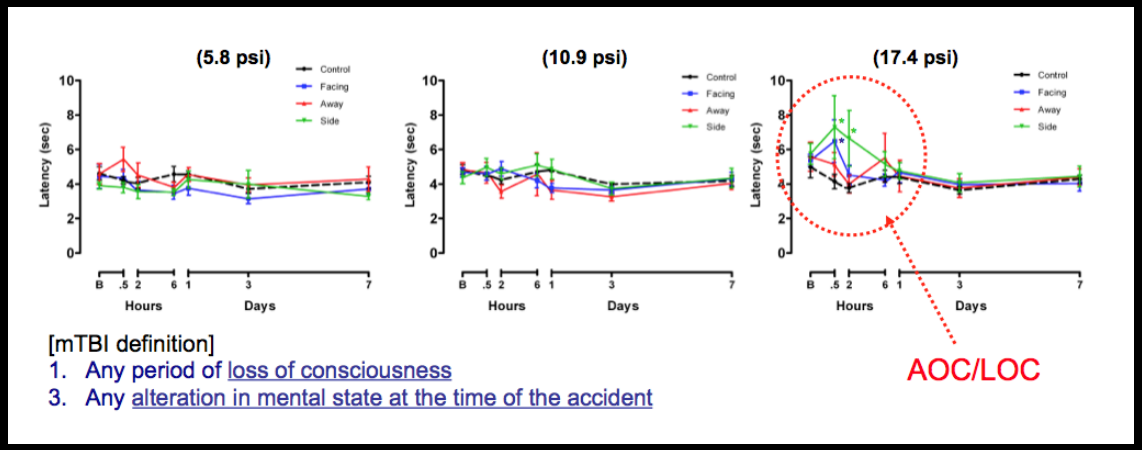
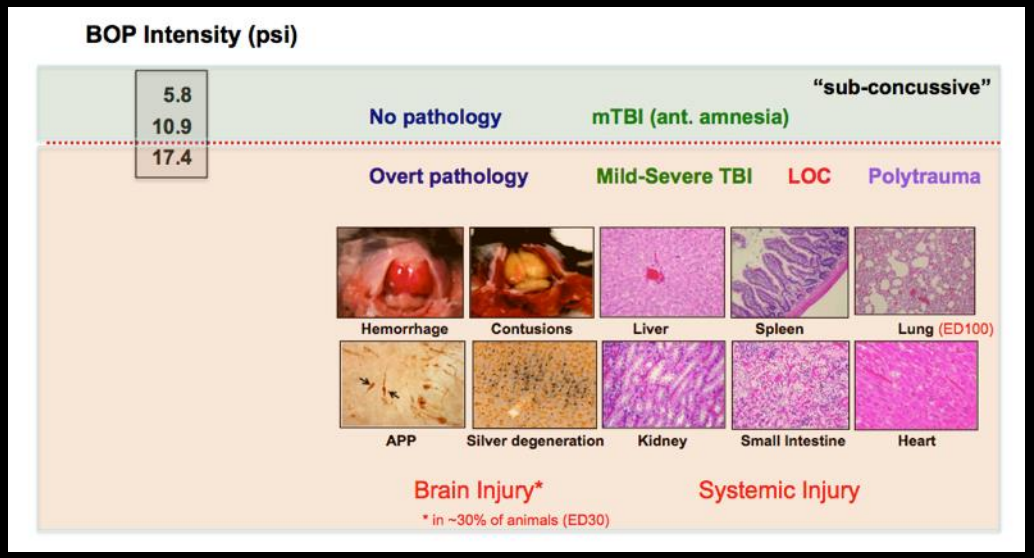
Vascular and inflammatory factors in the chronic pathophysiology of blast-induced brain injury

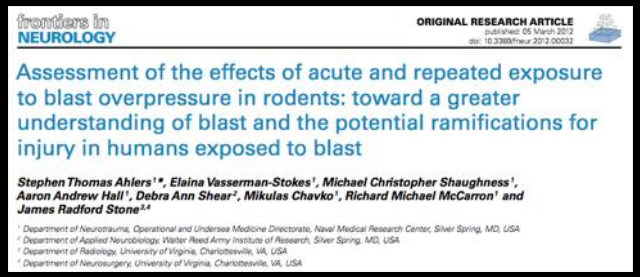
Blast Animal Model in Rats



- Blast intensity in relation to AOC/LOC



- Blast intensity in relation to pathology


frontiers in NEUROLOGY

ORIGINAL RESEARCH ARTICLE

Assessment of the effects of acute and repeated exposure to blast overpressure in rodents: toward a greater understanding of blast and the potential ramifications for injury in humans exposed to blast

Stephen Thomas Ahlers[1]*, Elaina Vasserman-Stokes[1], Michael Christopher Shaughness[1], Aaron Andrew Hall[1], Debra Ann Shear[2], Mikulas Chavko[1], Richard Michael McCarron[1] and James Radford Stone[3,4]

Rodent Model: No Obvious Pathology

No obvious CNS pathology (H&E, APP, GFAP, Cupric Silver, etc.)

BOP x 12 (5.6 psi)

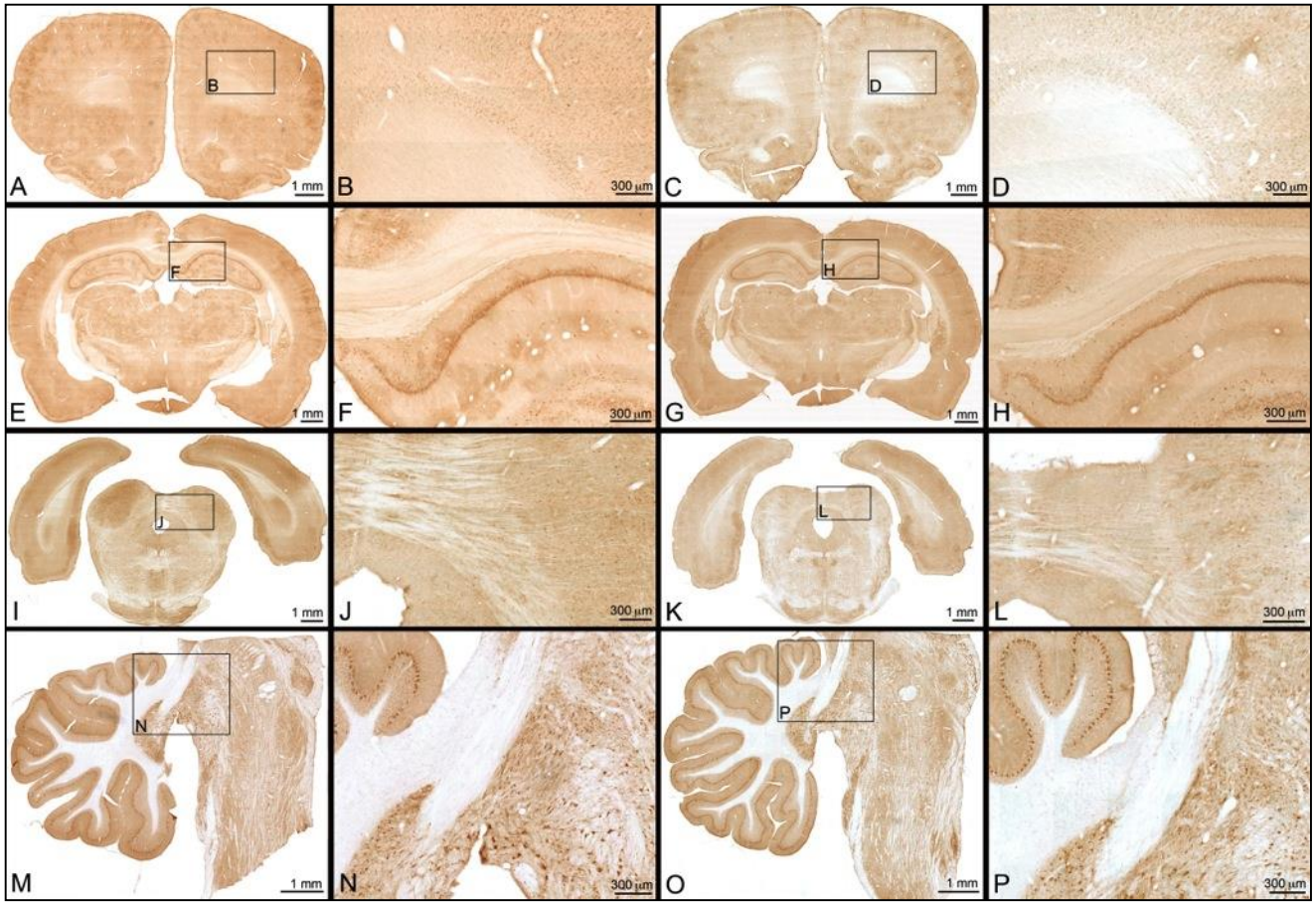
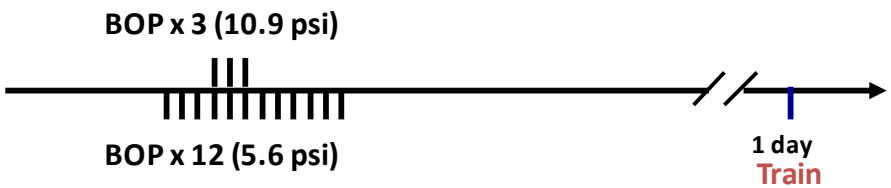
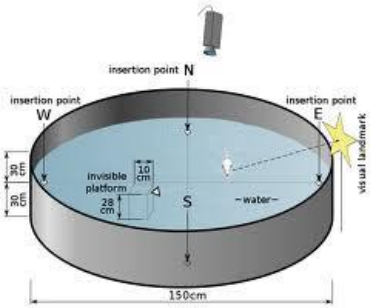


Figure 4: APP immunohistochemistry - frontal overpressure exposure:
APP immunohistochemistry is seen with animals exposed to 12 sessions of 36.6 kPa blast overpressure exposure (A, B, E, F, I, J, M, N) vs. SHAM injured controls (C, D, G, H, K, L, O, P). Photomontages of multiple photomicrographs of frontal (A, C), mid (E, G), and posterior (I, K) portions of the cerebrum are shown in coronal section. Sagittal photomicrograph of the brainstem is seen in plates M and O. Magnifications of corresponding boxes within photomontages are seen in plates B, D, F, H, J, L, N, and P. Within all of the plates, no evidence of traumatic injury or difference between experimentally injured and SHAM injured controls is seen.

