MICHAEL E. DeBAKEY VETERANS AFFAIRS MEDICAL CENTER

Neurorehabilitation: Neurons to Networks
Traumatic Brain Injury Center of Excellence

BCM
Baylor College of Medicine

Brain Imaging of Veterans and Service Members with Chronic Mild TBI

Harvey Levin, PhD

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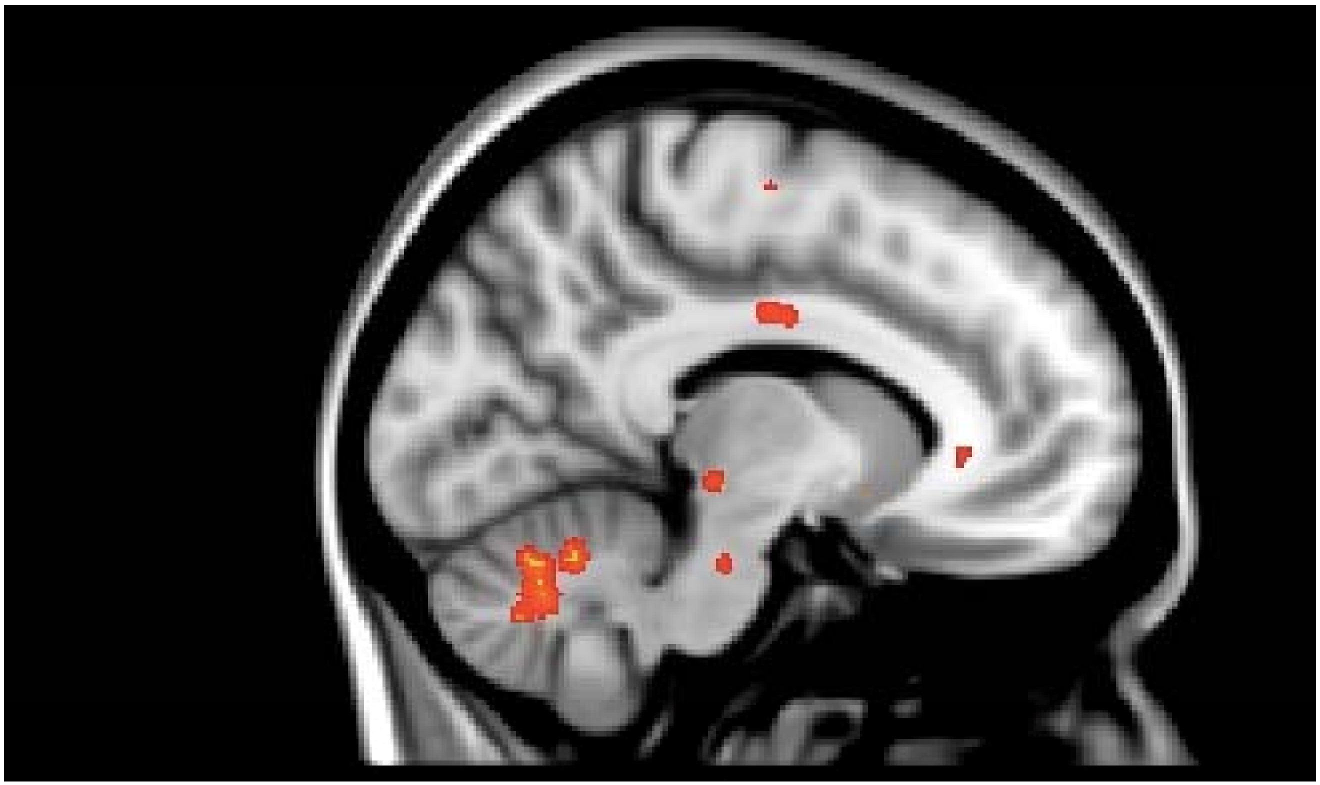
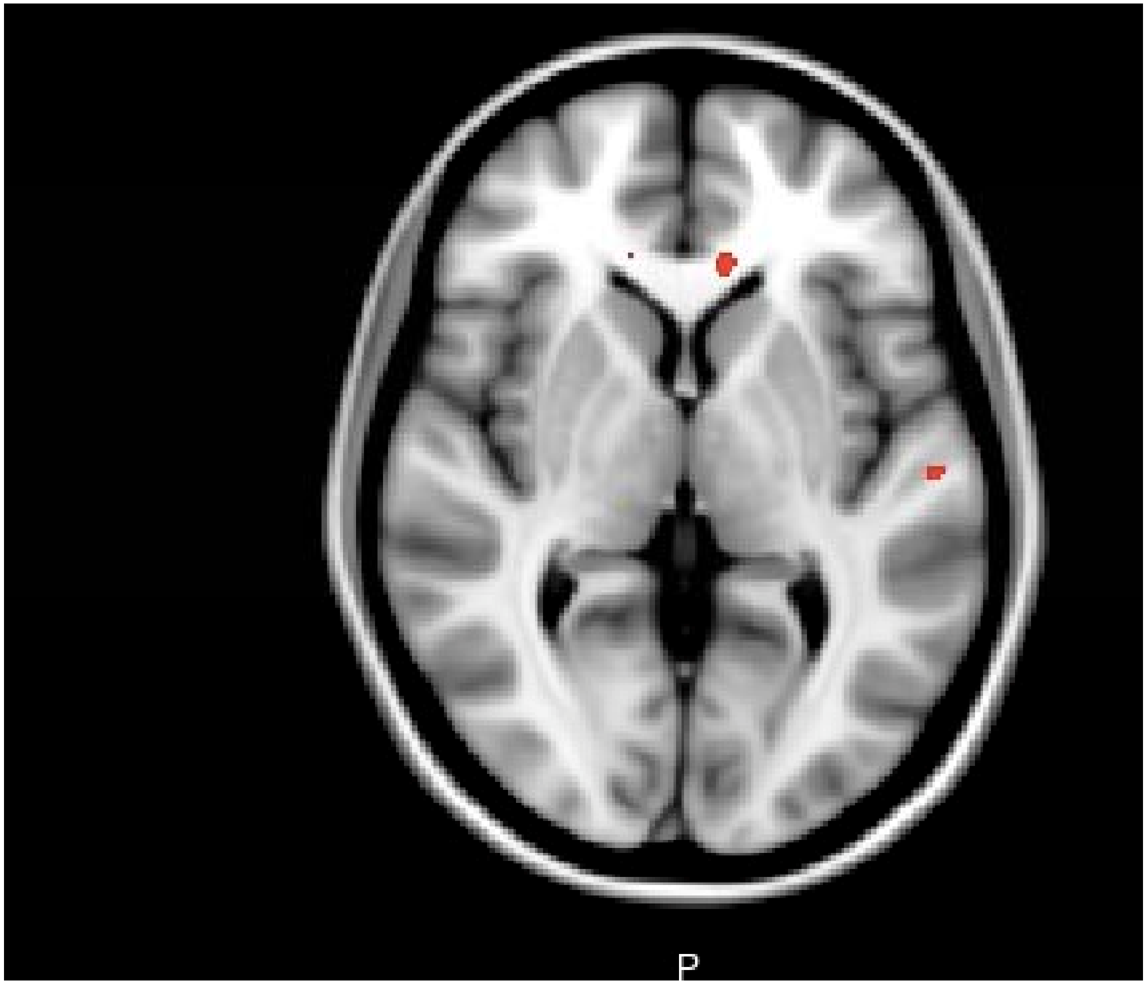
Challenges in Diagnosing Chronic mTBI in OEF/OIF/OND Veterans

- Diagnosis often relies on self-report without acute medical records; co-morbid PTSD/depression partially overlap in sx with mTBI. Substance abuse could affect MRI findings.
- Lack of reference data to identify subtle cortical atrophy and reduced brain region volumes on MRI; DTI metrics have similar issue.
- DTI metrics are potentially robust imaging biomarkers for mTBI, but center differences in equipment, software, QA, and method of analysis

DTI Data from Ongoing Merit Review Project of Chronic mTBI in Veterans

- Used tract based spatial statistics (TBSS) to compare mTBI (n=19) with post-deployed group without TBI (n=13) who were not exposed to blast.
- Fractional anisotropy (FA), a metric which reflects preferential diffusion of water parallel to tract, shows areas of reduced integrity of microstructure including corpus callosum, brain stem, and cerebellum.

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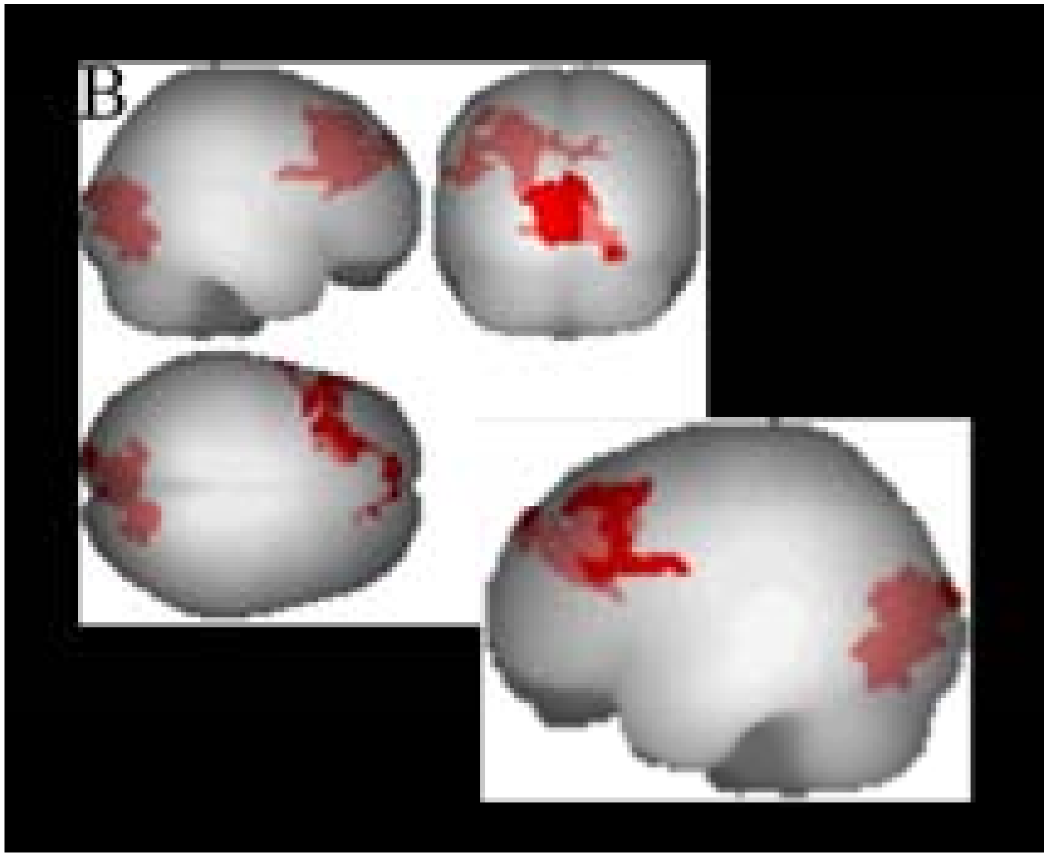
Preliminary fcMRI Findings

- Four male Veterans who sustained mTBI due to blast.
- Four male Veterans who were not exposed to blast and had no history of TBI served as control subjects.
- These small groups did not differ in age or education.
- In the scanner, subjects were instructed to close their eyes but not fall asleep.

Default Mode Network (DMN) mTBI>Controls



Note the atypical lateral region outside of the DMN reported in civilians with subacute mTBI (Mayer et al., 2011).

