Recent Research on Blast Injury, PTSD, and OIF/OEF Veterans

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December 7, 1941
USS Maryland and USS Oklahoma

Official Navy Photograph, National Archives Collection

The Nature of an Emerging and Unprecedented Problem

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

2 million Soldiers and Marines have been deployed to Iraq and Afghanistan as of 12/10; nearly 800,000 more than once; approximately 9-18% return with symptomatic mTBI.

What Makes the Current Wars in Iraq and Afghanistan Different From Previous U.S. Conflicts?

- Significant improvements in body armor
- Improvised explosive devices (IEDs) are the weapons of choice of insurgents
- Multiple deployments

An Example: One Stryker Brigade operating in Iraq over a 12 month period in 2004-2005.

Controlled IED detonation in Khan Bani Sa'ad, Iraq

Experienced 3056 enemy attacks, 1336 IEDs, 84 suicide vehicle-borne IEDs, 1513 direct fire attacks, and 631 indirect fire attacks. Those soldiers escaping immediate harm may have been exposed to hazardous blast overpressure (BOP) events roughly once every three days for the duration of their 12-month deployment.

Potential Consequences of Repetitive Mild Head Trauma

NFL Pro-Bowl 1988

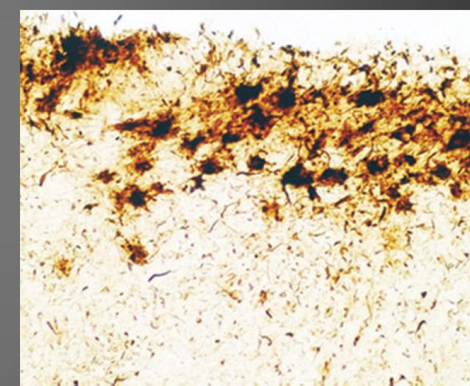


Photo provided to <u>Bostonian</u> (Winter/2009) by Virginia Grimsley

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

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 OIF/OEF 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 structural or functional brain changes?

Participants

- 35 male OIF Veterans with blast-induced mild traumatic brain injury
  - Mean age 31.5 ± 7.3 years (range 21-60)
- 13 non blast-exposed OIF Veterans
  - Mean age 31.8 ± 7.3 years (range 22-46; 12M, 1F)
- 12 cognitively normal community volunteers
  - Mean age 53.0 ± 4.6 years (range 49-56; 7M, 5F)

Participant Demographics

	mTBI (N=35)	OIF Control (N=13)
Education (years)	13.9 ± 1.5	13.8 ± 1.5
Race		
Caucasian	80%	62%
African-American	6%	15%
Pacific Islander	3%	8%
Other	11%	15%
Hispanic Ancestry	17%	23%
Military Service		
Army	69%[a]	54%
Marines	23%[a]	23%
Other	11%	23%

[a]One served in both Army and Marines

Neurologic Assessments

- Neurologic exam
  - mild eye movement, cerebellar signs
- Unified Parkinson's Disease Rating Scale
  - 2.5 ± 3.3 vs. 0.9 ± 1.9, $p=0.14$
- Brief Smell Identification Test
  - 65th percentile vs. 74th percentile

Neurocognitive Assessments

- Alzheimer’s Disease Research Center Uniform Dataset
- University of Pennsylvania Computerized Neurocognitive Battery
- Ruff 2 & 7 Selective Attention Test
- Controlled Word Association Test
- Sentence Repetition
- Wechsler Test of Adult Reading
- Effort assessment

Neurocognitive Assessments - Results

- 2 mTBI subjects excluded because of low scores on the effort test
- MMSE: 6/32 mTBI with score <28, 0/13 OIF controls
- Although there was individual variability, there were no group differences between blast and non-blast exposed OIF Veterans on:

Paragraph recall
Digit span forward
Digit span backward
Category fluency
WTAR

Trails A, Trails B
Wais Digit-symbol
Ruff 2 & 7
Sentence repetition

Genetic Markers in OIF mTBI and OIF Controls

	mTBI (N=34)	OIF Ctls (N=13)	p*
APOE Genotype			0.025
2,3	0	2 (15%)	
2,4	1 (3%)	0	
3,3	23 (68%)	4 (31%)	
3,4	9 (27%)	6 (46%)	
4,4	1 (3%)	1 (8%)	
At least 1 E4 allele	11 (32%)	7 (54%)	.2
BDNF Genotype			.7
C,C	21 (62%)	7 (54%)	
T,C	13 (38%)	6 (46%)	
TOMM-40 Poly-T length in (APOE-ε3/ε3)			.4
long/long	7 (30%)	2 (50%)	
short/long	14 (61%)	1 (25%)	
short/short	2 (9%)	1 (25%)	

Behavioral Assessments of OIF Veterans

- Clinician Administered PTSD Scale (CAPS)
- PTSD Checklist – Military (PCL-M)
- Patient Health Questionnaire (PHQ)-9
- Alcohol Use Disorders Identification Test – Consumption (AUDIT-C)
- Pittsburgh Sleep Quality Index (PSQI)
- Neurobehavioral Symptom Inventory (NSI)

Behavioral and Neurological Assessments of OIF Veterans

Measure	mTBI (N=34)	Ctls (N=13)	p*
CAPS Total Score	55.4 ± 31.2	5.0 ± 11.3	<.0001
PCL-M Total Score	49.9 ± 18.6	22.7 ± 4.6	<.0001
PHQ-9 Total Score	10.0 ± 7.5	2.5 ± 3.7	.0013
PSQI	9.4 ± 4.7	4.8 ± 3.9	.0027
AUDIT-C	4.9 ± 2.7	3.1 ± 1.8	.035
NSI Total Score	36.8 ± 23.1	7.4 ± 11.6	<.0001

*t-test

Neurobehavioral Symptom Inventory Item Frequency (%) Rated Moderate, Severe, or Very Severe in 35 OIF Veterans with mTBI and 13 OIF Veterans with No Blast Exposure

	TBI (N=35)	Control (N=13)	p*
Forgetfulness	71 %	31 %	.020
Difficulty falling or staying asleep	65 %	15 %	.0034
Feeling anxious or tense	65 %	15 %	.0034
Ringing in ears	65 %	0	<.0001
Irritability	62 %	15 %	.0078
Headaches	59 %	8 %	.0024
Hearing difficulty	53 %	0	.0006
Poor concentration/attention	53 %	8 %	.0067
Poor frustration tolerance	53 %	8 %	.0067
Sensitivity to noise	50 %	0	.0015
Feeling depressed/sad	50 %	15 %	.046

Quantification of Cumulative Blast Exposure (QCuBE)

- Numbers of exposures to blast
- Number of episodes of blast-concussion induced loss of consciousness (LOC)
- Date of first, last blast exposure
- History of non-blast head trauma (e.g., sports-related, motor vehicle accident)

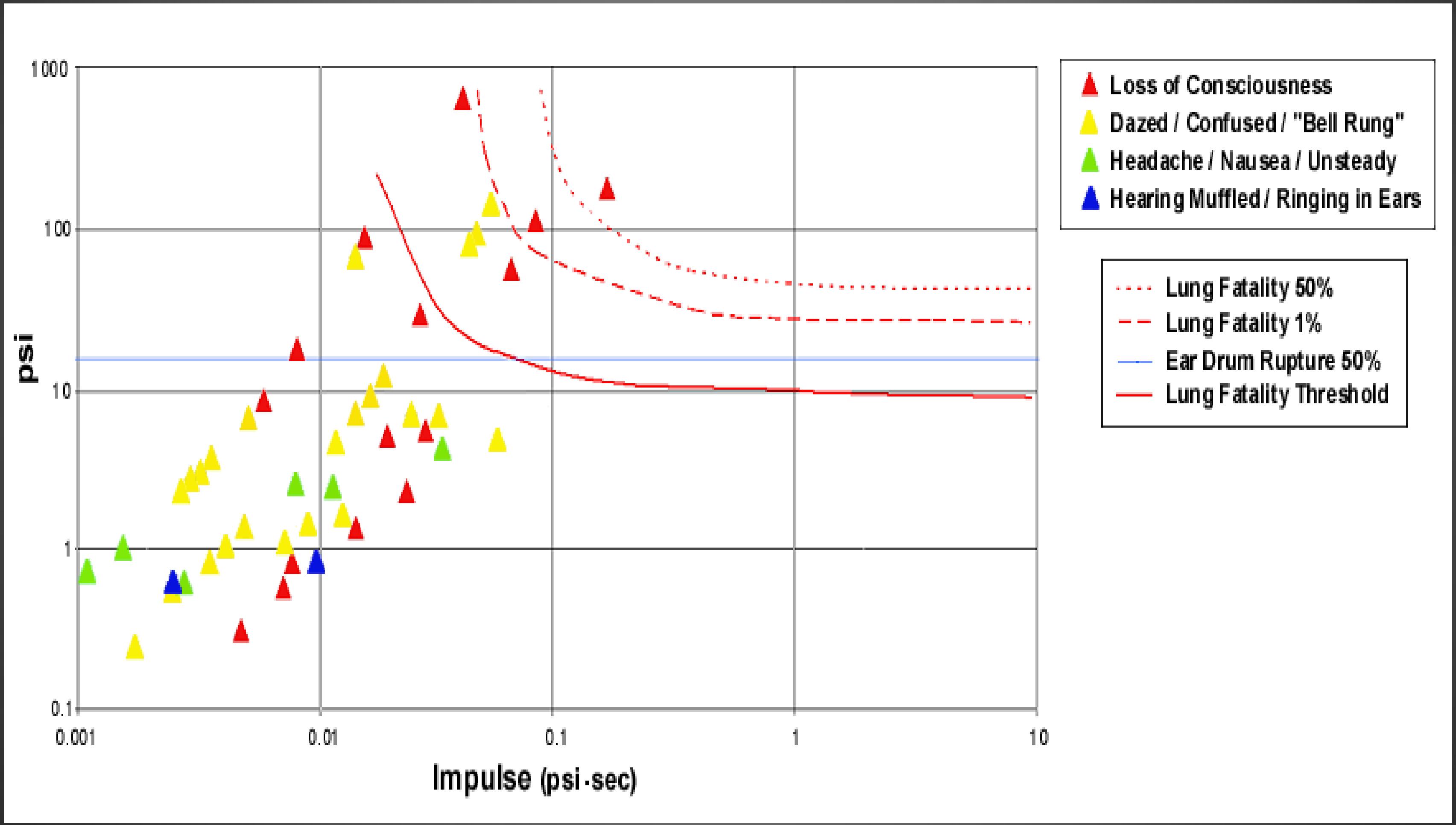
Quantification of Cumulative Blast Exposure (QCuBE) - continued

- Intensive characterization of worst 5 exposures
  - Type of explosive device
  - Distance from blast center
  - Tactical details, e.g.,:
    - Open air vs. in building or vehicle, head/body position relative to blast
    - Protective equipment
    - Secondary, tertiary TBI
  - Immediate symptoms
    - 4-point scale from LOC-severe-moderate-mild

