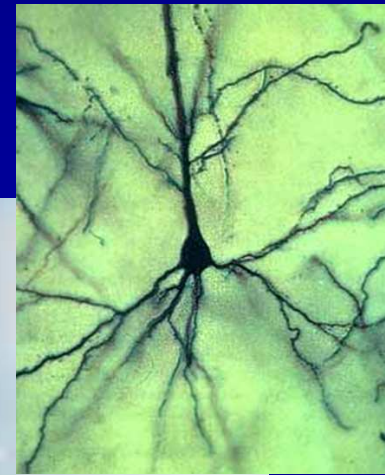
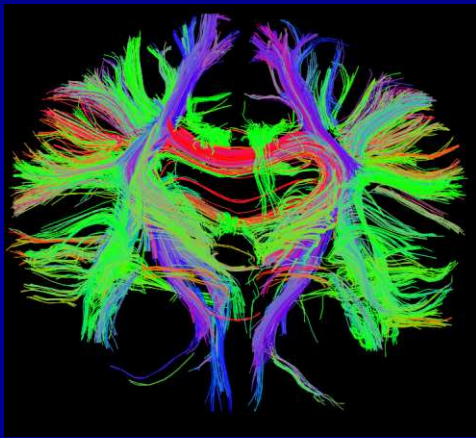
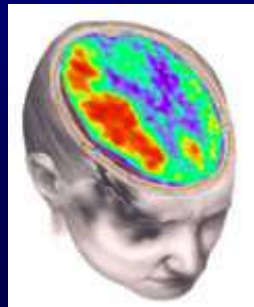


# Metabolism, Neural Activation and Plasticity after TBI: and Plasticity after TBI:

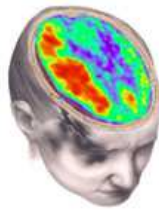
## A Developmental Perspective



Christopher C. Giza, M.D.  
UCLA Brain Injury Research Center  
Pediatric Neurology and Neurosurgery  
Mattel Children's Hospital – UCLA  
David Geffen School of Medicine



# Traumatic Brain Injury in Youth



## UCLA Brain Injury Research Center

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

### Basic Scientists

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Me

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Grace Griesbach, Ph.D.

Neil Harris, Ph.D.

Andrey Mazarati, M.D., Ph.D.

**Mayumi Prins, Ph.D.**

Raman Sankar, M.D., Ph.D.

### Residents/Fellows

Garni Barkoudarian, M.D.

Meeryo Choe, M.D.

Ivet Hartonian, M.D.

Daniel Shrey, M.D.

### Nurses

Maria Etchepare

**Sue Yudovin**

### Medical Students

Julia Breault

**Floyd Buen**

### Post-doc

Tiffany Greco

### Clinical Investigators

**Robert Asarnow, Ph.D.**

**Talin Babikian, Ph.D.**

Fabienne Cazalis, Ph.D.

Sarah DeBoard Marion, Ph.D.

John DiFiori, M.D.

Jason Lerner, M.D.

Michelle Leung, Programmer

Andy Madikians, M.D.

Joyce Matsumoto, M.D.

**David McArthur, Ph.D., M.P.H.**

### Lab Assistants

**Yan Cai, M.S.**

Sima Ghavim

Don Shin

### Graduate Students

Daya Alexander

Gretchen Miller

**Maxine Reger**

**Naomi Santa Maria**

**Hannah Valino**

### Undergrads/Postbac

Farbod Fazlollahi

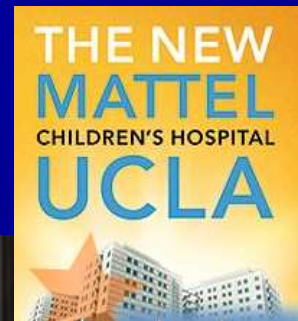
Phoebe Hua

Aditya Ponnaluri

### EEG Techs

Andrea Duran

Conrad Szeliga



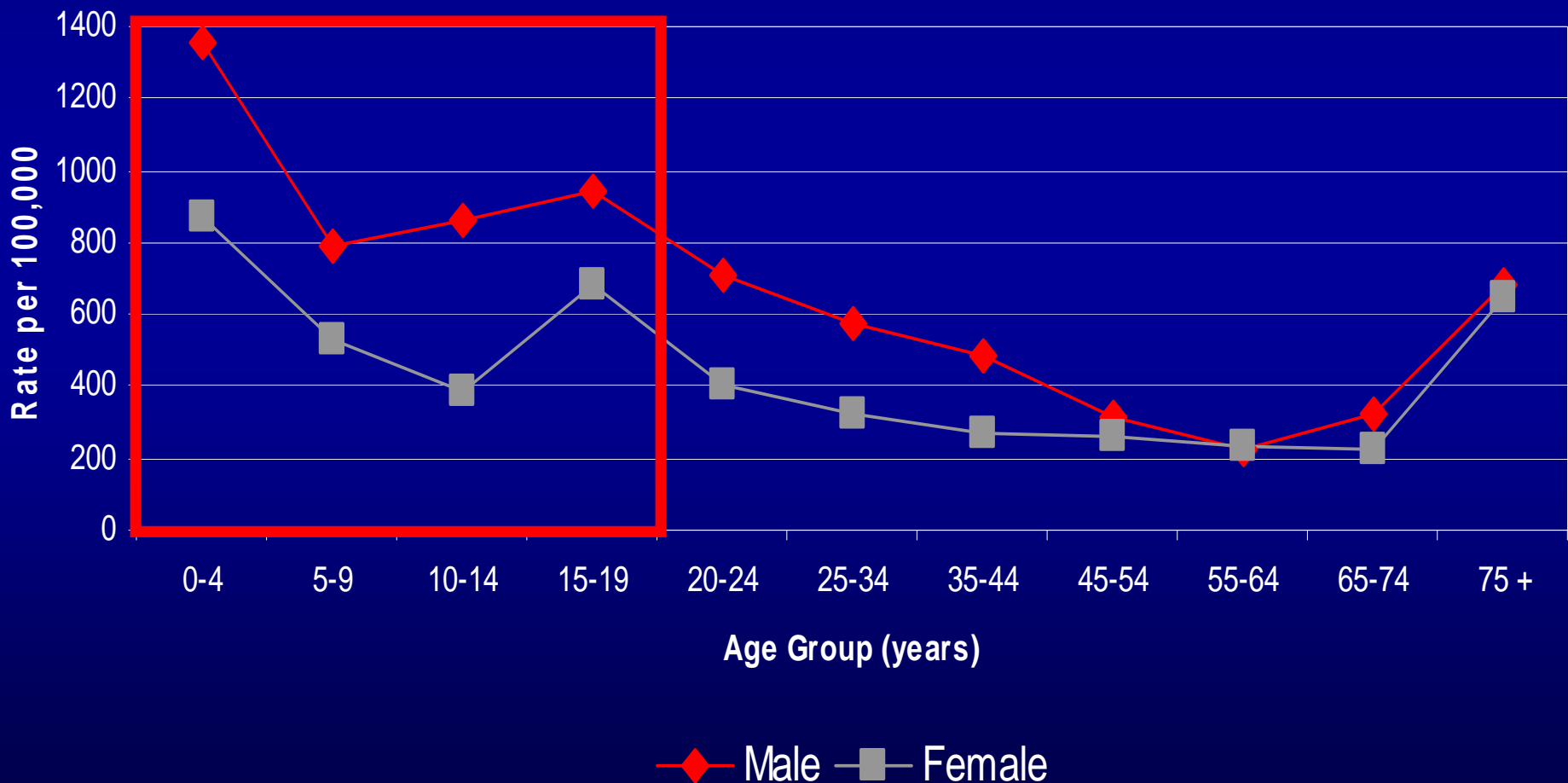
# Summary

1. Introduction to Pediatric TBI
2. Metabolism and Metabolic Therapy
3. Neural Activation and Pro-plasticity Therapy
4. Effects of Repeated Injury in Development
5. Conclusions



# Traumatic Brain Injury: Epidemiology

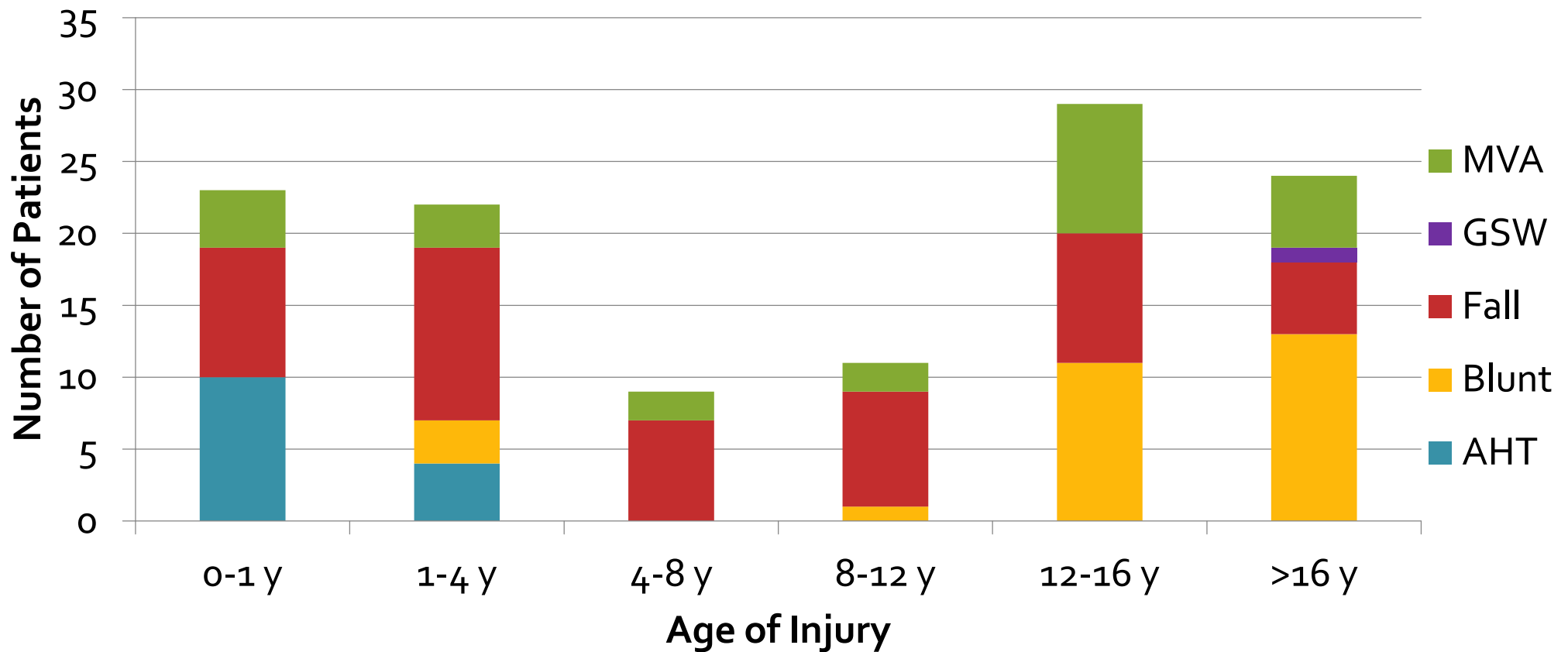
 *#1 cause of death and acquired disability in children and adolescents!!*



