



# **Neuropsychiatry of Traumatic Brain Injury**

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**Albert Eugene Sterne Professor of Psychiatry**

**Indiana University School of Medicine**

[www.mghcme.org](http://www.mghcme.org)

## Disclosures:

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**Royalties:** *American Psychiatric Assoc. Publishing, Inc. Textbook of Traumatic Brain Injury*

My spouse has no disclosures or conflicts of interest.

# Major Points

- Traumatic brain injury (TBI) greatly increases risk of developing several neuropsychiatric syndromes.
  - *Almost half develop neuropsychiatric disorders*
- Profile of TBI associated brain injury predicts the common neuropsychiatric sequelae.
- TBI alters the presentation and treatment of neurobehavioral syndromes in predictable ways



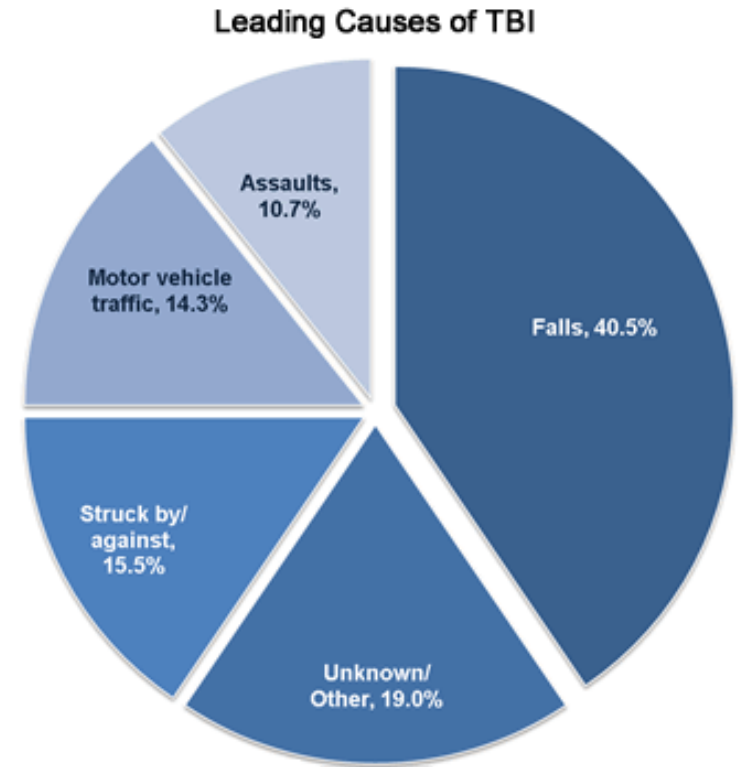
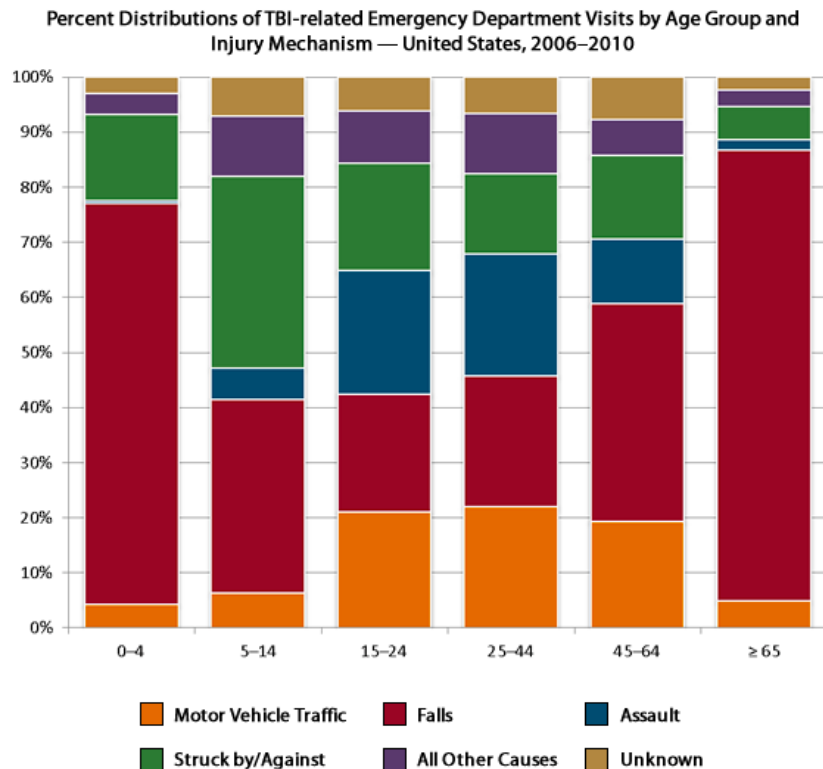
# TBI Definition

- “Force” acting on the brain
- Results in:
  - *Disturbance* in level of consciousness (loss of consciousness not required for the definition)
- This definition distinguishes TBI from:
  - Acquired brain injury (e.g. stroke)
  - Developmental disorders
- This definition encompasses “concussion”
  - Synonymous with term “mild TBI”



# Causes of TBI

- Falls - (elderly)
- Motor vehicle accident -Teens/young adults
- Assaults - Urban populations



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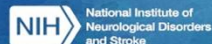
Injury Prevention & Control: Traumatic Brain Injury

# Metrics of Injury Severity

- Based on Time of Injury Parameters
  - Loss of consciousness (LOC)
  - Duration of post traumatic amnesia (PTA)
  - Glasgow Coma Scale (GCS) score
- Classified as: “Mild; Moderate; Severe”
  - 70-80% are “mild”
  - LOC < 30 min; PTA < 24hr; GCS 13-15
  - Determined by assessment at time of injury
  - Concussion - mild end of the mild spectrum



# Metrics of Injury Severity: Moving Beyond the GCS Score



## NINDS Traumatic Brain Injury (TBI) Classification and Nomenclature Workshop

January 22-23, 2024 | NIH Campus | Bethesda, MD



### A new characterisation of acute traumatic brain injury: the NIH-NINDS TBI Classification and Nomenclature Initiative

Geoffrey T Manley\*, Kristen Dams-O'Connor\*, Michael L Allosco, Hibah O Awwad, Jeffery J Bazarian, Peter Bragge, John D Corrigan, Adele Doperalski, Adam R Ferguson, Christine L Mac Donald, David K Menon, Molly M McNett, Joukje van der Naalt, Lindsay D Nelson, Dana Piscià, Noah D Silverberg, Nsini Umoh, Lindsay Wilson, Esther L Yuh, Henrik Zetterberg, Andrew I R Maast, Michael A McCreary, on behalf of the members of the NIH-NINDS TBI Classification and Nomenclature Initiative†

Lancet Neurol 2025; 24: 512-23

See Comment page 475

\*Joint first author

†Joint last author

‡Members are listed in the appendix (pp 7-9)

Neurological Surgery, University of California, San Francisco, CA, USA (Prof G T Manley MD, Prof A R Ferguson PhD); Department of Rehabilitation and Human Performance and

The clinical severity of traumatic brain injury (TBI) is commonly classified according to the Glasgow Coma Scale (GCS) sum score as mild (13–15), moderate (9–12), or severe (3–8). A new approach is needed for characterising TBI more accurately. In 2022, the US National Institutes of Health–National Institute of Neurological Disorders and Stroke launched an international initiative to address this need, with a focus on the acute phase of injury. Six working groups of TBI experts, implementation scientists, people with lived experience, and federal partners were established, involving 94 participants from 14 countries. The proposed new framework for the characterisation of acute TBI incorporates four pillars: a clinical pillar (full GCS and pupillary reactivity); a biomarker pillar (blood-based measures); an imaging pillar (pathoanatomical measures); and a modifier pillar (features influencing clinical presentation and outcome; CBI-M). The CBI-M framework provides a multidimensional characterisation of TBI to inform individualised clinical management and to improve scientific rigor. Research priorities include validation of the CBI-M framework, evaluation of its applicability beyond the acute phase of TBI, and strategies for clinical implementation.

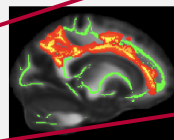
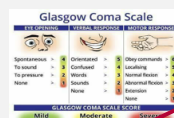
GCS; Pupillary responses

e.g. GFAP; UCHL-1

Clinical CT and/or MRI

Mental health hx; social disadvantage; medical hx

### NEW SYSTEM FOR CHARACTERIZATION & CLASSIFICATION OF TBI



C

CLINICAL

B

BIOMARKERS

I

IMAGING

M

MODIFIERS



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Slide courtesy of Michael McCreary, Ph.D.

# Injury Mechanisms in TBI

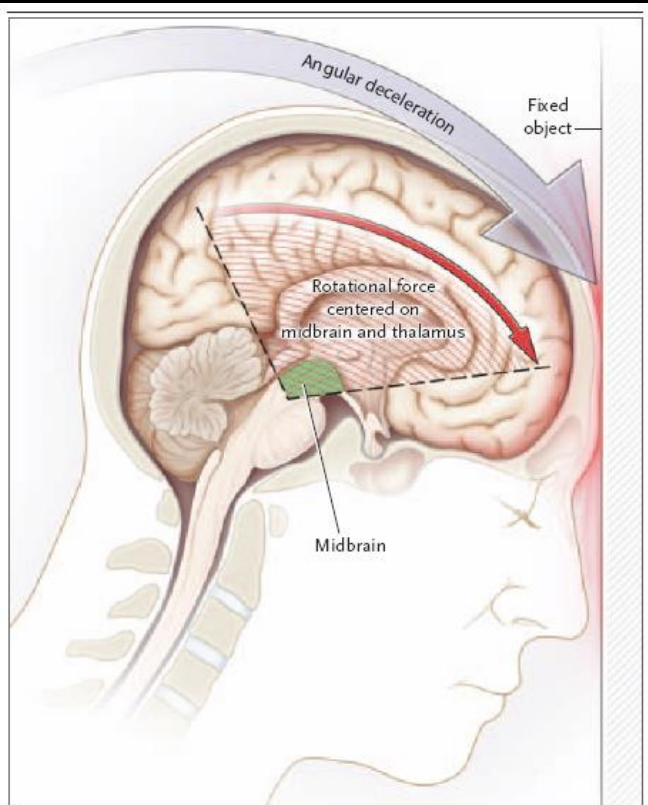


**Figure 1. Mechanism of Concussion.**

Biomechanical investigations dating back to the beginning of the 20th century suggest that concussion results from a rotational motion of the cerebral hemispheres in the anterior–posterior plane, around the fulcrum of the fixed-in-place upper brain stem. If the neck is restrained, concussion is difficult to produce. Concussions as portrayed in movies and cartoons, in which the back of the head is struck with a blunt object and no motion is transferred to the brain, are implausible. The modern view is that there is disruption of the electrophysiological and subcellular activities of the neurons of the reticular activating system that are situated in the midbrain and diencephalic region, where the maximal rotational forces are exerted. Alternative mechanisms for concussive loss of consciousness, such as self-limited cortical seizures or a sudden increase in intracranial pressure, have also been proposed, but with limited supporting evidence.

