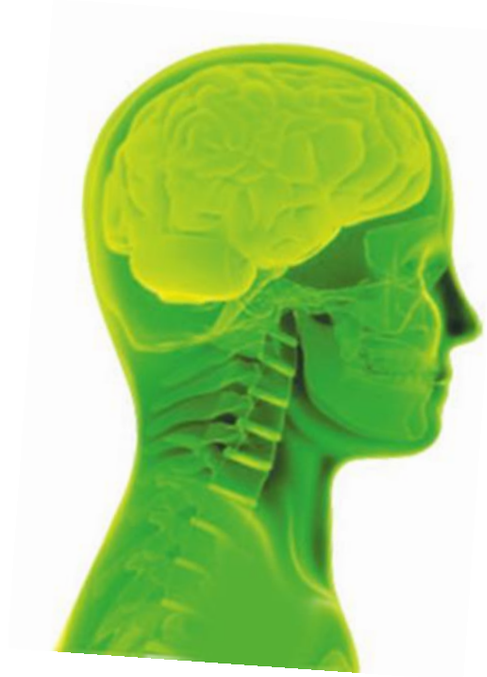
Pathophysiologic Insights and Implications for Return to Play Following TBI



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Sports Related Head Trauma Conference, WCMC, Thursday, June 5, 2014

Some slides adapted from presentations by Baxter Allen MD, Matthew McCarthy, MD and Jamshid Ghajar MD, PhD

