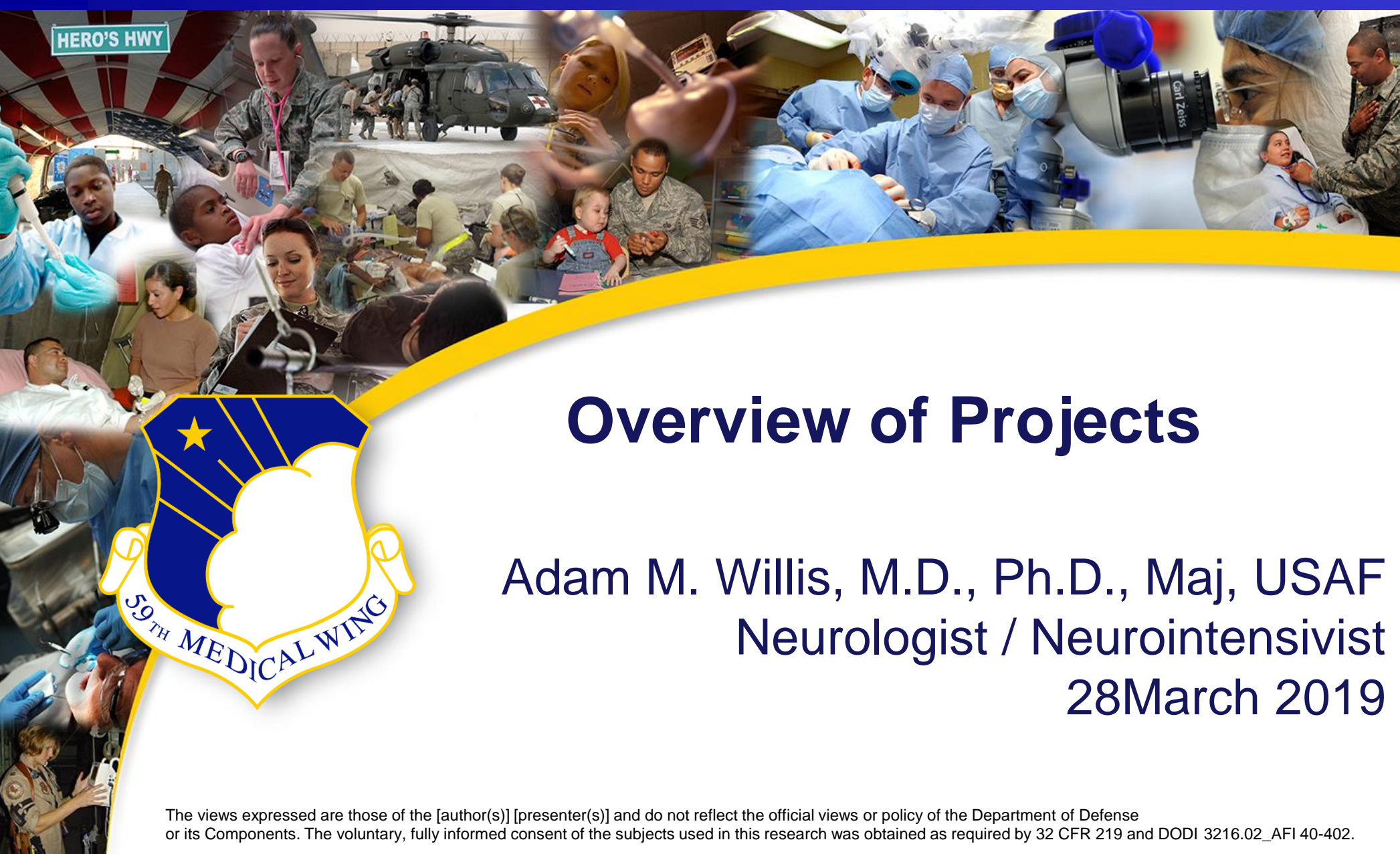




59th Medical Wing



Overview of Projects

Adam M. Willis, M.D., Ph.D., Maj, USAF
Neurologist / Neurointensivist
28March 2019

The views expressed are those of the [author(s)] [presenter(s)] and do not reflect the official views or policy of the Department of Defense or its Components. The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and DODI 3216.02_AFI 40-402.



Focus of research



Warrior Medics – Mission Ready – Patient Focused

- ***Post-traumatic stress disorder***. Signature wound of modern conflict:
- ***Severe blast traumatic brain injury***: second leading cause death in battlefield
- ***Non-compressible torso hemorrhage***: first leading cause of death in battlefield



PTSD and childhood trauma



Warrior Medics – Mission Ready – Patient Focused

RESEARCH ARTICLE

Open Access

Do adverse childhood experiences increase the risk of postdeployment posttraumatic stress disorder in US Marines?

Cynthia A LeardMann*, Besa Smith, Margaret AK Ryan

Journal of Traumatic Stress, Vol. 23, No. 2, April 2010, pp. 248–254 (© 2010)

The Impact of Childhood Abuse and Combat-Related Trauma on Postdeployment Adjustment

April M. Fritch
98th Medical Detachment (Combat Stress Control)

Matt Mishkind, Mark A. Reger, and Gregory A. Gahm
Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury

Research Articles

Childhood Adversity and Combat as Predictors of Depression and Post-Traumatic Stress in Deployed Troops

Oscar A. Cabrera, PhD, Charles W. Hoge, MD, Paul D. Bliese, PhD, Carl A. Castro, PhD, Stephen C. Messer, PhD

Am J Prev Med 2007;33(2)
© 2007 American Journal of Preventive Medicine

8300 Marines had hazard ratio of PTSD 1.57 with pre-deployment reporting of 2 or more ACE categories

1045 service members showed increased risk of PTSD, anxiety, and depression with childhood physical abuse.

Likelihood of screening positive for PTSD or depression significantly effected by ACE scores



PTSD and genetics and experience

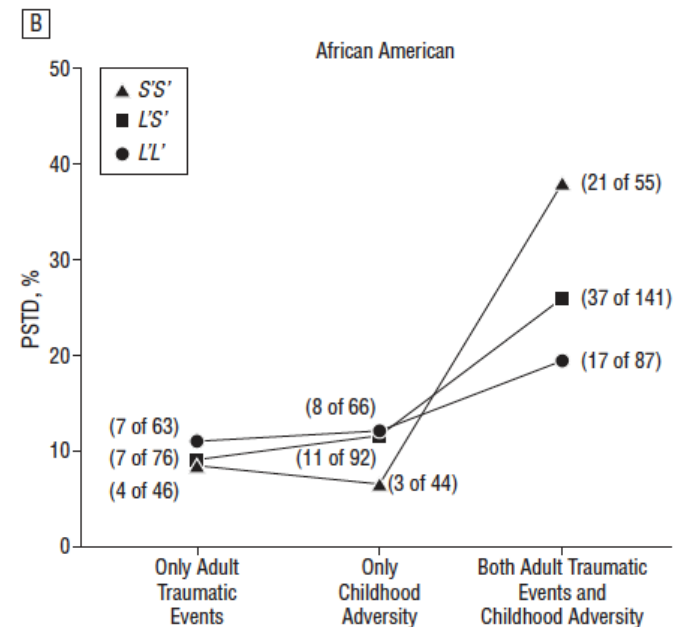
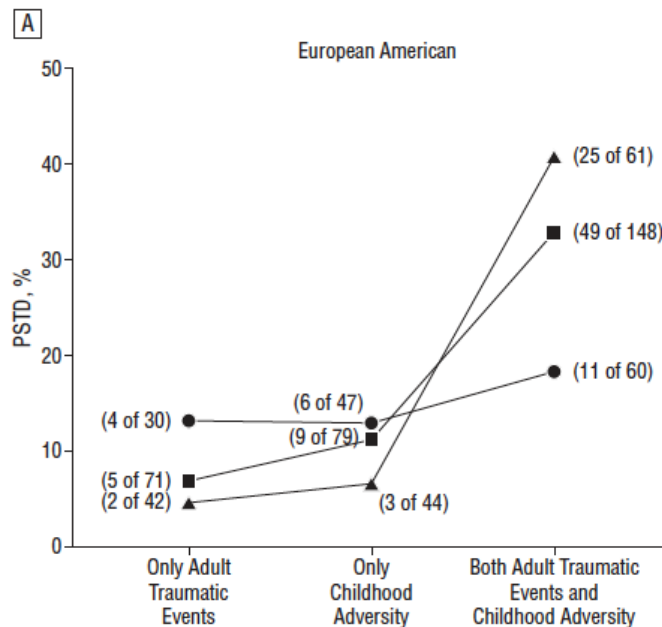


