

# Magnetoencephalography as a Potential Imaging Marker for Mild TBI and PTSD

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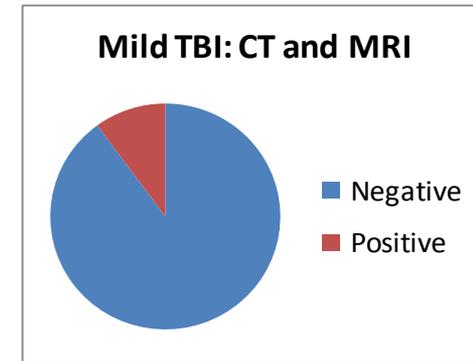


# Topics to be covered

- MEG's slow-wave and the detection of mild traumatic brain injury (mTBI)
- MEG functional connectivity research on blast mTBI
- MEG's application in Post-traumatic stress disorder (PTSD)

## 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).
- Diffuse axonal injury and neurochemical damages are leading factors in mTBI. Conventional CT and MRI are mainly sensitive to blood product
- 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, Huang et al., 2009, 2012, 2014).

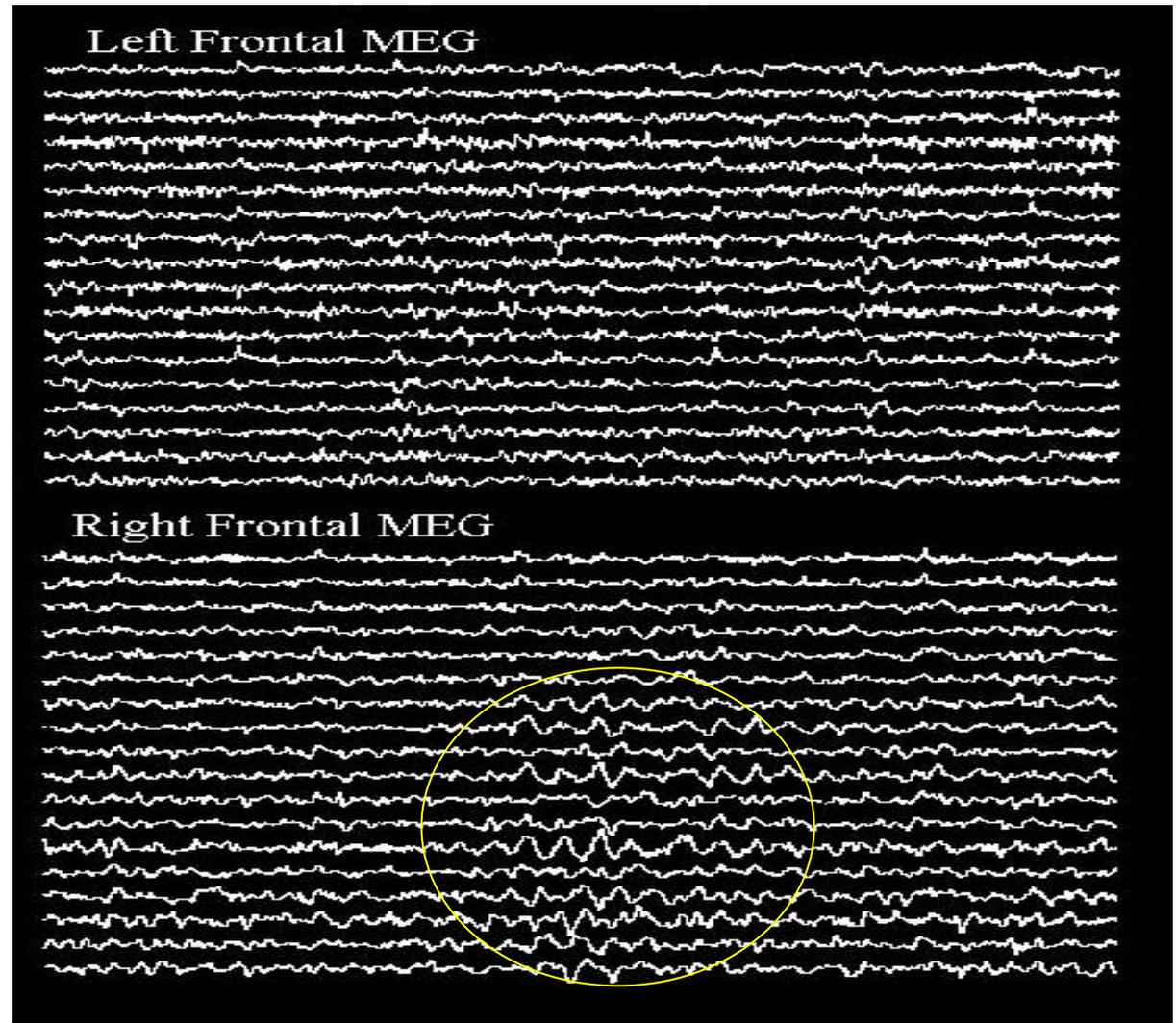


## What is the neurophysiology for resting-state MEG slow-wave generation (1-4 Hz) in TBI?

- Animal studies in cats revealed the slow-waves (delta-band 1-4Hz) were due to de-afferentation in gray-matter, caused by **injury in white matter tissue** (Gloor et al., Neurology, 1977, 27: 326–333; Ball et al., Electroencephalogr. Clin. Neurophysiol., 1977, 43: 346–361).
- In animals, slow-waves and de-afferentation can also be generated by applying atropine that blocks or limits **cholinergic transmissions** (Schaul et al., Brain Res. 1978, 143: 475-486).

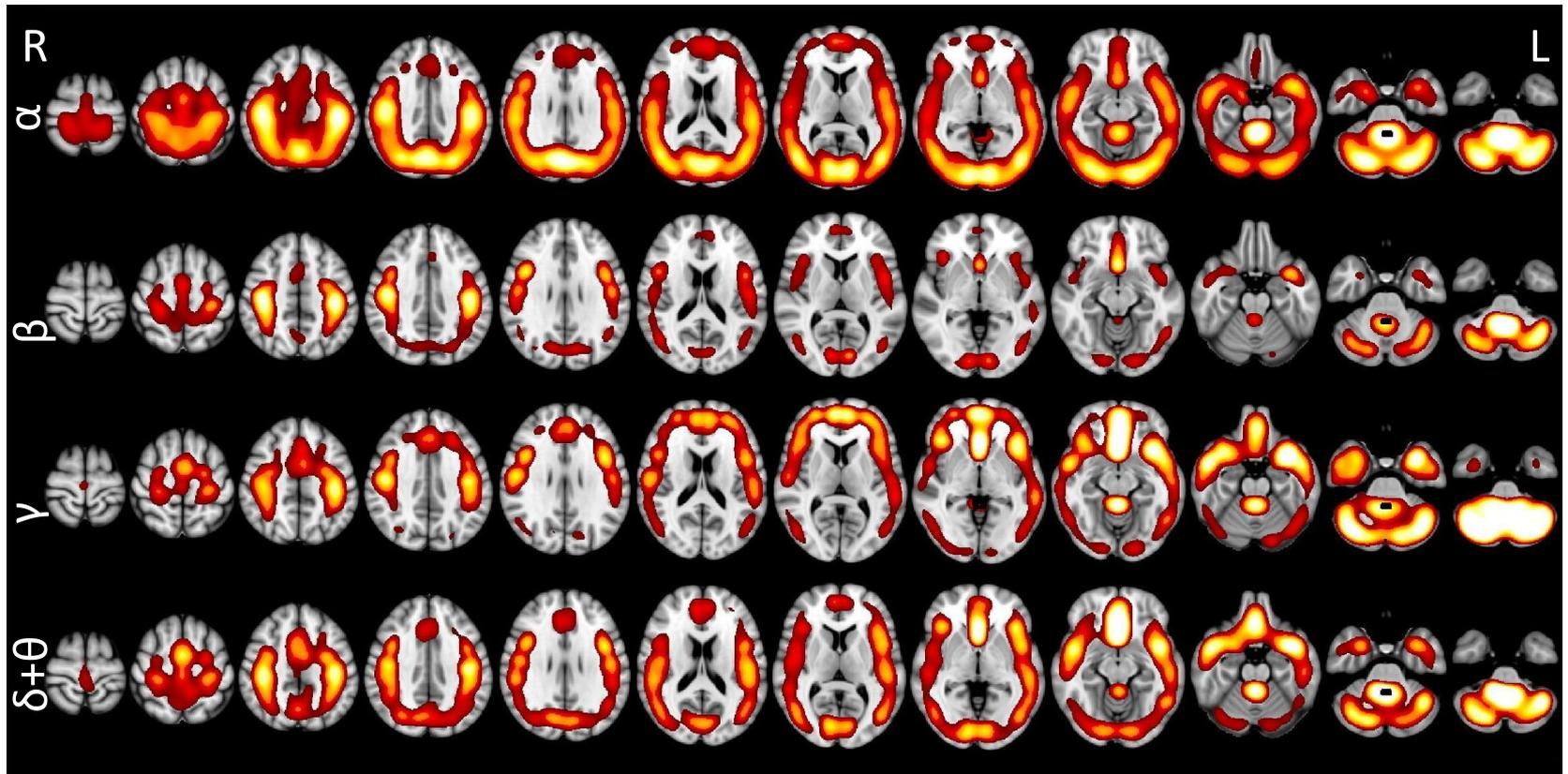
**Abnormal resting-state MEG slow-waves in gray matter (1-4 Hz, delta-waves) are characteristics of neurological injuries in the brain, resulting from white matter injury and/or cholinergic blockage**

