

DEPARTMENT OF DEFENSE
BLAST INJURY RESEARCH PROGRAM COORDINATING OFFICE

Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

3-5 NOVEMBER 2015

Chronic Traumatic Encephalopathy

Contact Sports and Blast Injuries

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FRONTLINE.

87 Deceased NFL Players Test Positive for Brain Disease

September 18, 2015, 10:27 am ET by Jason M.

**Family donates former
NHLer Todd Ewen's brain
to concussion study**

SEPT. 28, 2015



**Joint Chiefs chairman seeks
brain-injury limit**

9/28/2009



**New CDC Report Urges
Athletes to Report
Concussions**

9-22-15



**N.F.L. Acknowledges Long-Term
Concussion Effects**

By ALAN SCHWARZ, December 21, 2009

**As Worries Rise and Players Flee, a
Missouri School Board Cuts Football**

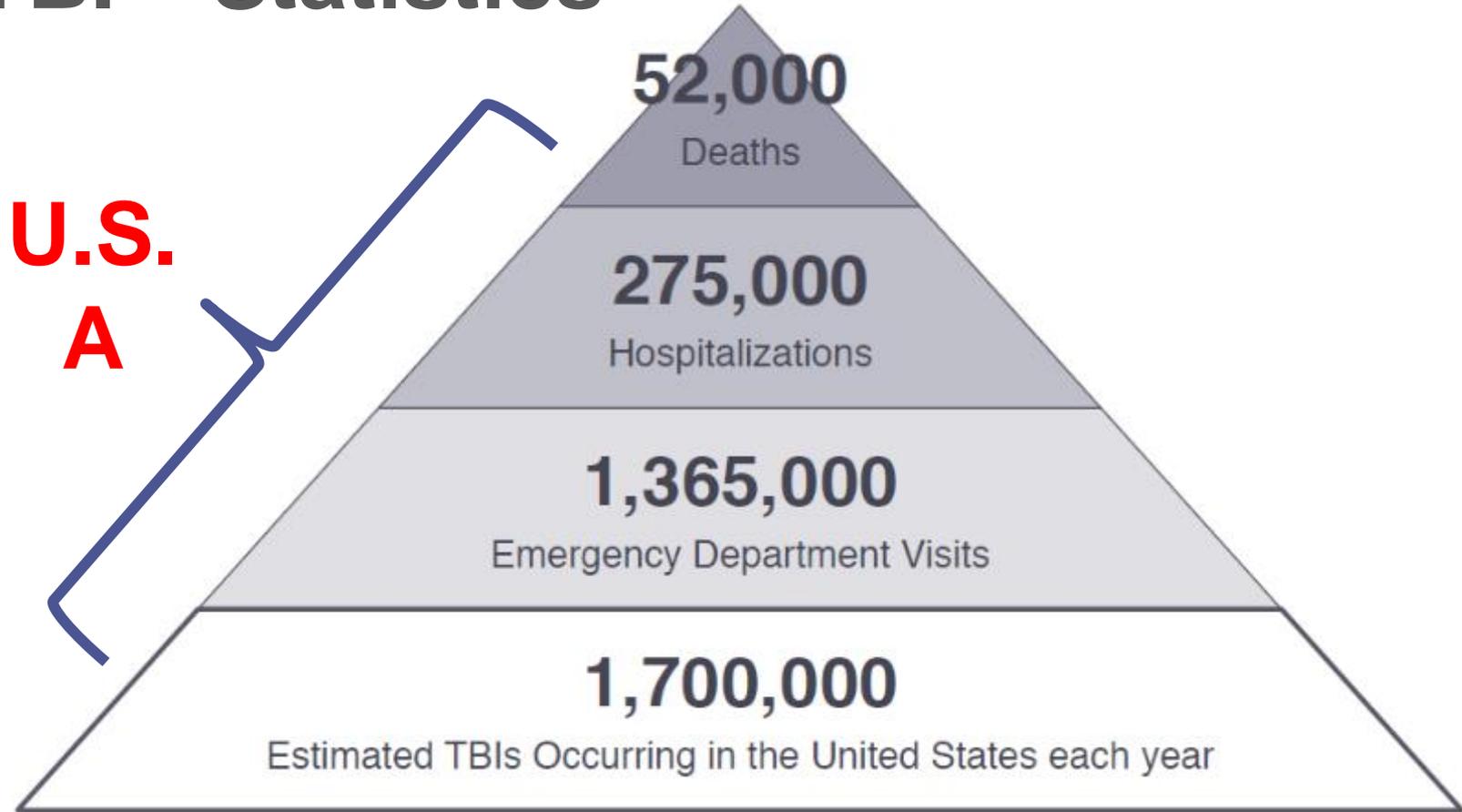
By [KEN BELSON](#) SEPT. 28, 2015

The New York Times



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

TBI – Statistics



Estimated Concussions Worldwide 51 Million/Year



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Study: Warriors may not recover from concussions as quickly as athletes do

By Jesse Bogan
St. Louis Post-Dispatch (Tribune News Service)
Published: March 5, 2015



ST. LOUIS (Tribune News Service) — A fifth of all servicemembers who served in Iraq and Afghanistan suffered concussions, mainly from being close to explosive blasts from roadside bombs. Doctors often refer to sports injuries to seek treatment options for the so-called signature wound of the long wars.



But new research signals that war-zone concussions are much different from concussions that happen playing football or hockey. Most athletes quickly recover brain function. Most soldiers and Marines do not, according to a study released Wednesday in *Brain: A Journal of Neurology*.

The findings will likely add to military discussions about who is fit to go back into the fight after suffering a concussion. And perhaps the recognition could lessen the stigma of mental health issues.

"We should be paying very careful attention to depression-type symptoms immediately after a concussion," says an associate professor of neurology at Washington State University.

Done in tandem with the Department of Defense, researchers followed 38 servicemembers who didn't pass field tests after surviving blasts in 2012 in southern Afghanistan. Sent to Camp Leatherneck or Kandahar Air Field for treatment and rest, data were collected from their cases within a few days of injury.

March 5, 2015

”..... that war-zone concussions are much different from concussions than happen playing football or hockey. **Most athletes quickly recover brain function. Most soldiers and Marines do not**, according to a study in *Brain: A Journal of Neurology*.”



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Comparison of MTBI (Concussions)

SPORTS

	NFL*	NHL*	High School*
# of Participants	1,696	690	1,050,000
Ave Concussions per year	144	71	63,750
Annual % per year	8.5%	10.3%	5.75%

MILITARY

	US Military ¹
Total # Deployed up until Oct 2007	1.6¹ million
Estimated # of Concussions	304,000
Post Deployment Survey Results	19%¹

* Approximation

¹RAND Corp, 2008

Ref: Pellman, EJ, Concussion in Football, Neurosurg Focus:21 (4) E12, 2006, Wennberg, RA, Concussion Incidence and Time Lost from Play in the NHL during the Past 10 years, Can J Neurol Sci, (35) 2008, Collins, M, Examining Concussion Rates and RTP in HS Football Players Wearing Newer Helmet Technology: A 3-yr Study, Neurosurgery, (58) No 2 Feb 2006

¹ RAND Corporation April 17, 2008 Invisible Wounds of War Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery

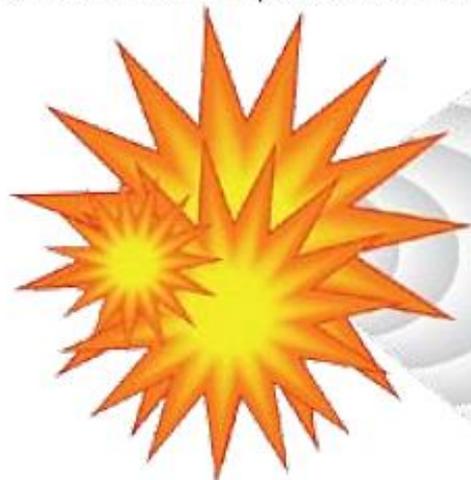


Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Blast-induced brain injury

Traumatic brain injury accounts for nearly 60 percent of all injuries among U.S. troops. A subset includes blast-induced injuries that could cause serious problems, even if shrapnel from the explosion never hits the soldier.

A shock wave from an explosion hits a person and moves through the body at a different speed than through air.



Body armor helps deflect some of the shock wave, preventing it from injuring internal organs, but does not protect the brain.



The wave propagates through tissues, bone and organs of different densities at different speeds. This makes the organs, such as the brain, more susceptible to tissue damage.

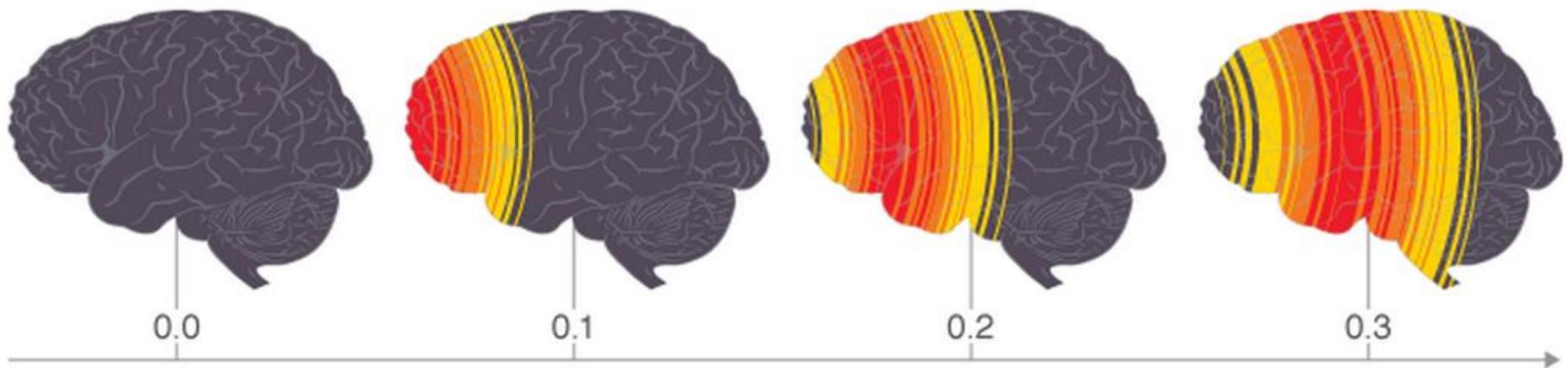
Blast-induced brain injuries include brain swelling and subarachnoid hemorrhage, which happens when a blood vessel just outside the brain spasms, putting pressure on the brain and starving it of oxygen and nutrients.



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Blast in the Brain

Studies show that the key mechanical factors associated with brain injury are an increase in intracranial pressure and the brain's motion relative to the skull. The blast wave, or overpressure, affects the brain immediately upon impact with the skull. Pressure in the brain returns to normal after only a few milliseconds, but brain motion can occur for hundreds of milliseconds after impact.



