Marked Increases in Resting-State MEG (Magnetoencephalography) Gamma-Band Activity in Combat-related Mild Traumatic Brain Injury

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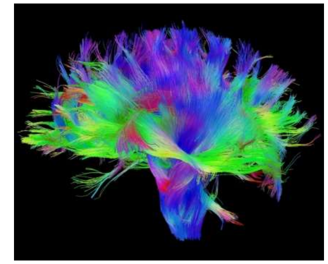
Traumatic Brain Injury

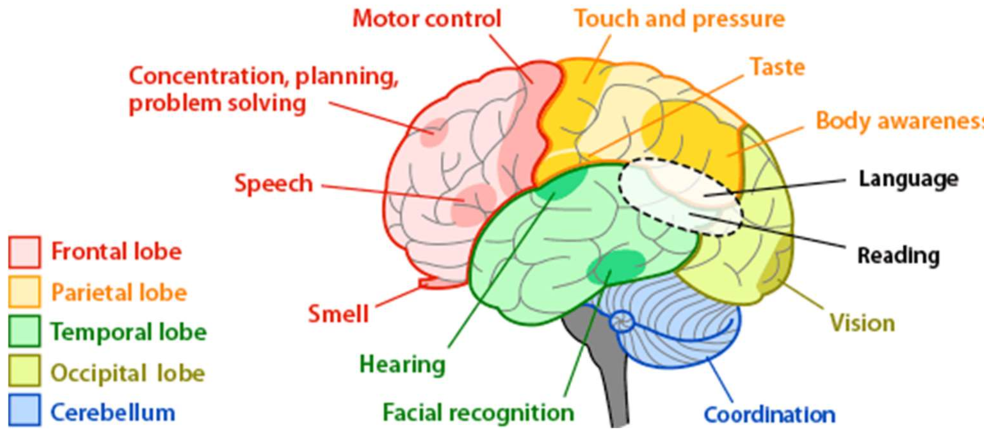
- Each year an estimated 1.5 million Americans sustain a TBI
- 230,000 people are hospitalized and survive.
- 50,000 people die.
- 80,000 to 90,000 people experience the onset of long-term disability.
- About 80% of all TBI are mild TBI (mTBI).
- Combat related mild TBI (mainly due to blast) is a major health issue in Veterans and active-duty service members.

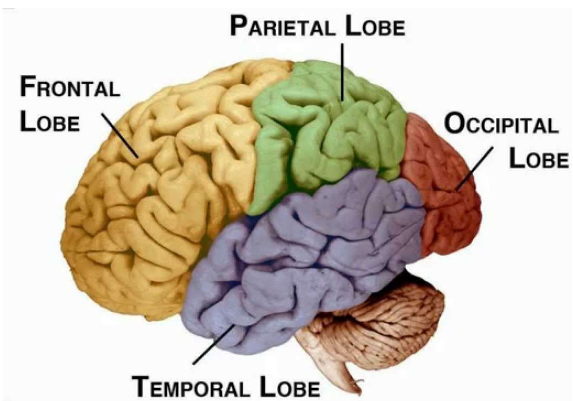
Diffusion-based MRI measurements of white matter integrity showed limited sensitivity and specificity for mild TBI

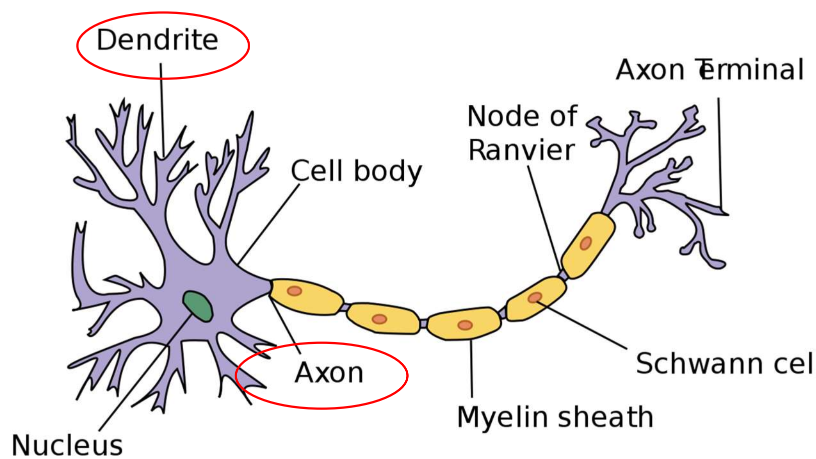


- In last over 20 years, diffusion-based MRI measurements of white matter integrity have achieved limited sensitivity / specificity for mild TBI, by assuming primary injury from white matter.
- Asken et al., 2018. Diffusion tensor imaging (DTI) findings in adult civilian, military, and sport-related mild traumatic brain injury (mTBI): a systematic critical review. Brain Imaging Behav. 12:585–612.
- Douglas et al., 2015. Diffusion Tensor Imaging of TBI: Potentials and Challenges. Top Magn Reson Imaging. 24:241–251.
- "DTI currently lacks the sensitivity and specificity necessary for meaningful clinical application in mTBI"
- Shall we carefully examine injuries in gray matter as well?

Human Brain Contains 100 Billion Neurons

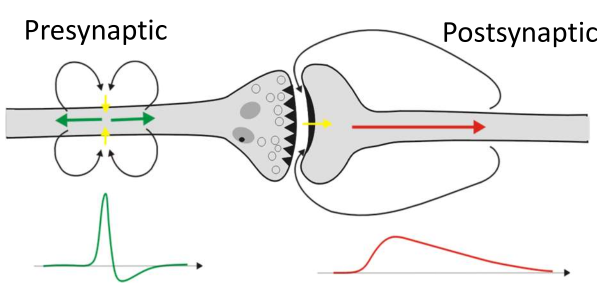




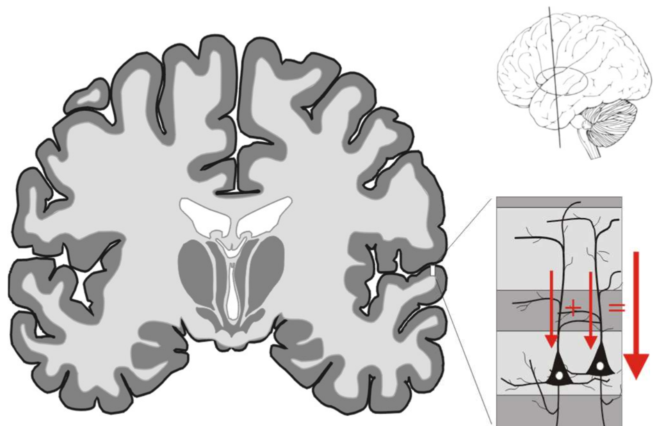


Magnetoencephalography (MEG) measures magnetic fields generated from postsynaptic current in gray matter, mainly from a population of pyramidal cells (~100,000) in a cortical column

