Effects of low-level blast exposure on the nervous system

HSR&D Cybersminar

Dr. Gregory Elder

Nov. 10, 2014

Disclosures

- Research support from the Department of Veterans Affairs, Veterans Health Administration, Rehabilitation Research and Development Service.

Poll Question #1

- What is your primary role in VA?
  - student, trainee, or fellow
  - clinician
  - researcher
  - manager or policy-maker
  - Other

Prominence of TBI in the wars in Iraq and Afghanistan

"the next time I come to, I'm at Walter Reed-like 10 days later"

Traumatic Brain Injury in the War Zone

Susan Okie, M.D.

Related article, page 2121

An interview with Dr. Okie can be heard at www.nejm.org.

Sergeant David Emme, a supply officer with a U.S. Army Stryker Brigade, was stationed at a submachine gun on a truck rolling through northern Iraq last November, in a convoy transporting Iraqi volunteers to Mosul for military training. As they entered the town of Talafar, Emme noticed that the streets were unusually quiet: no children were outdoors running toward the vehicles demanding sweets. Emme got on the radio and warned others in the convoy: "Something might happen. They might have some plan for us." Moments later, as they slowed at a traffic circle, an improvised explosive device (IED) went off right next to Emme's truck, knocking him out.

Emme's version of what happened next is patched together, from his own memories and what

Sergeant David Emme.

Jonathan Ernst

"The next time I come to, I'm at Walter Reed — like, 10 days later," he recalled.

NEJM 352: 2043-7, 2005

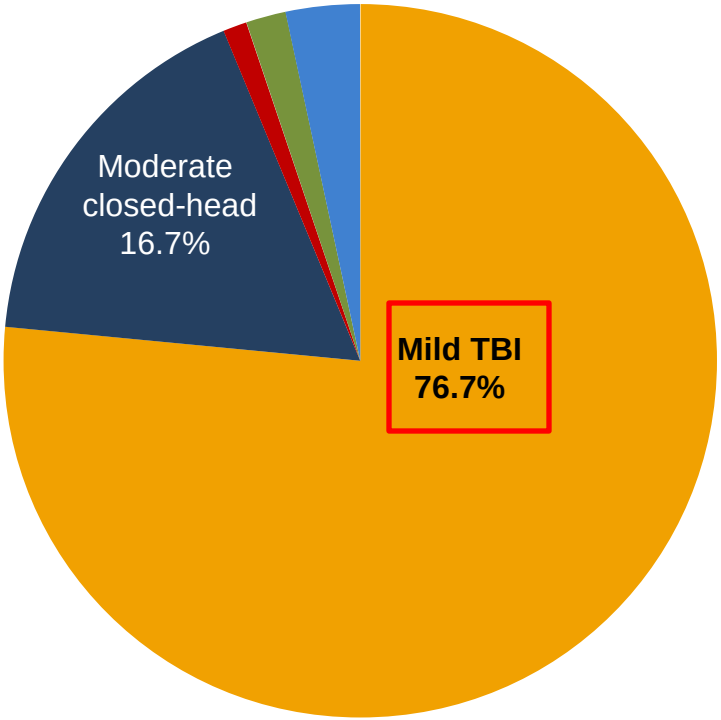
-TBI has been common with 10-20% of returning veterans having suffered a TBI.

-Initially most attention focused on moderate to severe TBIs recognized in theatre.

-The war in Iraq has lead to the highest number of military related severe TBIs since the Vietnam era.
-However, most TBIs were mild and many not recognized prior to discharge.

2000 – 2011 1st quarter

Penetrating	**3,573**
Severe	**2,235**
Moderate	**35,661**
Mild	**163,181**
Not Classifiable	**8,092**
TOTAL - All Severity	**212,742**



Source: Military Health System U.S. Dept of Defense
http://www.health.mil/Research/TBI_Numbers/

Diverse mechanisms have caused TBIs but in Iraq and Afghanistan blast exposure from improvised explosive devices (IEDs) most common cause of TBI.

For BBC Video of shock wave in slow motion see
http://www.youtube.com/watch?v=XIWeEWCvuyE

Current Questions

- What are the effects of low-level blast exposure (i.e. mTBI or subclinical blast)?
- Why is there a relationship between blast-related mTBI and post-traumatic stress disorder (PTSD)?
- Is there a relationship between low-level blast exposure and chronic neurodegenerative diseases?
- Is blast pathophysiologically different from non-blast TBI (e.g. civilian closed head injuries)?

What are the effects of low-level blast exposure (i.e. mTBI or subclinical blast)?

- Why does it matter?
- >75% of blast-related TBI is mTBI.
- Improved personal protective equipment mitigated the severity of other injuries (e.g. blast lung).
- Subclinical blast in operational settings such as Iraq common.
- Why is there a controversy?
- It’s so hard to separate mTBI from post-traumatic stress disorder (PTSD) and if they have blast-related mTBI they also have PTSD.

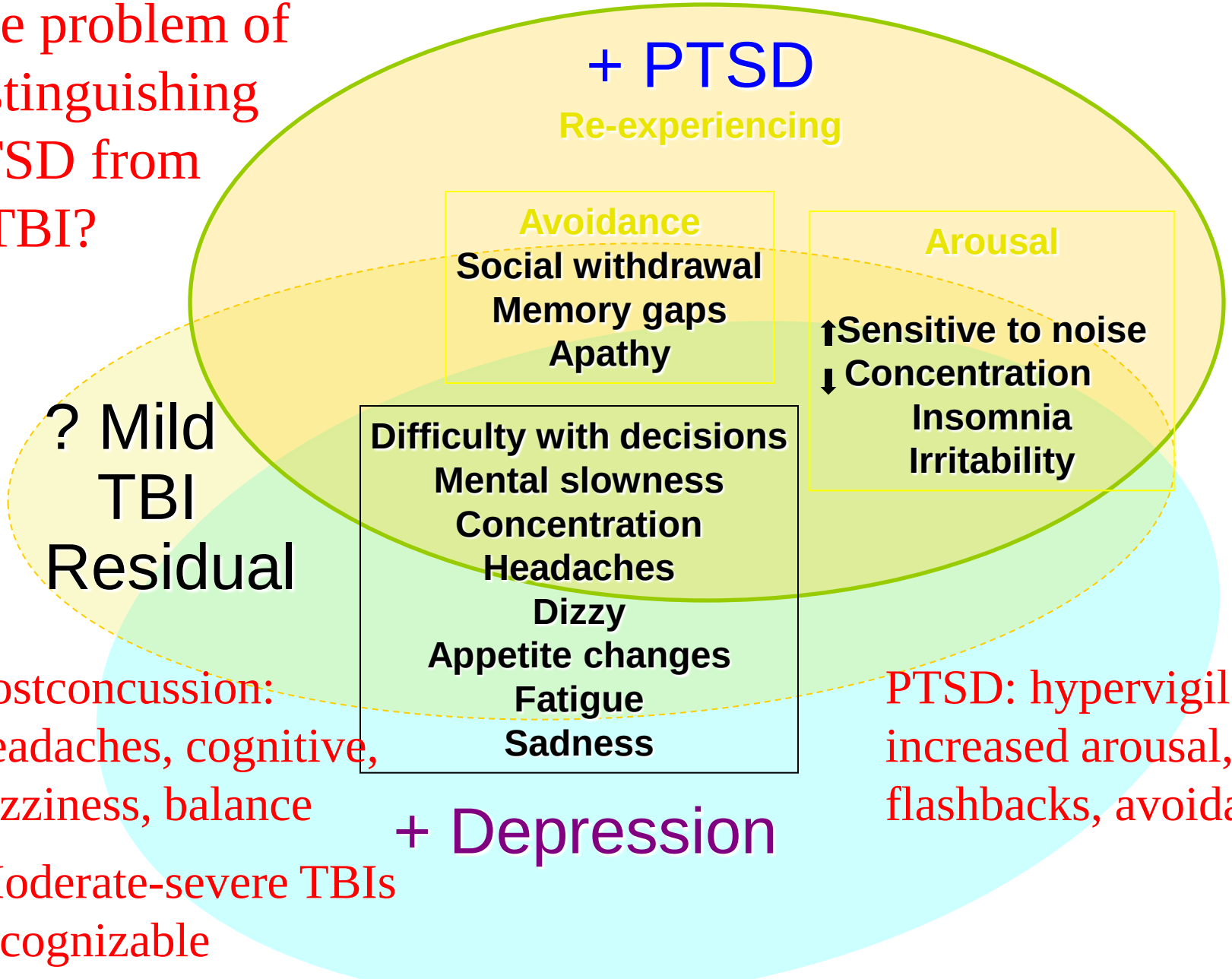
Distinguishing blast-related mild TBI from post traumatic stress disorder (PSTD)

-One of the striking features of the mTBI cases being seen in the current veterans is the high prevalence of PTSD seen in association with mTBI

-Population based studies 30-40%

-In clinic based populations >90%

The problem of distinguishing PTSD from mTBI?



Postconcussion: headaches, cognitive, dizziness, balance

PTSD: hypervigilance, increased arousal, flashbacks, avoidance

Moderate-severe TBIs recognizable by cognitive deficits (Neuropsych mTBI = PTSD)

-Distinction more complicated by the newer definition of “mild” TBI.
-TBI requires an event (some sort of head trauma).
-Historically concussion = loss of consciousness.
-Redefined to transient disturbance of neurological function including being “stunned, dazed or confused.”
-Lower threshold to labeling an “event” as “a TBI.”

Are we over diagnosing mTBI?

Care of War Veterans with Mild Traumatic Brain Injury — Flawed Perspectives

Charles W. Hoge, M.D., Herb M. Goldberg, B.A., B.Ed., and Carl A. Castro, Ph.D.

Researchers estimate that more than 300,000 U.S. veterans of the wars in Iraq and Afghanistan (20% of the 1.6 million) have sustained a mild traumatic brain injury (TBI), also known as concussion, with the majority going untreated.[1] In response, the Defense and the VA — a blow or jolt to the head resulting in brief alteration in consciousness, loss of consciousness (lasting less than 30 minutes), or post-traumatic amnesia — is inadequate for achieving the objectives of these well-intentioned initiatives. The

To identify those who sustained a concussion/mild TBI during deployment, the postdeployment screening form asks service members and veterans to recall whether they were "dazed" or "confused" at the time of an injury or blast "experience." Posi-

NEJM 360: 1588-1591, 2009

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ESTABLISHED IN 1812 JANUARY 31, 2008 VOL. 358 NO. 5

Mild Traumatic Brain Injury in U.S. Soldiers Returning from Iraq

Charles W. Hoge, M.D., Dennis McGurk, Ph.D., Jeffrey L. Thomas, Ph.D., Anthony L. Cox, M.S.W., Charles C. Engel, M.D., M.P.H., and Carl A. Castro, Ph.D.

ABSTRACT

BACKGROUND

An important medical concern of the Iraq war is the potential long-term effect of mild traumatic brain injury, or concussion, particularly from blast explosions. However, the epidemiology of combat-related mild traumatic brain injury is poorly understood.

METHODS

We surveyed 2525 U.S. Army infantry soldiers 3 to 4 months after their return from a year-long deployment to Iraq. Validated clinical instruments were used to compare soldiers reporting mild traumatic brain injury, defined as an injury with loss of consciousness or altered mental status (e.g., dazed or confused), with soldiers who reported other injuries.