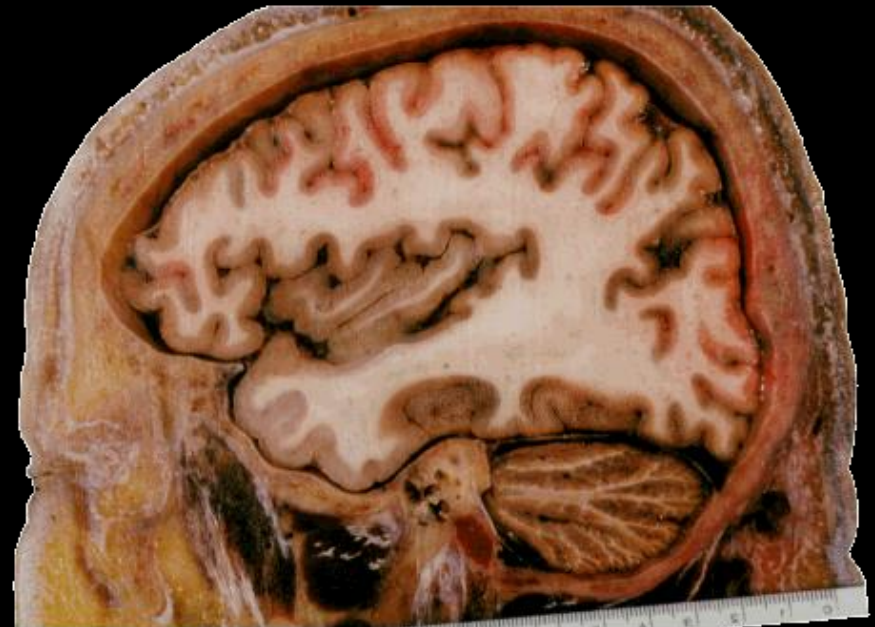


**FIGURE 26-1. Skull base.**

The skull cap has been removed, exposing the inner surface of the ventral base of the skull, with the various anatomic structures with the three cranial fossa clearly defined. The uneven surface of each fossa is clearly observable. The general location of the hippocampus (medial wall of the middle cranial fossa) and where the base of the frontal lobe is located (anterior cranial fossa) are depicted.

A = frontal crest; B = anterior cranial fossa; C = crista galli with cribriform plate beneath; D = sphenoid bone; E = petrous temporal bone; F = clinoid bone and area of the sella turcica; G = clivus; H = foramen magnum; I = middle cranial fossa; J = posterior cranial fossa.

Source. Reprinted with permission from Bigler ED: "Anterior and Middle Cranial Fossa in Traumatic Brain Injury: Relevant Neuroanatomy and Neuropathology in the Study of Neuropsychological Outcome." *Neuropsychology* 21:520, 2007.



# Frontal and Temporal Contusions

(from Gennarelli and Graham, in: *Textbook of Traumatic Brain Injury*)

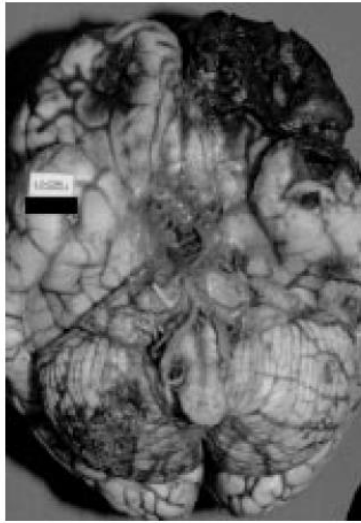
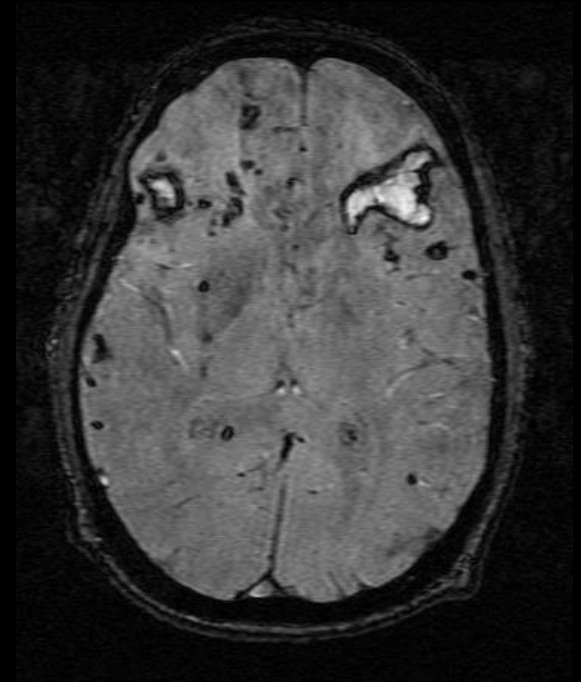


**FIGURE 2-1. Acute contusions: 18-hour survival.**

Base of brain to show hemorrhagic defects and associated subarachnoid hemorrhage on undersurfaces of frontal lobes and in relation to temporal poles.



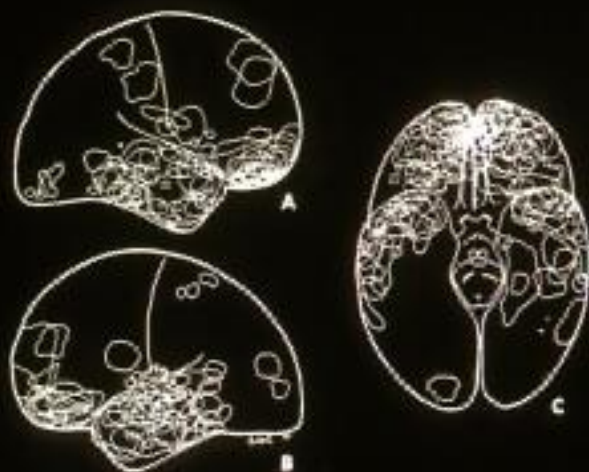
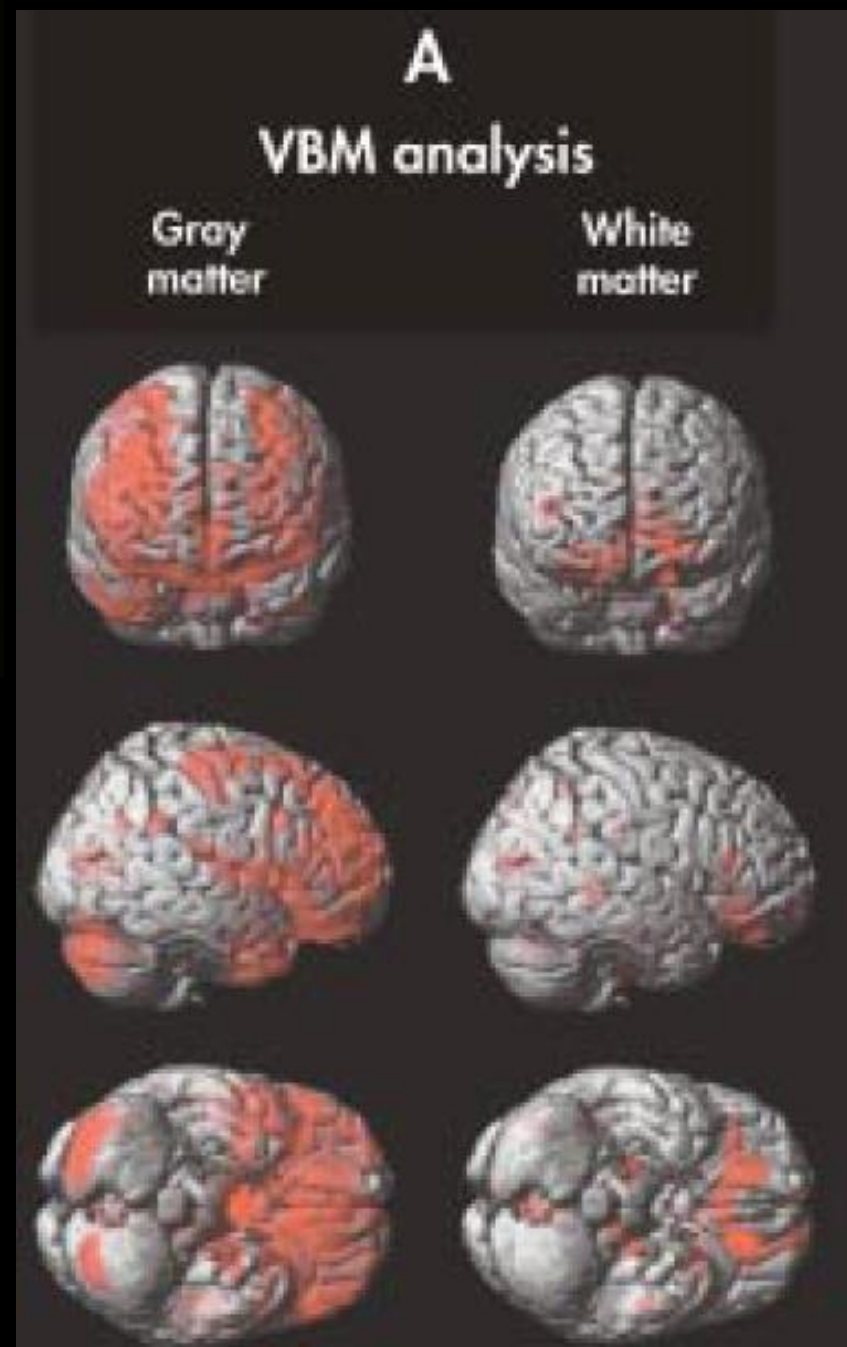


Figure 84-4

Composite drawing showing size and location of contusions found in a series of 40 consecutive cases. The tendency to localize in the subfrontal and temporal regions is clearly indicated. (From Courville.)

