

# Trajectory of Parvalbumin Cell Impairment and Loss of Cortical Inhibition in Traumatic Brain Injury

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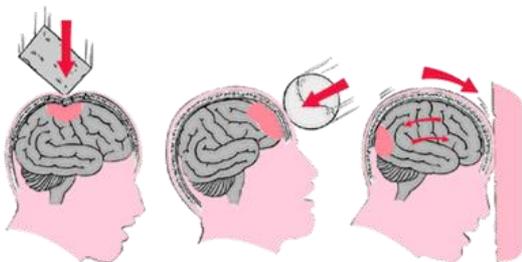
# Traumatic brain injury (TBI) & Neurologic symptoms

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- Many traumatic brain injury (TBI) survivors experience prolonged or even permanent neurocognitive dysfunction, with lasting changes in **cognitive and sensorimotor impairments**.

- ▣ chronic pain (Andary et al. 1997)
- ▣ mood disorders (Jorge et al. 2007)
- ▣ sleep disturbance (Hou et al. 2013)
- ▣ increased seizure susceptibility, and posttraumatic epilepsy (PTE) (Golarai et al. 2001)  
(Lucke-Wold et al. 2015)

- Those symptoms are referable to compromised cortical inhibition.



[https://en.wikipedia.org/wiki/Traumatic\\_brain\\_injury](https://en.wikipedia.org/wiki/Traumatic_brain_injury)



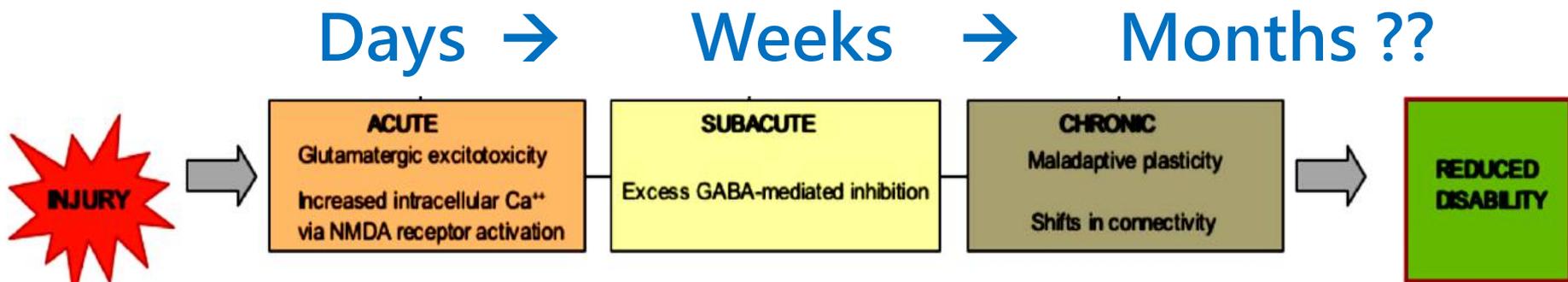
<http://lawyerforacaraccident.com/images/head-injury-car-accident-attorney.jpg>

# Cortical excitatory:inhibitory (E:I) Ratio

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- Previous studies indicate that the pathologic shift of cortical excitatory: inhibitory (E:I) ratio toward **excess excitation after TBI** is primarily due to **loss of synaptic inhibition** mediated by  $\gamma$ -aminobutyric acid (**GABA**) and a reduction of GABA related synapses in the cortex.

(Huusko and Pitkanen 2014; Cantu et al. 2015).



The temporal trajectory of cortical excitation or inhibition and its underlying mechanisms are still unknown.

