

Mild Traumatic Brain Injury: Pathophysiology & Recovery



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Mattel Children's Hospital

UCLA

Credit where credit deserved!



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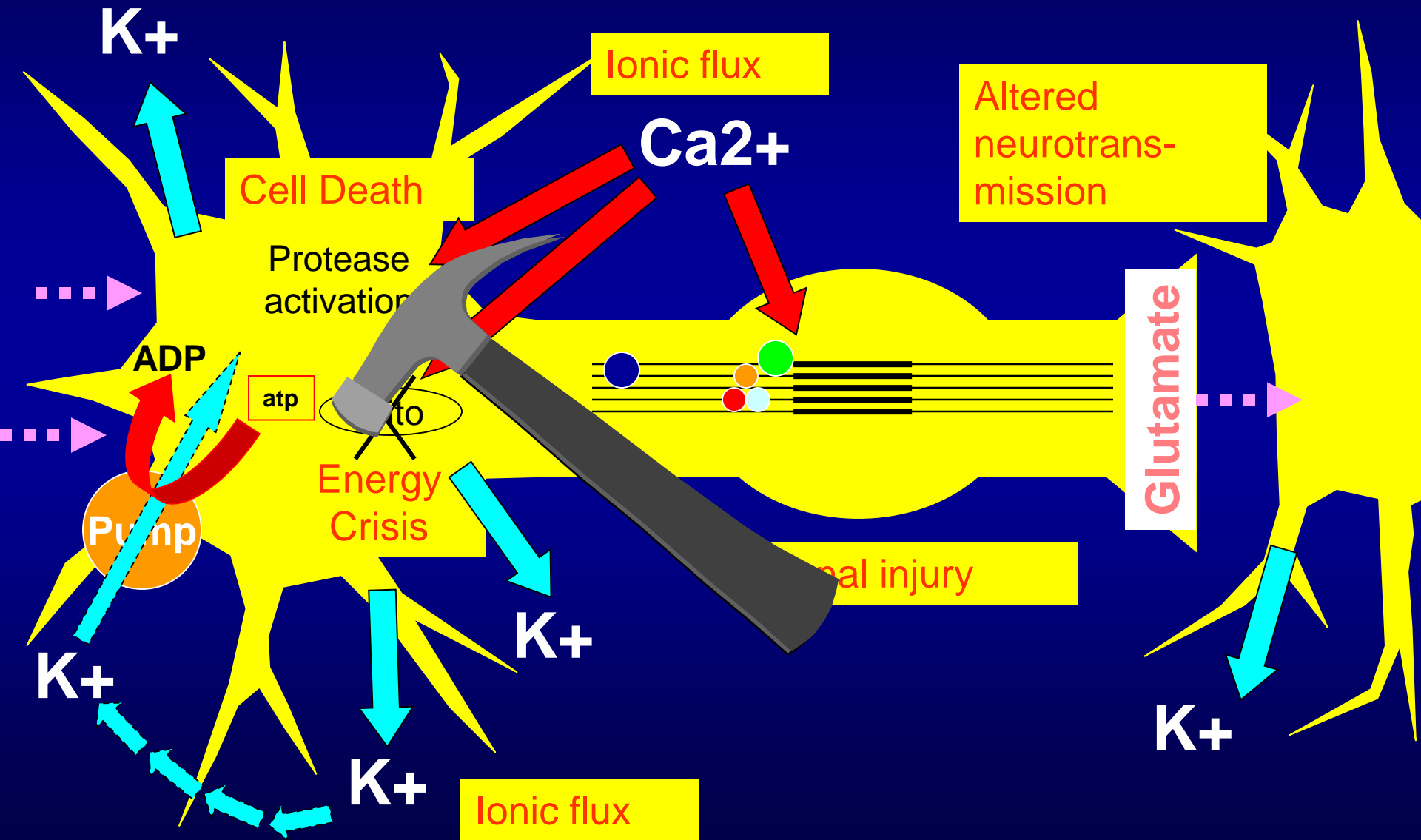
Twitter: @griz1

Why is it important to understand Concussion Pathophysiology?

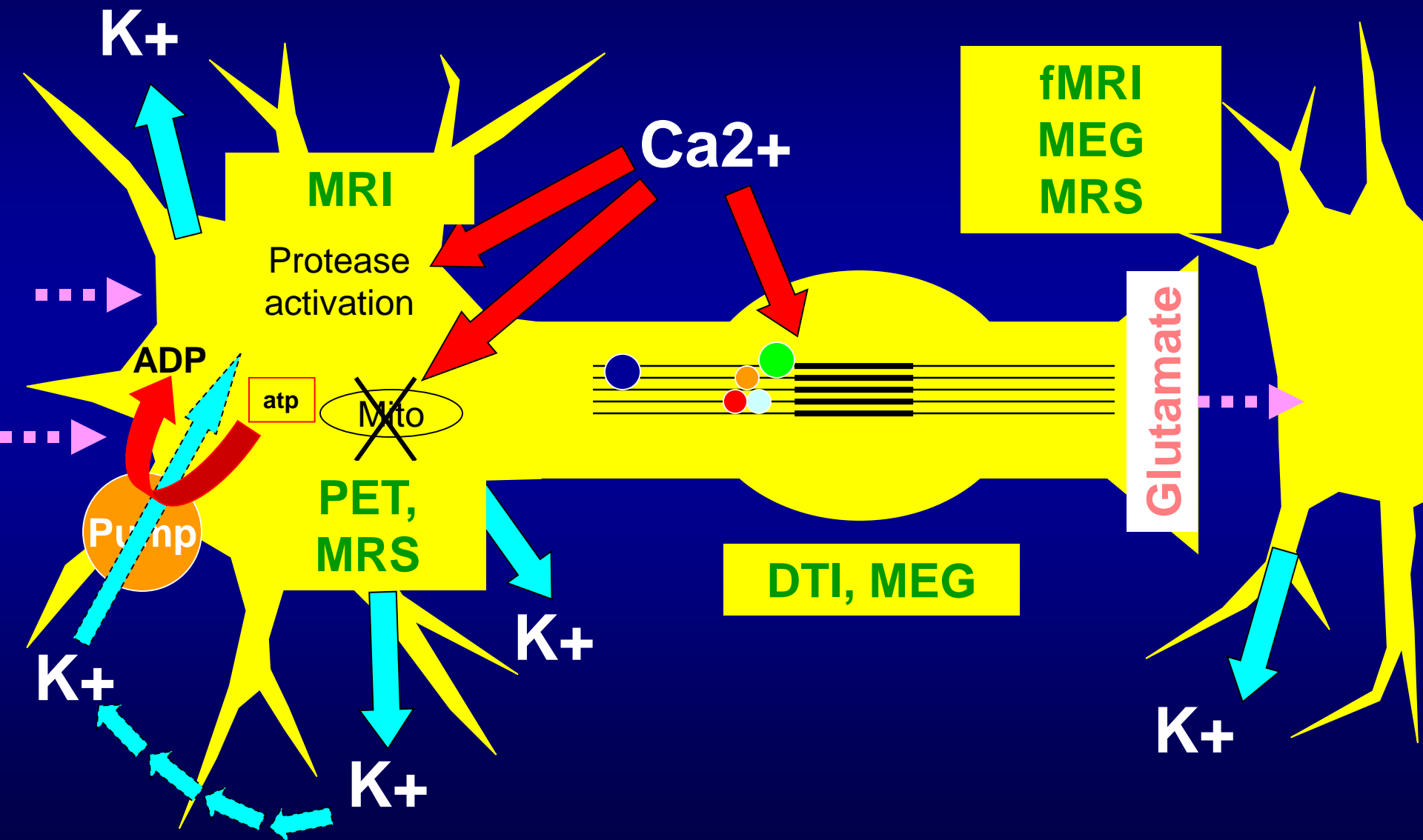


- 1. Concussion Pathophysiology can be detected using advanced neuroimaging in research studies**
- 2. It can explain vulnerability and repeat concussion risk**
- 3. It can determine when/how to activate the injured brain**
- 4. It can guide the development of therapeutic interventions**

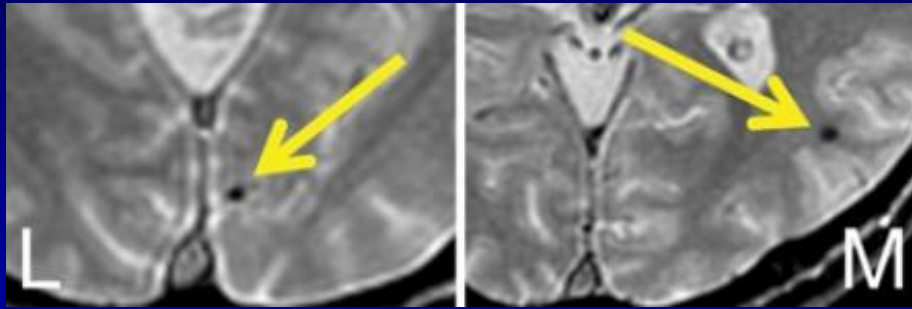
Neurometabolic Cascade of mTBI: Pathophysiology



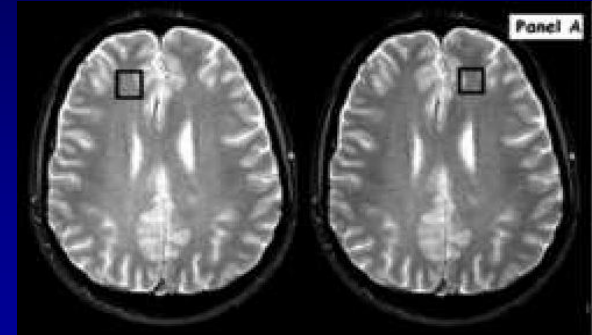
Seeing is Believing: Imaging mTBI Pathophysiology



