Post Concussion Syndrome: Cortisol, Allostatic Load, and "Neurologic Exhaustion."

Alternate Title: Post Concussion Syndrome "It's all in their head"

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“Disclosures”

- Received payment from Nyco Med, Purdue and Jannssen

- This “message” is about the relationship between Mild Traumatic Brain Injury (concussion) in *children* and PCS not:
  - Moderate to Severe Brain Injury
  - Second impact syndrome
  - Chronic Traumatic Encephalopathy
- This presentation used to be 220 slides
- I could also make a presentation with 220 slides explaining why PCS is entirely due to pure organic contributions.
- I use an incredible amount of analogies

Objective

1. To quickly describe what a concussion is at the clinical and pathophysiological level (Dispel the Great Concussion Mystery)
2. Explain why this is distinct from, and only indirectly related to, Post Concussion Syndrome (PCS)
3. Outline what I believe is the true etiology of PCS
   - 8 yrs and 2500 concussions to realize Concussions ≠ Post Concussion Syndrome
4. To propose an informal algorithm for working up patients with PCS
5. Explore possible treatment options
6. Not confuse, anger or bore anyone

What is a Concussion?

- *Concussion* is defined as
  - "A complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces"
  - My Definition: Any mental status change following trauma that cannot be attributed to extracranial factors or a preexisting condition

1. Short-lived.
   – Indeed *MOST* patients are symptom-free within 10 days.

2. Resolution typically follows a sequential course; symptoms may be prolonged.
   ✓ +/- LOC

3. Functional disturbance NOT a structural injury.

4. May be caused either by a direct blow to the head, face, neck or elsewhere on the body with an ''impulsive'' force transmitted to the head.

5. Due to contact and/or acceleration/deceleration forces of the head.

McCrory P, Meeuwisse W, Johnston K, Dvorak J, Aubry M, Molloy M, Cantu R. Consensus Stateent on Concussion in Sport: the 3rd International Conference on Concussion in Sport held in Zurich November 2008. Br J Sports Med. 2009 May;43 Suppl 1:i76-90.

The Basis Of Concussion Recovery: The Chemical Hypothesis

Barkhoudarian, G., Hovda, DA & CC Giza (2011). The Molecular Pathophysiology of Concussive Brain Injury. Clin Sports Med 30 (2011) 33–48

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Concussion vs Post Concussion Syndrome

- Amnesia
- Disorientation
- Appearing dazed
- Acting confused
- Memory Issues
- Emotional Liability
- Physical incoordination
- Seizure
- Slow verbal responses
- Personality changes
- Hallucinations
- Drowsiness
- Sadness

- Headache
- Dizziness
- Nausea or vomiting
- Vision changes
- Photophobia
- Phonophobia
- Feeling “out of it”
- Difficulty concentrating
- Tinnitus
- Nothing at all initially

Incidence? Waljias et al 2014 found 31% of healthy controls met criteria for PCS

Iverson 2006: 90% of patients with depression met self-report criteria for a PCS

Iverson, G Misdiagnosis of the persistent postconcussion syndrome in patients with depression. Archives of Clinical Neuropsychology 21 (2006) 303–310

As taken from “Concussion Supplement: Postconcussion Syndrome: A Physiatrist’s Approach Cara Camiolo Reddy, MD” available at http://now.aapmr.org/PMRJournals/201110_S396_PostconsussionSyndromeAPhysiatrists.pdf

Wäljas M[1], Iverson G, Lange R, Hakulinen U, Dastidar P, Huhtala H, Liimatainen S, Hartikainen K, Ohman J. J Neurotrauma. 2014 Nov 3. **A Prospective Biopsychosocial Study of the Persistent Post-Concussion Symptoms Following Mild Traumatic Brain Injury.**

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Symptom Etiology Changes Over Time

A great study by McNally et al 2013 concluded :

- Injury characteristics predict PCS in the first month following mild TBI but show a decreasing contribution over time.
- In contrast, noninjury factors are more consistently related to persistent PCS at 3 months
- Psychological and psychiatric symptoms tend to evolve over time, often weeks to months.
- Anxiety and affective symptoms may complicate the clinical picture if the initial symptoms do not rapidly dissipate.
- Irritability, insomnia and worry complicate and amplify pain (headache).

Macleod 2010 state that

- Rarely are the organic factors persistent
  - they may increase in intensity if accompanied by psychiatric morbidity.
- Incorrect diagnosis, fears of brain damage and over-solicitous medical attention may cause iatrogenic persistence of symptoms.
- Psychosocial factors amplify and maintain symptomatology, which may still retain a pseudoneurological signature.
- Post concussion syndrome: The attraction of the psychologic by the organic. Macleod. AD. 2010, Medical Hypotheses. 74 2010. 1033-1035

- Lishman (1988) also propose that organic factors are chiefly relevant in the earlier stages, whereas long-continued symptoms are largely due to “neurotic developments”.
- Lishman WA. Physiogenesis and psychogenesis in the ‘post-concussional syndrome’. Br J Psychiatry 1988;153:460–9.

- **CHRONIC ILLNESS**

Who gets PCS (There is no G Threshold)

- Stress/anxiety
- **High Achieving Teenagers**
- Women
- Those who live alone
- Smart/Not smart
- The Young/The Old
- **Those who get injured**
- Minorities
- Those with litigation involved (McNally et al 2013)

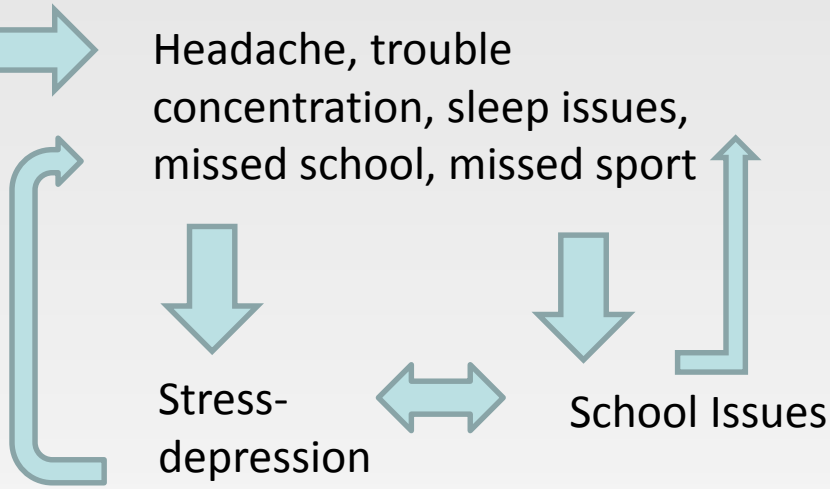
- MacLeod et al suggested
  - Physiological changes in the brain due to the *initial direct or indirect effects*
  - Depression due to the initial direct or indirect effects of concussion
    - Depression due to other factors
  - Chronic pain
  - Sleep disturbance and fatigue
  - Anxiety (generalized or specific or trauma-related)
  - Life stress, family and marital stress, and other psychosocial problems
  - Litigation stress
  - Numerous neurological conditions
  - Numerous psychiatric conditions
  - Malingering

