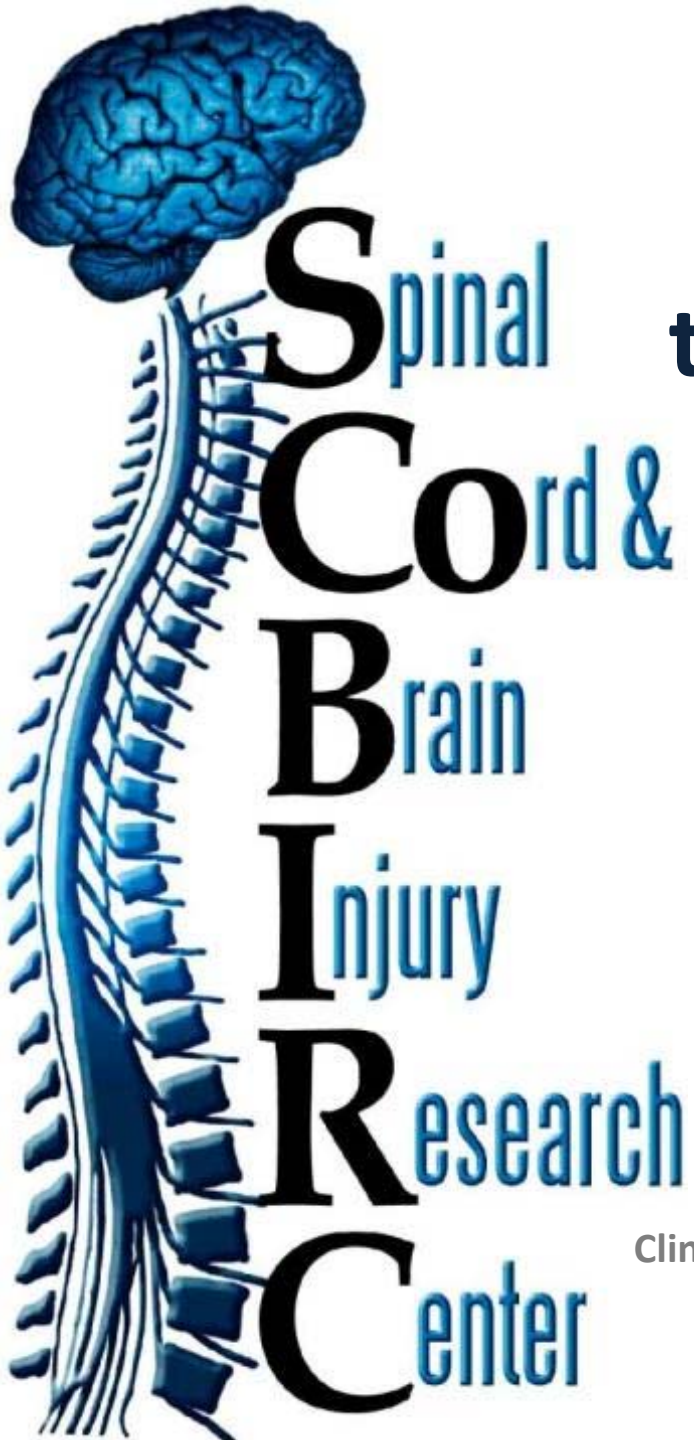

Diffuse brain injury causes up-regulation of thrombospondins in the rat thalamus:

Implications for a role in post-traumatic circuit reorganization

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Clinical and Molecular Biology of Acute and Chronic Traumatic Encephalopathies

Sports-Related TBI and CTE

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Thrombospondins 1 and 2 (TSP1/2) are involved in synaptogenesis