QCuBE Variables

	mTBI (N=35)
# Blast exposures during Iraq deployment(s)	16.4 ± 18.7
# Blast exposures during all military service	39.4 ± 42.4
# Blast exposures with LOC during Iraq deployment	1.1 ± 1.2
# LOC during lifetime	6.4 ± 5.9
Time since last blast exposure (years)	3.9 ± 1.4
Symptom characteristics for “worst” 5 blasts	
1 or more exposures with LOC	65%
1 or more exposures with severe symptoms	91%
1 or more exposures with moderate symptoms	29%
1 or more exposures with mild symptoms	24%

Most Acute Blast Overpressure (BOP) Injuries Can Be Understood In Terms of Pressure and Impulse



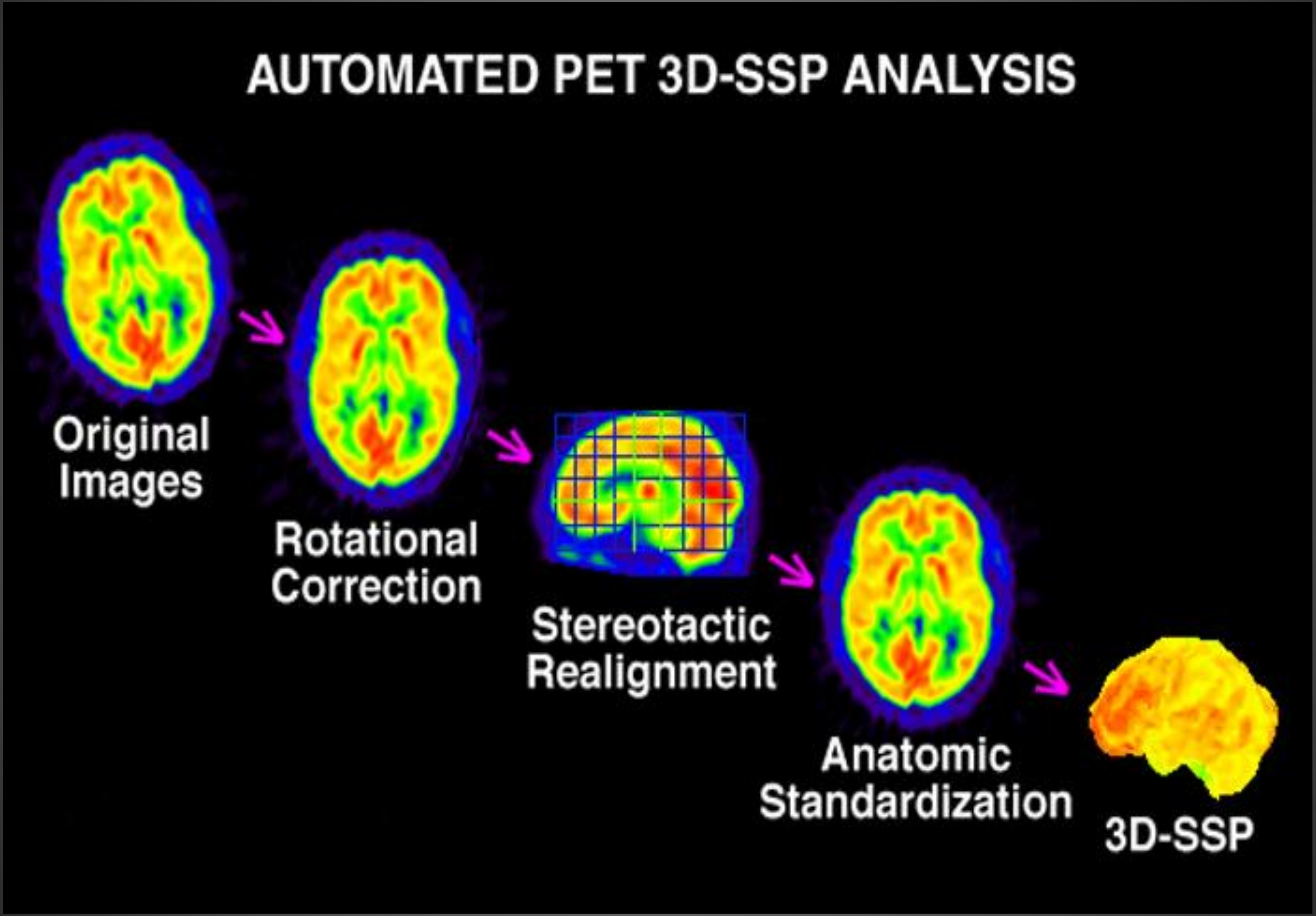
Neuroimaging Modalities

- Functional Neuroimaging:
  - [^{18}F]-Fluorodeoxyglucose Positron Emission Tomography ([^{18}F]-FDG-PET)
  - Resting State Blood Oxygen Level Dependent (BOLD)-functional Magnetic Resonance Imaging (fMRI)
- Structural Neuroimaging
  - Diffusion Tensor Imaging (DTI)
  - Cross Relaxation Imaging (CRI)

$[^{18}F]$-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

- Standard brain FDG-PET imaging protocol
  - 10 mCi $[^{18}F]$-FDG
  - 3D Image acquisition (GE Advance scanner)
- NEUROSTAT automated image pre-processing[1,2]
  - Automatic image co-registration
  - Linear scaling and non-linear warping to standard stereotactic coordinate space (Talairach & Tournoux)
  - 3-dimensional stereotactic surface projection (3D-SSP)
- Generation of 3D-SSP subtraction z-score images

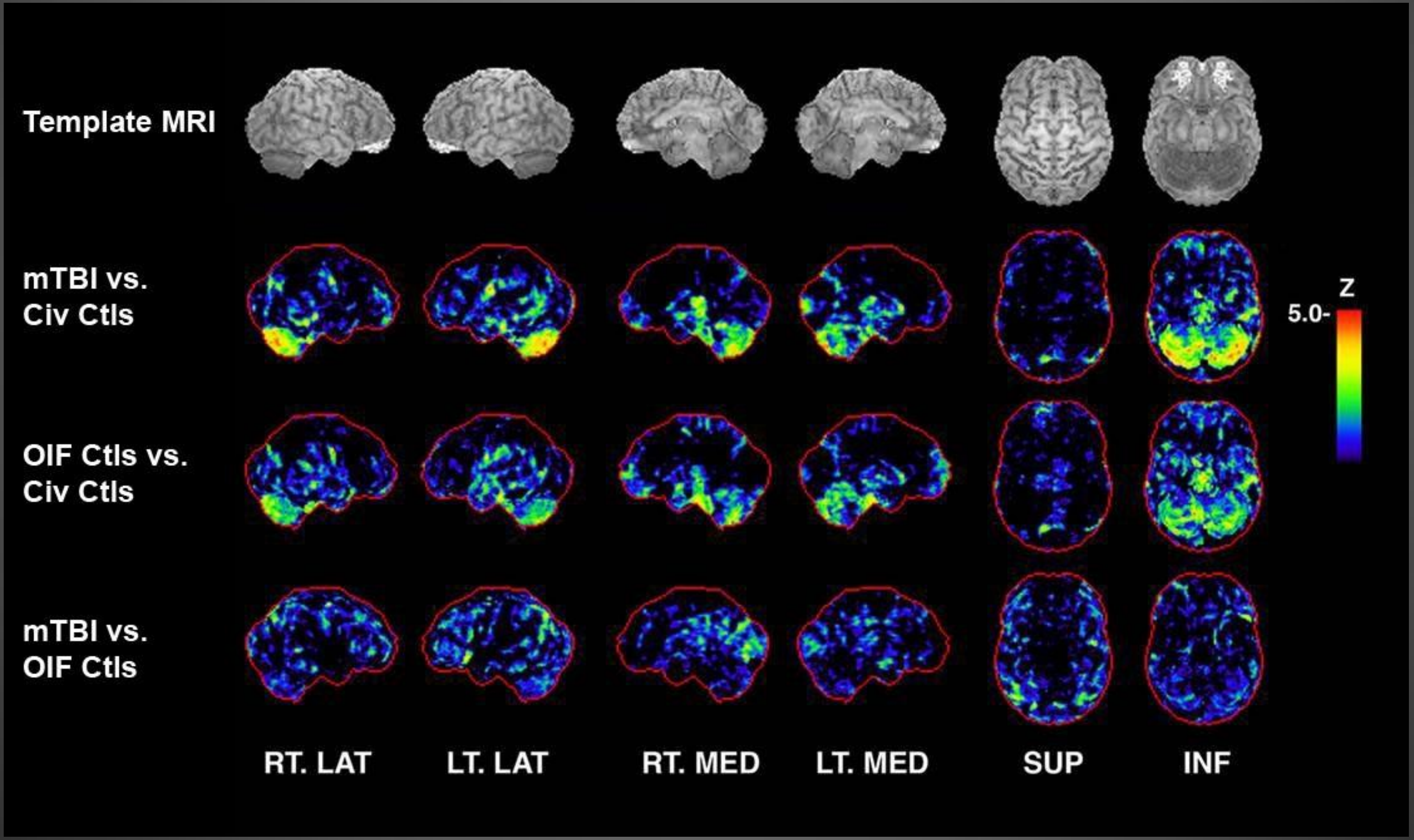
[1]Minoshima et al, J Nucl Med 35:1528-1536, 1994.
[2]Minoshima et al, J Nucl Med 36:1238-1248, 1995.


AUTOMATED PET 3D-SSP ANALYSIS
Original Images
Rotational Correction
Stereotactic Realignment
Anatomic Standardization
3D-SSP

[^{18}F]-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

- Data analysis:
  - Voxelwise analyses of differences between mTBI Veteran and control participants were performed with 2-sample t-tests; statistical significance evaluated using random fields approach to control Type I error rate approximately at p=0.05 (Z=3.5) for multiple comparisons
  - Significant differences and regional correlations in stereotactically-defined volumes-of-interest (VOIs) were compared with 2-sample t-tests and Bonferroni-corrected to control for multiple comparisons

