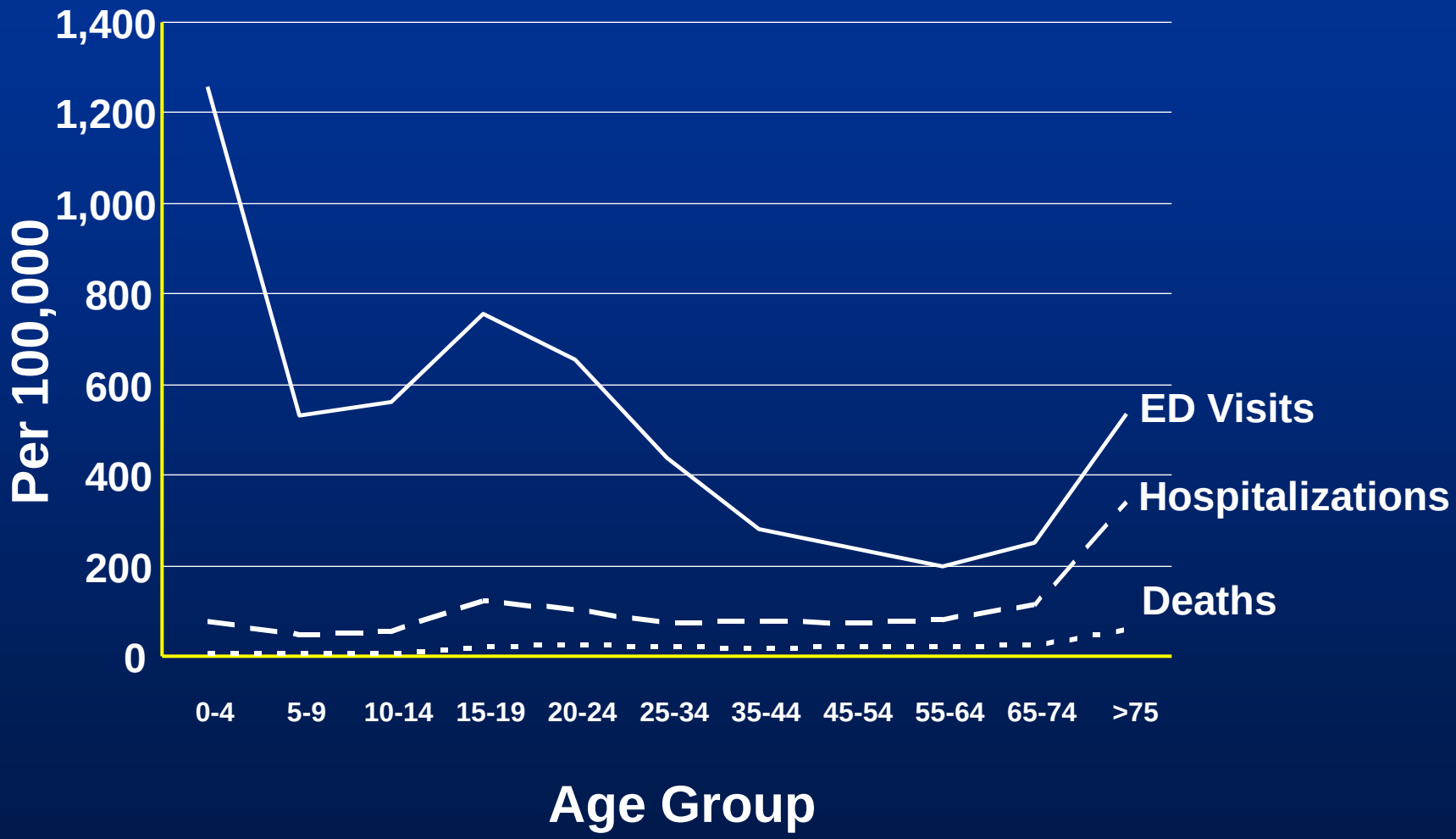
Tung, TA, *Am. J. Phys. Anthropol.* 133:941-956 (2007)
Torres-Rouff and Junqueira, *Am J. Phys. Anthropol.* 130:60-70 (2006)

Modern Epidemiology of TBI

- Incidence of 1.4 million ED visits per year in the United States
  - 80% mild, 10% moderate, 10% severe
- 50,000 fatalities annually
- 5.3 million Americans—2% of the U.S. population— live with disabilities resulting from TBI
- The single most common cause of death and permanent disability in young people (under age 45).
- Total costs estimated at $56.3 billion per year

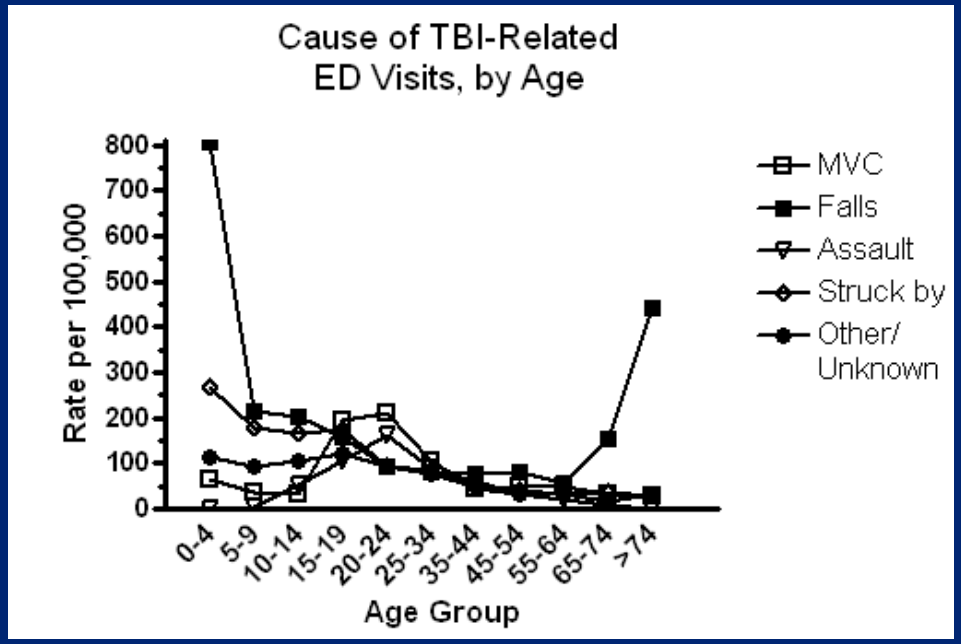
Thurman et al, *J Head Trauma Rehab* **(1999)** 14:602-615

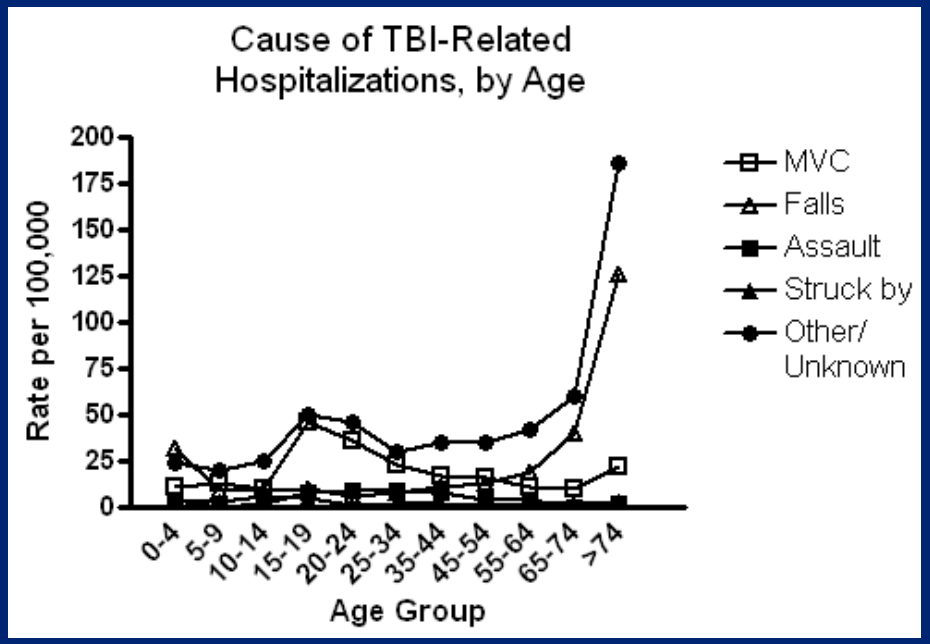
Modern Epidemiology of TBI



Division of Injury Response, National Center for Injury Prevention and Control
Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2010