Ahlers et. al., Frontiers Neurotrauma 2012

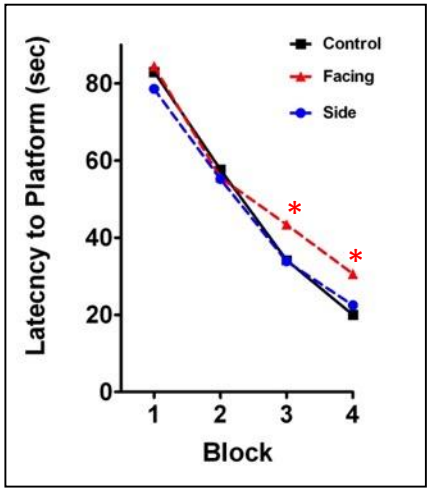
Repeated Low-intensity Blast Exposure





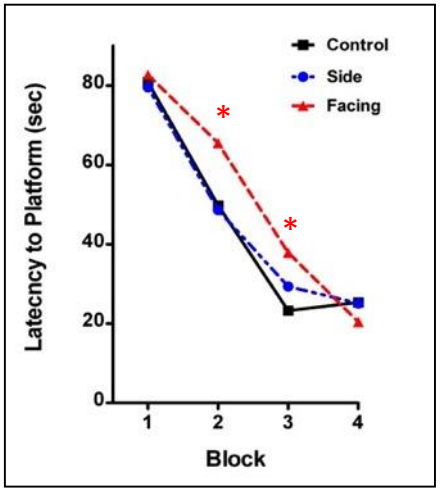
- 1 BOP exposure per day (facing or side orientation)
- Isoflurane anesthesia during BOP exposure

BOP x 3 (10.9 psi)



24 Hours post BOP

BOP x 12 (5.6 psi)

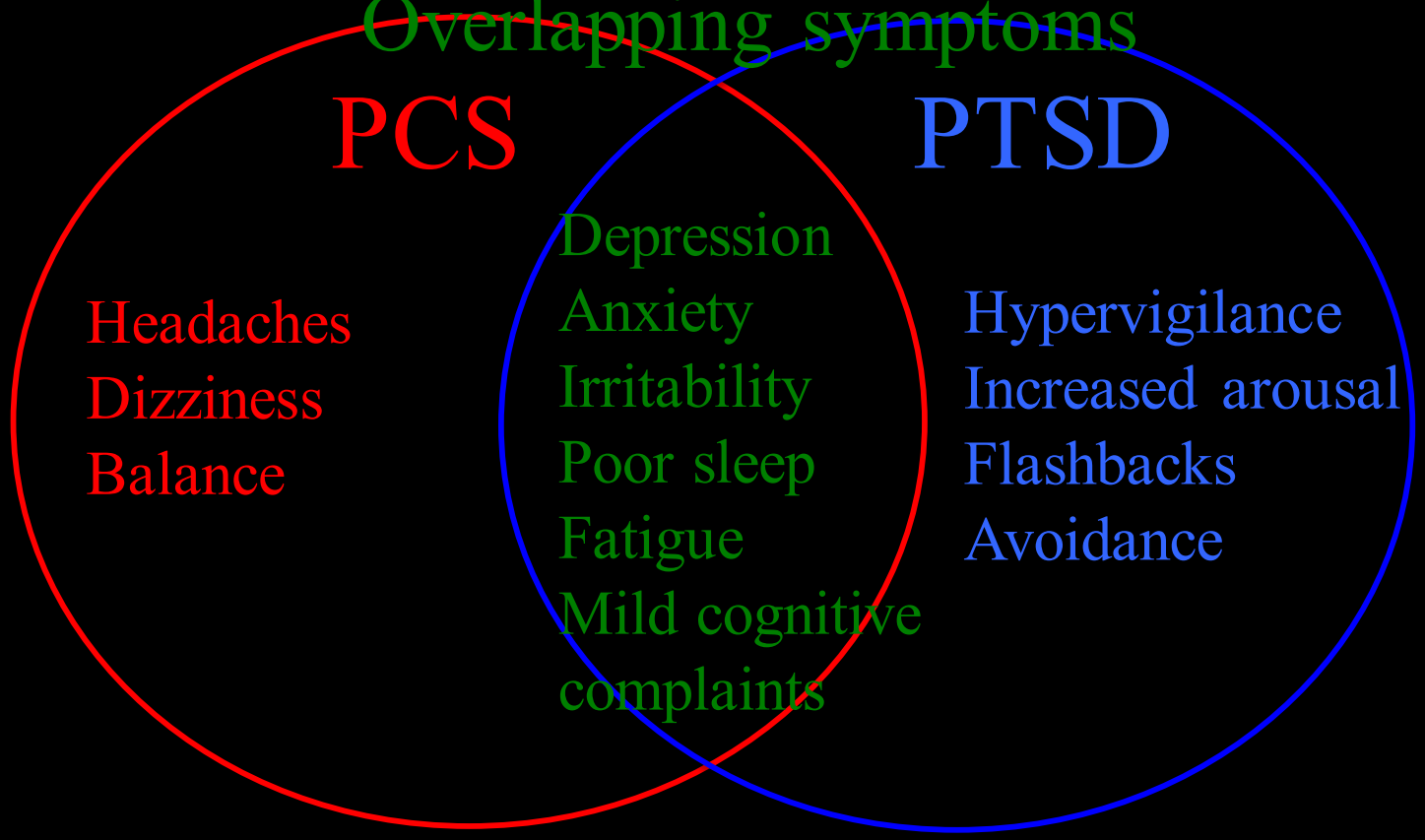


24 Hours post BOP

Ahlers et. al., Frontiers Neurotrauma 2012

- Blast induction of PTSD related traits
- Blast and Aβ production
- Blast-related vascular pathology and its possible relationship to inflammation

The problem of distinguishing PTSD from mTBI

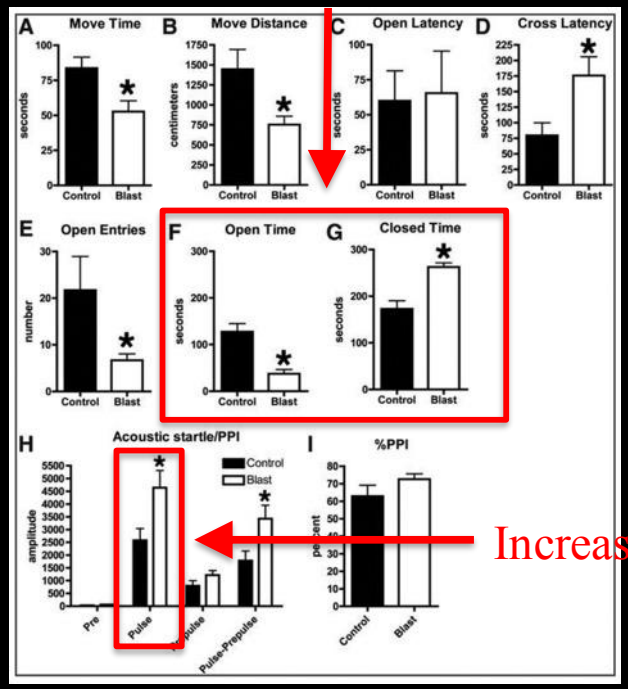


Moderate-severe TBIs recognizable by cognitive deficits (Neuropsych mTBI = PTSD)

Blast exposure induces PTSD related traits

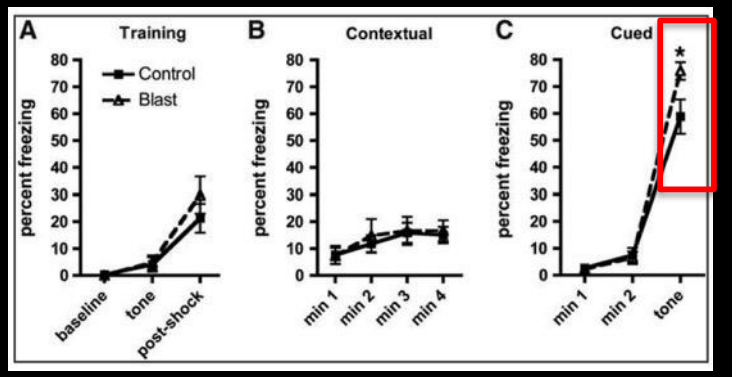
3 x 74.5 kPa blast exposures
Tested six months after blast exposure

Anxiety in EZM



Increased acoustic startle

Enhanced response cued fear

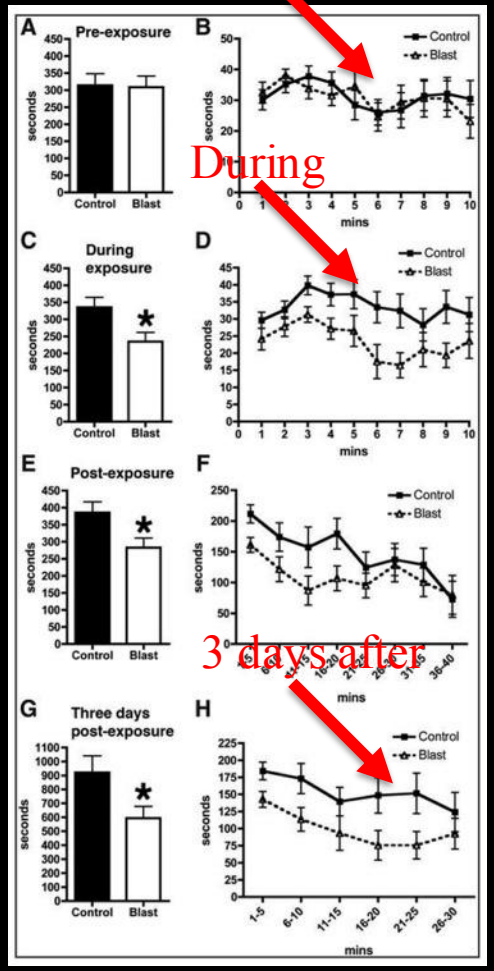


Response to predator scent (center time, open field)

