Multimodal Neuroimaging and Cerebrospinal Fluid Biomarkers of Neurodegeneration in Blast Concussion mTBI in Iraq and Afghanistan Veterans

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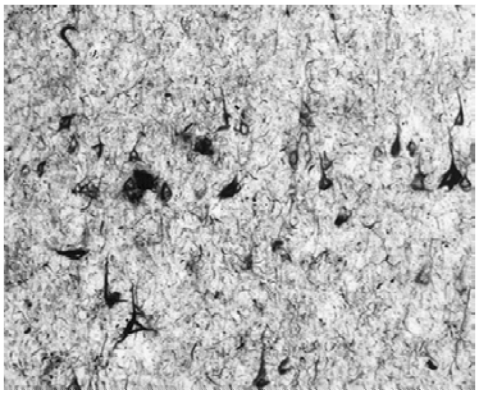
The Nature of an Emerging and Unprecedented Problem

Helmand Province, Afghanistan. July 13, 2009. (*MSNBC*)

3.5 million Soldiers and Marines have been deployed to Iraq and Afghanistan; approximately 9-18% return with symptomatic mTBI.

Potential Consequences of Repetitive Mild Head Trauma

NFL Pro-Bowl 1988



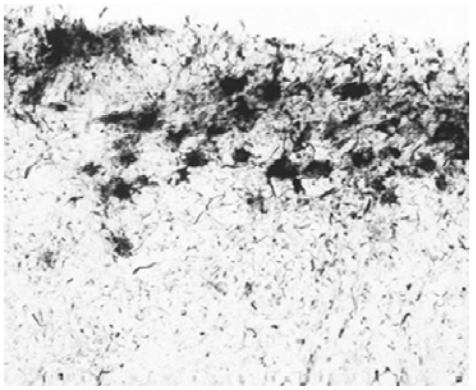


Photo provided to Bostonian (Winter/2009) by Virginia Grimsley

McKee et al., JNEN (2009)

There is growing concern that repetitive concussive and subconcussive head injuries can set in motion pathogenic processes that later emerge as neurodegenerative dementing disorders

McKee et al., *J Neuropathol Exp Neurol* 68:709-735, 2009

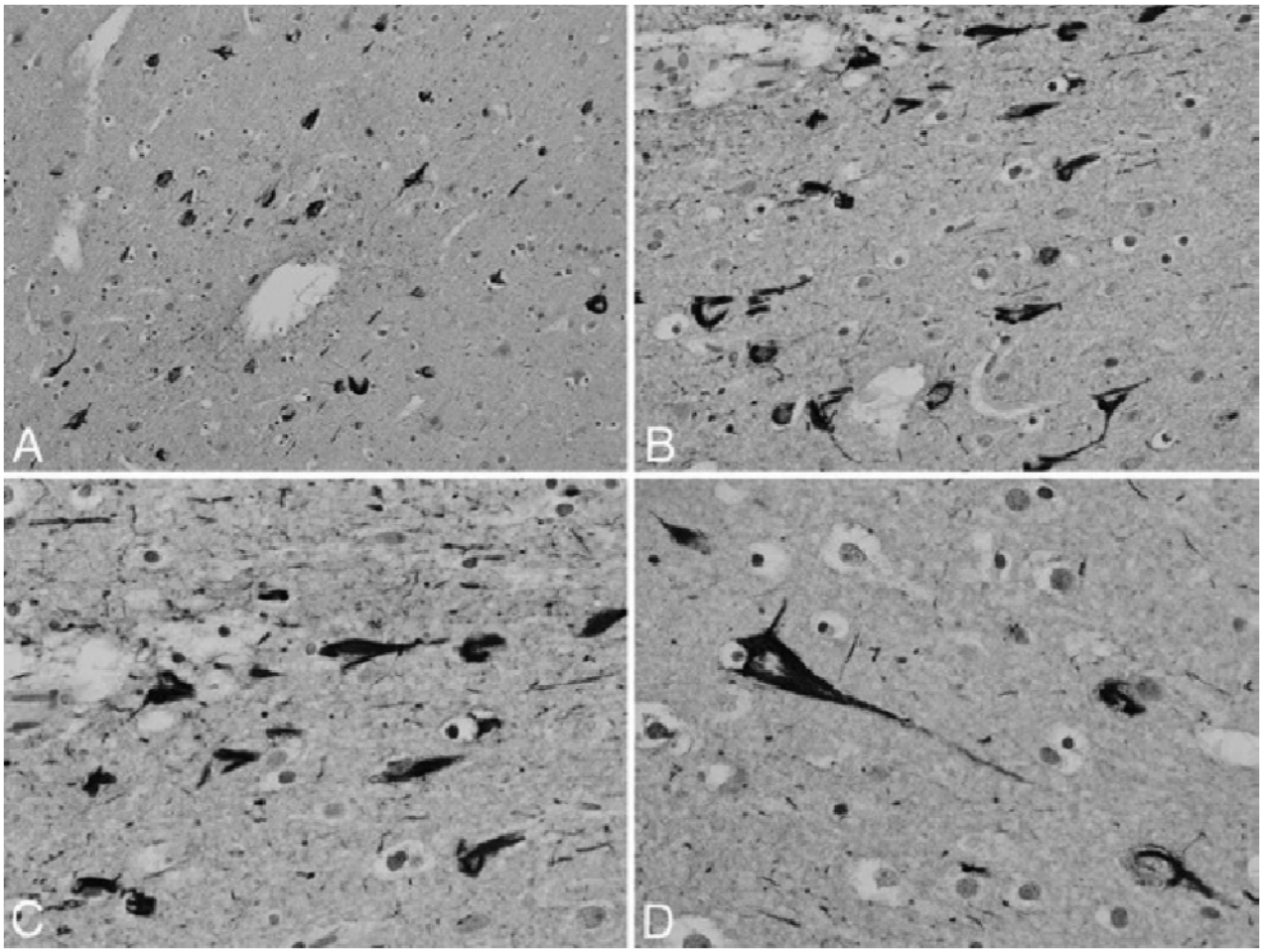
TRAUMATIC BRAIN INJURY

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]*

Goldstein et al., Sci Transl Med. 2012 May 16;4(134):134ra60.

Tau pathology in the brain of a 27 year old Iraq Veteran



Photomicrographs of tau-immunostained section of the frontal cortex showing frequent neurofibrillary tangles and neuritic threads (Omalu et al, *Neurosurg Focus* 31:E3, 2011).

Concussive and Subconcussive Head Injury and Risk of Neurodegeneration

- Repetitive sports concussion is associated with increased risk of the **rare** mid-life dementing disorder, chronic traumatic encephalopathy (CTE)

- Traumatic brain injury (TBI) is currently the best characterized environmental risk factor for developing the **common** late-life dementing disorder, Alzheimer's disease

The Controversy

- Controversy about etiology, course, and treatment of persistent somatic, cognitive, and behavioral symptoms in Iraq and Afghanistan Veterans following mTBI.
- An epidemiological study in military personnel found that symptoms of chronic mTBI (except for headache) more correlated with **PTSD** and **depression**.

The Controversy (continued)

- However, many skilled clinicians are convinced that war combatants' chronic symptoms of mTBI reflect real albeit subtle persistent brain damage.
- Do these chronic symptoms reflect persistent changes in brain **structure, function,** and/or cerebrospinal fluid biomarkers of neurodegeneration?

Participants

- 34 male Iraq/Afghanistan Veterans with blast-induced mild traumatic brain injury
  - Mean age 31.6 ± 9.2 years
- 16 non blast-exposed Iraq/Afghanistan Veterans
  - Mean age 32.8 ± 7.3 years (15M, 1F)
- 12 civilian community controls – FDG-PET only
  - Mean age 53 ± 2.0 years (7M, 5F)
- 55 male civilian community controls – CSF only
  - Mean age 31.8 ± 6.8 years

Participants

- 17 of the mTBI Veterans also met DSM-IV criteria (via CAPS interview) for combat operations posttraumatic stress disorder (PTSD).
- The mTBI group had higher scores for depression and alcohol use and had poorer sleep.
- Nearly all the mTBI Veterans had persistent postconcussive symptoms.

Neurobehavioral Symptom Inventory Item Frequency (%) Rated Moderate, Severe, or Very Severe in 34 Iraq/Afghanistan Veterans with mTBI and 16 Iraq/Afghanistan Veterans with No Blast Exposure

	TBI (N=33)	Control (N=15)	p*
Forgetfulness	67 %	20 %	.001
Feeling anxious or tense	67 %	13 %	<.0001
Difficulty falling or staying asleep	64 %	13 %	.002
Ringing in ears	64 %	0	<.0001
Irritability	61 %	13 %	<.0001
Headaches	61 %	7 %	<.0001
Sensitivity to noise	58 %	0	<.0001
Poor concentration/attention	52 %	13 %	.001
Hearing difficulty	52 %	0	<.0001
Slowed thinking	52 %	13 %	.001

Blast Exposure History

- Average time since last blast exposure was 4 years
- The average number of blast exposures resulting in loss of consciousness was 1.
- Majority had repetitive mTBI. Average number of blast exposures in Iraq or Afghanistan in the mTBI group was 14.

– single blast-mTBI	9%
– 2-5 blast mTBIs	29.4%
– 6-10 blast mTBIs	20.6%
– 11-15 blast mTBIs	6%
– 16-20 blast mTBIs	14.7%
– 21-50 blast mTBIs	9%
– 51-100 blast mTBIs	11.8%

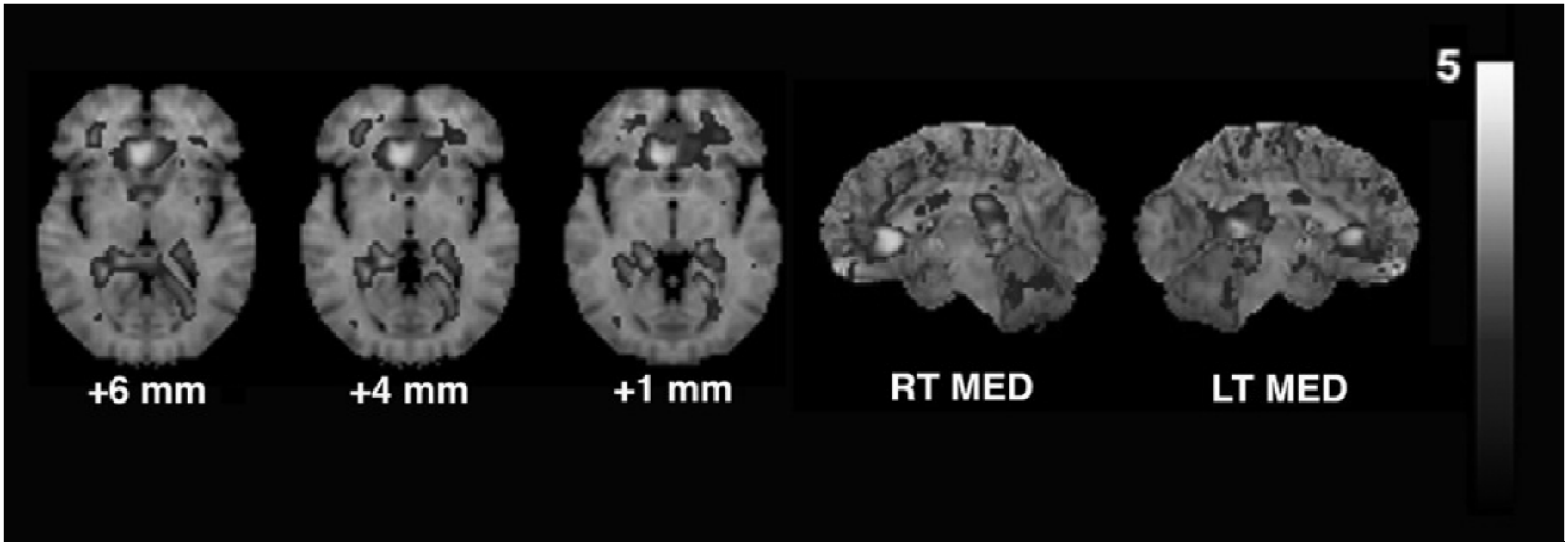
Multimodal Neuroimaging

- Structural Neuroimaging
  - Diffusion Tensor Imaging
  - Macromolecular Proton Fraction (MPF) Mapping
- Functional Neuroimaging:
  - [^{18}F]-Fluorodeoxyglucose Positron Emission Tomography ([^{18}F]-FDG-PET)

Neuroimaging of Blast-Trauma TBI: State-of-the-Art

- Magnetic Resonance (MR) Diffusion Tensor Imaging
  - Levin et al., *NeuroImage*, 2010
  - MacDonald et al., *New England Journal of Medicine*, 2011
  - Davenport et al., *Neuroimage*, 2012
  - Morey et al., *Human Brain Mapping*, 2012
  - Bazarian et al., *J Head Trauma Rehabil*, 2012

Diffusion Tensor Imaging: Composite Z-score subtraction maps of FA values in Blast-mTBI Veterans (N=15) compared to Nonblast Veterans (N=12)



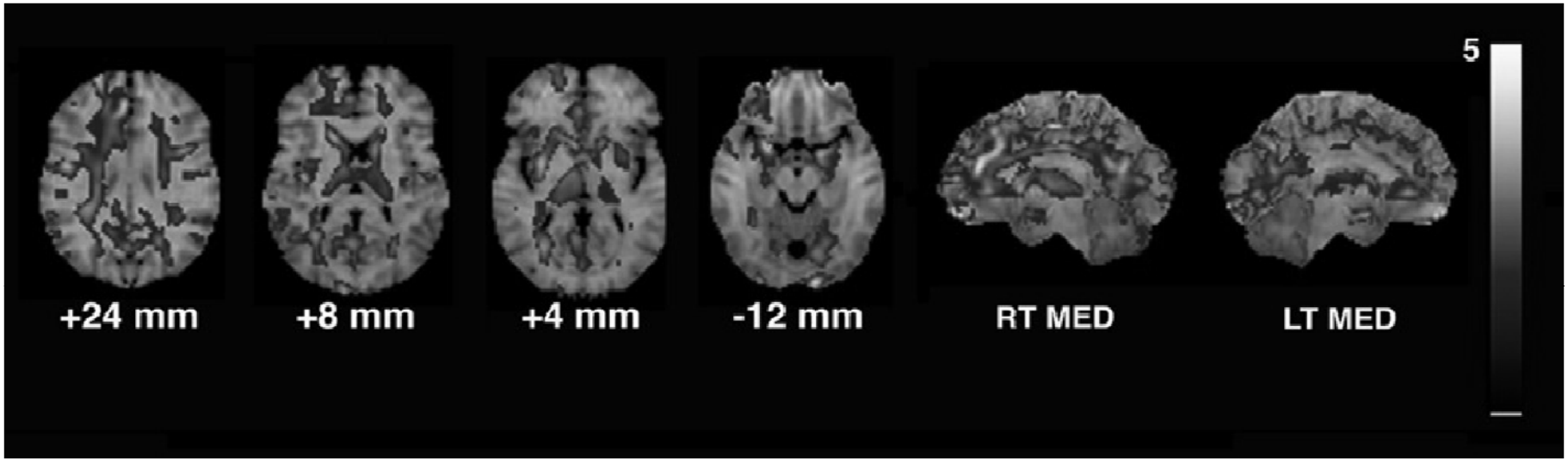
RESULTS:

- Decreased fractional anisotropy in genu of corpus callosum in mTBI Veterans compared to Nonblast Veterans ($p < 0.05$)
- Within mTBI group, no differences between Veterans with and without PTSD
- DTI studies in Iraq/Afghanistan Veterans vary among labs – both in Methods and Results

Macromolecular Proton Fraction (MPF) Mapping

- Are there other structural MRI techniques which may be more sensitive to chronic changes following blast concussion mTBI?
- MPF is a magnetization transfer structural imaging technique which provides an index of macromolecular composition.
- MPF correlates with indices of central myelin integrity in humans and in animal models of multiple sclerosis and spinal cord injury.