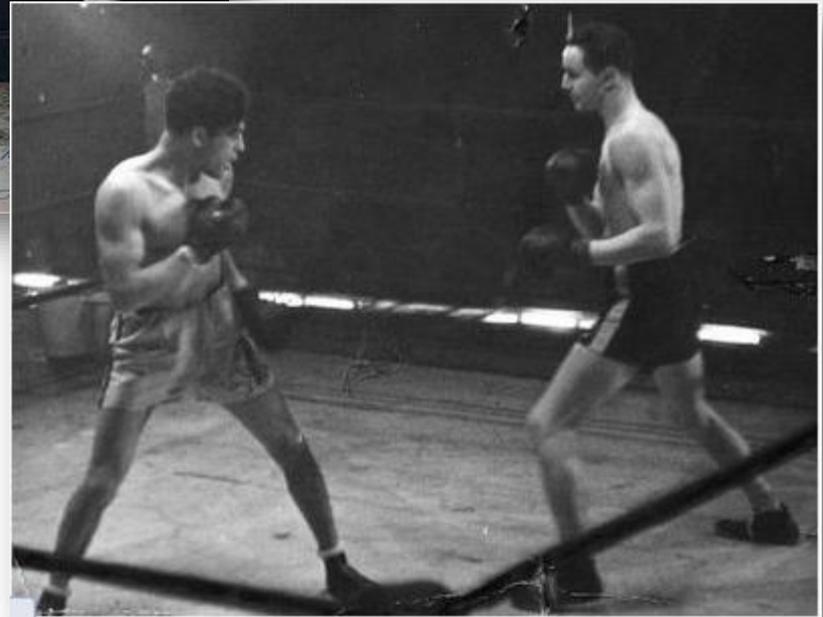
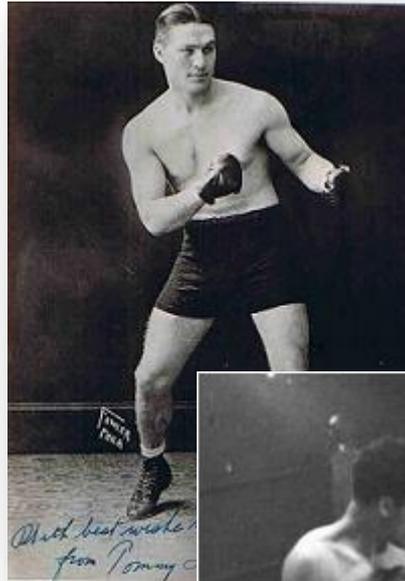
BLAST WAVE TRANSMISSION

in milliseconds



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

- Dr. Harrison Stanford Martland first described **Dementia Pugilistica** in 1928
- Symptoms only for diagnosis (no pathologic diagnosis performed)
 - Tremors
 - Slowed movement
 - Confusion
 - Speech problems



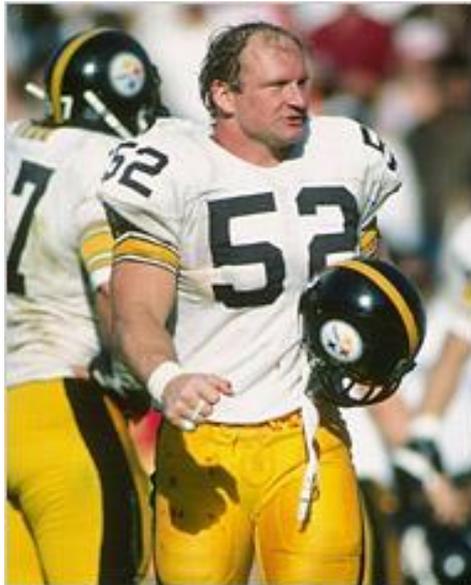


Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

CHRONIC TRAUMATIC ENCEPHALOPATHY IN A NATIONAL FOOTBALL LEAGUE PLAYER

**Bennet I. Omalu, M.D.,
M.P.H.**

Departments of Pathology
and Epidemiology,
University of Pittsburgh,
Pittsburgh, Pennsylvania



**Mike Webster
Steelers Center
1974-88**

OBJECTIVE: We present the results of the autopsy of a retired professional football player that revealed neuropathological changes consistent with long-term repetitive concussive brain injury. This case draws attention to the need for further studies in the cohort of retired National Football League players to elucidate the neuropathological sequelae of repeated mild traumatic brain injury in professional football.

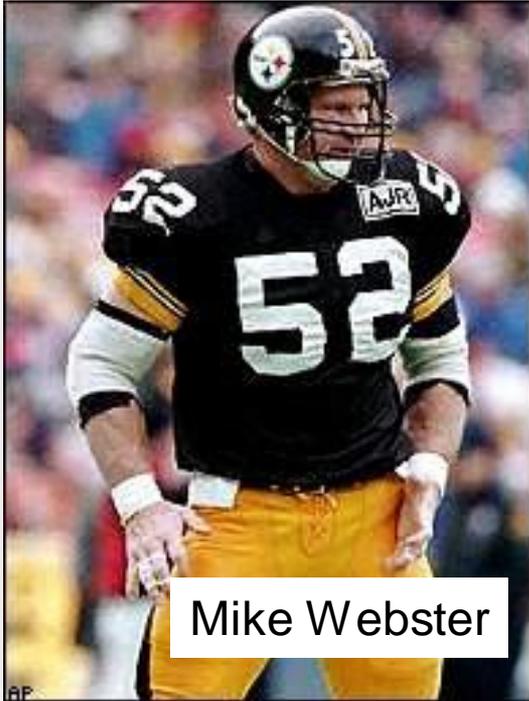
METHODS: The patient's premortem medical history included symptoms of cognitive impairment, a mood disorder, and parkinsonian symptoms. There was no family history of Alzheimer's disease or any other head trauma outside football. A complete autopsy with a comprehensive neuropathological examination was performed on the retired National Football League player approximately 12 years after retirement. He died suddenly as a result of coronary atherosclerotic disease. Studies included determination of apolipoprotein E genotype.

RESULTS: Autopsy confirmed the presence of coronary atherosclerotic disease with dilated cardiomyopathy. The brain demonstrated no cortical atrophy, cortical contusion, hemorrhage, or infarcts. The substantia nigra revealed mild pallor with mild dropout of pigmented neurons. There was mild neuronal dropout in the frontal, parietal, and temporal neocortex. Chronic traumatic encephalopathy was evident with many diffuse amyloid plaques as well as sparse neurofibrillary tangles and τ -positive neuritic threads in neocortical areas. There were no neurofibrillary tangles or neuropil

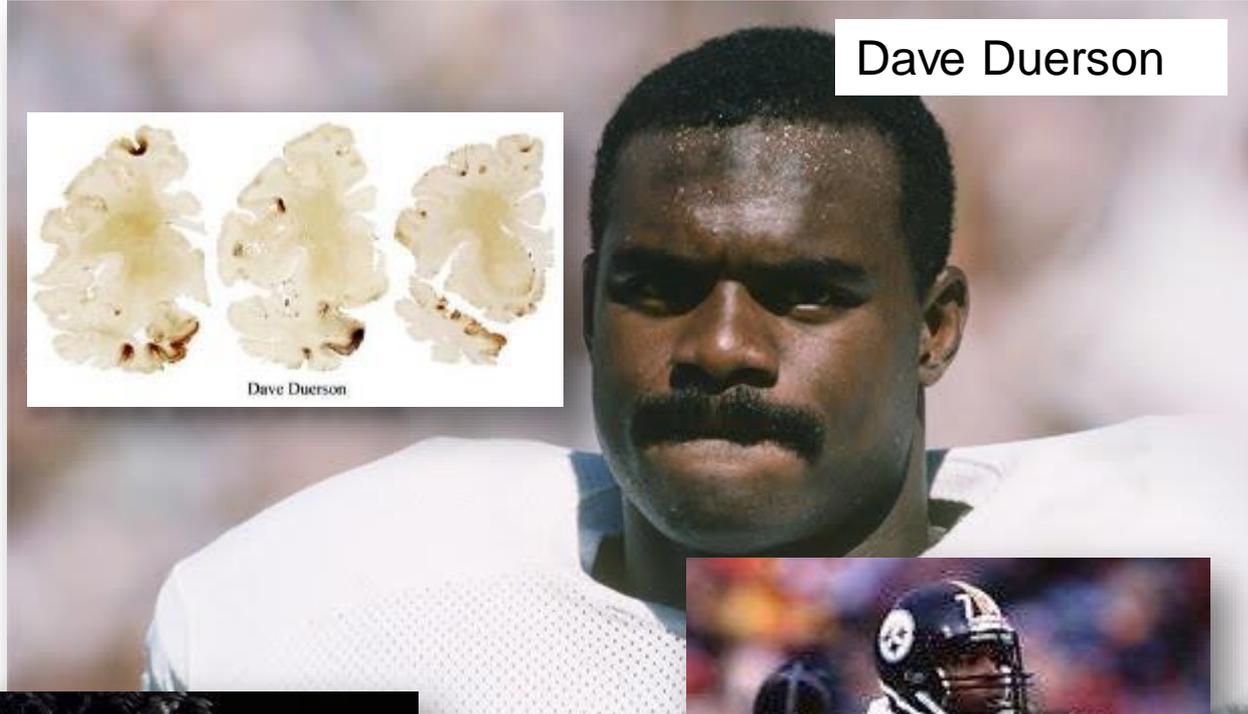
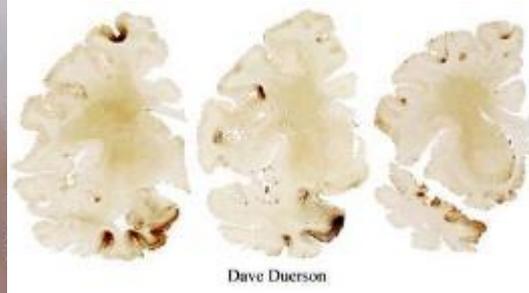
Neurosurgery 57:128-134, 2005



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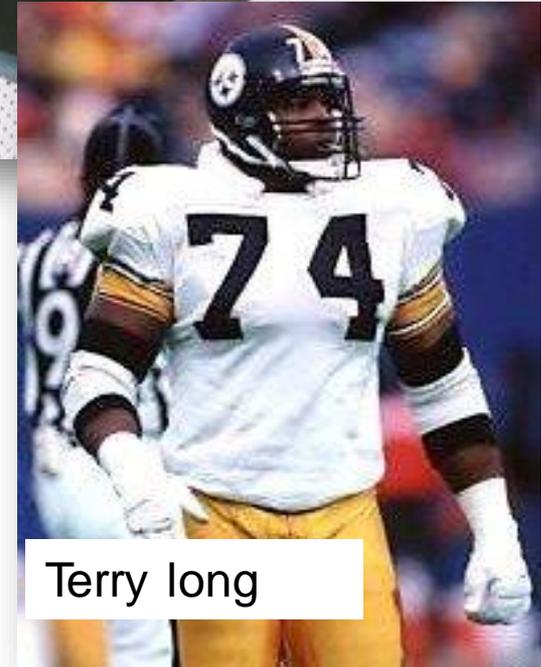
Mike Webster



Dave Duerson



Junior Seau



Terry Long



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

FACES OF CTE

THESE PLAYERS SHOWED SIGNS OF BRAIN DEGENERATION POSTMORTEM



NAME AND POSITION	Mike Webster Center	Justin Strzelczyk Offensive lineman	Andre Waters Defensive back	Chris Henry Wide receiver	Dave Duerson Defensive back	Junior Seau Linebacker
AGE	50	36	44	26	50	43
CAUSE OF DEATH	Heart attack 2002	Car chase 2004	Suicide 2006	Accident 2009	Suicide 2011	Suicide 2012
TEAM	Steelers, Chiefs	Steelers	Eagles, Cardinals	Bengals	Bears, Giants, Cardinals	Chargers, Dolphins, Patriots
SEASONS PLAYED	17 seasons; 4 Super Bowl wins	9 seasons	12 seasons; All-Pro in 1991	5 seasons	11 seasons; 4 Pro Bowls	20 seasons; 12 Pro Bowls



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J Neuropathol Exp Neurol. 2009 July ; 68(7): 709–735. doi:10.1097/NEN.0b013e3181a9d503.

Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy following Repetitive Head Injury

Ann C. McKee, MD^{1,2,3,4}, Robert C. Cantu, MD^{3,5,6,7}, Christopher J. Nowinski, AB^{3,5}, E. Tessa Hedley-Whyte, MD⁸, Brandon E. Gavett, PhD¹, Andrew E. Budson, MD^{1,4}, Veronica E. Santini, MD¹, Hyo-Soon Lee, MD¹, Caroline A. Kubilus^{1,3}, and Robert A. Stern, PhD^{1,3}

¹ Department of Neurology, Boston University School of Medicine, Boston, Massachusetts

² Department of Pathology, Boston University School of Medicine, Boston, Massachusetts

65-year-old control subject

NFL linebacker
John Grimsley

73 year old world champion boxer
with end stage CTE* and dementia

no abnormal tau
protein deposition



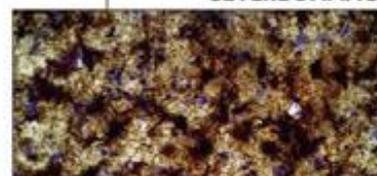
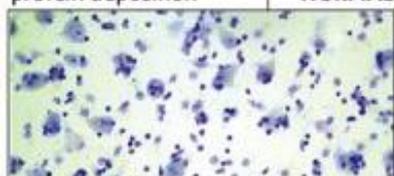
No abnormal tau
protein deposition

NORMAL

Abundant tau protein

*chronic traumatic
encephalopathy

SEVERE DAMAGE

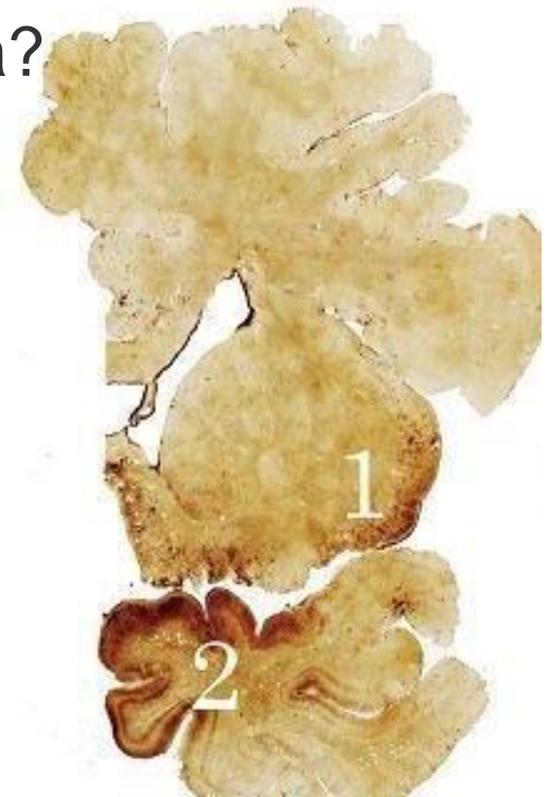




Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

CTE Questions

- What are the Risk Factors?
 - Prior “Priming” of Microglia Cells?
 - Severity and Frequency of Trauma?
 - Age?
 - Genetics (ApoE4)?
- How to Diagnosis?
- How to Treat?
- How to Prevent?
- What is the True Incidence?