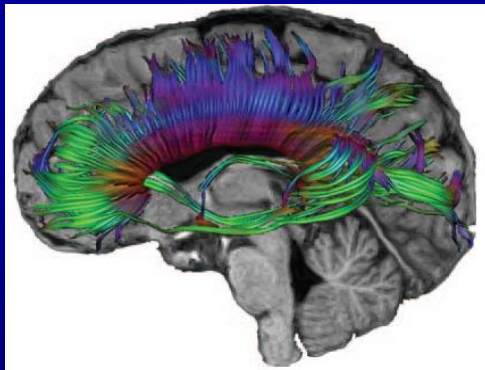
Imaging mTBI/Concussion



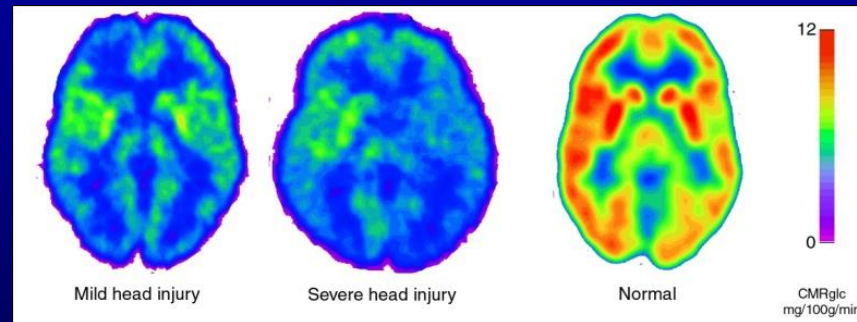
Yuh et al., Ann Neurol 2012



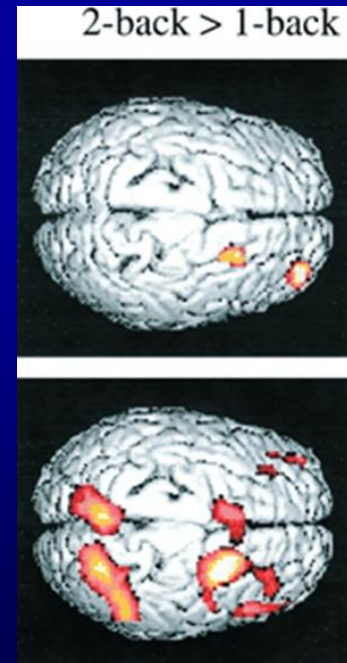
Vagnozzi et al., Neurosurg 2008



Wilde et al., Neurol 2008



Bergsneider et al., J Neurotrauma 2000



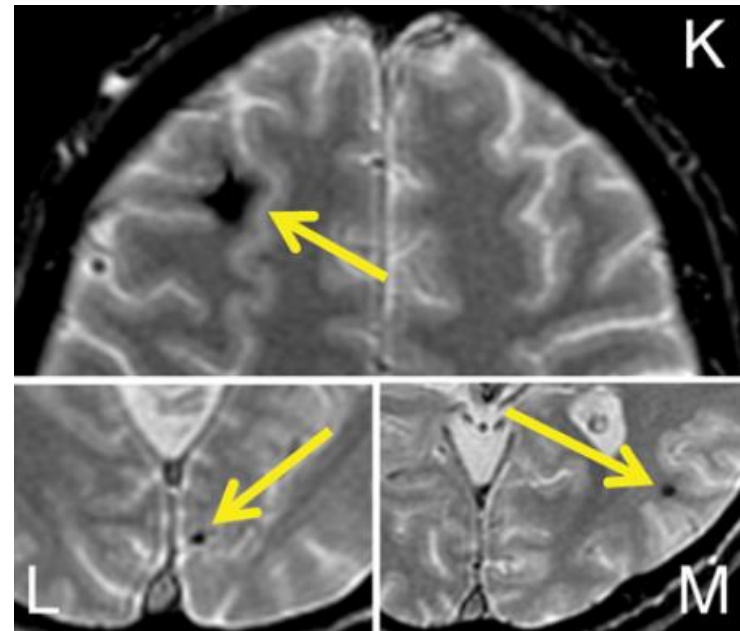
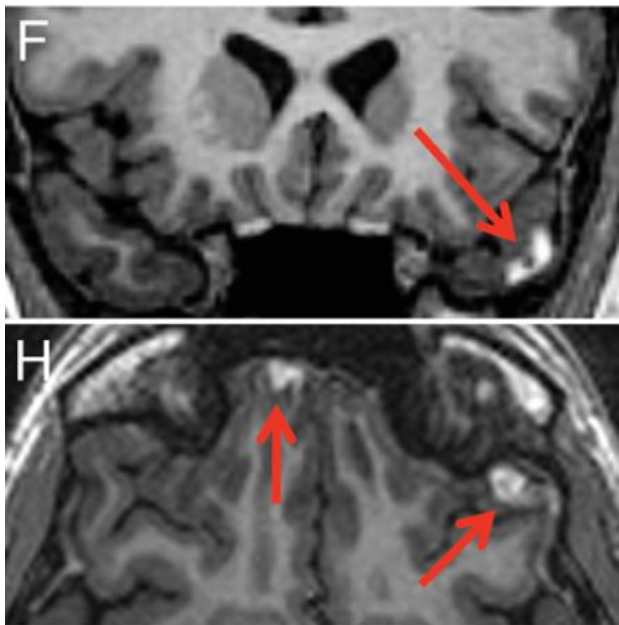
McAllister et al., Neurol 1999

Imaging Early mTBI: MRI/SWI

N=135

Prospective mTBI ED cohort, 3 centers

Time post-injury=12 days



≥ 1 brain contusion or ≥ 4 hemorrhagic foci on early MRI were associated with worse 3 month outcome

Afghanistan, January 2011



Effects of Blast

The NEW ENGLAND JOURNAL of MEDICINE

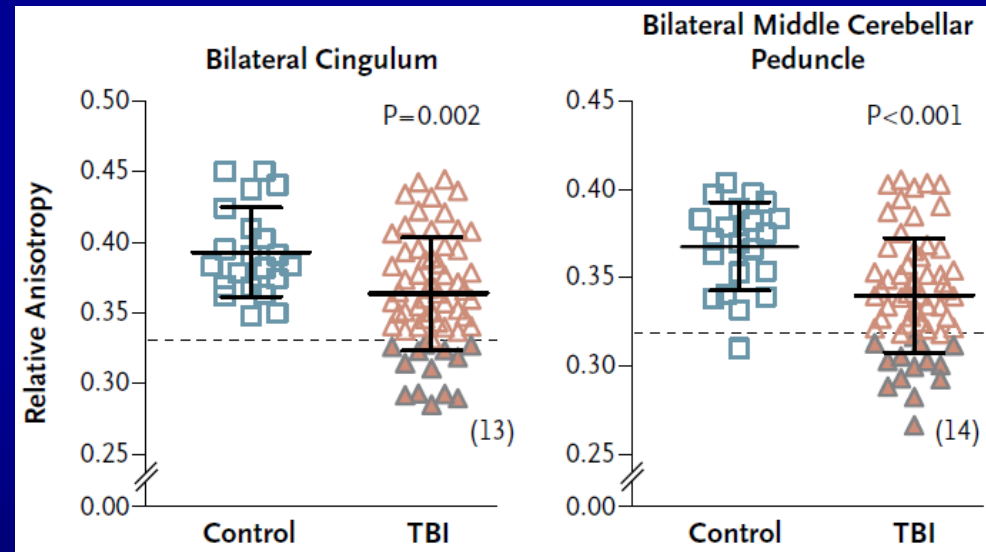
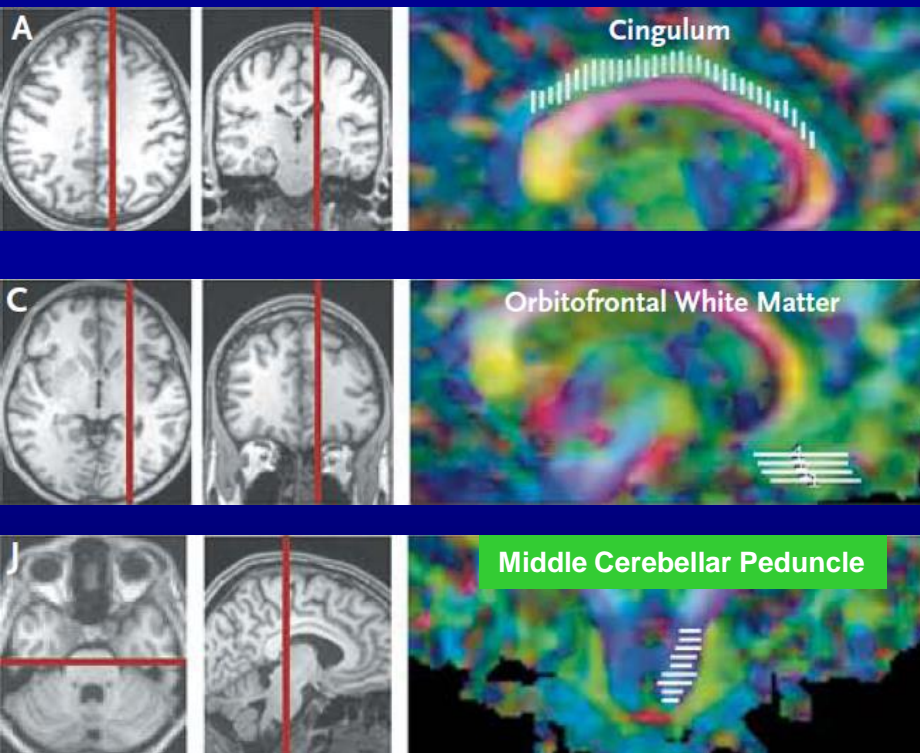
ESTABLISHED IN 1812

JUNE 2, 2011

VOL. 364 NO. 22

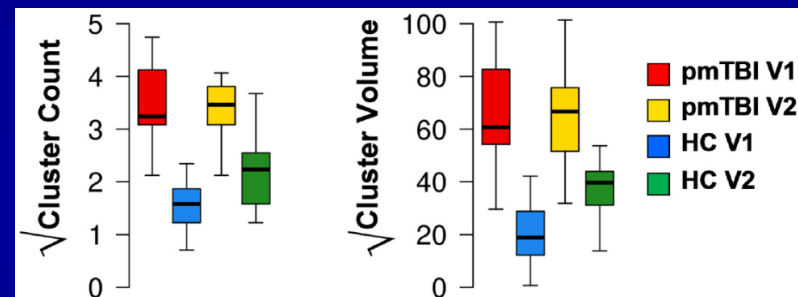
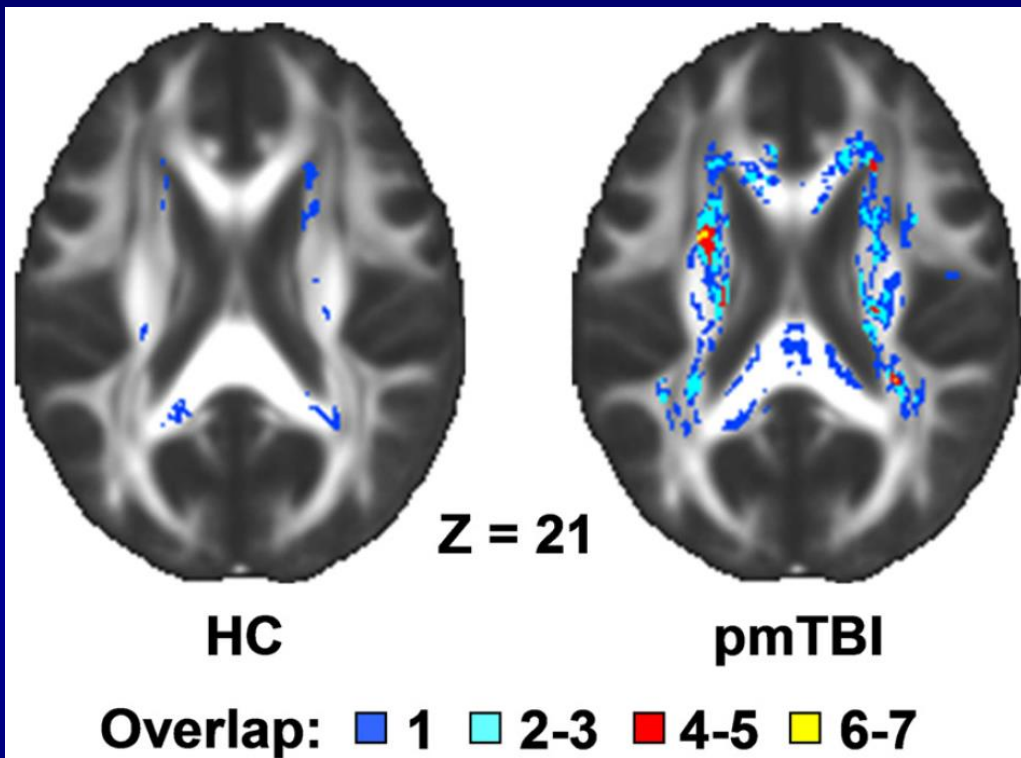
Mac Donald CL,
et al. NEJM 2011

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



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

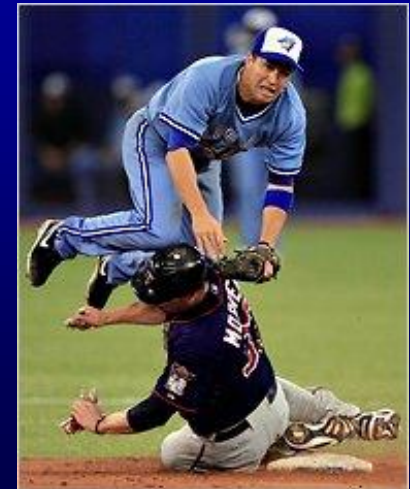
Axonal Damage in Ped mTBI: DTI



White matter differences seen after pediatric mTBI subacutely (2 wks) and chronically (4 mos). Symptom correlation only seen at 2 wks.

Why is it important to understand Concussion Pathophysiology?

