Traumatic Brain Injury: What Do We Know? What Should We Do?

Elaine R. Peskind, MD

Assoc. Director, Alzheimer's Disease Research Center
Friends of Alzheimer's Research Professor
Department of Psychiatry & Behavioral Sciences
University of Washington School of Medicine

Co-Director
VISN 20 Mental Illness Research, Education, and Clinical Center (MIRECC)

Staff Psychiatrist, Joint Base Lewis McChord, Tacoma WA

The Nature of an Emerging and Unprecedented Problem

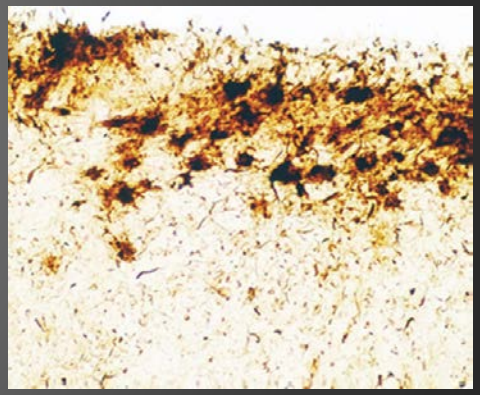
Helmand Province, Afghanistan. July 13, 2009. (*MSNBC*)

2.4 million Service Members 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

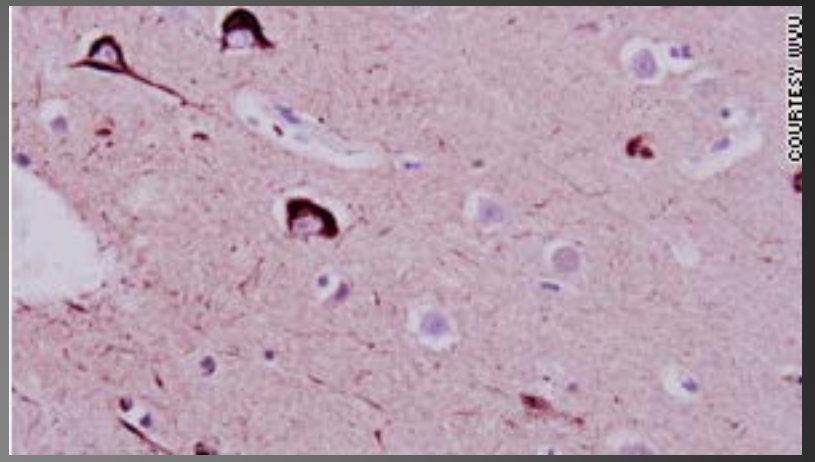
Photo provided to Bostonian (Winter/2009) by Virginia Grimsley