“Concussion Cycle” & Stress/Cortisol Effect and Neurologic Exhaustion

My argument is that it is not the aforementioned chemicals that cause PCS but something else that perpetuates the symptoms:

Injury, Depression, Anxiety, Sleep, Pain, Organic cause, Healthy Patient, Illness, SEIDS, Cortisol Effect

- **Concussion**



- **Leading to Neurochemical Alterations and “Vital Exhaustion”**

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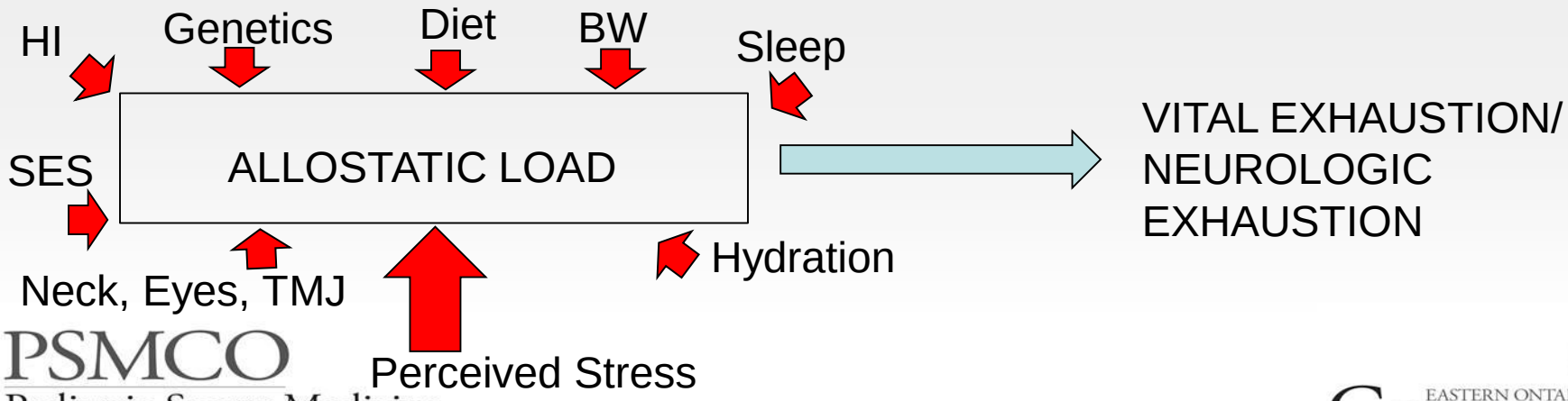
Allostatic Load and Neurologic Exhaustion



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Things At Play

1. Stress/Cortisol Response in Goulet Terms:
   I. My 8 year old self
   II. My Medical School Career
   III. Last Thursday Night
2. Empty Gas tank (unrefreshing sleep) “Duress”
3. Overtraining syndrome-use of antidepressants/Try and turn the table on stress
4. Prehistoric times: Prolonged levels of stress drives down serotonin/dopamine-
   1. phono/photo
5. Allostasis and Psychoneuroimmunology study of brain-behavior-immune interrelationships-microglial

Determining the Potential Contributors to PCS

- Organic/ "Physiogenesis"
  - Peristent Neurometabolic Anomaly ie "concussion"
  - Actual Brain Damage(?)
  - VestibuluOccular Reflex Dysfunction
  - Neck Injury
  - TMJ
  - Neuroendocrine Dysfunction/Hormonal
  - Autonomic Dysfunction
  - Sleep
  - Infectious
  - Autoimmune
- Psychologic/ "Psychogenesis"
  - Anxiety-Flight or Flight
  - Depression
  - Stress/Duress
  - PTSD
  - Iatrogenic
  - Premorbid Psych Functioning
  - Malingering
  - Coping Strategies
  - Support Structures

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If All "Organic" Causes are Ruled Out, One Must Then Equally Rule Out the Psychologic Contribution.

- Its hard to treat someone who is depressed/stressed who doesn't believe it (or who's parent doesn't believe it)
  - *that is where the ALLOSTATIC EXPLAINATION WORKS SO WELL*

Overtraining Syndrome, SEIDS, Fibromyalgia and PCS

- I see many similarities between PCS and Overtraining Syndrome and SEIDS (IL-6)
- In both conditions the body/nervous systems are exhausted and then the brain and body both break down

- Armstrong and VanHeest 2002 in their article **The unknown mechanism of the overtraining syndrome: clues from depression and psychoneuroimmunology**
  - There is no objective biomarker for OTS and the underlying mechanism is unknown
  - that OTS and clinical depression involve remarkably similar signs and symptoms, brain structures, neurotransmitters, endocrine pathways and immune responses.
  - Novel recommendations are proposed for the treatment of overtrained athletes with antidepressant medications, and guidelines are provided for psychological counselling.

- Armstrong, VanHeest 2001. **The unknown mechanism of the overtraining syndrome: clues from depression and psychoneuroimmunology.** Sports Med.2002;32(3):185-209.

Good Old Days Effect and How it Effects Incidence

Are some Post Concussive Patients actually already recovered?

- In a unique study Brooks et al 2014, they propose that some patients with post concussive symptoms overestimate their premorbid state.
  - This results in patients believing they are not recovered when in fact that have reached baseline measures.
- The "good old days" bias is present in pediatric mTBI by 1-month post-injury, influences retrospective symptom reporting, and has measureable implications for determining recovery in research and clinical practice.
- These other studies showed similar finding about attrition and overestimating previous premorbid state.

1. Ferguson RJ, Mittenberg W, Barone DF, Schneider B. Postconcussion syndrome following sports-related head injury: expectation as etiology. Neuropsychology 1999;13:582–589.

1. Gunstad J, Suhr JA. ‘‘Expectation as etiology’’ versus ‘‘the good old days’’: postconcussion syndrome symptom reporting in athletes, headache sufferers, and depressed individuals. Journal ofthe International Neuropsychological Society 2001;7:323–333.

