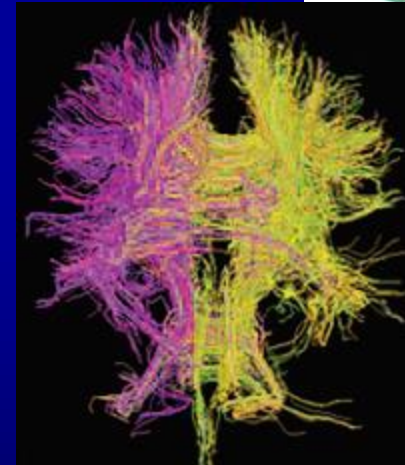
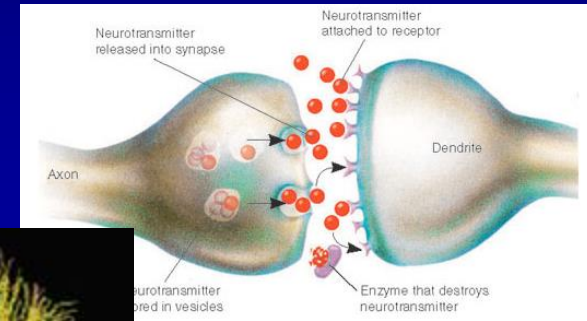


Neurobiology Matters: Mechanism-Based Intervention & Prognostication



November 6th, 2015
Austin, TX

35min

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

National Academy of Neuropsychology
Annual Meeting

Mattel Children's Hospital

UCLA

Credit where credit deserved!

Funded by: NS27544, HD061504, NCAA, Dept of Defense, NFL-GE, UCLA BIRC, UCLA FGP, UCLA Steve Tisch BrainSPORT

*Advisor: Love Your Brain, MLS, NBA, NCAA, USSF
Consultant: Neural Analytics Inc, NFL NCP, NHLPA*

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Mattel Children's Hospital **UCLA**



Outline

I. Post-Concussion Neural Activation

A. Synaptic dysfunction

B. Combination rehabilitative and pharmacotherapy

II. Post-Concussion Axonal Dysfunction

A. Axonal – white matter injury

B. Axonal plasticity?

III. Chronic Neurocognitive Impairment and Neurodegeneration

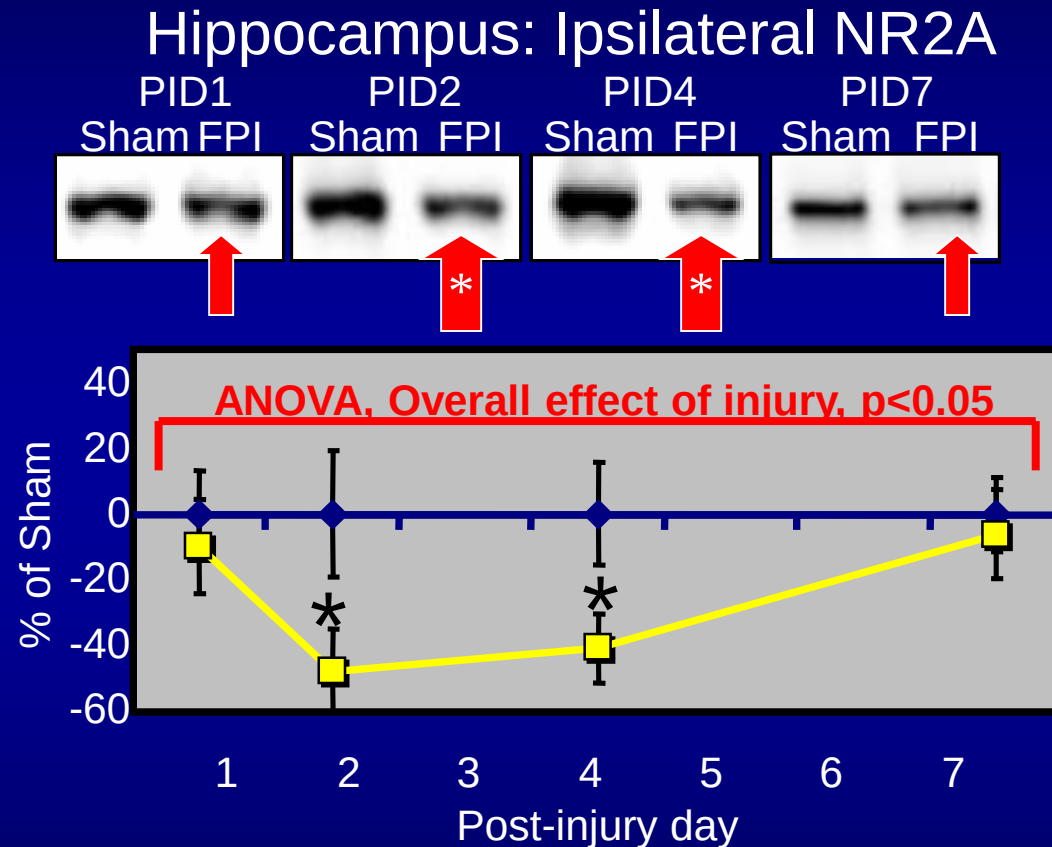


Developmental TBI: Glutamate-NMDAR dysfunction



N-methyl-D-aspartate (NMDA)
Receptor = IQ Gene?????

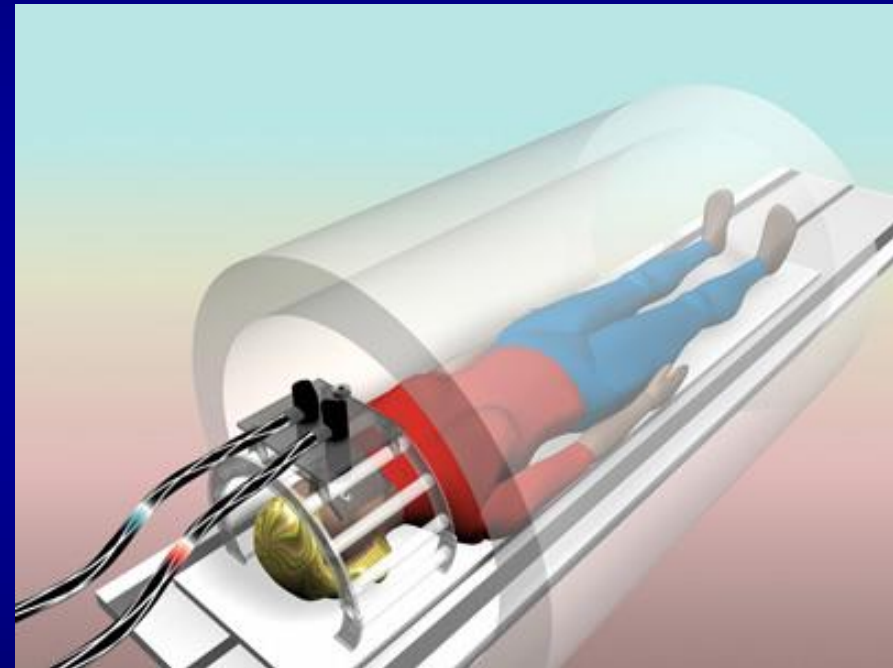
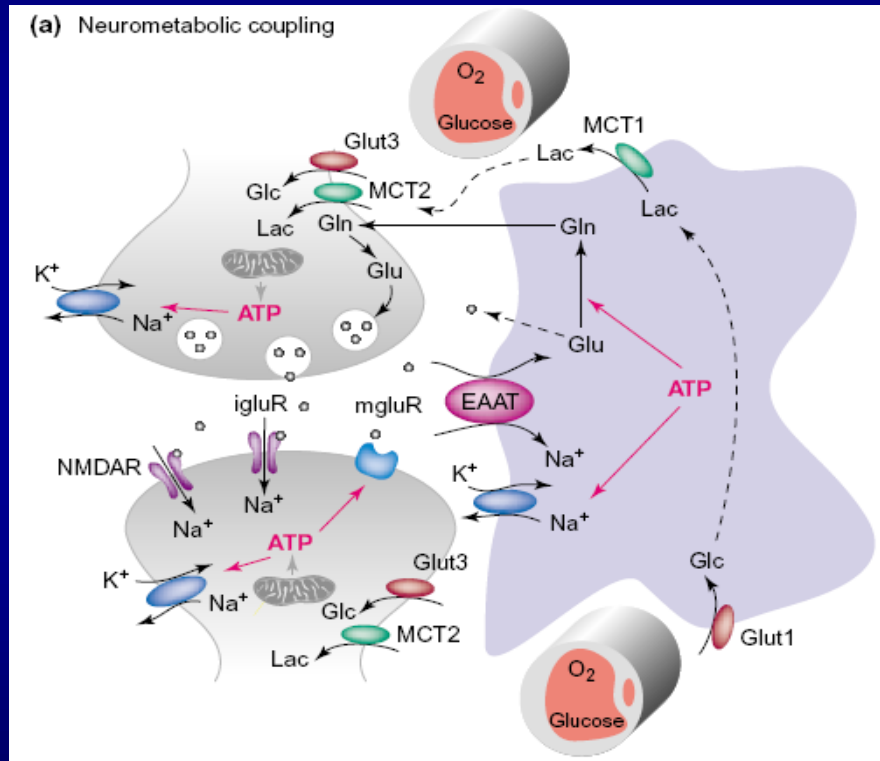
Different types: NR2A, NR2B



NR2A protein (IQ gene) is selectively reduced after developmental TBI.