- Stroke
- Brain tumor
- Epilepsy
- Traumatic brain injury



# Normative Database: Comprehensive Source Magnitude Images of Resting-state Brain Rhythms for Different Frequency Bands

Huang et al., NeuroImage, 84, 585-604, 2014



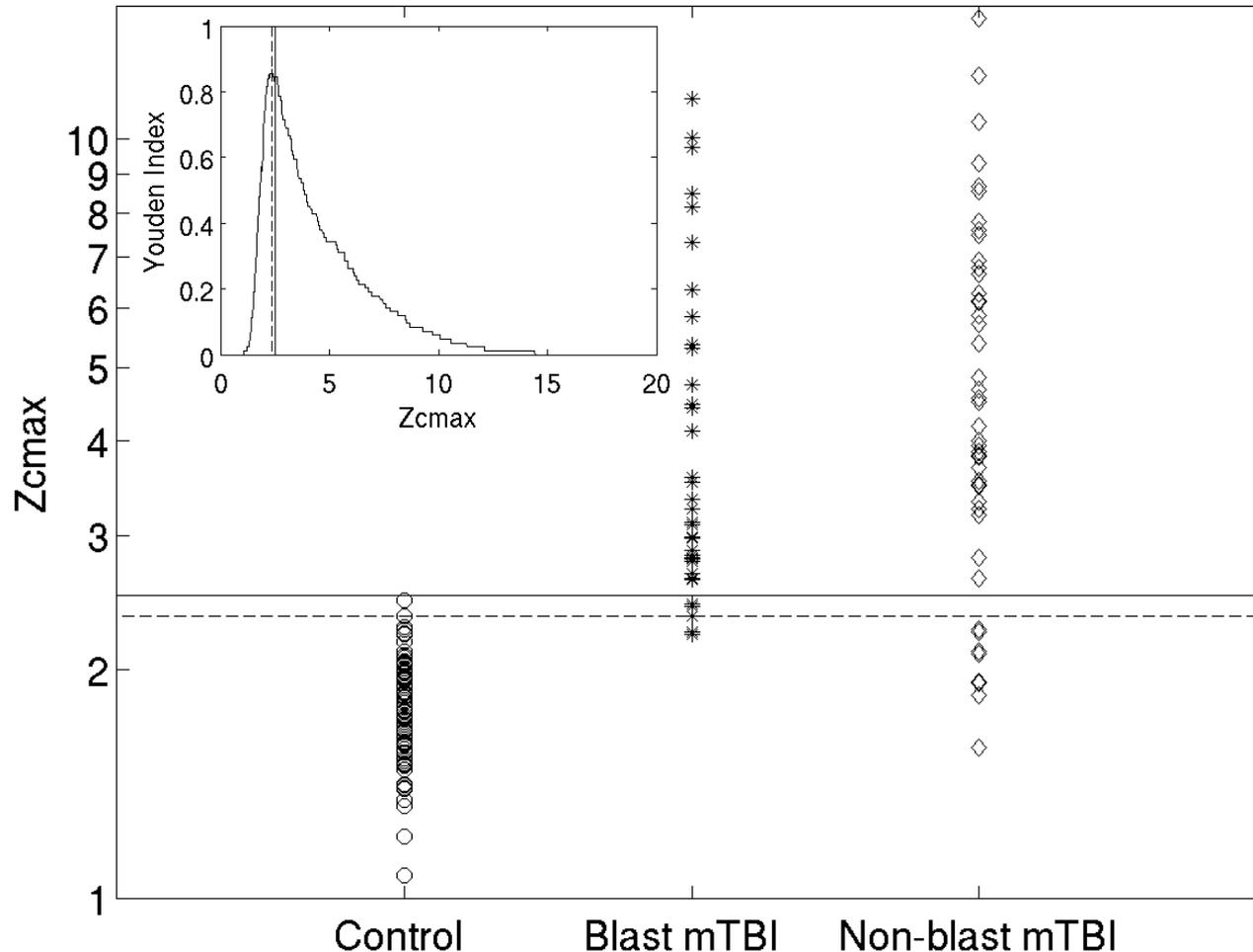
Whole brain rs-MEG source-amplitude images averaged from 41 healthy subjects in MNI-152 atlas coordinates from **Fast-VESTAL** in alpha (1<sup>st</sup> row), beta (2<sup>nd</sup> row), gamma (3<sup>rd</sup> row), and low-frequency (delta plus theta, 4<sup>th</sup> row) bands.

# Examining the positive detection rate of Mild TBI using automated resting-state MEG source imaging

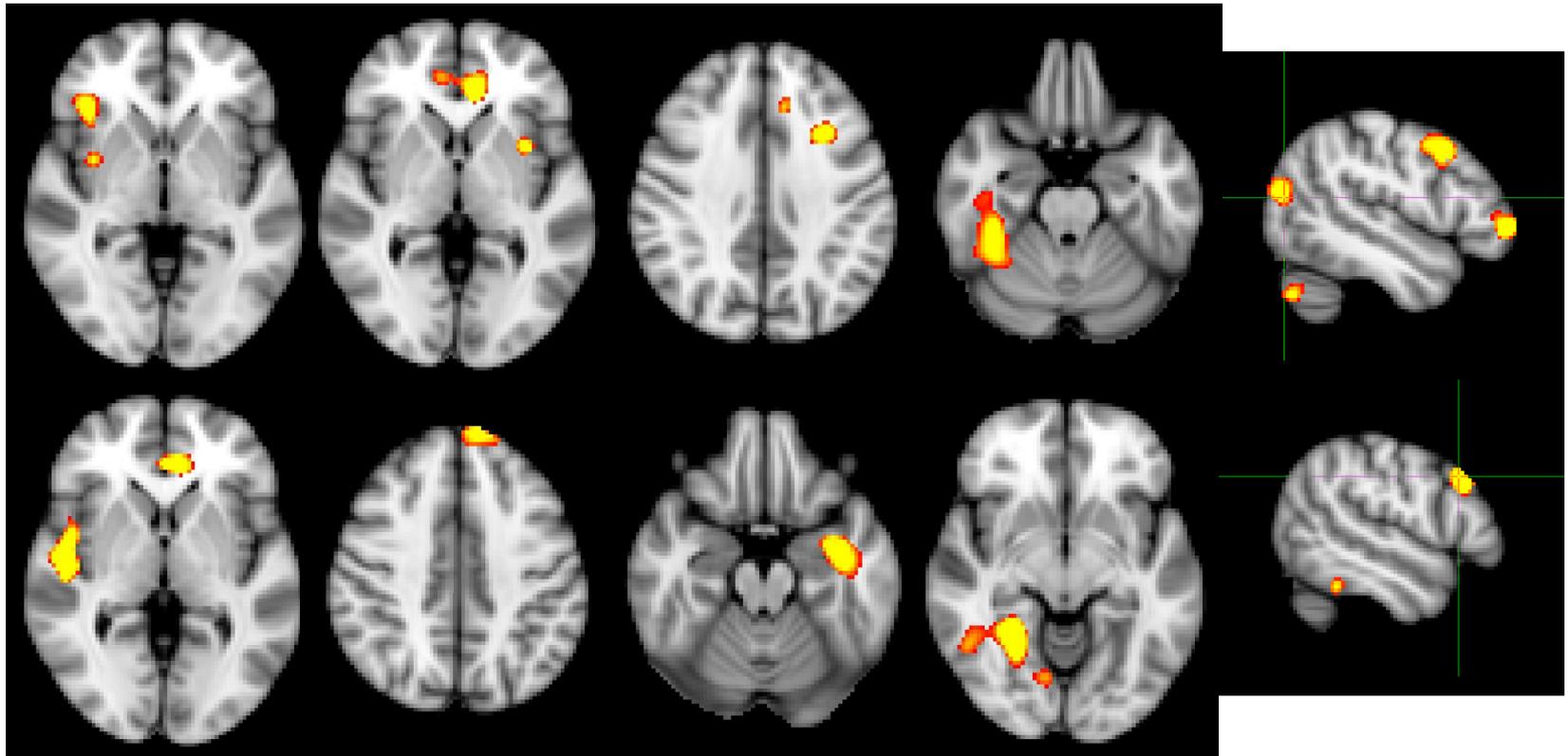
- Resting-state MEG data (spontaneous recording with eyes-closed) were collected using the Elekta-Neuromag VectorView MEG system.
- Group 1 contains 36 mild TBI patients whose injuries were caused by blast, all with persistent Post Concussion Symptoms (PCS).
- Group 2 contains the 48 mild TBI were injured with non-blast causes (i.e., motor vehicle accident, sports, and fall), all with PCS.
- On average, MEG exam was done ~7 months post injury.
- Group 3 contains 79 age-matched healthy control subjects.

# MEG slow-wave positive detection rates for mTBI: voxel-wise approach

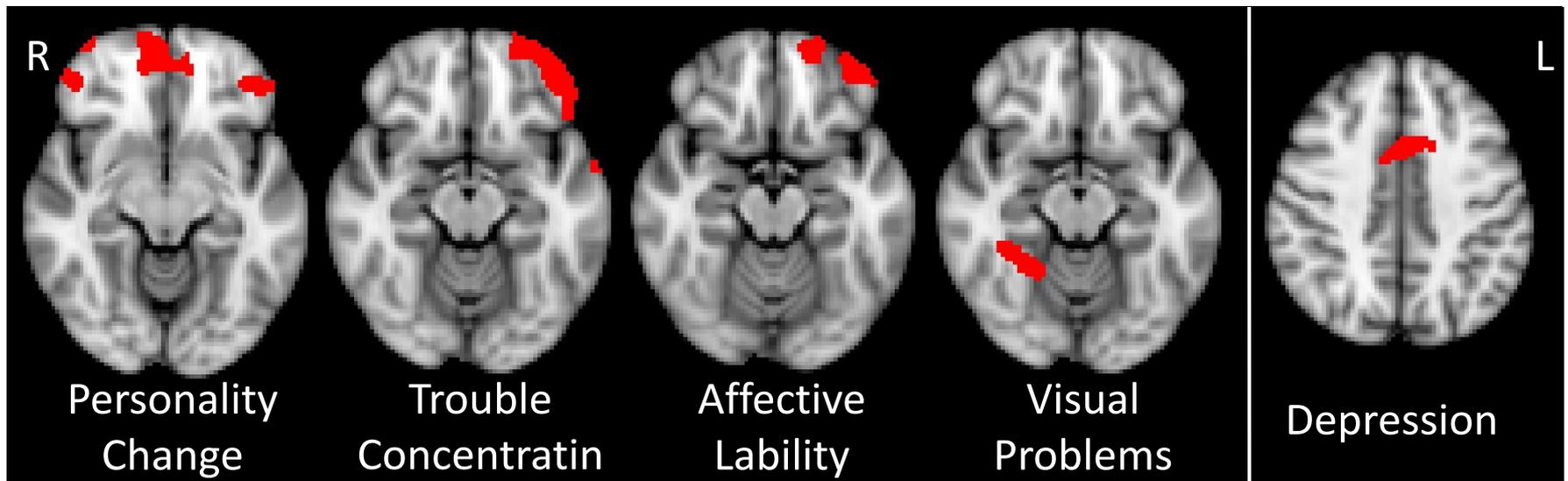
- The threshold of 0% false-positive rate in healthy control subjects.
  - In the blast mild TBI group, the MEG positive-finding rates was **86.1%**.
  - In the non-blast mild TBI group, the MEG positive-finding rates was **83.3%**.
  - In the combined mild TBI group (blast + non-blast), the MEG positive-finding rates was **84.5%**.



