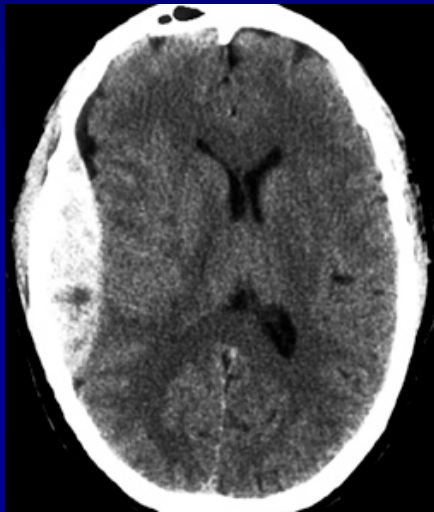


# Found in Translation:

## New Treatment Approaches for Pediatric Traumatic Brain Injury



Children's Discovery &  
Innovation Institute  
Los Angeles, CA  
May 28, 2015

20+5min

Christopher C. Giza, M.D.  
Pediatric Neurology and Neurosurgery



Mattel Children's Hospital

UCLA

# Credit where credit deserved!

*Funded by: NS27544, HD061504, NCAA, Dept of Defense, Joseph Drown Foundation, UCLA BIRC, UCLA Steve Tisch BrainSPORT*  
*Consultant: Alcobra, NHLPA, Pearson TLC*

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[www.birc.ucla.edu](http://www.birc.ucla.edu)

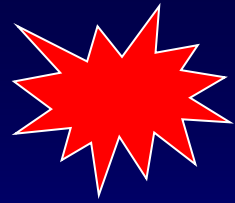
[cgiza@mednet.ucla.edu](mailto:cgiza@mednet.ucla.edu)

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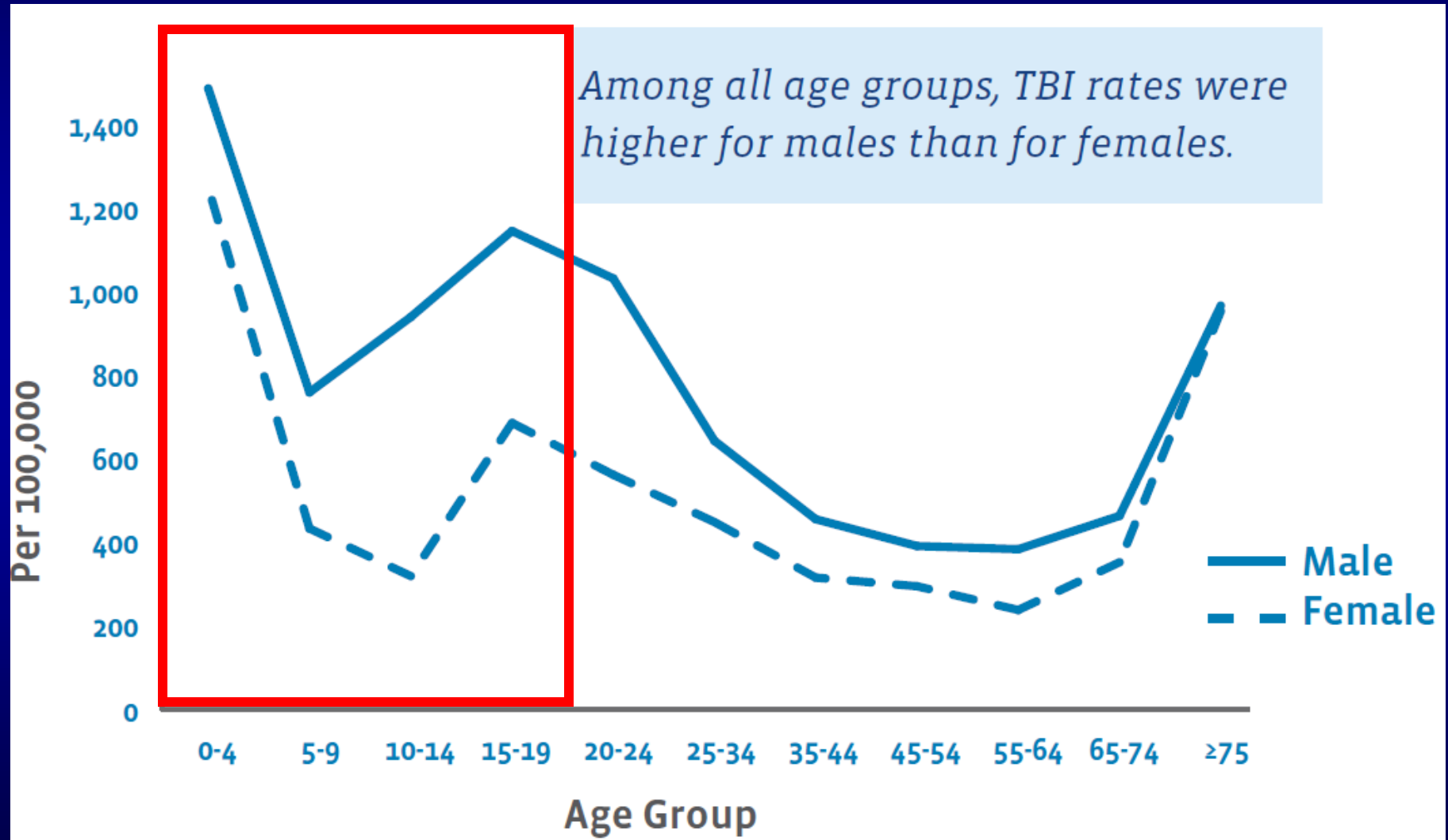
# What's Important?