Synaptic Impairment: Translation

**Does glutamate
image your thoughts?**



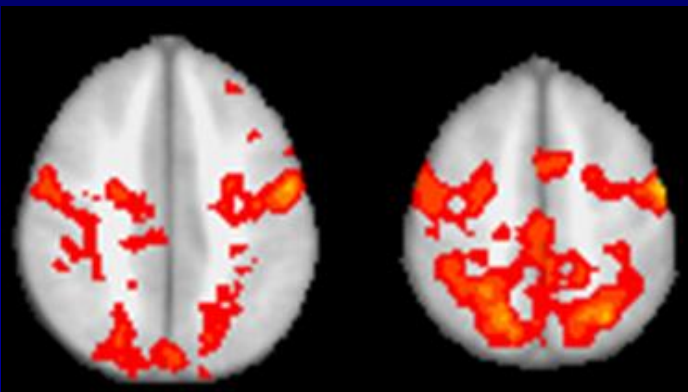
Glutamate neurotransmission drives the (BOLD) signal seen on fMRI



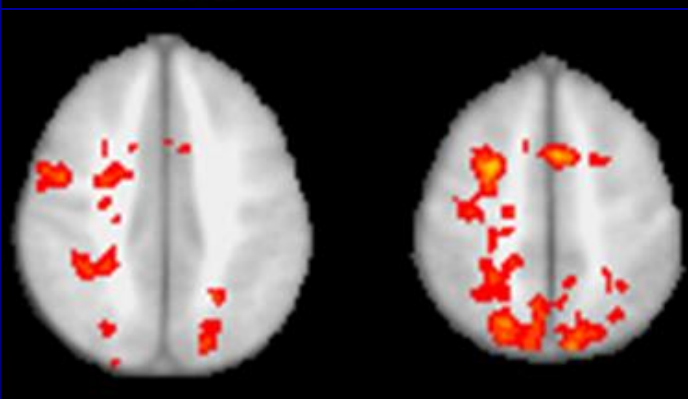
Post-TBI Impaired Activation: Translational Imaging



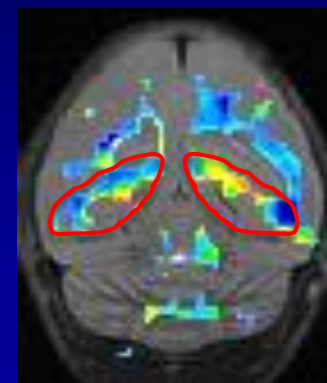
Controls



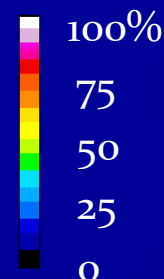
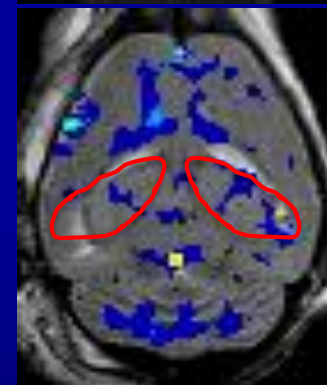
TBI



Control



TBI



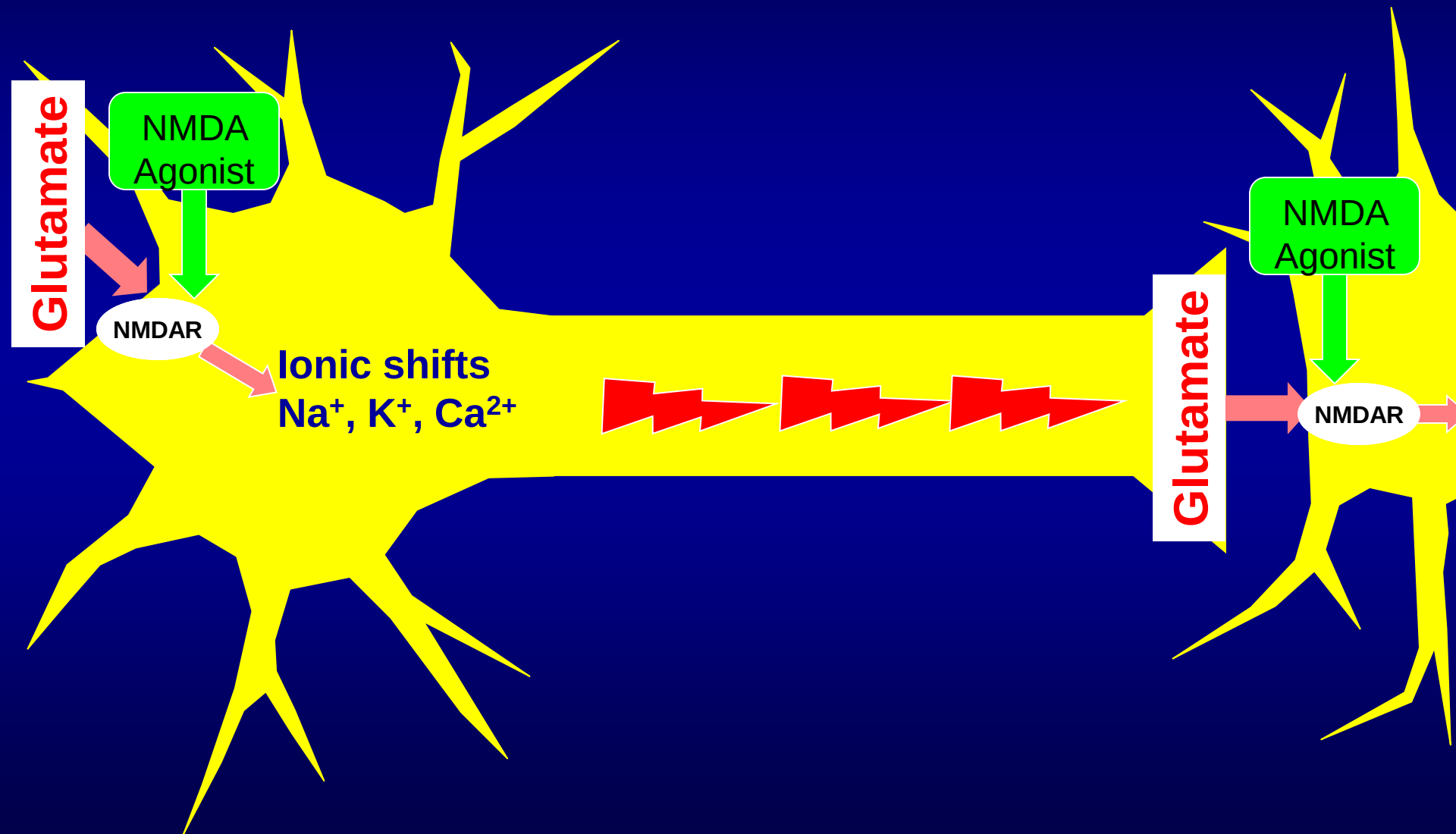
After TBI, children show much less network activation during a memory task

After TBI, immature rats show much less hippocampal activation when given glutamatergic meds.

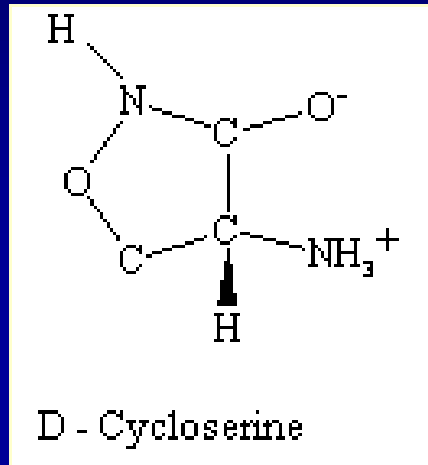
Prins, et al., in Ped TBI, Anderson & Yeates, eds 2010; Cazalis et al., Front Neurol 2011

Santa Maria N.S., et al., in revision 2013

Impaired Neurotransmission: Effect of excitatory therapy

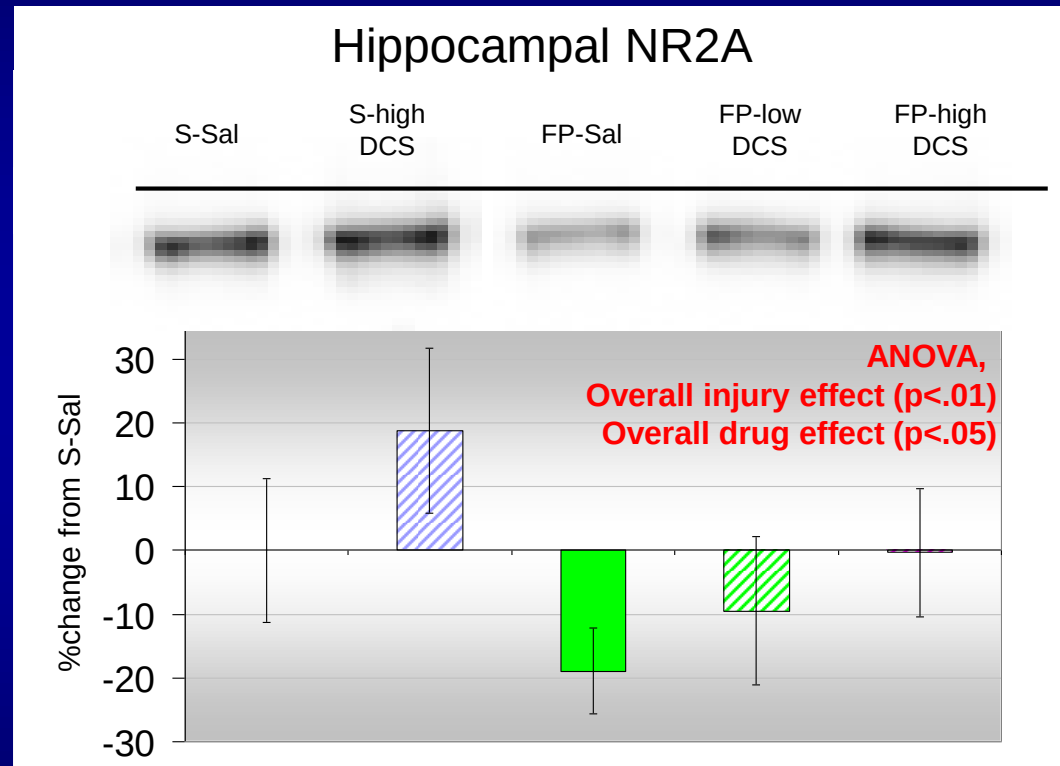


D-Cycloserine (DCS) Treatment Reverses TBI Dysfunction



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

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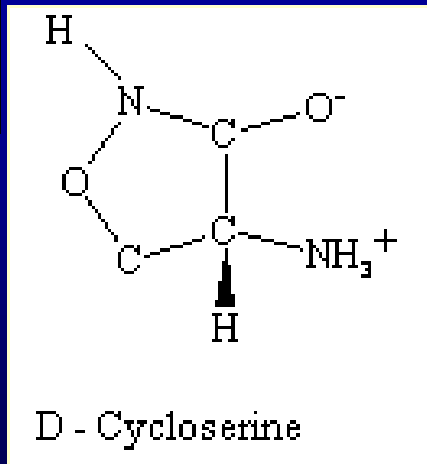
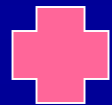
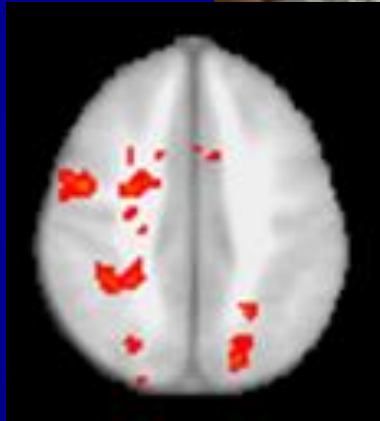
© Mike Baldwin / Corbis