Weill Cornell Medical College

NewYork-Presbyterian
Phyllis and David Komansky Center for Children's Health

I have no conflicts or disclosures

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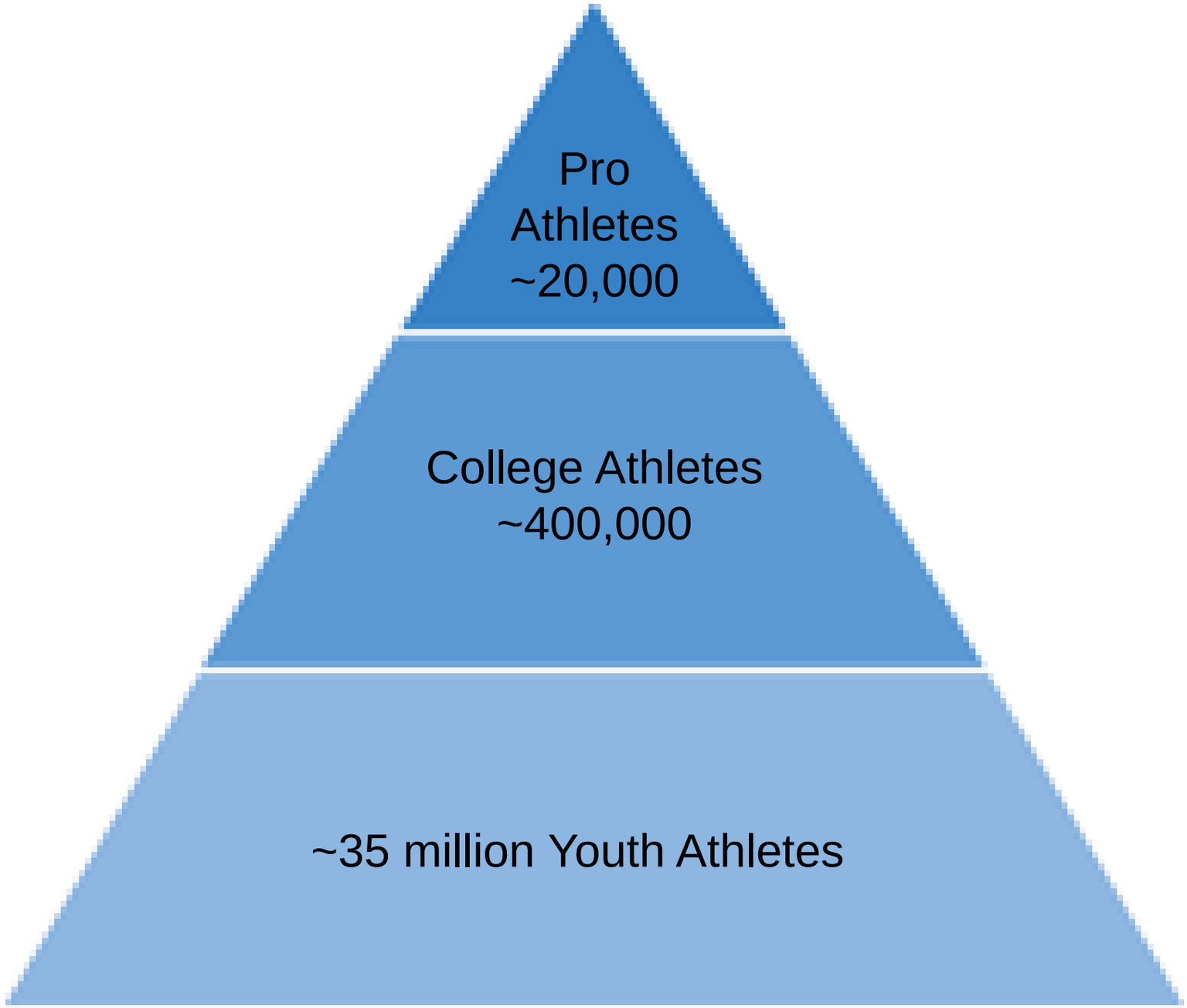
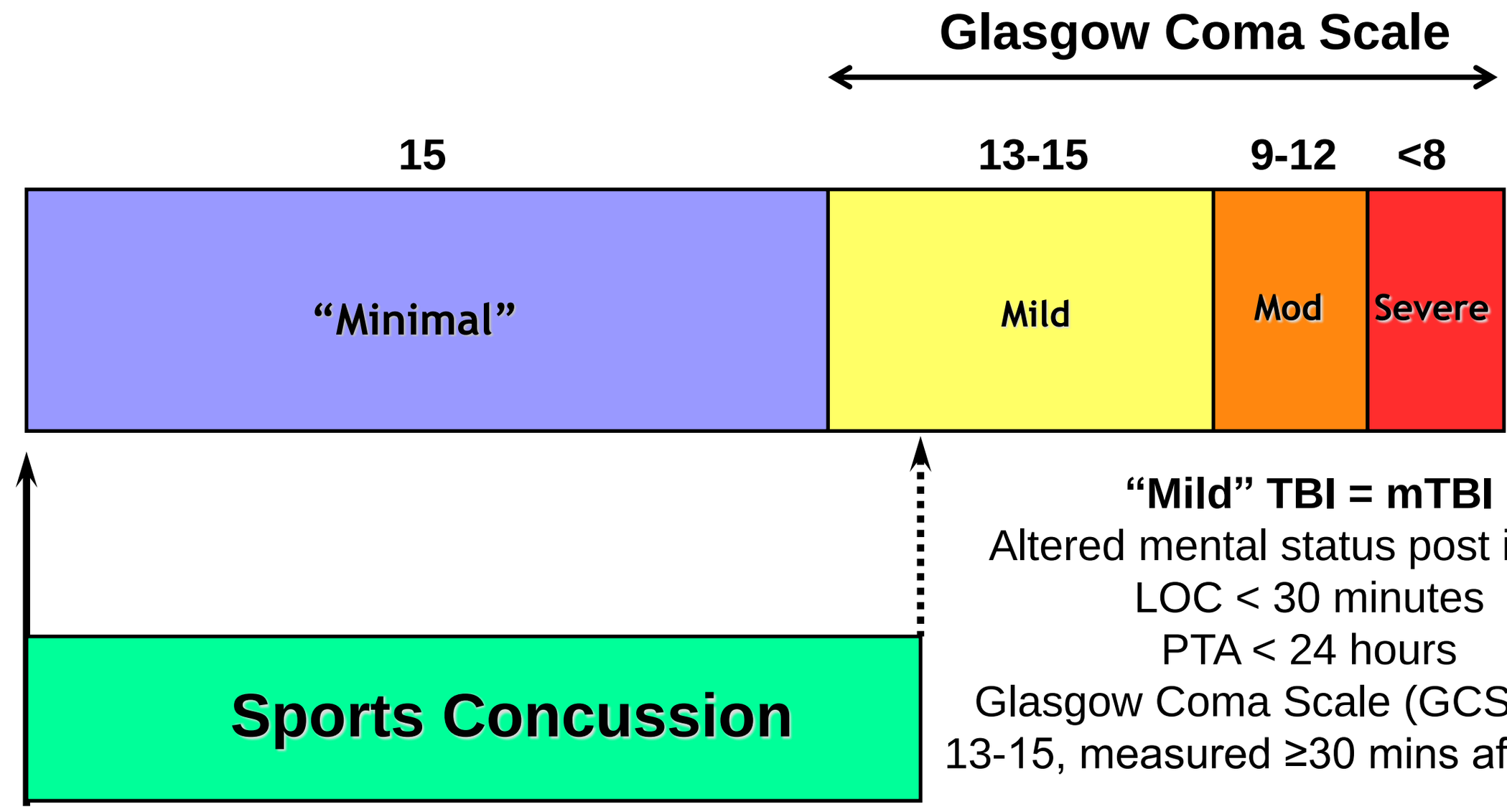
Why We Care About Pediatric Sports Concussions (#’s in the US)



Estimates from Bureau of Labor Statistics, NCAA, and statisticbrain.com.