1. **Why Pediatric TBI?**
2. Monitoring the Injured Brain
  - a) In the ICU
  - b) On the playing field
3. Activating the Injured Brain
  - a) After severe TBI
  - b) After concussion
4. Conclusions





# *TBI is the #1 cause of death and disability in kids and teenagers!!*





# What's Important?

1. Why Pediatric TBI?

**2. Monitoring the Injured Brain**

a) In the ICU

b) On the playing field

3. Activating the Injured Brain

a) After severe TBI

b) After concussion

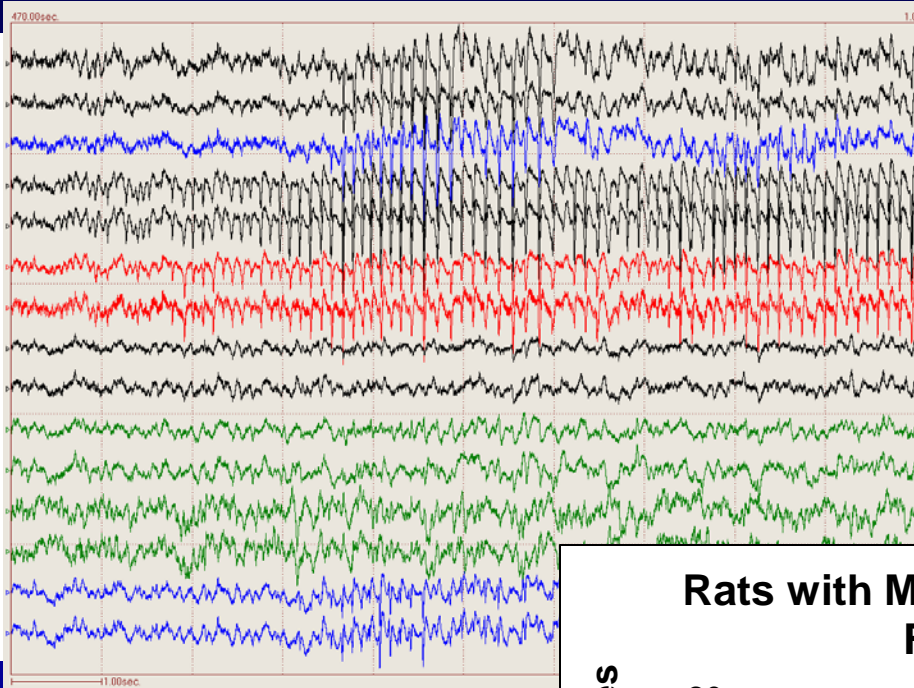
4. Conclusions



# Post-TBI seizures



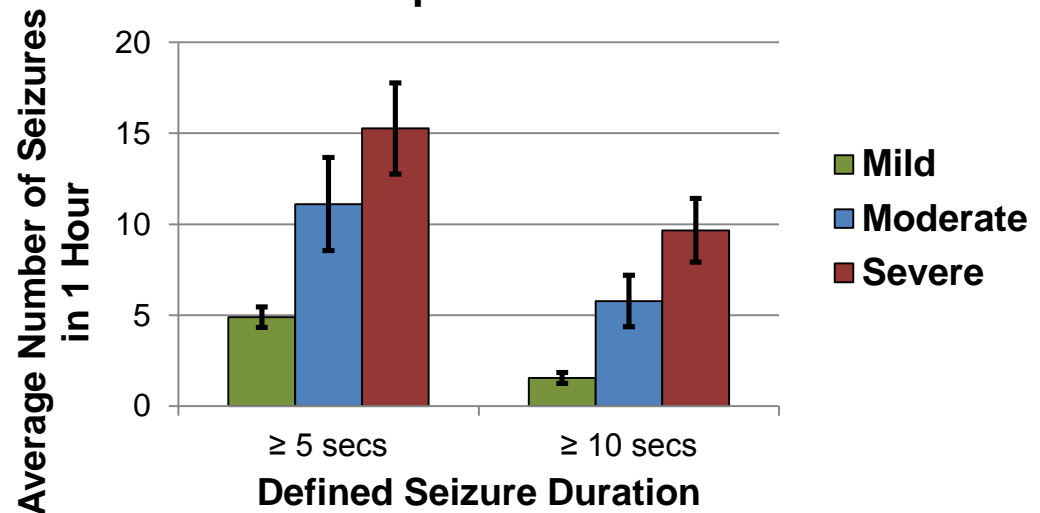
- 1: L Frontal
- 2: L Frontal
- 3: R Frontal
- 5: L Ant Parietal
- 6: L Ant Parietal
- 7: Lesion core
- 8: Lesion core
- 9: L Parietal
- 10: L Parietal
- 11: L Ant Hippo
- 12: L Ant Hippo
- 13: L Post Hippo
- 14: L Post Hippo
- 15: R Parietal
- 16: R Parietal



**47% of rats showed seizure activity after TBI.**

**More severe injury caused more frequent seizures**

**Rats with More Severe Injury Have More Frequent Seizures**



# Early post-traumatic seizures (EPTS)

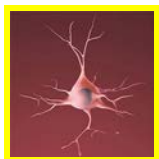


**FULL-LENGTH ORIGINAL RESEARCH**

## Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort

**\*<sup>1</sup>Daniel H. Arndt, †<sup>‡</sup>Jason T. Lerner, †<sup>‡</sup>Joyce H. Matsumoto, §Andranik Madikians,  
†<sup>‡</sup>Sue Yudovin, †<sup>¶</sup>Hannah Valino, †<sup>¶</sup>David L. McArthur, †<sup>‡</sup>Joyce Y. Wu, †<sup>¶</sup>Michelle Leung,  
†<sup>¶</sup>Farzad Buxey, †Conrad Szeliga, #Michele Van Hirtum-Das, †<sup>‡</sup>Raman Sankar,  
\*\*†<sup>‡</sup>Amy Brooks-Kayal, and †<sup>‡</sup>¶<sup>‡</sup>Christopher C. Giza**