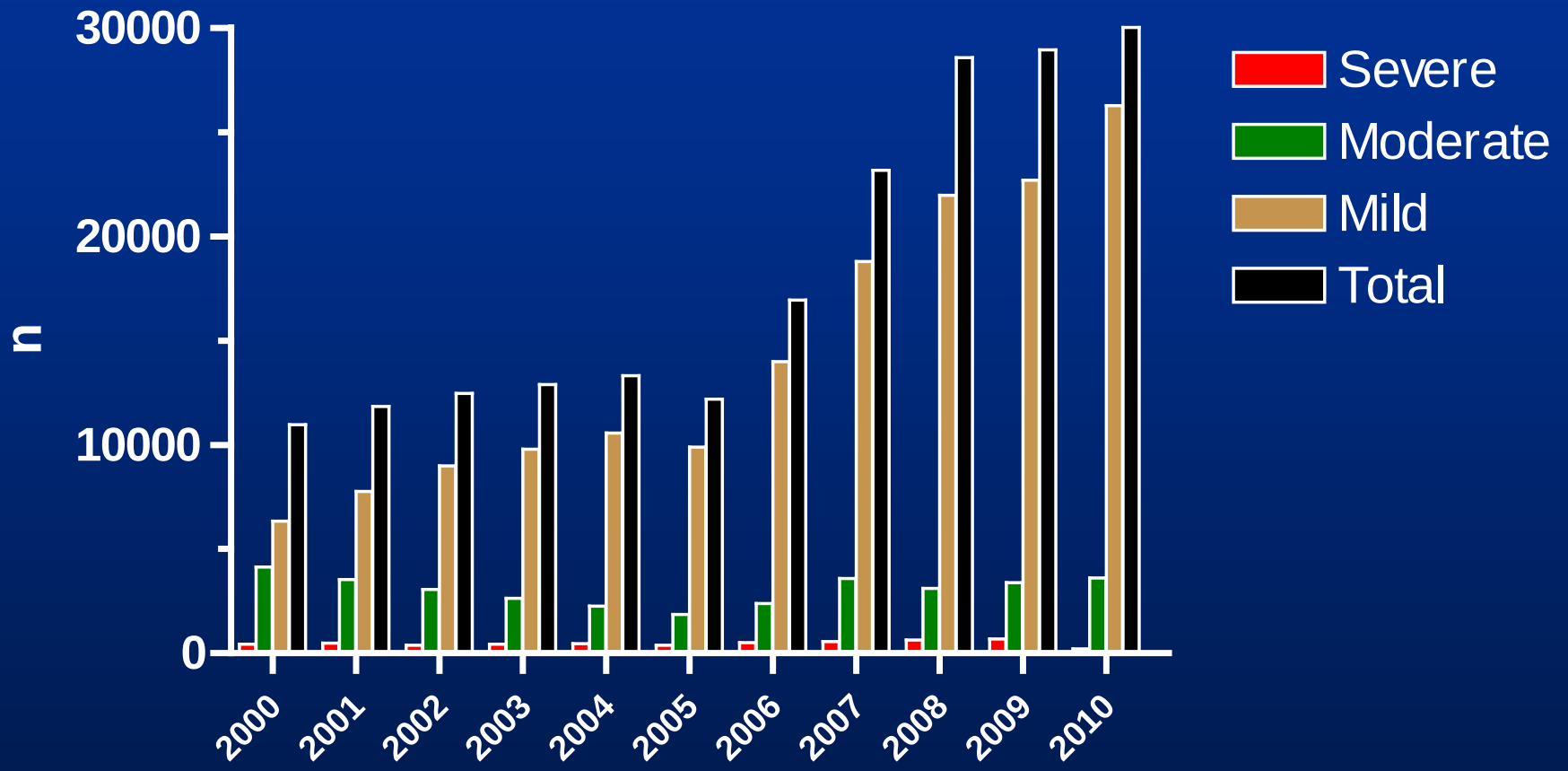
Causes of TBI





Division of Injury Response, National Center for Injury Prevention and Control
Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2010

TBI in the Modern Battlefield



Armed Forces Health Surveillance Center (www.DVBIC.org)

Outline of Presentation

- The concept of “mild” TBI
- Diagnosis and Management of mTBI in civilian Level I Trauma Centers
- Consequences of mTBI
- New insights from advanced neuroimaging
- Relevance of civilian experience to military mTBI

Concept of “mild” TBI

	Severity Classification		
Measure	**Mild**	**Moderate**	**Severe**
Glasgow Coma Scale	13-15	9-12	3-8
Loss of Consciousness	< 20 minutes	20 min – 36 hours	> 36 hours
Posttraumatic Amnesia	< 24 hours	1-7 days	> 7 days

Concept of “mild” TBI

	GCS	LOC	PTA	Other
ACRM	13-15	< 30”	< 24 hours	At least LOC, PTA, AMS, neuro deficit
CDC		< 30”	< 24 hours	AMS, amnesia, symptoms
WHO	13-15	< 30”	< 24 hours	At least 1 symptom; other causes r/o
DVBIC				Altered MS, symptoms

AAN	Grade 1: AMS, No LOC, Sx’s < 15”; Grade 2: AMS, Sx’s > 15”; Grade 3: LOC of any duration
CSG	Symptom-based; Simple (7-10 d.) vs. Complex (persistent sx’s or recurrent)
Cantu	Grade 1 (mild): No LOC, PTA < 30”, Sx’s < 24 hours Grade 2 (moderate): LOC < 1” or PTA > 30” < 24 hrs or Sx’s > 24 hrs < 7 d Grade 3 (severe): LOC > 1” or PTA > 24 hours, Sx’s > 7 days

Concept of “mild” TBI

What is used in the Emergency Department

- Uncomplicated mTBI
  - GCS 13 – 15
  - At least one of the following:
    - Loss of consciousness
    - Amnesia for event
    - Short-term memory deficit
    - Post-traumatic seizure, headache, vomiting or neurologic deficit
  - Normal cranial CT scan within 24 hours
- Complicated mTBI
  - Same as above, with ABNORMAL cranial CT

Smits et al, *AJNR* 29:506-13 (2008)

Management of mTBI in ED

- Diagnosis
  - Who requires a neurosurgeon?
  - Who requires hospital admission?
- Counseling about return to regular activities
  - Return to work
  - Sports—return to play
  - Military—return to duty
- Medical management of post-traumatic symptoms