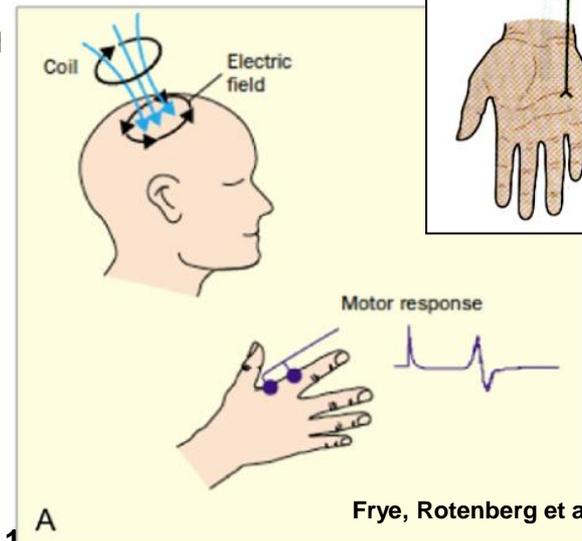
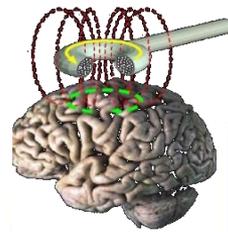
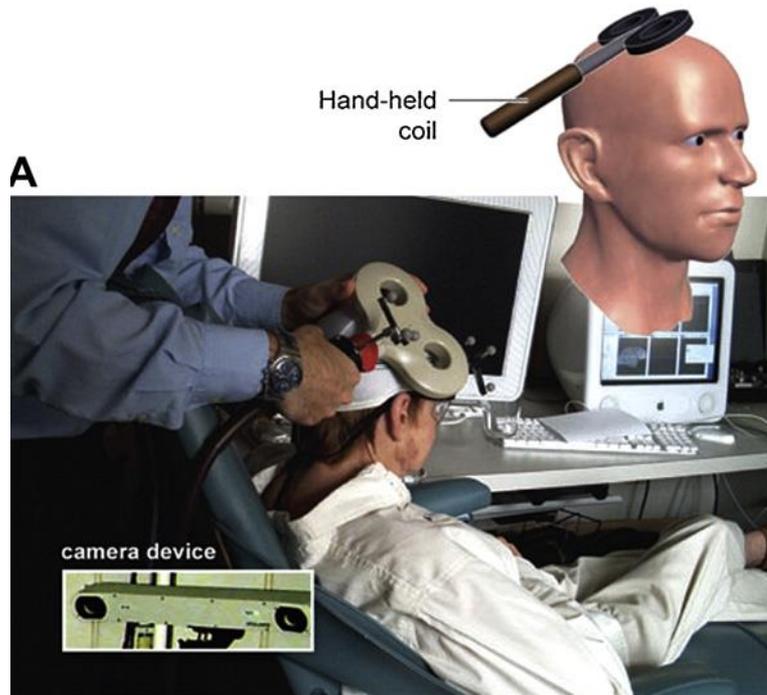
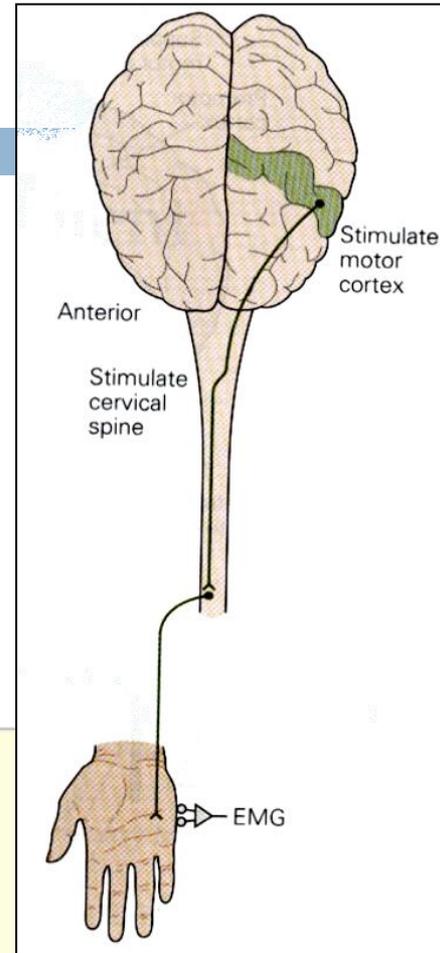
# Measures of Cortical Excitatory:Inhibitory (E:I) Ratio in Human

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## Electrophysiological method for assessing cortical excitability

### TMS & Motor evoked potential (MEP)

- Approach to assess corticospinal tract excitability induced by transcranial magnetic stimulation (TMS)