Traumatic Brain Injury



“Mild” TBI = mTBI

Altered mental status post impact

LOC < 30 minutes

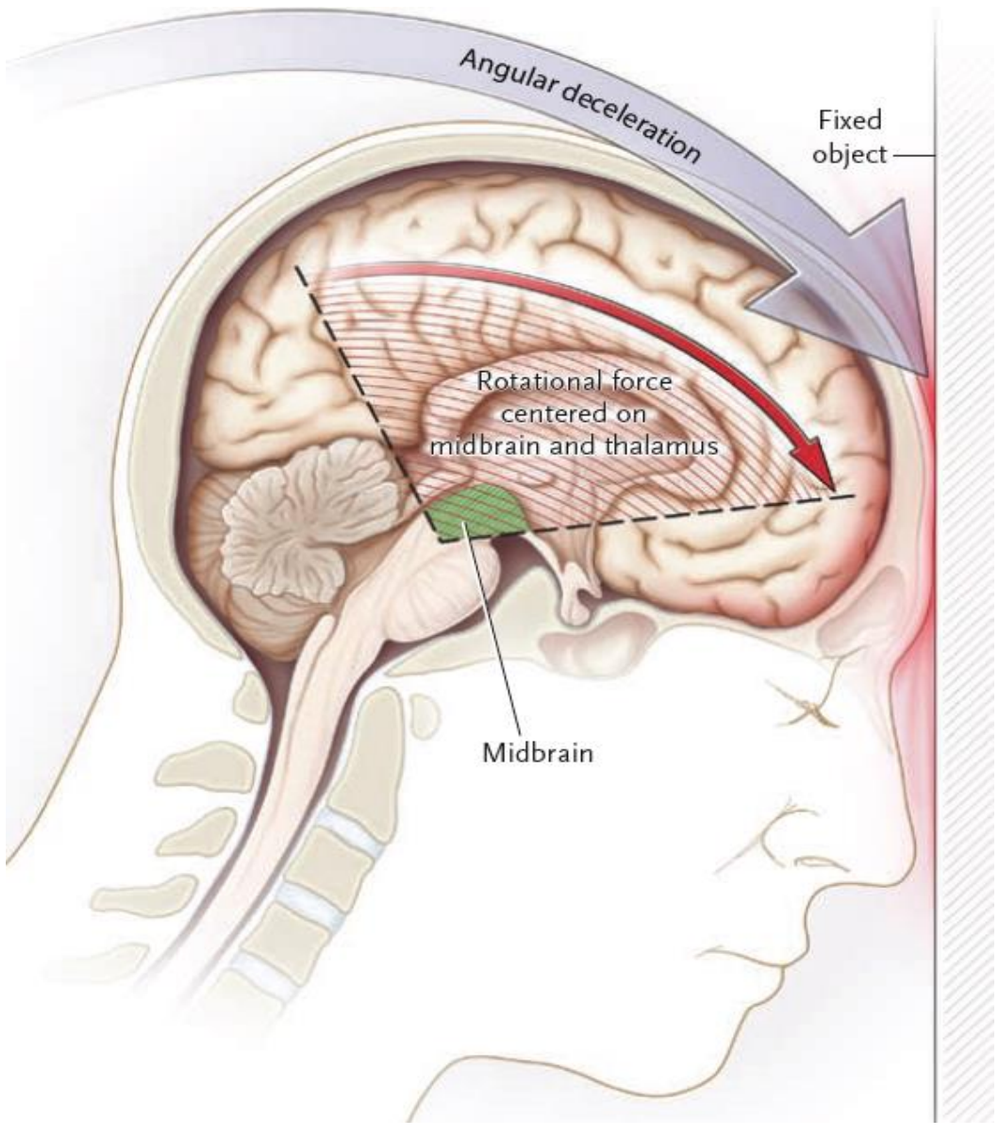
PTA < 24 hours

Glasgow Coma Scale (GCS) score 13-15, measured ≥30 mins after injury

Consensus Statement on Concussion in Sport. 3rd International Conference on Concussion in Sport held in Zurich, Nov 2008