Warrior Medics – Mission Ready – Patient Focused

ORIGINAL ARTICLE

Interactive Effect of Stressful Life Events and the Serotonin Transporter 5-HTTLPR Genotype on Posttraumatic Stress Disorder Diagnosis in 2 Independent Populations

Pingxing Xie, BS; Henry R. Kranzler, MD; James Poling, PhD; Murray B. Stein, MD, MPH; Raymond F. Anton, MD; Kathleen Brady, MD, PhD; Roger D. Weiss, MD; Lindsay Farrer, PhD; Joel Gelernter, MD





PTSD and genetics and experience



Warrior Medics – Mission Ready – Patient Focused

Early Intervention May Prevent the Development of PTSD: A Randomized Pilot Civilian Study with Modified Prolonged Exposure

Barbara Olasov Rothbaum, Ph.D.¹, Megan C. Kearns, Ph.D.¹, Matthew Price, Ph.D.², Emily Malcoun, Ph.D.¹, Michael Davis, Ph.D.¹, Kerry J. Ressler, M.D., Ph.D.^{1,5}, Delia Lang, Ph.D.³, and Debra Houry, M.D., M.P.H.¹

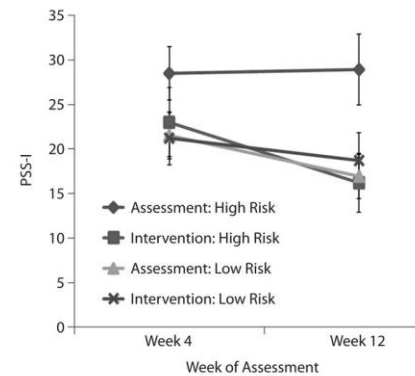
Early Intervention Following Trauma May Mitigate Genetic Risk for PTSD in Civilians: A Pilot Prospective Emergency Department Study

Drs. Barbara O. Rothbaum, PhD, Drs. Megan C. Kearns, PhD, Mss. Emily Reiser, BS, Mss.

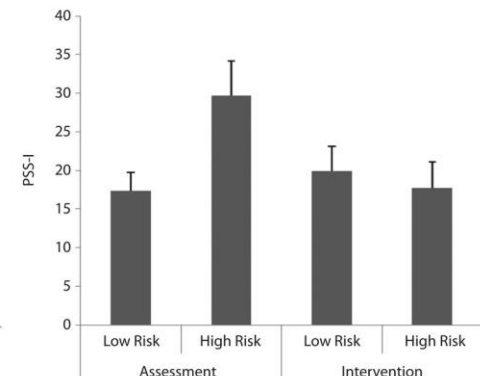
Gene	SNP	Risk Genotype
ADCYAP1R1	Rs2267735	CC
COMT	Rs4680	GG
CRHR1	Rs7209436	CC
DBH	Rs1611115	CC
DRD2	Rs6277	TT
FAAH	Rs324420	CC
FKBP5	Rs1360780	TT
NPY	Rs16147	GG
NTRK2	Rs1867283	GG
PCLO	Rs2522833	AA
TPH2	Rs4570625	AA
TPH2	Rs1386494	CC
DAT1	Rs40184	CC
DRD2	Rs1800497	TT

	Intervention (n=69)	Assessment (n = 68)	Effect size
Primary Outcomes			
PSS			
Week 4*	<i>a,y</i> 19.09±1.83 (15.51-22.68)	<i>b,y</i> 24.54±1.70 (21.22-27.87)	0.38
Week 12*	<i>a,z</i> 15.47±1.98 (11.60-19.34)	<i>b,z</i> 20.33±1.80 (16.79-23.87)	0.34
BDI			
Baseline	<i>a,y</i> 18.60±1.51 (15.64-21.55)	<i>a,y</i> 21.26±1.47 (18.38-24.14)	
Week 4*	<i>b,z</i> 15.04±1.70 (11.72-18.37)	<i>a,y</i> 21.37±1.63 (18.38-24.14)	0.35
PDS			
Baseline	<i>a,y</i> 18.90±1.80 (15.35-22.39)	<i>a,y</i> 19.46±1.78 (15.97-22.95)	
Week 4	<i>a,y</i> 18.90±2.34 (14.30-23.50)	<i>a,y</i> 23.76±2.29 (19.27-28.24)	0.11

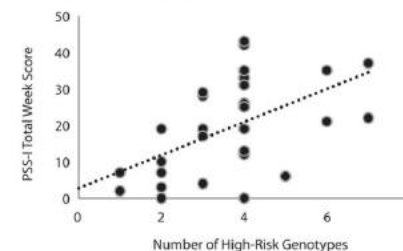
PTSD, ADCYAP1R1 Genetic Risk, and Intervention^a



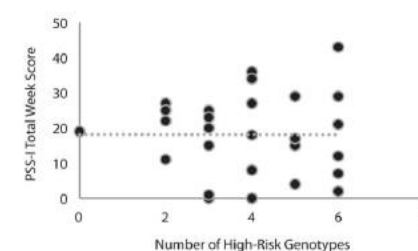
ADCYAP1R1 (PACAP receptor) PSS-I Week 12^b



G. Assessment: Total PSS-I^c



H. Intervention: Total PSS-I^c





Building the ACES framework



Warrior Medics – Mission Ready – Patient Focused

Recruitment

- Prospective case-control study
 - 70 patients with PTSD and 210 patients w/o PTSD
- Inclusion criteria
 - Active duty
 - Deployed for greater than 3 months
 - “Seen combat”
- Exclusion criteria
 - Known history of structural brain damage as demonstrated by imaging (CT head / MRI)
 - History TBI resulting in loss of consciousness
 - Pre-deployment diagnosis of PTSD or anxiety disorder
 - Pre-deployment prescription of a selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), or tricyclic antidepressants (TCA).



Results – Exposure, Genetics, and Outcomes



Warrior Medics – Mission Ready – Patient Focused

Pearson Correlation coefficients for exposure and outcome variables

	PTSD	PCL-M	CES	ACES
PTSD	1.00			
PCL-M	0.6734 (<0.0001)	1.00		
CES	0.2627 (<0.0001)	0.3057 (<0.0001)	1.0	
ACES	0.14747 (<0.0001)	0.2309 (0.001)	-0.0427 (0.4713)	1.0

Significant Genetic Outcomes

Rs7209436	PTSD (0)	PTSD (1)	Odds Ratio (95% CI)	p
2	63 (29.7%)	26 (42.6%)	1.00	
1	100 (47.2%)	20 (32.8%)	0.47 (0.24 – 0.92)	0.03
0	49 (23.1%)	15 (24.6%)	0.67 (0.31 – 1.42)	0.29
Total	212	61		

No other significant interactions between experience and genetics tested



Results- Methylation Analysis



Warrior Medics – Mission Ready – Patient Focused

	PTSD (cases)	No PTSD (controls)
	70	100
Gender		
Male	53	87
Female	17	13
Age (mean)	38.7	35.1
Ethnicity		
Caucasian	21	50
African American	21	22
Hispanic/Latino	17	20
Asian	4	4
Other	7	4
Anti-depressant use*	50 (p< 0.0001)	21
ACES score (mean)	2.8 (p=0.0015)	1.7
Combat Exposure Scale [0-41] (mean)	17.5 (p <0.0001)	11.3
PCL-M score [0-85] (mean)	56.9 (p <0.0001)	27.8



Results – Methylation Analysis



Warrior Medics – Mission Ready – Patient Focused

Significant hypomethylation differences found on all methylation sites for ***BDNF*** and ***NR3C1*** and ***MAN2C1***.