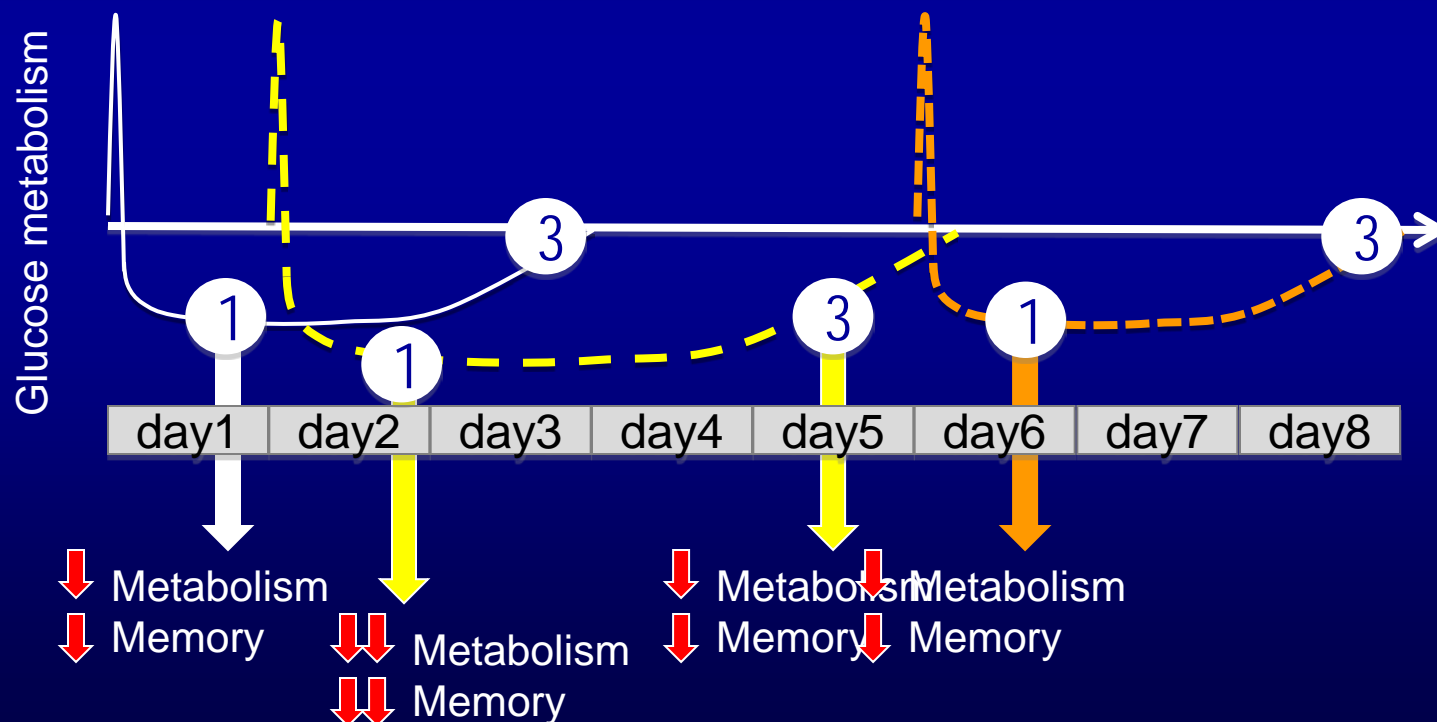
# Repeated Mild Traumatic Brain Injury: Mechanisms of Cerebral Vulnerability



Mayumi L. Prins,<sup>1,4,5</sup> Daya Alexander,<sup>4,5</sup> Christopher C. Giza,<sup>1,2</sup> and David A. Hovda<sup>1,3-5</sup>

**2<sup>nd</sup> concussion before full recovery results in worse brain metabolism & memory**

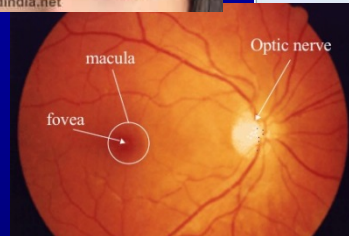
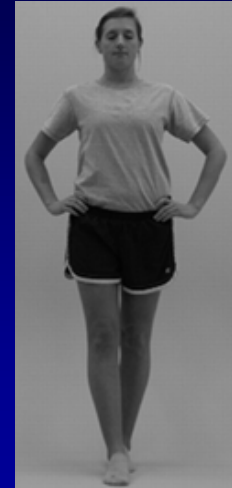
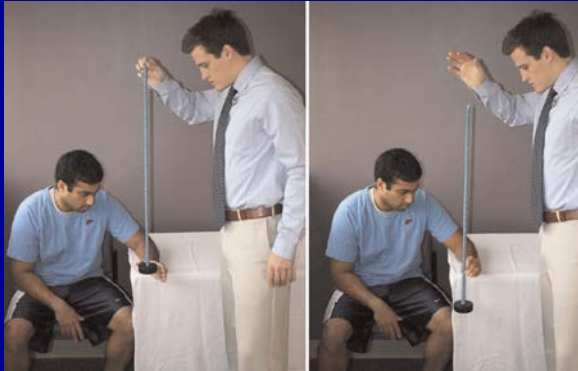
- Single TBI
- - 2<sup>nd</sup> TBI BEFORE recovery from 1<sup>st</sup> TBI
- ... 2<sup>nd</sup> TBI AFTER recovery from 1<sup>st</sup> TBI