Altered brain activation in military personnel after ≥1 TBI from blast. Scheibel et al (JINS 2012, 18:89-100)

- Compared OEF/OIF groups with TBI (n=15) vs no TBI on stimulus-response compatibility task.
- TBI was co-morbid with high PTSD symptoms
- Pressed button on side pointed to by blue arrows, but opposite of red arrow direction
- TBI group had more activation in mesial prefrontal cortex, anterior cingulate gyrus and posterior regions after statistically controlling for group differences in PTSD, depression and RT .
- PTSD dampened frontal-temporal activation

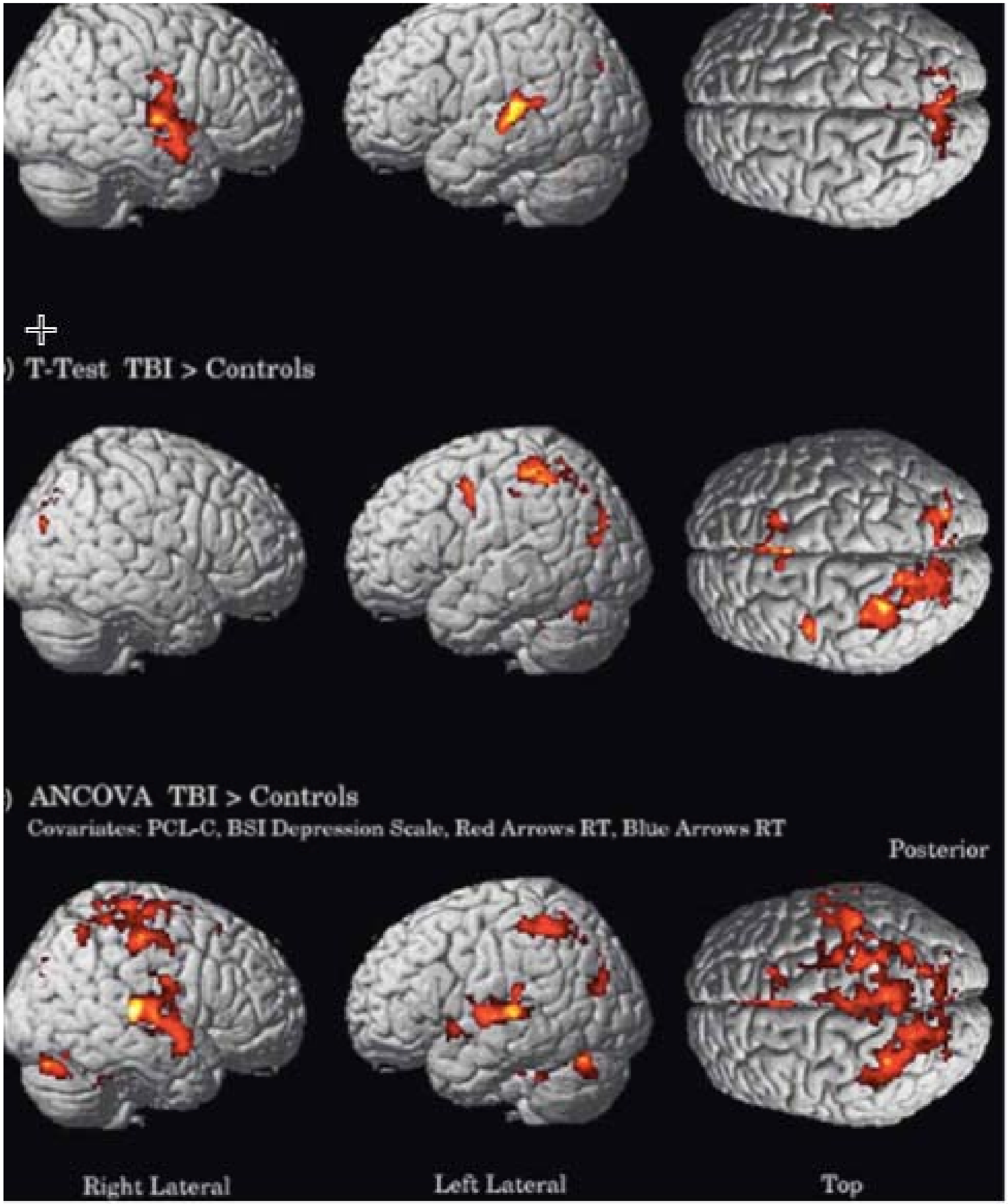
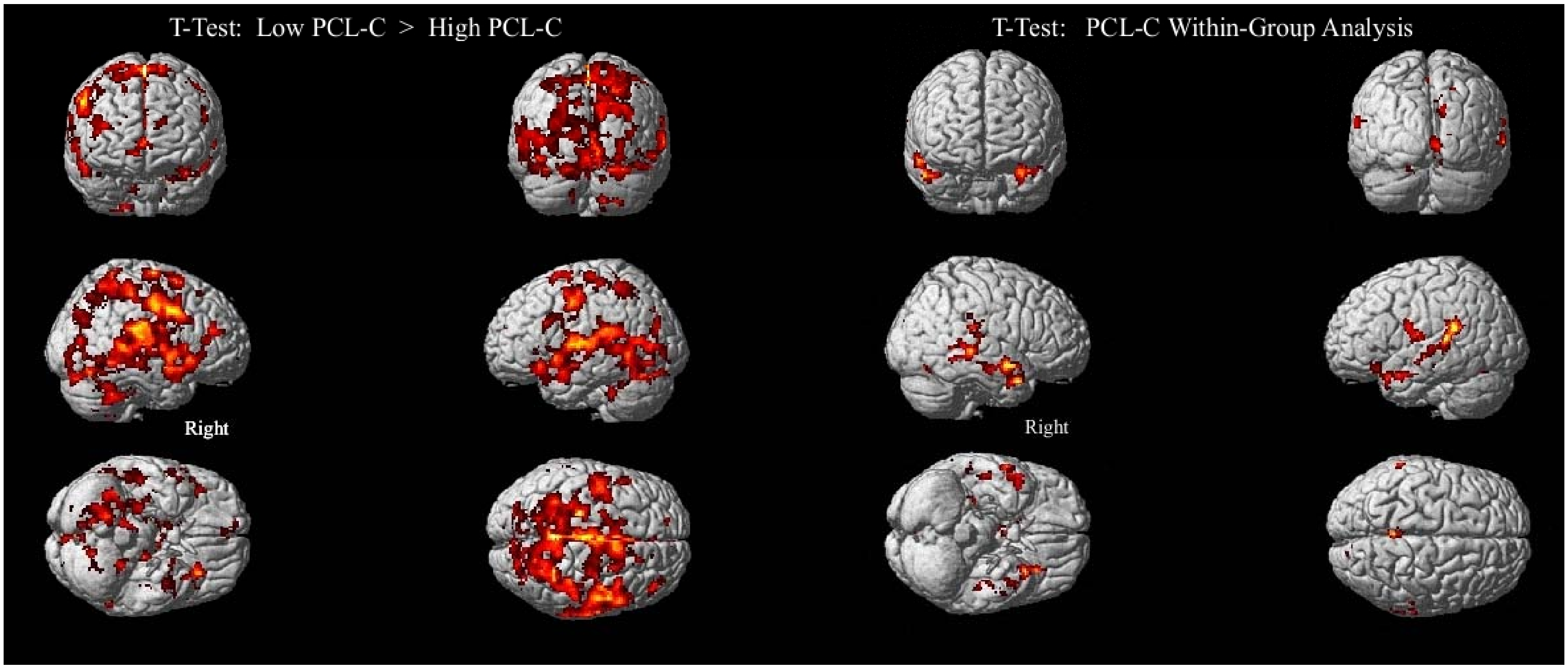

) T-Test TBI > Controls
) ANCOVA TBI > Controls
Covariates: PCL-C, BSI Depression Scale, Red Arrows RT, Blue Arrows RT
Posterior
Right Lateral
Left Lateral
Top

Figure 2 Modulation of cognitive control activation by PTSD symptom severity. Images on the left depict areas where veterans with lower scores on the PCL-C had greater Arrows task activation, relative to veterans with higher PCL-C scores. Figures on the right indicate brain areas where veterans with lower PCL-C scores had significant activation during the Arrows task.
(Scheibel et al., 2011)



Summary

- DTI, resting state fMRI and task-related fMRI are sensitive to chronic effects of predominantly mild TBI primarily due to blast
- Co-morbid PTSD clearly affects task-related fMRI, but effects on resting state and task fMRI are under investigation.
- DTI effects may be more specific to axonal injury than PTSD
- Cautious interpretation of findings because studies are still in progress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Making the invisible injury visible: MEG low-frequency source imaging for mild and moderate Traumatic Brain Injury (TBI)

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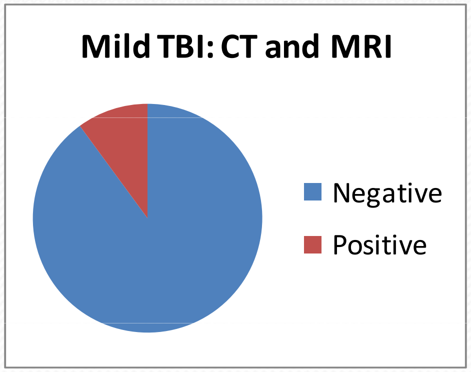
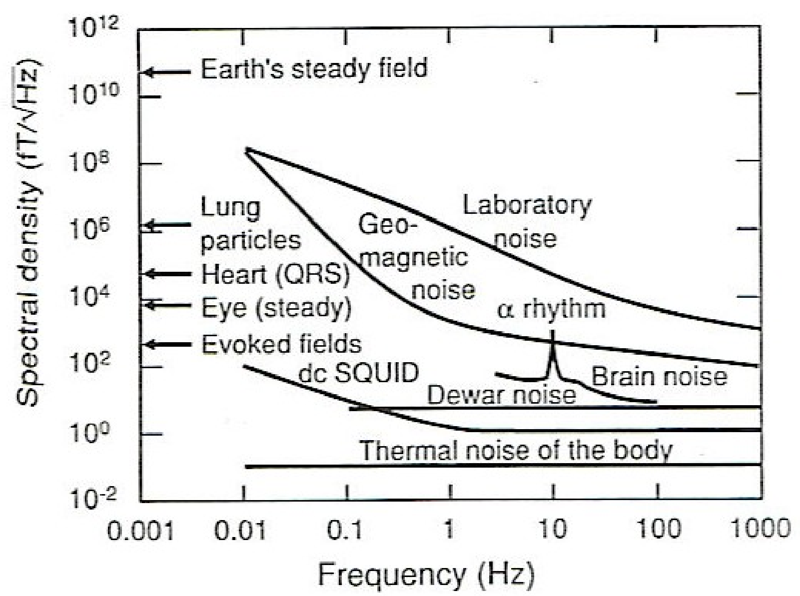
Mild TBI is often referred as *invisible* injuries: Detecting Mild TBI is Challenging using Conventional Neuroimaging Methods

- Traumatic brain injury (TBI) is a leading cause of sustained impairment in veterans, military personnel, and civilian populations.
- Mild TBI (mTBI): injuries are difficult to detect (injuries visible on only 10% of conventional MRIs or CTs).
- Axonal injury is a leading factor in mTBI. Conventional CT and MRI are mainly sensitive to blood product, and less sensitive to axonal damage itself, hence they underestimate the presence of axonal injury, especially in mild TBI cases.
- Injured brain tissues in mTBI patients generate pathological slow-wave magnetic signal that can be measured and localized by MEG (Lewine et al., 1999, 2007).
- Integrate gray-matter MEG slow-wave with white-matter diffusion tensor imaging (DTI) findings in mTBI (Huang et al., 2009)



Non-invasive MEG Technique with 1 ms Temporal Rresolution and several mm Spatial Resolution in Cortex

MEG signal is weak



IMEDCO Multiple Layer Magnetic Shielded Room Installed at UCSD

Shielding factors:

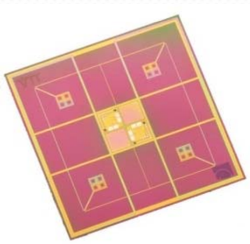
0.01Hz: 65dB

0.1 Hz: 73dB

1 Hz: 108dB

10Hz: 160dB

MEG SQUID Sensor Array

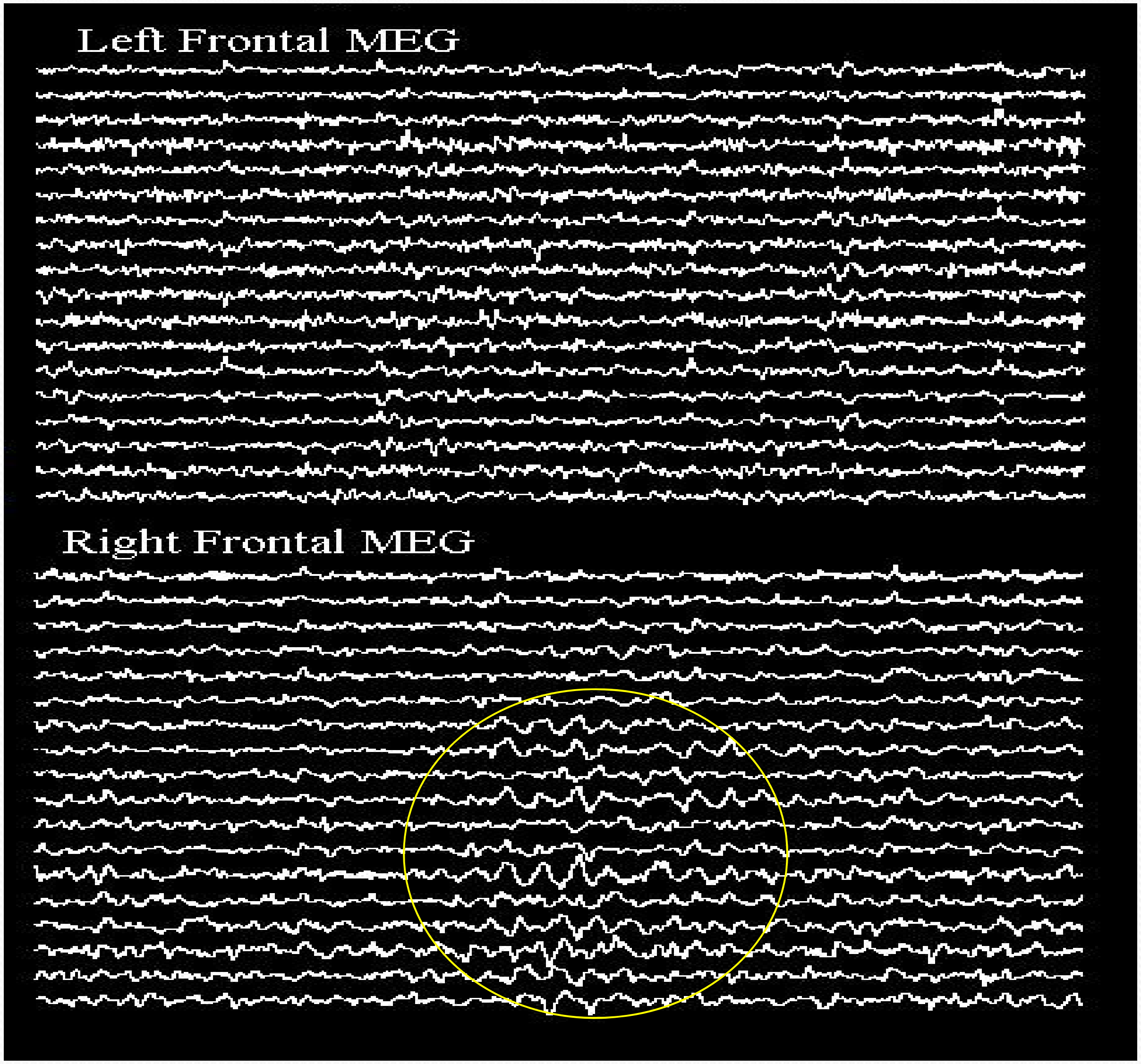


Elekta/Neuromag VectorView Whole Head MEG System with 306 Channels at the UCSD MEG Center

M.X. Huang, Ph.D., mxhuang@ucsd.edu

Abnormal MEG Slow-waves in gray-matter (1-4 Hz, delta-waves) are Characteristics of Neurological Injuries in the Brain, resulting from axonal injury

- Stroke
- Brain tumor
- Epilepsy
- Traumatic brain injury



What is the neurophysiology for MEG slow-wave generation (1-4 Hz) in TBI?

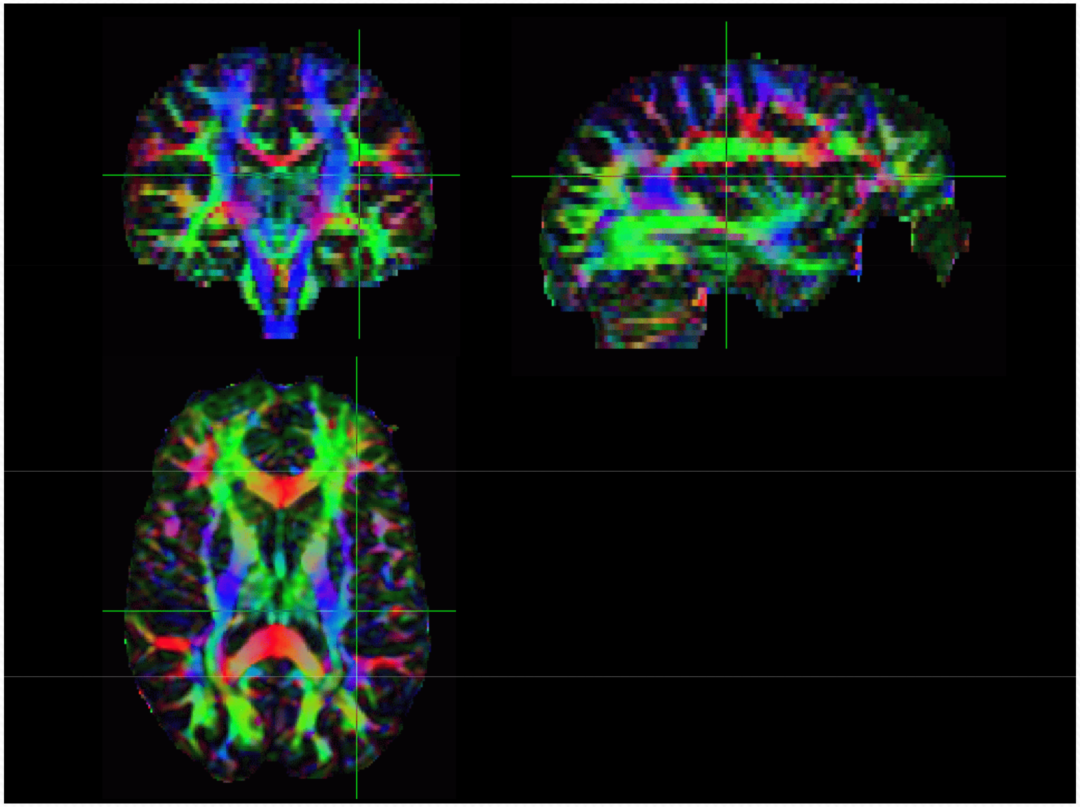
- Animal studies in cats revealed the slow-wave (delta-band 1-4Hz) were due to De-afferentation in gray-matter, caused by axonal lesions in white matter (Gloor et al., Neurology, 1977; Ball et al., Electroencephalogr. Clin. Neurophysiol., 1977).
- Is it possible that abnormal MEG slow-waves in mTBI patients are also due to de-afferentation from axonal injury?
- Our MEG-DTI integration study examines slow-wave in gray-matter and axonal injury in white matter (Huang et al., Journal of Neurotrauma, 2009)

Diffusion Tensor Imaging (DTI)

- DTI is an MR imaging technique based on the Brownian motion of water through tissues
- It measures how easy that water molecules move along the direction of white matter fibers versus the directions perpendicular to the fibers.
- TBI causes tissue shearing in the white matter fibers that leads to reduction of DTI signal.

$$D = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}$$

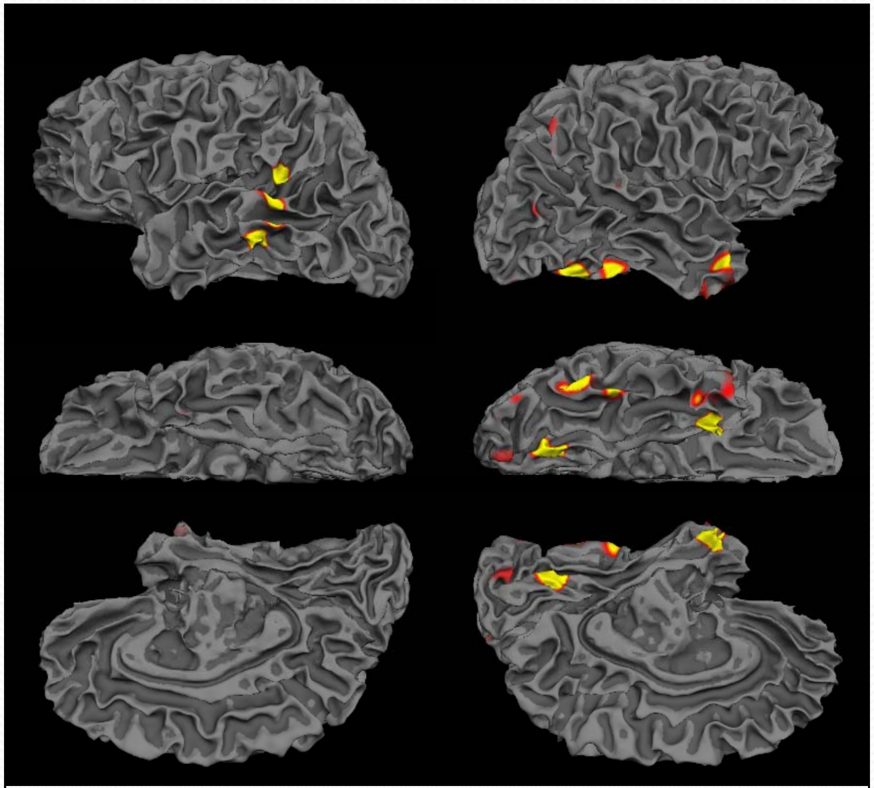
$$FA = \frac{\sqrt{3\left[(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2\right]}}{\sqrt{2\left(\lambda_1^2 + \lambda_2^2 + \lambda_3^2\right)}}$$



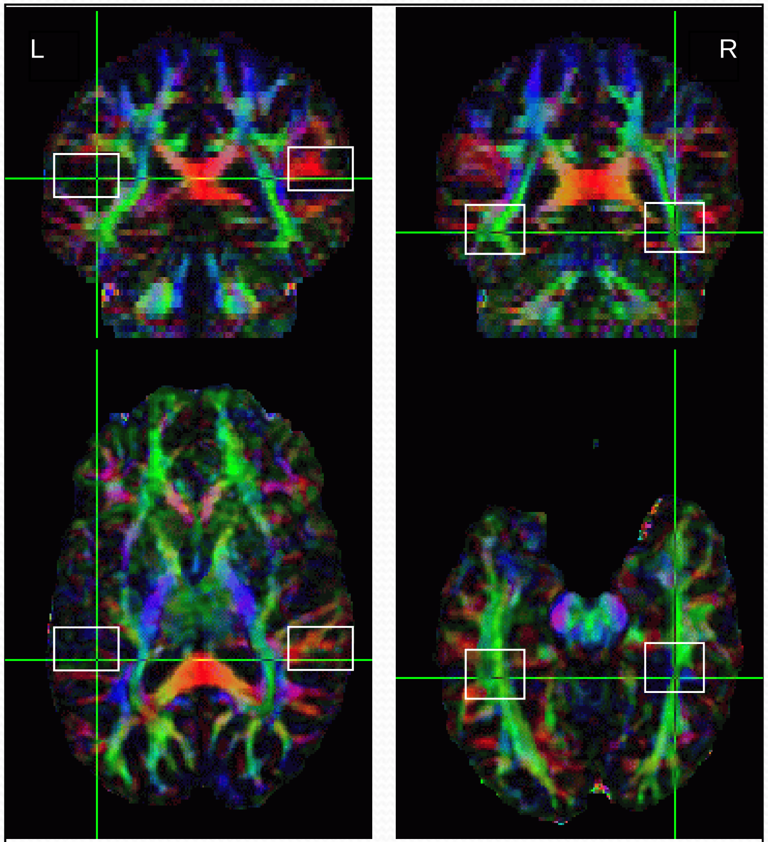
MEG-DTI Findings in Mild TBI due to Sport-related Accidents

History: 17-year old football player, 3 mTBIs. Symptoms: progressive headaches. dizziness, extreme fatigue while performing any mental task, altered sleep, memory problems, changes in speech.

Evaluation: Multiple CT & MRI scans negative.



MEG results show abnormal slow-waves generated from two regions in a TBI patient: 1) left column -- left lateral superior-posterior temporal region, 2) right column --- right inferior-temporal areas. Color threshold p<0.01.