1. Brooks BL[1], Kadoura B, Turley B, Crawford S, Mikrogianakis A, Barlow KM. Arch Clin Neuropsychol. 2014 Mar;29(2):186-93**Perception of recovery after pediatric mild traumatic brain injury is influenced by the "good old days" bias: tangible implications for clinical practice and outcomes research.**

1. Belanger HG[1], Barnick EM, Kim KE, Kretzmer T, Vanderploeg RD. 2013 **Postconcussive symptom complaints and potentially malleable positive predictors.** Clin Neuropsychol. ;27(3):343-55.
Mittenberg W, Tremont DV, Perrin S, Bass AE. Symptoms following mild head injury: expectation as aetiology. Journal of Neurology, Neurosurgery & Psychiatry 1992;55:200–204.

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Attribution/Expectation of Symptoms

- The tendency to attribute common current symptoms to a past concussion has been called 'expectation as aetiology' and was first coined by Mittenberg et al. 1992
  - The individuals with head injury reported 60% fewer symptoms pre-injury relative to the base rate in the healthy controls,
    AGAIN overestimating their premorbid state
- Mittenberg et al. proposed
  - "the expectation of symptoms after head injury results in the misattribution of common symptoms and complaints to the injury and minimization of preinjury symptoms and minimization of other aetiologies, such as stress."
- Bleanger et al 2013 based on their study of 91 patients with mTBI found
  - "Those who attribute their symptoms to TBI are more likely to report greater symptom severity overall.
  - Taken together, **knowledge, self-efficacy, and attributions contribute independently to PCS severity**.

McNally KA, Bangert B, Dietrich A, Nuss K, Rusin J, Wright M, Taylor HG, Yeates KO. 2013. Injury versus noninjury factors as predictors of postconcussive symptoms following mild traumatic brain injury in children. Neuropsychology. Jan 2013; 27(1): 1–12.

Education

- Wasldron et al 2015 found that educating undergrad students about a positive recovery may result in less symptom persistence

- Nygren de Boussard et al found that early, reassuring educational information is beneficial after MTBI.

- Kemp et al 2013 found that the terminology used by clinicians can impact the recovery of concussions

- Nygren-de Boussard C[1], Holm LW[2], Cancelliere C[3], Godbolt AK[4], Boyle E[5], Stålnacke BM[6], Hincapié CA[7], Cassidy JD[8], Borg J[4]. **Nonsurgical interventions after mild traumatic brain injury: a systematic review. Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis.** Arch Phys Med Rehabil. ; 95(3 Suppl):S257-64
- Kempe CB[1], Sullivan KA, Edmed SL. **CE the effect of varying diagnostic terminology within patient discharge information on expected mild traumatic brain injury outcome.** Clin Neuropsychol. 2013;27(5):762-78.
- Waldron-Perrine B[1], Tree HA, Spencer RJ, Suhr J, Bieliauskas L. 2015 **Informational literature influences symptom expression following mild head injury: An analog study.** Brain Inj.2015 Jul 16:1-5.

Education:

- Miller et al. found that a single psychoeducational session is a key factor in preventing or shortening PCS
  - Provide supportive reassurance
  - Educate about the symptoms of concussion,
  - Describe the expected recovery course
  - Emphasize the appropriate attribution of symptoms to benign aetiologies,
  - Explain the gradual resumption of activities can be highly effective in reducing symptoms.

It is Not the Injury But the Presence of Injury

- Meares et al. **Mild traumatic brain injury** does not **predict acute** postconcussion **syndrome**. (n 175)
- Diagnosis of acute PCS was not specific to mTBI (mTBI 43.3%; controls 43.5%).
- Pain was associated with acute PCS in mTBI.
- Females were 3.33x more likely (95% CI 1.20 to 9.21).
- **The strongest effect for acute PCS was a previous affective or anxiety disorder (OR 5.76, 95% CI 2.19 to 15.0).**
- **These results were confirmed at the 3 month mark**

- Yeates et al. (2009) studied 2 subgroups of children,
  - 1 group of children orthopedic injury and the other of children with mild TBI,
  - They found that persistent PCS unrelated to brain insult

- Keightley et al 2014 *A systematic review by the International Collaboration on Mild Traumatic Brain Injury Prognosis.*
  - After 1 year, the prevalence of PCS is similar between children w MTBI and children w orthopedic injuries
  - Children with MTBI experience greater rates of psychiatric illness during the 3 years after their injury.

- Asarnow et al., 1995 and Bijur & Haslum 1995 studied behavioral outcomes after injury:
  - They found that there were not more **behavioural problems** in children with mTBI relative to children with other **traumatic** injuries.

Meares S, Shores EA, Taylor AJ, Batchelor J, Bryant RA, Baguley IJ, Chapman J, Gurka J, Dawson K, Capon L, Marosszeky JE. **Mild traumatic brain injury** does not **predict acute** postconcussion **syndrome**. J Neurol Neurosurg Psychiatry. 2008 Mar;79(3):300-6.

Yeates KO, Taylor HG, Rusin J, Bangert B, Dietrich A, Nuss K, Wright M, Nagin DS, Jones BL. 2009. Longitudinal trajectories of postconcussive symptoms in children with mild traumatic brain injuries and their relationship to acute clinical status Pediatrics. 123(3):735-43

•Arch Phys Med Rehabil. 2014 Mar;95(3 Suppl):S192-200. doi: 10.1016/j.apmr.2013.12.018.

•**Psychosocial consequences of mild traumatic brain injury in children: results of a systematic review by the International Collaboration on Mild Traumatic Brain Injury Prognosis.**

•Keightley ML[1], Côté P[2], Rumney P[3], Hung R[3], Carroll LJ[4], Cancelliere C[5], Cassidy JD[6].

Bijur PE, Haslum M. Cognitive, behavioral, and motoric sequelae of mild head injury in a national birth cohort. In: Broman S, Michel ME, editors. Traumatic head injury in children. Oxford University Press; 1995. pp. 147–164.

Satz PS, Alfano MS, Light RF, Morgenstern HF, Zaucha KF, Asarnow RF, Newton S. Review Persistent Post-Concussive Syndrome: A proposed methodology and literature review to determine the effects, if any, of mild head and other bodily injury. J Clin Exp Neuropsychol. 1999 Oct; 21(5):620-8.

Light R, Asarnow R, Satz P, Zaucha K, McCleary C, Lewis R Mild closed-head injury in children and adolescents: behavior problems and academic outcomes. J Consult Clin Psychol. 1998 Dec; 66(6):1023-9.