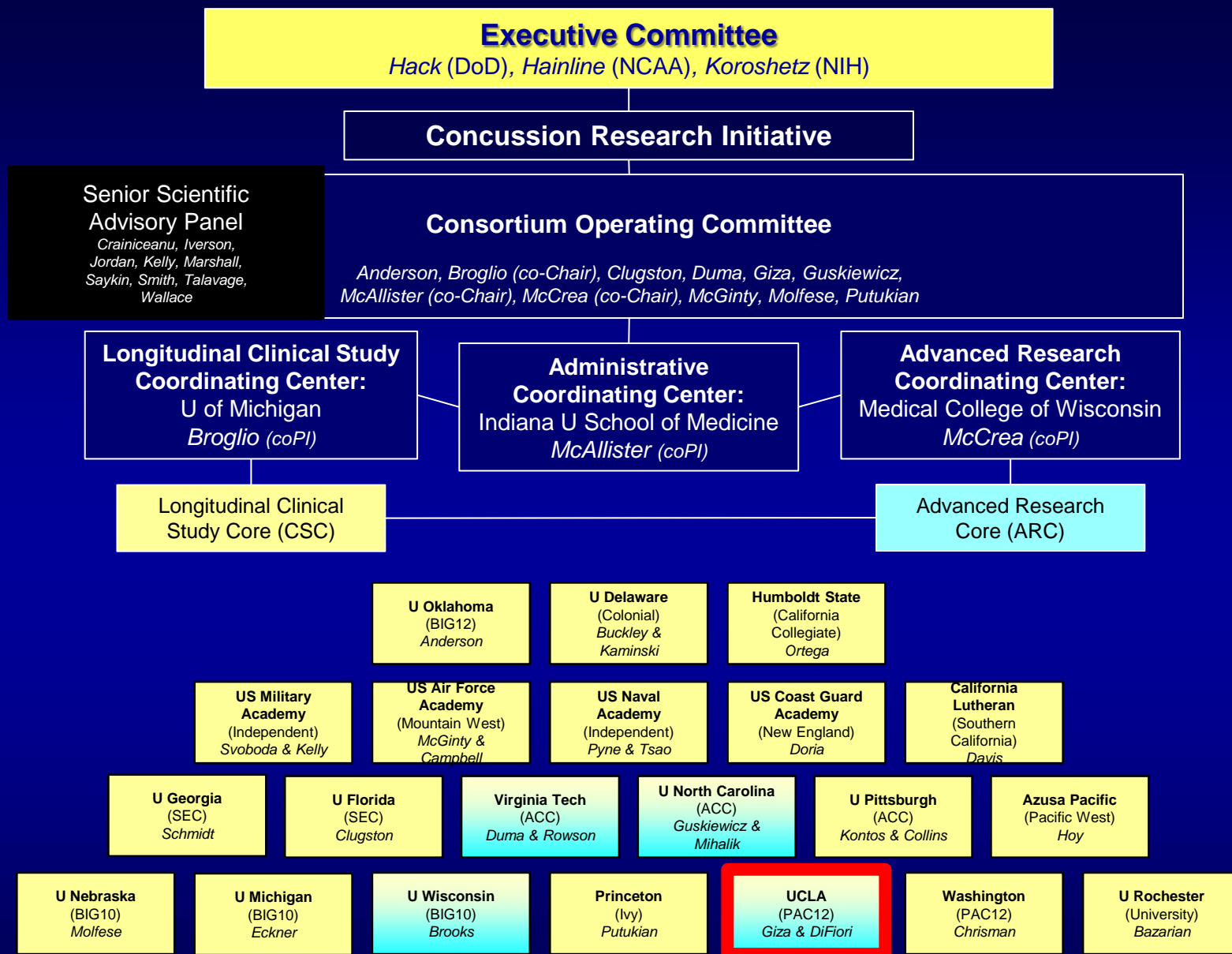
# Diagnosing Concussions

- *There is NO SINGLE test to diagnose concussion*



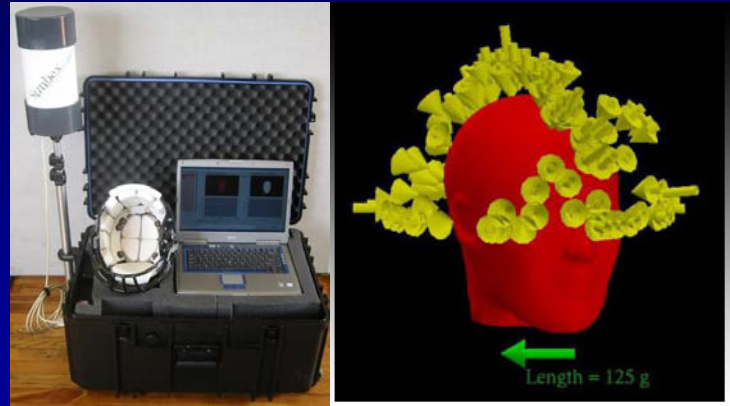
3 - 7 - 5 - 9 - 0  
2 - 5 - 7 - 4 - 6  
1 - 4 - 7 - 6 - 3  
7 - 9 - 3 - 9 - 0  
4 - 5 - 2 - 1 - 7  
5 - 3 - 7 - 4 - 8  
7 - 4 - 6 - 5 - 2  
9 - 0 - 2 - 3 - 6