Magnetization Transfer Molecular Proton Bound Fraction (MPF): Z-score subtraction maps of MPF values in Blast-mTBI Veterans (N=27) compared to Nonblast Veterans (N=16)



RESULTS:

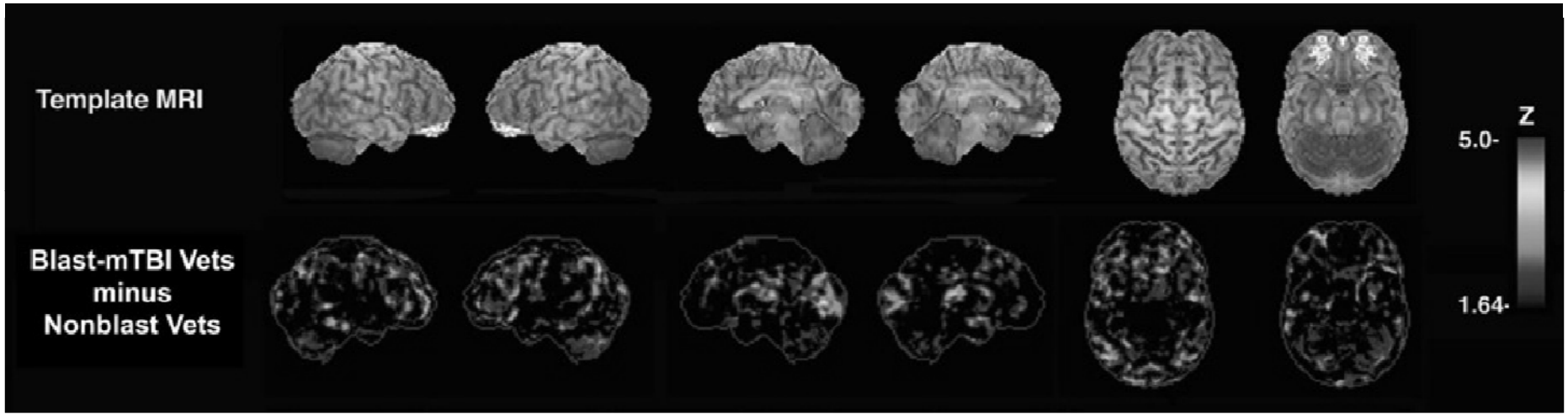
Reduced MPF in numerous subgyral, cortical-subcortical, and longitudinal white matter (WM) tracts (Zs>4.0, all p's <0.05)

•Within mTBI group, no differences between Veterans with and without PTSD

•Findings consistent with the mechanism of **diffuse axonal injury** and suggest **alterations of myelin structure** in white matter tracts known to be vulnerable to damage in diffuse axonal injury.

•**Potential** as prospective quantitative biomarker of blast-induced mTBI

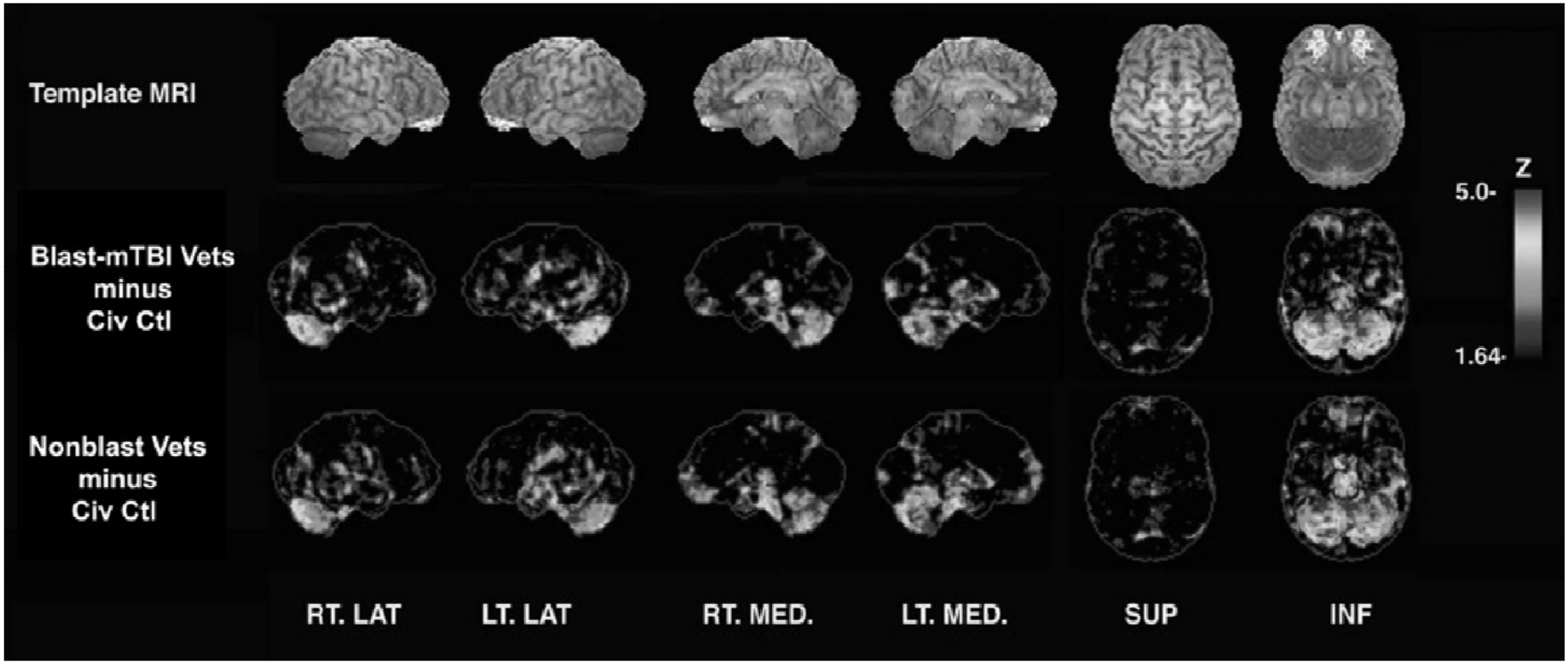
Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET): Composite Z-score subtraction maps of regional brain glucose metabolism in Blast-mTBI Veterans (N=33) vs. Nonblast Veterans (N=16)



RESULTS:

- Regional glucose hypometabolism in parietal lobes bilaterally, left sensorimotor cortex and right visual cortex in mTBI Veterans (all p's < 0.05)
- Within mTBI group, no differences between Veterans with and without PTSD

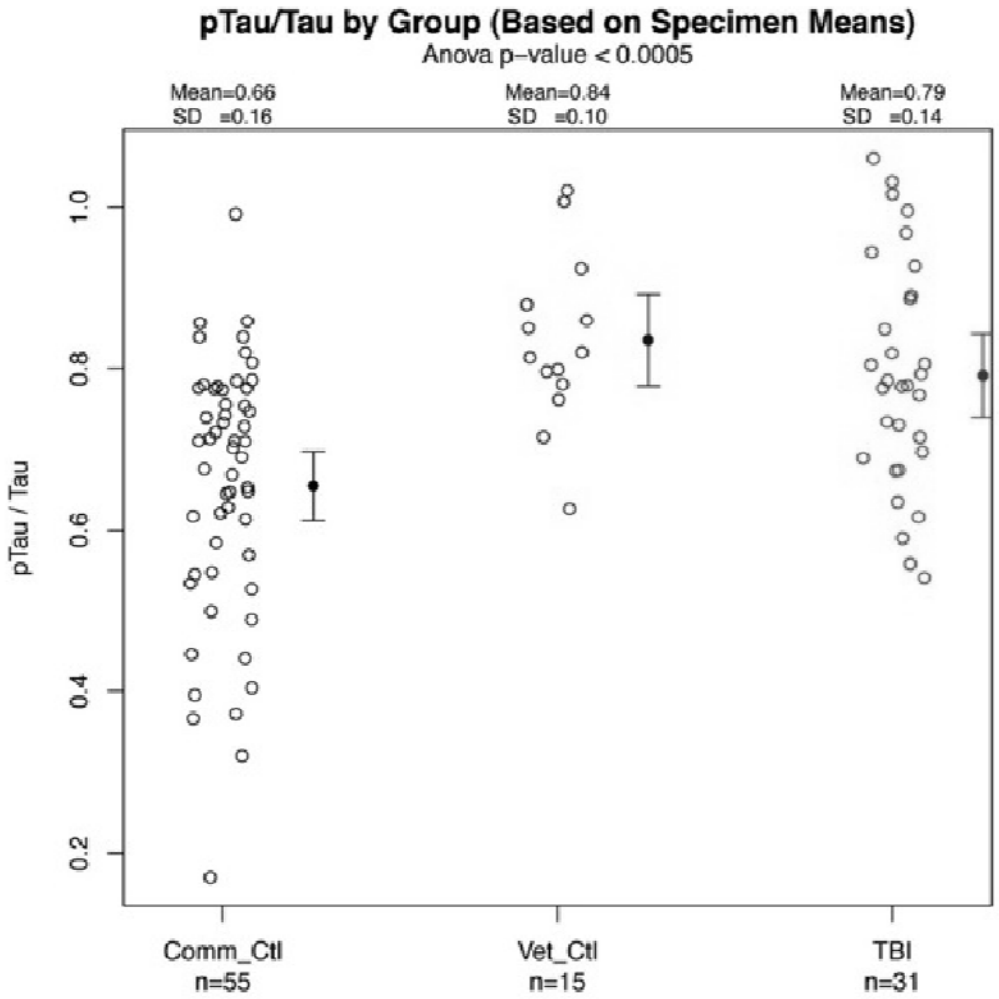
FDG-PET: Composite Z-score subtraction maps of regional brain glucose metabolism in Blast-mTBI Veterans vs. civilian controls (N=12) and Nonblast Veterans vs. civilian controls



RESULTS:

• Compared to civilian community controls, both Blast-mTBI and Nonblast Veterans have glucose hypometabolism in the cerebellum, pons, thalamus and medial temporal lobes bilaterally (all p's < 0.05).

CSF $ptau_{181}$:tau Ratio is Elevated in Iraq/Afghanistan Veterans Compared to Community Controls*



*p<0.0005, one-way ANOVA

Results/Conclusions – Regional Glucose Hypometabolism and CSF p-tau$_{181}$:tau Ratio in Iraq and Afghanistan Veterans Unrelated to TBI

- Hypotheses/Speculation about etiology:
  - Pre-military (and post-military) vulnerabilities and military "lifestyle" (including other head trauma, alcohol misuse, bodybuilding supplements)
  - Effects of military training (e.g., combatives)
  - Hyperthermia in Iraq combat operations environment
  - Other environmental/behavioral combat zone exposures including stress
  - High % of Non-blast Veterans with APOE-ε4 allele

Summary and Conclusions

- Both structural and functional imaging modalities suggest a coherent picture of **diffuse axonal injury** in Iraq/Afghanistan Veterans with blast (and impact) concussion mTBI specific to TBI and not attributable to PTSD.
- Unexpected brain abnormalities in Iraq and Afghanistan Veterans independent of head trauma exposure
  - Glucose hypometabolism in cerebellum, pons, thalamus, medial temporal lobes
  - Elevation in CSF p-tau$_{181}$:tau ratio suggests possible neurodegenerative changes
- Long-term consequences of these brain abnormalities make long-term follow-up of these Veterans essential.

