Brain Amygdala Volume Changes in Veterans and Active-Duty Military Personnel With Combat-Related Posttraumatic Stress Disorder and Mild Traumatic Brain Injury

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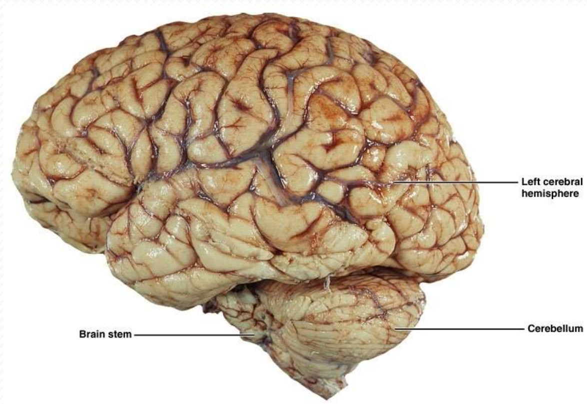
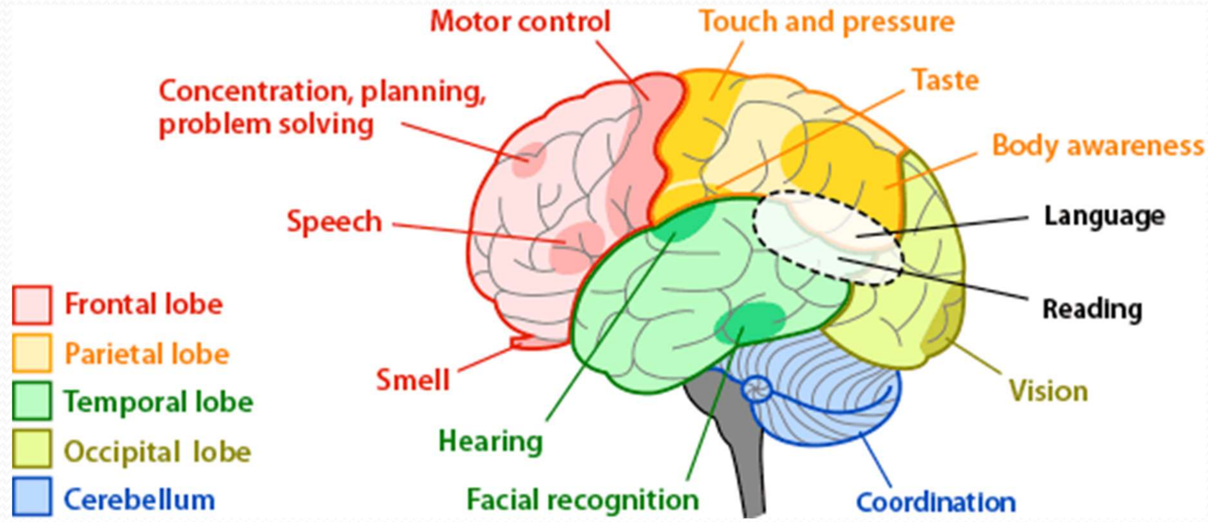
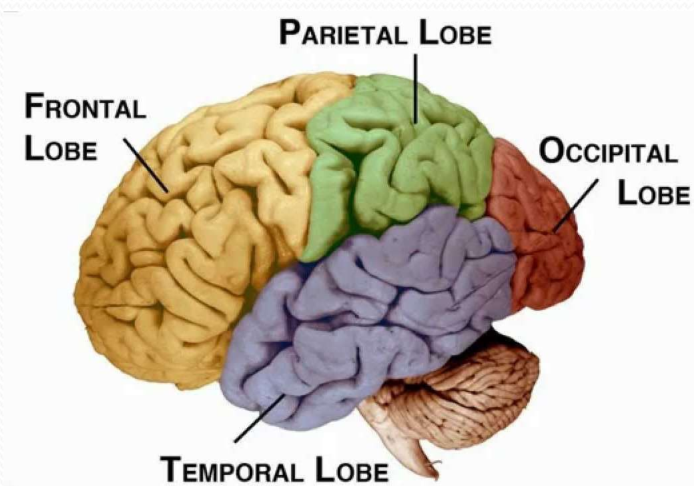
Combat-related PTSD vs. Co-morbidity of PTSD and mTBI

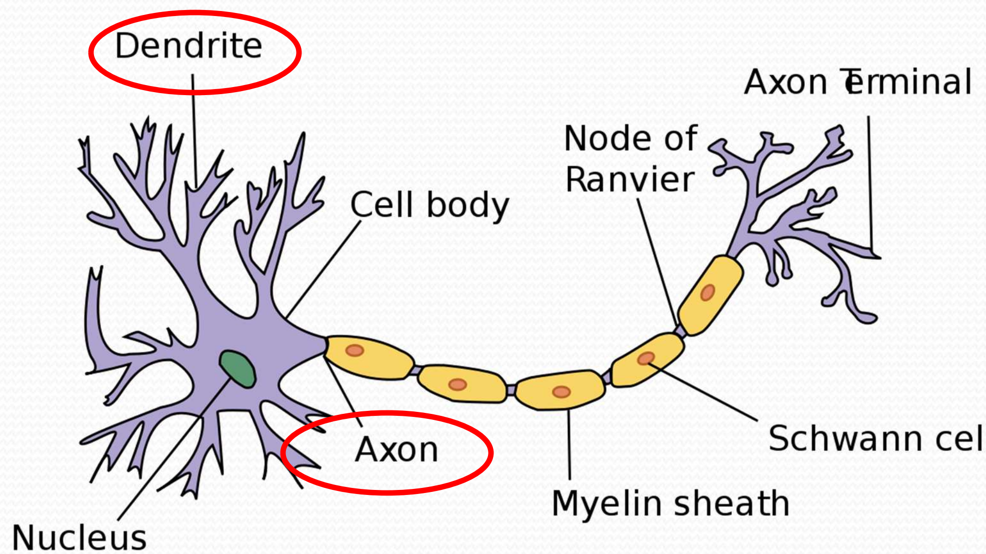
- Combat-related post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) are leading healthcare issues in veterans and active-duty military personnel.
- The co-occurrence of PTSD in OEF/OIF service members with mTBI has been reported at rates of 33% - 66% in various studies.
- PTSD and mTBI share some similar symptoms, including depression, sleep disturbances, and cognitive and neuropsychiatric impairments.
- Neural mechanisms of PTSD, mTBI, and particularly the co-morbidity of PTSD and mTBI have not been fully understood.

