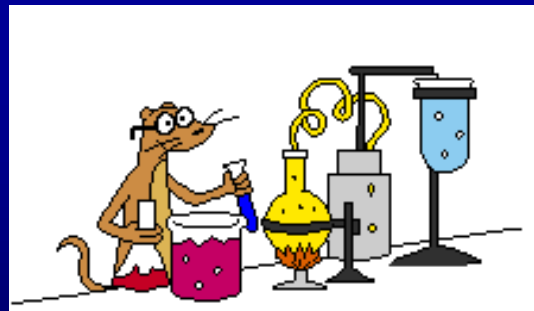


The New Neurometabolic Cascade

Pathophysiology & Neurobiology of mTBI



November 6th, 2015
Austin, TX

35min

National Academy of Neuropsychology
Annual Meeting

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, 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***

Basic Scientists

David Hovda, Ph.D.
Me
Fernando Gomez-Pinilla, Ph.D.
Neil Harris, Ph.D.
Mayumi Prins, Ph.D.
Raman Sankar, M.D., Ph.D.
Rick Staba, Ph.D.

Residents/Fellows

Adam Darby, M.D.
Josh Kamins, M.D.
Anish Patel, M.D.
Doug Polster, Ph.D.
Raj Rajaraman, M.D.

Clinical Investigators

Robert Asarnow, Ph.D.
Talin Babikian, Ph.D.
Meeryo Choe, M.D.
John DiFiori, M.D.
Jason Lerner, M.D.
Andy Madikians, M.D.
Joyce Matsumoto, M.D.
David McArthur, Ph.D., M.P.H.

Program Manager
Constance Johnson

Lab Assistants

Yan Cai, M.S.
Sima Ghavim

Research Assistants

Alma Martinez
Briana Meyer
Sonal Singh
Max Zeiger

Nurse Practitioners

Kristina Murata
Sue Yudovin

Graduate Students

Daya Alexander
Chaitali Biswas, Ph.D.

Post-docs

Emily Dennis, Ph.D.
Tiffany Greco, Ph.D.
Annie Hoffman Ph.D.

Students

Isaac Gadinsky
Akash Patel

Medical Student

Kyla Sherwood

www.birc.ucla.edu
cgiza@mednet.ucla.edu
Twitter: @griz1



Mattel Children's Hospital **UCLA**





What is a Concussion?

“A Brain Movement Injury”

- A biological process affecting the brain induced by physical forces

- Symptoms start quickly
- Don't have to be knocked out
- Gets better with time if you don't get whacked again
- CAT scans are normal

Outline

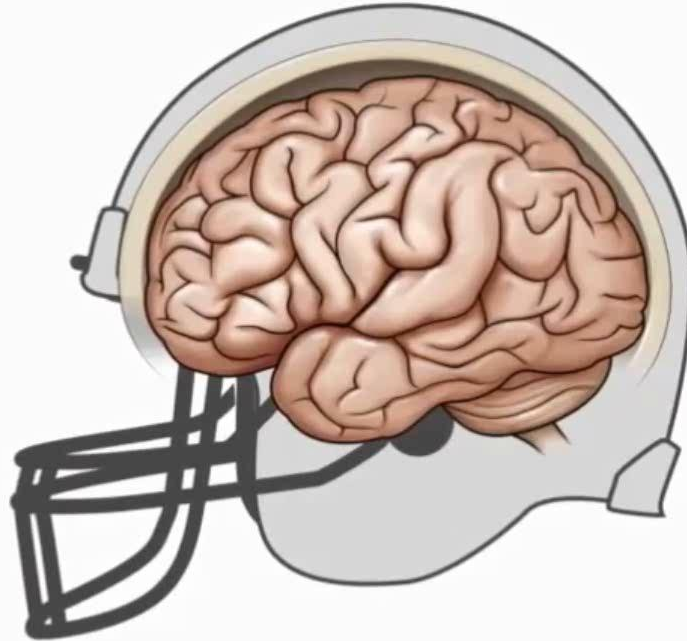
- I. **Basic Pathophysiology**
- II. Symptoms and Time Course
- III. Advanced Neuroimaging to Detect Concussion
- IV. Post-Concussive Vulnerability
 - A. Repeat Concussions
 - B. Second Impact Syndrome
 - C. Persistent Symptoms



Gray Matters Video

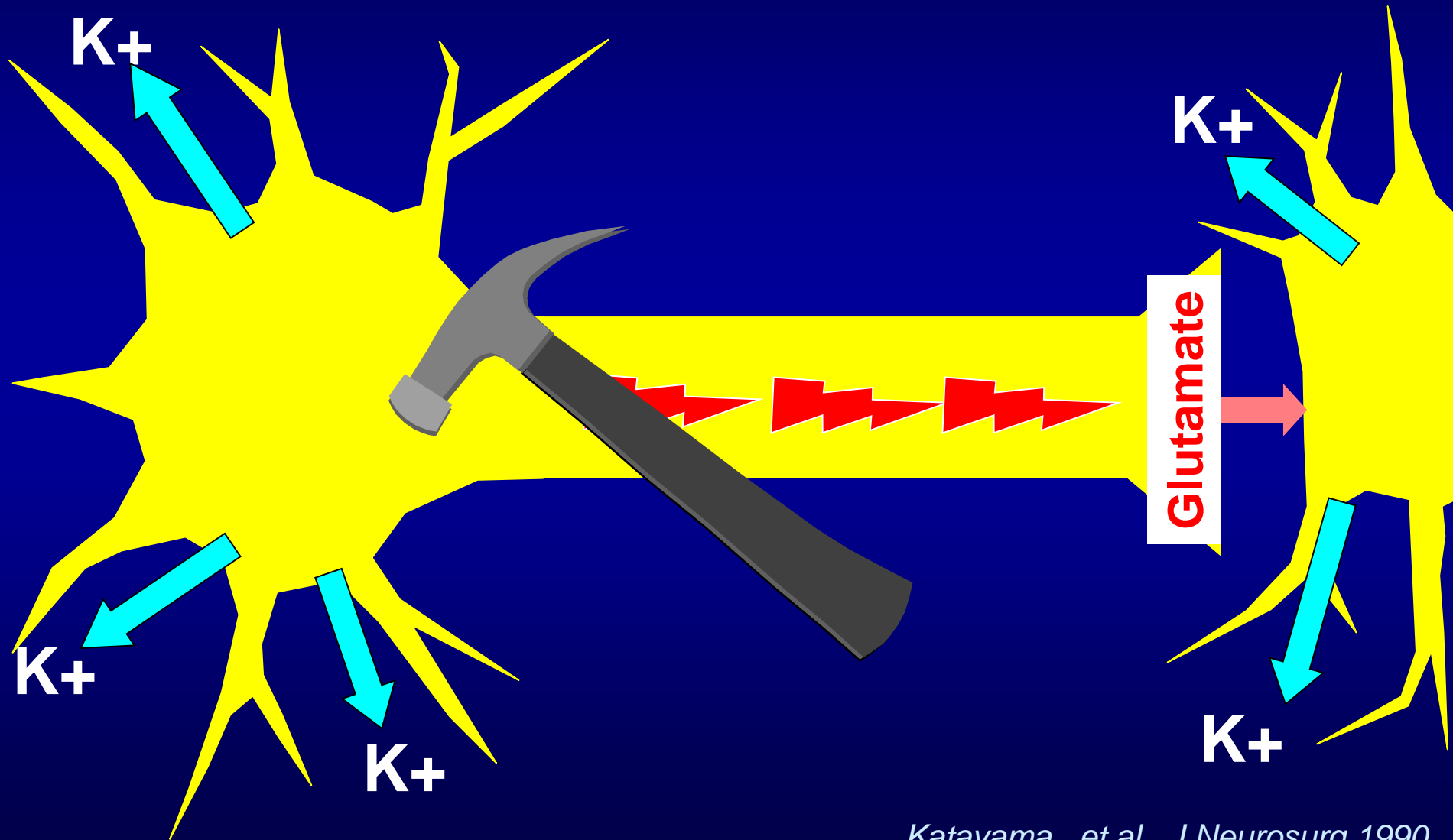
Understanding concussion on the cellular level