# Age of Injury and Mechanism



## Mechanism of Injury varies by Age



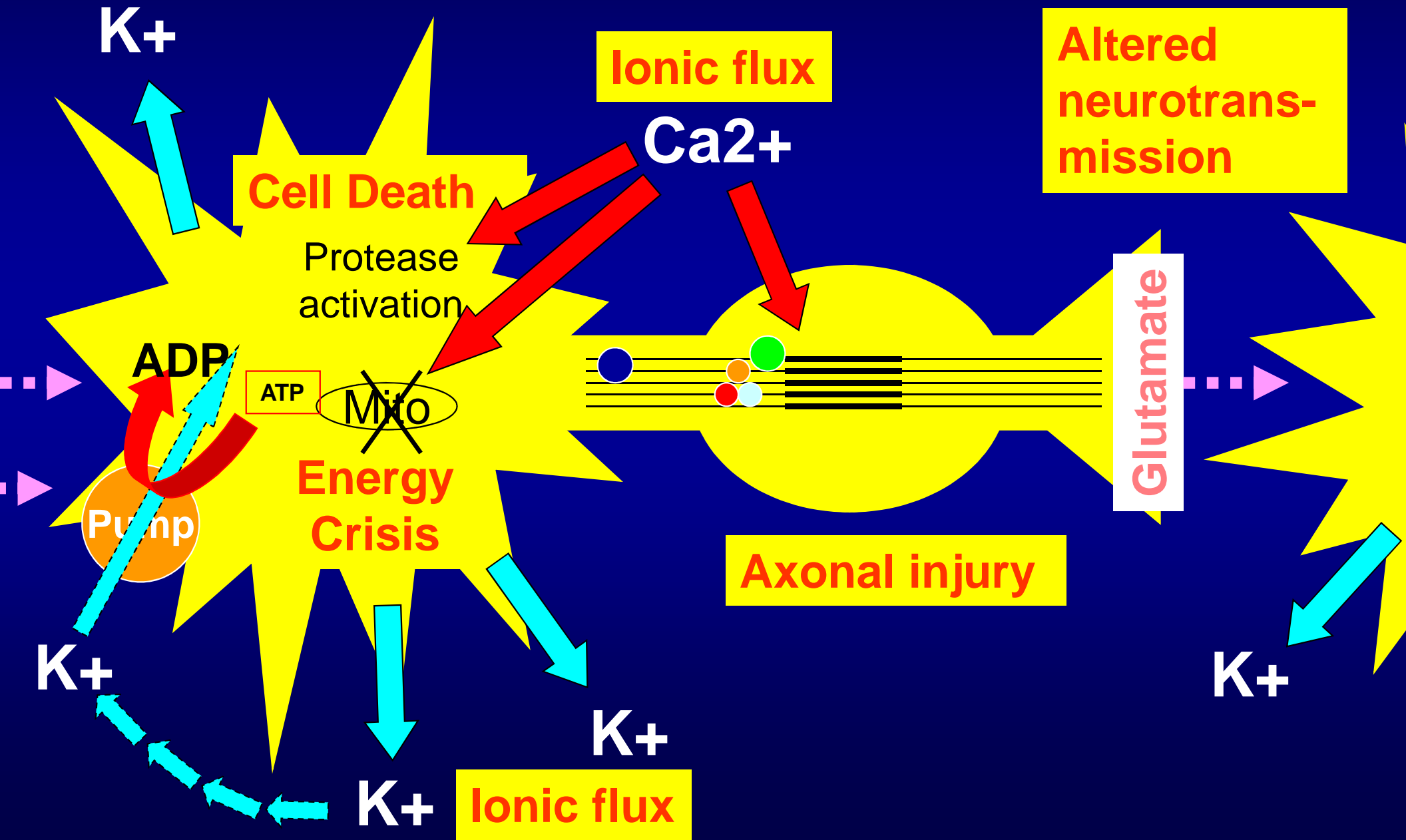
\*ANOVA,  $p < 0.0001$

# Summary

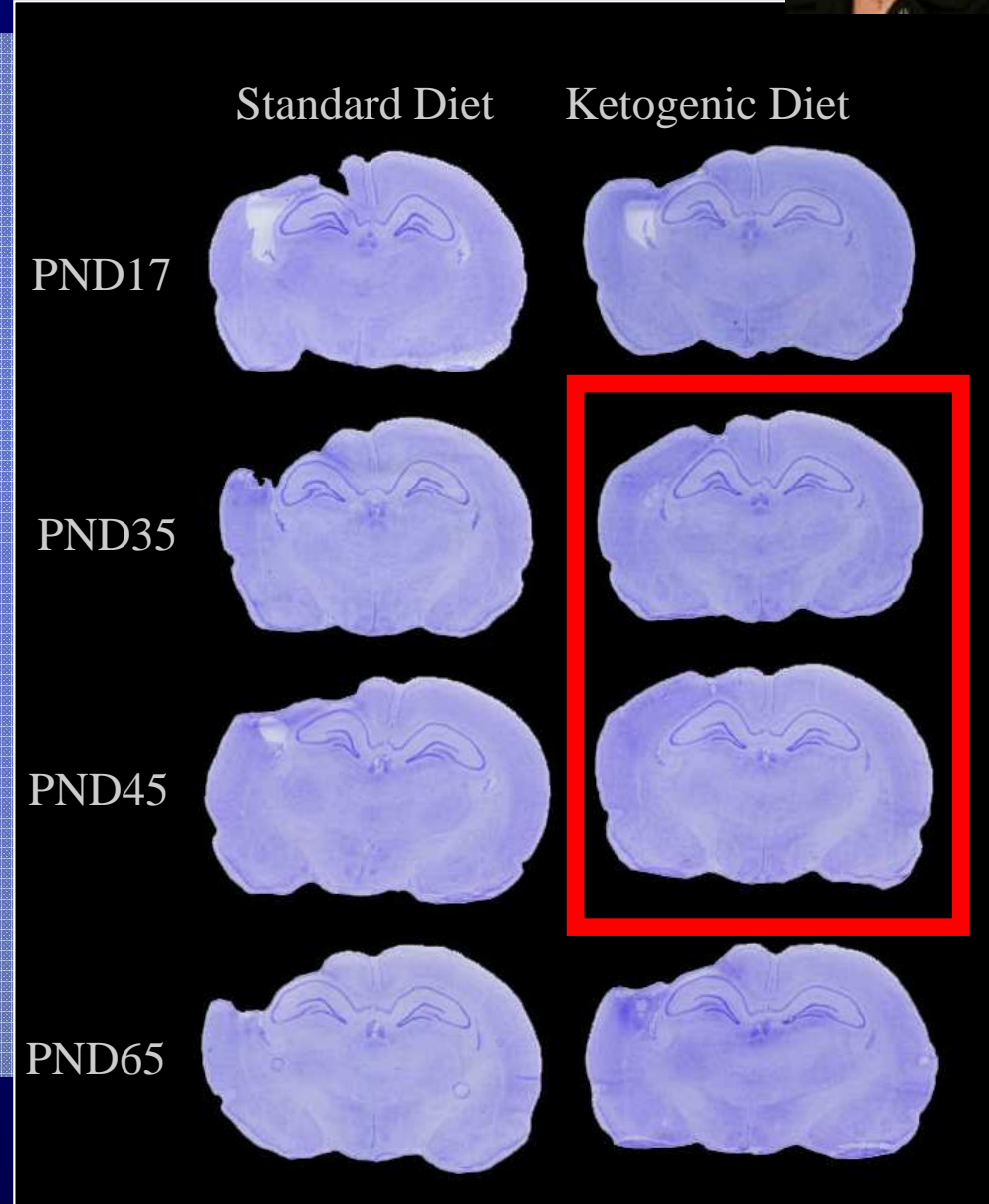
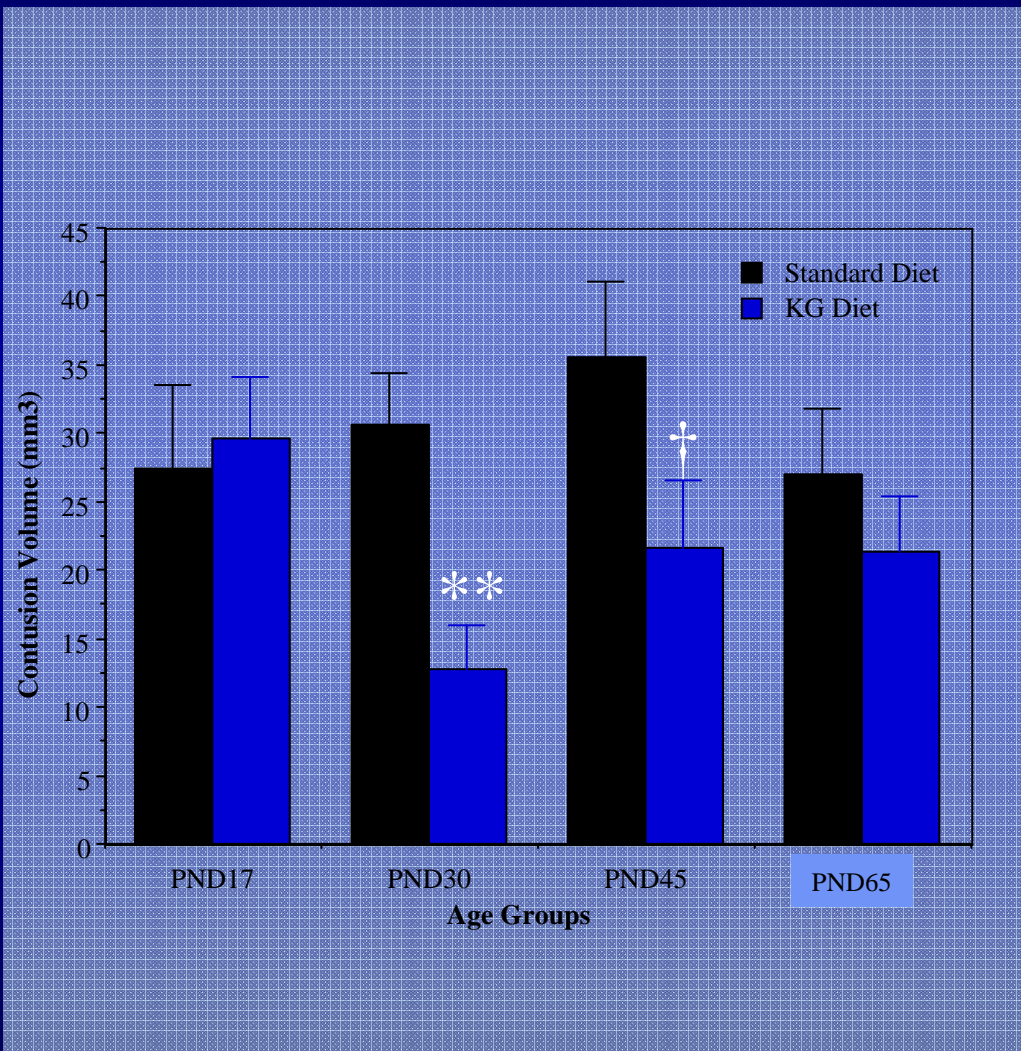
1. Introduction to Pediatric TBI
- 2. Metabolism and Metabolic Therapy**
  - a) Neurometabolic Cascade**
  - b) Alternative Fuel Metabolic Therapy**
3. Neural Activation and Pro-plasticity Therapy
4. Effects of Repeated Injury in Development
5. Conclusions