## Voxel-wise MEG slow-wave imaging for individual mild TBI patients

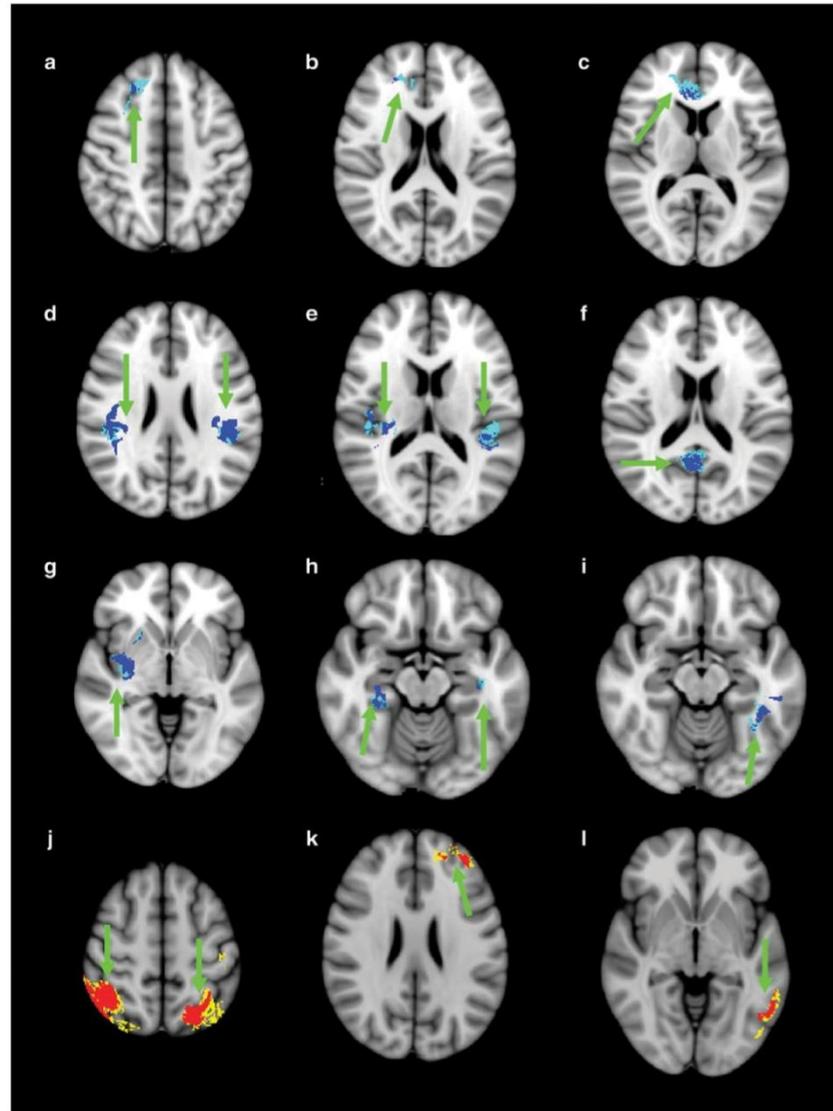


# MEG slow-wave source magnitude significantly correlated with PCS



Huang et al., NeuroImage: Clinical, 2014, 5:109-119.

# MEG slow-wave source correlates with Delis-Kaplan Executive Function System (D-KEFS) Color Word Interference Inhibition Scaled



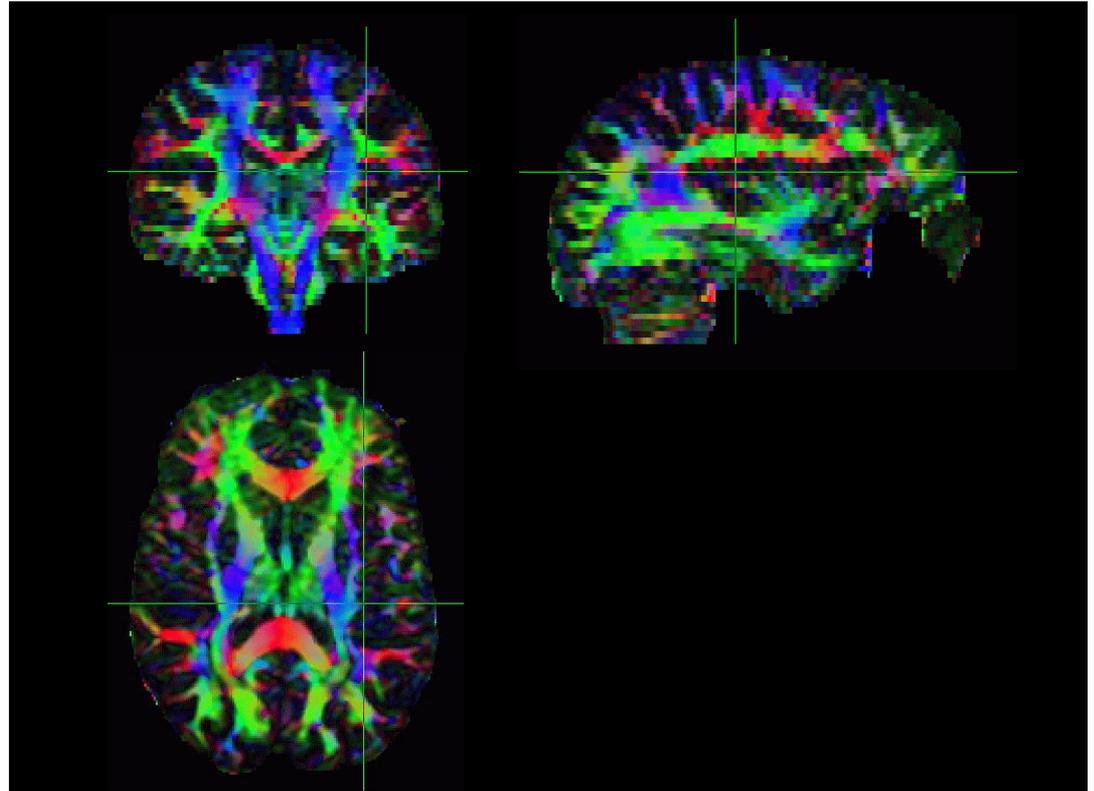
Swan et al., Journal of Neurotrauma, 2015, 32:1510–1521.

# 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.

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

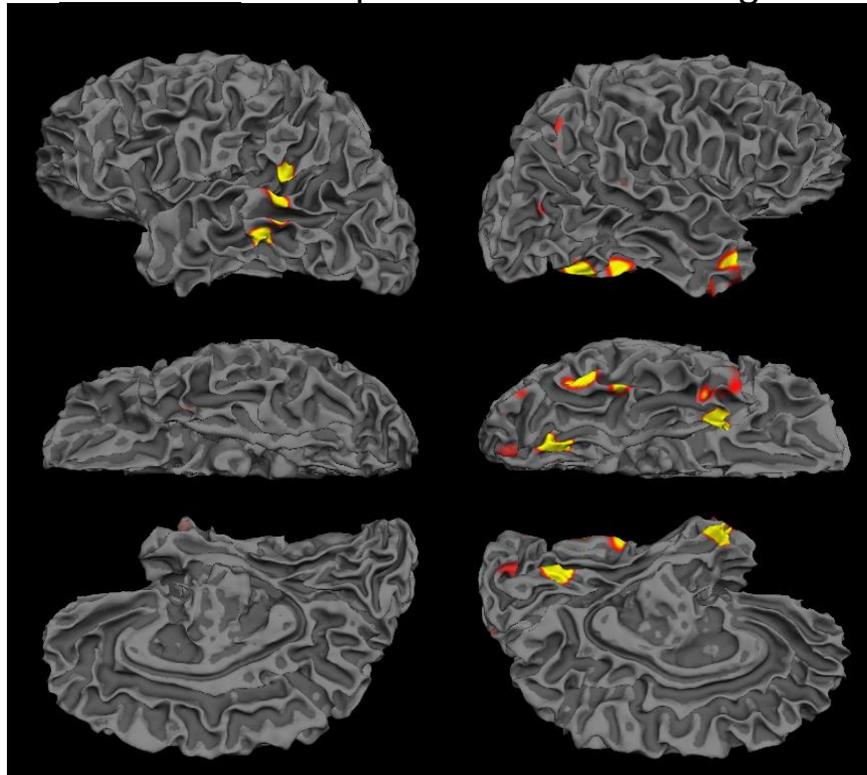
$$FA = \frac{\sqrt{3[(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2]}}{\sqrt{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$



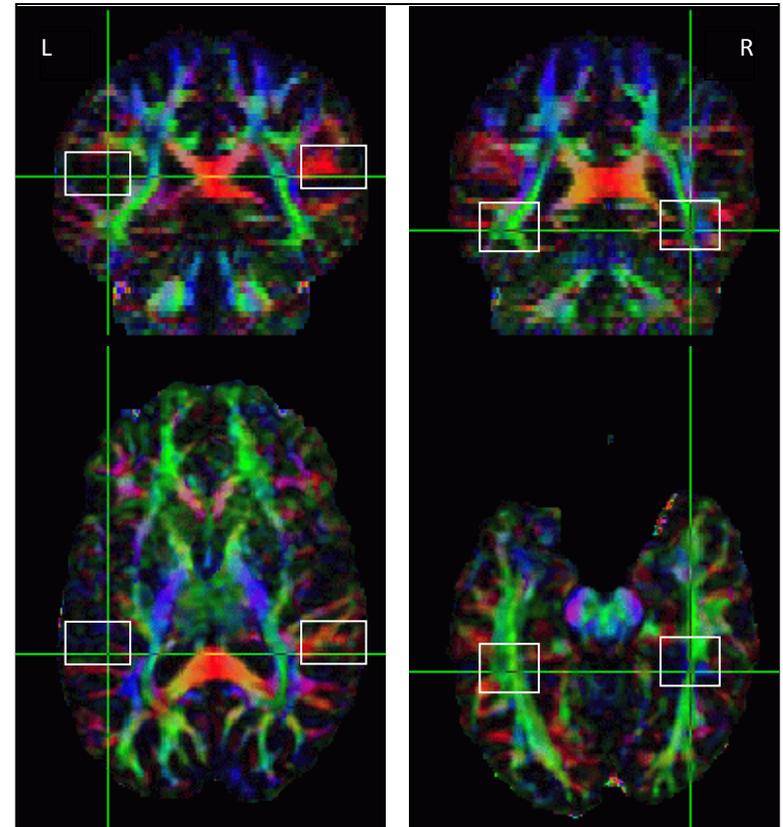
# Consistent MEG-DTI Findings in 25% Mild TBI

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.



rs-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  $p < 0.01$ .