Before

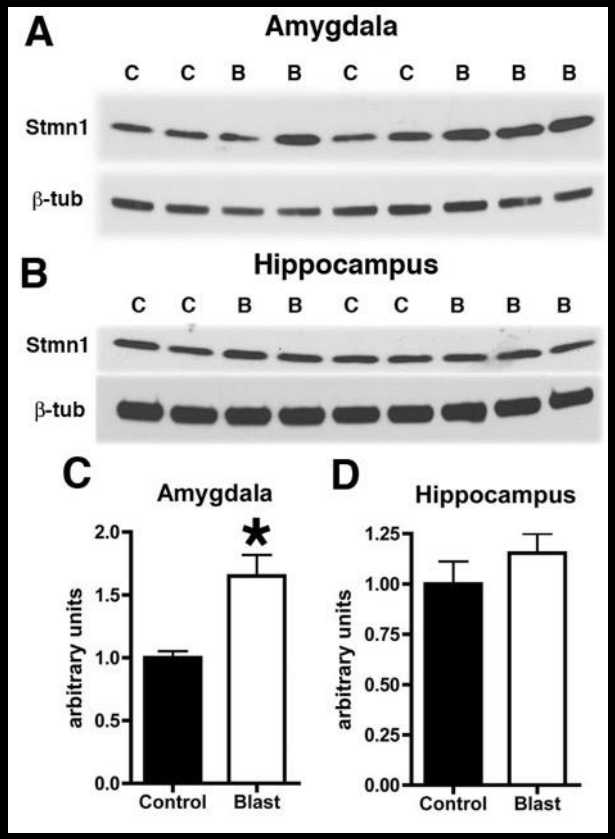
During

3 days after

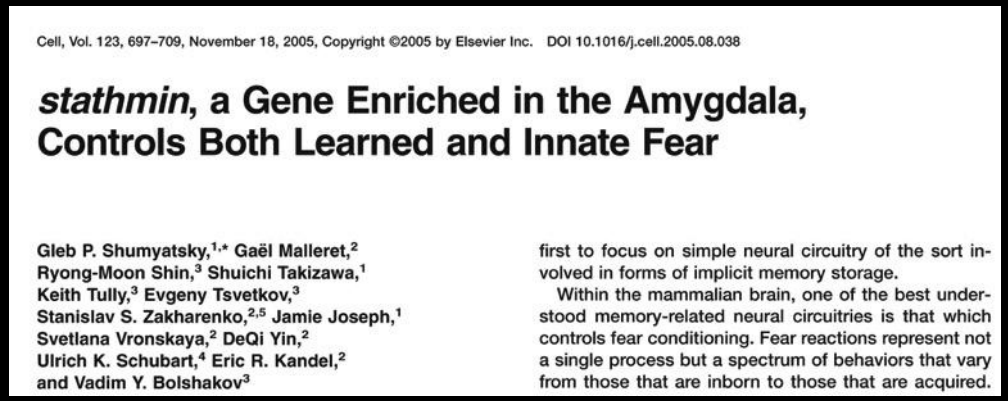


Blast exposure induces stathmin 1 in the amygdala

stathmin 1



C = control
B= blast exposed



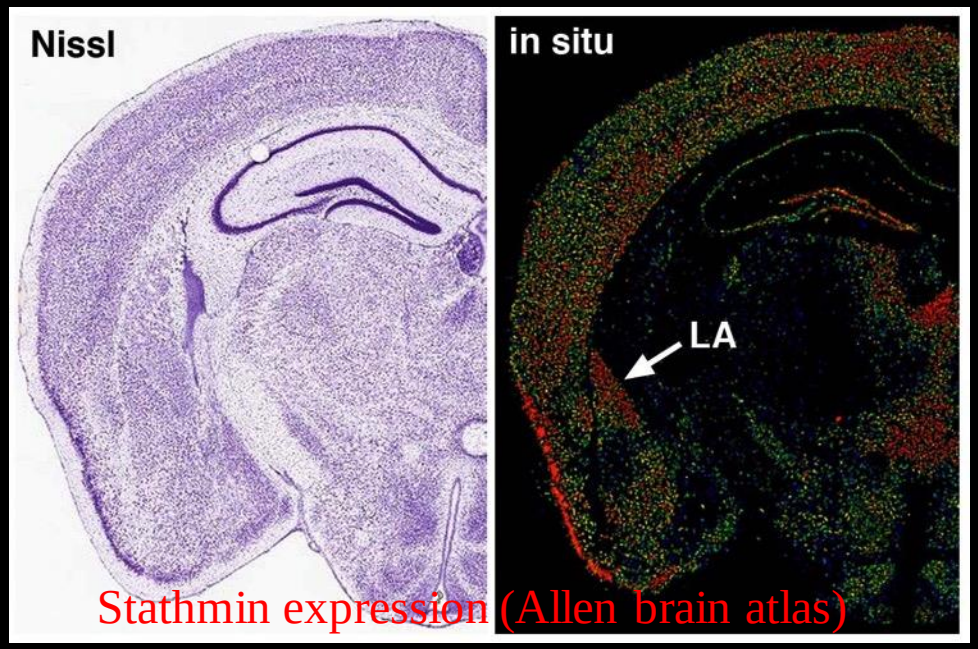
Cell, Vol. 123, 697–709, November 18, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.cell.2005.08.038

***stathmin*, a Gene Enriched in the Amygdala, Controls Both Learned and Innate Fear**

Gleb P. Shumyatsky,[1,*] Gaël Malleret,[2] Ryong-Moon Shin,[3] Shuichi Takizawa,[1] Keith Tully,[3] Evgeny Tsvetkov,[3] Stanislav S. Zakharenko,[2,5] Jamie Joseph,[1] Svetlana Vronskaya,[2] DeQi Yin,[2] Ulrich K. Schubart,[4] Eric R. Kandel,[2] and Vadim Y. Bolshakov[3]

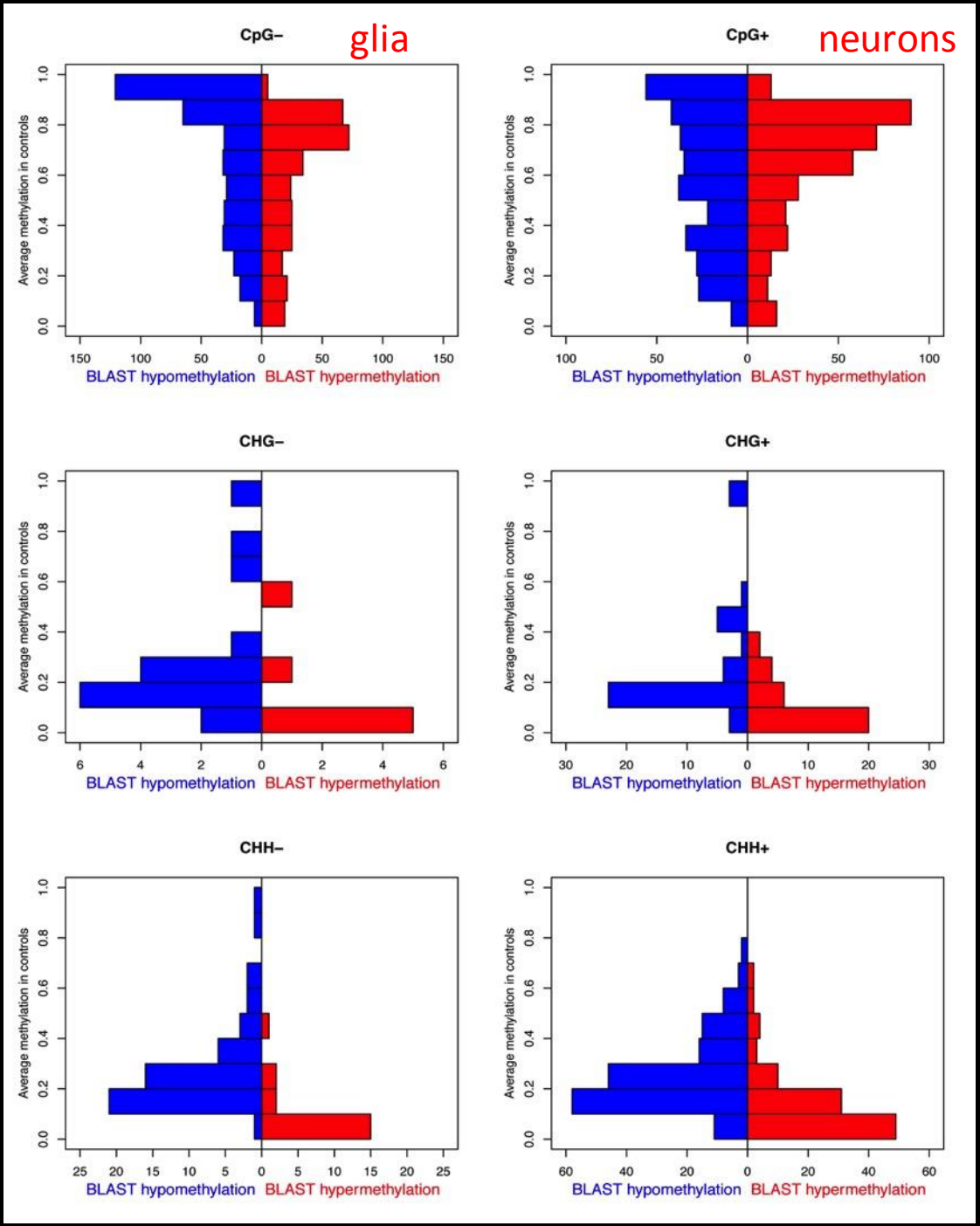
first to focus on simple neural circuitry of the sort involved in forms of implicit memory storage.

Within the mammalian brain, one of the best understood memory-related neural circuitries is that which controls fear conditioning. Fear reactions represent not a single process but a spectrum of behaviors that vary from those that are inborn to those that are acquired.



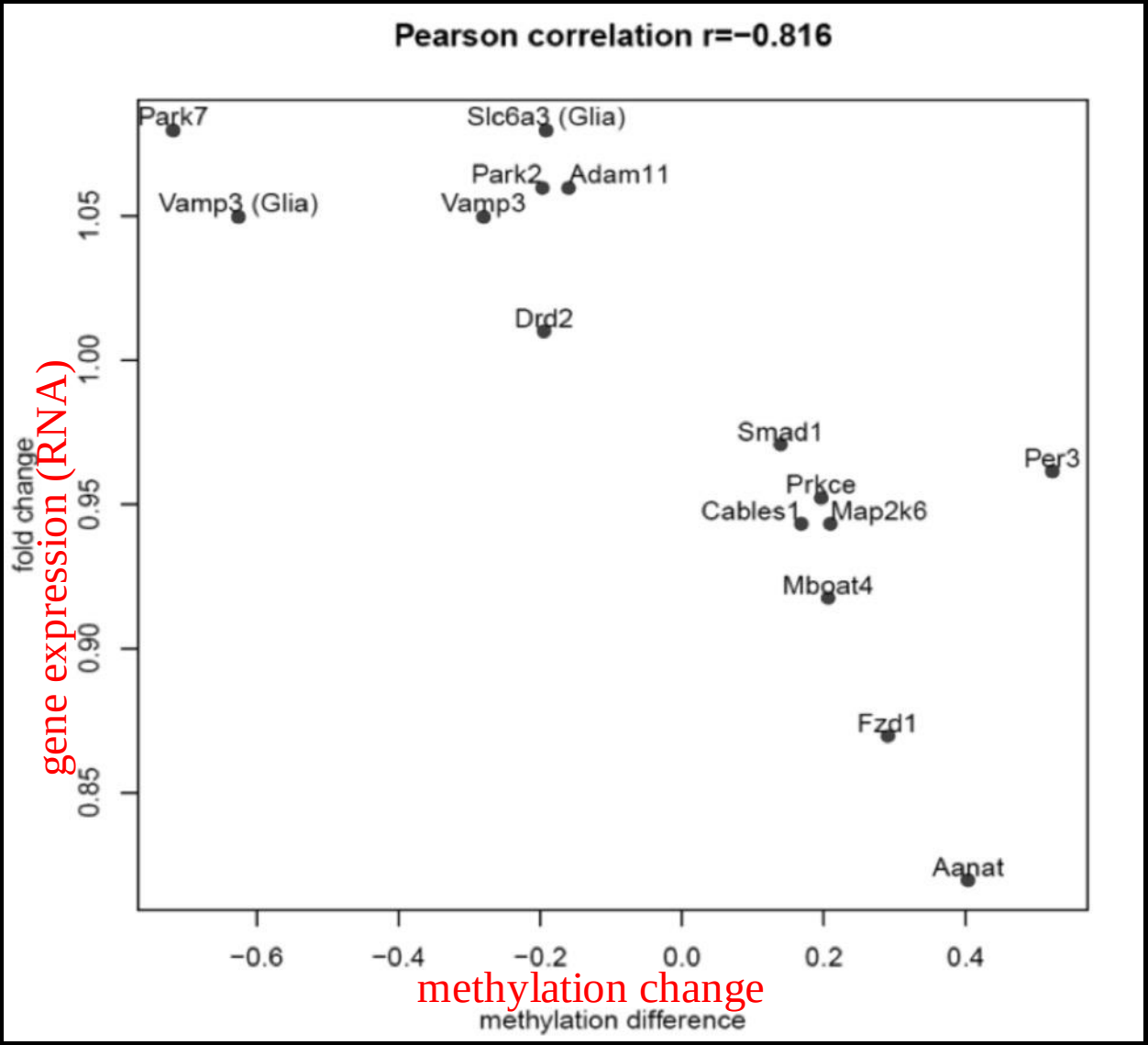
Stathmin expression (Allen brain atlas)

DNA Methylation Profiling of Blast-related TBI using expanded reduced representation bisulfite sequencing on sorted neuronal (NeuN+) and glial (NeuN-) populations from rats 8 months following blast exposure.



Haghighi et al.
Journal Neurotrauma
32: 1200, 2015

-Methylation site changes in 458 neuronal and 379 glial genes
-Pathways effected enriched for:
cell death and survival, nervous system development and function, transforming growth factor β (TGF- β)
nitric oxide signaling
-Gene expression analysis of 30 differentially methylated neuronal and glial genes showed correlation with methylation.



Haghighi et al. *Journal Neurotrauma* 32: 1200, 2015

Blast-related TBI and chronic neurodegenerative diseases: could there be a connection to elevated Aβ?