Najib et al., 2011

Frye, Rotenberg et al., 2007

# Diagnostic application: Measures of Cortical Function by Paired-Pulse TMS (ppTMS)

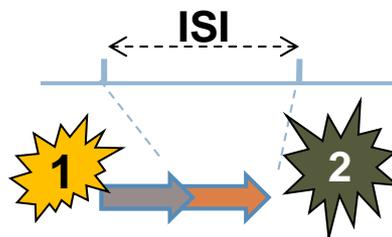
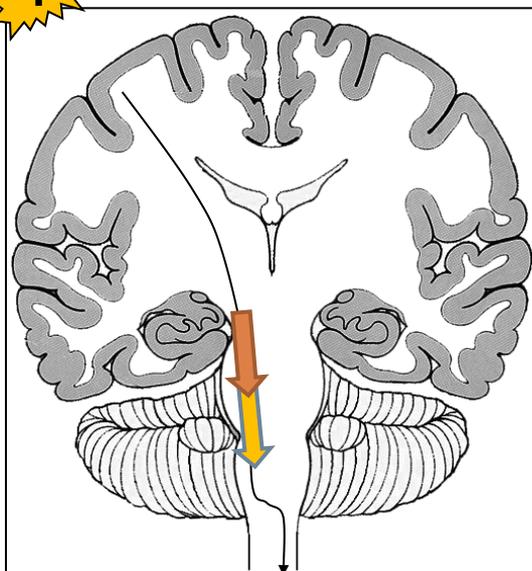


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Test TMS

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Conditioning TMS



Rotenberg and Pascual-Leone, 2010

Control

SICI; 1-6 ms ISI

ICF; 10-25 ms ISI

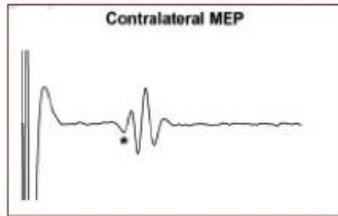
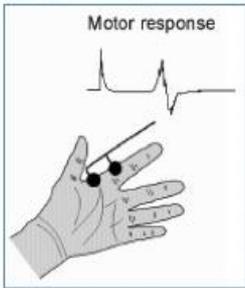
LICI; 50-200 ms ISI

SICI is likely mediated by  $\gamma$ -aminobutyric acid (GABA) receptors

ICF could be mediated by GABA, NMDA receptors

LICI is likely mediated by  $\gamma$ -aminobutyric acid receptors

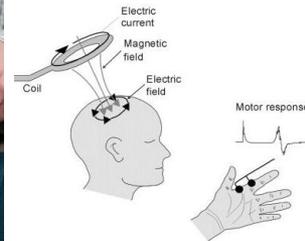
# Translation from Human to Animal Research