## Distribution of Structural Lesions From Contact Mechanisms is not Random

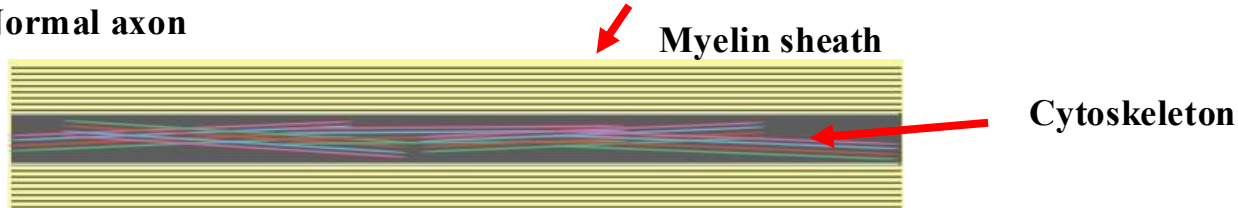
Bigler, ED. Structural Imaging. In Silver JM, McAllister TW, Yudofsky SC. (eds) *Textbook of Traumatic Brain Injury*, American Psychiatric Publishing, Inc. 2005 p 87



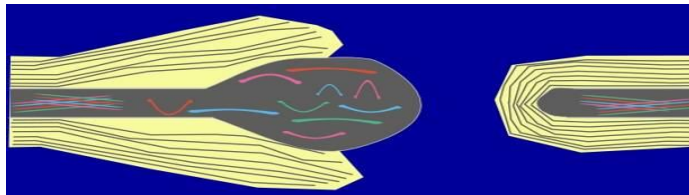
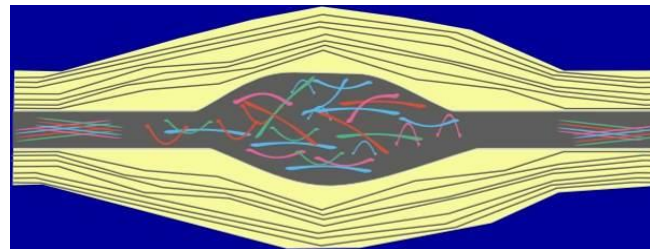
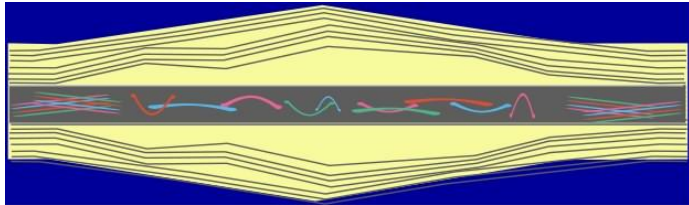
# Inertial Forces: Diffuse Axonal Injury(DAI)

*(borrowed from Robin Hurley, M.D.)*

Normal axon

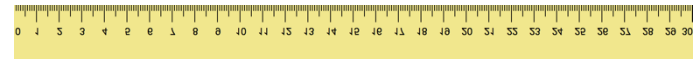


Injured axon



## Injury Sequence:

- Axon is stretched
- ~5-7mm displacement can exceed tissue tolerance



## Increased permeability

- Calcium influx
- Damage to cytoskeleton
- Impaired axoplasmic transport
- Axonal swelling
- Detachment and axonal death



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# Diffuse Axonal Injury

Although it is diffuse,  
DAI particularly  
effects:

Sub-cortical  
frontal white  
matter and  
Corpus callosum

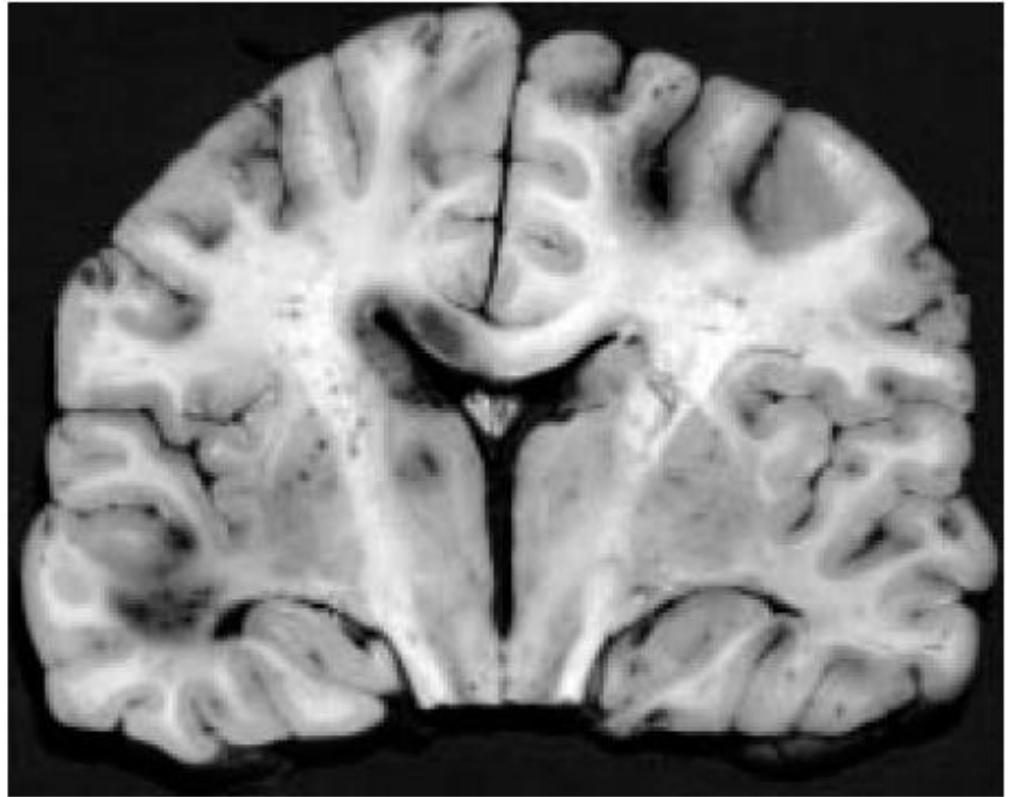
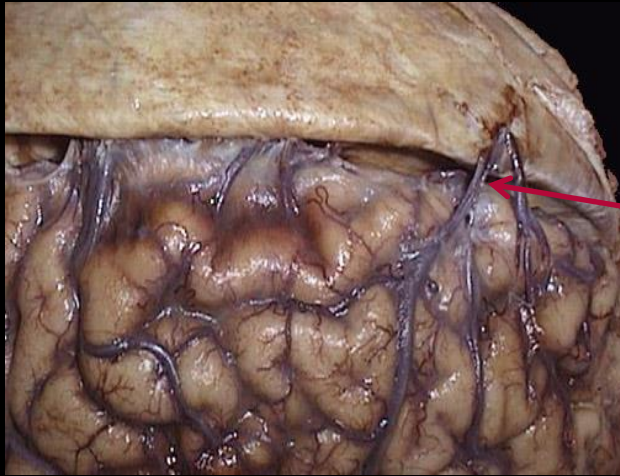


**FIGURE 2-5.** Traumatic diffuse axonal injury (DAI): 5-day survival.

Note absence of surface contusions and midline hemorrhages in the corpus callosum and in the left thalamus. Hemorrhages were also seen in the dorsolateral sector of the upper brainstem. Microscopy revealed widely distributed axonal damage, with a severity grading of DAI 3.

# Vascular Injuries

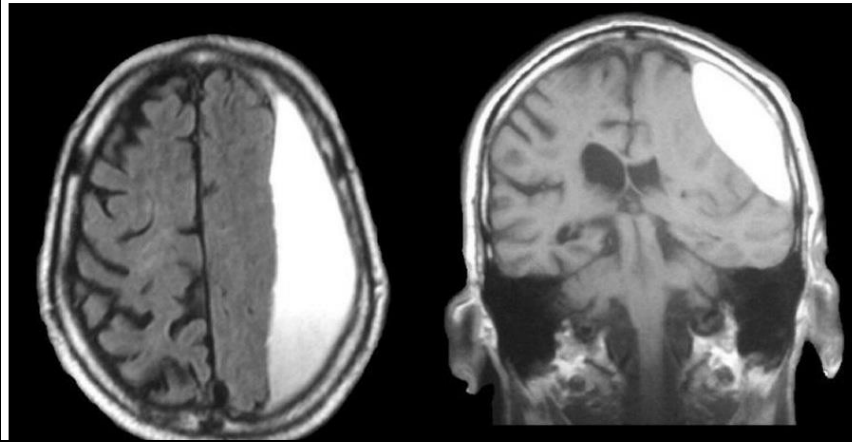


Bridging veins

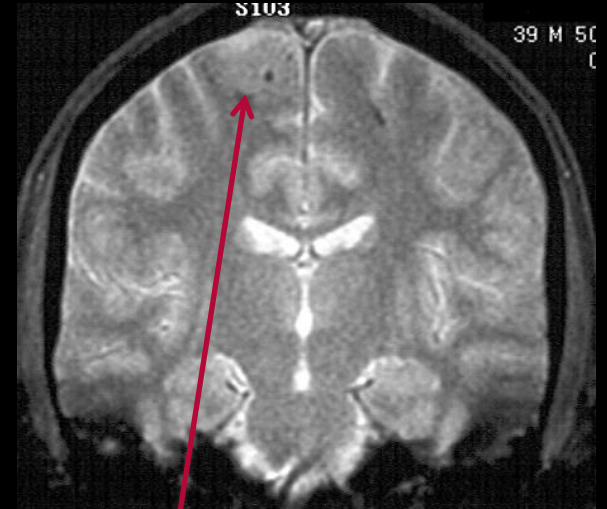
<http://medlib.med.utah.edu/WebPath/CNSHTML/CNS315.html>

## Subdural Hematoma - Unilateral Acute - Case 1

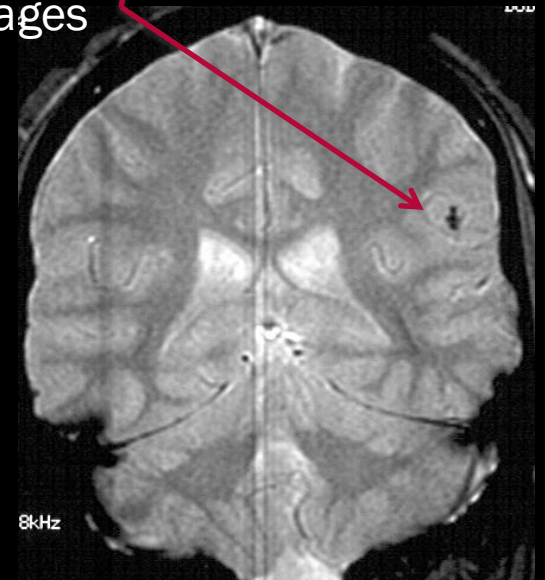
An 82 year-old man developed progressive confusion and weakness of the right arm and leg.