From the Division of Psychiatry and Neuroscience, Walter Reed Army Institute of Research, U.S. Army Medical Research and Materiel Command, Silver Spring, MD (C.W.H., D.M., J.L.T., A.L.C., C.A.C.); and the Deployment Health Clinical Center and Uniformed Services University of Health Sciences, Washington, DC (C.C.E.). Address reprint requests to Dr. Hoge at the Division of Psychiatry and Neuroscience, Walter Reed Army Institute of Research, 503 Robert Grant Ave., Silver Spring, MD 20910, or at charles.hoge@us.army.mil.

"When PTSD and depression were included in the analysis, the associations between loss of consciousness and the multiple physical symptoms disappeared, except for two, (headache and heart pounding)."

Subsequent studies

"persistent postconcussive symptoms only in those whose TBI involved LOC and not in the majority of MTBI cases as currently defined."

Mild Traumatic Brain Injury (Concussion) During Combat: Lack of Association of Blast Mechanism With Persistent Postconcussive Symptoms

Joshua E. Wilk, PhD; Jeffrey L. Thomas, PhD; Dennis M. McGurk, PhD; Lyndon A. Riviere, PhD; Carl A. Castro, PhD; Charles W. Hoge, MD

J. Head Trauma Rehabil 25: 9-14, 2010

"postconcussive symptoms are common in returning troops and while some may be related to blast exposure, the association is not specific."

Symptoms of post-concussional syndrome are non-specifically related to mild traumatic brain injury in UK Armed Forces personnel on return from deployment in Iraq: an analysis of self-reported data

N. T. Fear[1]*, E. Jones[2], M. Groom[3], N. Greenberg[1], L. Hull[2], T. J. Hodgetts[4] and S. Wessely[2]

[1] *Academic Centre for Defence Mental Health, King's College London, London, UK*
[2] *King's Centre for Military Health Research, King's College London, London, UK*
[3] *Defence Medical Services, Ministry of Defence, London, UK*
[4] *Royal College of Defence Medicine, Ministry of Defence, Birmingham, UK*

Psychological Medicine 39: 1379-1387, 2009

“in terms of long-term adverse health outcomes in humans there is sufficient evidence of a causal relationship to blast only for penetrating eye injuries and some long-term effects on the genitourinary organ. For postconcussion symptoms and persistent headaches following blast-related mTBI… only sufficient evidence for an association”.

Institute of Medicine, 2014

Gulf War and Health, Volume 9
Long-Term Effects of Blast Exposures

Committee on Gulf War and Health: Long-Term Effects of Blast Exposures

Board on the Health of Select Populations

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Could it all be PTSD?

Poll Question #2

- What is your primary specialty or primary area of interest in VA?
  - Primary care
  - Neurology/Neurosurgery
  - Rehabilitation Medicine
  - Mental Health
  - Other

Other studies have suggested that the link may be more than coincidental

Posttraumatic Stress Disorder in Combat Casualties With Burns Sustaining Primary Blast and Concussive Injuries

Alejandra G. Mora, BS, Amber E. Ritenour, MD, Charles E. Wade, PhD, John B. Holcomb, MD, Lorne H. Blackbourne, MD, and Kathryn M. Gaylord, PhD, APRN, BC

J. Trauma 66: S178-S185, 2009

"*greater prevalence of PTSD in burn patients with primary blast injury and MTBI than in burn patients injured by other mechanisms*".

Head Injury as a PTSD Predictor Among Oklahoma City Bombing Survivors

Timothy Walilko, PhD, Carol North, MD, MPE, Lee Ann Young, MA, Warren E. Lux, MD, Deborah L. Warden, MD, Michael S. Jaffee, MD, FC USAF, and David F. Moore, MD, PhD

J. Trauma 67: 1311-1319, 2009

"*significant association between PTSD and head/brain injuries*" while PTSD was not highly correlated with other injuries.

-Vietnam veterans TBI is associated with more severe PTSD (Vanderploeg et al. Arch Phys Med Rehabil 90: 1084-93, 2009)

-OIF/OEF veterans, PTSD is more prevalent in veterans reporting mTBI, as compared to veterans who suffered no injury (Schneiderman et al. Am J Epidemiol 167: 1446-52, 2008)

-Relationship between TBI and PTSD-different ends of a spectrum with TBI an organic brain disease and PTSD a psychologically based reaction to a stressor that was not associated with physical injury.
-Suggested that the post-traumatic amnesia associated with TBI may protect against PTSD.
-A neural insult may alter reactions to psychological stressors and increase the likelihood that PTSD will develop?
-Could blast damage brain structures that are involved in the development of PTSD?

-Functional neuroimaging data: heightened amygdala activity…decreased hippocampal and orbital frontal activity…inadequate frontal inhibition of the amygdala…lead to exaggerated amygdala responses to psychological threats

Biological Models of PTSD

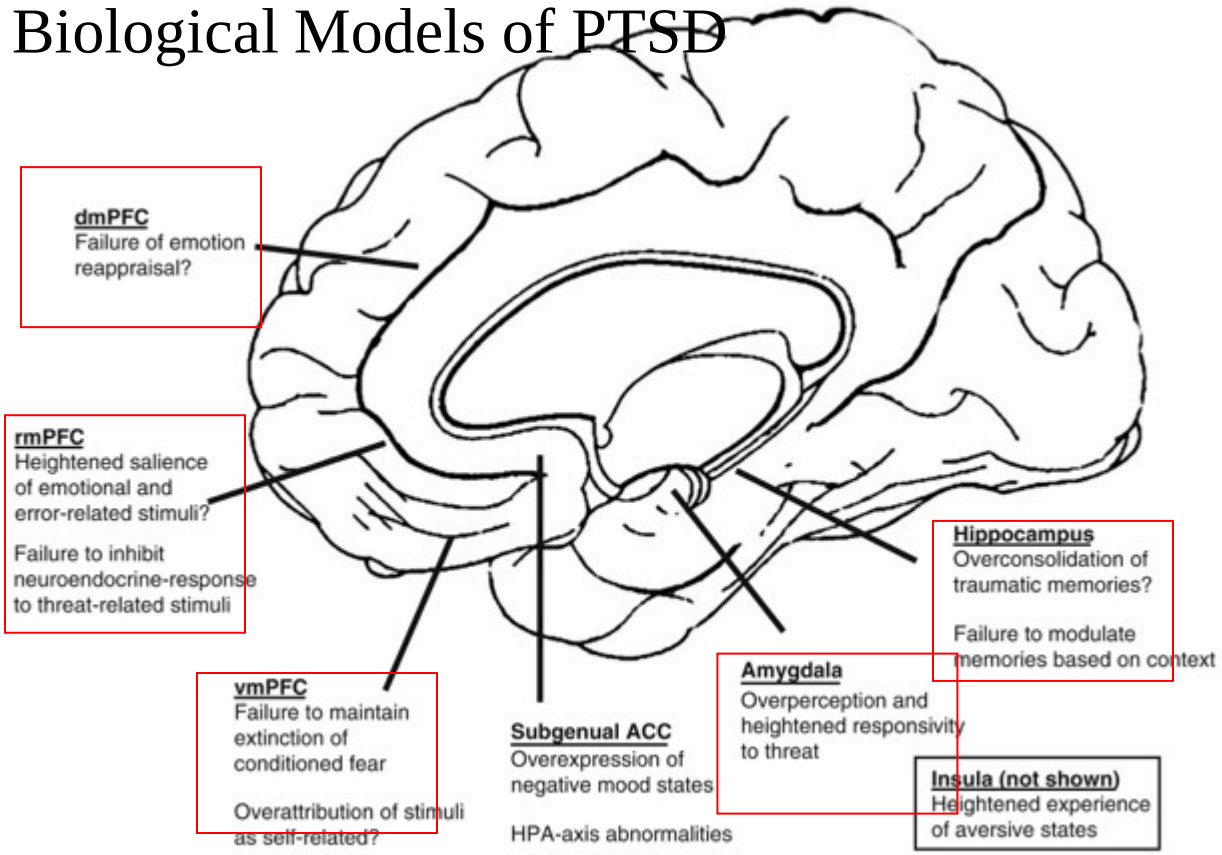


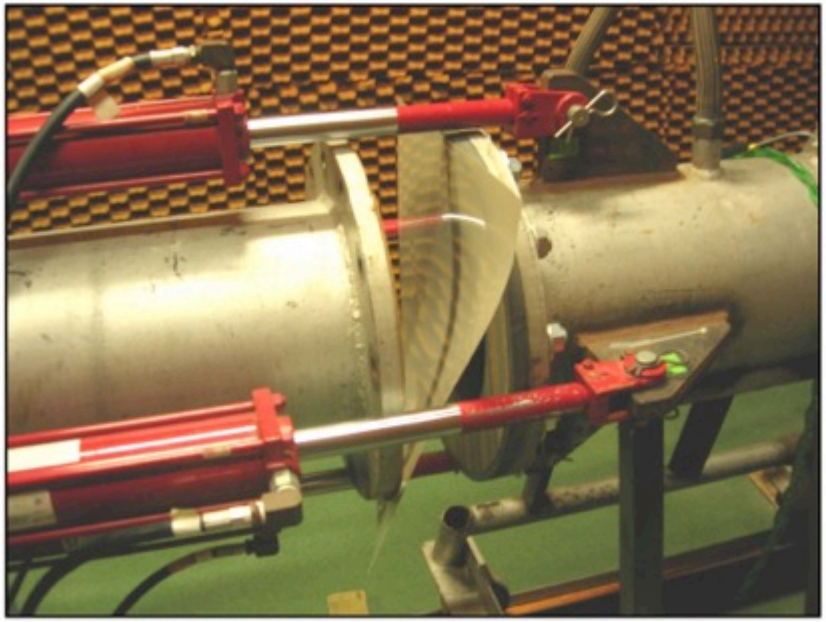
Fig. 1. Neural regions implicated in PTSD, dmPFC = dorsomedial prefrontal cortex, rmPFC = rostral medial prefrontal cortex, vmPFC = ventromedial prefrontal cortex, ACC = anterior cingulate cortex.