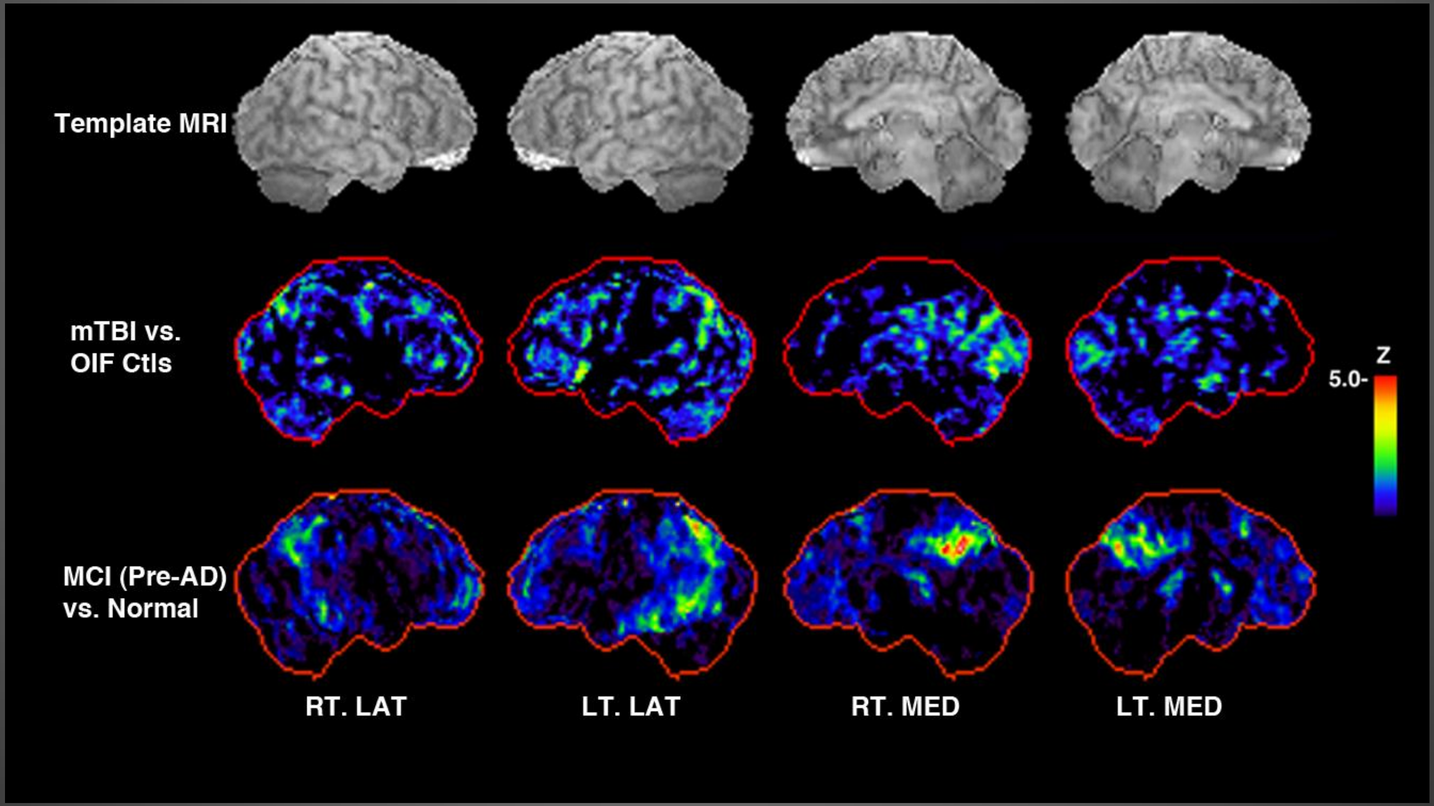
Composite Z-Score Map of Brain Glucose Hypometabolism in OIF mTBI Subjects (N=31) Compared to Community Volunteers (N=12) and to OIF-deployed Non-Blast Exposed Veterans (N=11)



Peskind et al, *Neuroimage* (2010 Apr 10, e-published ahead of print)

Results/Conclusions – FDG-PET Imaging

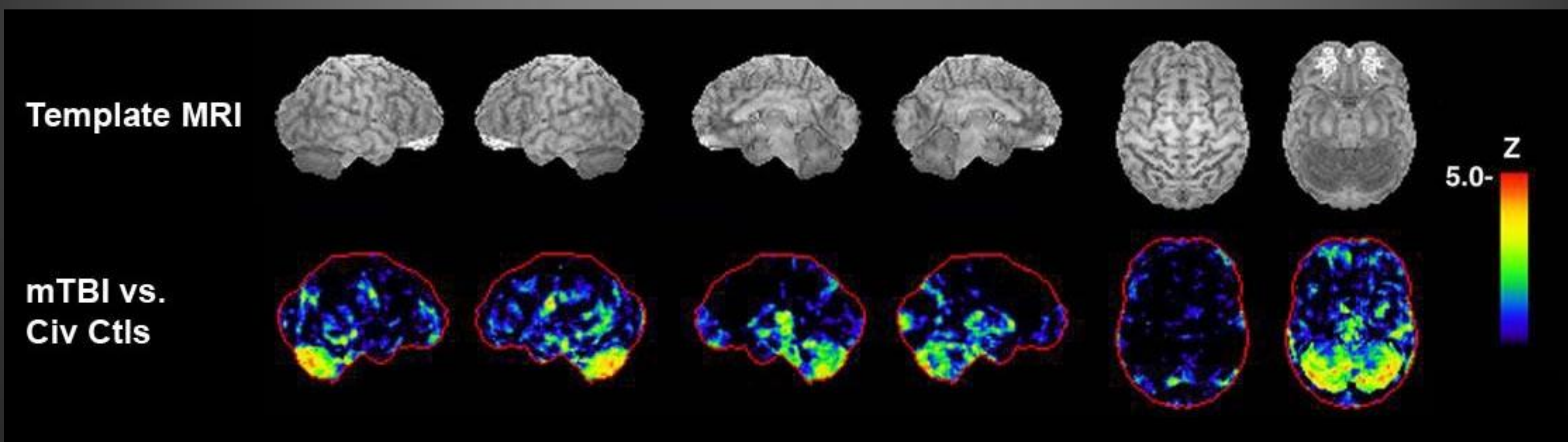
- Blast-exposed OIF Veterans compared to non blast-exposed OIF Veterans had significantly decreased metabolism in:
  - posterior cingulate (3.6%, p=0.005)
  - parietal cortex (2.6%, p=0.01)



MCI data from Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol* 1997; 42:85-94

Results - FDG-PET Imaging

- Compared to community controls, mTBI Veterans also showed hypometabolism in:
  - **medial temporal lobe** (4.3%, p=0.03)
  - **thalamus** (2.0%, p=0.003).



Results/Conclusions – FDG-PET Imaging

- 8 of 31 blast-exposed OIF Veterans did **not** meet DSM-IV criteria for PTSD using SCID-IV and Clinician Administered PTSD scale criteria.
- We performed a separate analysis within the blast exposed OIF veterans comparing those with and without PTSD.
- No differences in glucose metabolism were found in any brain region between OIF Veterans with blast-exposure who did or did not have PTSD.
- Changes in brain metabolism in the entire group were not the result of PTSD.

Results/Conclusions – FDG-PET Imaging

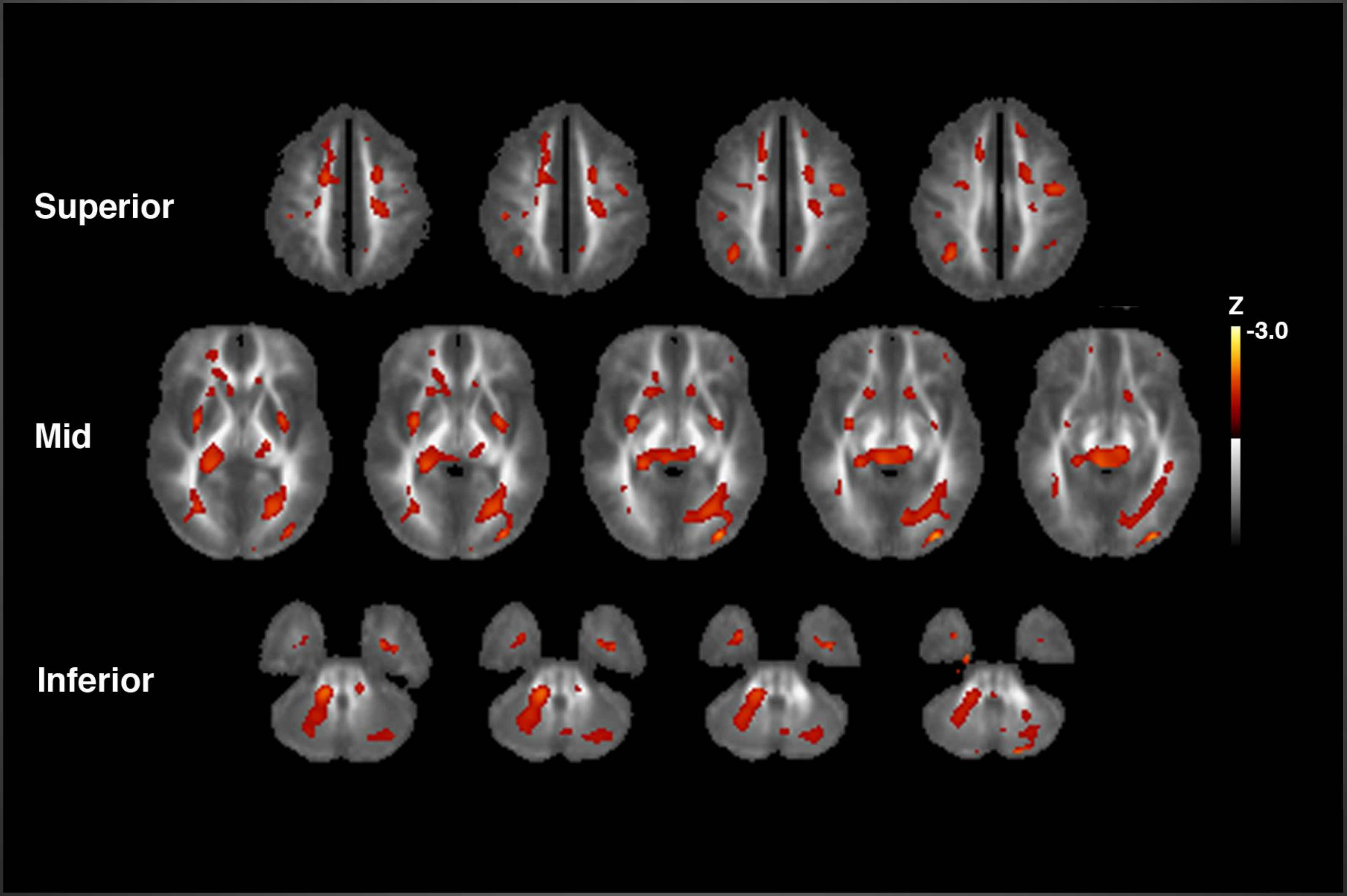
- Hypometabolism was found for both blast-exposed and non blast-exposed OIF Veterans compared to community controls in:
  - cerebellum (7.3%, $p=0.0003$)
  - **pons** (7.5%, $p=0.001$)
- Hypotheses/Speculation about etiology:
  - Pre-military vulnerabilities and military “lifestyle” (including other head trauma, alcohol misuse)
  - Effects of military training (e.g., combatives)
  - Hyperthermia in Iraq combat operations environment
  - High % of OIF non blast exposed controls with APOE-ε4 allele

Diffusion Tensor Imaging (DTI)

- Image acquisition:
  - 3T MR scanner (Achieva, Philips Medical Systems)
  - single-shot echo-planar sequence; TR=10.56 sec; TE=60ms; flip angle=80°; matrix size=128x128; FOV=240x240; slice thickness=3mm; 32 gradient directions, non-diffusion weighted b0 map, and b-factor set at 1000 s/mm^2.
- Image Processing (NEUROSTAT[1,2])
- Correction for motion and eddy current artifacts
- B0 map unwarping performed and tensors fit using b-factor and diffusion direction matrix with DTIfit toolbox.
- FA indices calculated for each voxel, producing whole brain diffusion weighted FA maps.
- Automated image linear scaling/non-linear warping to Talairach stereotactic coordinate space

[1]Minoshima et al, J Nucl Med 35:1528-1536, 1994.
[2]Minoshima et al, J Nucl Med 36:1238-1248, 1995.