Subdural Hematoma

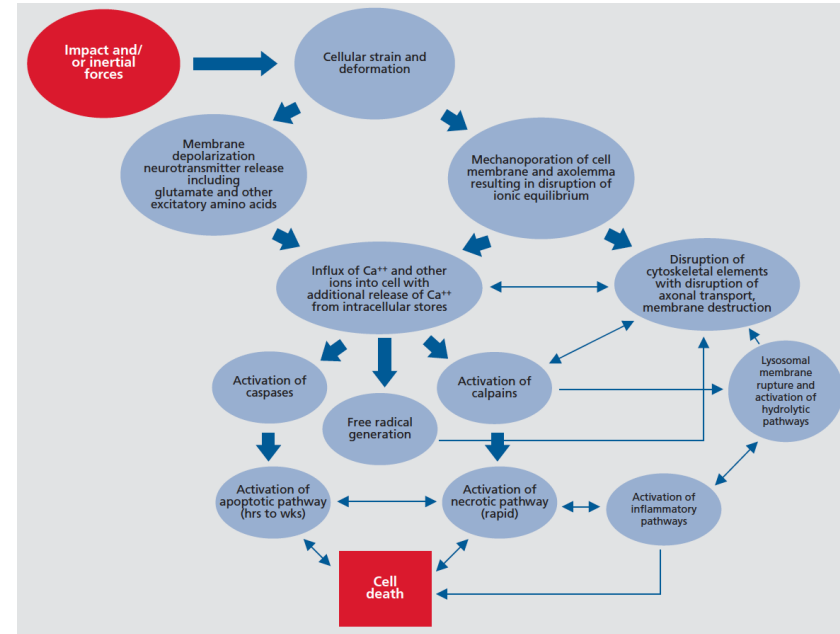


Shear Hemorrhages



# Neuropathology of TBI

- Combination of:
  - Diffuse and focal
  - Primary and secondary
  - Immediate and evolving
- ***Non-random geographic distribution of injury burden within the brain***
- ***Selectively impacts regions and neurotransmitters critical to behavior modulation***



## Brain regions vulnerable to TBI and relationship to neurobehavioral sequelae

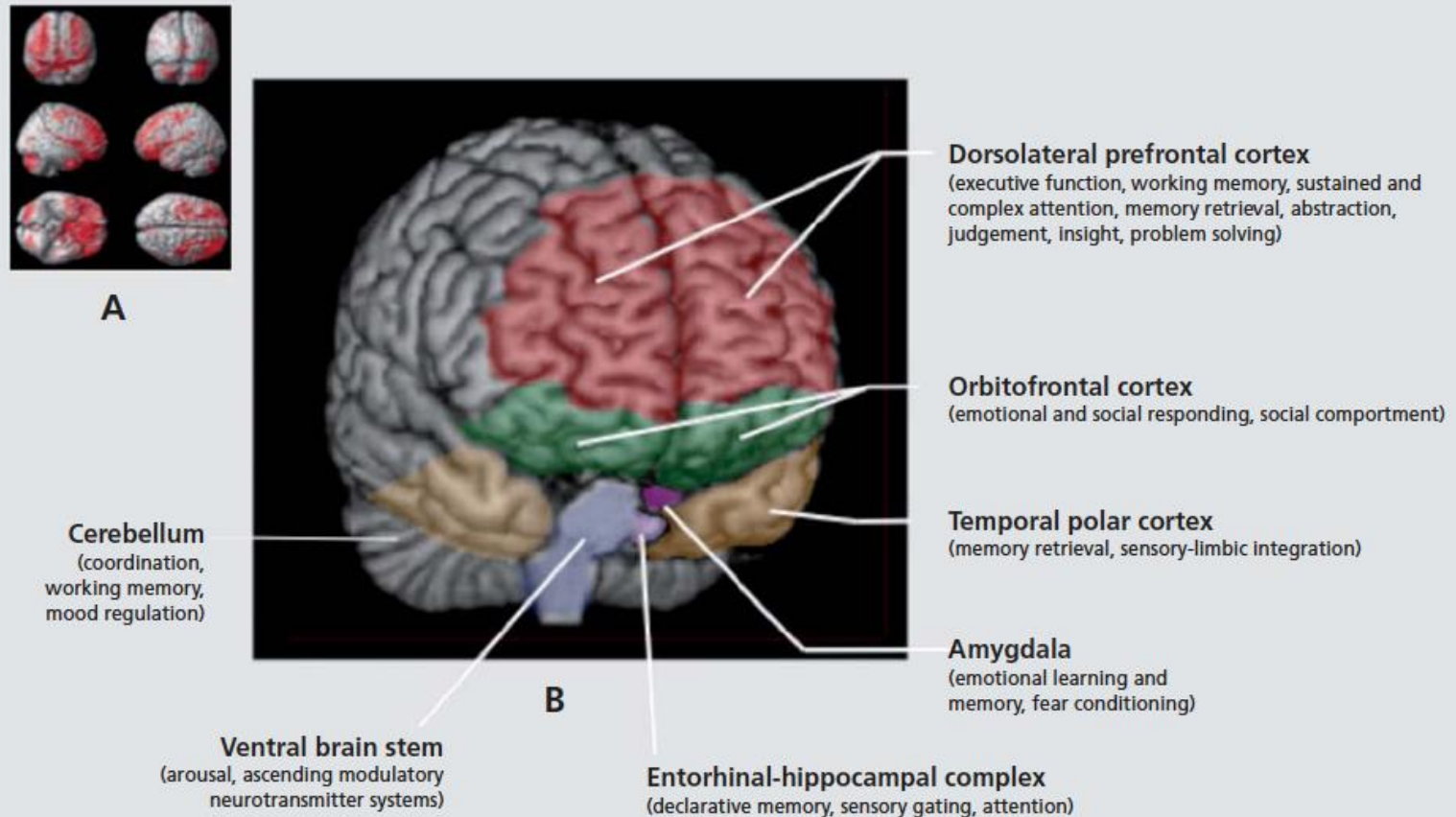


**Figure 3.** (A) Brain regions vulnerable to damage in a typical traumatic brain injury (TBI, from ref 112 ); (B) Relationship of vulnerable brain regions to common neurobehavioral sequelae associated with TBI.

(B) Adapted from ref 111: Arciniegas DB, Beresford TP. *Neuropsychiatry: an Introductory Approach*. Cambridge, UK: Cambridge University Press; 2001:58. Copyright © Cambridge University Press, 2001

# Major Categories of Neuropsychiatric Sequelae

- Dysexecutive Syndromes (“personality changes”)
  - Disorders of Social comportment
  - Disorders of Motivation
  - Disorders of executive cognitive functions
- Cognitive Deficits
  - Memory/attention/speed of information processing
  - Dementia?
- Psychiatric Disorders
- Neurological & Medical Complications



# Dysexecutive Syndrome Vignette: 44 yo male: bike vs. truck

44 cyclist struck by pickup truck on rural road

- Moderate to severe TBI
- Progressive recovery
- Marked agitation, disinhibition & “inappropriate” behaviour, “psychotic behavior”
- Requested psychiatry consult



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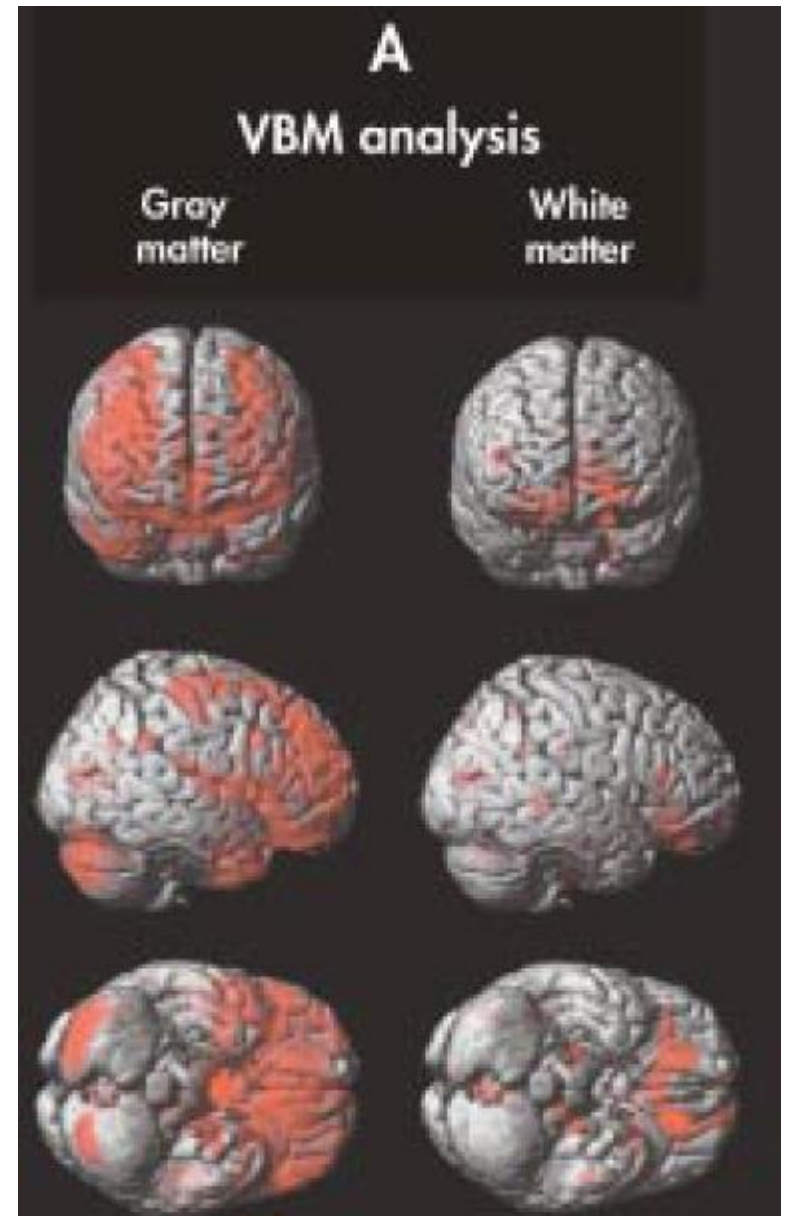
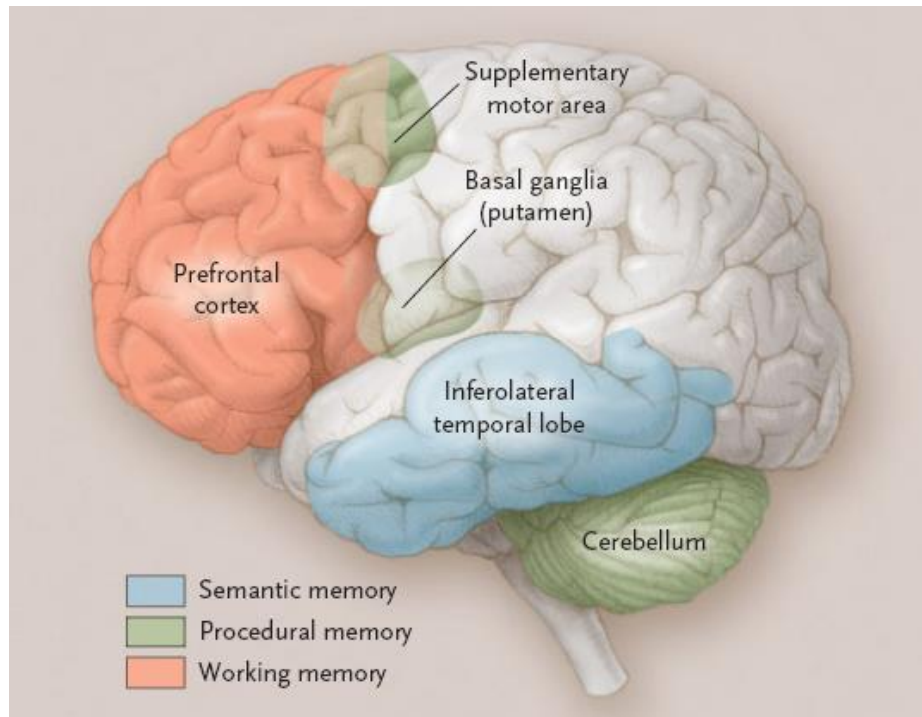
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# Cognitive Deficits After TBI