- **TSP1/2** are astrocyte-secreted glycoproteins that help promote ultra-structurally normal synapses (*in vitro* & *in vivo)* (Christopherson et al., 2005)
  - induce synapse formation
  - stabilizing synapse
  - presynaptically active and post-synaptically silent (unidentified astrocyte signal necessary)
- TSP1/2 bind with the **α2δ-1 subunit** of voltage-gated calcium channels to exert synaptogenic effect (Eroglu et al., 2009)
  - Independent of calcium mediated function
- TSP1/2:α2δ-1 interactions form **excitatory** synapses (Hughes et al., 2010)
- Overexpression of α2δ-1 increases synaptogenesis (*in vitro* & *in vivo)*
  - ❖ Knockdown of α2δ-1 decreases synaptogenesis *(in vitro)* (Eroglu et al., 2009)

TSP1/2 knockout mice support role for synaptogenesis

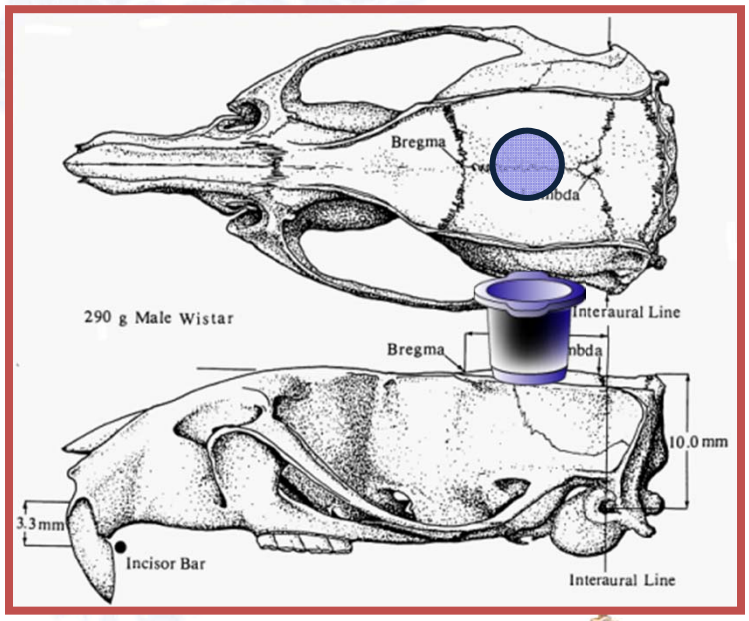
- TSP1/2 KO mice form fewer synapses
  (Christopherson et al., 2005)

- Post-stroke, TSP1/2 KO mice were compared to WT
  - significantly **decreased synaptic density**
  - significantly **decreased axonal sprouting**
  - significantly **reduced ability to recover function**
    (Liauw et al., 2008)

Is it possible TSPs reorganize circuits after diffuse TBI?

Experimental Diffuse Brain Injury

Midline fluid percussion injury (FPI)



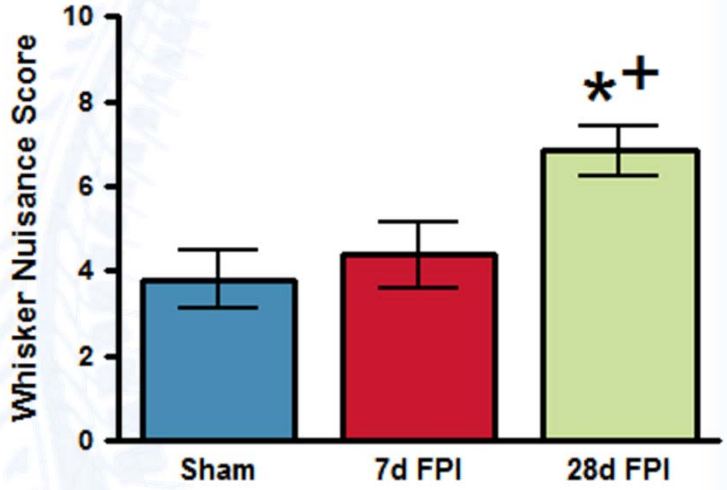
- adult, male SD rats
- 1.8-2.1 atm
- 6-10 min righting time