ACADEMIC EMERGENCY MEDICINE 2006
Current Pharmaceutical Design, 2001, 7, 1475

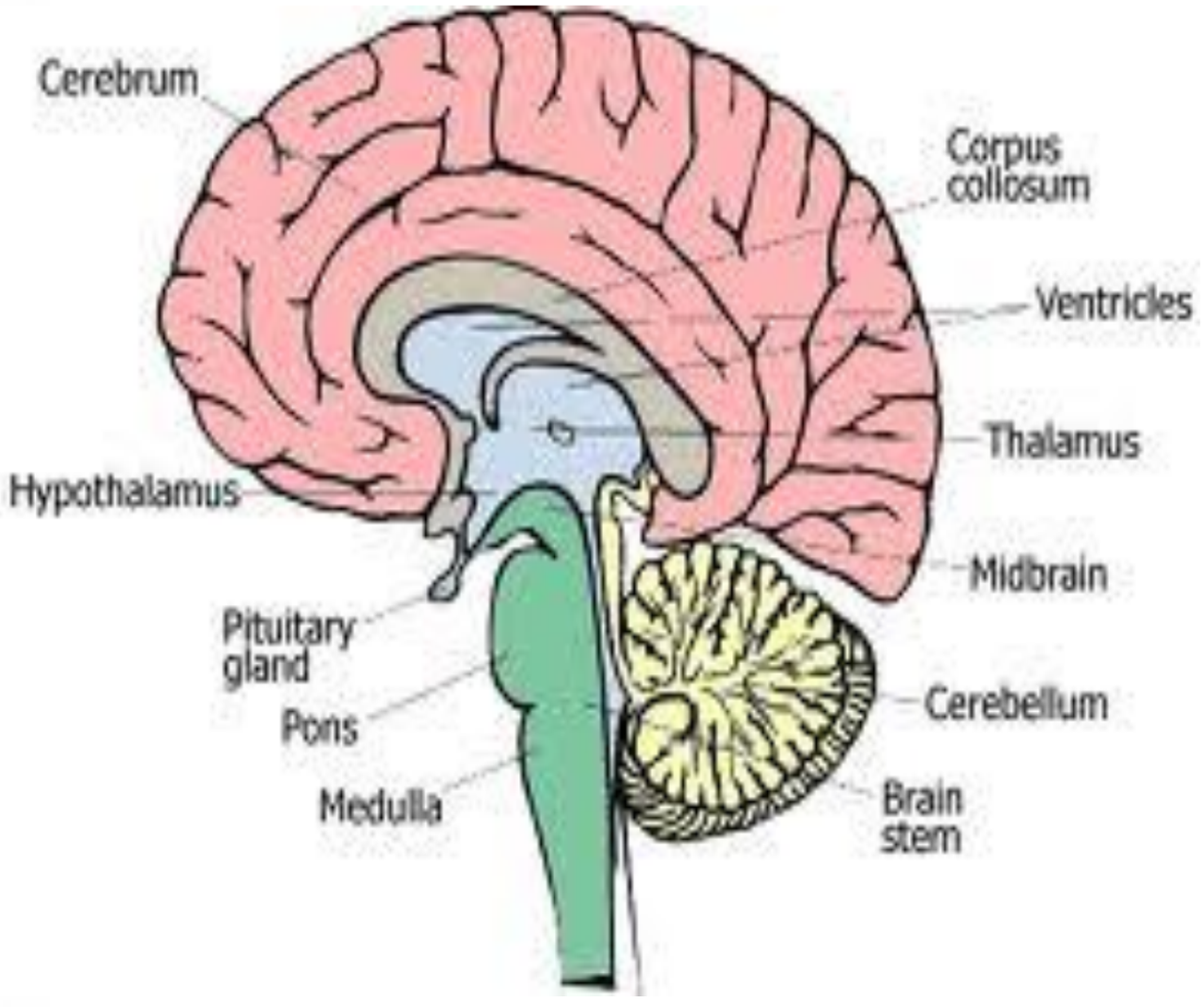
Mechanisms Underlying TBI



Biomechanical investigations dating back to the beginning of the 20th century suggest that concussion results from a rotational motion of the cerebral hemispheres in the anterior–posterior plane, around the fulcrum of the fixed-in-place upper brain stem.

N Engl J Med 2007;356:166-72.

Mechanism of Traumatic Brain Injury



Concussion vs. mTBI

1.74 million U.S. civilians suffer a mild TBI each year (1/2 are under the age of 18)

- Awake- GCS 13-15. Of all grades of TBI 90% is “mild”. Concussion is a useful term for reversible condition. Mild TBI useful in context of TBI spectrum of injury.
- Most have “normal CT and MRI”- 7% have intracranial lesion on CT and <1% will require neurosurgery
- Approximately 30% of mild TBI go on to have ongoing somatic (headache), cognitive (attention and memory), and emotional (lability) problems
- No clear neurobiological explanation: Anatomy: Behavior: Neurophysiology
- No firm diagnostic test: MRI: Neuropsychology: EEG
- No predictors regarding “return to play”: IMPACT is not helpful

Signs and Symptoms of Concussion

- -**Physical/Somatic:** headache, sensitivity to light/noise, nausea, vomiting, fatigue, numbness/tingling, visual problems, balance problems, dizziness

- **-Cognitive**: feeling “in a fog” mentally, problems concentrating, impaired memory, decreased attention, problems with predictive timing, feeling “slowed down”

- **-Emotional**: irritability, sadness, nervousness

- **-Sleep**: drowsiness, sleeping more or less than usual, trouble falling asleep

2012 AMSSM position statement: concussion in sport

Primary Brain Injury:
Glutamate Release and Ionic Flux

- Membrane deformation leads to potassium efflux and release of excitatory amino acids, especially glutamate
- Glutamate binds NMDA and AMPA ionic channels
  - Calcium influx and further depolarization
  - Depolarization leads to neuron suppression resembling spreading depression
- ATP-dependent Na+/K+ pumps work to restore ionic balance
  - High levels of glucose metabolism due to high energy needs (lasts from .5 – 4 hours in rat TBI experiments)
  - Lactate production is increased, leading to local acidosis, increased membrane permeability, and cerebral edema