Baldwin

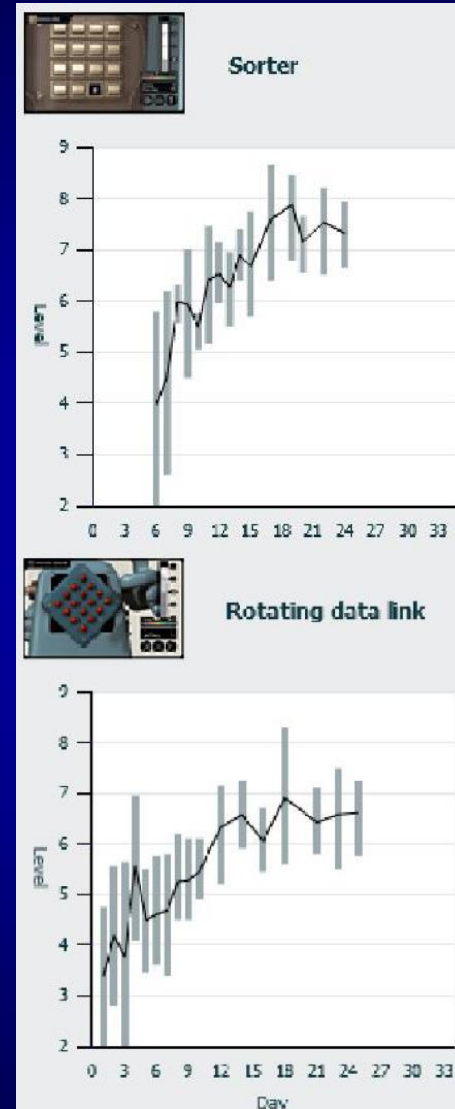
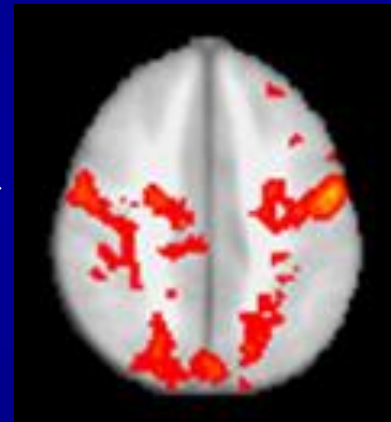


"I go home today. They cured me using this new miracle drug. I'm afraid it'll be years before it's approved for humans."

Translation: Combined Cognitive & Pharmacotherapy



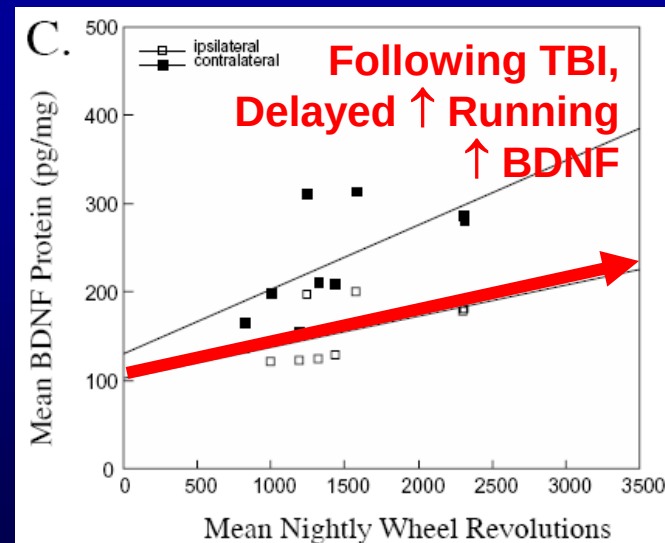
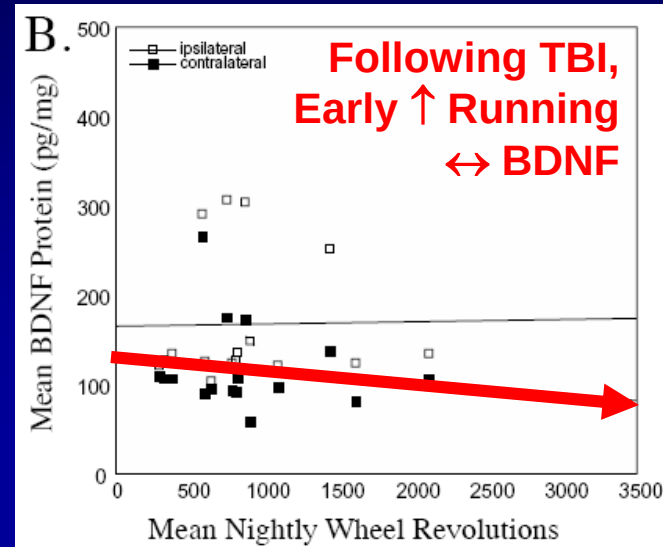
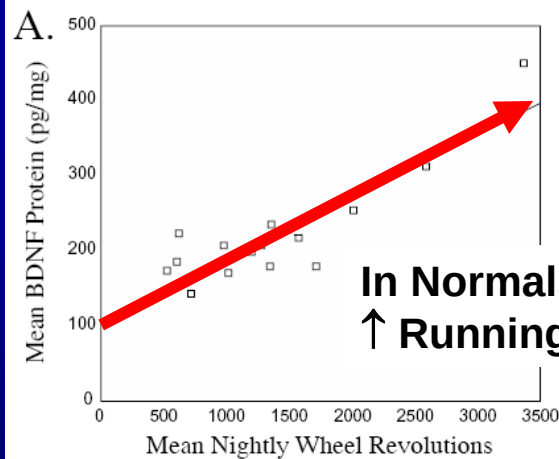
D-cycloserine



Post-mTBI Impaired Activation



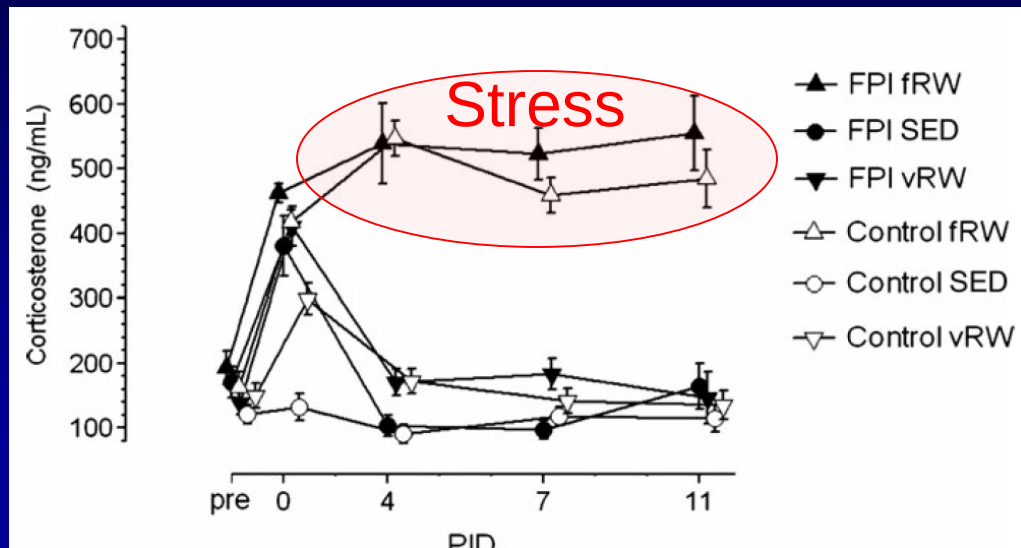
Also...
Worse
cognition



Better
cognition

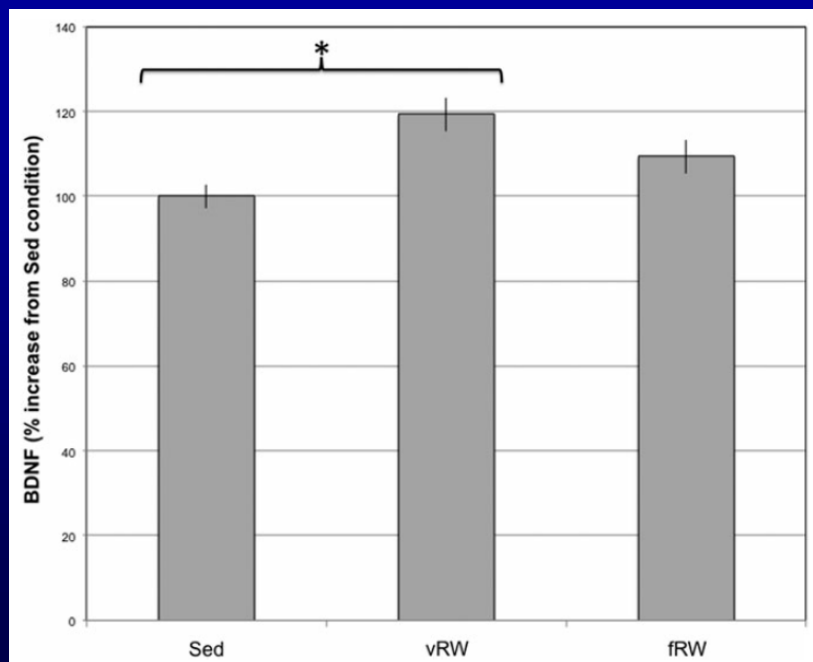
Exercise immediately post-injury worsens outcome;
but delayed exercise helps.