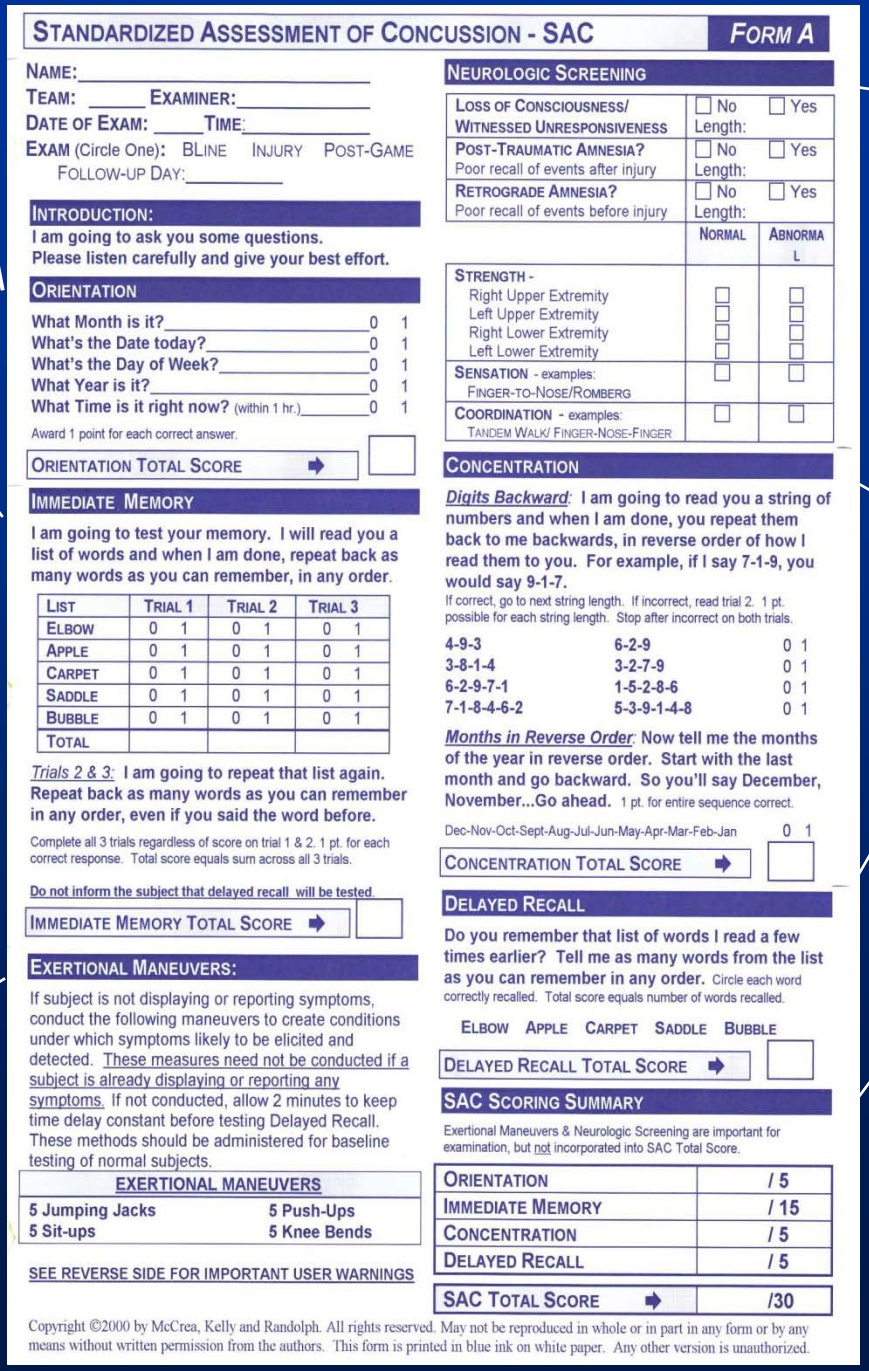
Diagnosis

- Glasgow Coma Score
- Less common, but better for mTBI
  - Standardized Assessment of Concussion (SAC)
- Military Acute Concussion Evaluation (MACE)

Orientation:
Day, Month, Date, Year, Time

Immediate Memory:
Repeated List Learning Paradigm

Exertional Maneuvers:
Provocative conditions



STANDARDIZED ASSESSMENT OF CONCUSSION - SAC — FORM A

NAME:_____
TEAM: _____ EXAMINER:_____
DATE OF EXAM: _____ TIME:_____
EXAM (Circle One): BLINE INJURY POST-GAME
FOLLOW-UP DAY:_____

INTRODUCTION:
I am going to ask you some questions.
Please listen carefully and give your best effort.

ORIENTATION
What Month is it?_____ 0 1
What's the Date today?_____ 0 1
What's the Day of Week?_____ 0 1
What Year is it?_____ 0 1
What Time is it right now? (within 1 hr.)_____ 0 1
Award 1 point for each correct answer.
ORIENTATION TOTAL SCORE ➡ ☐

IMMEDIATE MEMORY
I am going to test your memory. I will read you a list of words and when I am done, repeat back as many words as you can remember, in any order.

LIST	TRIAL 1	TRIAL 2	TRIAL 3
ELBOW	0 1	0 1	0 1
APPLE	0 1	0 1	0 1
CARPET	0 1	0 1	0 1
SADDLE	0 1	0 1	0 1
BUBBLE	0 1	0 1	0 1
TOTAL			

Trials 2 & 3: I am going to repeat that list again. Repeat back as many words as you can remember in any order, even if you said the word before.
Complete all 3 trials regardless of score on trial 1 & 2. 1 pt. for each correct response. Total score equals sum across all 3 trials.
Do not inform the subject that delayed recall will be tested.
IMMEDIATE MEMORY TOTAL SCORE ➡ ☐

EXERTIONAL MANEUVERS:
If subject is not displaying or reporting symptoms, conduct the following maneuvers to create conditions under which symptoms likely to be elicited and detected. These measures need not be conducted if a subject is already displaying or reporting any symptoms. If not conducted, allow 2 minutes to keep time delay constant before testing Delayed Recall. These methods should be administered for baseline testing of normal subjects.

EXERTIONAL MANEUVERS	
5 Jumping Jacks	5 Push-Ups
5 Sit-ups	5 Knee Bends

SEE REVERSE SIDE FOR IMPORTANT USER WARNINGS

NEUROLOGIC SCREENING

LOSS OF CONSCIOUSNESS/ WITNESSED UNRESPONSIVENESS	☐ No Length:	☐ Yes
POST-TRAUMATIC AMNESIA? Poor recall of events after injury	☐ No Length:	☐ Yes
RETROGRADE AMNESIA? Poor recall of events before injury	☐ No Length:	☐ Yes

	NORMAL	ABNORMAL
STRENGTH - Right Upper Extremity	☐	☐
Left Upper Extremity	☐	☐
Right Lower Extremity	☐	☐
Left Lower Extremity	☐	☐
SENSATION - examples: FINGER-TO-NOSE/ROMBERG	☐	☐
COORDINATION - examples: TANDEM WALK/ FINGER-NOSE-FINGER	☐	☐

CONCENTRATION
Digits Backward: I am going to read you a string of numbers and when I am done, you repeat them back to me backwards, in reverse order of how I read them to you. For example, if I say 7-1-9, you would say 9-1-7.
If correct, go to next string length. If incorrect, read trial 2. 1 pt. possible for each string length. Stop after incorrect on both trials.

4-9-3	6-2-9	0 1
3-8-1-4	3-2-7-9	0 1
6-2-9-7-1	1-5-2-8-6	0 1
7-1-8-4-6-2	5-3-9-1-4-8	0 1

Months in Reverse Order: Now tell me the months of the year in reverse order. Start with the last month and go backward. So you'll say December, November...Go ahead. 1 pt. for entire sequence correct.
Dec-Nov-Oct-Sept-Aug-Jul-Jun-May-Apr-Mar-Feb-Jan 0 1
CONCENTRATION TOTAL SCORE ➡ ☐

DELAYED RECALL
Do you remember that list of words I read a few times earlier? Tell me as many words from the list as you can remember in any order. Circle each word correctly recalled. Total score equals number of words recalled.
ELBOW APPLE CARPET SADDLE BUBBLE
DELAYED RECALL TOTAL SCORE ➡ ☐

SAC SCORING SUMMARY
Exertional Maneuvers & Neurologic Screening are important for examination, but not incorporated into SAC Total Score.