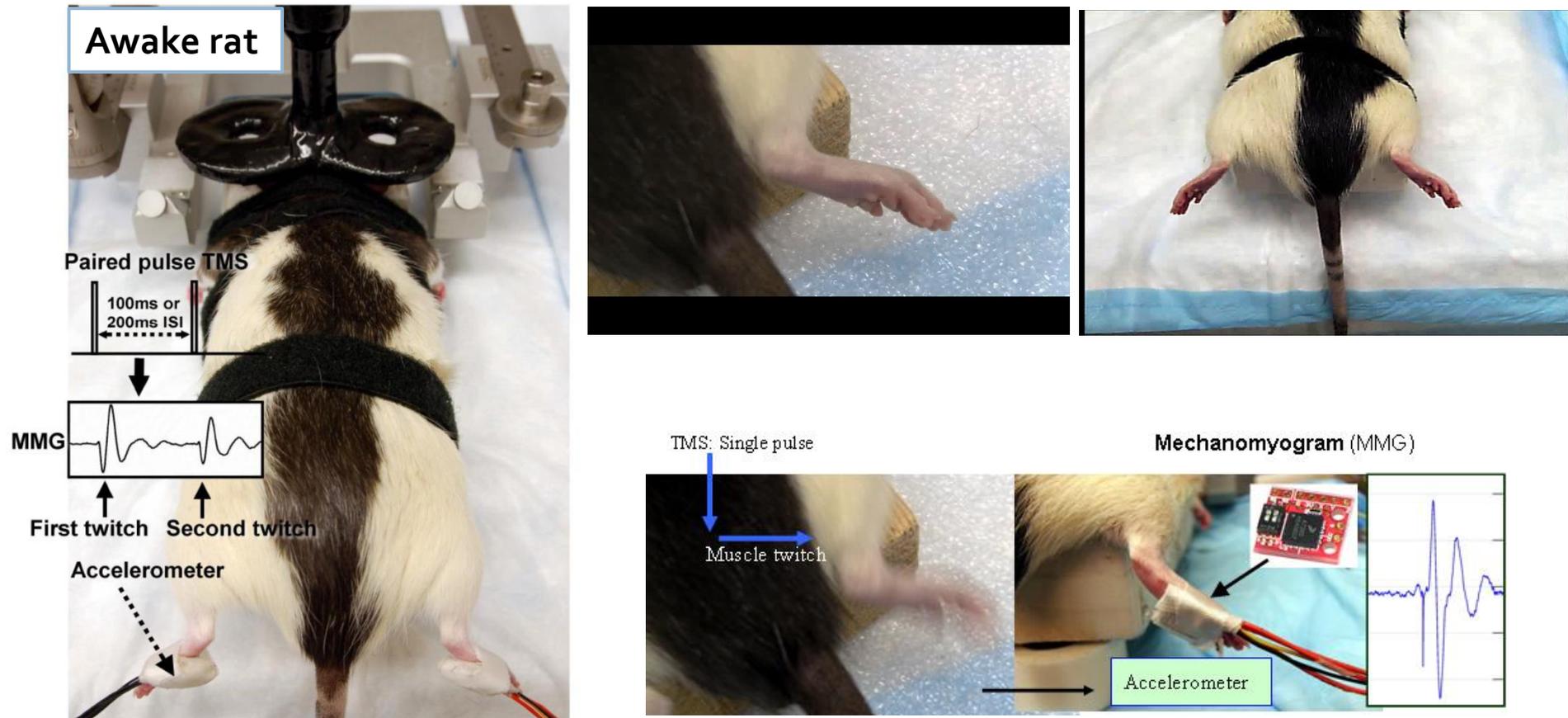
Rotenberg et al., 2010

Frye, Rotenberg et al., 2007

- ❑ An animal disease models may provide mechanistic insight into the ppTMS physiology and into disease processes
- ❑ To enable translational research in rat disease models, we recently adapted ppTMS methods to rats



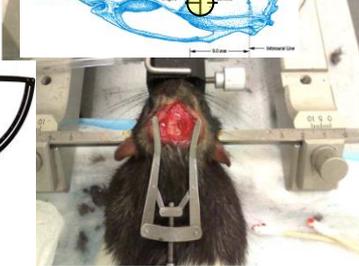
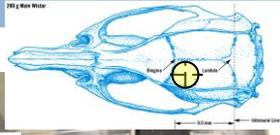
# A new measure of cortical inhibition by mechanomyography and paired-pulse transcranial magnetic stimulation in unanesthetized rats



