Sex and *Concussion*

Rock n Role of the Brain

David Baron, MSEd, DO, FACP, FRSM
Fulbright, Distinguished Chair in Brain Science
Youth Sports Concussion, Univ of Calgary
ACP Annual Meeting Feb. 2018

Disclosures

- Independent Consultant
  - NCAA
  - NFL
  - LA Rams
  - LA Chargers
  - IOC
  - World Rugby
- President, Brain Injury Research Strategies
  - Side line eye tracking
- Copyright- BDSA

What is a concussion?

- The Centers For Disease Control and Prevention
  - "*type of traumatic brain injury caused by a bump, blow, or jolt to the head or by a hit to the body that causes the head and brain to move rapidly back and forth. This sudden movement can cause the brain to bounce around or twist in the skull, stretching and damaging the brain cells and creating chemical changes in the brain.*"

Definition of Concussion

(International Consensus)

- ***A complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces***
  - Caused by direct blow to the head, face, neck, or elsewhere on the body with "impulsive" force transmitted to the head

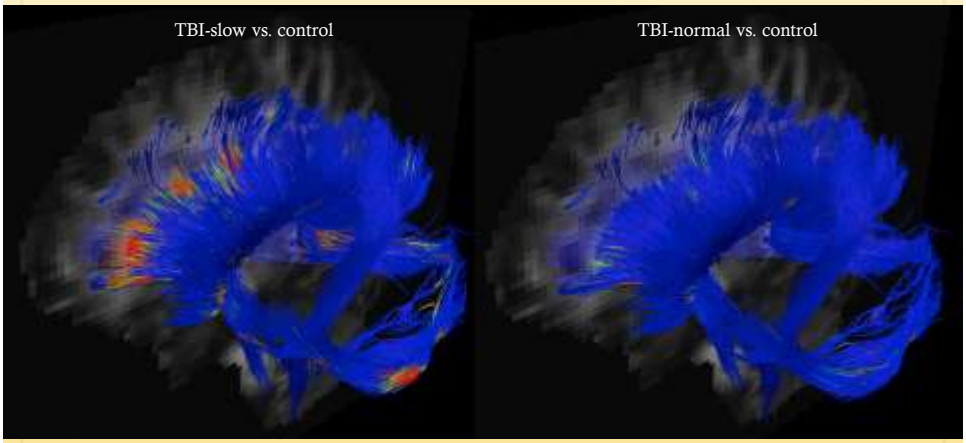
TBI vs Concussion

- Baron Sunburn Analogy
  - Age-younger brain
  - ***Sex***
  - Dose effect-number of impacts
    - Concussive vs sub-concussive
  - Risk factors(genetic)
    - Prior brain insult
- Treatment
  - No proven tx concussion /PCS

Pathophysiology

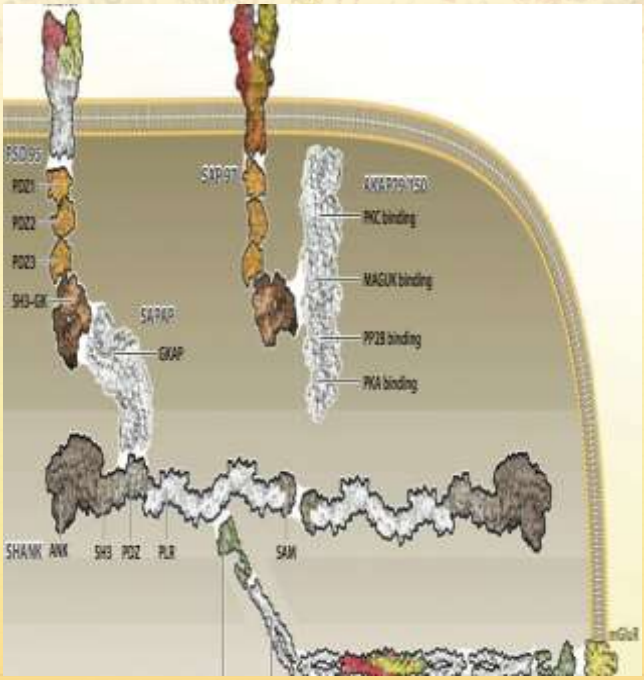
- Dysregulation of ions
  - Causes strain on ion pumps
    - Leads to increased energy demand
- *Hypermetabolic state*
  - Larger than normal amounts of glucose consumed
- Reduction of cerebral blood flow
  - Combined with hypermetabolic state, results in "***energy crisis***"
- Disruption of brain connectivity
  - DTI
- White tract thickness??
- Inflammosome

Cross-sectional results



Dennis, Ellis et al., 2015 J Neuroscience

This is a thresholded *p*-map, where blue are areas at or above threshold (not significantly different), while green-red are areas of significantly lower WM integrity.