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3. It can determine when/how to activate the injured brain
4. It can guide the development of therapeutic interventions



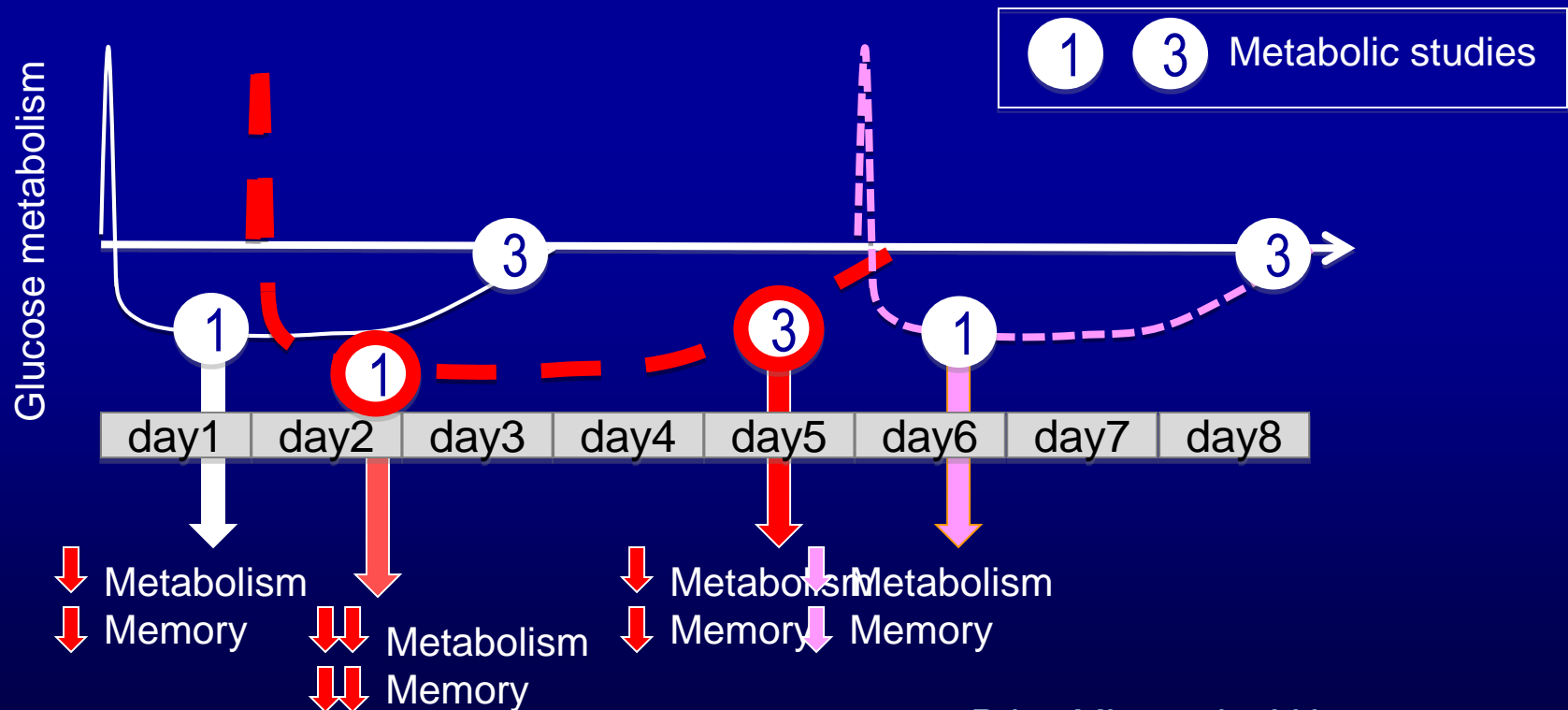
Repeated Mild Traumatic Brain Injury: Mechanisms of Cerebral Vulnerability



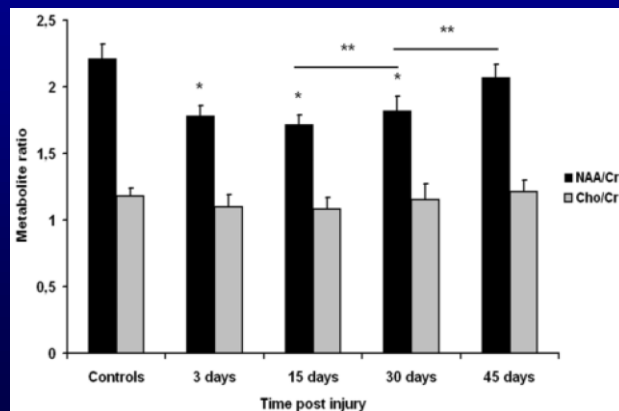
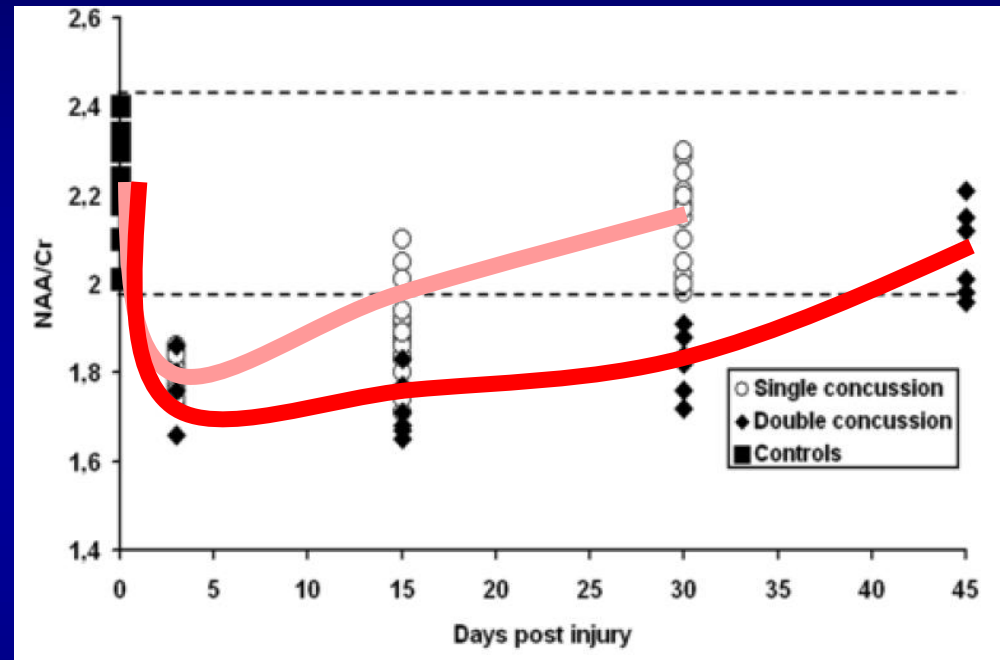
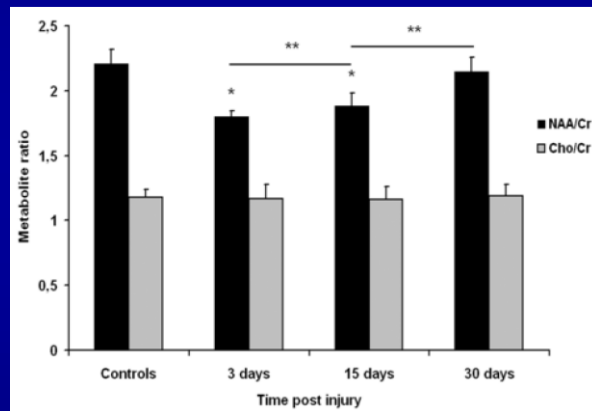
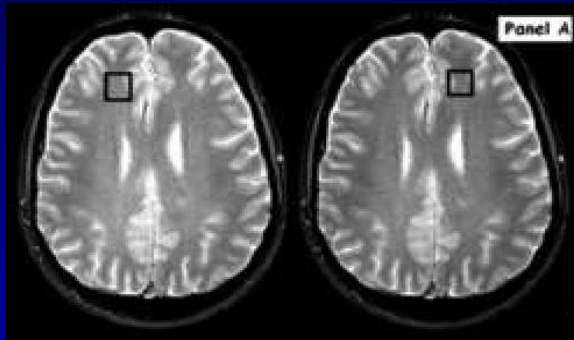
Mayumi L. Prins,^{1,4,5} Daya Alexander,^{4,5} Christopher C. Giza,^{1,2} and David A. Hovda^{1,3-5}

2nd concussion before full recovery results in worse brain metabolism and worse memory

- Single Impact
- 2nd TBI BEFORE recovery from 1st TBI
- 2nd TBI AFTER recovery from 1st TBI



Vulnerability: Metabolism & MRS



There were significant reductions of NAA/Cr for 30 days after 1 concussion and 45 days after 2 concussions.

Vagnozzi, et al., Neurosurgery, 2008

Vagnozzi, et al., Brain 2010

Vulnerability: Repeat Concussion Risk

Concussed athletes are 3x more likely to get another concussion!!!

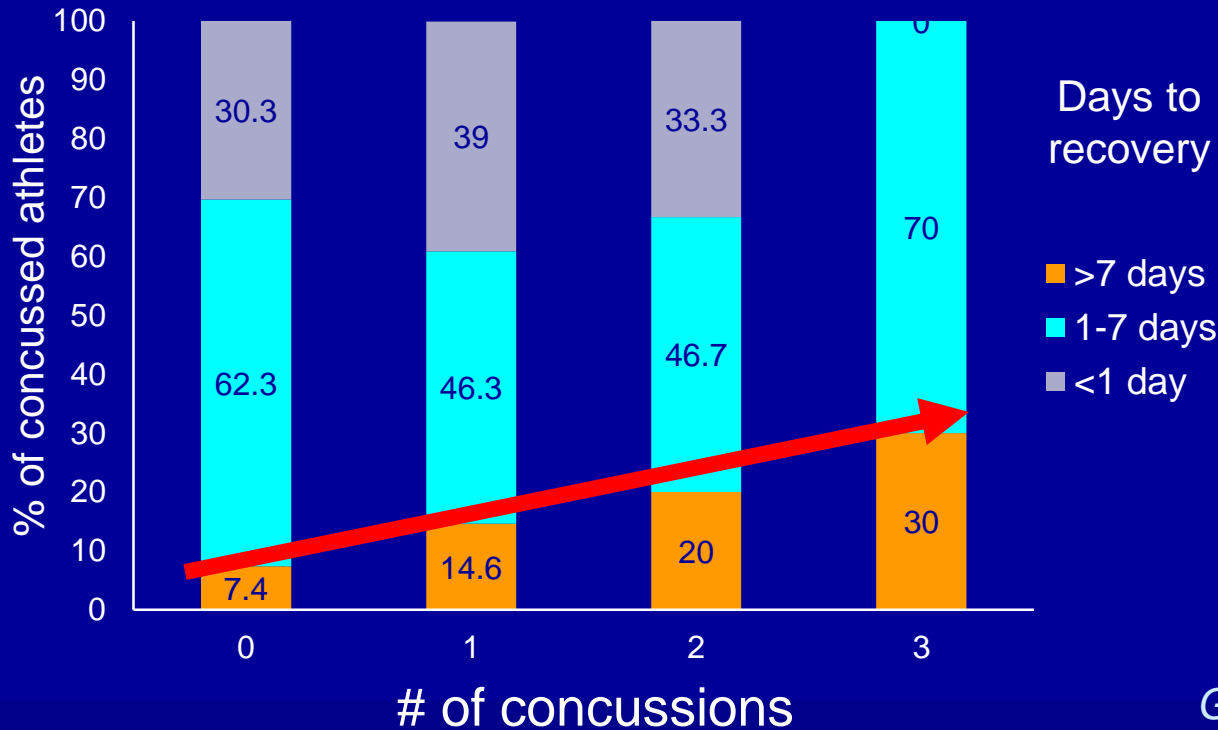
1. Brain energy crisis
2. Slow reflexes and reaction time
3. Slower thinking
4. Poor playing style
5. Genetic risk



92% of repeat in-season concussions occurred within 10 days of 1st concussion.