**TMS-MMG setup.** Unanesthetized rat is restrained under brief isoflurane anesthesia.

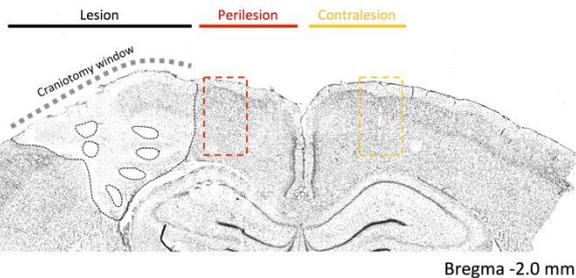
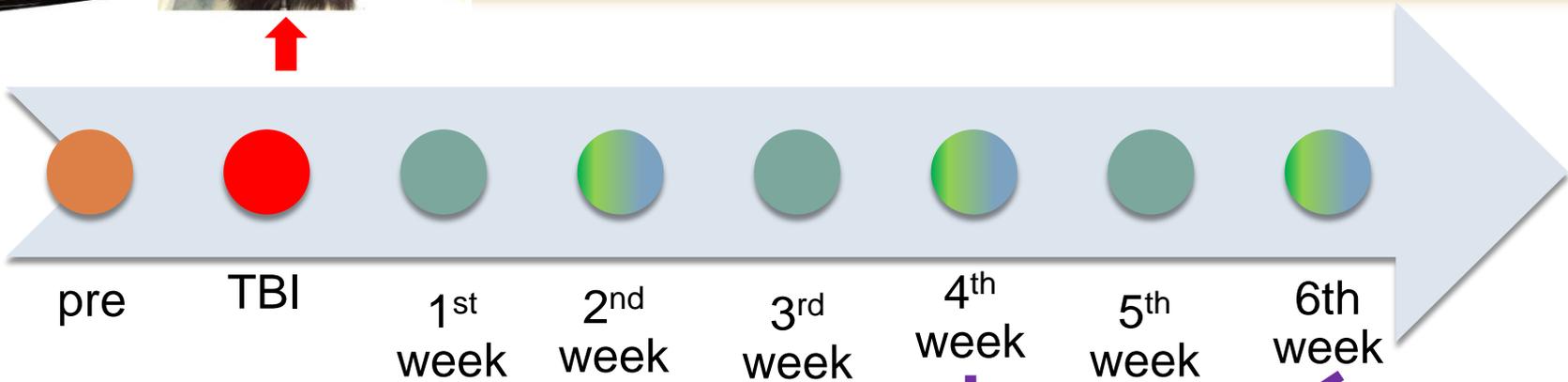
- The MMG is obtained by two 3-axis accelerometer elements on bilateral foot.
- The figure-of-eight TMS coil is centered over the dorsal scalp at the interaural line.