ORIENTATION	/ 5
IMMEDIATE MEMORY	/ 15
CONCENTRATION	/ 5
DELAYED RECALL	/ 5
SAC TOTAL SCORE ➡	/30

Neurologic Exam:
Strength, Sensation, Coordination
Record LOC, PTA

Concentration:
Digits Backward
Months Backward

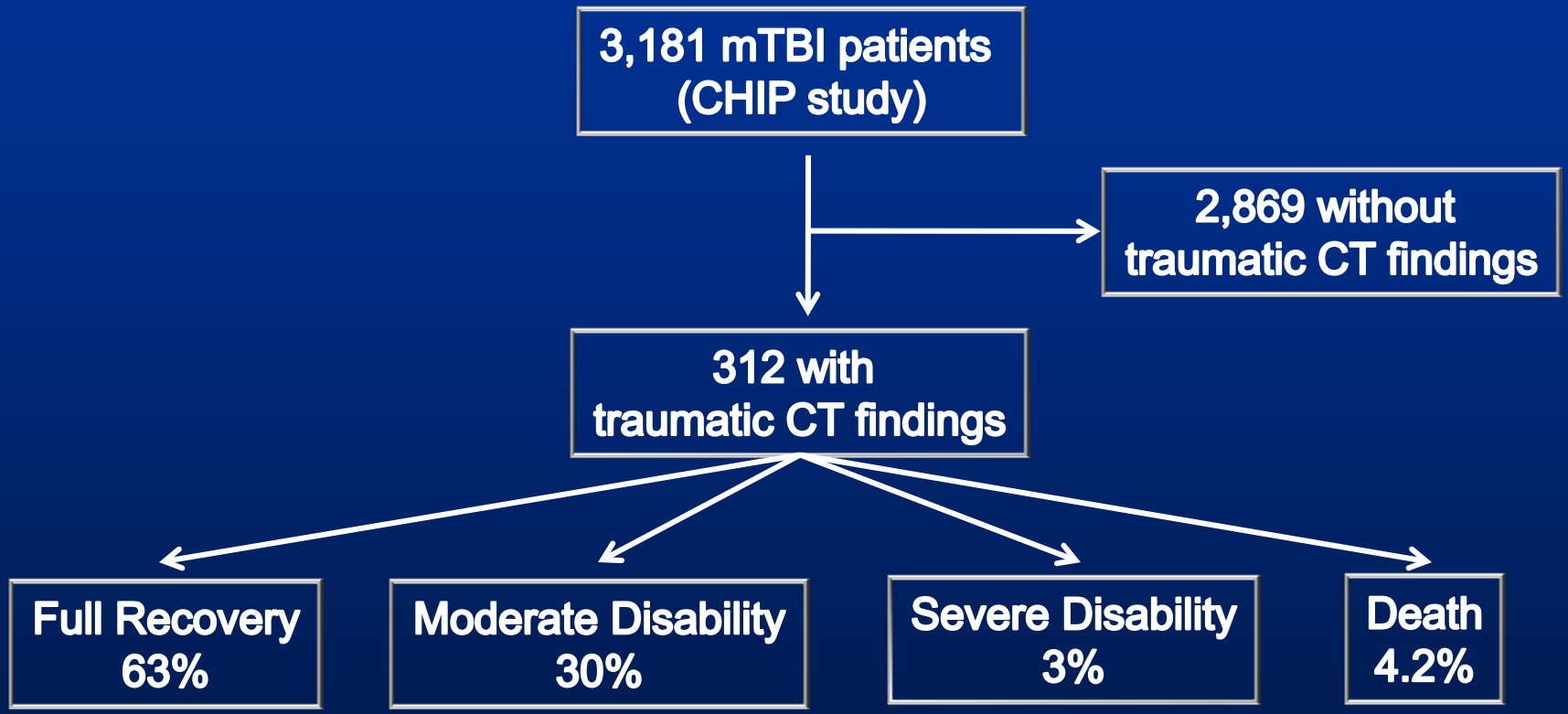
Delayed Recall:
Word List Recall

Total Score (30)
Orientation /5
Im. Memory /15
Concentration /5
Delayed Recall /5

Cranial CT Scanning

- Very useful for assessing need for neurosurgical intervention
- Rough and imperfect relationship with
  - Post-concussive symptoms
  - Long-term neuropsychological deficits

CT in Head Injury Patients (CHIP)



Smits et al, *AJNR* 29:506-13 (2008)

CT Scan Findings in mTBI

SAH

Contusion

EDH

SDH

All patients with GCS 15 at presentation to ED

Consequences of mTBI
Outcome in Uncomplicated mTBI

- Generally favorable
  - University of Washington Longitudinal TBI Studies (Dikmen, Temkin, et al)
    - Subtle neuropsychologic impairment at 1 month
    - No difference from control group at 1 year
- Confounders a big problem
  - Premorbid functioning
  - Premorbid EtOH and substance abuse
  - Secondary gain

Consequences of mTBI
Studies of Sports Concussion

- Studies of athletes offers advantages
  - High frequency of concussion
  - Ability to do pre-injury testing in large sample
  - Injuries are usually witnessed
  - Systematic followup feasible
  - Lower frequency of confounders
- Disadvantage
  - Mechanical forces generally lower than in motor vehicle or combat settings

Football: The Moral Equivalent of War

- American Football
  - Derived from British prep school game of Rugby
  - Started in 1870s in the Ivy League
  - Faculty and administrators (all Civil War veterans) wanted to provide students the moral formation that combat provides
  - “Moral Equivalent of War”

- 1870’s - 1905
  - Collegiate football spread rapidly to Midwest, and specially the defeated South
  - Evolved into a very brutal game, with frequent injuries and deaths
    - 18 collegiate football players died in 1905 alone
  - Banned at Columbia, NYU, Northwestern, California, Stanford by 1906
  - Rules committee named at the request of President Theodore Roosevelt
    - Legalized forward pass; outlawed flying wedge formation
    - Committee grew into the National Collegiate Athletic Association

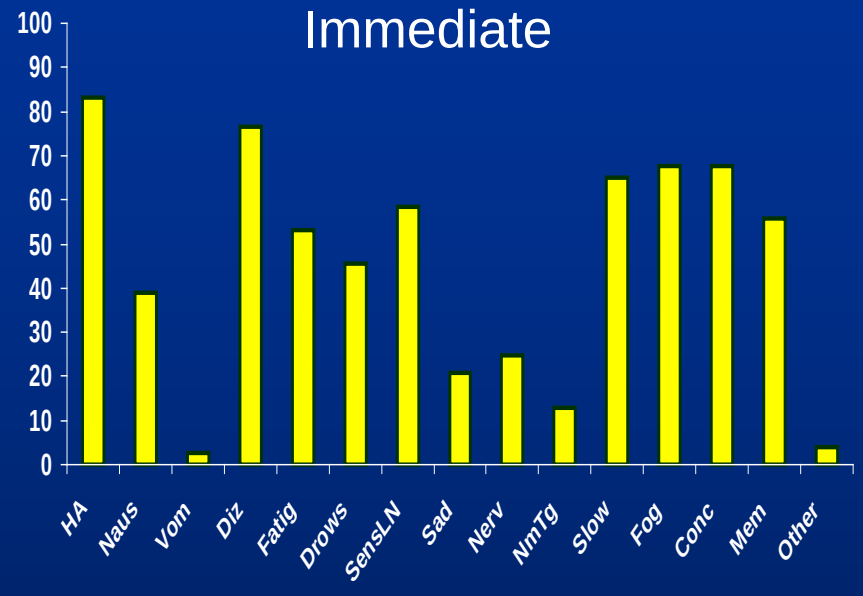
NCAA, Project Sideline & CDC Concussion Studies

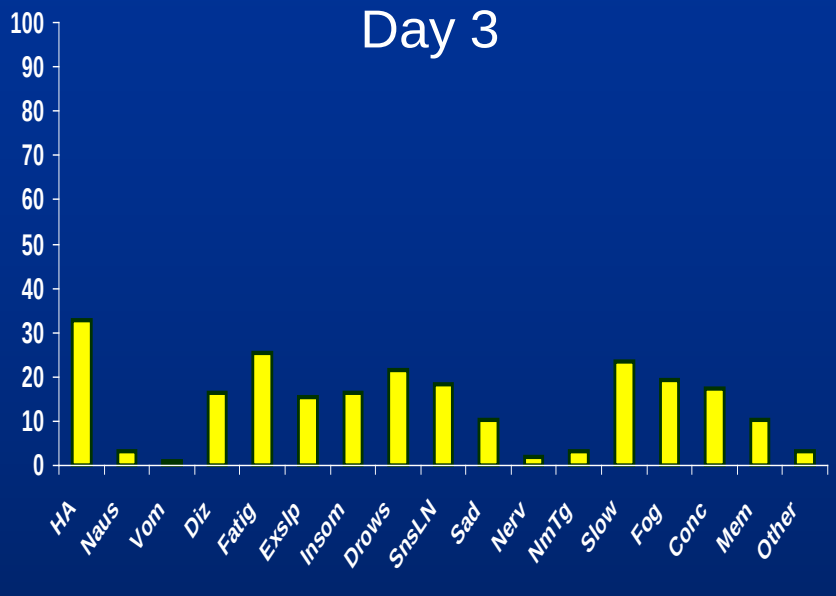
	NCAA	Project SL	CDC
Teams	25	20	124
Player Seasons	4,251	3,279	9,094
Concussions	196	87	375
AAN Grade 1-2 AAN Grade 3	93.2% 6.8%	82.1% 17.9%	80.7% 9.3%
LOC	6.8%	17.9%	9.3%
PTA	19.1%	37.3%	21.9%
RGA	7.4%	29.9%	17.3%
No LOC/PTA	77.8%	49.1%	64.5%
% Complete Protocol	84%	98%	80%

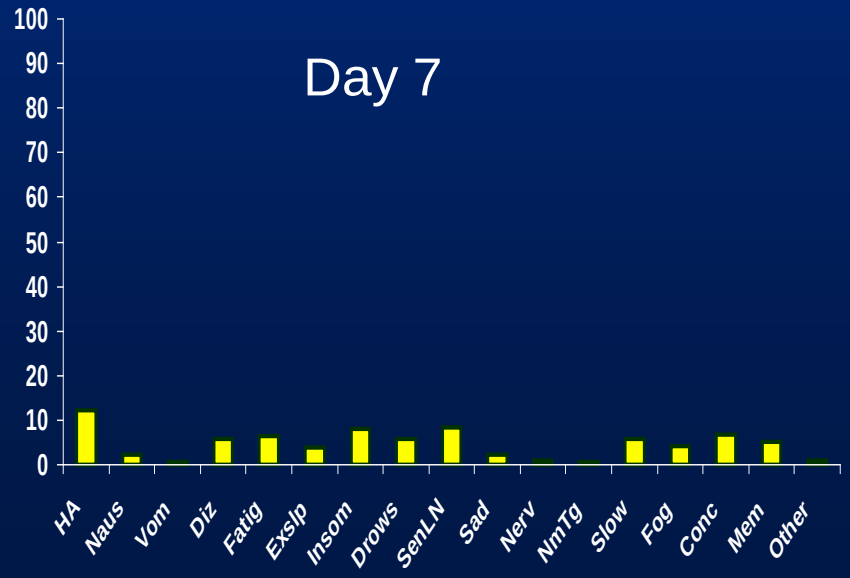
Totals: 16,624 Player Seasons, 658 Concussions Studied (3.9% IR)