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



Tau staining in Chris Henry's Brain. Age 26.
Images from CNN

Los Angeles Times

Junior Seau had degenerative brain disease when he committed suicide

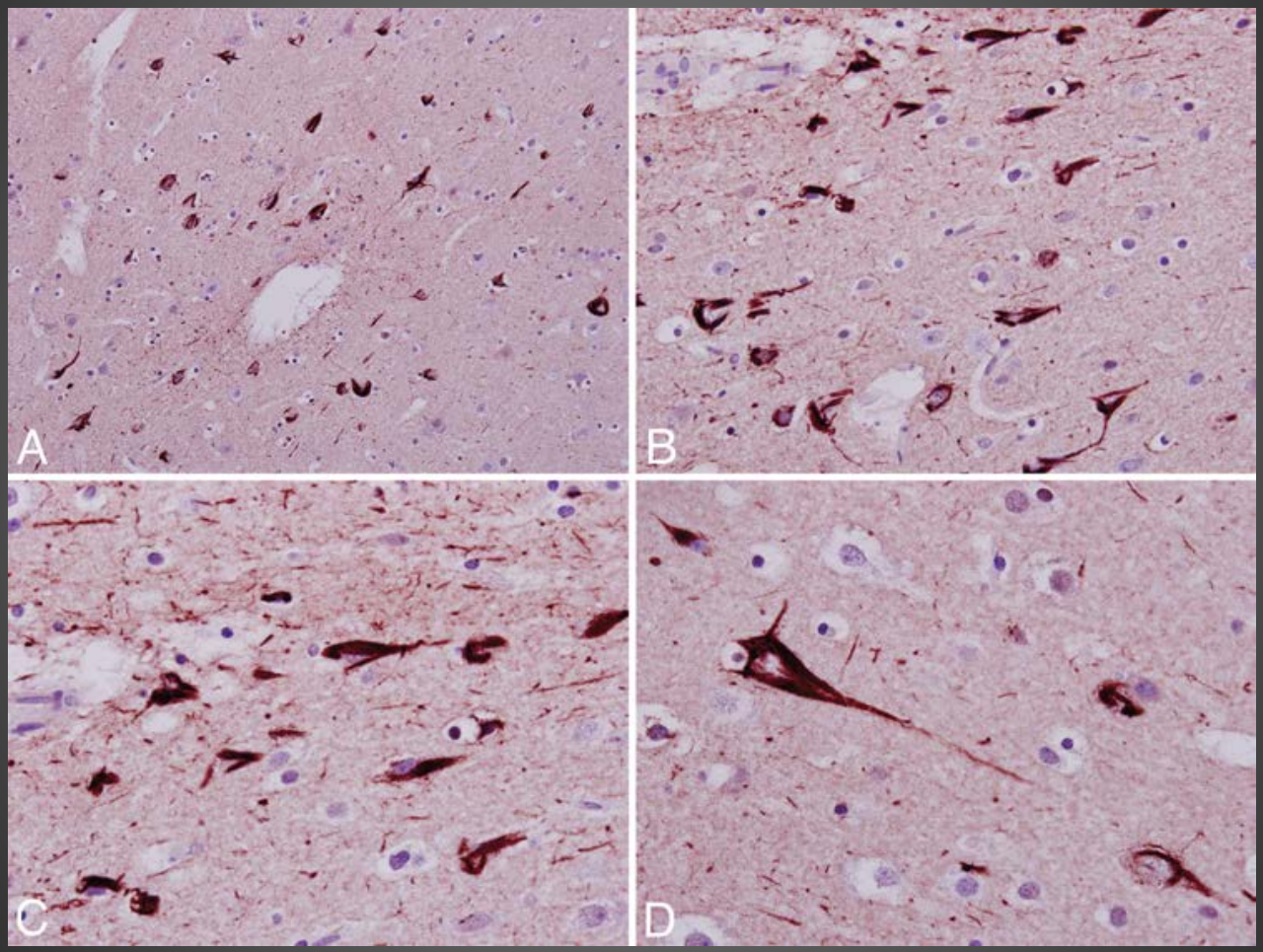
TRAUMATIC BRAIN INJURY

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]*

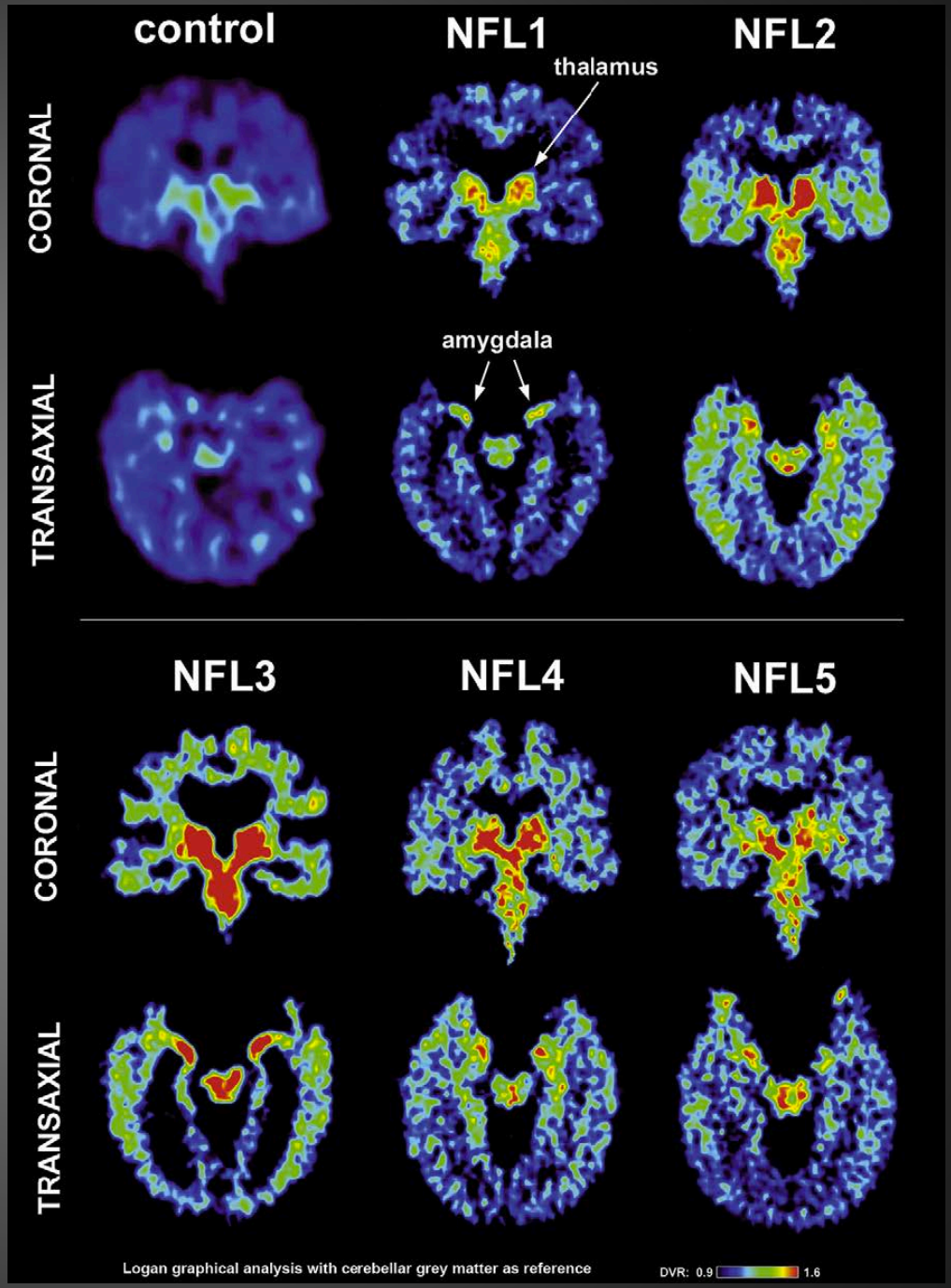
Goldstein et al., Sci Transl Med. 2012 May 16;4(134):134ra60.

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



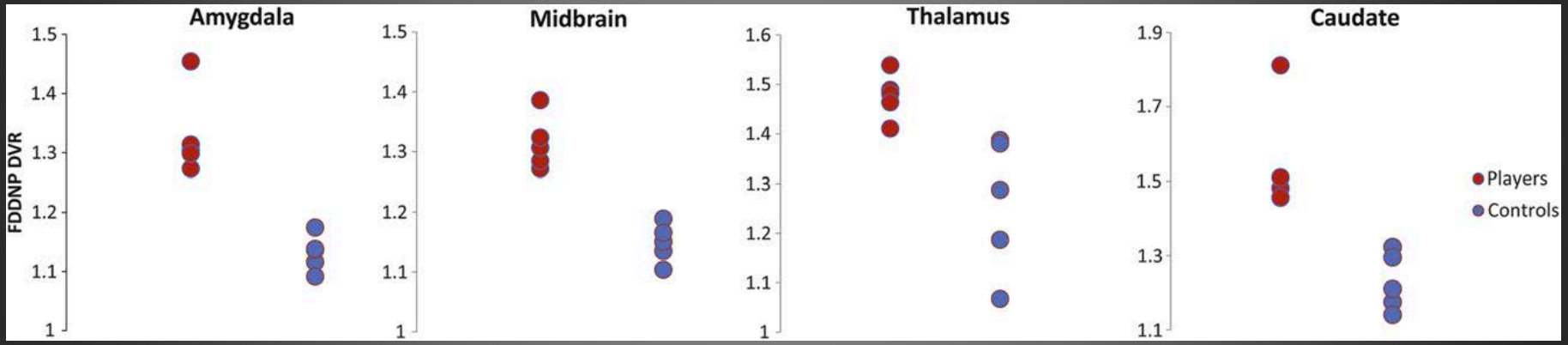
Photomicrographs of tau-immunostained section of the frontal cortex showing frequent neurofibrillary tangles and neuritic threads (Omalu et al, *Neurosurg Focus* 31:E3, 2011).

