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AUSTRALIA
CREATE CHANGE

Concussion in childhood: Mechanisms and management

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CHRC, University of Queensland

Declarations

Motor Accident Insurance Commission (QLD) – funding of university position

Children's Hospital Foundations – QLD and Calgary

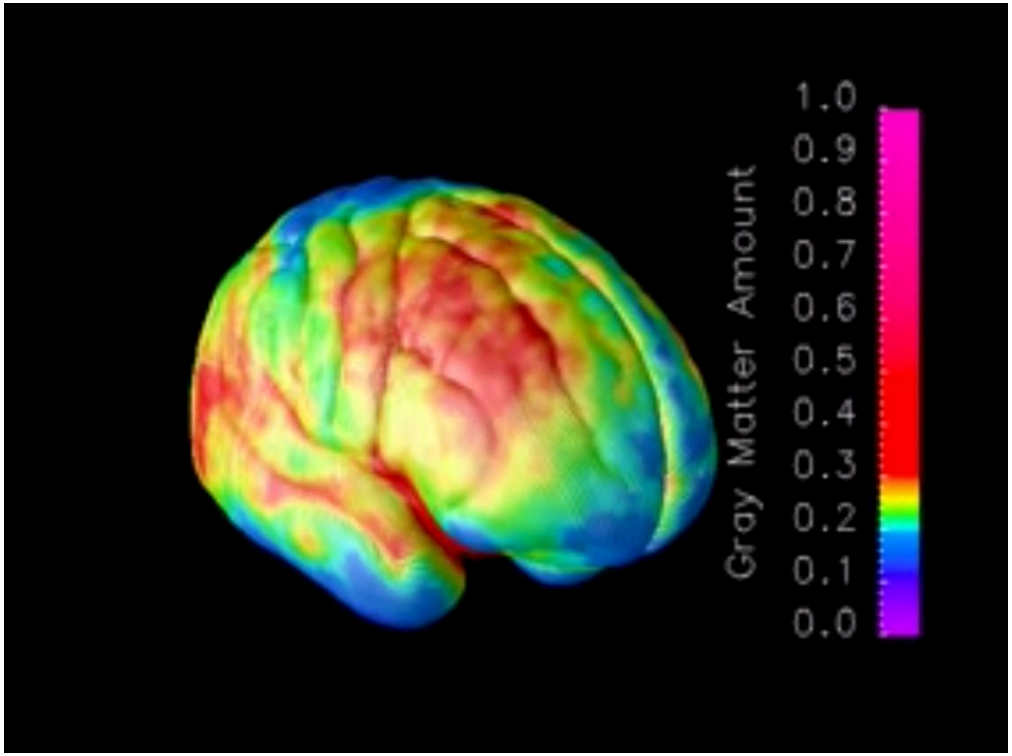
No conflicts of interest

Objectives

- Discuss outcome of pediatric concussion
- Examine mechanisms of symptom persistence
  - Use of neuroimaging “biomarkers”

- Management of children with persistent symptoms
- Results of RCT of melatonin to treat persistent symptoms
- Brain connectivity to assess treatment response

Childhood: a **critical time of brain development**



- Cortical development in childhood
  - pruning of synapses and dendritic spines
- Pronounced in prefrontal regions
  - differs between cortical layers
- Puberty associated with
  - More pruning and myelination
- Developmental synchronization between connected regions
  - Synaptic tuning
- Different biomechanical properties
  - Increased brain water content, decreased myelination
  - Decreased neck strength
  - **Increased susceptibility to injury**

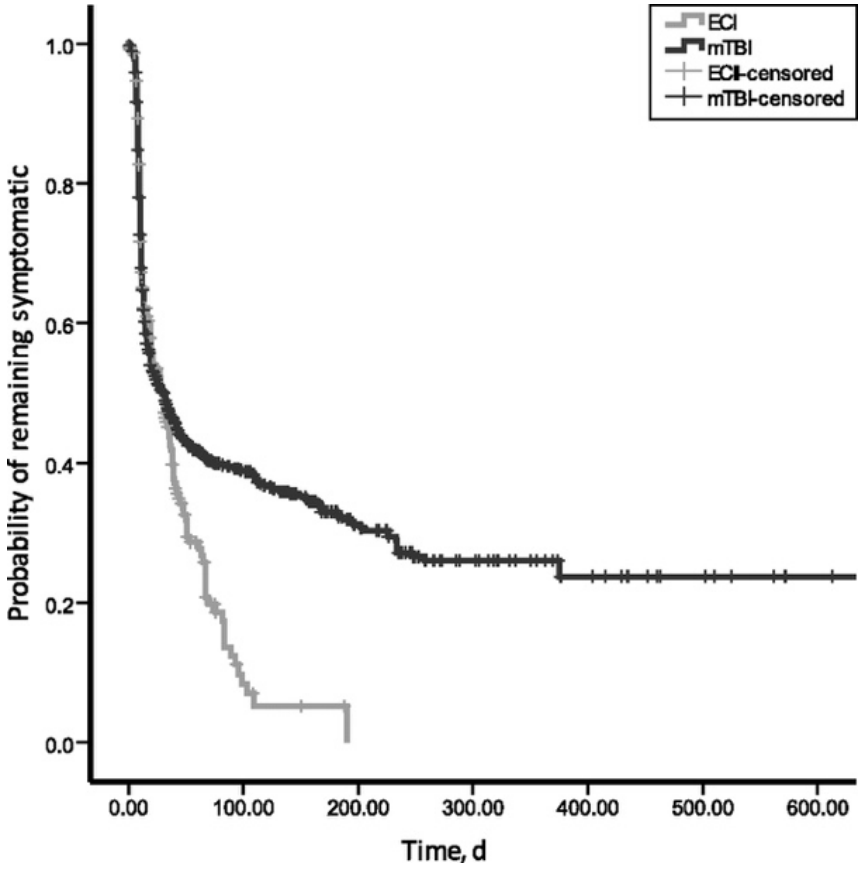
Giedd and Rapoport, Neuron. 2010

Krongold et al, Cereb. Cortex (2015)

Paediatric mTBI

- 15% of children sustain TBI by 16 years
- 80% may present to GP only
- Present later for medical attention compared to mod/severe TBI
- Diagnosis can be challenging

- Natural history is recovery for majority
- 25% have symptoms 1 month
- 11% at 3 months, 3% by 1 year
- Significant impairments in HRQoL
- NNT considerations



McKinlay, Brain Injury, 2008
Barlow et al, Pediatrics 2010
Zemek, JAMA Peds 2016

RISK FACTORS

- Female;
- Youth > Adult
- Certain sports (Rugby, Football, Hockey, Boxing!)

  Certain positions on the team

  Using caffeinated beverages
- Migraine;
- Previous concussion (3 x higher)
- ADHD
- Genotypes?