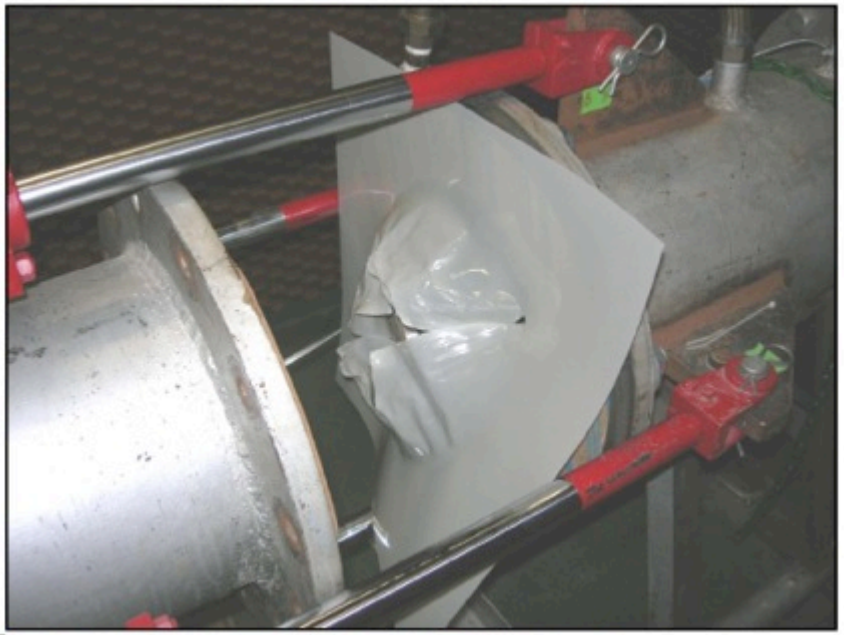
Liberzon and Sripada, Prog Br Res 167: 151-169, 2008

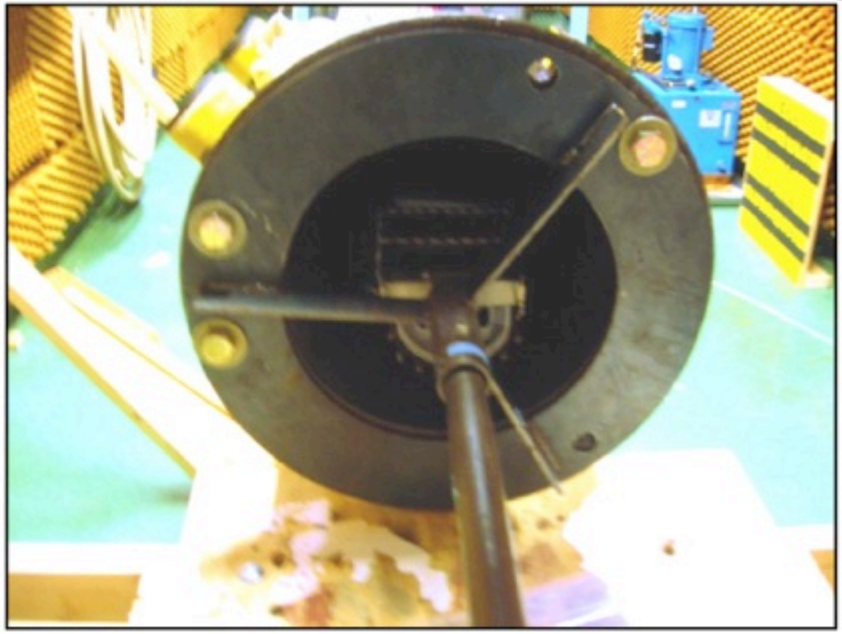
-Service personnel in a war zone inevitably have exposure to PTSD stressors independent of TBI events, making it hard to sort out.

Shock tube at the Naval Medical Research Center, Silver Spring MD

Courtesy Steve Ahlers and Miklus Chavko







Courtesy Dr. Steve Ahlers
Naval Medical Research Center
Silver Spring MD

Exposure	Motor	Cognitive	Pathology
0 kPa	None	None	No overt pathology
40 kPa (5.8 psi)	None	None	No overt pathology
75 kPa (10.9 psi)	None	mild anterograde amnesia on passive avoidance task (frontal orientation only)	No overt pathology
120 kPa (17.4 psi)	Transient loss of the righting reflex; impairment of gross motor function as judged by balance beam performance	anterograde amnesia on a passive avoidance task	30% gross cerebral and subdural hemorrhages and contusions; all pulmonary hemorrhages

10.9 psi and 17.4 psi dividing line between mild transient disturbances/no pathology (= low level blast) vs. overt pathology/polytrauma

Blast Exposure (psi)

0
5.8
10.9
17.4

No pathology | Mild TBI

Overt pathology | Moderate/Severe TBI | Polytrauma | AOC/LOC

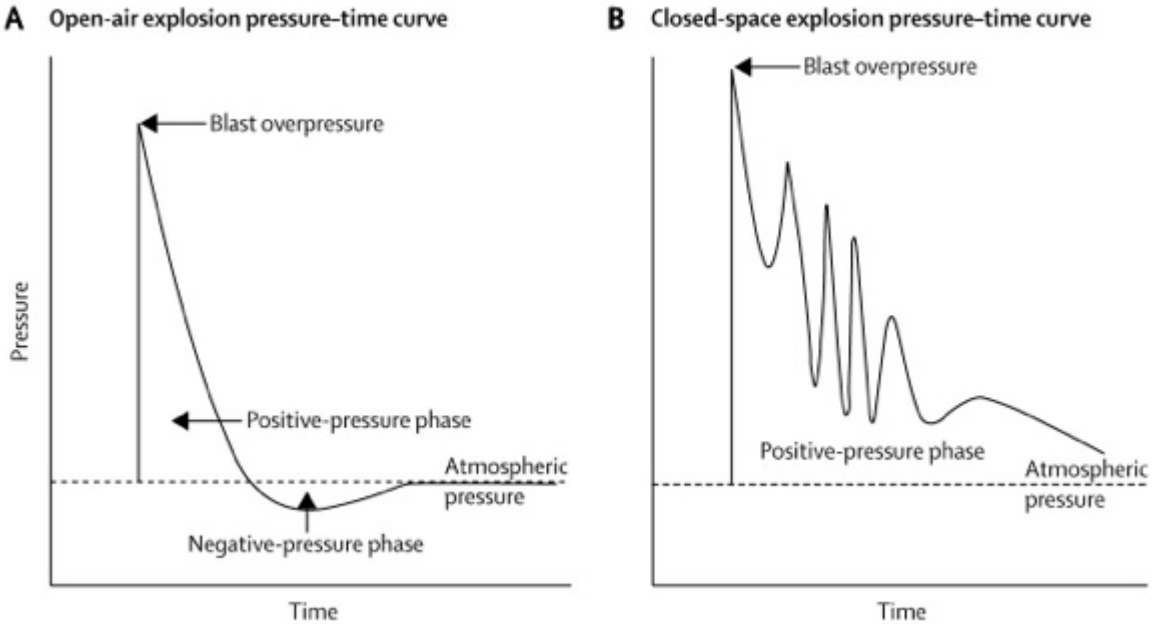
What is a relevant exposure in humans?

-Blast wave peak overpressure

-Distance from detonation

-Environmental factors- explosions within enclosed structures or adjacent to walls become amplified by shockwave reflection causing greater injury than if exposure had occurred in an open space

Wolf et al. Lancet 374: 405-415, 2009



Best controlled data on human blast exposure from breacher studies

Maximum breacher exposure = 12.9 psi

Courtesy of S. Ahlers and the Breacher Consortium

-Coincident exposures hard to control for in clinical studies.

In animals:

-Control over conditions

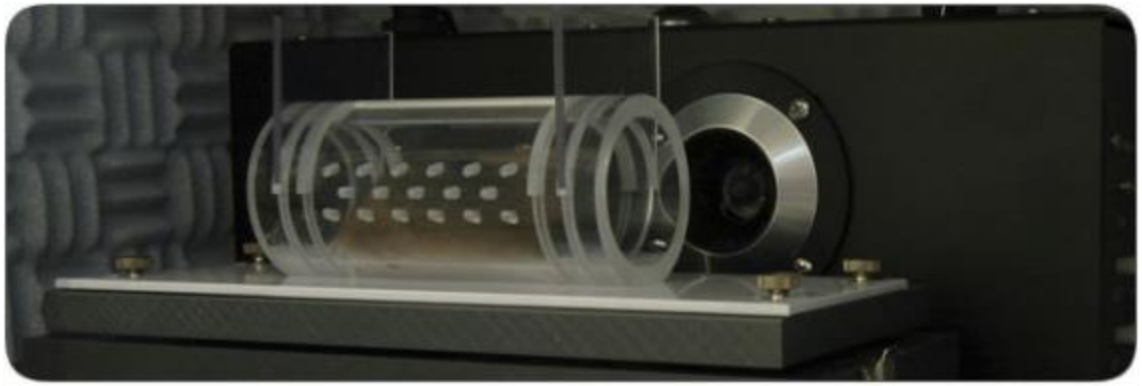
-Studies under anesthesia (no psychological stressor)

-Question: would blast exposure induce PTSD-related traits?

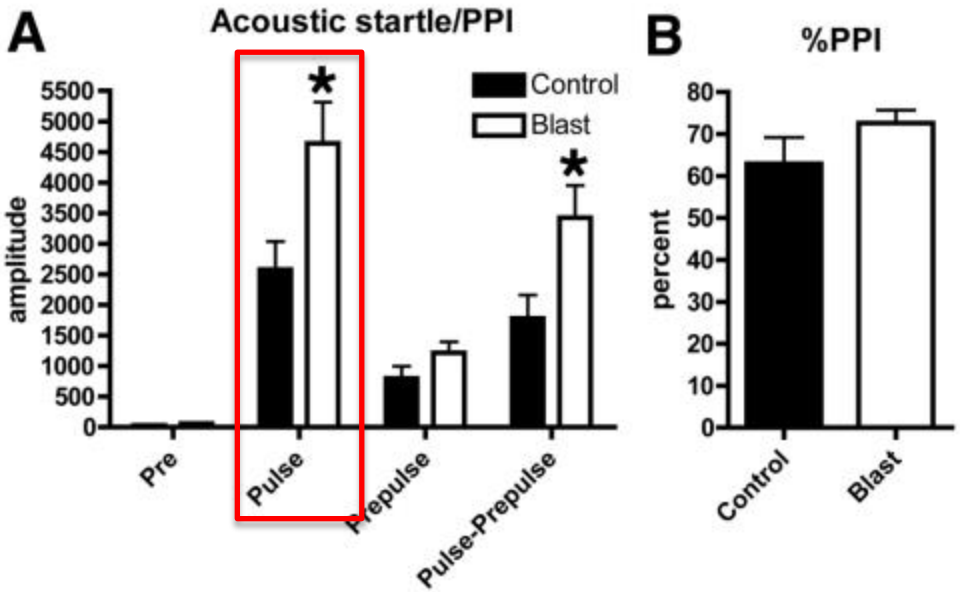
Core features of PTSD grouped into three categories:
-Re-experiencing (flashbacks, nightmares, thoughts)
-Avoidance (crowds, reminders)
-Hyperarousal (hypervigilance, easy startle)

Associated features:
Anxiety, mood, cognitive, sleep, somatic

acoustic startle (hyperarousal)



Increased acoustic startle in blast exposed rats



Pre = background
Pulse = acoustic startle (120 dB)
Prepulse = acoustic startle after prepulse (79 dB)
%PPI = degree to which the prepulse dampened the acoustic startle
* indicates p = 0.02

PTSD = prolonged and exaggerated response to a threat.
Are blast exposed rats more responsive to a PTSD related stressor?