MA McCrea, *Mild TBI and Postconcussion Syndrome*, Oxford Univ. Press, 2008

Post-Concussive Symptoms



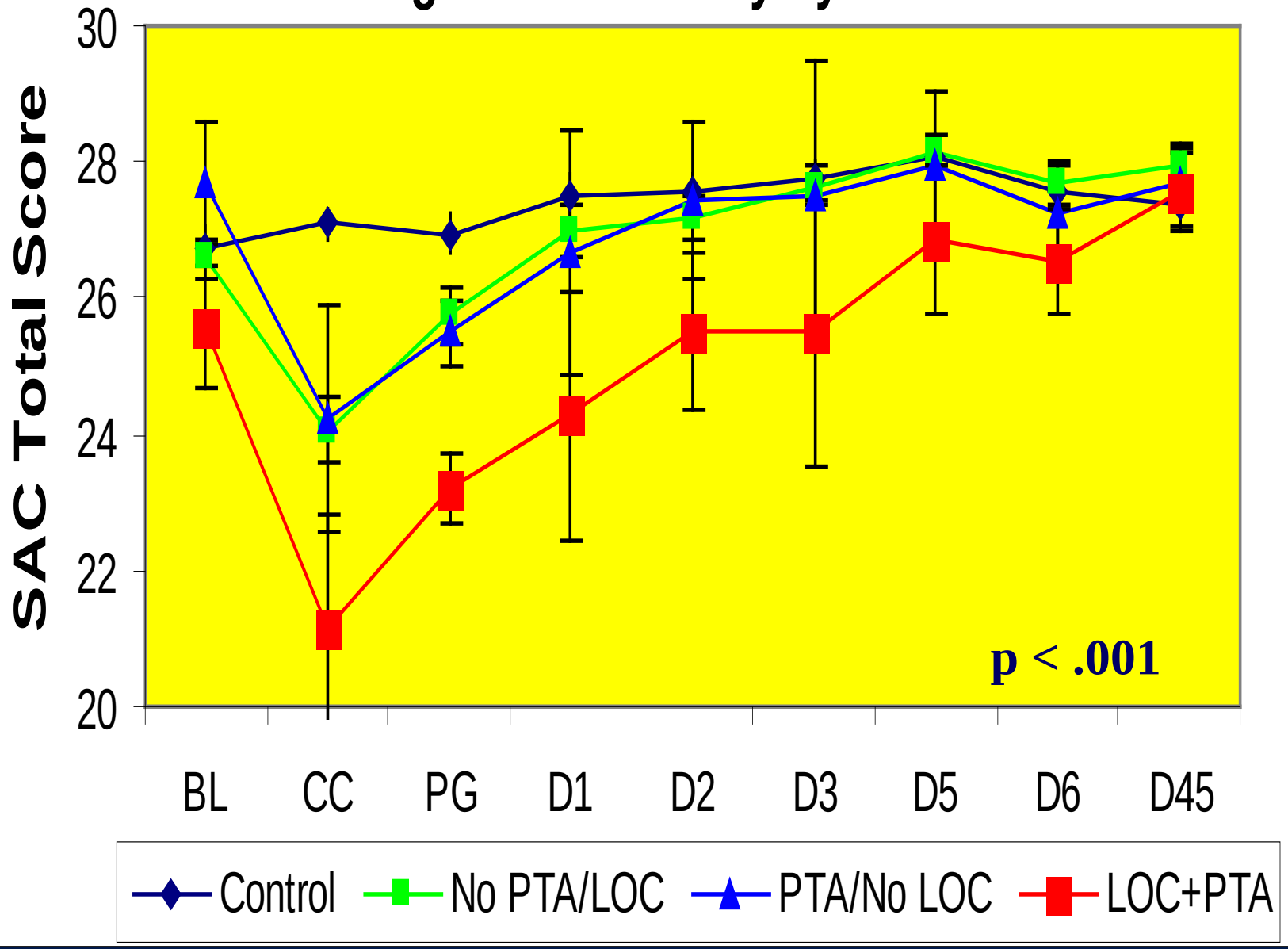




85 % of subjects full symptom recovery within 1 week

MA McCrea, *Mild TBI and Postconcussion Syndrome*, Oxford Univ. Press, 2008

Cognitive Recovery by LOC/PTA



Consequences of mTBI
Second Impact Syndrome

- Second injury occurring before full recovery from first injury
- Rare cases of lethal malignant cerebral edema and herniation
- Common: Second impact results in:
  - Delayed recovery of post-concussion symptoms
  - Greater risk of long-term consequences

Consequences of mTBI
Risk of Dementia after single TBI

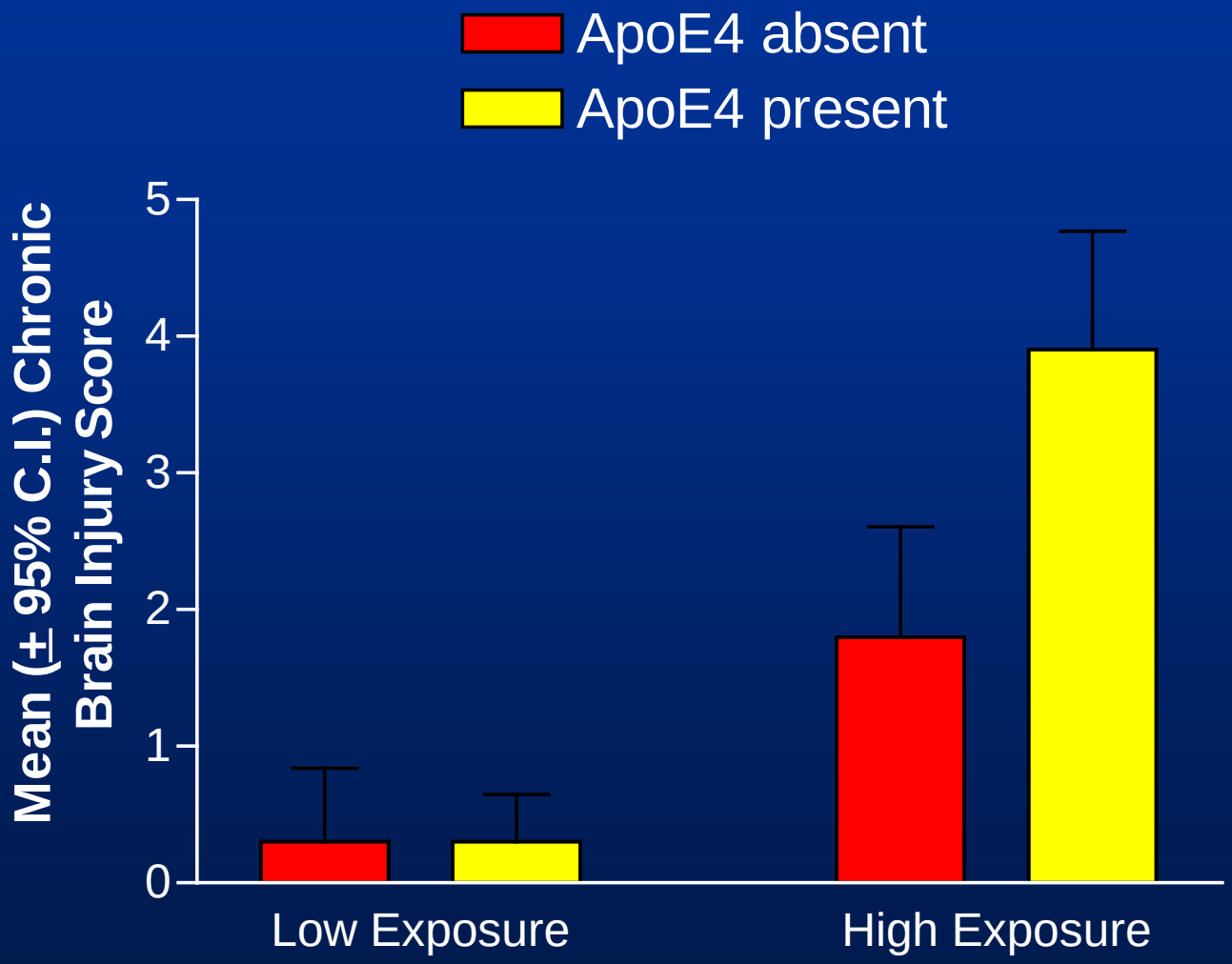
- WW II Navy and Marine Veterans 1944 - 1945
  - 548 hospitalized for non-penetrating TBI
  - 1228 hospitalized for non-TBI injuries
  - Evaluated 1996 – 1997 through telephone interviews and clinical assessments
- Severe TBI (LOC or PTA > 24 hours)
  - HR 4.51 (95% CI 2.09 – 9.63) for AD
- Moderate TBI (LOC or PTA > 30 min, < 24 h)
  - HR 2.39 (95% CI 1.24 – 4.58) for AD
- Mild TBI (LOC or PTA < 30 min)
  - HR 0.76 (95% CI 0.51 – 3.47)