- Executive Function
- Attention
- Speed of Information Processing
- Speech and language
- **Memory**
  - Static impairment
  - Dementia?



Comparison of regional substrates of memory, and regions of decreased cortical gray matter after TBI. Note in particular the overlap with working memory regions



# Vignette:

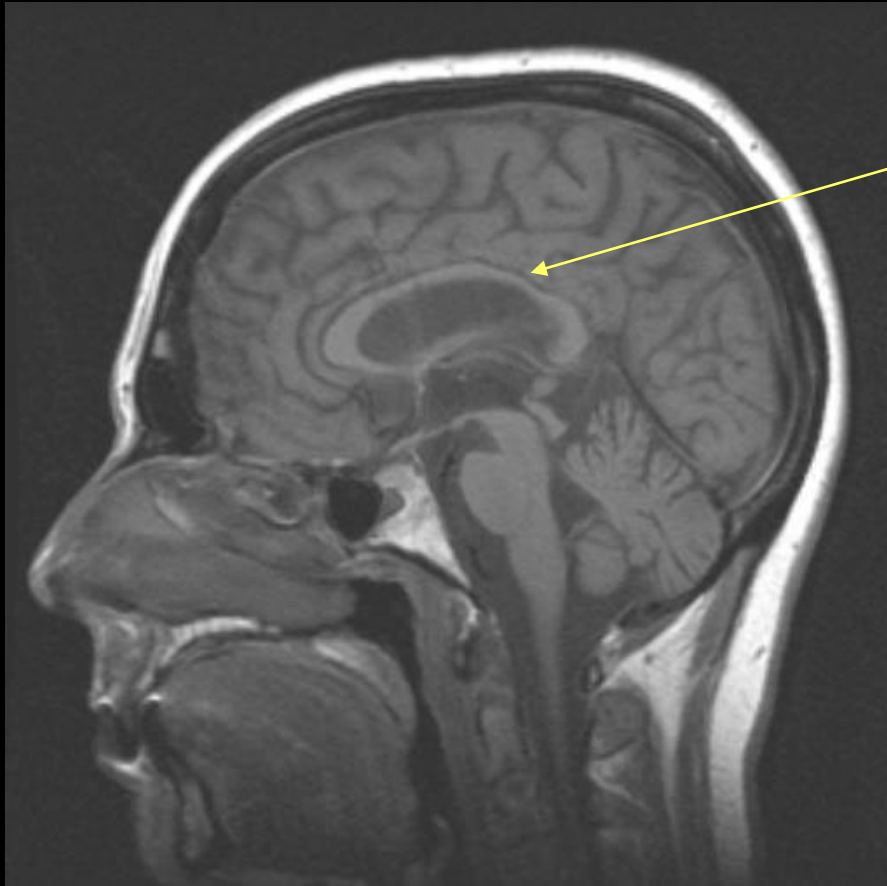
## Severe TBI with Memory Deficits

- Mrs. A was a healthy 35 yr old until MVA
- Severe TBI, coma for 5 weeks, then gradual recovery.
- Ongoing problems with memory, comprehension, speech and ambulating
  - “My short-term memory is gone... but I can remember things from 10 years ago”
  - Unable to read, multi-task, or follow through with projects.



### Neuroimaging Findings:

- Thinning of Corpus Callosum
- Hippocampal/mesiotemporal atrophy



# Treatment

- Started on Rivastigmine 6mg BID
- Reported gradual but significant improvement:
  - reading, concentration, and memory
  - felt “sharper mentally”, able to recall people's faces, events from the past, and improved short-term memory
  - Overall rated herself a 2 or 3 in terms of improvement on a 0-4 Scale. Husband concurs with assessment.
  - working again part time

Clinical Trial > [Neurology](#). 2006 Sep 12;67(5):748-55.

doi: 10.1212/01.wnl.0000234062.98062.e9.

## Effects of rivastigmine on cognitive function in patients with traumatic brain injury

J M Silver <sup>1</sup>, B Koumaras, M Chen, D Mirski, S G Potkin, P Reyes, D Warden, P D Harvey, D Arciniegas, D I Katz, I Gunay

Affiliations + expand

PMID: 16966534 DOI: [10.1212/01.wnl.0000234062.98062.e9](#)

Randomized Controlled Trial > [J Neuropsychiatry Clin Neurosci](#). 2025 Spring;37(2):102-114.

doi: 10.1176/appi.neuropsych.20230055. Epub 2024 Dec 4.

## Multicenter Evaluation of Memory Remediation in Traumatic Brain Injury With Donepezil: A Randomized Controlled Trial

David B Arciniegas <sup>1</sup>, Emily J Almeida <sup>1</sup>, Angelle M Sander <sup>1</sup>, Jay A Bogaards <sup>1</sup>, Joseph T Giacino <sup>1</sup>, Flora M Hammond <sup>1</sup>, Cynthia L Harrison-Felix <sup>1</sup>, Tessa Hart <sup>1</sup>, Jessica M Ketchum <sup>1</sup>, David C Mellick <sup>1</sup>, Mark Sherer <sup>1</sup>, John Whyte <sup>1</sup>, Ross D Zafonte <sup>1</sup>

Affiliations + expand

PMID: 39628282 DOI: [10.1176/appi.neuropsych.20230055](#)

# TBI and Dementia

- Two Broad Concerns:
  - Increased risk of Alzheimer's Disease
  - Chronic Traumatic Encephalopathy (CTE) related to concussion(s) and/or repetitive head impacts
- Risk of AD - Some evidence for increased rates after TBI:
  - Recent meta-analysis of 32 studies with 2M subjects found increased RR for both any dementia (RR=1.63) and AD (RR=1.51)
    - Li, Y., Li, Y., Li, X., Zhang, S., Zhao, J., Zhu, X., & Tian, G. (2017). Head Injury as a Risk Factor for Dementia and Alzheimer's Disease: A Systematic Review and Meta-Analysis of 32 Observational Studies. PLoS ONE, 12(1), e0169650.  
<http://doi.org/10.1371/journal.pone.0169650>
  - Possible interaction between TBI and genotype
  - Accelerated course: reduced cognitive reserve vs. risk factor
  - Does it occur after a single TBI?
  - Relationship to injury severity and frequency?



## Dementia Risk Seen in Players in N.F.L. Study

By ALAN SCHWARZ  
Published: September 29, 2009

A study commissioned by the [National Football League](#) reports that Alzheimer's disease or similar memory-related diseases appear to have been diagnosed in the league's former players more than in the national population — including a rate nearly double the normal rate for men ages 30 through 49.



The N.F.L. has long existed of reliable cognitive decline and These numbers would league's first public connection. though



ANNALS OF MEDICINE

### OFFENSIVE PLAY

How different are dogfighting and football?

BY MALCOLM GLADWELL

OCTOBER 19, 2009



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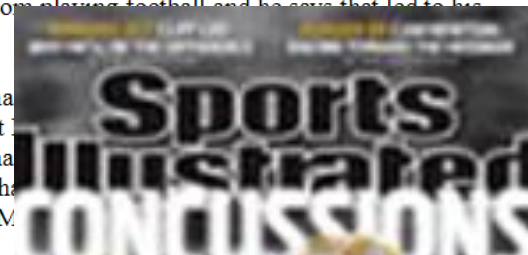
## Expert Ties Ex-Player's Suicide to Brain Damage

January 18, 2007

By ALAN SCHWARZ

Since the former National Football League player Andre Waters killed himself in November, an explanation for his suicide has remained a mystery. But after examining a specimen of Mr. Waters's brain, a neuropathologist in Pittsburgh is claiming that Mr. Waters had sustained brain damage from playing football and he says that led to his suicide and ultimate death.

Neuropathologist, Dr. Bennet Omalu, a forensic neuropathologist, determined that the 37-year-old man with similar characteristics. Dr. Omalu said he believed that the damage was by successive concussions M



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### Prevalence of chronic traumatic encephalopathy at death in National Football League players: retrospective population based cohort study, 2008-21

Daniel H Daneshmandi,<sup>1,2,3</sup> Christopher J Nowinski,<sup>4</sup> Bobak Abdolmohammadi,<sup>5</sup> Charlotte B Luster,<sup>3</sup> Madeline Uretsky,<sup>6</sup> Brett M Martin,<sup>7</sup> Joseph N Palmisano,<sup>7</sup> Jennifer Weuve,<sup>8</sup> Michael D McClean,<sup>9</sup> Jonathan D Cherry,<sup>9,10,11</sup> Brigid Dwyer,<sup>12</sup> Evan D Feigel,<sup>3</sup> Michael J Mastroiaca,<sup>3</sup> Victor E Alvarez,<sup>10</sup> Gil D Rabinovici,<sup>13</sup> William W Seeley,<sup>13</sup> Lea T Grinberg,<sup>13,14,15</sup> John F Cray,<sup>16</sup> Thor D Stein,<sup>9,10,11</sup> Lee Goldstein,<sup>17</sup> Douglas I Katz,<sup>12</sup> Ross D Zafonte,<sup>18</sup> Yorghos Tripodis,<sup>7</sup> Robert C Cantu,<sup>5,19,20</sup> Robert A Stern,<sup>5,12,19</sup> Michael L Alisco,<sup>5,12</sup> Ann C McKee,<sup>5,12,21</sup> Jesse Mez<sup>5,12,21</sup>

#### ABSTRACT

##### OBJECTIVES

To determine the range of possible prevalences of chronic traumatic encephalopathy (CTE) at death among National Football League (NFL) players and examine the association between CTE severity and risk of dementia.