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

# Conclusion: MEG and Diffusion MRI for mild TBI

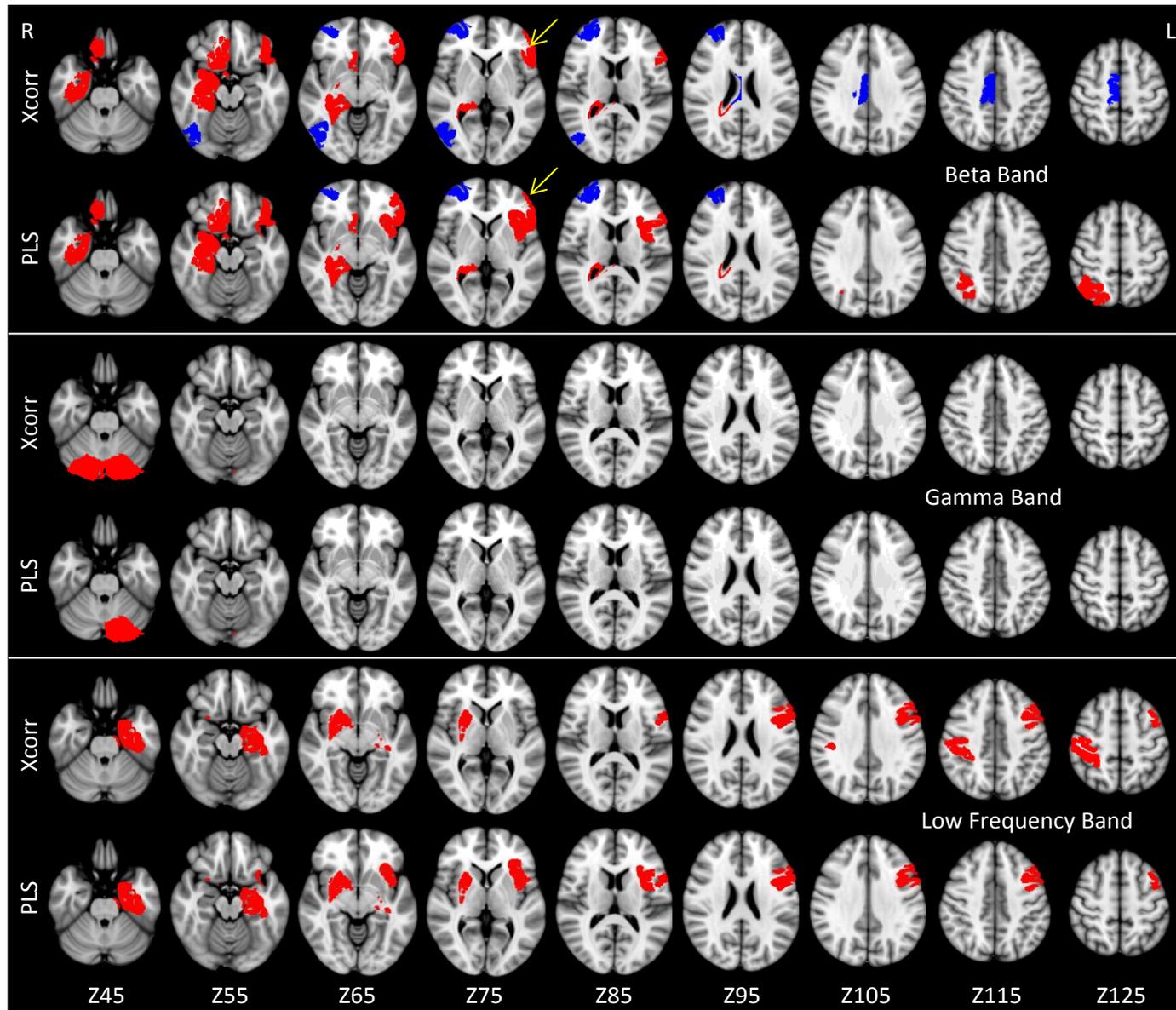
- MEG slow-waves from gray-matter result from de-afferentation, due to axonal injury and/or neuro-chemical damage in white-matter.
- For mild TBI, MEG slow-wave imaging has high sensitivity (~85%).
- In ~25% mTBI cases, MEG slow-wave imaging findings in gray-matter are consistent with reduced FA in white-matter tracks.
- Both **decreased** and **increased** fractional anisotropy (FA) were reported with diffusion MRI, with overall sensitivity 25%-30%.
- “Despite the continued advancements in DTI and related diffusion techniques over the past 20 years, DTI techniques are sensitive for mTBI at the group level only and there is insufficient evidence that DTI plays a role at the individual level.” (Douglas, et al., (2015). Top. Magn Reson. Imaging 24(5):241-251)
- Are we limiting ourselves to diffuse axonal injury model for the past 20 years in Diffusion MRI studies in mTBI?

## Confusing functional connectivity findings in mild TBI using fMRI and MEG

- Among 26 resting-state fMRI studies in mTBI
  - 6 showed functional connectivity **increases**
  - 9 showed functional connectivity **decreases**
  - 15 showed **increases** in some regions/net-works, but **decreased** in the others.
  - 4 /26 were blast mTBI
- Resting-state MEG functional connectivity studies in mTBI showed **increases** and/or **decreases**, similar to fMRI
  - Tarapore et al., J. Neurosurgery, (2013), 118:1306-1316
  - Alhourani et al., (2016), J. Neurophysiol. jn.00513.2016.
  - Antonakakis et al., (2016), Int. J. Psychophysiol. Off. J. Int. Organ. Psychophysiol. 102, 1–11.
  - Dimitriadis et al., (2015), NeuroImage Clin. 9, 519–531
  - No MEG functional connectivity study for blast mTBI

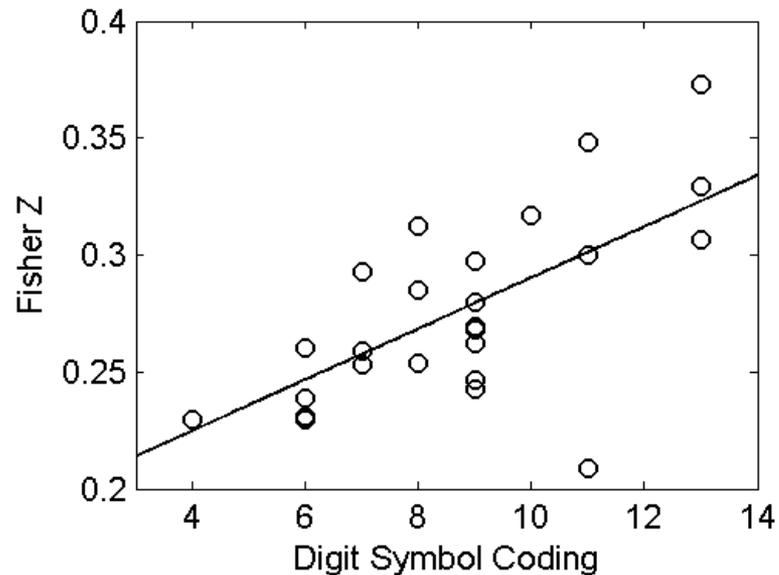
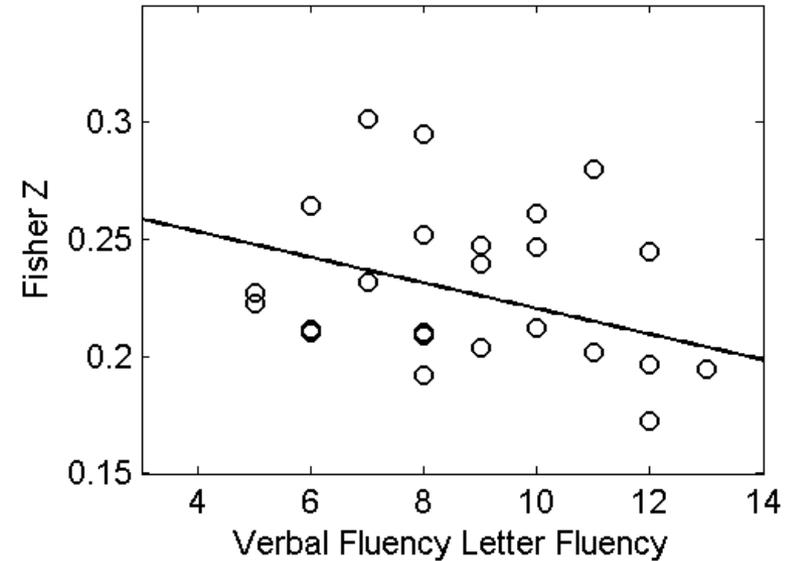
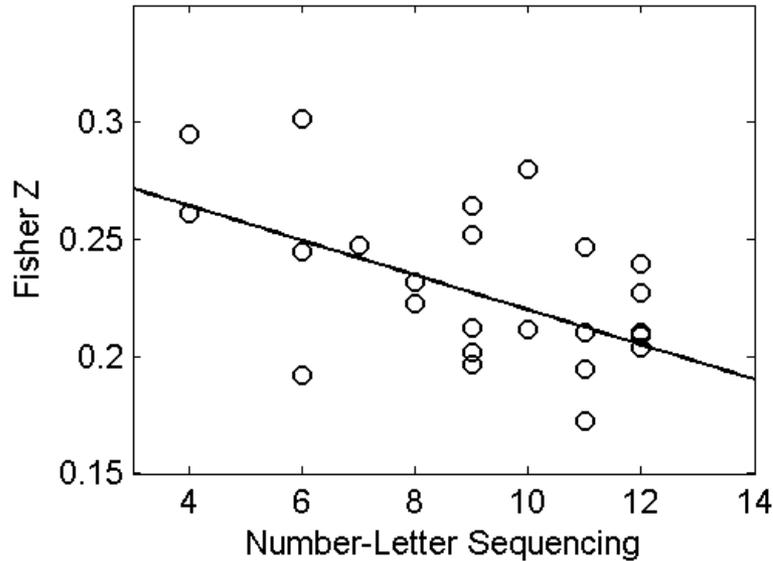
To decrease or to increase, that is the question!