Significance remained in ***BDNF*** and ***NR3C1*** after controlling for antidepressant use

In this clean PTSD population – we see changes in methylation of ***immune*** systems and products associate with ***cortical connectivity***

... how can we move forward



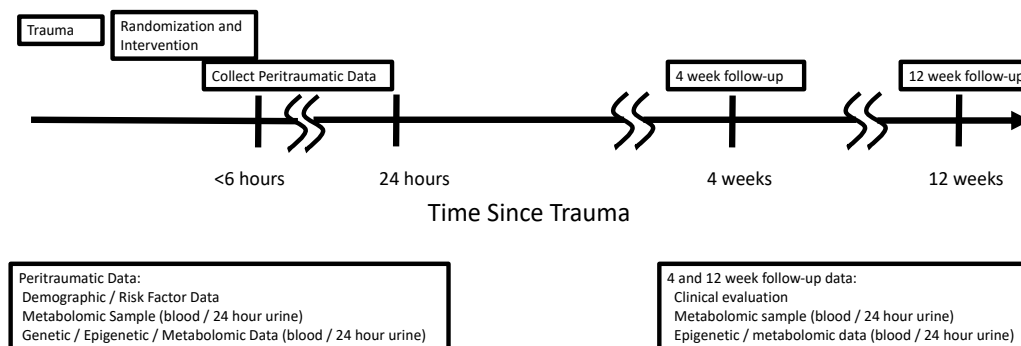
PR-ICBM



Warrior Medics – Mission Ready – Patient Focused

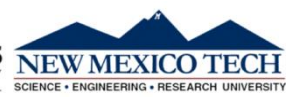
Post-traumatic stress disorder **R**eduction via **I**ntravenous **C**orticosteroids with analysis of **B**iomarkers using **M**etabolomics. (PR-ICBM)

- Only treatment to reduce PTSD following trauma is early administration of hydrocortisone
- We will test this via double blind randomized control trial with immediate hydrocortisone (100 – 140 mg IV) supplementation after trauma
- Goal recruitment 150 subjects
- Primary outcome PTSD diagnosis at 12 weeks
- Secondary outcome - identify via metabolomics subjects who benefit from hydrocortisone supplementation



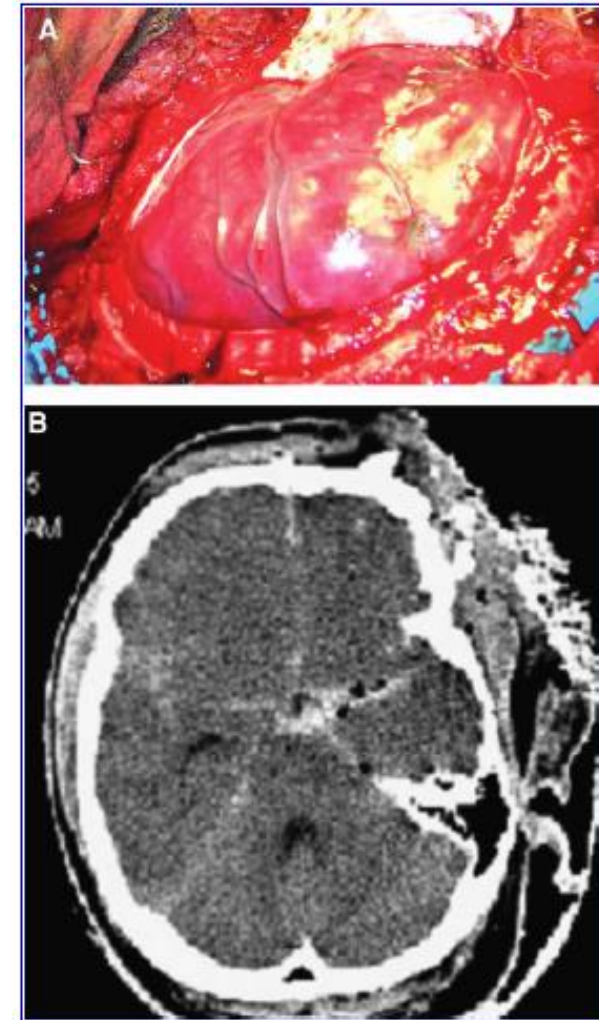


Blast TBI – severe vascular dysfunction



Warrior Medics – Mission Ready – Patient Focused

- Severe edema in acute setting (minutes to hours)
- Subarachnoid hemorrhage, pseudo-aneurysm,
- Delayed vasospasm – not always associated with subarachnoid hemorrhage



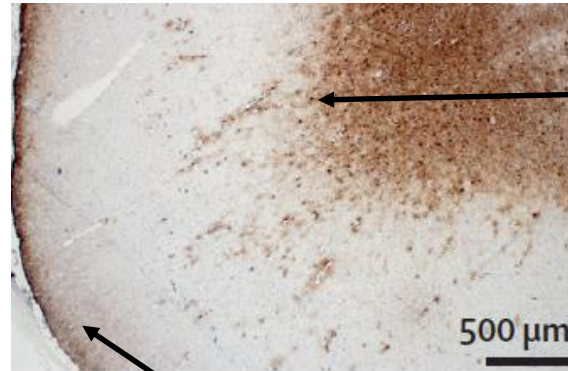
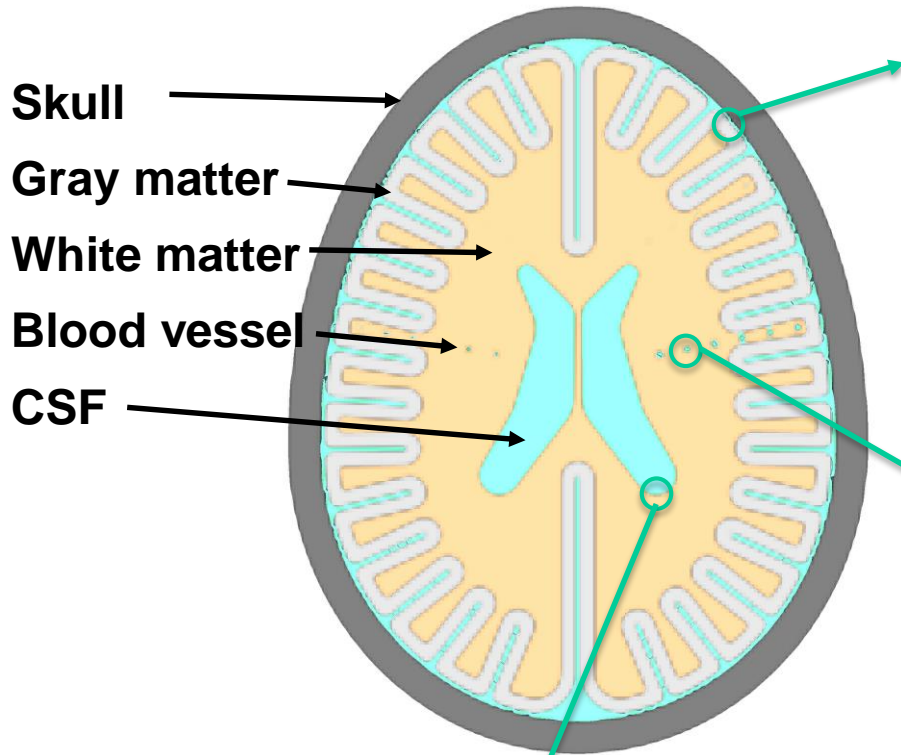
Ling 2009



Blast TBI – unique interfacial injury

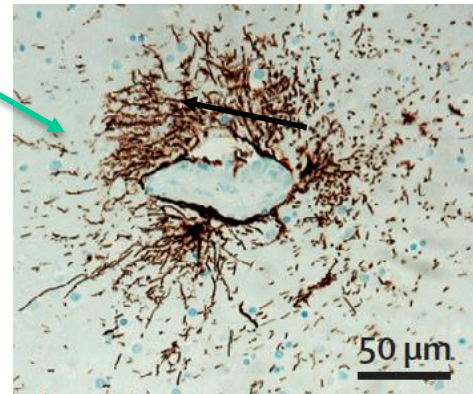


Warrior Medics – Mission Ready – Patient Focused

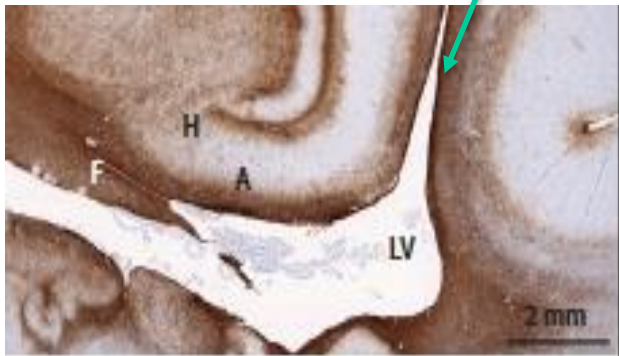


Gray-white

CSF – brain (sub-pial)



Peri-vascular



CSF-brain
(Peri-ventricular)



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

Lancet Neurol 2016; 15: 944-53



Kinematic localization of blast TBI?