Setting Apart the Affected: The Use of Behavioral Criteria in Animal Models of Post Traumatic Stress Disorder

Hagit Cohen*[,1], Joseph Zohar[2], Michael A Matar[1], Kaplan Zeev[1], Uri Loewenthal[1] and Gal Richter-Levin[3]

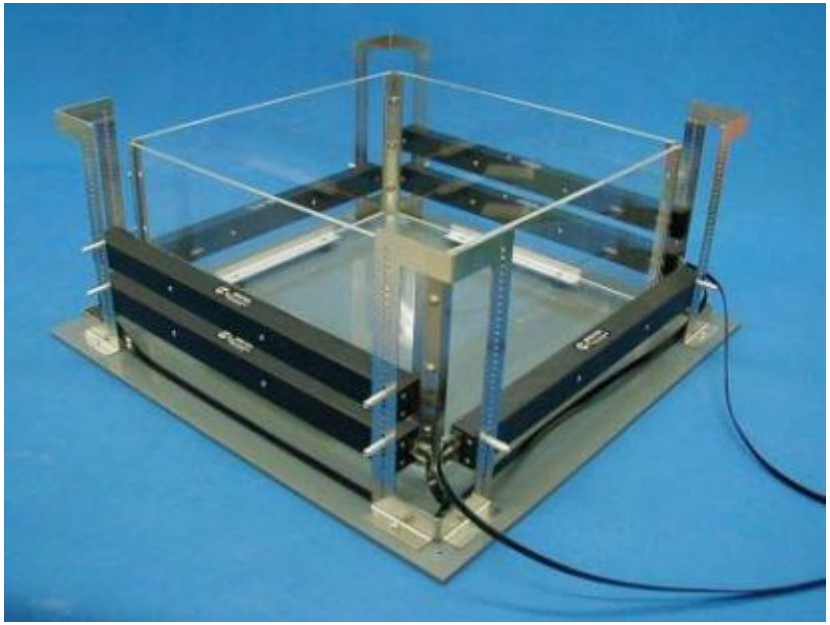
[1]Anxiety and Stress Research Unit, Ministry of Health Mental Health Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer- Sheva, Israel; [2]The Chaim Sheba Medical Center, Sackler Medical School, Tel-Aviv University, Israel; [3]Department of Psychology, University of Haifa, Israel

Post-traumatic stress disorder (PTSD) affects about 20–30% of exposed individuals. Clinical studies of PTSD generally employ stringent criteria for inclusion in study populations, and yet in animal studies the data collection and analysis are generally expressed as a function of exposed *vs* nonexposed populations, regardless of individual variation in response. Prior data support an approach to animal models analogous to inclusion criteria in clinical studies. This series of studies sought to assess prevalence rates of maladaptive *vs* adaptive responses determined according to a more stringent approach to the concept of inclusion/exclusion criteria (cutoff behavioral criteria—CBC), consisting of two successive behavioral tests (elevated plus maze and acoustic startle response tests). The rats were exposed to stressors in two different paradigms; exposure to a predator and underwater trauma. The prevalence rates of maladaptive responses to stress in these two distinct models dropped over time from 90% in the acute phase to 25% enduring/maladaptive response at 7 days, to remain constant over 30 days. As setting the affected individuals apart from the unaffected approximates clinical studies, it might also help to clarify some of the pending issues in PTSD research.

Neuropsychopharmacology (2004) **29,** 1962–1970, advance online publication, 14 July 2004; doi:10.1038/sj.npp.1300523

Keywords: post-traumatic stress disorders; animal models; anxiety; predator stress; acoustic startle response; elevated plus maze; maladapted; well adapted

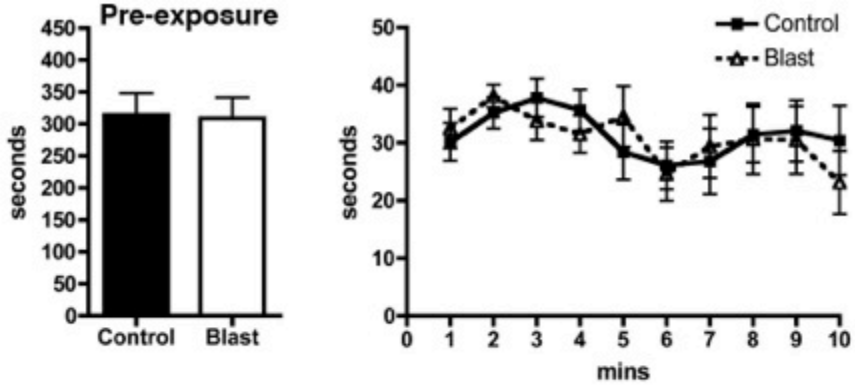
Exposure to cat urine-EZM/acoustic startle readouts



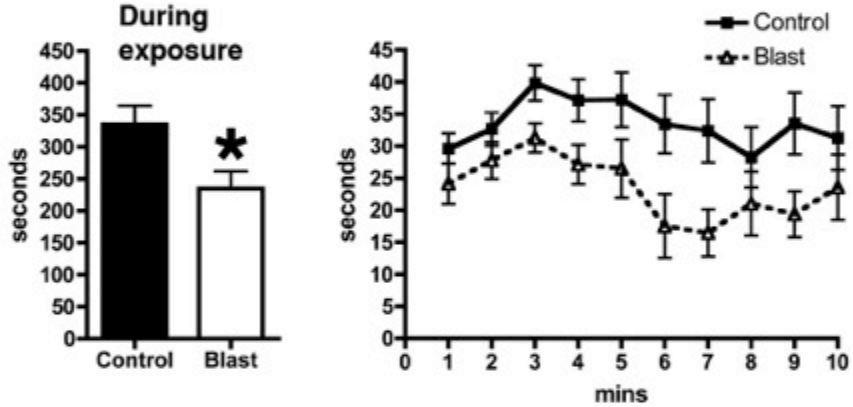
Predator scent protocol:
-Activity in open field recorded for 10 min.
-10 min exposure to cage bedding (standard corn husk) well soiled with cat urine (20mL urine in 100mL bedding, shaken together in a flask) in an open field.
-Following exposure, transferred to a clean open field cage and activity was recorded for an additional 40 min.
-Three days post-exposure: open field activity recorded for 30min

Center Time

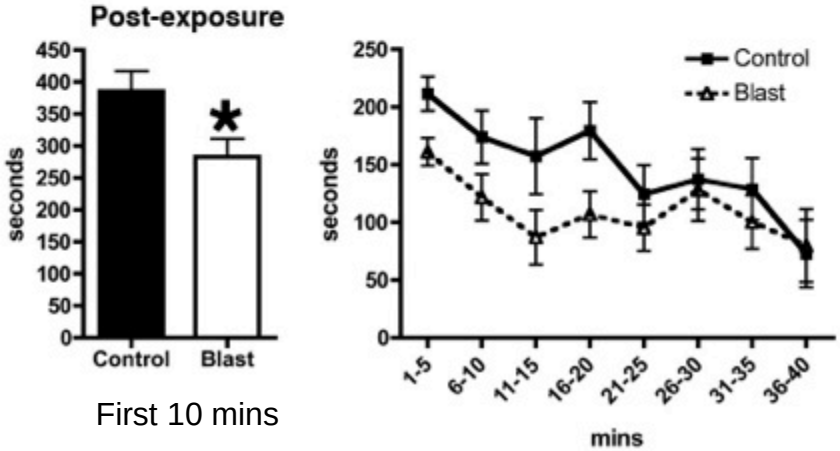
10 mins
pre-exposure



10 mins
during
exposure



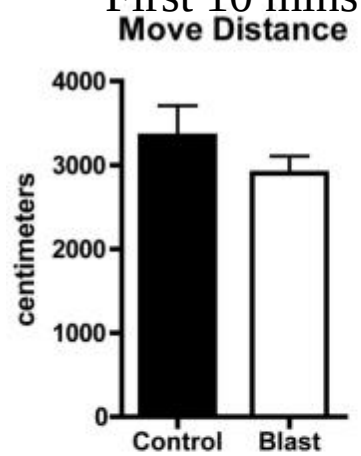
post-exposure

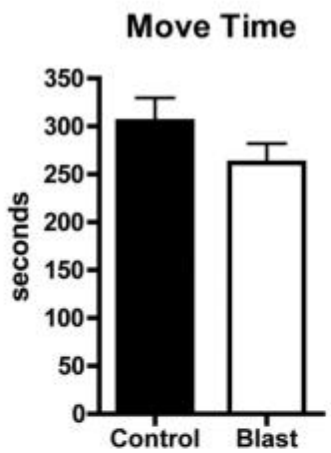


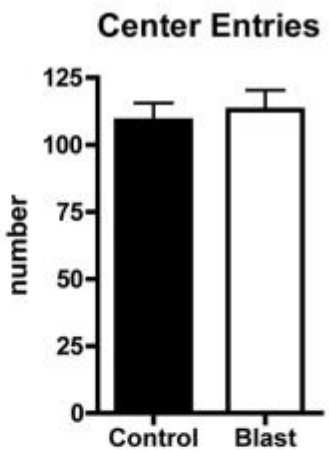
First 10 mins

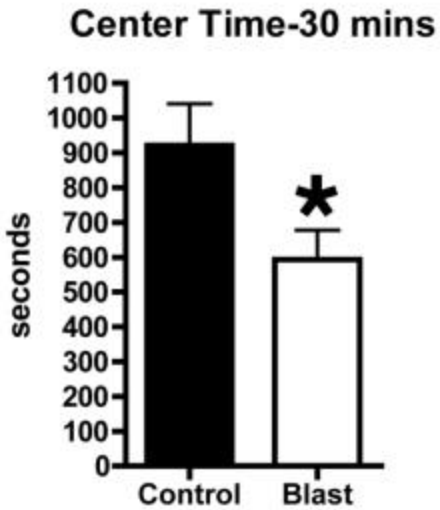
Open field three days post predator scent exposure

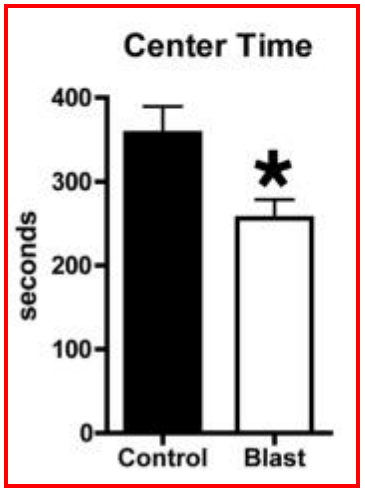
First 10 mins

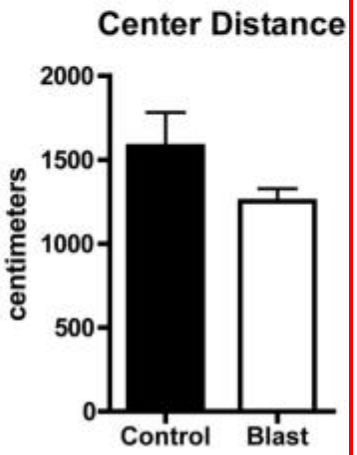


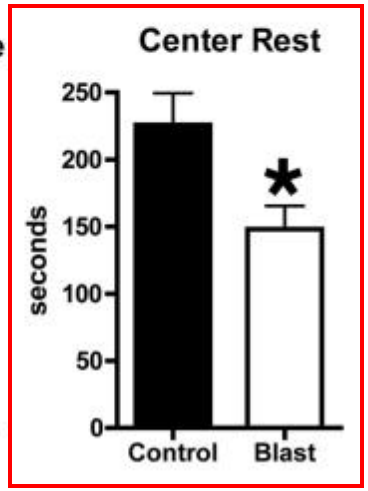


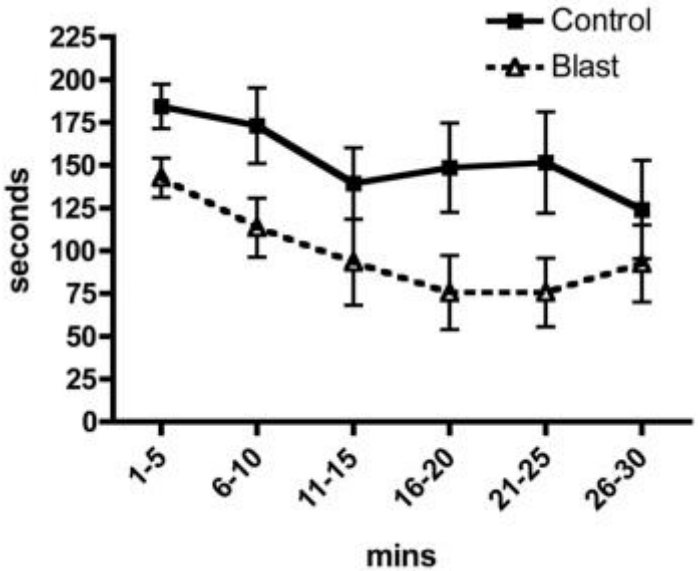












frontiers in NEUROLOGY

ORIGINAL RESEARCH ARTICLE
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A novel closed-head model of mild traumatic brain injury caused by primary overpressure blast to the cranium produces sustained emotional deficits in mice