FDDNP-PET scan results for five retired NFL players and one control subject



Small G, Kepe V, Siddarth P, Ercoli L, Merrill D, Donoghue N, Bookheimer S, Martinez J, Omalu B, Bailes J, Barrio J. PET Scanning of Brain Tau in Retired National Football League Players: Preliminary Findings. Am J Geriatr Psychiatry 2013; 21:138e144.

Scatter plots of FDDNP binding values in players and controls



Small G, Kepe V, Siddarth P, Ercoli L, Merrill D, Donoghue N, Bookheimer S, Martinez J, Omalu B, Bailes J, Barrio J. PET Scanning of Brain Tau in Retired National Football League Players: Preliminary Findings. Am J Geriatr Psychiatry 2013; 21:138e144.

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

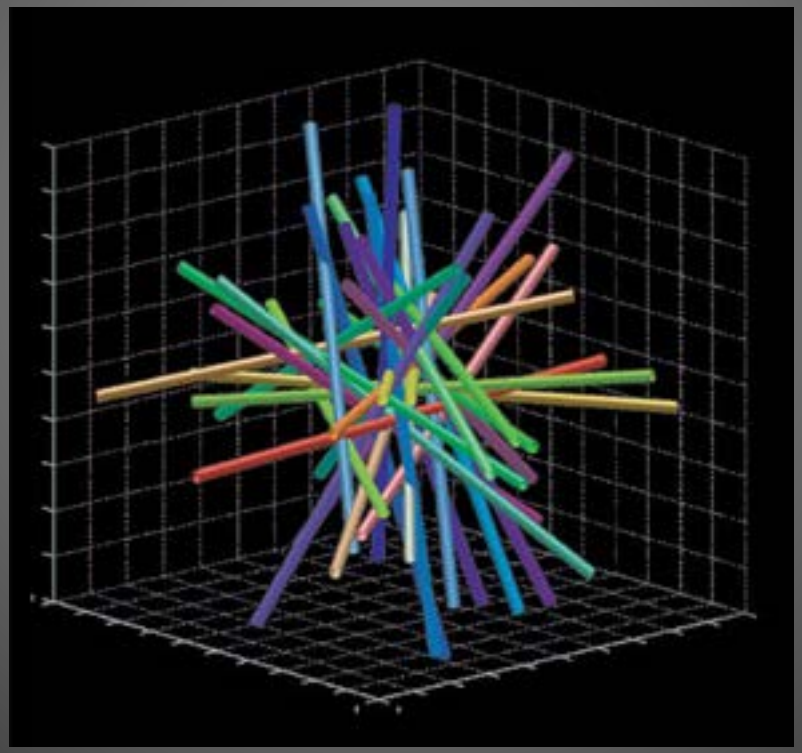
- Average time since last blast exposure was 4 years
- The average number of blast exposures resulting in loss of consciousness was 1.
- Majority had repetitive mTBI. Average number of blast exposures in Iraq or Afghanistan in the mTBI group was 14.

– 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

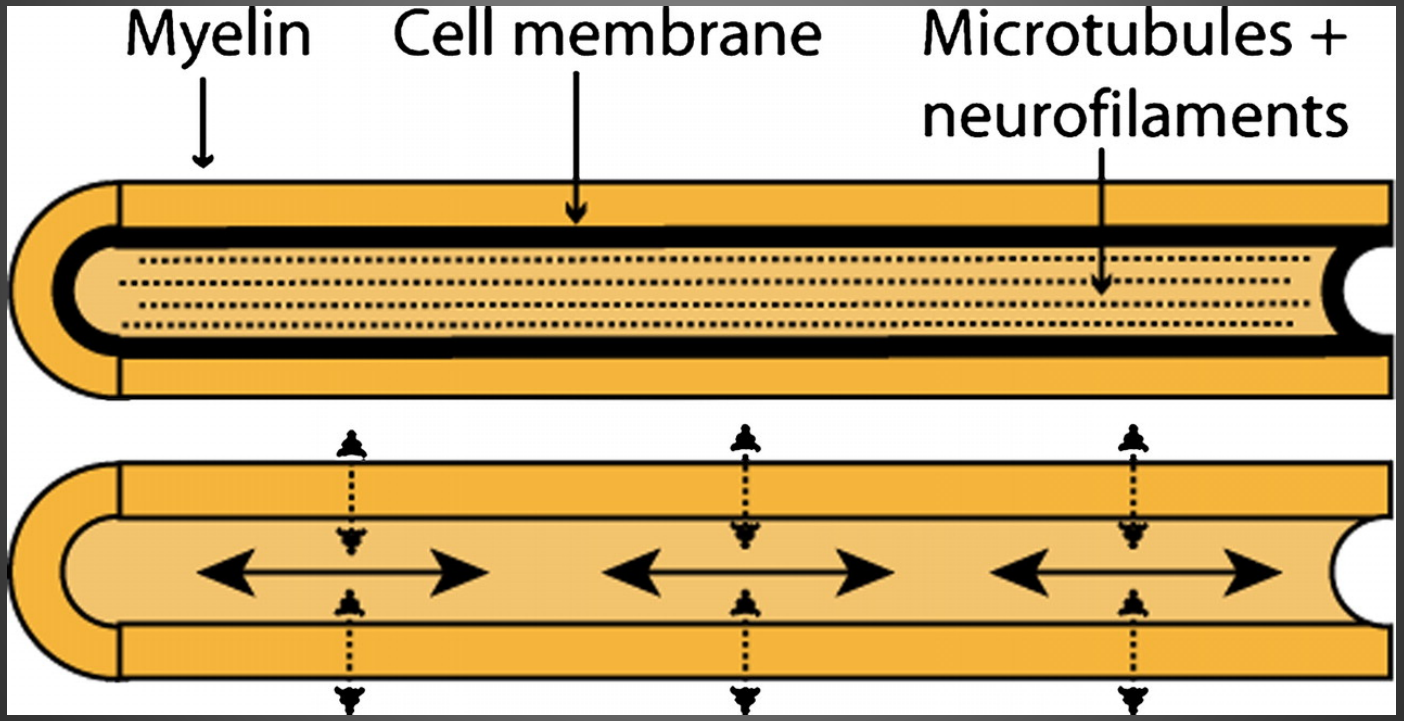
- Structural Neuroimaging
  - Diffusion Tensor Imaging
  - Macromolecular Proton Fraction (MPF) Mapping
- Functional Neuroimaging:
  - [^{18}F]-Fluorodeoxyglucose Positron Emission Tomography ([^{18}F]-FDG-PET)