Diagnosis can be difficult

Alteration in brain function

- Easier if there has been LOC or transient focal neurological deficit
  - But this occurs only in 10%
- Loss of memory, confusion and/or disorientation
  - can be influence by traumatic stress too
- Or evidence of brain pathology e.g. on CT scan
  - (although imaging is not usually indicated)

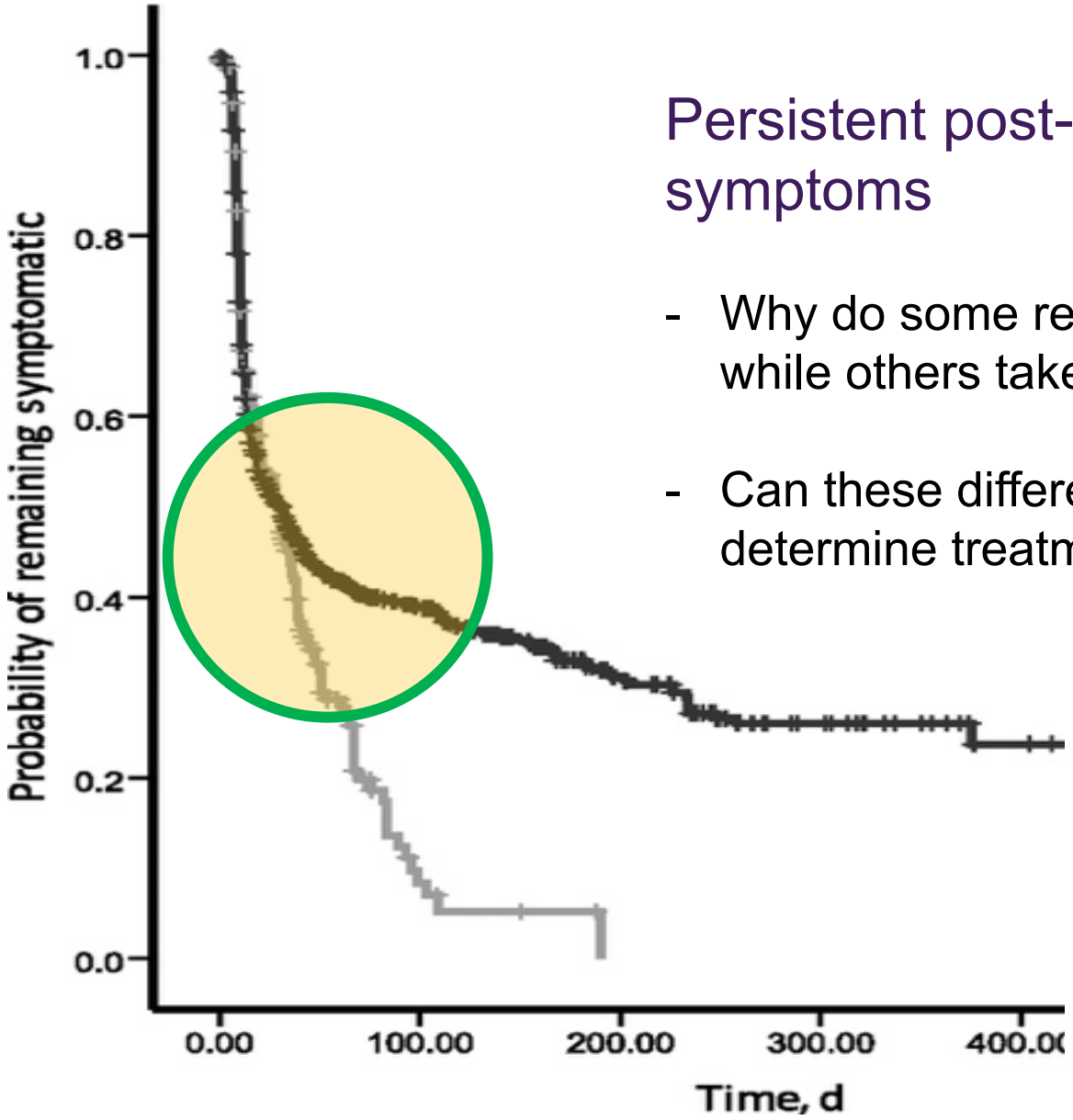
GCS not < 13
LOC not > 30min
PTA not > 24 hours

External force

- a reasonable force which could cause pathology

Symptoms should have a temporal relationship

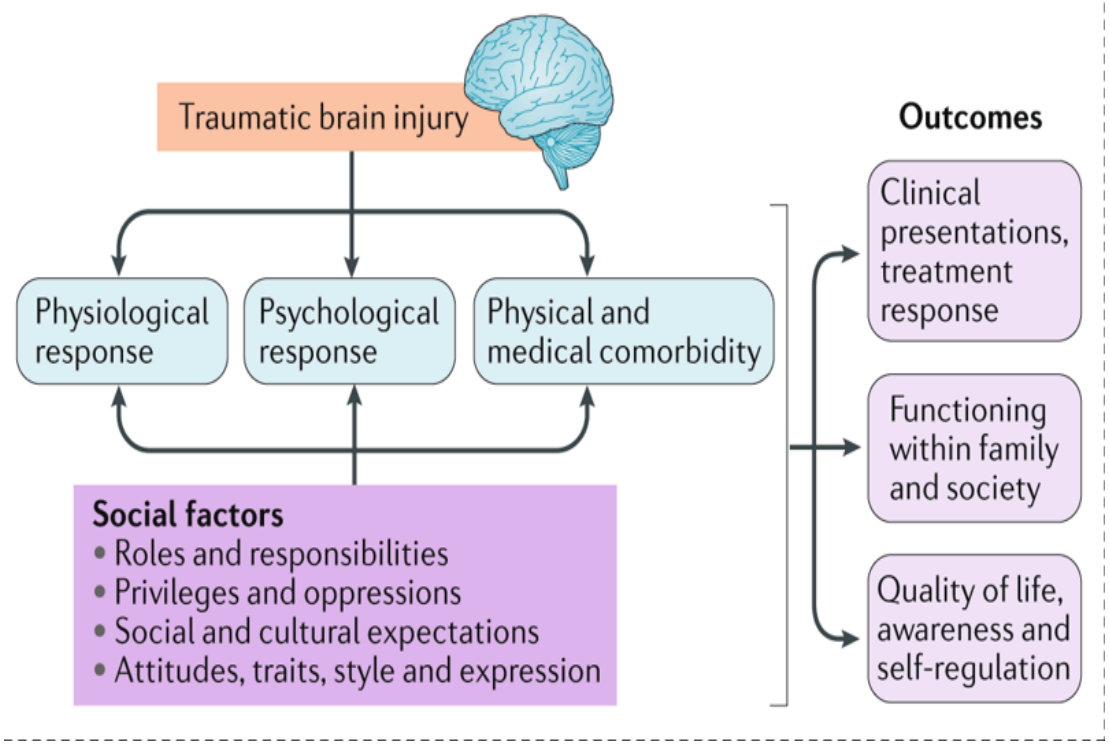
- usually immediately, headache can occur within a couple of days



Persistent post-concussion symptoms

- Why do some recover quickly while others take a long time?
- Can these differences help determine treatments?