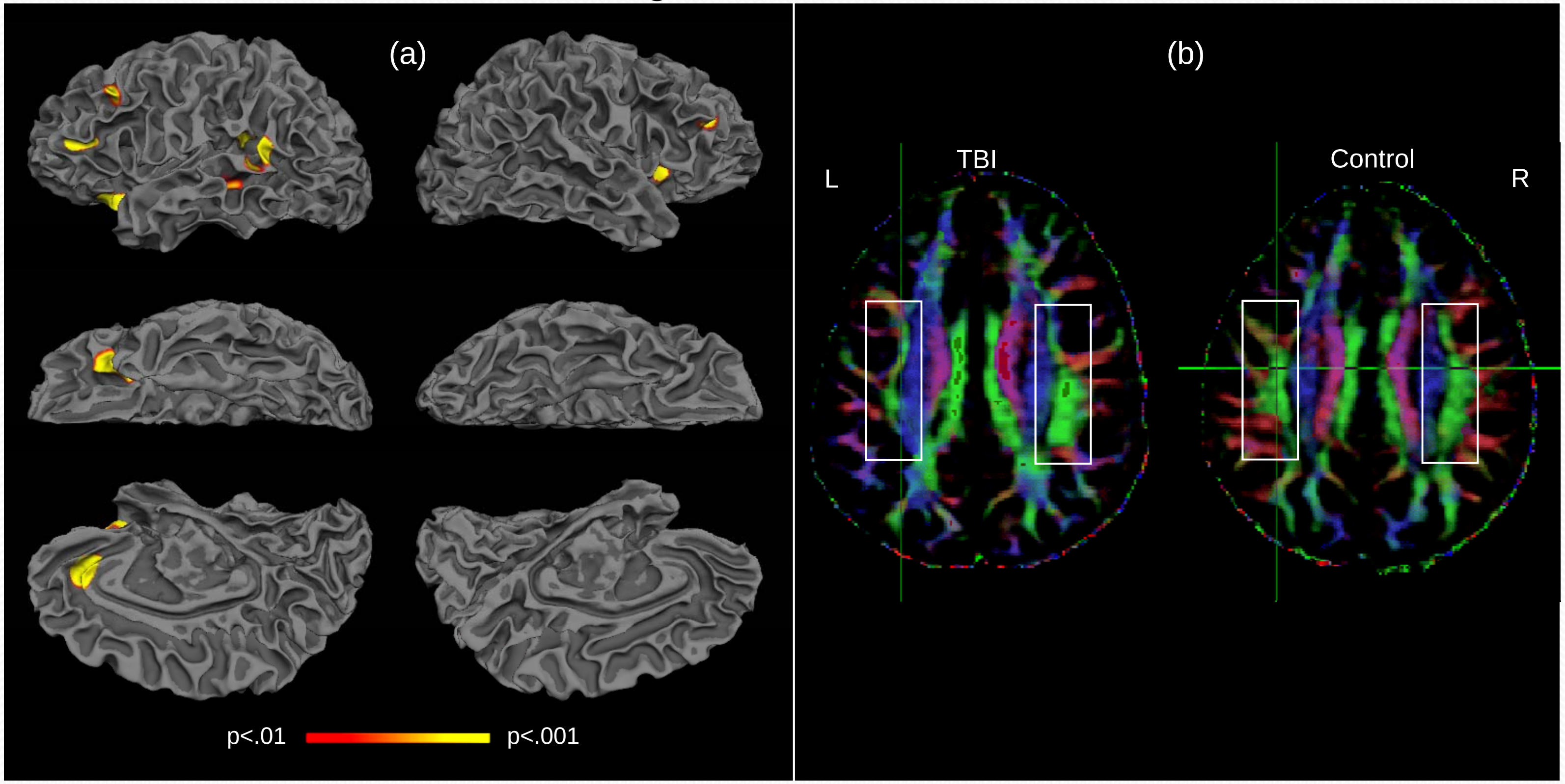


Left column: coronal and axial view show abnormal DTI in superior-posterior temporal lobe of the left hemisphere in a TBI patient. Right column: abnormal DTI in inferior-temporal lobe as part of the inferior longitudinal fasciculus of the right hemisphere.

Huang et al., J Neurotrauma. 2009 Aug;26(8):1213-1226.

MEG-DTI Findings in Mild TBI Blast

History: 27 year old Veteran, IED mTBI with loss of consciousness.
Symptoms: fatigue, disordered sleep, dizziness, irritability, anxiety, psychosocial and personality disturbances, memory loss.
Evaluation: CT and MRI scans negative.



Multiple neuronal sources that generated MEG slow-waves in a mild TBI patient. Bilateral LPFC, left OFC, left ACC, and left temporal areas regions showed abnormal slow-wave activities. DTI reveals profound abnormality of left SLF in a TBI patient. The normal control showed much thicker anterior-posterior oriented diffusion in SLF (green color) than the TBI patient in the left hemisphere.

Huang et al., J Neurotrauma. 2009 Aug;26(8):1213-1226.

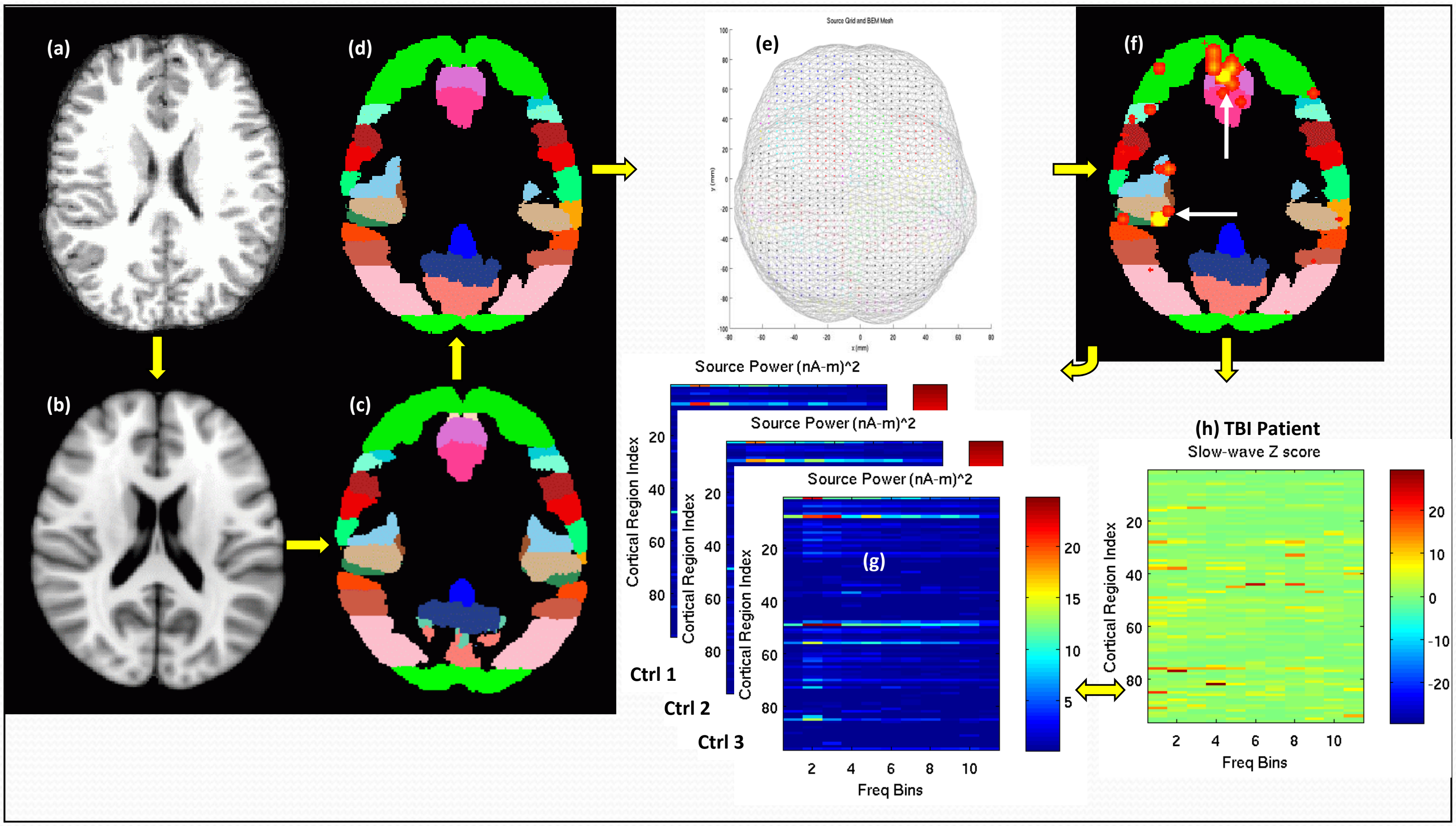
Examining the Positive Detection Rate of Mild TBI using MEG

- Resting-state MEG data (spontaneous recording for slow-wave detection) were collected using the Elekta-Neuromag VectorView whole-head MEG system with 306 MEG channels at the UCSD MEG Center.
- Group 1 contains 23 mild TBI patients whose injuries were caused by blast, all with PCS;
- Group 2 contains the 22 mild TBI were injured with non-blast causes (i.e., motor vehicle accident, sports, and fall), all with PCS
- Group 3 contains 10 moderate TBI that were not blast-related, all with PCS.
- Group 4 contains 44 age-matched healthy control subjects.

Huang et al., NeuroImage, 2012, 61(4):1067-1082.

MEG Slow-wave Source Imaging

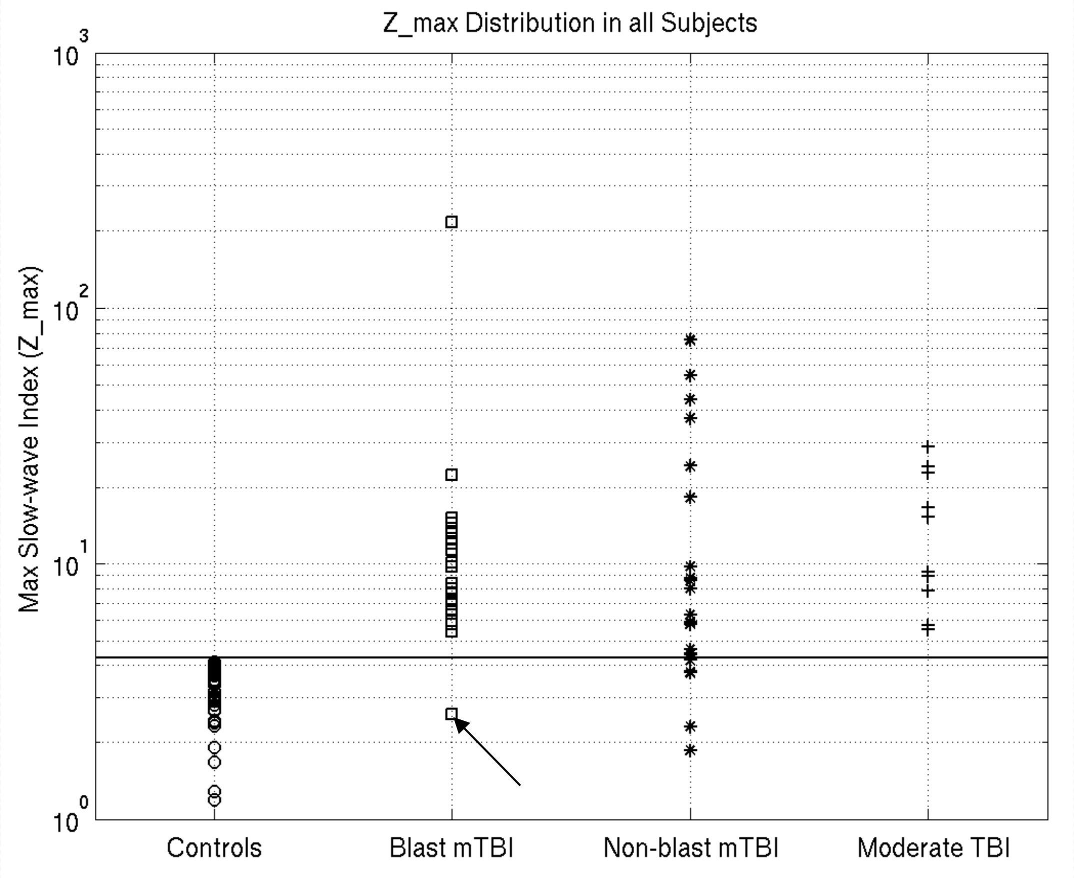
- Resting-state MEG data were analyzed using our new improved frequency-domain VESTAL method to obtain the source images for the low-frequency range (1-4Hz). Normative Database from healthy control subjects were used to detect abnormal slow-wave generation in TBI patients.



Huang et al., NeuroImage, 2012, 61(4):1067-1082.

