Interface Astroglial Scarring, a Pattern of Brain Damage in Blast-Exposed Service Members with Prominent Persistent Behavioral/Neurologic Symptomatology, Including Suicide

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The opinions expressed herein are those of the presenter(s) 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 (we) have no conflicts to report.

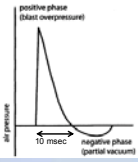
TBI Among Military Personnel

- 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 and the Naval Academy!!)

Improvised Explosive Devices (IEDs)

- Current weapon of choice of the enemy
- Inexpensive, unsophisticated technology, requires little training to build
- Effective, especially with remote detonation
- 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 Symptoms In Post-Blast TBI Subjects

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

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

Behavioral/emotional: depression, anxiety, agitation, irritability, impulsivity, aggression, substance abuse, suicide

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 pathological lesions in the brains of post-blast TBI patients with significant persistent symptomatology.

Acute Effects after Blast Exposure

What do we know about the acute (immediate) effects on the human brain after exposure to an high explosive, like an IED?

One would think that this question has been extensively researched and that we can answer it in detail.

Trinitrotoluene (TNT)
The Prototype High Explosive

- First synthesized in 1863 as a yellow dye
- Its properties as an extremely potent explosive were not recognized until many years later.
- In 1902, TNT was first added to the core of artillery shells, producing projectiles that could deliver a powerful explosive force on impact.
- The widespread use of such explosive artillery shells was introduced in World War I.

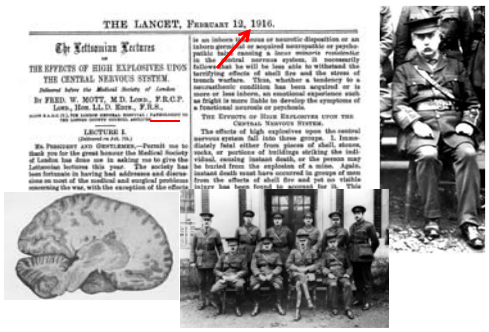

World War I (The Great War)
1914-1918

The war quickly evolved into trench warfare, especially on the Western Front with the battles of Ypres, Somme and Verdun. These battles involved lengthy exchanges of artillery shells.


The Battle of Verdun (Feb. 21-Dec. 18, 1916)

- A prolonged artillery battle in which a total of 40,000,000 artillery shells were exchanged!
- Total Allied and German casualties were estimated at 500,000+ (306,000 deaths).
- 70% of the casualties was caused by artillery fire.
- Many deaths occurred in the vicinity of the artillery blast, yet with no overt signs of injury to the head.

Major Frederick W. Mott, MD


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., Hon. LL.D. Edin., F.R.S.,

LECTURE I.

Mr. PRESIDENT AND GENTLEMEN,—Permit me to thank you for the great honour the Medical Society of London has done me in asking me to give the Lettsomian lectures this year. The society has been fortunate in having had addresses and discussions on most of the medical and surgical problems concerning the war, with the exception of the effects

is an inborn defect or neurotic disposition or an inborn germ or acquired neuropathic or psychopathic taint causing a lower minority resistance in the central nervous system. It necessarily follows that he will be less able to withstand the terrifying effects of shell fire and the stress of trench warfare. Thus, whether a tendency to a neurasthenic condition has been acquired or is more or less inborn, an emotional experience such as fright is more liable to develop the symptoms of a functional neurosis or psychosis.

THE EFFECTS OF HIGH EXPLOSIVES UPON THE CENTRAL NERVOUS SYSTEM.

The effects of high explosives upon the central nervous system fall into three groups. 1. Immediately fatal either from pieces of shell, stones, rocks, or portions of buildings striking the individual, causing instant death, or the person may be buried from the explosion of a mine. Again, instant death must have occurred in groups of men from the effects of shell fire and yet no visible injury has been found to account for it. This

Long-term Effects after Blast Exposure

What do we know about the <u>long-term</u> effects on the human brain after exposure to an high explosive?

World War I

In World War I, large numbers of combatants (>100,00 British soldiers) developed a spectrum of behavioral symptoms which precluded continuation to serve on the battlefield. Most of these patients were categorized as either having NYDN (Not Yet Diagnosed, Neurologic), neurasthenia or simply “shell shock.”