This injury causes circuit disruption without causing destruction

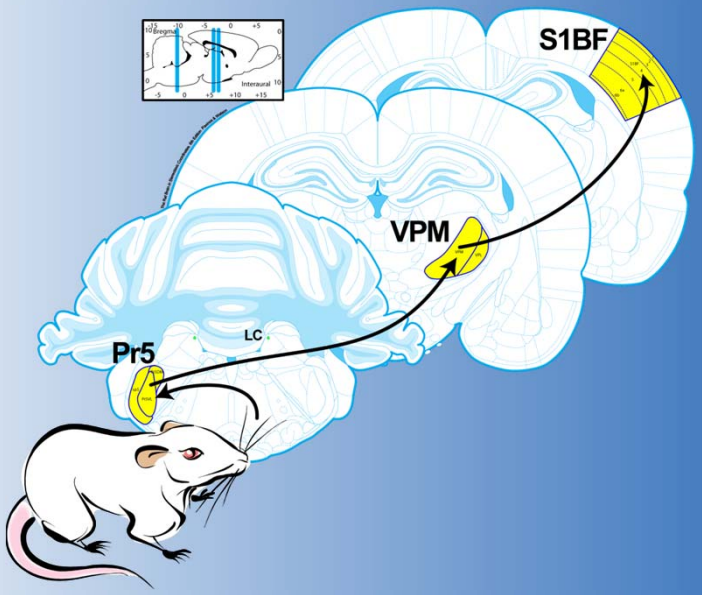
FPI induces late-onset behavioral, neurochemical and morphological changes in the thalamus

Whisker nuisance task

Late-onset sensory sensitivity to manual whisker stimulation



Whisker barrel circuit



Thalamocortical circuit

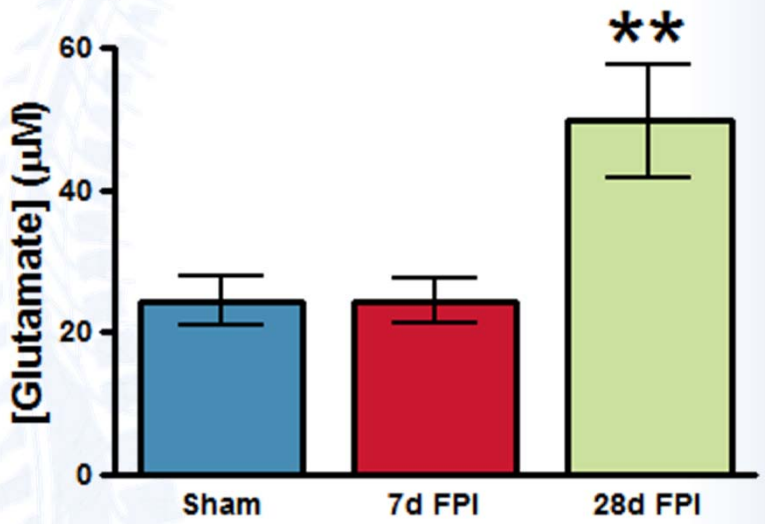
VPM: Ventral posterior medial nucleus of the thalamus

S1BF: Primary somatosensory barrel fields

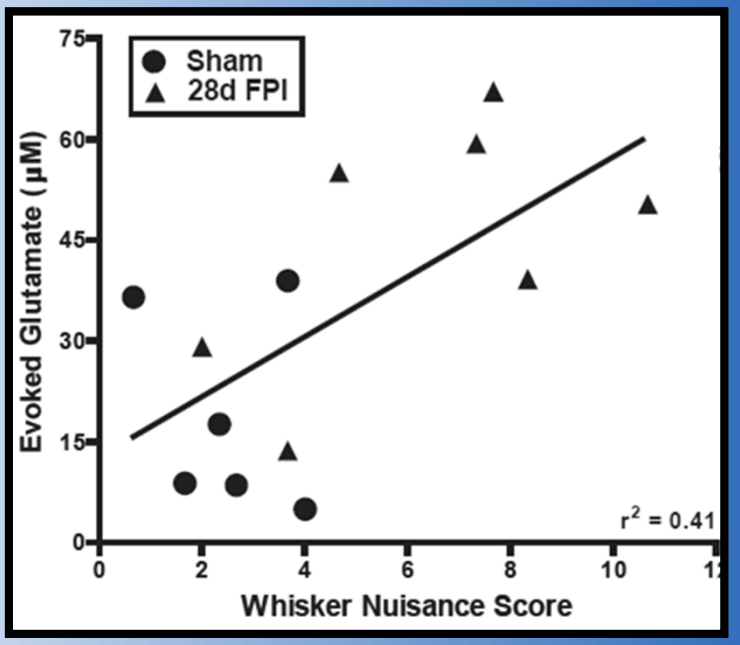
McNamara et. al., 2010; Thomas et. al., 2012