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Surgical Neurology International

OPEN ACCESS

Editor-in-Chief:

James I. Ausman, MD, PhD
University of California, Los Angeles, CA, USA

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<http://www.surgicalneurologyint.com>

Review Article

Immunoexcitotoxicity as a central mechanism in chronic traumatic encephalopathy—A unifying hypothesis

Russell L. Blaylock, Joseph Maroon¹

Theoretical Neurosciences, LLC Visiting Professor of Biology, Belhaven University, Jackson, MS 315 Rolling Meadows Rd, Ridgeland, MS 39157, ¹Department of Neurosurgery, Heindl Scholar in Neuroscience, University of Pittsburgh Medical Center, Team Neurosurgeon, The Pittsburgh Steelers

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*Corresponding author

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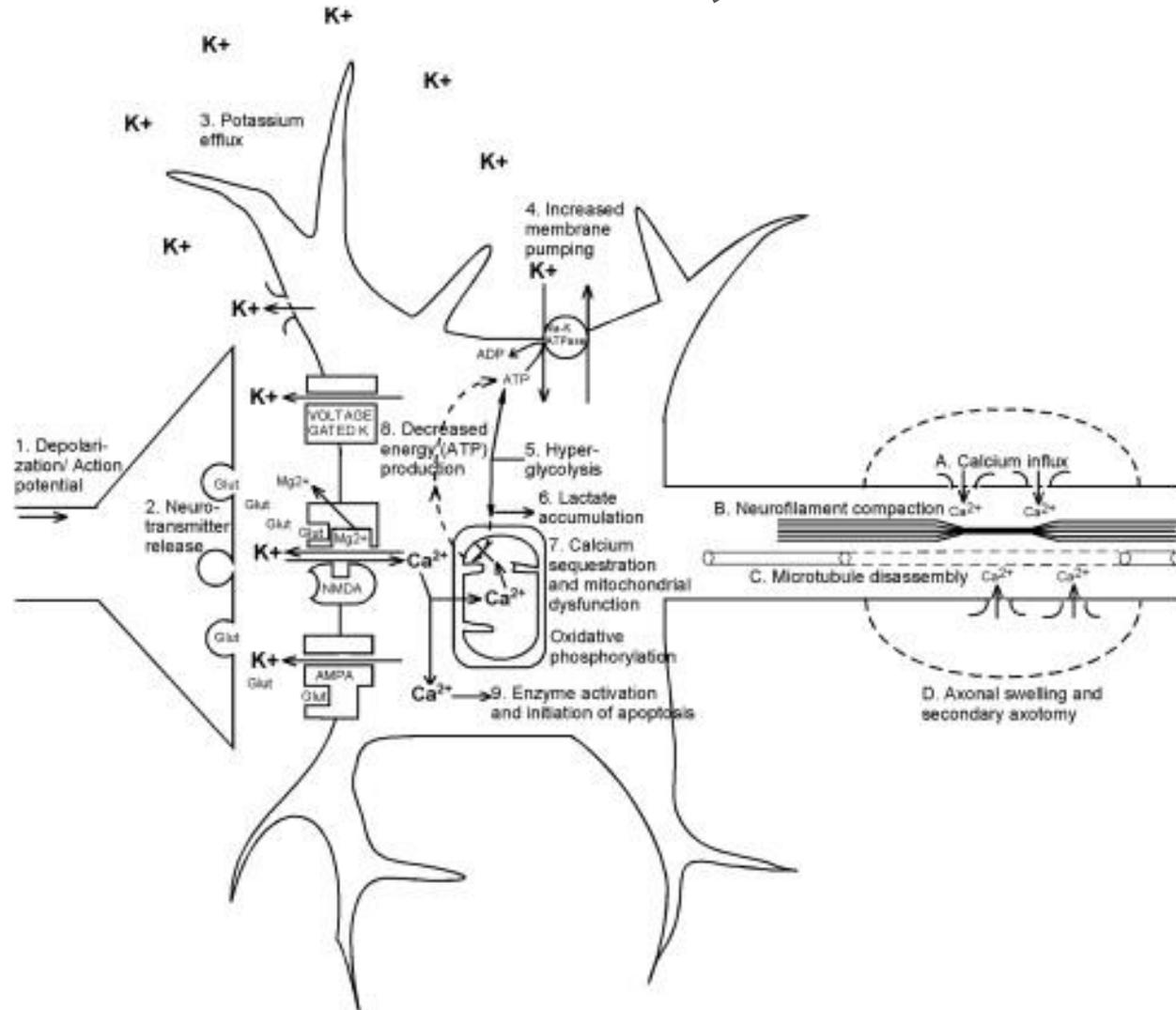
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Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

PATHOGENESIS of Concussion, PTSD and CTE

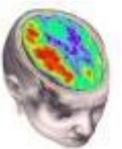
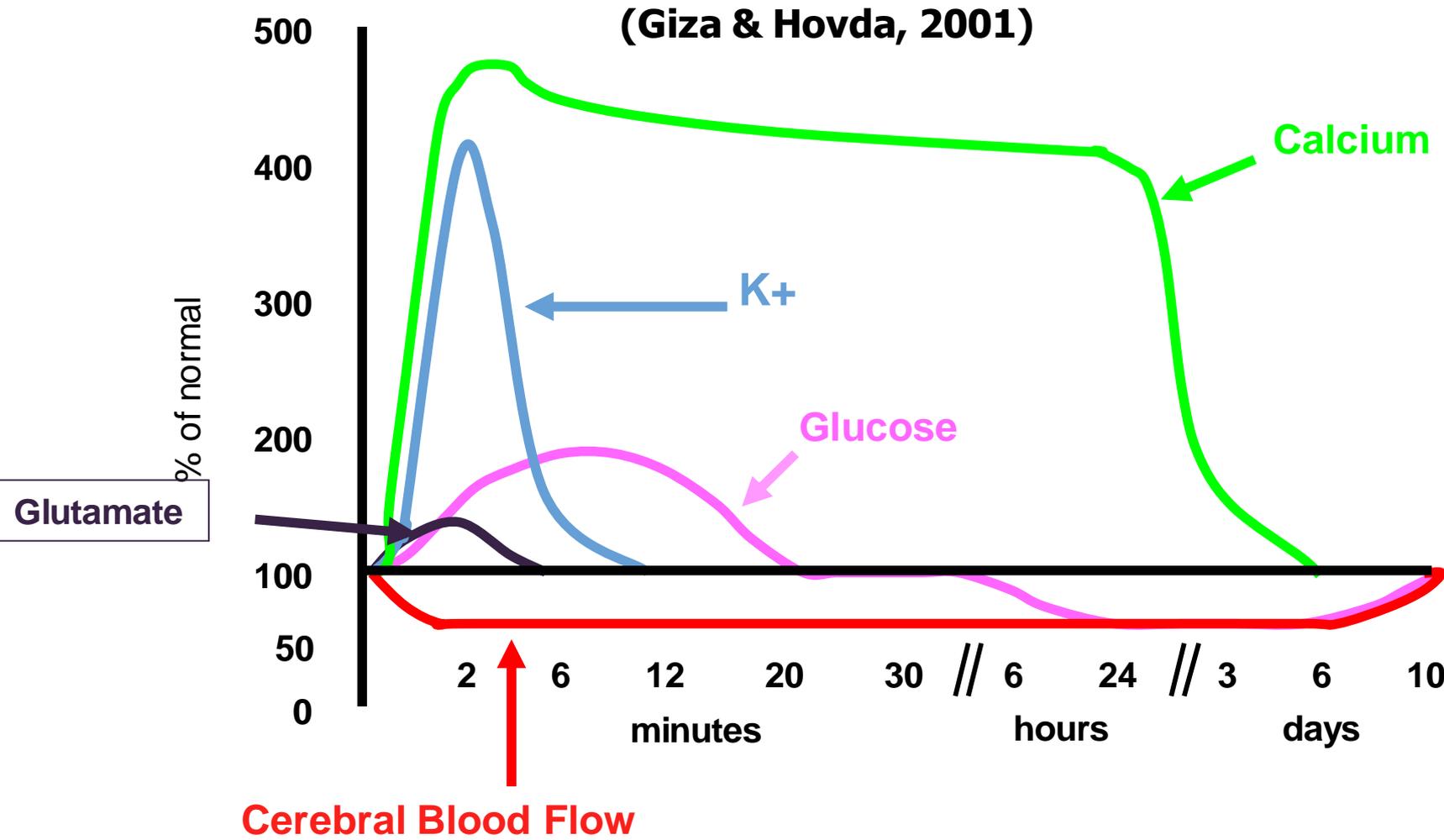
- Metabolic
- Excitotoxic
- Immunologic





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Concussion Metabolic "Mismatch"





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

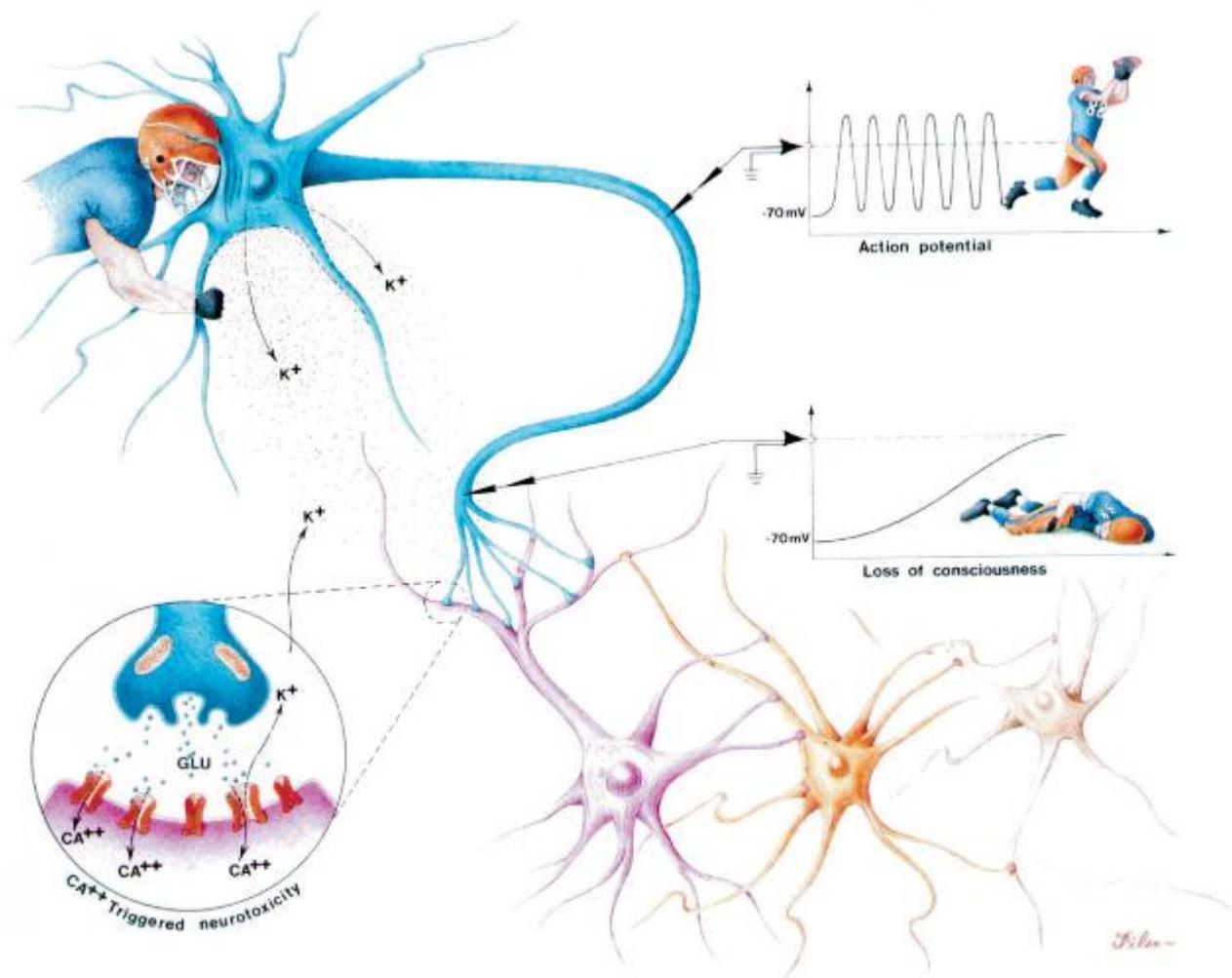


FIGURE 1. Changes in the extracellular potassium concentration after concussion. A percussive injury to nerve cells leads to the rapid release of intracellular potassium (*upper left*). When the extracellular potassium concentration increases beyond the physiological limit of 4 to 5 mmol/L, to levels of 20 to 50 mmol/L and above, inhibition of the action potential and loss of consciousness may occur (*lower right*). This injury-mediated potassium release can initiate a variety of pathways that lead to secondary brain injury. Depolarization of nerve terminals produced by the elevated extracellular potassium concentration can trigger the release of glutamate, resulting in calcium-mediated neurotoxicity (*lower left*).