# Neurometabolic Cascade of mTBI: Basic Pathophysiology



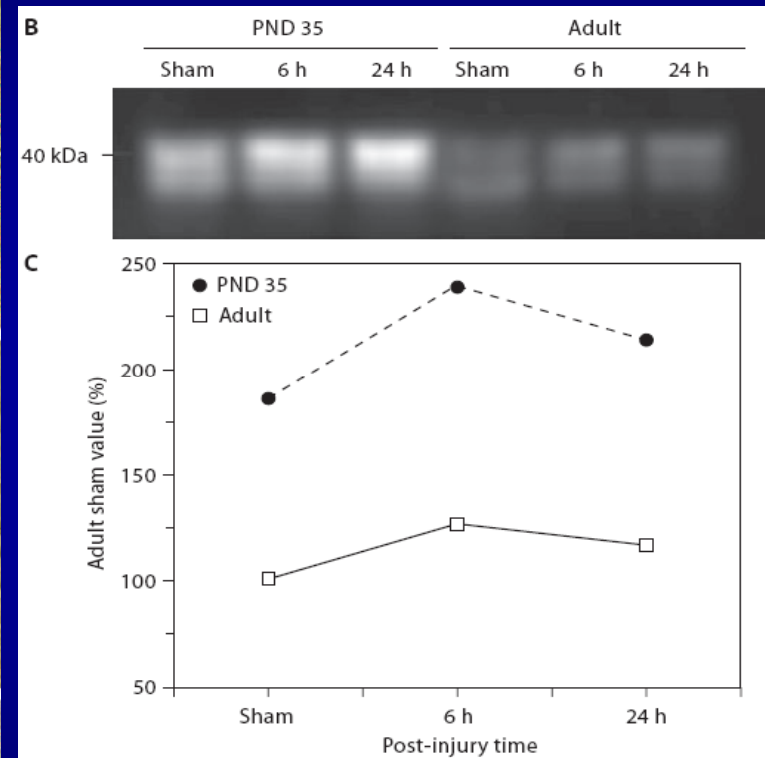
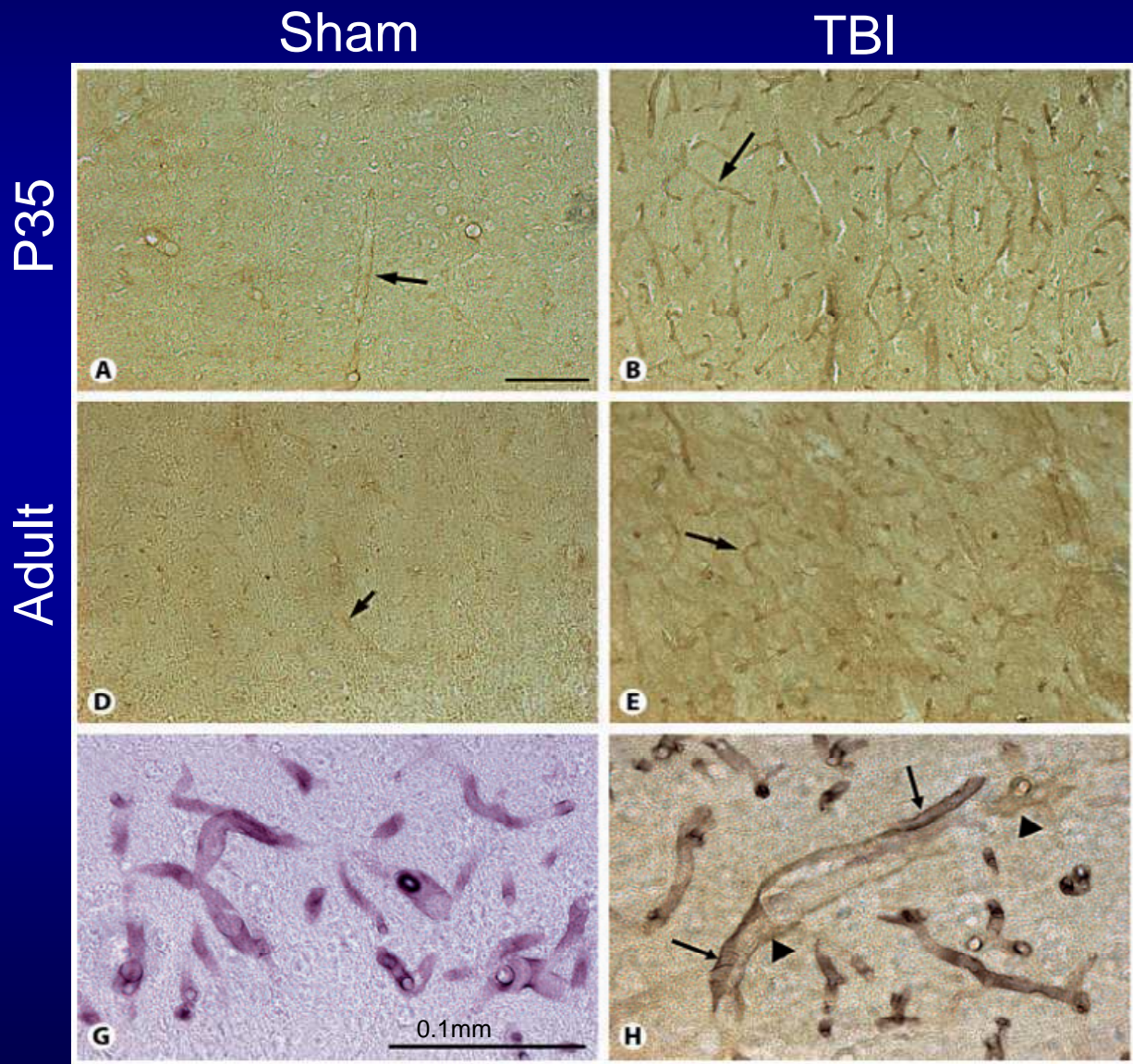
# Treating for Neuroprotection: Ketones as Fuel