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 elevated after TBI in humans
-Plaques appear within hours of a severe TBI

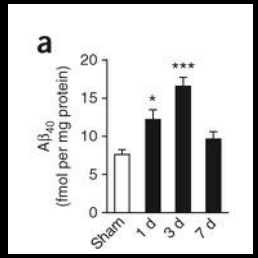
nature medicine

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.

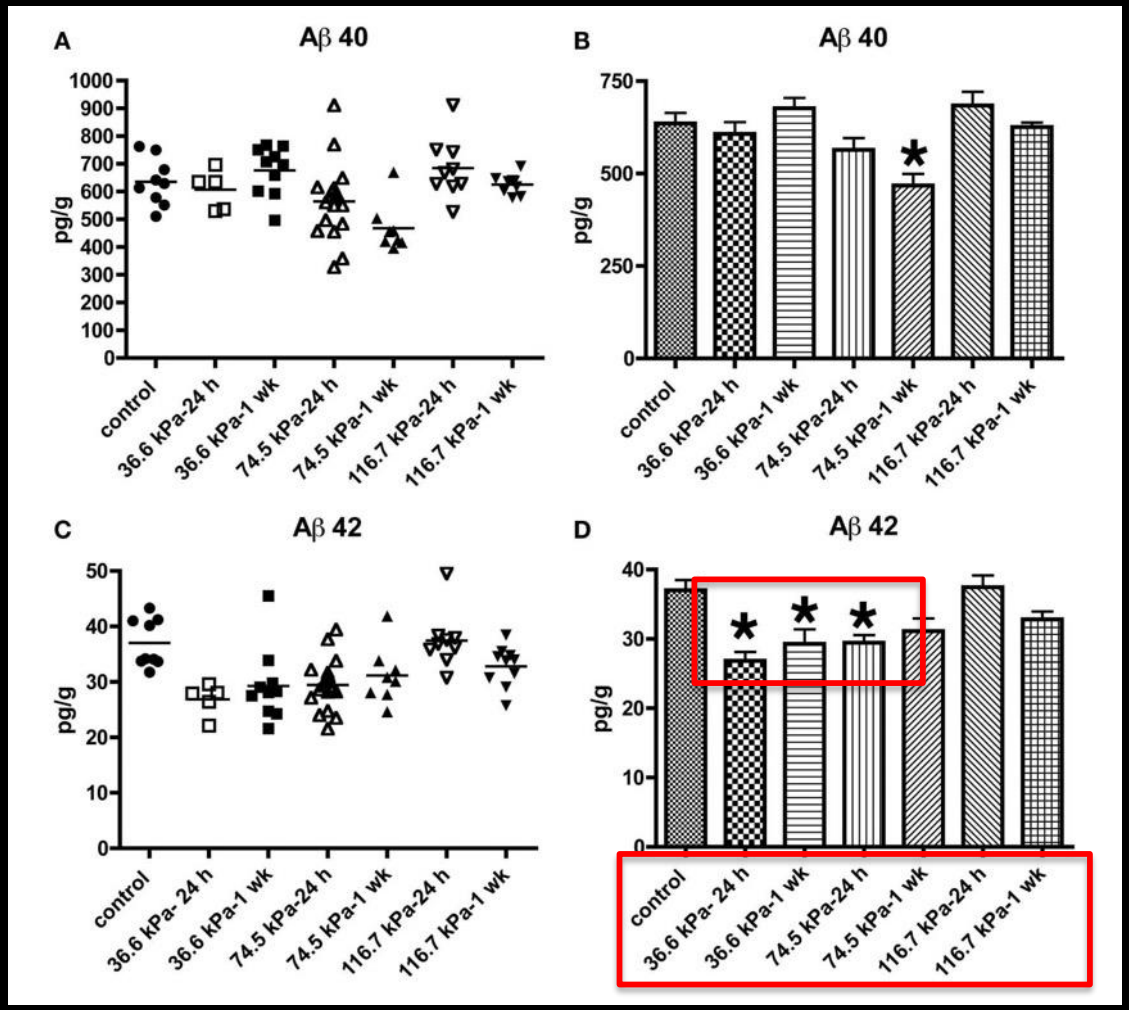
All rights reserved.



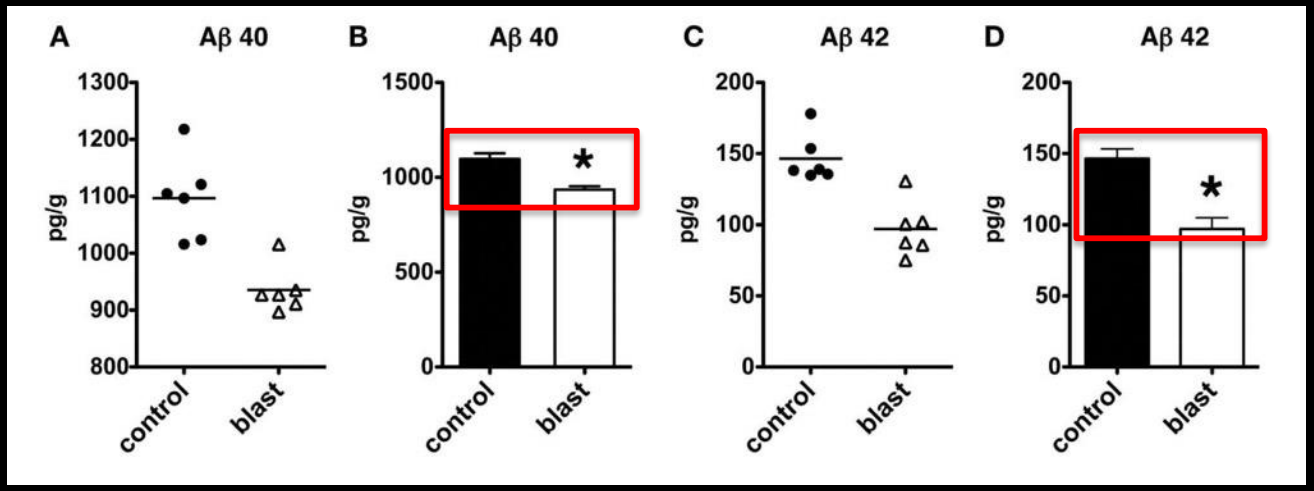
-Aβ is increased in impact animal models of TBI (controlled cortical impact, weight drop).
-Mice that are unable to generate Aβ (BACE KO) show less cortical volume loss and less impairment in a spatial memory tasks

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

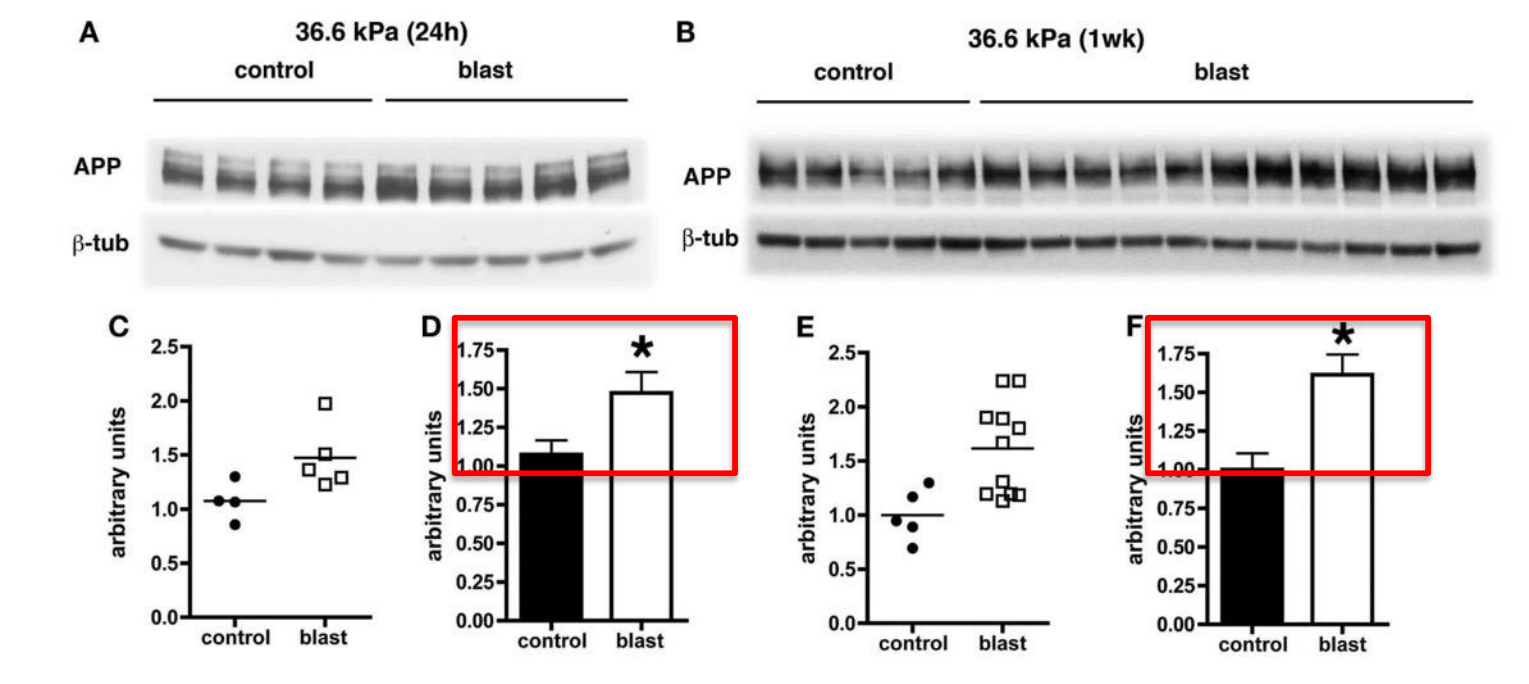
Brain Aβ 42 is decreased following blast exposure in rats



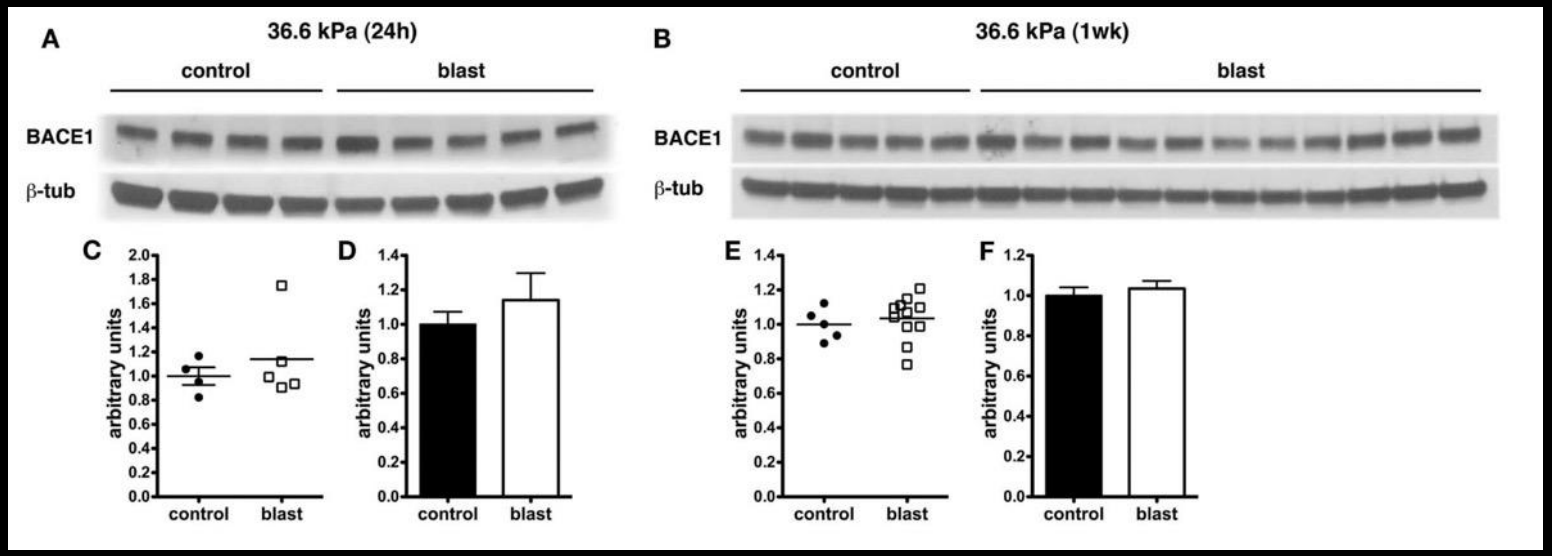
Brain Aβ 40 and 42 are decreased 24 hr following blast exposure in mice (147 kPa)

