Viewing the Invisible Wound:
The Effects of Blast Traumatic Brain Injury (TBI) on the Human Brain

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Daniel P. Perl, MD

Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD

Center for Neuroscience and Regenerative Medicine (CNRM)

daniel.perl@usuhs.edu

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The opinions expressed herein are those of the presenter and are not necessarily representative of those of the government of the United States, the Uniformed Services University of the Health Sciences (USUHS), the Department of Defense (DoD); or, the United States Army, Navy or Air Force.

I have no conflicts to report.

Traumatic Brain Injury (TBI)
A Major Public Health Issue

- 2.5 million emergency department visits annually
- 280,000 hospital admissions
- 52,000 deaths

Acute Effects of TBI

Colon Ca = 50,000; Breast Ca = 40,000; Pancreas Ca = 42,000

- There are 5.3 million Americans living with long-term disability related to prior TBI

Long-Term Effects of TBI

Equal to the current number of cases of Alzheimer's disease

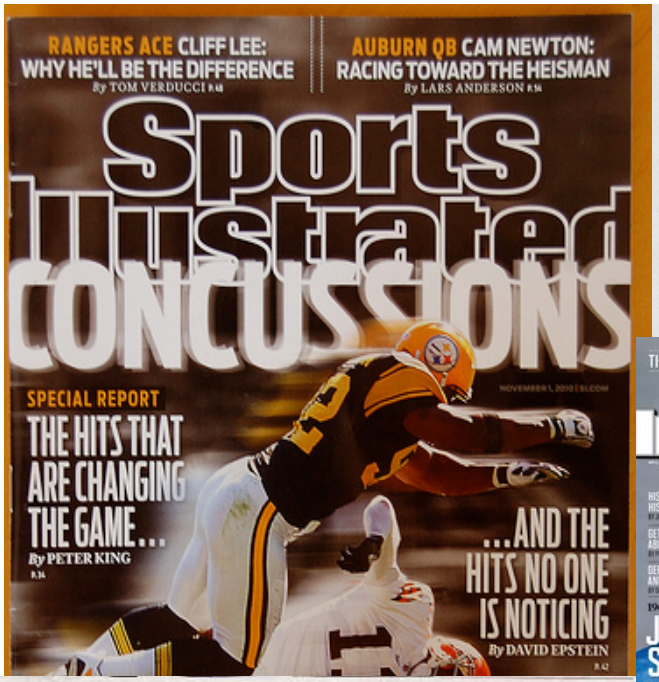
Source - Centers for Disease Control, Atlanta, GA

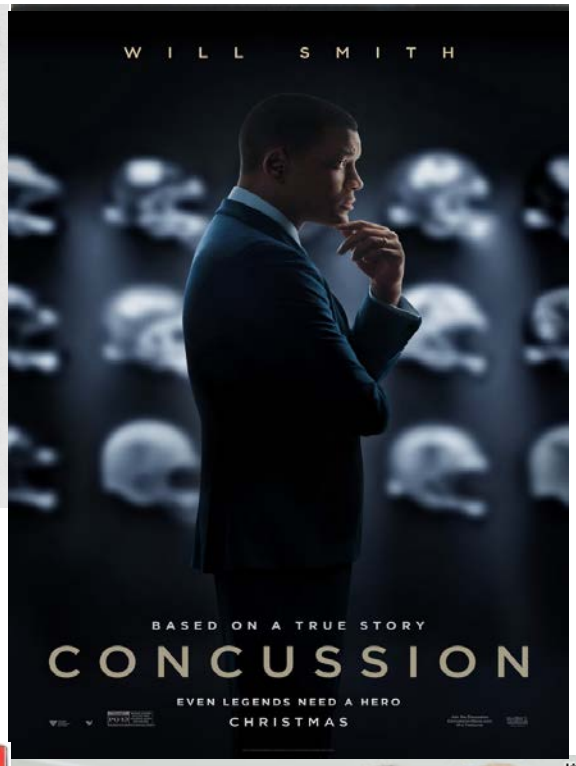
Acute Effects of TBI

Almost all of the classic lesions related to the acute effects of TBI were first described many years ago and relatively little has been added in recent years. This was mostly achieved through the study of autopsy-derived brain specimens.

Long-Term Effects of TBI

Very little is known of the long-term effects of TBI, especially the long-term effects of single episodes of moderate to severe impact TBI. However, the long-term effects of repeated impact TBI (in the context of contact sports) is a topic of daily discussion in the media.





Hockey Brawler Paid Price, With Brain Trauma

By ALAN SCHWARZ

TECUMSEH, Ontario — For 16 seasons, Bob Probert's fists were two of hockey's most notorious weapons, winning most of his 246 fights and feeding the N.H.L.'s fondness for bare-knuckle brawling.

But the legacy of Probert, who died last July of heart failure at 45, could soon be rooted as much in his head as his hands. After examining Probert's brain tissue, researchers at Boston University said this week that they found the same degenerative disease, chronic traumatic encephalopathy, whose presence in more than 20 deceased professional football players has prompted the National Football League to change some rules and policies in an effort to limit dangerous head impacts.

Although the National Hockey League has taken steps recently to reduce brain trauma — ban-

FRED JEWELL/ASSOCIATED PI

Bob Probert, left, played 16 N.H.L. seasons and was rated t greatest enforcer in hockey history in a 2007 Hockey News po