**Post-TBI ketogenic diet reduces  
lesion volume in immature rats**



# Post-TBI transporter upregulation



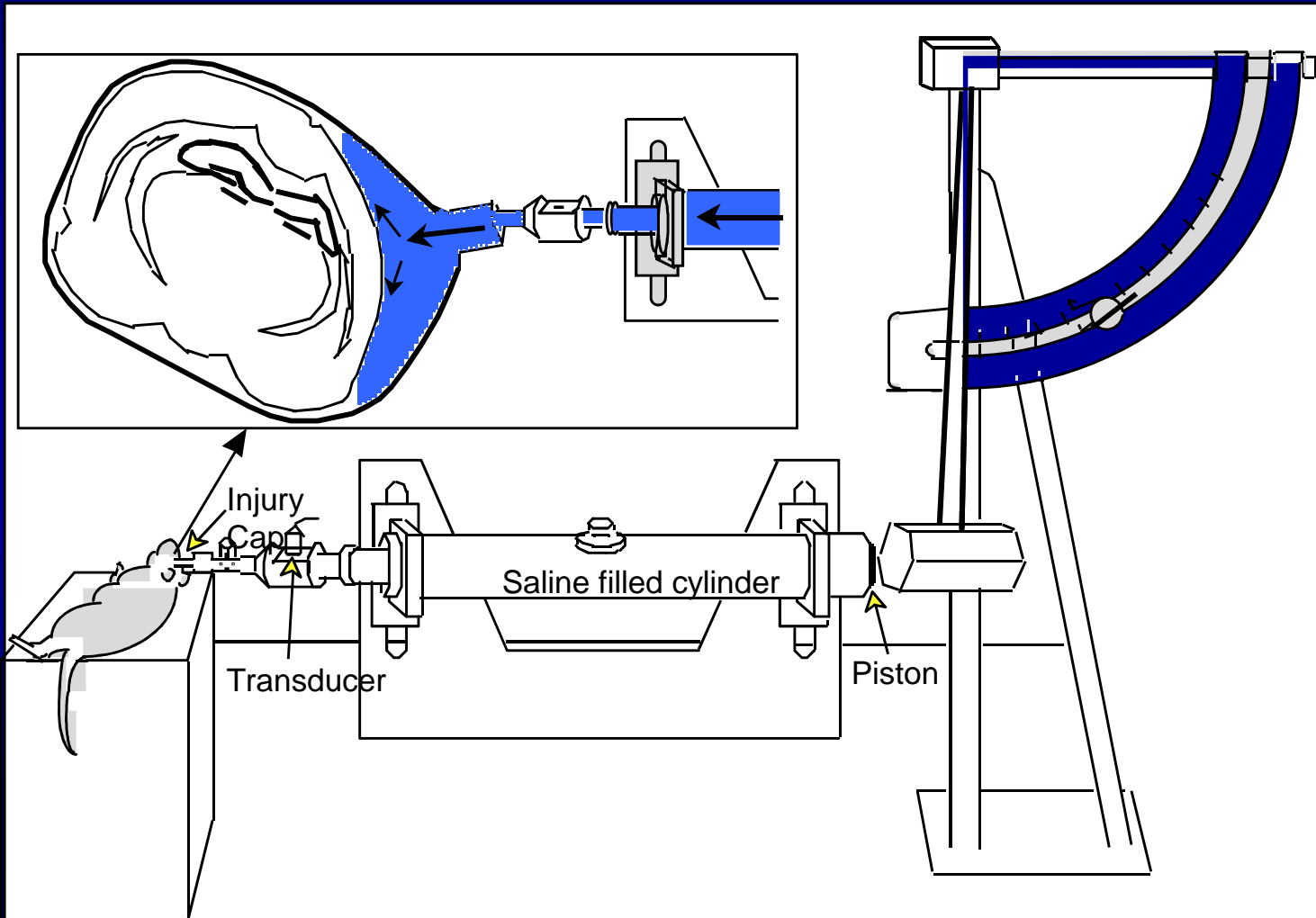
**TBI induces vascular endothelial expression of monocarboxylate transporter 2 (MCT2)**

# Summary

1. Introduction to Pediatric TBI
2. Metabolism and Metabolic Therapy
- 3. Neural Activation and Pro-plasticity Therapy**
  - 1. Impaired glutamatergic neurotransmission and experience-dependent plasticity**
  - 2. Restoration of plasticity using glutamate agonist**
4. Effects of Repeated Injury in Development
5. Conclusions



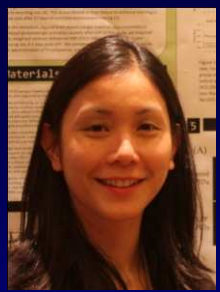
# Traumatic Brain Injury: Fluid Percussion



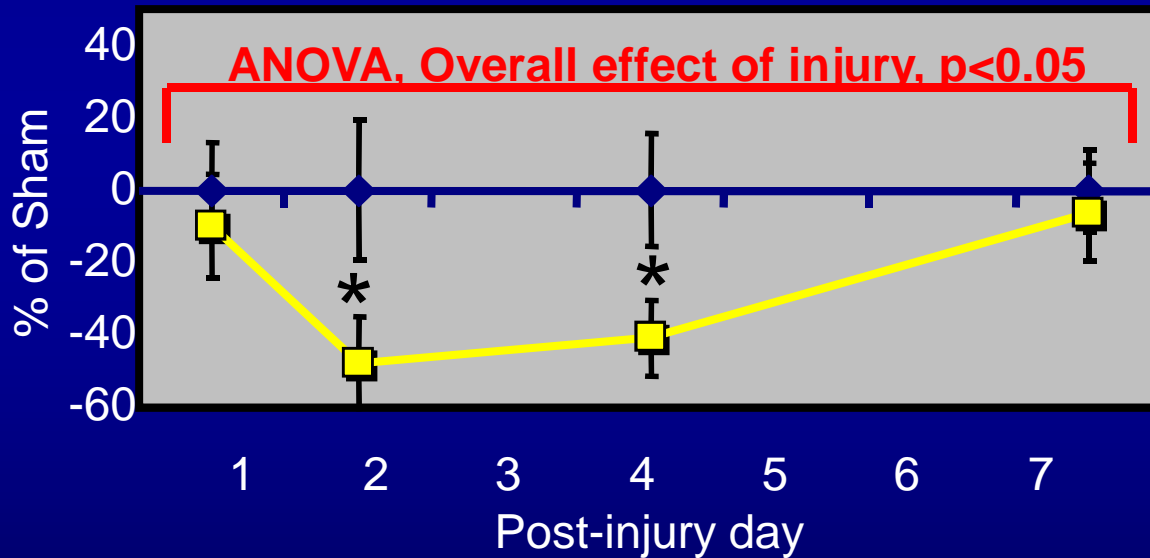
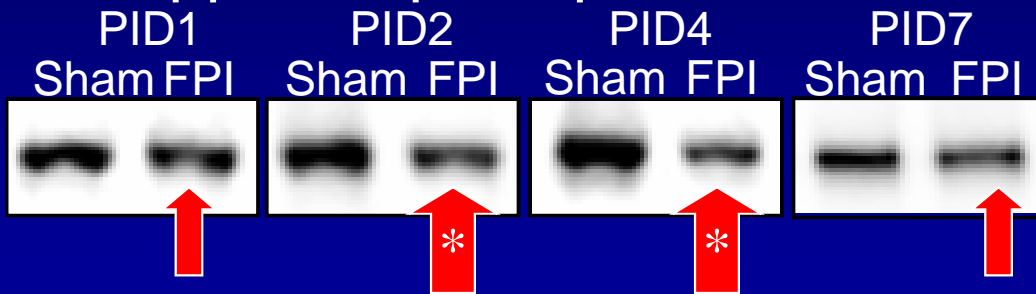
## Fluid percussion injury effects

- Diffuse concussive injury
- Dura intact
- Followed by apnea and unresponsiveness to toe pinch
- Normal open-field behavior as early as 1 day post-injury
- *Little, if any overt cell death in developing animals*

# Developmental TBI: NMDARs

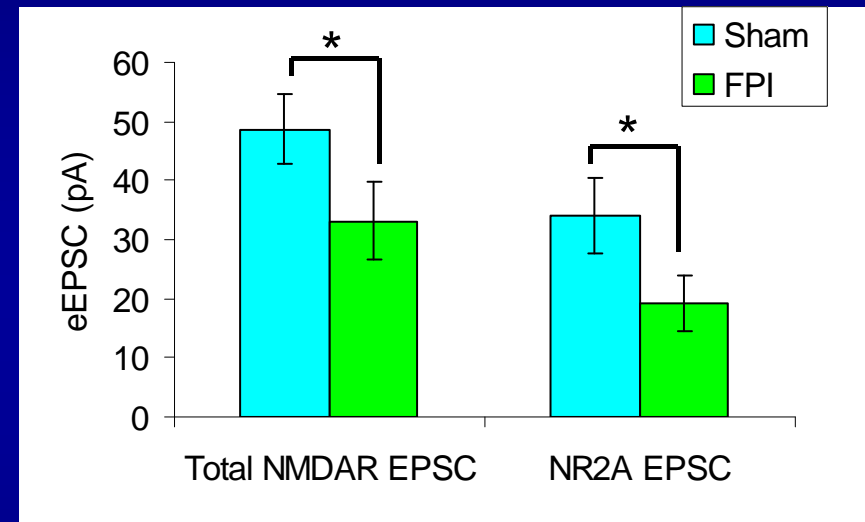


## Hippocampus: Ipsilateral NR2A



Protein levels of the NR2A subunit are selectively *reduced* after developmental TBI. NR1 & NR2B show little change.