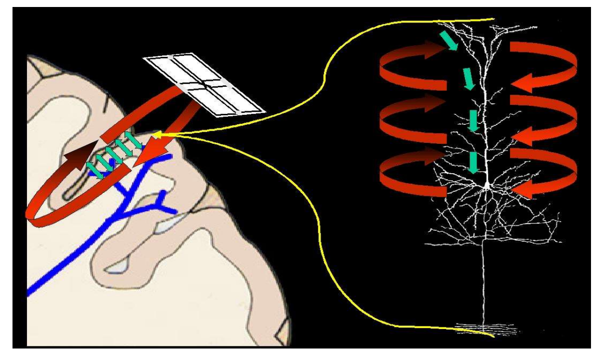
Neuronal currents in axons and dendrites



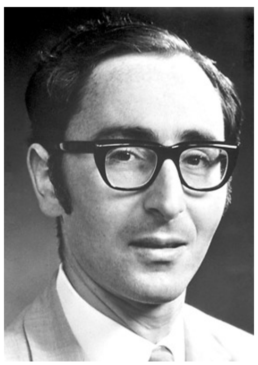
Parallel dendrites



Pyramidal cells: parallel orientation => spatial summation

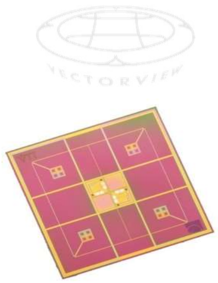


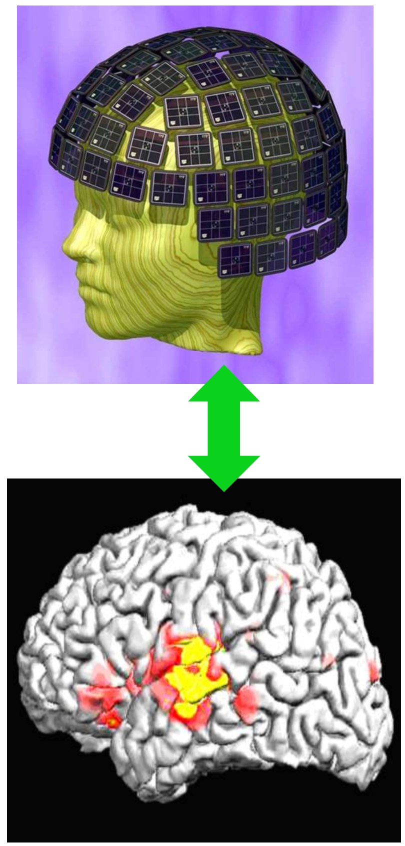
Magnetoencephalography (MEG): non-invasive functional imaging technique for gray matter activity with 1 ms time resolution and 2-3 mm spatial resolution in cortex



Brian Josephson

MEG SQUID Sensor Array





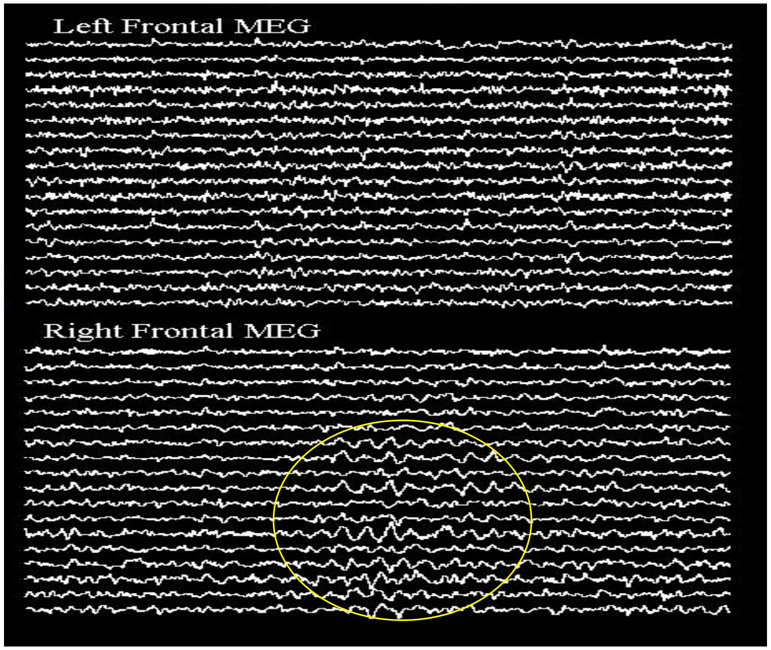
Topics to cover today

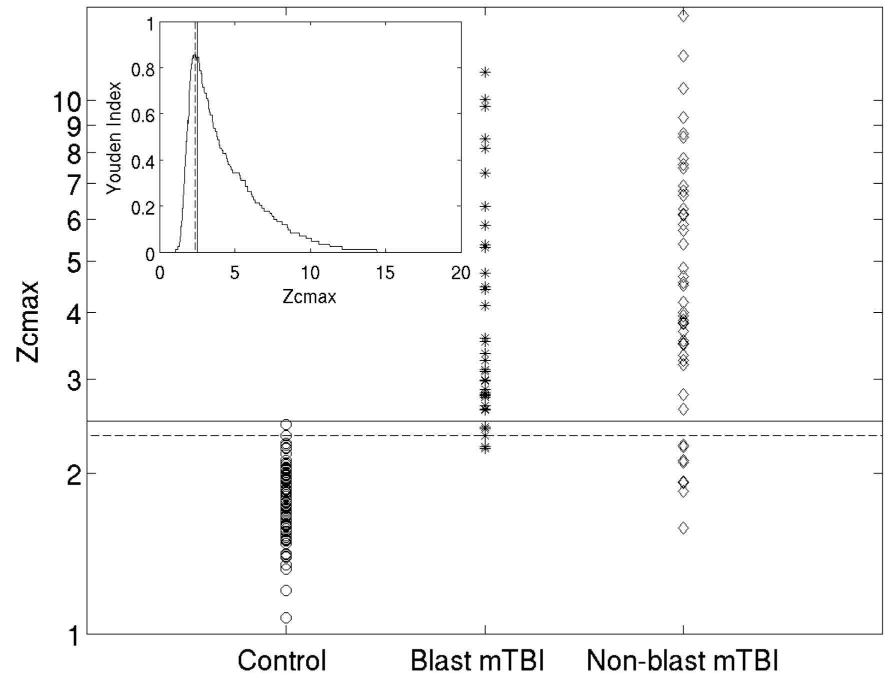
- Resting-state MEG delta-wave / slow-wave (1-4 Hz) source imaging in mild TBI (Huang et al., NeuroImage: Clinical, 2014, 5:109-119).
- Resting-state MEG gamma-band (30-80 Hz) activity in combat-related mild TBI (Huang et al., Cerebral Cortex, January 2020;30: 283–295).
- MEG working memory N-Back task evokes functional deficits in combat-related mild TBI (Cerebral Cortex, May 2019;29: 1953–1968).