Asarnow RF, Satz P, Light R, Zaucha K, Lewis R, McCleary C. The UCLA study of mild head injury in children and adolescents. In: Michel ME, Broman S, editors. Traumatic head injury in childre

Depression and PCS

- "Depression is the best example of a psychiatric condition that can seriously complicate our understanding of recovery following mild head injury"

- Prevalence of 13% -77% and is a risk factor for poor recovery[1-6]
- Maeres et al 2011 found that preinjury depression/anxiety and acute post-traumatic stress (at 5-days post-injury) were predictive of post-concussive symptoms at 3-months.
- mTBI Patients who are depressed report lower QoL, lower satisfaction with life and poor memory abilities[7]
- Depressed patients have more severe PCS compared to non-depressed TBI patients
  - headache, blurred vision, dizziness, and memory impairment[8,9]

- Similarly Hutchinson found that pre-existing psychosocial and/or learning disabilities resulted in significantly longer recovery times.

- A great recent review by Broshek et al 2015 demonstrates that pre-morbid and concurrent anxiety increases the risk PCS.
  - propose that neurobiological abnormalities may serve as a pre-disposition for the expression of affective distress following a traumatic brain injury (i.e. diathesis/stress model).

1. Iverson, G Misdiagnosis of the persistent postconcussion syndrome in patients with depression. Archives of Clinical Neuropsychology 21 (2006) 303–310.
2. Rapoport MJ, McCullagh S, Streiner D, Feinstein A. The clinical significance of major depression following mild traumatic brain injury. Psychosomatics. 2003 Jan-Feb;44(1):31–7.
3. Mooney G, Speed J. The association between mild traumatic brain injury and psychiatric conditions. Brain Inj. 2001 Oct;15(10):865–77.
4. Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Harding HP, Matthews A, Mihalik JR, Cantu RC. Recurrent concussion and risk of depression in retired professional football players. Med Sci Sports Exerc. 2007 Jun;39(6):903–9.
5. Jain A, Mittal RS, Sharma A, Sharma A, Gupta ID. Study of insomnia and associated factors in traumatic brain injury. Asian J Psychiatr 2014;8:99-103.
6. Kim E, Lauterbach EC, Reeve A, Arciniegas DB, Coburn KL, Mendez MF, *et al.* Neuropsychiatric complications of traumatic brain injury: A critical review of the literature (A report by the ANPA Committee on Research). J Neuropsychiatry Clin Neurosci 2007;19:106-27.
7. O'Donnell ML, Creamer M, Pattison P, Atkin C. Psychiatric morbidity following injury. Am J Psychiatry 2004;161:507-14.
8. Goverover Y[1], Chiaravalloti N. 2014. **The impact of self-awareness and depression on subjective reports of memory, quality-of-life and satisfaction with life following TBI.** Brain Inj. 2014;28(2):174-80
9. Fann, J.R., Katon, W.J., Uomoto, J.M., Esselman, P.C. (1995). Psychiatric disorders and functional disability in outpatients with traumatic brain injuries. Am. J. Psychiatry 152, 1493–1499.
10. Rutherford, W.H. (1977). Sequelae of concussion caused by minor head injuries. Lancet 1, 1–4.

Alexander MP. Neuropsychiatric correlates of persistent postconcussive syndrome. J Head Trauma Rehabil. 1992;7:60–69. Kumar RG[1], Bracken MB, Clark AN, Nick TG, Melguizo MS, Sander AM. **2014 Relationship of Preinjury Depressive Symptoms to Outcomes 3 mos After Complicated and Uncomplicated Mild Traumatic Brain Injury.** Am J Phys Med Rehabil. Ahead of print

Broshek DK[1], De Marco AP, Freeman JR. Brain Inj.2015;29(2):228-37. **A review of post-concussion syndrome and psychological factors associated with concussion.**

Depression and PCS

- In a review by Busch and Alpern 1998 they conclude that MTBI is the triggering event for a set of pathophysiological changes and a concomitant depressive episode in a vulnerable population-

- Directional relationship between depression and mtbi:
- Vassallo et al found that remote psychiatric difficulties, individuals with mood, anxiety, and conduct disorders were 2.5, 1.6, and 1.7 times, respectively, more likely to sustain TBI

- *Very interestingly, mTBI subjects have higher rates of depression, postconcussive syndrome and poor global outcome than those with more severe TBI*[10]

- Uomoto and Esselman reported:
  - 95% of individuals that had sustained a MTBI reported *chronic pain* while only
  - 22% of those having suffered a moderate- to-severe TBI did so[11]

- Kumar found that preexisting depression is a risk factor for
  - poor affective/behavioral, cognitive, and mental health-related QOL outcomes at 3 months

Busch CR[1], Alpern HP. Neuropsychol Rev. 1998 Jun;8(2):95-108. **Depression after mild traumatic brain injury: a review of current research.**
Hutchinson M[1], Comper P, Csenge B, Richards D. **Psychosocial and psychological factors related to delayed recovery from concussion in high school students.** Br J Sports Med. 2014 Apr;48(7):610
Broshek DK[1], De Marco AP, Freeman JR. **A review of post-concussion syndrome and psychological factors associated with concussion.** Brain Inj.2015;29(2):228-37.

Uomoto JM, Esselman PC 1993. Traumatic brain injury and chronic pain: differential types and rates by head injury severity. Arch Phys Med Rehabil. 1993 Jan; 74(1):61-4.
Meares S, Shores EA, Taylor AJ, Batchelor J, Bryant RA, Baquley IJ, Chapman J, Gurka J, Marosszeky JE. The prospective course of postconcussion syndrome: the role of mild traumatic brain injury. Neuropsychology 2011;25:454–465.
Vassallo JL, Proctor-Weber Z, Lebowitz BK, Curtiss G, Vanderploeg RD. Psychiatric risk factors for traumatic brain injury. Brain Inj 2007; 21 (6) 567-573
Moore EL, Terryberry-Spohr L, Hope DA. **Mild traumatic brain injury and anxiety sequelae: a review of the literature.** *Brain Inj.* 2006;20:117–132

Anxiety and Concussions:

- We already know that pre-existing Depression and Anxiety are the greatest predictors of PCS
- Bryant and colleagues studied 1,084 patients with mTBI for 1 yr. They found:
  - generalized anxiety disorder 13.4%, posttraumatic stress disorder 13.0%, agoraphobia 12.8%, social phobia 9.0%, OCD 4.0%.

Anxiety Sensitivity

- Is considered a personality trait
- fearful response ass with an individual's own bodily sensations
- arises from the belief that these sensations are signs of impending harmful consequences(NOCEBO?)
- has been demonstrated to influence how individuals perceive pain following a concussion **
- Heightened anxiety sensitivity may contribute to how clinical populations, (especially mTBI), perceive their injuries. ***

Negative cognitive loop

- In this model, the initial concussion symptoms disrupt cognition
  - in vulnerable individuals, these transient symptoms can cause anxious and fearful reactions,
  - which can cause further cognitive disruption(in flight or flight mode)
- This alternating pattern of cognitive slips followed by anxiety which exacerbates cognitive disruption creating greater levels of anxiety can create a dysfunctional feedback loop.