Warrior Medics – Mission Ready – Patient Focused

- Clinically:
 - Large vessels : **CSF – vessel interface**
 - Small vessels : **brain – vessel interface**
- Pathology:
 - Small vessels: **brain – vessel interface**
 - Gray-white interface: **interface**
 - Periventricular: **CSF – brain interface**
 - Subpial: **CSF – brain interface**

	Density	Bulk Modulus	Shear Modulus
Skull	1.21 (g/cc)	4672 (MPa)	3270 MPa
White Matter	1.04	2371	41 kPa- G_o , 7.8 kPa- G_{inf} , $B = 40 \text{ s}^{-1}$
Gray Matter	1.04	2371	34 kPa- G_o , 6.4 kPa- G_{inf} , $B = 40 \text{ s}^{-1}$
CSF	.9998	1960	



Computational Modeling



Warrior Medics – Mission Ready – Patient Focused

Domain: 14.4374cm x 18.7166cm x 10.4cm

Gray Matter

White Matter

CSF

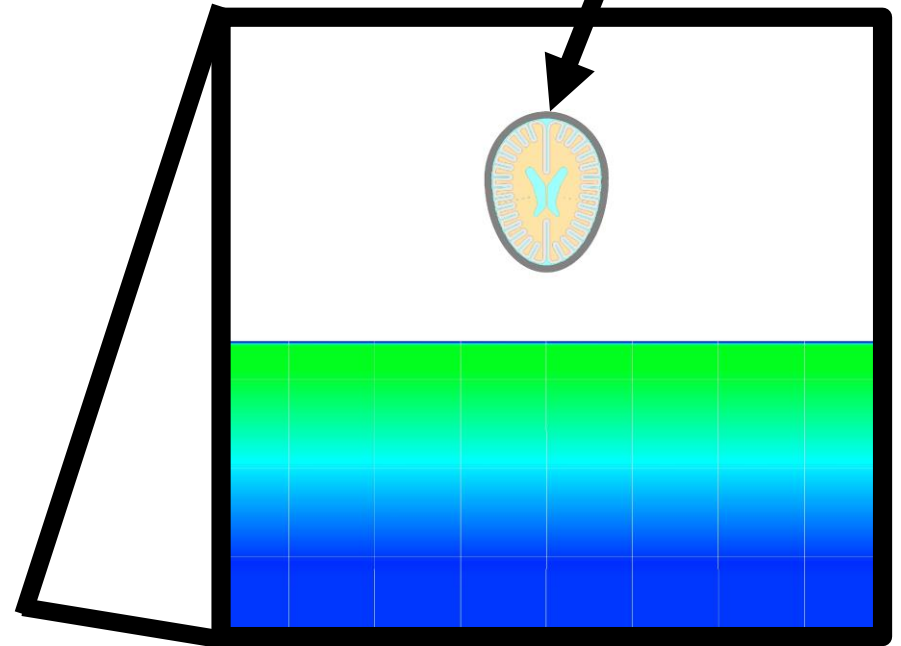
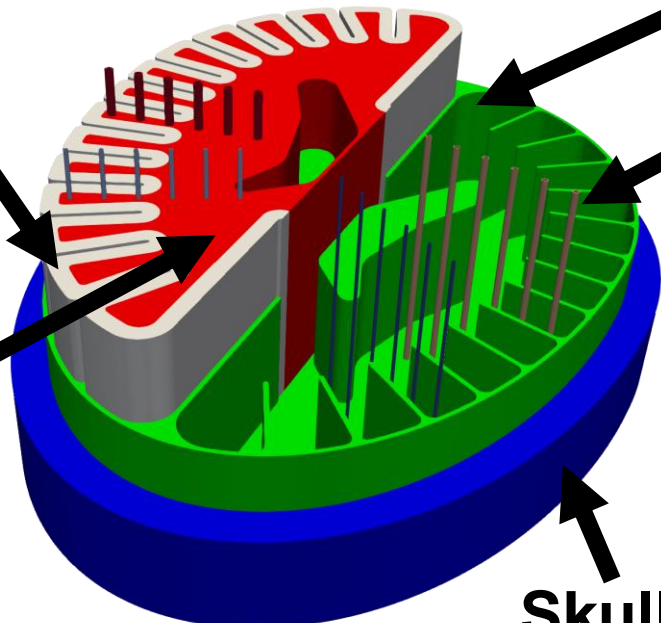
Vessel

Skull

Finite Element Solver (Sierra Mechanics)

Gas Dynamics Solver (CTH)

Fully coupled with Zapotec



Number of nodes: 2,419,095
Number of elements = 2,368,704

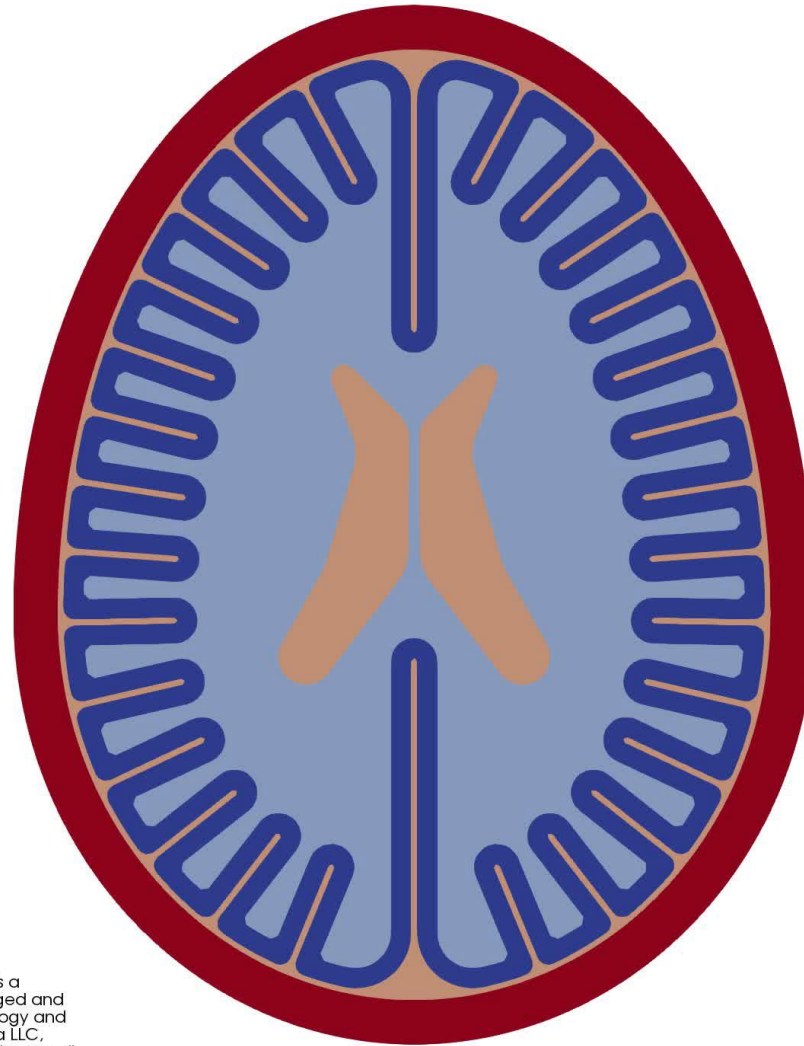
Skull: 820,432 elements
CSF: 351,152
White: 531,824
Gray: 665,296



Computational Modeling



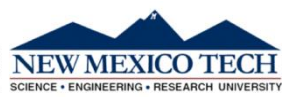
Warrior Medics – Mission Ready – Patient Focused



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International Inc. for the U.S.
Department of Energy's National
Nuclear Security Administration
under contract DE-NA0003525.

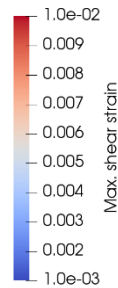
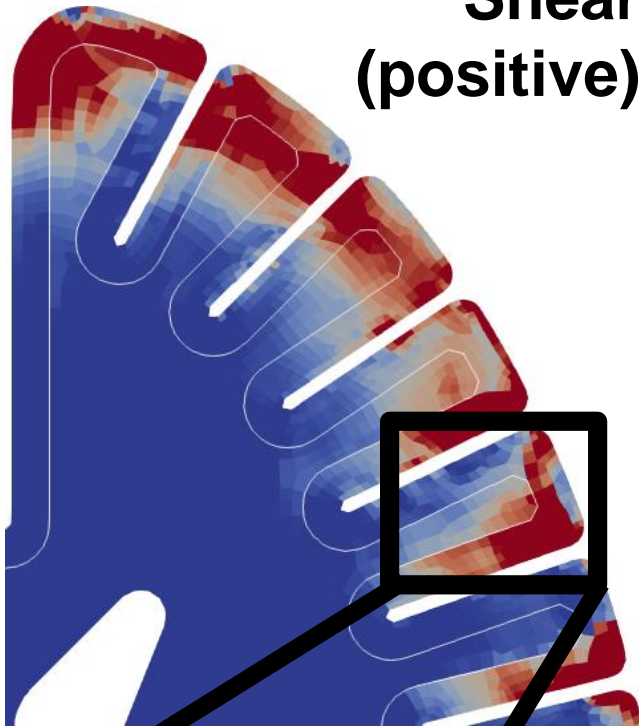