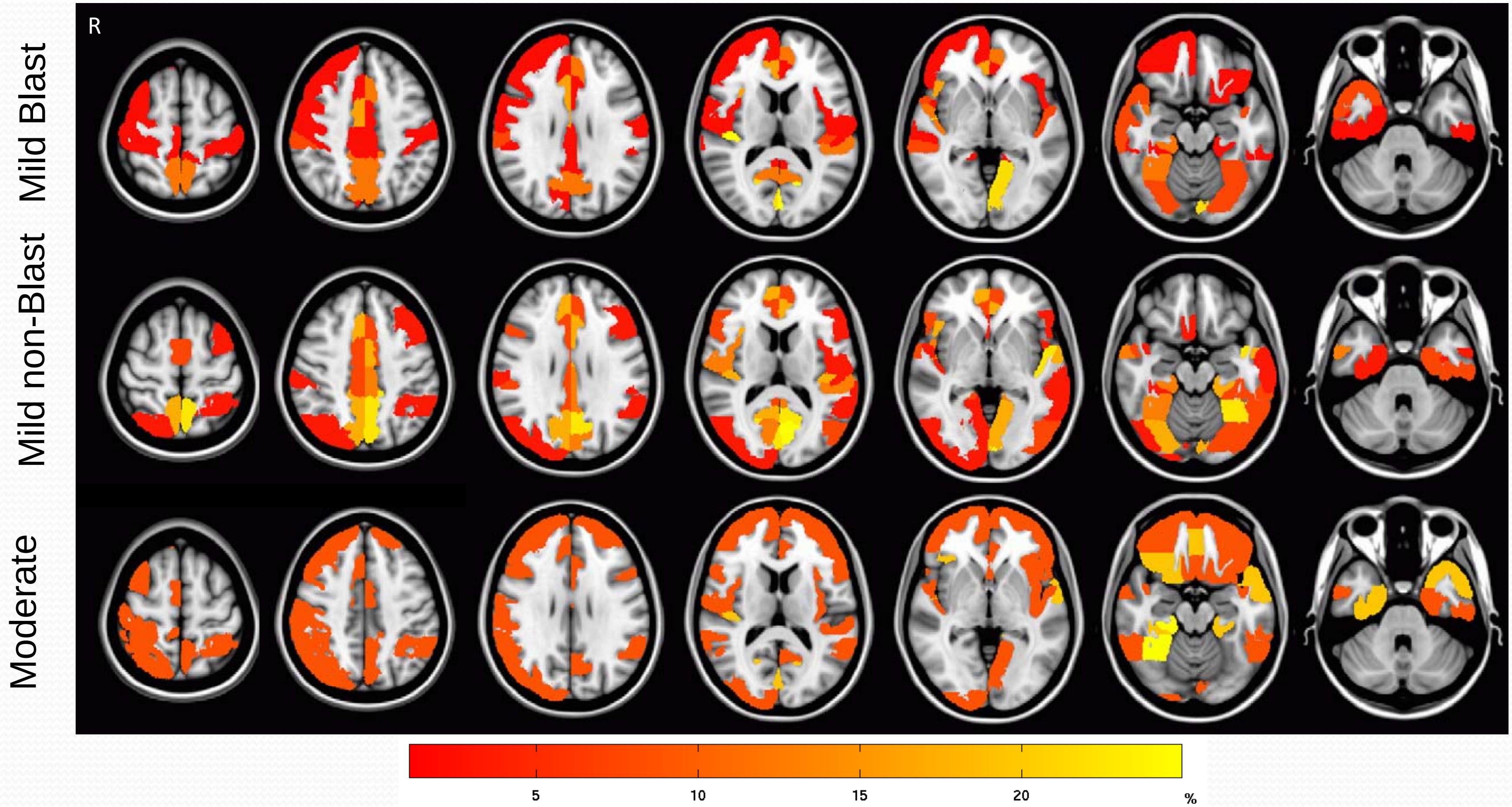
MEG Slow-wave Positive Detection Rates for TBI

- MEG positive-finding rates for different TBI groups were calculated at the threshold of 0% false-positive rate in healthy control subjects.
  - In the mild TBI group caused by blast, the MEG positive-finding rates was **96%**.
  - In the mild TBI group with non-blast causes, the MEG positive-finding rates was **77%**.
  - In the moderate TBI group, the MEG positive-finding rate was **100%**.
  - In the combined mild TBI group (blast+non-blast), the MEG positive-finding rates was **87%**.



Huang et al., NeuroImage, 2012, 61(4):1067-1082.

Percent-likelihood of MEG Slow-wave Generation across Brain regions



Huang et al., NeuroImage, 2012, 61(4):1067-1082.

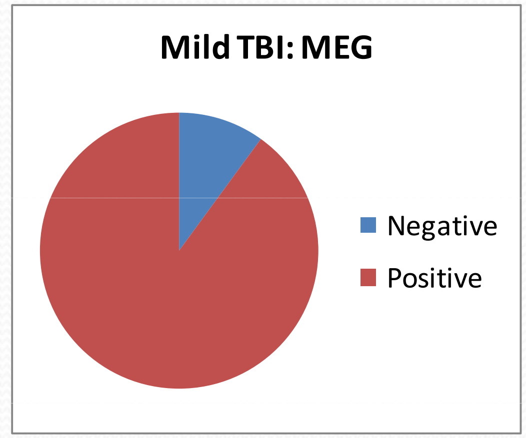
MEG Slow-wave Exam Correlates with Post-concussive Symptoms

- $N_{slow\text{-}wave\_sum}$ is significantly correlated with N_{PCS_sum} (r=+0.27, p<0.05) in 55 TBI patients
- Regarding Individual PCS, $N_{slow\text{-}wave\_sum}$ significantly correlated with Personality Changes (e.g., social problems) (r=+0.32, p<0.05), Apathy, (r=+0.36, p<0.01), and other visual difficulties (r=+0.27, p<0.05).
- 1) headaches, 2) dizziness, 3) fatigue, 4) memory difficulty, 5) irritability, lack of patience, lose temper easily 6) anxiety, 7) trouble with sleep, 8) hearing difficulties, 9) blurred vision and other visual difficulties, 10) personality changes (e.g., social problems), 11) apathy, 12) lack of spontaneity, 13) affective lability (quick-changing emotions), 14 depression, 15) trouble concentrating, 16) bothered by noise, 17) bothered by light, 18) coordination and balance problems, 19) motor difficulty, 20) difficulty with speech, 21) numbness/tingling.

Huang et al., NeuroImage, 2012, 61(4):1067-1082.

Making the invisible injury Visible

- <u>Positive-detection Rates</u>: MEG slow-waves in TBI patients has **87**% positive-finding rate in mild TBI and **100**% for moderate TBI groups.
- <u>Injury Patterns</u>: The patterns of slow-wave generation between mild blast TBI and mild non-blast TBI patients were highly correlated.
- <u>MEG slow-wave findings correlate with post-concussive symptoms</u>

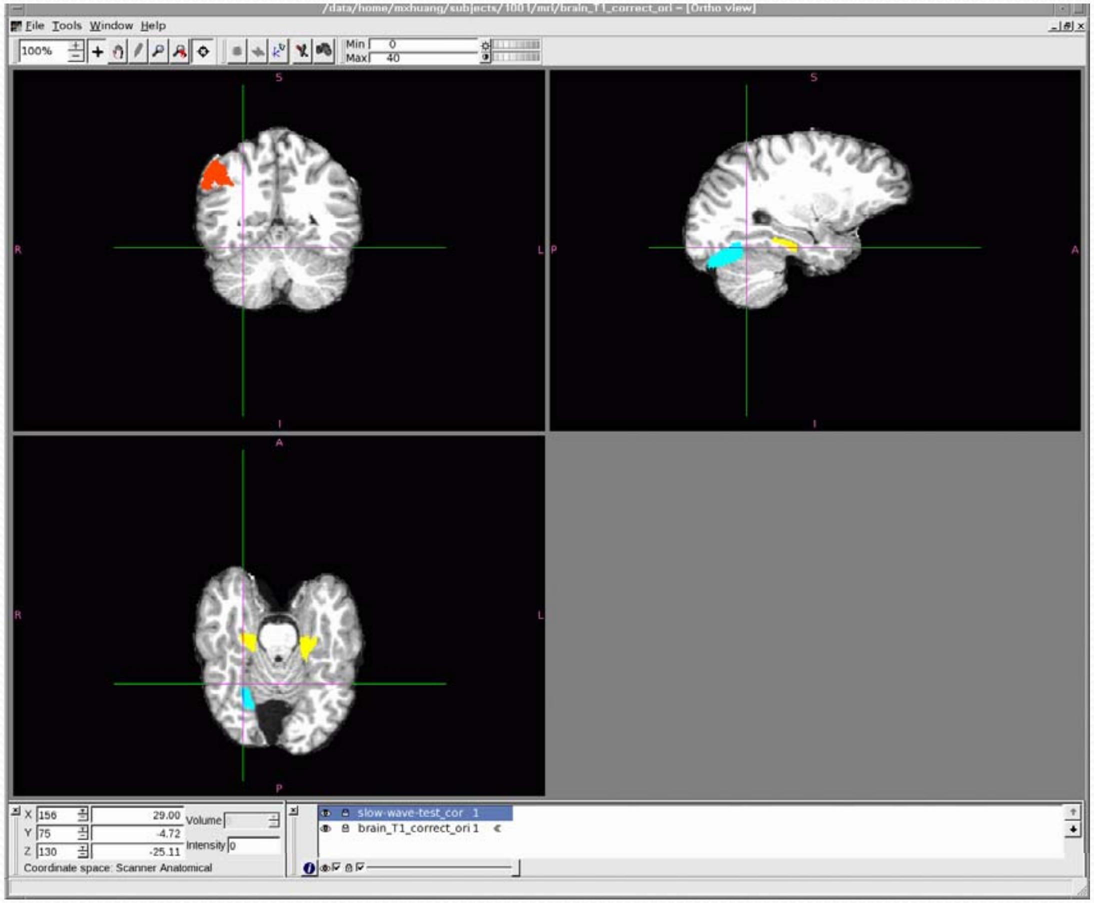


Huang et al., NeuroImage, 2012, 61(4):1067-1082.

Invisible Injuries become not so Invisible

TV Interview with Col G.I. Wilson with KPBS:

http://www.youtube.com/watch?v=uhlANIGAJXA



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  - Investigator Collaboration: VA San Diego Healthcare System, UCSD, Naval Medical Center San Diego.

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Catherine Cheung

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Rebecca Theilmann
Michael Levy
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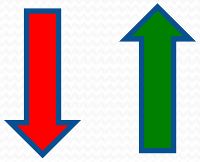
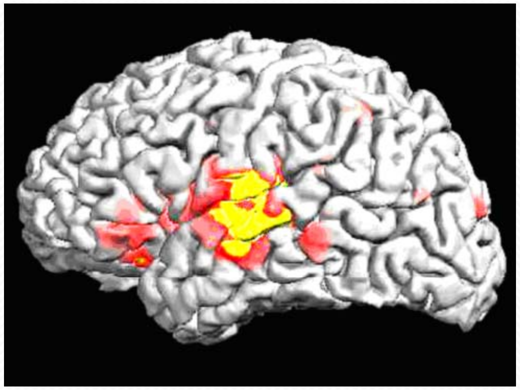
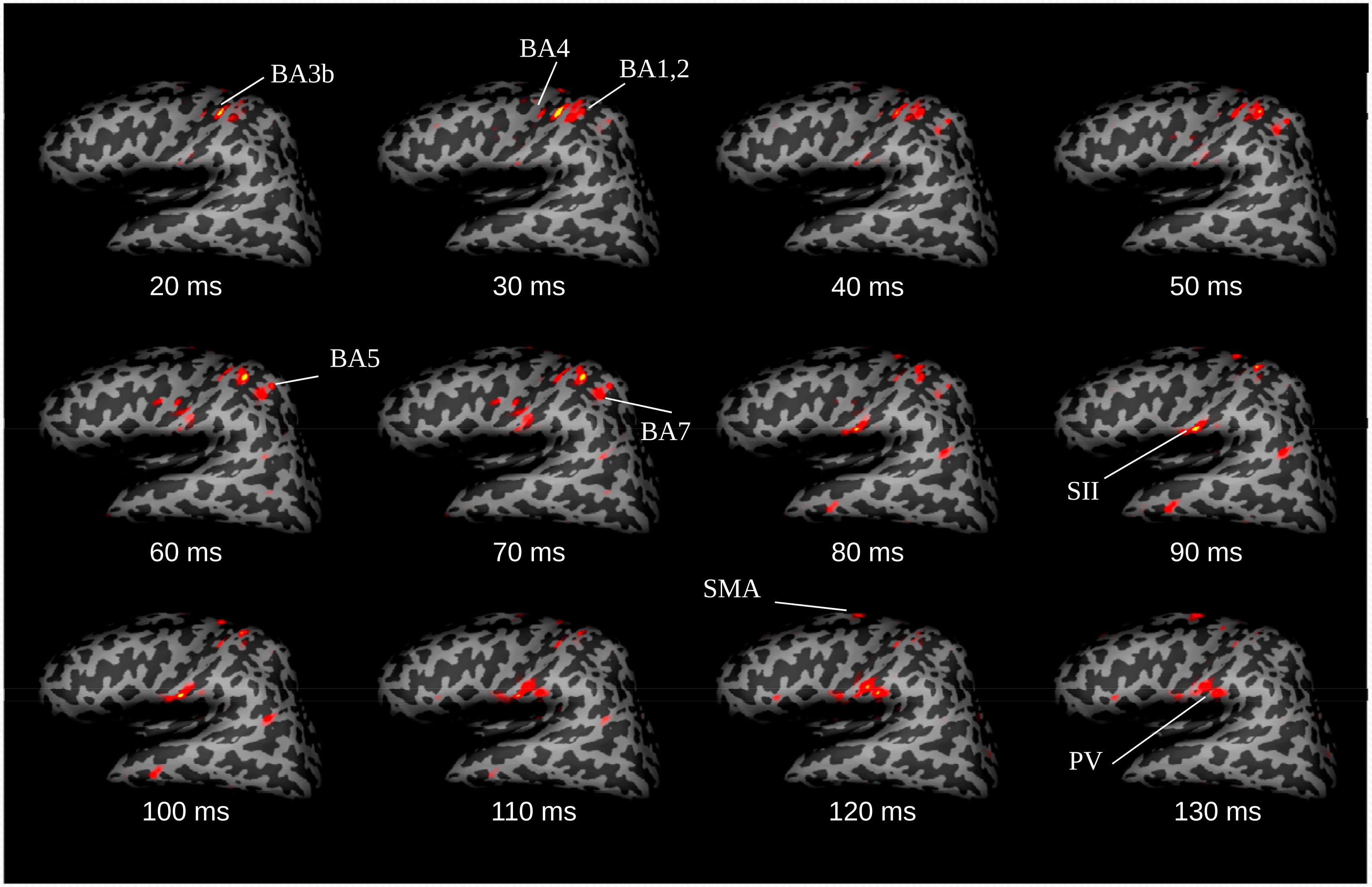
MEG: Forward and Inverse Modeling