Shell Shock

- No accepted clinical definition
- In one study, 60% had been "concussed."
- Clinical symptoms included:
  - Persistent headaches
  - Poor concentration
  - Amnesia
  - Difficulty sleeping
  - Abrupt mood swings
  - Impulsive acts, including suicide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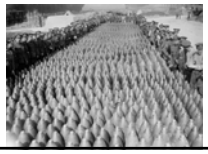
LECTURE I.

The Mott Hypothesis

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



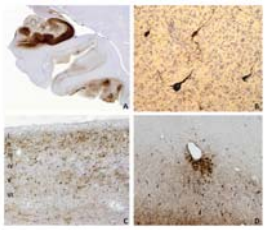
Chronic Traumatic Encephalopathy (CTE); Punch Drunk Syndrome; Dementia Pugalistica


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 (NFL football, ice hockey, etc.)
- However, is CTE seen in symptomatic blast exposed Service Members?



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

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Recent Literature on the Long-Term Effects of Blast TBI on the Human Brain: Does it Lead to CTE?

- Omalu, et al. 2011 - 1 case of CTE following deployment to Iraq with blast TBI (plus multiple impact TBIs)
- Goldstein, et al. 2012; McKee, Robinson 2014 – 4 or 5 cases of CTE in veterans with blast TBI
- Ryu, et al. 2014; 6 cases with blast TBI
  - Evidence of injury to axons
  - No *tau* pathology (that is, no CTE seen)

Articles

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

Sharon Baughman Shively*, Jnen 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.

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See Online/Comment
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The Joint Pathology Center

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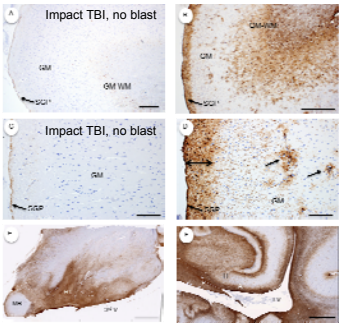
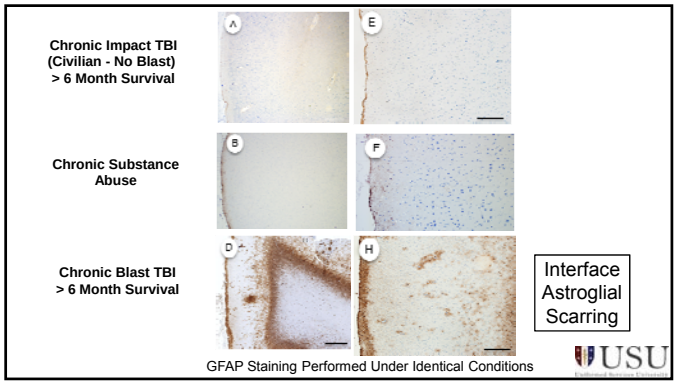
UNIVERSITY OF MARYLAND BRAIN & TISSUE BANK

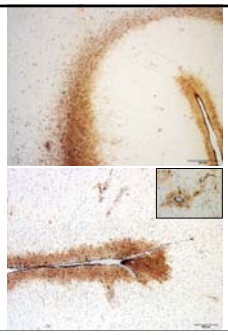
We identified a pattern of **Interface Astroglial Scarring** that we believe represents an unique pattern of repair from injury related to the blast wave interacting with the brain. It is **not** seen following civilian impact TBI with survival, chronic substance abuse or in athletes with CTE (without blast exposure). This pattern fits known concepts of blast biophysics that blast wave energy is released at differing tissue density interfaces.