Computational Modeling: Shear

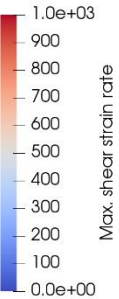
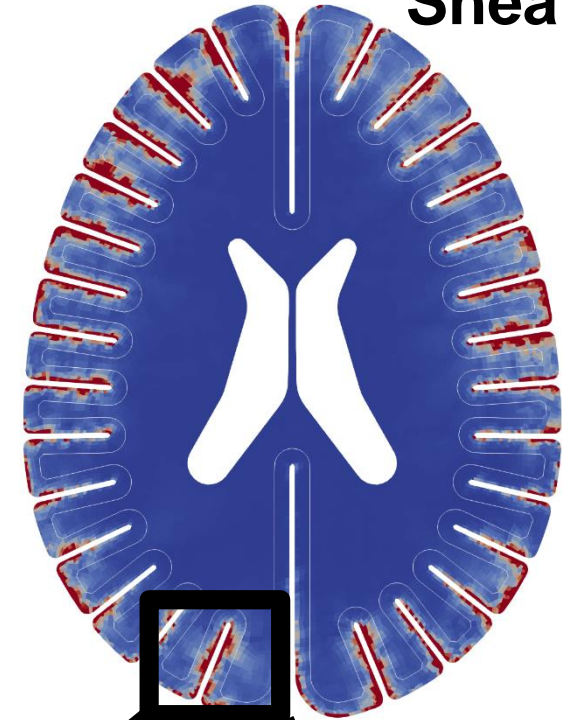


Warrior Medics – Mission Ready – Patient Focused

Shear (positive)

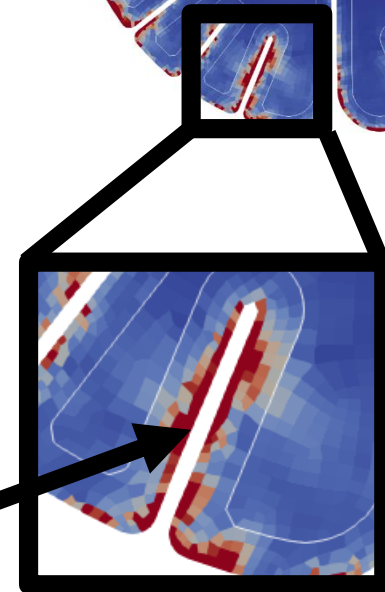
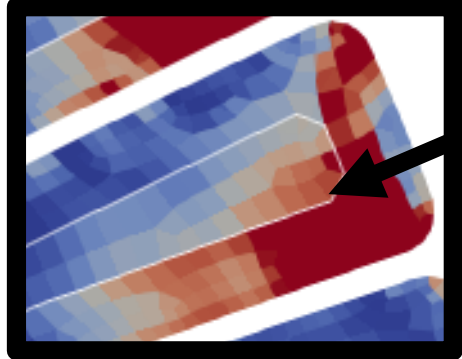


Shear rate



Gray-white interface

Sub-pial glial plate

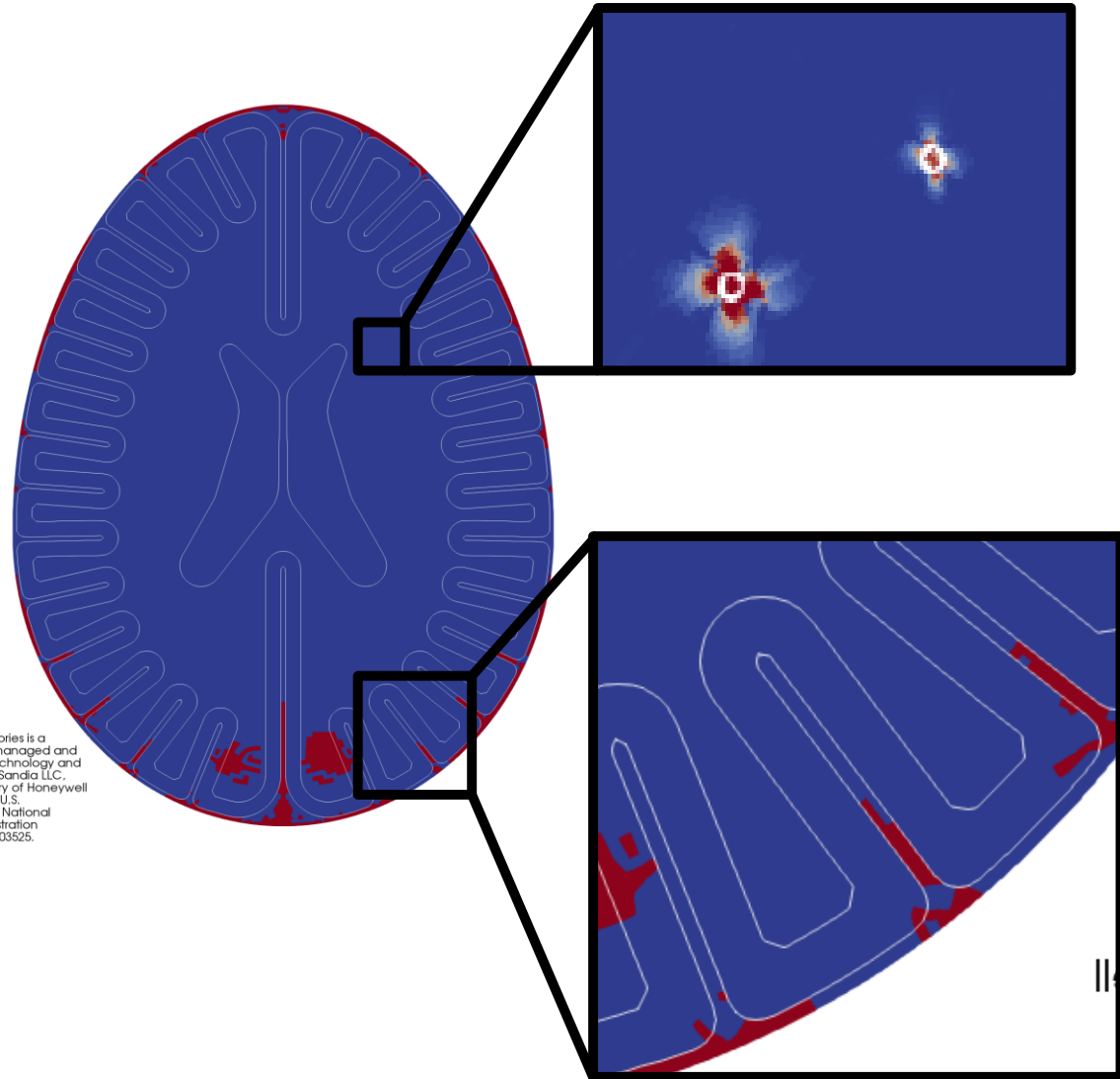




Computational Modeling - Cavitation



Warrior Medics – Mission Ready – Patient Focused



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11



What to minimize?



Warrior Medics – Mission Ready – Patient Focused

- Clinically:
 - Large vessels : **cavitation in CSF**
 - Small vessels : **cavitation in penetrating vessels**
- Pathology:
 - Small vessels: **cavitation in penetrating vessels**
 - Gray-white interface: **shear strain**
 - Periventricular: **?**
 - Subpial: **cavitation in CSF, shear strain rate**

	Density	Bulk Modulus	Shear Modulus
Skull	1.21 (g/cc)	4672 (MPa)	3270 MPa
White Matter	1.04	2371	41 kPa- G_o , 7.8 kPa- G_{inf} , $B = 40 \text{ s}^{-1}$
Gray Matter	1.04	2371	34 kPa- G_o , 6.4 kPa- G_{inf} , $B = 40 \text{ s}^{-1}$
CSF	.9998	1960	