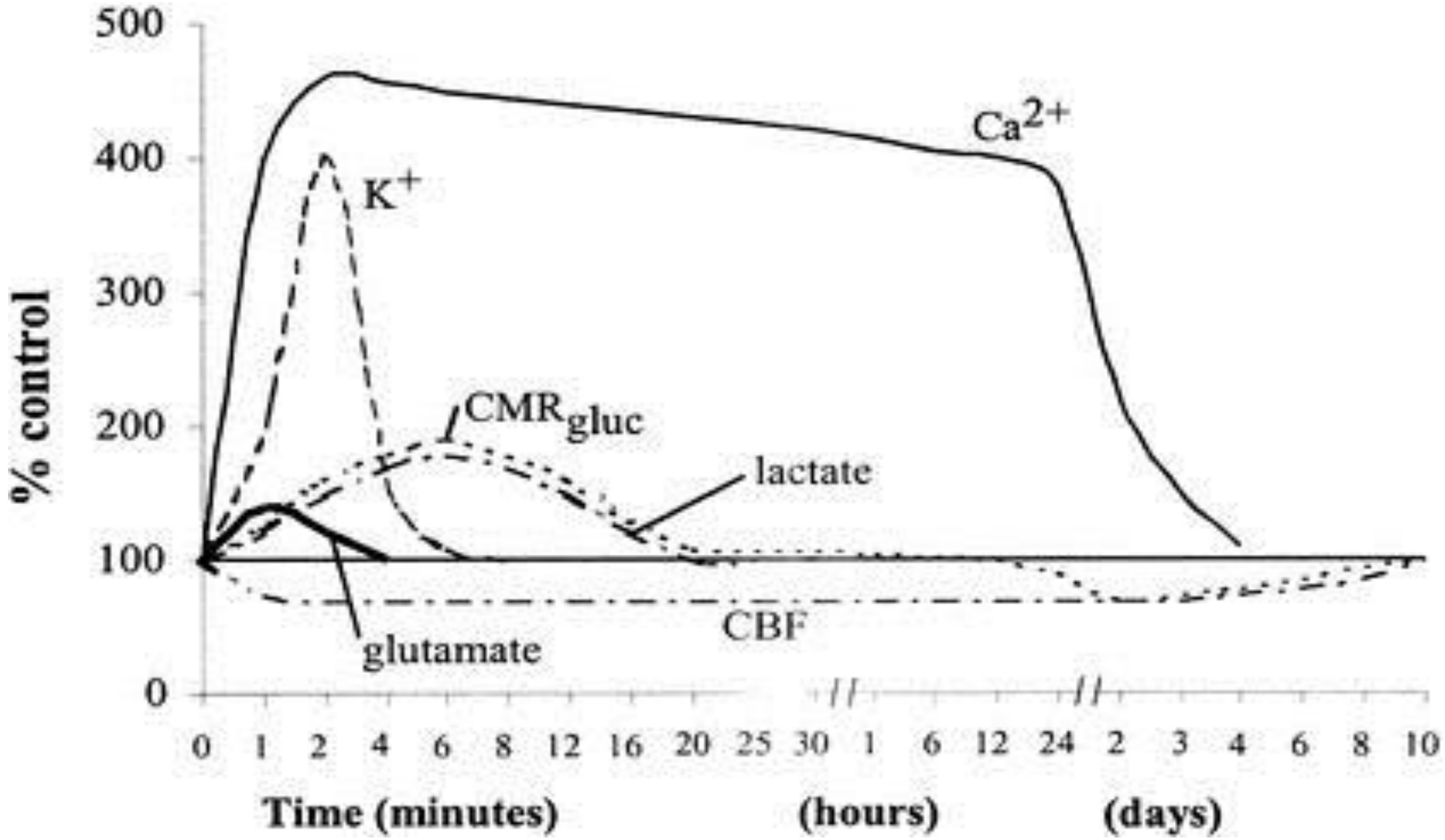
Barkhoudrain G et al. The Molecular Pathophysiology of Concussive Brain Injury. Clin Sports Med 30 (2011): 33-48.

Functional Secondary Brain Injury: Glucose Metabolism, Mitochondrial Function, and Cerebral Blood Flow

- Altered Cellular Energetics: Initial hyper-glycolysis followed by prolonged period of hypo-metabolism (up to 5 days in rat study)
  - NMDA channel activation leads to influx of Ca++
  - Ca++ accumulates in mitochondria
  - Leads to glucose oxidative dysfunction
- Impaired Cerebral Blood Flow: Triphasic alteration in severe TBI, but not well studied in mild TBI
  - Initial cerebral hypoperfusion (day 0)
  - Cerebral hyperemia (days 1-3)
  - Cerebral vasospasm (days 4-15)

Barkhoudrain G et al. The Molecular Pathophysiology of Concussive Brain Injury. Clin Sports Med 30 (2011): 33-48.

Time-course of Functional Brain Injury Following TBI in Animal Models



Giza CC, Hovda DA. Ionic and metabolic consequences of concussion.

Biomarkers of Primary & Secondary mTBI

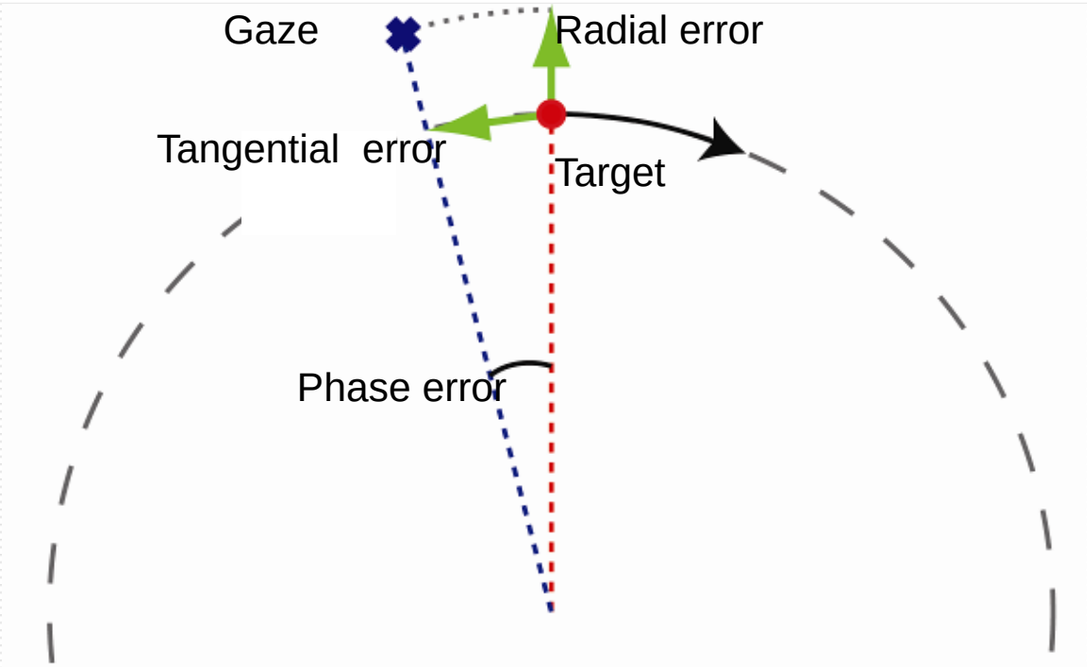
- Glutamate release and Ionic Flux (MRS)
- Alterations in Glucose Metabolism and Mitochondrial Function (MRS)
- Alterations in Cerebral Blood Flow (MRI/ASL)
- Axonal Injury (DTI)
- Alterations in Brain Activation (2DG PET)
- Neuropsychological computerized tests
  (e.g., Impact, Anam4)
- Attention and working memory tests
  (e.g., ANT, CVLT)
- Eye tracking (predictive timing)