##### DESIGN

Retrospective population based cohort study.

##### SETTING

NFL players from the era of hard-shell helmets

records and informant based clinical histories, to adjudicate a dementia diagnosis.

##### MAIN OUTCOME MEASURES

The main outcome measures were the minimum (number of donors with CTE/total number of NFL deaths) and maximum (1 (number of donors without CTE/total number of NFL deaths)) CTE prevalence at death during the study period and the six years (2016-21) when brain donation was most frequent. To account for selection pressure of brain donation status, inverse probability weighting was used to

For numbered affiliations see end of the article.  
Correspondence to: D H Daneshmandi (dhaneshmandi@bwh.harvard.edu or gbraindian@u.wisc.edu ORCID 0000-0003-3691-9513).  
Additional material is published online only. To view please visit the journal online.  
Cite this as: BMJ 2026;394:e100418  
http://dx.doi.org/10.1136/bmj-2026-100418

's brain is being donated to the Boston University School of Medicine to

#### LIGHTS

on, former NFL  
himself in the chest

CNN Chief Medical Correspondent Dr David Duerson's survivors and brain e  
Gupta, M.D. -- Head Games: The Tru



## The Army Said Tank Blasts Don't Harm Troops. His Case Raises Doubts.

Researchers say troops' brains may be injured by blasts from firing M1 Abrams tank guns and other weapons, even if they measure below the Pentagon's ceiling for safe exposure.

# Changing Paradigm

- Initial view:
  - Minor event with uniformly good prognosis - “Bell rung”
- Modified view:
  - Some injuries result in bad outcome
- Emerging concern:
  - Not an event – more of a process
  - Single event initiates chronic illness?
    - CTE

## Original Investigation

July 25, 2017

### Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football

Jesse Mez, MD, MS<sup>1,2</sup>; Daniel H. Daneshvar, MD, PhD<sup>1,3</sup>; Patrick T. Kiernan, BA<sup>1,2</sup>; et al

» Author Affiliations | Article Information

JAMA. 2017;318(4):360-370. doi:10.1001/jama.2017.8334

*J Neuropathol Exp Neurol* • Volume 68, Number 7, July 2009

*Chronic Traumatic Encephalopathy in Athletes*

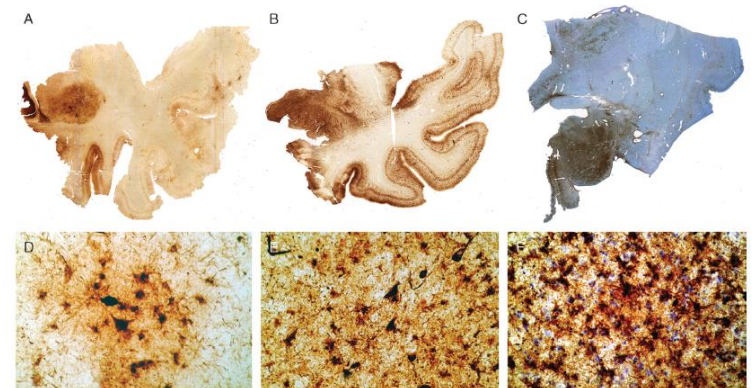


FIGURE 4. (A–C) Whole-mount 50-μm-thick coronal sections immunostained for tau (AT8) from Case A (A), Case B (B), and Case C (C) counterstained with cresyl violet showing extremely dense deposition of tau protein in the amygdala with increasing severity from left to right. (D–F) Microscopically, there is a moderate density of neurofibrillary tangles and astrocytic tangles in Case A (D), the density is increased in Case B (E), and extremely marked in Case C (F). Original magnification: 350×.

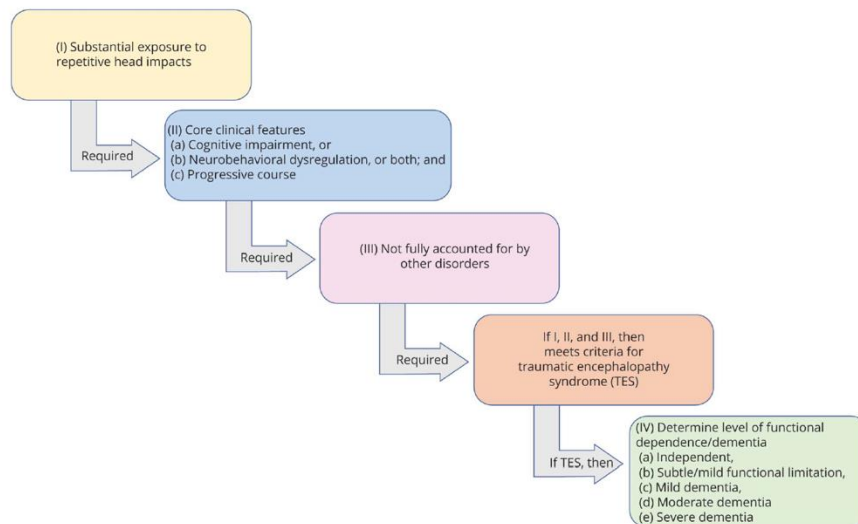


**NCAA•DOD**  
Grand Alliance  
CARE Consortium

# Traumatic Encephalopathy Syndrome (TES)

- NINDS Consensus Conference
- Modified Delphi process

**Figure 1** Stepwise Process for Using the NINDS Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome



The first step is to determine whether the individual meets criteria for substantial exposure to repetitive head impacts (table 1). If yes, core clinical features (table 2) are determined, and if criteria are met, those features must be not fully accounted for by other disorders (table 3). If yes, the TES criteria are met and the final step is to determine level of functional dependence/dementia (table 4). NINDS = National Institute of Neurological Disorders and Stroke; TES = traumatic encephalopathy syndrome.

## VIEWS & REVIEWS

### National Institute of Neurological Disorders and Stroke Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome

Douglas I. Katz, MD, Charles Bernick, MD, David W. Dodick, MD, Jesse Mez, MD, Megan L. Mariani, BS, Charles H. Adler, MD, PhD, Michael L. Alisco, PhD, Laura J. Balcer, MD, Sarah J. Banks, PhD, William B. Barr, PhD, David L. Brody, MD, PhD, Robert C. Cantu, MD, Kristen Dams-O'Connor, PhD, Yonas E. Geda, MD, Barry D. Jordan, MD, Thomas W. McAllister, MD, Elaine R. Peskind, MD, Ronald C. Petersen, MD, PhD, Jennifer V. Wethe, PhD, Ross D. Zafonte, DO, Eimear M. Foley, MS, Debra J. Babcock, MD, PhD, Walter J. Koroshetz, MD, Yorghos Tripodis, PhD, Ann C. McKee, MD, Martha E. Shenton, PhD, Jeffrey L. Cummings, MD, Eric M. Reiman, MD, and Robert A. Stern, PhD

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**Table 1** Primary Diagnostic Criteria for TES: I. Substantial Exposure to Repetitive Head Impacts

History of substantial exposure to repetitive impacts to the head is required. These impacts may or may not have been associated with clinical symptoms or signs of concussion or TBI. Individuals should be screened for multiple possible sources of exposure over a lifetime. Examples of sources of substantial exposure to RHIs include the following:

**Involvement in high-exposure contact or collision sports** such as (but not limited to) boxing, American (tackle) football, ice hockey, soccer, rugby, professional wrestling, mixed martial arts, and some other sports with high risk of exposure to RHIs (e.g., motocross and bull riding).

For American football, a minimum of 5 y of organized play is required. This minimum should include ≥2 y at the high school level or beyond. [The inclusion of level of play (i.e., high school) is based on clinical judgment, with limited evidence]. Nearly all of the participants in a published study establishing the 5-y threshold played at least high school level football<sup>1</sup>

Exposure risk thresholds for other contact or collision sports, or combinations of contact/collision sports, have not yet been established but should be a substantial number of years (e.g., ≥ 5 y) at a level of play involving routine RHIs.

**Military service involving RHIs**, including (but not limited to) combat exposure to multiple blast and other explosions, noncombat exposure to explosions (including breacher training—blasting and forced opening of locked doors), or multiple blows to the head over an extended period of time (e.g., pugil stick training—repeated blows with a padded military training weapon).

Exposure risk thresholds for military service have not yet been established.

**Other sources involving multiple head impacts** over an extended period of time, including (but not limited to) domestic violence (or intimate partner violence), head banging, and vocational activities such as breaching locked doors and other barriers by first responders.

Exposure risk thresholds for other sources have not yet been established.

Abbreviations: RHI = repetitive head impact; TBI = traumatic brain injury; TES = traumatic encephalopathy syndrome.



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# Key Questions

- What is the level of impact exposure?
  - Across sports, gender, age, level of play
- Is there an injury threshold?
  - Variable across individuals?
  - Are there injury-specific biomechanical components?
- Does context matter?
  - Past concussions, recent impact history
- How good are we at identifying “injury”
  - Is concussion the appropriate metric?



# BIOMARKERS OF ACUTE CONCUSSION

## ACUTE ELEVATION IN GFAP & UCH-L1

JAMA Network | Open

Original Investigation | Neurology

### Association of Blood Biomarkers With Acute Sport-Related Concussion in Collegiate Athletes

Findings From the NCAA and Department of Defense CARE Consortium

Michael McCrea, PhD, ABPP; Steven P. Broglio, PhD; Thomas W. McAllister, MD; Jessica Gill, PhD; Christopher C. Giza, MD; Daniel L. Huber, MPH; Jaroslaw Harezlak, PhD; Kenneth L. Cameron, PhD; Megan N. Houston, PhD; Gerald McGinty, DPT; Jonathan C. Jackson, MD; Kevin Guskiewicz, PhD; Jason Mihalik, PhD; M. Alison Brooks, MD, MPH; Stephan Duma, PhD; Steven Rowson, PhD; Lindsay D. Nelson, PhD; Paul Pasquina, MD; Timothy B. Meier, PhD; and the CARE Consortium Investigators

#### Abstract

**IMPORTANCE** There is potential scientific and clinical value in validation of objective biomarkers for sport-related concussion (SRC).