Human Brain Contains 5 Lobes and 100 Billion Neurons

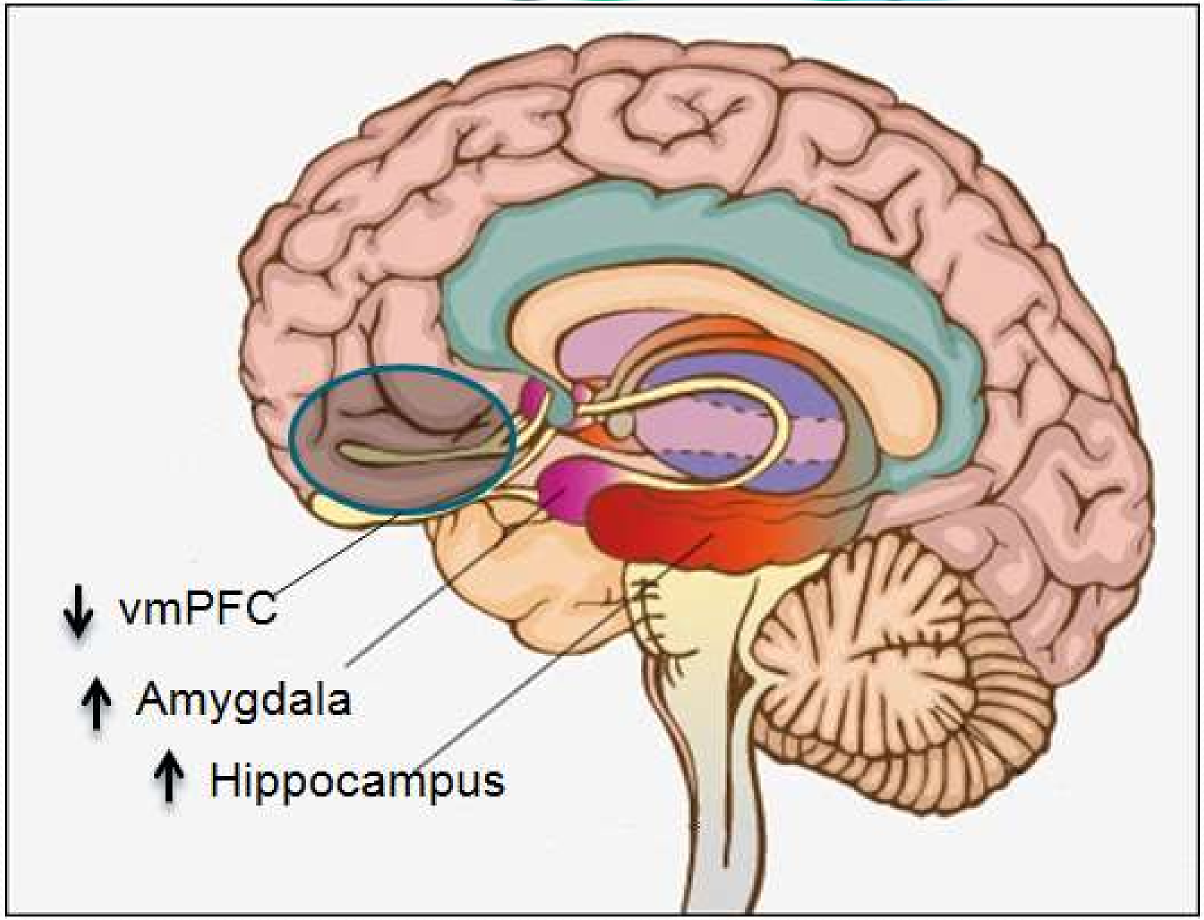






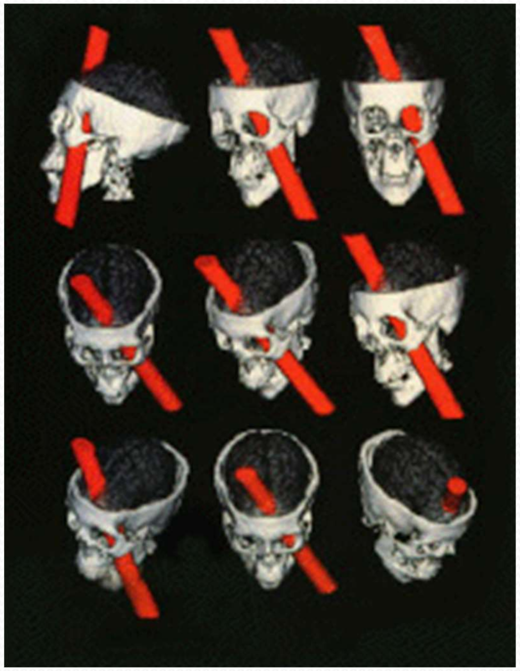


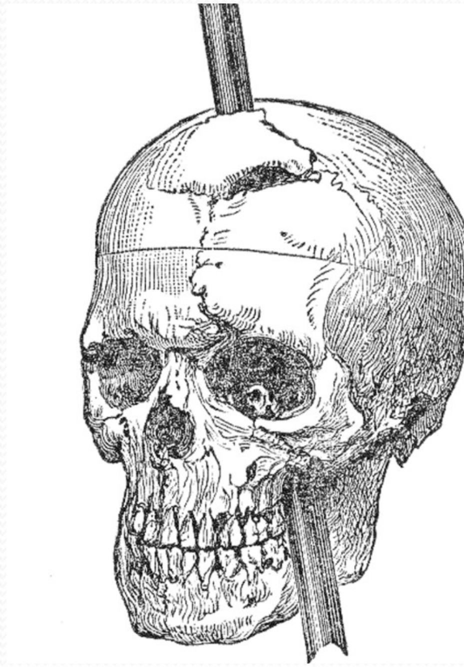
PTSD and its Neurocircuitry

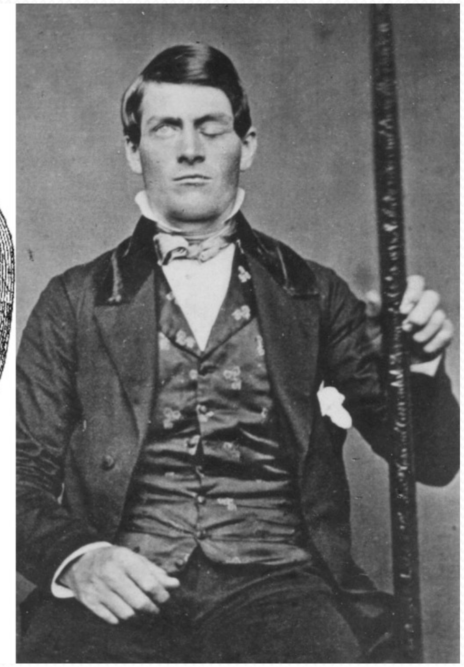


- Rauch, Shin, Phelps. Biol. Psychiatry 60, 376-382, 2006; Shin and Liberzon. Neuropsychopharmacology 35: 169-191, 2010
- Hyper-responsive Amygdala
- Hyper-responsive Hippocampus
- Hypo-responsive ventromedial prefrontal cortex (vmPFC)

Severe Traumatic Brain Injury – Phineas Gage

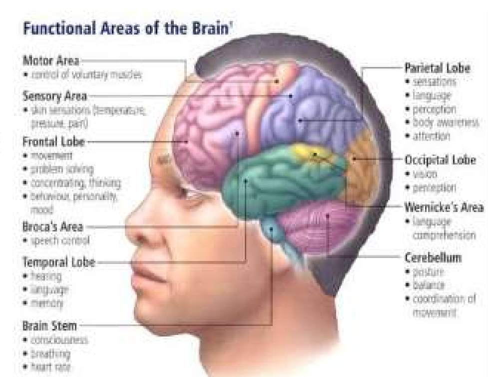






The Effects

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**

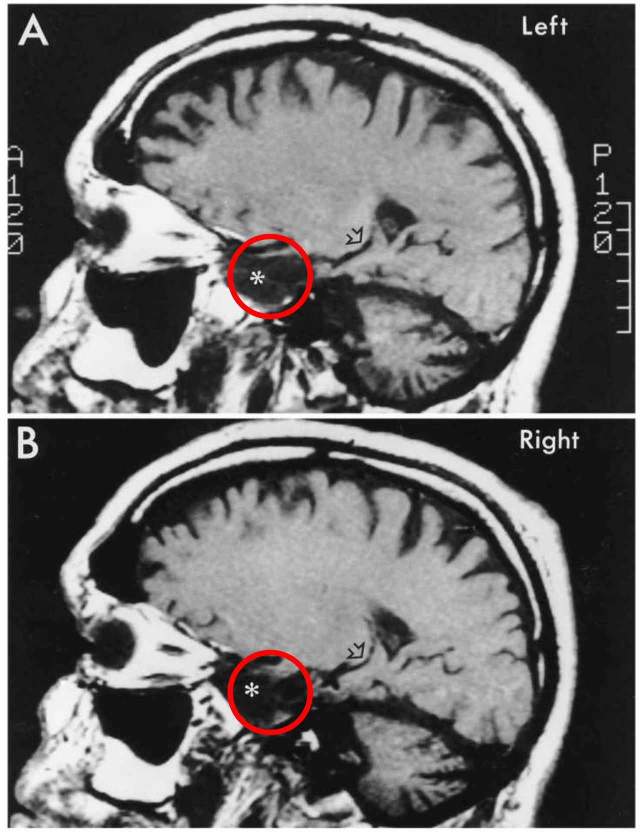


Figure 3. T1-weighted parasagittal sections from the left (*A*) and right (*B*) sides of H. M.'s brain. The resected portion of the anterior temporal lobes is indicated bilaterally with an *asterisk*. The remaining portion of the intraventricular portion of the hippocampal formation is indicated with 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 at MNI

Notorious Dr. Walter Freeman and his Lobotomy

Portuguese neurologist António Egas Moniz, Nobel Prize for Physiology or Medicine of 1949

Studies to cover today

- Brain amygdala volume changes in veterans and active-duty military personnel with combat-related posttraumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI).
- Resting-state magnetoencephalography (rs-MEG) study in combat-related PTSD neurocircuitry.