Plassman et al, *Neurology* 2000;55:1158-1166

Consequences of mTBI
Risk of Dementia after Repeated mild TBI

- Dementia Pugilistica (Martland 1928)
  - "Punch drunk syndrome"
  - Current term: Chronic Traumatic Encephalopathy
- Prevalence in boxers estimated at 20%
  - No Class I studies
- Higher risk in professional boxers, compared to amateur

Association of apoE ε4 allele with chronic brain injury in boxers



$p < 0.001$

Jordan et al, *JAMA* 1997;278:136

Does Chronic Traumatic Encephalopathy occur in Football Players?

Center for the Study of Traumatic Encephalopathy

NATIONAL FOOTBALL LEAGUE PLAYERS ASSOCIATION

SPORTS MEDICINE RESEARCH LABORATORY

sportslegacy INSTITUTE

BOSTON UNIVERSITY

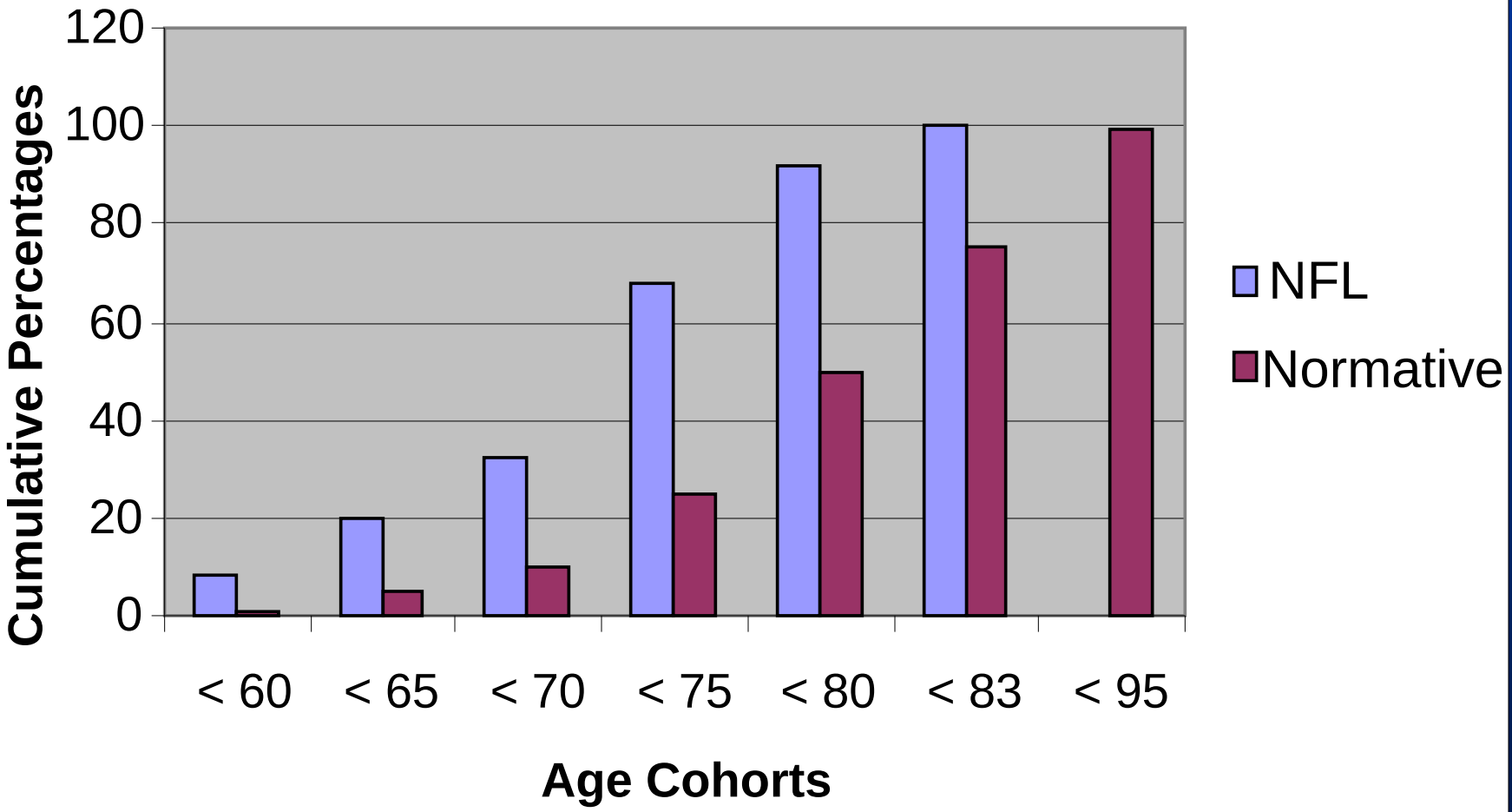
2001 Health Survey of Retired NFL Players

History of concussion from participating in professional football: 61% of all respondents

- Ave no. concussions during pro football career: 2.1
- 24% of respondents sustained 3 or more concussions
- 12% of respondents sustained 5 or more concussions
- 71% reported having returned to play on the same day as their concussion (18% reported this occurrence 3+ times)
- 16% reported that concussions have a permanent effect on thinking/ memory skills as they get older

Recurrent Concussion as Risk for Dementia

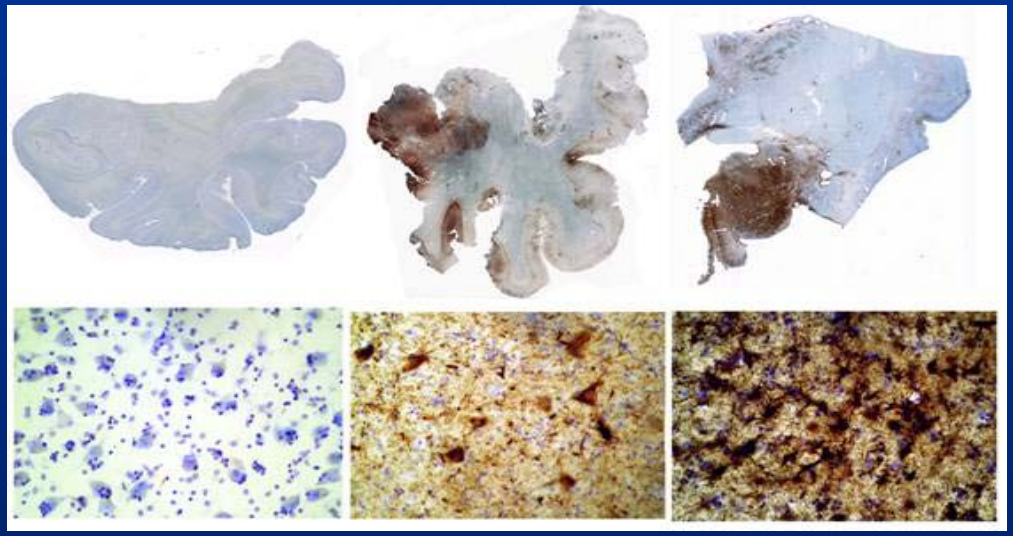
NFL vs. Normative PAD Age Distribution



MA McCrea, *Mild TBI and Postconcussion Syndrome*, Oxford Univ. Press, 2008

Pathology of CTE

- JG died at age of 45 from an accidental gunshot wound to the chest while cleaning a gun
- Had played football in high school, 3 years in college, and 10 in the NFL
- Concussed 3 times in college and at least 8 in the NFL. Only 1 was medically confirmed
- Never required hospitalization and never had LOC longer than few seconds