Isotropic diffusion within a single voxel



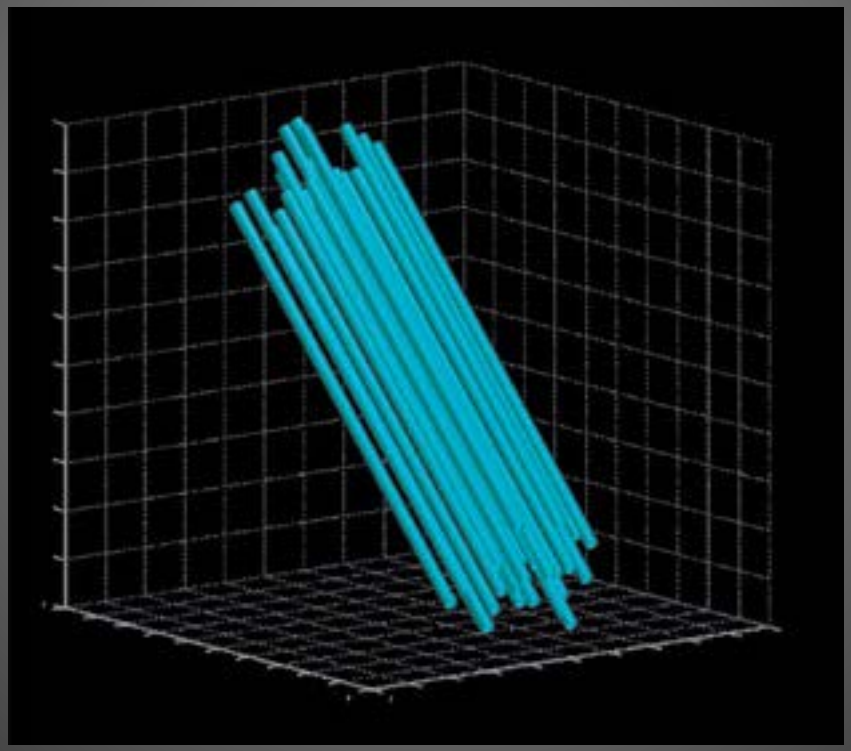
Hagmann Radiographics 2006;26:S205-S223

Cellular elements that contribute to diffusion anisotropy



Hagmann, P. et al. Radiographics 2006;26:S205-S223

Anisotropic diffusion within a single voxel

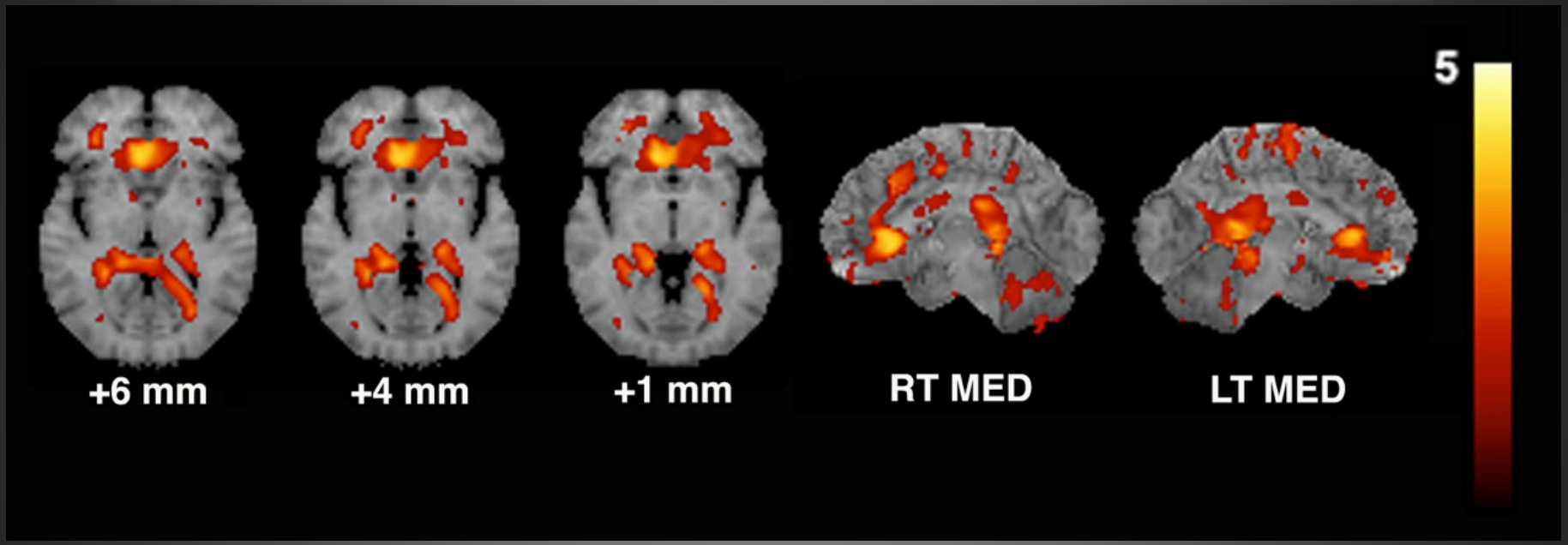


Hagmann Radiographics 2006;26:S205-S223

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
  - Jorge et al., *Am J Psychiatry*, 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