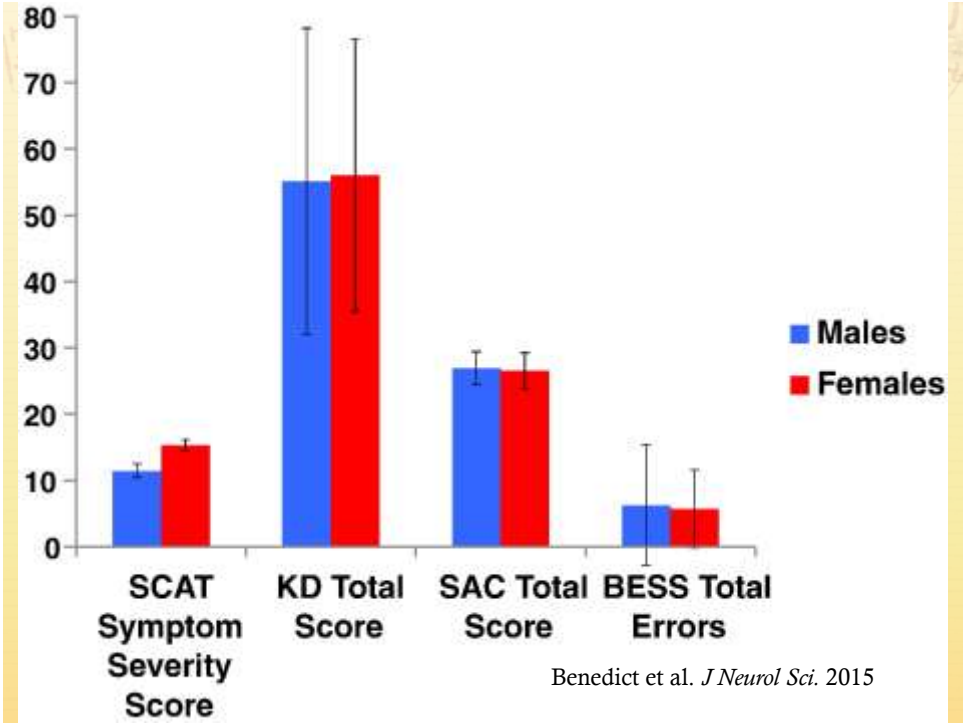
Baron and DeFranco 2011

Baseline Symptoms

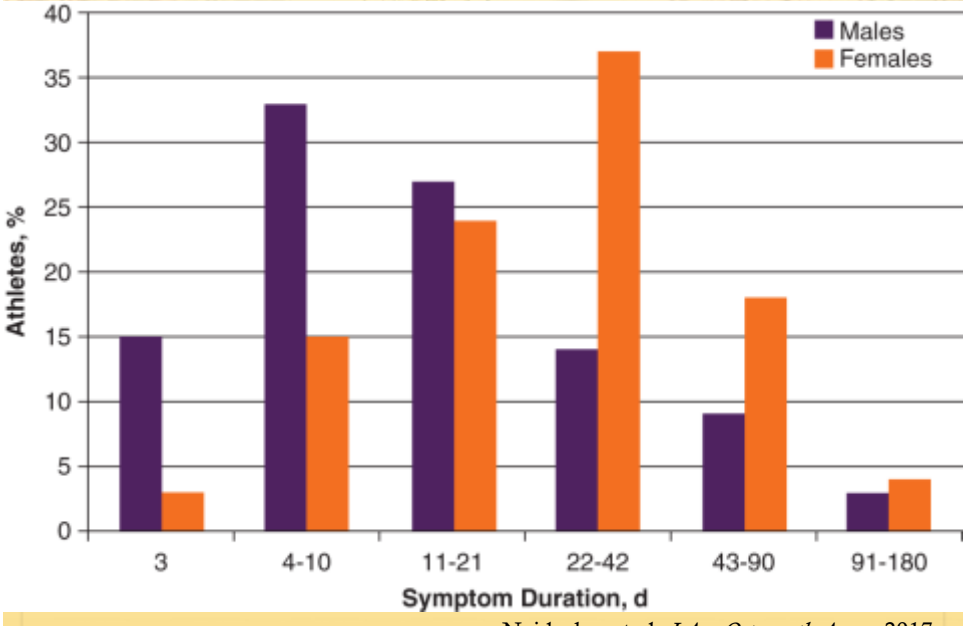
Symptom Type Sex Differences

- Males reported more cognitive symptoms, females reported more neurobehavioral and somatic symptoms
  - Males reported amnesia and confusion/disorientation more often, ***females reported drowsiness and sensitivity to noise more often***
- ***Women had greater symptom severity***, being a woman was significant predictor of symptom severity score when accounting for age