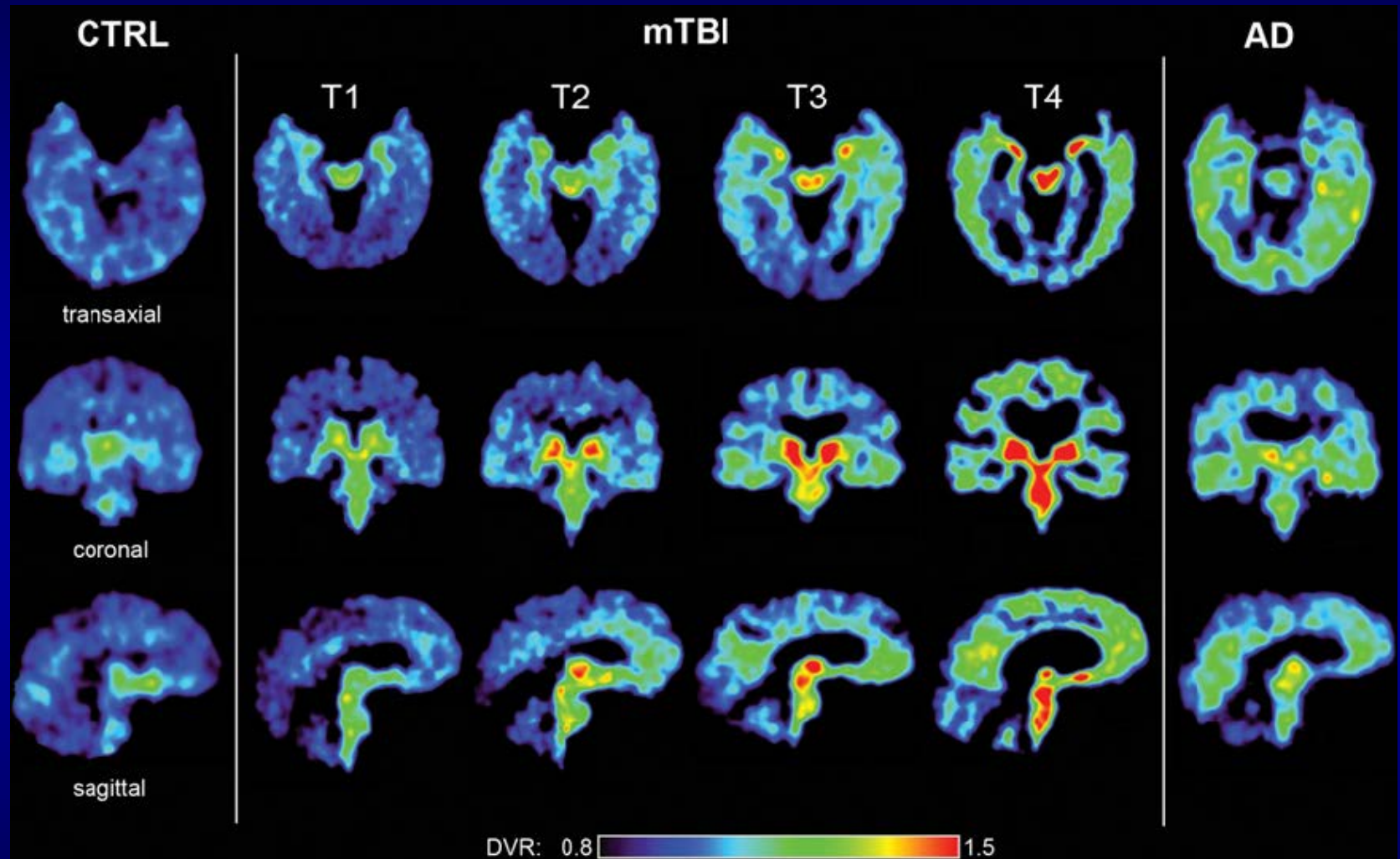
# Concussion Exposure: Sports

Helmet-based systems





# Imaging Chronic Concussions?



**FDDNP-PET is a marker for amyloid and tau protein; in retired NFL players it may be a marker for chronic brain damage.**



# What's Important?

1. Why Pediatric TBI?
2. Monitoring the Injured Brain
  - a) In the ICU
  - b) On the playing field
- 3. Activating the Injured Brain**
  - a) After moderate-severe TBI**
  - b) After concussion**
4. Conclusions

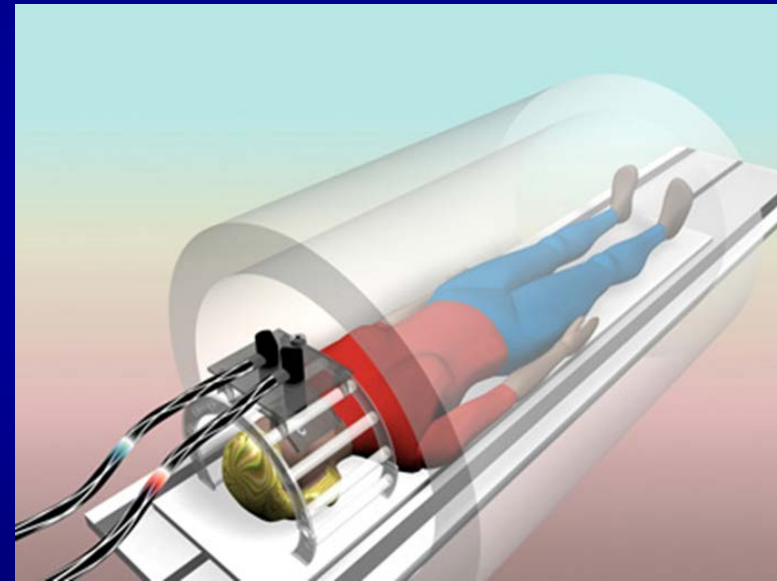




# Pediatric TBI: Glutamate-NMDA receptor dysfunction



Does glutamate  
image your thoughts?



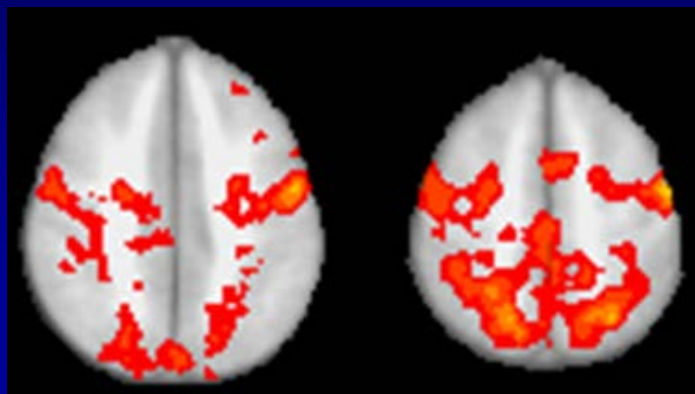
Glutamate neurotransmission  
drives the (BOLD) signal seen  
on fMRI



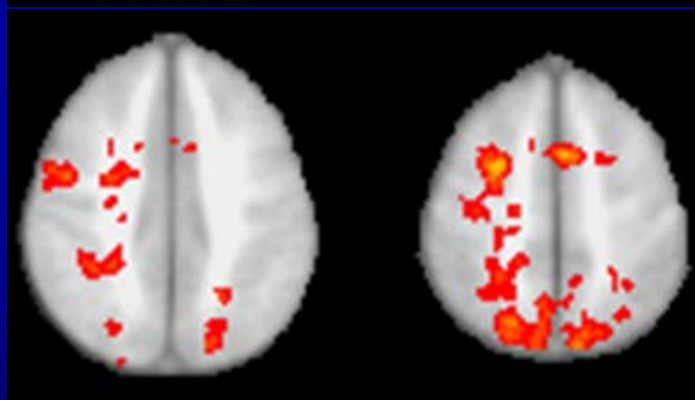
# Post-TBI Impaired Activation: Translational Imaging