# MEG functional connectivity in blast mTBI vs Ctrl



Huang, et al., J. Neurotrauma in press. ■ mTBI > Ctrl; ■ mTBI < Ctrl; corrected  $p < 0.05$

# MEG vIPFC FC correlate with neuropsychological exams in blast mild TBI



Huang, et al., J. Neurotrauma (in press) PMID: 27762653, DOI: 10.1089/neu.2016.4581

## Conclusion for MEG source imaging based functional connectivity findings in mTBI

- MEG Fast-VESTAL approach is sensitive in detecting abnormal functional connectivity in mTBI.
- High degree of similarity across different measures (lagged cross correlation, phase locking synchrony (Lachaux et al., 1999))
- Blast mild TBI group showed **decreases** and **increases** in functional connectivity over the controls.
- Three mechanisms in mTBI
  - Diffuse axonal injury predicts functional connectivity **decreases**
  - GABA-disinhibition leads to over-excitation in gray matter predicts functional connectivity **increases**.
  - Functional reorganization and compensation also predicts functional connectivity **increases**.

Increased in excitation and dis-inhibition after TBI and higher chance for developing post-traumatic epilepsy

- Prince et al., (2009). *Epilepsia* 50 Suppl 2:30-40.
- Song et al., (2015). *Brain Connect.* 5(5):276-283.

# Is Slow-wave Associated with Healing Mechanism?

- Is slow-wave generation in wakefulness merely a negative consequence of neuronal injury?
- Or, is the slow-wave a signature of ongoing neuronal rearrangement and healing that occurs at the site of the injury?
- Morawska et al., (2016). Sleep Modulation Alleviates Axonal Damage and Cognitive Decline after Rodent Traumatic Brain Injury. *J Neurosci* 36, 3422–3429.
- Xie et al., (2013). Sleep drives metabolite clearance from the adult brain. *Science* 342, 373–377.
- Mander et al., (2015).  $\beta$ -amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat Neurosci* 18, 1051–1057.

# Post-Traumatic Stress Disorder: PTSD

OEF/OIF/OND  
Military Service  
Members and  
Veterans in the U.S.

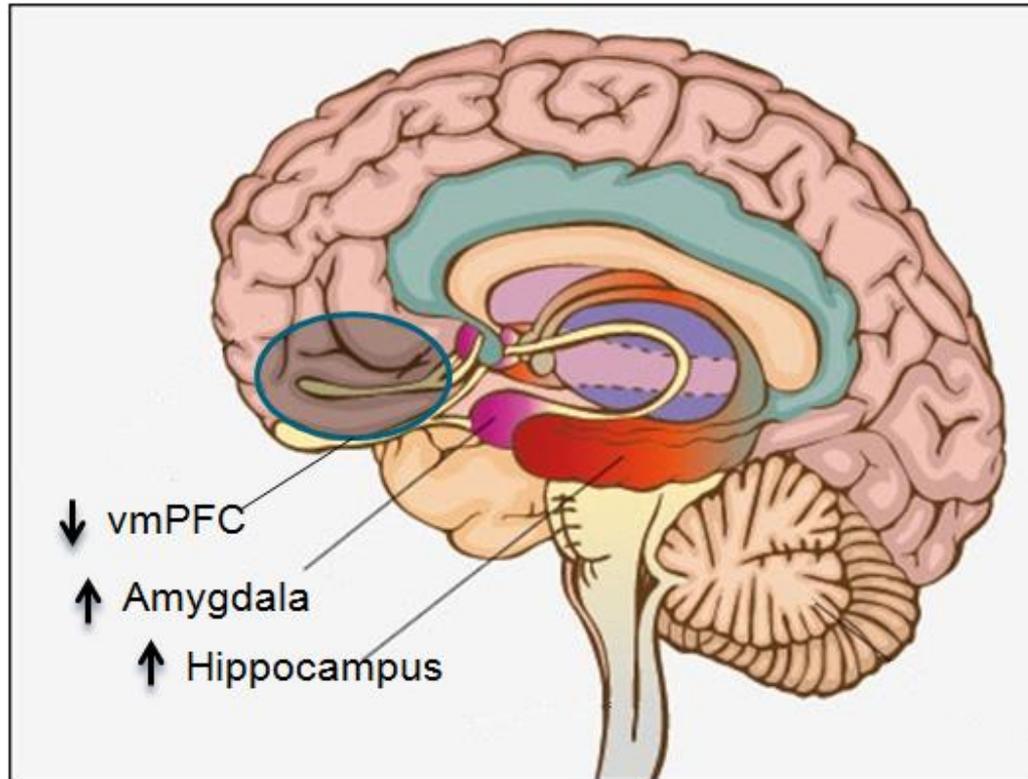


Devastating Earthquake  
and Tsunami, Japan, 2011



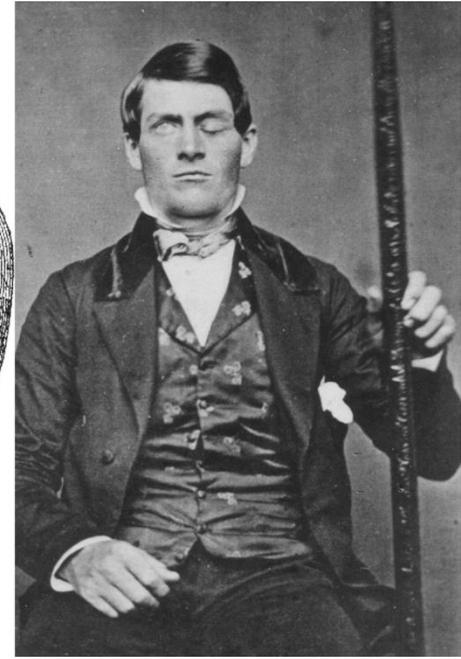
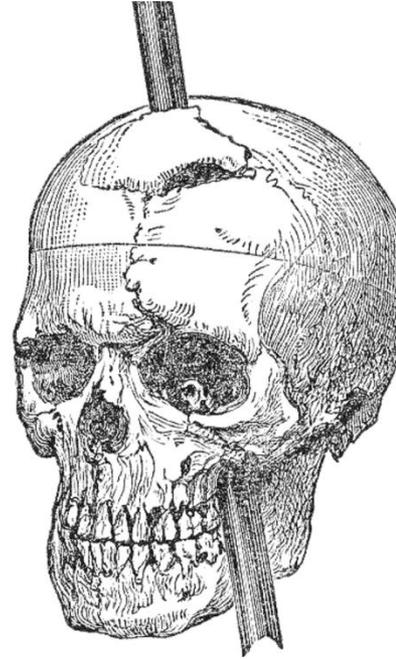
Tiananmen Square Massacre,  
Beijing, China, 1989

# The neurocircuitry of PTSD



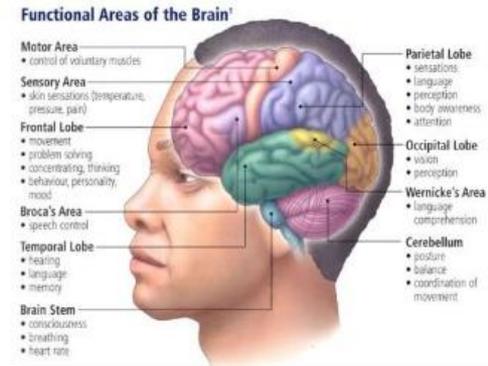
- Hyper-responsive Amygdala
- Hyper-responsive Hippocampus
- Hypo-responsive ventromedial prefrontal cortex (vmPFC)

# Severe Traumatic Brain Injury – Phineas Gage



## The Effects

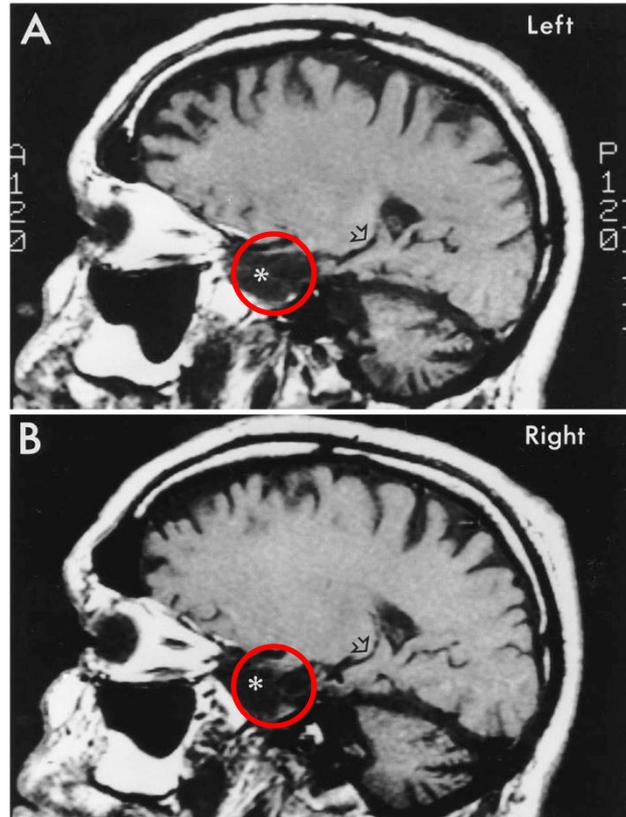
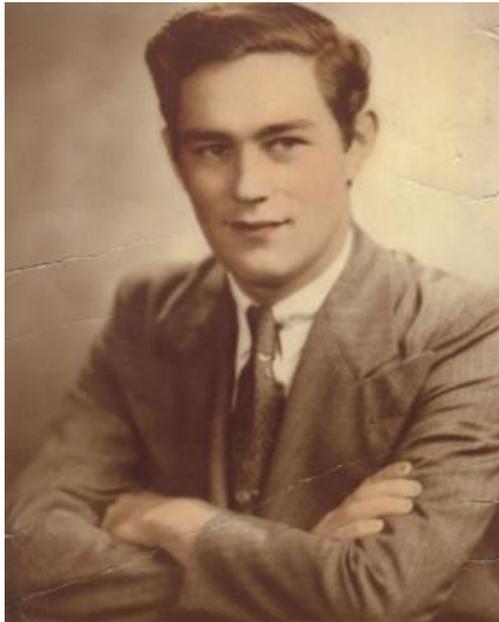
The parts of the frontal lobes essential to intellectual, motor and language function, the motor strip and Broca's area, were undamaged, leaving his ability to move, talk, and understand language intact. The major damage caused to the **ventromedial** region is likely responsible for the majority of the personality changes.