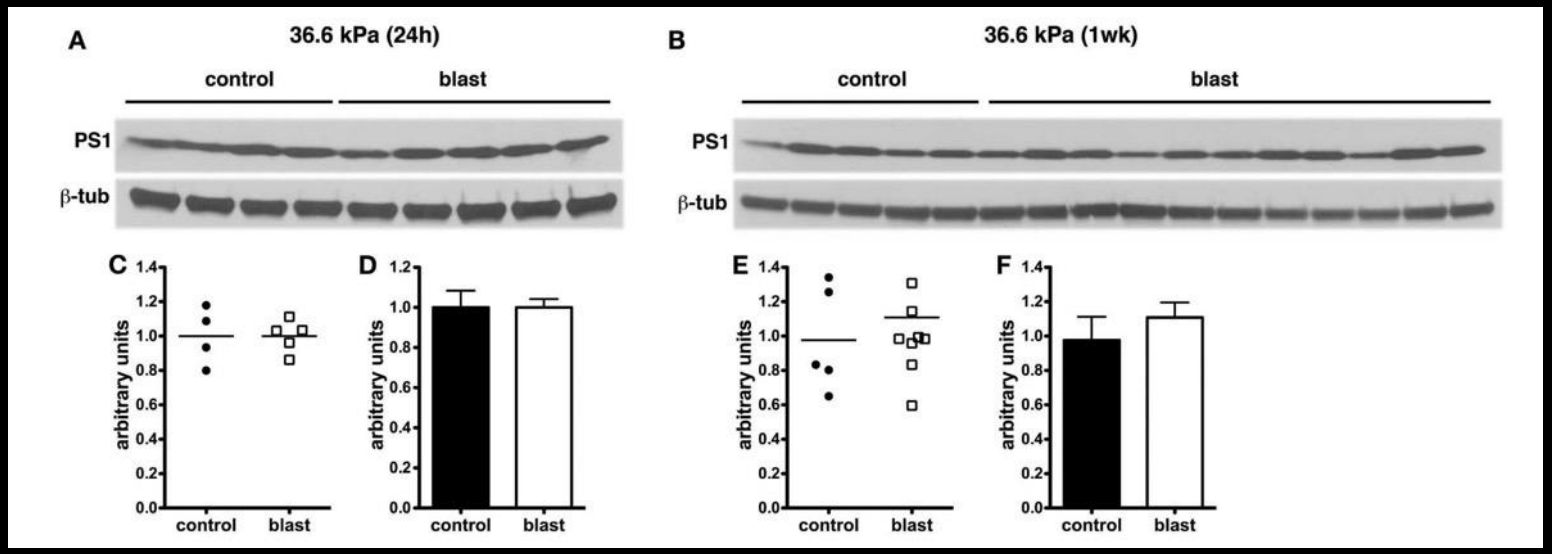


APP levels are elevated in rats following blast at 24 hours and one week



No change in levels of BACE 1 or presenilin-1





Blast-related tauopathy?

RESEARCH ARTICLE www.ScienceTranslationalMedicine.org 16 May 2012 Vol 4 Issue 134 134ra60

TRAUMATIC BRAIN INJURY

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]*

Journal of Alzheimer's Disease 37 (2013) 309–323 309
DOI 10.3233/JAD-130182
IOS Press

Blast Exposure Causes Early and Persistent Aberrant Phospho- and Cleaved-Tau Expression in a Murine Model of Mild Blast-Induced Traumatic Brain Injury

Bertrand R. Huber[a,1], James S. Meabon[b,c,1], Tobin J. Martin[c], Pierre D. Mourad[d,e,f], Raymond Bennett[g], Brian C. Kraemer[c,h], Ibolja Cernak[i], Eric C. Petrie[a,b], Michael J. Emery[j], Erik R. Swenson[j,k], Cynthia Mayer[a], Edin Mehic[f], Elaine R. Peskind[a,b] and David G. Cook[c,h,l,*]

Blast-related vascular pathology

frontiers in NEUROLOGY

REVIEW ARTICLE
published: 10 December 2010
doi: 10.3389/fneur.2010.00151

The importance of systemic response in the pathobiology of blast-induced neurotrauma

*Ibolja Cernak**

Biomedicine Business Area, National Security Technology Department, Johns Hopkins University Applied Physics Laboratory, Laurel, MD, USA

JOURNAL OF NEUROTRAUMA 31:1292–1304 (July 15, 2014)
© Mary Ann Liebert, Inc.
DOI: 10.1089/neu.2013.3016

Exposure of the Thorax to a Sublethal Blast Wave Causes a Hydrodynamic Pulse That Leads to Perivenular Inflammation in the Brain

J. Marc Simard,[1–3] Adam Pampori,[1] Kaspar Keledjian,[1] Cigdem Tosun,[1] Gary Schwartzbauer,[1] Svetlana Ivanova,[1] and Volodymyr Gerzanich[1]

frontiers in NEUROLOGY

REVIEW ARTICLE
published: 16 March 2015
doi: 10.3389/fneur.2015.00048

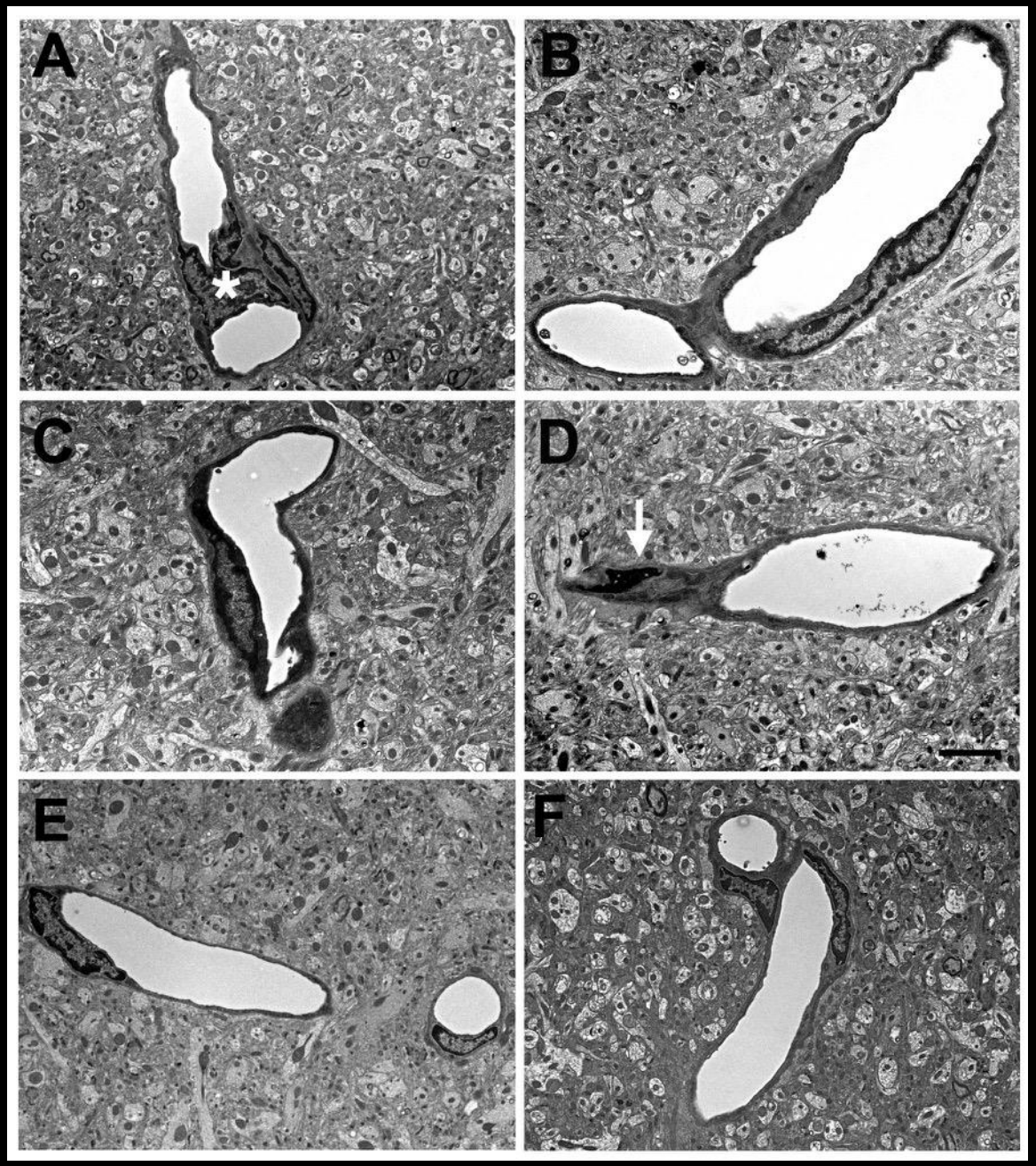
Vascular and inflammatory factors in the pathophysiology of blast-induced brain injury

Gregory A. Elder[1,2,3,4]*, Miguel A. Gama Sosa[2,4,5], Rita De Gasperi[2,4,5], James Radford Stone[6,7], Dara L. Dickstein[4,8,9], Fatemeh Haghighi[2,4,5,8], Patrick R. Hof[4,8,9] and Stephen T. Ahlers[10]