Diffusion Tensor Imaging: Conclusions

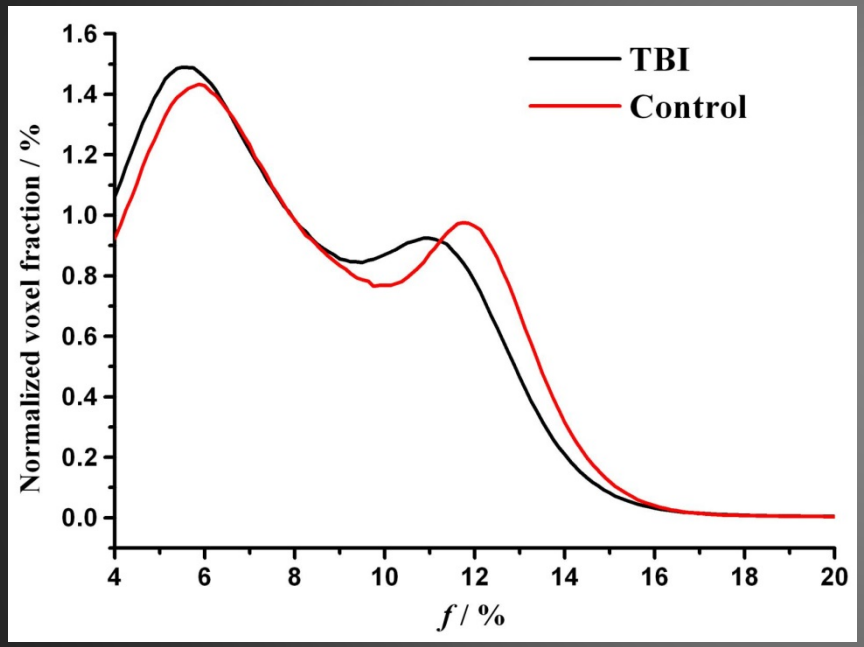
- Preliminary results from our laboratory show decreased FA in corpus callosum an average of 4 years following last blast exposure in Iraq and Afghanistan Veterans with mTBI vs. deployed control Veterans without TBI, consistent with diffuse axonal injury.
- These results could not be attributed to PTSD.
- DTI studies in Iraq/Afghanistan Veterans vary among labs – both in Methods and Results
- Are there other structural MRI techniques which may be more sensitive to chronic changes following blast concussion mTBI?

Macromolecular Proton Fraction (MPF) Mapping

- 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.

Macromolecular Proton Bound Fraction (f): Whole-Brain Histogram Analysis Results

Macromolecular Proton Fraction (*f*) Histogram Parameters for blast-exposed (N=27) vs. non-blast exposed Iraq/Afghanistan Veterans (n=16)

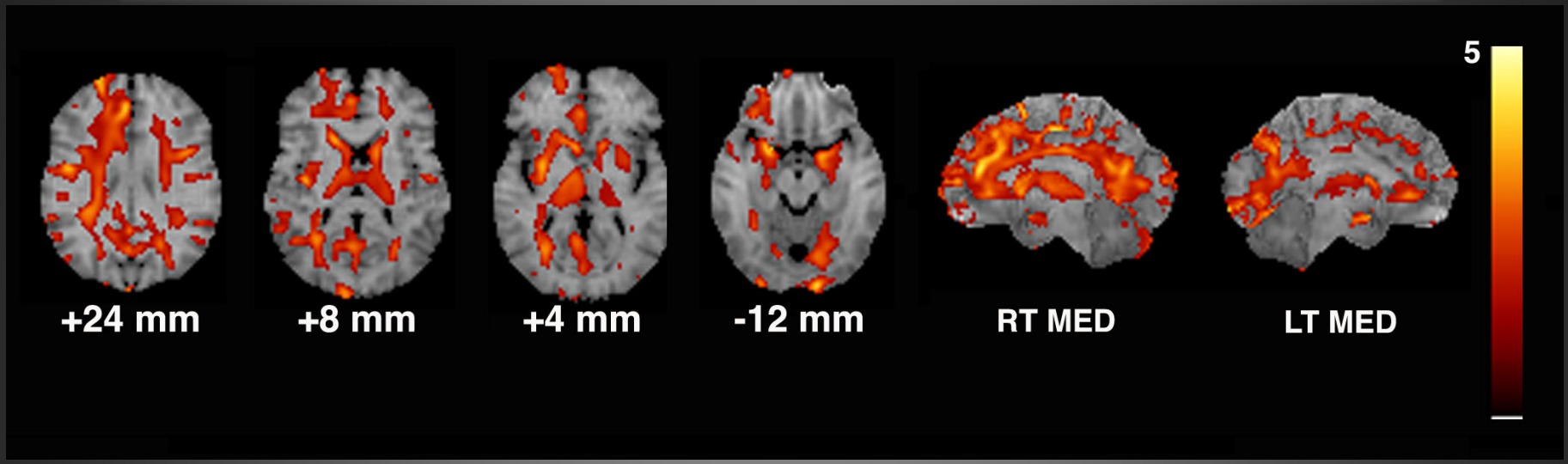


Plot of group mean whole-brain MPF (*f*) histograms for Iraq/Afghanistan mTBI (n=27) vs. Iraq/Afghanistan non blast-exposed (n=16) Veterans

Macromolecular Proton Fraction (*f*) Histogram Parameters (mean ± SD)				
Parameter		mTBI	Controls	P-value[a]
GM	**f_1 (%)**	**5.56±0.35**	5.86±0.22	**<0.001**
WM	**f_2 (%)**	**11.17±0.66**	**11.87±0.33**	**<0.001**
Mixed	**f_3 (%)**	**8.36±0.60**	**9.01±0.30**	**<0.001**