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

SURGICAL
NEUROLOGY
INTERNATIONAL

AN OPEN ACCESS, INTERNATIONAL JOURNAL OF NEUROSURGERY

Dear Colleague,

SNI has published a paper that will change the course of Neurology and Neurosurgery. After an extensive review of the literature and personal experience in war and sports injuries, Russell Blaylock and Joe Maroon have developed a hypothesis for the development of Chronic Traumatic Encephalopathy extending from concussion to the damage seen after multiple injuries to the brain. This concept is based on a primed

inflammation
can explain
players,
depression
molecular
Immun
messengers
which lead
[in chronic](#)
hypothesis
appear and
published

“This paper will change the course of Neurology and Neurosurgery. After an extensive review of the literature and personal experience in war and sports injuries, Russell Blaylock and Joe Maroon have developed a hypothesis for the development of Chronic Traumatic Encephalopathy from concussion.”

been recently presented. (*JAMA* August 2, 2011-Traumatic Brain Injury...Medical News). This concept will change the understanding of many CNS diseases.

James I Ausman, MD, PhD

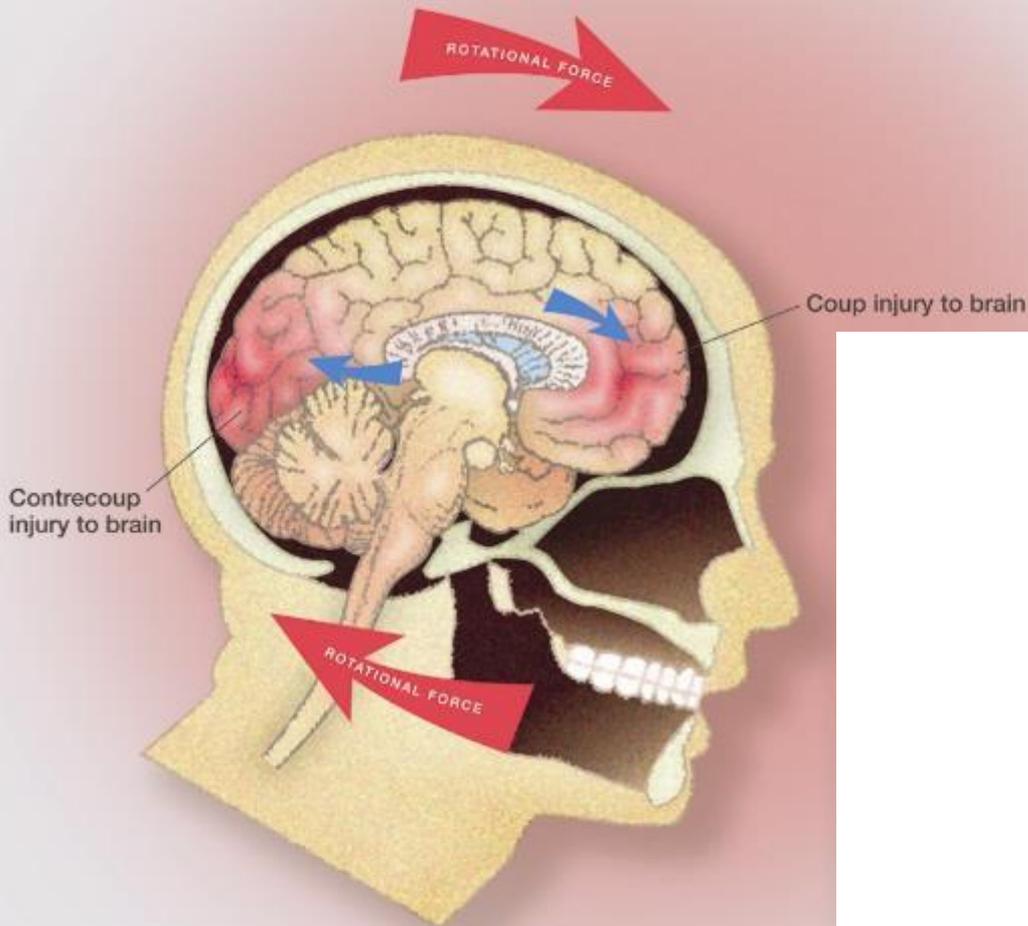
Editor-in-Chief

Surgical Neurology International



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Concussion - Acute Cellular Inflammation



Transient Release of high levels of

- ROS/RNS
- lipid peroxidation products
- Prostaglandins
- nitric oxide

All can then activate microglia

Activation of Microglia Macrophage will stimulate

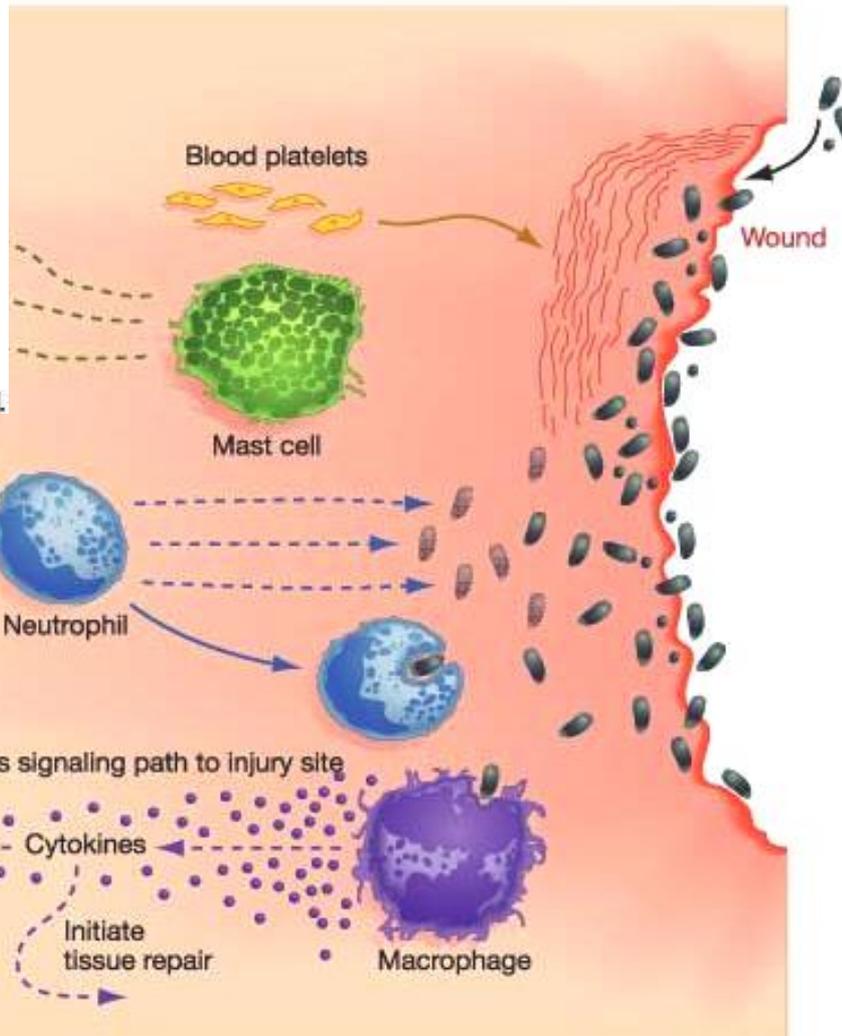
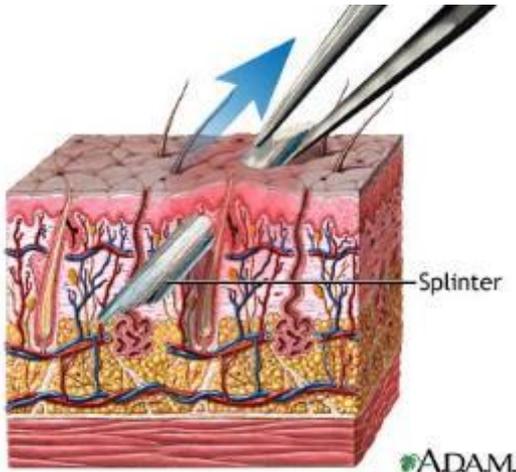
- Immune mediated Inflammation
- Genetic upregulation of chemokines
- \uparrow tumor necrosis factor alpha (TNF α)
- \uparrow NFK-B

Typically Acute Inflammation response will abate and healing will occur



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Immunologic (Inflammatory Response)



1. Bacteria and other pathogens enter wound.
2. Platelets from blood release blood-clotting proteins at wound site.
3. Mast cells secrete factors that mediate vasodilation and vascular constriction. Delivery of blood, plasma, and cells to injured area increases.
4. Neutrophils secrete factors that kill and degrade pathogens.
5. Neutrophils and macrophages remove pathogens by phagocytosis.
6. Macrophages secrete hormones called cytokines that attract immune system cells to the site and activate cells involved in tissue repair.
7. Inflammatory response continues until the foreign material is eliminated and the wound is repaired.



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

*Nature Reviews
Neuroscience* **8**,
57–69 (January
2007)

Microglia-mediated neurotoxicity: uncovering the molecular mechanisms

*Michelle L. Block**, *Luigi Zecca[†]* and *Jau-Shyong Hong**

Abstract | Mounting evidence indicates that microglial activation contributes to neuronal damage in neurodegenerative diseases. Recent studies show that in response to certain environmental toxins and endogenous proteins, microglia can enter an overactivated state and release reactive oxygen species (ROS) that cause neurotoxicity. Pattern recognition receptors

“Microglia overactivated cause neurotoxicity through two mechanisms. First, microglia can initiate neuron damage by recognizing pro-inflammatory stimuli, such as lipopolysaccharide (LPS), becoming activated and producing neurotoxic proinflammatory factors.

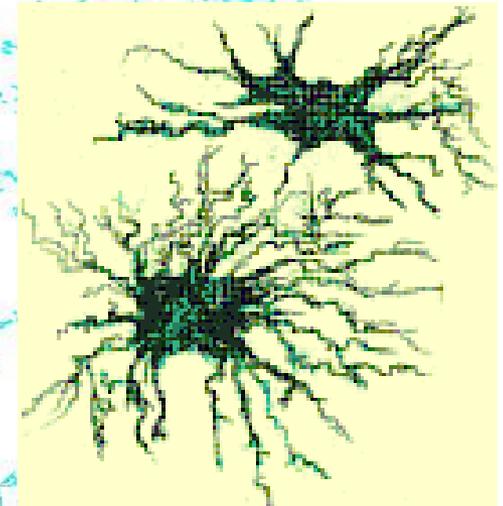
Second, microglia can become overactivated in response to neuronal damage (reactive microgliosis), which is then toxic to neighbouring neurons, resulting in a perpetuating cycle of neuron death. Reactive microgliosis could be an underlying mechanism of progressive neuron damage across numerous neurodegenerative diseases, regardless of the instigating stimuli.”