Collaborators

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Collaborators

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  - –First Sgt (ret) Creed McCaslin

First Stryker Brigade (Lancers), 25th Infantry Division, Mosul, Iraq, 2004-2005

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ADAMS

Biomarker discovery through neurobehavioral, neuropathological and molecular characterization of mouse models of TBI

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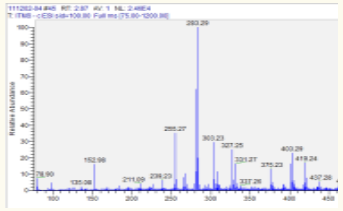
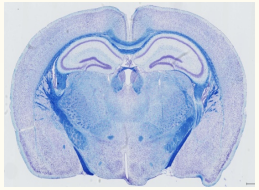
Rodent models of TBI:–
CCI; mild TBI

Neurobehavior

Molecular profiling of brain tissue and blood



Neuropathology



Identify and validate molecular targets and biomarkers

Deliverables:

- TBI-targeted therapeutics
- Diagnostic and prognostic markers

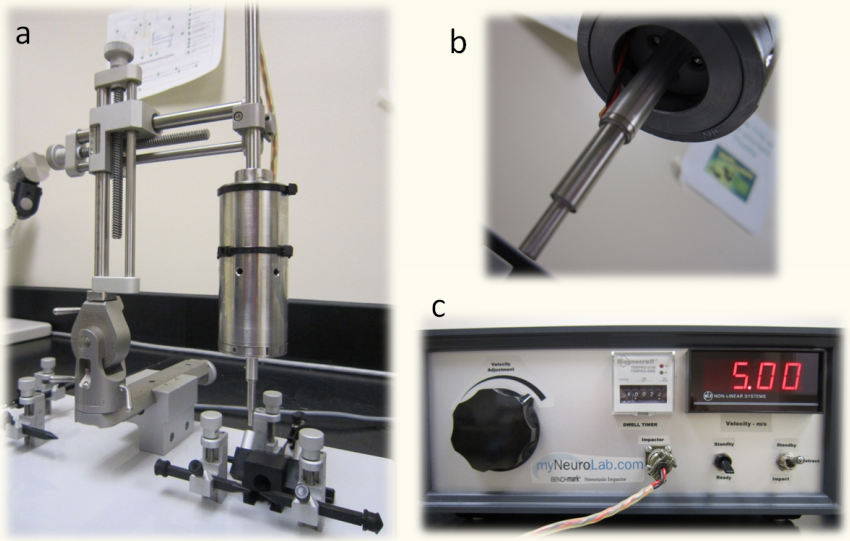
Active military

Blood biomarker profiling

TBI patients

Mouse Models

- Controlled Cortical Impact – CCI
  - APOE genotype
- Mild Closed Head Injury TBI model - mTBI
  - Single injury
  - Repetitive injury (5 hits over 9 days with an inter-injury interval of 48hrs)



CCI and APOE

- ApoE has 3 main isoforms - ApoE2, ApoE3, ApoE4
- Human APOE4 carriers show poorer acquisition and recall following TBI compared to those without an APOE4 allele (Crawford 2002, Friedman 1999, Sabo 2000, Smith 2006)
- Used LC-MS approaches to compare brain and plasma proteomic profiles of mice transgenic for human APOE3 and APOE4 over a null background at multiple time points post-TBI
- Extensive and complex datasets – focus on APOE influence on TBI profiles – the INTERACTIVE term –
  to determine favorable versus unfavorable responses to TBI

Proteomic Analysis

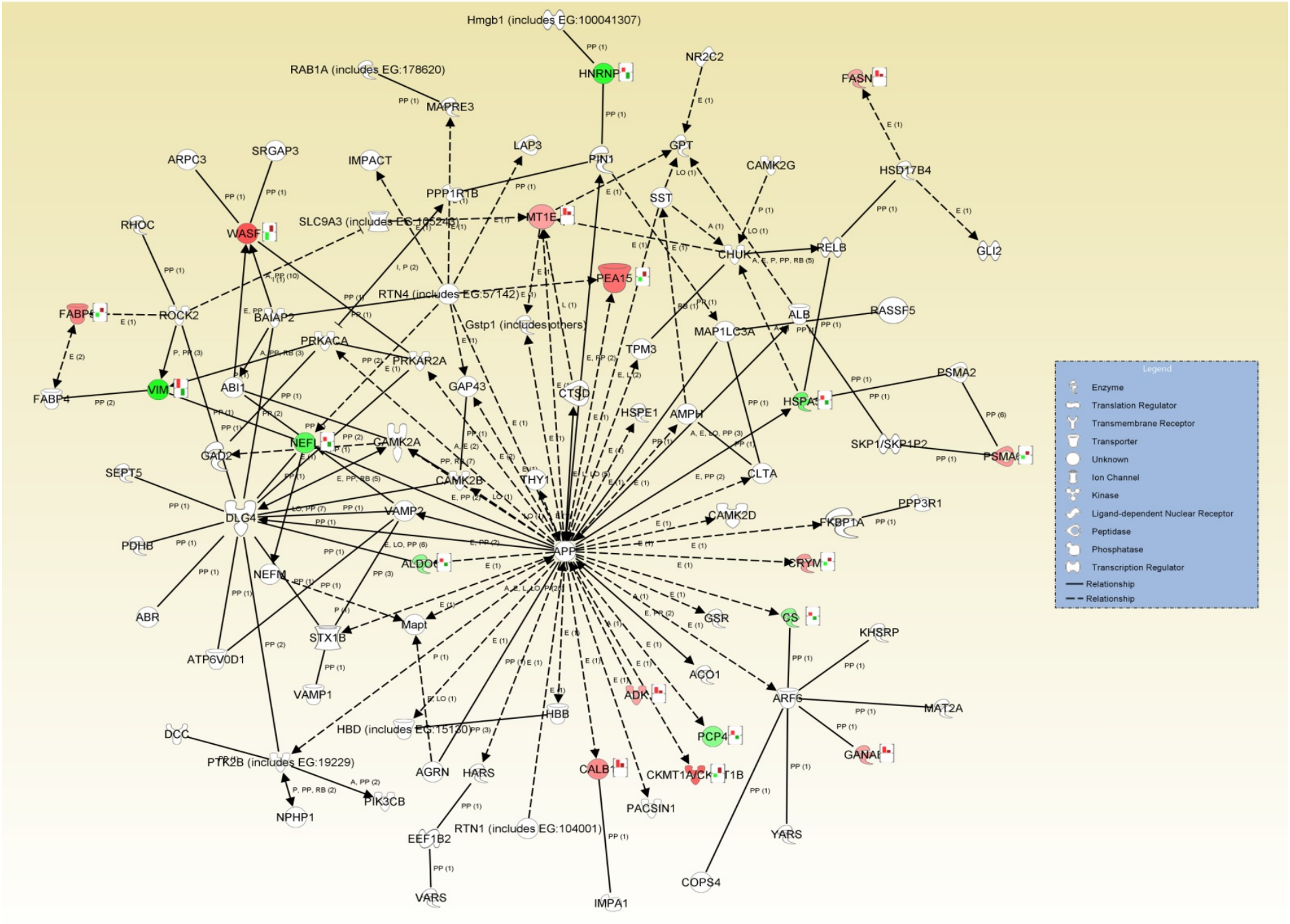
- Samples were collected from APOE transgenic mice at multiple timepoints after CCI
  - Severe and mild injuries (1.8mm depth or 1.3 mm depth at 5m/s)
  - 24 hours, 1 month, and 3 months (severe only) after surgery
  - Plasma and ipsilateral Hippocampus and Cortex were analyzed
- We used iTRAQ labeling to enable quantitative as well as qualitative proteomic profiling
- Statistical analyses were used to determine the differential response of APOE3 and APOE4 to TBI
- Ingenuity Pathway Analysis was used to attribute functional significance to the observed proteomic responses

Plasma Datasets

(Crawford, J Neurotrauma 2011)

IPI Accession	Protein description	Symbol	24 hour				1 month				3 months	
			Mild		Severe		Mild		Severe		Severe	
			Injury	Interaction	Injury	Interaction	Injury	Interaction	Injury	Interaction	Injury	Interaction
IPI00377351.2	Apolipoprotein A-IV	APOA4	.	.	.		.	.	.	.	3.62E-02	8.01E-04
IPI00311147.1	Complement C1q subcomponent subunit B	C1QB	2.73E-02	.	.		.	.	.	.	.	.
IPI00121274.2	Isoform 1 of Complement component C8 beta chain	C8B	3.22E-02	1.41E-02	.		.	.	.	.	.	.
IPI00118437.1	Complement component 8, gamma subunit, isoform CRA_b	C8G	.	.	.		.	.	.	3.18E-02	.	.
IPI00468757.2	Cerebellin-1	CER*	.	.	.		4.87E-02	.	.	.	.	.
IPI00320420.3	Clu Clusterin	CLU	.	.	.		.	8.12E-03	.	.	.	.
IPI00421014.8	Anti-carcinoma embryonic antigen light chain variable region	EALC*	.	.	.		.	.	.	.	.	1.21E-04
IPI00352901.3	EP3-6 light chain variable region	EP3-6*	1.41E-02	1.03E-02	.		.	.	3.62E-02	1.33E-02	.	.
IPI00114206.1	F2 Prothrombin (Fragment)	F2	.	.	1.76E-02		.	.	.	.	.	.
IPI00115522.3	Fga fibrinogen, alpha polypeptide isoform 2	FGA	.	.	.		4.77E-02	.	.	.	.	.
IPI00279079.1	Fibrinogen beta chain	FGB	.	.	.		2.25E-02	.	.	.	.	.
IPI00108285.3	Fibroblast growth factor 13	FGF13	.	.	.		.	.	.	.	.	2.62E-02
IPI00133536.2	Glutathione peroxidase 3	GPX3	.	.	.		.	.	.	.	1.15E-02	.
IPI00110658.1	Hba-a1;Hba-a2	HBA1	.	8.60E-04	.		.	.	.	8.95E-03	.	.
IPI00762198.2	Hbb-b1 Beta-globin	HBB	5.44E-08	3.28E-08	.		.	.	.	.	.	.
IPI00553333.2	Hemoglobin subunit beta-1	HBB	2.90E-03	1.45E-04	.		.	.	.	.	.	.
IPI00316491.4	Hemoglobin subunit beta-2	HBD	.	.	.		.	.	.	.	8.97E-05	9.40E-05
IPI00885376.1	Hbb-b1 Beta-2-globin (Fragment)	HBD	7.95E-05	6.62E-05	.		.	.	.	.	.	1.02E-02
IPI00128484.1	Hemopexin	HPX	2.85E-02	.	.		.	.	.	.	.	2.15E-02
IPI00117022.3	AI324046 Isoform 2 of Ig gamma-3 chain C region	IGG3C*	.	.	.		.	.	.	.	.	1.27E-04
IPI00459201.1	Igh-2 Igh protein	IGH2*	.	.	.		.	.	.	3.29E-02	.	.
IPI00109910.4	Igh-1b;Igh-1a Ighg protein	IGHG	.	2.71E-02	.		.	.	.	.	.	.
IPI00177214.2	Igh-6 Ig mu chain C region membrane-bound form	IGHM	.	.	.		.	1.17E-03	.	.	.	.
IPI00137967.3	EG434025 Ig kappa chain V-V region MOPC 41	IGK5*	5.13E-04	1.56E-04	.		.	.	.	.	.	.
IPI00464399.3	Ig kappa chain V-III region PC 3741\TEPC 111	IGK8*	.	.	.		4.79E-02	.	.	.	.	.
IPI00380178.7	Ig lambda-3 chain C region	IGL3C*	.	.	.		4.10E-02	.	.	.	.	.
IPI00406213.4	Similar to Chain L, Structural Basis Of Antigen Mimicry In A Clinically Relevant Melanoma Antigen System isoform 1	LOC100047628	.	9.07E-04	.		.	.	.	.	.	.
IPI00123223.2	Murinoglobulin-1	MUG1	.	1.33E-02	.		.	1.89E-02	.	.	.	.
IPI00752840.2	13 kDa protein	Not available	.	.	.		.	.	.	.	.	2.09E-02
IPI00672861.5	13 kDa protein	Not available	.	2.71E-02	.		.	.	.	.	.	.
IPI00319986.2	Rhomboid domain-containing protein 1	RHBDD1	.	.	.		.	.	5.11E-03	.	.	.
IPI00131830.1	Serine protease inhibitor A3K	SERPINA3K	.	2.66E-03	.		.	2.71E-02	.	.	.	.
IPI00403993.5	Synaptic nuclear envelope 1 isoform 3	SYNE1	1.03E-02	.	.		.	.	.	.	.	.
IPI00139788.2	Serotransferrin	TF	.	.	.		.	.	.	.	8.35E-03	.

APP Interactive 2 Iterations



Functional Clustering (1)

Pathway no.	Ingenuity Canonical Pathways	Mild				Severe					
		Injury		Interaction		Injury			Interaction		
		24 hr	1 Month	24 hr	1 Month	24 hr	1 Month	3 Months	24 hr	1 Month	3 Months
1	Actin Cytoskeleton Signaling					(F2) 1.35E-02					
2	Acute Phase Response Signaling		(FGB, FGA) 3.24E-04			(F2) 1.05E-02		(TF) 4.07E-02			(HPX) 4.07E-02
3	Arachidonic Acid Metabolism							(GPX3) 3.39E-02			
4	B Cell Development				(IGHM) 6.76E-03						
5	Bladder Cancer Signaling										(FGF13) 2.19E-02
6	Clathrin-mediated Endocytosis Signaling					(F2) 1.0E-02		(TF) 3.89E-02			(FGF13) 3.89E-02
7	Coagulation System		(FGB, FGA) 1.41E-05			(F2) 2.19E-03					
8	Complement System	(C8B, C1QB) 6.17E-05		(C8B) 1.02E-02						(C8G) 4.17E-03	
9	Extrinsic Prothrombin Activation Pathway		(FGB, FGA) 2.82E-06			(F2) 1.0E-03					
10	FGF Signaling										(FGF13) 2.09E-02
11	Glutathione Metabolism							(GPX3) 1.62E-02			
12	Gα12/13 Signaling					(F2) 7.41E-03					
13	Intrinsic Prothrombin Activation Pathway		(FGB, FGA) 1.02E-05			(F2) 1.86E-03					
14	LXR/RXR Activation							(APOA4) 1.91E-02			(APOA4) 1.91E-02
15	p70S6K Signaling					(F2) 7.59E-03					
16	Primary Immunodeficiency Signaling				(IGHM) 1.0E-02						
17	Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	(C1QB) 0.0288									
18	Role of Tissue Factor in Cancer		(FGB, FGA) 1.38E-04			(F2) 6.76E-03					
19	Systemic Lupus Erythematosus Signaling				(IGHM) 2.57E-02						
20	Thrombin Signaling					(F2) 1.17E-02					
21	TR/RXR Activation		(FGA) 1.58E-02								

Functional Clustering (2)

Biomodules	Mild				Severe					
	Injury		Interaction		Injury			Interaction		
	24hr	1 month	24hr	1 month	24hr	1 month	3 months	24hr	1 month	3 months
Amino acid metabolism							11			
Cancer		18			18					5
Cardiovascular signaling		9,13			9, 13, 20					
Cellular growth, proliferation and development				4	15					10
Cellular Immune response	17			16	6		6			6
Cellular stress and injury		7,9,13			7, 9, 13, 15					
Cytokine signaling		2			2		2			2
Disease-Specific pathways				16, 19						5
Growth factor signaling										10
Humoral Immune response	8		8	4, 16					8	
Ingenuity Toxicity List Pathways		2, 21			2		2, 14			2, 14
Intracellular and second messenger signaling					12					
Lipid metabolism							3			
Nuclear receptor signaling		21					14			14
Organismal growth and development					1, 6		6			6
Pathogen-influenced signaling	17				6		6			6

Mouse – Human translation

Detailed characterization of behavior, brain pathology and plasma profiles in mouse models at a range of timepoints after injury




Time since TBI

Correlation of plasma profiling in mouse models with human plasma profiling will identify diagnostic and potentially prognostic biomarkers for TBI.