Amygdala volume changes due to combat-related PTSD

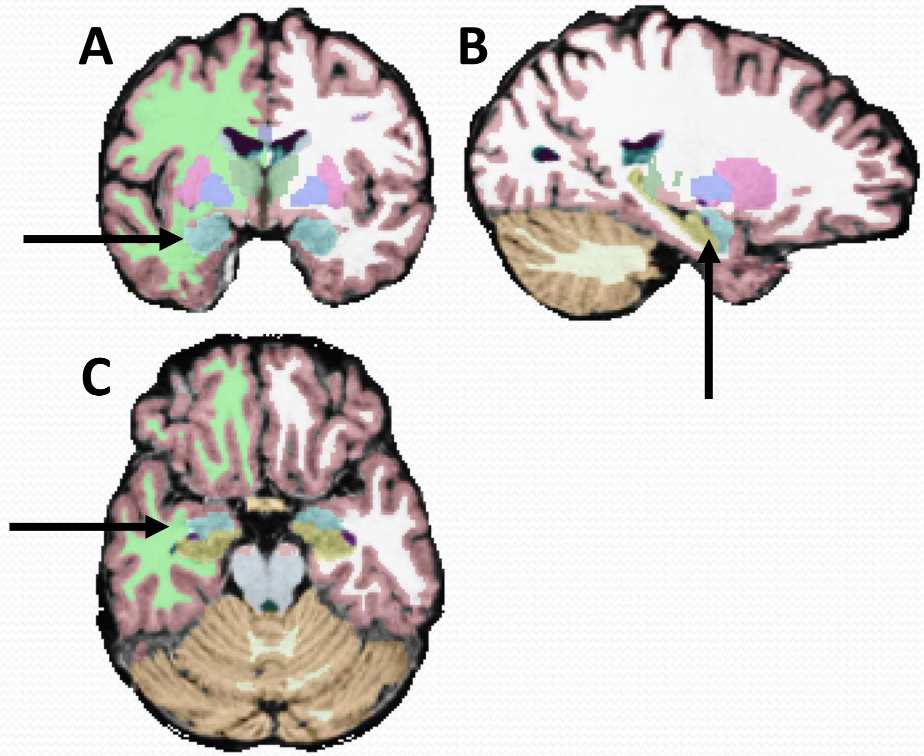
- Inconsistency exists in literature regarding amygdala volume changes in PTSD where **increase** (e.g., Kuo et al., Arch. Gen. Psychiatry 2012; 69:1080–1086: combat PTSD vs no PTSD) or **decrease** (e.g., Morey et al., Arch.Gen.Psychiatry 2012; 69:1169–1178; PTSD vs HC) in amygdala volume were reported.
- Key issues that need to be systematically studied:
- 1). Combat-related comorbid PTSD with mTBI vs combat-related mTBI, with matching the combat-experience
- 2). The effects of intracranial volume (ICV) on amygdala volumetric measures.

Subject demographics of the clinical groups: The mTBI-only and co-morbid mTBI/PTSD groups show no significant difference in any demographic characteristic or handedness.

Characteristic	mTBI (n=60)	Co-morbid mTBI/PTSD (n=29)
Age (SEM)	29.1 (0.7)	32 (1)
Years Education (SEM)	12.9 (0.2)	13.2 (0.3)
Race (% White)	73.3%	75.9%
Gender (% Male)	100%	96.6%
Handedness (% Right)	100%	100%
Post-injury period (Days)	2425.8 ± 2705.9	1937.2 ± 1785.2

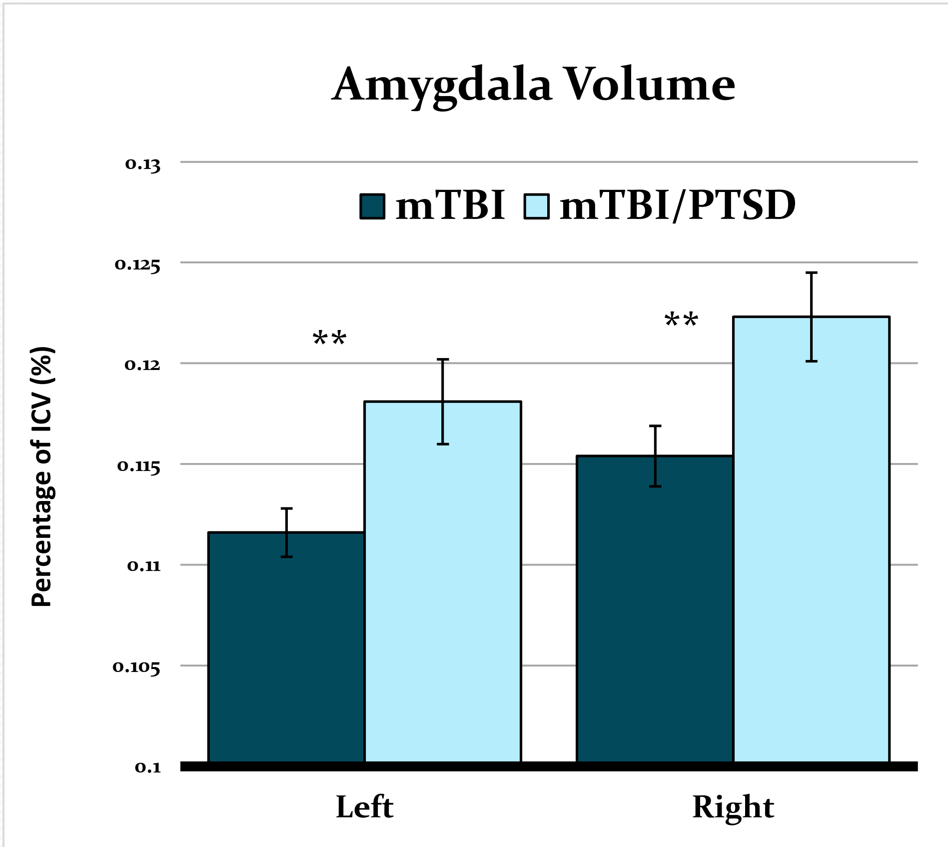
Pieper et al. J Head Trauma Rehabil. 2020 Jan-Feb; 35(1): E1–E9.