Frommer et al. *J Athl Train.* 2011
Benedict et al. *J Neurol Sci.* 2015



Benedict et al. *J Neurol Sci.* 2015



Neidecker et al. *J Am Osteopath Assoc.* 2017

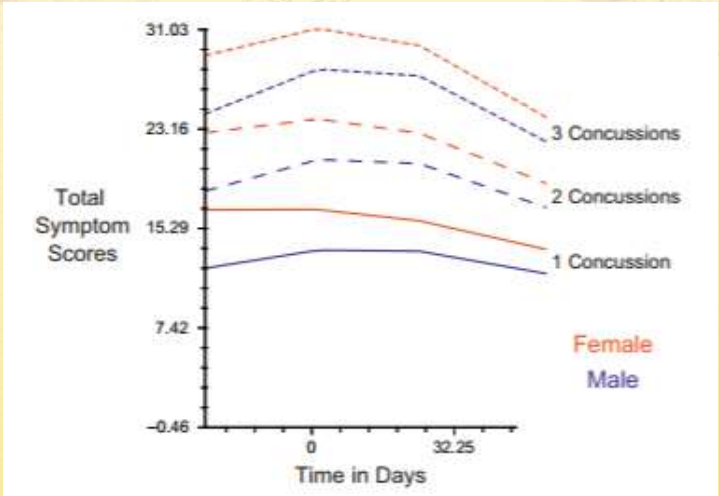


Figure 1. Sex-based differences as a predictor of recovery in total symptoms after a concussion.

Ono et al. *Am J Sports Med.* 2016

Concussion Reporting Intention

Reporting Concussions

- Girls more likely than boys to report a concussion before and after having an educational lecture
- Females have greater intention to report a future concussion
  - Females also experienced more impacts resulting in symptoms, and were more likely to have been diagnosed with concussion previously
- Reporting intention greater in athletes who conform less strongly to traditionally masculine norms of self-reliance and winning

Miyashita et al. *Sports Health.* 2016
Kroshus et al. *J Adolesc.* 2017

Cognitive Deficits and Symptom Reporting in Adolescents

- After concussion, females performed worse across all neurocognitive measures and reported greater symptoms relative to baseline testing, regardless of sport, as measured by ImPACT
- Female athletes more likely than males to have scores predictive of protracted recovery

Sandel et al. *Am J Sports Med.* 2017

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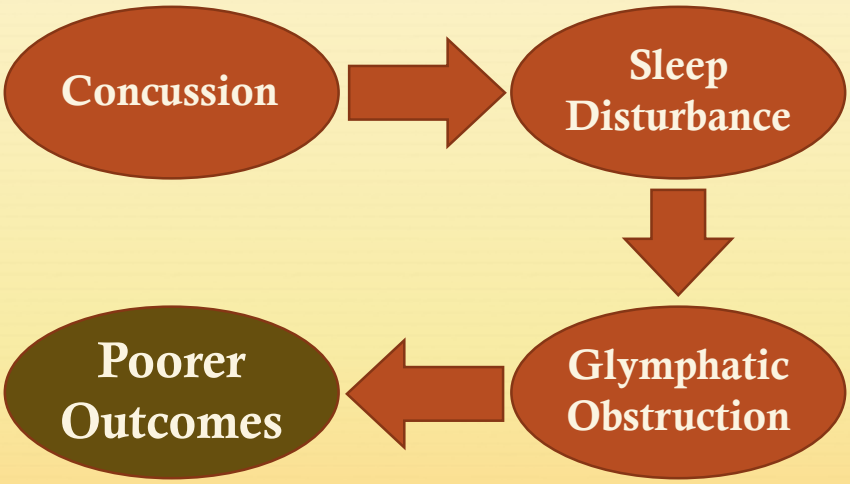
Symptoms and Return to Baseline