McCrea et al., Neurosurgery 2009, Guskiewicz et al., JAMA 2003

Vulnerability: Repeat Concussion Severity



Guskiewicz et al., JAMA 2003

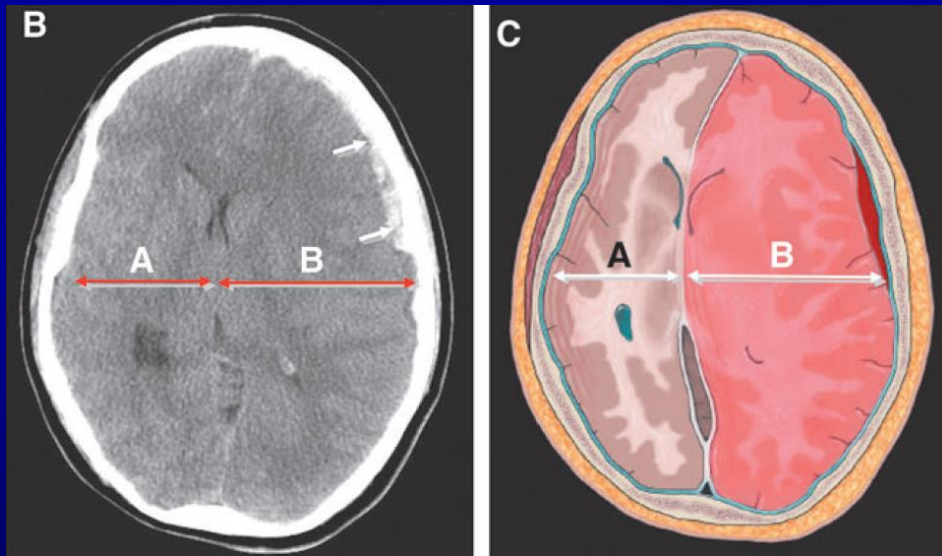
Athletes with repeated concussions take longer to recover – and miss more school and more games.

Age and 'Second Impact Syndrome'

Probable second impact syndrome: N=5 Age: 17.2y

Non-second impact syndrome (but cerebral edema or other neurological problems): N=11 Age: 19.0y

McCrary & Berkovic, Neurology, 1998



Rare post-concussive cerebral edema seems to occur more commonly in younger athletes

Second impact syndrome + small subdural hematoma:

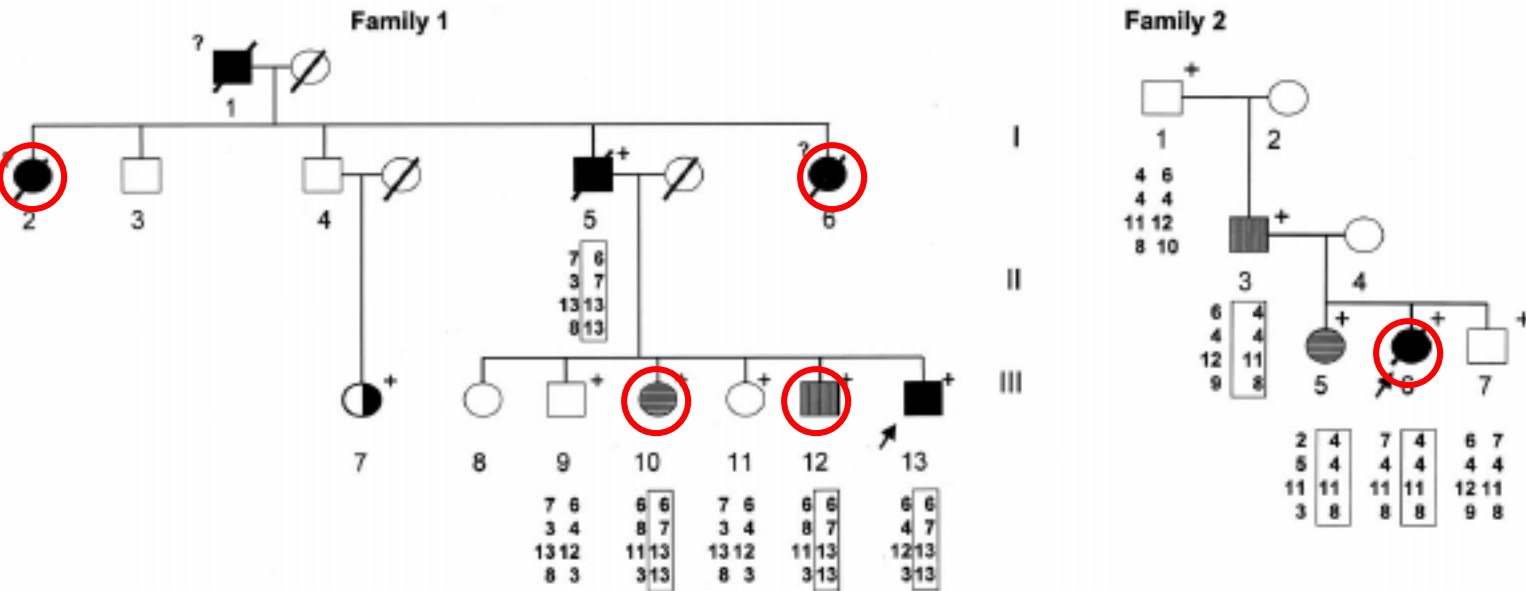
N=10 Age: 15.4y

Cantu & Gean, J Neurotrauma, 2010

Delayed Cerebral Edema and Fatal Coma after Minor Head Trauma: Role of the CACNA1A Calcium Channel Subunit Gene and Relationship with Familial Hemiplegic Migraine

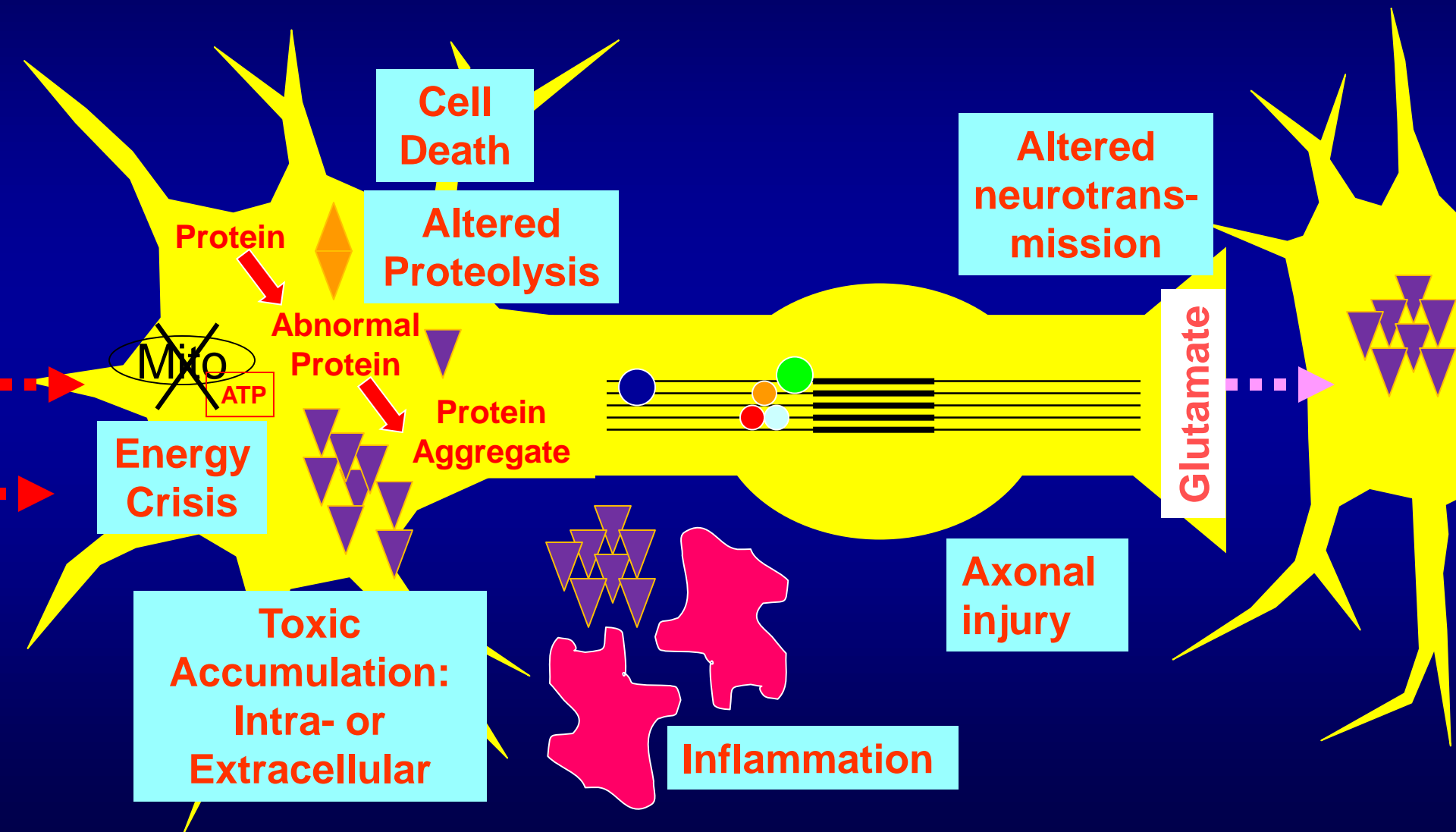
Esther E. Kors, MD,¹ Gisela M. Terwindt, MD, PhD,¹ Frans L.M.G. Vermeulen,²

Robin B. Fitzsimons, MBBS, BSc(Med), PhD, FRACP,³ Philip E. Jardine, MD, FRCPC,⁴ Peter Heywood, MD,⁵
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 Rune R. Frants, PhD,² and Michel D. Ferrari, MD, PhD¹



Black = coma
 Stripes = ataxia, migraine
 1/2 black = migraine only
 Red circle = mTBI induced AMS