By relating human plasma to mouse plasma to mouse brain we may be informed regarding ongoing pathogenic processes in the human brain.

Plasma profiling in human samples

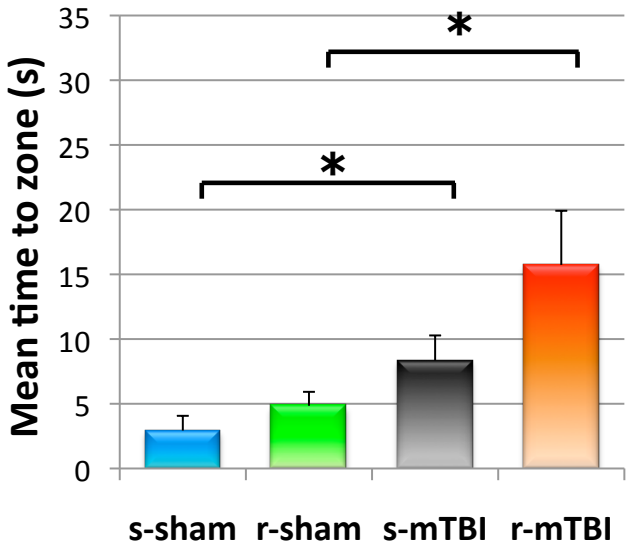
mTBI model

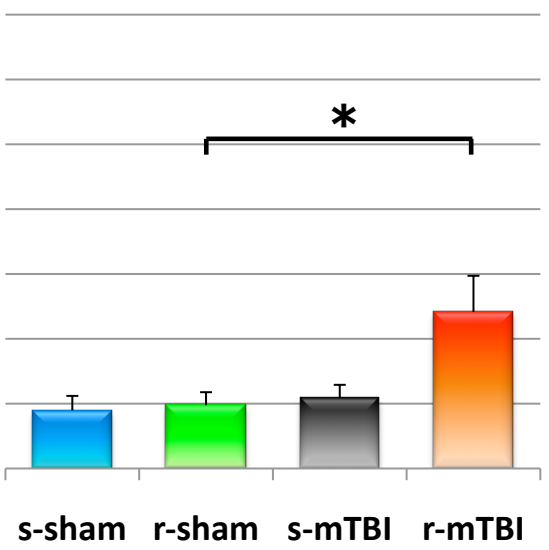
(Mouzon J Neurotrauma 2012)

- Greater relevance to human conditions
- Mild but progressive pathology
- Axonal injury, inflammation, developing tau pathology
- Acute cognitive deficits in both single-mTBI and repetitive-mTBI models compared to anesthesia controls
- Persistent cognitive deficits in repetitive-mTBI, analyses to date show impaired Barnes Maze performance at 18 months post injury.