Stress, exercise & mTBI



Forced exercise induces a sustained stress response not seen with voluntary exercise

Griesbach et al., J Neurotrauma, 2012



Forced exercise induces

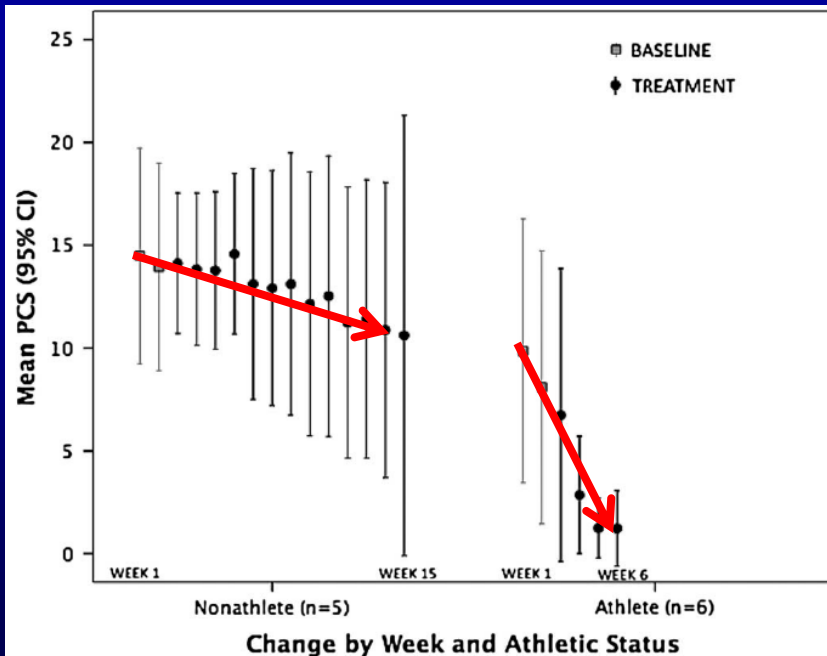
- increase HPA activity,
- higher core temperature and
- reduced HR elevation in response to exercise

Voluntary subacute exercise does not induce stress response & increased BDNF

Griesbach et al., J Neurotrauma, 2014

Exercise as Treatment?

- Active exercise improves symptoms
- Athletes may improve more rapidly
- Exercise tolerance improves with training



Leddy JJ, et al., Clin J Sport Med 2010

Scand J Med Sci Sports 2015; **; **; **
doi: 10.1111/sms.12441

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SCANDINAVIAN JOURNAL OF
MEDICINE & SCIENCE
IN SPORTS

A pilot study of active rehabilitation for adolescents who are slow to recover from sport-related concussion

I. Gagnon^{1,2,3}, L. Grilli², D. Friedman^{2,3,4}, G. L. Iverson^{5,6,7,8}

Gagnon I, et al., Scand J Med Sci Sport 2015

Active rehab for concussion?

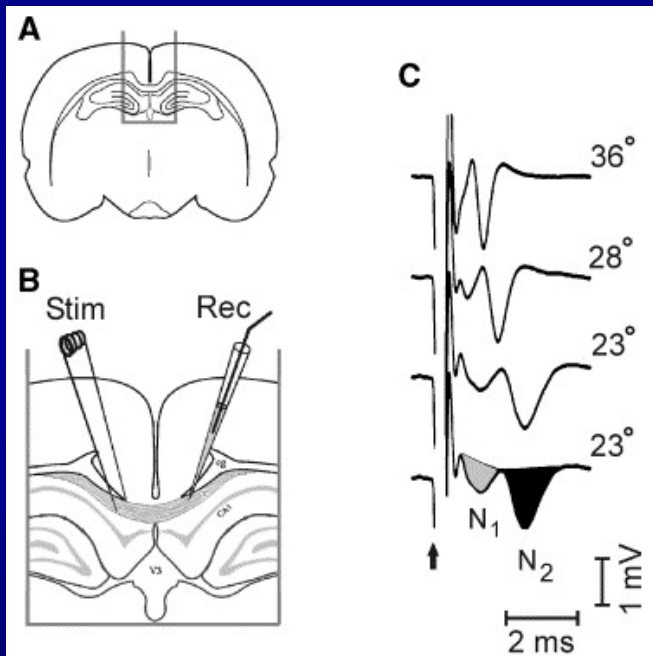


Outline

- I. Post-Concussion Neural Activation
 - A. Synaptic dysfunction
 - B. Combination rehabilitative and pharmacotherapy
- II. Post-Concussion Axonal Dysfunction**
 - A. Axonal – white matter injury**
 - B. Axonal plasticity?**
- III. Chronic Neurocognitive Impairment and Neurodegeneration