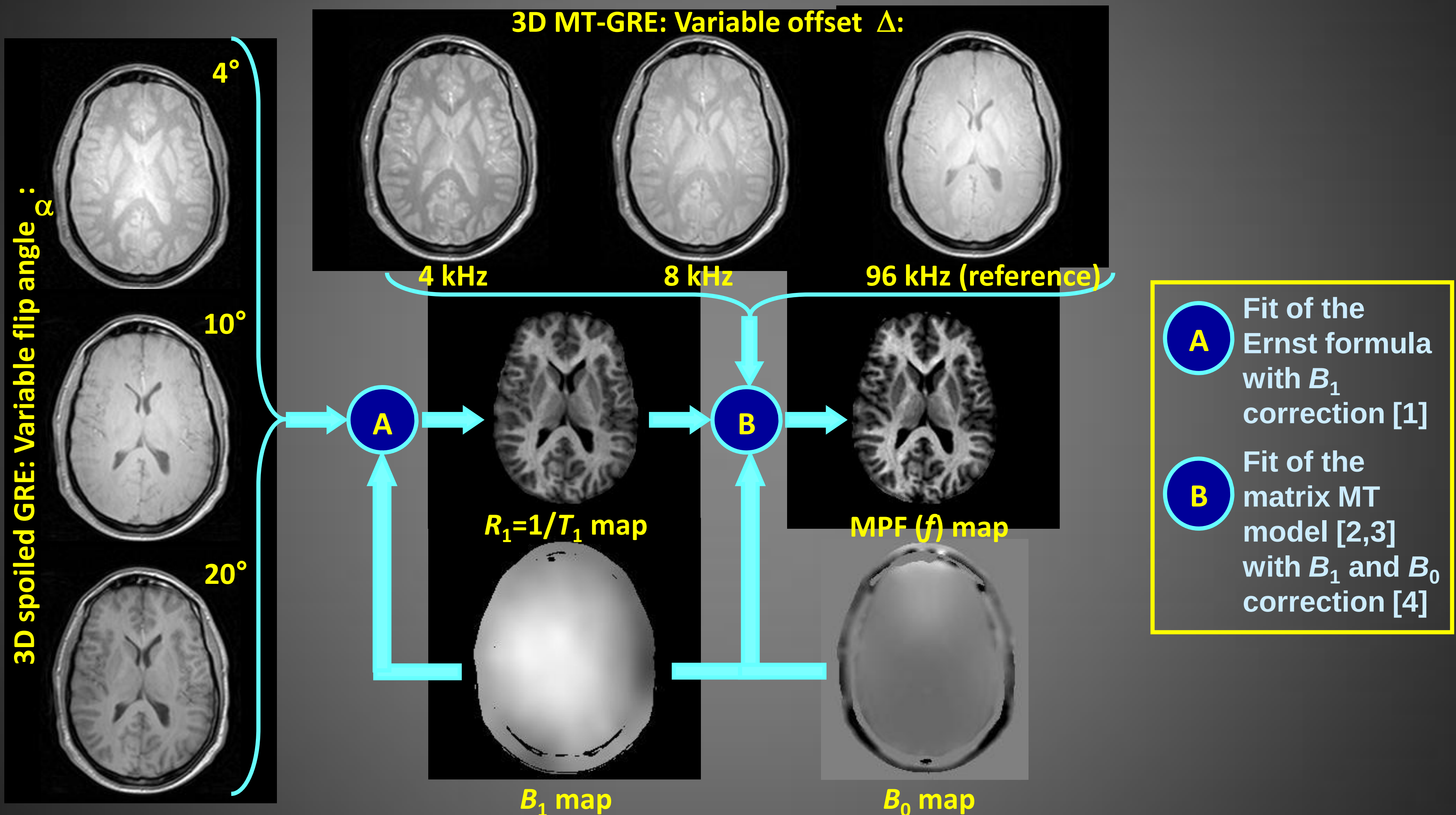
DTI detects significant decreases in white matter structural integrity in OIF blast-exposed veterans (N=21) compared to OIF non-blast exposed veterans (N=10)



Results/Conclusions – DTI

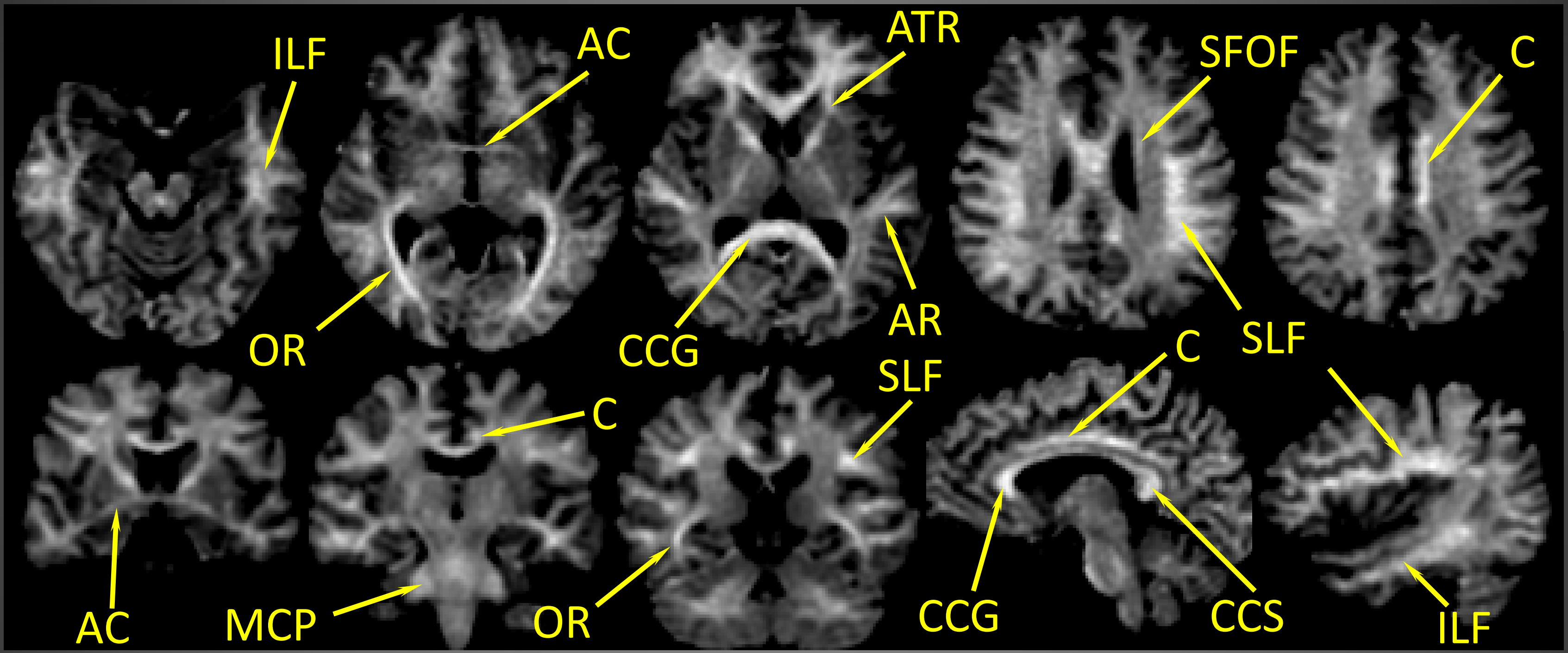
- Results: FA maps suggest white matter dysintegrity in:
  - optic radiations $p=0.00025$
  - cerebellar peduncles $p=0.0004$
  - inferior longitudinal fasciculus $p=0.001$
  - brainstem $p=0.005$
- Conclusions:
  - Preliminary findings from groupwise analysis of white matter integrity suggest underlying white matter substrate for glucose metabolic differences
  - These relationships need to be explored further

Cross-Relaxation Imaging (CRI) method: Fast Macromolecular Proton Fraction (*f*) mapping



[1]Yarnykh VL. *Magn Reson Med* 2007; 57: 192. [2]Yarnykh VL. *Magn Reson Med* 2002;47:929. [3]Yarnykh VL, Yuan C. *NeuroImage* 2004;23:409. [4]Underhill HR et al. *NeuroImage* 2009;47:1568

Macromolecular proton fraction maps reveal detailed anatomy of fiber tracts

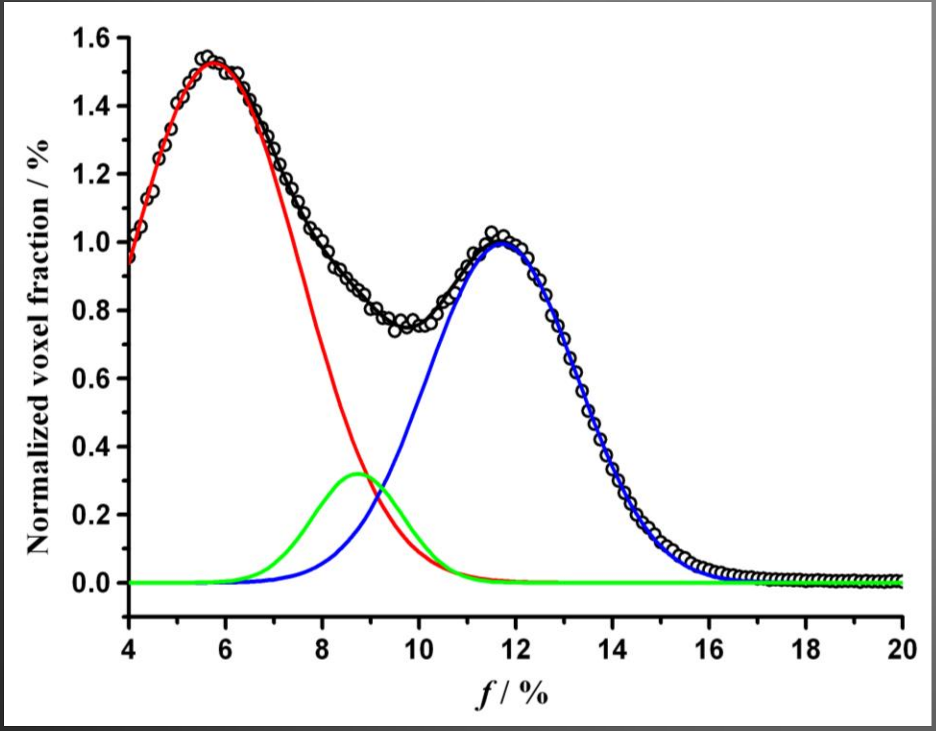


ILF-inferior longitudinal fasciculus; OR-optic radiations; AC-anterior commissure; CCG-corpus callosum, genu; CCS-corpus callosum, splenium; AR-auditory radiations; ATR-anterior thalamic radiations; SLF-superior longitudinal fasciculus; SFOF-superior fronto-occipital fasciculus; C-cingulum; MCP-middle cerebellar peduncle.