Single 74.5 kPa blast exposure, sacrificed 24 hours later

Blast

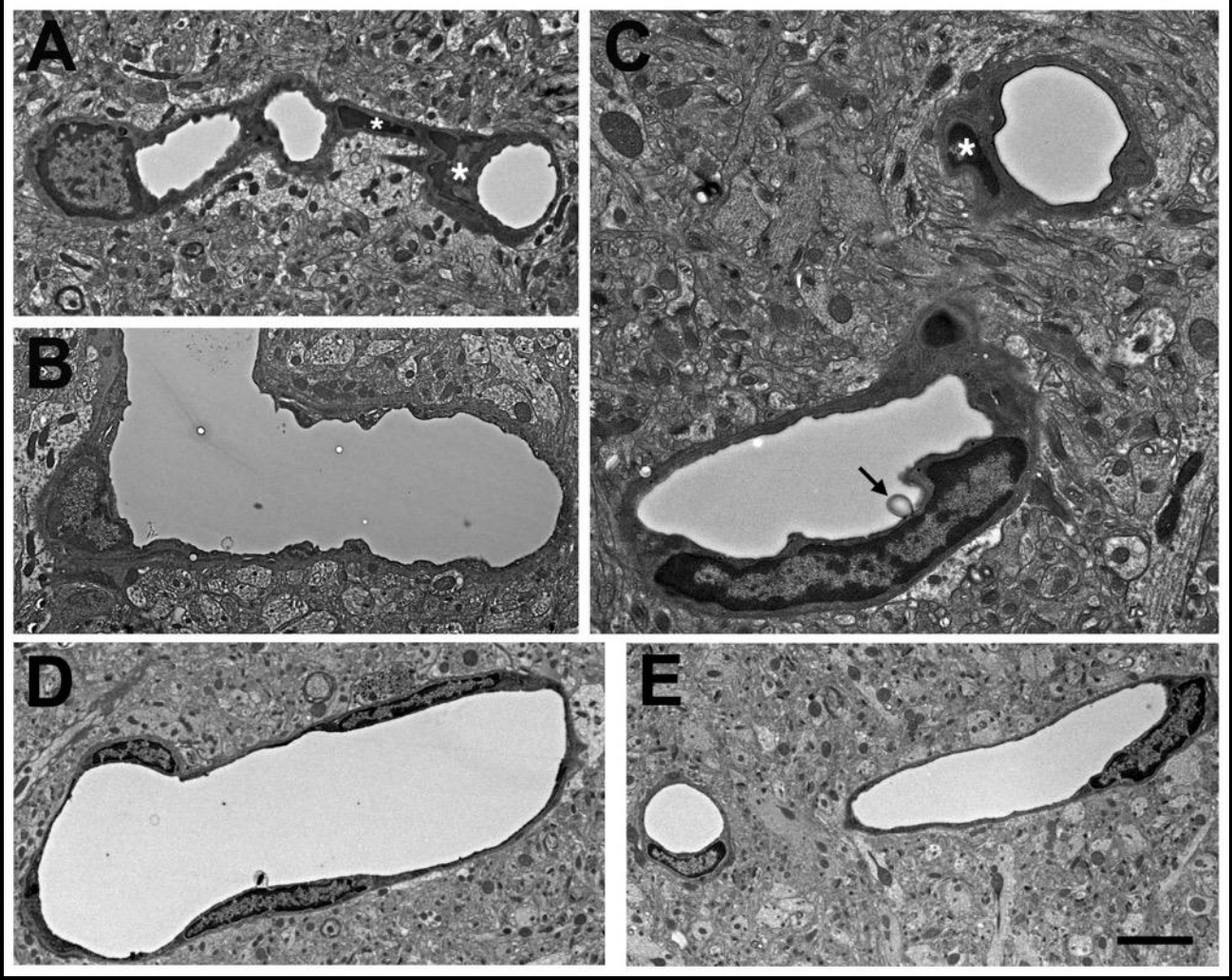
Controls



Three 74.5 kPa blast exposures, sacrificed 24 hours later

Blast

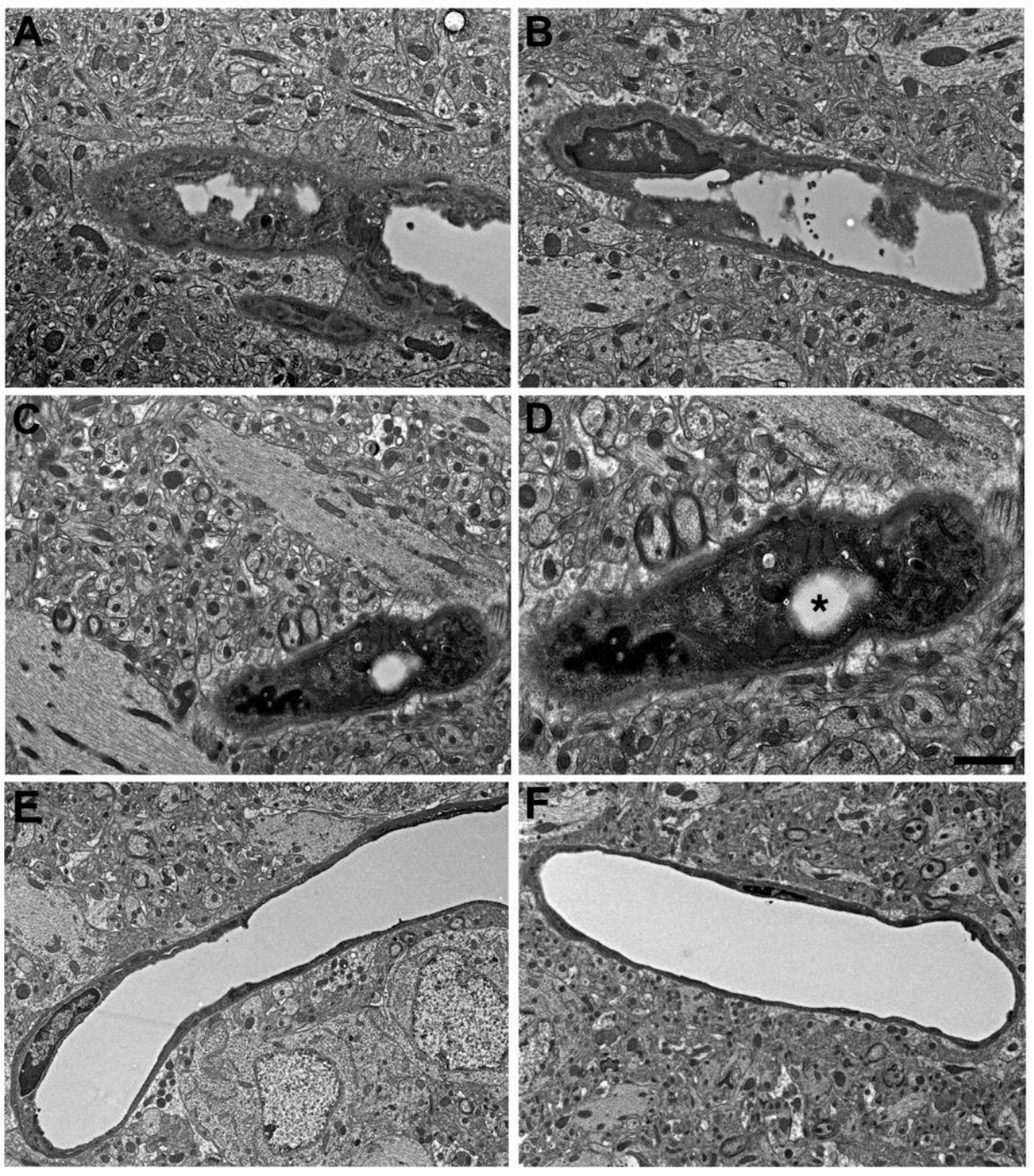
Controls



Three 74.5 kPa blast exposures, sacrificed 24 hours later

Blast

Controls

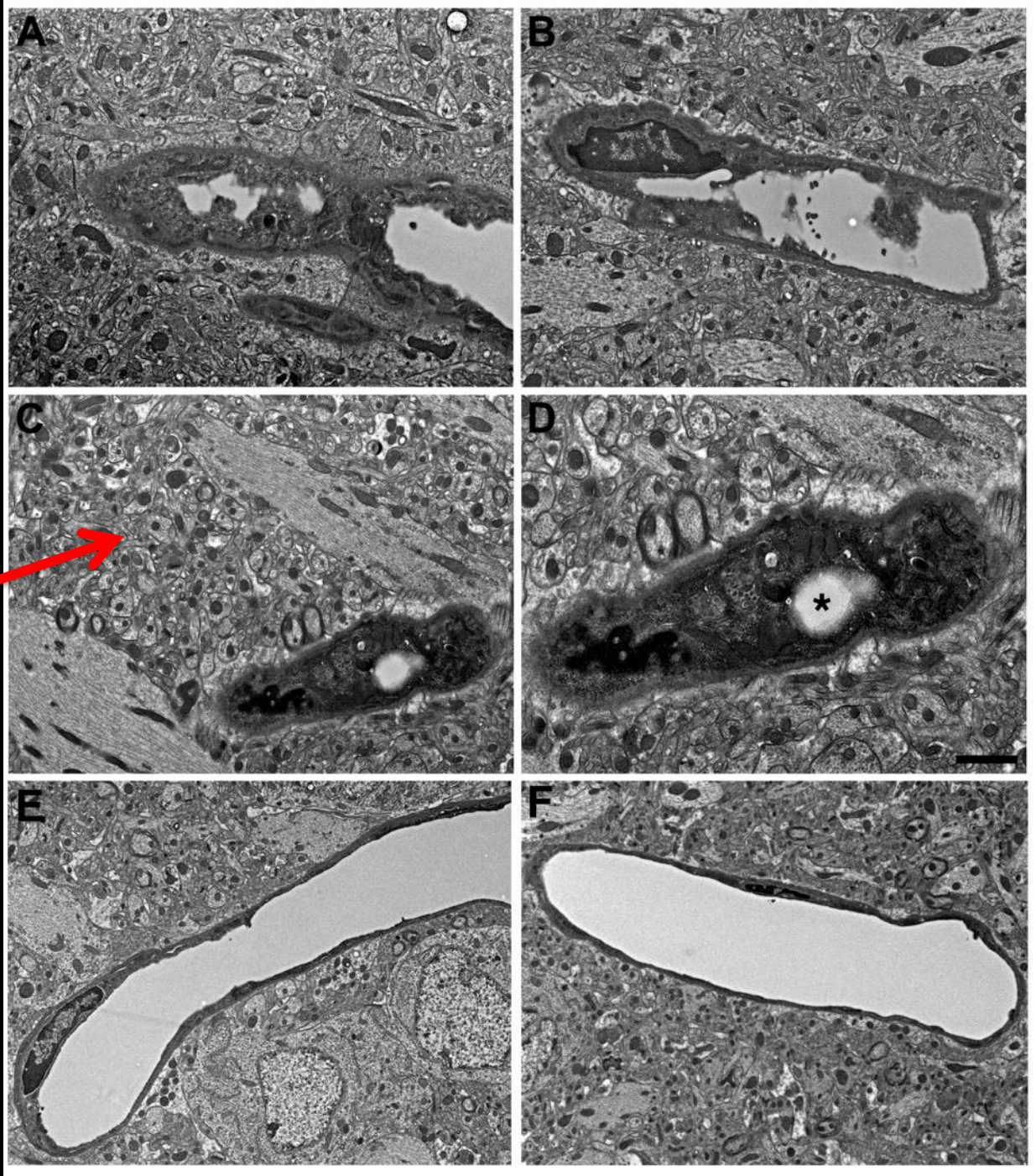


Three 74.5 kPa blast exposures, sacrificed 24 hours later

Blast

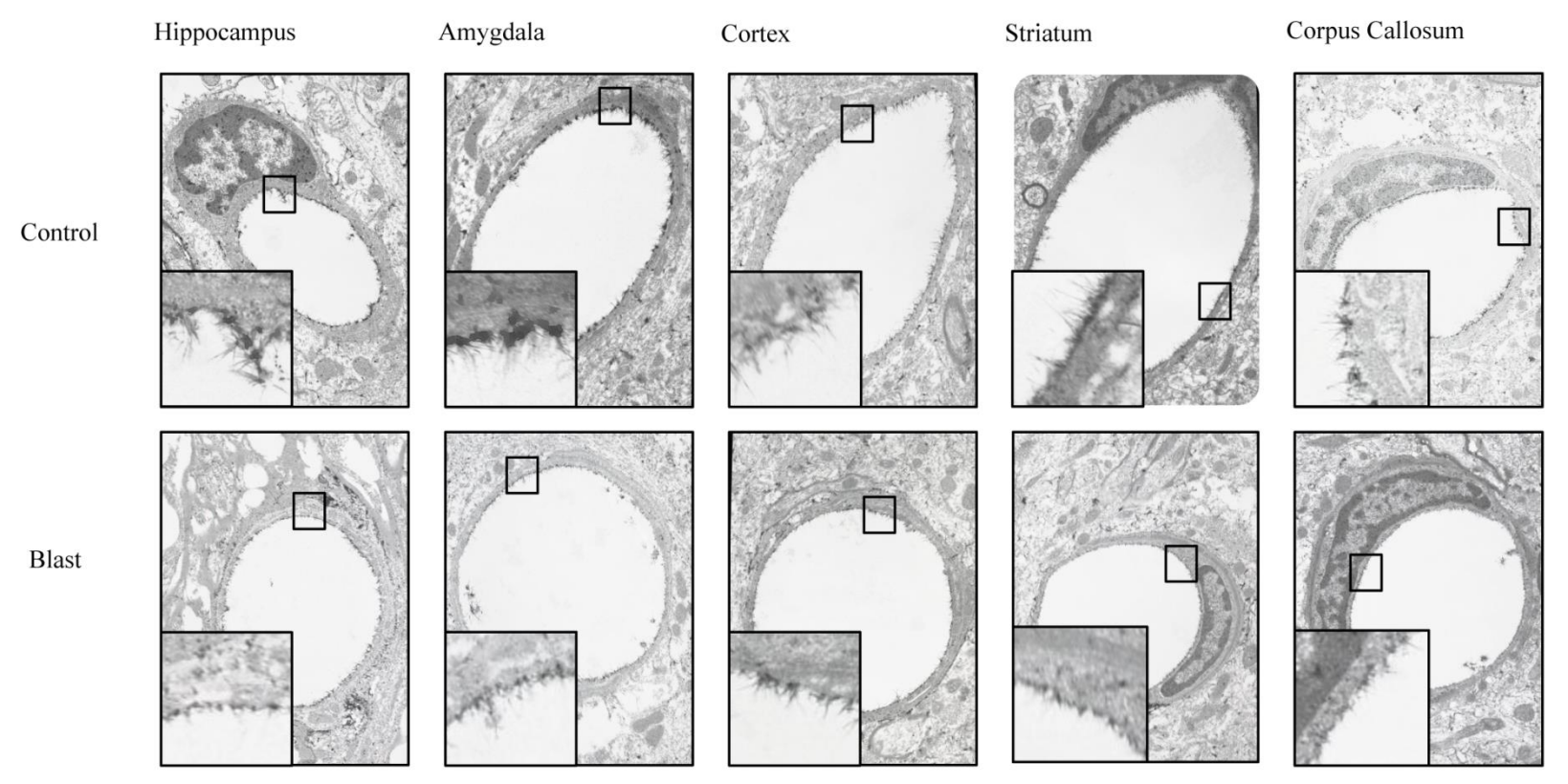
Normal neuropil

Controls

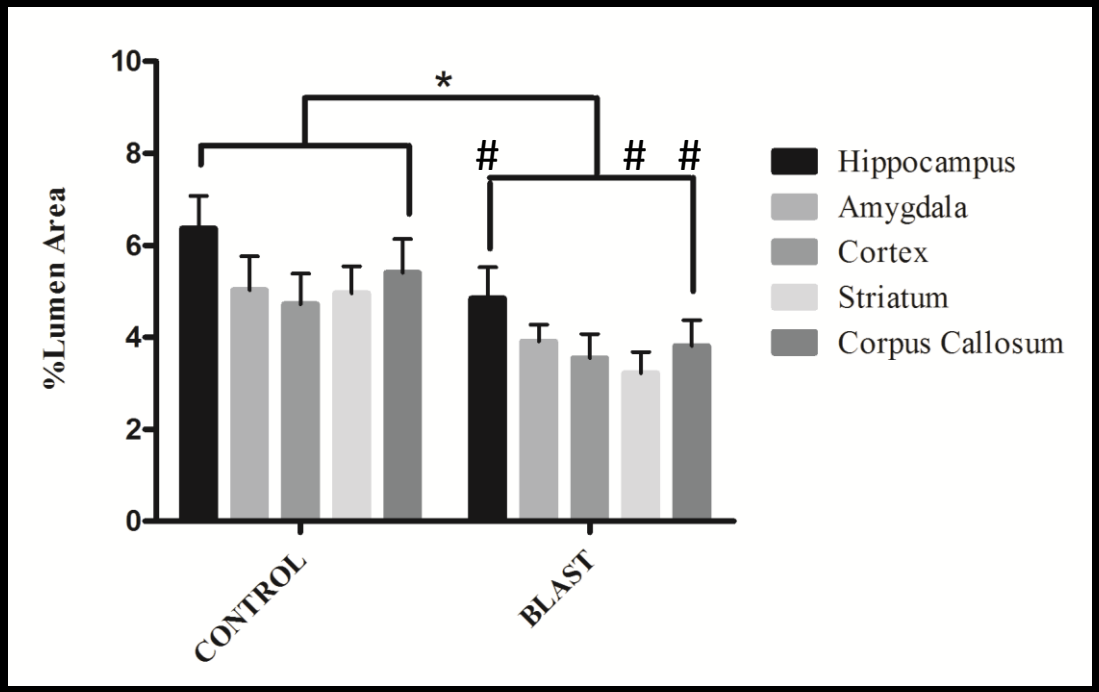