## Hippocampus: Ipsilateral CA1

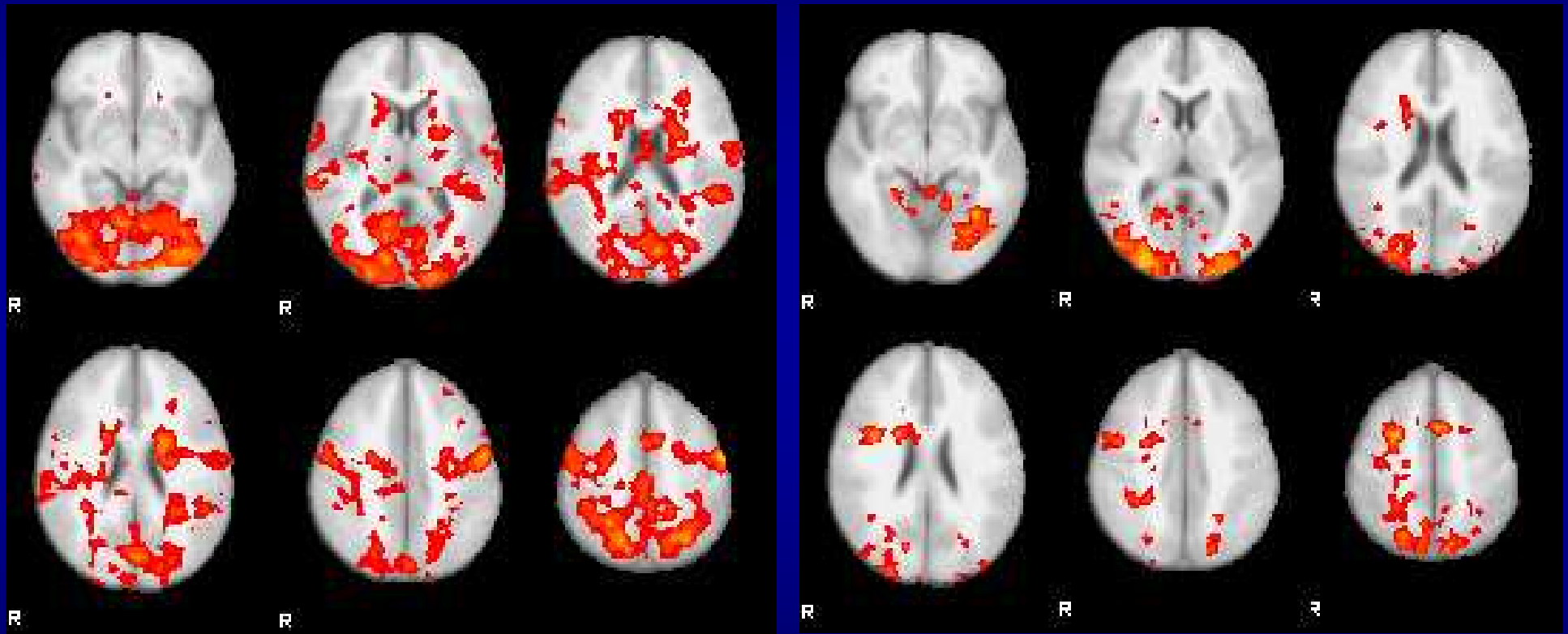


\* p < 0.05

NR2A mediated postsynaptic currents are selectively *reduced* after developmental TBI.

# Post-TBI Impaired Activation: Functional MRI

Condition 1 vs 3

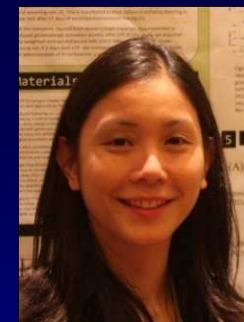


Controls

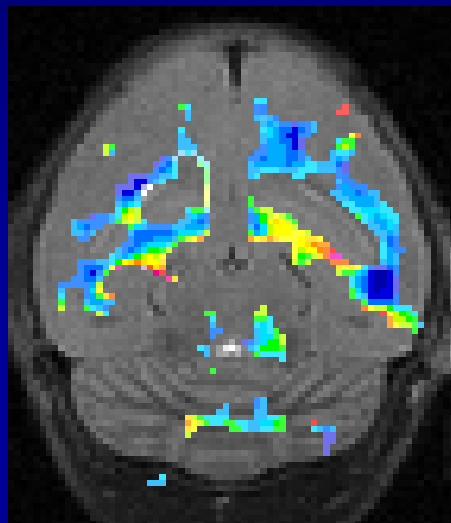
TBI

**During a spatial working memory task, children post-acutely following moderate-severe TBI show much less network activation**

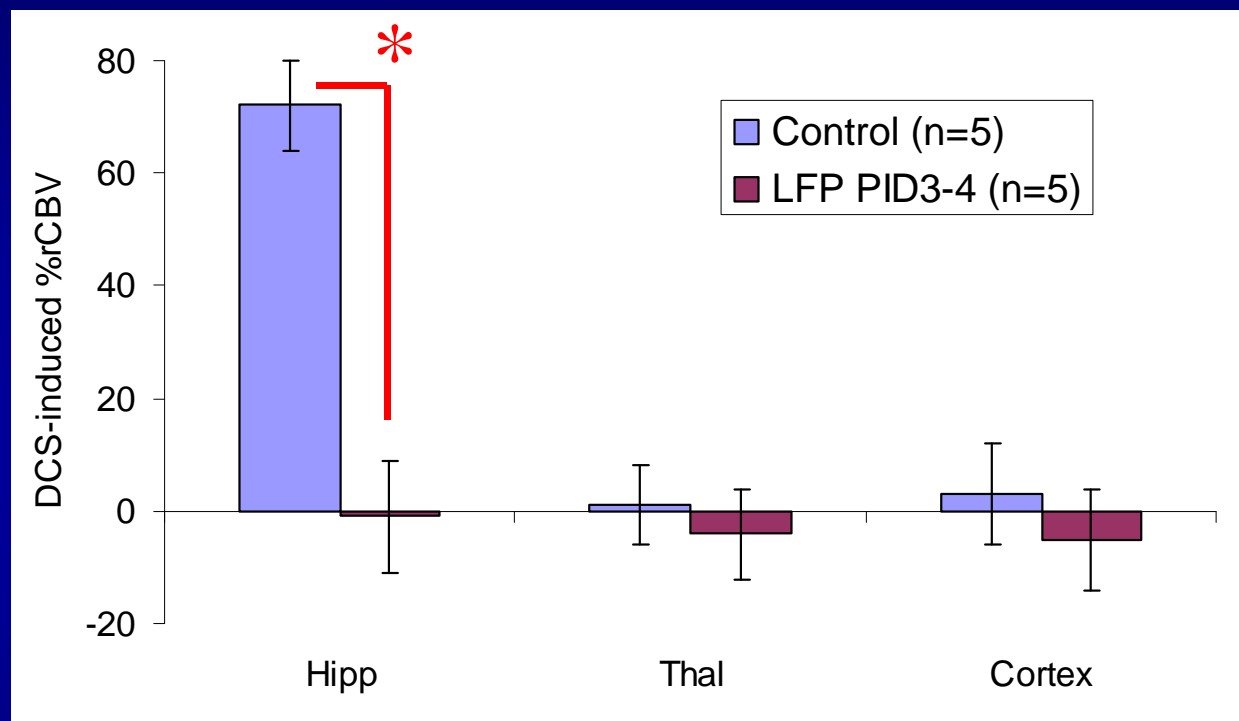
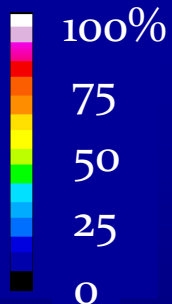
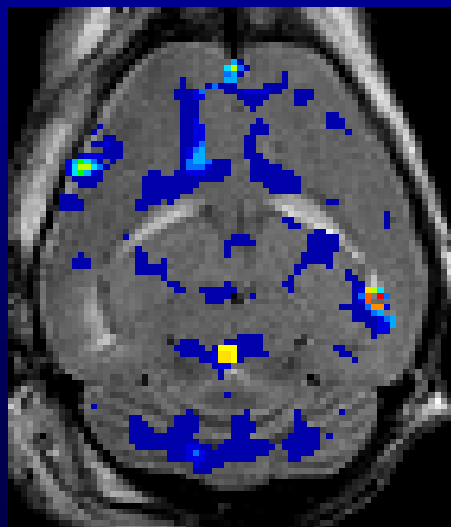
# Imaging Post-TBI NMDAR Activation with phMRI: Rat



Control PID3-4



LFP PID3-4



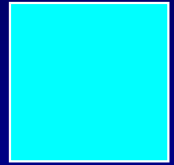
**DCS administration selectively increases hippocampal rCBV. This activation is abolished 3-4 days after developmental TBI.**

# Experimental Design:

SHAM  
SURGERY



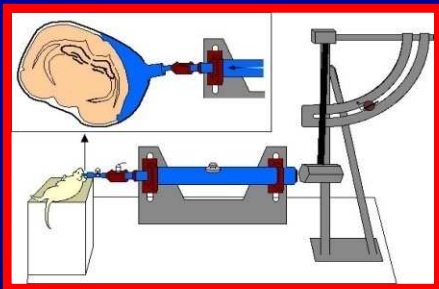
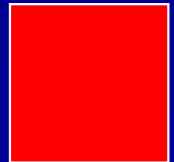
STANDARD  
ENVIRONMENT



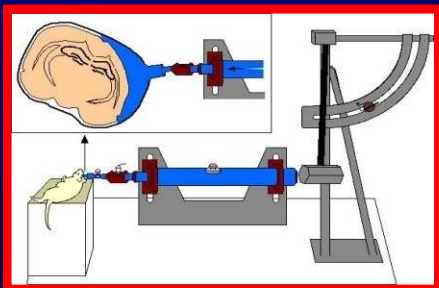
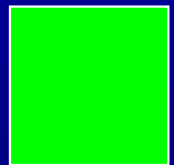
SHAM  
SURGERY



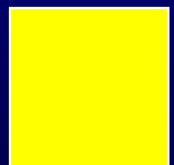
Enriched  
environment  
rearing for 17  
days