Neurometabolic Cascade of mTBI: Chronic Pathophysiology



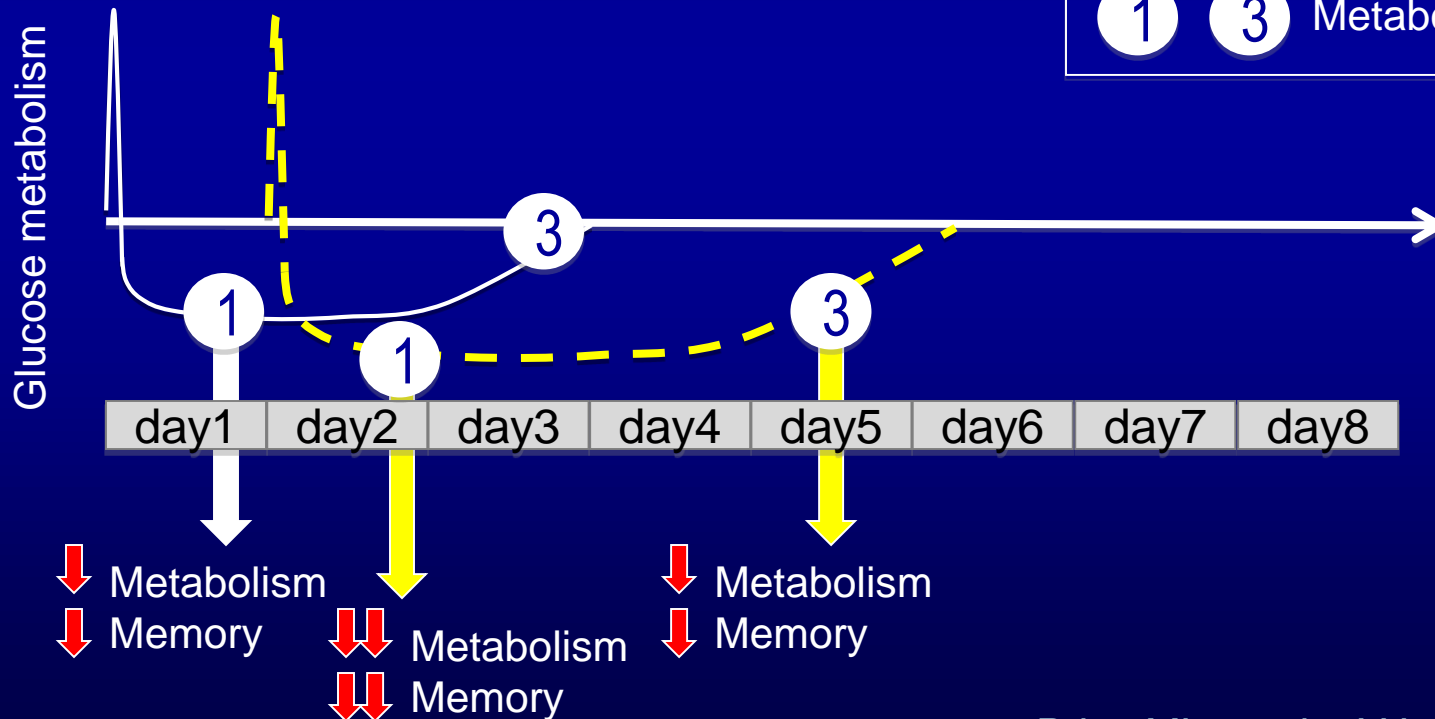
Repeat mild TBI: Metabolism & Timing



**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

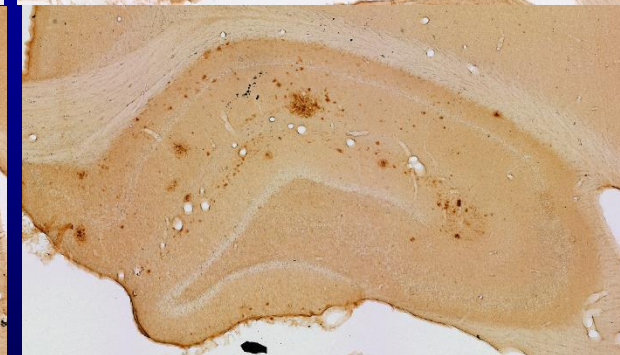
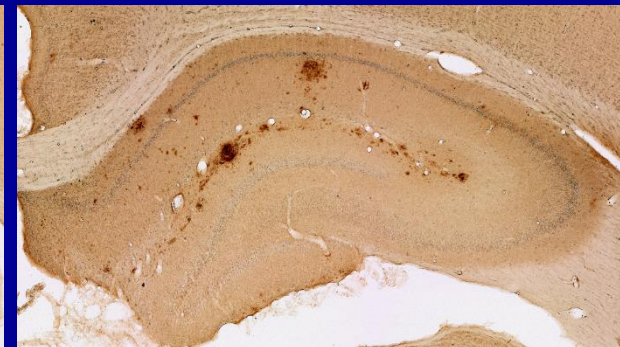
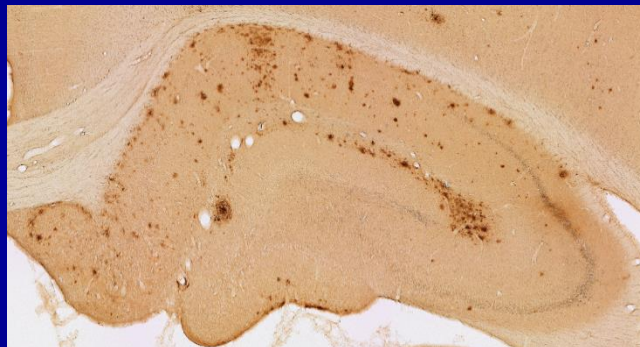
72h intervals 



Sham

4RTBI_{24h}

4RTBI_{72h}



Repeat mTBI in youth worsens amyloidosis. Impact Interval Matters.

Chronic Neurocognitive Impairment (CNI)

*Dose response

	Professional		Amateur	
CNI?	Yes	No	Yes	No
Class I	<ol style="list-style-type: none"> 1. Wall JNNP 2006 (horseracing)* 2. Shuttleworth-Edwards Arch Clin NP 2008 (rugby) 		<ol style="list-style-type: none"> 1. Collins JAMA 1999 2. Jordan SE AJSM 1996 3. Shuttleworth-Edwards Arch Clin Neuropsych 2008 4. Thornton J Clin Exp NP 2008 	<ol style="list-style-type: none"> 1. Rutherford J Clin Exp NP 2009 2. Bruce Neurosurg 2009 3. Collie BJSM 2006 4. Priess-Farzanegan PMR 2009 5. Stephens Child NP 2005
Class II	<ol style="list-style-type: none"> 1. Guskiewicz Med Sport Sci Ex 2005 (football)* 2. Guskiewicz Neurosurg 2005 (football)* 3. Jordan JAMA 1997 (boxing)* 4. Kutner Neurosurg 2000 (football)* 5. Matser Neurol 1998 (soccer)* 		<ol style="list-style-type: none"> 1. Killiam Arch Clin NP 2005 2. Kuehl CJSM 2010 3. Covassin JNNP 2010 4. Moser Nsurg 2005 5. Chen Arch Gen Psych 2008 	<ol style="list-style-type: none"> 1. Gysland Ann Biomed Eng 2012 2. Guskiewicz AJSM 2002 3. Mihalik J Nsurg 2005 4. Baillargeon Brain Inj 2012
Class III	<ol style="list-style-type: none"> 1. Amen J NP Clin Nsci 2011 (football) 		<ol style="list-style-type: none"> 1. Iverson Brain Inj 2004 	<ol style="list-style-type: none"> 1. Schatz Nsurg 2011

CNI is consistent in pro sports, with a 'dose response', but inconsistent in amateur sports, about 1/2 showing problems and 1/2 not.

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)

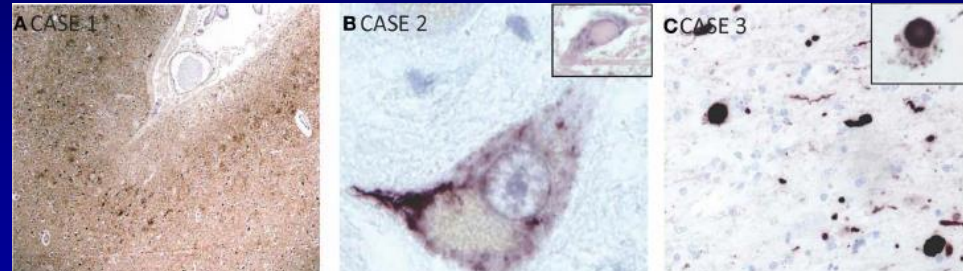
Chronic Traumatic Encephalopathy



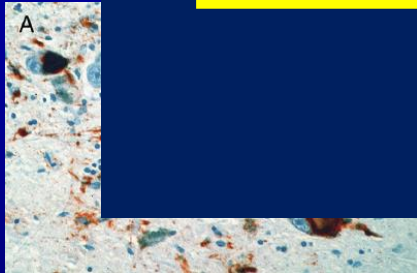
CTE +
severe AD

ALS

CTE +
DLBD



Incidence / Risk is unknown!

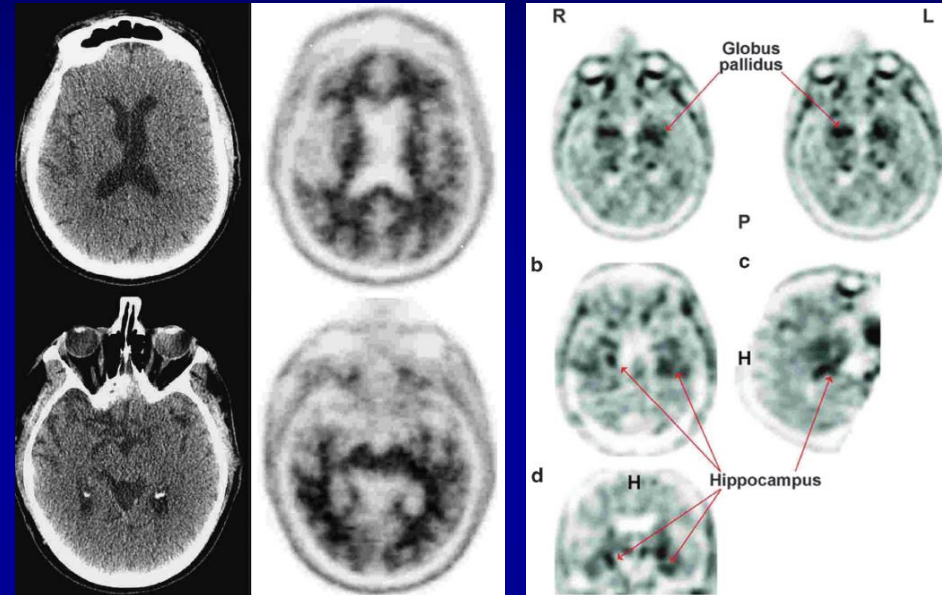
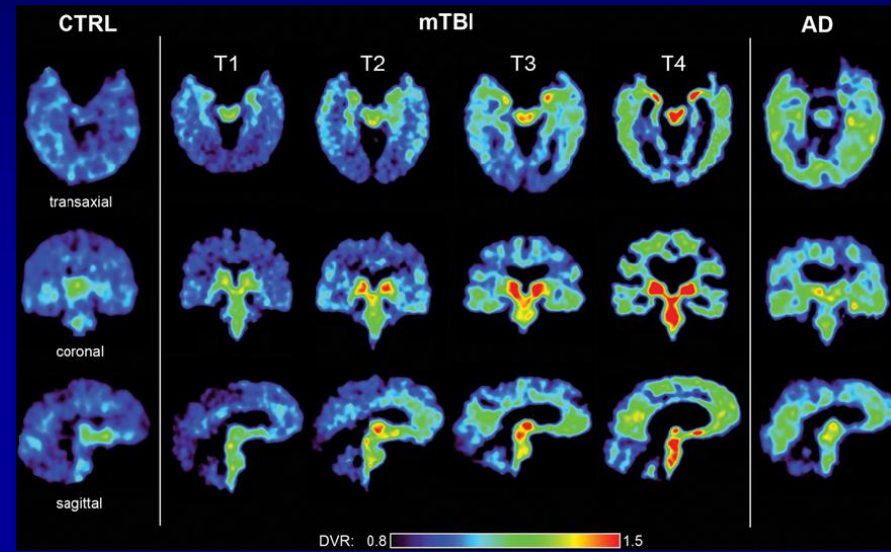


PD

reported in
68/85 brains of
athletes and
military
personnel

3/6 had CTE + other
neurodegeneration
0/6 had only CTE

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 F¹⁸-T807 but not F¹⁸-Florbetapir was detected in vivo in a symptomatic retired NFL player

Why is it important to understand Concussion Pathophysiology?

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To Rest or Not to Rest?