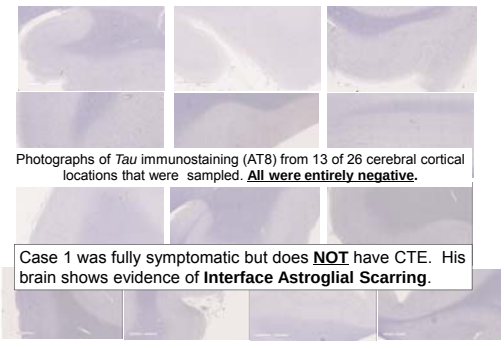


Case 1

- Navy Seal deployed multiple times to Iraq, Lebanon, Afghanistan
- Numerous blast exposures with multiple episodes of ruptured tympanic membranes. Participated in missions in which team members died of acute blast exposure
- Severe, intractable sleep disturbance
- Hearing loss, headache, depression, anxiety, PTSD (nightmares, hyper-vigilance, agitation, avoidance).
- Severe alcohol abuse
- Died of suicide (hanging) at age 29



GFAP Stain Shows Interface Astroglial Scarring



Photographs of *Tau* immunostaining (AT8) from 13 of 26 cerebral cortical locations that were sampled. **All were entirely negative.**

Case 1 was fully symptomatic but does **NOT** have CTE. His brain shows evidence of **Interface Astroglial Scarring**.

Case 2

- Navy Seal
- Multiple deployments
- Alcohol abuse
- Severe sleep disturbance, headaches, memory problems
- Diagnosed with PTSD
- Wife obtained court order of protection and sought involuntary psychiatric evaluation
- Died of drowning (likely suicidal) at age 35

GFAP staining of Case 2 reveals evidence of **interface astroglial scarring.**

CASE 2: Photomicrographs of Multiple Neocortical Samples with Negative *Tau* Immunohistochemical (AT8) Results

Photomicrographs of Negative *Tau* Immunohistochemistry (AT8) Hippocampus (CA1)

Single *Tau*-Immunoreactive Neuron (AT8) Cingulate Cortex

Case 3

- US Army medic
- In very close proximity to IED
- Alcohol abuse
- Depression, headaches, sleep disorder, impulsiveness, outbursts of anger, PTSD
- Died – gunshot wound to head at age 36

Neuropathology Results:

Interface Astroglial Scarring

Negative tau staining

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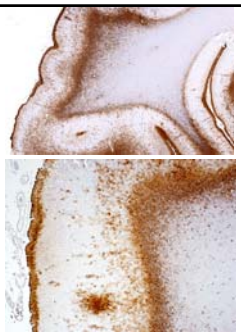
Case 4

- Former Navy Seal who served in Desert Storm, OIF and OEF where he was considered to be highly competent, reliable and emotionally stable.
- In combat and training exercises, exposed to numerous blasts at close proximity.
- Wrestled in high school (no football), 3 MVAs
- Developed persistent headaches, sleep disturbance, short-term memory problems, jumbled speech, trouble maintaining mental focus.
- Following discharge from service, clinicians described poor eye contact, flat affect and low voice tone and diagnosed PTSD.
- He died of a self-inflicted gunshot wound (age 45).



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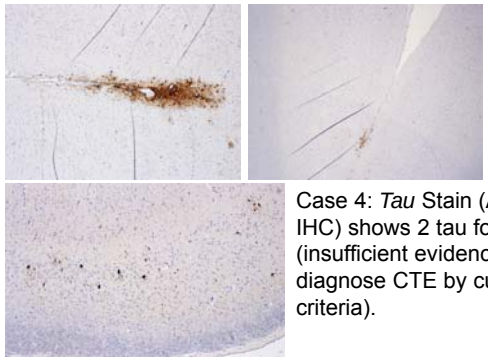

Case 4: *Tau* Stain (AT8 IHC) shows 2 tau foci (insufficient evidence to diagnose CTE by current criteria).

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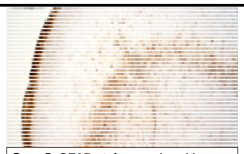
Case 5

- Navy Seal, numerous blast exposures in training and missions.
- Drinking excessively, headaches, sleep disorder, erratic behavior, lack of organization, anxiety, depression, diagnosed with PTSD.
- NICOE workup revealed 10 deployments, exposure to over 300 breeches, 100 mortar launches, 6-7 incoming rocket propelled grenade blasts and 20-30 other nearby grenade blasts.
- Death from self-inflicted gunshot wound (age 46)

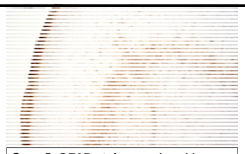


Case 5: **GFAP stain** reveals evidence of **interface astroglial scarring.**

Case 5: **tau stain** also shows evidence of **very "early" CTE** (McKee Stage I CTE).