FPI induces late-onset behavioral, neurochemical and morphological changes in the thalamus

Increase in evoked glutamate release over 28 days post-FPI



Positive correlation between the [glutamate] released and aberrant response to whisker stimulation

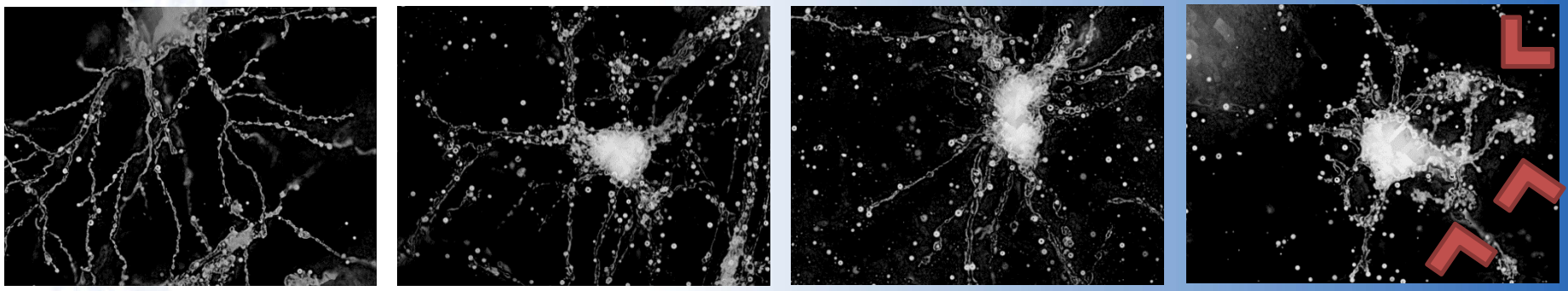


Thomas et. al., 2012

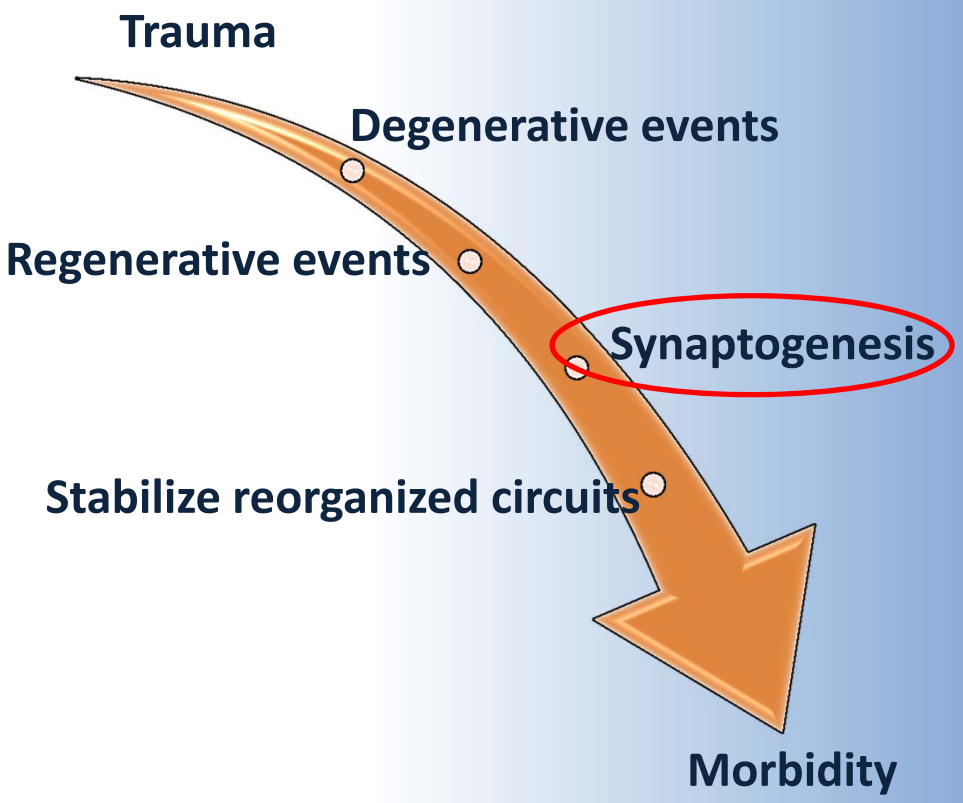
FPI induces late-onset behavioral, neurochemical and morphological changes in the thalamus