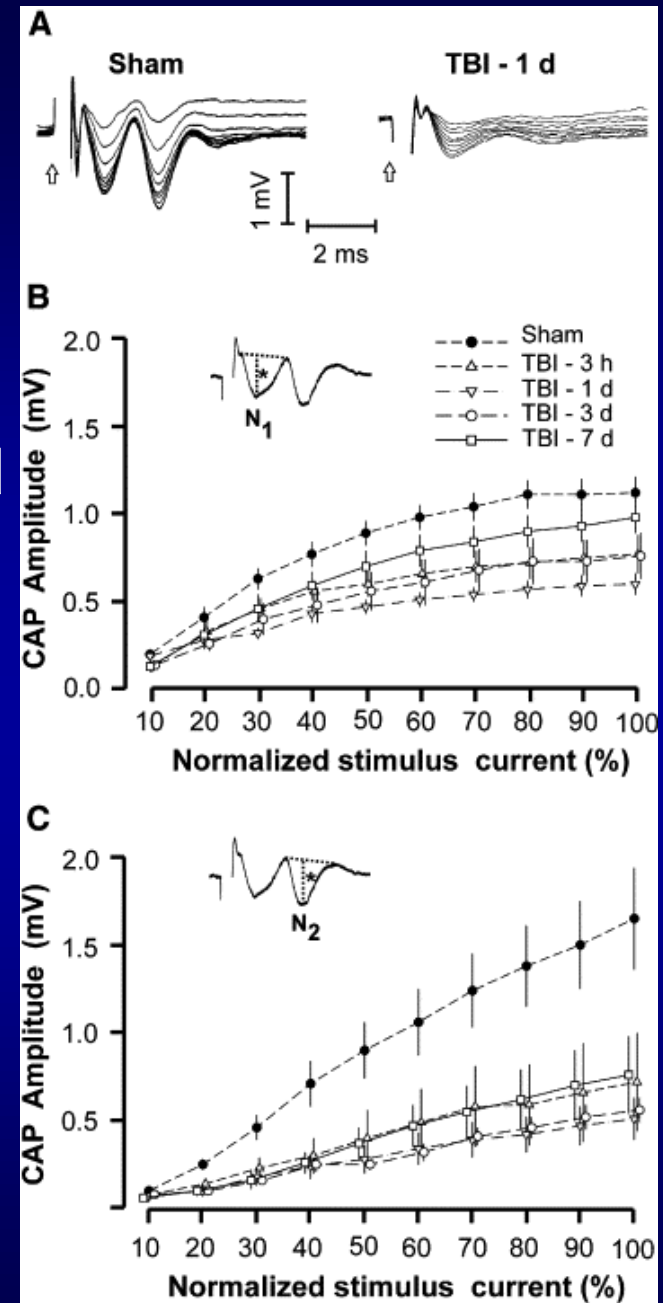


Unmyelinated axons are more vulnerable than myelinated

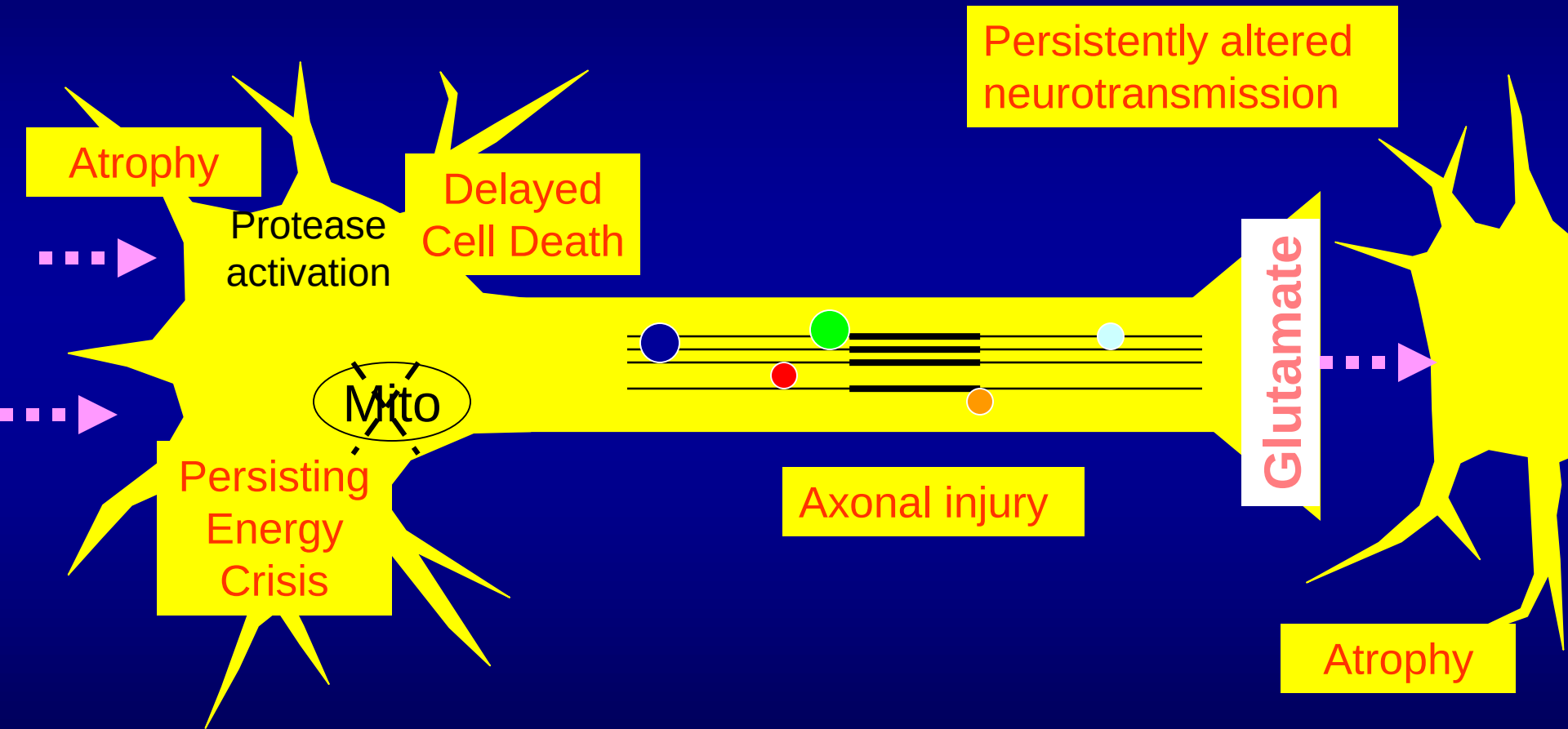


N1 = myelinated
shows recovery

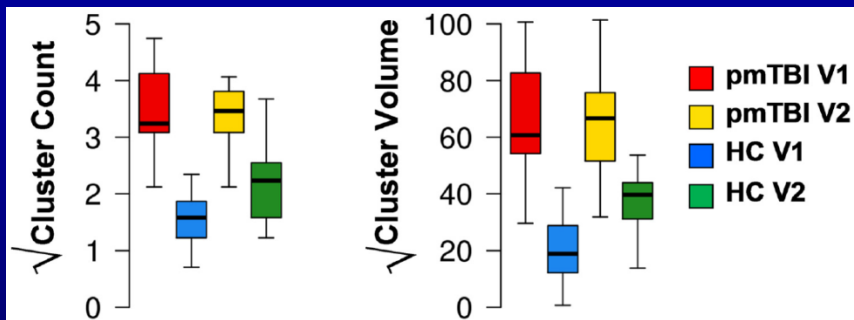
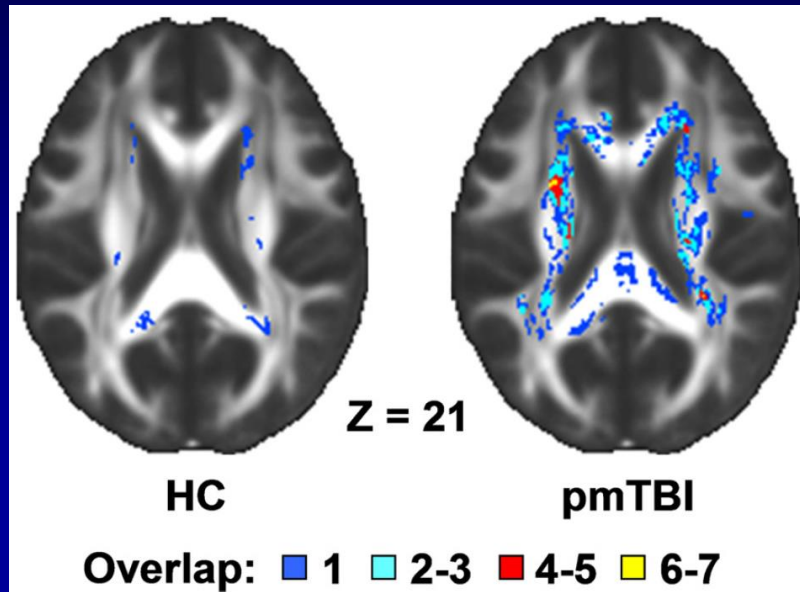
N2 = unmyelinated
does not show
recovery



Neurometabolic Cascade of mTBI: Chronic Pathophysiology

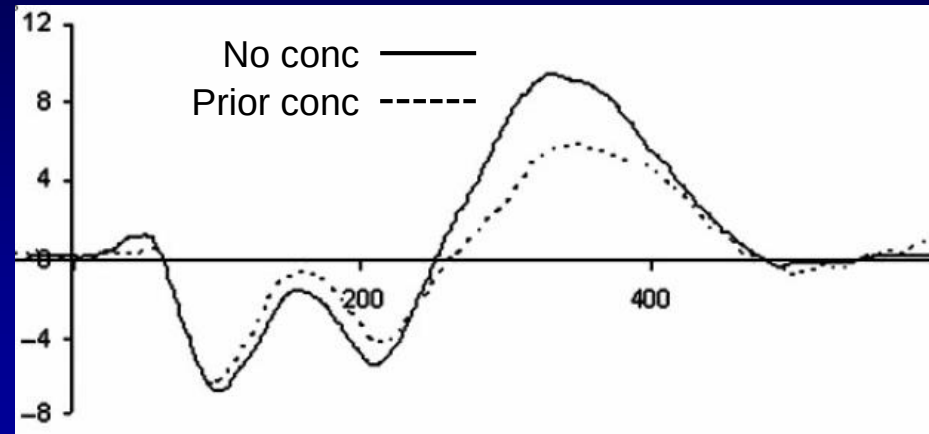


Chronic Pathophysiology?



White matter abnormalities seen after pediatric mTBI subacutely (2 wks) and chronically (4 mos).

Mayer AR et al., J Neurosci 2012

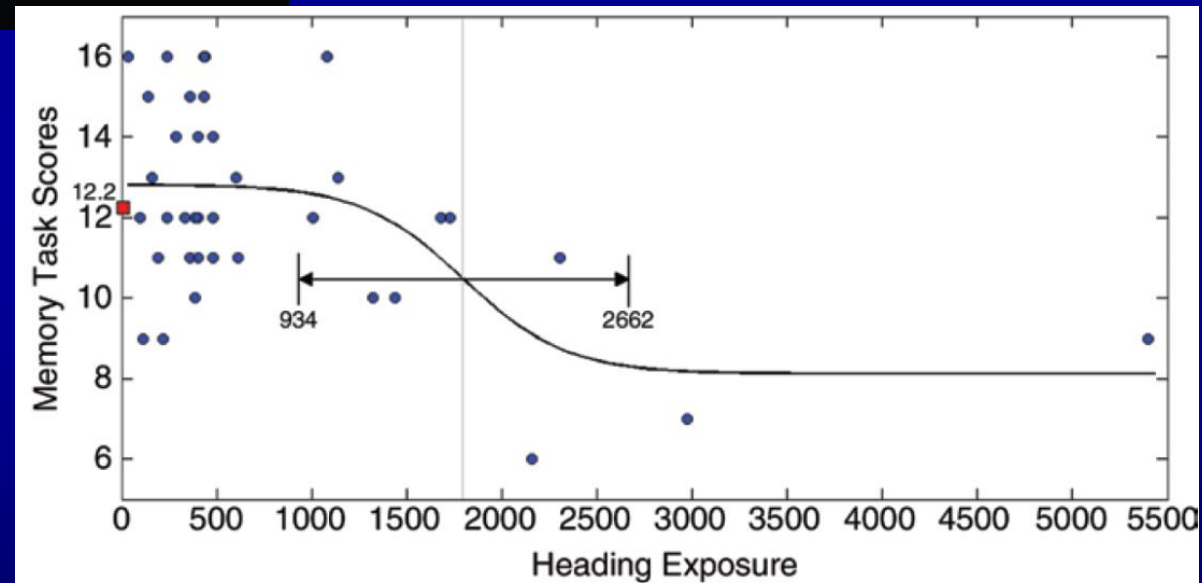
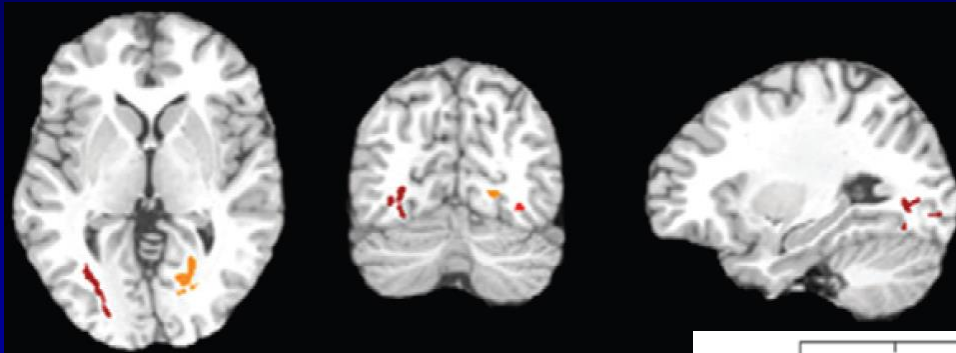


Measures	Controls Mean (SD)	Concussed Mean (SD)	F	P
P3a				
Amplitude	4.50 (2.32)	2.94 (1.67)	5.67	<0.05
Latency	359.6 (35.5)	387.2 (44.9)	4.43	<0.05
P3b				
Amplitude	5.25 (2.11)	4.18 (1.99)	2.57	>0.05
Latency	362.9 (28.9)	397.6 (57.0)	5.58	<0.05

Decreased electrophysiological potentials, NP scores and movement speed in subjects with remote concussion (>25+ yrs) vs controls.

DeBeaumont L et al., Brain 2009

Axonal Damage in Subconcussion: DTI



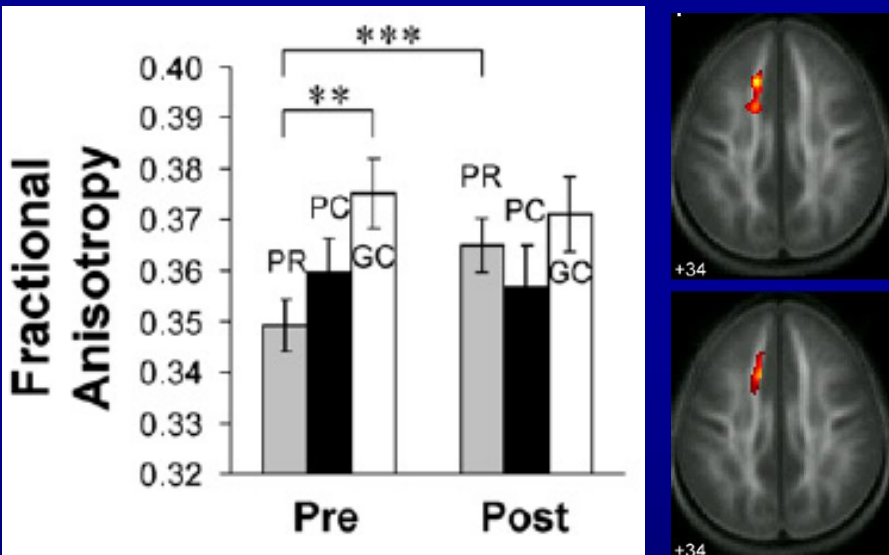
Heading exposure was related to decreases in white matter integrity (FA) in 3 regions, and in memory test scores.

Treatment:

Training & White Matter Plasticity

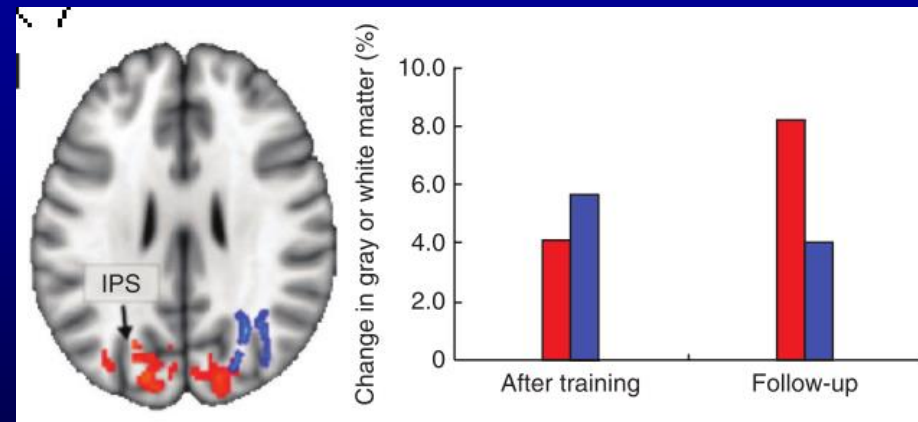
Altering Cortical Connectivity: Remediation-Induced Changes in the White Matter of Poor Readers

Timothy A. Keller^{1,*} and Marcel Adam Just¹



In WM regions associated with reading ability, training increased FA (and reading performance).