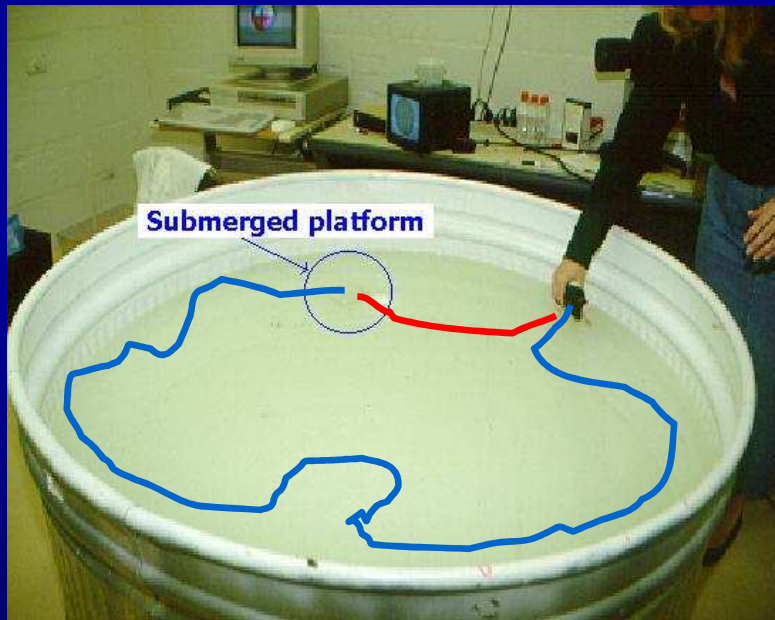
STANDARD  
ENVIRONMENT



Enriched  
environment  
rearing for 17  
days

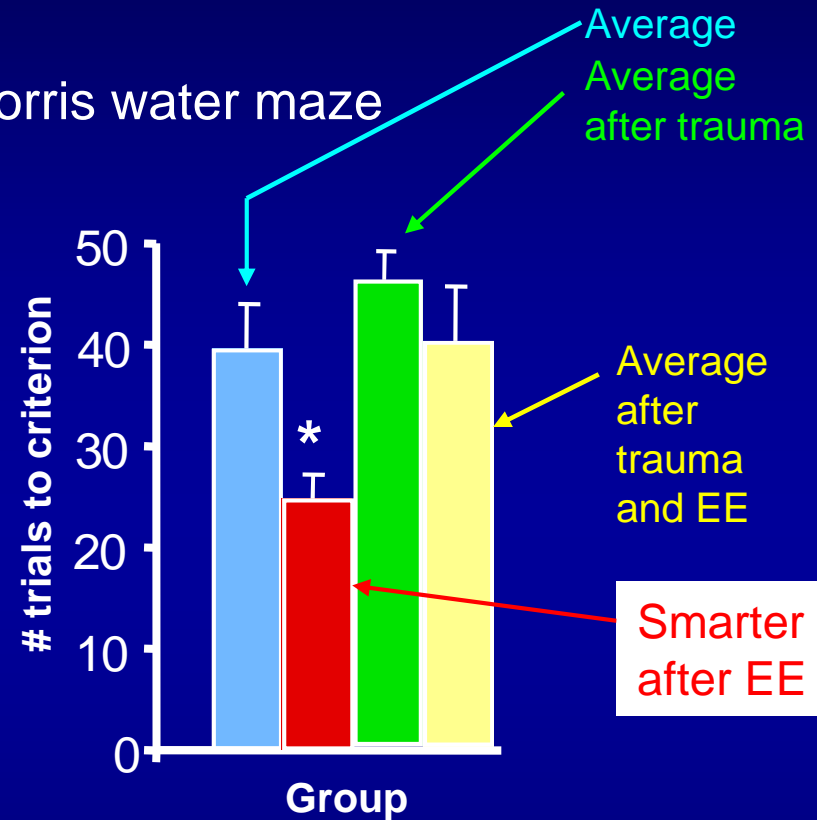


# TBI Early in Life Results in a Loss of Developmental Potential



- Control/STD
- FP/STD
- Sham/EE
- FP/EE

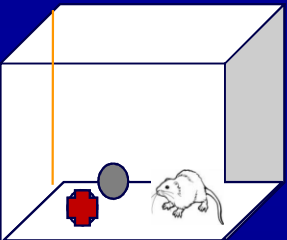
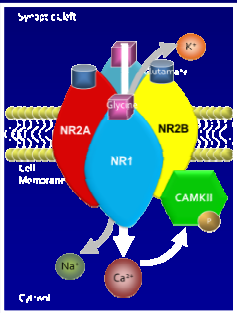
Morris water maze



Morris water maze performance *improves* after enrichment, but **does NOT** improve with enrichment after developmental TBI.



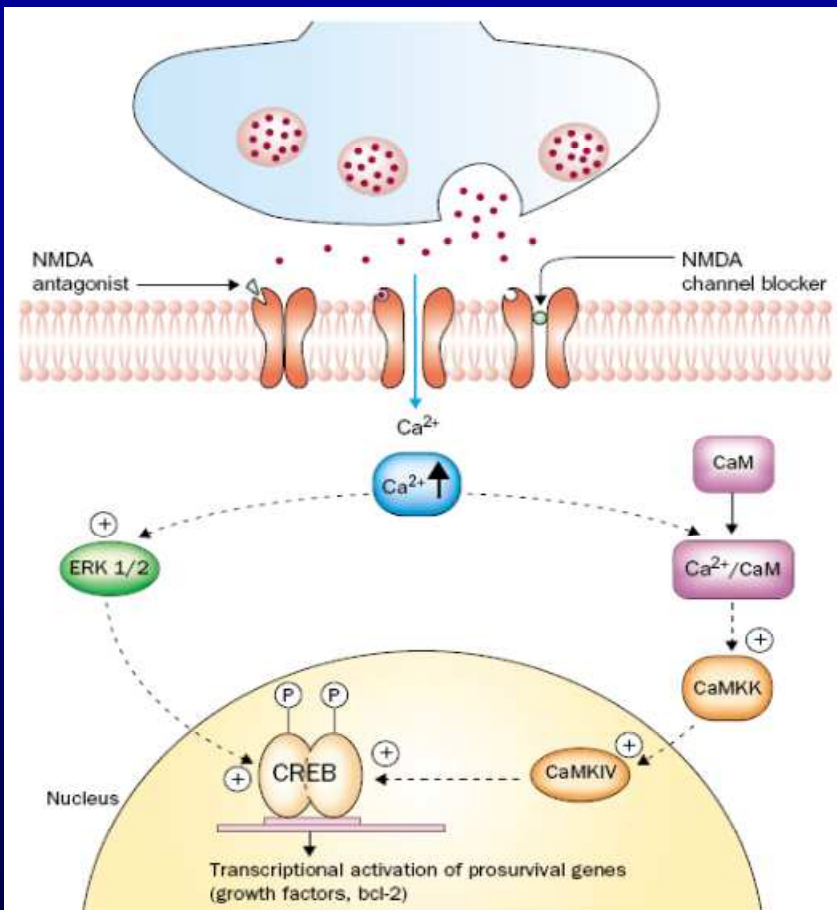
# What we have: FPI and NMDAR Summary



Measure	P19 FPI	
Molecular	NR2A (PID4) Phos/total CAMKII (PID4)	↓
Electro-physiological	Evoked EPSC (PID4)	↓
Behavioral (subacute)	NOR (PID4)	↓
Behavioral (chronic)	MWM Trials to Criterion (PID40)	↓
phMRI (subcute)	$\Delta$ rCBV (evoked) (PID3-5)	↓

# Why did NMDA receptor antagonists fail clinical trials for stroke and traumatic brain injury?

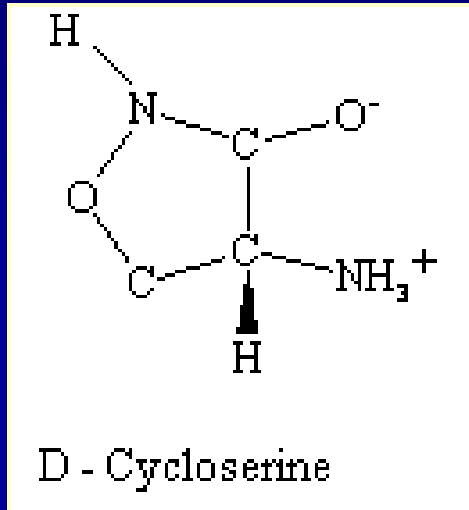
Chrysanthy Ikonomidou and Lechoslaw Turski



The concept of excitotoxicity led to the general idea that **GLUTAMATE WAS BAD** post-injury and should be blocked.