Computation Model Validation



Warrior Medics – Mission Ready – Patient Focused

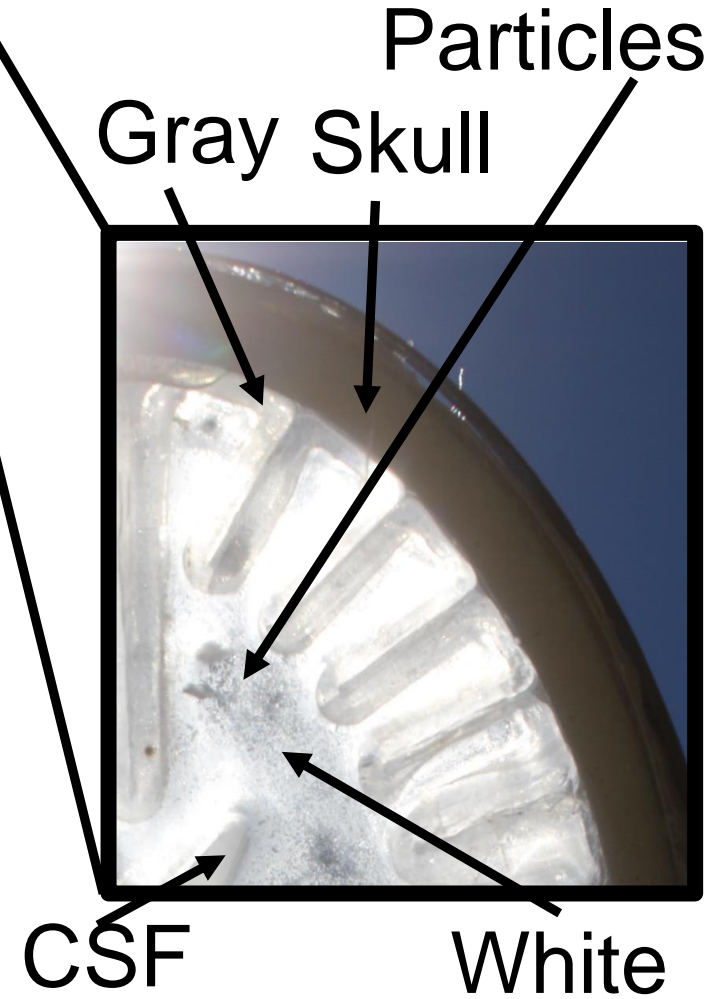
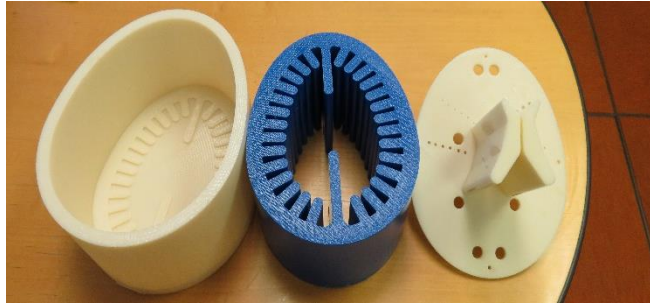
- Make a test object
- Blast test object and quantify kinematics (particle image velocimetry)



Making test object



Warrior Medics – Mission Ready – Patient Focused

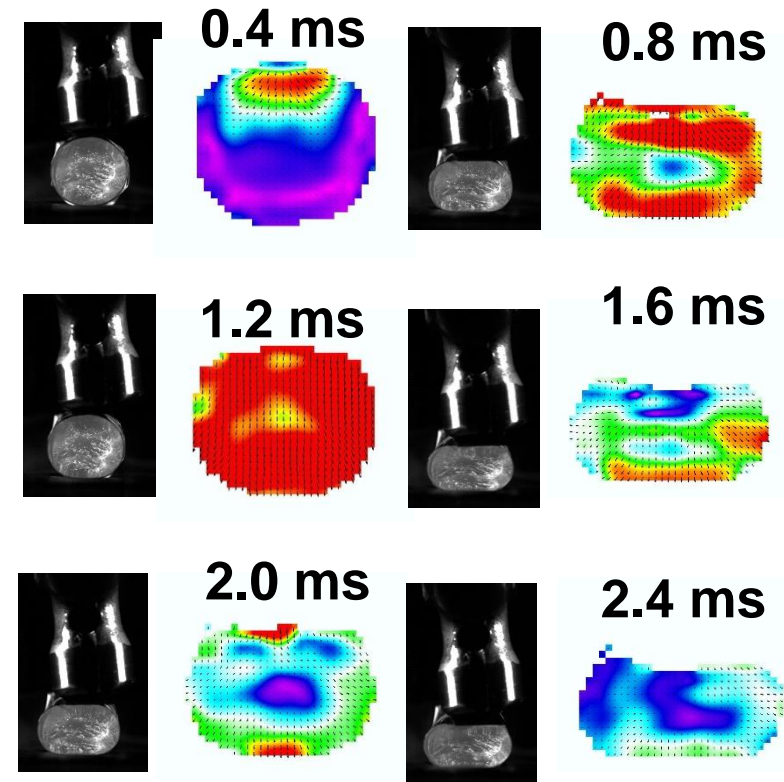
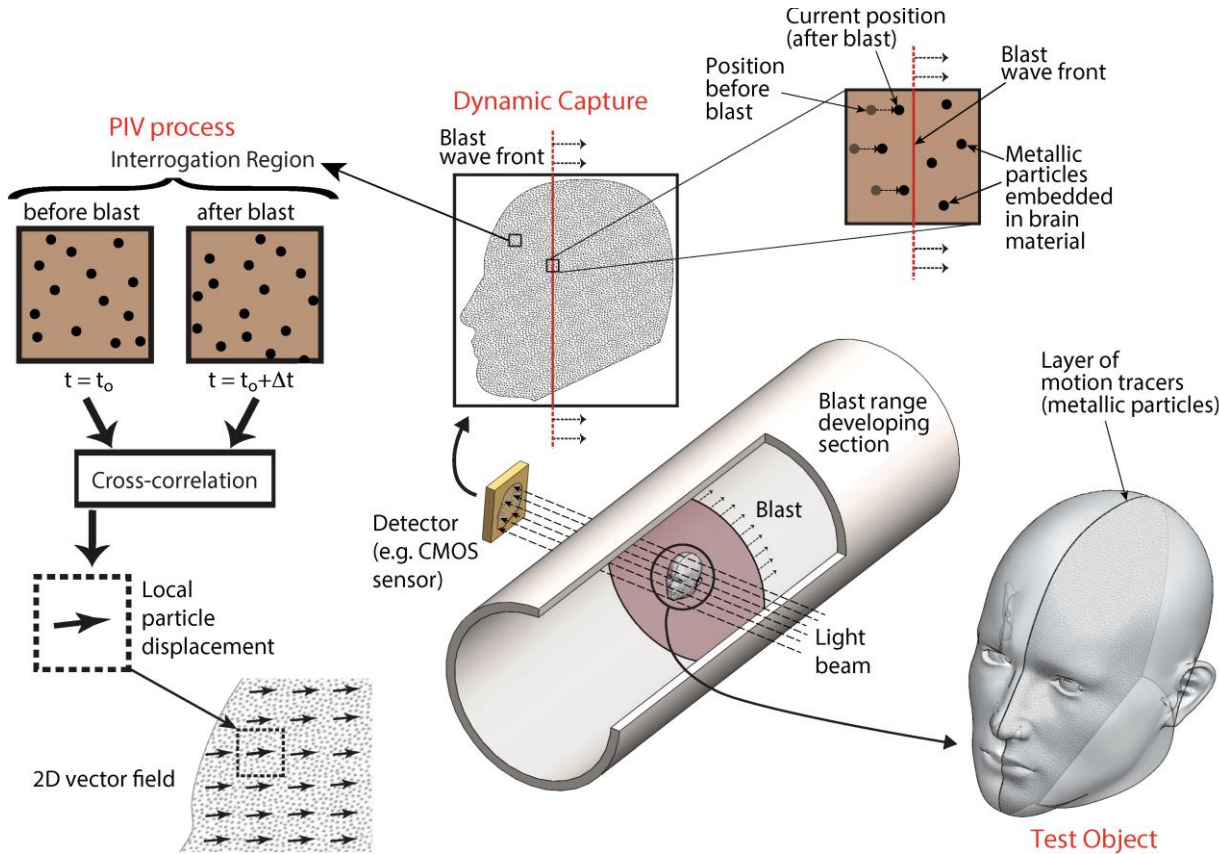