Scott A. Heldt[1], Andrea J. Elberger[1], Yunping Deng[1], Natalie H. Guley[1], Nobel Del Mar[1], Joshua Rogers[1], Gy Won Choi[1], Jessica Ferrell[1], Tonia S. Rex[2,3], Marcia G. Honig[1] and Anton Reiner[1,2]*

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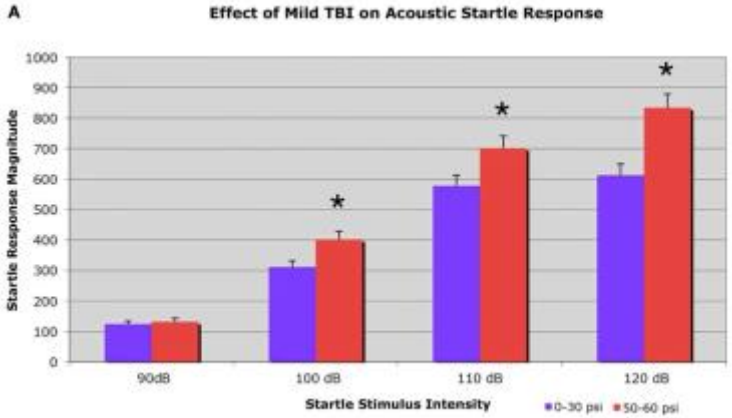
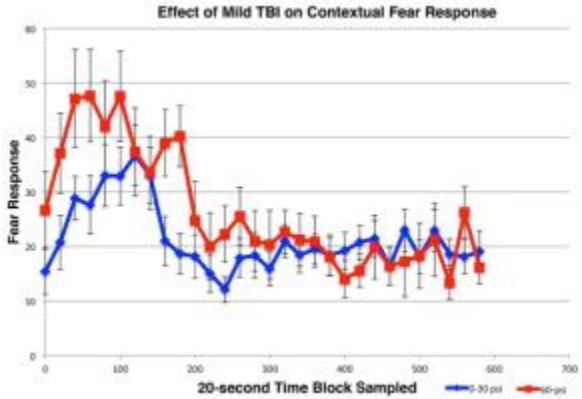
[2] Department of Ophthalmology, The University of Tennessee Health Science Center, Memphis, TN, USA
[3] Department of Ophthalmology and Visual Sciences, Vanderbilt University, Nashville, TN, USA

-Increased acoustic startle
-Enhanced contextual fear response
-Reduced extinction of a learned fear response.
-Diminished prepulse inhibition
-Depression-like behavior in a forced swim test





Blast related injury in a rat model of mTBI:

-No general histopathology

-Chronic persistent behavioral changes that mimic traits seen in PTSD

-Effects seen in anesthetized animals suggesting that no psychological stressor is necessary

-Suggest that blast injury may induce PTSD traits without a PTSD stressor and may produce a heightened reactivity to PTSD stressors

Maybe it’s not all PTSD
rather maybe blast can induce
a state that looks like PTSD?

Human neuroimaging in blast related TBI

-Diffusion tensor imaging (DTI),
-Functional MRI (fMRI)
-Positron emission tomography (PET) with fluoro-deoxyglucose.
-Most imaged mTBI
-Mostly months to years after injury

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Detection of Blast-Related Traumatic Brain Injury in U.S. Military Personnel

Christine L. Mac Donald, Ph.D., Ann M. Johnson, Dana Cooper, B.S., Elliot C. Nelson, M.D., Nicole J. Werner, Ph.D., Joshua S. Shimony, M.D., Ph.D., Abraham Z. Snyder, M.D., Ph.D., Marcus E. Raichle, M.D., John R. Witherow, M.D.,* Raymond Fang, M.D., Stephen F. Flaherty, M.D., and David L. Brody, M.D., Ph.D.

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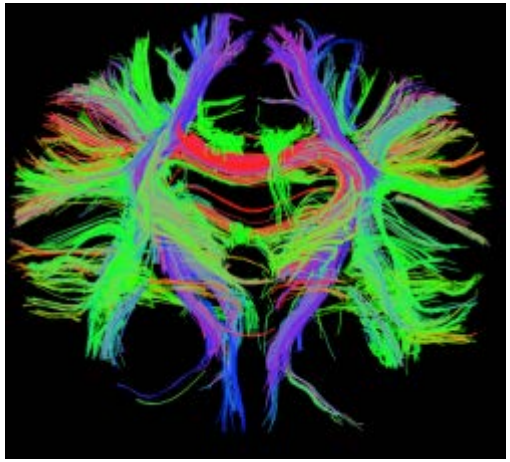
Original Articles

Neuroimaging, Behavioral, and Psychological Sequelae of Repetitive Combined Blast/Impact Mild Traumatic Brain Injury in Iraq and Afghanistan War Veterans

Eric C. Petrie,[1–3] Donna J. Cross,[3] Vasily L. Yarnykh,[3] Todd Richards,[3] Nathalie M. Martin,[3] Kathleen Pagulayan,[1,2] David Hoff,[1] Kim Hart,[1] Cynthia Mayer,[1] Matthew Tarabochia,[1] Murray A. Raskind,[1,2] Satoshi Minoshima,[3] and Elaine R. Peskind[1,2]



Most consistent finding:
Diffuse axonal injury (DAI) on DTI

DTI in PTSD?

DEPRESSION AND ANXIETY 30:207–216 (2013)

Theoretical Review

WHITE MATTER INTEGRITY AND ITS RELATIONSHIP TO PTSD AND CHILDHOOD TRAUMA—A SYSTEMATIC REVIEW AND META-ANALYSIS

Judith K. Daniels, Ph.D.,[1]* Jan-Peter Lamke,[1] Michael Gaebler,[1] Henrik Walter, Ph.D.,[1] and Michael Scheel, Ph.D.[2]

-Adult onset PTSD is associated with clusters of both increased and decreased FA in various structures

-Within blast related TBI studies findings do not differ between veterans with versus without PTSD suggesting that the abnormalities are not related to comorbid PTSD.

Poll Question #3

- Does it matter whether we call it PTSD or TBI?
  - Yes
  - No
  - Maybe

Current Questions

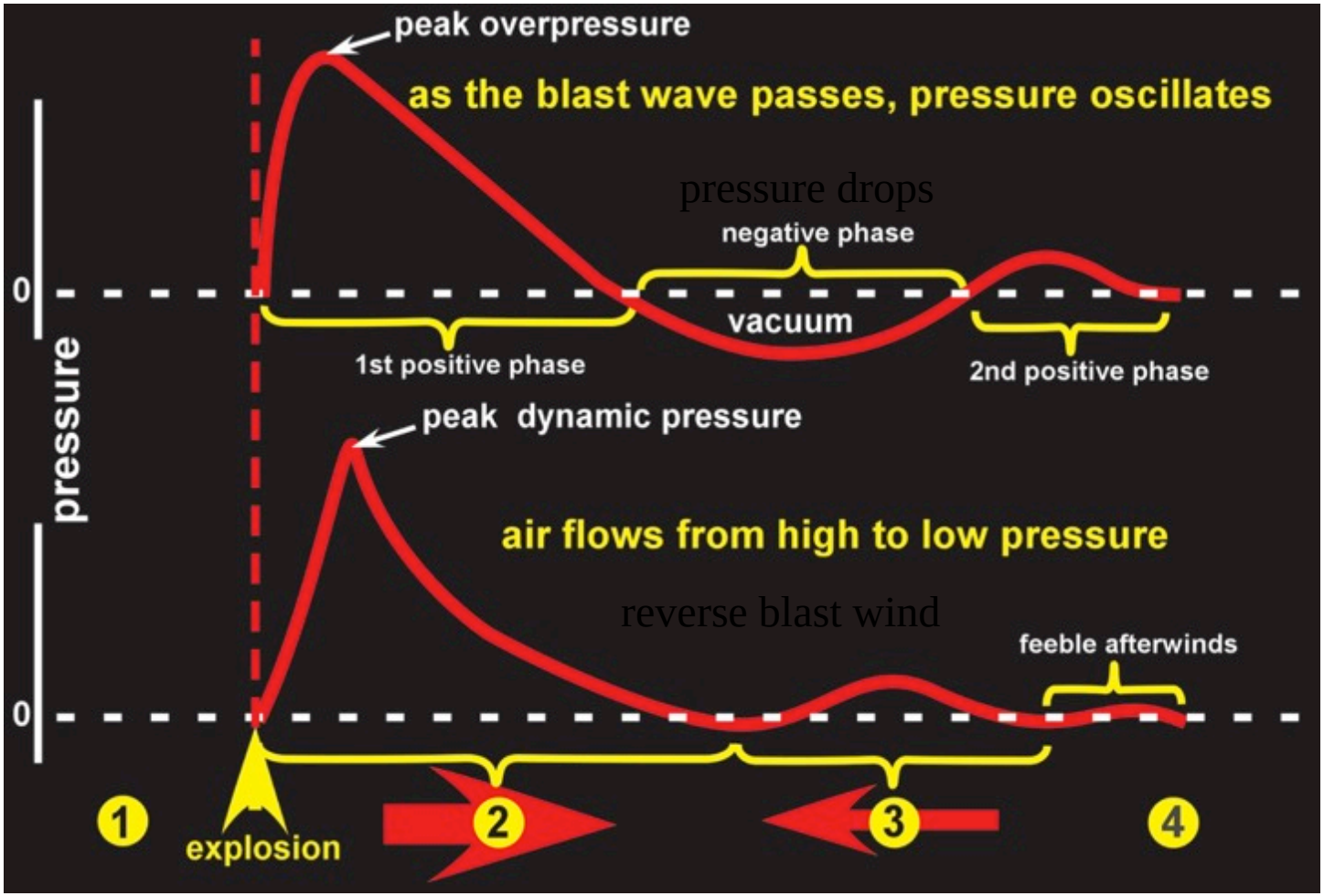
- What are the effects of low-level blast exposure (i.e. mTBI or subclinical blast)?
- Why is there a relationship between blast-related mTBI and post-traumatic stress disorder (PTSD)?
- Is there a relationship between low-level blast exposure and chronic neurodegenerative diseases?
- Is blast pathophysiologically different from non-blast TBI (e.g. civilian closed head injuries)?