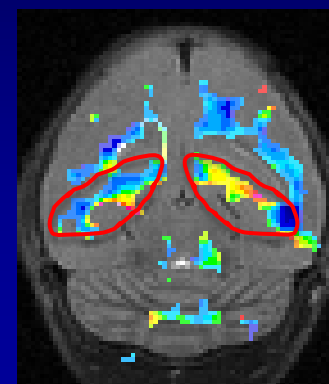
Controls



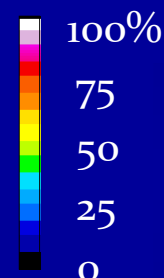
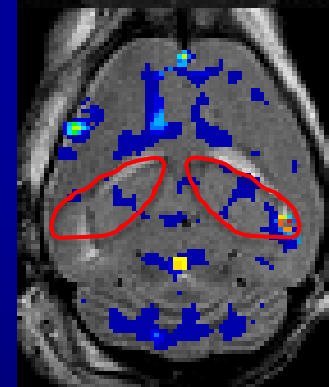
TBI



Control



TBI



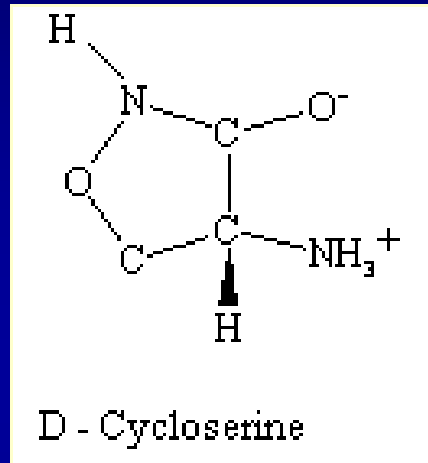
**Children with TBI show less network activation during memory**

**Immature rats with TBI show less hippocampal activation and more memory impairment**

*Prins, et al., in Ped TBI, Anderson & Yeates, eds 2010; Cazalis et al., Front Neurol 2011*

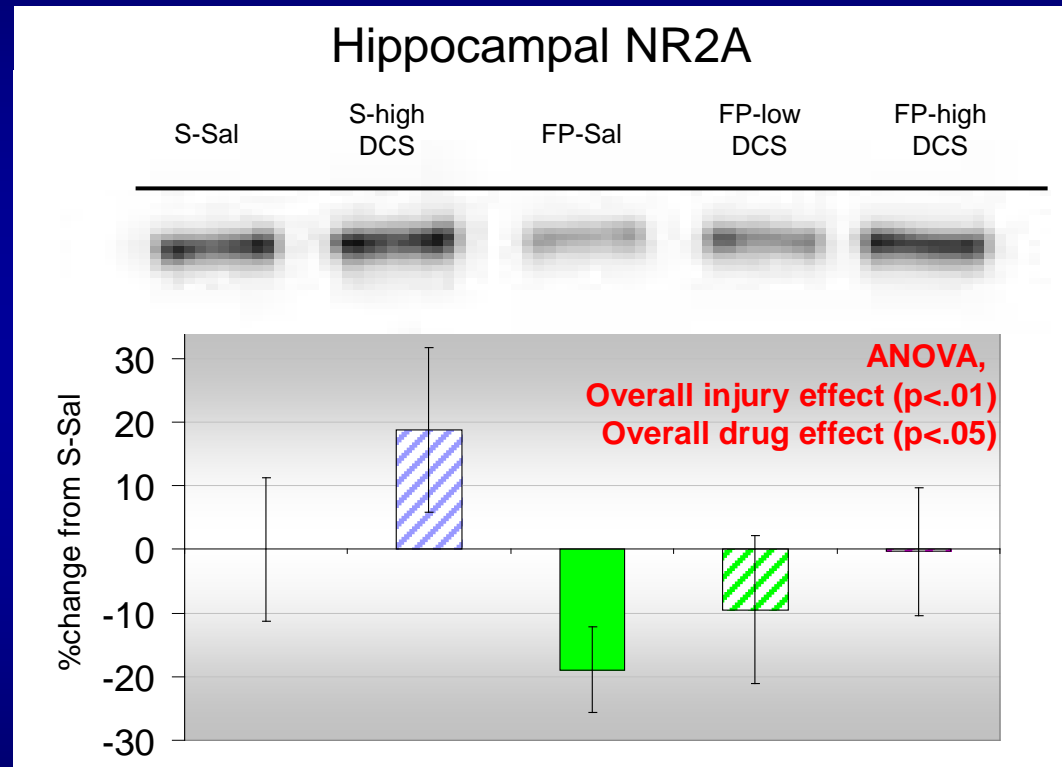
*Santa Maria N.S., et al., in revision 2015*