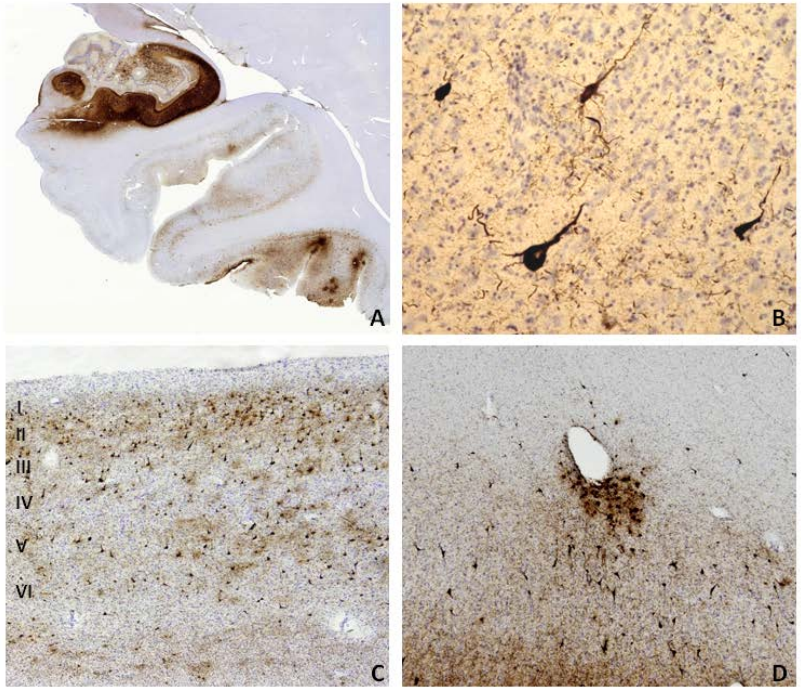
Chronic Traumatic Encephalopathy (CTE); Punch Drunk Syndrome; Dementia Pugalistica

Harrison Martland

Bennet Omalu

Ann McKee

- CTE is a chronic, progressive neurodegenerative disease involving accumulation of pathologic *tau* protein in the brain.
- CTE is almost exclusively seen in patients with a history of repeated TBIs, especially following participation in contact sports.
- These lesions cannot be visualized by MRI and currently CTE can only be definitively diagnosed at autopsy.



from Shively, et al. *Arch. Neurol*. 2012

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Clinical Features of Autopsy Proven Cases of CTE

- Early Symptoms:
  - Headache, loss of attention and ability to concentrate, short-term memory problems, impulsivity, abrupt mood swings, substance abuse, depression.
- Later manifestations:
  - Cognitive impairment to frank dementia and/or parkinsonism.

From: McKee, AC, Stern, RA, et al. *Brain* 136;43-69, 2013

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Issues to resolve with respect to CTE:

- **Clinical Diagnosis:** **No** currently available clinical diagnostic criteria. Neuroimaging unable to make definitive diagnosis. **No** scientific data available on the overall prevalence of CTE in the general population.
- **Prevention:**
  - **No** clear concept of the dose of TBI needed to trigger CTE (relative importance of concussive vs. subconcussive blows is unclear).
  - Is this dose reached in recreational sporting activities (the "Soccer-Mom" question)?
  - Return-to-play guidelines (allow brain time to "heal" after a concussion). **No** data to show that this prevents CTE.
- **Treatment:** **No** effective therapies available.
- **Biology:** The biologic mechanism by which a blow to the head triggers the onset of a neurodegenerative process (i.e., progressive *tau* accumulation) is **not** known.

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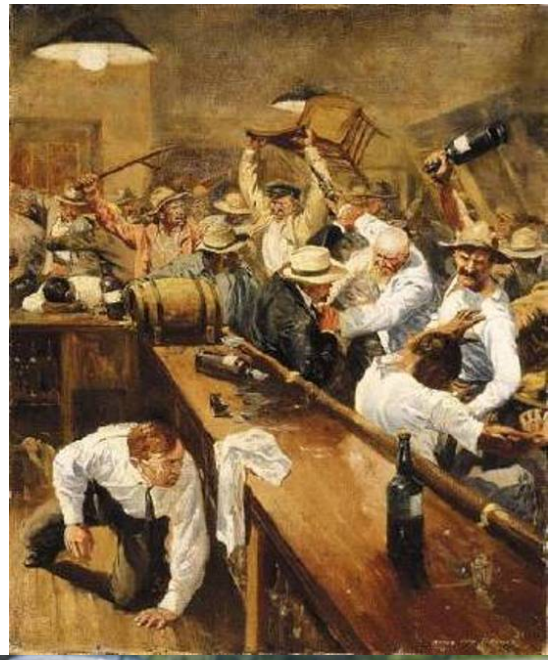
TBI Among Military Personnel

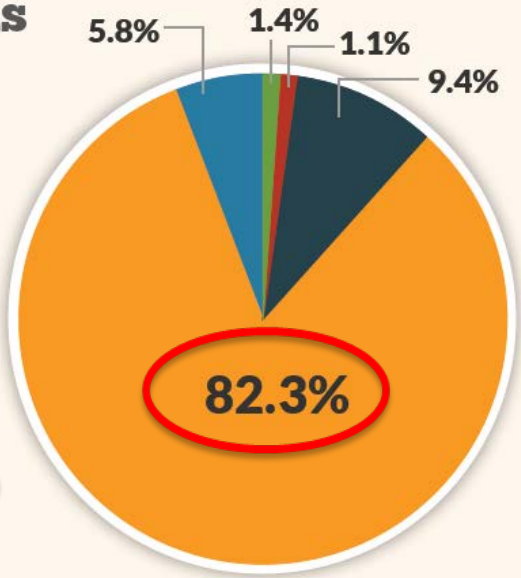
- 50% of military recruits have already experienced at least one TBI prior to starting their military career.
- About 80% of all TBIs experienced by active duty service members occur off the battlefield.
  - Contact sports
  - Motor vehicle accidents
  - Falls
  - Fights (NOTE: boxing is a required course at West Point!!)



DoD Numbers for Traumatic Brain Injury
Worldwide – Totals

2000 - 2017 (Q1-Q2)

Penetrating	5,131
Severe	3,895
Moderate	34,926
Mild	305,140
Not Classifiable	21,596
Total - All Severities	**370,688**



Source: Defense Medical Surveillance System (DMSS), Theater Medical Data Store (TMDS) provided by the Armed Forces Health Surveillance Center (AFHSB)

Prepared by the Defense and Veterans Brain Injury Center (DVBIC)

2000-2017(Q1-Q2), as of August 10, 2017

*Percentages do not add up to 100% due to rounding

TBI Level→	Mild	Moderate	Severe	{Penetrating}
GCS	12-15	9-12	3-8	(any)
AoC	</= 24 hrs	>24 hrs	>24 hrs	(any)
LoC	0-30 min	31 min-24 hrs	>/=24 hrs	(any)
PTA	</=24 hrs	24H - 7 days	>/=7 days	(any)

GCS, Glasgow Coma Scale; AoC, period of altered consciousness; LOC, period of loss of consciousness; PTA, duration of post-traumatic amnesia.