# Experimental design: To validate the translational relevance of the ppTMS-MMG in the traumatic brain injury model



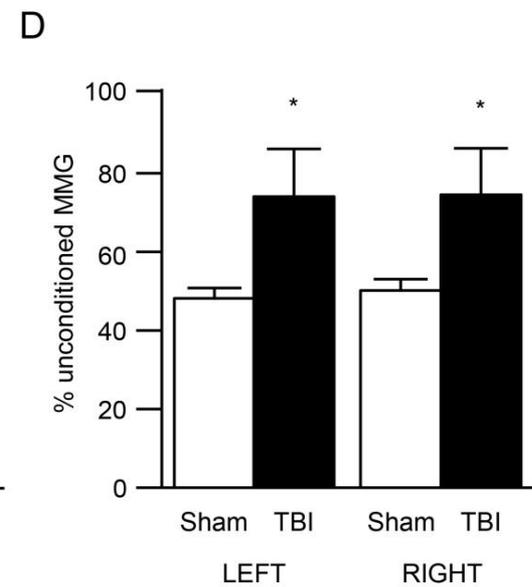
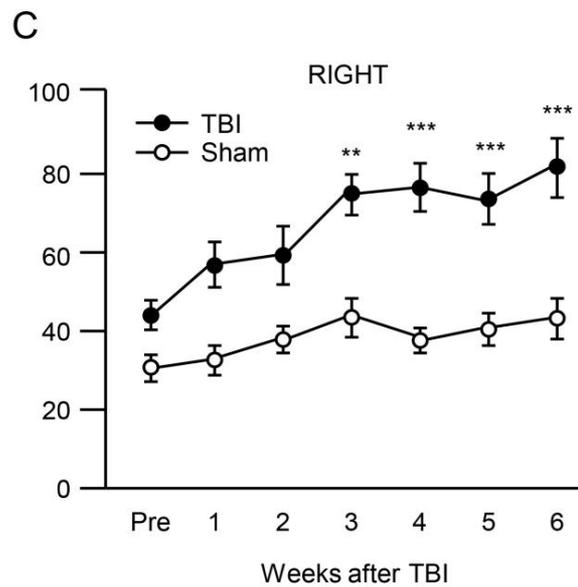
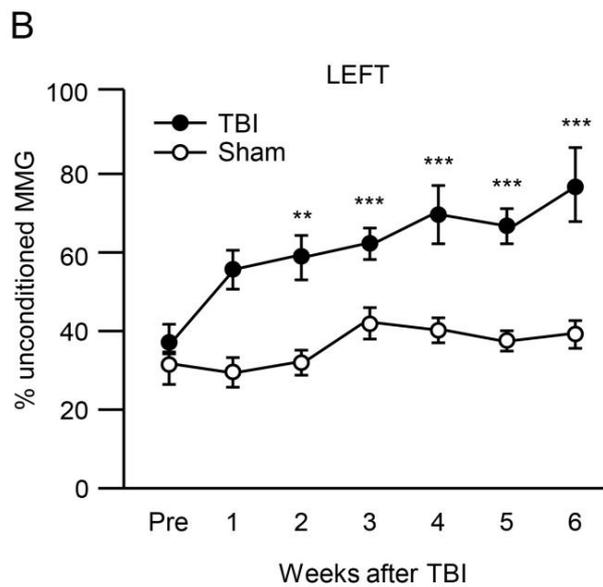
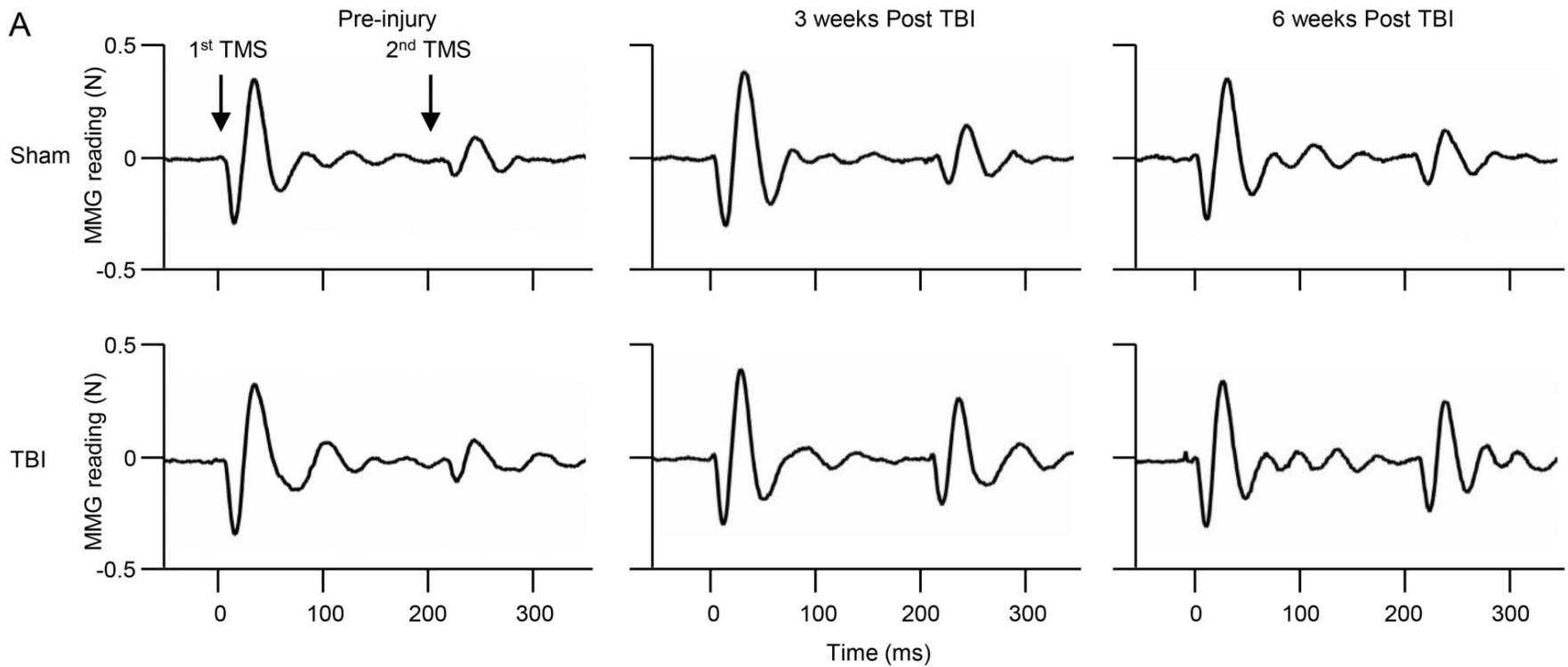
**Experiment 1:** Perform LI-ppTMS every week

- We tested whether loss of cortical inhibition after TBI in rats is reflected in ppTMS metrics of cortical inhibition.