Visual evidence of corresponding changes in neuronal projections (Golgi stain)

Sham | 1d FPI | 7d FPI | 28d FPI

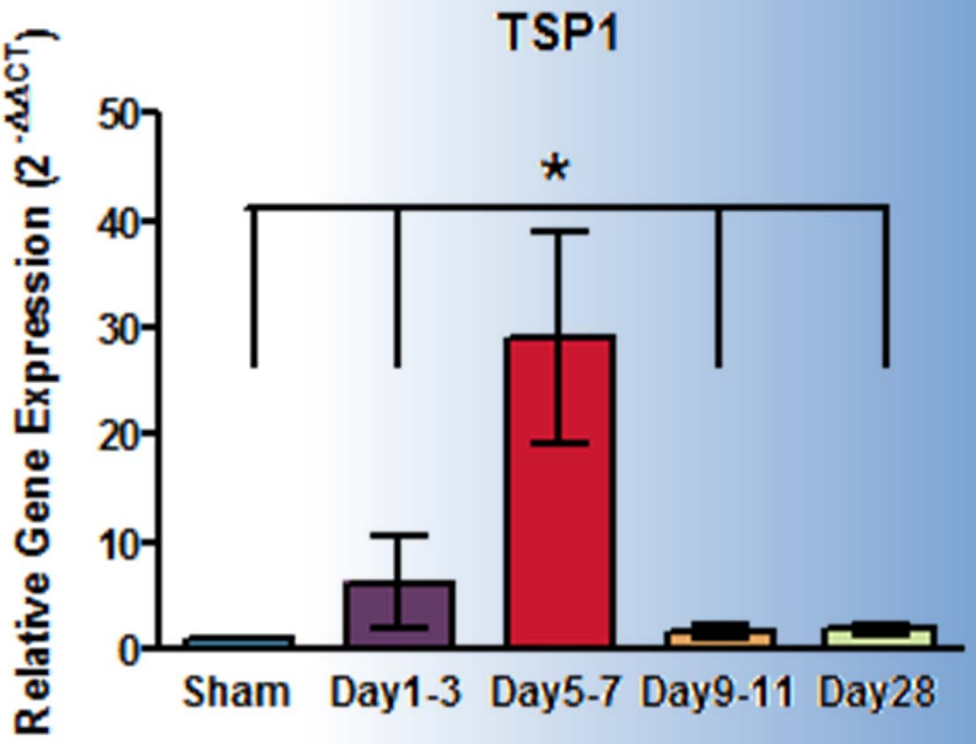


Is TSP-mediated synaptogenesis involved in maladaptive circuit reorganization resulting in late-onset sensory sensitivity?