# D-Cycloserine (DCS) Treatment: Reverses TBI Dysfunction



## D-cycloserine

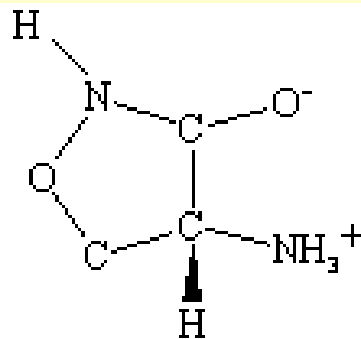
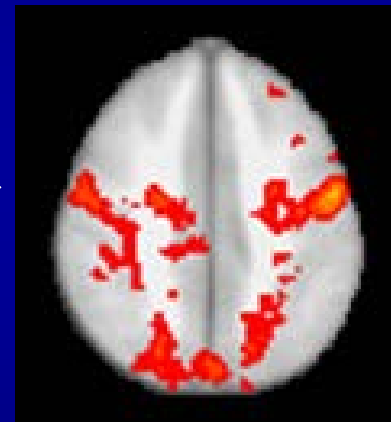
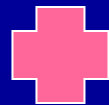
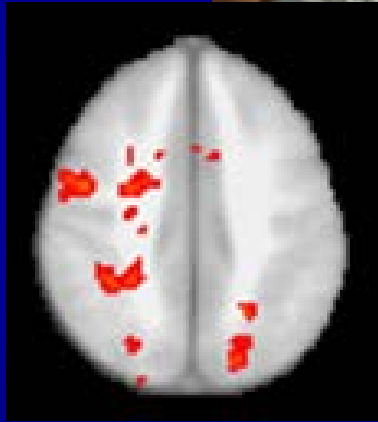
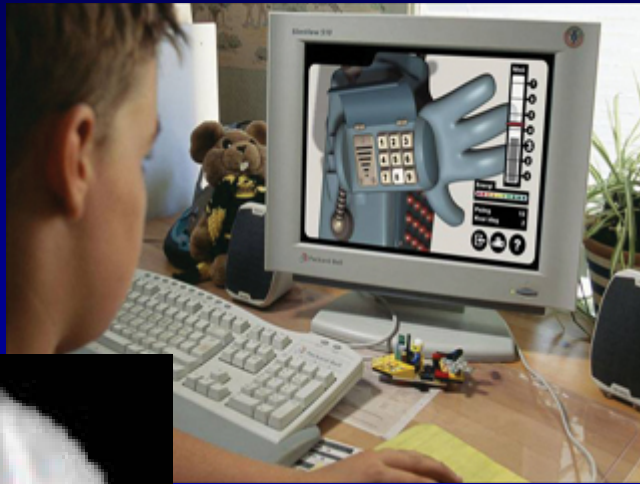
- NMDAR co-agonist
- Binds at glycine site
- FDA approved agent
- Good bioavailability
- Penetrates BBB



**Treatment with DCS restores normal NR2A (IQ gene) levels in rats**

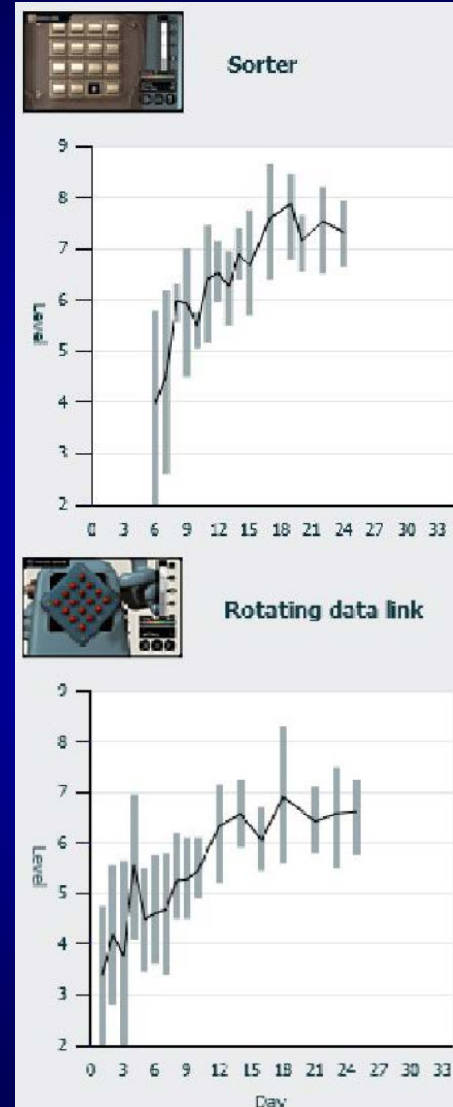


# Clinical Trial: Cognitive Tx + DCS

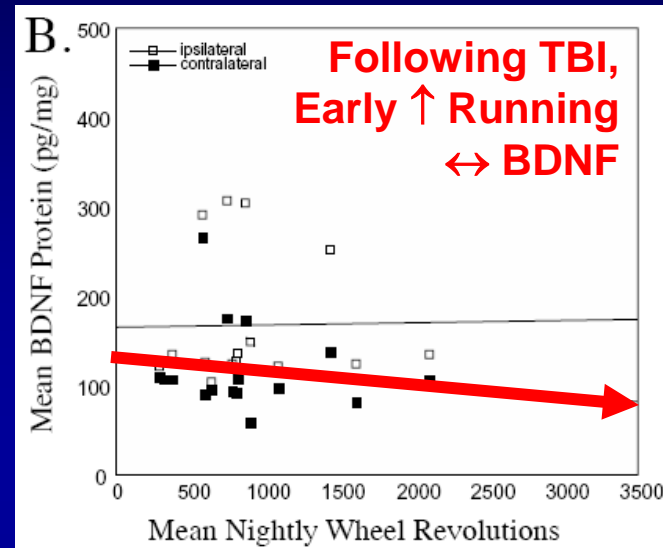
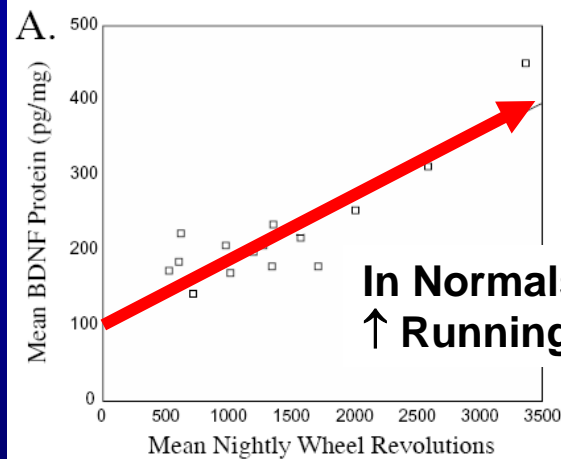