Novel mTBI model shows persistent cognitive problems after repetitive injury

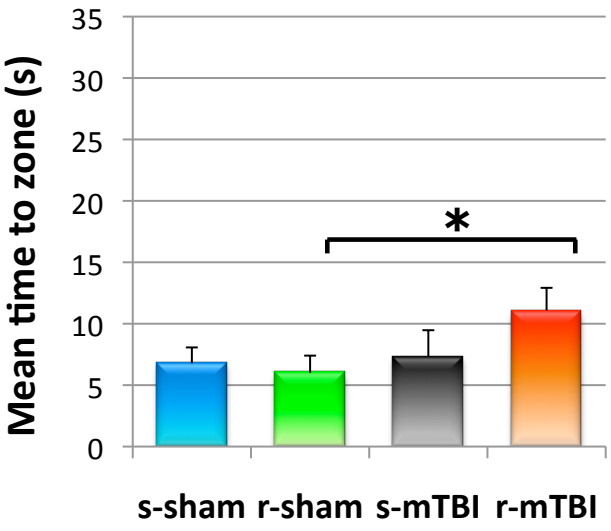
24 hours after last injury

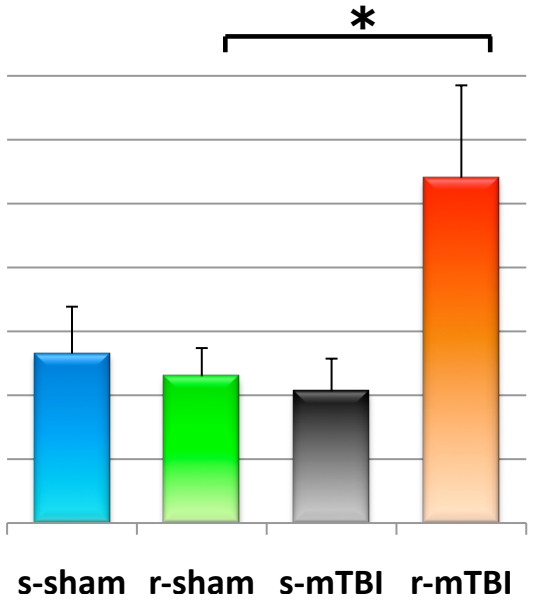




6 months after last injury

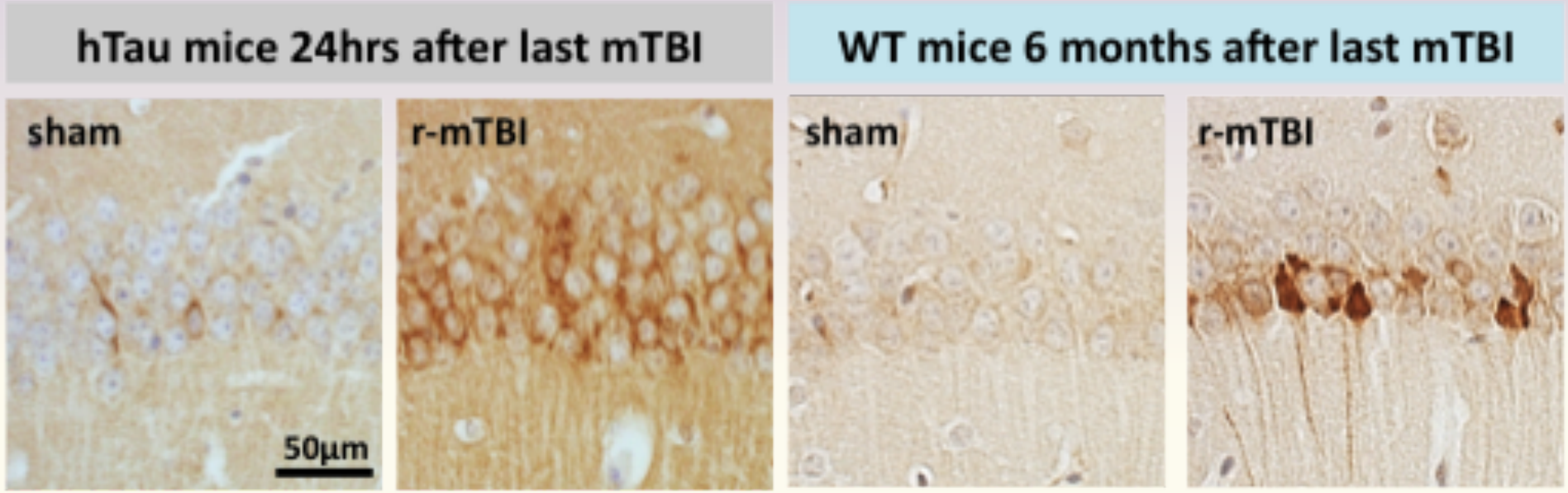
12 months after last injury



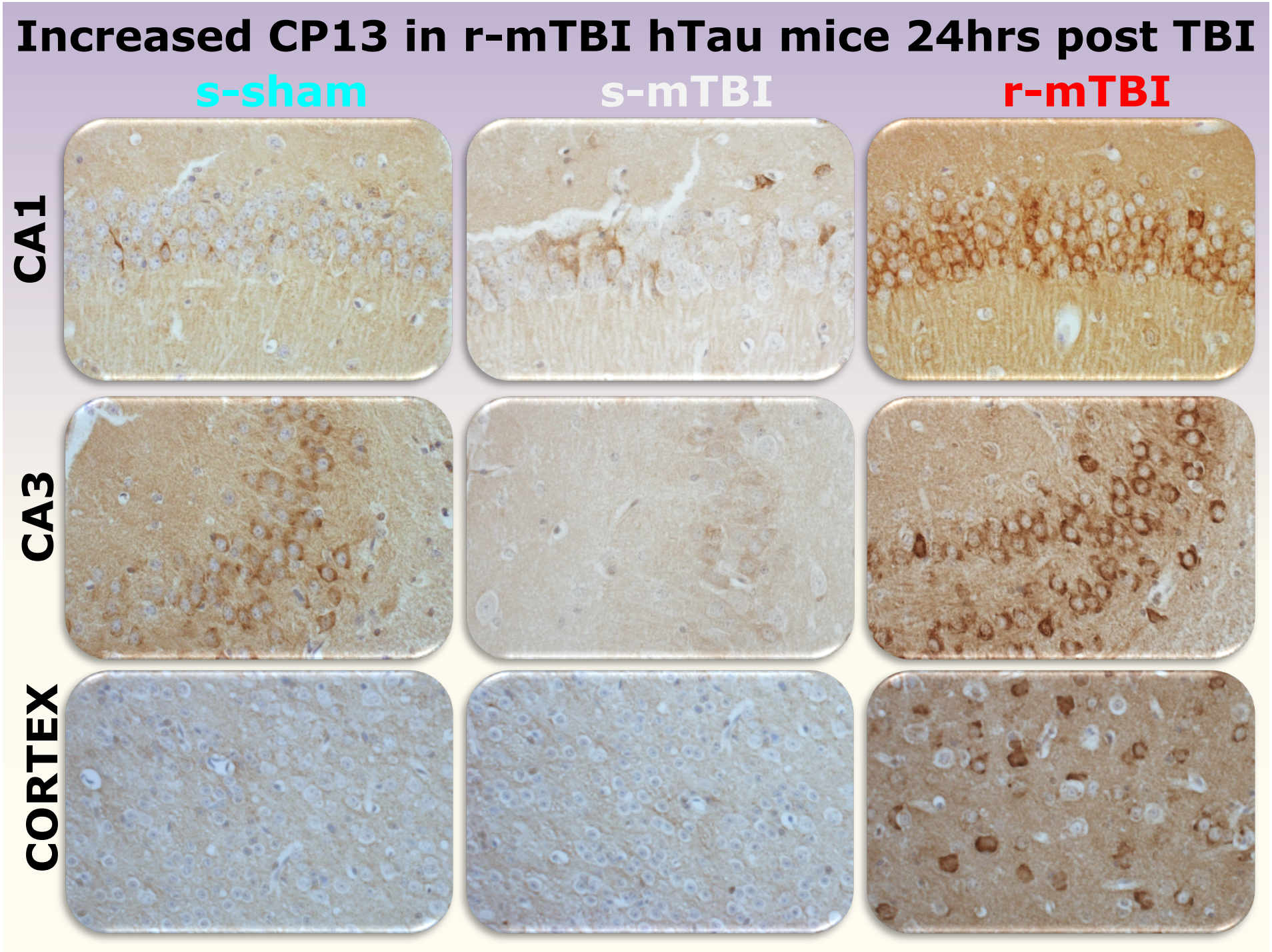


18 months after last injury

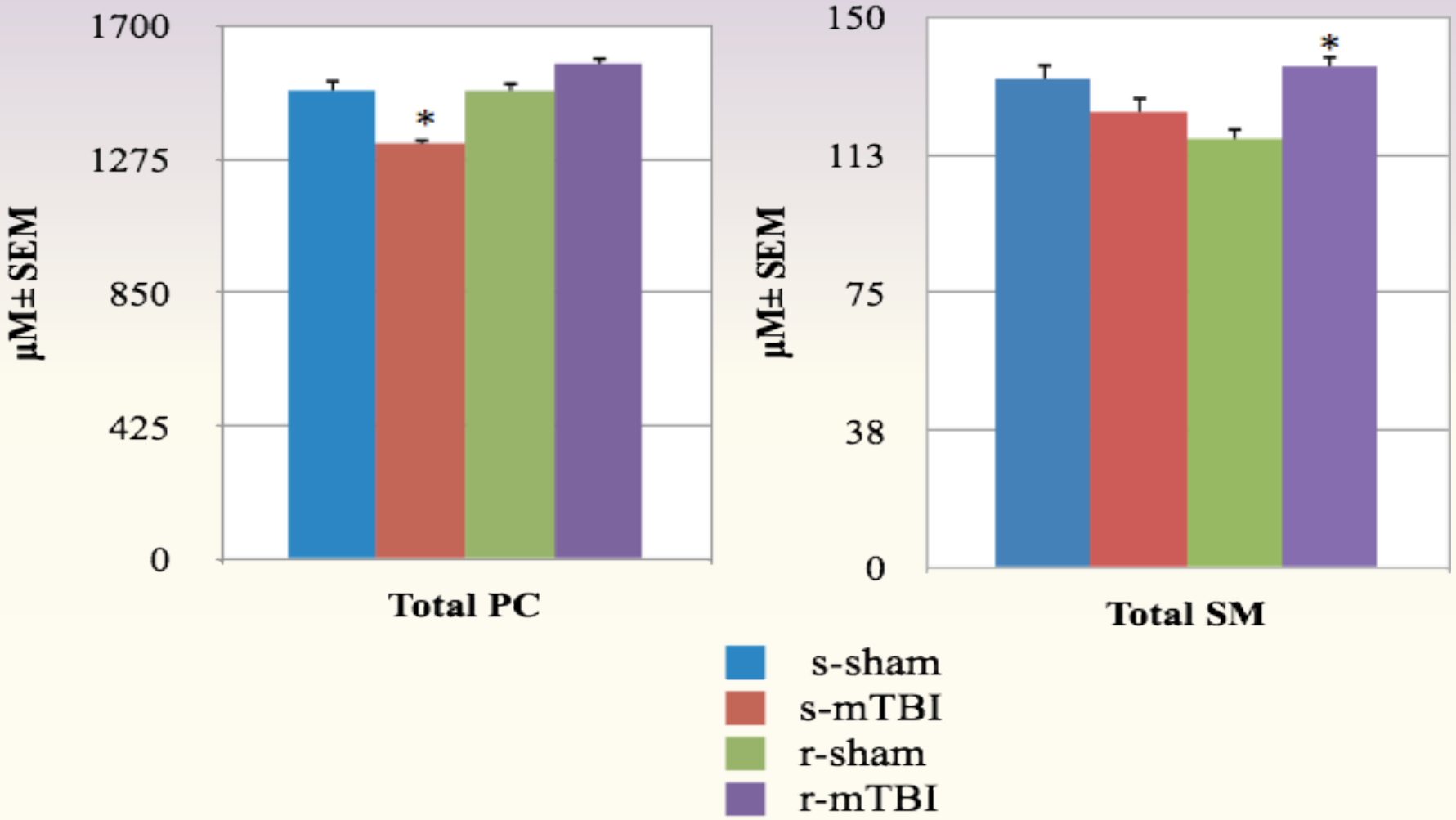
Tau pathology (CP13) in the CA1 in the repetitive mTBI model



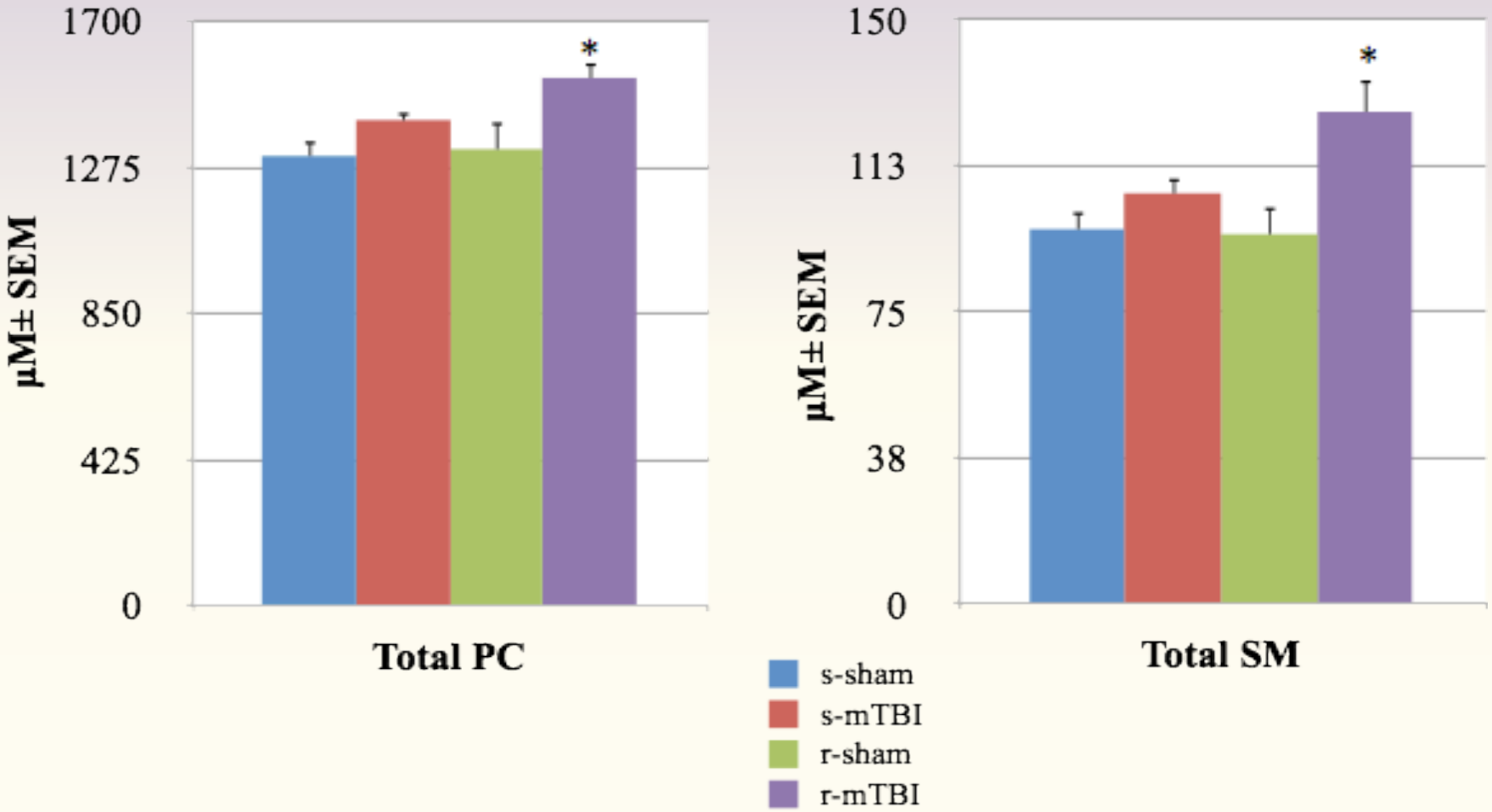
Increased CP13 in r-mTBI hTau mice 24hrs post TBI



Plasma lipidomic analyses in the wild type mTBI model at 24hrs post-TBI



Plasma lipidomic analyses in the wild type mTBI model 12 months post-TBI



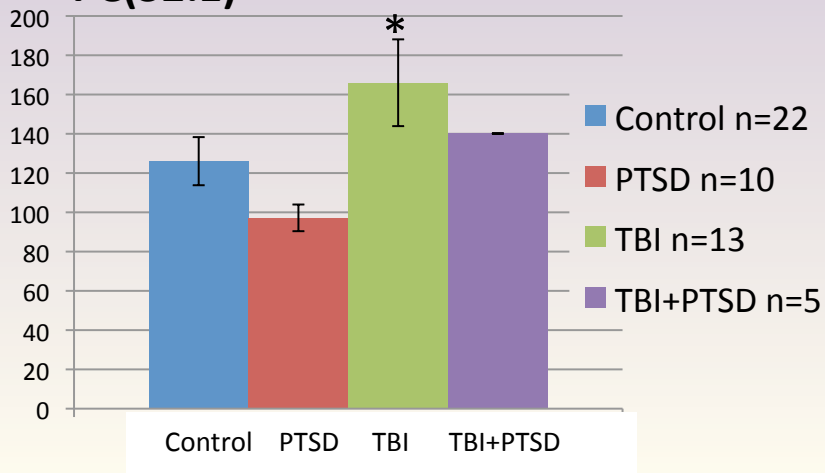
Active Duty Troop study

(Captain/Dr. Michael Dretsch at USAARL)

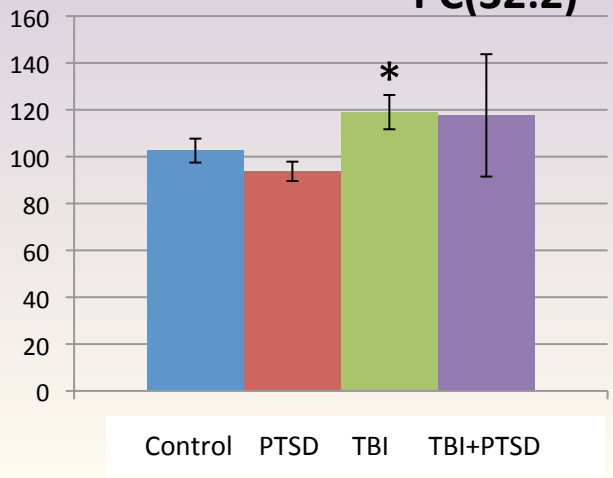
- 470 troops recruited through Ft. Riley and Camp Shelby – full neuropsychological assessment and blood samples for genetic and omic analyses
- Pre- and Post-deployment evaluations
- Pilot data in a cohort of 50 troops to detect deployment related changes in plasma profiling correlating with clinical grouping

Pilot blood profiling from troops pre- and post- deployment reveals changes in lipid species specific to clinical subgroups

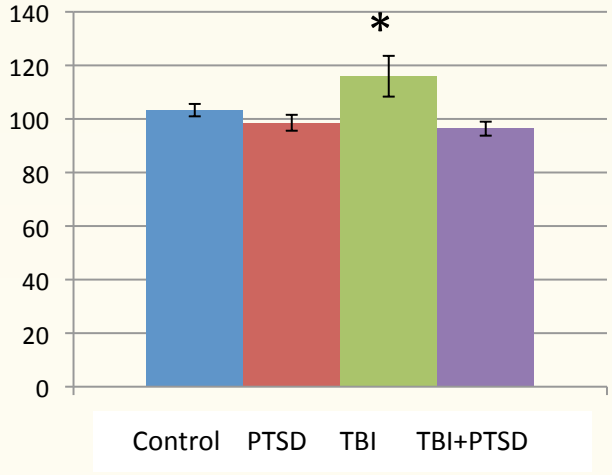
PC(32:1)



PC(32:2)



PC(34:4)



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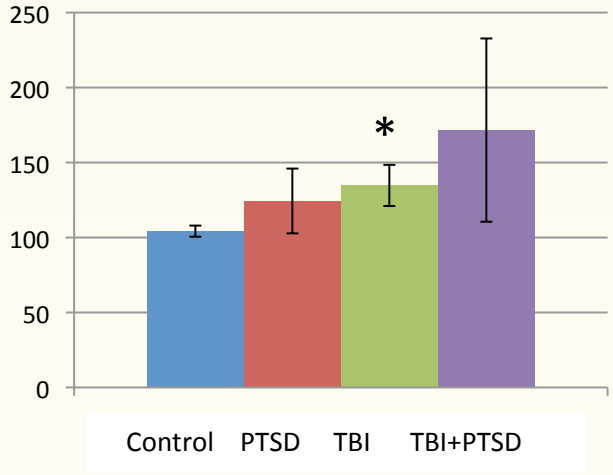

Conclusions

- Multi-disciplinary approaches are essential to tackle the complexity of TBI and attempt translation from laboratory models to humans;
- Detailed characterization of laboratory models of TBI will provide a more complete understanding of pathogenesis and a platform for translation of biomarkers and potential therapeutics to human populations;
- Omics technology is a powerful tool with which to identify molecular signatures of TBI;
- Immune, inflammatory and lipid pathways are significantly disrupted in response to TBI;
- Plasma and brain molecular responses to TBI progress and persist after the injury, affording larger detection and therapeutic windows than originally anticipated.

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Diagnosing Residual Brain Injury following mTBI among OIF/OEF Veterans

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- None

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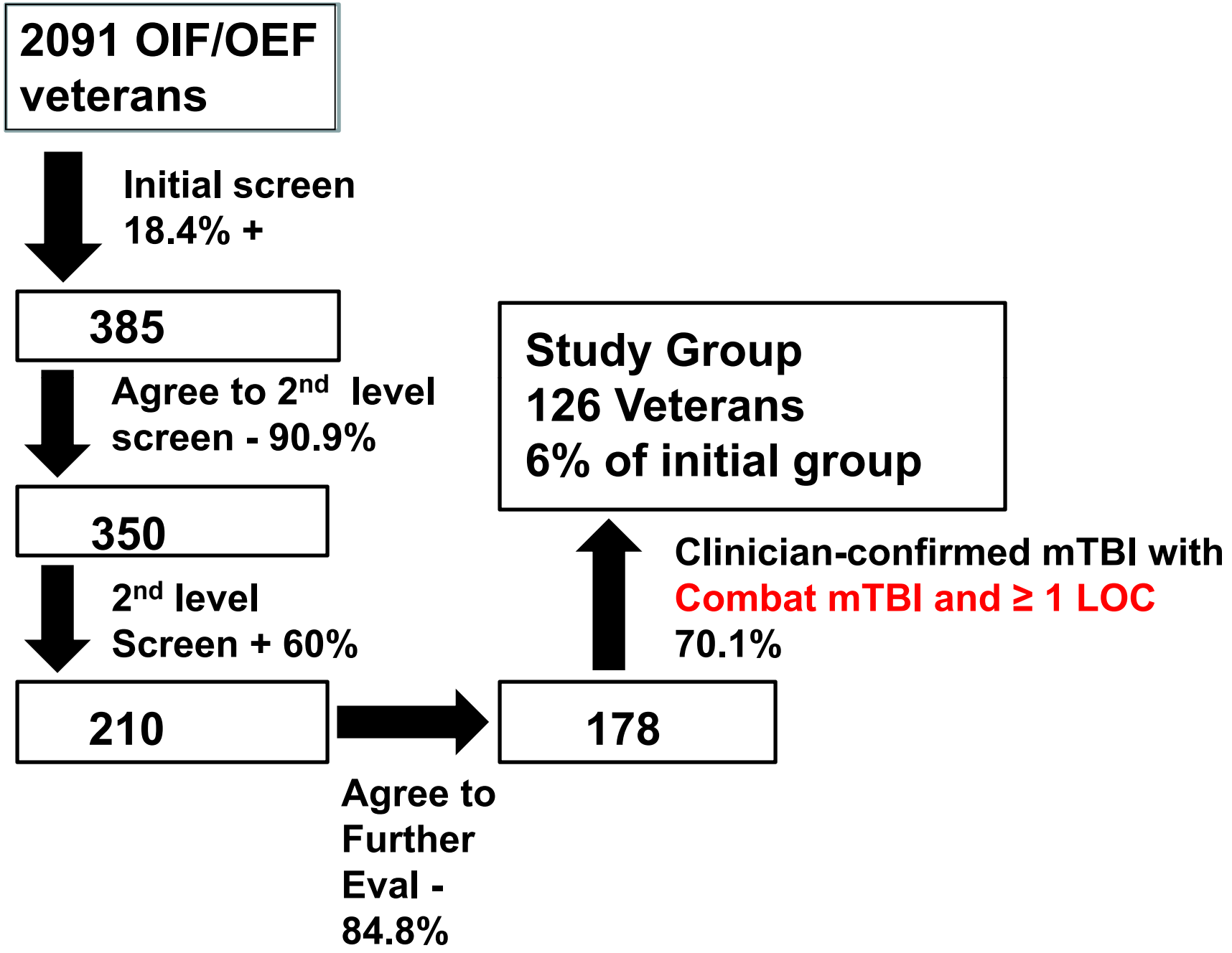
- Any opinions or conclusions presented are those of the author and do not necessarily reflect those of the Department of Veterans Affairs.