**Experiment 2:** Immuno-staining every 2 weeks

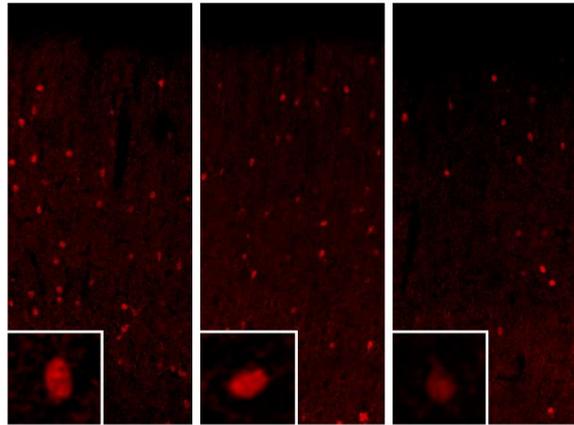
- We examined the relative temporal trajectory of these molecular entities (PV+ cell count, oxidative stress level) after FPI



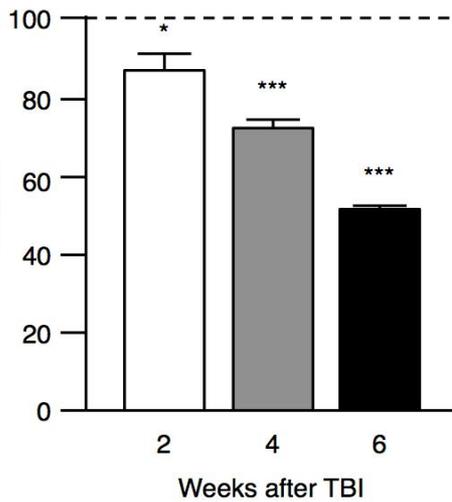
## PV+ cell loss after TBI

Post-TBI (perilesion)

2 4 6



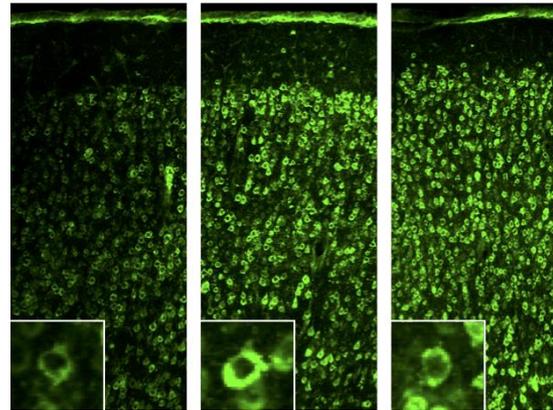
Perilesion



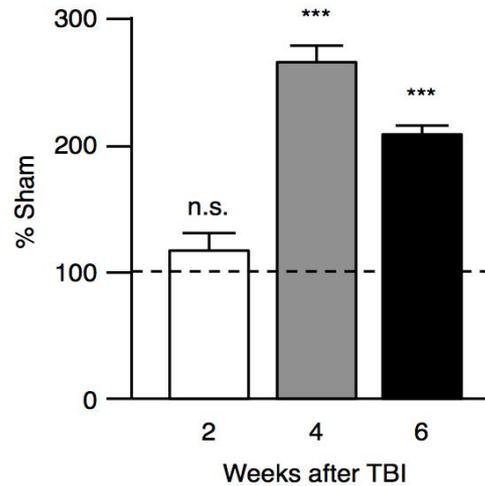
## Increased oxidative stress after TBI

Post-TBI (perilesion)