# Patient H.M. (Henry Molaison 1926-2008) and the Function of Hippocampus

Corkin et al. • MRI of H. M.'s Brain

J. Neurosci., May 15, 1997, 17(10):3964-3979 3969

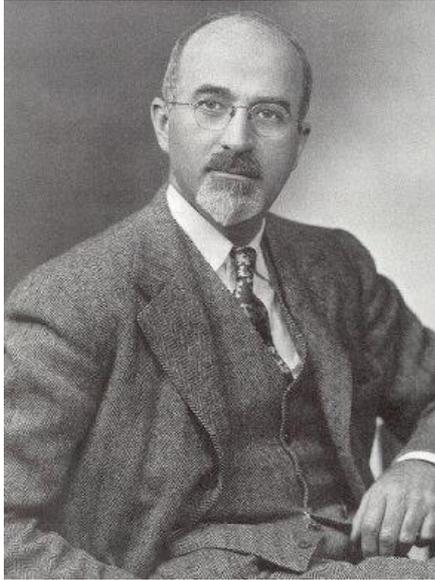


*Figure 3.* T1-weighted parasagittal sections from the left (A) and right (B) sides of H. M.'s brain. The resected portion of the anterior temporal lobes is indicated bilaterally with an asterisk. The remaining portion of the intraventricular portion of the hippocampal formation is indicated with an open arrow. Scale bar (right of A), 5 cm in 1 cm increments. Approximately 2 cm of preserved hippocampal formation is visible bilaterally. Note also the substantial cerebellar degeneration obvious as enlarged folial spaces.



Dr. Brenda Milner

# Notorious Dr. Walter Freeman and his Lobotomy



# Questions to be Addressed by Current MEG Study

- Is MEG source imaging able to directly detect abnormal electromagnetic signals in PTSD neurocircuitry?
- If yes, at what frequency bands?
- How similar are the MEG source imaging findings to the PET/fMRI findings in PTSD?

Huang et al., Voxel-wise resting-state MEG source magnitude imaging study reveals neurocircuitry abnormality in active-duty service members and veterans with PTSD. *NeuroImage: Clinical*, 5:408-419, 2014

# MEG protocol for imaging the neurocircuitry of PTSD

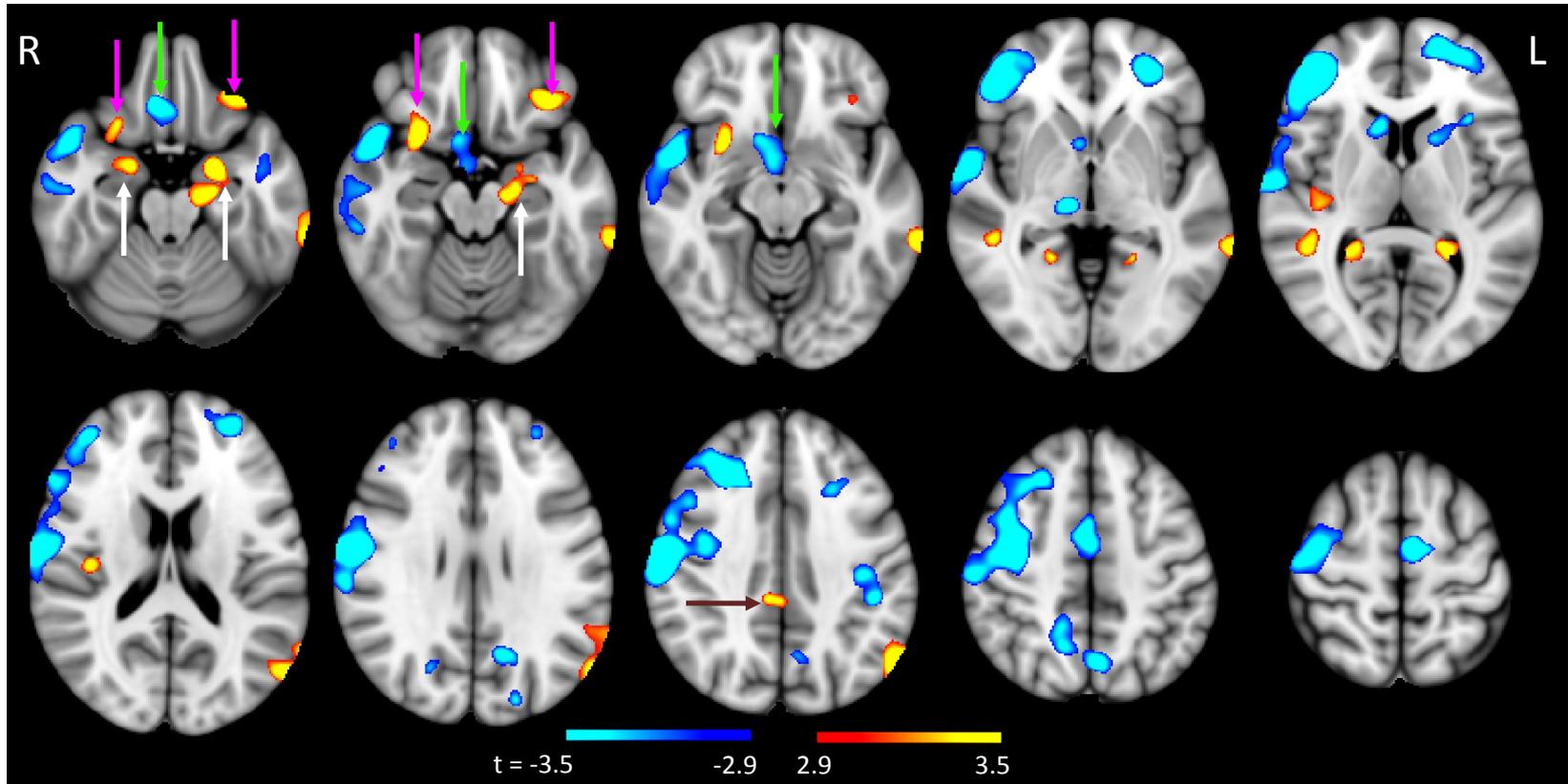
- Resting-state MEG recording with eyes-closed
- 25 active-duty and Veterans diagnosed with PTSD (CAPS total: 41-81)
- 30 Healthy Controls
- MEG source imaging for different frequency bands
- Hypothesis 1: hyper-activity in amygdala and hippocampus
- Hypothesis 2: hypo-activity in ventromedial prefrontal cortex (vmPFC)

Huang et al., Voxel-wise resting-state MEG source magnitude imaging study reveals neurocircuitry abnormality in active-duty service members and veterans with PTSD. *NeuroImage: Clinical*, 5:408-419, 2014

# MEG data processing

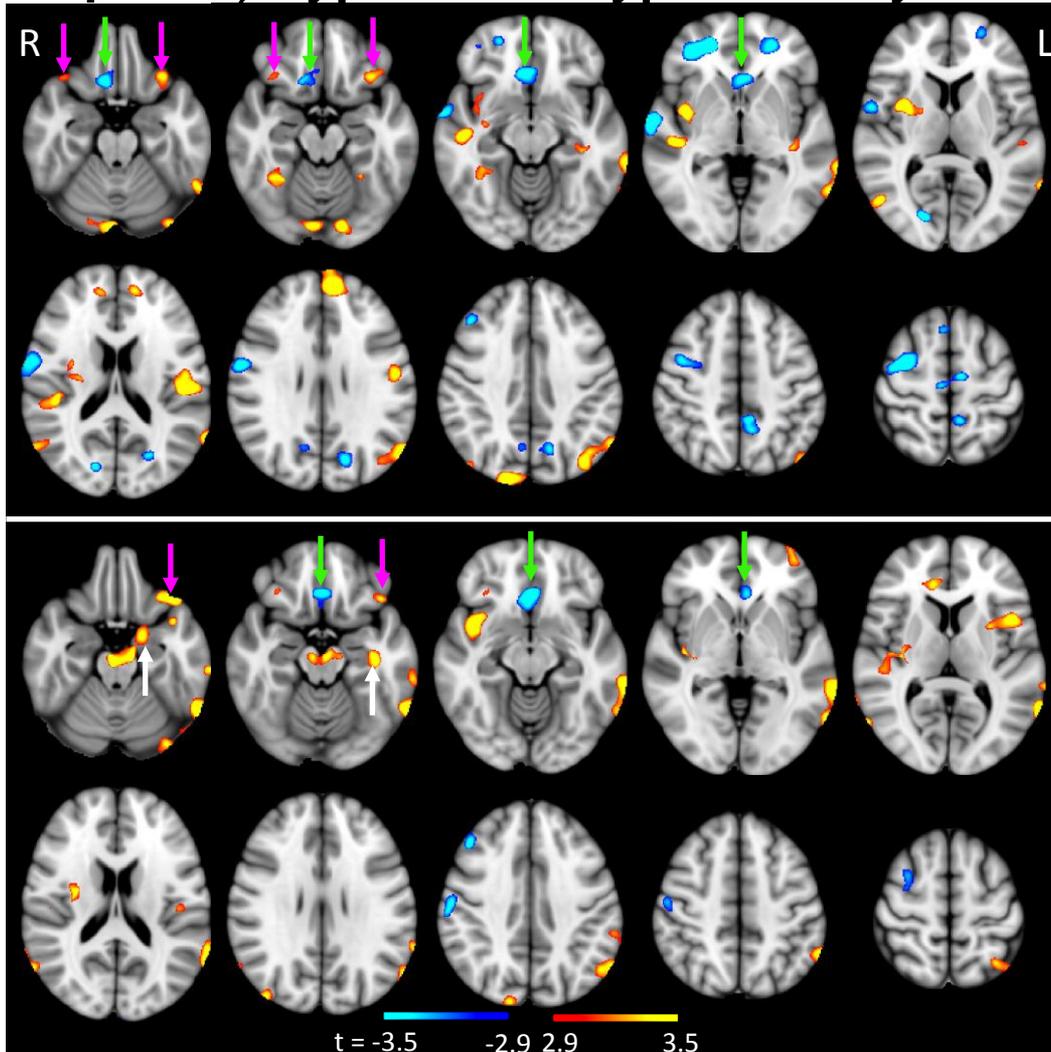
- MaxFilter and ICA for removing noise and artifacts
- Data were divided into 2.5 sec epochs
- Apply DC correction, band-pass filter for alpha (8-12 Hz), beta (15-30 Hz), gamma (30-80 Hz), high-gamma (80-150 Hz), and low-frequency (1-7 Hz) bands.
- Calculate sensor waveform covariance matrix
- Run Fast-VESTAL to obtain voxel-wise source images
- Run spatial smoothing, then registered to MNI space.
- Perform logarithm transformation
- Voxel-wise comparison between PTSD and healthy controls
- Statistical analysis and correct for family-wise error