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Microglia

- Resident Macrophages of CNS
- Primary Active Immune Defense CNS
- 20% of Total Glial Cells
- **Pro-inflammatory** → **Neuro-inflammation**
 - Cytokines – IL-1a, IL-1B, IL-6, TNF-a
 - Chemokines – MCP-1
 - Proteases – Cathepsins, MMP
 - Amyloid Precursor Protein –APP
 - Inflammatory Prostaglandins – PG-1, PG-6





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?



Available online at www.sciencedirect.com



Journal of Psychiatric Research 41 (2007) 744–752

JOURNAL OF
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Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder

Roland von Känel ^{a,b,*}, Urs Hepp ^c, Bernd Kraemer ^c, Rafael Traber ^c,
Marius Keel ^d, Ladislav Mica ^d, Ulrich Schnyder ^c

^a Department of General Internal Medicine, Division of Psychosomatic Medicine, University Hospital//INSELSPITAL,

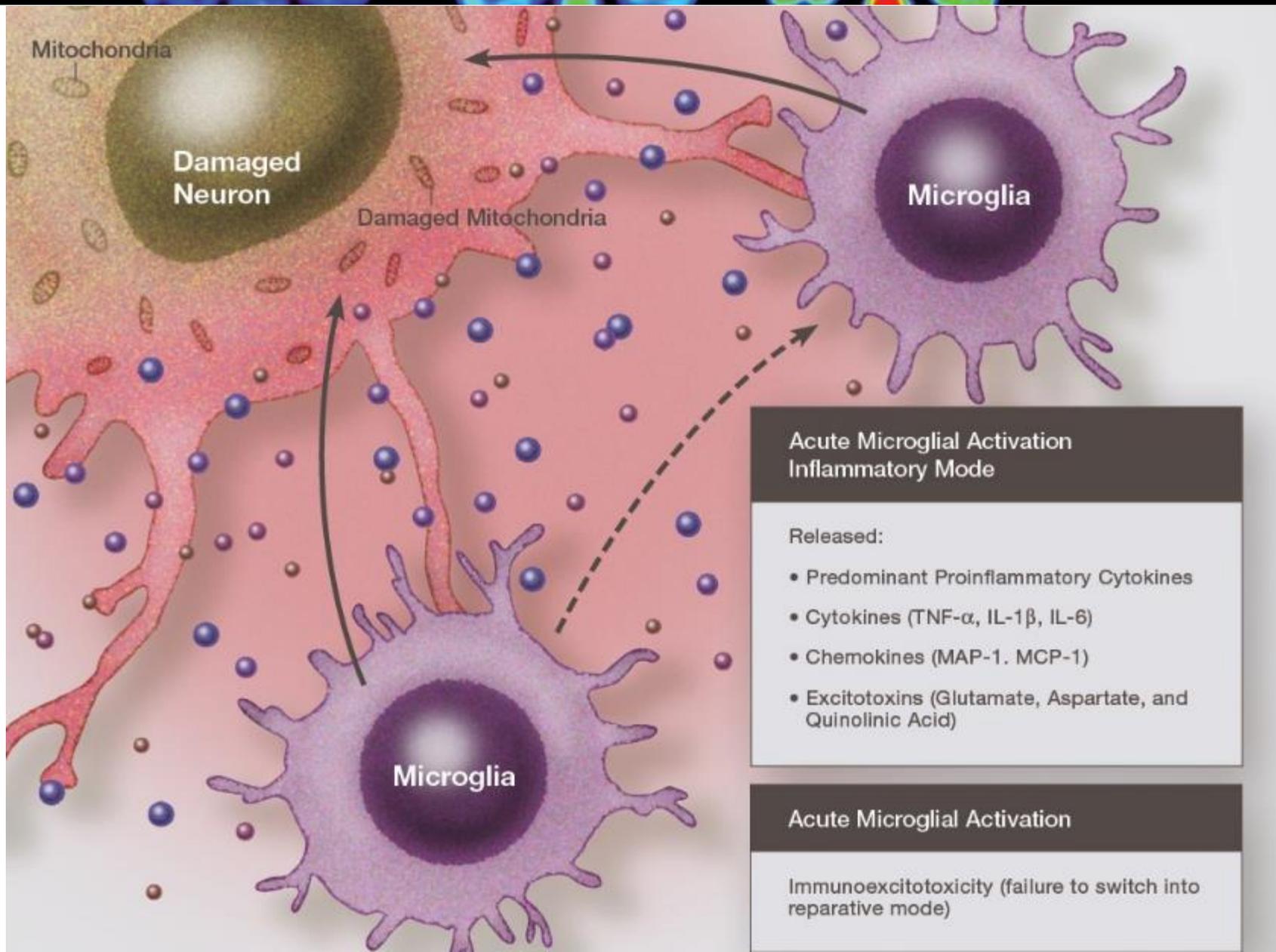
“Levels of TNF- α and of IL-1 β were higher in (PTSD) patients than in controls.”

Abstract

Posttraumatic stress disorder (PTSD) may increase cardiovascular risk but the psychophysiological mechanisms involved are elusive. We hypothesized that proinflammatory activity is elevated in patients with PTSD as diagnosed by the Clinician Administered PTSD Scale (CAPS) interview. Plasma levels of proinflammatory C-reactive protein (CRP), interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF)- α , and of anti-inflammatory IL-4 and IL-10 were measured in 14 otherwise healthy PTSD patients and in 14 age- and gender-matched healthy non-PTSD controls. Levels of TNF- α ($p = 0.038$; effect size Cohen's $d = 0.58$) and of IL-1 β ($p = 0.075$, $d = 0.68$) were higher in patients than in controls. CRP ($d = 0.10$), IL-6 ($d = 0.18$), IL-4 ($d = 0.42$), and IL-10 ($d = 0.37$) were not significantly different between groups. Controlling for traditional cardiovascular risk factors, mood, and time since trauma revealed lower IL-4 in patients than in controls ($p = 0.029$) and rendered group differences in TNF- α and IL-1 β insignificant. In all subjects, TNF- α correlated with total (frequency and intensity) PTSD symptom cluster of re-experiencing ($r = 0.49$, $p = 0.008$), avoidance ($r = 0.37$, $p = 0.050$), and hyperarousal ($r = 0.42$, $p = 0.026$), and with PTSD total symptom score ($r = 0.37$, $p = 0.054$). Controlling for time since trauma attenuated