Particle Image Velocimetry



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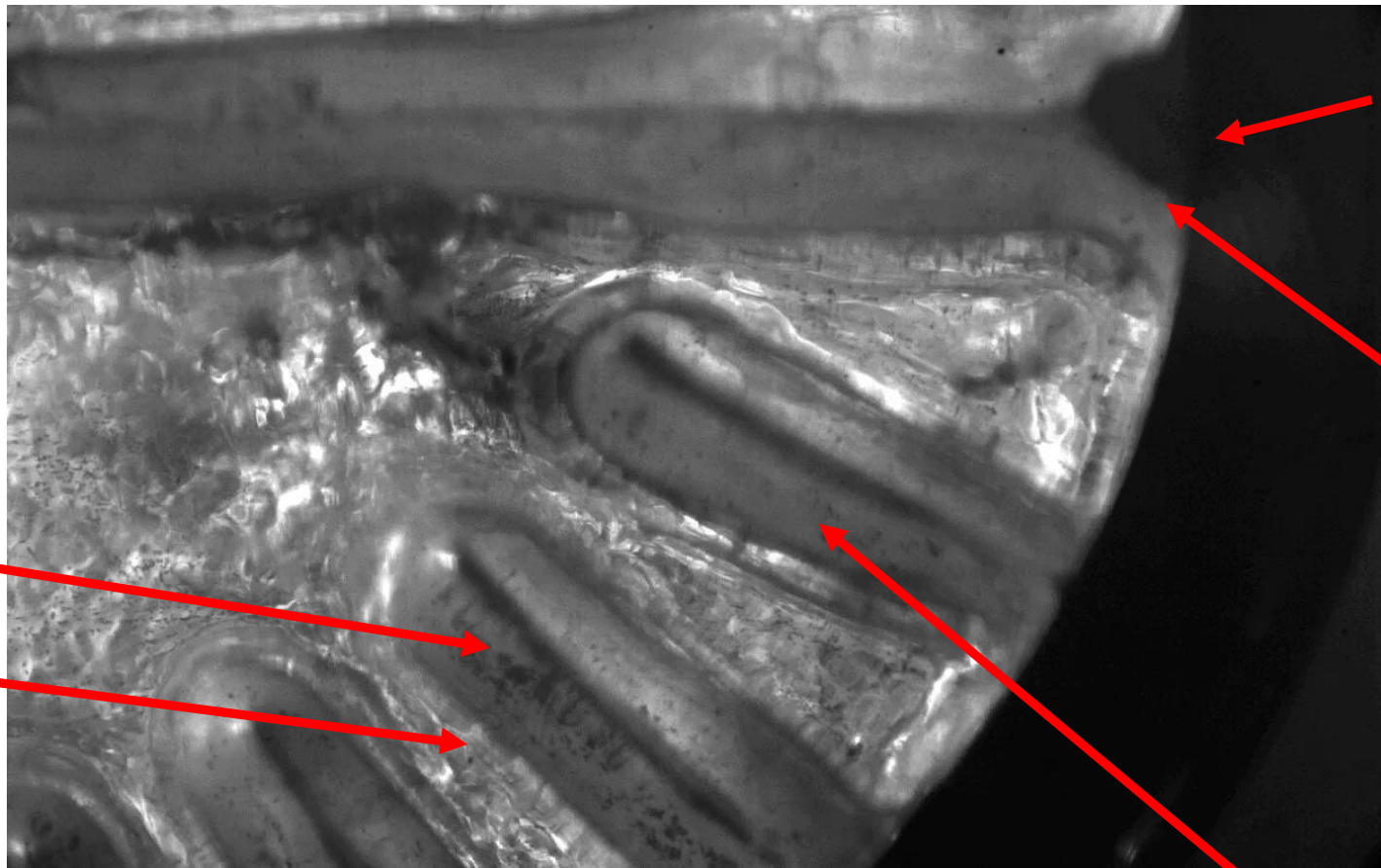




First 0.4 seconds of blast



Warrior Medics – Mission Ready – Patient Focused



Skull

CSF

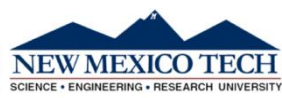
Gray

White

Particles

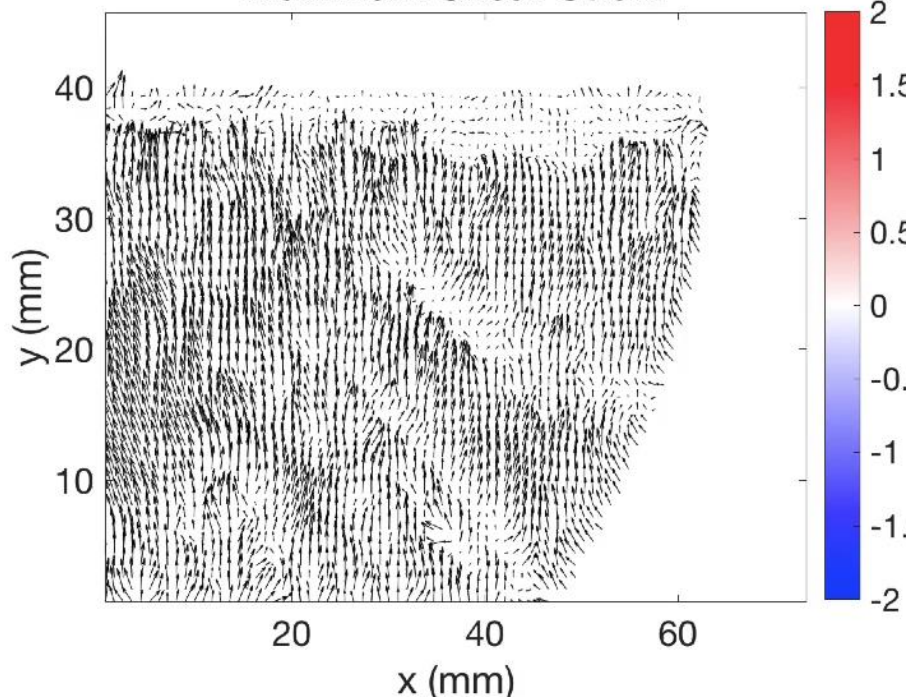


PIV analysis of first 0.02 seconds of blast

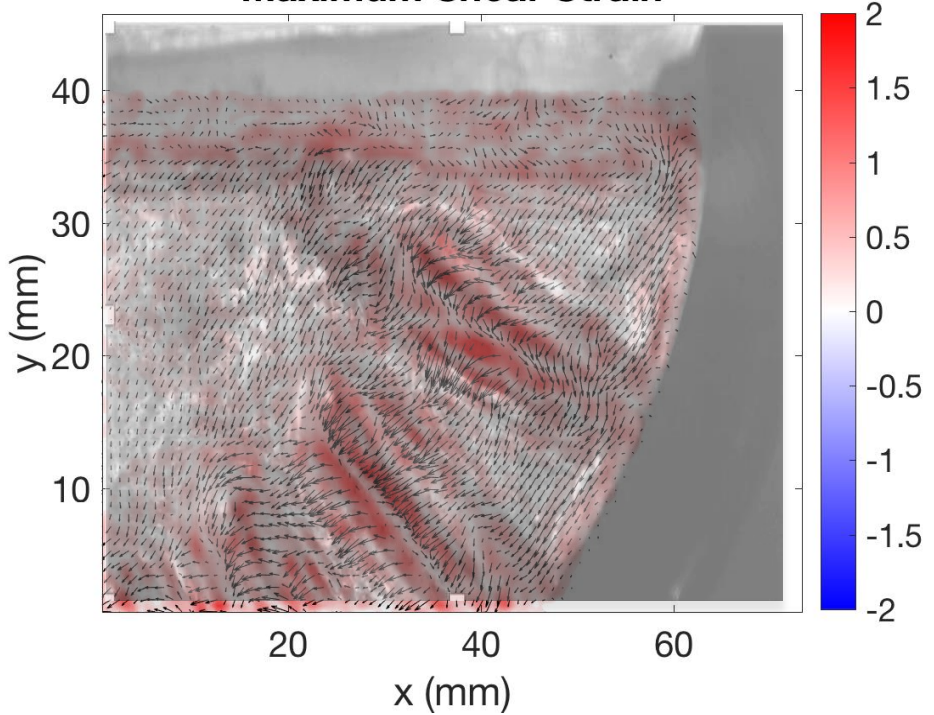


Warrior Medics – Mission Ready – Patient Focused

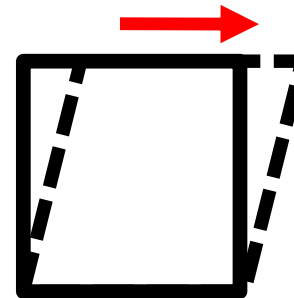
Maximum Shear Strain



Maximum Shear Strain



Shear





Next Steps - Funded



Warrior Medics – Mission Ready – Patient Focused

- Verify cavitation hypothesis experimentally
- Use computer to design new helmets to minimize cavitation
- Demonstrate reduction of cavitation with new helmet experimental