Impact



Concu

Neurometabolic Cascade: Potassium & Glutamate Flux



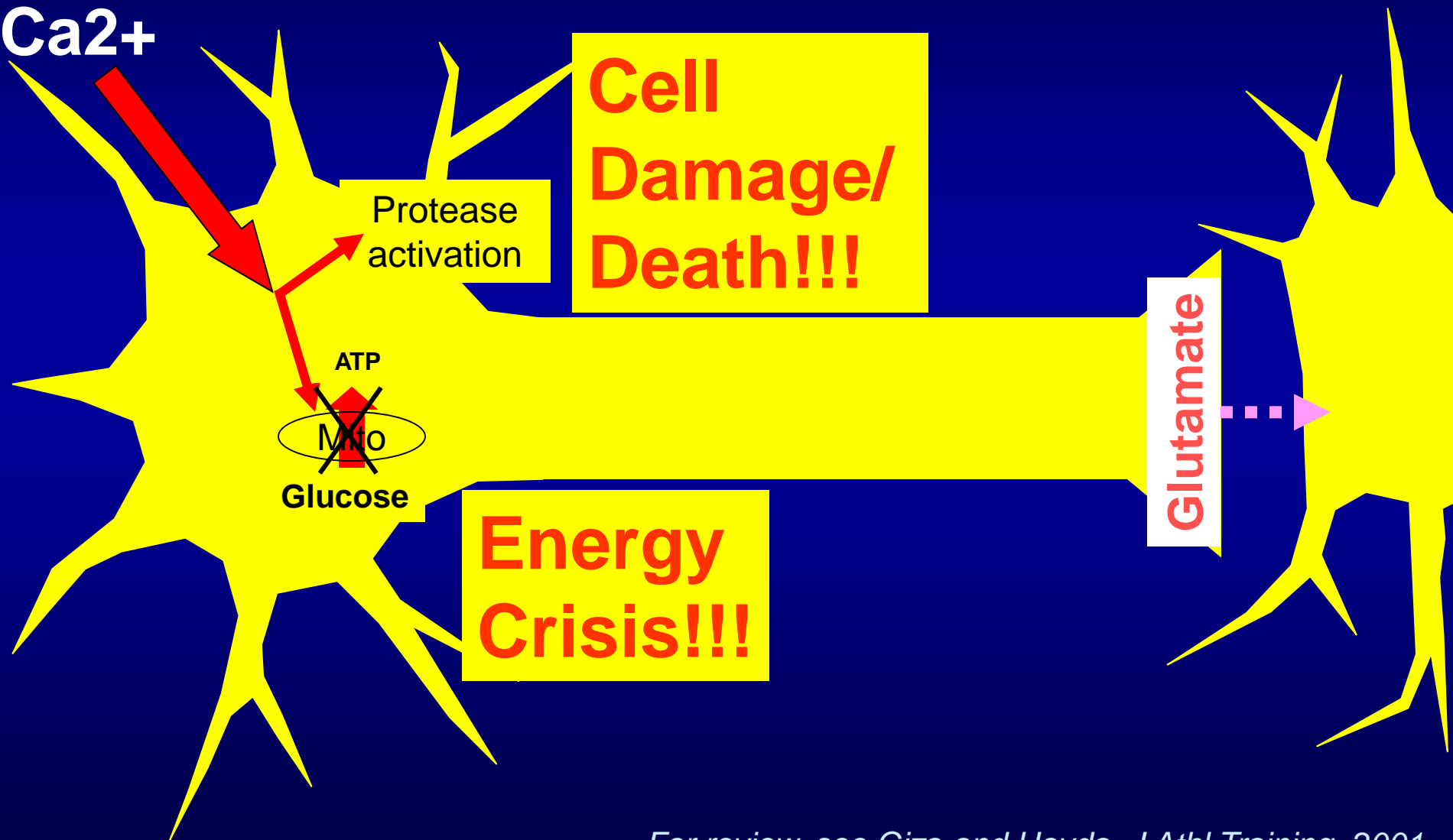
Neurometabolic Cascade: Hyperglycolysis and Energy Crisis



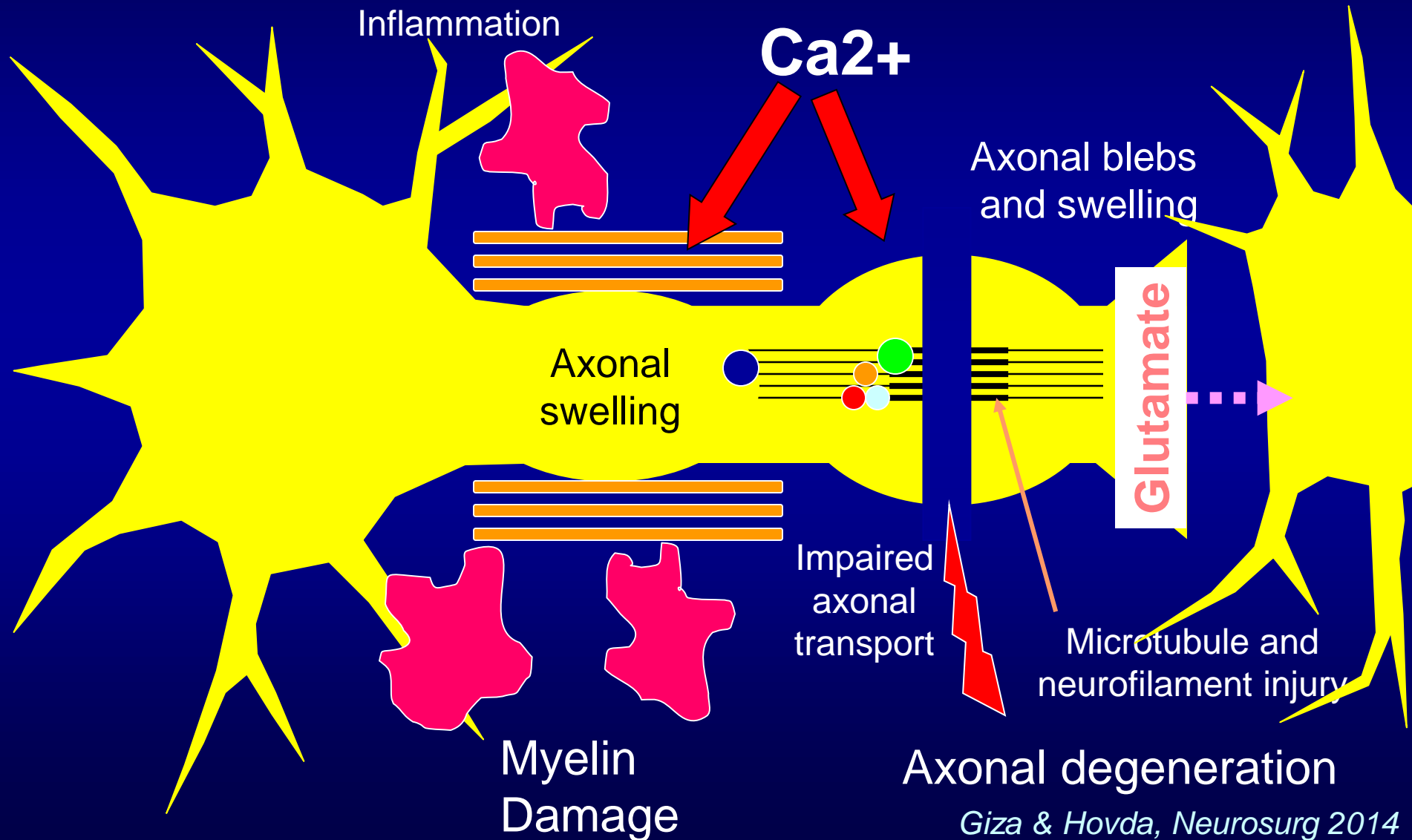
Neurometabolic Cascade:

Calcium, mitochondrial dysfunction and death

Ca^{2+}



Neurometabolic Cascade: Axonal Injury



Outline

- I. Basic Pathophysiology
- II. Symptoms and Time Course**
- III. Advanced Neuroimaging to Detect Concussion
- IV. Post-Concussive Vulnerability
 - A. Repeat Concussions
 - B. Second Impact Syndrome
 - C. Persistent Symptoms