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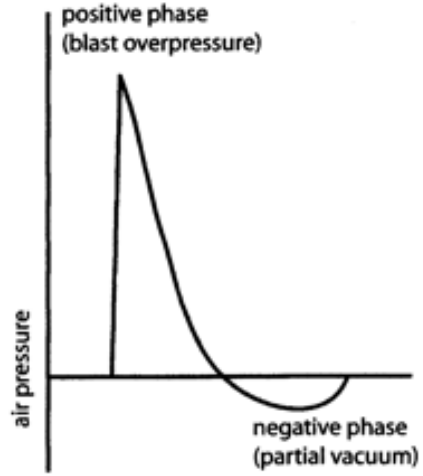
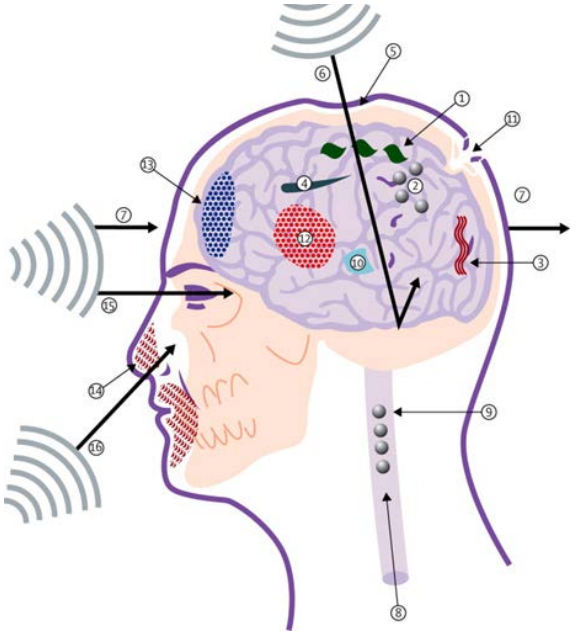
Improvised Explosive Devices (IEDs)

- Current weapon of choice of the enemy
- Inexpensive (~$100 to build), unsophisticated technology, requires little training to build
- Effective, especially with remote detonation
- The Pentagon has spent about $75 billion on armored vehicles and other tools that deal with IEDs
- Responsible for at least 60% of battlefield casualties

The Blast Wave





- Blast wave is a very quick (≈10 msec) pulse of high pressure that spreads in all direction at greater than the speed of sound.
- The blast wave can enter the skull and pass through the brain. What effect on structure and function does this have?

Common Persistent Post-Concussive Symptoms (commonly seen after IED exposure)

Physical: headache, nausea, vomiting, dizziness, fatigue, blurred vision, sleep disturbance, sensitivity to light/noise, balance problems, hearing difficulties/loss, seizure

Cognitive: impaired attention, concentration, recent memory, speed of processing, judgment, executive function

Behavioral/emotional: depression, anxiety, agitation, irritability, impulsivity, aggression

VA/DoD Clinical Guidelines For Management of Concussion/mTBI, 2009

Can Neuroimaging Studies of Post-Blast TBI Patients Provide Answers?

To date, **no** routine neuroimaging studies have provided a consistent signal alteration to indicate the presence of pathologic lesions in the brains of post-blast TBI patients with significant persistent symptomatology.

MRI

- Can be used on live patients. Studies can be performed longitudinally (at multiple time points)
- Can detect structural abnormalities as small as 1-2 mm in diameter.

Neuropathology

- Can only be performed only once, following the death of the subject.
- Can detect structural abnormalities 0.5 micron in diameter (0.0005 mm). Can also be used to identify specific constituents (proteins, lipids, etc.) of such structural abnormalities.

This is a 2000 to 4000-fold difference in resolution!!

Neuropathology Literature on the Effects of High Explosives (blast TBI) on the Human Brain

World War I

- First experience with widespread use of high explosives in warfare
- Maj. Frederick Mott, 1916 (WWI) – published 3 cases of acute death following high explosive exposure (focal hemorrhages). Mott also hypothesized that “shell shock” could represent a persistent problem caused by brain damage related to blast exposure.

Recent Literature on the Long-Term Effects of Blast TBI on the Human Brain

- Omalu, et al. 2011 - 1 case of CTE following deployment in OIF
- Goldstein, et al. 2012; McKee, Robinson 2014 - 4 cases of CTE in Veterans

- Ryu, et al. 2014; 6 cases with blast TBI
  - Evidence of injury to axons
  - No *tau* pathology (that is, no CTE seen)

Characterisation of interface astroglial scarring in the human brain after blast exposure: a post-mortem case series

Sharon Baughman Shively, Iren Horkayne-Szakaly*, Robert V Jones, James P Kelly, Regina C Armstrong, Daniel P Perl*

Summary

Background No evidence-based guidelines are available for the definitive diagnosis or directed treatment of most blast-associated traumatic brain injuries, partly because the underlying pathology is unknown. Moreover, few neuropathological studies have addressed whether blast exposure produces unique lesions in the human brain, and if those lesions are comparable with impact-induced traumatic brain injury. We aimed to test the hypothesis that blast exposure produces unique patterns of damage, differing from that associated with impact-induced, non-blast traumatic brain injuries.

Lancet Neurol 2016

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See Online/Comment
http://dx.doi.org/10.1016/S1474-4422(16)30058-8

Lancet Neurology 15: 944-953, 2016

The Joint Pathology Center

CNRM BRAIN TISSUE REPOSITORY

UNIVERSITY OF MARYLAND BRAIN & TISSUE BANK
A Brain and Tissue Repository of the NIH NeuroBioBank

Long-term Effects of Exposure to Multiple Blasts (Index Case)

- The patient is a former Special Operations combatant who died at age 45 of suicide. The patient served in Desert Storm, OIF and OEF where he was considered to be highly competent, reliable and emotionally stable.
- In combat and training exercises, he had been exposed to numerous blasts at close proximity. The effects of these episodes were not disclosed to his superiors for fear of being deemed unfit for duty.
- Once separated from the military he complained of persistent headaches, sleep disturbance, memory problems, and trouble maintaining mental focus.
- The patient had wrestled and boxed in his school years, and had experienced 3 MVAs.