Solid or liquid explosive converted to a gas

Creating a blast overpressure wave

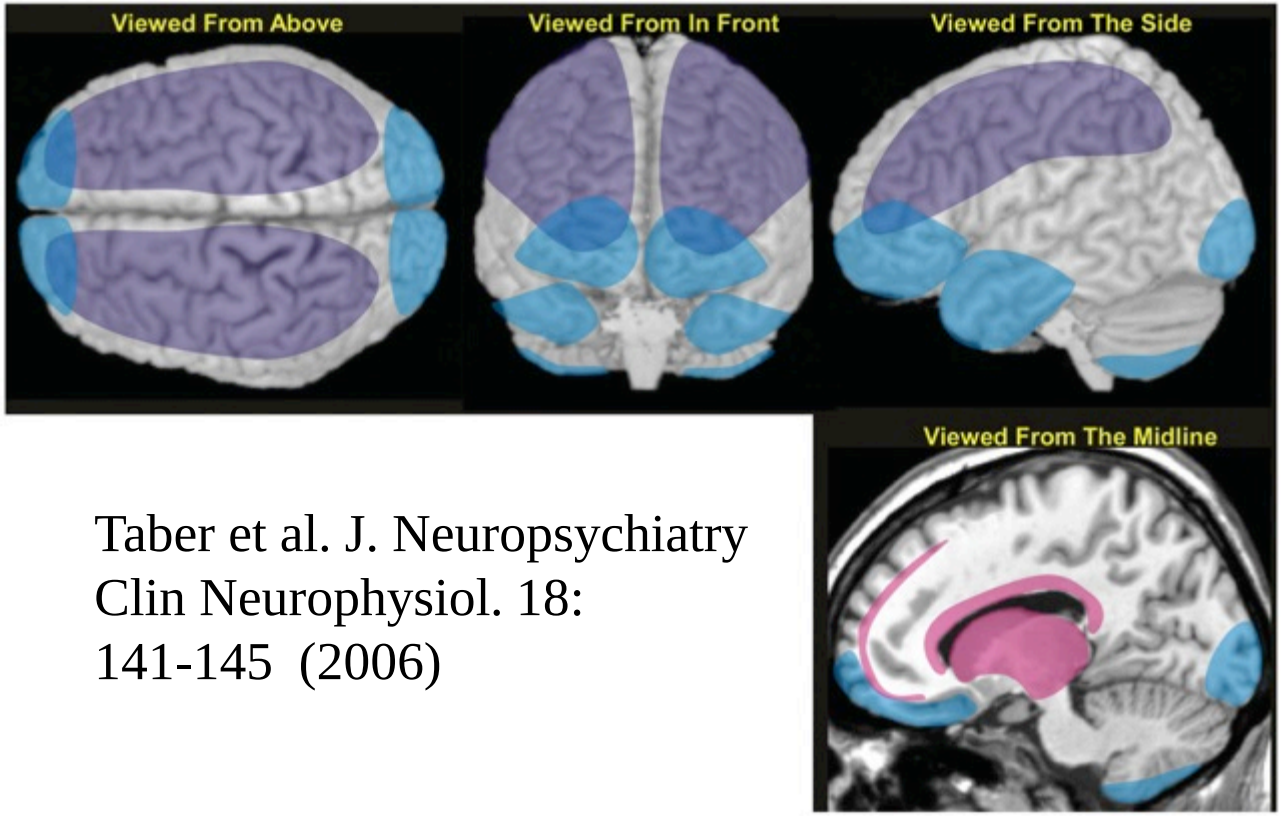
Propagates at supersonic speeds

Followed by a blast wind



Taber et al. J. Neuropsychiatry Clin Neurophysiol. 18: 141-145 (2006)

The pathophysiology of blast induced TBI (is it different from civilian TBI?)

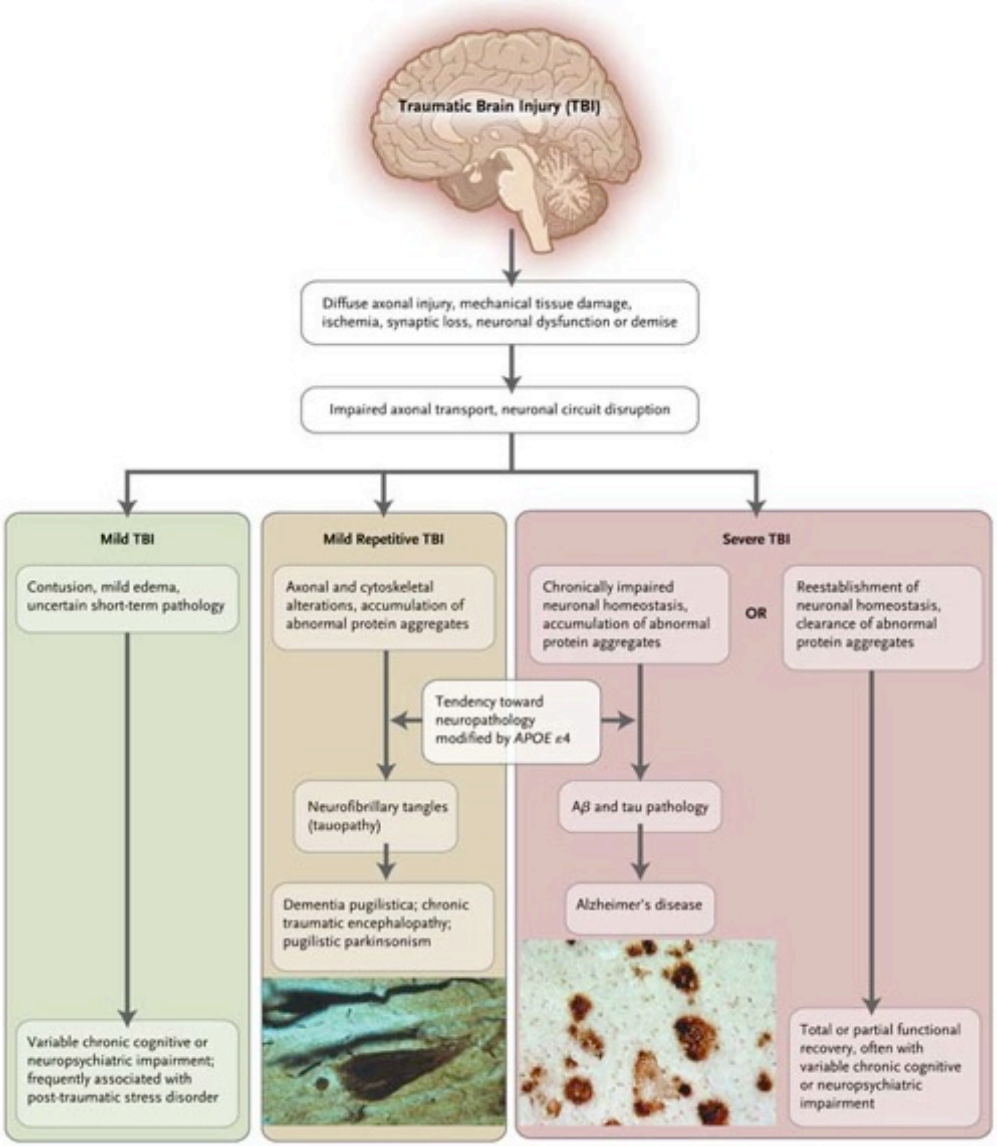


Taber et al. J. Neuropsychiatry Clin Neurophysiol. 18: 141-145 (2006)

-Blast = pressure wave
-Mechanisms in closed impact head injury (e.g. MVA):
-Bleeding/contusions
-Coup/contracoup injury most affecting the fronto-temporal regions and occipital lobes
-Diffuse axonal injury (DAI)
-Activation of secondary cascades/oxidative stress/inflammation
-Similar mechanisms are involved in moderate to severe blast-related TBI but what about the primary blast wave and mTBI?

Are there chronic effects of blast?

-Single severe TBI
= AD
Repetitive mTBI
= Chronic traumatic encephalopathy (CTE)
-Boxers (dementia pugilistica); NFL football players and others
-CTE has a different pathological basis from AD
-Long-term effects of repetitive mTBI common in Iraq and Afghanistan?



DeKosky, Ikonomovic and Gandy NEJM 2010

Neurosurg Focus 31 (5):E3, 2011

Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide

Bennet Omalu, M.D., M.B.A., M.P.H., C.P.E.,[1,2] Jennifer L. Hammers, D.O.,[1,3] Julian Bailes, M.D.,[1,4] Ronald L. Hamilton, M.D.,[5] M. Ilyas Kamboh, Ph.D.,[6] Garrett Webster,[1,2] and Robert P. Fitzsimmons, J.D.[1,7]

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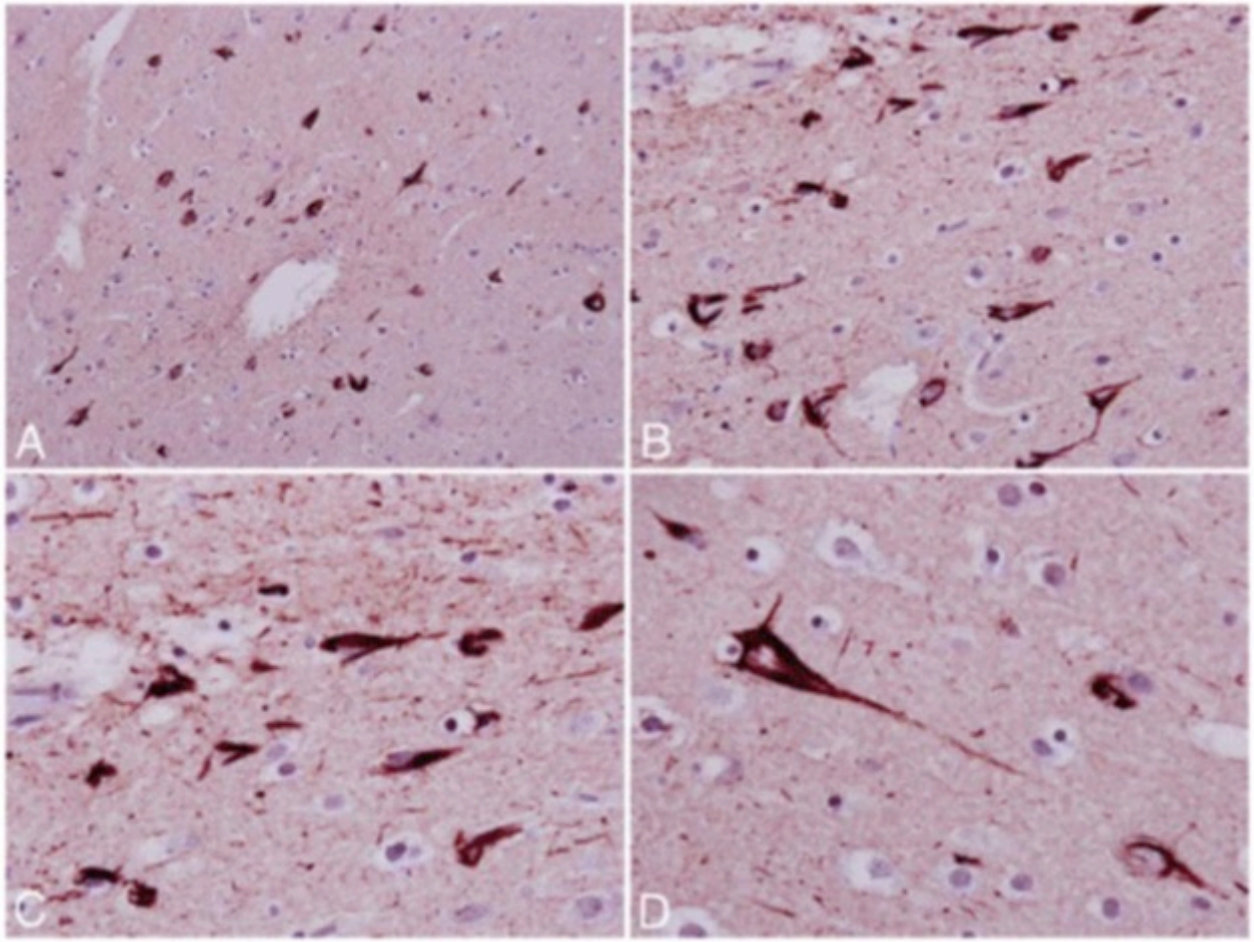
TRAUMATIC BRAIN INJURY