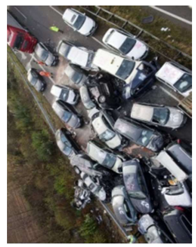
What is the neurophysiology for resting-state MEG delta-wave generation (1-4 Hz) in TBI?

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

MEG delta-wave / slow-wave (1-4 Hz) source imaging for detecting mild Traumatic Brain Injury (mTBI) : >80% sensitivity



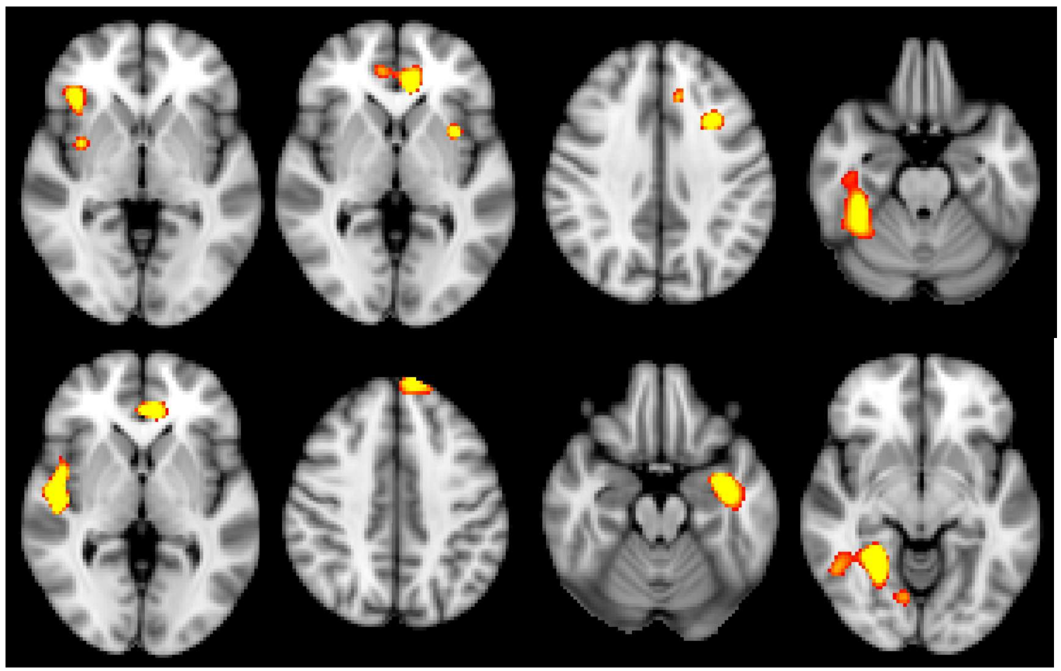




- N1=79 (Healthy controls); N2=36 (Blast mTBI); N3=48 (Non-blast mTBI)
- The threshold of 0% false-positive rate in healthy control subjects.
- In the blast mild TBI group, the MEG sensitivity was **86.1%**.
- In the non-blast mild TBI group, the MEG sensitivity was **83.3%**.
- In the combined mild TBI group (blast + non-blast), the MEG sensitivity was **84.5%**.

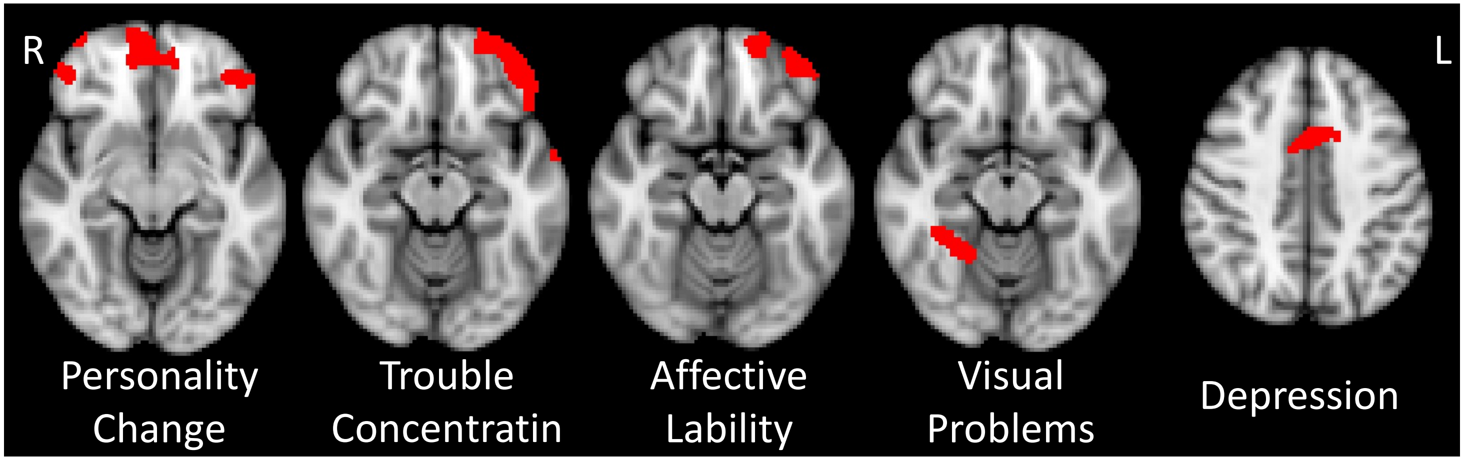
Huang et al., NeuroImage: Clinical, 2014, 5:109-119.