Background

- **Combat mild TBI in OIF/OEF is often associated with PTSD , neurological deficits, impaired sleep and pain (headache)**
- **There can be confusion between having had a TBI (historical diagnosis) and having residual deficits from a TBI (important to VBA)**
- **Epidemiological connection between mTBI and PTSD**
- **Questions – 1) What is the most sensitive physical exam test for residual deficits from a mTBI?**
- **2) How Can CNS damage predispose to PTSD?**

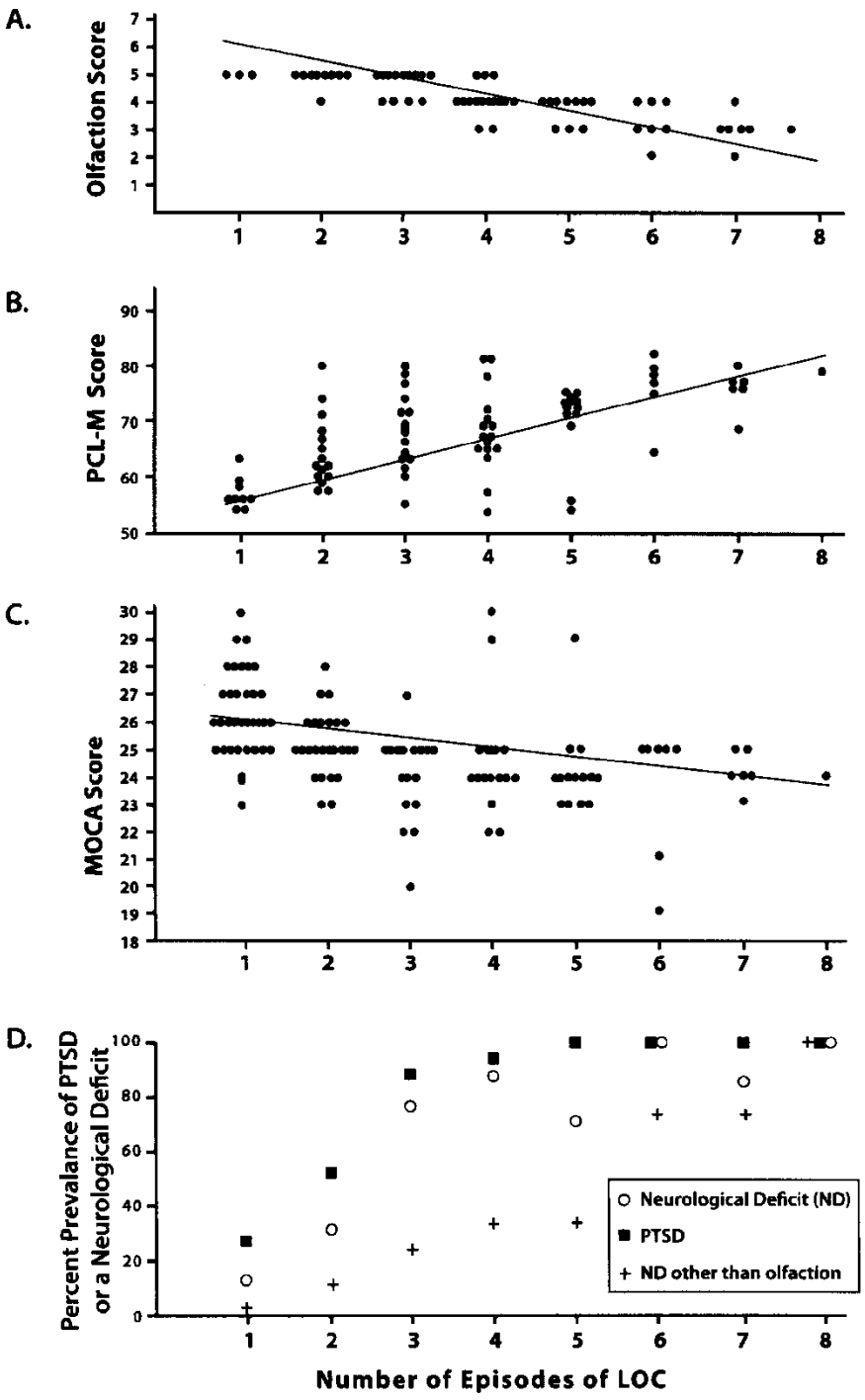

2091 OIF/OEF veterans
Initial screen 18.4% +
385
Agree to 2nd level screen - 90.9%
350
2nd level Screen + 60%
210
Agree to Further Eval - 84.8%
178
Clinician-confirmed mTBI with Combat mTBI and ≥ 1 LOC 70.1%
Study Group 126 Veterans 6% of initial group

A - OIF/OEF mTBI + LOC Group (n=126)
B - OIF/OEF mTBI w/o LOC Group (n=21)
C - OIF/OEF injury w/o TBI (n=52)
D - Civilians with mTBI + LOC (n=21)
E - Civilians without TBI (n=21)

- Neurological examination included a quantitative olfaction test (BSIT-12, Sensonics, Haddon Hts NJ).
- PTSD severity assessed by PCL-M
- Montreal Cognitive Assessment test (MOCA), Epworth sleepiness scale (ESS), headache pain level rated from 0 to 10 and number of headaches/month.
- mTBI + LOC - Neurological Deficits: olfaction – 63, balance – 14, eye movements – 13, motor – 2 and sensory – 2.

Frequencies of abnormalities on neurological testing, PTSD and MOCA scores
Probabilities for comparisons to veterans who had mTBI + LOC in combat.

Patient Group	**Deficit on Neurological Examination**	**Neurological Deficits other than olfaction**	**PTSD**	**MOCA Scores**
Combat mTBI & LOC	65 (52%)	29 (23%)	83 (66%)	25.1 ± 0.18
Combat mTBI w/o LOC	0 (0%)	0 (0%)	2 (9.5%)	28.8± 0.29
Combat w/o TBI	0 (0%)	0 (0%)	5 (9.6%)	28.7 ± 0.31
Civilian mTBI & LOC	2 (9.5%)	1 (4.8%)	1 (4.8%)	28.4 ± 0.23
Civilian w/o mTBI	0 (0%)	0 (0%)	0 (0%)	28.9± 0.29



Olfaction severity related to # of episodes of mTBI with LOC

PTSD severity related to # of episodes of mTBI with LOC

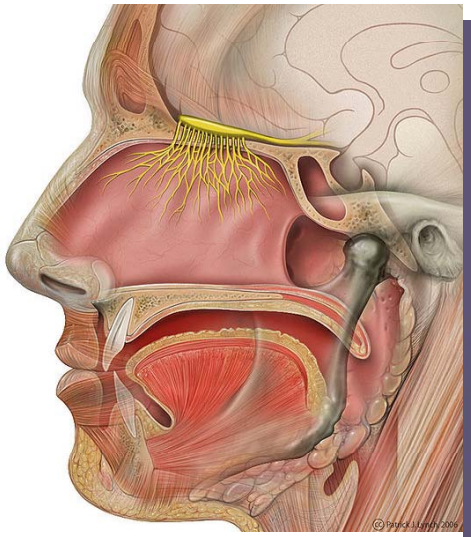
Cognitive performance inversely related to # episodes of mTBI with LOC

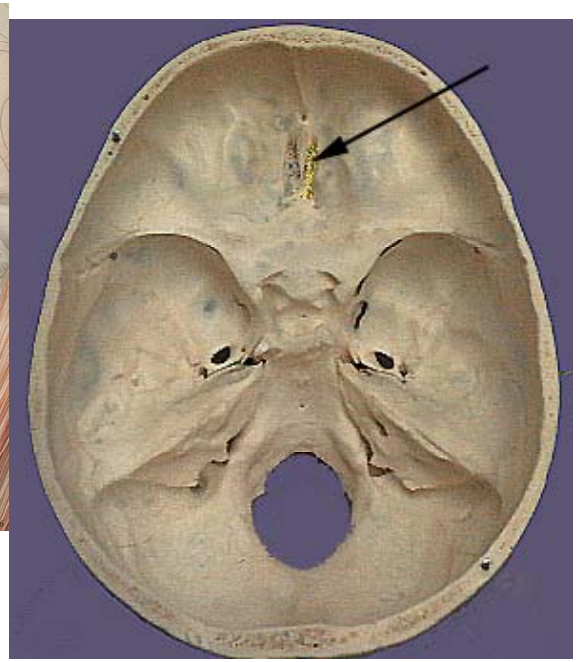
The likelihood of PTSD, ND related to # episodes of mTBI with LOC