- MEG forward problem
  - For given neuronal current configuration and head conductivity distribution (head models), how to calculate MEG field distribution at sensor space.
  - Spherical MEG head model
  - Boundary Element Method (BEM)
  - Multi-sphere head model (Huang et al., Phys Med Biol, 1999)
- MEG inverse problem
  - For given MEG sensor measurements, how to estimate neuronal current distribution inside the brain.
  - No unique solution
  - Additional constraints need to be imposed to make a unique solution (source models)
  - 1) Dipole fit, MUSIC, MSST; 2) minimum L2- / L1-norm, VESTAL, 3) Beamformer, etc.



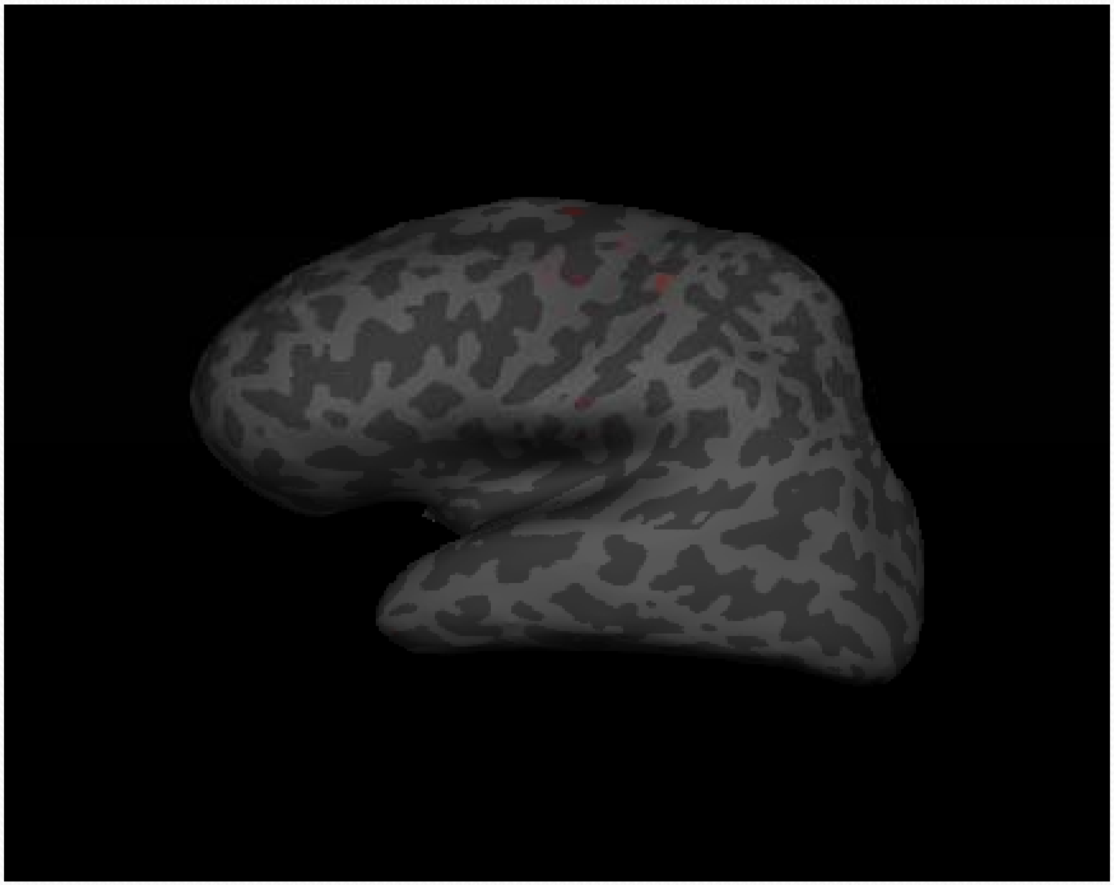


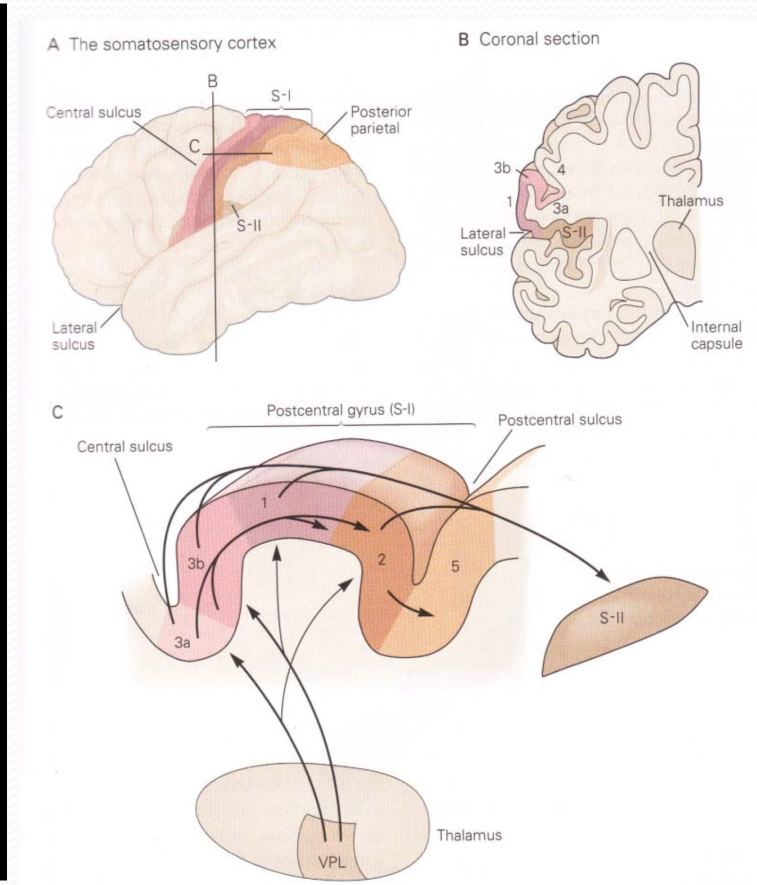
VESTAL's performance on human MEG response evoked by right median-nerve stimulation: snap shots of the source map



Huang, et al., NeuroImage, 31(3):1025-1037. 2006.

VESTAL's performance on human MEG response evoked by right median-nerve stimulation (cont.): activation movie





Source: Kandel et al., *Principles of Neural Science*, pg. 453

Huang, et al., NeuroImage, 31(3):1025-1037. 2006.

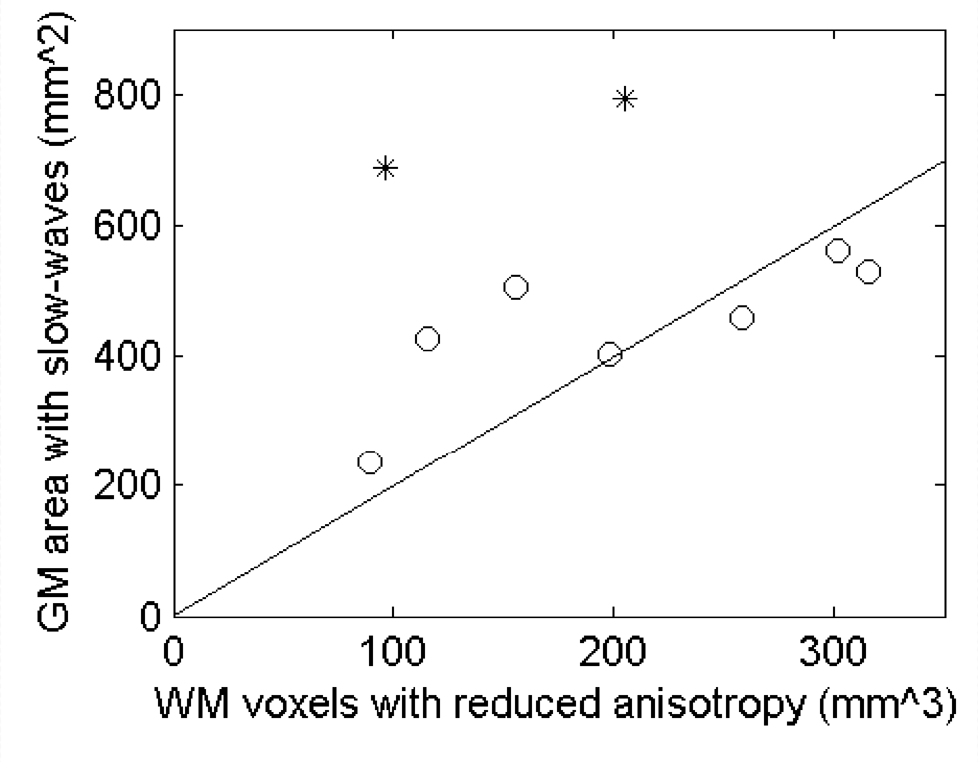
Table 1: Regions that generated MEG delta-waves and showed DTI abnormalities in mTBI with "normal" CT/MRI (partial list, 25 TBI patients total)

	Cause of TBI	MEG slow-wave foci	Foci with DTI abnormalities
Case 1, Male, Age 43	Blast	R posterior-temporal & anterior-occipital lobe	R posterior-temporal & anterior-occipital lobe
Case 2, Male, Age 17	Sport (Football), three incidents	L posterior superior temporal lobe; R inferior temporal-occipital regions (3 areas)	L posterior superior temporal lobe; R inferior longitudinal fasciculus
Case 3, Male, Age 14	Sport (Hockey), hit to R temporal	R inferior temporal–occipital lobe	R inferior longitudinal fasciculus in temporal lobe.
Case 4, Male, Age 27	Blast	L lateral prefrontal lobe; L temporal-parietal junction; L orbital frontal lobe; L anterior cingulate; R lateral prefrontal lobe	L Superior longitudinal fasciculus
Case 5, Female, Age 12	Sport (Soccer), fall on back of the head	L and R occipital lobes; L posterior temporal lobe	L-R asymmetry in optical tracts in the occipital lobes; L posterior temporal lobe
Case 6, Male, Age 16	Sport (Football)	R inferior parietal lobe	Within normal range
Case 7, Male, Age 21	Motor Vehicle Accident	R lateral prefrontal cortex; R central sulcus; R inferior posterior parietal area; R ventral temporal area	DTI findings within normal range, but PET shows abnormal metabolic signals in: R lateral prefrontal cortex; R parietal lobe; R temporal lobe; R occipital lobe

1) Abnormal DTI in small local fiber tracts
2) Abnormal DTI in major fiber tracts
3) DTI within normal range, MEG abnormal

Huang et al., J Neurotrauma. 2009 Aug;26(8):1213-1226.