# MEG Beta-band hyper- and hypo-activity in PTSD versus healthy controls. PTSD



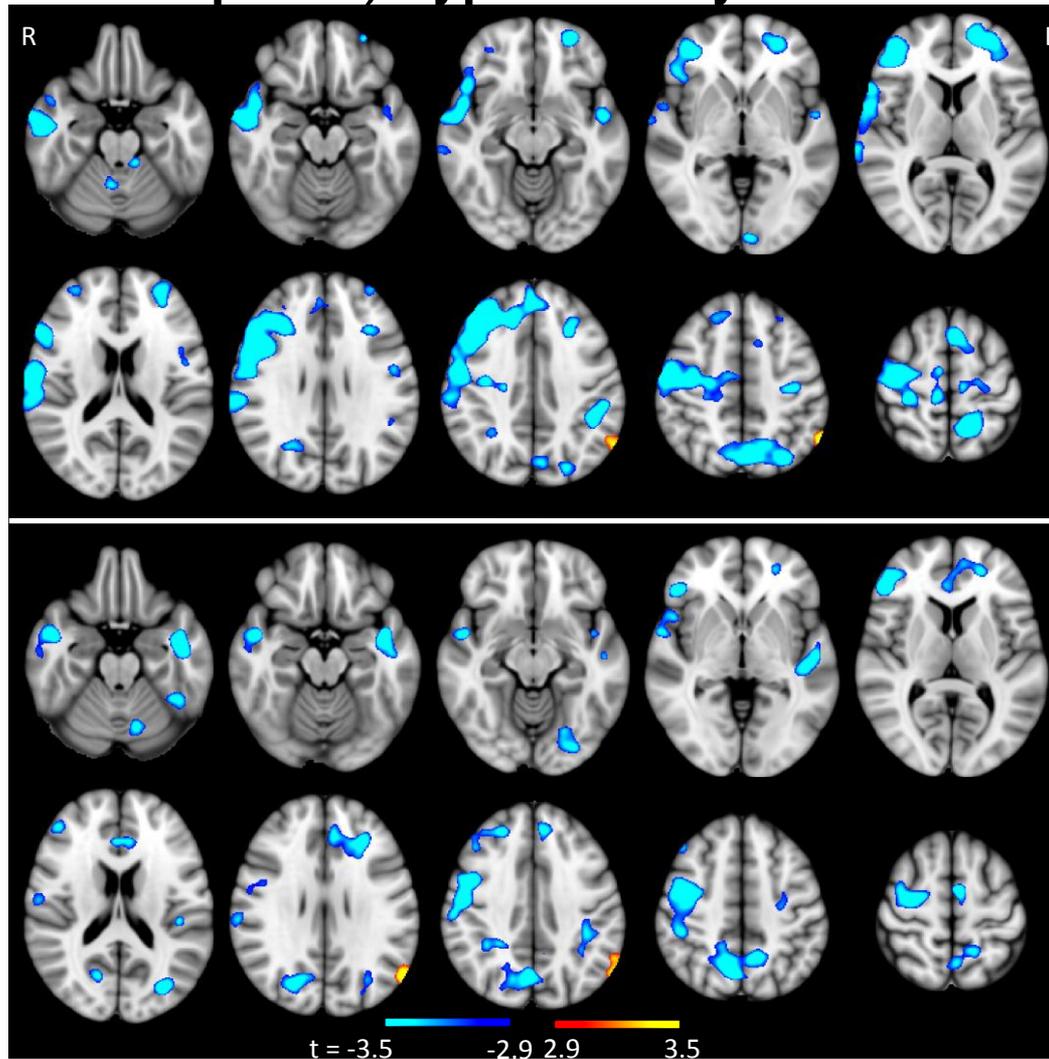
- Hyper-activity: L+R Amygdala (white arrows), L hippocampus, L+R posterolateral OFC (magenta arrows), R insular cortex, PCC, etc.
- Hypo-activity: vmPFC (green arrows), L+R dlPFC, precuneus cortex, L+R frontal poles, L temporal poles, etc.

# MEG gamma-band (upper panel) and high gamma band (lower panel) hyper- and hypo-activity in PTSD



- Hypo-activity: vmPFC (green arrows), L dlPFC, precuneus cortex, etc.
- Hyper-activity: L+R Amygdala (white arrows), L hippocampus, L+R posterolateral OFC (magenta arrows), L+R insular cortex, dmPFC, etc.

# MEG alpha-band (upper panel) and low-freq band (lower panel) hypo-activity in PTSD



Hypo-activity: bilateral FPs, bilateral dlPFC, right superior frontal gyrus, bilateral anterior temporal lobes, bilateral precuneus cortices, and bilateral sensorimotor cortices.

# PTSD Symptoms (CAPS) Correlating with MEG Source Magnitude

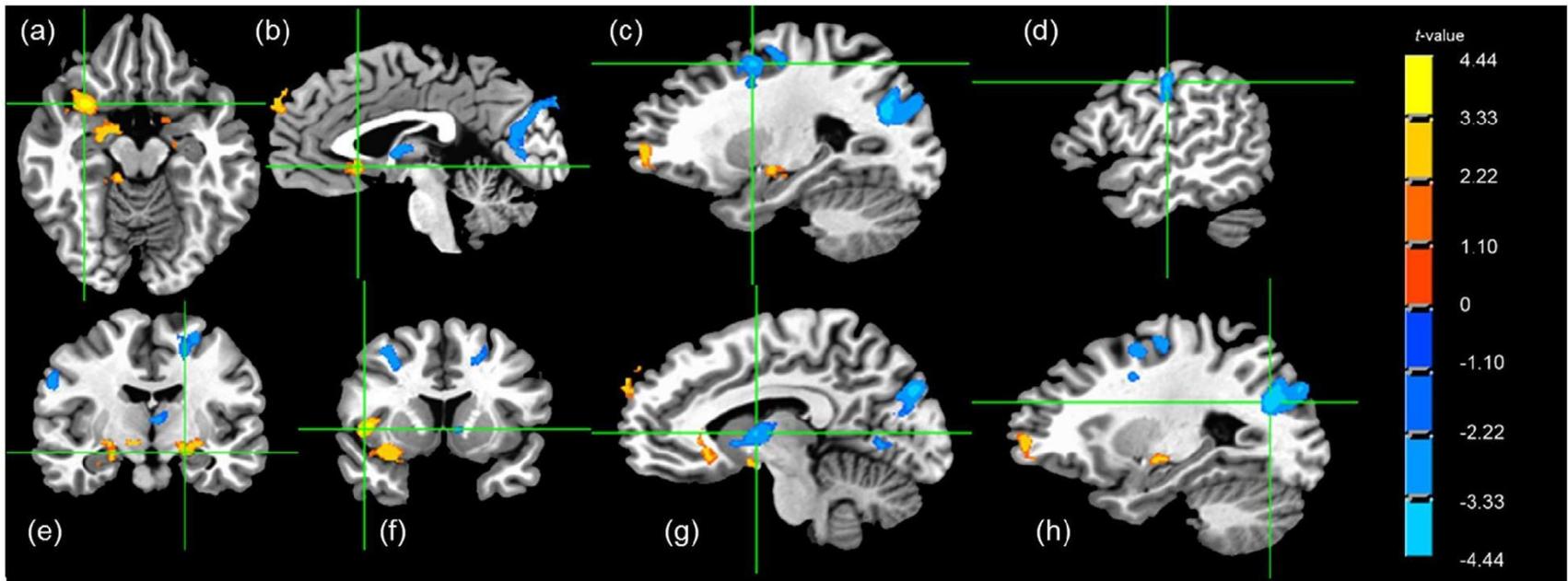
- Positively correlated with MEG left amygdala (beta band,  $r = +0.51$ ,  $p < .05$ ).
- Positively correlated with left posterolateral OFC (beta band,  $r = +0.55$ ,  $p < .05$ )
- Negatively correlated with vmPFC (beta band,  $r = -0.58$ ,  $p < .01$ ; gamma band,  $r = -0.63$ ,  $p < .01$ ; and high-gamma band,  $r = -0.60$ ,  $p < .01$ ).
- Negatively correlated precuneus (alpha band,  $r = -0.48$ ,  $p < .05$ )
- Using the MEG source magnitude from the above areas, support vector machine (SVM) correctly classified PTSD patients with 93% accuracy, and healthy controls with 95% accuracy.