The biopsychosocial model
Complex interplay between environment, injury and outcome



- Injury severity
- Age, Gender
- Pre-injury Function
- Socioeconomic circumstances important moderator of outcome
- Family dysfunction also effects outcome
- “Double hazard” theory

Mollayeva et al, Nature Reviews Neurology 2018
Crowe et al, J Ped Psych, 2012
Escalana, 1982; Anderson, 2005

Persistent Post Concussion Symptoms

Combined or in isolation

- Physical (headache, dizziness)
- Cognitive (Memory/concentration)
- Emotional (Depression/anxiety)
- Sleep disruption
- For 4 weeks or more

No diagnostic test or biomarker

Subject to attribution biases e.g. good old days bias

Brooks B, Mikrogianakis, Barlow Arch Clin Neuropsychol. 2014.
Barlow, J Child Neur, 2014
Barlow, Ped Neur (2015)

JAMA The Journal of the American Medical Association
March 8, 2016, Vol 315, No. 10 >

Original Investigation | March 8, 2016

Clinical Risk Score for Persistent Postconcussion Symptoms Among Children With Acute Concussion in the ED

Roger Zemek, MD[1]; Nick Barrowman, PhD[2]; Stephen B. Freedman, MDCM, MSc[3]; Jocelyn Gravel, MD[4]; Isabelle Gagnon, PhD[5]; Candice McGahern, BA[2]; Mary Aglipay, MSc[2]; Gurinder Sangha, MD[6]; Kathy Boutis, MD[7]; Darcy Beer, MD[8]; William Craig, MDCM[9]; Emma Burns, MD[10]; Ken J. Farion, MD[1]; Angelo Mikrogianakis, MD[11]; Karen Barlow, MD[12]; Alexander S. Dubrovsky, MDCM, MSc[5]; Willem Meeuwisse, MD, PhD[13]; Gerard Gioia, PhD[14]; William P. Meehan III, MD[15]; Miriam H. Beauchamp, PhD[16]; Yael Kamil, BSc[2]; Anne M. Grool, MD, PhD, MSc[2]; Blaine Hoshizaki, PhD[17]; Peter Anderson, PhD[18]; Brian L. Brooks, PhD[19]; Keith Owen Yeates, PhD[20]; Michael Vassilyadi, MDCM, MSc[21]; Terry Klassen, MD[8]; Michelle Keightley, PhD[22]; Lawrence Richer, MD[23]; Carol DeMatteo, MSc[24]; Martin H. Osmond, MDCM[1] ; for the Pediatric Emergency Research Canada (PERC) Concussion Team

Risk factors for symptoms at 1 month

- female
- age ≥8 years,
- migraine history
- previous concussion symptoms lasting >1 week,

- Lots of acute symptoms:
  - headache, noise sensitivity, fatigue, answering questions slowly
- ≥4 errors on BESS

Concussion

R—Reassurance

Normalize symptoms & educate about recovery process. Typically symptoms subside within 7-10 days.

E—Ease into things

Promote sleep hygiene, adequate hydration and regular meals with snacks. First 2 days rest and then return to school with modified activities.

S—Seek Help

Drowsiness, weakness, severe headaches, or persistent symptoms.

T—Treat & Comfort

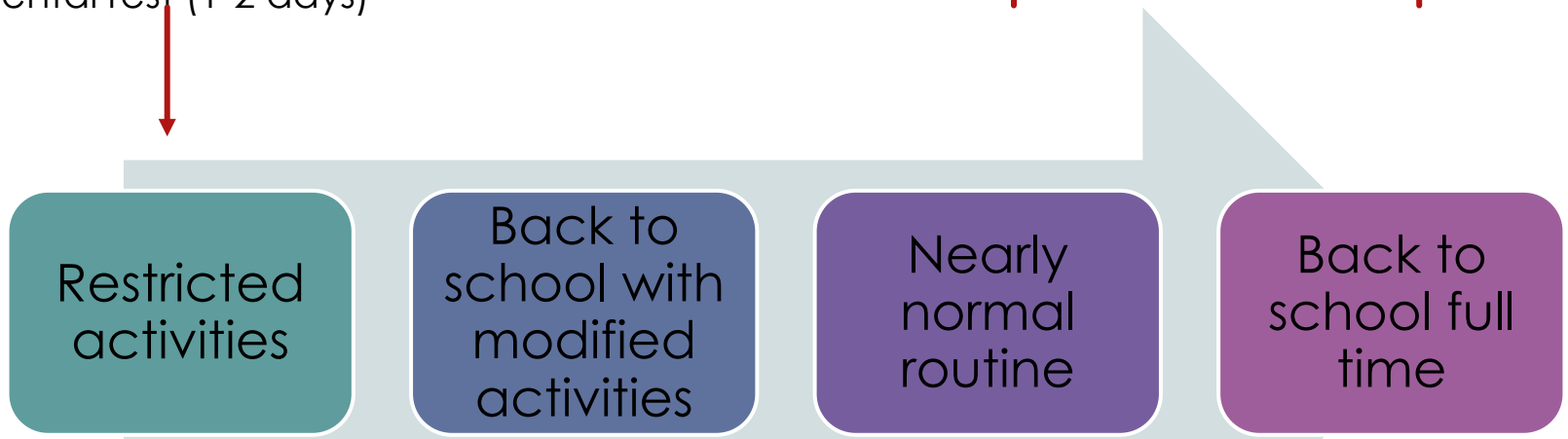
For headaches use cold compresses, Advil or Tylenol (for 1st two weeks).

SEND FAMILY HOME WITH CONCUSSION TEACHING SHEETS

"Return to Learn"