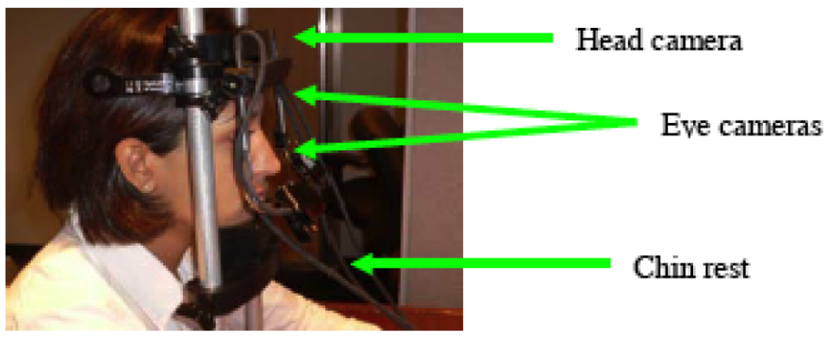
Barkhoudrain G et al. The Molecular Pathophysiology of Concussive Brain Injury. Clin Sports Med 30 (2011): 33-48.

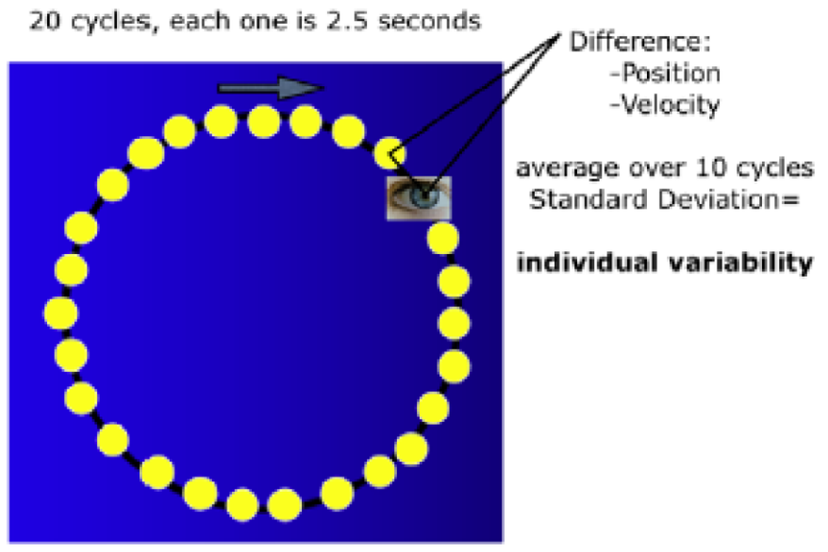
Quantification of Eye Tracking Performance Variability

Visual Tracking Performance Variability ≡ Standard Deviation (SD) of eye position error

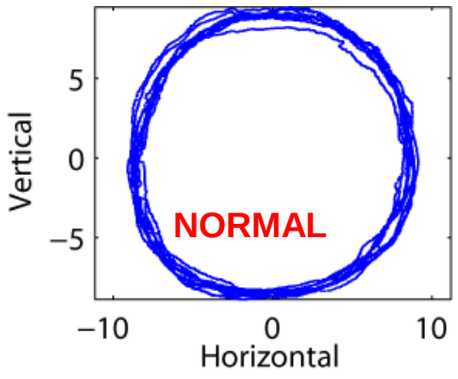
- Circular trajectory of target is predictable
- Predictive timing in maintaining target on fovea of eye is learned
- Predictive timing error is measured by variability of eye position relative to target