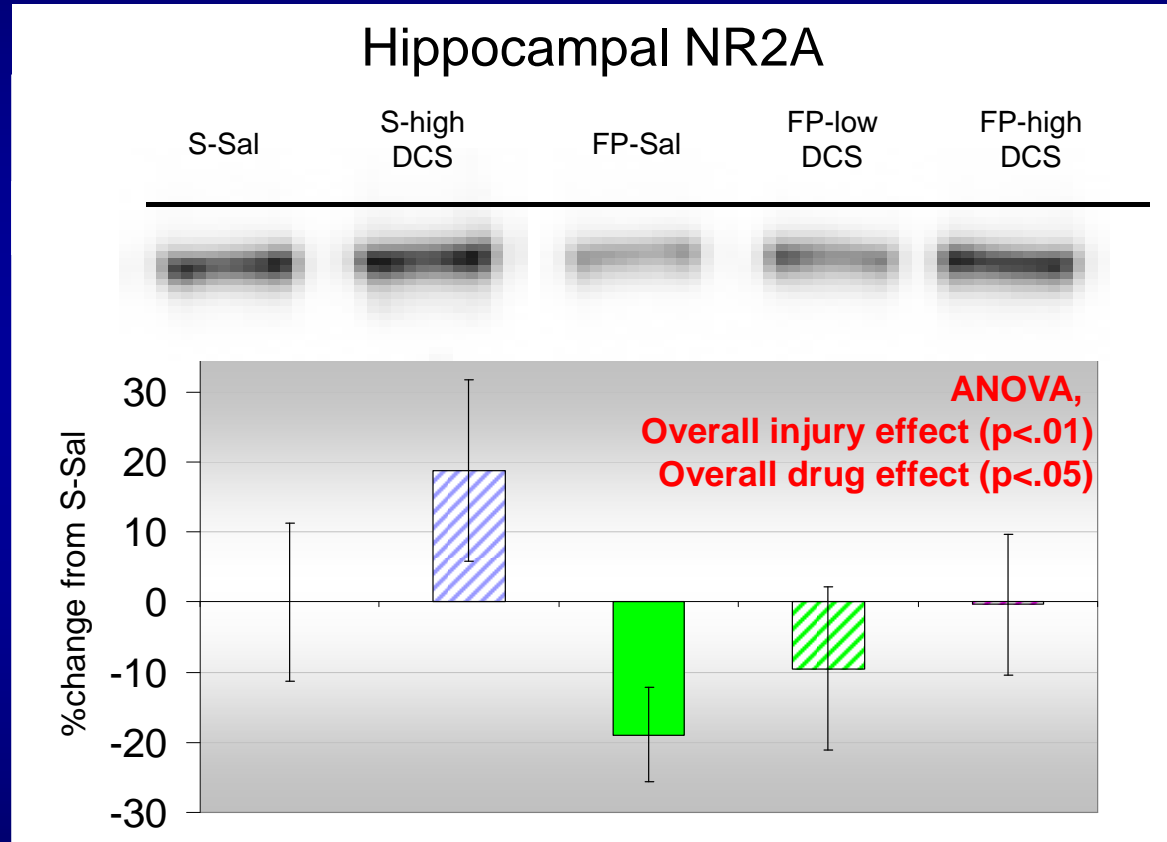
However, it is increasingly apparent that **GLUTAMATE CAN ALSO BE GOOD.**

# D-Cycloserine (DCS) Treatment Reverses TBI Dysfunction



## D-cycloserine

- NMDAR co-agonist
- Binds at glycine site
- FDA approved agent (for TB)
- Good bioavailability
- Penetrates BBB



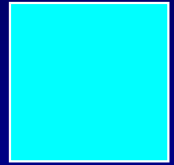
**Treatment with DCS restores normal NR2A levels in rats**

# Experimental Design:

SHAM  
SURGERY



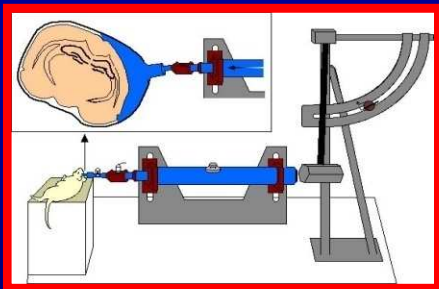
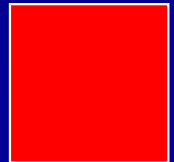
STANDARD  
ENVIRONMENT



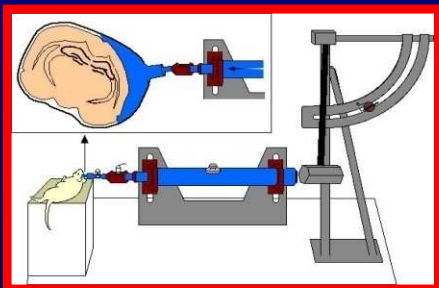
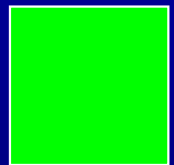
SHAM  
SURGERY



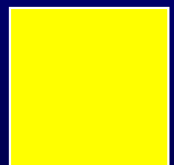
Enriched  
environment  
rearing for 17  
days



STANDARD  
ENVIRONMENT

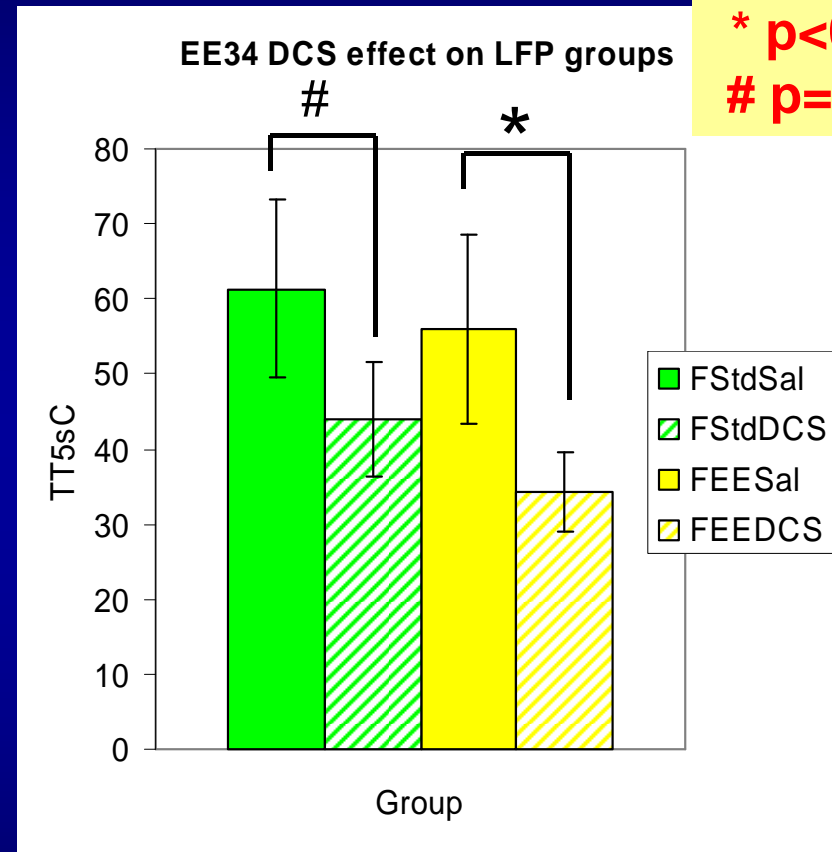
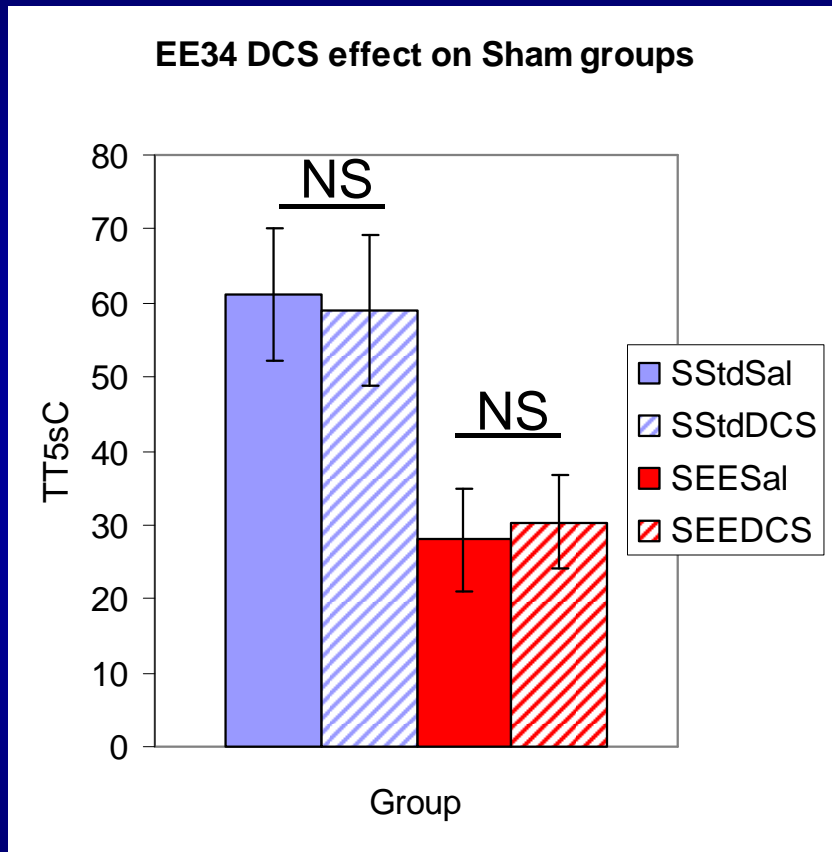


Enriched  
environment  
rearing for 17  
days



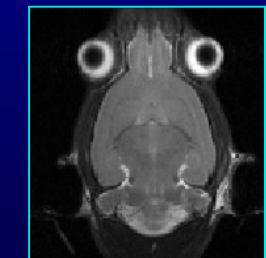
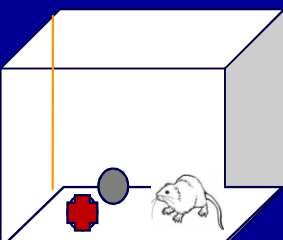
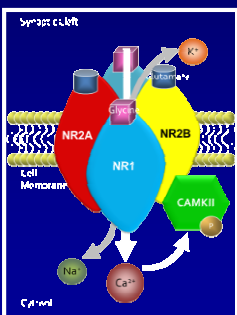
# D-Cycloserine (DCS) Treatment Restores post-TBI Plasticity

One-way ANOVA  
\*  $p < 0.05$   
#  $p = 0.19$



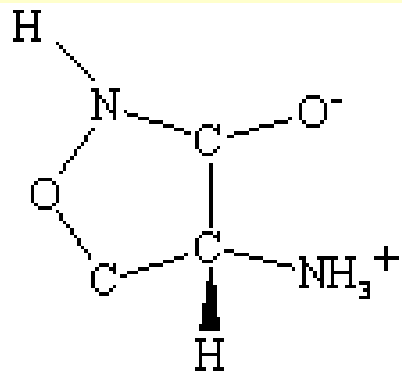
Treatment with DCS has no effect in sham rats, but given after developmental TBI, DCS improves spatial memory in adulthood preferentially in EE reared animals