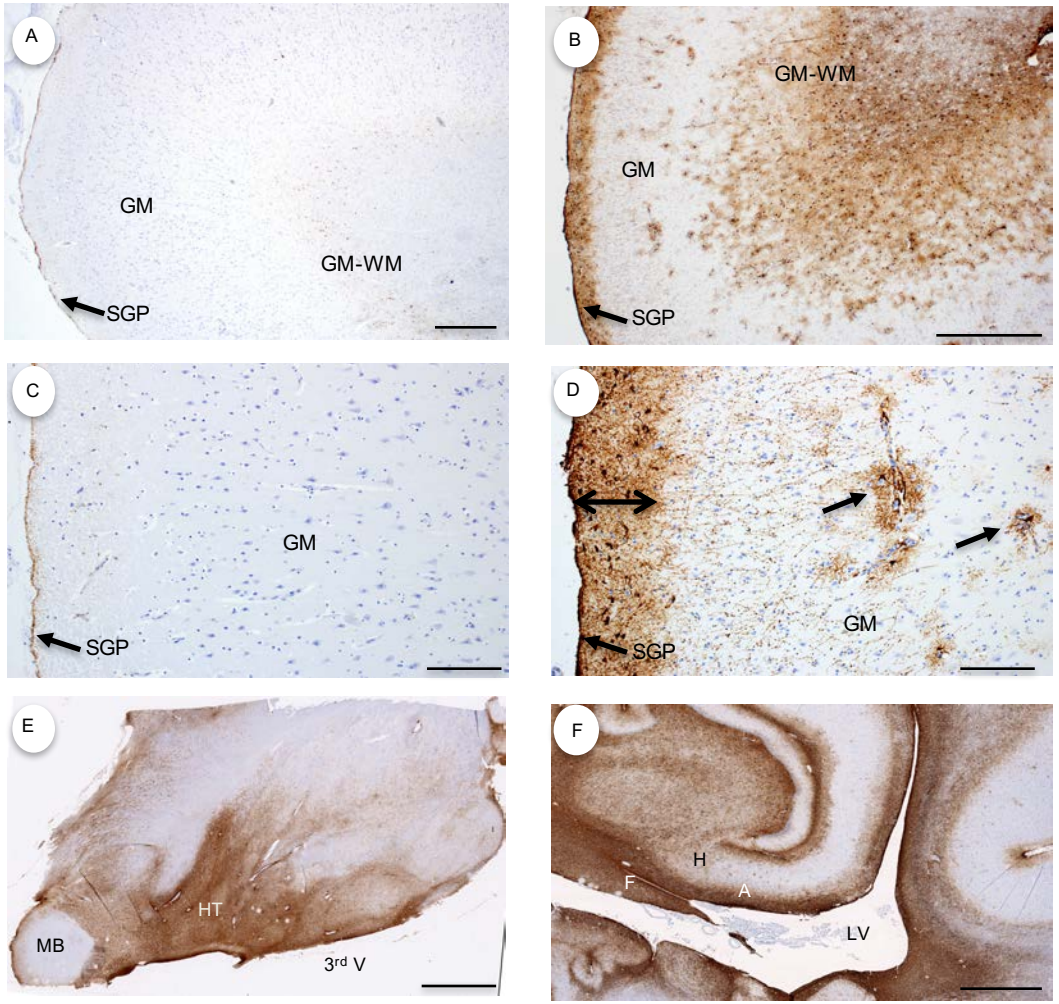
Long-term Effects of Exposure to Multiple Blasts (Index Case)

- He often lost coherence of thought and jumbled speech.
- His wife confirmed short-term memory problems and other cognitive and behavioral changes.
- Following discharge, clinicians described poor eye contact, flat affect and low voice tone and treated him for PTSD, depression and anxiety.
- There was no indication of substance abuse by history or postmortem toxicology screening.

Interface Astroglial Scarring

1. Sub-pial plate
2. Cortical penetrating blood vessels
3. Gray-white matter junction
4. Periventricular structures

This pattern of damage adheres to basic principles of blast biophysics (interface).

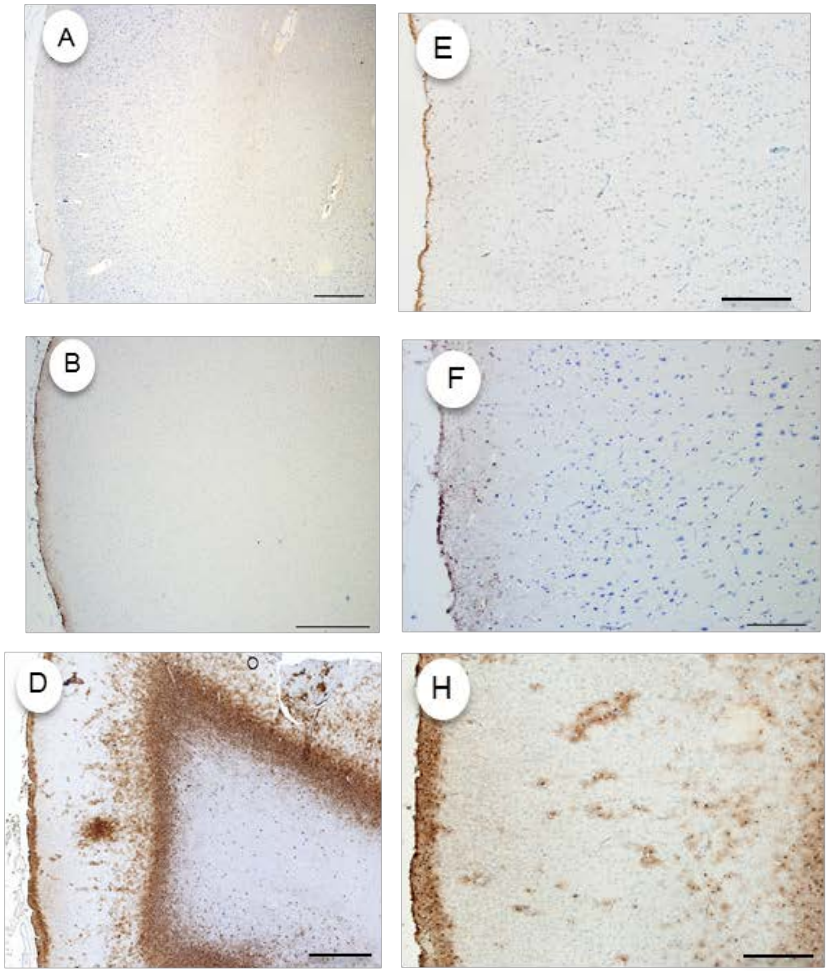


A, C – Civilian Impact TBI; B,D,E,F – Chronic blast TBI (Case 1)