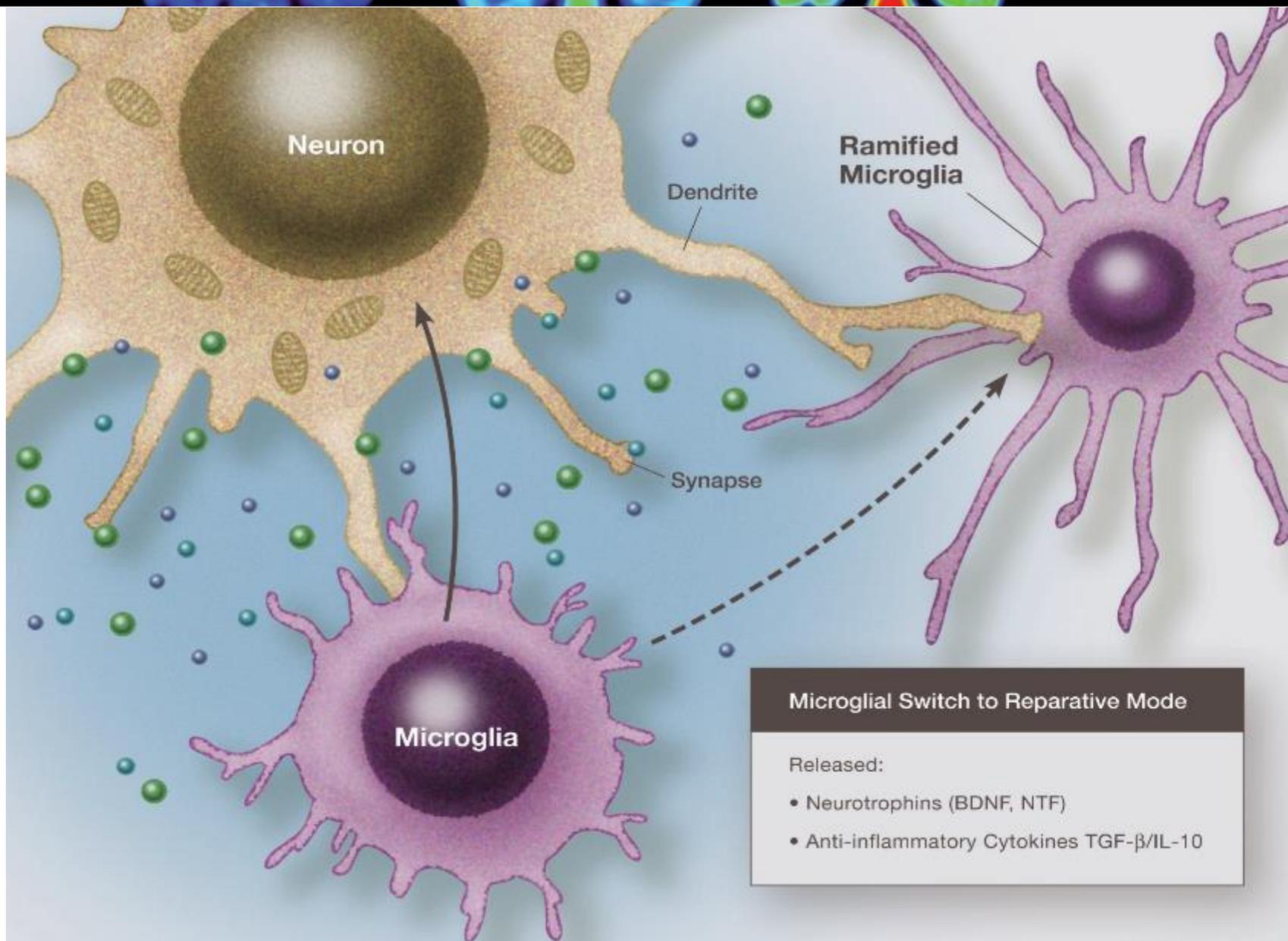


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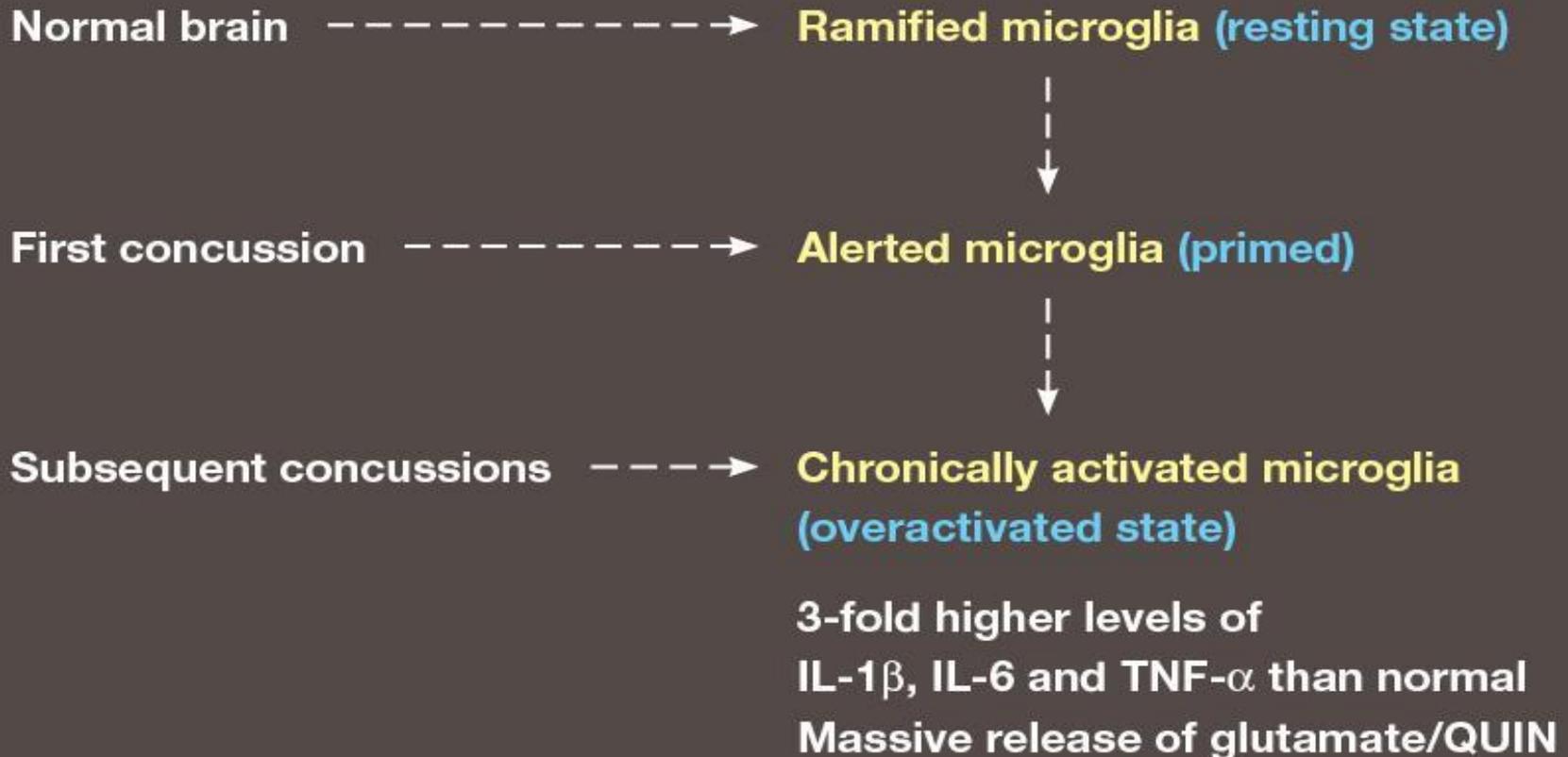
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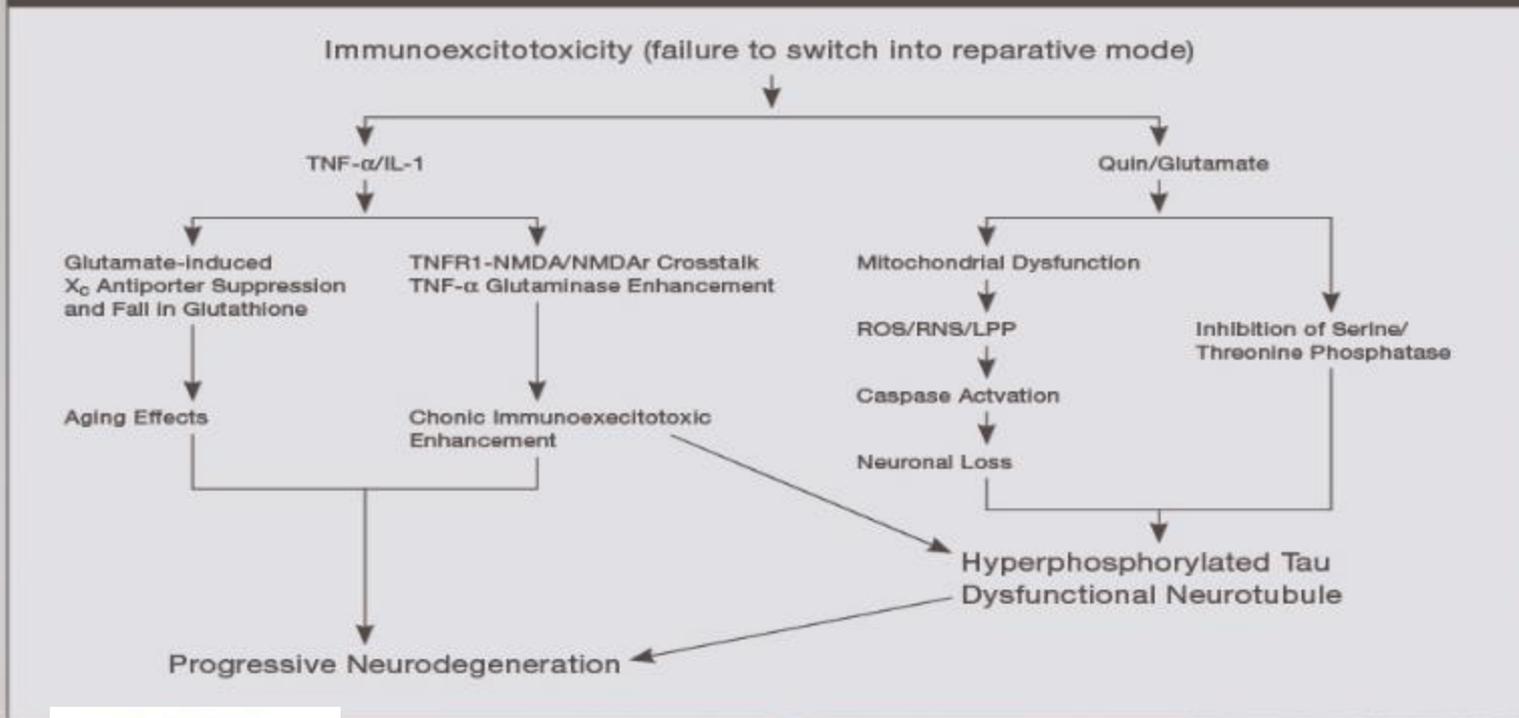
Microglial Priming





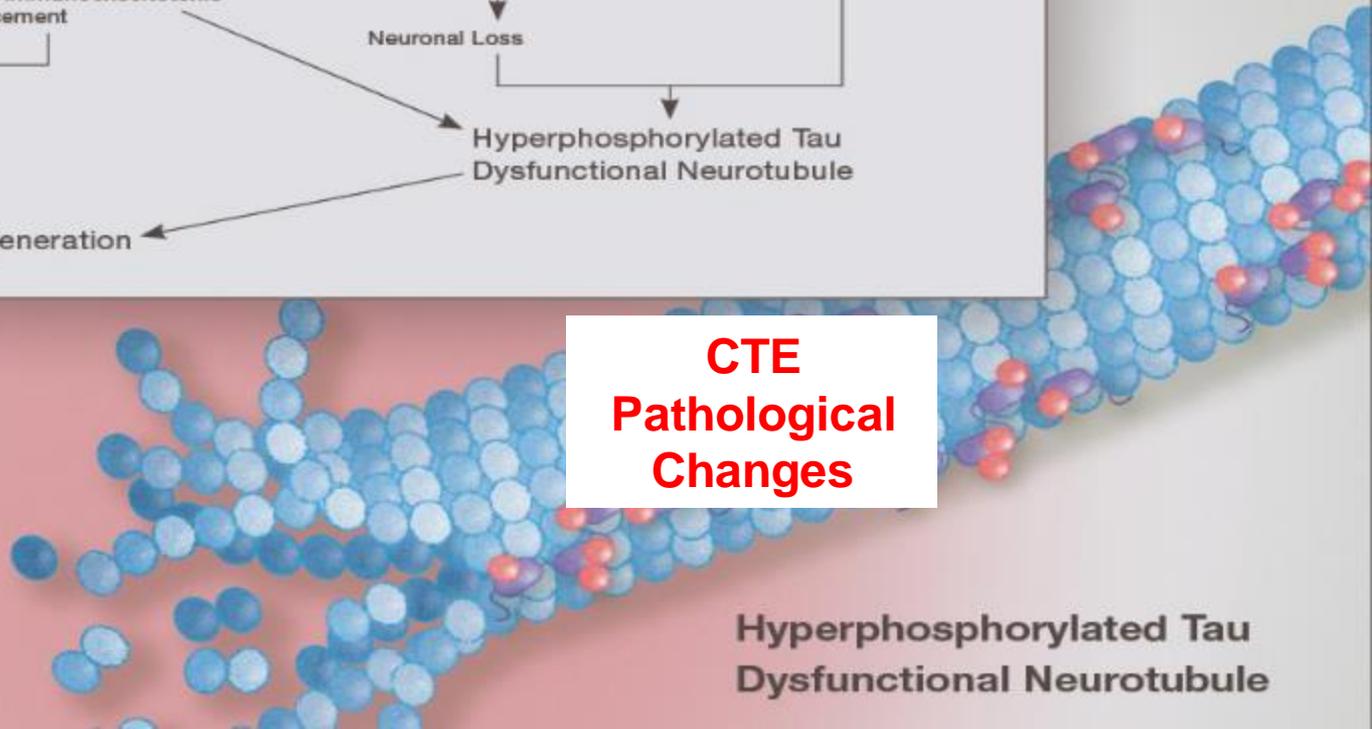
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Acute Microglial Activation



**CTE
Pathological
Changes**

**Hyperphosphorylated Tau
Dysfunctional Neurotubule**





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Long-term Consequences of Repetitive Brain Trauma: Chronic Traumatic Encephalopathy

Robert A. Stern, PhD, David O. Riley, BS, Daniel H. Daneshvar, MA, Christopher J. Nowinski, BA, Robert C. Cantu, MD, Ann C. McKee, MD

Abstract: Chronic traumatic encephalopathy (CTE) has been linked to participation in contact sports such as boxing and American football. CTE results in a progressive decline of memory and cognition, as well as depression, suicidal behavior, poor impulse control, aggressiveness, parkinsonism, and, eventually, dementia. In some individuals, it is associated with motor neuron disease, referred to as chronic traumatic encephalomyelopathy, which appears clinically similar to amyotrophic lateral sclerosis. Results of neuropathologic

PM R 2011;3:S460-S467

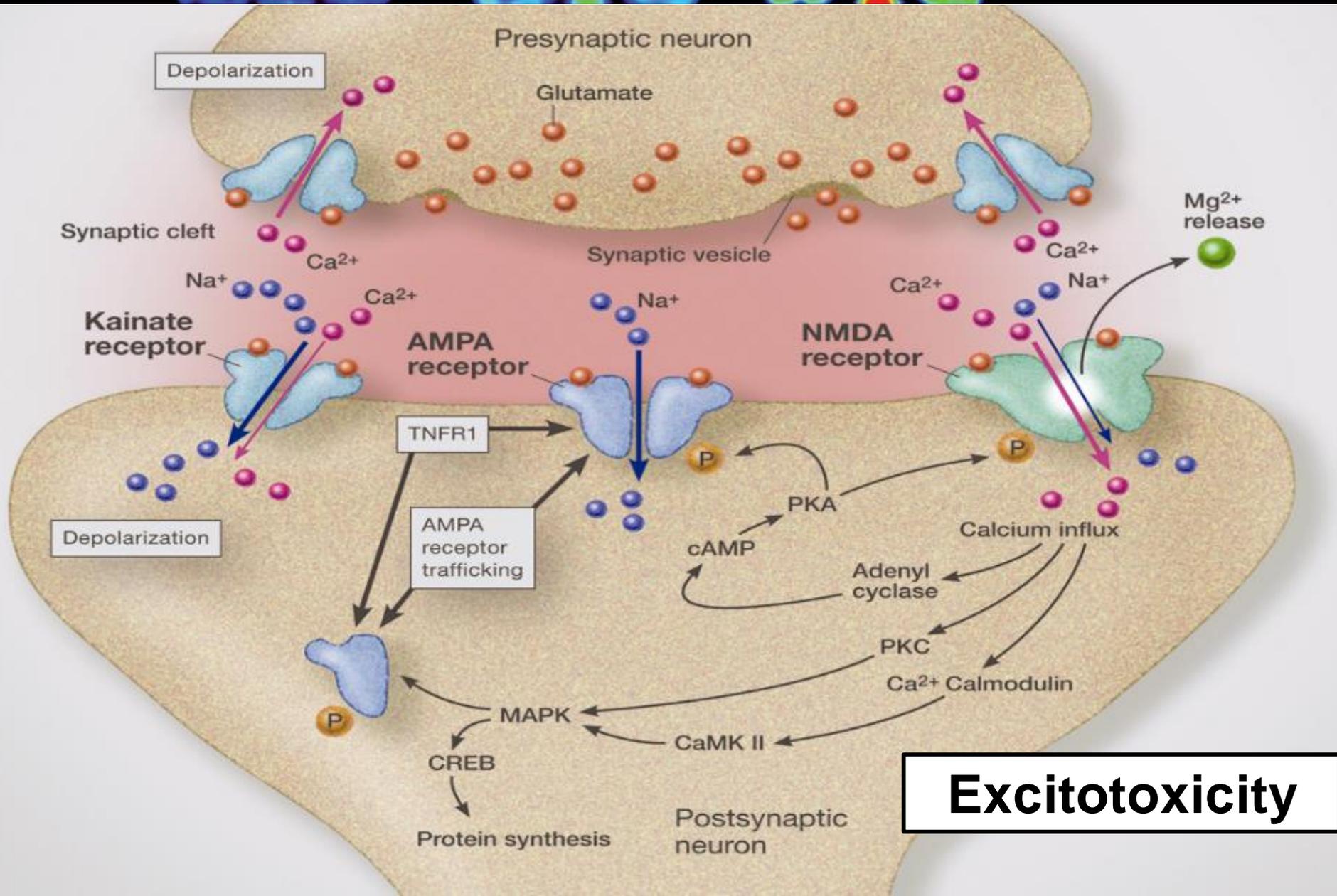
Table 5. Potential additional risk factors for chronic traumatic encephalopathy

Potential General Risk Factor	Specific Examples and/or Questions
Genetics	APOE ε4; MAPT; GRN; TARDP
Family history	First- and/or second-degree relatives with history of dementia
Type of brain trauma exposure	Symptomatic concussions; asymptomatic subconcussive blows; blast wave; minimum gravitational force; degree of axonal injury and/or microhemorrhages
Age and duration of brain trauma exposure	Susceptibility period during youth; years of overall exposure
Frequency of brain trauma exposure	Minimum number of injuries (eg, can one moderate-severe TBI lead to CTE, without any additional repetitive concussions or subconcussive exposure history?); amount of "rest" (and overall time interval) between injuries
Chronic inflammation	Obesity, hypertension, diabetes, and heart disease may exacerbate neurodegeneration and NFT formation
Cognitive reserve	Greater cognitive reserve (or brain reserve capacity) may be less likely to display the clinical symptoms associated with the neurodegeneration or exhibit them later in the neuropathologic process
Gender	Are women at greater risk if they had the same exposure as men?
Race	Are there racial differences in risk?