**OBJECTIVE** To investigate the association of acute-phase blood biomarker levels with SRC in collegiate athletes.

**DESIGN, SETTING, AND PARTICIPANTS** This multicenter, prospective, case-control study was conducted by the National Collegiate Athletic Association (NCAA) and the US Department of Defense Concussion Assessment, Research, and Education (CARE) Consortium from February 20, 2015, to May 31, 2018, at 6 CARE Advanced Research Core sites. A total of 504 collegiate athletes with concussion, contact sport control athletes, and non-contact sport control athletes completed clinical testing and blood collection at preseason baseline, the acute postinjury period, 24 to 48 hours after injury, the point of reporting being asymptomatic, and 7 days after return to play. Data analysis was conducted from March 1 to November 30, 2019.

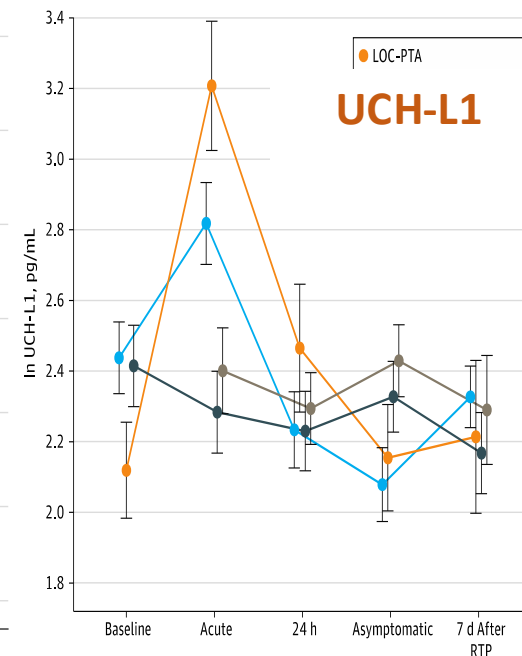
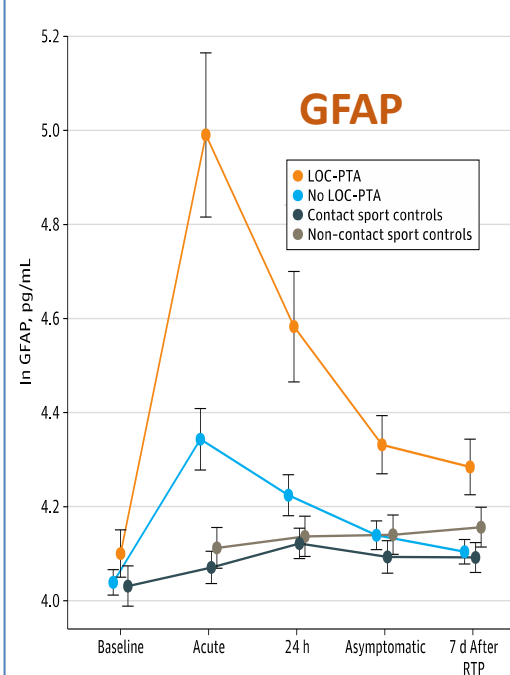
**MAIN OUTCOMES AND MEASURES** Glial fibrillary acidic protein (GFAP), ubiquitin C-terminal hydrolase-L1 (UCH-L1), neurofilament light chain, and tau were quantified using the Quanterix Simoa multiplex assay. Clinical outcome measures included the Sport Concussion Assessment Tool-Third Edition (SCAT-3) symptom evaluation, Standardized Assessment of Concussion, Balance Error Scoring System, and Brief Symptom Inventory 18.

#### Key Points

**Question** Is sport-related concussion associated with levels of traumatic brain injury biomarkers in collegiate athletes?

**Findings** In this case-control study of 504 collegiate athletes with concussion, contact sport control athletes, and non-contact sport athletes, the athletes with concussion had significant elevations in multiple traumatic brain injury biomarkers compared with preseason baseline and with 2 groups of control athletes without concussion during the acute postinjury period.

**Meaning** These results suggest that blood biomarkers can be used as research tools to inform the underlying pathophysiological mechanism of concussion and provide additional support for future studies to optimize and validate biomarkers for potential clinical use in sport-related concussion.



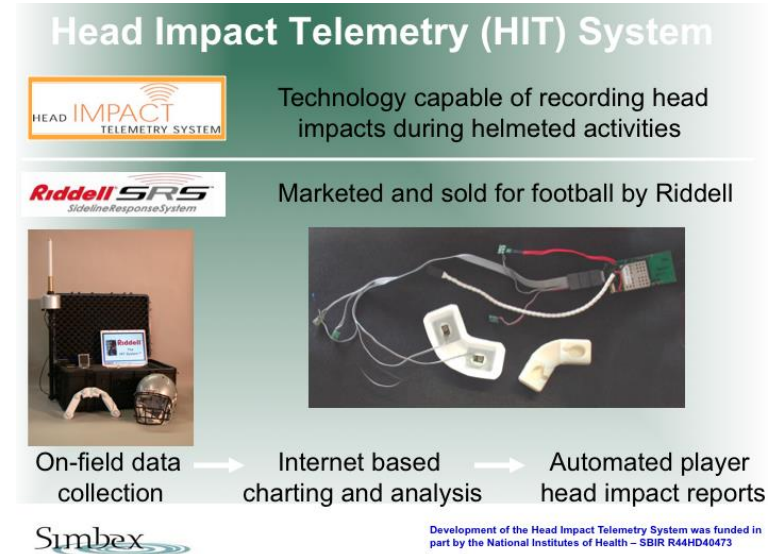
ACUTE BIOMARKERS CORRELATE WITH CLINICAL SEVERITY, RECOVERY, RTP



NCAA-DOD  
Grand Alliance  
CARE Consortium

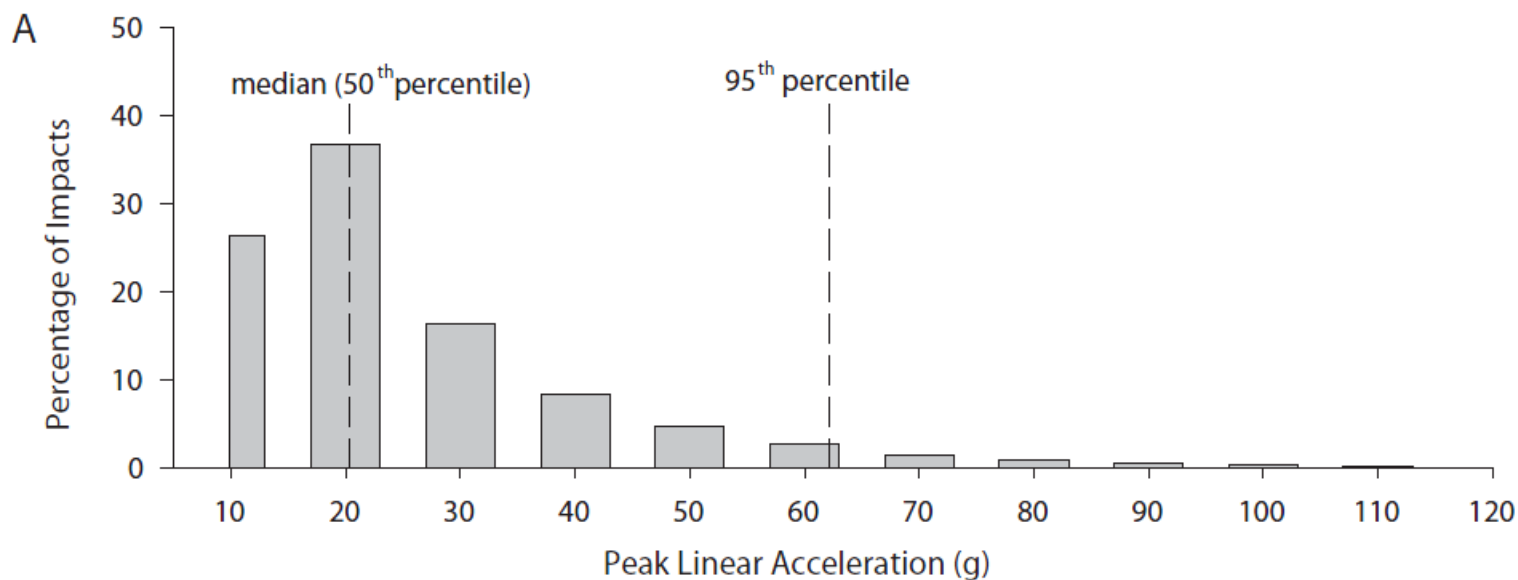
# “Career” Exposure to Repetitive Head Impacts

- ~500 hits over 5 years of youth football
- ~3000 hits over 4 years of high school
- ~5000 hits over 4 years of college
- ~8500 total over 13 year amateur “career”
- ~1200 per year of NFL career
- Adapted from Broglio et al.(2011) *J of Neurotrauma*; Bailes et al (2013) *J of Neurosurgery*; Daniel et al. (2012) *Ann Biomed Eng* 40:976-981



# Exposure

(n=254, Impacts = 184,000)



Journal of Athletic Training 2010;45(6):549-559  
© by the National Athletic Trainers' Association, Inc.  
www.nata.org/jat

original research

~500 -1500 impacts per season

## Frequency and Location of Head Impact Exposures in Individual Collegiate Football Players

Joseph J. Crisco, PhD\*; Russell Fiore, MEd, ATC†; Jonathan G. Beckwith, MS‡; Jeffrey J. Chu, MS‡; Per Gunnar Brolinson, DO§; Stefan Duma, PhD||; Thomas W. McAllister, MD¶; Ann-Christine Duhaime, MD#; Richard M. Greenwald, PhD‡\*\*



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# 100g Hit and 49g Hit



Slide courtesy of Jonathan Beckwith, Simbex  
Video courtesy of Oklahoma Univ. for Research Purposes

**Linear Acceleration: 44.2 g**  
**Rotational Acceleration: 1624.51 rad/ss**  
**Athlete: #75**



Slide courtesy of Drs. Brian Stemper and Alok Shaw, CARE Head Impact Measurement Core  
Medical College of Wisconsin  
Video courtesy of University of Wisconsin for Research Purposes

# Revelations

## Long-Term Cognitive and Neuropsychiatric Consequences of Repetitive Concussion and Head-Impact Exposure

Thomas McAllister, MD\*; Michael McCrea, PhD, ABPP†

\*Department of Psychiatry, Indiana University School of Medicine, Indianapolis; †Department of Neurosurgery, Medical College of Wisconsin, Milwaukee

- Lots of hits
- No clear concussion “threshold”
  - some after modest hits
  - lots of really hard hits without concussion dx
- Not always clear which impact causes concussion
  - Not always a “smoking gun”
- About a third of diagnosed concussions are “late reporters”



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# TBI and Relative Risk of Psychiatric Disorders...