Anatomical location of amygdala



A) Coronal, B) sagittal, and C) axial sections showing automated segmentation of subcortical structures using Freesurfer software. The amygdala is shown in light teal

Co-morbid mTBI/PTSD group had **significantly larger amygdala** volumes when normalized to ICV. The statistical false discovery rate (FDR) corrected p-value is < 0.05 in the co-morbid mTBI/PTSD compared to mTBI-only group.



However, non-normalized amygdala volumes showed no significant difference between groups.

Pieper et al. J Head Trauma Rehabil. 2020 Jan-Feb; 35(1): E1–E9.

ICV-normalized volume for different brain regions in the mTBI-only and co-morbid mTBI/PTSD groups. ** indicates significant statistical differences.

Brain Regions	ICV normalized volume (%) in mTBI (n=60)	ICV normalized volume (%) in Co-morbid mTBI/PTSD (n=29)	t-value	p-value
L Caudate	0.231 ± 0.027	0.238 ± 0.027	-1.12	0.26
L Hippocampus	0.271 ± 0.022	0.279 ± 0.028	-1.48	0.14
L Amygdala	0.112 ± 0.009	0.118 ± 0.011	-2.73	0.01**
L ACC	0.152 ± 0.021	0.144 ± 0.019	1.82	0.07
R Caudate	0.231 ± 0.027	0.242 ± 0.030	-1.64	0.11
R Hippocampus	0.286 ± 0.022	0.296 ± 0.026	-1.79	0.08
R Amygdala	0.115 ± 0.012	0.122 ± 0.012	-2.61	0.01**
R ACC	0.146 ± 0.021	0.143 ± 0.023	0.50	0.62

Pieper et al. J Head Trauma Rehabil. 2020 Jan-Feb; 35(1): E1–E9.

Summary of amygdala volume study on comorbid PTSD and mTBI vs only mTBI

- Combat-exposed individuals with co-morbid mTBI and PTSD have significantly larger normalized amygdala volumes compared to those with mTBI only.
- Overall, amygdala volumes in the co-morbid mTBI and PTSD group were 6% larger when normalized to ICV.
- Right amygdala was larger than the left in our sample.
- Our findings are also consistent with a large number of previous studies in animal models (see reviews by Cacciaglia et al., Psychoneuroendocrinology 2017; 76:19–28) that showed a persistent amygdala hypertropy was associated with prolonged multiple traumatic stresses.
- Potential factors / mechanisms: prolong stress induces dendritic remodeling, enhances synaptic connectivity, etc.

Pieper et al. J Head Trauma Rehabil. 2020 Jan-Feb; 35(1): E1–E9.

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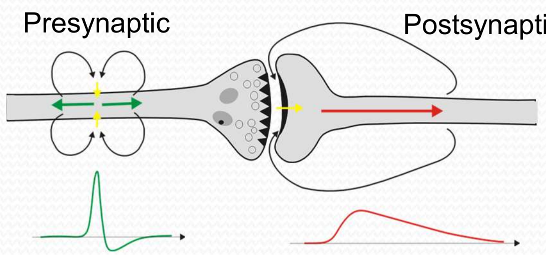
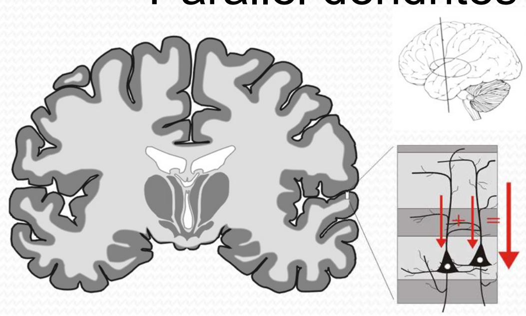
Magnetoencephalography (MEG): non-invasive functional imaging technique for gray matter activity with 1 ms time resolution and 2-3 mm spatial resolution in cortex

Neuronal currents in axons and dendrites

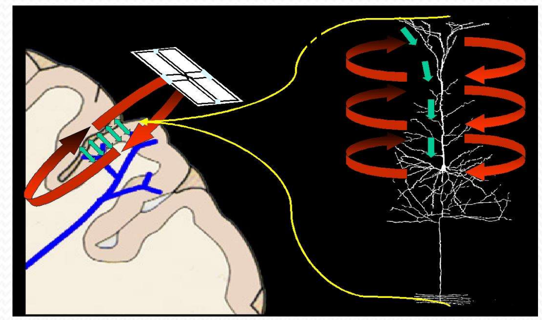


Parallel dendrites

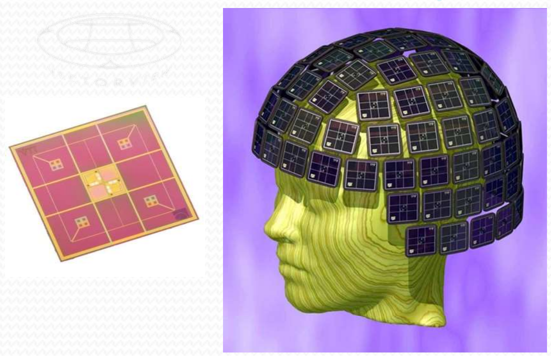


Pyramidal cells: parallel orientation
=> spatial summation

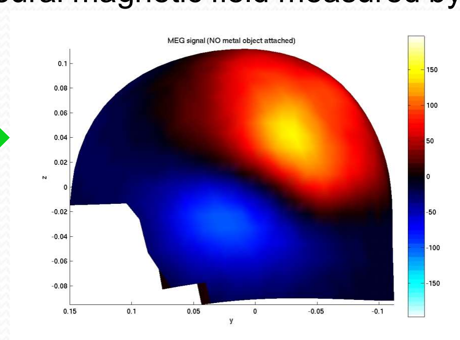
Neuromagnetic



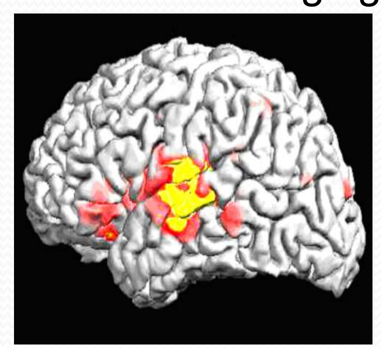
MEG SQUID Sensor Array



Neural magnetic field measured by MEG



MEG source imaging



Non-invasive MEG System and the best Magnetic Shielded Room for MEG at UCSD

UCSD 6-Layer Magnetic Shielded Room

Shielding factors:

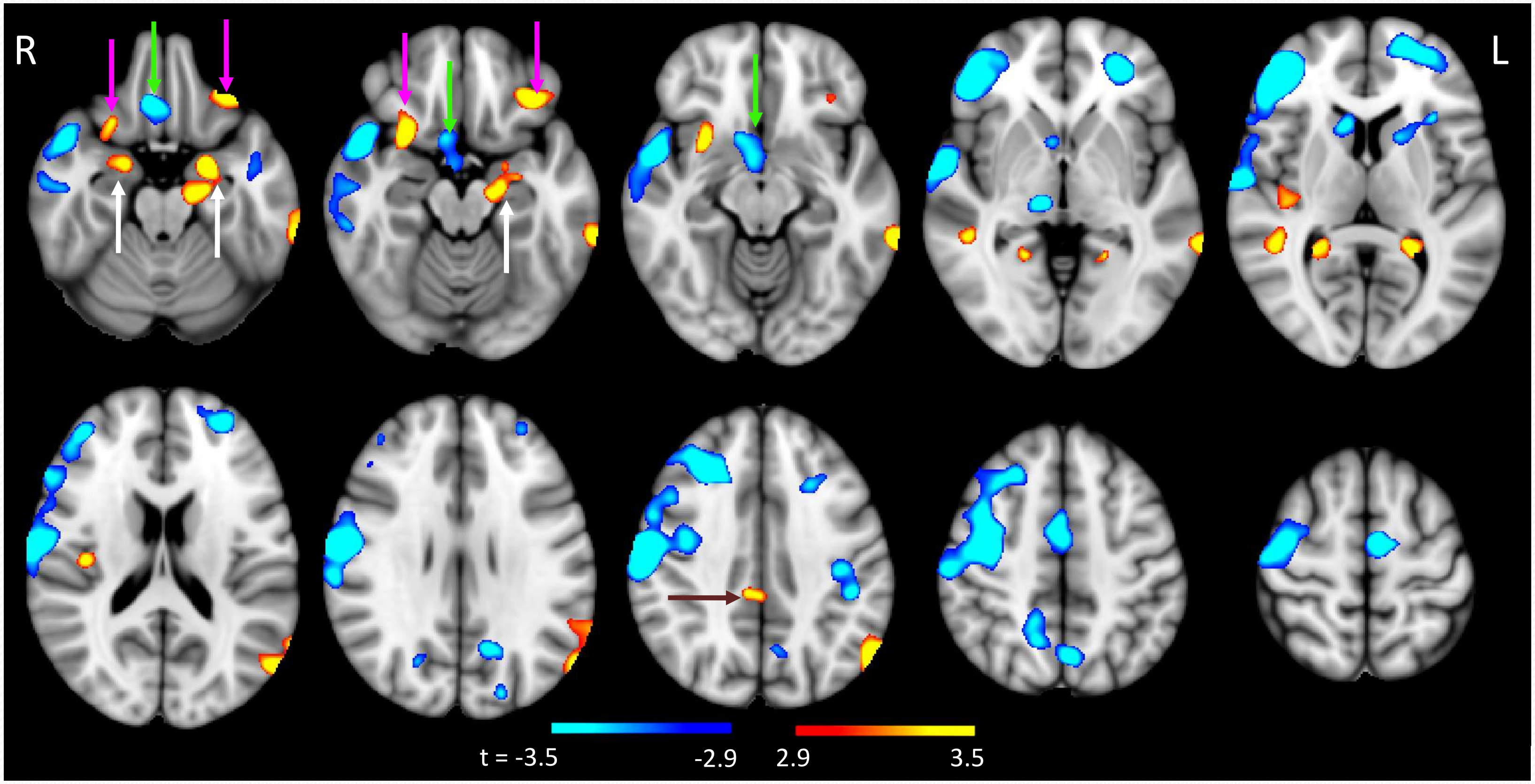
0.01Hz: 65dB

0.1 Hz: 73dB

1 Hz: 108dB

10Hz: 160dB

Rs-MEG Beta-band hyper- and hypo-activity in PTSD (n=25) versus healthy controls (n=30)