Yarnykh VL, Yuan C. *NeuroImage* 2004; 23:409

CRI: Analysis of Whole-brain Macromolecular Proton Fraction (f) Histograms

Superposition of three Gaussian components:



Fitted parameters:

- **peak positions f_i**
- **peak widths w_i**
- **peak areas A_i**

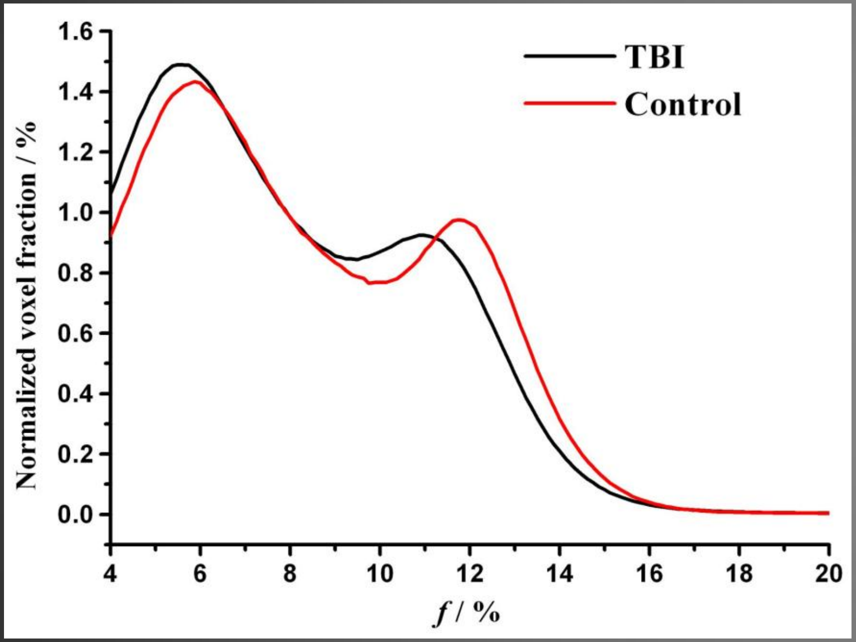
Components describe:

- **White matter (WM)**
- **Gray matter (GM)**
- **Mixed WM and GM (Mixed) such as GM structures with high axonal density (e.g., thalamus) or WM-GM junction regions**

Yarnykh VL et al. *Proc ISMRM* 2010: 4342

Cross-Relaxation Imaging Analysis

Macromolecular Proton Fraction (*f*) Histogram Parameters for OIF blast-exposed OIF Veterans (N=27) vs. non-blast exposed OIF Veterans (n=12)



Plot of group mean whole-brain MPF (*f*) histograms for OIF mTBI (n=27) vs. OIF-non blast-exposed (n=12) Veterans

Macromolecular Proton Fraction (*f*) Histogram Parameters (mean ± SD)				
	Parameter	mTBI	Controls	p[a]
GM	f_1 (%)	**5.56±0.35**	5.86±0.26	**0.014[b]**
	w_1 (%)	3.73±0.58	3.99±0.64	0.20
	A_1	6.91±0.68	7.04±0.53	0.50
WM	f_2 (%)	**11.17±0.66**	**11.90±0.38**	**0.0001[b]**
	w_2 (%)	3.00±0.58	2.85±0.40	0.40
	A_2	3.59±0.68	3.38±0.30	0.30
Mix	f_3 (%)	**8.36±0.60**	**9.03±0.35**	**0.0001[b]**
	w_3 (%)	1.87±0.53	1.84±0.31	0.90
	A_3	0.70±0.47	0.78± 0.48	0.60

[a]Independent two-tailed t-test
[b]Significant after Bonferroni correction

Conclusions - CRI

- Observed reductions of bound pool fractions in white matter, gray matter, and mixed white-gray matter histogram components is consistent with the mechanism of diffuse axonal injury.
- These reductions suggest alterations of myelin structure in white matter tracts known to be vulnerable to damage in diffuse axonal injury.
- Histogram parameters of the macromolecular proton fraction have potential as prospective quantitative biomarkers of blast-induced mTBI.

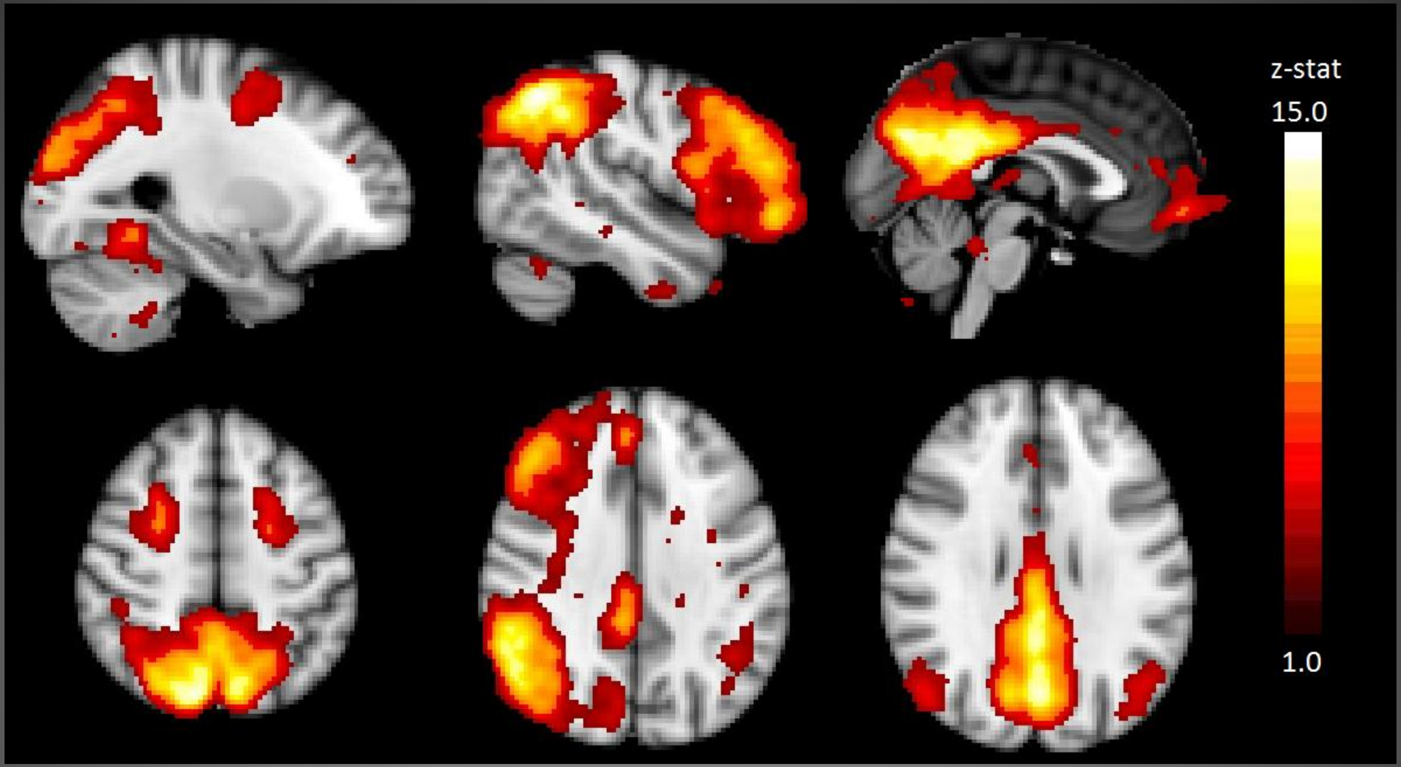
Resting State BOLD-fMRI - Methods

- Participants
  - 20 blast-exposed OIF mTBI Veterans and 6 non-blast exposed OIF Veterans (controls)
- Resting state (task free or default-state) BOLD- fMRI scans collected
  - 225 volumes/7 min 30s each
- Preprocessing step
  - High pass filter cutoff: 100 sec
  - MCFLIRT: Image Registration
  - Spatial Smoothing 5mm
  - CSF filtering for physiological correction
  - Created separate masks of each network

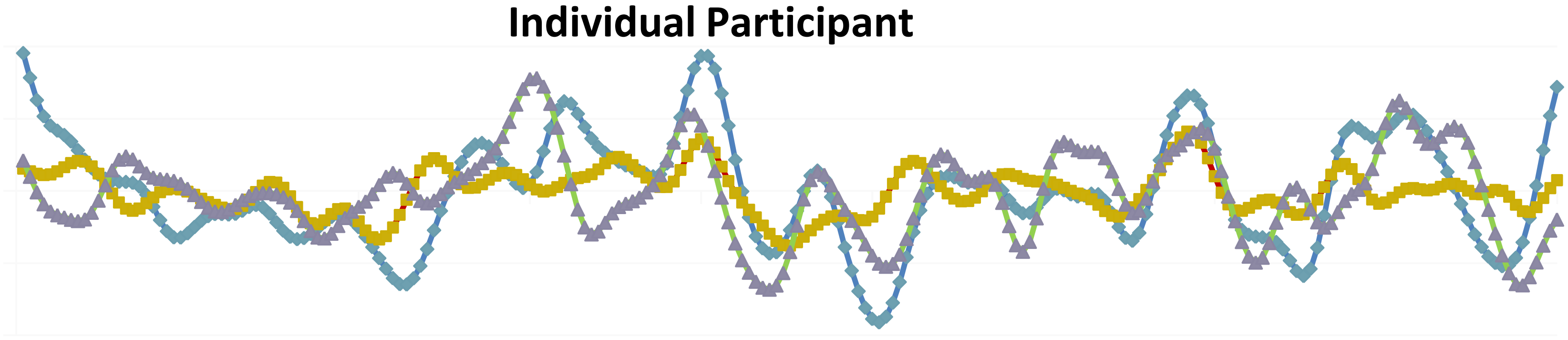
Resting State BOLD-fMRI - Methods

- Created masks of Resting State Networks (RSN) for seed point analyses
  - Group MELODIC Multi-session temporal concatenation (ICA approach)
    - Identifies components with common spatial patterns without assuming a consistent temporal response between participants
    - Identified the default network (DN), the dorsal attention network (DAN), and right lateralized ventral attention network (VAN)
    - Created separate masks of each network
- Conducted Seed point–based functional connectivity analyses within FSL
    - Extracted the fMRI timeseries from the voxels included in the mask for each participant
    - Entered the normalized timeseries as a model into FEAT FMRI expert analysis tool
    - Performed between-group comparisons of each RSN
    - Performed correlations between RSN and neuropsychological variables in the TBI group