Blast exposure reduces glycocalyx thickness in capillaries

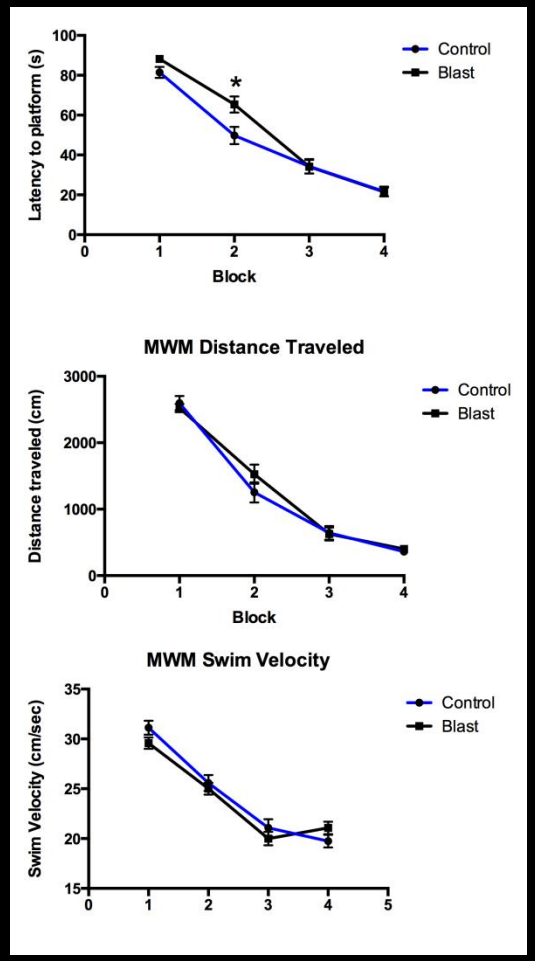
Rats, 12 x 40 kPa blast exposures spaced over 2.5 weeks; sacrificed 24 hours after last exposure



20% decrease in capillary glycocalyx thickness

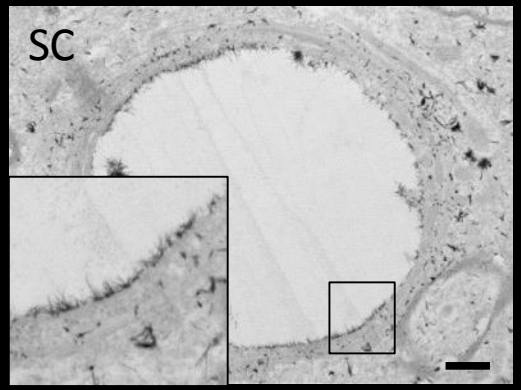


Blast-related impairment in Morris water maze

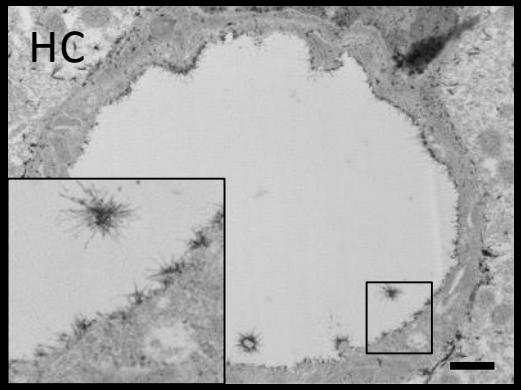


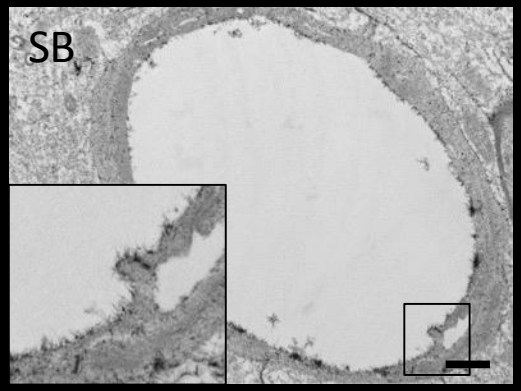
Hyaluronidase infusion during blast exposure causes glycocalyx thickening and improves MWZ performance