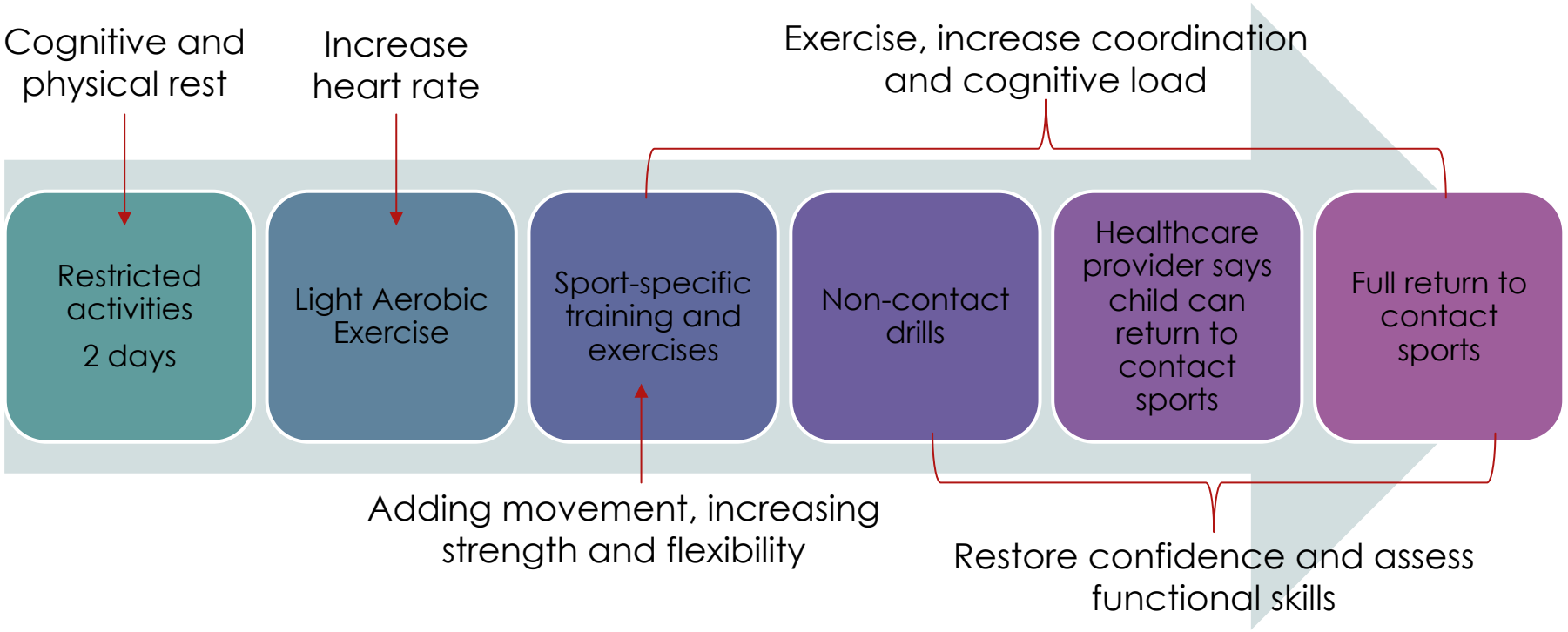
No physical activities. Allowing cognitive and mental rest (1-2 days)

Attempting longer days at school with introduction of previously restricted activities



Attempting half days at school with some activities requiring cognitive and mental efforts

"Return to Play"