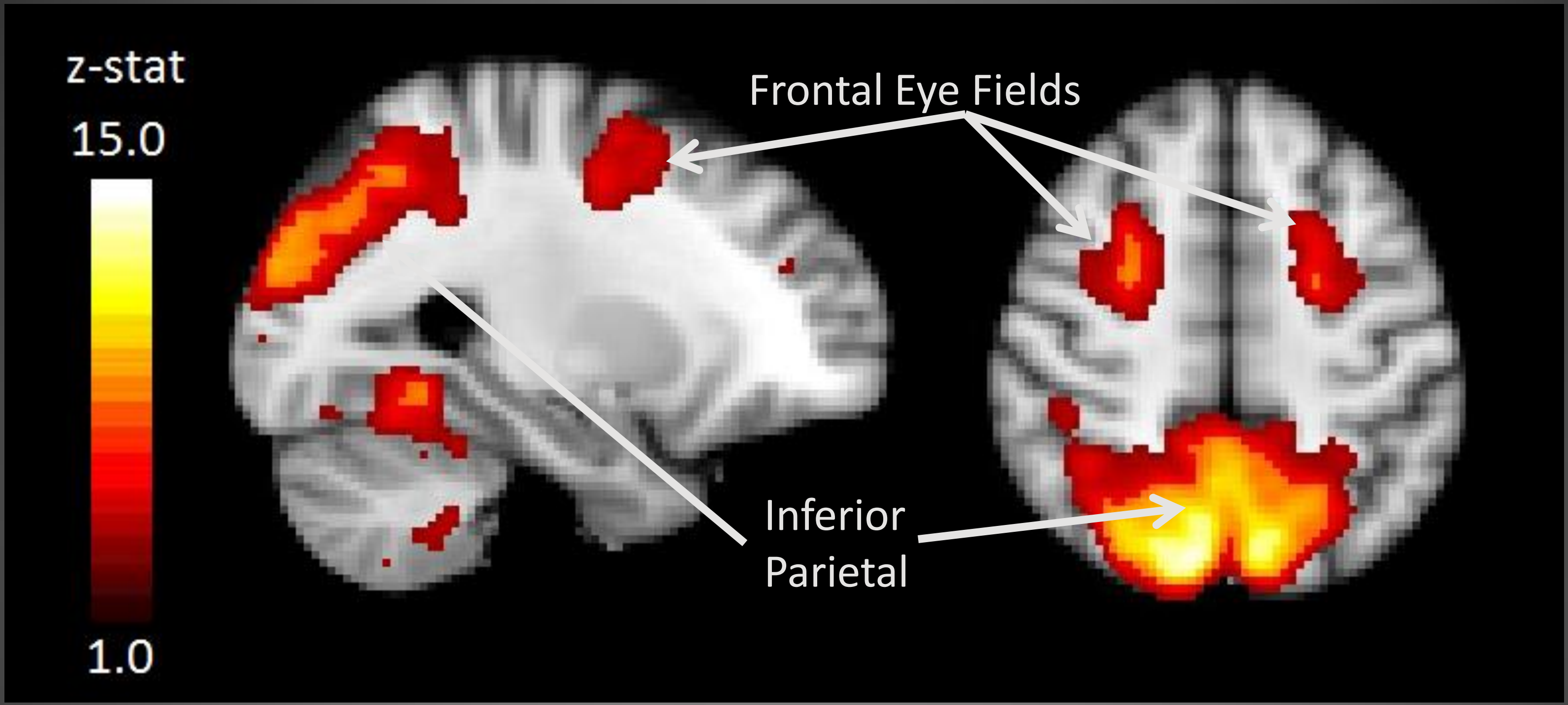
TBI Group Resting Networks

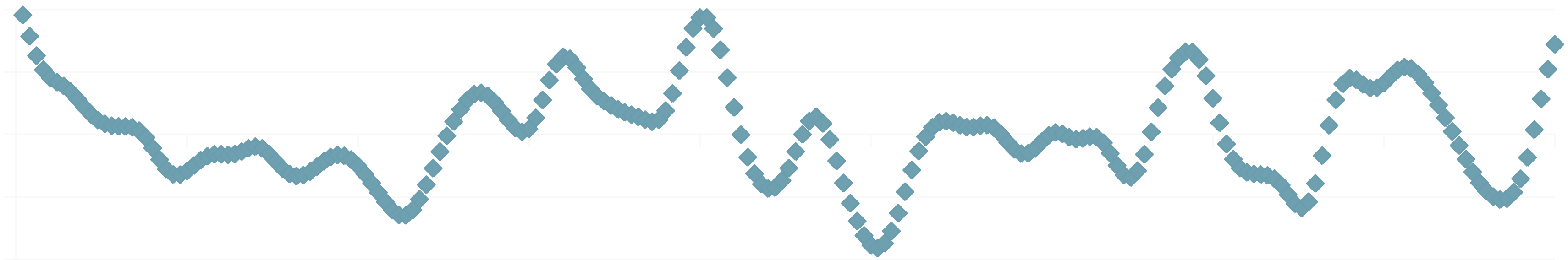


DAN VAN DN

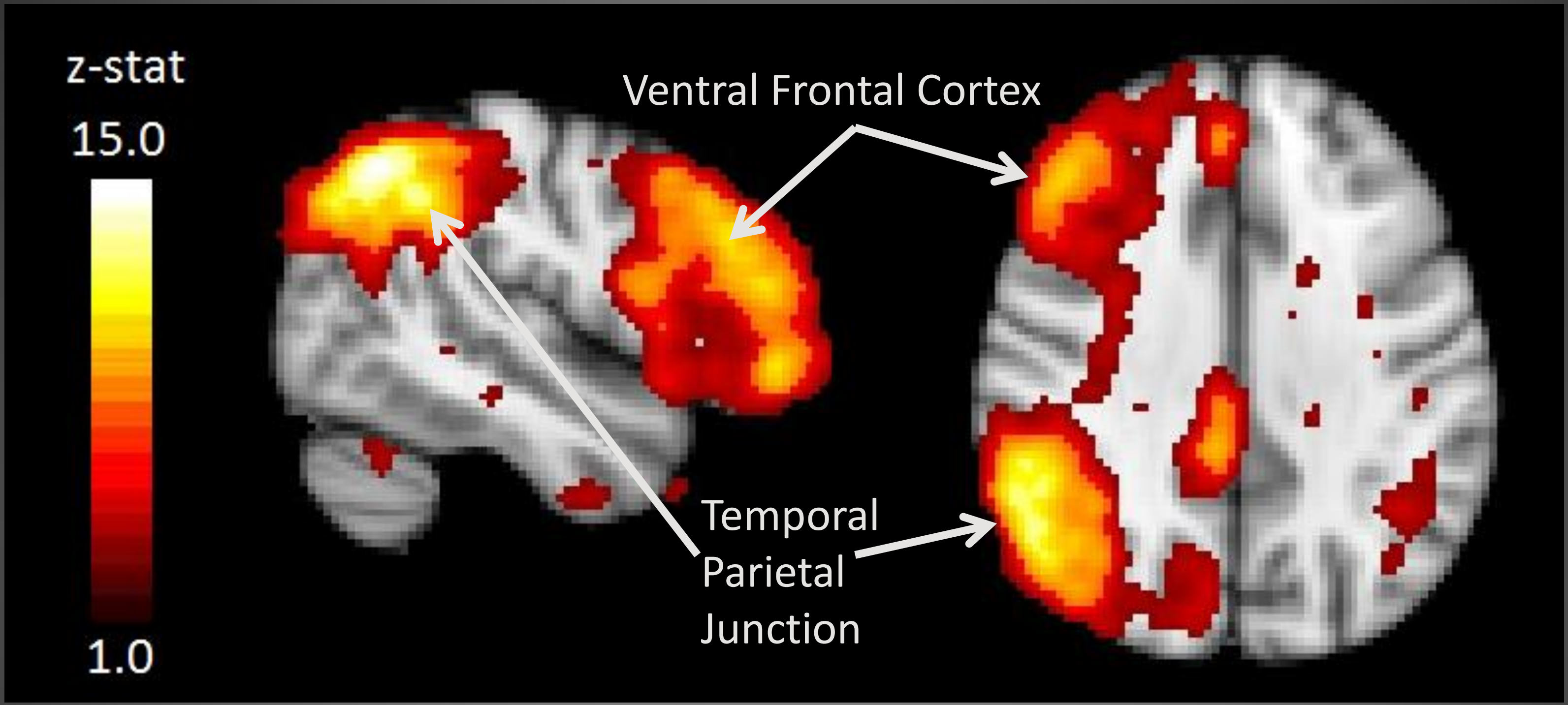


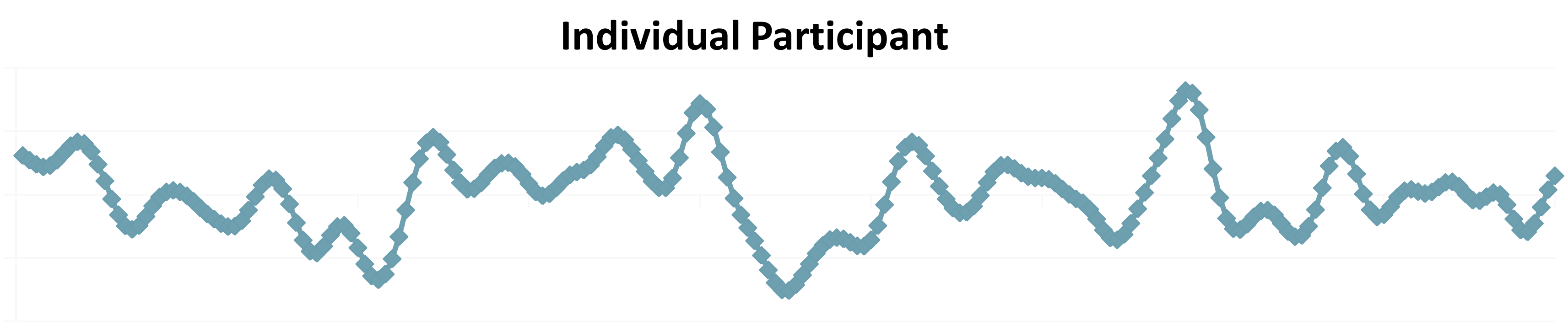
TBI Group Dorsal Attention Network (DAN)



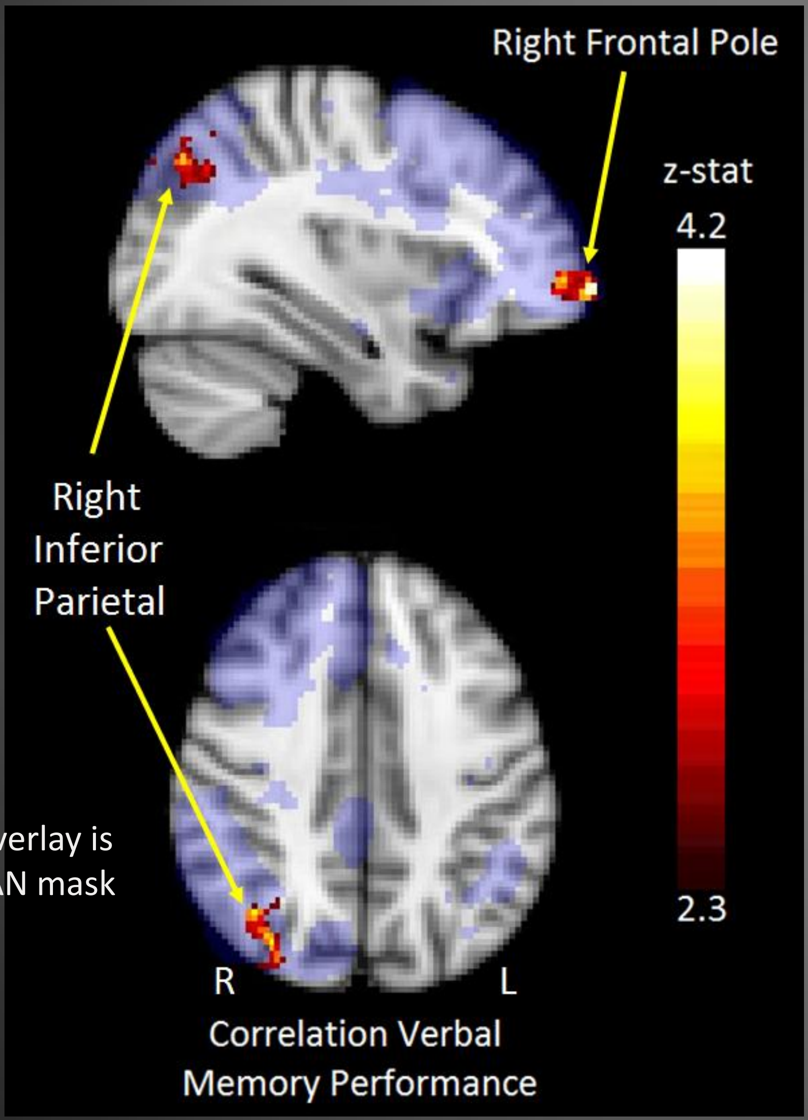


TBI Group Ventral Attention Network (VAN)