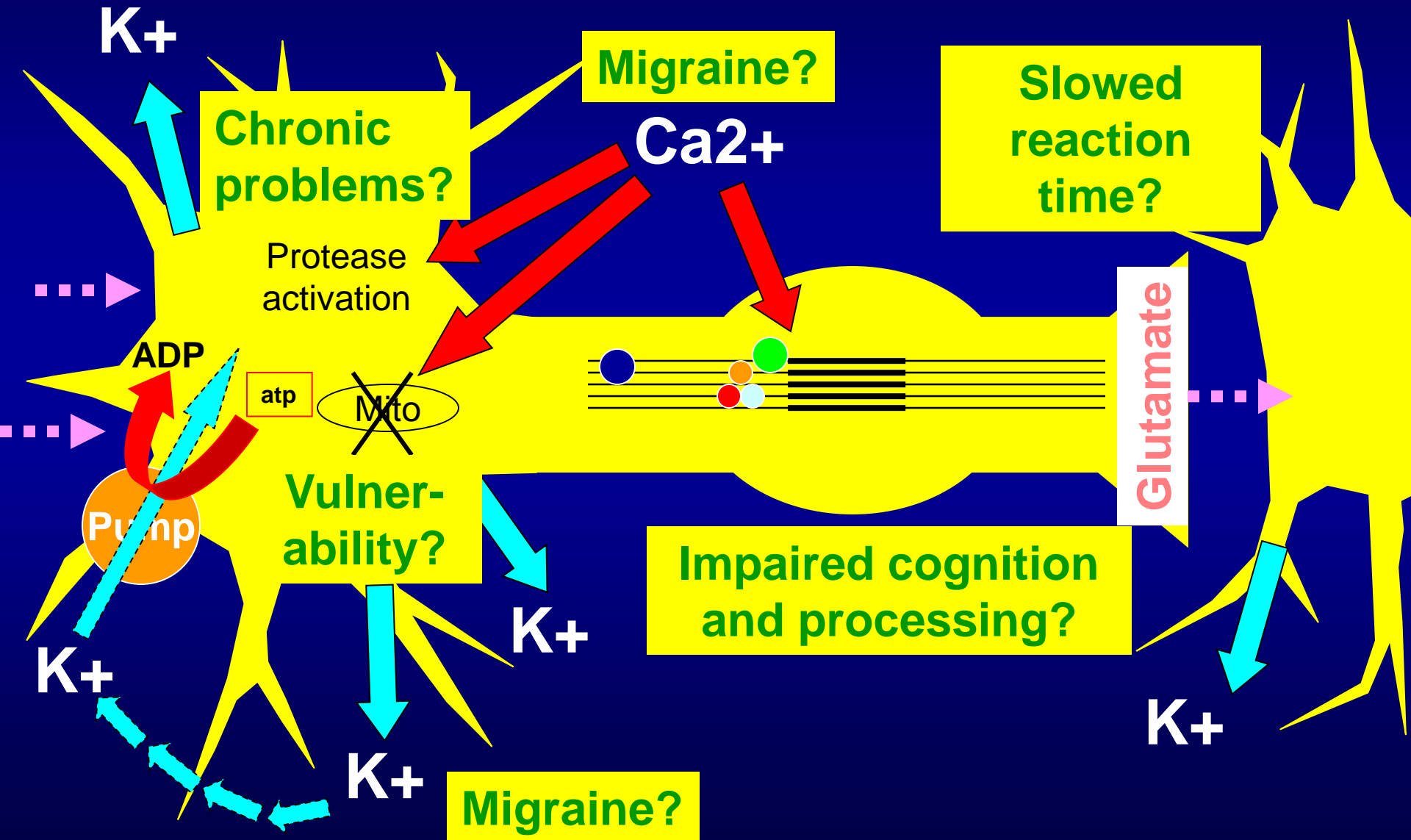


Signs/Symptoms of Concussion

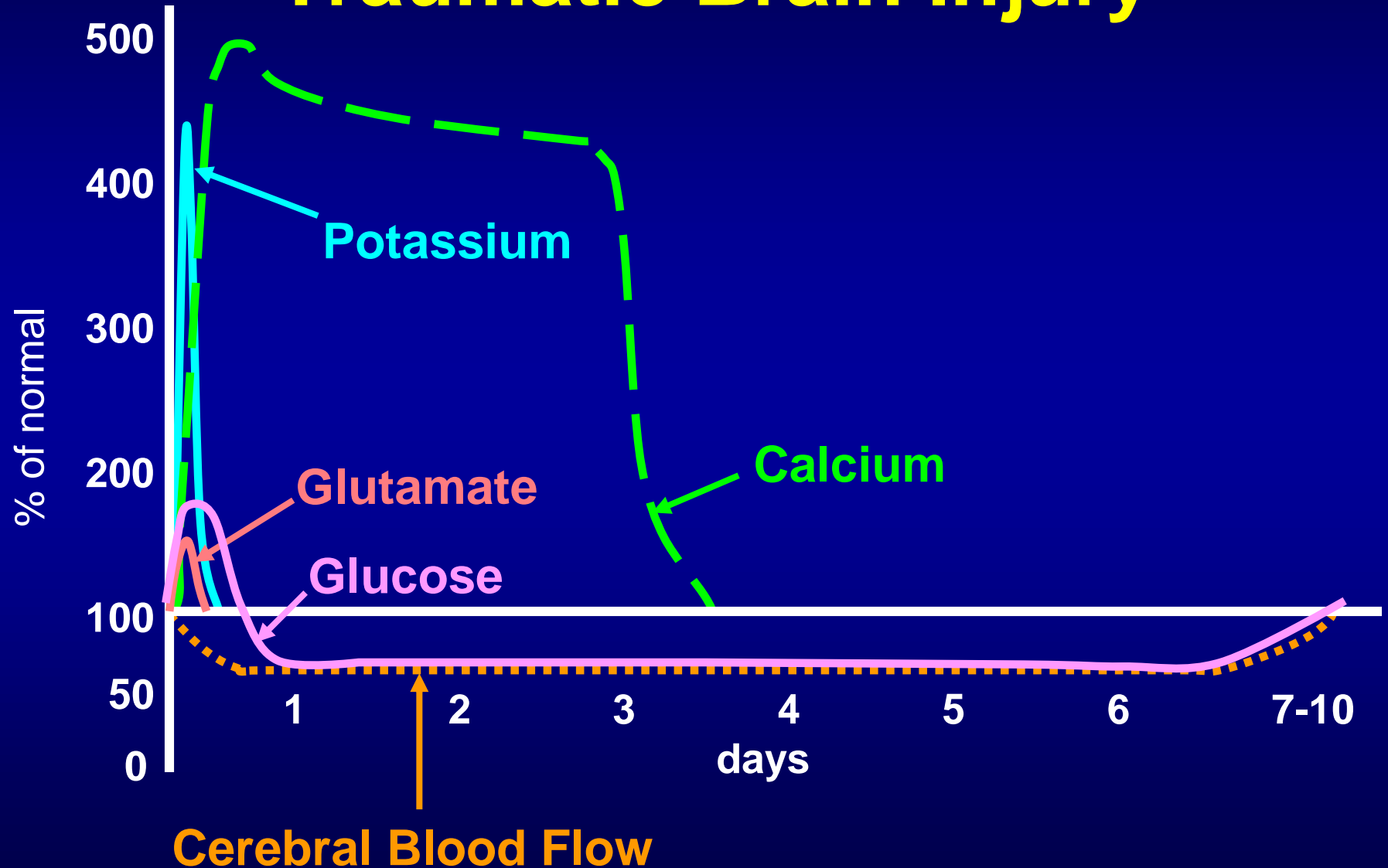
- Headache
- Dizziness
- Nausea and Vomiting
- Vacant stare (looks 'out of it')
- Slow to talk or do things
- Confusion and inattention
- Disorientation
- Slurred or incoherent speech
- Loss of coordination
- Emotions out of proportion
- Memory loss (amnesia)
- Any period of unconsciousness



Neurometabolic Cascade of mTBI: Pathophysiology Meets Symptoms



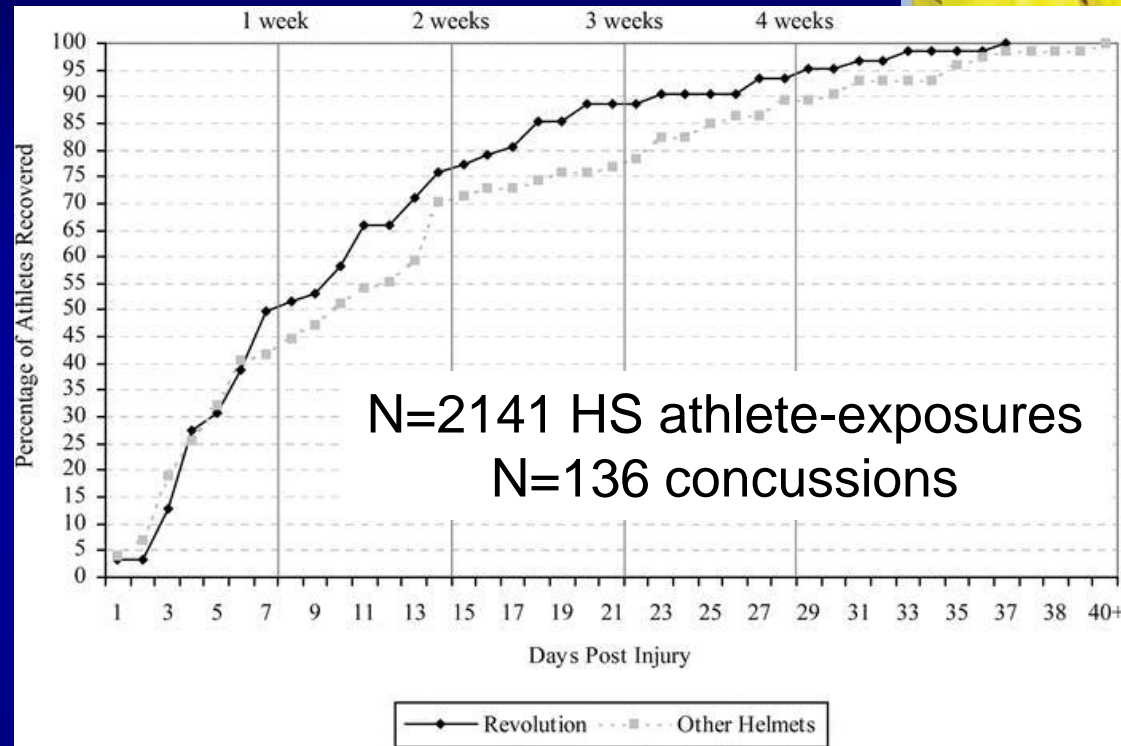
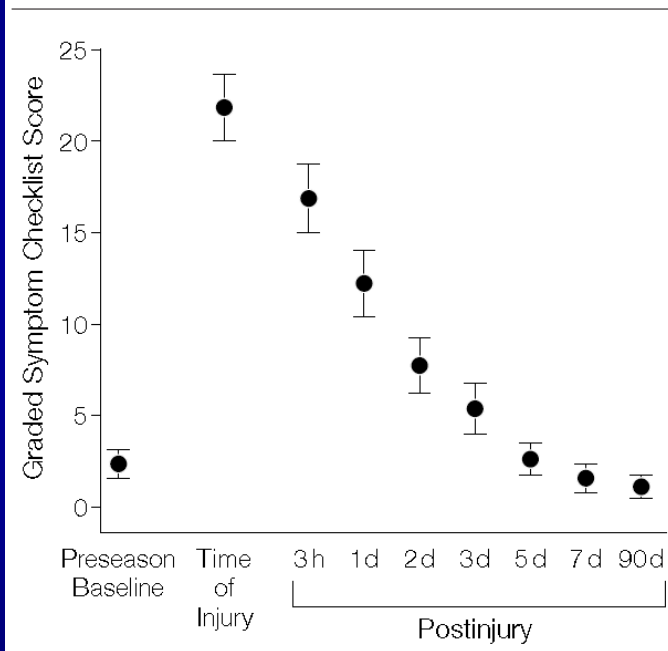
Neurometabolic Cascade Following Traumatic Brain Injury