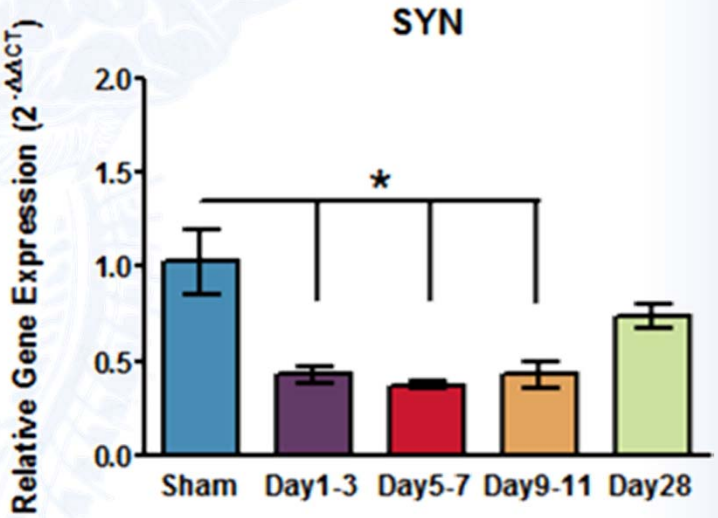
The temporal profile of these events are unknown!

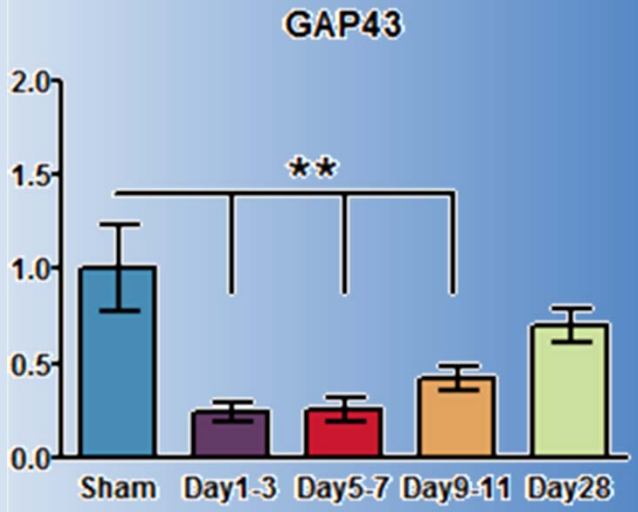
Thrombospondin1 gene expression changes after diffuse TBI

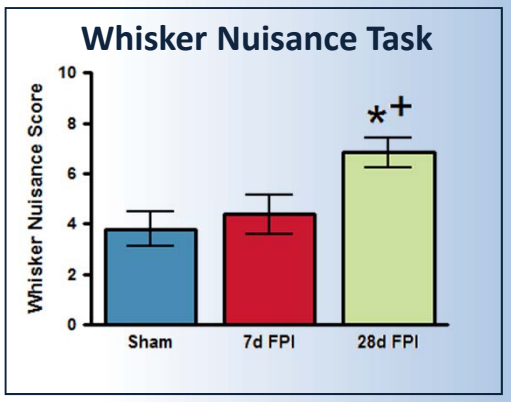


One-way ANOVA; Tukey's post-hoc; *p<0.05; **p<0.01; $^{+}$compared to 7d; mean ±SEM; n=3-5/group

Synaptic gene expression decreases and rebounds over 28 days post-FPI







One-way ANOVA; Tukey's post-hoc; *p<0.05; **p<0.01; +compared to 7d; mean ±SEM; n=3-5/group

Summary

- Identification of a temporal profile of synaptogenic gene expression after diffuse TBI
  - TSP1 increases 30-fold between days 5-7 post-injury

- “Rebound” at 28 days post-injury corresponds to late-onset behavioral morbidity, altered neurochemistry and neuron morphology

Significance

- Synaptogenic events are ongoing at 1 month post-injury which may impact repetitive trauma and return-to-play criteria.

- A temporal profile may identify a therapeutic window for treatment of diffuse brain injury by focusing on synaptogenesis as the pivotal process in circuit reorganization.

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