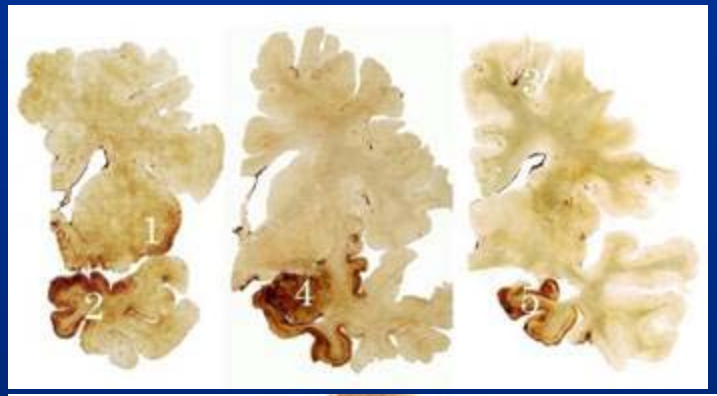
Tau immunohistochemistry

- At age 40, family started to notice impairment in short-term memory, concentration, planning, and organization
- Symptoms radually increased over the next 5 years. By the end of his life he became irritatable and aggressive over insignificant issues, was more emotionally labile, and began to consume more alcohol

AC McKee et al, *J Neuropath Exp Neurol* 2009;68:709-735

Clinicopathologic Features of CTE

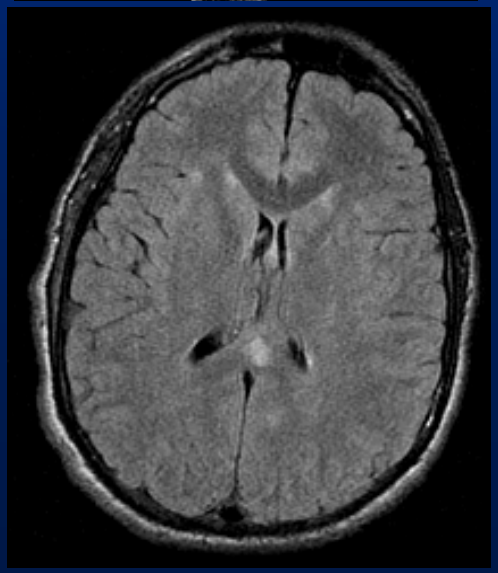
- Clinical Features of CTE
  - Onset typically in 5th and 6th decades
  - Mood and behavioral symptoms are prominent, in addition to short term memory problems
  - Motor symptoms are common (Parkinsonism and Motor Neuron Disease)
  - Progression over several decades (mean 18.6 y)
- Pathologic Features of CTE
  - Globbal atrophy, thinning of corpus callosum, cavum septum pellucidum
  - Tau neurofibrillary deposits in hippocampus, temporal and frontal cortex, substantia nigra, hypothalamus, mammillary bodies



Tau immunohistochemistry

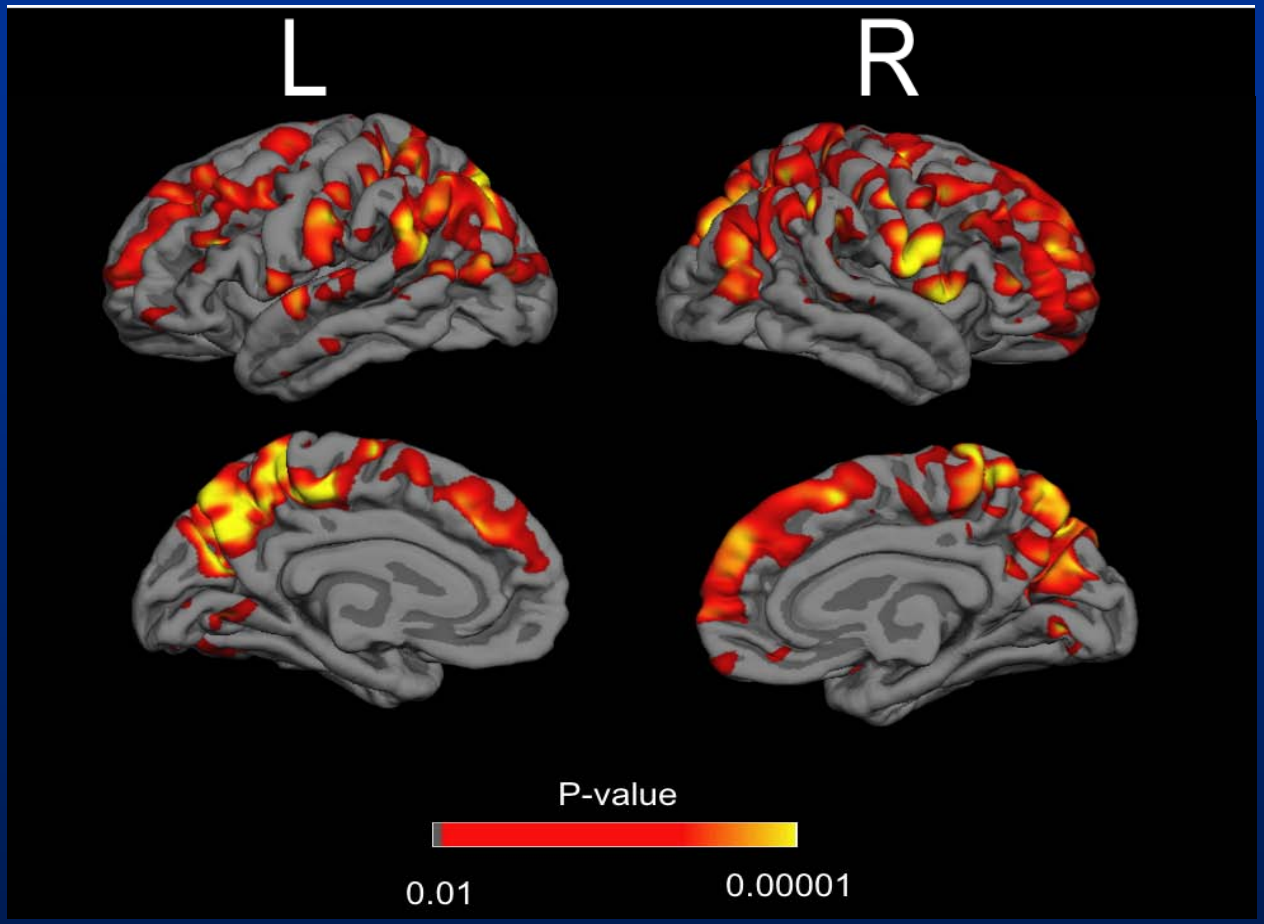
AC McKee et al, *J Neuropath Exp Neurol* 2009;68:709-735

New Insights from Advanced Neuroimaging
MRI abnormalities in TBI



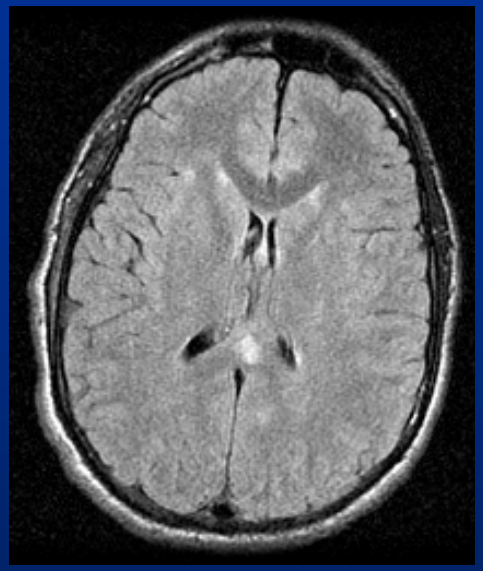
- Cranial CT abnormal in 10 – 20% of mTBI
- MRI 30% more sensitive
  - Abnormal 10 – 57% in mTBI
  - No head – to –head large studies comparing with CT
- MRI may be useful for:
  - Counseling
  - Medico-legal issues
  - Research