CTE = chronic traumatic encephalopathy; NFT = neurofibrillary tangles; TBI = traumatic brain injury.



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Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

mTBI

Inflammatory

Immuno-excitotoxicity

Concussion

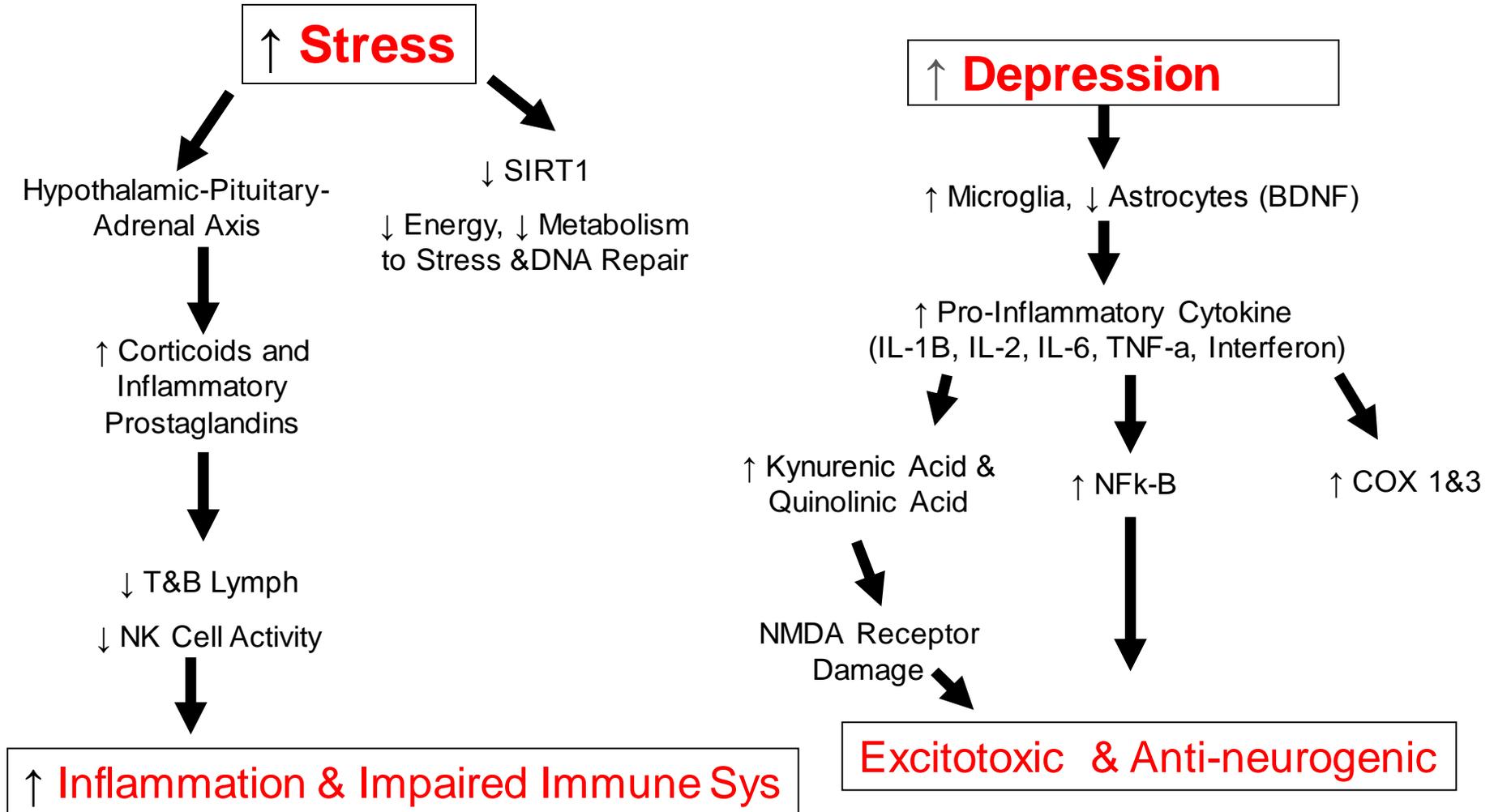
**Post-Traumatic Stress
Disorder (PTSD)**

**Chronic Traumatic
Encephalopathy (CTE)**



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

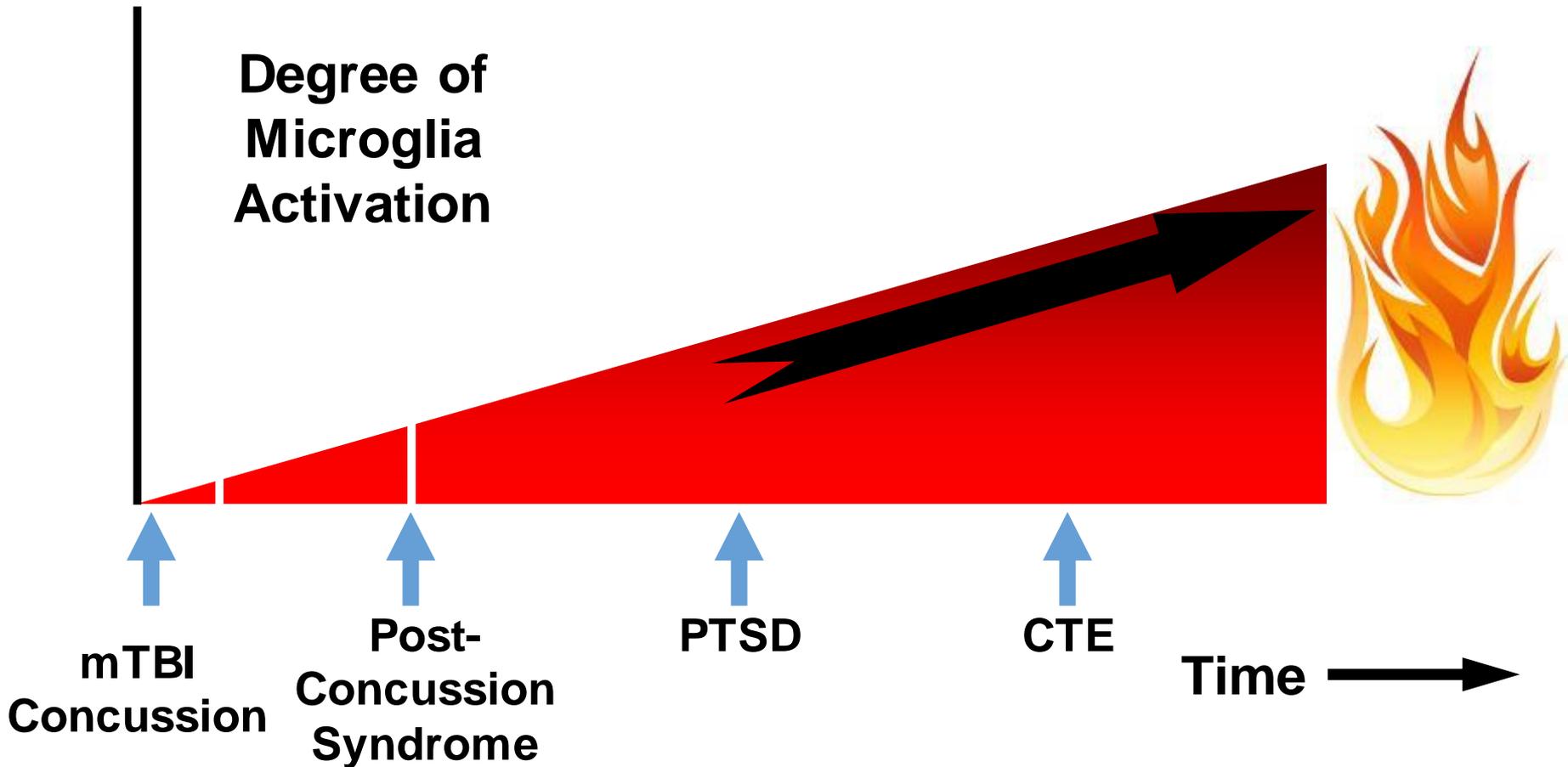
Immunoexcitotoxicity & PTSD Increased Cytokines in PTSD





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Spectrum of Immunoexcitotoxicity





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Risk Factors for Chronic Traumatic Encephalopathy

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RESEARCH ARTICLE

Chronic Traumatic Encephalopathy in Contact Sports: A Systematic Review of All Reported Pathological Cases

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Abstract

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with head trauma. Although initially believed to affect only boxers, the at-risk population has expanded to encompass a much wider demographic, including American football players, hockey players, wrestlers, and military veterans. This expansion has garnered considerable media attention and public concern for the potential neurodegenerative effects of head trauma. The main aim of this systematic review is to give a complete overview of the common findings and risk factors for CTE as well as the status quo regarding the incidence and prevalence of CTE. This systematic review was performed using PubMed and MEDLINE and includes all neuropathologically confirmed cases of CTE in the medical literature to date, from the first published case in 1954 to August 1, 2013 (n = 153). The demographics, including the primary source of mTBI (mild Traumatic Brain Injury), age and cause of death, ApoE genotype, and history of substance abuse, when listed, were obtained from each case report. The demographics of American football players found to have CTE are also presented separately in order to highlight the most prevalent group of CTE cases reported in recent years. These 153 case reports of CTE represent the largest collection to date. We found that a history of mTBI was the only risk factor consistently associated with CTE. In addition, we found no relationships between CTE and age of death or abnormal ApoE allele. Suicide and the presence of pre-morbid dementia was not strongly associated with CTE. We conclude that the incidence of CTE remains unknown due to the lack of large, longitudinal studies. Furthermore, the neuropathological and clinical findings related to CTE overlap with many common neurodegenerative diseases. Our review reveals significant limitations of the current CTE case reporting and questions the widespread existence of CTE in contact sports.

OPEN ACCESS

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

1954-2012 Demographic Breakdown of Neuropathologically Confirmed Cases

Neuropathologically Confirmed Cases of CTE (n = 153)						
Primary TBI Exposure	Boxing	Football	Hockey	Wrestling	Military	Misc. ¹
Professional	43	47 ²	4	3	-	-
Amateur	11	16 ³	1	-	-	-
Other/Not Specified	15	-	-	-	6	7
Total	69	63	5	3	6	7
Percentage	45.1%	41.2%	3.3%	2.0%	3.9%	4.6%

¹ The miscellaneous category includes one victim of physical abuse, three individuals of self-injury behaviors, a circus clown, and an amateur soccer player

² Professional football category includes 41 former National Football League player (NFL), 4 Canadian Football League players, 1 Semi-Pro Football player

³ The amateur football category includes 9 collegiate football and 7 high school football players



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Results		
Total	153	
Athletes	143	
Football	63	
Deaths	Natural	74 (70.3%)
	Accidental	18 (17.1%)
	Suicide	14 (12.6%)
Age at death	17 to 91 yrs,	
Co-morbid neurodegenerative disease	25 cases (16.7%)	
Substance Abuse	37 cases (25%)	
ApoE Genotype	79 cases (52%)	Same as General Population
Football position	Offense lineman and Defensive linebacker	

Conclusions

- All 153 are case reports
- **No** randomized studies
- **No** relationship between CTE and age of death
- **No** significant association of CTE and abnormal ApoE allele
- **Suicide and premorbid dementia** not strongly associated with CTE.
- Prior mTBI **only risk factor** significantly associated with CTE.