D - Cycloserine

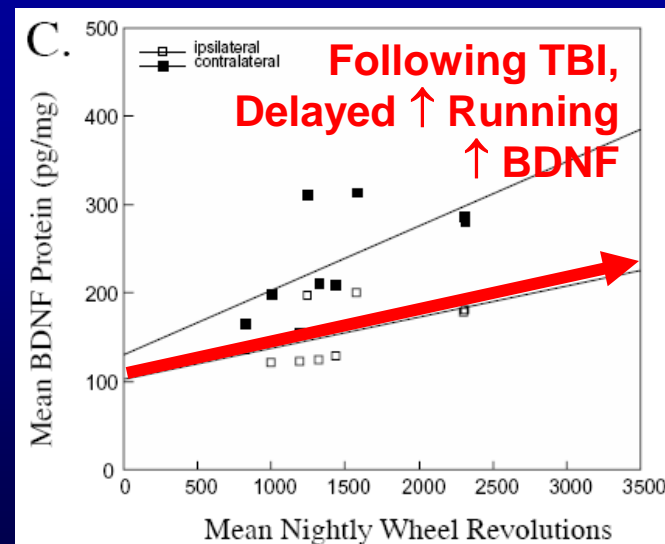
**D-cycloserine**



# Post-concussive Impaired Activation



Also...  
Worse  
cognition



Better  
cognition

**Exercise immediately post-injury worsens outcome;  
but delayed exercise helps.**

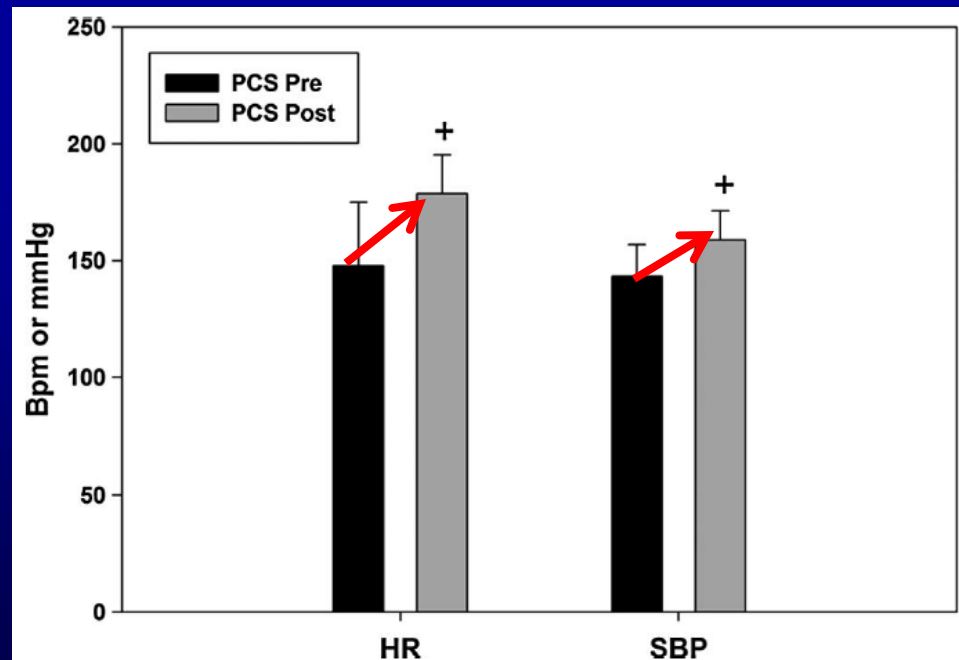
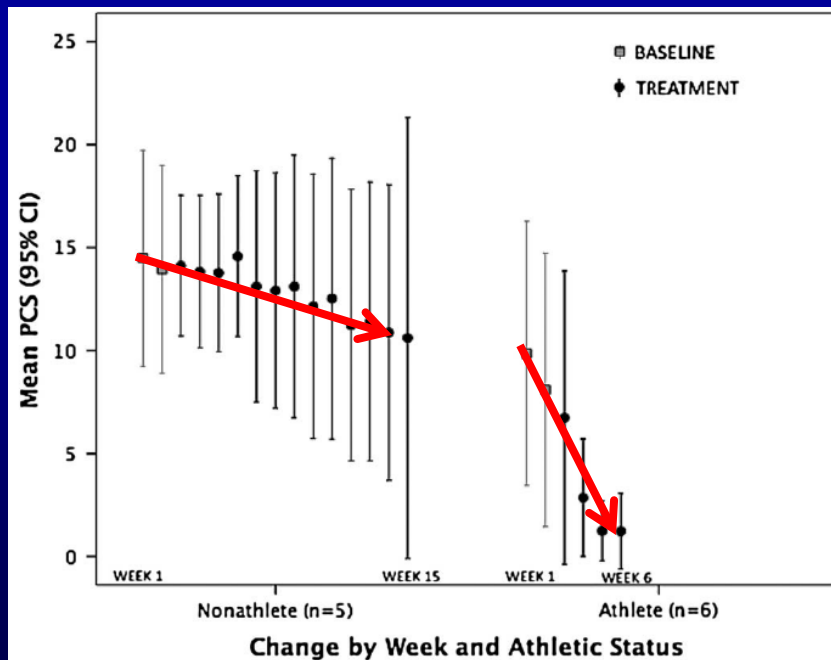
# Exercise as Treatment?

## SubSymptom Threshold Exercise Training

N=12 refractory PCS patients  
(6 athletes, 6 non-athletes)

All subjects exercised near HR max  
w/o symptom exacerbation. No  
adverse reactions or drop-outs

- **Symptoms improved**
- **Athletes improved more rapidly**
- **Heart rate & blood pressure at maximal exercise improved**



# The Future of Pediatric TBI?

1. **Monitoring the injured brain** in the ICU will allow more **rapid intervention for seizures** & secondary brain injury.
2. **Baseline testing** the brain will allow **better diagnosis & treatment** of sports concussion.
3. **Combinations of pharmacological and behavioral therapies** can be synergistic in enhancing TBI outcome.
4. **Properly timed exercise / activity may be therapeutic** for achieving optimal concussion outcomes in athletes.





# UCLA Steve Tisch BrainSPORT

## Baseline assessments



## Sports concussion clinic

12<sup>th</sup> and Wilshire, Santa Monica

200 Medical Plaza, Westwood

**OPENING in 2015...**

**Wasserman Building, Westwood**

Email: [concussioncare@mednet.ucla.edu](mailto:concussioncare@mednet.ucla.edu)

Website: Google “UCLA BrainSPORT”

## Safe return to play



## Comprehensive care



## Education & Research