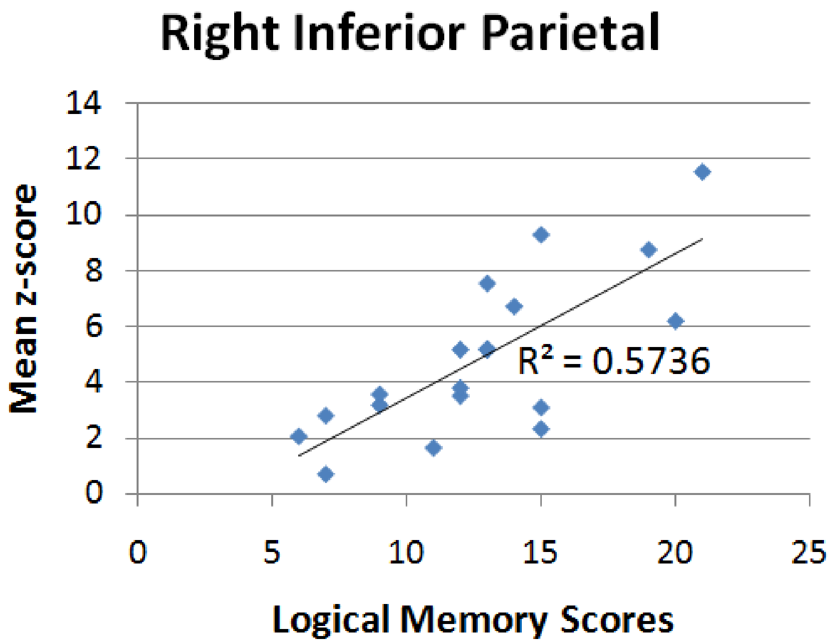


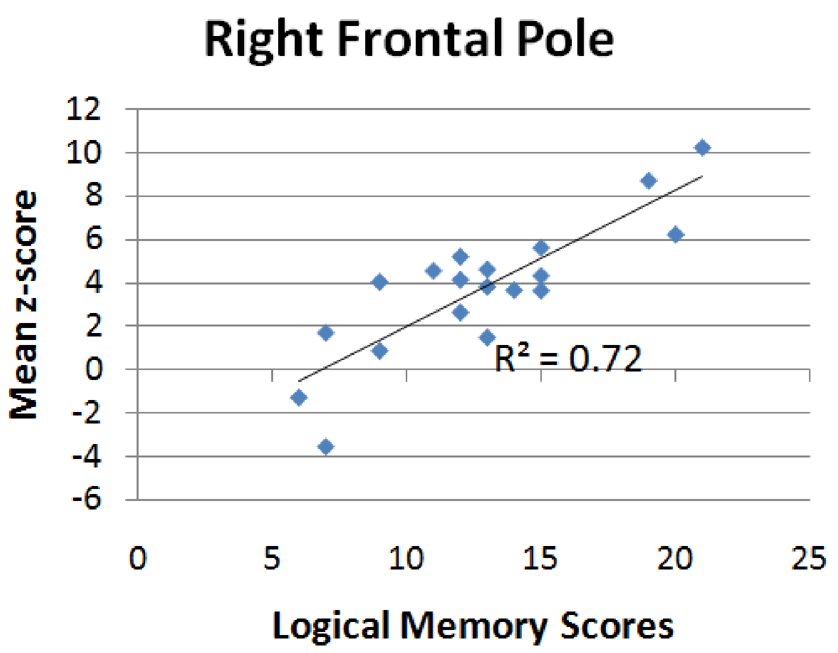


Reduced VAN Connectivity and Memory Impairment in TBI

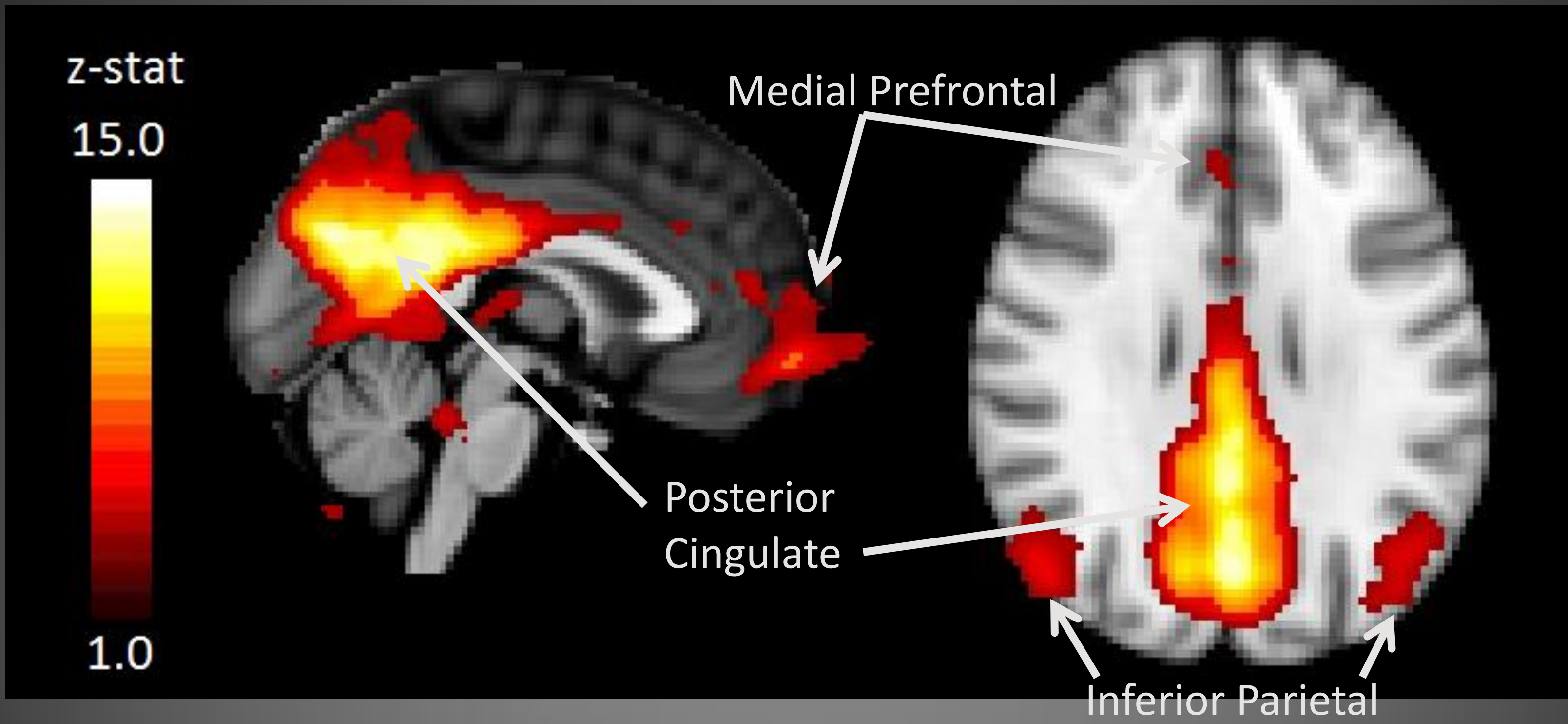


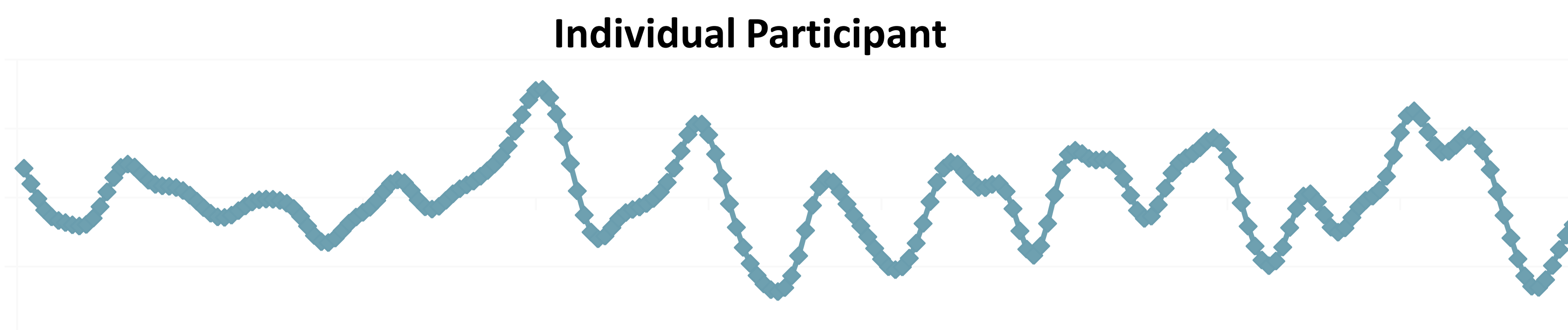
Blue overlay is the VAN mask



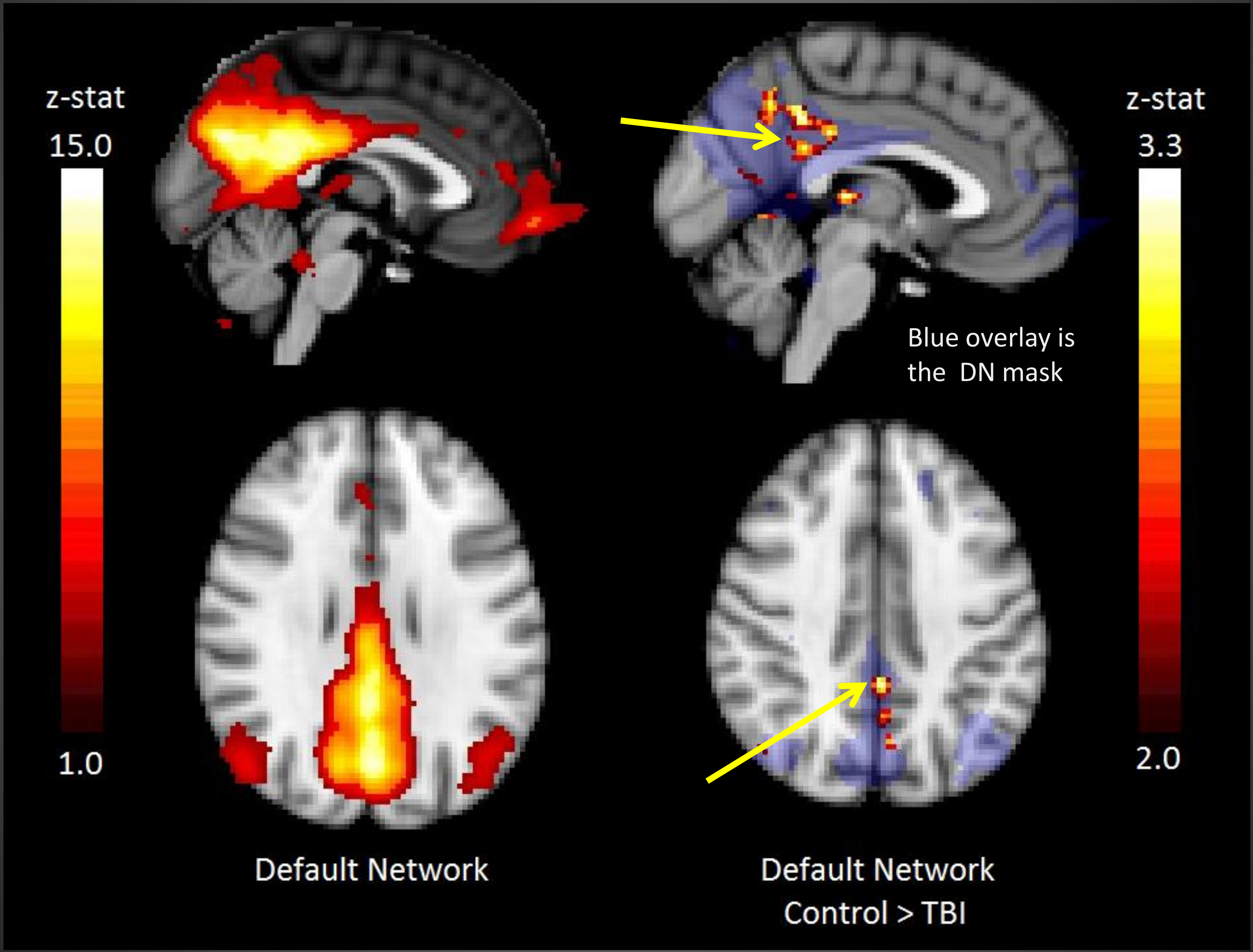


TBI Group Default Network (DN) component





Reduced Connectivity in the Default Network



Conclusions – BOLD-fMRI

- Evidence for reduced connectivity within the Ventral Attention Network, which correlates with performance on an immediate memory task.
- Preliminary evidence of reduced connectivity in the posterior cingulate and parietal lobes in mTBI in which FDG-PET showed glucose hypometabolism.
- This strong preliminary evidence is consistent with findings on FDG-PET, DTI, and CRI.
- However, there are limitations:
  - Small sample size, particularly for non blast-exposed OIF Veterans
  - Potential other sources of variability: psychiatric comorbidities, military training, hyperthermia, etc., etc.

Cerebrospinal Fluid Biomarkers in OIF mTBI and OIF Controls

	mTBI (n=26)	**OIF Ctls (N=8)**	**p***
Protein	45.6 ± 21.1	31.2 ± 11.7	.078
Glucose	60.6 ± 4.5	58.2 ± 4.0	.2
RBCs	3 ± 4	1 ± 1	.3
$A\beta_{42}$	480 ± 168	422 ± 136	.4
Total tau	63 ± 19	58 ± 19	.5
P-tau_{181}	61 ± 15	57 ± 19	.5

Summary and Conclusions

- The structural imaging modalities, both CRI and DTI, and functional imaging with FDG-PET are starting to provide a coherent picture of **diffuse axonal injury** and corresponding focal **hypometabolism** in brain regions of high connectivity.
- BOLD-fMRI suggests complementary decreased connectivity in these brain regions.
- The pattern of **functional** deficits is **reminiscent** of very early changes seen in Alzheimer's disease