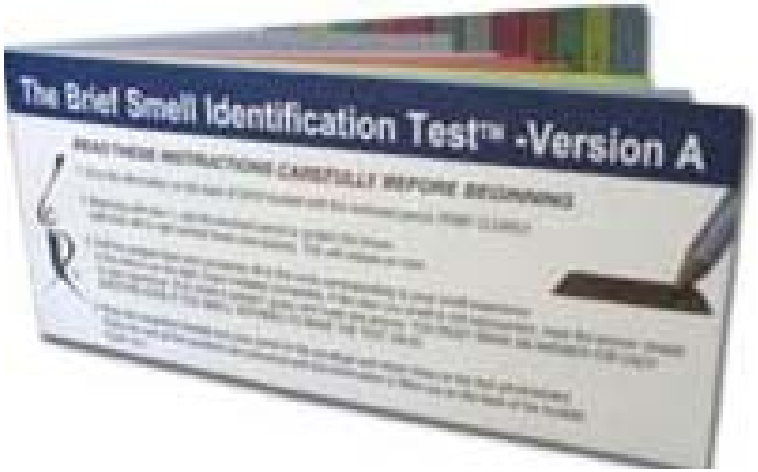
Olfactory Dysfunction

- Regional Vulnerability
- Alcohol swab not acceptable
- http://sensonics.com/

Neuro Deficit	Number
Olfaction	65
Balance	14
Eye movements	13
Motor	2
Sensory	2



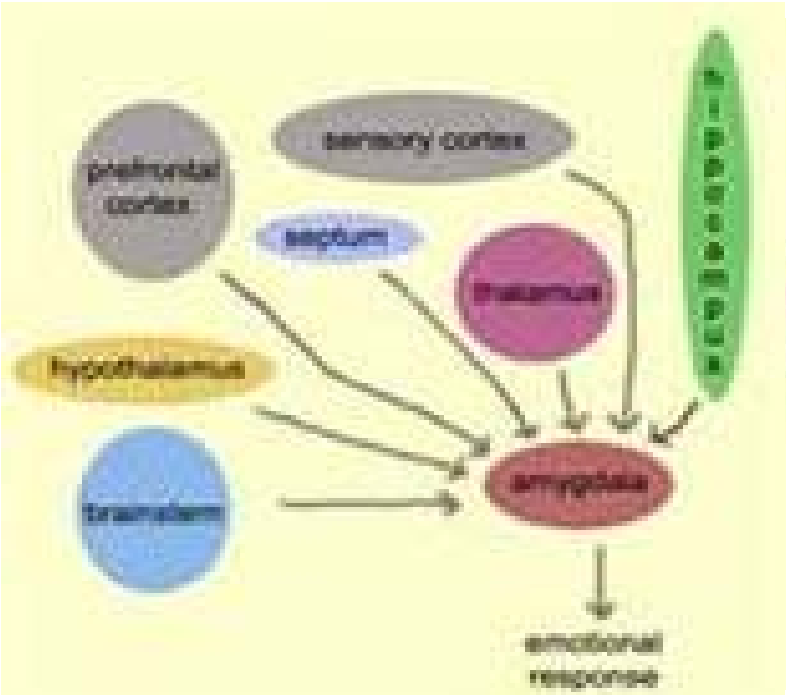


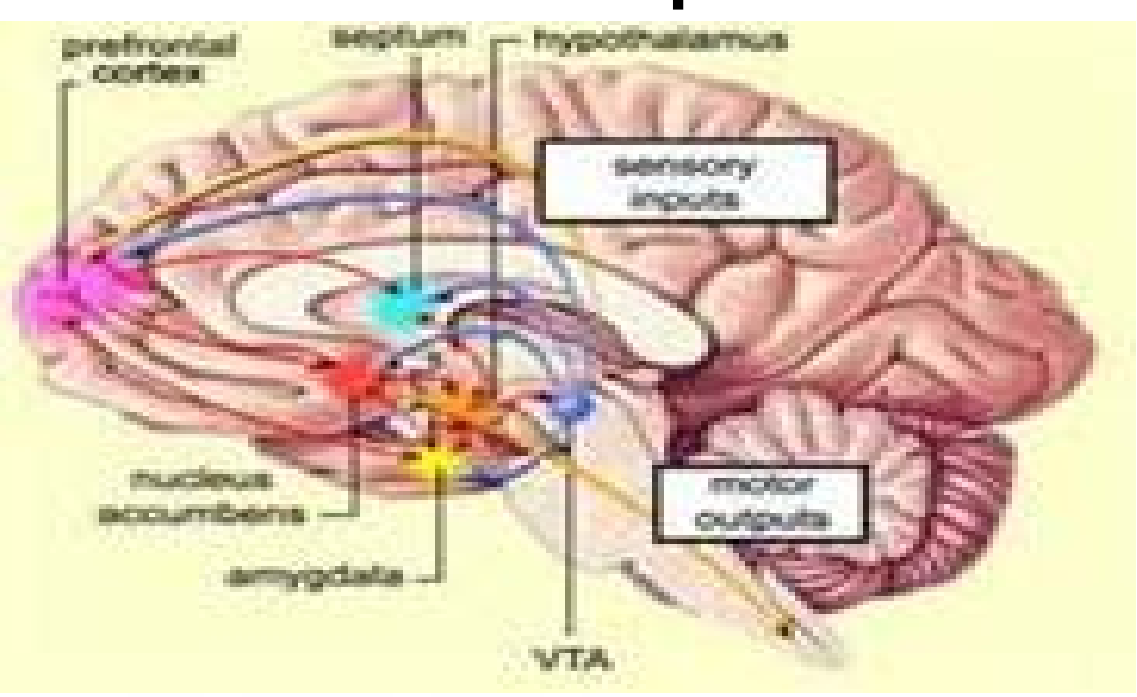


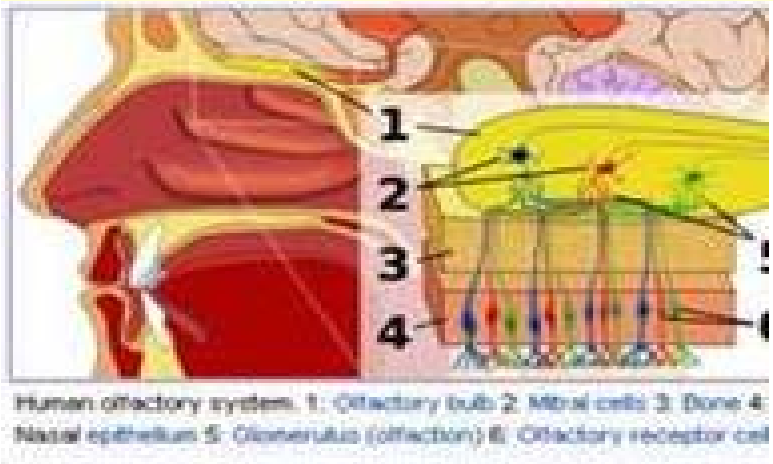
Amygdala and VMpfc Associated with PTSD

- Model –
  - PTSD associated with dysregulated amygdala activity
  - VMpfc and to a lesser extent hippocampus regulate amygdala activity
  - VMpfc regulation of amygdala is complex – not purely inhibitory
  - Damaging the amygdala/VMpfc interaction can facilitate PTSD genesis
  - Obliterating amygdala or both pfc can protect against PTSD (block the emotional excess).

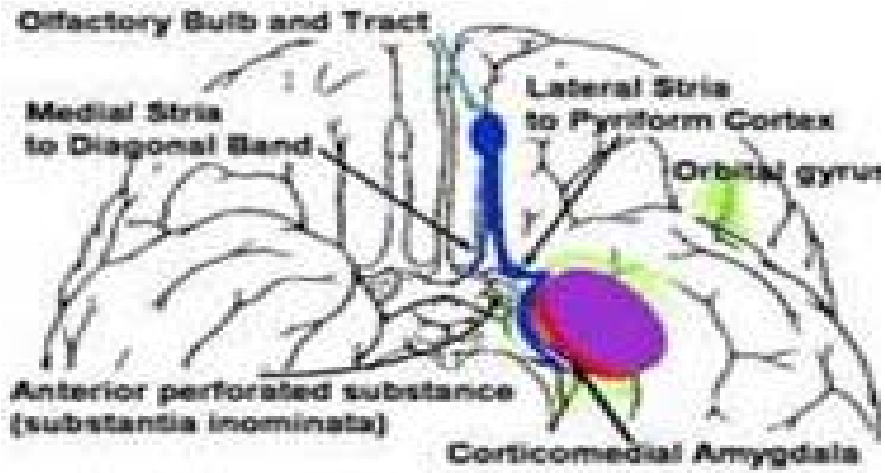
Anatomic Relationships



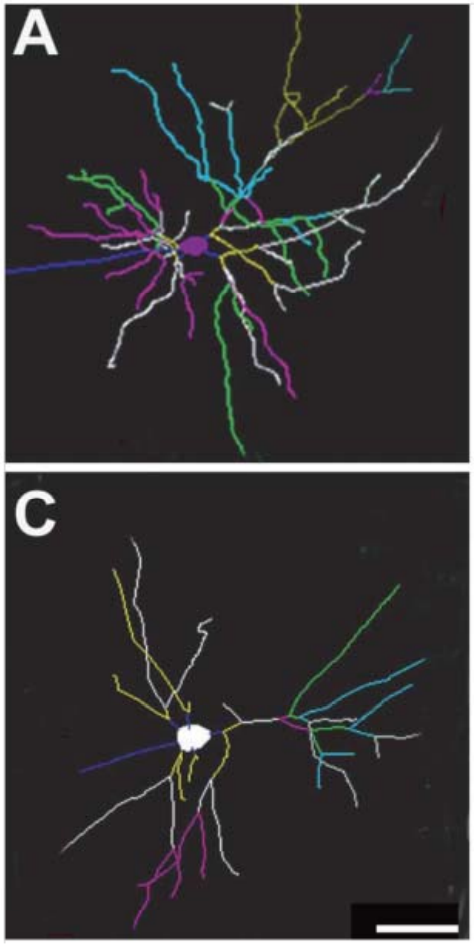




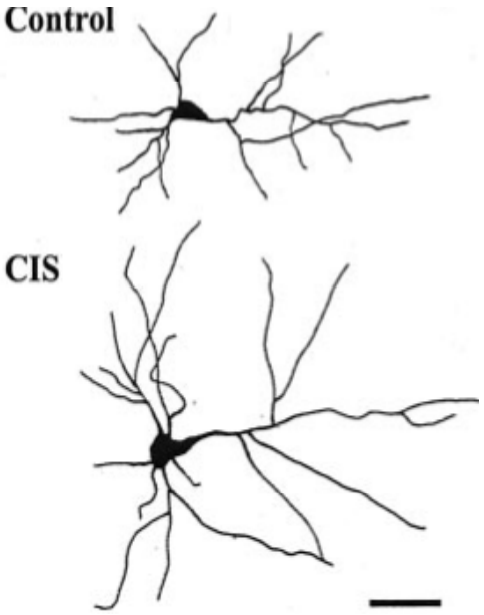
Human olfactory system. 1: Olfactory bulb 2: Mitral cells 3: Bone 4: Nasal epithelium 5: Glomerulus (olfaction) 6: Olfactory receptor cell



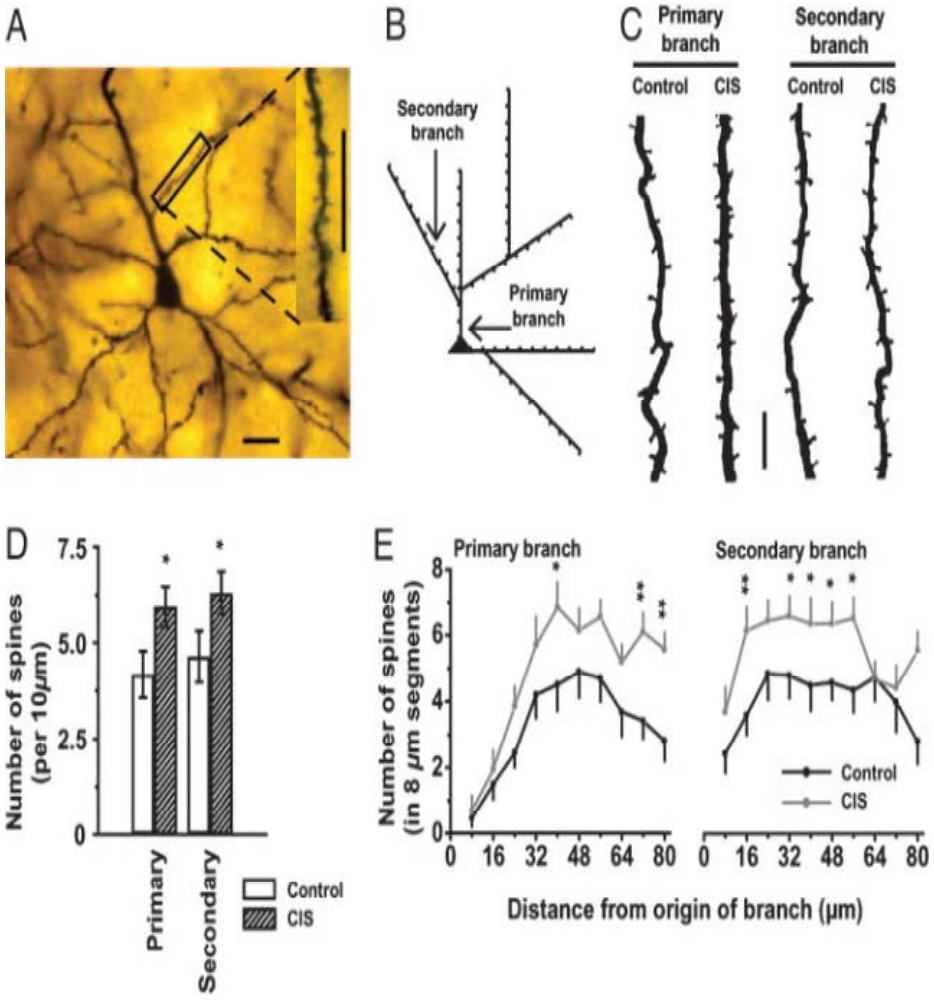
Ψ Stress Alters VMpfc and Amygdala neuron structure



J. J. Radley et al. / Neuroscience 125 (2004) 1–6 (pfc pyramidal cell)

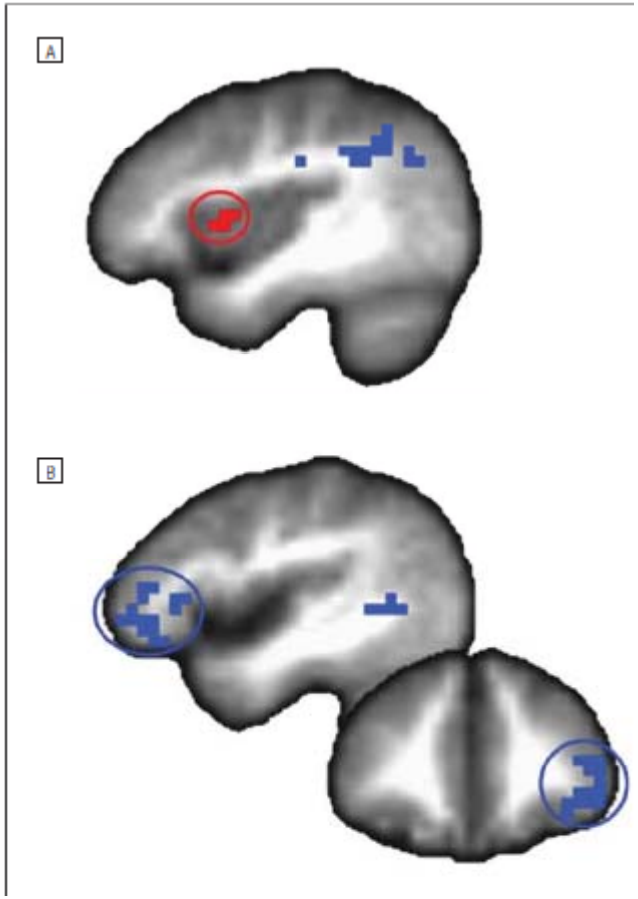


The Journal of Neuroscience, 2002, 22(15):6810–6818
Chronic Stress Induces Contrasting Patterns of Dendritic Remodeling in Hippocampal and Amygdaloid Neurons
A Vyas, R Mitra, S Rao, S Chattarji