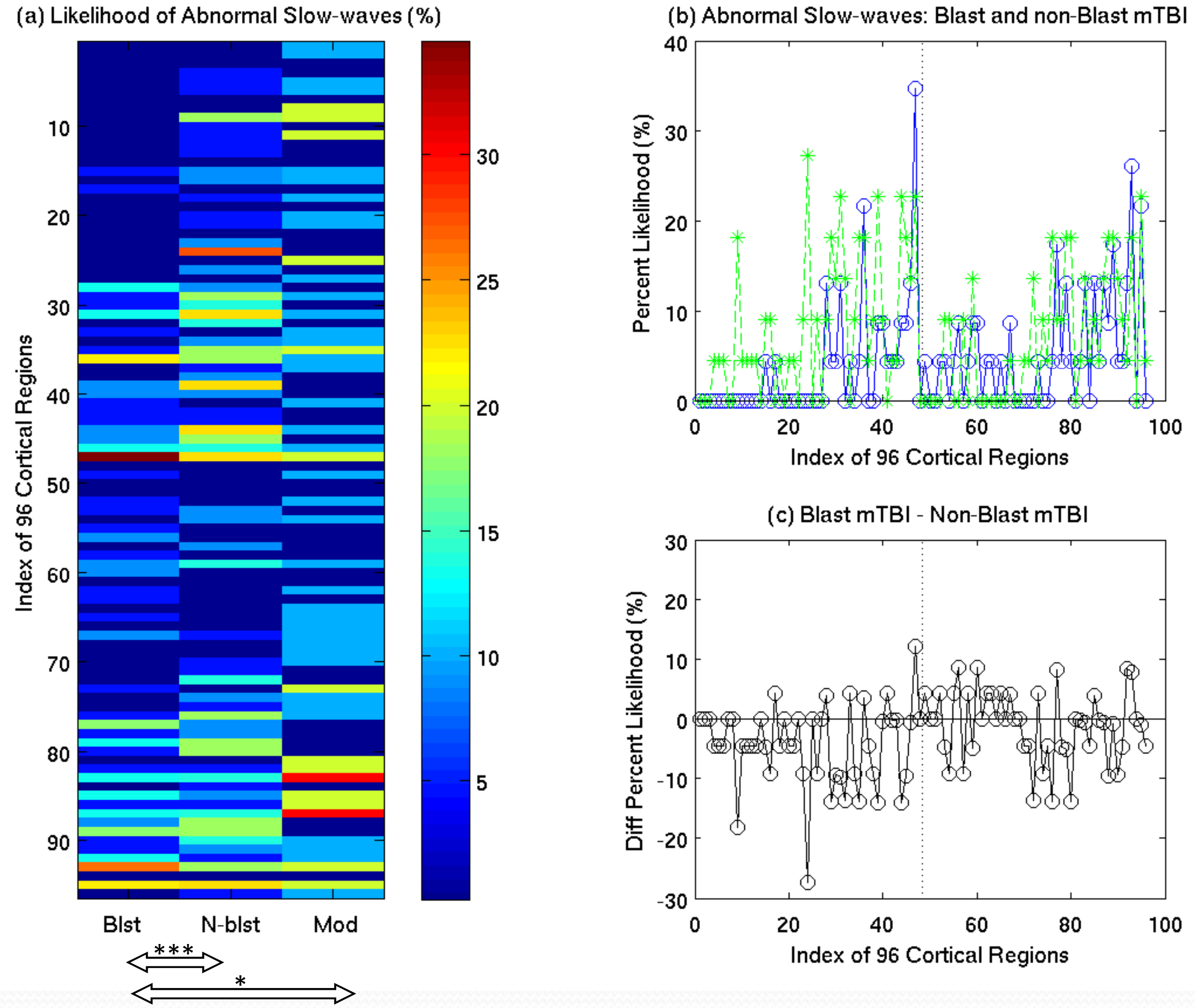
MEG and DTI correlation



Huang et al., J Neurotrauma. 2009 Aug;26(8):1213-1226.

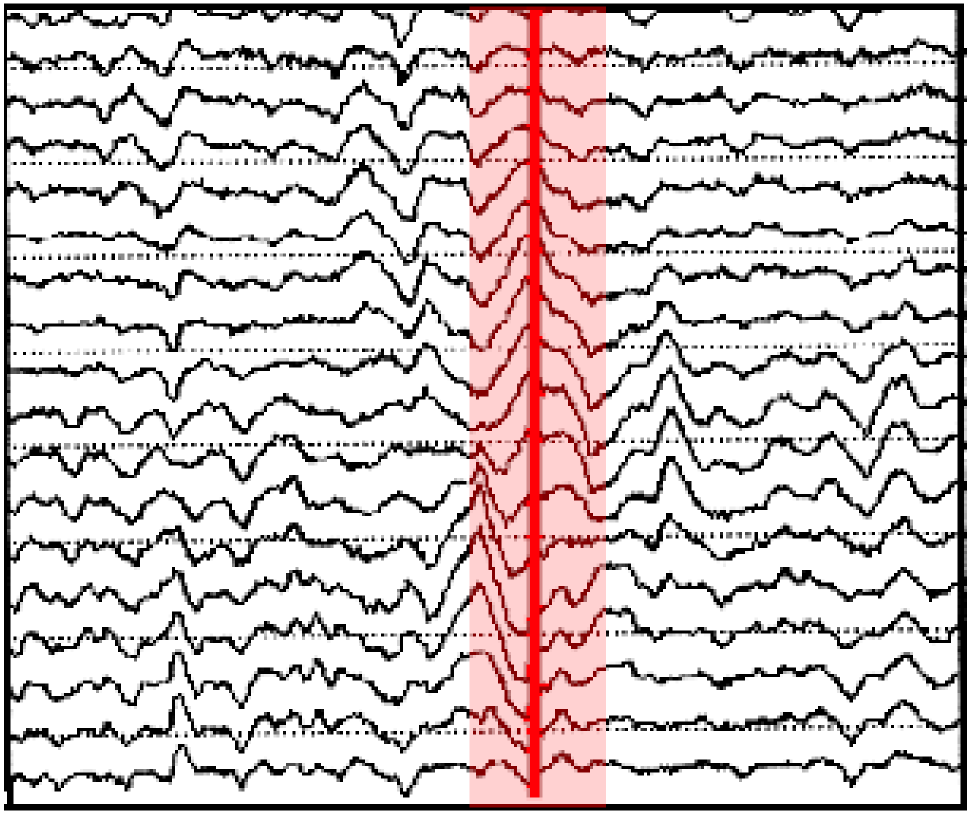
Areas and Patterns of Injuries for Different TBI Groups

- MEG identifies brain areas likely to be injured in each TBI group.
- Slow-wave generation in mild blast TBI group is highly correlated with mild non-blast TBI group.
- Slow-wave generation in moderate TBI group correlate with blast mild blast but not with non-blast mild TBI groups.

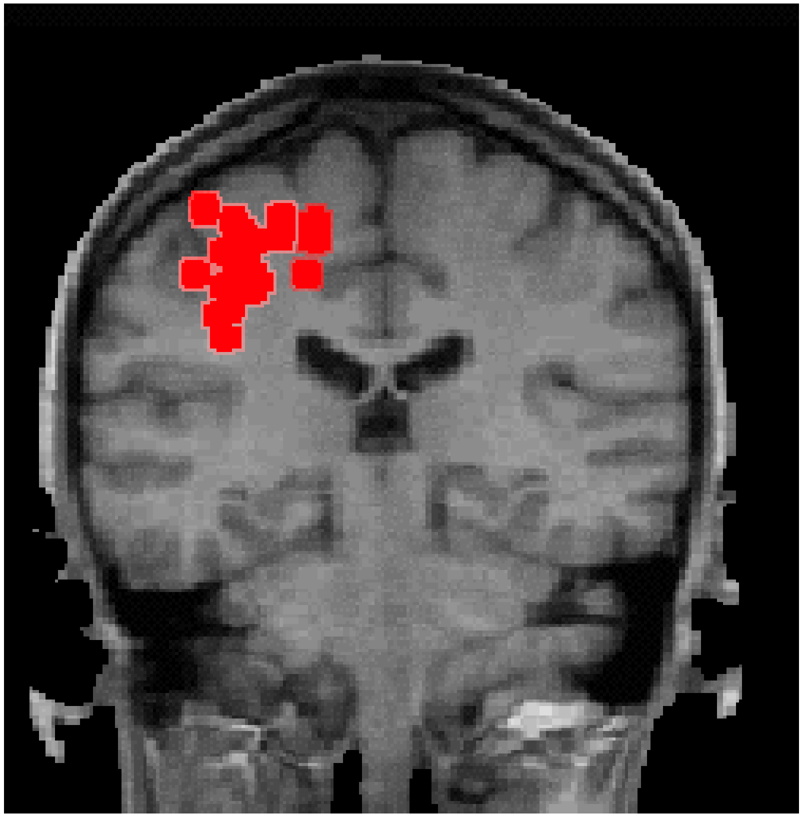


Huang et al., NeuroImage, 2012, 61(4):1067-1082.

MEG Slowing in mild head trauma patients with normal MRI (from Dr. Jeff Lewine)



Dipolar Slow Wave



Mild Head Trauma

Mid-Atlantic

MIRECC

Mental Illness Research, Education & Clinical Center

Neurobehavioral sequelae of mild TBI

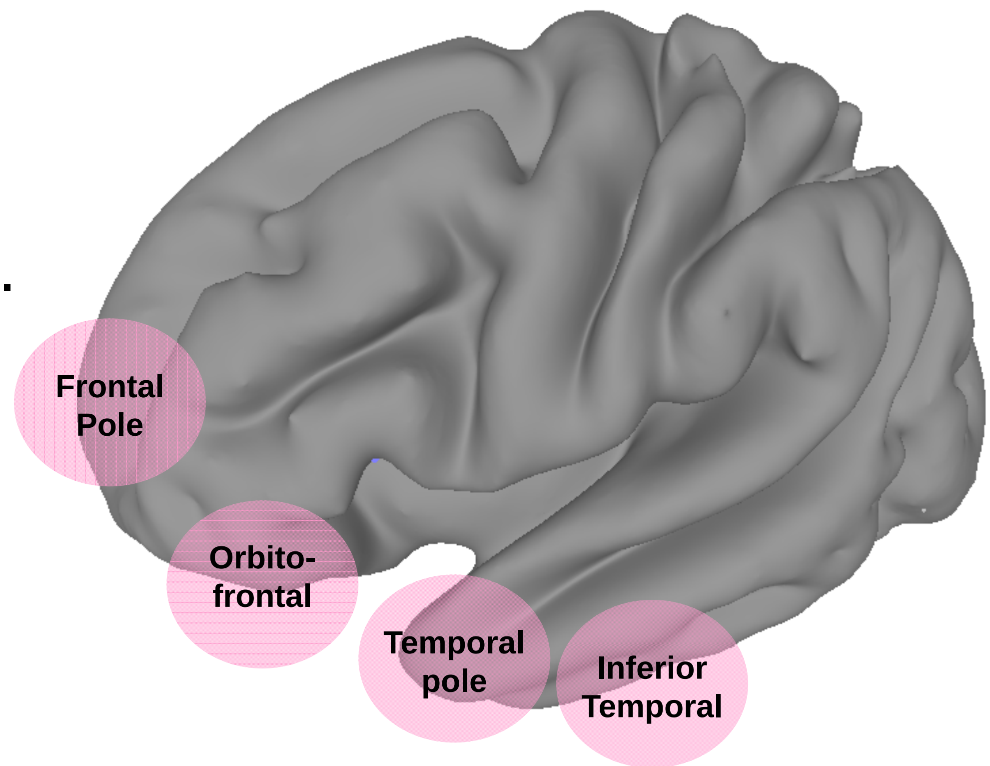
Rajendra Morey MD, MS

Durham VA Medical Center

Duke University

Profile of Injury

- Impact or concussive injury
- Inertial injury – acceleration and deceleration
- Blast injury – high energy, high velocity pressure wave.
- Secondary injury – hypoxia, edema, neurotransmitters, various neurotoxic agents
- Psychological trauma – acute exposure



Mechanism of tissue damage

- Hypoxia
- Edema
- Increased intracranial pressure
- Mechanical distortions
- Neurotransmitter release
- Excitotoxic cascade and injury
- Neuronal apoptosis
- Tauopathy – chronic traumatic encephalopathy

Changes in Cognition

- Inattention – impaired concentration and focus
- Executive Function – working memory, decision making.
- Memory – short-term
- Learning
- Information processing
- Speech and Language functions
- Impulsivity
- Poor Judgment
- Insight – lack of awareness of changes

Changes in Affect

- Irritability
- Affect – labile affect
- Aggression
- Apathy

Somatic and Neurological sequelae

- Headache
- Dizziness, loss of balance
- Nausea, vomiting
- Sensory disturbances - blurred vision, tinnitus
- Sensitivity to light or sound
- Fatigue or drowsiness
- Insomnia
- Hypersomnia

Profile of Injury and Personality Change

- Dorsolateral PFC damage – impairs executive function, working memory, decision making, problem solving, mental flexibility.
- Orbitofrontal damage – impairs intuitive reflexive social behavior, self monitoring, ability to self correct in a social contexts.
- Anterior cingulate –motivated and reward-related behaviors.
- Medial temporal damage – assessment of stimulus salience, memory, integration of emotional memory.