2 4 6



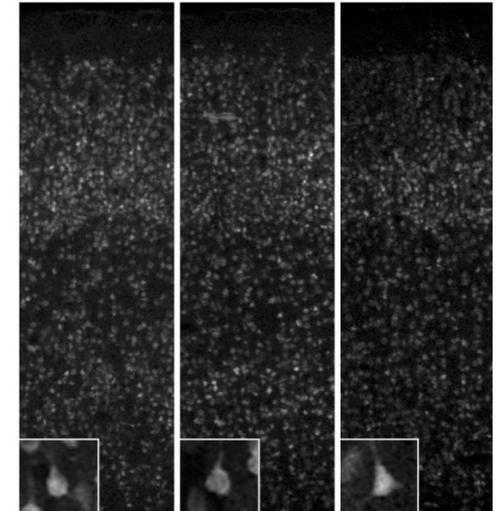
Perilesion



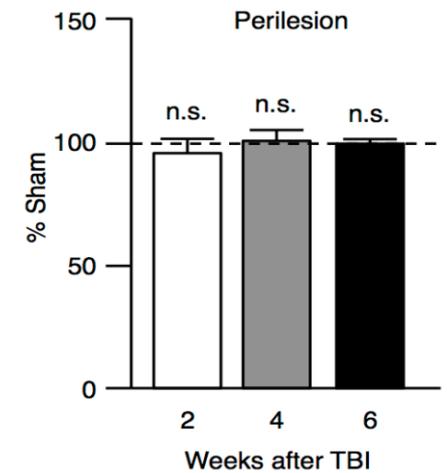
## Unchanged neuronal cell counts after TBI

Post-TBI (perilesion)

2 4 6



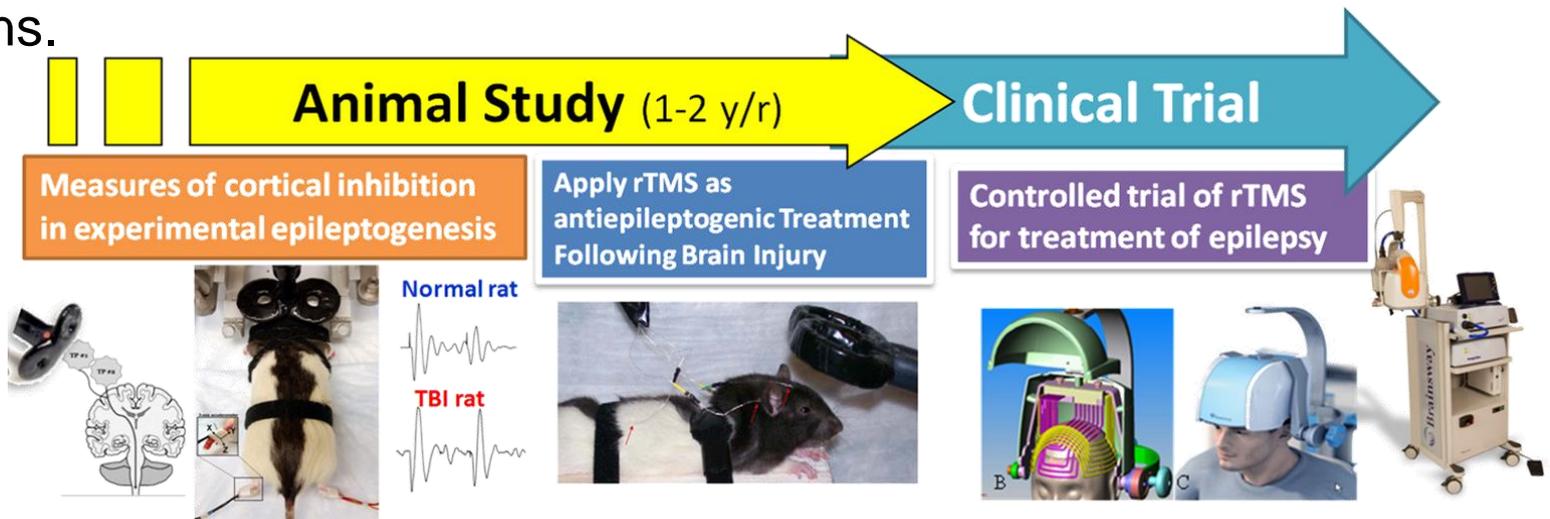
**B NeuN+ cell count**



# Discussion & Conclusion

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- We demonstrate for the first time that progressive functional loss of cortical inhibition correlates with cortical inhibitory interneurons (PV+ cells) following TBI in rats.
- Since non-invasive ppTMS is available to humans, our findings can be readily translated to head trauma patients for the prognosis of posttraumatic symptoms.
- We expect that these neurobiological insights into the post-TBI loss of cortical inhibition will provide valuable opportunities for translation to humans.



# Thank You!



Dr. Alexander Rotenberg Dr. Alvaro Pascual-Leone Dr. Hing Cheong Lee Dr. Mustafa Hameed Dr. Takao K. Hensch