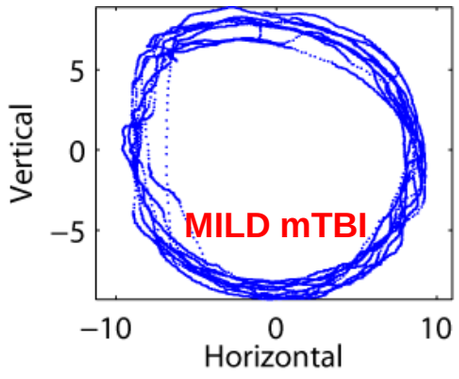


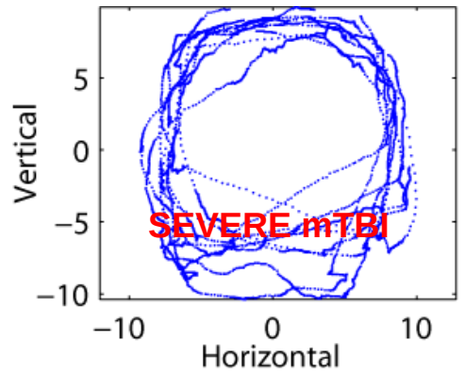


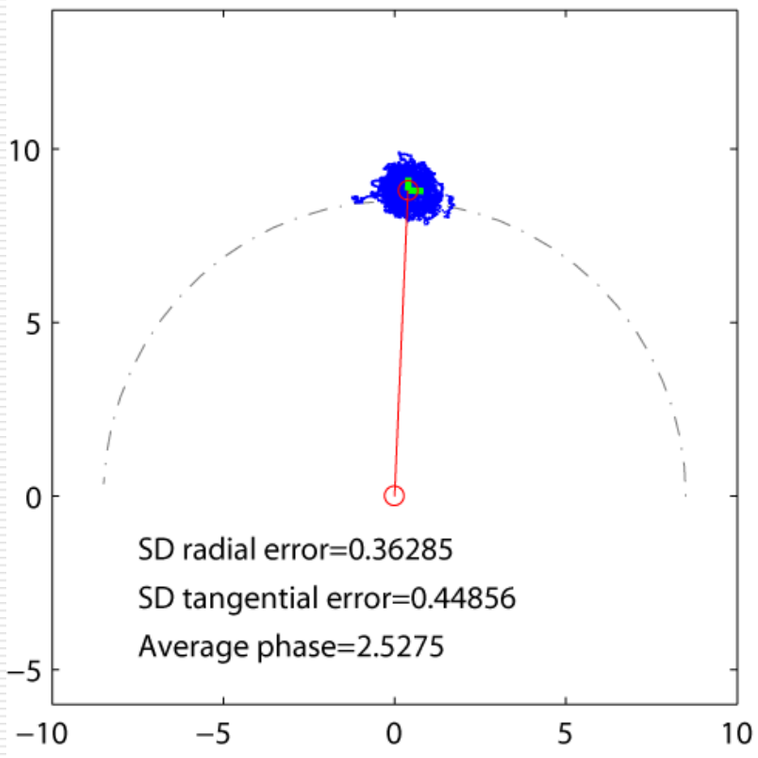


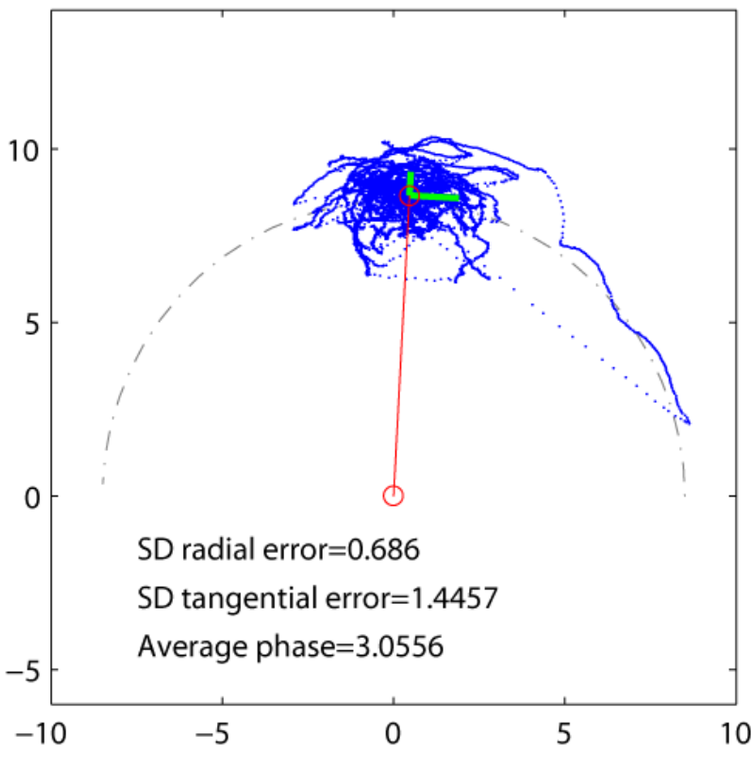
Different Grades of Eye Tracking Performance Correlates with Severity of TBI