MEG delta-wave / slow-wave (1-4 Hz) imaging for individual mild TBI patients



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

MEG delta-wave (1-4 Hz) source magnitude significantly correlated with PCS



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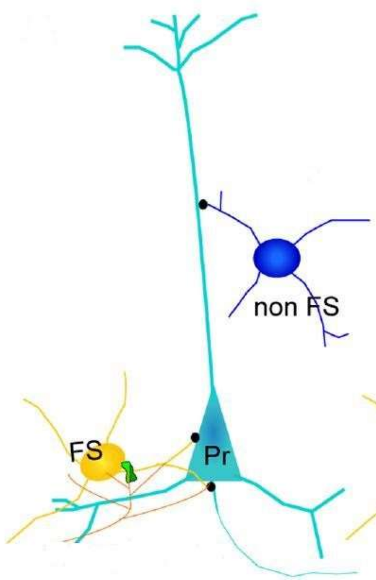
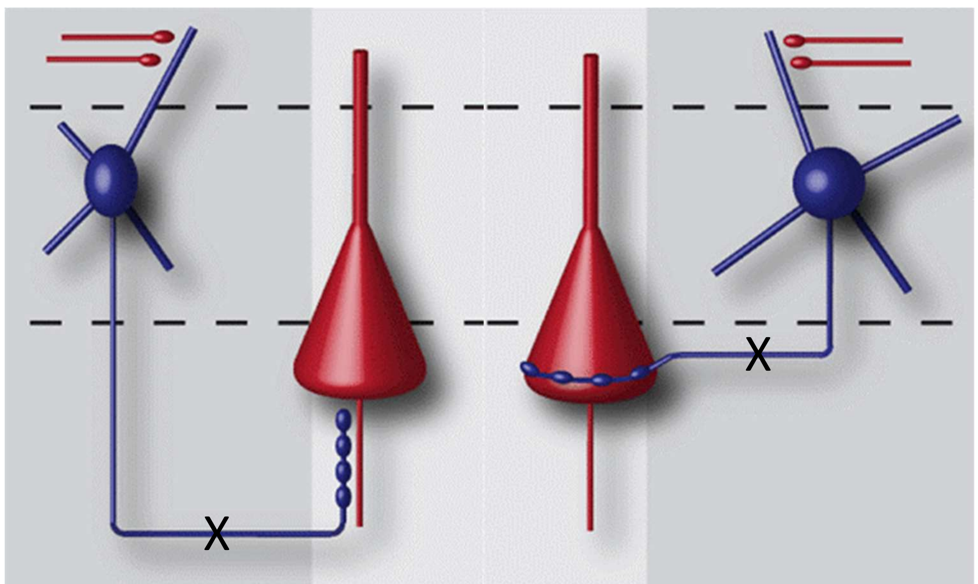
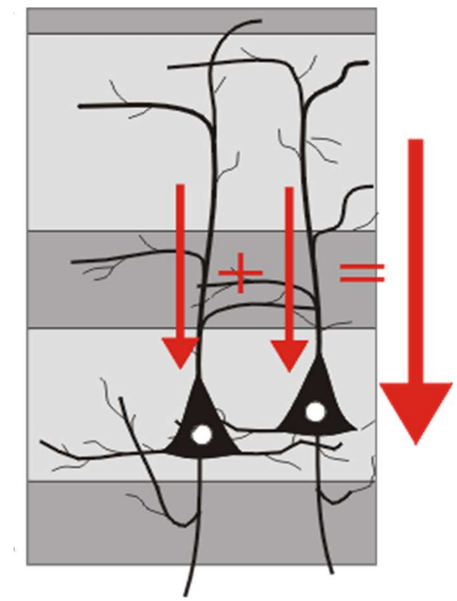
Injury to GABA-ergic Inhibitory Interneurons in Gray Matter Plays a major role in mTBI, which Leads to Abnormal Gama-band (30 – 80 Hz) Activity

- GABA-ergic (fast-spiking) inhibitory interneurons in gray matter are vulnerable to brain injuries, including mTBI.
- Animal studies showed that injury to GABA-ergic inhibitory interneurons (fast-spiking or FS) leads to reduction of inhibition and **increases** in gamma-band spontaneous / baseline / background activity from the primary excitatory neurons.
- It also leads to **decreases** in synchronized gamma-band responses evoked by stimuli with regular patterns



GABA-ergic inhibitory interneurons (blue) vs excitatory pyramidal neurons (red)





Vascak et al., Cerebral Cortex, 2018; 28:1625–1644

Mild Traumatic Brain Injury Induces Structural and Functional Disconnection of Local Neocortical Inhibitory Networks via Parvalbumin Interneuron Diffuse Axonal Injury