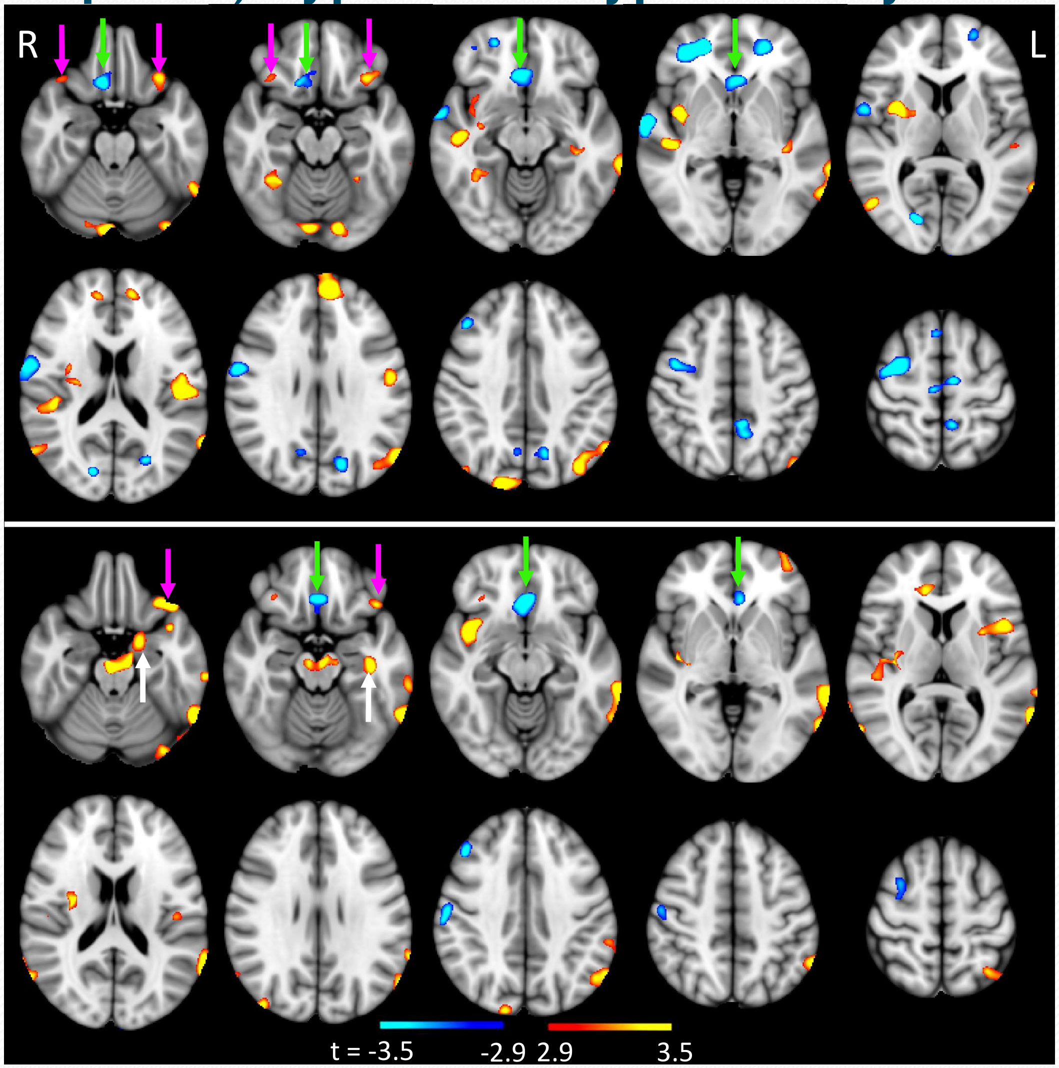


•Hyper-activity: L+R Amygdala (white arrows), L hippocampus, L+R posterolateral OFC (magenta arrows), R insular cortex, PCC (brown arrow), etc.

•Hypo-activity: vmPFC (green arrows), L+R dlPFC, precuneus cortex, L+R frontal poles, L temporal poles, etc.

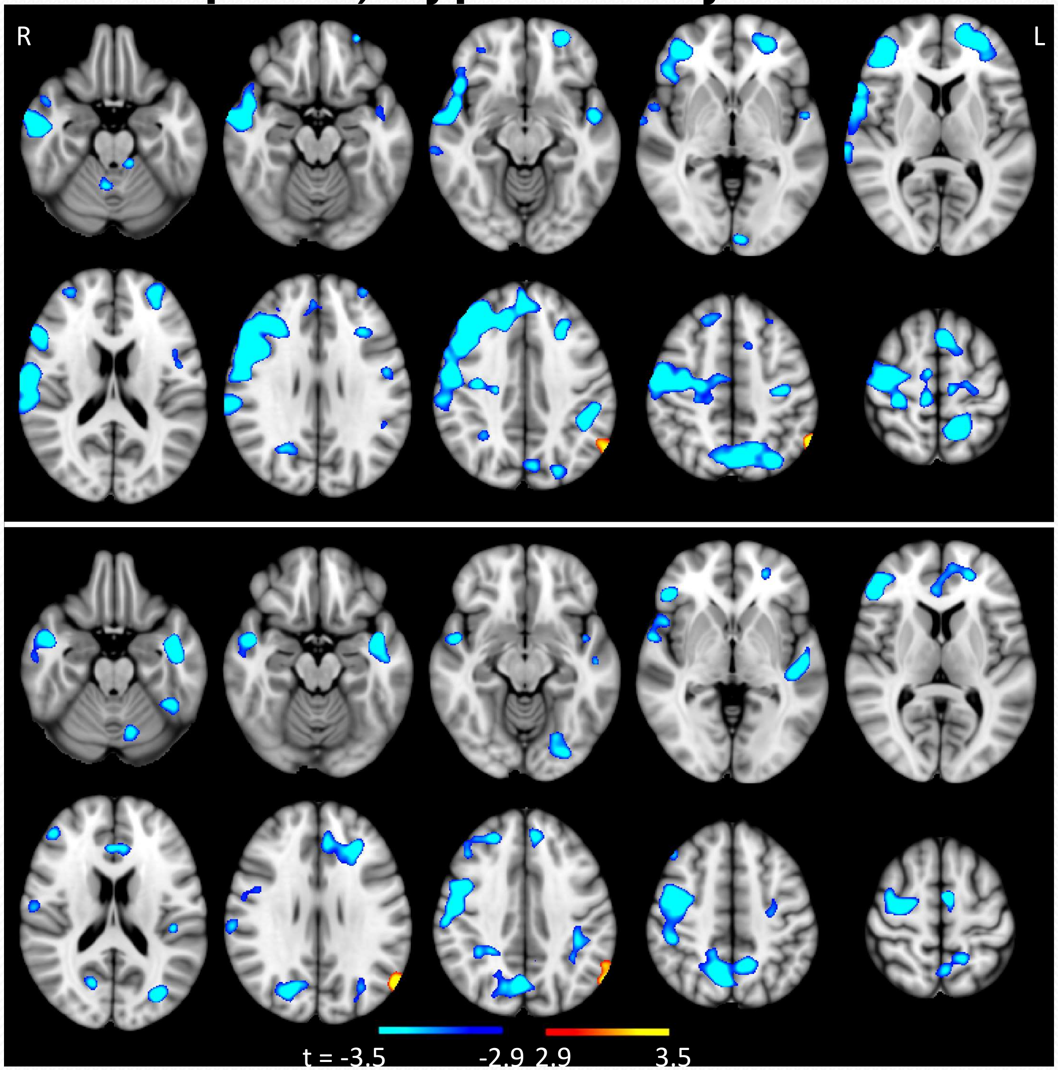
Huang et al., NeuroImage: Clinical, 5:408-419, 2014