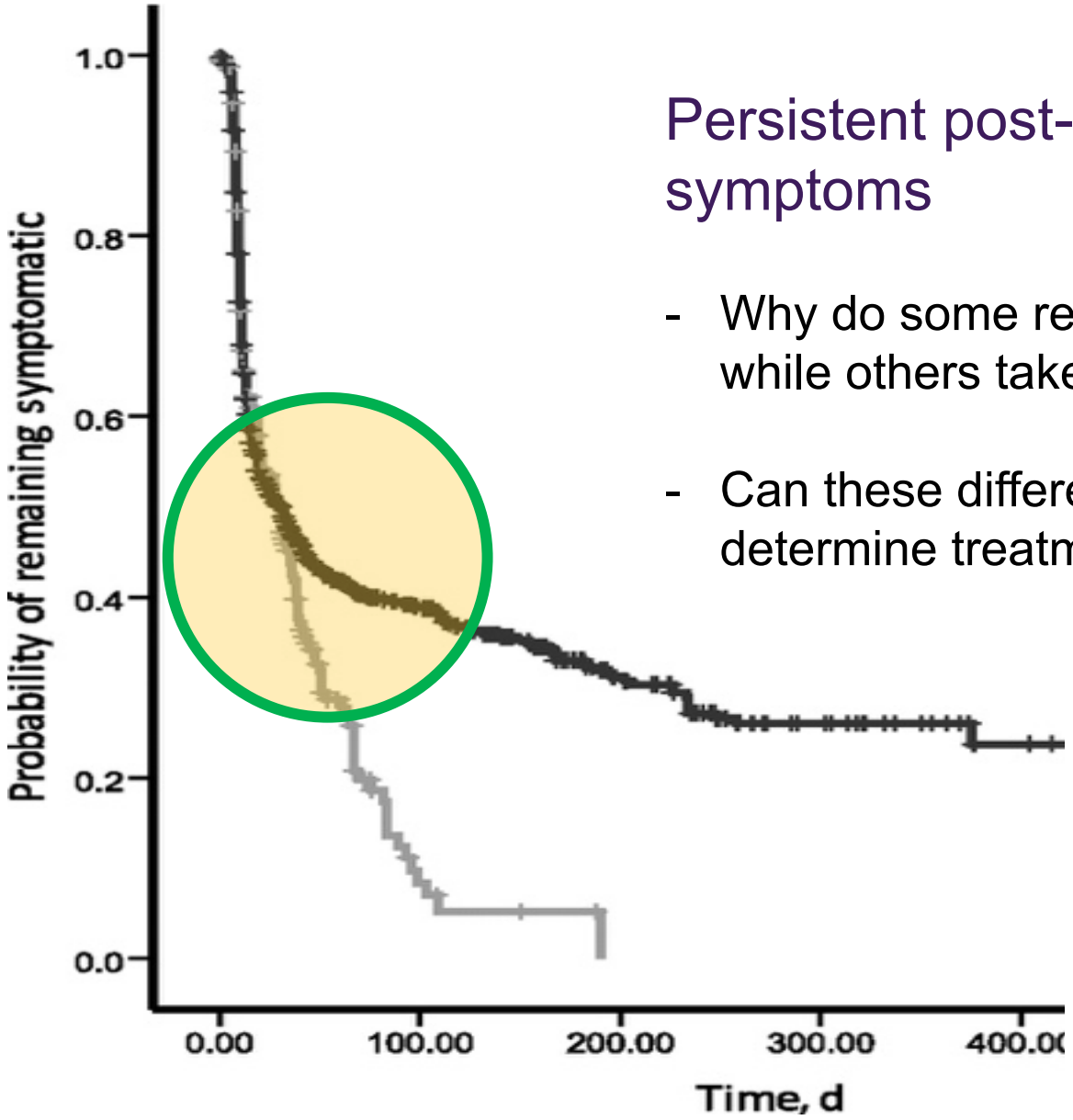


Keys to a Good Recovery

Regular bedtimes and good sleep hygiene practices

Balance meals and snacks, with adequate hydration

Avoiding medication overuse



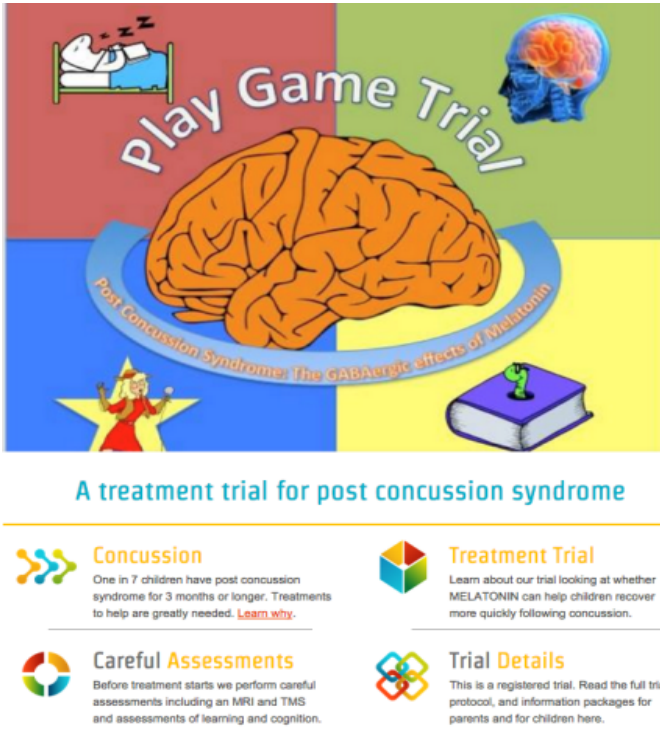
Persistent post-concussion symptoms

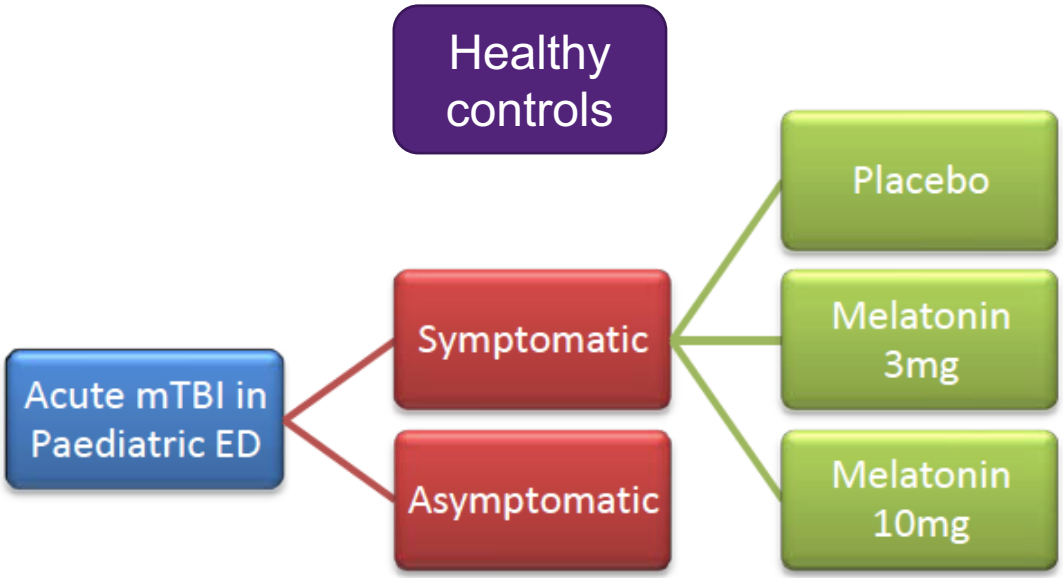
- Why do some recover quickly while others take a long time?
- Can these differences help determine treatments?

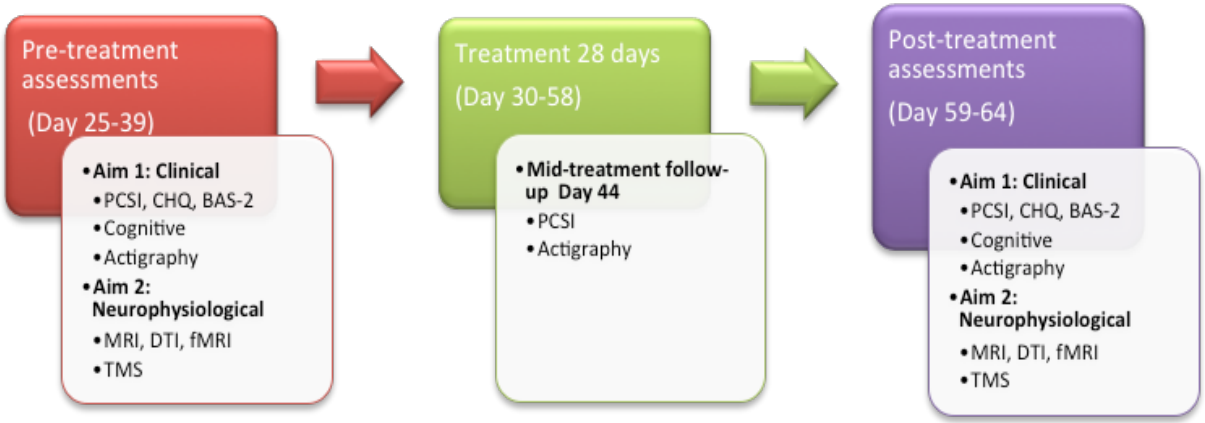
Exploring why some children have persistent symptoms PLAY GAME trial

- Randomized double blind controlled trial
- Dose dependent response assessment, three parallel group design
  - **Placebo**
  - **3mg melatonin**
  - **10mg melatonin**
  - 33 per group

- Use adjunctive techniques (*integrating* fMRI, DTI and TMS) to elucidate alterations in neuronal function and circuitry.