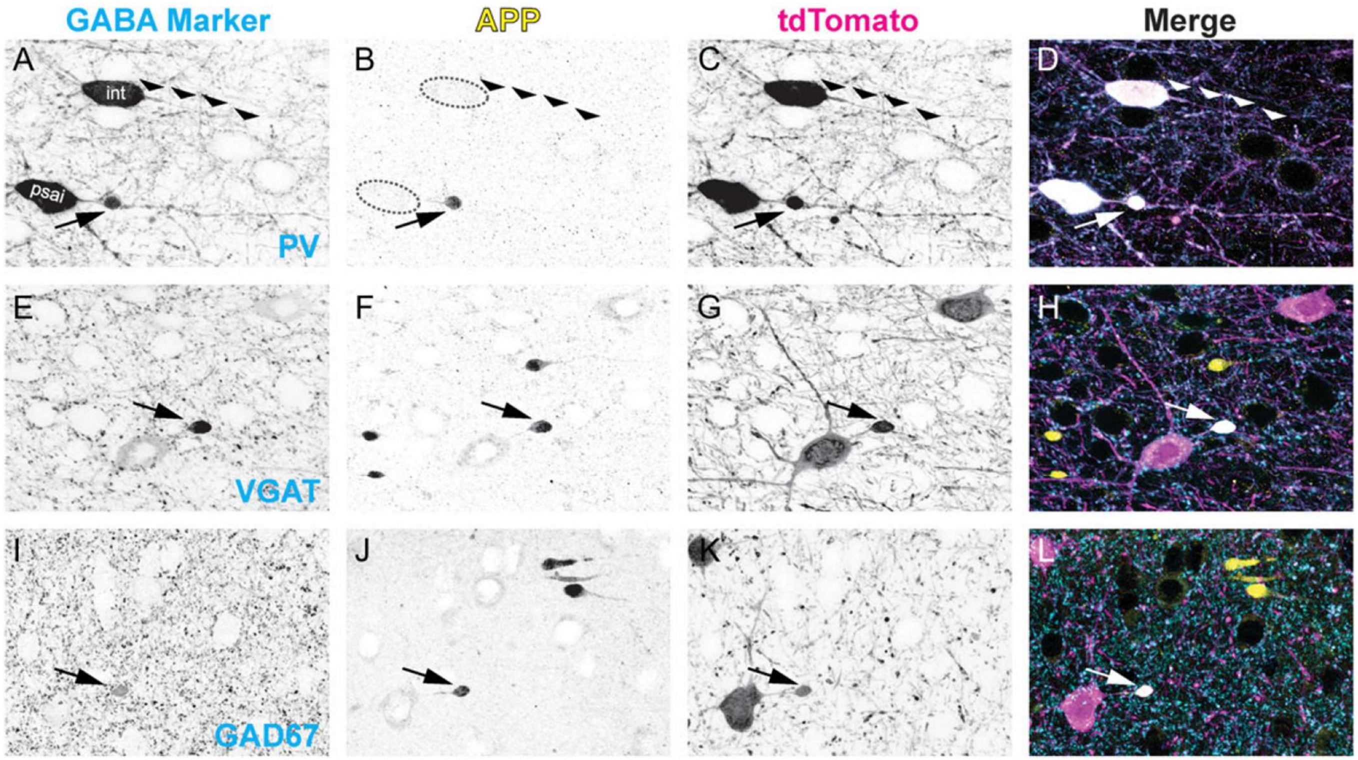


Figure 4. GABAergic markers accumulate in APP+/tdTomato+ perisomatic axonal swellings. Representative images at 3 h post-mTBI showing GABAergic markers (*A*, *E*, *I*) with respect to APP immunoreactivity (*B*, *F*, *J*), which accumulates at focal sites of impaired axonal transport (arrows). Colocalization of tdTomato+ PSAI with PV (*A–D*), VGAT (*E–H*), and GAD67 (*I–L*) immunoreactivity confirms GABAergic interneuron axonal injury. (*A*) Normal uninjured intact (int) axonal profile (wide arrowheads) juxtaposed by PV+ interneuron PSAI (arrow). (*B*) APP is not detected within the intact axonal profile, while robust APP immunoreactivity colocalizes with tdTomato+/PV+ interneuron PSAI (*C*, *D*). Within sites of tdTomato+ PSAI (*C*,*G*,*K*), the immunoreactive profiles of VGAT (*E*) and GAD67 (*I*) are similar to APP+ axonal swellings (*F* and *J*, respectively). Qualitatively, the GAD67+ axonal swelling profile (*I*, *L*) has a better signal-to-noise than VGAT (*E*, *H*). Note non-GABAergic APP+ axonal swellings have opposite trajectories.

Carlen et al., Molecular Psychiatry (2012) 17, 537–548

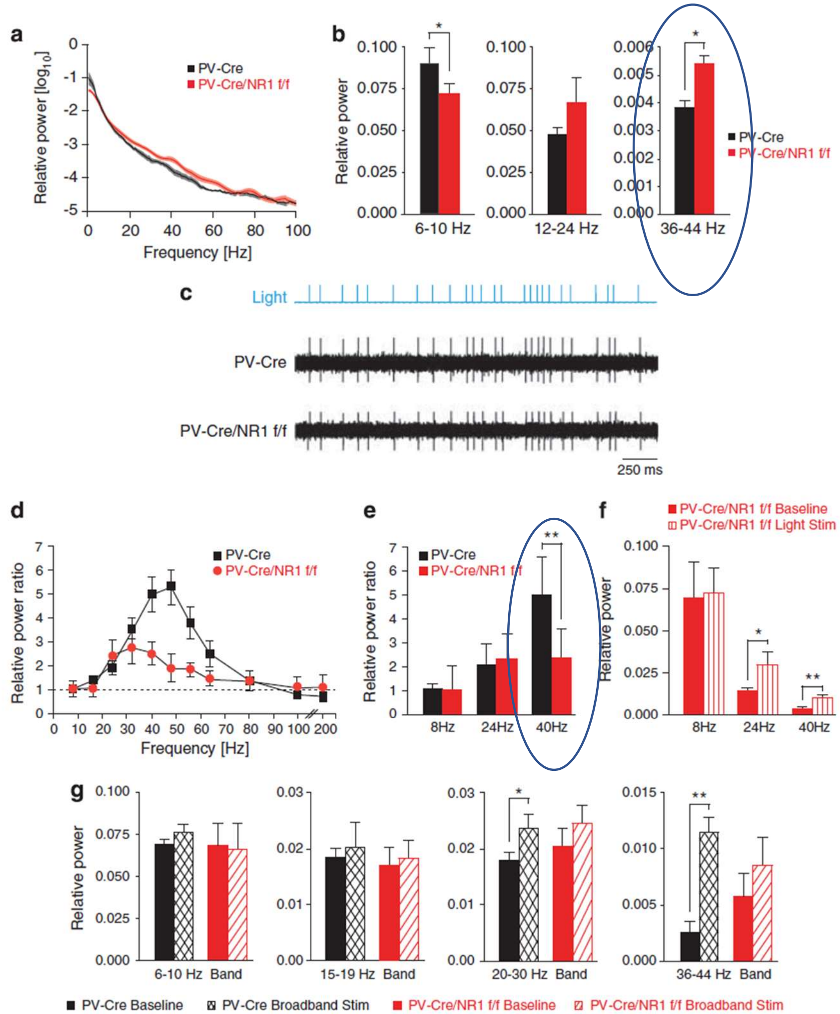


Figure 2 Spontaneous and induced cortical gamma oscillations require NMDA receptor (NMDAR) in parvalbumin (PV) interneurons. (**a, b, d–g**) Local field potential (LFP) activity in anesthetized control (black) and PV-Cre/NR1f/f (red) mice.

Demographic characteristics in the control and blast mTBI groups.

	Control (n=35)		mTBI (n=25)		t-test
	Mean	SD	Mean	SD	p-value
Age	29.00	5.00	28.00	7.52	0.307
Years of education	14.00	1.48	13.00	1.89	0.126

Table 1B: Percentage of subjects showing individual symptoms in mTBI and control groups:

Symptoms	mTBI (%)	Control (%)	Symptoms	mTBI (%)	Control (%)
Headaches	84.0	14.3	Lack of Spontaneity	4.0	0.0
Dizziness	56.0	11.4	Affective Lability	8.0	2.9
Fatigue	48.0	14.3	Depression	28.0	14.3
Memory Difficulty	88.0	14.3	Trouble Concentrating	16.0	20.0
Irritability	64.0	20.0	Bothered by Noise	12.0	2.9
Anxiety	64.0	20.0	Bothered by Light	12.0	17.1
Trouble with sleep	60.0	14.3	Coordination/ Balance Problems	20.0	11.4
Hearing difficulties	60.0	14.3	Motor difficulty	0.0	0.0
Blurred vision Other visual difficulties	16.0	2.9	Difficulty with speech	4.0	2.9
Personality Changes	20.0	2.9	Numbness/Tingling	20.0	11.4
Apathy	4.0	0.0			

Huang et al., Cerebral Cortex, January 2020;30: 283–295.

Neuropsychological test performance in the control and blast mTBI groups.