Bimanual motor training (juggling) increased gray matter density (red) and white matter FA (blue)





Afghanistan, January 2011



Effects of Blast

The NEW ENGLAND JOURNAL of MEDICINE

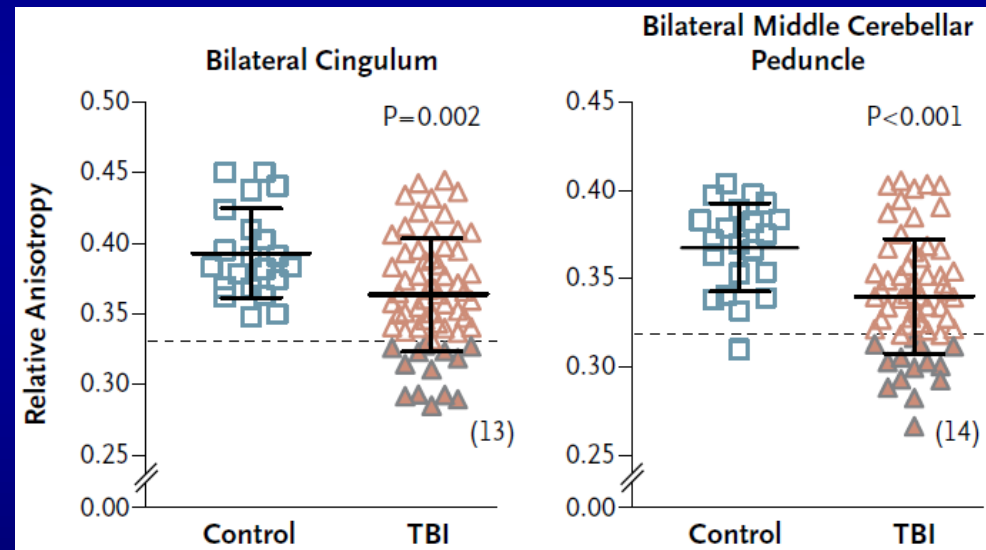
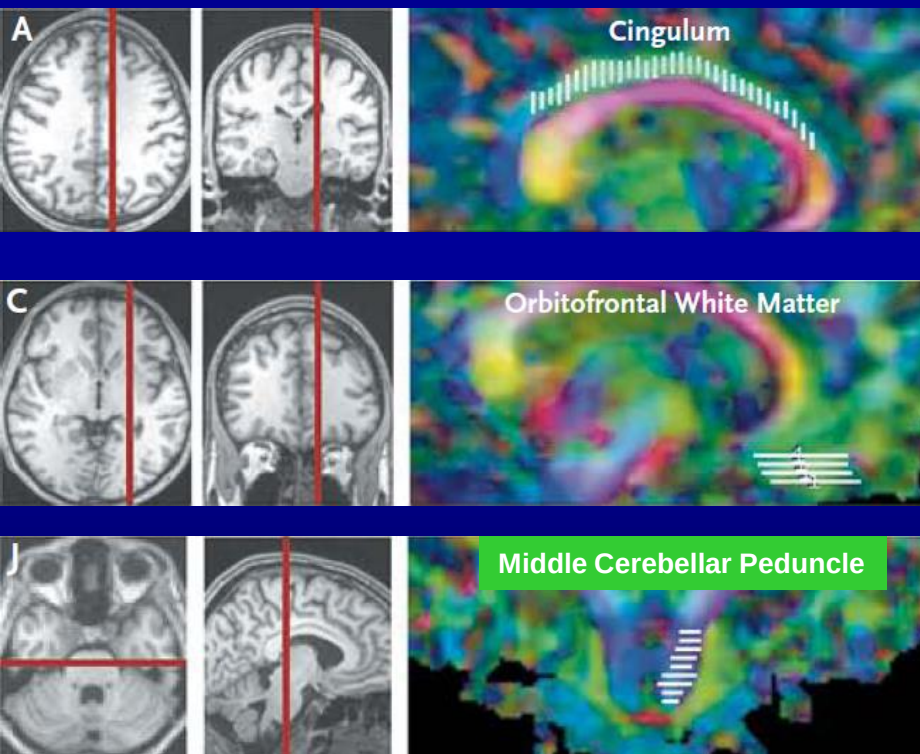
ESTABLISHED IN 1812

JUNE 2, 2011

VOL. 364 NO. 22

Mac Donald CL,
et al. NEJM 2011

Detection of Blast-Related Traumatic Brain Injury in U.S. Military Personnel



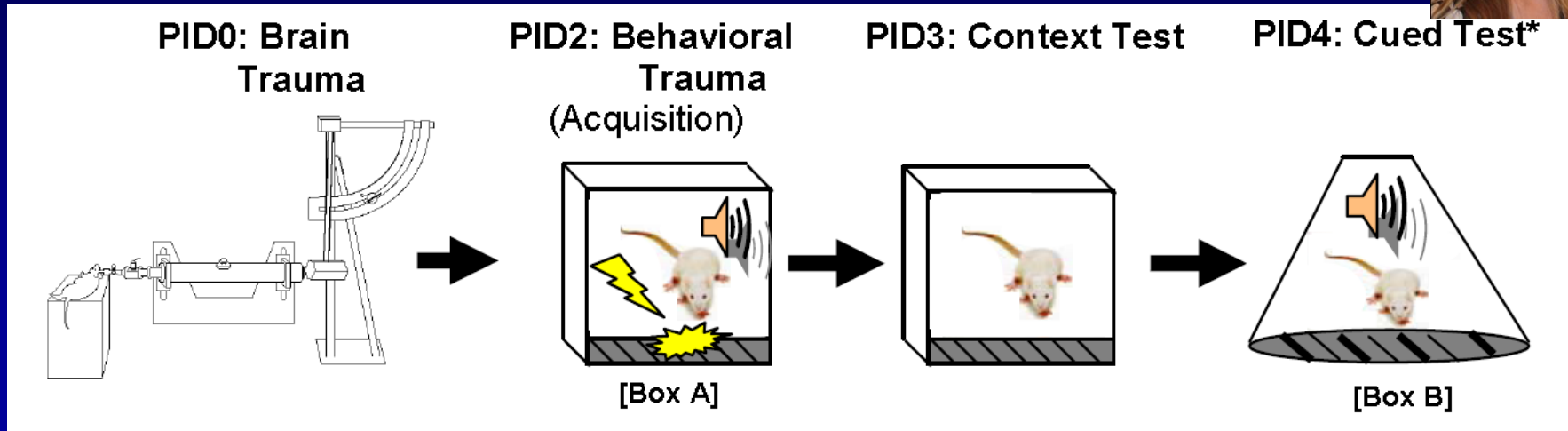
White matter injury is detectable in distinct brain regions following blast TBI.

Outline

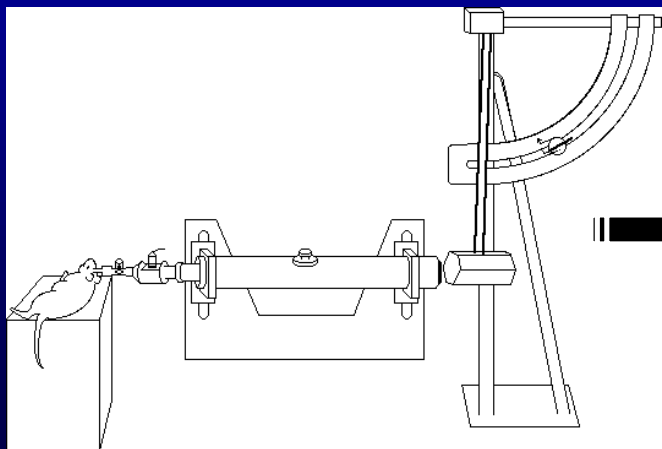
- I. Post-Concussion Neural Activation
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mTBI followed by Fear Conditioning



Day0: Concussive Injury (LFPI)
(unconscious 3-7min)

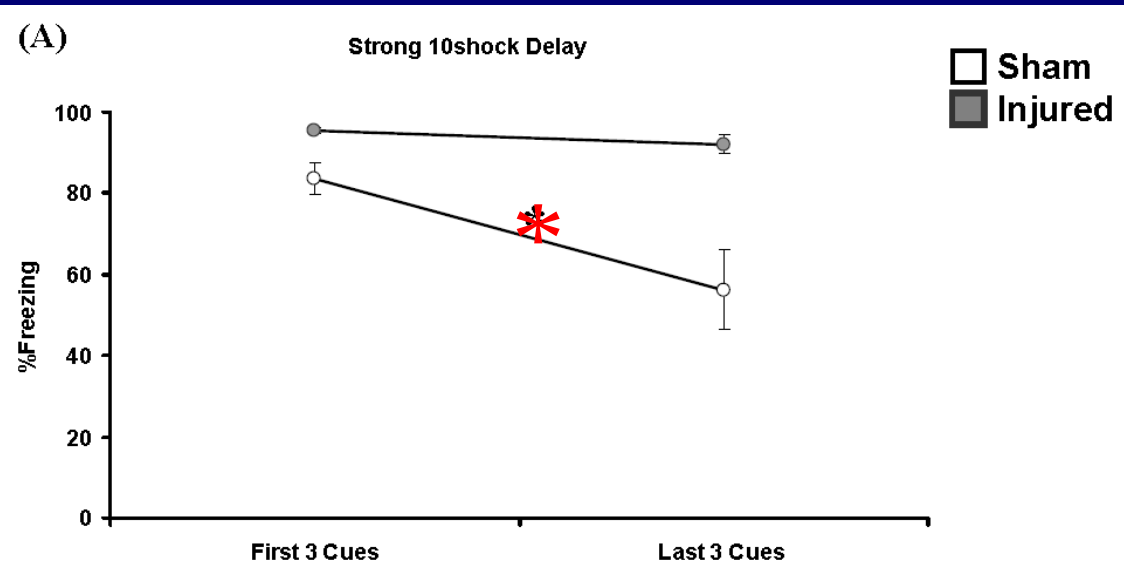
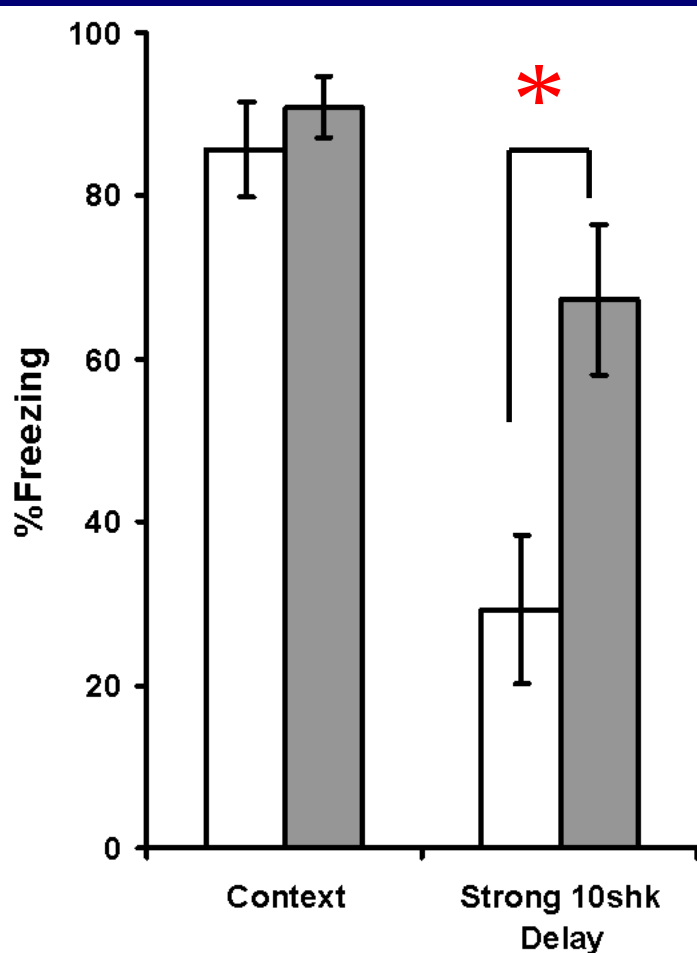