PEDIATRICS®

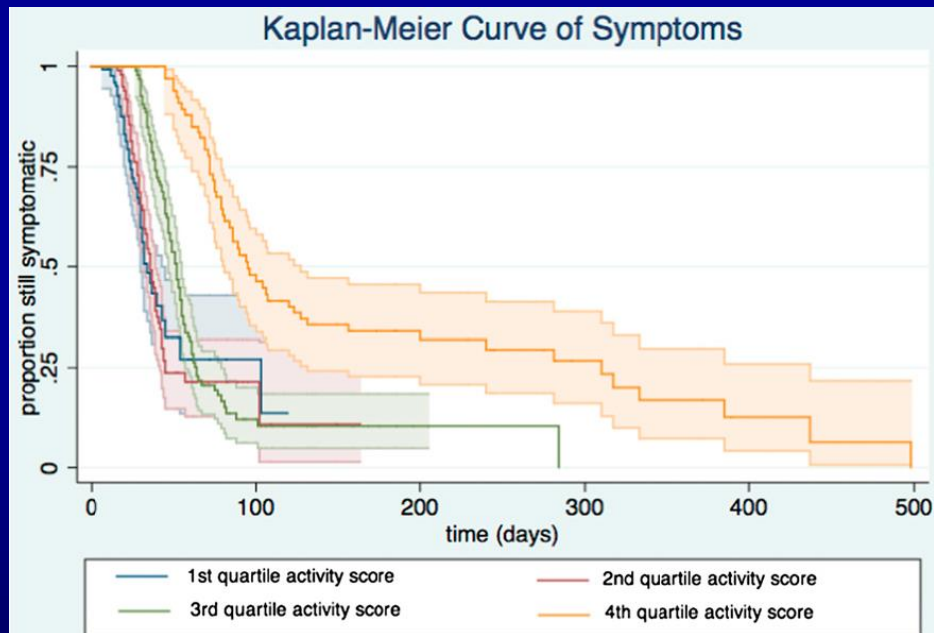
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Effect of Cognitive Activity Level on Duration of Post-Concussion Symptoms

Naomi J. Brown, Rebekah C. Mannix, Michael J. O'Brien, David Gostine, Michael W. Collins and William P. Meehan III

Pediatrics; originally published online January 6, 2014;
DOI: 10.1542/peds.2013-2125

Prospective; n=335; age=15y (8-23)

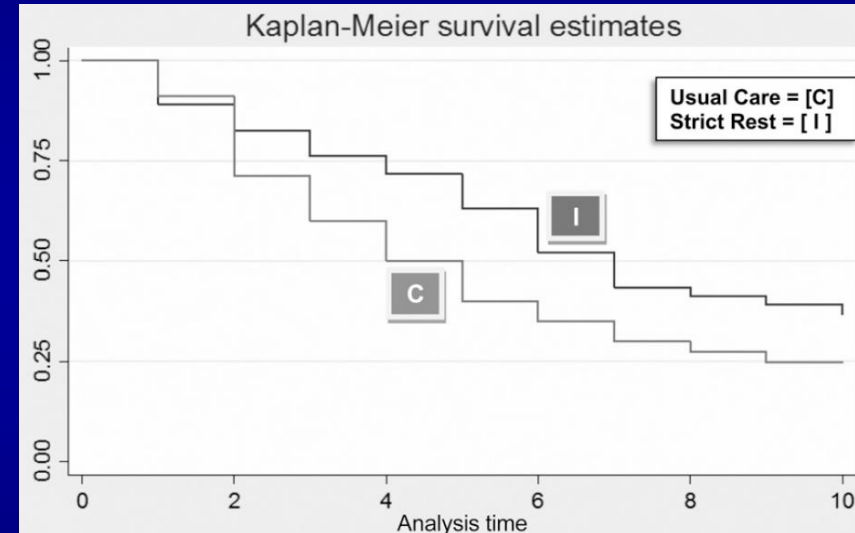


Only highest cognitive activity level predicted longer recovery.

Brown, et al., Pediatrics 2014

Benefits of Strict Rest After Acute Concussion: A Randomized Controlled Trial

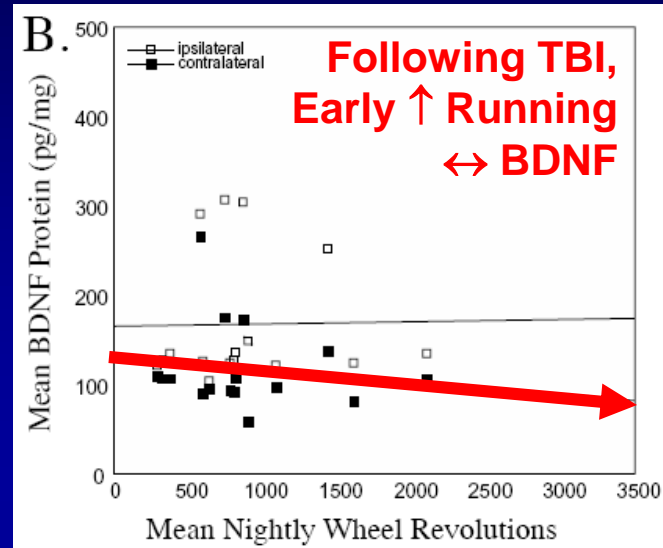
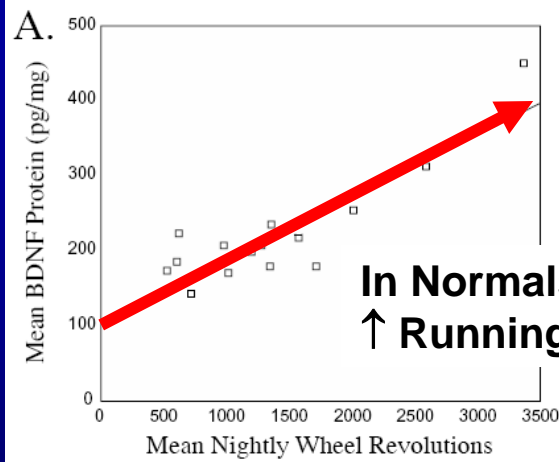
Danny George Thomas, MD, MPH^a, Jennifer N. Apps, PhD^b, Raymond G. Hoffmann, PhD^a, Michael McCrea, PhD^a, Thomas Hammeke, PhD^b



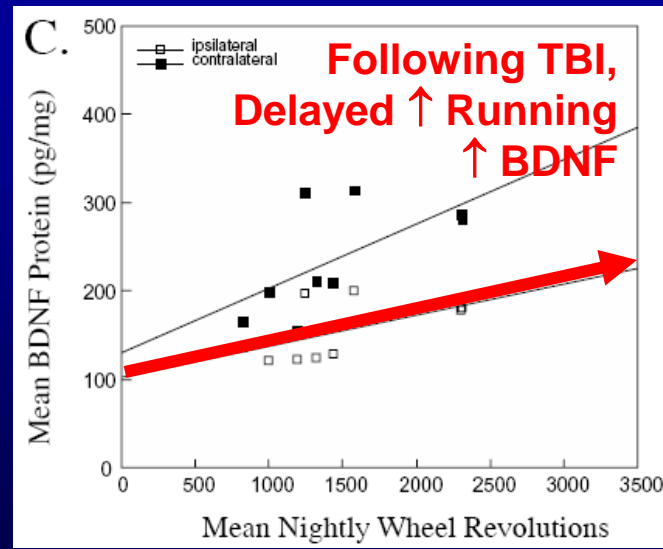
Strict rest (5d) took 3d longer than usual care (1-2d rest) for 50% to recover. But more symptoms reported at all times in strict rest group.

Thomas DG, et al, Pediatrics 2015

Post-concussive Impaired Activation



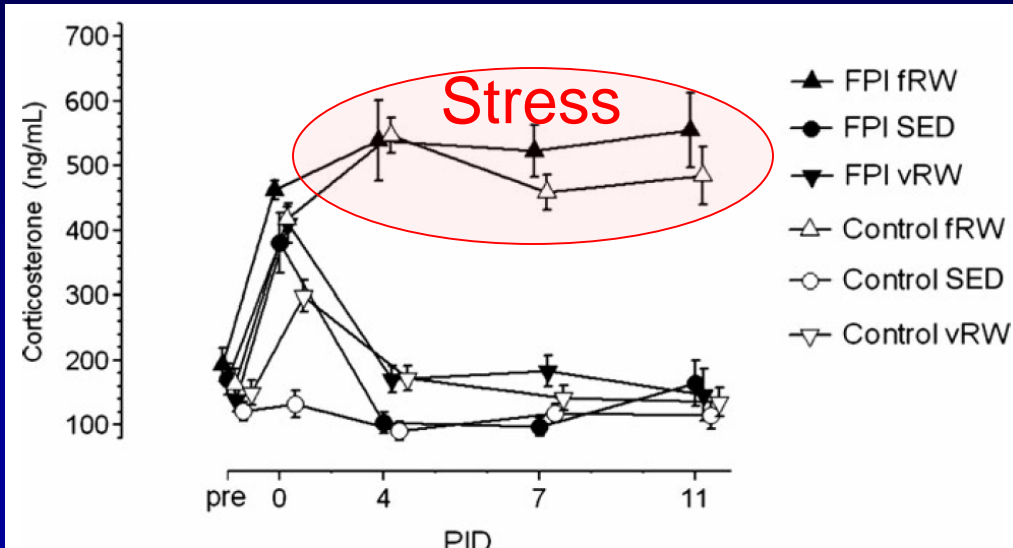
**Also...
Worse
cognition**



**Better
cognition**

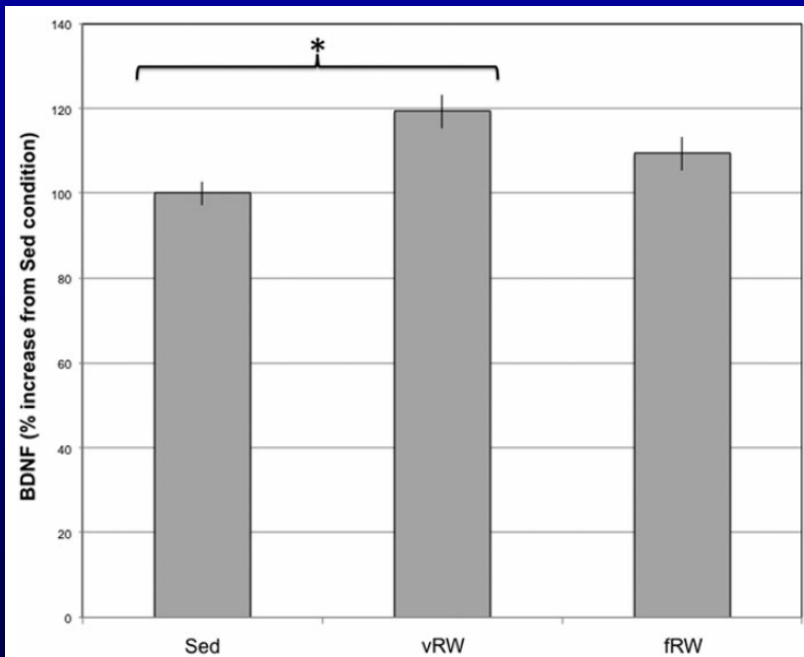
Exercise immediately post-injury worsens outcome; but delayed exercise helps.

Stress, exercise & TBI



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

Griesbach et al., J Neurotrauma, 2012



Forced exercise induces

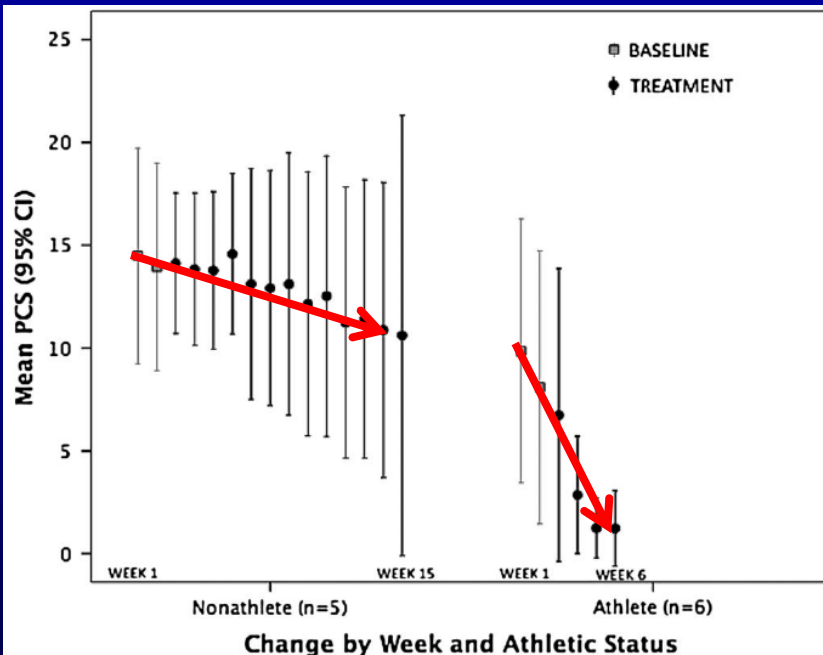
- increase HPA activity,
- higher core temperature and
- reduced HR elevation in response to exercise