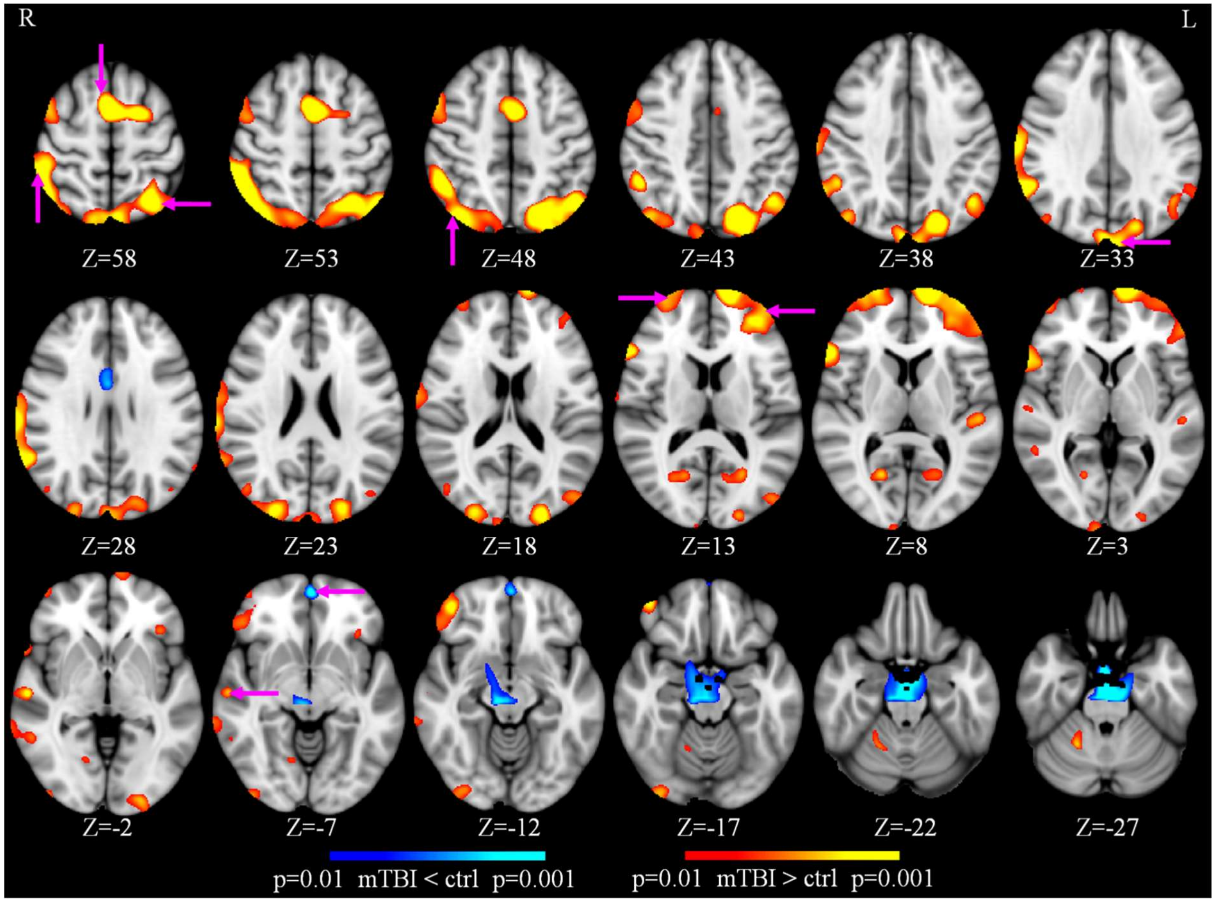
	Control, N=35		mTBI, N=25				
	Mean	**SD**	**Mean**	**SD**	***t*-Value**	***p*-value**	**Cohen's *d***
D-KEFS Trail Making Test							
Number-Letter Switching	11.09	1.98	9.08	2.55	3.30	**0.002***	1.37
D-KEFS Verbal Fluency Test							
Letter Fluency	10.83	3.21	9.08	2.74	2.27	**0.027***	0.59
Category Switching	11.54	2.62	10.16	2.75	1.96	0.056	0.51
WAIS							
Digit Symbol Coding†	10.34	2.82	8.83	2.66	2.09	**0.042***	0.55

- Group differences on the measures reported in the table were tested using independent *t*-tests.
- Neuropsychological measures are scaled scores (mean=10, standard deviation=3) .
- * Statistically significant ($p < 0.05$).
- † An outlier in the mTBI group was removed from this assessment (see main text)

Resting-state MEG source imaging showed gamma-band (30-80 Hz) hyper-activity in blast mTBIs versus controls

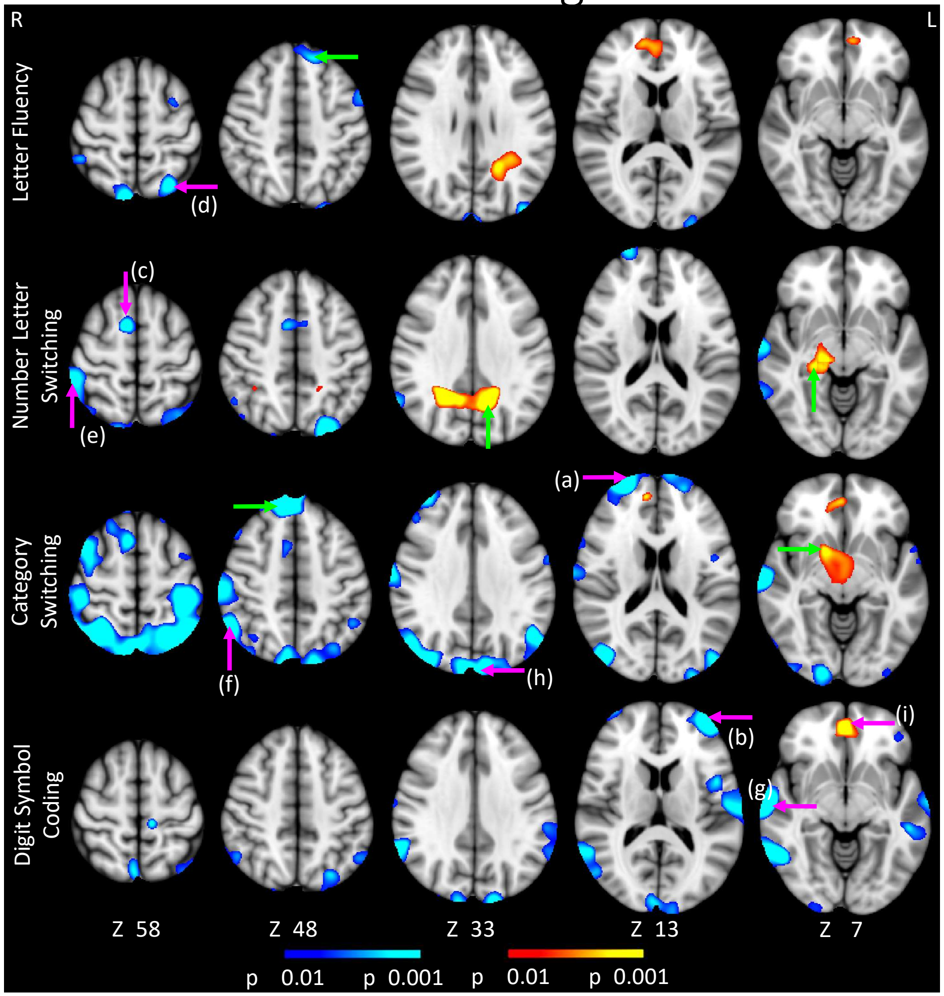
<u>Group 1</u> N=25 symptomatic active-duty service members or Veterans with combat-related mTBI

<u>Group 2</u> N=35 healthy controls active-duty service members or Veterans with similar combat experiences.