Day2: Train



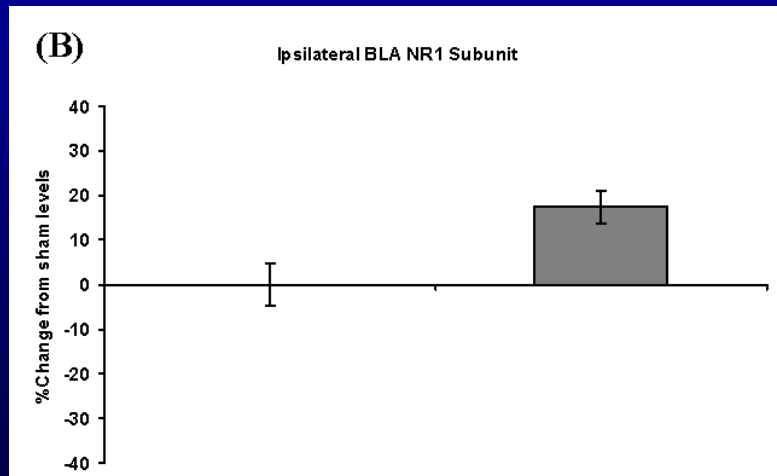
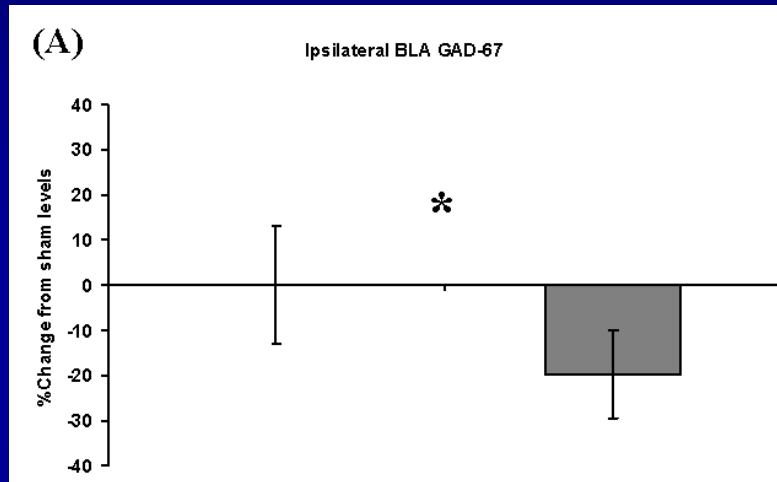
- ✓ No Freezing Prior to Shock
- ✓ Learning Curves Normal
- ✓ Reactivity to Shock Normal

Enhanced Fear-Based Learning after mTBI

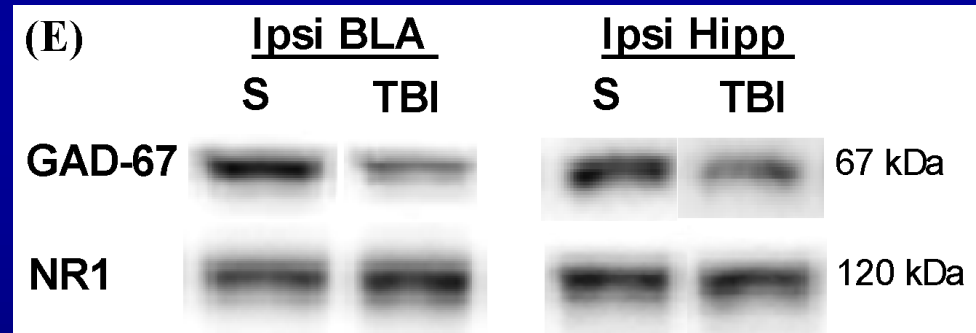


Experimental TBI results in enhanced fear-based learning that, like PTSD, generalizes to new contexts and is difficult to extinguish.

Potential Mechanisms of Enhanced Fear post-mTBI



Experimental TBI followed by fear conditioning results in excitatory-inhibitory imbalance.



Chronic Neurocognitive Impairment (CNI) vs. Chronic Traumatic Encephalopathy (CTE)

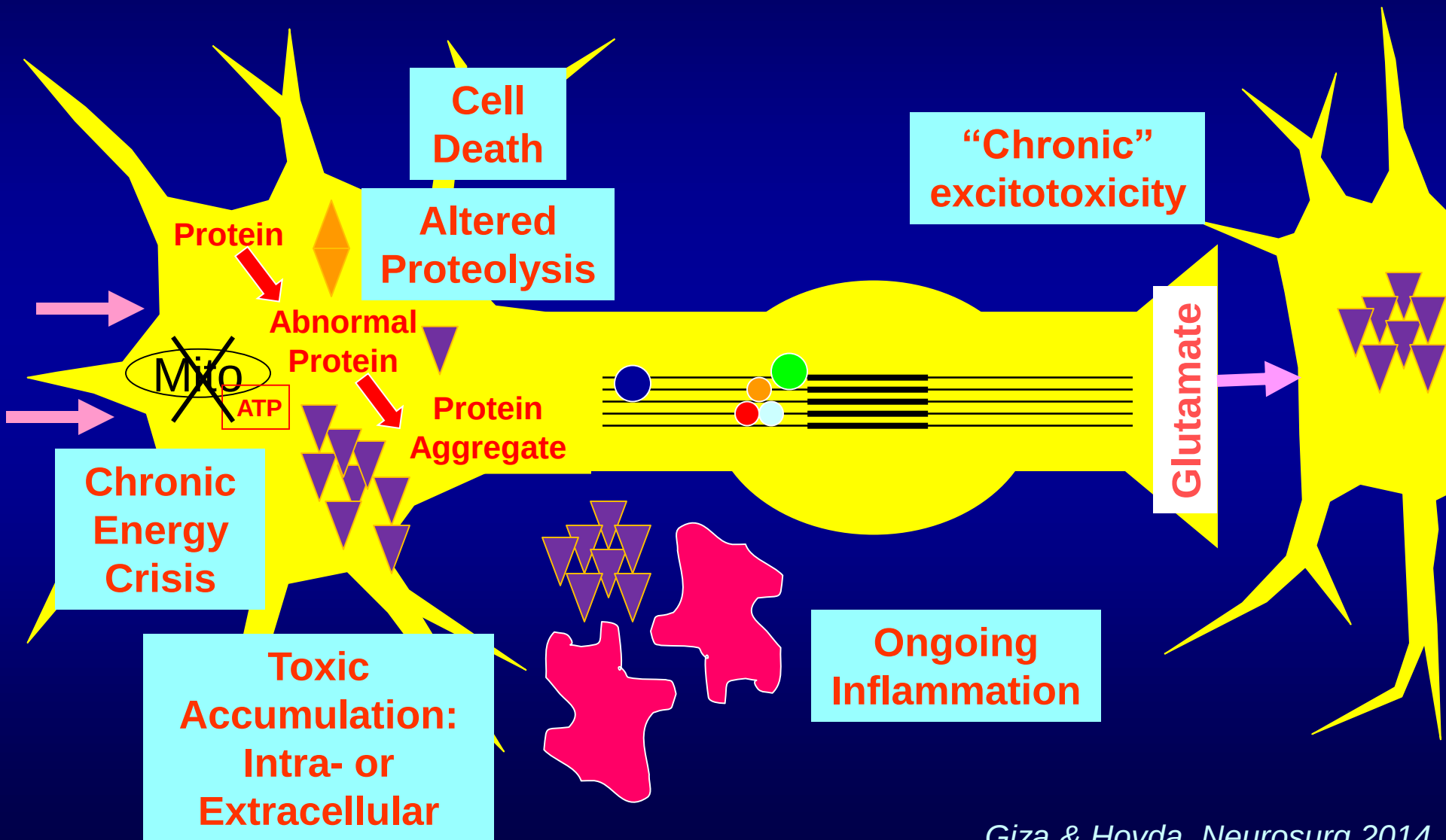
Chronic Neurocognitive Impairment (CNI)

- Decrement in function
- May be static
- Detected in **living patients**
- May be measured by **neuropsych testing, neurological measures or behavioral screening** questionnaires.
- **Causal link not established, but suggested by dose-dependent risk** in studies of professional athletes (Class I-II).