[a]Independent one-tailed t-test

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

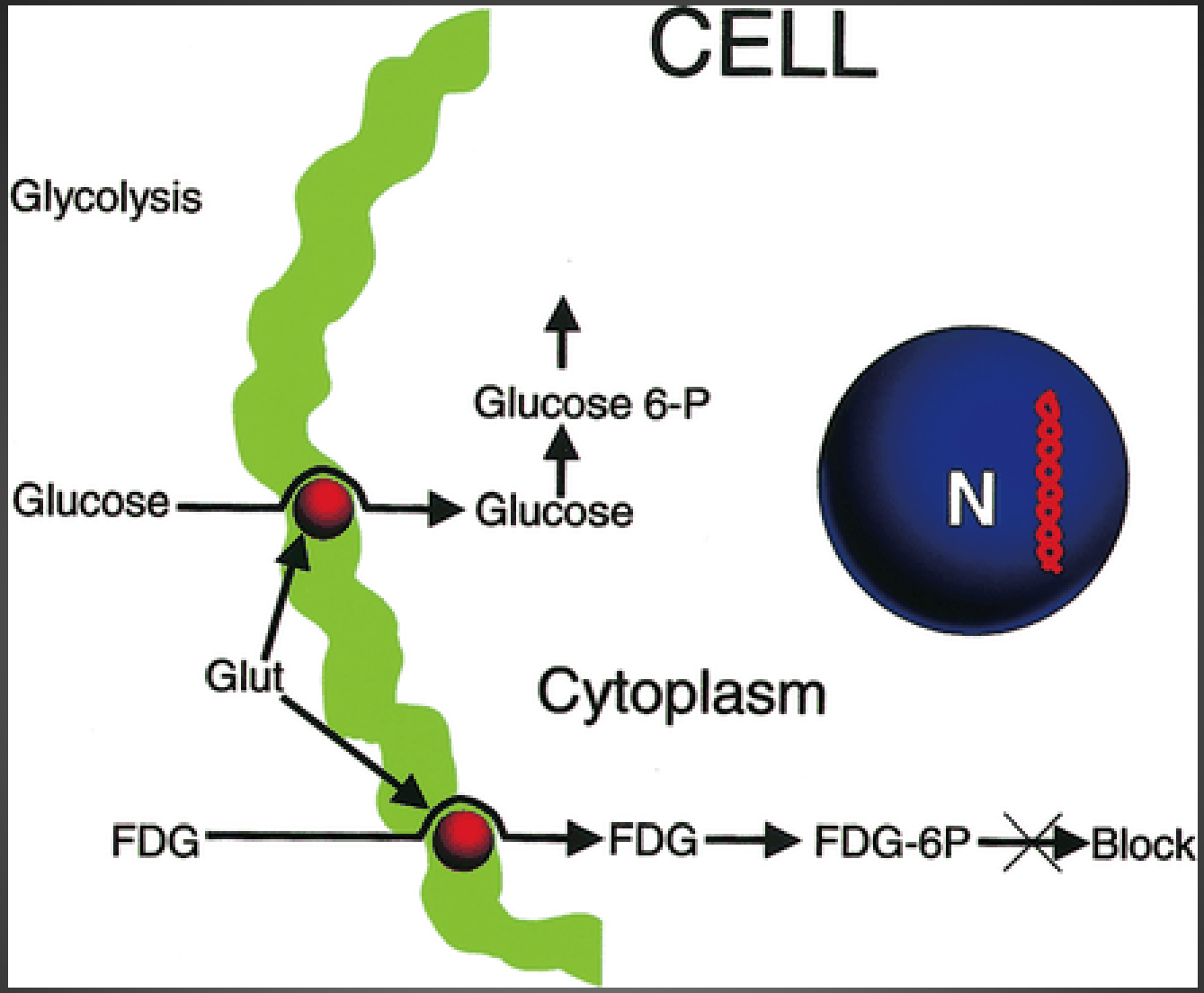
Macromolecular Proton Bound Fraction (f): Voxelwise Subtraction Analysis Results

Structure*	Tissue Component	Coordinates (mm)¶	Z score	Reduction (%)@
R External Capsule	WM	(-30, -1, 0)	4.4	10.5 ‡
R Internal Capsule, Anterior Limb	WM	(-17, 17, 9)	4.0	12.3 §
R Superior Longitudinal Fasciculus	WM	(-44, -6, 27)	4.1	16.3 ‡
R Superior Frontal Gyrus	GM WM GM/WM Border GM/WM Border GM	(-24, 59, 22) (-17, -13, 45) (-17, 8, 58) (-6, 32, 27) (-24, 66, 7)	4.6 4.4 4.0 4.0 4.0	35.8 § 7.2 § 27.0 § 17.6 ‡ 36.4 ‡
R Middle Frontal Gyrus	WM GM GM/WM Border	(-39, 1, 47) (-46, 50, -2) (-37, 48, -4)	4.4 4.1 4.3	19.6 ‡ 28.1 † 16.7 ‡
L Inferior Frontal Gyrus	GM/WM Border	(42, 5, 20)	4.3	24.3 §
R Medial Orbital Gyrus	GM GM	(-26, 37, -16) (-21, 5, -11)	4.2 4.1	30.5 ‡ 18.4 ‡
R Precentral Gyrus	WM GM	(-19, -17, 45) (-46, -13, 43)	4.4 4.1	8.1 § 19.6 ‡
R Anterior Cingulate Gyrus	GM	(-3, 41, 18)	4.5	23.6 §
L Subcallosal Gyrus	GM	(15, 3, -14)	4.3	32.5 §
L Superior Parietal Lobule	WM	(15, -62, 32)	4.0	15.6 §
R Precuneus	WM	(-21, -58, 38)	4.2	16.8 §
L Lingual Gyrus	GM	(12, -91, -11)	4.2	20.2 §

† $p<0.05$, ‡ $p<0.01$, § $p<0.001$ (Independent groups t-test, one-tailed)