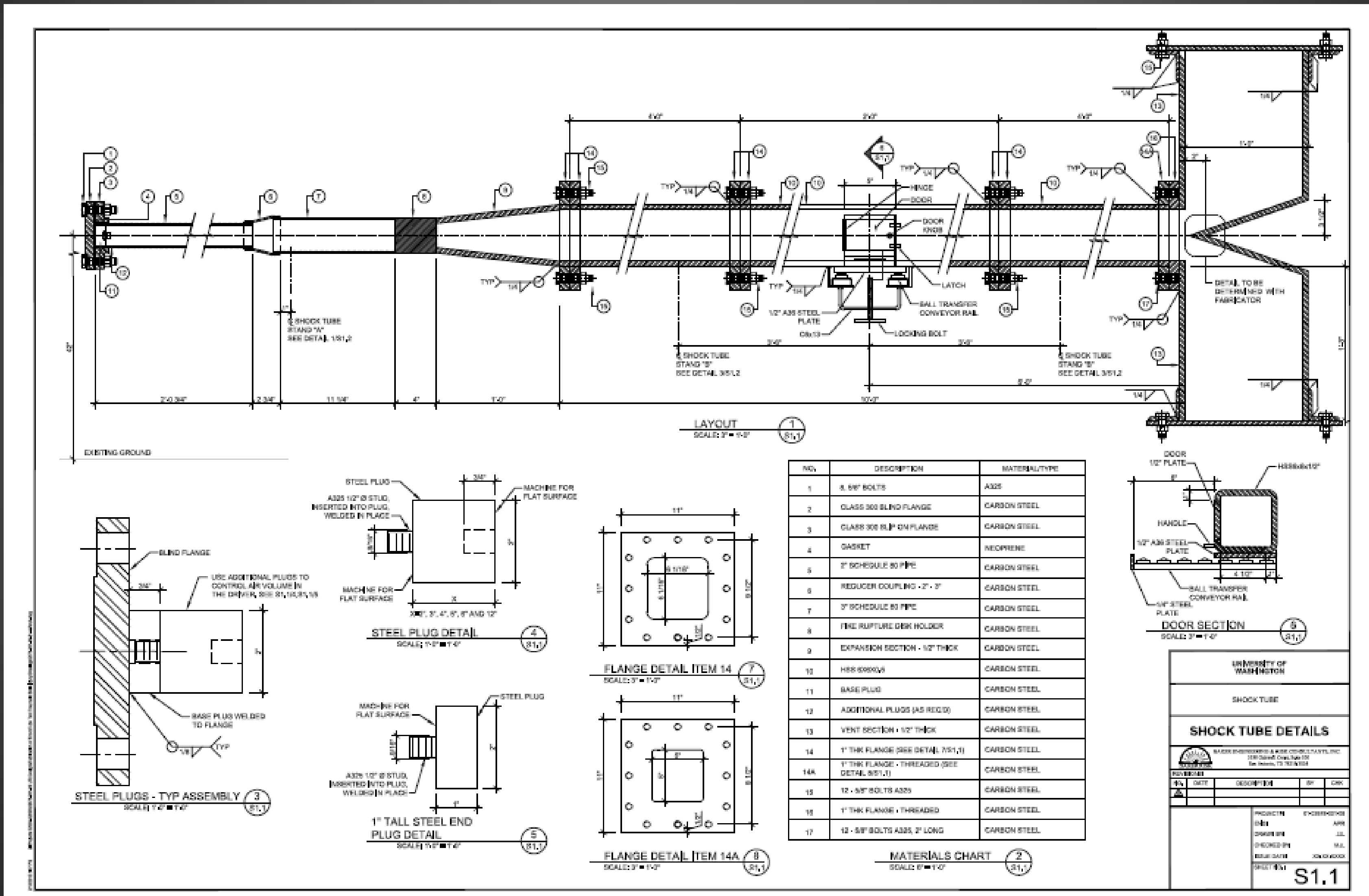
Summary and Conclusions

- Caution needed!
  - no evidence of convincing neuropsychological test performance deficits at the group level
  - 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!

Future Plans

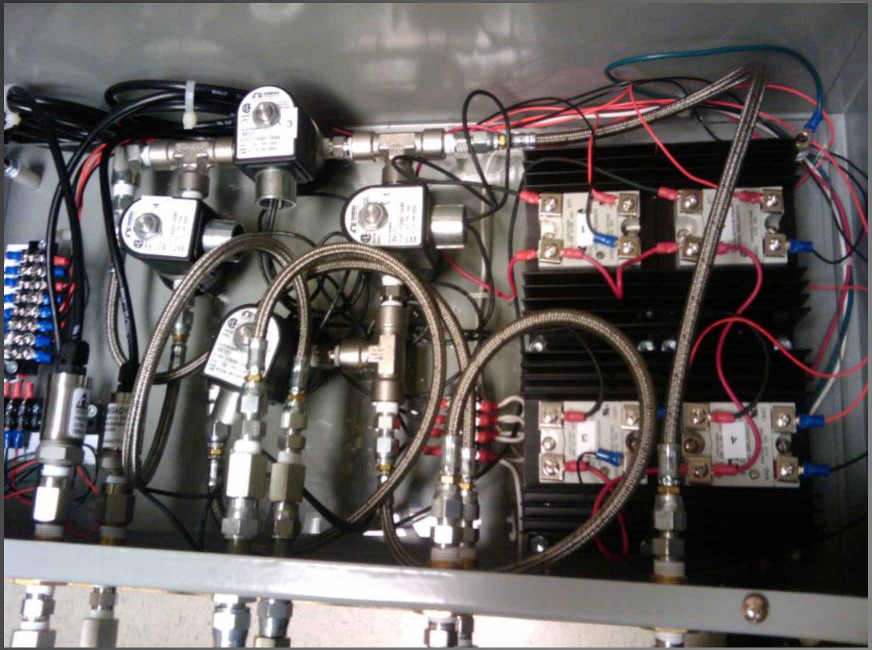
- Additional control groups: mTBI without PTSD, PTSD without mTBI, aged-matched community controls, repetitive sports-related concussion
- Further CSF biomarker measurements
  - Normative sample of >150 community controls (age 21-50) already collected
  - Measurements of neurofilament low molecular weight protein, F-2 isoprostanes, BDNF, IL-6, IL-8, β_2 macroglobulin, broad scale proteomics.
- Assessment of pituitary function
- Longitudinal follow-up
- Mouse model of repetitive blast concussion

A novel shock tube currently under construction has been designed to replicate the blast forces OIF/OEF Veterans with mTBI have experienced



NO.	DESCRIPTION	MATERIAL/TYPE
1	8, 5/8" BOLTS	A325
2	CLASS 300 BLIND FLANGE	CARBON STEEL
3	CLASS 300 SLIP ON FLANGE	CARBON STEEL
4	GASKET	NEOPRENE
5	2" SCHEDULE 80 PIPE	CARBON STEEL
6	REDUCER COUPLING - 2" - 3"	CARBON STEEL
7	3" SCHEDULE 80 PIPE	CARBON STEEL
8	FIKE RUPTURE DISK HOLDER	CARBON STEEL
9	EXPANSION SECTION - 1/2" THICK	CARBON STEEL
10	HSS 6X6X0.5	CARBON STEEL
11	BASE PLUG	CARBON STEEL
12	ADDITIONAL PLUGS (AS REQ'D)	CARBON STEEL
13	VENT SECTION - 1/2" THICK	CARBON STEEL
14	1" THK FLANGE (SEE DETAIL 7/S1.1)	CARBON STEEL
14A	1" THK FLANGE - THREADED (SEE DETAIL 8/S1.1)	CARBON STEEL
15	12 - 5/8" BOLTS A325	CARBON STEEL
16	1" THK FLANGE - THREADED	CARBON STEEL
17	12 - 5/8" BOLTS A325, 2" LONG	CARBON STEEL

Shock Tube Control Unit



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

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