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

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VIEWS & REVIEWS

Chronic traumatic encephalopathy and athletes

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ABSTRACT

Recent case reports have described athletes previously exposed to repetitive head trauma while participating in contact sports who later in life developed mood disorders, headaches, cognitive difficulties, suicidal ideation, difficulties with speech, and aggressive behavior. Postmortem discoveries show that some of these athletes have pathologic findings that are collectively termed chronic traumatic encephalopathy (CTE). However, it remains unclear whether the pathologic findings perhaps blow the diagnosis of CTE. The pathologic findings may develop the full spectrum of mood disorders, cognitive difficulties, and aggressive behavior. It has been proposed that those current case-control studies of the neuropathology of CTE are subject to recall bias in that they are based on postmortem cases. The current evidence and the associated limitations. *Neurology*® 2015;85:1-8

Given the potential for referral and recall bias in available studies, it remains unclear whether or not the pathologic findings made postmortem cause the presumed neurobehavioral sequela and whether the presumed risk factors, such as sports activity, cerebral concussions, and subconcussive blows, are solely causative of the clinical signs and symptoms



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

FOCUS ON TRAUMATIC BRAIN INJURY

Chronic neuropathologies of single and repetitive TBI: substrates of dementia?

Douglas H. Smith, Victoria E. Johnson and William Stewart

Abstract | Traumatic brain injury (TBI) has long been recognized to be a risk factor for dementia. This association has, however, only recently gained widespread attention through the increased awareness of 'chronic traumatic encephalopathy' (CTE) in athletes exposed to repetitive head injury. Originally termed 'dementia pugilistica' and linked to a career in boxing, descriptions of the neuropathological features of CTE include brain atrophy, cavum septum pellucidum, and amyloid- β , tau and TDP-43 pathologies, many of which might contribute to clinical syndromes of cognitive impairment. Similar chronic pathologies are also commonly found years after just a single moderate to severe TBI. However, little consensus currently exists on specific features of the pathology. Moreover, the review the cu

Smith, D. H. et al

Robust diagnostic criteria permitting confident differentiation from other, better-characterized neurodegenerative syndromes remain elusive. Indeed, owing to the lack of large-scale controlled studies, our understanding of the pathology of CTE has advanced little since the landmark study by Corsellis *et al.* in 1973. Furthermore, at least some pathological features are common to survival from single and repetitive TBI, raising the possibility that they represent manifestations along a spectrum of common pathology, perhaps with a phenotype influenced by severity and frequency of exposure

Smith, D. H. *et al.* *Nat. Rev. Neurol.* 9, 211–221 (2013);



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

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REVIEW ARTICLE

Chronic Effects of Mild Neurotrauma: Putting the Cart Before the Horse?

Rudy J. Castellani, MD, George Perry, PhD, and Grant L. Iverson, PhD

Abstract

Accumulation of phosphorylated tau (p-tau) is accepted by many as a long-term consequence of repetitive mild neurotrauma based largely on brain findings in boxers (dementia pugilistica) and, more recently, former professional athletes, military service members, and others exposed to repetitive head trauma. This concept is also largely accepted and suggests that repetitive mild or subconcussive head trauma can produce a deleterious neuroinflammatory process that leads to p-tau templating, transsynaptic neurodegeneration, and associated clinical features. However, before accepting these concepts, it is important to note that the association between findings of p-tau at autopsy and clinical features reported in chronic traumatic encephalopathy are poorly defined. Much additional research in chronic traumatic encephalopathy is needed to determine if it has unique neuropathology and clinical features, the extent to which the neuropathologic alterations cause the clinical features, and whether it can be identified accurately in a living person.

Key Words: Athletes, Chronic traumatic encephalopathy, Dementia pugilistica, Head trauma, Neuropathology, Tau protein.

INTRODUCTION

The association between the history of concussion and findings of p-tau at autopsy is unclear. Concussions and subconcussive head trauma exposure are poorly defined in available cases, and the clinical features reported in chronic traumatic encephalopathy are not at present distinguishable from other disorders. Much additional research in chronic traumatic encephalopathy is needed to determine if it has unique neuropathology and clinical features, the extent to which the neuropathologic alterations cause the clinical features, and whether it can be identified accurately in a living person.



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

REVIEW

Neurodegeneration and Sport

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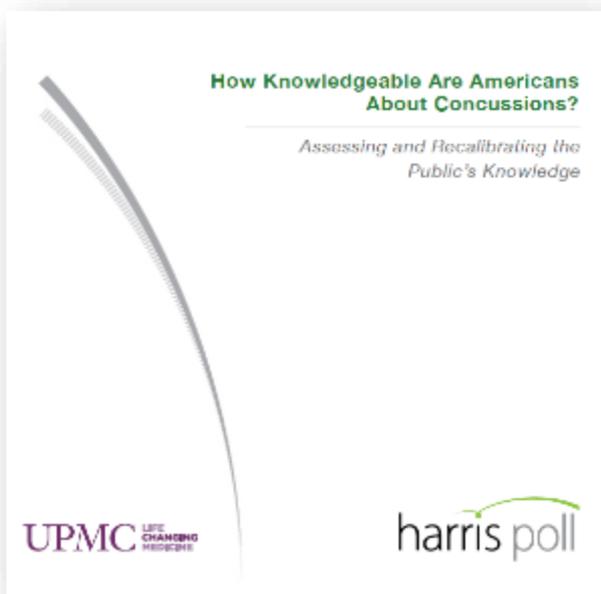
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The recent interest in concussion in sport has resulted in significant media focus about chronic traumatic encephalopathy (CTE), although a direct causative link(s) between concussion and CTE is not established. Typically, sport-related CTE occurs in a retired athlete with or without a history of concussion(s) who presents with a constellation of cognitive, mood, and/or behavioral symptoms and who has postmortem findings of tau deposition within the brain. There are many confounding variables, however, that can account for brain tau deposition, including genetic mutations, drugs, normal aging, environmental factors, postmortem brain processing, and toxins. To understand the

The article also reviews pathological changes identified with normal aging, and reviews the pathological findings of CTE in light of all these factors. While many of these athletes have a history of exposure to head impacts as a part of contact sport, there is insufficient evidence to establish causation between sports concussion and CTE. It is likely that many of the cases with neuropathological findings represent the normal aging process, the effects of opiate abuse, or a variant of frontotemporal lobar degeneration.



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

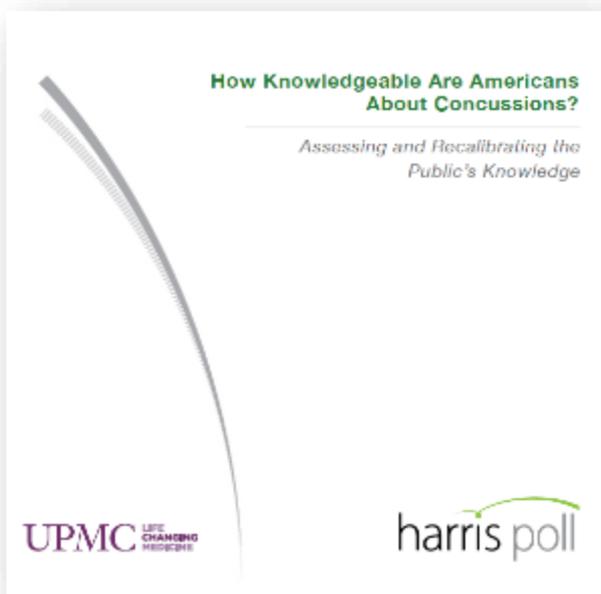


Survey conducted online within the by Harris Poll on behalf of UPMC
April 16-23, 2015,
2,012 U.S. adults age 18 or older

- **89%** believe concussions are a moderate or serious health concern
- **2%** say it is not a health concern at all
- **41%** feel that getting a concussion is living a nightmare
- **24%** scared it would change their life forever will get a concussion
- **25%** of parents do not let their kids play some contact sports because of fear of concussions



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?



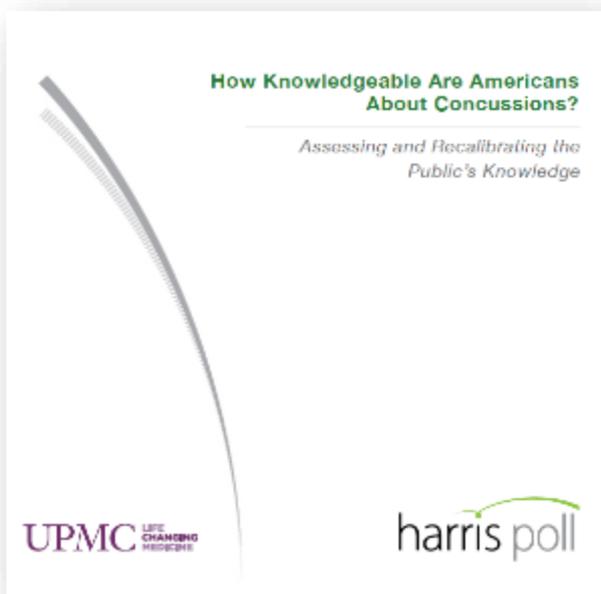
22% anxious that they wouldn't be able to live their life the way they want to.

- **18%** feel that concussions aren't as bad as people think they are.
- **83%** feel that people generally do not take concussions seriously enough
- **32%** of parents live in fear that their child will get a concussion

Survey conducted online within the by Harris Poll on behalf of UPMC
April 16-23, 2015,
2,012 U.S. adults age 18 or older



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?



Many Overstate the Long-term Impact and Understate the Treatability

- **79%** believe that there is no real way to cure a concussion; the symptoms can only be lessened
- Only **29%** of Americans believe that all concussions are treatable.
- **32%** believe that most concussions are life- threatening
- **22%** feel anxious that they wouldn't be able to live their life the way they wanted to if they sustained a concussion

Survey conducted online within the by Harris Poll on behalf of UPMC
April 16-23, 2015,
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Conclusion

CTE Neuropathology– no comprehensively determined unique factors

- Head injury– single versus multiple?
- Impact versus non-impact?
- Severity?
- Time between injuries?
- Incidence?
- Clinical symptoms overlap with other neurodegenerative diseases



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Existing Data

- Observational (Case-reports and small series)
- Major selection bias
- Methodological concerns
- No firm agreement on pathologic findings



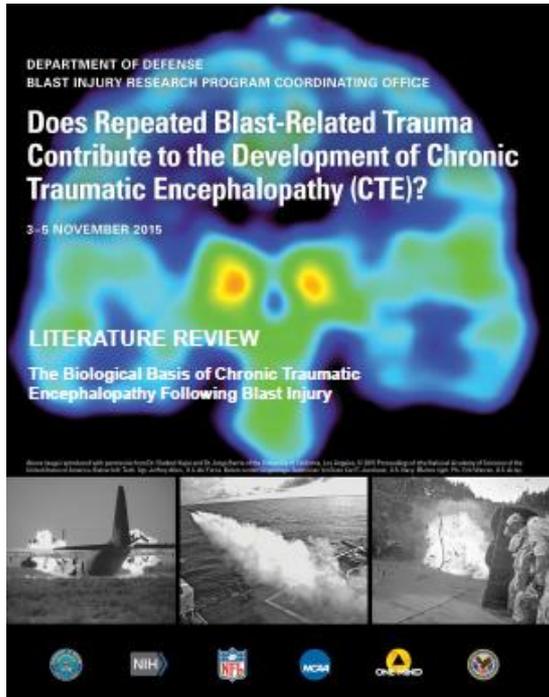
Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Required

- Population based studies– athletes compared to demographic controls
- Standardized pathological protocols
- Agreed upon clinical diagnostic criteria
- Further biomarker development– PET scans, blood, etc.



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?



- The current state of the science does not allow for a conclusive determination of whether exposure to head injury is associated with the development of CTE pathology or clinical symptoms.
- Existing clinical data are limited, observational in nature, and subject to several methodological concerns, leading some researchers to question whether CTE is a unique neurodegenerative disease.
- CTE has drawn significant public and media attention given the large at-risk population (e.g., military service members, contact sport athletes).
- Experts have noted concern over the potential clinical and legal consequences of widespread misunderstanding of CTE.
- In light of these factors, the need for additional research is clear, particularly population-based studies, the use of standardized pathology protocols, and the development of clinical diagnostic criteria.



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Thank you