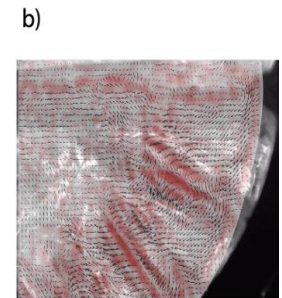
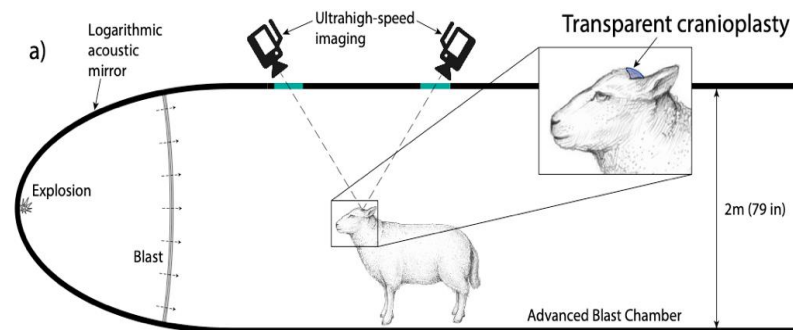
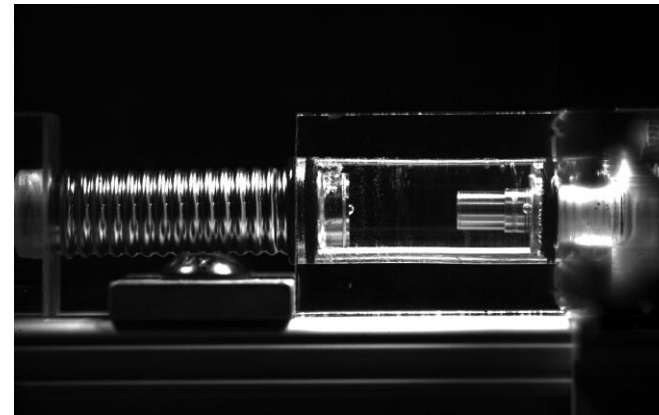
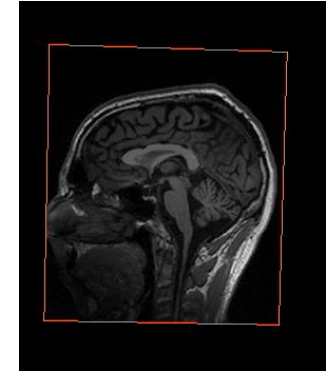
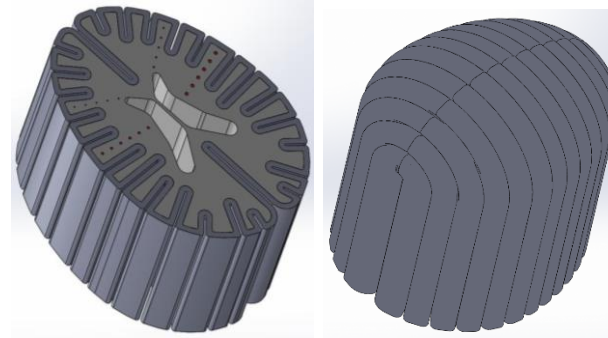


Next Steps – In Development



Warrior Medics – Mission Ready – Patient Focused

1. Improve geometry and import human anatomy (IRB pending)
2. Develop methods to expose *in vitro* cultures blast stresses / strains (preliminary testing of living brain slices and neuronal cells)
3. Visualization of *in vivo* models and correlate with biomarkers (under review for MULTI 2019)



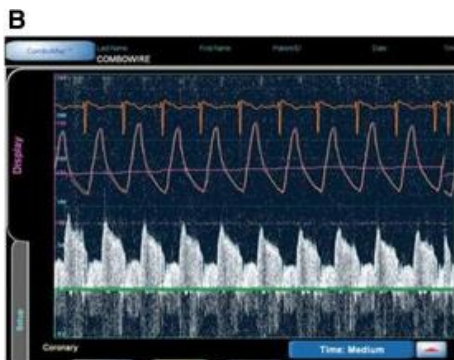
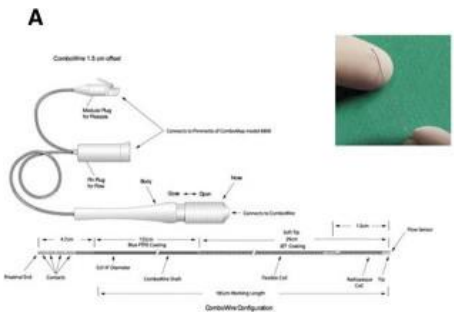


Localizing non-compressible torso hemorrhage

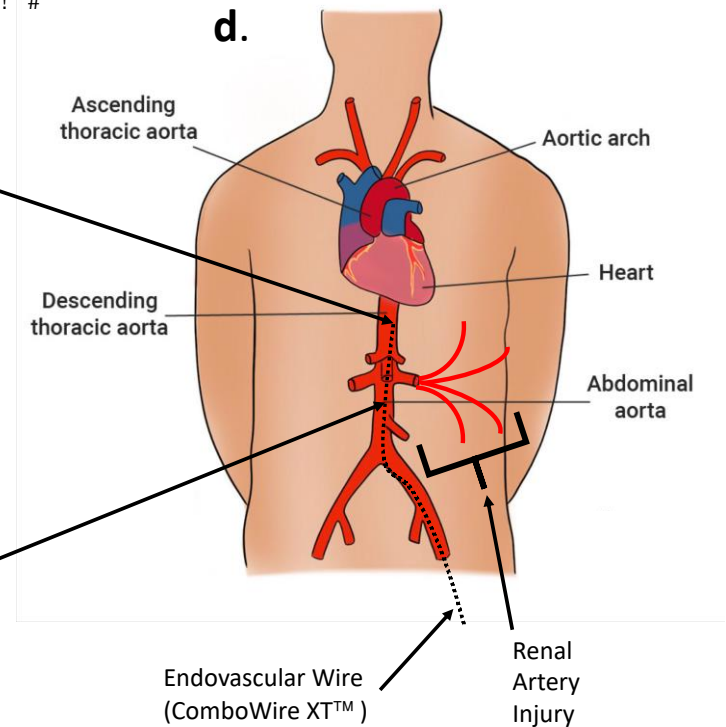
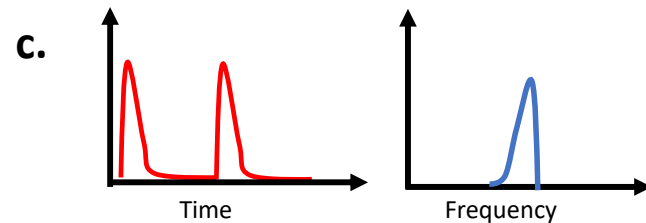
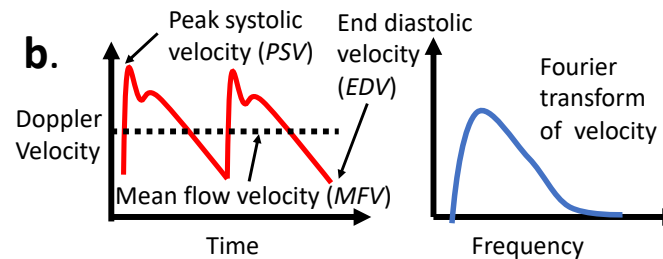


Warrior Medics – Mission Ready – Patient Focused

- Just received funding Air Force Medical Service Fiscal Year 2019 (FY19) 6.2 Research & Development Funding



a. Pulsatility Index = $\frac{PSV - EDV}{MFV}$; Resistivity Index = $\frac{PSV - EDV}{PSV}$





In Summary



Warrior Medics – Mission Ready – Patient Focused

We focus on significant injuries in modern conflict

- PTSD
 - Experiential risk factors may dominate and immune risk
 - PR-ICBM RCT to reduce PTSD with deployable intervention
- Severe blast traumatic brain injury
 - Developed new tools computational and experimental tools
 - Efforts reduce hypothesized injury mechanism – cavitation
 - Developing techniques to dose living tissue with blast
- Non-compressible torso hemorrhage
 - Testing hypothesis with existing and deployable technology
 - If successful would be ready for 6.3 funding for field testing



Thanks to Collaborators



Warrior Medics – Mission Ready – Patient Focused

- **San Antonio Military Medical Center**
 - David Kavour, M.D., LTC, USA
 - Matthew Brock, M.D., Maj, USAF
 - Michael Hossak, M.D., Capt, USAF
 - Jon Williams, M.D., Maj, USAF
 - Jono Thomas, M.D., Maj, USAF
 - Paul Elsbernd, M.D., M.S.
 - Matthew Reid, Ph.D.
- **Center For Advance Molecular Detection**
 - Sandra Valtier, Ph.D.
- **Clinical Research Division**
 - Jody Noe, Ph.D.
 - Thomas Gibbons, Ph.D.
- **Michigan State University**
 - Ricardo Mejia-Alvarez, Ph.D.
 - Joseph Kerwin
 - Faezeh Masoomi
 - Suhas Vidhate
- **Sandia National Laboratories**
 - Scott Miller, Ph.D.
 - Candice Cooper, M.S.
 - Chad Hovey, Ph.D.
- **New Mexico Tech**
 - Michaelann Tartis, Ph.D.
 - Kelsea Welsh
 - Ann Wermer



Questions?



Warrior Medics – Mission Ready – Patient Focused



HERO'S HWY





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