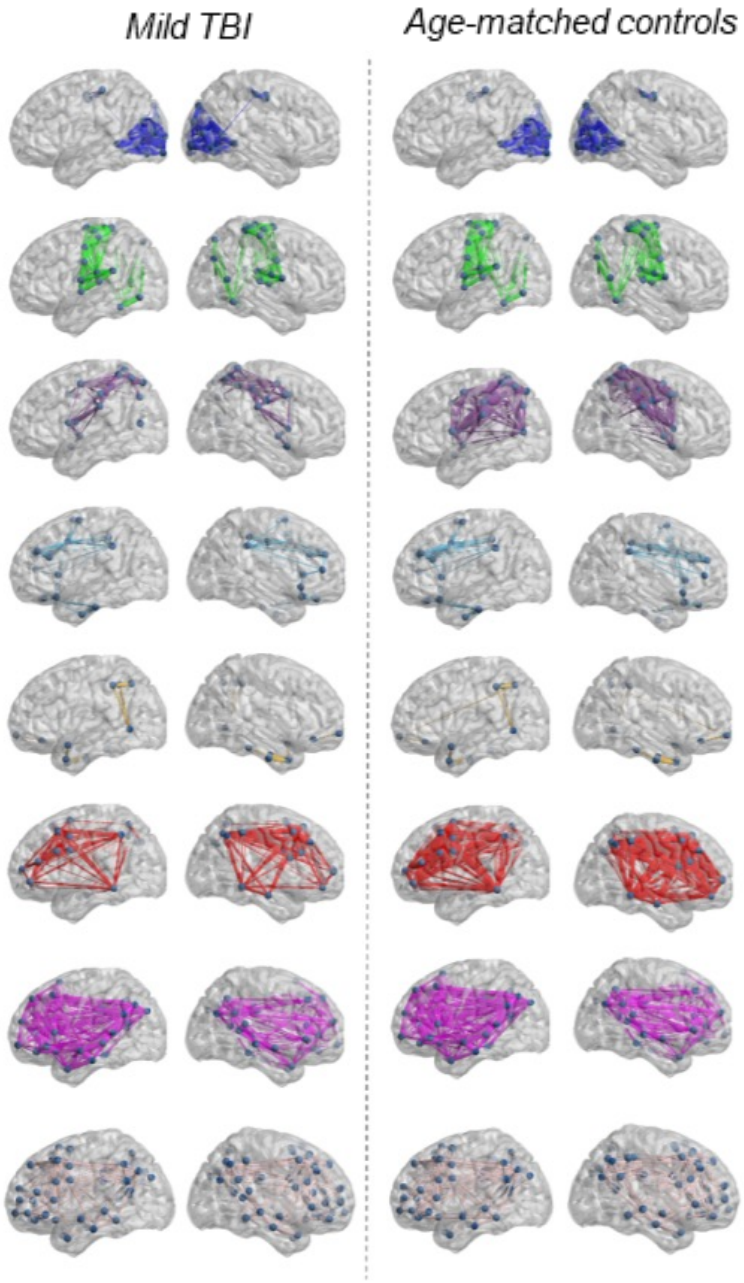

Healthy controls
Acute mTBI in Paediatric ED
Symptomatic
Asymptomatic
Placebo
Melatonin 3mg
Melatonin 10mg


Pre-treatment assessments
(Day 25-39)
•Aim 1: Clinical
•PCSI, CHQ, BAS-2
•Cognitive
•Actigraphy
•Aim 2: Neurophysiological
•MRI, DTI, fMRI
•TMS
Treatment 28 days
(Day 30-58)
•Mid-treatment follow-up Day 44
•PCSI
•Actigraphy
Post-treatment assessments
(Day 59-64)
•Aim 1: Clinical
•PCSI, CHQ, BAS-2
•Cognitive
•Actigraphy
•Aim 2: Neurophysiological
•MRI, DTI, fMRI
•TMS

Exploring Persistent Symptoms with Advanced Neuroimaging

Micro-Structural	Functional	Cerebral blood flow	Metabolic	Neurotransmission
• Grey matter volume/thickness • White matter hyperintensities • White matter anisotrophy • WM Tracts	• Resting state fMRI • Task-related fMRI • (dynamic connectivity)	• Arterial spin labelling fMRI	• MRS	• Brain connectivity • TMS

Brain networks
- structural
- dynamic



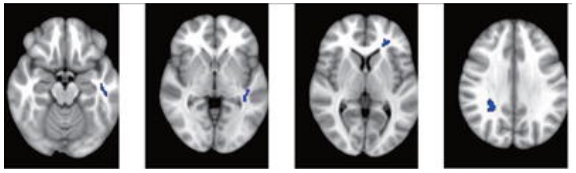
Default mode network

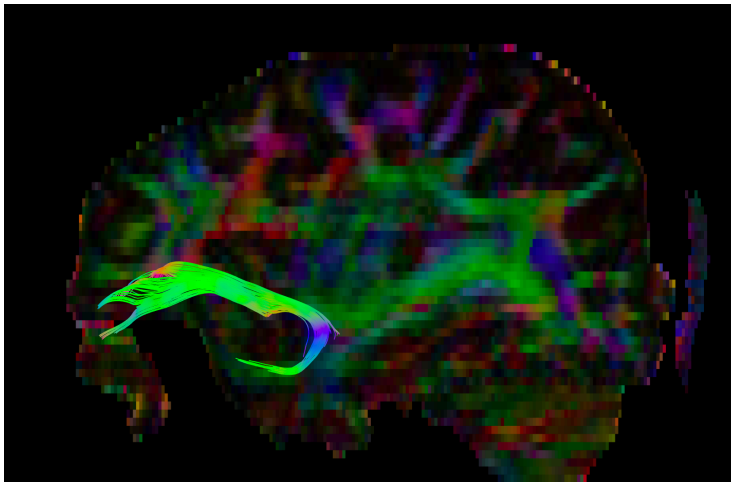
Structural brain changes in group analyses

- some tracts more vulnerable

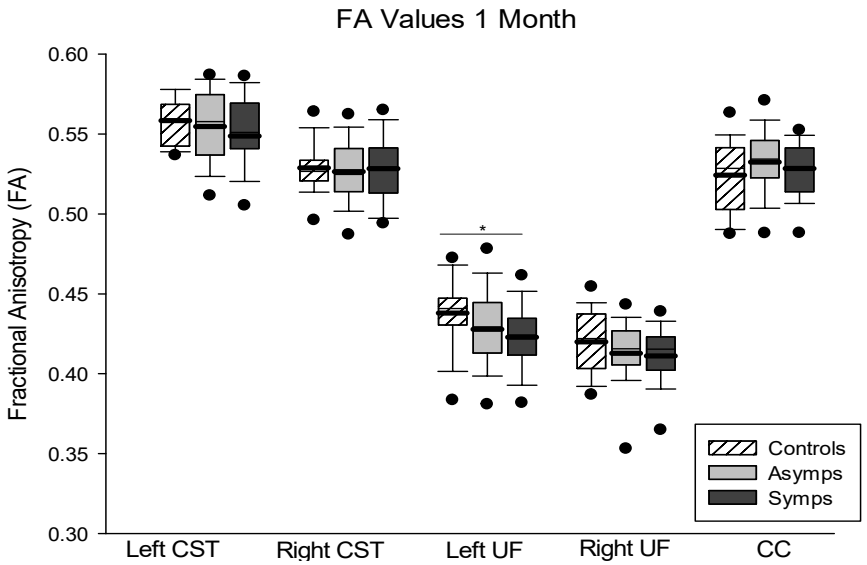
ACUTE: Heterogenous evidence of increased water diffusion in mTBI