- *Peterson RA, Heilbronner RL. The anxiety sensitivity index: construct validity and factor analytic structure. Anxiety Disorders 1987;1:117–121.
- **Whittaker R, Kemp S, House A. Illness perceptions and outcome in mild head injury: a longitudinal study. Journal of Neurology, Neurosurgery & Psychiatry 2007;78:644–646.
- *** Wood RL, McCabe M, Dwakins J. The role of anxiety sensitivity in symptom perception after minor head injury: an exploratory study. Brain Injury 2011;25:1296–1299.

Silver JM, Kay T. Persistent symptoms after a concussion. In: Arciniegas DB, Zasler ND, Vanderploeg RD, Jaffee MS, editors. Management of adults with traumatic brain injury.Arlington, VA: American Psychiatric Publishing; 2013. p 475–500.

Bryant RA, O'Donnell ML, Creamer M, McFarlane AC, Clark CR, Silove D. The psychiatric sequelae of traumatic injury. Am J Psychiatry 2010; 167 (3) 312-320

Kay et al 1992 Cognitive Impairment

When cognitive symptoms persist the individual may develop a “shaken sense of identity”1, Extra Motivated TEEN

Kay et al propose a model that psychological distress

- can create further cognitive compromise by suppressing attention, mental efficiency, learning and memory,
- this creates cognitive symptoms above and beyond those accounted for by the concussion.
- **avoidance of anxiety provoking situations (school avoidance!),**

The anxiety and avoidant behaviours may also lead to depression.

The psychological overlay accumulates and intensifies and may become more disabling than the initial injury.

Kay et al. also identified psychosocial factors that can affect recovery, including work or school demands, as well as pressure from teammates and coaches to return to competition.

THE CONCUSSION CYCLE

Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based alogorithms for diagnosis and optimized treatment. British Medical Bulletin 2003; 65:193–207.

Meyers JE[1], Grills CE, Zellinger MM, Miller RM 2014. **Emotional distress affects attention and concentration: the difference between mountains and valleys.** Appl Neuropsychol Adult. 2014;21(1):28-35..

Kay T, Newman B, Cavallo M, Ezrachi O, Resnick M. Toward a neuropsychological model of functional disability after mild traumatic brain injury. Neuropsychology 1992;6:371–384.

Anxiety & the *"Evolutionary Faux Pas"*

- The way I see it and explain it to child is that teenagers are an evolutionary "faux pas"
- This is one of the most stressful times in their lives and they have very little coping strategies in place

- Sources of stress:
  - School
  - Work
  - Career Aspirations
  - College University
  - Sport
  - Very Little Autonomy
  - Bullying
  - Body Image
  - Sexual Orientation

PTSD

- Carelson et al 2010 looked at 836 patients who had confirmed TBI,
  - 63.9% also had PTSD and 35.6% were given a diagnosis of an anxiety disorder other than PTSD.
- PTSD following mTBI has been linked to increased PCS *
- PTSD in children is driving the presence of pain, and not vice versa.**
- PTSD is strongly associated with CDH, suggesting that traumatic stress may lead to headache chronification.

- **Sawyer et al** 212 prospectively enrolled individuals within one week of mTBI who were hospitalized. Participants were assessed at baseline, 3, 6, and 12 months
  - Univariate regression revealed a significant ass btwn PTSD and worse recovery (p<.001).
  - Headache is more common in persons with PTSD
  - "Further research is needed to examine whether PTSD symptoms exacerbate headaches, or whether problematic headache symptoms exacerbate PTSD."

- Carlson KF, Nelson D, Orazem RJ, Nugent S, Cifu DX, Sayer NA. Psychiatric diagnoses among Iraq and Afghanistan war veterans screened for deployment-related traumatic brain injury. J Trauma Stress 2010; 23 (1) 17-24
- Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. N Engl J Med 2008; 358 (5) 453-463
- Arch Phys Med Rehabil. 2015 Jul 25. pii: S0003-9993(15)00589-4. doi: 10.1016/j.apmr.2015.07.006. [Epub ahead of print]
- **A Longitudinal Study of Headache Trajectories in the Year Following Mild TBI: Relationship to PTSD Symptoms.**
- Sawyer K[1], Bell KR[2], Ehde D[3], Temkin N[4], Dikmen S[5], Williams RM[6], Dillworth T[7], Hoffman JM[2].

- *Ponsford J, Cameron P, Fitzgerald M, Grant M, Mikocka-Walus A, Schönberger M 2012. Predictors of postconcussive symptoms 3 months after mild traumatic brain injury. Neuropsychology. 2012 May; 26(3):304-13.
- **Brown EA[1], Kenardy JA, Dow BL.2014 **PTSD Perpetuates Pain in Children With Traumatic Brain Injury.** J Pediatr Psychol. (ahead of print)
- ***Theeler BJ, Flynn FG, Erickson JC. **Chronic daily headache in U.S. soldiers after concussion.** Headache. 2012 May;52(5):732-8.

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FEAR and PCS

- In an interesting study using a rat model Reger et al. induced head injury.
  - They found that injured rodents demonstrated increased fear conditioning and an over-generalization of learned fear to conditioned and novel conditions
  - Flight or Fight?.

- Broshek et al 2015 discuss the implication of fear of concussion in the context of sports related concussion.
  - fear of re-injury,
  - fear of being perceived as weak,
  - fear of losing or not achieving a desired role,
  - fear of isolation
  - loss of affiliation with the team
  - fear of losing financial stability (income or scholarship),
  - pressure from teammates coaches etc
- They contend that patients can be functionally disabled by their concern about their symptoms

THIS DRIVES THE PERPETUAL FIGHT FLIGHT RESPONSE

- Emotional Intelligence Goleman 2006

- Reger ML, Poulos AM, Buen F, Giza CC, Hovda DA, Fanselow MS. Concussive brain injury enhances fear learning and excitatory processes in the amygdala. Biological Psychiatry 2012;71: 335–343
- Broshek, DK De Marco, AP & Freeman JR 2015. A review of post-concussion syndrome and psychological factors associated with concussion Brain Inj, 2015; 29(2): 228–237

To Summarize Thus Far

- What I believe happens is that many children at this age often barely able to cope with all of those stressors
- They then have a head injury where they miss school(get stressed and socially isolated), have their sport taken away from them(depressed), and have to deal with constant pain (effecting mood, ability to concentrate etc)
  - ALLOSTATIC LOAD
- This becomes too much for them and they become psychologically/emotionally exhausted and neurochemical changes ensure
  - VITAL EXHAUSTION/NEUROLOGY EXHAUSTION
- This is the true source of many of their symptoms
- Not the Sodium Potassium Glutamate etc imbalance that we know a concussion to be

Dopamine: The Unification of the Organic and Psychologic

- Bales et al 2015 calls Dopamine the Gatekeeper of cognitionDA is critical for a number of physiologic functions including hormone secretion, movement control, motivation, emotion, and cognitive processing (Jackson and Westlind-Danielsson, 1994; Floresco and Magyar, 2006).