Chronic Impact TBI (Civilian - No Blast) > 6 Month Survival

Chronic Substance Abuse

Chronic Blast TBI > 6 Month Survival



GFAP Immunohistochemistry Performed Under Identical Staining Conditions

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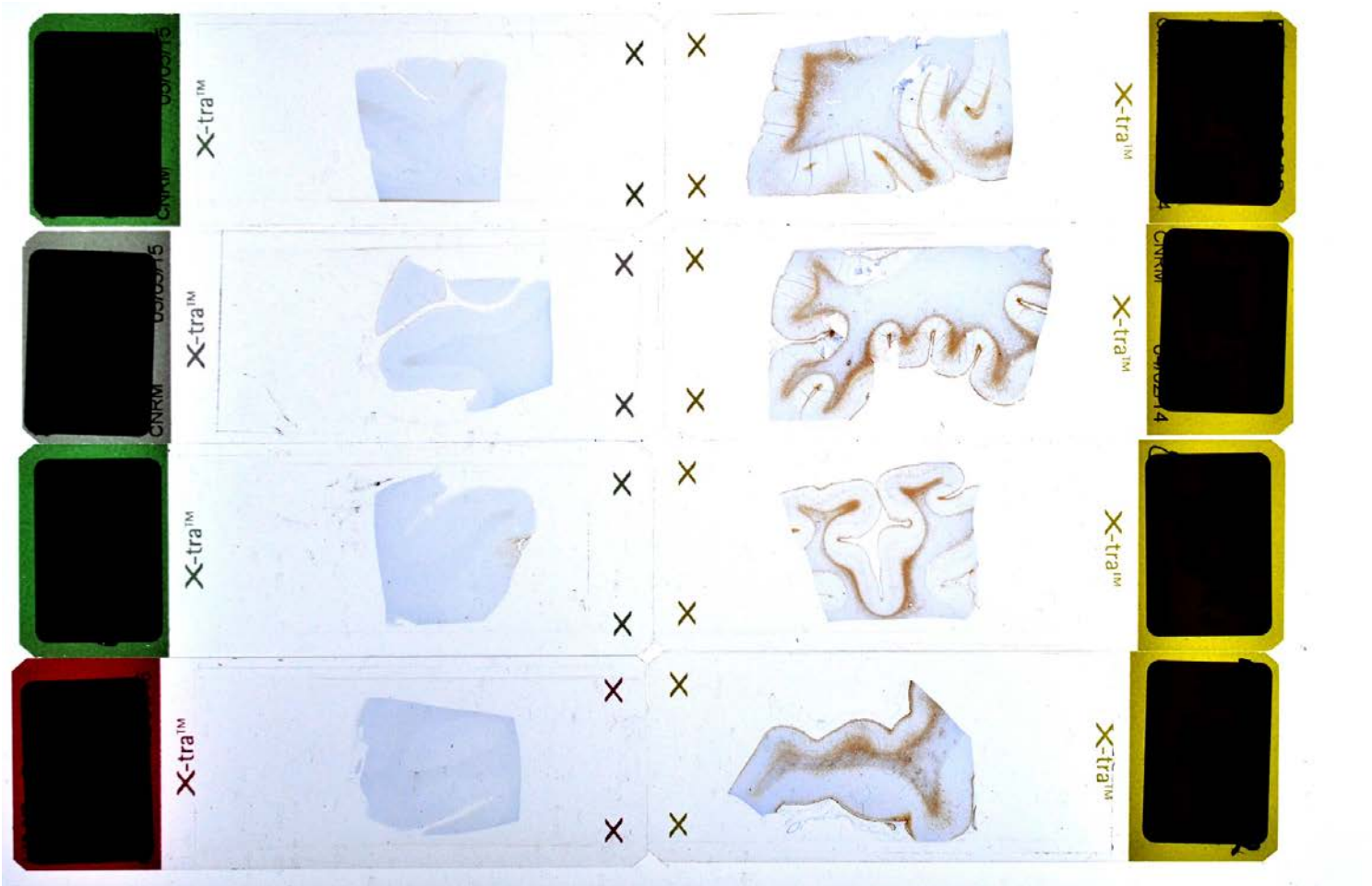
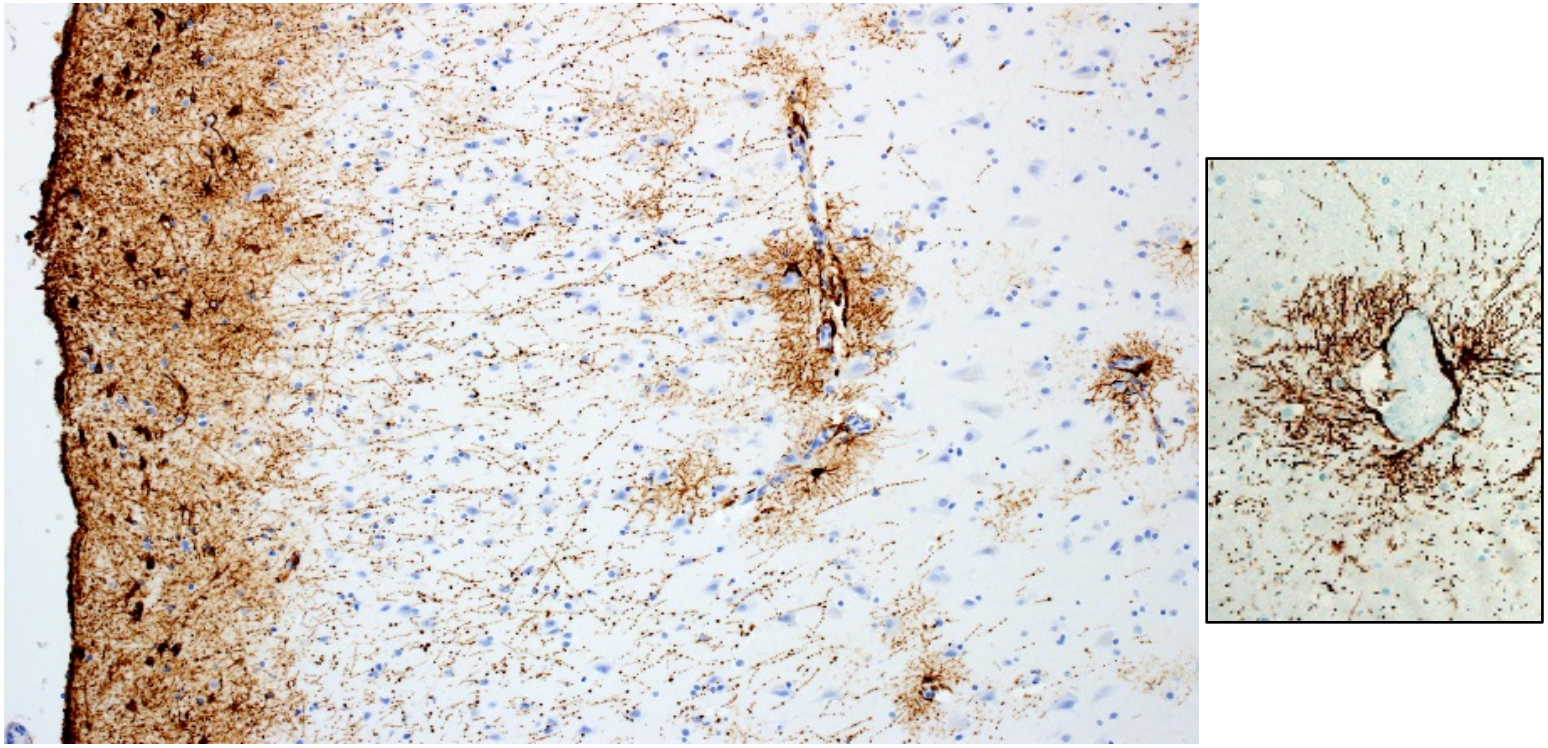
Impact TBI (no blast)