Expect to Get Better



Figure 2. Mean Reported Graded Symptom Checklist Total Scores for Players With Concussion (n=196) Across Repeated Assessments

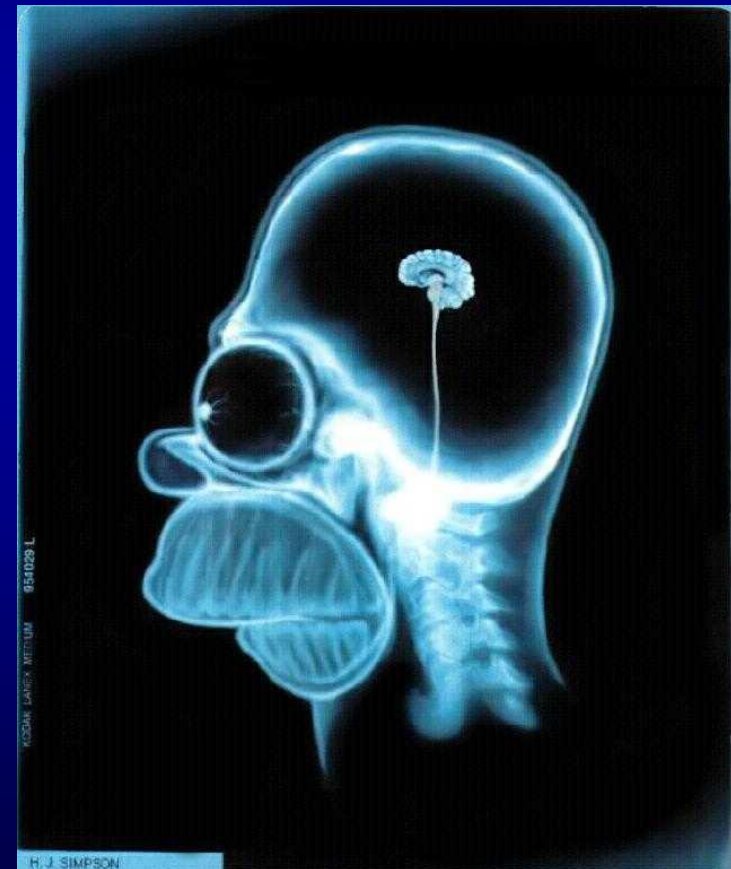


90-95% of college athletes with concussions get better in 7-10 days.

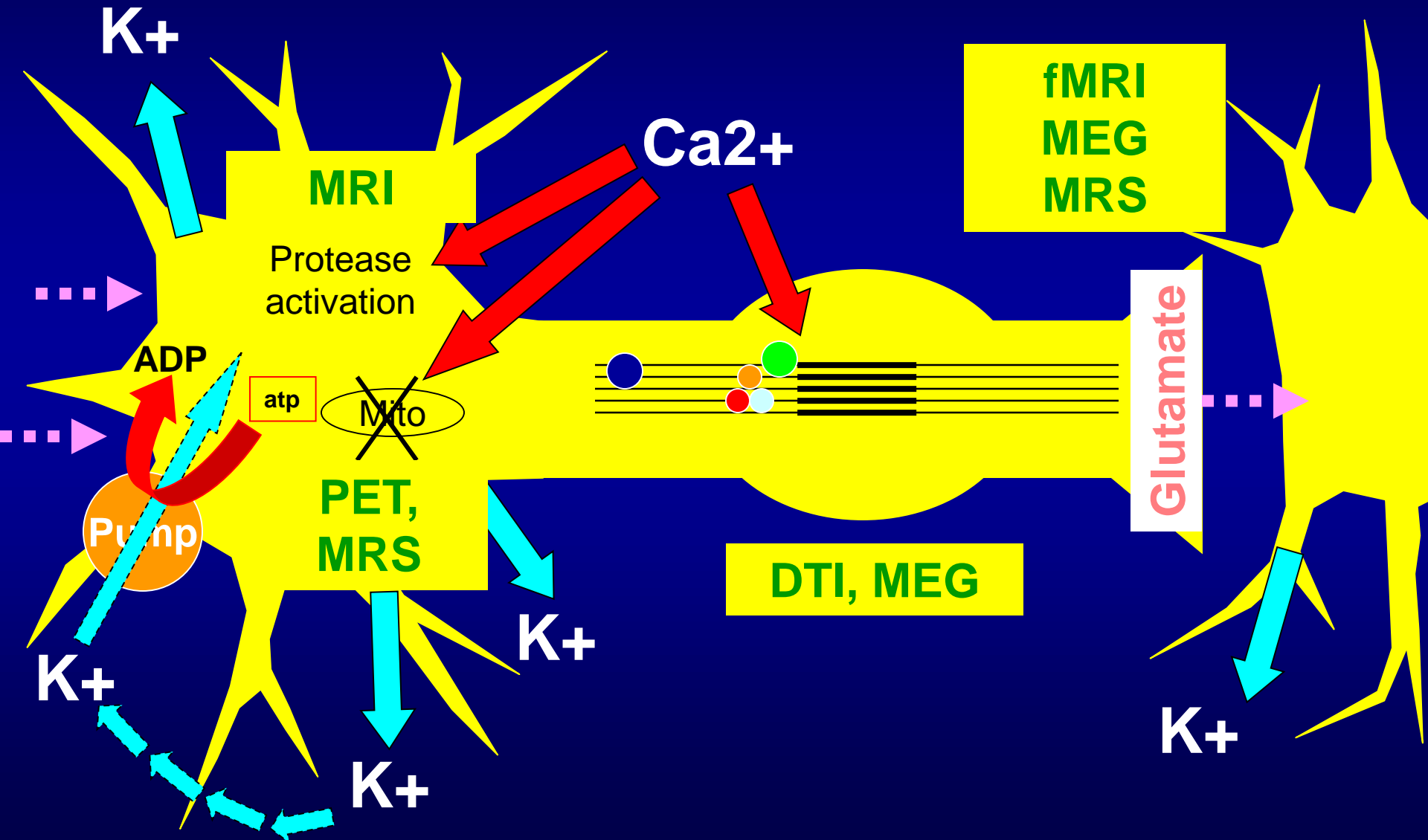
70-75% of high school athletes with concussions get better in 14 days; 80-85% in 21 days.

Outline

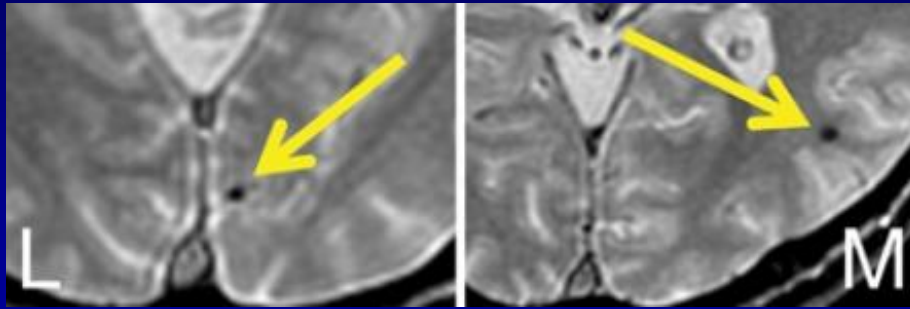
- I. Basic Pathophysiology
- II. Symptoms and Time Course
- III. Advanced Neuroimaging to Detect Concussion**
- IV. Post-Concussive Vulnerability
 - A. Repeat Concussions
 - B. Second Impact Syndrome
 - C. Persistent Symptoms



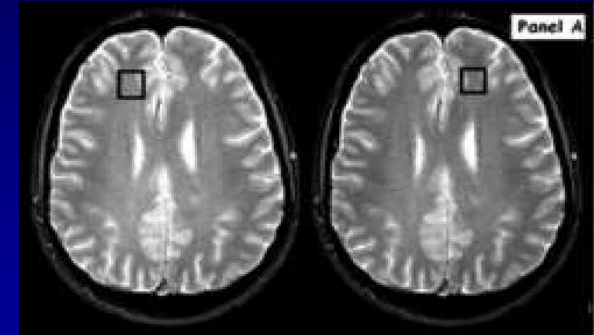
Seeing is Believing: Imaging Early mTBI Pathobiology