# Resting-state fMRI findings in PTSD

Yan et al., Neuroscience Letters. 547: 1-5, 2013

X. Yan et al. / Neuroscience Letters 547 (2013) 1–5

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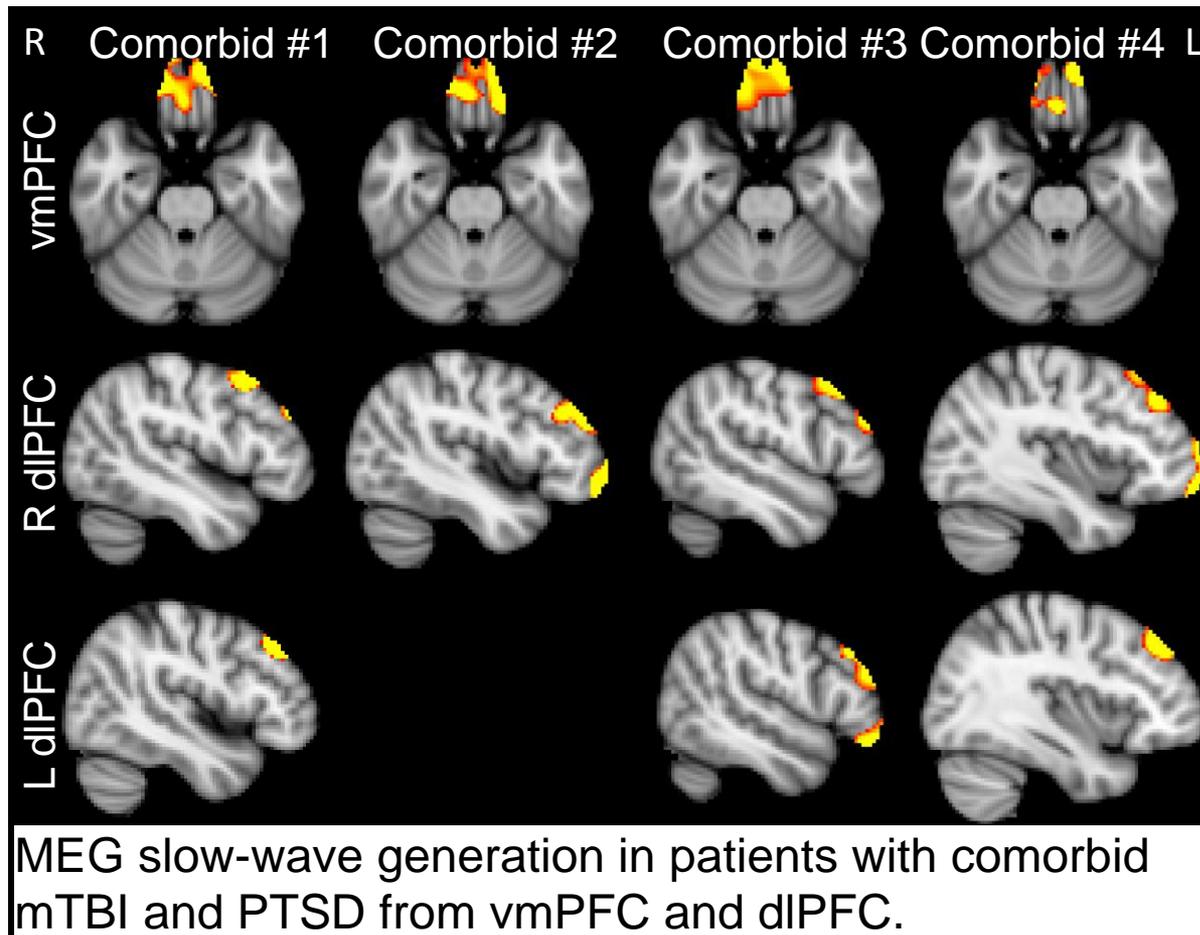


**Fig. 1.** Brain regions showing significant group differences between PTSD and controls in terms of magnitudes of spontaneous activity. The crosshairs are focused at the following brain regions: (a) orbital frontal gyrus, (b) anterior cingulate cortex, (c) superior frontal gyrus, (d) dorsal lateral prefrontal cortex, (e) amygdala, (f) insula, (g) thalamus and (h) precuneus. Warm colors (red and yellow) represent increased spontaneous activity in the PTSD group compared to the control group, whereas cold color (blue) represents decreased spontaneous activity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

# Conclusion of MEG Study in PTSD

- In MEG beta and gamma bands, PTSD showed **hyperactivity** in amygdala, hippocampus
- PTSD showed **hypoactivity** in vmPFC, dlPFC, precuneus, frontal poles, anterior temporal lobes
- New finding: hyperactivity from posterolateral OFC
- MEG abnormal activity correlated with PTSD symptom scores.
- MEG findings are similar to fMRI findings, but MEG offers markedly more information in terms of new abnormal areas, frequency-bands, etc.

# Abnormal MEG Slow-waves from vmPFC and dlPFC in Patients with Comorbid mTBI and PTSD



# Acknowledgement

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- ❑ Investigator Collaboration: VA San Diego Healthcare System, UCSD.



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Annemarie Angeles  
Ashley Robb  
Angela Drake**



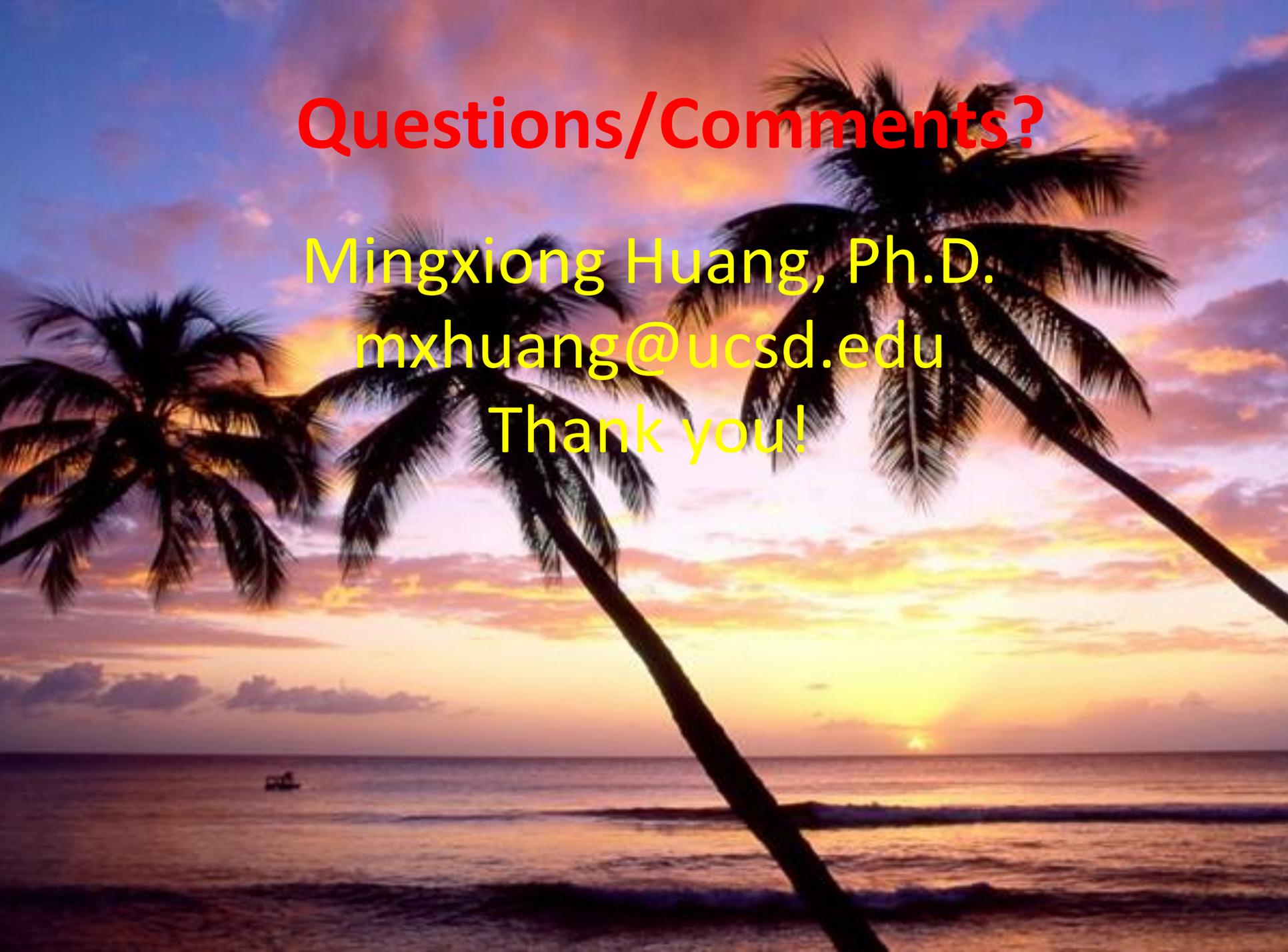
**Roland Lee  
Sharon Nichols  
Mithun Diwakar  
Deborah Harrington  
Tao Song**

# Resources

- “Invisible Injuries become not so Invisible”  
TV Interview with Col G.I. Wilson by KPBS:  
<http://www.youtube.com/watch?v=uhIANIGAJXA>
- National Public Radio interview “War Studies Suggest A Concussion Leaves The Brain Vulnerable To PTSD”:  
<http://www.npr.org/sections/health-shots/2016/09/26/495074707/war-studies-suggest-a-concussion-leaves-the-brain-vulnerable-to-ptsd>
- More publications from our lab:  
<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/48074704/?sort=date&direction=descending>

# Poll Question

- Which field(s) describes your interests in TBI / PTSD (select all that apply)?
  - \_\_ diagnosing TBI / PTSD
  - \_\_ treating TBI / PTSD
  - \_\_ animal research of TBI / PTSD
  - \_\_ human research of TBI / PTSD
  - \_\_ social work or other support to TBI / PTSD

A tropical sunset scene with palm trees and a boat on the ocean. The sky is filled with soft, colorful clouds in shades of orange, yellow, and blue. The sun is low on the horizon, casting a warm glow over the water. Several palm trees are silhouetted against the sky, and a small boat is visible on the ocean in the distance.

**Questions/Comments?**

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Thank you!