Babcock L, J Pediatr Rehabil Med. 2015





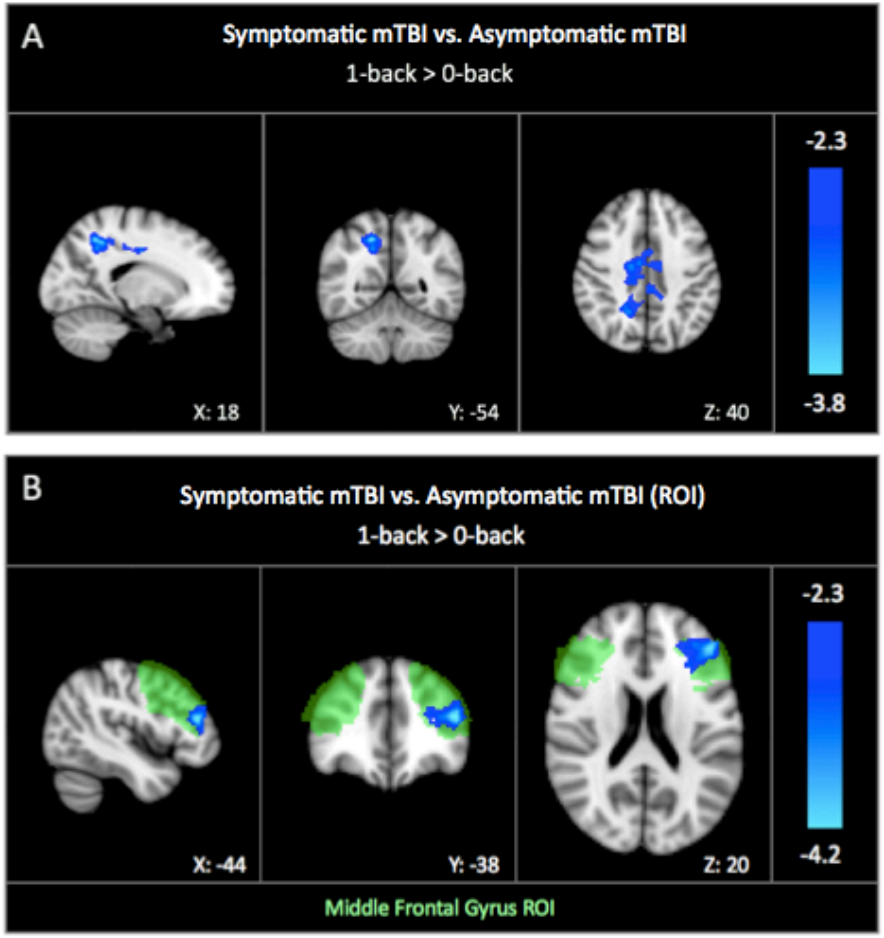
King, R Barlow KM Neuroimage Clinical, 2019



Subtle evidence of microstructural injury in the uncinate fasciculus in persistent post concussion symptoms

Functional connectivity

- During a working memory task fMRI
  - Decreased activation of the frontal lobe (DLPFC)
  - Increased default mode network deactivation
  - Suggesting dysregulation of network activation
  - Similar performance on task



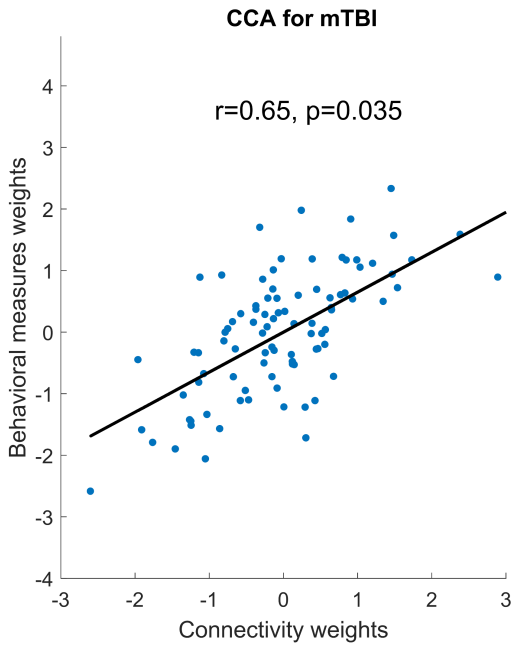
Khetani et al, J Neurotrauma 2019 Dec
(Mayer et al., 2011; Sours et al., 2013; Zhou et al., 2012).

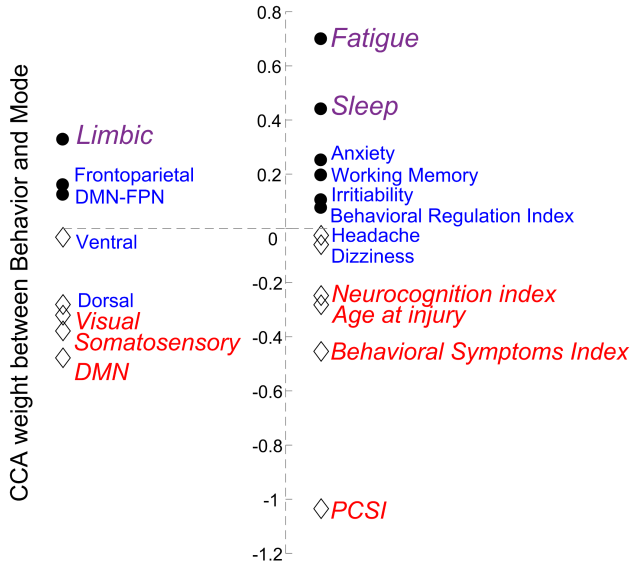
Relating symptoms to connectivity in pediatric PPCS

CCA Analysis

- A single “positive-negative” dimension linked post-concussive symptoms with functional connectivity within key brain networks.

Meaning: enables the development of new prognostic markers, as well as potential novel targeted interventions.