Quantitative Volumetric MRI



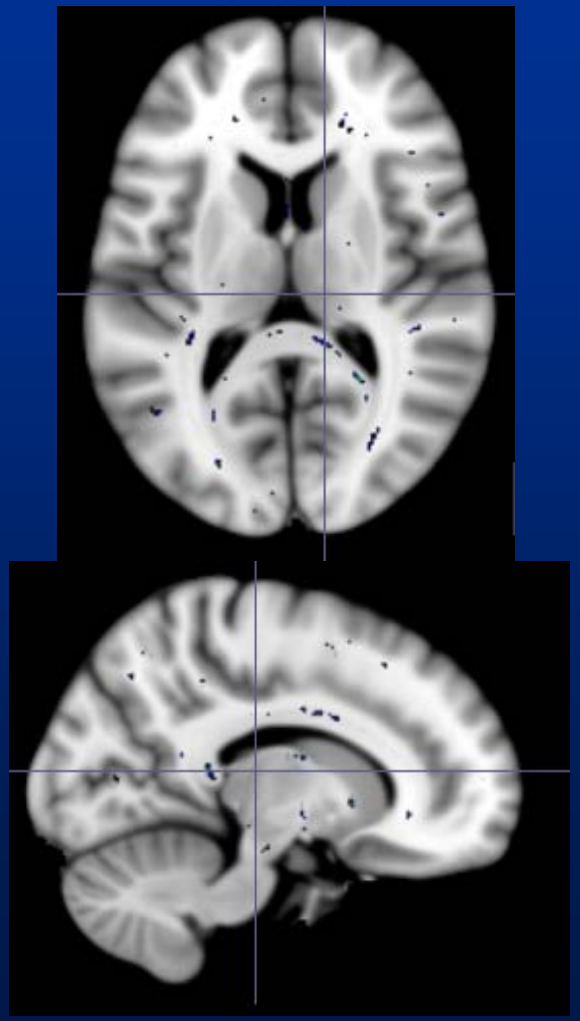
Warner et al, *Arch Neurol.* 2010;67(11):1336-44.

Diffusion Tensor Imaging



FLAIR

VBM

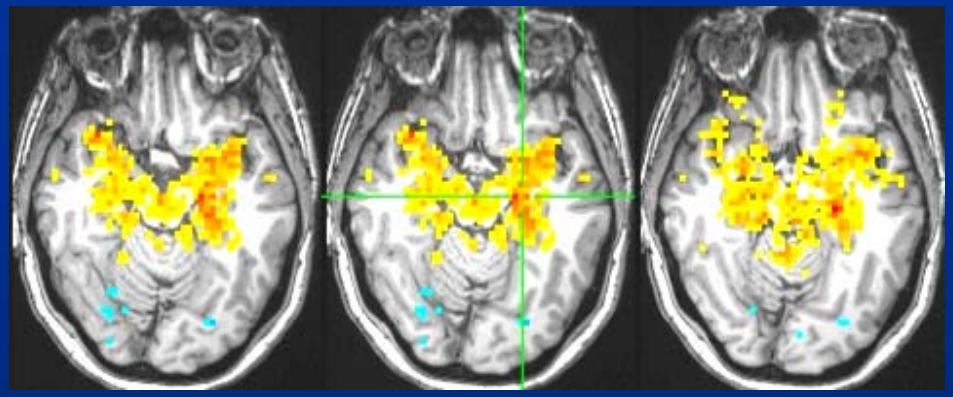


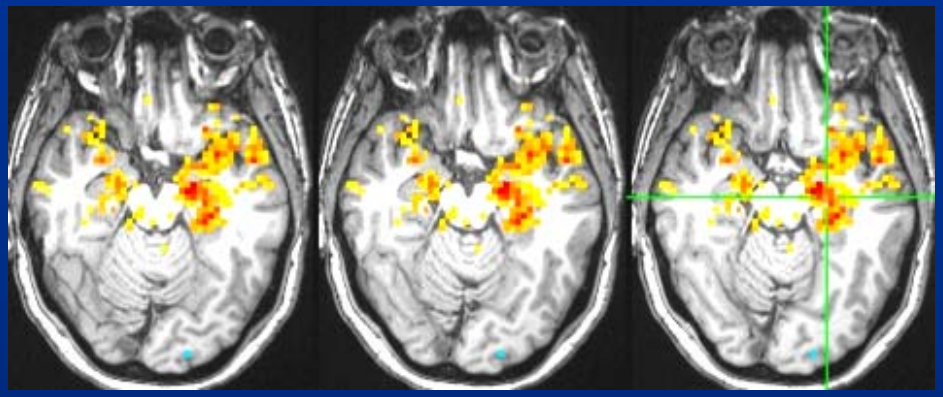
TBSS

Three different patients with mTBI (GCS 15) scanned within 2 days of injury

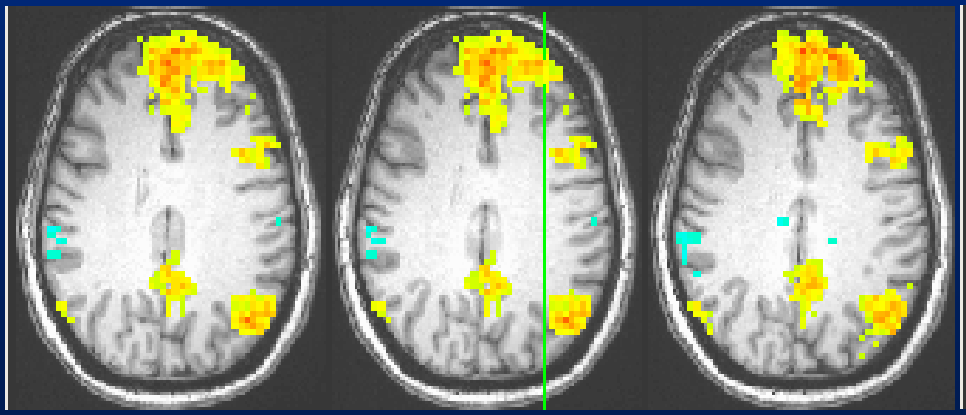
Resting State Functional Connectivity

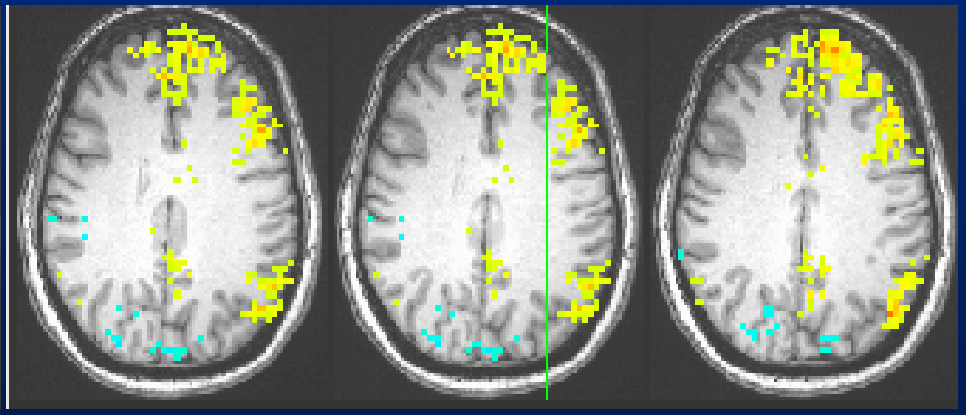
Left Hippocampus Seed





Left Dorsolateral Prefrontal Cortex Seed





Controls (n = 17)

TBI Patients (n = 16)

Marquez de la Plata, et al, *Arch Neurol* [in press, 2010]

Relevance of Civilian Experience to Military TBI

- Symptom complex quite similar
  - Biomechanical details may differ
- Prevalence of symptoms may be higher in military setting
  - Severity of injury likely higher
  - Higher incidence of repeated mTBI
  - Risk of second impact syndrome
- Possible increased vulnerability to mTBI in the setting of combat stress
- Effective therapies are likely to be effective across populations

Collaborators

- **UT Southwestern**
  - Caryn Harper
  - Carol Moore
  - Carlos Marquez de la Plata
  - Lifang Peng
  - Nasreen Sayed
  - Christopher Paliotta
  - Kan Ding
  - Jun-Yi Wang
  - Khamid Bakhadirov
  - Matthew Warner
  - Katherine Oldenkamp
  - Yale Gong

- **UT Southwestern**
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  - Mark Agostini
  - Paul Van Ness
  - Anne Hudak
  - Mike Devous
  - Roderick McColl
  - Tony Whittemore

- **Baylor Institute for Rehabilitation**
  - Mary Carlile
  - Stuart Yablon
  - Cindy Dunklin
  - Elizabeth Callender

- **NIH**
  - R01 HD48179
  - U01 HD42652
  - R01 AG17861
- **US Dept. of Education**
  - HD133A020526