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



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

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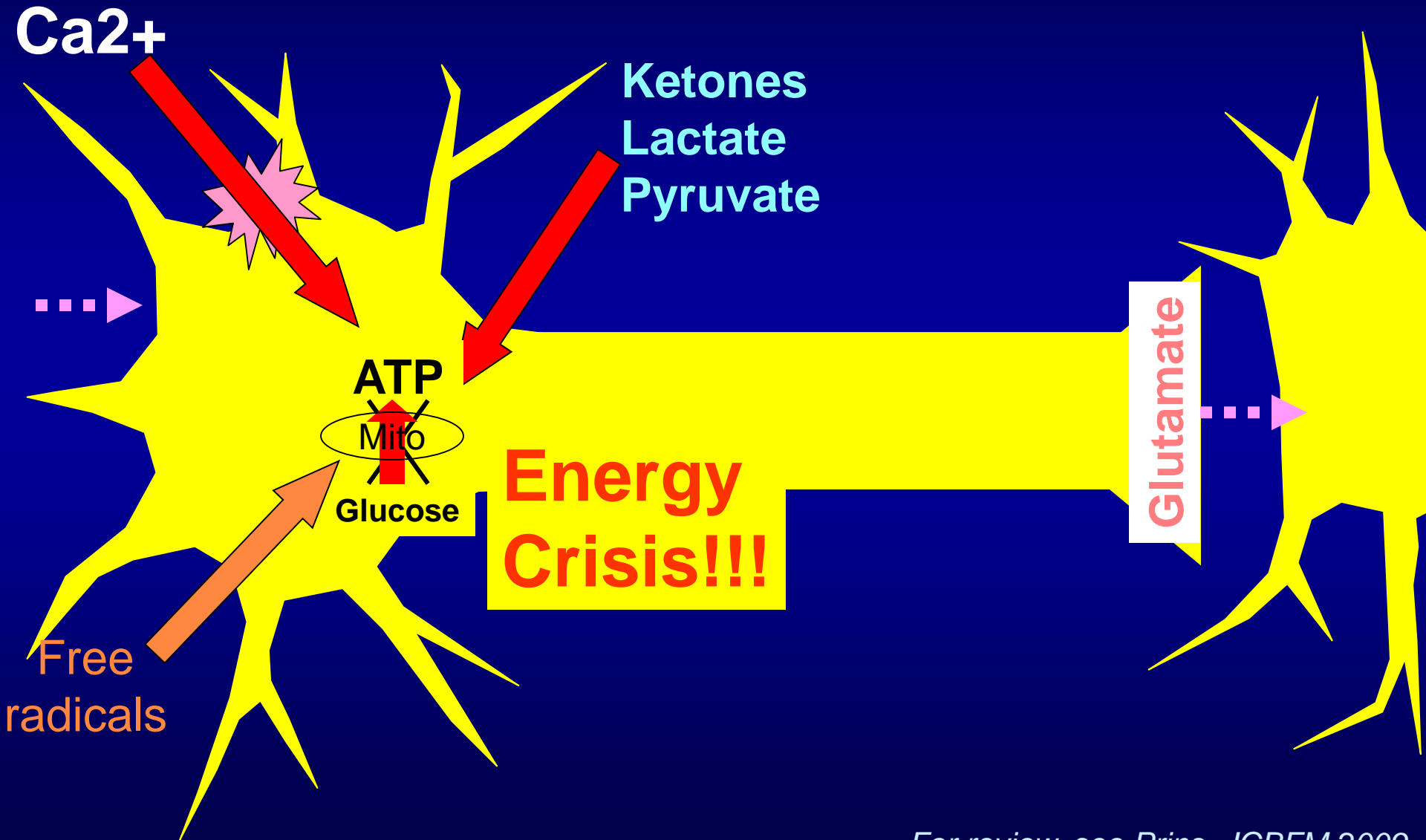
A pilot study of active rehabilitation for adolescents who are slow to recover from sport-related concussion

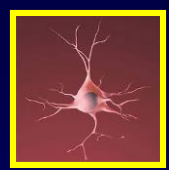
I. Gagnon^{1,2,3}, L. Grilli², D. Friedman^{2,3,4}, G. L. Iverson^{5,6,7,8}

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Neurometabolic Cascade of mTBI: Improving metabolism with alternative fuels

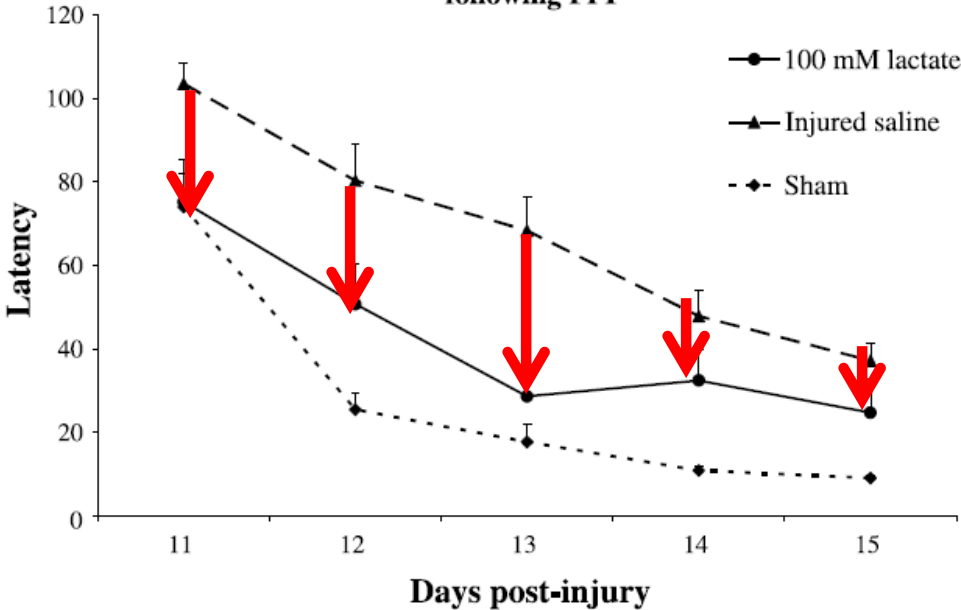




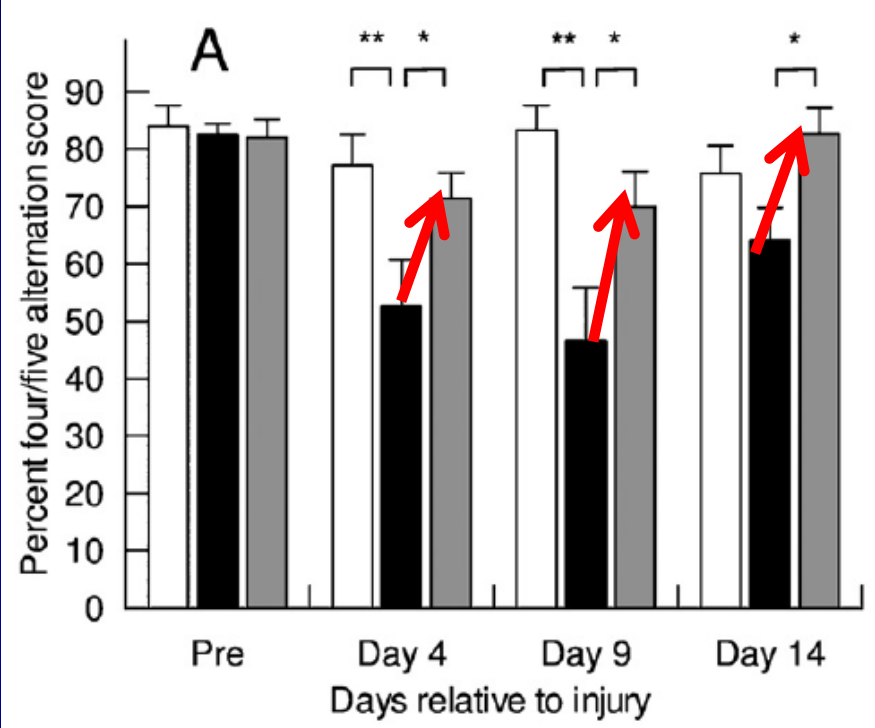
Lactate and Pyruvate after TBI

□	Sham-Veh
■	CCI-Veh
■	CCI-SP

Effect of 100 mM L-lactate dose on cognitive recovery following FPI



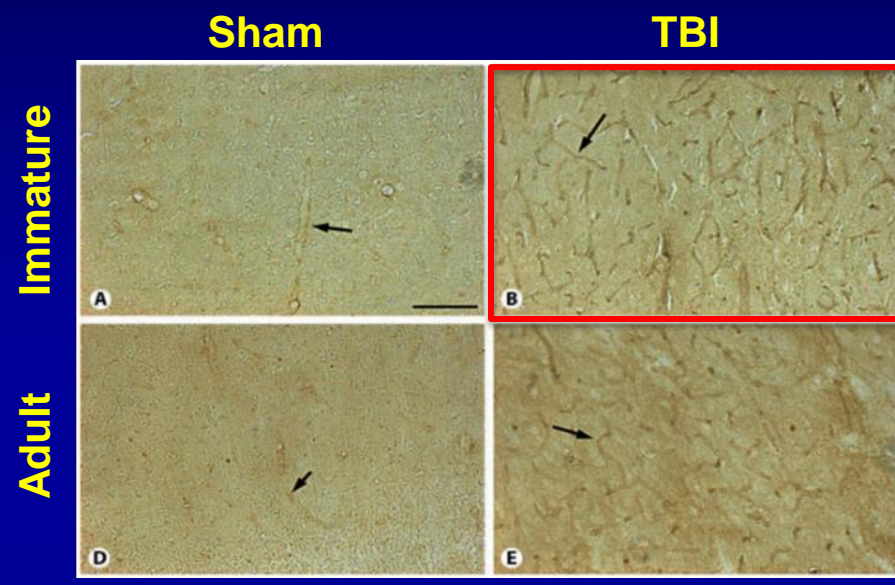
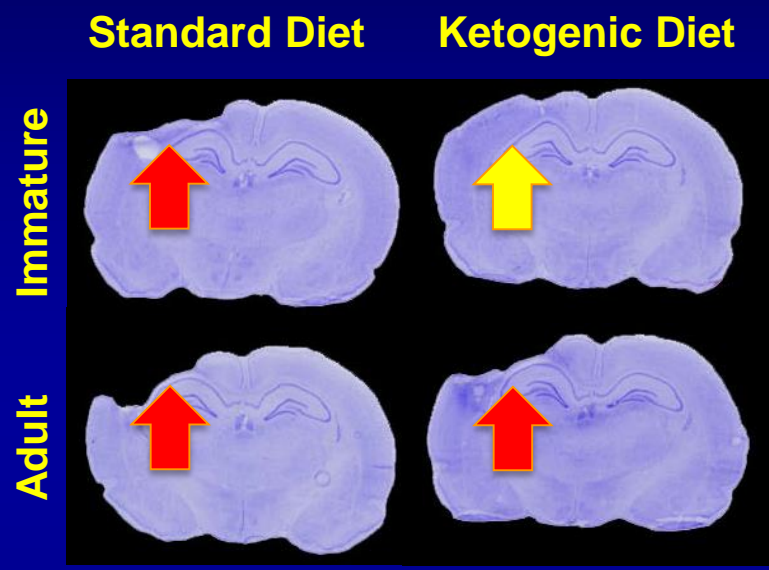
Intravenous lactate improved cognitive recovery after experimental TBI.



Intraperitoneal pyruvate improved cognitive recovery after experimental TBI.