Association with psychiatric disorders

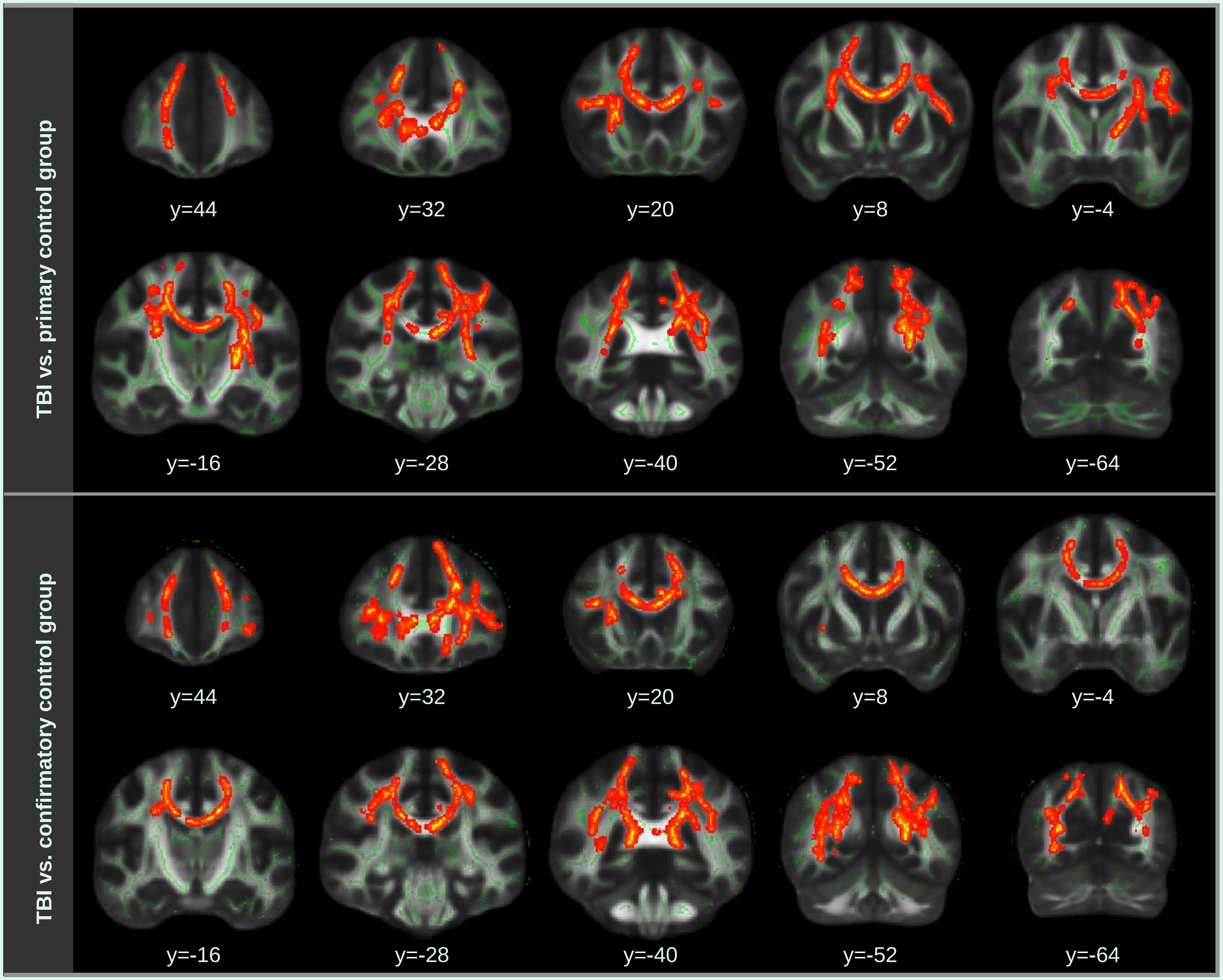
- Depression
- PTSD*
- Panic disorder
- Substance use disorders
- MCI and Dementia

White matter integrity : Mild TBI

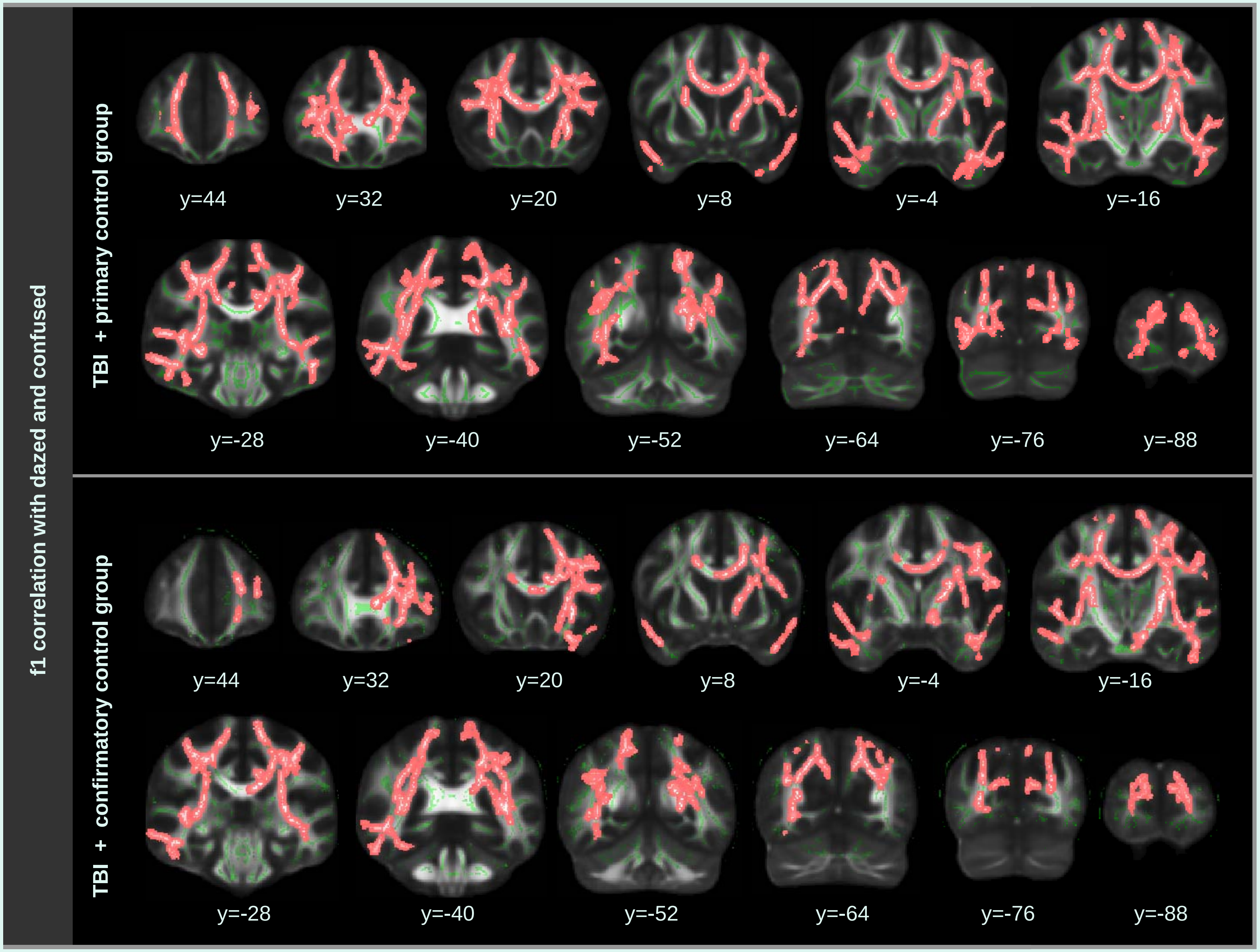
- Total sample size of n=100
- 30 Veterans with mild TBI and PTSD
- 42 Veterans in primary control group.
- 28 Veterans in secondary control group
- HARDI – 55 gradient directions
- Crossing fiber analysis with TBSS-X

Morey, R.A., Haswell, C.C., Selgrade, E., Massaglia, D., Liu, C., Weiner, J., *et al.* (2012). Effects of chronic mild traumatic brain injury on white matter integrity in Iraq and Afghanistan Veterans. *Human Brain Mapping* In press.

Effect of mild TBI; no effect of PTSD

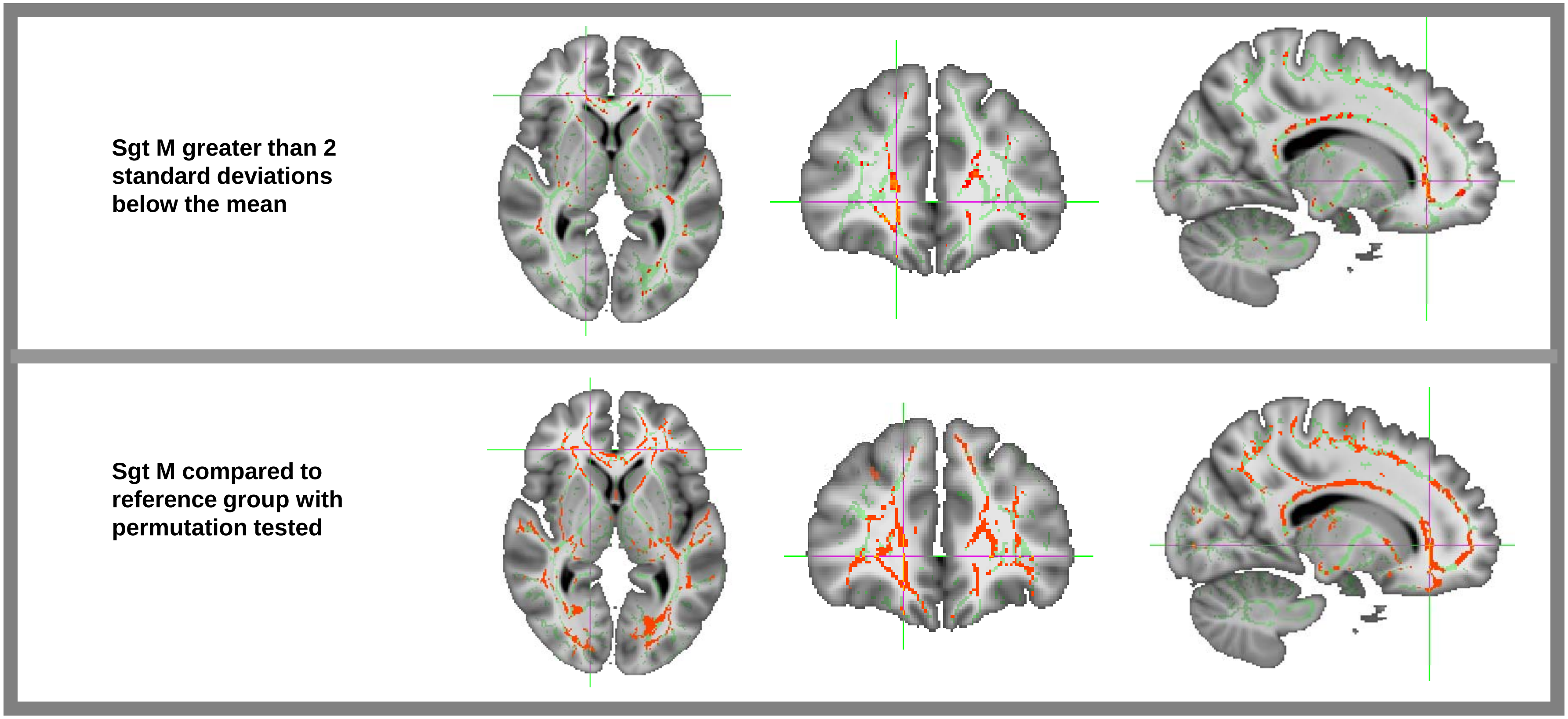


Effect of feeling dazed and confused



Single subject approach for TBI diagnosis

- Sgt M compared to a reference group of 37 non-TBI subjects.
- Z-statistic based analysis without correction for multiple correction (upper panel)
- Permutation testing followed by *threshold free cluster enhancement* (lower panel)



Hayes, J.P., Morey, R.A., and Tupler, L.A. (2011). A case of frontal neuropsychological and neuroimaging signs following multiple primary-blast exposure. *Neurocase*.

Questions

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