control + saline

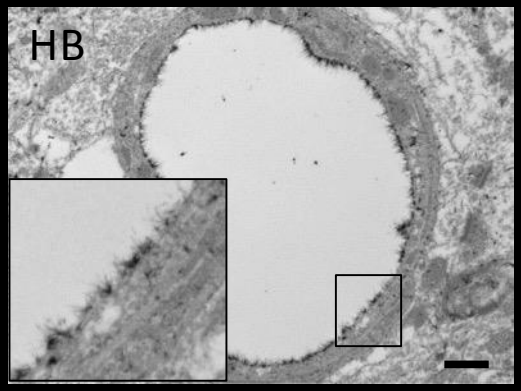


control + hyaluronidase

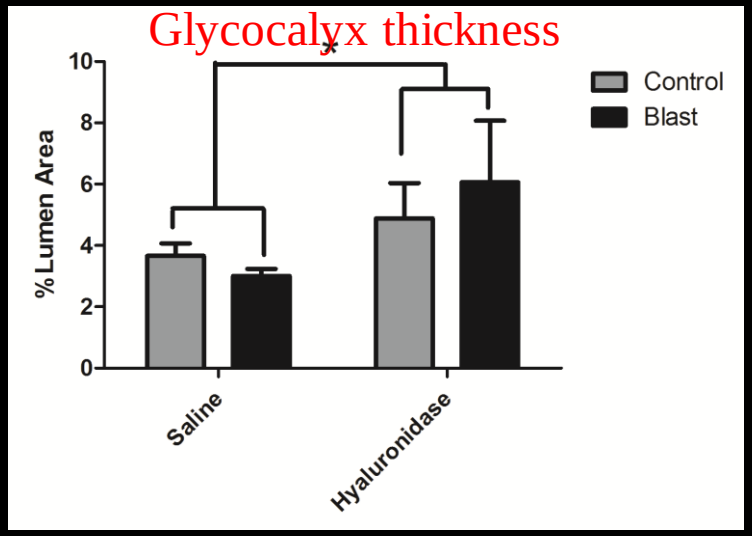


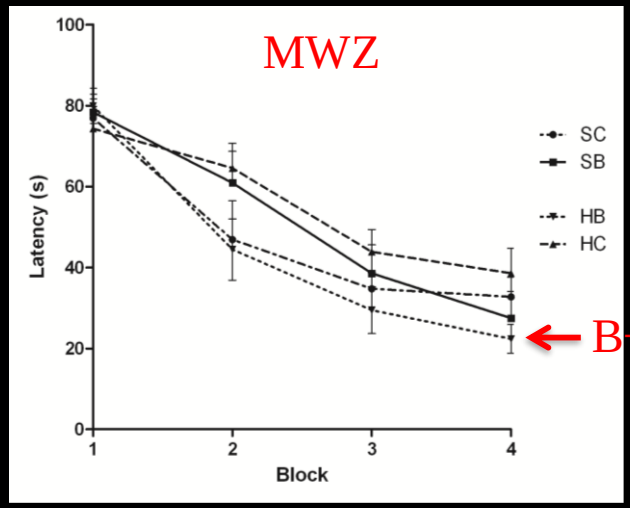


blast + saline



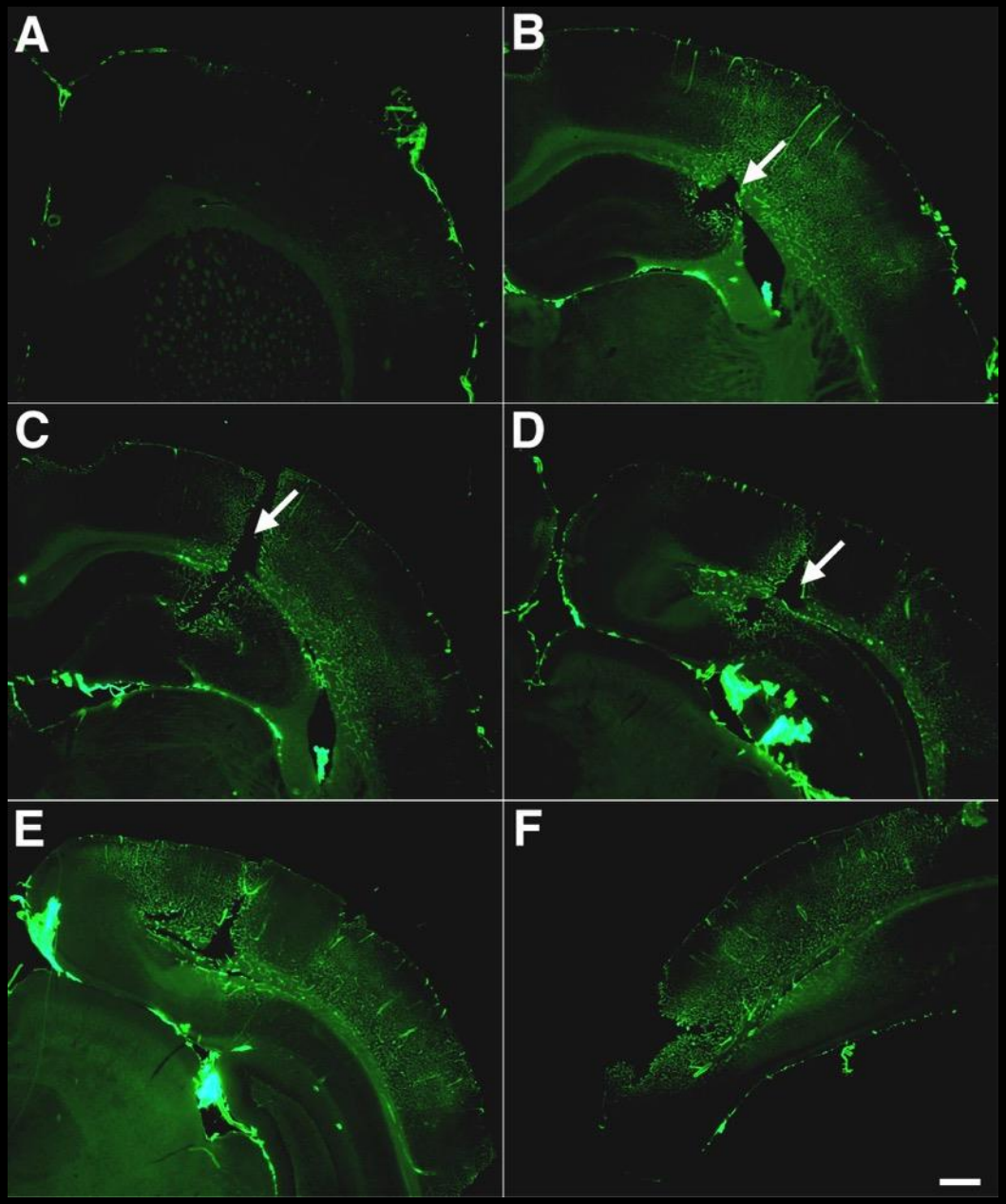
blast + hyaluronidase





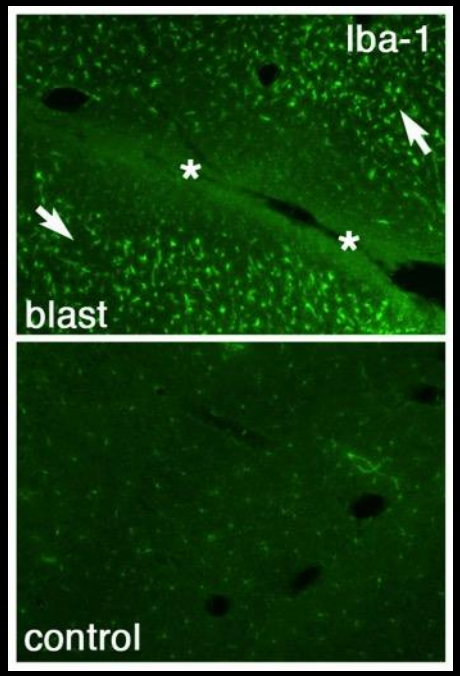
Chronic remodeling of the extracellular matrix after blast exposure

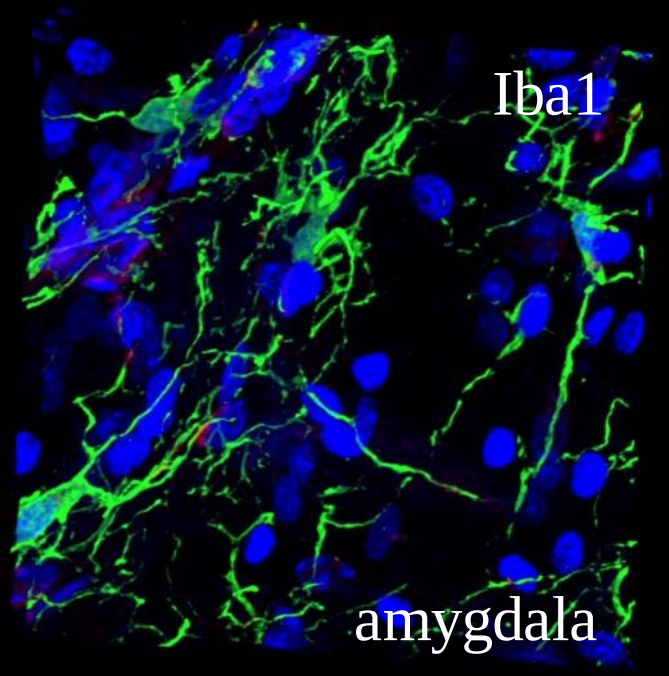
-3 x 74.5 kPa blasts at 2 months age
-Collagen IV staining 10 months later without pepsin



A vascular/inflammatory connection?

Chronic microglial activation





Vascular

↓

Inflammation

↓

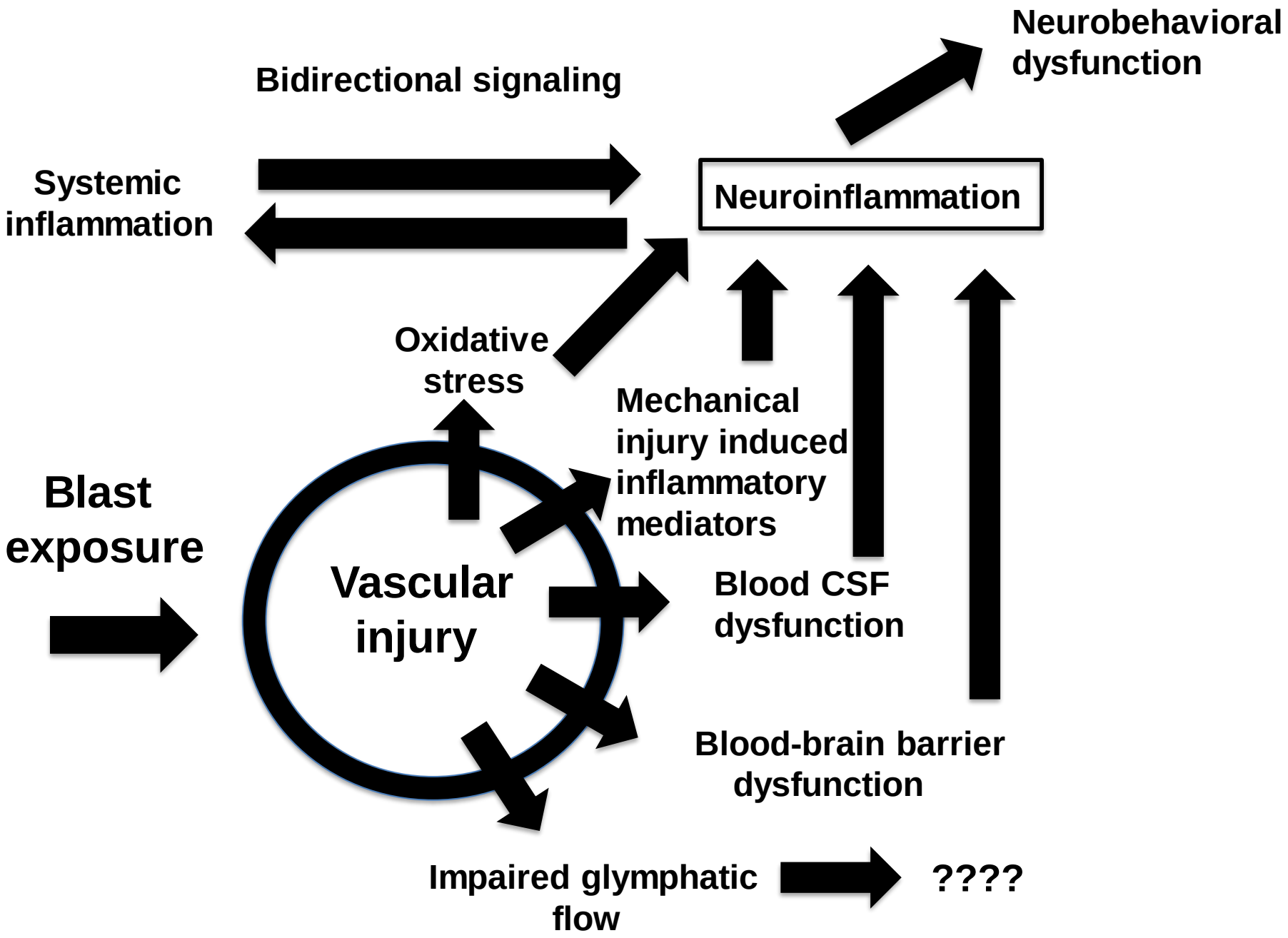
Neuronal Dysfunction

frontiers in NEUROLOGY

REVIEW ARTICLE
published: 16 March 2015
doi: 10.3389/fneur.2015.00048

Vascular and inflammatory factors in the pathophysiology of blast-induced brain injury

Gregory A. Elder[1,2,3,4]*, Miguel A. Gama Sosa[2,4,5], Rita De Gasperi[2,4,5], James Radford Stone[6,7], Dara L. Dickstein[4,8,9], Fatemeh Haghighi[2,4,5,8], Patrick R. Hof[4,8,9] and Stephen T. Ahlers[10]


Neurobehavioral dysfunction
Bidirectional signaling
Systemic inflammation
Neuroinflammation
Oxidative stress
Mechanical injury induced inflammatory mediators
Blast exposure
Vascular injury
Blood CSF dysfunction
Blood-brain barrier dysfunction
Impaired glymphatic flow
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