Case 5

- Age 18: assaulted, hit on head with iron mallet with LOC
- Played football in high school, college and arena (post-college), several concussions, no LOC
- Navy Seal, numerous blast exposures in training and missions.
- Drinking excessively, headaches, sleep disorder, erratic behavior, lack of organization, anxiety, depression, diagnosed with PTSD.
- NICOE workup revealed 10 deployments, exposure to over 300 breeches, 100 mortar launches, 6-7 incoming rocket propelled grenade blasts and 20-30 other nearby grenade blasts.
- Death from self-inflicted gunshot wound (age 46)



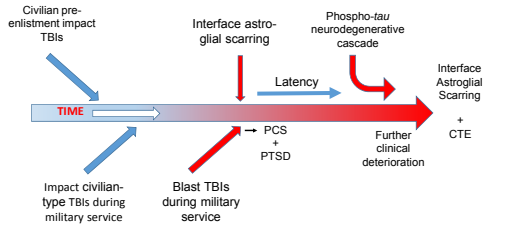
Case 5: **GFAP stain** reveals evidence of **interface astroglial scarring.**

Case 5: **tau stain** also shows evidence of **very "early" CTE** (McKee Stage I CTE).

Neuropathologic Evaluation Of 5 Cases of Service Members With Blast TBI Who Died of Suicide

Case	Age at Death	Mil. Service	PTSD	Other TBI exposure	NP Diagnosis
Case 1	29 years	Navy Seal	Yes	Wrestling	**IAS**, no tau (no CTE)
Case 2	35 years	Navy Seal	Yes	None known	**IAS,** no tau (no CTE)
Case 3	36 years	Army Medic	Yes	None known	**IAS**, no tau (no CTE)
Case 4	**45 years**	Navy Seal	Yes	Wrestling, MVA	**IAS**, **2 foci of tau** (not sufficient for CTE diagnosis)*
Case 5	**46 years**	Navy Seal	Yes	Football, TBI	**IAS**, **early (Stage I) CTE***

* The extent of tau pathology identified in cases 4 and 5 was not considered sufficient to significantly contribute to the symptoms noted clinically.



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?
- 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

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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 could 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.

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. This problem will undoubtedly 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.

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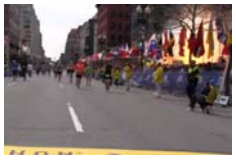
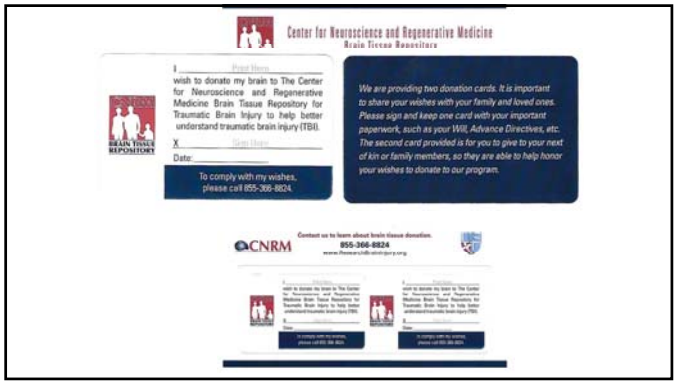
Blast TBI – No Longer a Strictly Military Issue

With episodes, such as the bombing of the Alfred P. Murrah Building (Oklahoma City), Boston marathon, and the recent Paris and Brussels attacks, the long-term effects of blast TBI are no longer strictly a military issue. Increasing numbers of civilians are also being exposed to these weapons.





We need to pause to thank the Service Members and their families who have agreed to brain donation.

Without this precious gift, we could not do our work.

Many of our donor families have expressed the feeling that although their loved ones have made the ultimate sacrifice, through brain donation, they continue to serve their Country.

CNRM BRAIN TISSUE REPOSITORY

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www.researchbraininjury.org