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. Huang et al., NeuroImage: Clinical, 5:408-419, 2014

Resting-state fMRI findings in PTSD

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

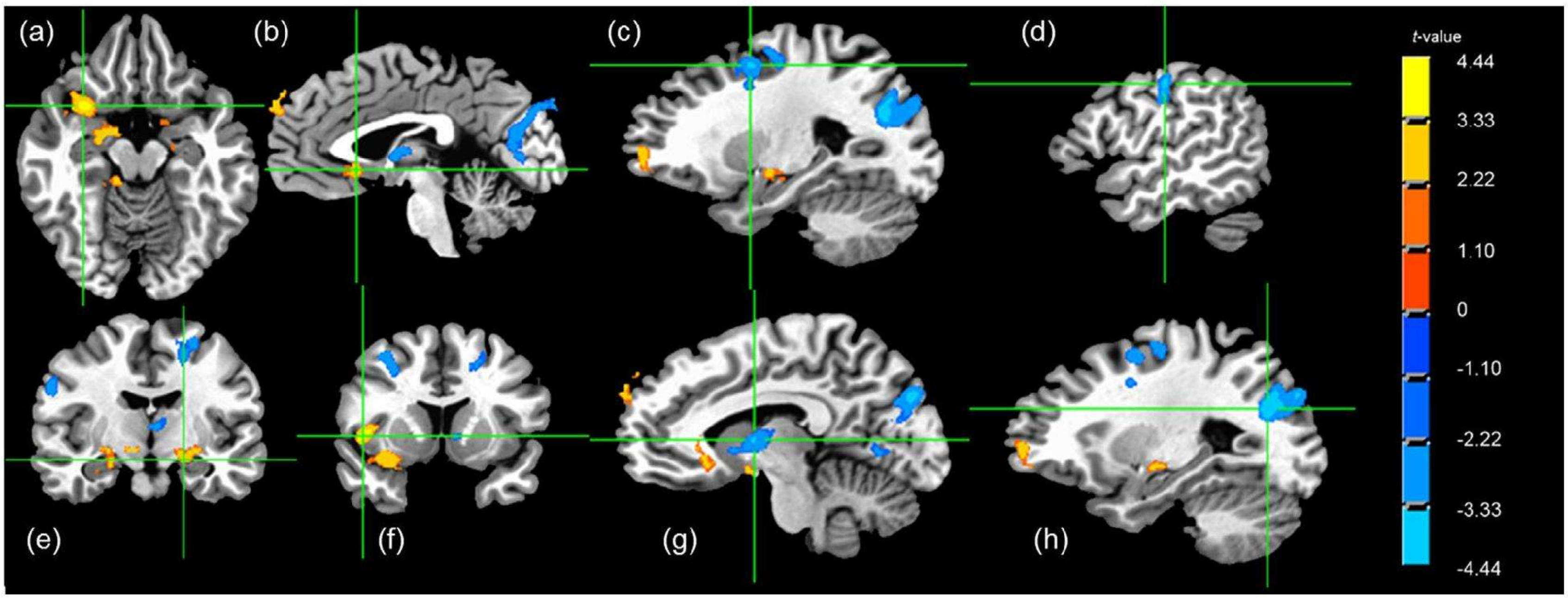


Fig. 1. Brain regions showing significant group differences between PTSD and controls in terms of magnitudes of spontaneous activity. The crosshairs are focused at the following brain regions: (a) orbital frontal gyrus, (b) anterior cingulate cortex, (c) superior frontal gyrus, (d) dorsal lateral prefrontal 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.)

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.

Huang et al., NeuroImage: Clinical, 5:408-419, 2014

Summary of MEG Study on 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.

Huang et al., NeuroImage: Clinical, 5:408-419, 2014

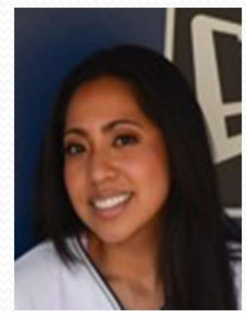
Acknowledgement

- Funding: VA Merit Review Grants (PI: Huang, I01-CX000499, B1988-I, I01-RX001988, MHBA-010-14F, NURC-022-10F, NEUC-044-06S), Marine Resilience Study-II (PI: Baker, Exploratory Project PI: Huang), NFL (PIs: Huang, Lee), McDonnel Foundation via Brain Trauma Foundation (PI: Ghajar; site PIs: Lee, Huang)
- Investigator Collaboration: VA San Diego Healthcare System, UCSD.









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Thank you!
Questions?