Blast TBI



Appearance of GFAP scarring on immunostained slides



Perivascular gliosis of penetrating cerebral cortical blood vessels

Development of vascular migraine days following blast exposure

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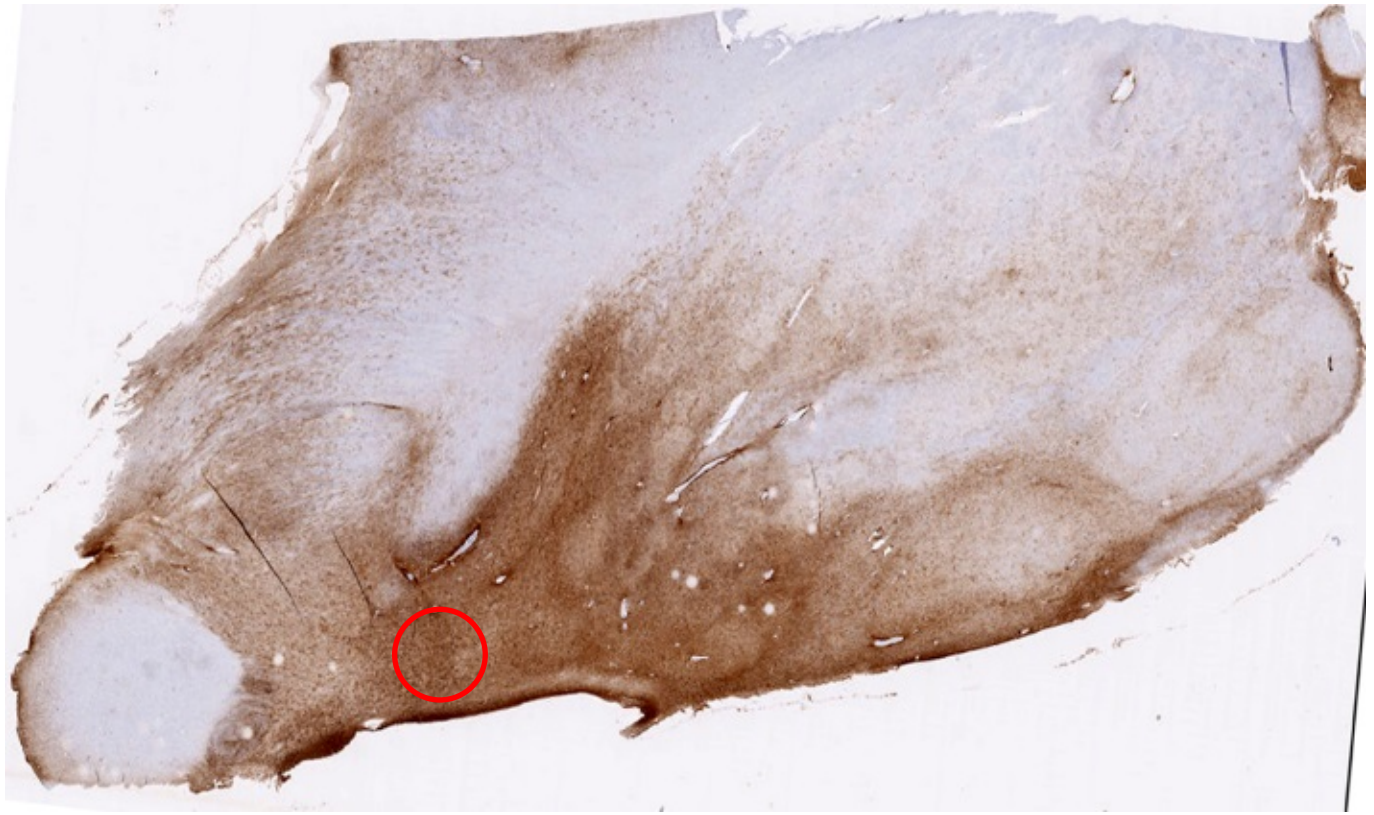

Glial scarring of hypothalamic areas controlling sleep/wake cycles

Persistent sleep disorder that is intractable to medication

Additional Recently Donated Interface Astroglial Scarring Case

- 31 year-old former Special Operations combatant
- Deployed multiple times, including Iraq and Afghanistan
- Multiple blast exposures with several episodes of ruptured tympanic membranes. Participated in several missions in which team members died of acute blast exposure.