Hyperactivity in lateral frontal pole cortex (lFPC), inferior frontal gyrus (IFG), supplementary motor cortex (SMA), superior parietal lobule (SPL) / intra-parietal sulcus (IPS), supramarginal gyrus (SMG), angular gyrus (AG), superior temporal gyrus (STG), and superior lateral occipital cortex. To a much lesser extent, aberrantly reduced gamma (hypoactivity) were also observed in ventomedial prefrontal cortex (vmPFC). **(Huang et al., Cerebral Cortex, January 2020;30: 283–295).**

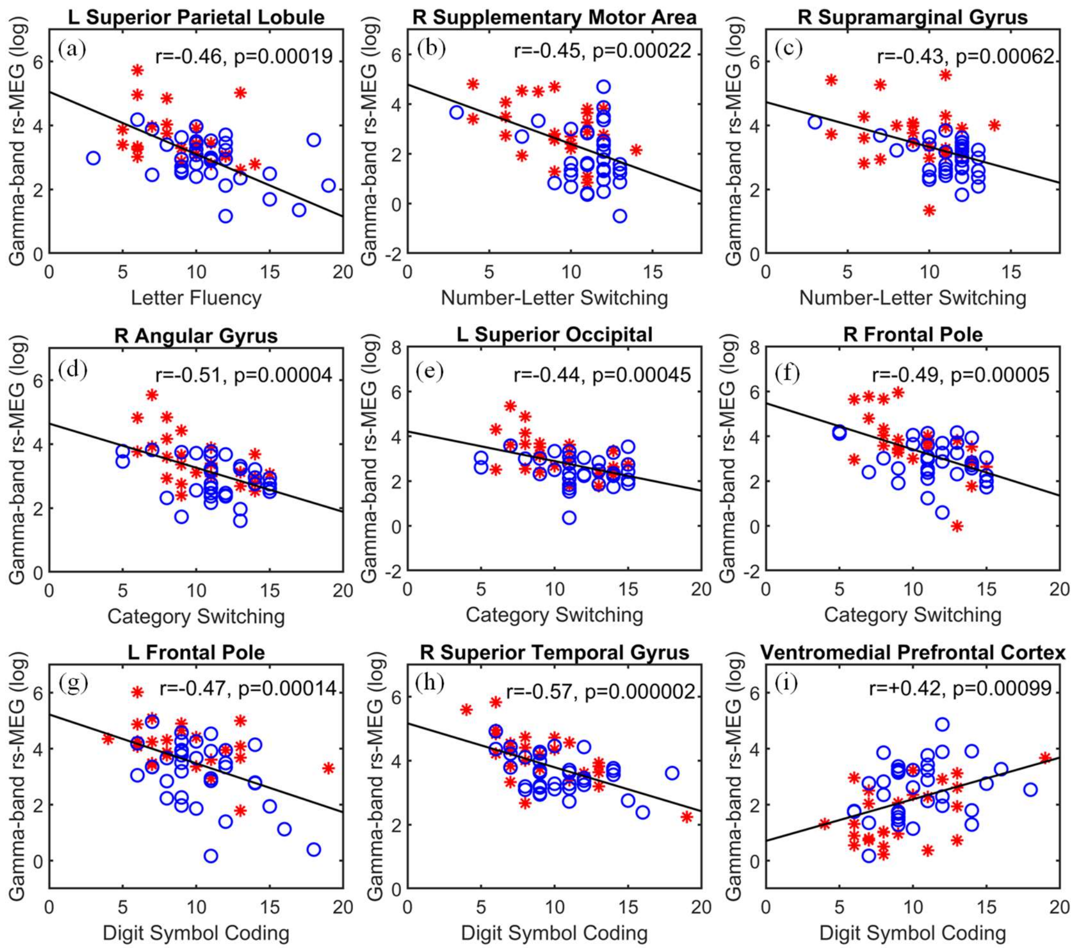
Correlations (r-maps) between gamma-band rs-MEG activity and cognitive functioning



Huang et al., Cerebral Cortex, January 2020;30: 283–295.

MEG gamma-band signals correlate with three neuropsychological scores

* mTBIs
o Ctrls



DKEFS Number-letter switching, DKEFS Verbal fluency, WAIS Digit symbol coding
(Huang et al., Cerebral Cortex, January 2020;30: 283–295).

Summary of Gamma-band MEG study in combat-related mTBI

- Combat-related mTBI participants showed profound gray matter gamma-band hyper-activity from frontal area (lFPC, IFG, SMA), parietal areas (SPL/IPS, SMG, AG), superior temporal gyrus, and superior lateral occipital cortex.
- To a much lesser extent, aberrantly reduced gamma (hypoactivity) were also observed in vmPFC.
- MEG hyper-activity in lFPC, SMA, SPL/IPS, STG, etc. negatively correlated with NP performances.
- MEG hypo-activity in vmPFC positively correlated with NP performances.
- More details see: Huang et al., Cerebral Cortex, January 2020;30: 283–295.
- Applications to epilepsy, schizophrenia, Alzheimer's disease, etc.