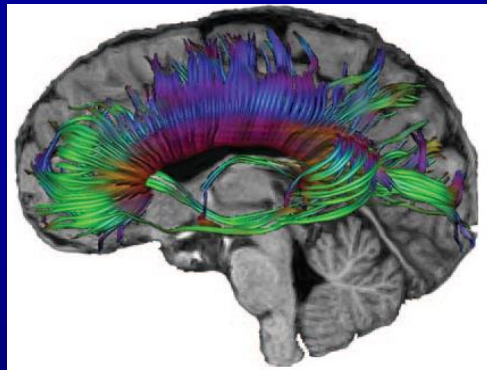
Imaging mTBI/Concussion Biomarkers



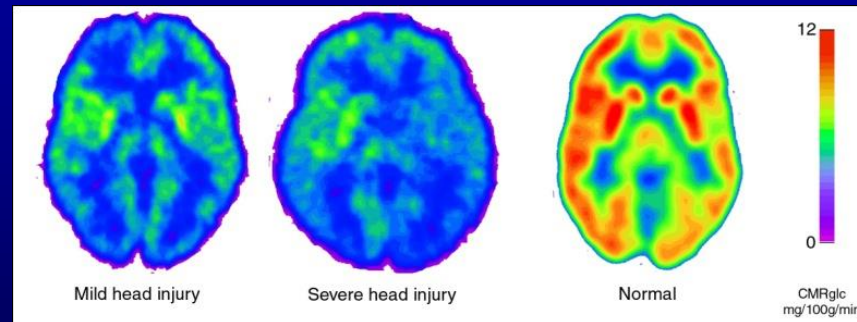
Yuh et al., Ann Neurol 2012



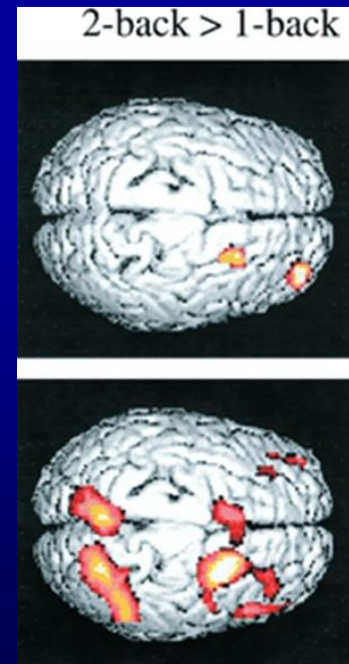
Vagnozzi et al., Neurosurg 2008



Wilde et al., Neurol 2008



Bergsneider et al., J Neurotrauma 2000



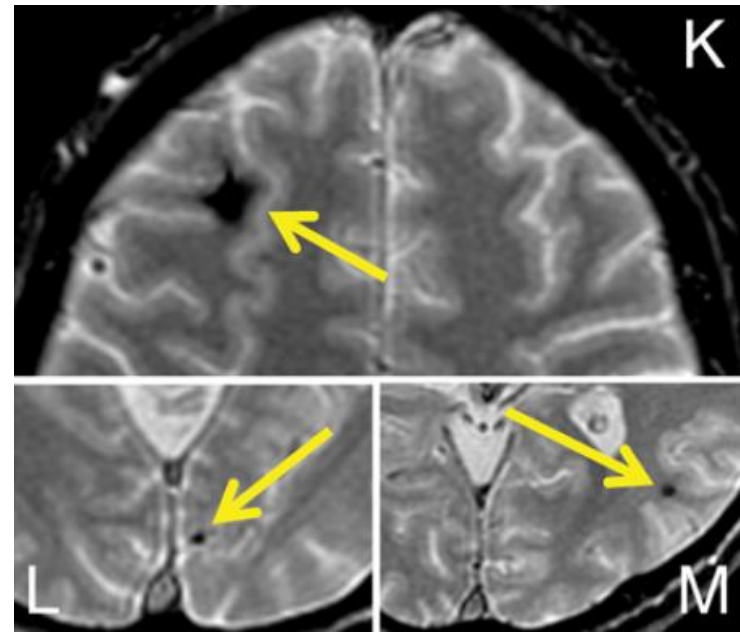
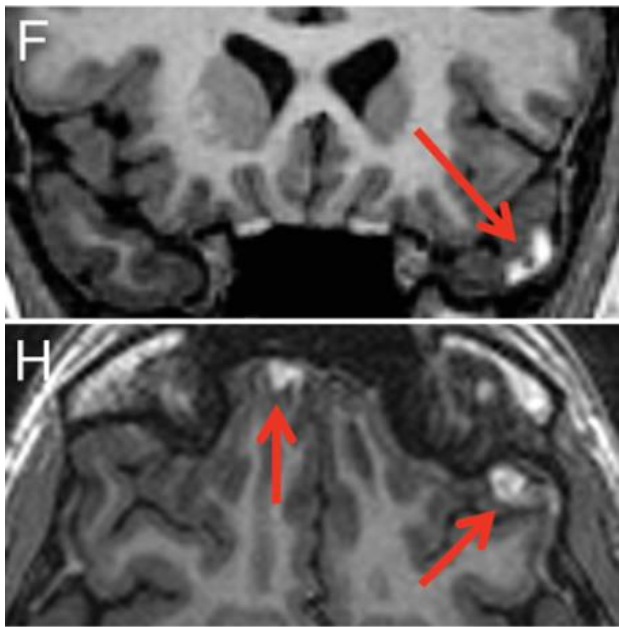
McAllister et al., Neurol 1999

Imaging Early mTBI: MRI/SWI

N=135

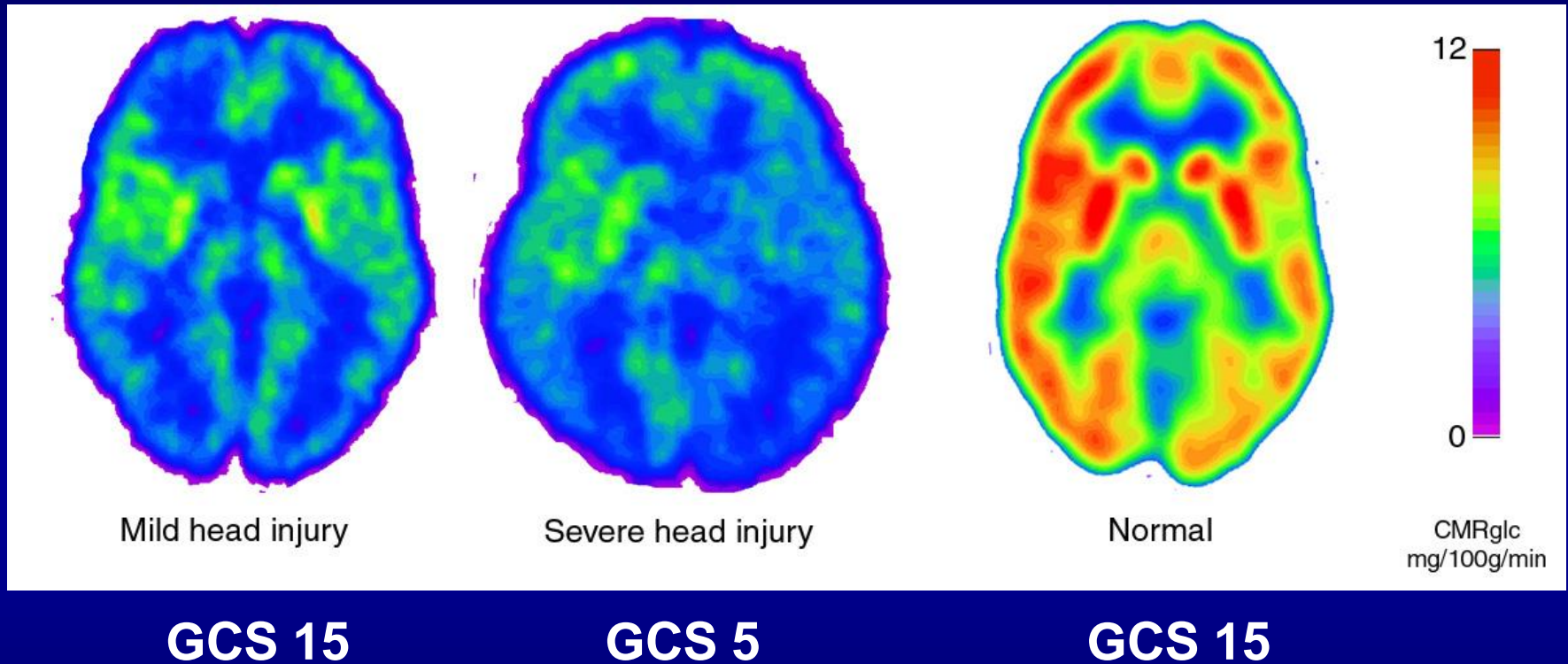
Prospective mTBI ED cohort, 3 centers

Time post-injury=12 days



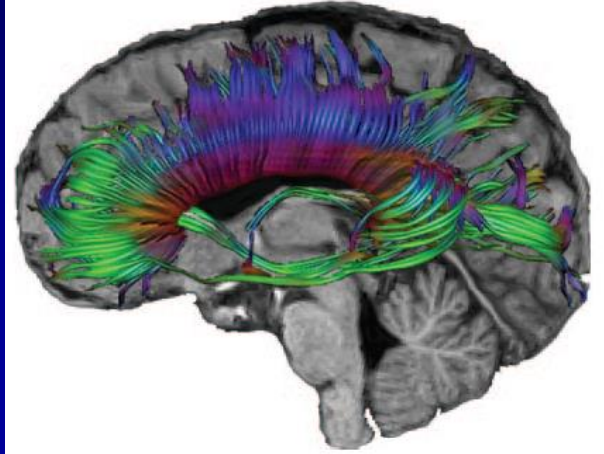
≥ 1 brain contusion or ≥ 4 hemorrhagic foci on early MRI were associated with worse 3 month outcome

Imaging Early mTBI: PET



Glucose metabolism may show profound abnormalities in humans, even after mild TBI.