- At baseline, females reported greater severity for "sleeping less than usual," more sleep-arousal symptoms, higher odds of reporting sleep disturbances
  - More problems with cognitive-sensory symptoms
- Females took longer to return to baseline total symptom score

Zuckerman et al. *J Neurosurg Pediatr.* 2014
Brooks et al. *Appl Neuropsychol Child.* 2016
Brown et al. *Sports Med.* 2015

Post-Concussion Symptomology

Possible Mechanism of Action



Recovery

Recovery Trajectories after SRC

- ***Female athletes reported more total symptoms at baseline*** and post-concussion (particularly somatic and emotional)
  - Possible differences in protracted female recovery due to greater number of symptoms reported
- ***Female gender associated with poorer outcome*** after mild head injury in 5/6 studies
- Female middle and high school athletes take significantly longer for symptoms to resolve after their first concussion

Ono et al. *Am J Sports Med.* 2016
King. *Brain Inj*. 2014
Neidecker et al. *J Am Osteopath Assoc.* 2017

Relation to Menstrual Cycle

mTBI, Progesterone Withdrawal Hypothesis

- Women injured during luteal phase had significantly lower health rating scores than women injured during follicular phase or women on oral contraceptives
- mTBI in setting of high progesterone results in sudden decrease
  - Women taking synthetic progestin had high levels during and after injury, with health rating scores similar to follicular phase women

Wunderle et al. *J Head Trauma Rehabil.* 2014

Concussion Symptoms and Menstrual Phase

- ***Eumenorrheic females had greater total symptom severity score and number of symptoms than OCP users***
  - Clinical measures of concussion remained consistent through menstrual cycle
- Prior studies have reported TBI can cause amenorrhea and irregular cycles
- ***Young women have significantly greater risk of developing abnormal menstrual patterns after concussion*** compared to orthopedic injuries
  - No patients developed amenorrhea

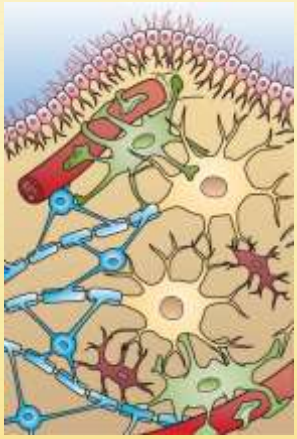
Mihalik et al. *J Sci Med Sport.* 2009
Snook et al. *JAMA Pediatr.* 2017

Table 3. Types of Abnormal Bleeding Patterns by Injury Group

Outcome	Patient Group, No. (%)		
	Concussion (n = 68)	Orthopedic Injury (n = 60)	OR (95% CI)
Primary			
Abnormal patterns (≥2)	16 (23.5)	3 (5.0)	5.85 (1.61-21.22)
Secondary			
Intermenstrual interval, d			
<21	11 (16.2)	2 (3.3)	5.60 (1.19-26.38)
>35	26 (38.2)	24 (40.0)	0.93 (0.46-1.89)
Bleeding duration <3 d	5 (7.4)	2 (3.3)	2.30 (0.43-12.30)

Snook et al. *JAMA Pediatr.* 2017

Glymphatics



Intro to Glymphatics

- Glymphatic system is peri-arterial CSF influx and peri-venous clearance
  - Functions like lymphatics in rest of body
  - CSF flow supported by aquaporin 4 channels in astrocytes
- Glymphatic flow is enhanced during sleep due to increase of cortical interstitial fluid space
  - Disrupted sleep leads to less waste clearance
  - Buildup of amyloid

Benveniste et al. *Neuroscientist*. 2017

Brain Injury, Sleep, and Glymphatics

- Traumatic brain injuries are often associated with onset of sleep disruption
- Sleep is necessary for proper function of the glymphatic system
  - ***Brain injury limits removal of hyperphosphorylated tau by glymphatic system during sleep***
- Failure for waste removal in the brain can lead to neuronal damage and death

Luck-Wold et al. *Neurosci Biobehav Rev.* 2015

Common Themes

- Females report more symptoms and greater symptom severity than males, at baseline and after injury
  - Somatic and emotional. Sleep disturbances
  - Protracted recovery in females?
  - Menstrual cycle phase
    - Luteal phase worse
- Females have greater intention to report concussions

Moving Forward

- Prospective trials
  - Better clinical science-
  - Control for confounding variables, larger "n"
- Change culture re concussion (smoking)
- Education
  - Providers
  - Trainees
  - Coaches
  - Players
- Other high risk pt populations
  - SA
  - Military/police
  - elderly

References and Further Reading

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