Chronic Traumatic Encephalopathy (CTE)

- **Neurodegenerative disease**
- **Presumed progressive**
- Detected **post-mortem**
- Characterized **pathologically** by tau accumulation in brain
- **Causal link not yet established, current data is only case reports/series** (Class IV)

Neurometabolic Cascade of mTBI: Hypothesized Acute-Chronic Linkage



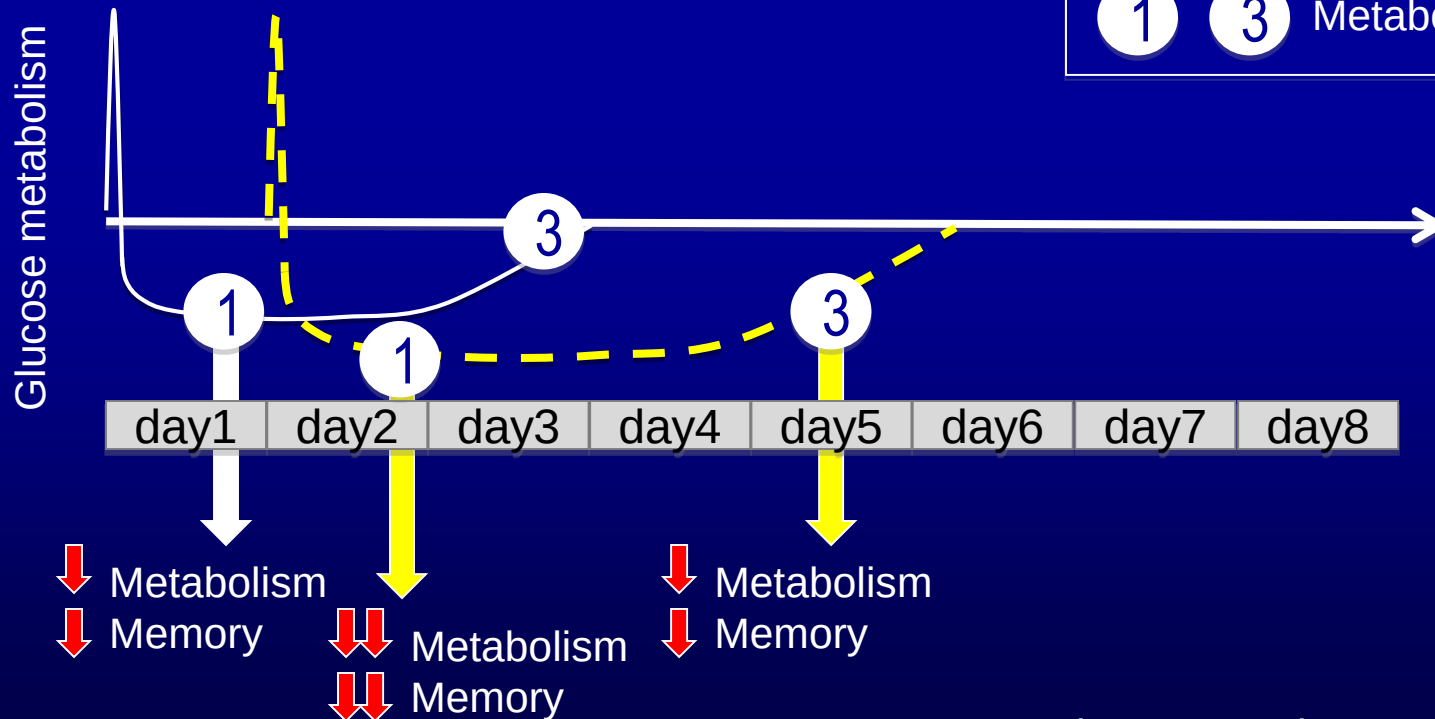
Repeat mild TBI: Metabolism & Timing



**2nd concussion during
metabolic impairment results
in worse metabolic disruption
and cognition**

— Single Impact
- - - 2nd TBI induced DURING the depressed
metabolic phase from the 1st TBI

① ③ Metabolic studies



Repeat mild TBI: Acute-to-chronic linkage

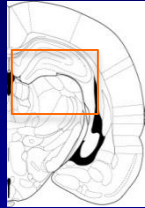


24h intervals  Using 3xTg AD rat model to address effects of RmTBI on amyloid deposition

Adolescent

Adult

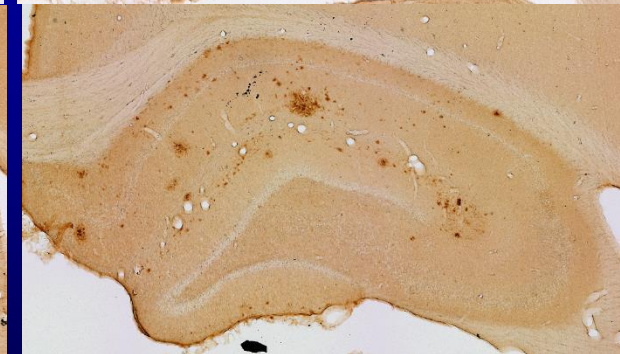
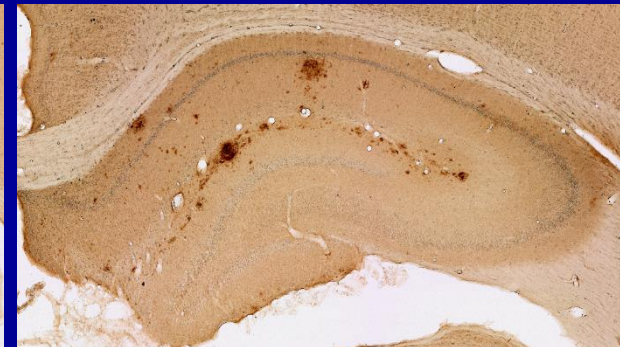
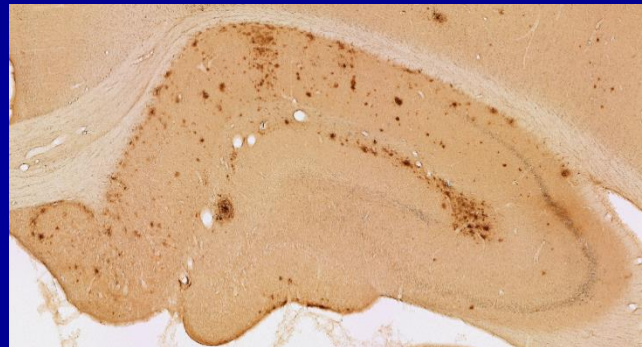
72h intervals 



Sham

4RTBI_{24h}

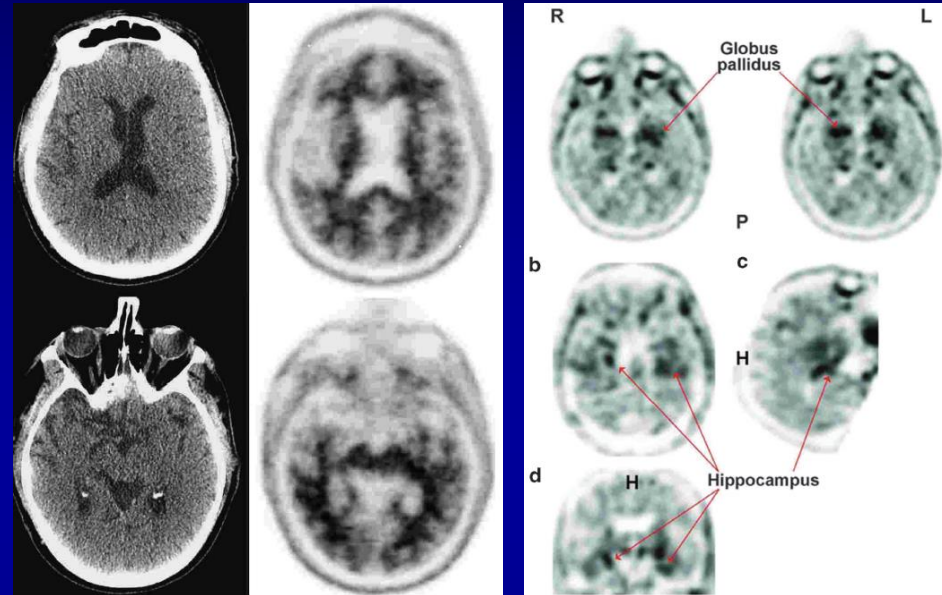
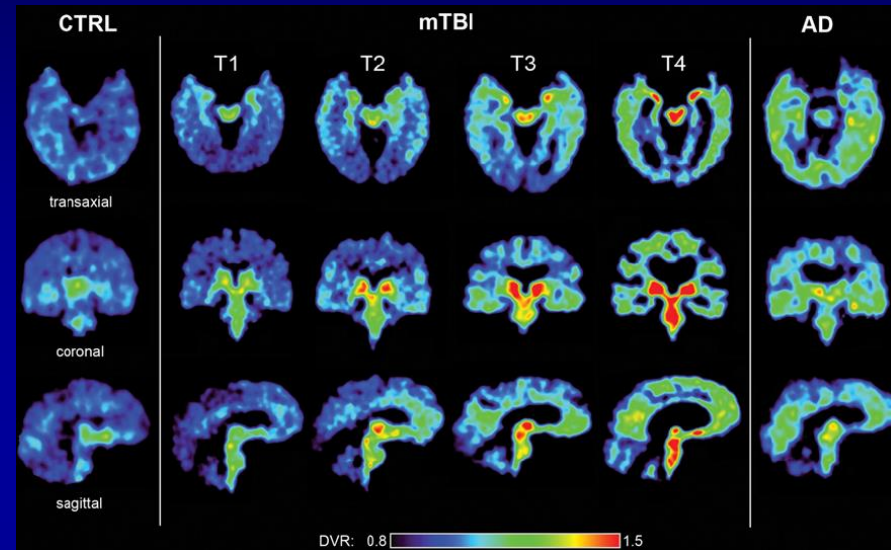
4RTBI_{72h}



Repeat mTBI in youth worsens amyloidosis. Impact Interval Matters.

Alexander D, et al. J Neurotrauma abstract 2014

Imaging Tau in vivo



FDDNP-PET binds both amyloid & tau; but signal in mesial temporal structures is more likely to be tau & differs from pattern seen in Alzheimers

Increased F^{18} -T807 but not F^{18} -Florbetapir was detected in vivo in a symptomatic retired NFL player

Why Biology is Important

-
- control NFL1 NFL2
- thalamus
- amygdala
- CORONAL
- TRANSAXIAL
1. Neural activation is impaired following TBI
 2. Recovery after TBI may be enhanced by combination of behavioral and pharmacological activation
 3. Network connectivity and axonal integrity is damaged after TBI
 4. Active rehabilitation may restore axonal damage and/or improve functional recovery
 5. Chronic post-TBI outcomes are not the same: Post-concussion syndrome, cognitive impairment, behavioral impairment (anxiety, PTSD, depression), CTE
 6. Causal linkages need to be proven between acute TBI/concussion and chronic neurobehavioral deficits

It's Just a Game