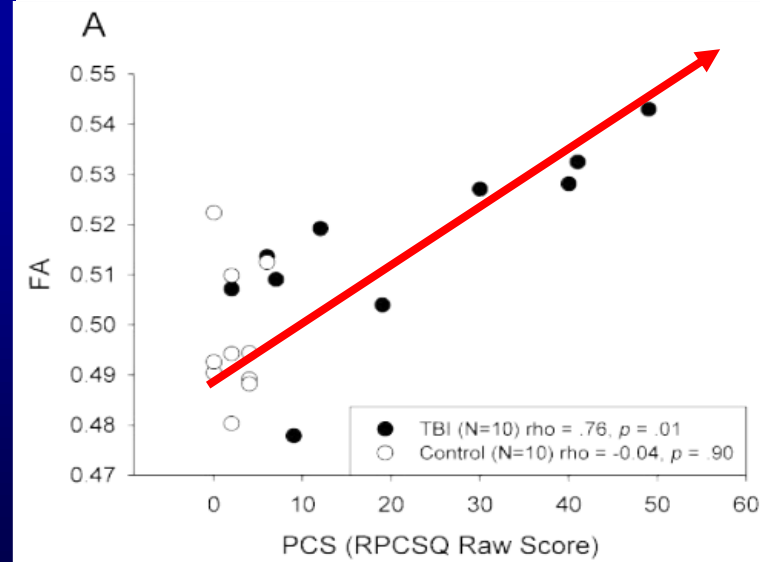
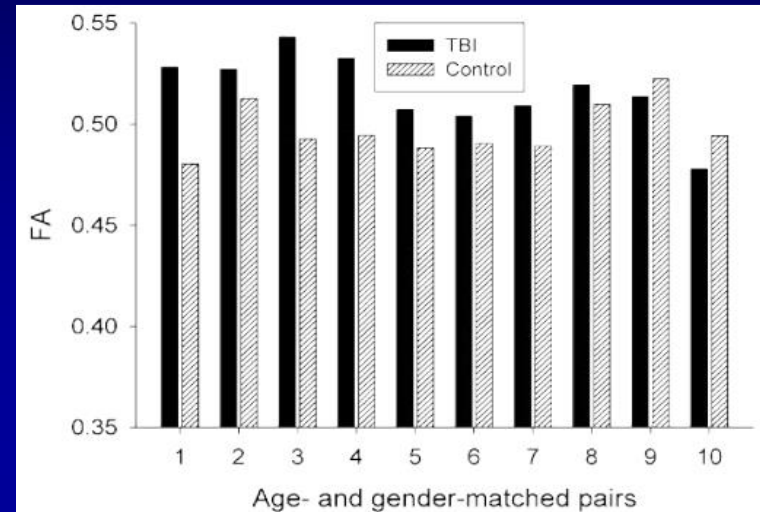
Imaging Early mTBI: Symptoms & DTI



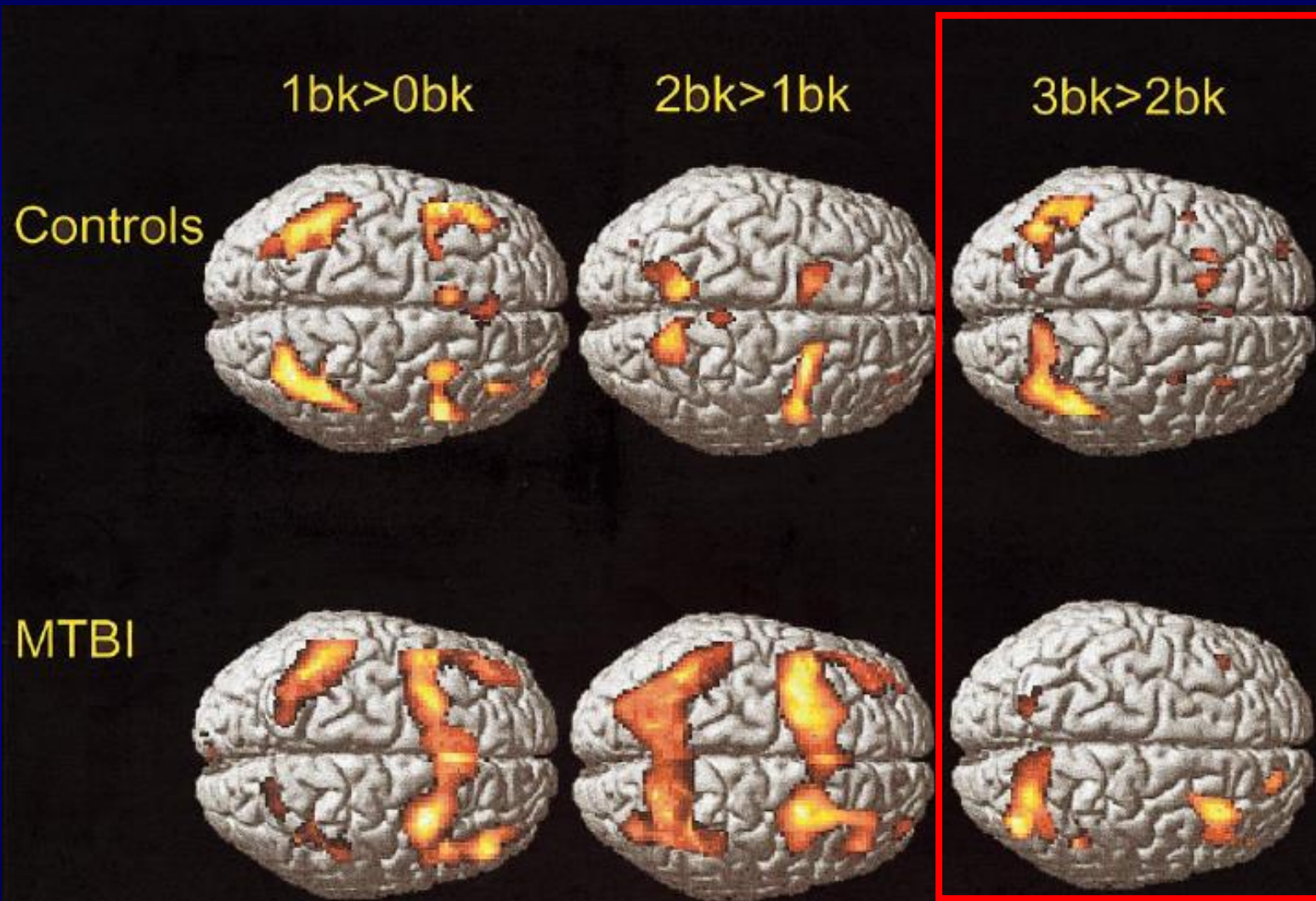
In adolescents with mTBI, DTI of the CC performed within 6 days showed increased FA and decreased diffusivity.

These abnormalities in DTI correlated well with post-concussion symptoms.

But results from many different DTI studies have shown a wide range of results.



Impaired Neurotransmission: fMRI



Mild TBI results in abnormal task-related BOLD activation patterns.

Outline

- I. Basic Pathophysiology
- II. Symptoms and Time Course
- III. Advanced Neuroimaging to Detect Concussion
- IV. Post-Concussive Vulnerability**
 - A. Repeat Concussions**
 - B. Second Impact Syndrome
 - C. Persistent Symptoms