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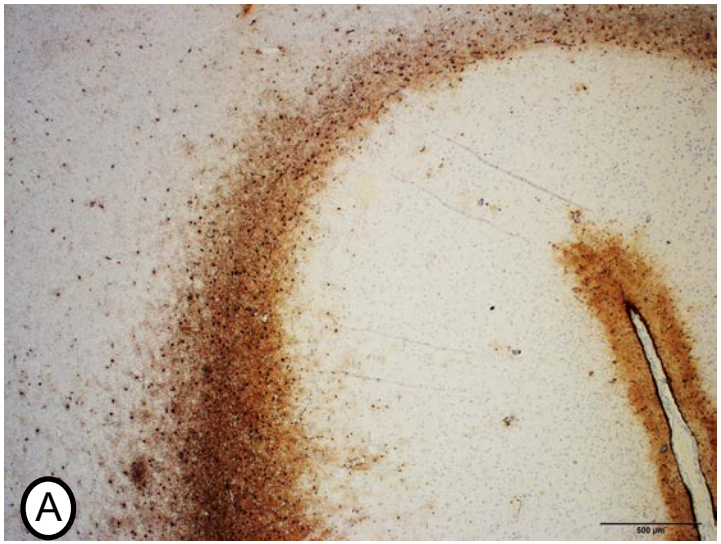
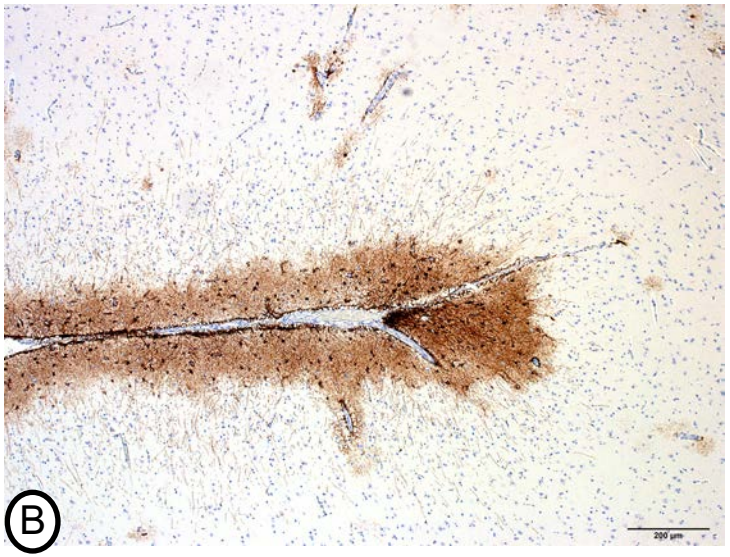
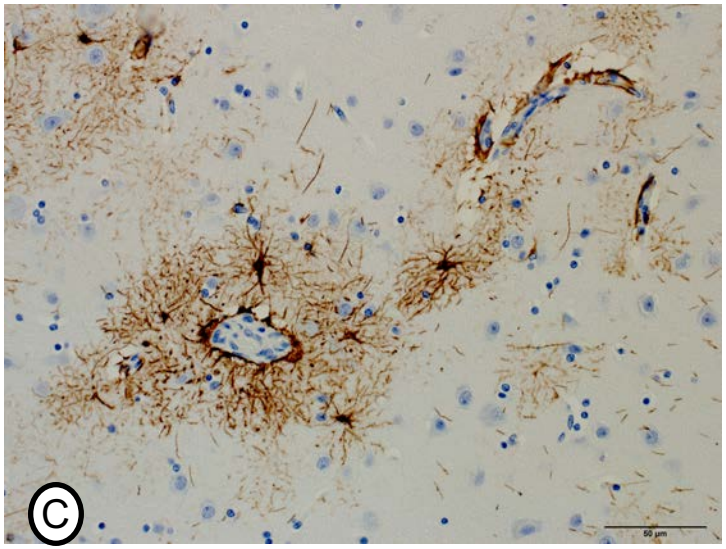
Additional Case (continued)

- Severe, intractable sleep disturbance
- Hearing loss, headaches, depression, anxiety, PTSD, alcohol abuse.
- More recently, increasing anxiety, memory issues, fear, paranoia, irritability, sleeplessness with nightmares
- Died of suicide at age 31







GFAP immunohistochemistry reveals the pattern of **interface astroglial scarring** (A, B and C)

No evidence of abnormal tau deposits despite extensive sampling and AT8 immunostaining.

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This is a 'Game Changer'…

(def. – an event, idea or procedure that effects a significant shift in the current manner of doing or thinking about something)

- Currently, Interface Astroglial Scarring can only be diagnosed at autopsy
  - Need to find a means to diagnose it in living individuals (Neuroimaging or other biomarkers?)
- How common is it among active duty and retired Service Members? SOF combatants?
- Interface Astroglial Scarring could affect a large percentage of post-deployed Service Members who have persistent symptoms following significant blast exposure.