- DAergic pathways in the CNS can be divided into two predominant systems:
- (1) the nigrostriatal pathway and
- (2) the mesocorticolimbic pathway projecting to the prefrontal cortex (PFC), hippocampus, amygdala, and nucleus accumbens (Alexander and Crutcher, 1990; Graybiel, 1990)

- DA receptors are abundantly expressed in brain areas known to be damaged after TBI, (prefontal frontal cortex and striatum), which are important for cognitive function

- DAergic system dysfunction within the PFC has been strongly tied to attentional and cognitive symptoms associated with schizophrenia and attention deficit hyperactivity disorder (ADHD; Heilman et al., 1991; Tassin, 1992; Knable et al., 1997; Tanaka, 2006).

- Dopamine levels have been shown to fluctuate greatly with head injury (McIntosh et al., 1994).
  - Donnemiller et al. (2000) used single photon emission computed tomography (SPECT) to show that striatal DAT binding is decreased in patients 4–5 months after severe TBI, even in cases where no anatomical evidence of direct striatal injury exists

- The efficacy of DA receptor agonists suggests that TBI patients benefit from the promotion of central DAergic transmission.
  - This could be a sign that DA release is suppressed after injury, that DA uptake is over active, or some combination of the two.
  - Alternatively, it might be the case that DA activity remains normal after injury, but that basal DA activity is inadequate in the face of the injury-induced disruptions. Bales etcI (Donnemiller et al., 2000).

- As quoted by **Persistent cognitive dysfunction after traumatic brain injury: A dopamine hypothesis James W. Bales**a,b,c,d,e, **Amy K. Wagner**a,b,c,f, **Anthony E. Kline**a,b,c,d,f,g, and **C. Edward Dixon**a,b,c,e,f,* *Neurosci Biobehav Rev*. 2009 July ; 33(7): 981–1003.
- Chen J, Johnston KM, Petrides M, Ptito A. Neural substrates of symptoms of depression following concussion in male athletes with persisting postconcussion symptoms. Archives of General Psychiatry 2008;65:81–89.
- **Persistent cognitive dysfunction after traumatic brain injury: A dopamine hypothesis James W. Bales**a,, **Amy K. Wagner**a,b,c,f, **Anthony E. Kline**a,b,c,d,f,g, and **C. Edward Dixon**a,b,c,e,f,* *Neurosci Biobehav Rev*. 2009 July ; 33(7): 981–1003.
- Vecht CJ, van Woerkom CA, Teelken AW, Minderhoud JM. 1975. Homovanillic acid and 5-hydroxyindoleacetic acid cerebrospinal fluid levels: a study with and without probenecid administration of their relationship to the state of consciousness after head injury. Arch Neurol 32: 792–797.
- 10.1016/j.neubiorev.2009.03.011

Dopamine: PFC the Unification of the Organic and Psychologic

- The PFC and hippocampus, are essential for memory formation.
- Mild traumatic brain injury often involves damage to the prefrontal cortex due to shearing forces of the frontal regions against the skull.
  - Effects on the PFC include **decreased glucose metabolism** (Fontaine et al., 1999), changes **in frontal lobe blood flow** during memory tasks (Ricker et al., 2001), and hypoactivation with memory tasks (Sanchez-Carrion et al., 2008).
  - Gould et al 2014 and Kinsella et al 1988 hypothesize anxiety from head injury is secondary to focal and diffuse injury that can perturb **the inhibitory functioning of the prefrontal cortex and lead to over-activation of the amygdala** and other subcortical limbic structures.
  - PTSD involves an exaggerated response of the amygdala-resulting in impaired regulation by the medial prefrontal cortex.

- Koenigs et al 2008 propose that the neurobiological basis of anxiety disorders may be due to a complex interaction between PFC and the amygdala
  - TBI causes an imbalance in excitatory and inhibitory components of these circuits.

- **In terms of Microglia and Dopamine…**we know that microglial can cause both healing and damage to the brain. Its activity is increased by head injury and stress.
- In a study by Brew et al 2015 they found that dopamine can be protective to the developing brain as it was asscoaited with decreased apoptosis, oxidative stress and decreased neuroinflammtion in white matter and caudate nucleus

- **James W. Bales**, **Amy K. Wagner**, **Anthony E. Kline**a, and **C. Edward Dixon 2009 Persistent cognitive dysfunction after traumatic brain injury: A dopamine hypothesis** *Neurosci Biobehav Rev*. 2009 July ; 33(7): 981–1003.
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- **James W. Bales**, **Amy K. Wagner**, **Anthony E. Kline**a, and **C. Edward Dixon 2009 Persistent cognitive dysfunction after traumatic brain injury: A dopamine hypothesis** *Neurosci Biobehav Rev*. 2009 July ; 33(7): 981–1003.
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- Levita L, Bois CC, Healey A, Smyllie E, Papakonstantiou E. The behavioural inhibition system, anxiety and hippocampal volume in a non-clinical population. Biology of Mood & Anxiety Disorders 2014;4:1–10
- Brew N[1], Azhan A[1], den Heijer I[1], Boomgardt M[1], Davies GI[1], Nitsos I[1], Miller SL[1], Walker AM[1], Walker DW[2], Wong FY. **Dopamine treatment during acute hypoxia is neuroprotective in the developing sheep brain.** Neuroscience. 2015 Dec 19. pii: S0306-4522(15)01107-0. doi: 10.1016/j.neuroscience.2015.12.022

Hippocampus and Dopamine

- Hippocampus, and limbic structures have albeen shown to be sensitive to damage after TBI (Dixon et al., 1987; Lighthall, 1988; Lighthall et al., 1989, Stuss et al., 1985; Levin, 1990; Ponsford and Kinsella, 1992; McDowell et al., 1997).
  - The hippocampus, which is also critical for cognitive function does not have a high level of DA receptor expression, but is dependent on DA activity to modulate function
- Mild TBI models show diffuse white matter damage, cortical cell loss, and **hippocampal** cell loss (Hicks et al., 1993; Sanders et al., 2001),
  - DA receptors in the hippocampus are the physiologic basis for memory formation and consolidation (Li et al., 2003; Lemon and Manahan-Vaughan, 2006).
  - In experimental TBI the hippocampus is exquisitely sensitive to both acute apoptotic events and excitotoxicity (Kotapka et al., 1991; Hicks et al., 1993; Dietrich et al., 1994; Smith et al., 1994).
  - Damage to the hippocampus causes reproducible deficits in spatial and temporal memory processing (Buckley, 2005).
  - Bremmer et al found a connection between reduced hippocampal volumes and in trauma-exposed populations.
- Sapolsky propose high levels of glucocorticoids can decrease hippocampal volume (STRESS RESPONSE).
- Levita et al. show decrease hippocampal may cause anxiety
- Decreased hippocampal volume has also been associated with depressive episodes, and increased volumes ass w symptom resolution