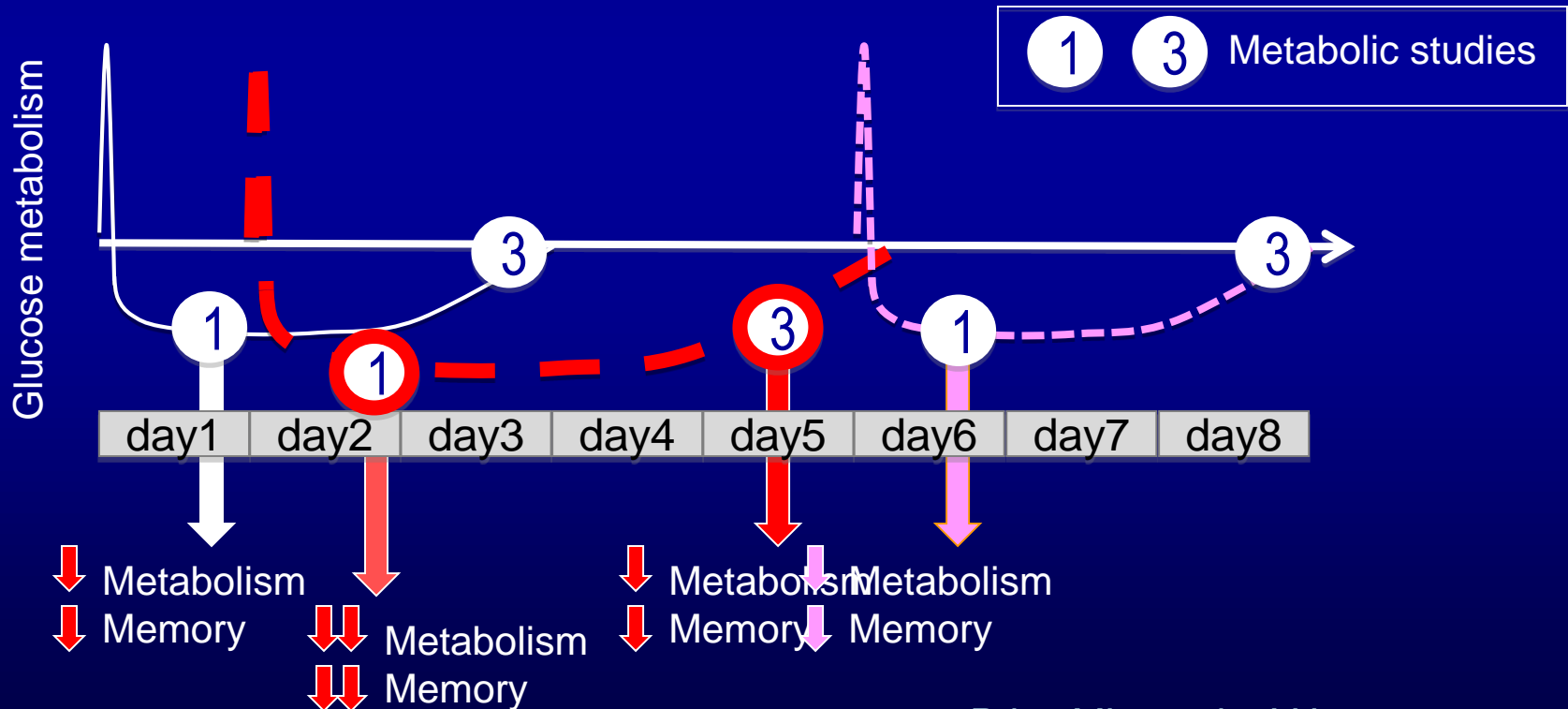


Vulnerability: Metabolism & Timing

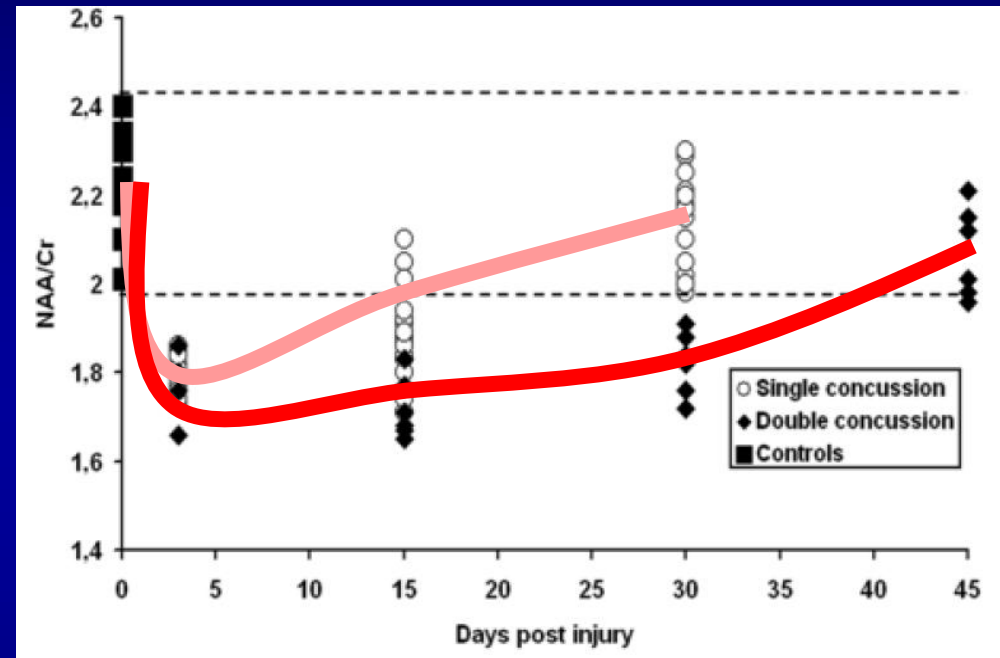
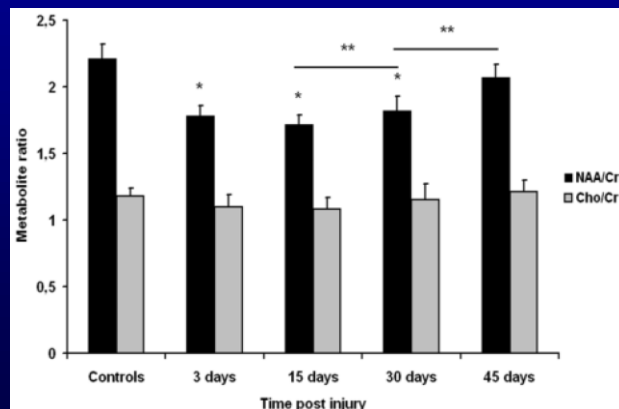
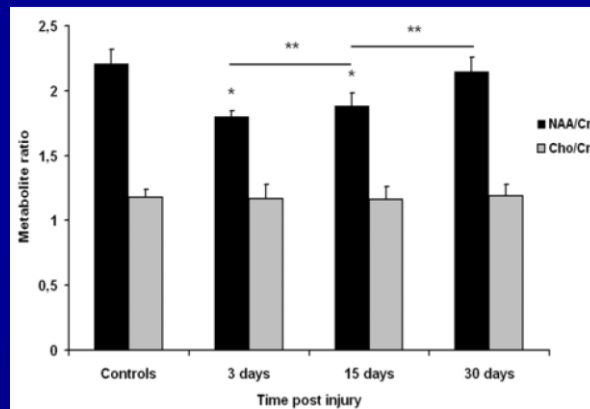
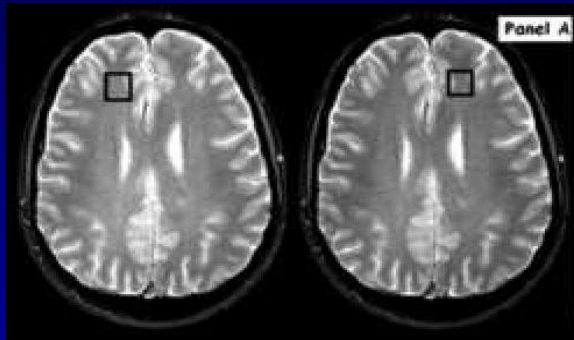


**2nd concussion during
metabolic impairment results
in worse metabolic disruption
and cognition**

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

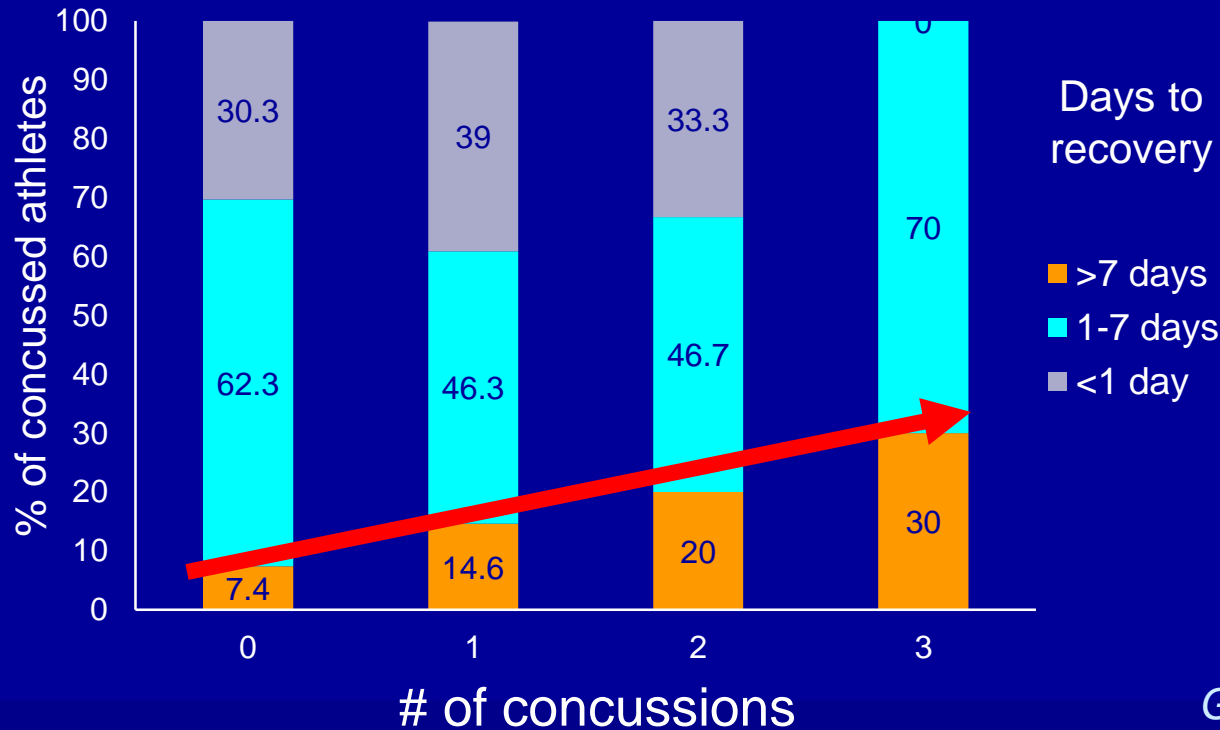
1. Brain energy crisis
2. Slow reflexes and reaction time
3. Slower thinking
4. Poor playing style
5. Genetic risk



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.