# What we have: FPI and NMDAR Summary

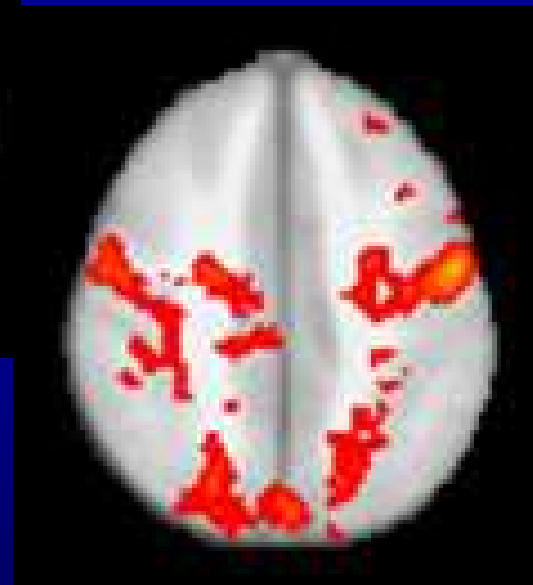
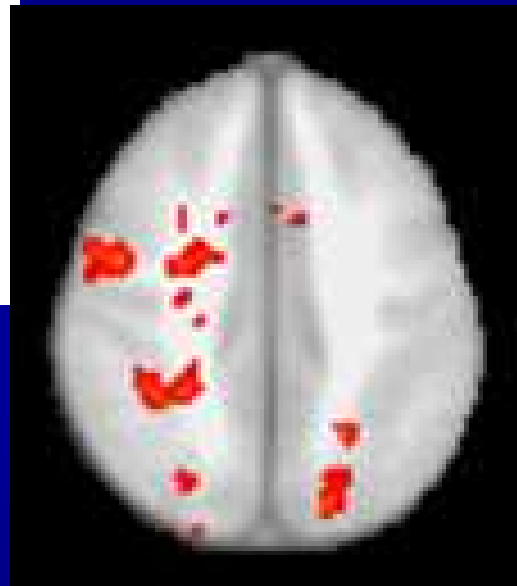


Measure	P19 FPI		DCS	
Molecular	NR2A (PID4) Phos/total CAMKII (PID4)	↓	<b>Restored NR2A (PID4)</b> <b>Restored phos/total CAMKII (PID4)</b>	↑
Electro-physiological	Evoked EPSC (PID4)	↓	-	
Behavioral (subacute)	NOR (PID4)	↓	<b>Restored NOR (PID4)</b>	↑
Behavioral (chronic)	MWM Trials to Criterion (PID40)	↓	<b>Restored MWM Trials to Criterion</b> <b>Restored MWM Probe Trial (PID40-50)</b>	↑
phMRI (subcute)	$\Delta$ rCBV (evoked) (PID3-5)	↓	-	

# Future Clinical Directions



D - Cycloserine



....this?

# Summary

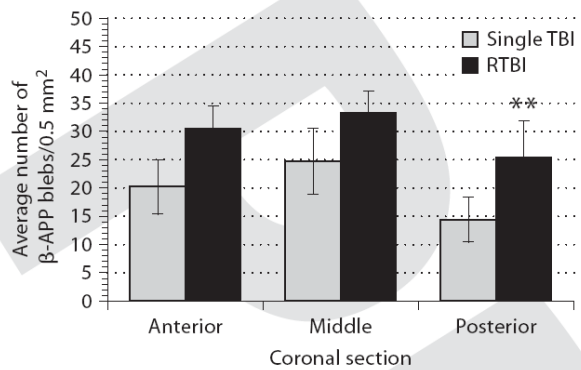
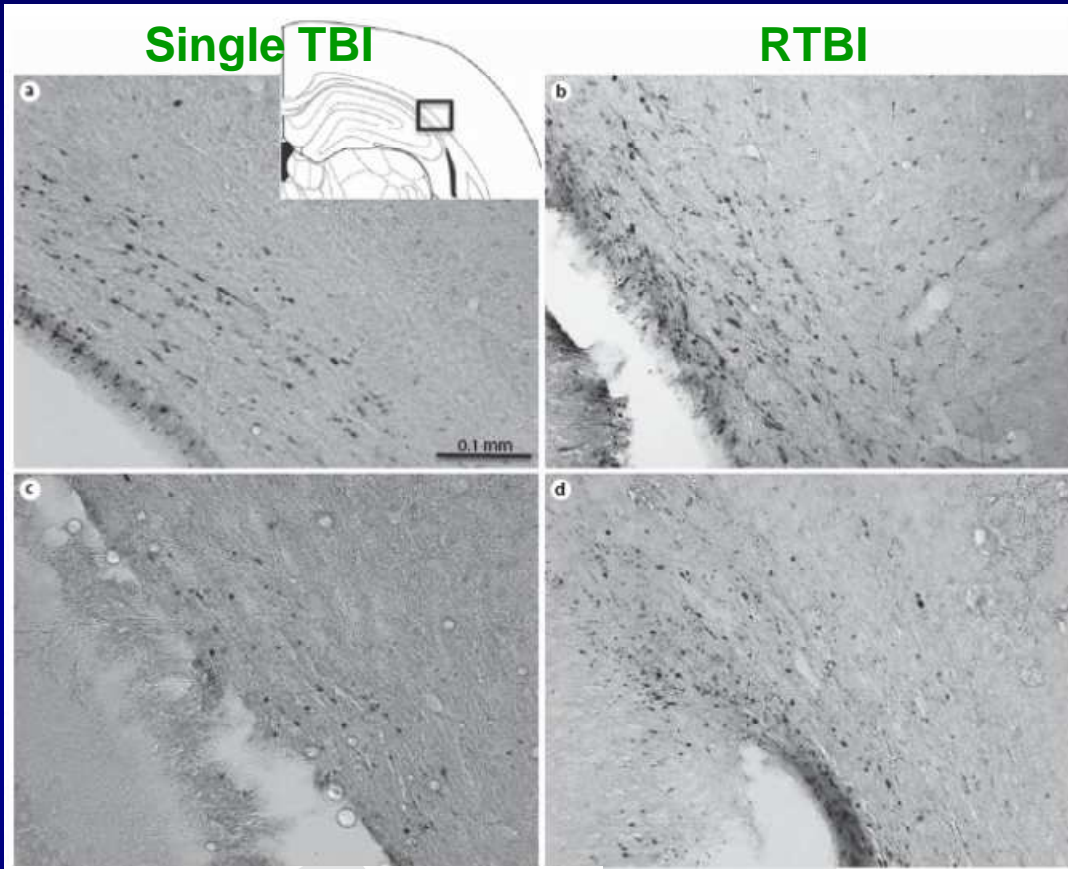
1. Introduction to Pediatric TBI
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5. Conclusions



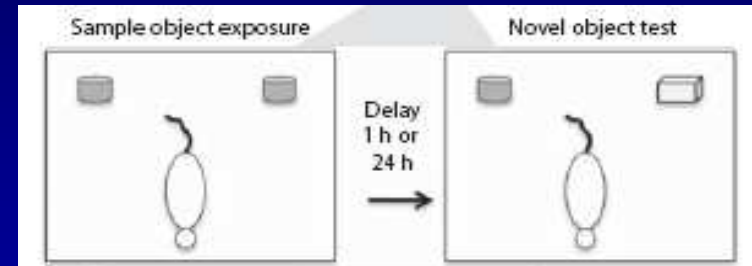


# Concussion in juvenile rat

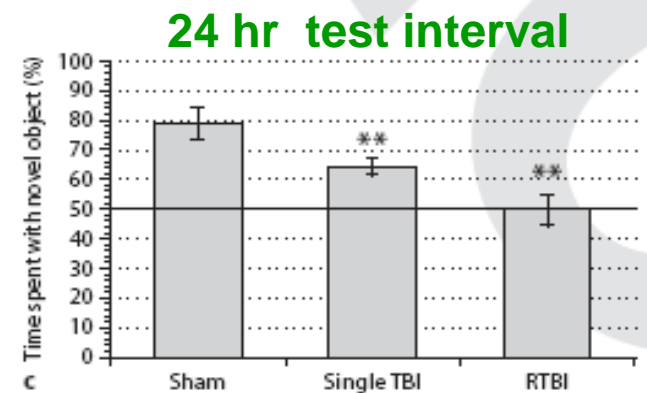
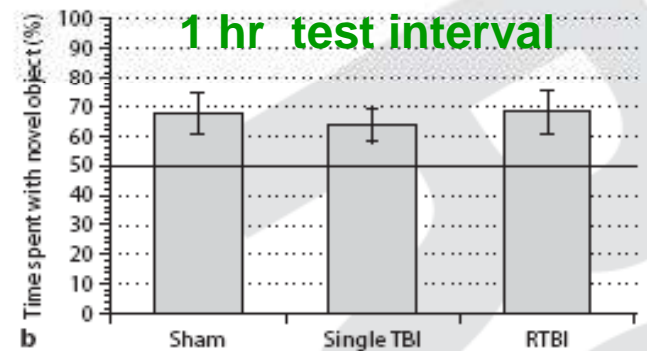
APP staining at Post-injury day 1



**Axonal injury and working memory impairment after repeat TBI can be modeled in rats.**



Post-injury day 2



# Conclusions



1. The developing brain has both resiliencies and vulnerabilities to TBI.
2. The neurometabolic cascade of TBI is distinct in the young brain, and metabolic therapy with alternative substrates may be an age-specific treatment.
3. The young brain is resilient to TBI but shows altered / impaired neural activation and plasticity.
4. Judicious use of glutamate agonists coupled with behavioral interventions can restore experience-dependent plasticity after TBI.
5. Repeated injury in the young brain can result in worse sequelae, depending upon the timing of the injuries.

# PROTECT ALL THE BRAINS!!!

Protected Brains

Unprotected Brain