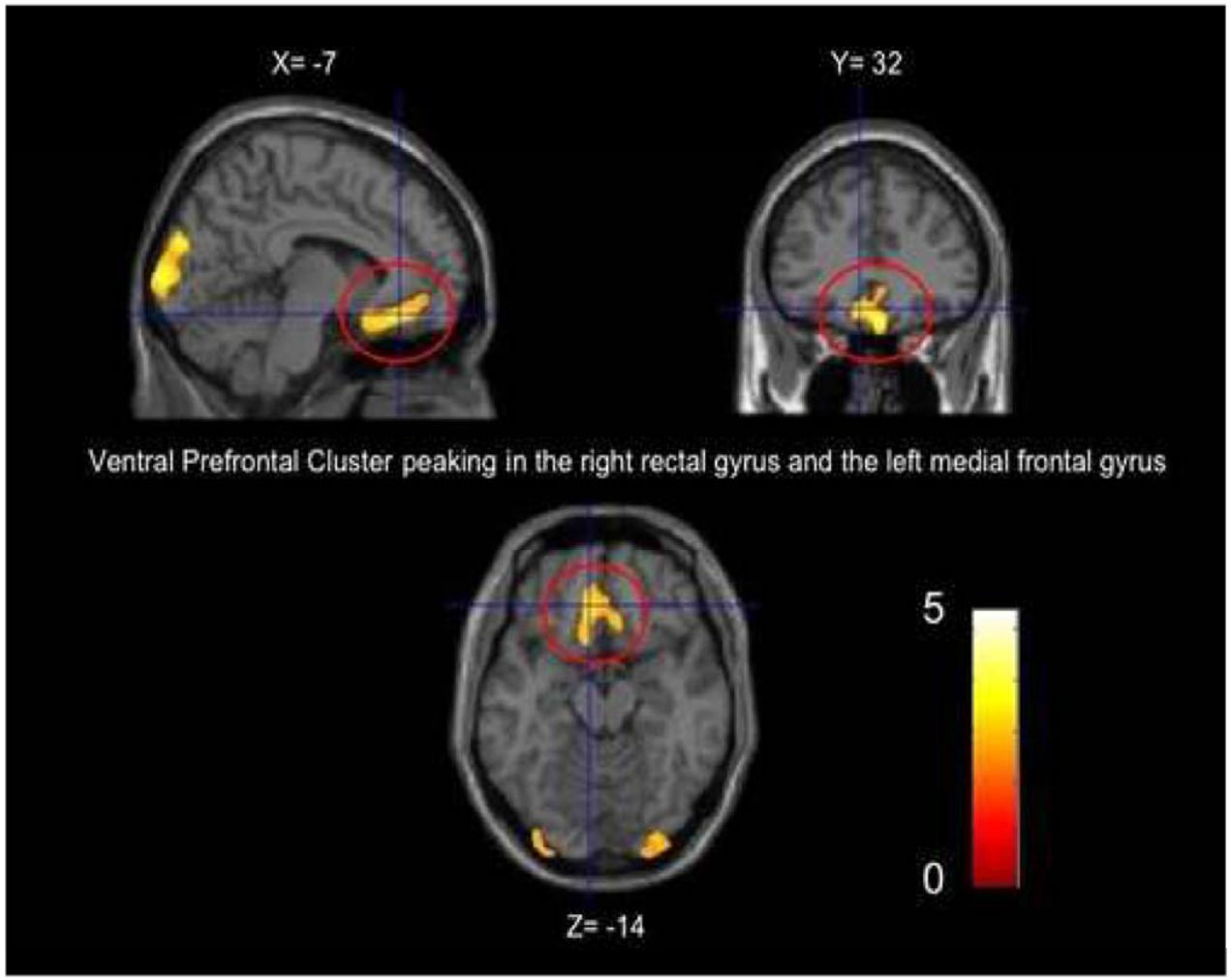


PNAS June 28, 2005 vol. 102 no. 26 9371–9376

PTSD: Amygdala & pfc

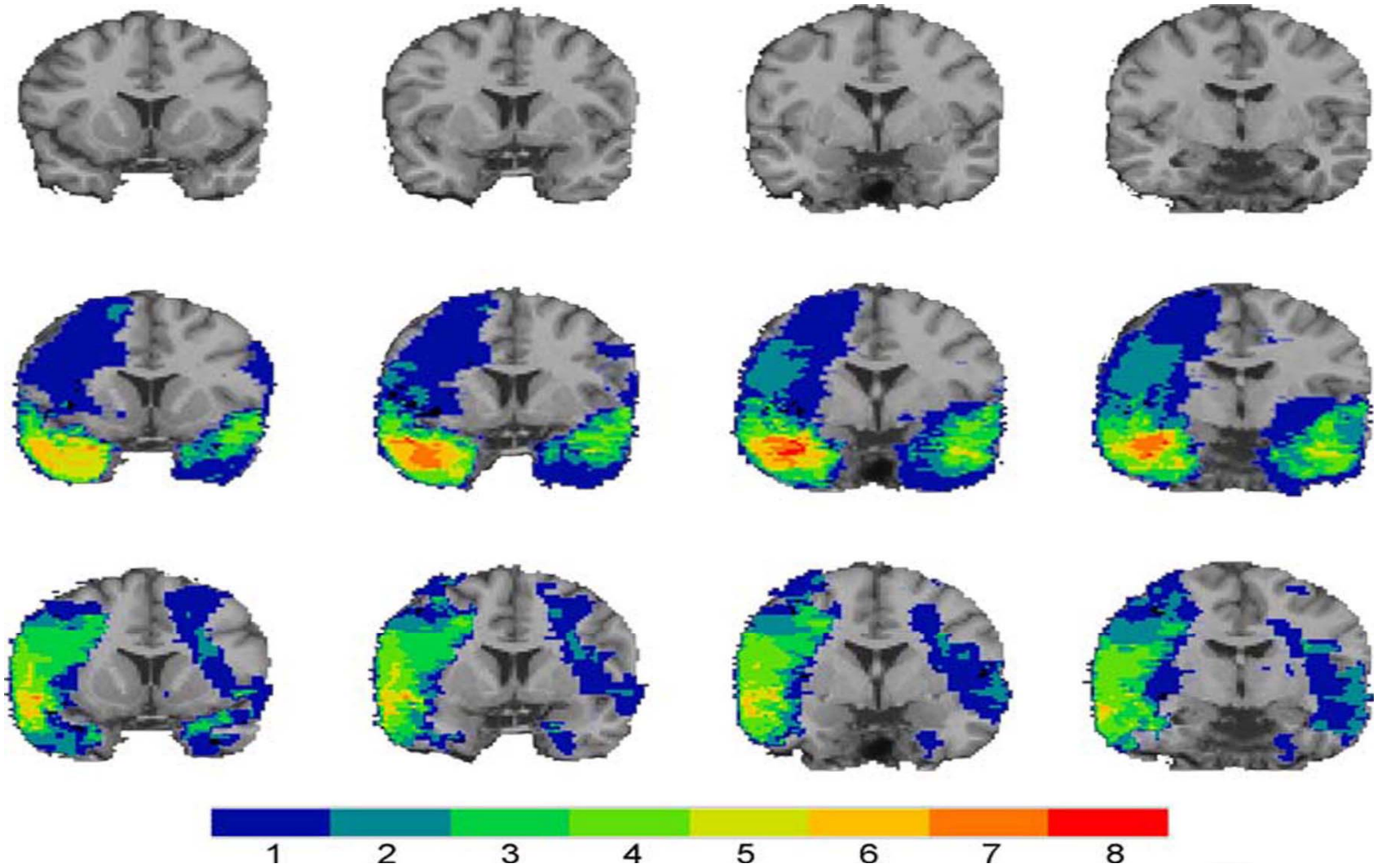


Arch Gen Psychiatry. 2012;69(4):360-371
Women with PTSD due to Partner violence - fMRI



Psychiatry Res. 2009 June 30; 172(3): 226–234
Pediatric PTSD – MRI study – note partial trauma pattern

Damage to Amygdale ↓PTSD



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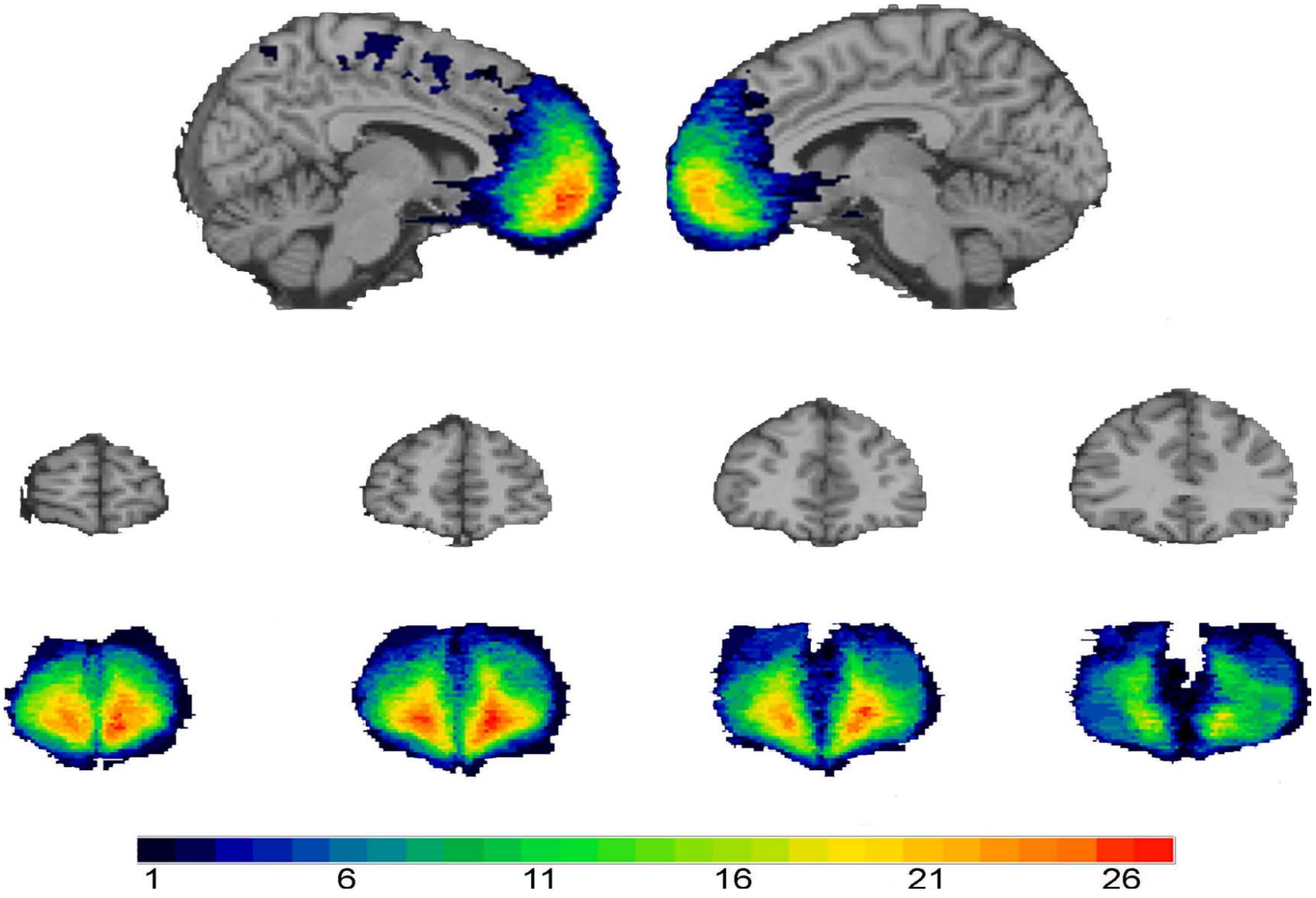
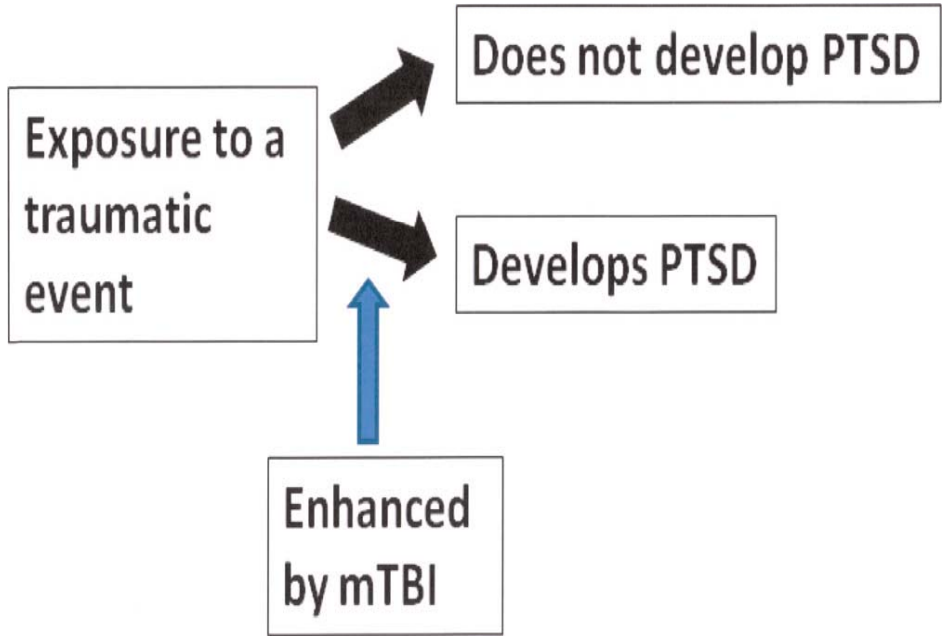
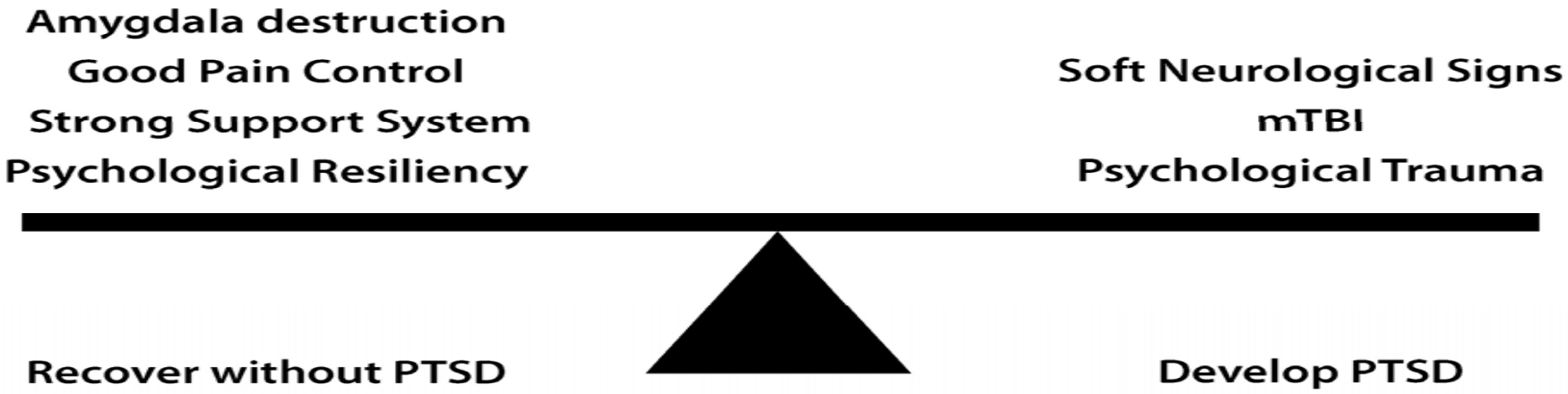
Damage to superior pfc ↓PTSD



Role of TBI in PTSD Genesis?





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Thank You and Questions

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