- Koenigs M, Huey ED, Raymont V , et al. Focal brain damage protects against post-traumatic stress disorder in combat veterans. Nat Neurosci 2008; 11 (2) 232-237
- Gould KR, Ponsford JL, Spitz G. Association between cognitive impairments and anxiety disorders following traumatic brain injury. J Clin Exp Neuropsychol 2014; 36 (1) 1-14
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- Vertes RP. Interactions among the medial prefrontal cortex, hippocampus and midline thalamus in emotional and cognitive processing in the rat. Neuroscience 2006;142:1–20.

Serotonin and Head Injury

- Vecht et al., 1975 found levels of dopamine and serotonin were reduced in the cerebrospinal fluid of patients with TBI

- Mobayed M, Dinan TG found patients who were depressed following mTBI have blunted prolactin response to buspirone,
  - They propose there is altered serotonin function and this is what differentiates depressed vs non depressed TBI patient
- More recently Booji 2015 looked at serotonin and head Injury
  - Serotonin plays an important role in the etiology of depression.
  - Serotonin is also crucial for brain development.
  - animal studies have demonstrated that early disruptions in the serotonin system affect brain development and emotion regulation in later life.

- A plausible explanation is that environmental stressors reprogram the serotonin system through epigenetic processes by altering serotonin system gene expression.
- This in turn may affect brain development, including the hippocampus, a region with dense serotonergic innervations and important in stress-regulation.

- These results suggest that serotonin transporter methylation may be involved in physiological gene-environment interaction in the development of stress-related brain alterations.

- Booij L[1], Szyf M[2], Carballedo A[3], Frey EM[4], Morris D[3], Dymov S[2], Vaisheva F[2], Ly V[2], Fahey C[5], Meaney J[6], Gill M[7], Frodl T[8]**DNA methylation of the serotonin transporter gene in peripheral cells and stress-related changes in hippocampal volume: a study in depressed patients and healthy controls.** **PLoS One.** 2015 Mar 17;10(3):
- Mobayed M, Dinan TG. Buspirone/prolactin response in post head injury depression. J Affect Disord 1990;19:237-41.

Sleep from Rao et al 2015

- In a great review by Rao et al:
  - Sleep disturbances are common after TBI, and disrupt recovery.
  - Sleep disturbances can be secondary to brain injury or caused by secondary factors
    - medical comorbidities, pain, medication side effects, stress etc.
  - They identify sleep issues like insomnia, sleep apnea, hypersomnia, circadian rhythm sleep–wake cycle disorders and parasomnias

- Ouellet et al found 50% of TBI patients have been found to experience chronic insomnia.
  - This study also found Milder severity of injury, severe depressive symptoms, severe pain, and fatigue have been found to be predictors of insomnia

- In a more recent study Towns et al 2015 found
  - 92% of patients with mTBI reported poor sleep.
  - Sleep quality significantly accounted for the variance in PCS, ($p < 0.001$),

- **They Conclude**
  - While sleep is associated with PCS severity, psychological distress is a more potent predictor

- Studies by Ponsford et al 2012, Fogelberg et 2012 and Mathis and Alvaro 2012 sleep problems after TBI have been linked to anxiety, depression, cognitive difficulties, and trouble with rehab.
- **Ponsford** JL, Ziino C, Parcell DL, Shekleton JA, Roper M, Redman JR, Phipps-Nelson J, Rajaratnam SM. 2012 Fatigue and **sleep** disturbance following traumatic brain injury--their nature, causes, and potential treatments. J Head Trauma Rehabil. 2012 May-Jun;27(3):224-33
- **Fogelberg** DJ, Hoffman JM, Dikmen S, Temkin NR, Bell KR. Association of **sleep** and co-occurring psychological conditions at 1 year after traumatic brain injury.
- Arch Phys Med Rehabil. 2012 Aug;93(8):1313-8..
- **Mathias** JL, Alvaro PK. 2012 Prevalence of **sleep** disturbances, disorders, and problems following traumatic brain injury: a meta-analysis. **Sleep** Med. 2012 Aug;13(7):898-905

Rao V[1], Koliatsos V[1], Ahmed F[1], Lyketsos C[1], Kortte K[2]. **Neuropsychiatric disturbances associated with traumatic brain injury: a practical approach to evaluation and management** Semin Neurol. 2015 Feb;35(1):64-82. doi: 10.1055/s-0035-1544241. Epub 2015 Feb 25.

Ouellet MC, Beaulieu-Bonneau S, Morin CM. Insomnia in patients with traumatic brain injury: frequency, characteristics, and risk factors. J Head Trauma Rehabil 2006; 21 (3) 199-212

The Concept of Resilience/Adaptation

- Resilience is defined as the ability to rebound and recover after insult.
  - It has been proposed that those with less resilience are more likely to develop PCS [1, 2]
- Losoi et al found that: Resilience prevents fatigue after mtbi
- Merritt el al: 142 military: higher resilience reported fewer PCS and PTSD-related symptoms
- Sullivan et al 2015: perceived psychological resilience was the strongest predictor of PCS-like symptomatology
  - even more than a history of mtbi.