Outline

- I. Basic Pathophysiology
- II. Symptoms and Time Course
- III. Advanced Neuroimaging to Detect Concussion
- IV. Post-Concussive Vulnerability**
 - A. Repeat Concussions
 - B. Second Impact Syndrome**
 - C. Persistent Symptoms



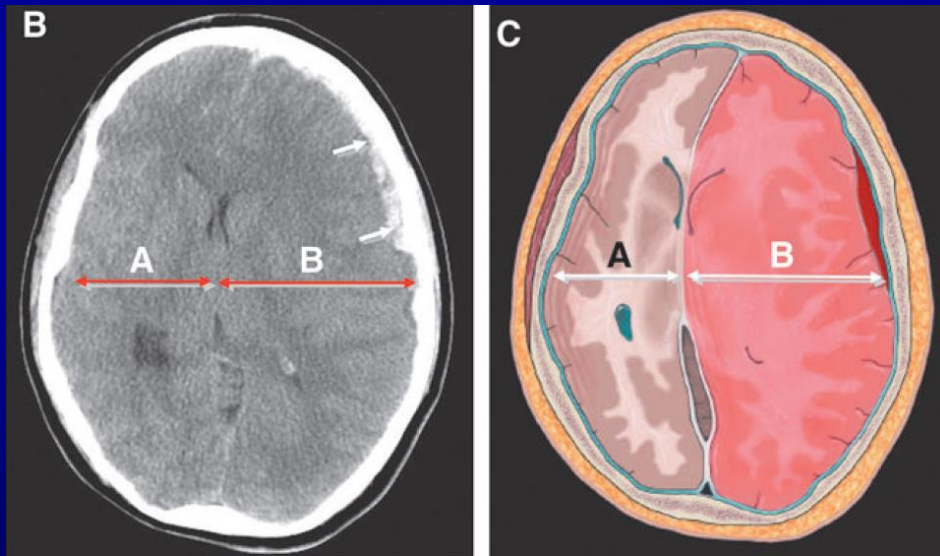
<http://abcnews.go.com/Health/impact-syndrome-high-school-football-player-normal-ct/story?id=18102534>

Vulnerability: '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

McCorry & 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

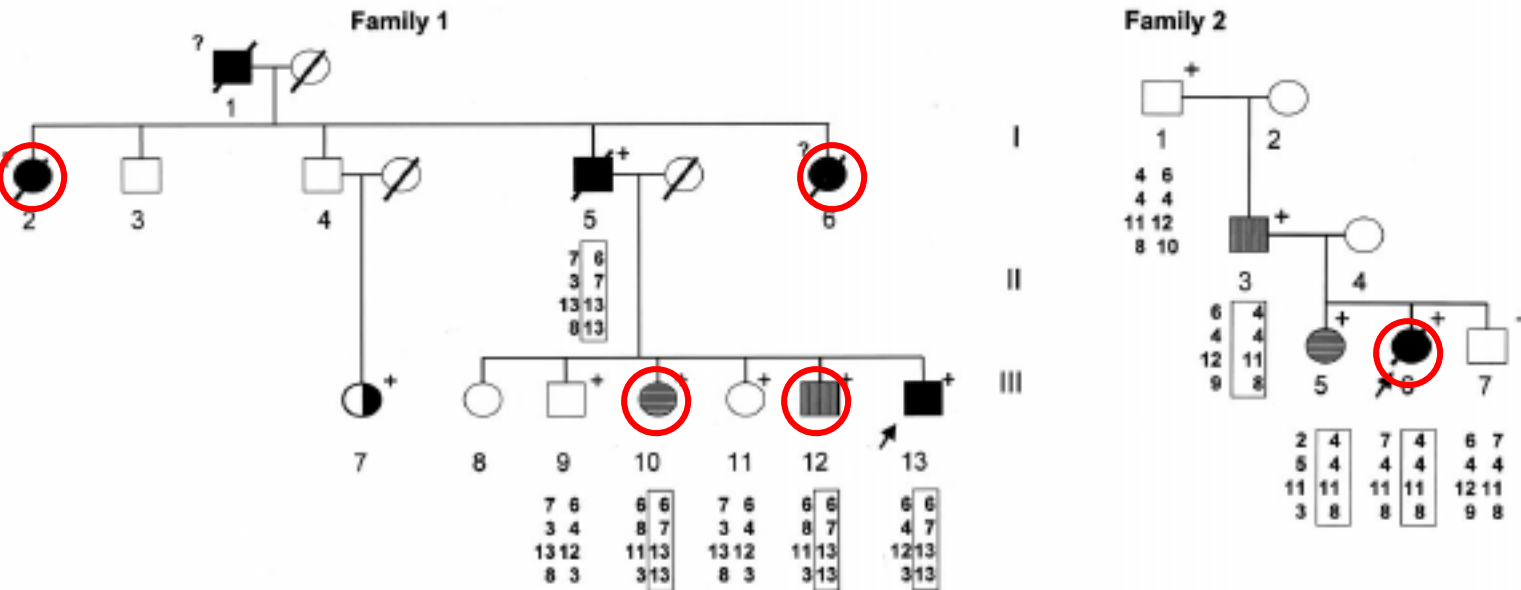
Delayed Cerebral Edema and Fatal Coma after Minor Head Trauma: Role of the CACNA1A Calcium Channel Subunit Gene and Relationship with Familial Hemiplegic Migraine

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

Seth Love, MBBCh, PhD, FRCP, FRCPath,⁶ Arn M.J.M. van den Maagdenberg, PhD,² Joost Haan, MD, PhD,^{1,7}

Rune R. Frants, PhD,² and Michel D. Ferrari, MD, PhD¹

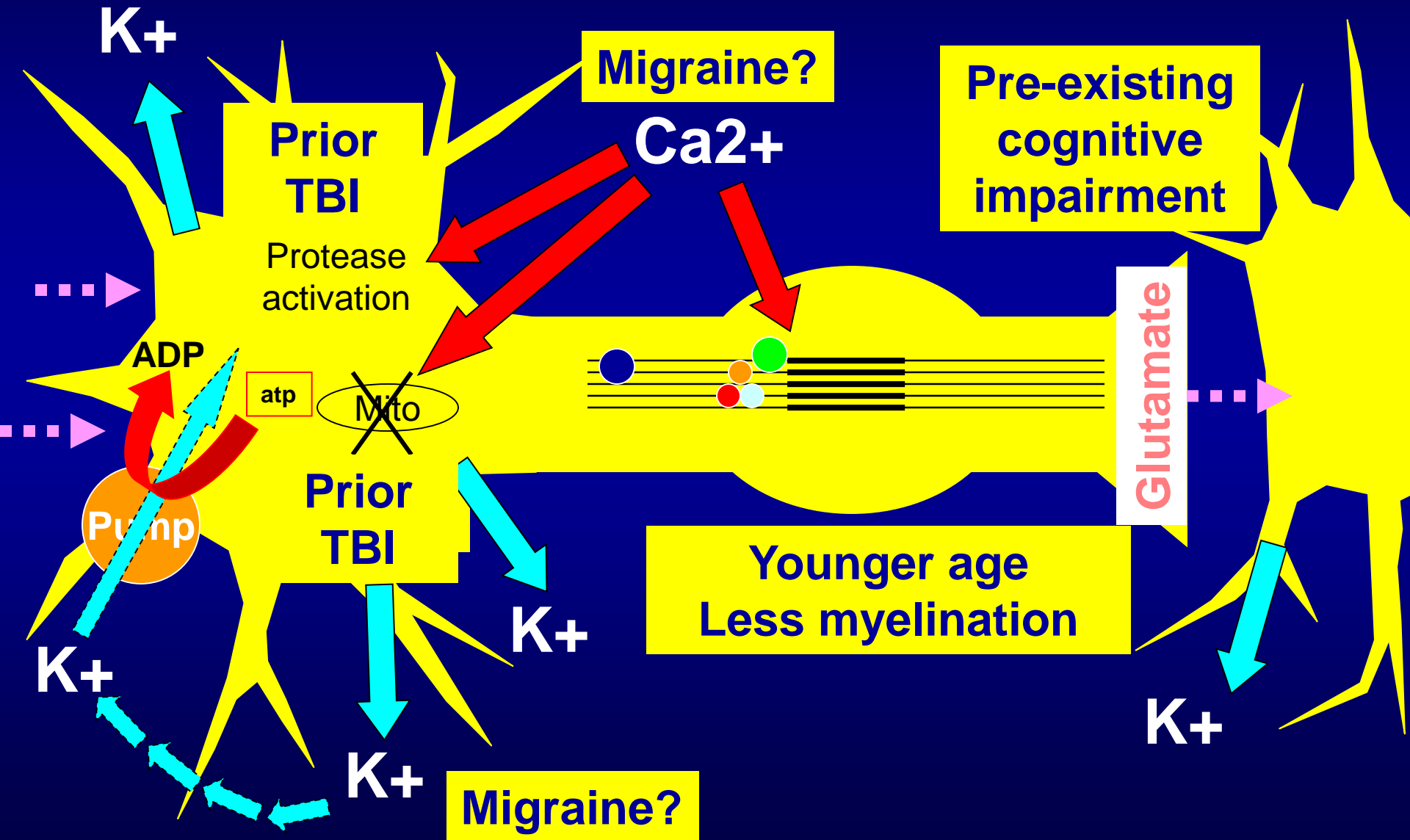


Outline

- I. Basic Pathophysiology
- II. Symptoms and Time Course
- III. Advanced Neuroimaging to Detect Concussion
- IV. Post-Concussive Vulnerability**
 - A. Repeat Concussions
 - B. Second Impact Syndrome
 - C. Persistent Symptoms**



Neurometabolic Cascade of mTBI: Pathophysiology Meets Risk Factors



Risk Factors for Prolonged Recovery

Prior concussion



Younger age

Headache



Fogginess



On-field AMS



Prior headaches



Learning disability / ADHD

Dizziness



Why Biology is Important

-
1. Acute pathophysiology is related to early symptoms and generally recovers over 7-14 days
2. Advances in neuroimaging support basic science understanding of concussion neurobiology. However, advanced MRI remains a research tool
3. Concussed athletes are more vulnerable to a second injury
4. Repeat concussions rarely cause second impact syndrome
5. Acute and subacute pathobiology may also be related to vulnerability to more persistent symptoms and development of post-concussion syndrome

Reaction time is Important