- Several estimates suggest that 40-50% of those who sustain a TBI will develop a *new* neuropsychiatric disorder.
  - Depression
  - Anxiety
  - PTSD
  - Somatoform syndromes

## Article

### Axis I and II Psychiatric Disorders After Traumatic Brain Injury: A 30-Year Follow-Up Study

Salla Koponen, M.D.

Tero Taiminen, M.D., M.Sc.D.

Raija Portin, Ph.D.

Leena Himanen, M.A.

Heli Isoniemi, M.D.

Hanna Heinonen, M.D.

Susanna Hinkka, Ph.Lic., M.Sc.

Olli Tenovu, M.D., M.Sc.D

**Objective:** Patients who had suffered traumatic brain injury were evaluated to determine the occurrence of psychiatric disorders during a 30-year follow-up.

**Method:** Sixty patients were assessed on average 30 years after traumatic brain injury. DSM-IV axis I disorders were diagnosed on a clinical basis with the aid of the Schedules for Clinical Assessment in Neuropsychiatry (version 2.1), and axis II disorders were diagnosed with the Structured Clinical Interview for DSM-III-R Personality Disorders. Cognitive impairment was measured with a neuropsychological test battery and the Mini-Mental State Examination.

**Results:** Of the 60 patients, 29 (48.3%) had had an axis I disorder that began after traumatic brain injury, and 37 (61.7%) had had an axis I disorder during their lifetimes. The most common novel disorders after traumatic brain injury were ma-

jor depression (26.7%), alcohol abuse or dependence (11.7%), panic disorder (8.3%), specific phobia (8.3%), and psychotic disorders (6.7%). Fourteen patients (23.3%) had at least one personality disorder. The most prevalent individual disorders were avoidant (15.0%), paranoid (8.3%), and schizoid (6.7%) personality disorders. Nine patients (15.0%) had DSM-III-R organic personality syndrome.

**Conclusions:** The results suggest that traumatic brain injury may cause decades-lasting vulnerability to psychiatric illness in some individuals. Traumatic brain injury seems to make patients particularly susceptible to depressive episodes, delusional disorder, and personality disturbances. The high rate of psychiatric disorders found in this study emphasizes the importance of psychiatric follow-up after traumatic brain injury.

(Am J Psychiatry 2002; 159:1315-1321)



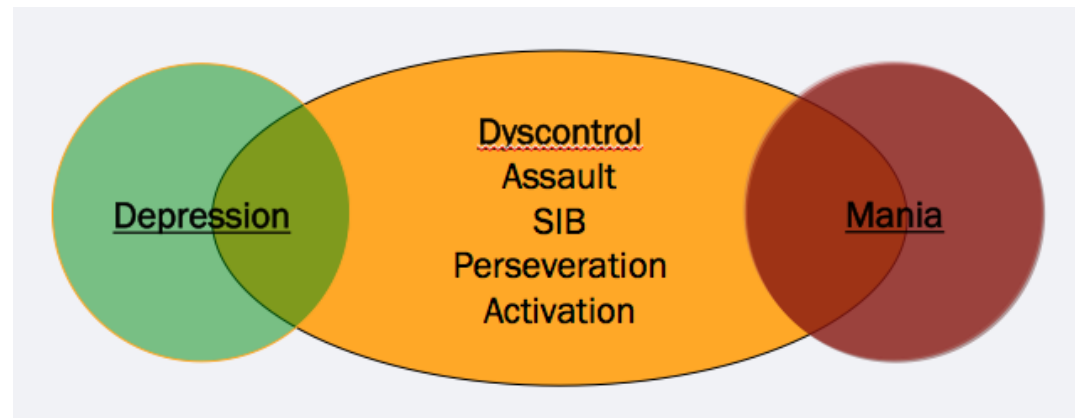
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# Depression and TBI

- Most common psychiatric disorder after TBI
- Impacts short and long-term outcome
  - *Cognition*
  - *Quality of Life*
  - *Vocational Function*
  - *Social Function*



# Neural Network of Mood Regulation

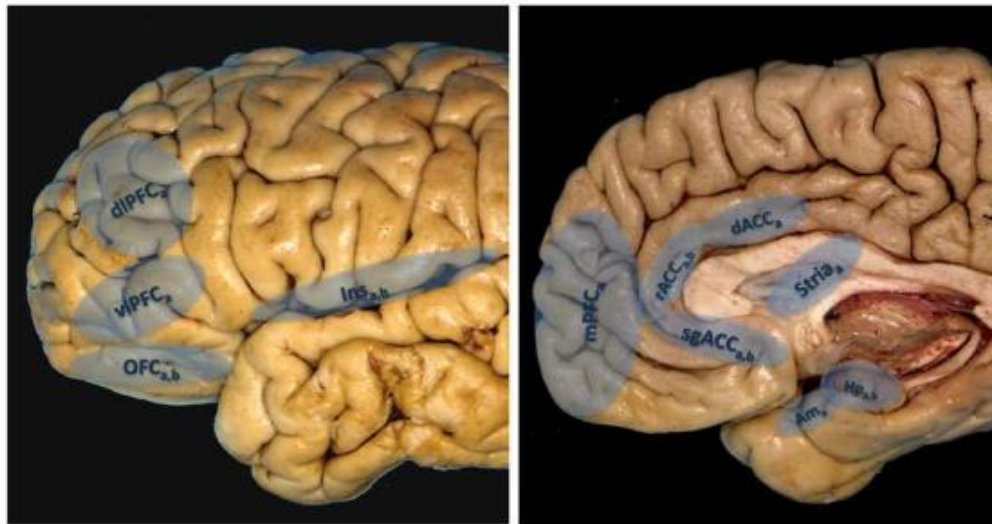


**Figure 1.** Brain regions implicated in structural and functional studies as potential illness and treatment biomarkers in major depressive disorder. (A) Lateral view of the cortical surface of the brain, showing the dorsolateral prefrontal cortex (dlPFC), ventrolateral PFC (vlPFC), orbitofrontal cortex (OFC), and insular cortex (ins). (B) Mid-sagittal view of the brain, showing the medial PFC (mPFC), anterior cingulate cortex (subgenual (sgACC), rostral (rACC), dorsal (dACC)), striatum (stria), amygdala (Am), and hippocampus (Hp). Regions are implicated as a potential (a) illness or (b) treatment biomarker. Of note, the striatum, amygdala, and insula are deep to the region indicated and are not seen on the specimen. Photographs of anatomical specimens courtesy of T.P. Naidich, M.E. Fowkes, and C.Y. Tang.

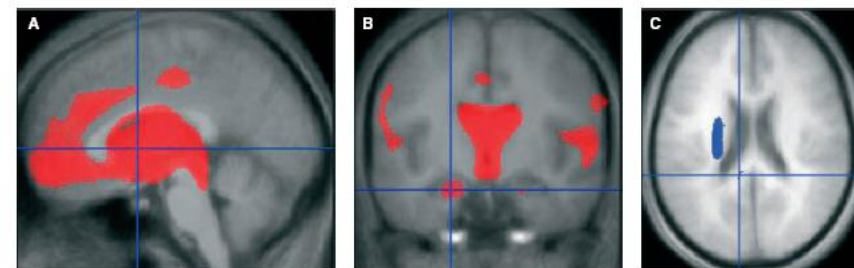
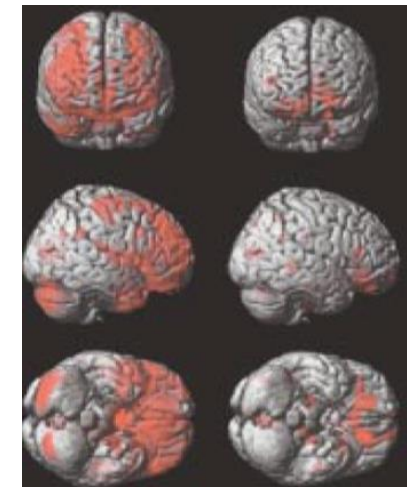


**Fig. 2** Representative results from VBM analysis. Red indicates areas of decreased grey matter density. Blue indicates areas of decreased white matter density. Images thresholded at FDR  $P < 0.01$  (grey matter) and FDR  $P < 0.05$  (white matter) (A) septal nuclei, diagonal band of Broca, nucleus basalis of Meynert ( $-24\ 2$ ), (B) bilateral hippocampal formation ( $-21\ -11\ -22$ ) and (C) medial pathway ( $-8\ -41\ 21$ ) (lateral capsular pathway abnormality also visible).

# Vignette: Neurobehavioral Complications After Sport-related Concussion

- 21-year old collegiate soccer player with 3<sup>rd</sup> concussion
  - Poor recovery trajectory after 10 months
    - Fatigue, headache, recurrent symptoms with exertion, disturbed sleep, academic and cognitive difficulties
  - Multiple sports medicine specialists and neurodiagnostic procedures
  - Effect of injury on his life (social network; identity; family)
  - Treatment

# Neuropsychiatric Evaluation

- Accurate history
  - Psychological trauma history
  - Biomechanical trauma history
  - Trajectory of symptoms
  - Meaning of the injury & the head that is injured
- Attribution pitfalls
  - Exposure not the same as cause
  - Non-specific symptoms can be final common pathway for lots of things
- Goodness of fit:
  - Profile of injury vs. presenting neurobehavioral profile
  - Timecourse



# Treatment: When Using Medications

- No FDA approved meds for TBI-specific conditions
  - Most clinicians favor use of conventional algorithms with some adaptation
- Consider lower/slower approach
- Have a hypothesis about what you are treating
- Adequate trial length
- Be alert to effects on
  - Cognition
  - Arousal
  - Sleep
  - Neurological function (gait, balance, strength, coordination)
- Be alert to other co-morbid conditions



# When Using Psychotherapy/Cognitive Therapies

- Know the individual's cognitive capacity
  - Adjust therapy accordingly
- May need:
  - Slower pace
  - More repetition
  - Know where the minefields are
- Be alert to other co-morbid conditions



# Summary: Evaluation

- Problems in the neurobehavioral domain (mood, emotions, behavior, cognition) are a major challenge to most survivors and family/caregivers
- Profile of injury predicts neuropsychiatric sequelae
- Clinical assessment and conclusions should make sense
  - “Goodness of fit” between complaints, deficits, and injury profile
- Understand “the head that is injured”....