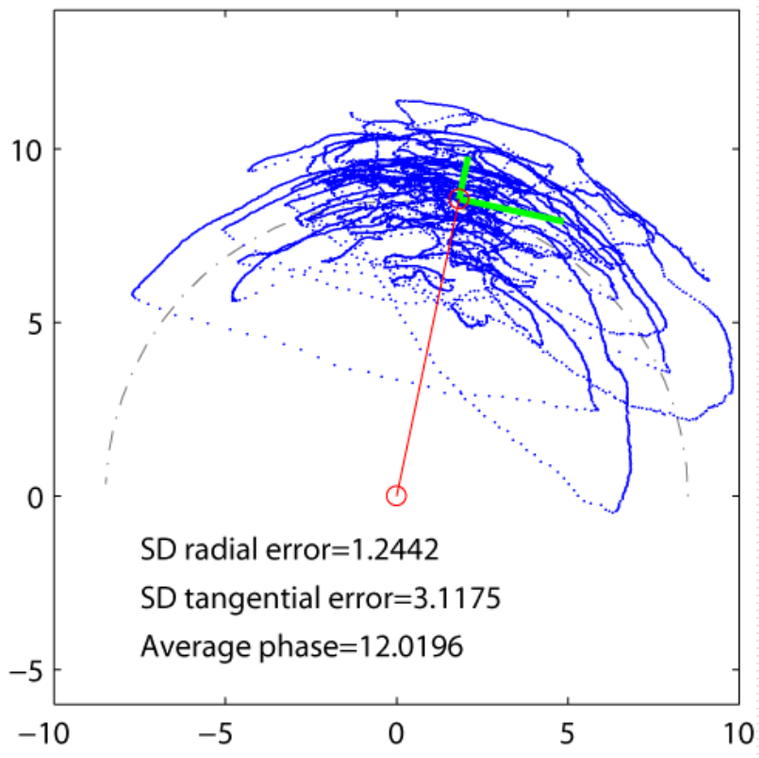












Return to Play/Learn

When can children return to cognitive/physical activity after a concussion?

- Barry Kosofsky, MD (Child Neurologist): Cognitive Concerns
- Jim Kinderknecht, MD (Pediatric Sports Medicine): Athletic Concerns

Return to Play/Learn

This is a **VERY** important question that is **VERY** difficult to answer!

We know that immediately after a concussion there is an increased risk of repeat concussion that may be associated with worse outcomes.

We lack quality evidence/research to support any specific guideline, especially in children

There is NO SINGLE DIAGNOSTIC TEST TO DETERMINE RESOLUTION OF CONCUSSION (including the Impact test)

Each individual will have a different course with concussion, so we need to approach every case individually

Symptoms of concussion may be present to some degree in people prior to injury (prior history of headache or anxiety)

People (especially athletes) do not always report symptoms they are experiencing

Our Approach at WCMC

-Initial period of cognitive/physical rest until initial acute concussion symptoms resolve

- Never return to physical exercise until mental exercise is well tolerated

-Spend 1-2 weeks ensuring that mental exercise does not induce symptoms

-Approach return to full mental activity in a graded fashion, increasing level of mental exertion and concentration in a step-wise progression, being vigilant for ‘inducible’ headache

-If the escalating level of mental activity causes symptoms, stop and return to previous level for 48-72 hours (do NOT power through inducible headache)

-Cognitive/Neuropsychiatric assessments can be helpful as an adjunct, especially with baseline test results, but cannot definitively predict readiness to return, and school performance is a more sensitive indicator.

-Keep headache/symptom diary. Medication may be required to return to school, but should not be started for at least 2 weeks. Should be asymptomatic off of medications prior to return to play.

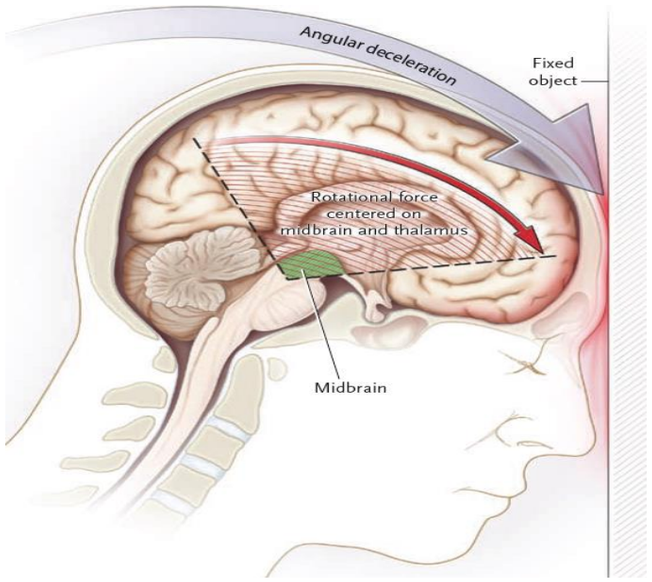
Strategies Regarding Identification of Circulating Biomarkers of mTBI

- Requires a definition of which phase of mTBI is most relevant

- Symptomatic phases:
  - Acute (first 72 hours): constant or positional headache resulting from increased ICP
  - Subacute (days/weeks/months): Mental- or physical exertion-induced headaches secondary to functional changes (lack of cerebrovascular auto-regulation)
  - Chronic (month/years/decades): Long-term cognitive deficits including risk of chronic traumatic encephalopathy (CTE) secondary to structural changes (immediate or delayed)

- Goal of circulating biomarkers would include:
  - Early identification (during the first 24-48 hours following injury) of risk for ongoing damage (high sensitivity AND specificity for identifying those patients at risk for subacute and chronic signs and symptoms)
  - Actionable: would identify subset(s) of mTBI subjects who when treated during the acute phase of injury would minimize subacute symptoms and potentially chronic disabilities

Actionable Biomarkers: To Prevent Secondary Brain Injury s/p mTBI



Intervention

Improved Functional Outcome

Improved Structural Outcome

Actionable Biomarkers

- **Circulating Biomarkers**
  - Blood
  - CSF

Validate with non-invasive biomarkers