1. Losoi H[1], Wäljas M, Turunen S, Brander A, Helminen M, Luoto TM, Rosti-Otajärvi E, Julkunen J, Ohman J 2014 J Head Trauma Rehabil. 2014 May 16. **Resilience Is Associated With Fatigue After Mild Traumatic Brain Injury.**
2. Merritt VC[1], Lange RT, French LM. 2015 **Resilience and symptom reporting following mild traumatic brain injury in military service members.** Brain Inj. Jul 23:1-12.
- Losoi H[1], Wäljas M, Turunen S, Brander A, Helminen M, Luoto TM, Rosti-Otajärvi E, Julkunen J, Ohman J 2014 J Head Trauma Rehabil. 2014 May 16. **Resilience Is Associated With Fatigue After Mild Traumatic Brain Injury.**
- Sullivan KA[1], Edmed SL[1], Allan AC[2], Smith SS[2], Karlsson LJ[1]. **The role of psychological resilience and mTBI as predictors of postconcussional syndrome symptomatology.** Rehabil Psychol. 2015 May;60(2):147-54

Coping Strategies and Cognition

- It has been postulated that a lack of coping skills or neural reserve influence the development of PCS in children (Dennis, Yeates, Taylor, & Fletcher, 2007)

- Woodrome et al 2011 go as far as to say that
  - "interventions designed to prevent or ameliorate post-concussive symptoms should focus on identification of children with mild TBI who use maladaptive coping strategies"
  - They identify emotion-focused strategies and problem-focused disengagement as detremental

- Stacey E. Woodrome, Keith Owen Yeates, H. Gerry Taylor, Jerome Rusin, Barbara Bangert, Ann Dietrich, Kathryn Nuss, and Martha Wright. 2011. **Coping Strategies as a Predictor of Post-concussive Symptoms in Children with Mild Traumatic Brain Injury *versus* Mild Orthopedic Injury.** J Int Neuropsychol Soc. Mar 2011; 17(2): 317–326.
- Dennis M, Yeates KO, Taylor HG, Fletcher JM. Brain reserve capacity, cognitive reserve capacity, and age-based functional plasticity after congenital and acquired brain injury in children. In: Stern Y, editor. Cognitive reserve. New York: Taylor & Francis; 2007. pp. 53–83.
- Gasquoine PG. 1997 Review Postconcussion symptoms. Neuropsychol Rev; 7(2):77-85.

Is PCS Due to The Pain?

- Uomoto and Esselman report that 95% of individuals that had sustained a MTBI reported chronic pain
  - only 22% of those having suffered a moderate- to-severe TBI did so
  - "These results underscore the high frequency of chronic pain problems in the mild head injury population and implicate the need for avoiding the mislabeling of symptoms such attentional deficits or psychological distress as attributable only to head injury sequelae in those with coexisting chronic pain.
- Recently Weyer et al 2013 in their study of chronic pain and PCS found that
  - high chronic pain exacerbates the emotional aspect of PCS .
- Taylor et al 2010 propose that physical discomfort or difficulties in adjusting to the effects of injury, are likely to contribute to PCS after mTBI.
- Pain is known to be associated with a variety of cognitive, emotional, and behavioral symptoms (Beaupre, De Guise, McKerral, 2012).
- Hart et al in their review report those with chronic pain have impairments on measures of attention, processing speed, and psychomotor speed were often present in the chronic pain
- Eccleston and Crombez 1999 propose pain may compete with other attentional demands, leading to difficulties with attention

- Weyer Jamora C[1], Schroeder SC, Ruff RM**Pain and mild traumatic brain injury: the implications of pain severity on emotional and cognitive functioning.** Brain Inj. 2013;27(10):1134-40. doi: 10.3109/02699052.2013.804196. Epub 2013 Jul 29.
- H. Gerry Taylor, Ann Dietrich, Kathryn Nuss, Martha Wright, Jerome Rusin, Barbara Bangert, Nori Minich, and Keith Owen Yeates. 2010. **Post-Concussive Symptoms in Children with Mild Traumatic Brain Injury.** Neuropsychology. Mar 2010; 24(2): 148–159.
- Hart RP, Martelli MF, Zasler ND 2000. Review Chronic pain and neuropsychological functioning. Neuropsychol Rev. 2000 Sep; 10(3):131-49.
- Eccleston C, Crombez G. 1999. Review Pain demands attention: a cognitive-affective model of the interruptive function of pain. Psychol Bull. 1999 May; 125(3):356-66.
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- Beaupré M, De Guise E, McKerral M. 2012. The Association between Pain-Related Variables, Emotional Factors, and Attentional Functioning following Mild Traumatic Brain Injury. Rehabil Res Pract. 2012; 2012():924692.

Post Concussion Syndrome: Bringing it Home

- At the end of the day It starts with a concussion/organic injury but at some point (1 month/three month?) the influence changes-its just hard to tell when
- Perpetual flight or flight
- In large part its almost inconsequential as you cant treat a concussion anyway-you manage a concussion.
- You have to rule out all other causes and treat symptoms
- You can treat mood and optimize mental health, sleep and eating
- Anxiety stress, and pain issues cause the prolongation of symptoms and must be addressed
- What I believe is that one cannot separate mind from body and when one is “broken” the other will eventually break (Overtraining syndrome)

- Physical injury can lead to psychological injury which then in turn can lead back into physiologic injury.

- There is a strong tie between physical and psychological symptoms
  - the more one has of one, the more one has of the other (simon et al 1999)

– Simon G, Von Korff M, Picinelli M, Fullerton C, Ormel J. An international study N Engl J Med 1999;341:1329–55.

Workup/Treatment

- All About the History
- Physical Exam
- At 4 weeks
  - Blood work
  - Ensure all possible physical contributors are dealt with
  - Get a sense of how full their plate is

- 3-6 months consider imaging looking for Chiari or evidence of previous brain bleed

- Starts with supplements
- Eating, sleeping, and drinking optimization
- Education
- Break the cycle
  - Elavil vs other headache treatments
  - Adjust the neurochemicals
    - Stimulants or Antidepressants

Treatment

PSMCO
Pediatric Sports Medicine
Clinic of Ottawa

EASTERN ONTARIO
Concussion
CLINIC

MPH and TBI

1) Acta Neurol Scand.2016 **Long-term treatment with methylphenidate for fatigue after traumatic brain injury.**

Johansson B, Wentzel AP, Andréll P, Rönnbäck L, Mannheimer C.

- Methylphenidate can be a treatment option for long-term mental fatigue and cognitive impairment after a TBI.

2) Brain Inj. 2014;28(3):304-10. **Evaluation of dosage, safety and effects of methylphenidate on post-traumatic brain injury symptoms with a focus on mental fatigue and pain.**

Johansson B, Wentzel AP, Andréll P, Odenstedt J, Mannheimer C, Rönnbäck L.

- Methylphenidate decreased mental fatigue for subjects suffering a traumatic brain injury, the treatment is considered to be safe and is recommended, starting with a low dose.

3) Brain Inj. 2015;29(6):758-65. doi: 10.3109/02699052.2015.1004747. Epub 2015 Mar 20.

Methylphenidate reduces mental fatigue and improves processing speed in persons suffered a traumatic brain injury.

Johansson B, Wentzel AP, Andréll P, Mannheimer C, Rönnbäck L.

- Methylphenidate was generally well-tolerated and it improved long-lasting mental fatigue and processing speed after traumatic brain injury.

Thank You

- "Now this is not the end. It is not even the beginning of the end, but it is, perhaps, the end of the beginning." November 1942