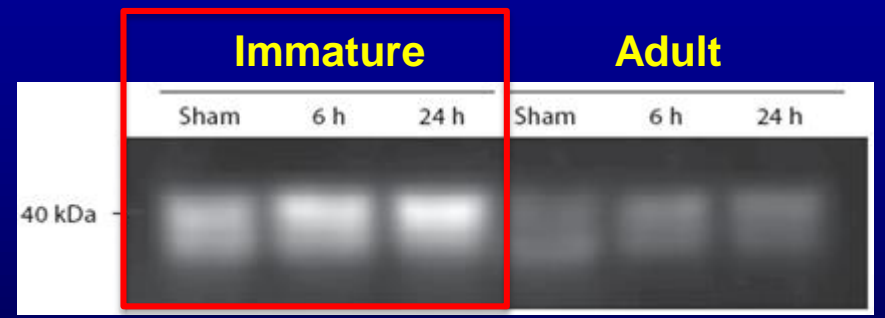


Ketones after TBI: Rats



Ketogenic diet is neuroprotective after developmental TBI. Ketone transporters are upregulated more rapidly in the immature brain.

Prins, et al., J Neurosci Res, 2005



Prins & Giza, Dev Nsci 2006

Ketogenic diet reduces damage after TBI in immature rats



Ketogenic diet

- Very high fat, very low carbohydrate
- Strictly weighed portions
 - Fixed number of calories per day
 - Protein required for growth
 - Composition of all meals abide by diet ratio
- Typical diet ratio 3:1 to 4:1
- Diet typically initiated in hospital

The New York Times

July 6, 1922 **TBI?**

FASTING AS ~~EPILEPSY~~ CURE.

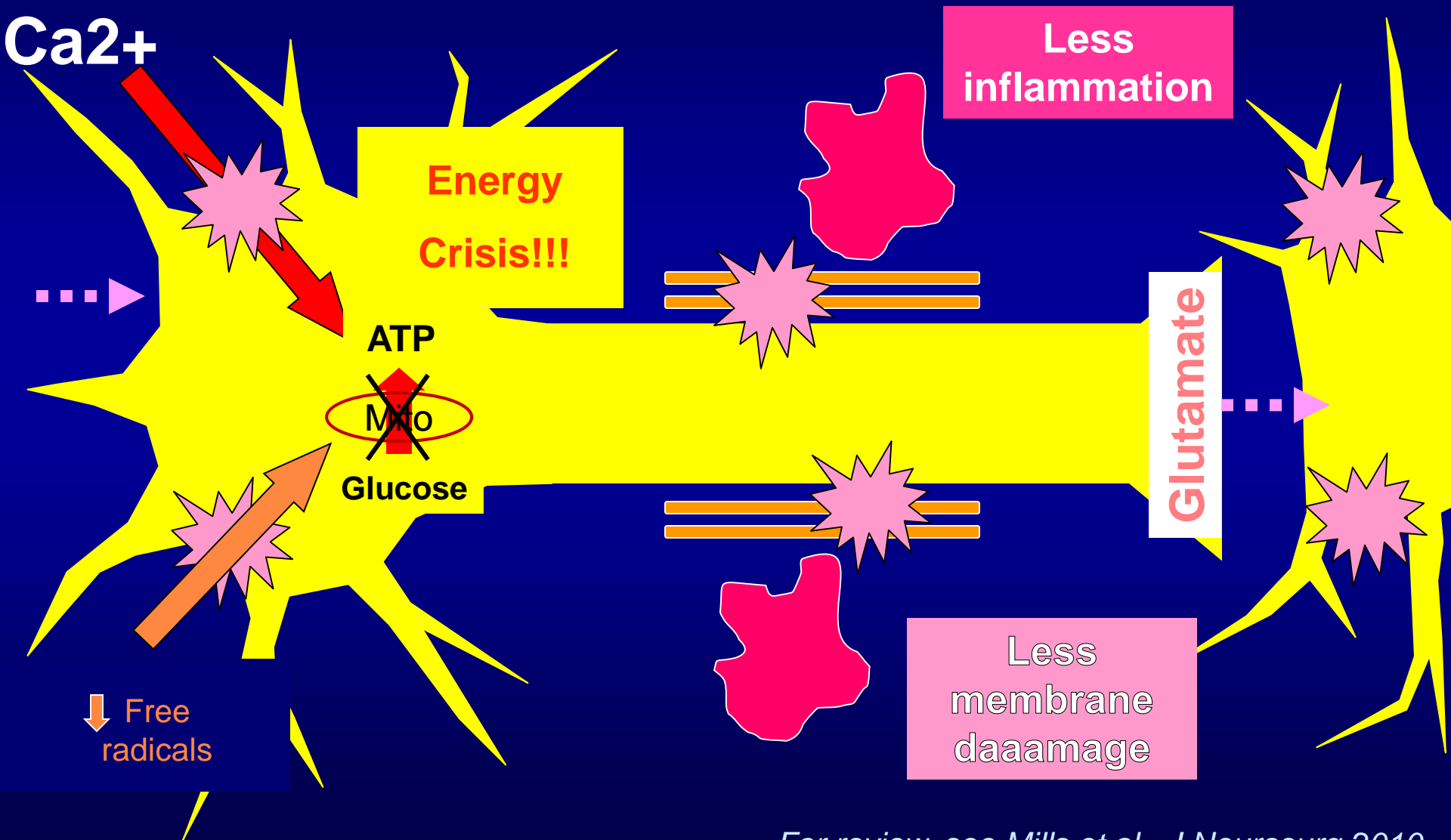
Osteopaths Hear That 22 Days on Water Usually End Fits.

LOS ANGELES, July 5.—Epilepsy may be cured by fasting, Dr. Hugh Conklin told the twenty-sixth annual convention of the American Osteopathic Association, now in session here. Epilepsy, according to Dr. Conklin, is caused by the improper functioning of certain glands in the bowels. By fasting for twenty-two days, taking only water, a cure may be effected, he said.

"Many people," added Dr. Conklin, "fast thirty days and are never afflicted by fits again. The longest fast which any patient ever took under my direction lasted sixty days. Out of thirty-seven tests in which children were used as patients, only two still are affected by the disease. The children all were under the age of 11 years, but we effect cures in older patients in from 50 to 60 per cent. of the cases we undertake."

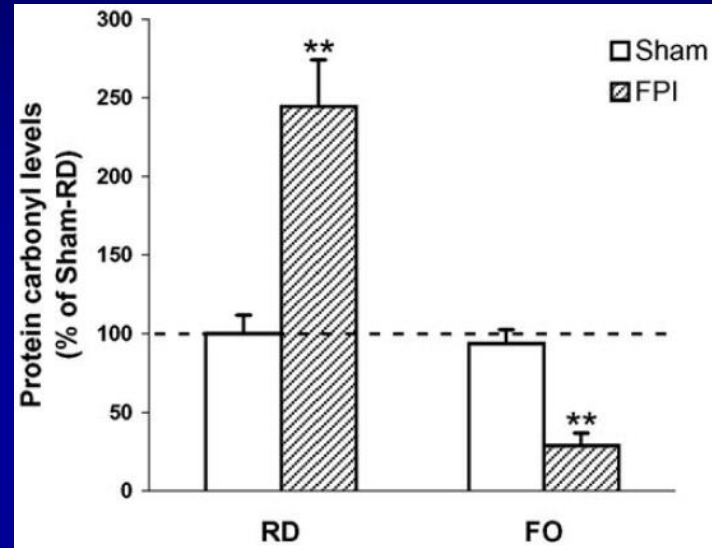
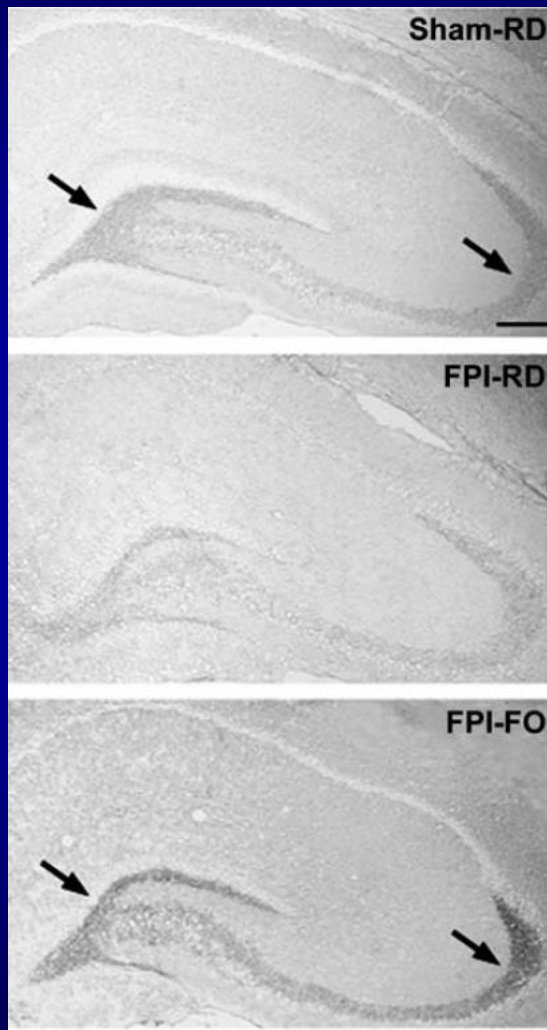
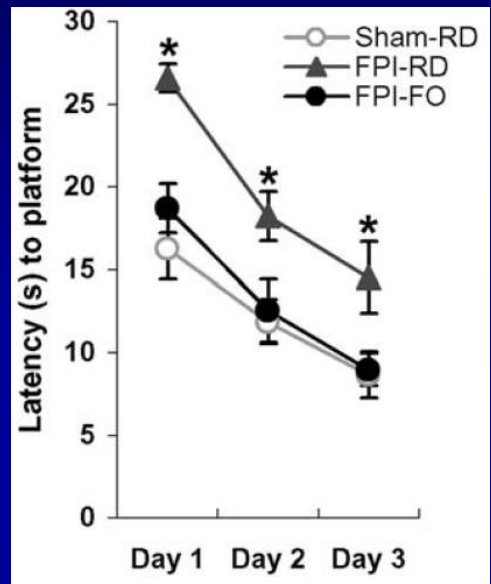
Neurometabolic Cascade of mTBI & DHA: Potential Mechanisms of Protection

Ca²⁺





Fish oil after TBI: Rats



Fish oil improved learning after TBI

Fish oil increased BDNF levels and reduced oxidative stress after TBI

Fish oil diet 4 weeks prior and 1 week after TBI

Wu A, et al., J Neurotrauma, 2004

Some Nutrients that Affect Cognition after Injury

Nutrient	Effects	Food sources
Omega-3 fatty acids (e.g. docosahexaenoic acid–DHA)	Improves cognition for expt TBI & expt Alzheimers ; reduces cognitive decline in human aging	Fish, flaxseed, krill, kiwi fruit, walnuts
Ketones	Improves cognition for expt TBI ; reduces seizures in human epilepsy	Ketogenic diet/supplements; Atkins diet
Lactate, pyruvate	Improves cognition for expt TBI	Intravenous infusion
Curcumin	Improves cognition for expt TBI & expt Alzheimers	Turmeric (curry spice)
Saturated fat	Worsens cognition for expt TBI & human aging	Butter, suet, lard, coconut oil, cottonseed oil, dairy, meat
Vitamin E	Improves cognition for expt TBI ; reduces cognitive decline in human aging	Asparagus, avocado, nuts, peanuts, olives, spinach
Choline	Improves cognition for expt seizures ; may be related to human cognitive function	Egg yolks, chicken, veal, turkey, liver, lettuce

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(PAC12)
Chrisman

U Rochester
(University)
Bazarian

CSC enrollment as of 9/15/15

• Baseline

- Total = 975
 - Unique = 14,120
 - Repeat = 1,855
 - ≈50% Cadets

• Concussions

- Total = 399
 - <6 hr = 235
 - 24-48 hr = 336
 - Asymptomatic = 287
 - Return to Play = 287
 - 6 month = 110



20,953,668 data points

Why Biology is Important to YOU... and your athletes

1. Acute pathophysiology may be visualized using advanced imaging.
2. Although repeat concussions rarely cause second impact syndrome, concussed athletes are more vulnerable to a second injury.
3. Premature activity may be bad, but so may complete inactivity; moderate activity can be beneficial.
4. Understanding pathophysiology may lead to mechanism based therapies. Clinical and translational studies are needed!