Science Translational Medicine 4:134ra60 (2012)

Chronic Traumatic Encephalopathy in Blast-Exposed Military Veterans and a Blast Neurotrauma Mouse Model

Lee E. Goldstein,[1,2,3,4]* Andrew M. Fisher,[1,4] Chad A. Tagge,[1,4] Xiao-Lei Zhang,[5] Libor Velisek,[5] John A. Sullivan,[5] Chirag Upreti,[5] Jonathan M. Kracht,[4] Maria Ericsson,[6] Mark W. Wojnarowicz,[1] Cezar J. Goletiani,[5] Giorgi M. Maglakelidze,[5] Noel Casey,[1,3] Juliet A. Moncaster,[1,3] Olga Minaeva,[1,3,4] Robert D. Moir,[7] Christopher J. Nowinski,[8] Robert A. Stern,[2,8] Robert C. Cantu,[8,9] James Geiling,[10] Jan K. Blusztajn,[2] Benjamin L. Wolozin,[2] Tsuneya Ikezu,[2] Thor D. Stein,[2,11] Andrew E. Budson,[2,11] Neil W. Kowall,[2,11] David Chargin,[12] Andre Sharon,[4,12] Sudad Saman,[13] Garth F. Hall,[13] William C. Moss,[14] Robin O. Cleveland,[15] Rudolph E. Tanzi,[7] Patric K. Stanton,[5] Ann C. McKee[2,8,11]*

CTE like pathology in military case of blast exposure



Gandy et al. Molecular Neurodegeneration 9:37, 2014

The causal connection between TBI and AD: elevated Aβ?

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Available online at www.sciencedirect.com

SCIENCE DIRECT

Experimental Neurology 190 (2004) 192–203

Experimental Neurology

www.elsevier.com/locate/yexnr

Alzheimer's pathology in human temporal cortex surgically excised after severe brain injury

Milos D. Ikonomovic[a,b], Kunihiro Uryu[c], Eric E. Abrahamson[a], John R. Ciallella[a], John Q. Trojanowski[c], Virginia M.-Y. Lee[c], Robert S. Clark[d], Donald W. Marion[e], Stephen R. Wisniewski[f], Steven T. DeKosky[a,b,*]

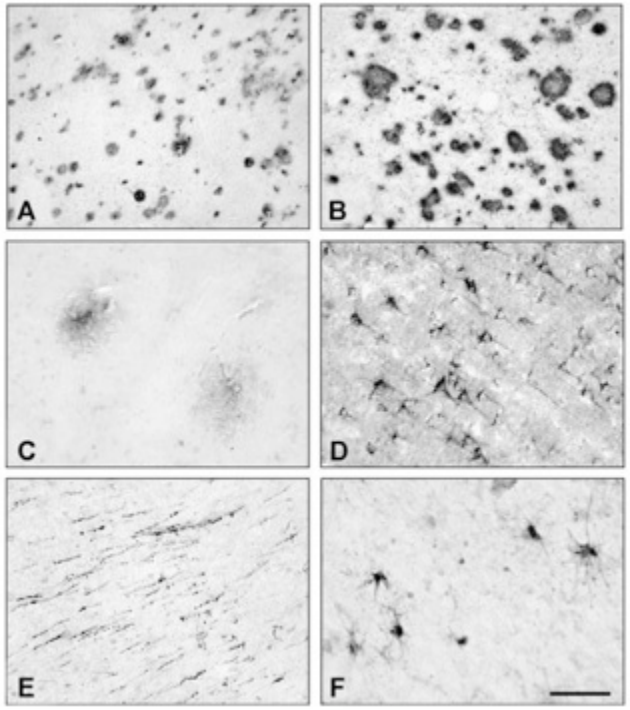
-Aβ is elevated after TBI

-Plaques appear within hours of a severe TBI

Association of Increased Cortical Soluble $A\beta_{42}$ Levels With Diffuse Plaques After Severe Brain Injury in Humans

Steven T. DeKosky, MD; Eric E. Abrahamson, PhD; John R. Ciallella, PhD; William R. Paljug, MS; Stephen R. Wisniewski, PhD; Robert S. B. Clark, MD; Milos D. Ikonomovic, MD

Arch Neurol 64: 541 (2007)



-Aβ is increased after TBI in experimental animals
-Mice that are unable to generate Aβ show less cortical volume loss and less impairment
in a spatial leaning tasks
-Administration of a γ-secretase inhibitor to wild type mice after TBI limits tissue damage and normalizes behavior

nature medicine

Amyloid precursor protein secretases as therapeutic targets for traumatic brain injury

David J Loane[1], Ana Pocivavsek[1], Charbel E-H Moussa[1], Rachel Thompson[1], Yasuji Matsuoka[2], Alan I Faden[1], G William Rebeck[1] & Mark P Burns[1]

Amyloid-β (Aβ) peptides, found in Alzheimer's disease brain, accumulate rapidly after traumatic brain injury (TBI) in both humans and animals. Here we show that blocking either β- or γ-secretase, enzymes required for production of Aβ from amyloid precursor protein (APP), can ameliorate motor and cognitive deficits and reduce cell loss after experimental TBI in mice. Thus, APP secretases are promising targets for treatment of TBI.

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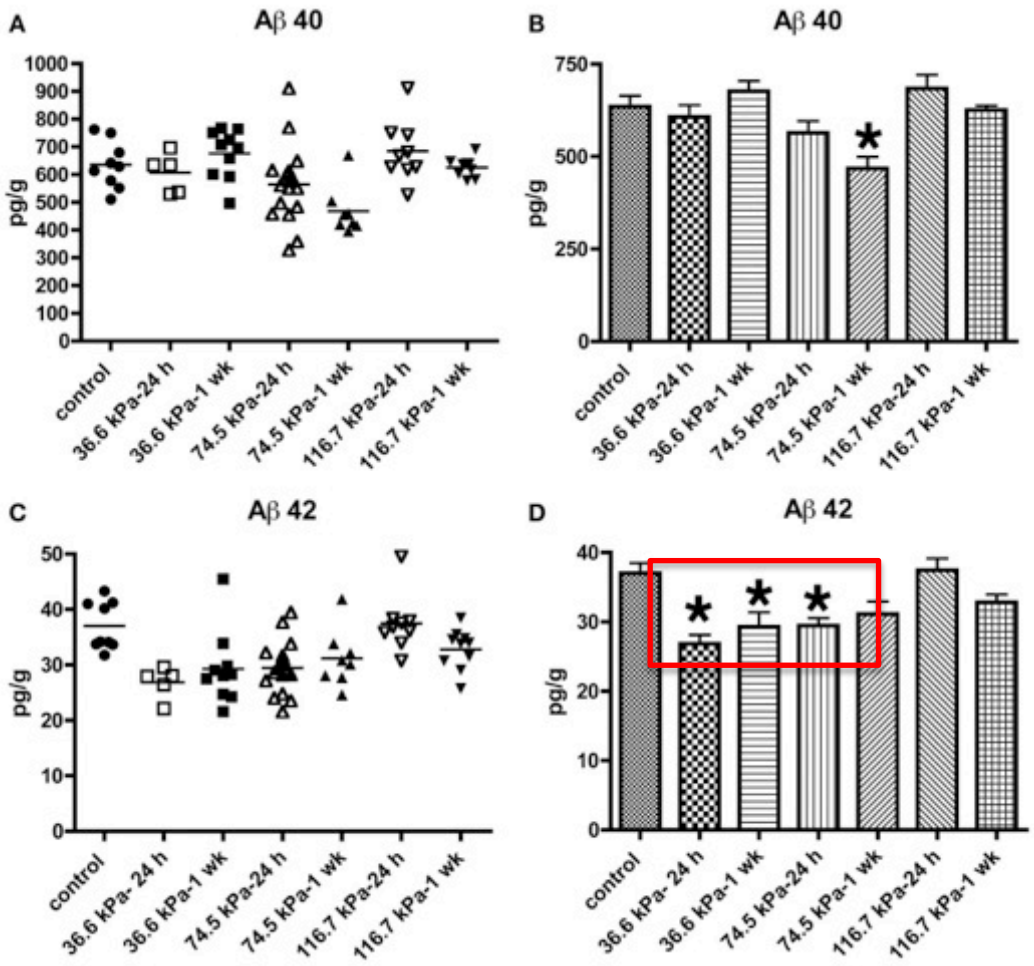
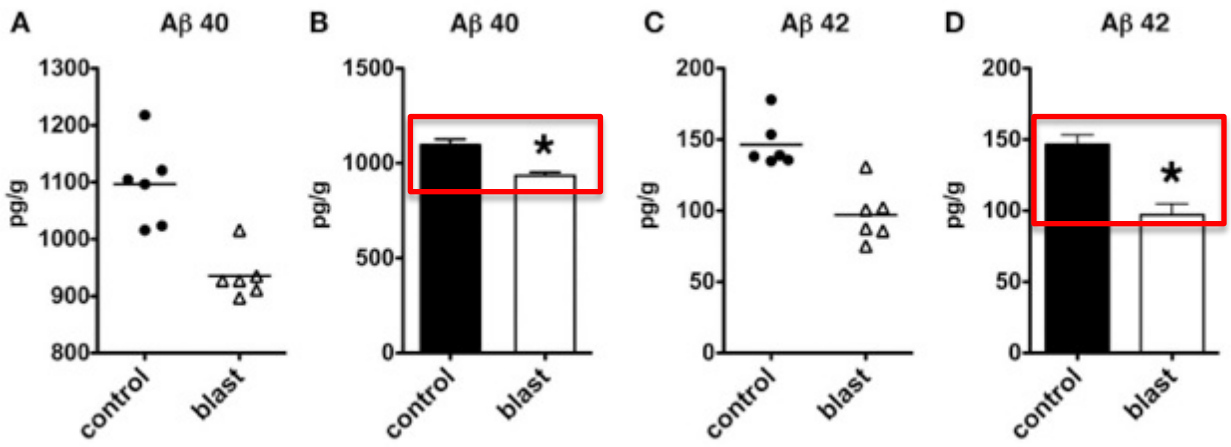
Loane et al. Nature Medicine, 15: 377 (2009)

Brain Aβ 42 is decreased following blast exposure in rats



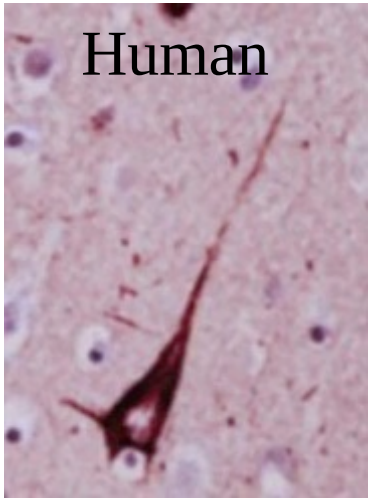
De Gasperi et al. *Frontiers Neurology* 3:177. 2012.