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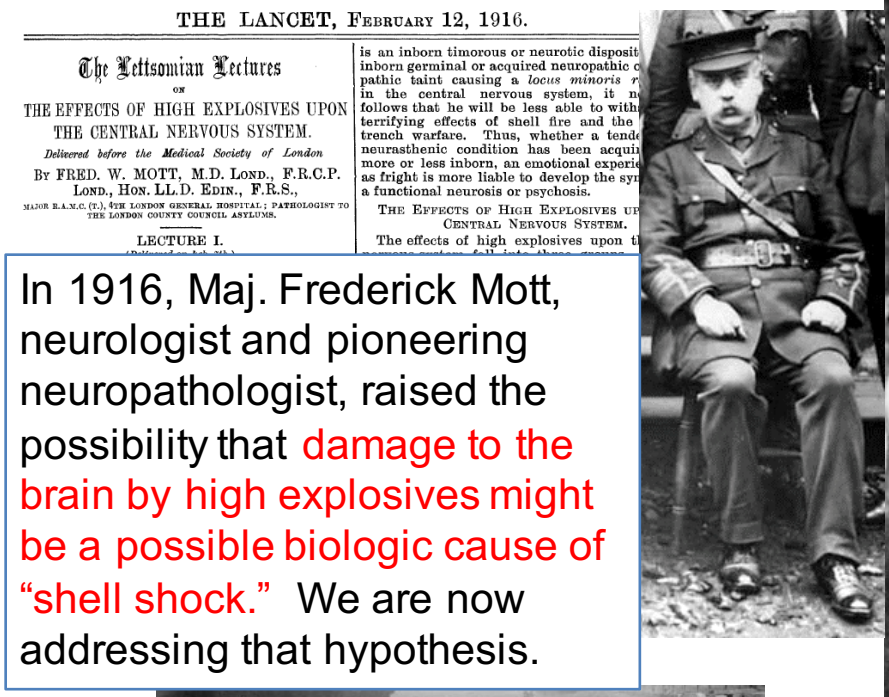
- What dose of blast exposure is required to produce Interface Astroglial Scarring? Do multiple smaller doses = a single larger dose? Do exposures experienced during SOF training exercises contribute to its development?
- What role does Interface Astroglial Scarring play in the high risk of blast-exposed Service Members to develop PTSD, suicide and other behavioral issues?
- Develop an animal model to investigate its biology (real progress being made)
- Devise new targeted prevention (helmet/armor design) and treatment strategies



THE LANCET, FEBRUARY 12, 1916.

The Lettsomian Lectures

ON

THE EFFECTS OF HIGH EXPLOSIVES UPON THE CENTRAL NERVOUS SYSTEM.

Delivered before the Medical Society of London

BY FRED. W. MOTT, M.D. LOND., F.R.C.P. LOND., HON. LL.D. EDIN., F.R.S.,

MAJOR R.A.M.C. (T.), 4TH LONDON GENERAL HOSPITAL; PATHOLOGIST TO THE LONDON COUNTY COUNCIL ASYLUMS.

LECTURE I.

is an inborn timorous or neurotic disposit
inborn germinal or acquired neuropathic c
pathic taint causing a *locus minoris r*
in the central nervous system, it n
follows that he will be less able to with
terrifying effects of shell fire and the
trench warfare. Thus, whether a tende
neurasthenic condition has been acquir
more or less inborn, an emotional experie
as fright is more liable to develop the syn
a functional neurosis or psychosis.

THE EFFECTS OF HIGH EXPLOSIVES UP
CENTRAL NERVOUS SYSTEM.

The effects of high explosives upon t

In 1916, Maj. Frederick Mott, neurologist and pioneering neuropathologist, raised the possibility that damage to the brain by high explosives might be a possible biologic cause of "shell shock." We are now addressing that hypothesis.

Structural Brain Damage vs "Mental Health" Problem

- Many of the issues blast-exposed Service members are currently struggling with may not strictly be related to "mental health" problems.
- Symptomatic blast-exposed Service Members diagnosed with PTSD may have distinctive microscopic brain abnormalities (lesions) that cannot be detected by current brain imaging studies.
- The presence of these brain abnormalities can contribute to both the neurologic and behavioral symptoms exhibited by these patients.
- Approaches to diagnosis and treatment of affected individuals need to now consider the potential presence and significance of these brain lesions.

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The Way Forward…

We have recently seen two additional cases with Interface Astroglial Scarring (both were SOF combatants, both died by suicide and both had been diagnosed with PTSD).

1. Operationalize a program to promote brain donation among active duty and retired SOF personnel.
2. Using data obtained from such donations, determine the relationship between brain pathology, clinical symptoms and neuroimaging results. Need to consider a study of SOF combatants with baseline and then periodic longitudinal assessments (including neuroimaging).
3. Using these data, determine which aspects of training and carrying out the duties of being in the SOF correlate with the development of these outcomes.
4. Characterize those who are resistant to such changes. What have their blast exposures been?

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Exactly 100 years ago, on the Western front of World War I

The War to End All Wars, sadly, did not accomplish the goal of ending war. We continue to struggle with the long-term effects of military TBI. Undoubtedly, this problem will continue to be encountered in the future. Hopefully, our ongoing studies will provide new avenues towards dealing with these difficult and lasting consequences of participation in warfare.

1916

2016

- We need to pause and thank the Service members and their families who have agreed to donate the brain to our Repository.
- Without this precious gift, we could not do our research.
- Our donor families often express the feeling that although their loved ones have made the ultimate sacrifice, through brain donation, they continue to serve their Country. We are pleased to know that this has provided considerable comfort to them.

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BRAIN TISSUE REPOSITORY

Center for Neuroscience and Regenerative Medicine
Brain Tissue Repository

BRAIN TISSUE REPOSITORY

I _____ Print Here _____
wish to donate my brain to The Center for Neuroscience and Regenerative Medicine Brain Tissue Repository for Traumatic Brain Injury to help better understand traumatic brain injury (TBI).

X _____ Sign Here _____

Date: _____

To comply with my wishes, please call 855-366-8824.

We are providing two donation cards. It is important to share your wishes with your family and loved ones. Please sign and keep one card with your important paperwork, such as your Will, Advance Directives, etc. The second card provided is for you to give to your next of kin or family members, so they are able to help honor your wishes to donate to our program.

Contact us to learn about brain tissue donation.

855-366-8824

www.ResearchBrainInjury.org

Acknowledgments

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daniel.perl@usuhs.edu
www:ResearchBrainInjury.org
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