Conclusions - MPF

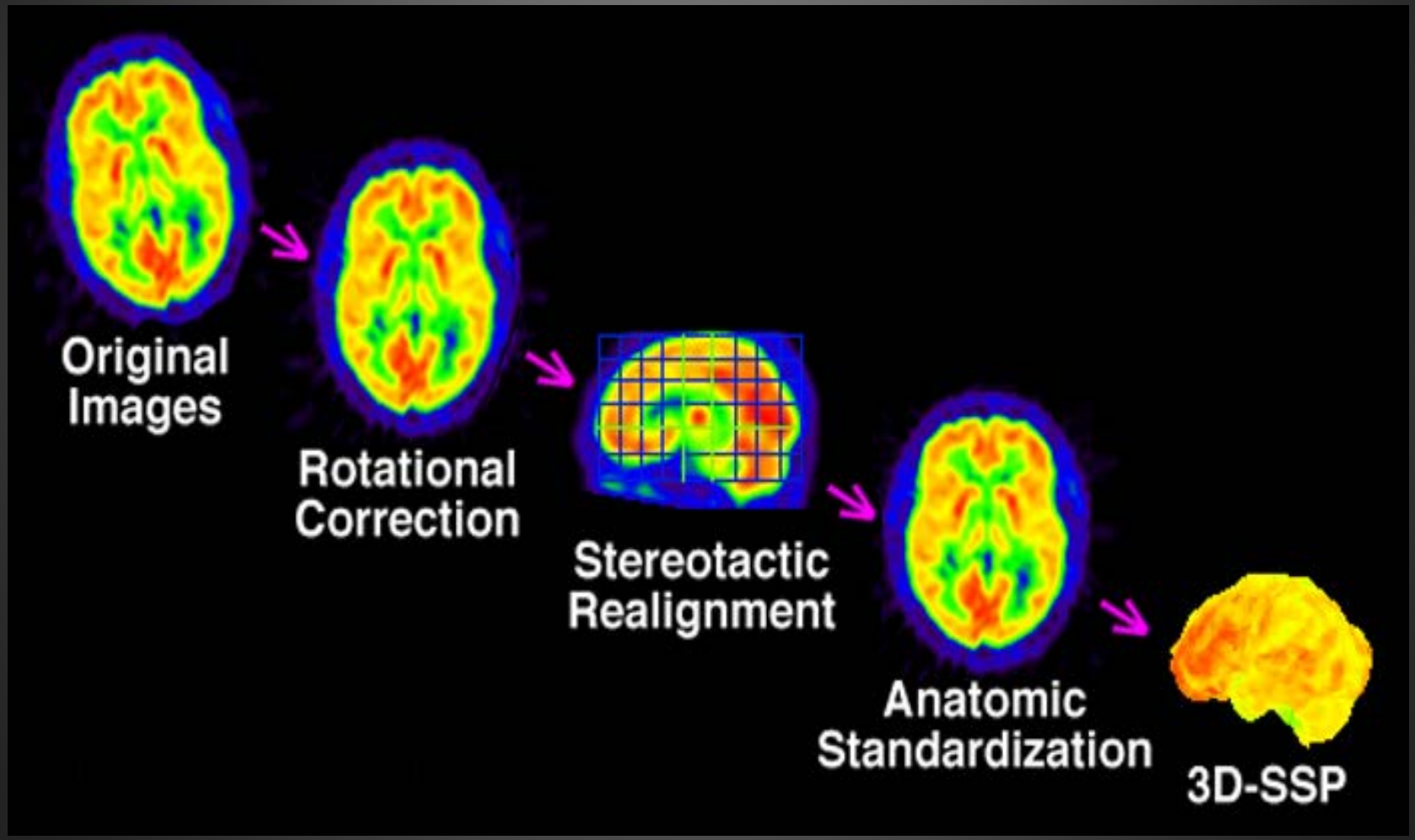
- Observed reduction of bound pool fraction in white matter on whole brain analysis is consistent with the mechanism of **diffuse axonal injury**.
- Voxelwise analysis of MPF images suggests **alterations of myelin structure** in white matter tracts known to be vulnerable to damage in diffuse axonal injury.
- Altered MPF parameters have **potential** as prospective quantitative biomarkers of blast-induced mTBI.



Uptake of FDG. FDG is a glucose analog that is taken up by metabolically active cells by means of facilitated transport via glucose transporters (*Glut*) in the cell membrane. In the cell cytoplasm, FDG undergoes phosphorylation to form FDG-6-phosphate (*6P*), which, unlike glucose, cannot undergo further metabolism and becomes trapped within the cell. *N* = nucleus.

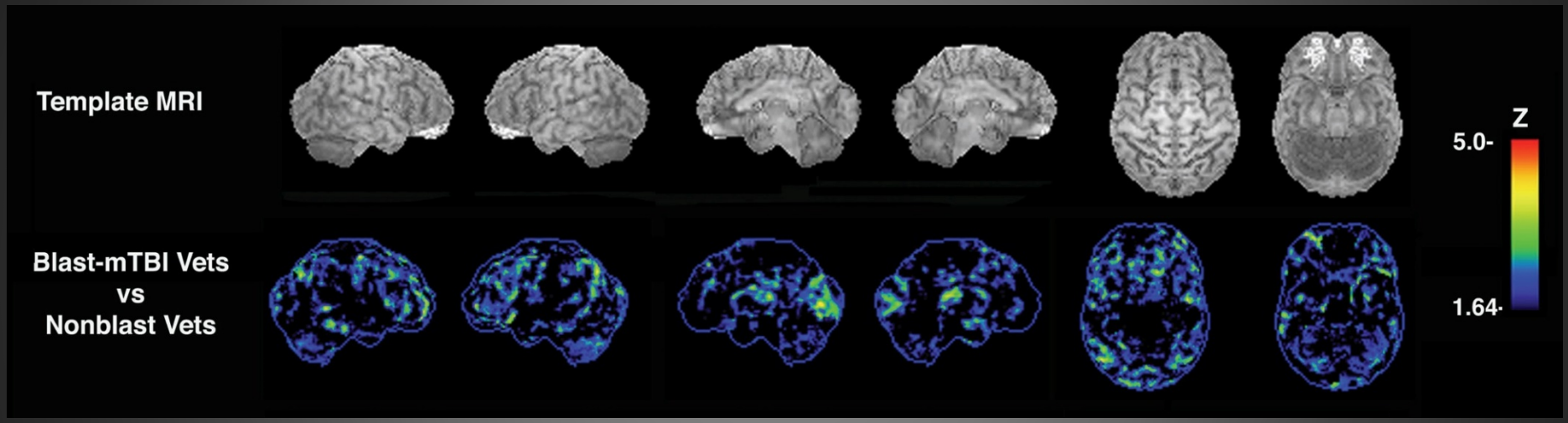
RadioGraphics 2004;24:523-543

FDG-PET Spatial Normalization and Transformation to Standard Stereotactic Coordinate Space



Talairach J, Tournoux P. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme, 1988.