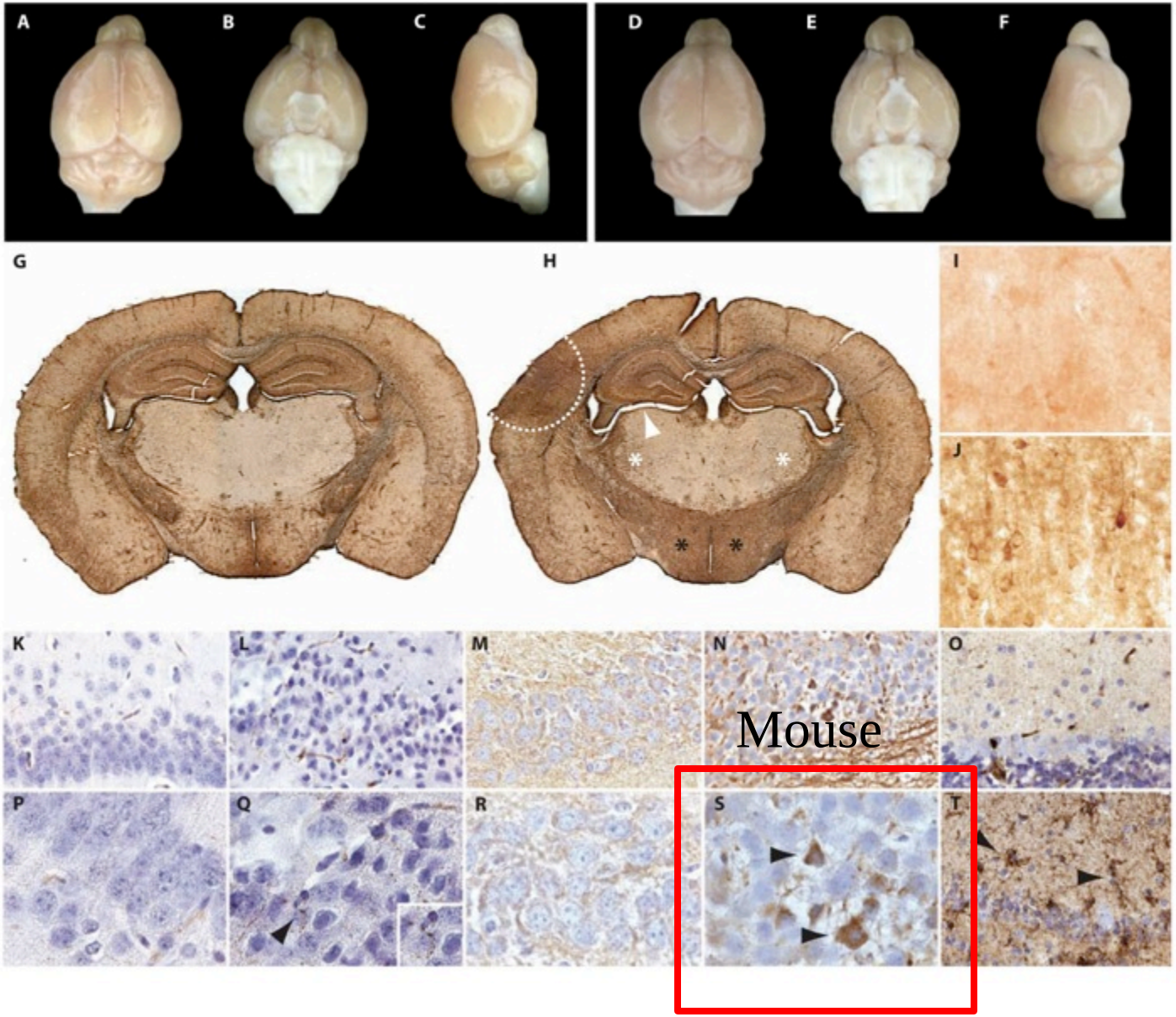
Brain Aβ 40 and 42 are decreased 24 hr following blast exposure in mice (147 kPa)



De Gasperi et al. *Frontiers Neurology* 3:177. 2012.

Blast related tauopathy?





Goldstein et al. Science Translational Medicine 4:134ra60 (2012)

Contents lists available at SciVerse ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Changes in mouse cognition and hippocampal gene expression observed in a mild physical- and blast-traumatic brain injury

David Tweedie [a,*], Lital Rachmany [b], Vardit Rubovitch [b], Yongqing Zhang [c], Kevin G. Becker [c], Evelyn Perez [d], Barry J. Hoffer [e,1], Chaim G. Pick [b,1], Nigel H. Greig [a,1]

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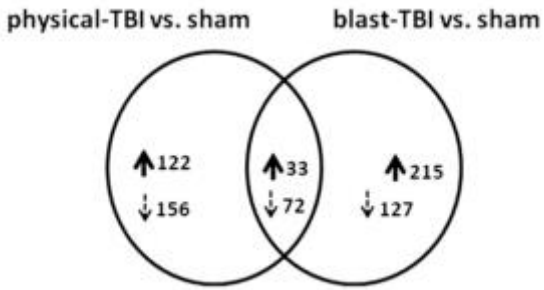
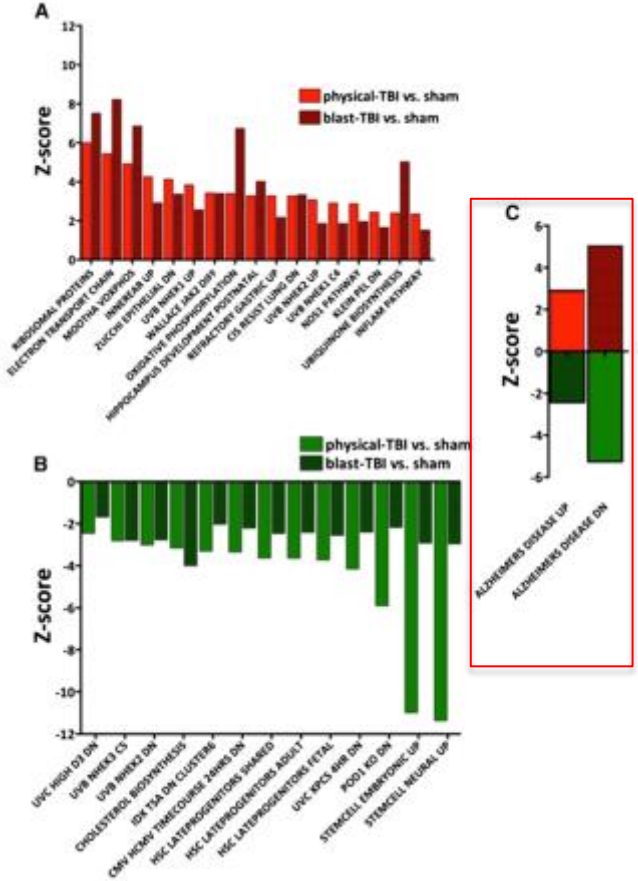
[e] Department of Neurosurgery, Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA

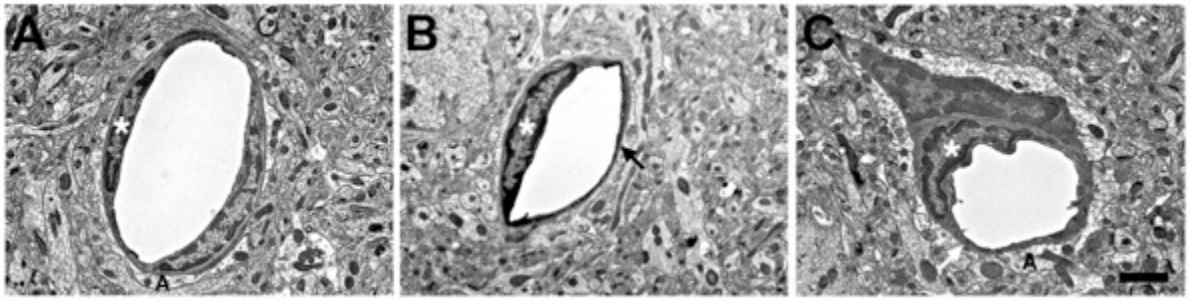
Neurobiol Dis 2013, **54**:1-11.





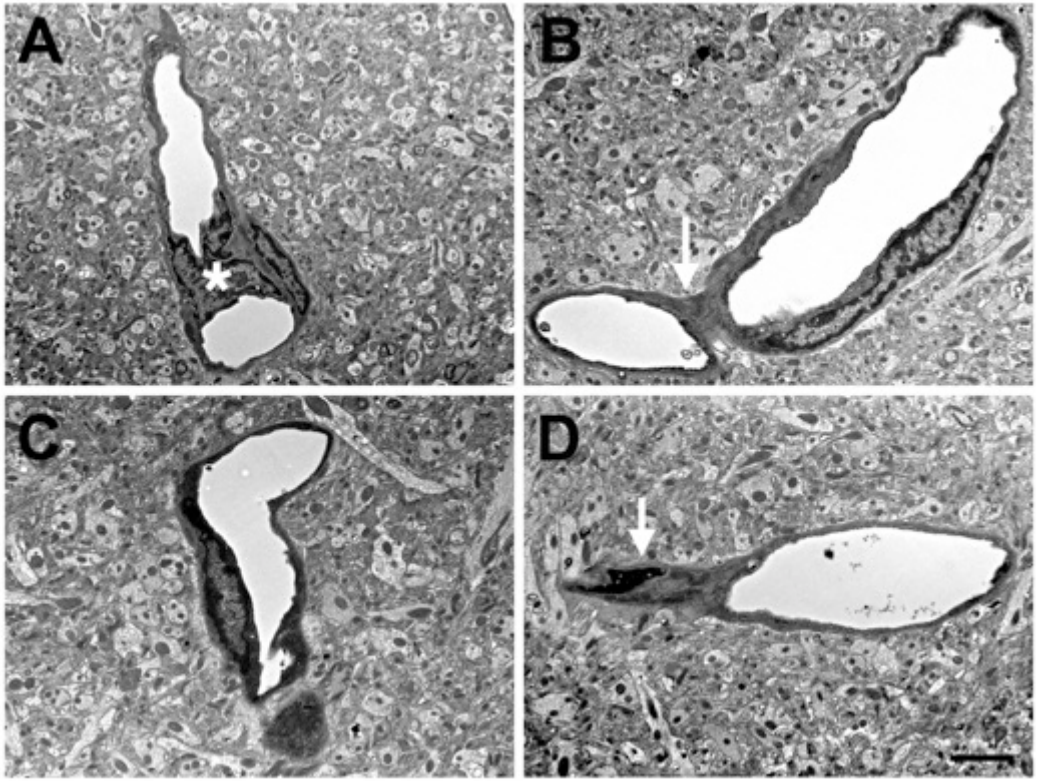
-Compared transcriptome changes between a weight drop model designed to approximate an mTBI or mice exposed to a 17.2 kPa (2.5 psi) blast.
-A common set of up regulated or down regulated RNAs found but most changes were different.
-Functional pathway analysis showed genes up regulated or down regulated in in Alzheimer's disease were regulated in similar directions by nbTBI while the opposite was seen following blast with the "Alzheimer's Disease Up" pathway down regulated by blast and the "Alzheimer's Disease Down" up regulated by blast.

Selective vulnerability of the cerebral vasculature to blast?



Control

Blast



Gama Sosa et al.
Acta Neuropathologica Communications
2014, 2:67

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Additional Reading

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