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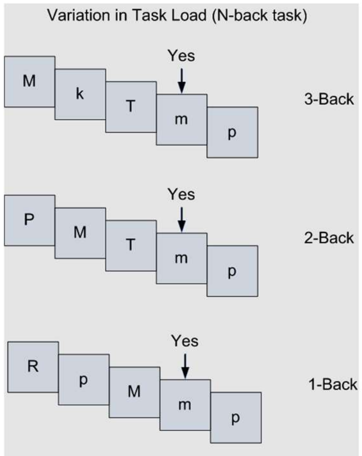
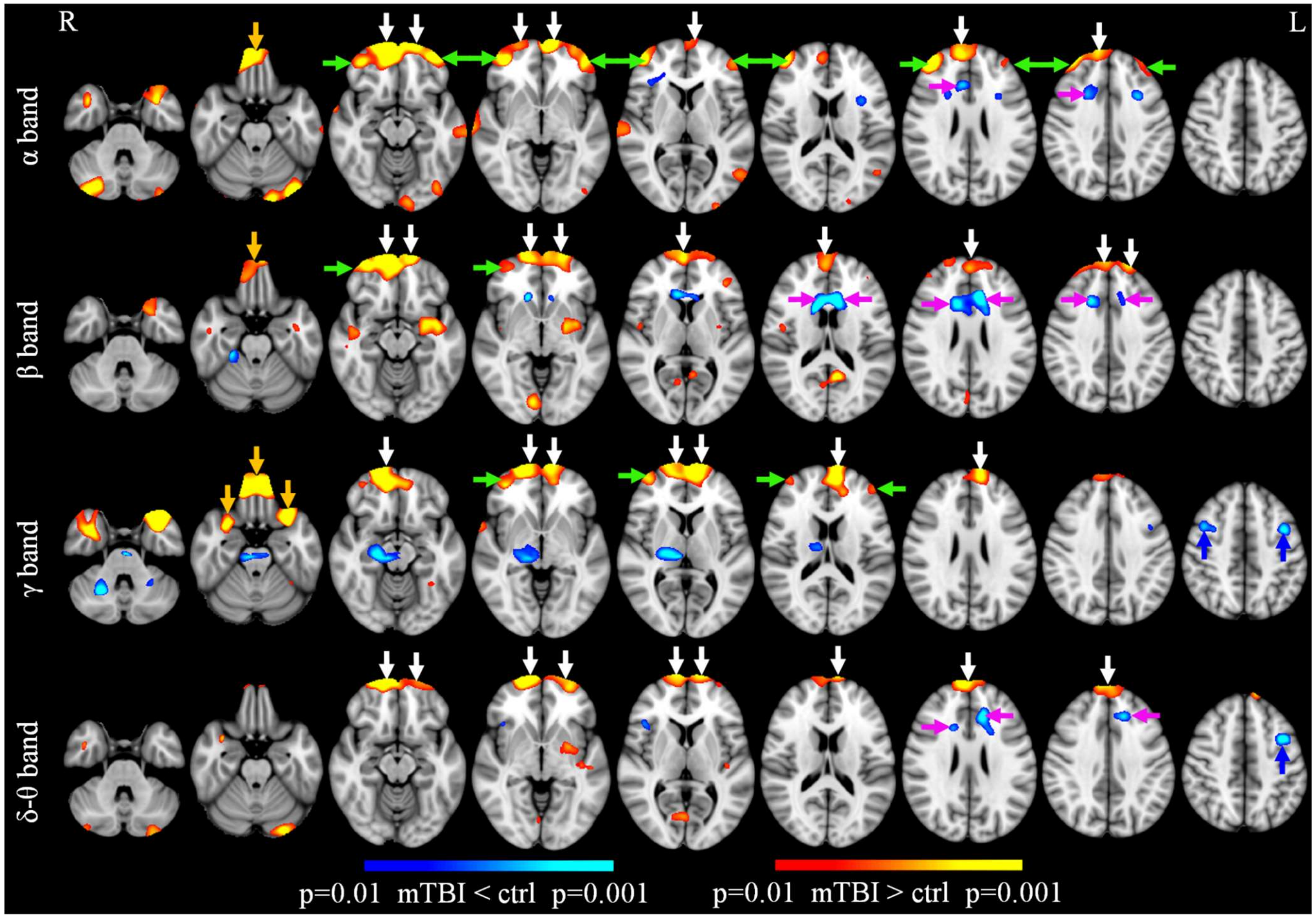
MEG source imaging showed hyper- and hypo-activations in blast mTBIs versus controls evoked by N-back working-memory test



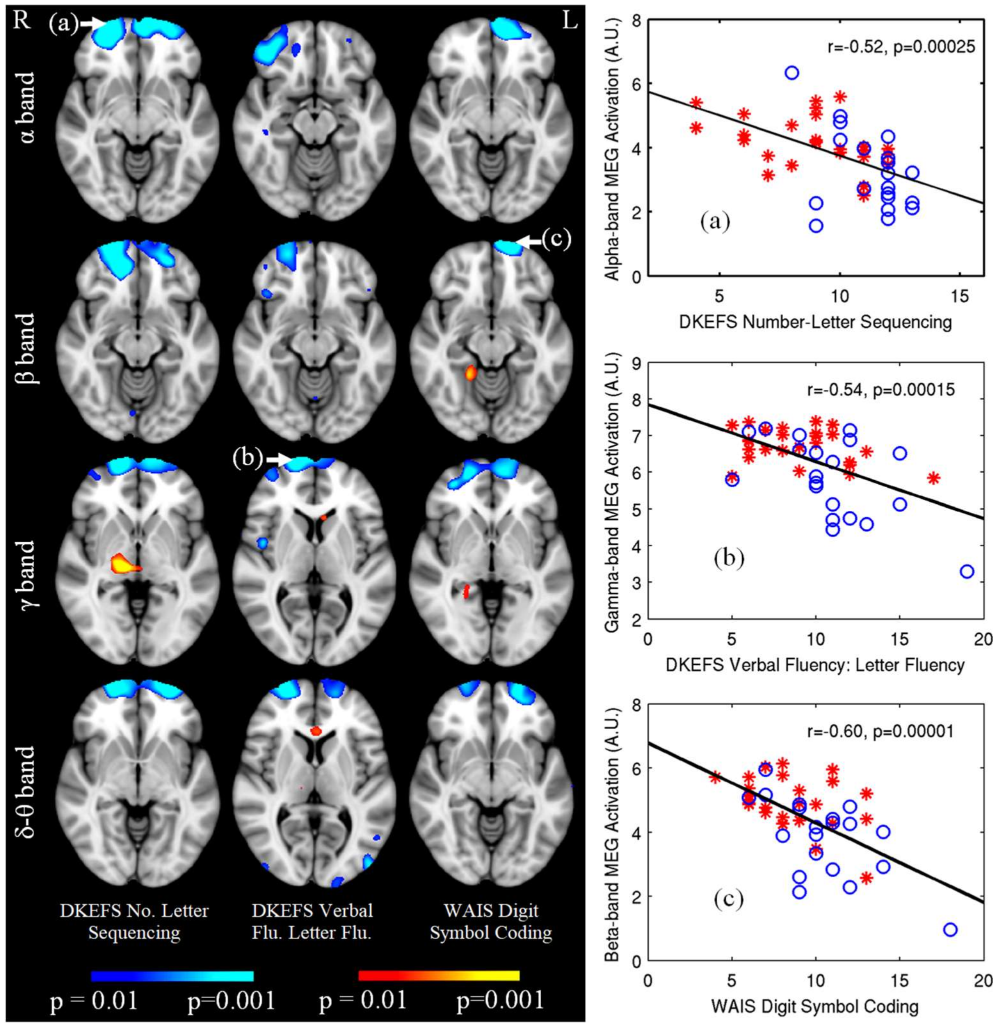


Group 1 N=25 symptomatic active-duty service members or Veterans with combat-related mTBI

Group 2 N=20 healthy controls active-duty service members or Veterans with similar combat experiences.

Huang et al., Cerebral Cortex 2019, 29(5): 1953-1968.

MEG N-back signals correlate with three neuropsychological scores



Huang et al., Cerebral Cortex 2019, 29(5): 1953-1968.

Summary: Evoked MEG source imaging working memory study in mTBI

- Compared with healthy combat controls, mTBI participants showed reduction in evoked MEG activity (e.g., gamma-band in proper working memory regions, such DLPFC and ACC.
- MTBI showed MEG hyper-activations across frequency bands outside proper working memory network in FP, vlPFC, OFC, but decreased MEG signals in ACC and posterior dlPFC
- Hyper-activations in FP, OFC, etc. were associated with slower reaction times.
- MEG activations in lateral FP also negatively correlated with performance on tests of letter sequencing, verbal fluency, and digit symbol coding.

Huang et al., Cerebral Cortex 2019, 29(5): 1953-1968.

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Thank you!
Questions?