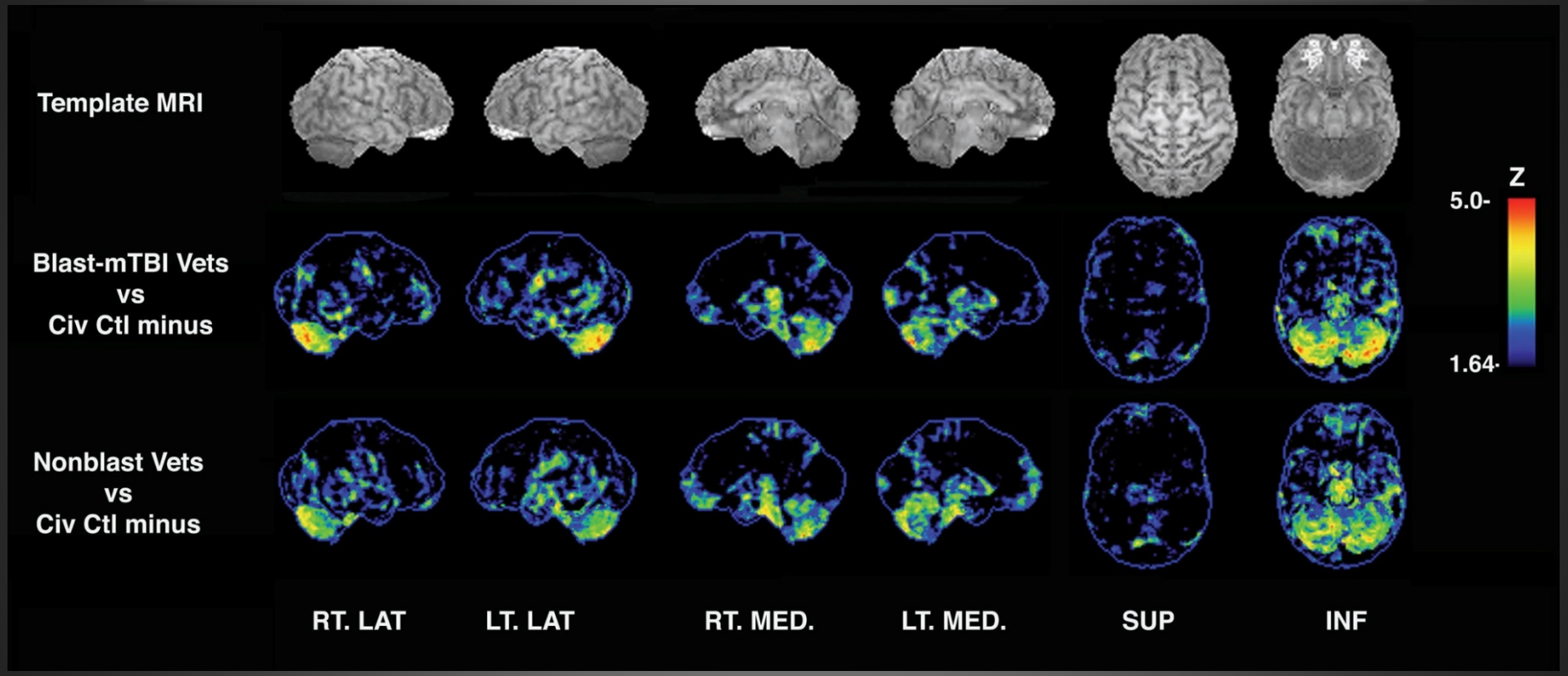
Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET): Composite Z-score subtraction maps of regional brain glucose metabolism in Blast-mTBI Veterans (N=33) vs. Nonblast Veterans (N=16)



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).

Summary and Conclusions

- Caution needed!
  - neuropsychological test performance deficits only with difficult executive tasks
  - no differences in CSF biomarkers between blast exposed OIF Veterans and non blast-exposed OIF Veterans
  - more data, analysis, and replication needed
  - must be careful about selection of control groups – need multiple control groups to determine what is specifically blast-related
  - longitudinal follow-up essential!

What Should We Do?

- Much more research needed:
  - DoD ADNI
  - DoD/VA TBI Consortium
- Reducing your own risk
  - Avoid head trauma: wear seatbelt, helmet
- Are contact sports safe?
  - Youth sports, collegiate and professional sports

Collaborators

- **VA MIRECC**
  - Eric Petrie, MD
  - Murray Raskind, MD
  - Kathleen Pagulayan, PhD
  - Jim Leverenz, MD
  - Cynthia Mayer, DO
  - Kim Hart, PA-C
  - David Hoff, PA-C
  - Jane Shofer, MS
- **VA GRECC**
  - David Cook, PhD
  - Charles Wilkinson, PhD
  - Chang-En Yu, PhD
- **University of Washington**
  - Donna Cross, PhD
  - Satoshi Minoshima, MD, PhD
  - Vasily Yarnykh, PhD
  - Natalia Kleinhans, PhD
  - Todd Richards, PhD
  - Raimondo D'Ambrosio, PhD
  - Tom Montine, MD, PhD
  - Jing Zhang, MD, PhD

Ray Bennett, PhD, Baker Risk, San Antonio, TX

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Collaborators

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