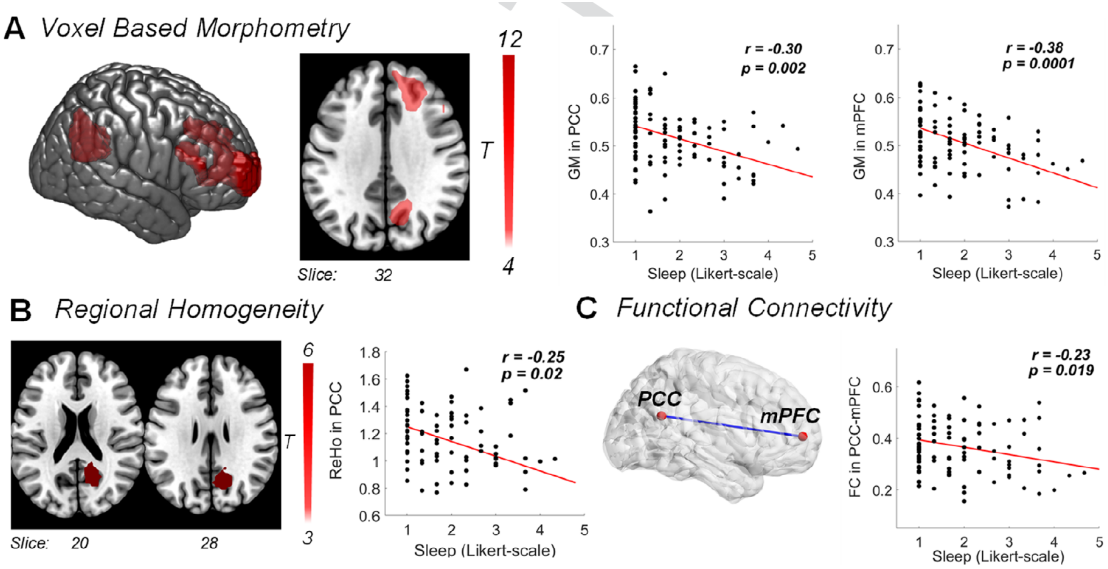


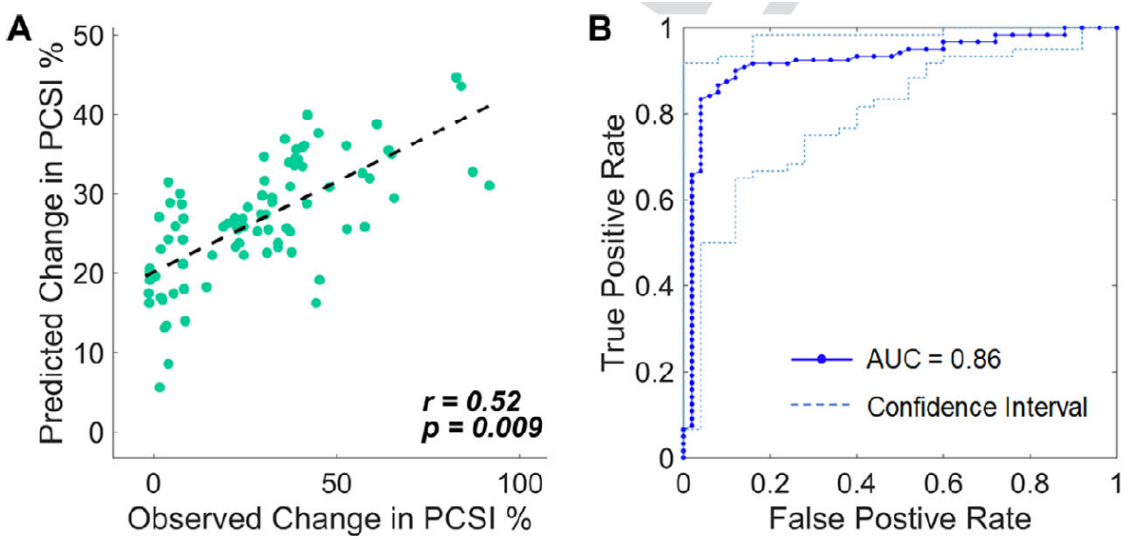


Iyer, K. et al, Annals of Clin Trans Neurology. 2019

Combining connectivity modalities to predict recovery

- machine learning





Iyer, Annals of Clinical and Translational Neurology In press 2019

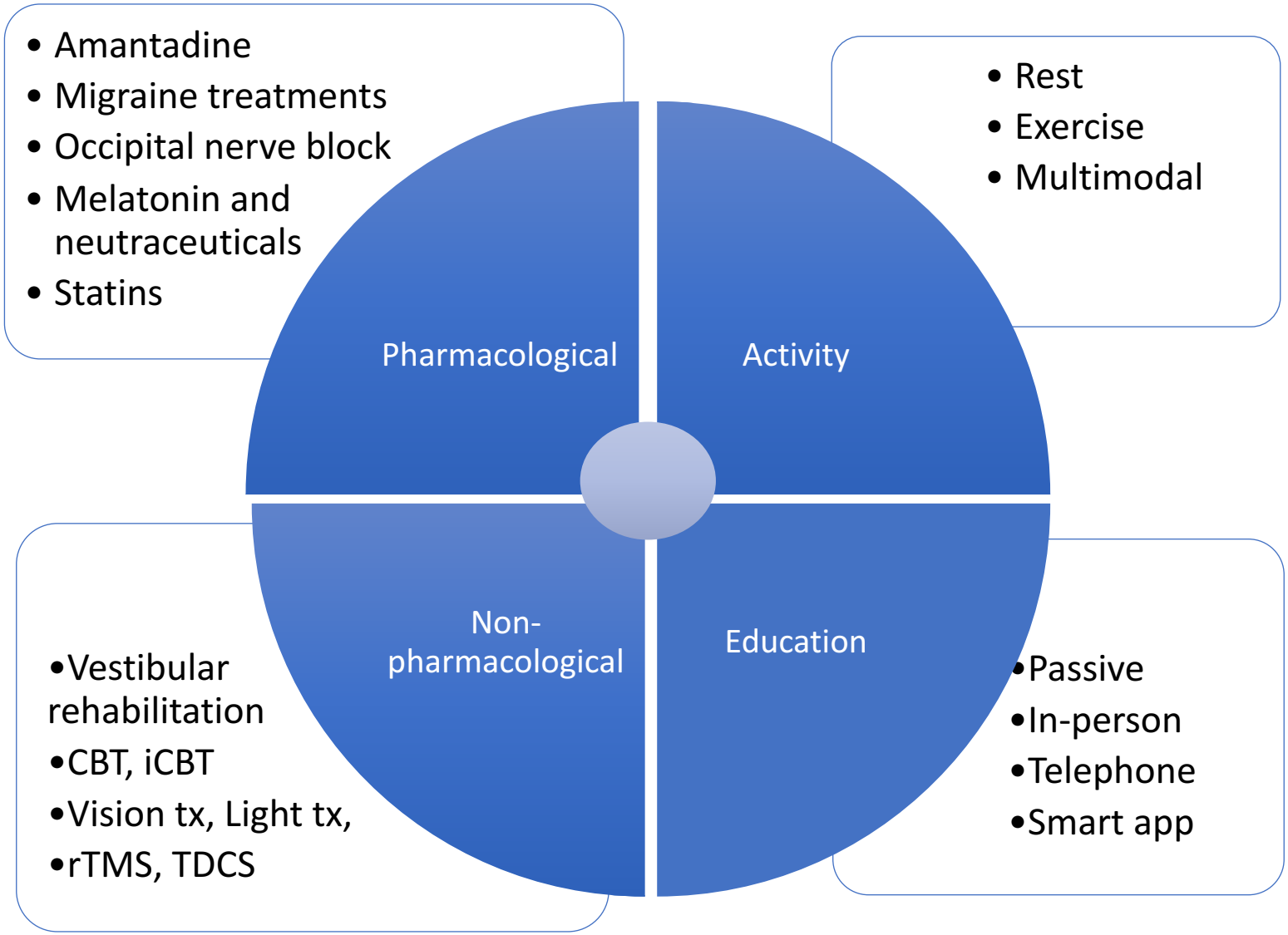
How to treat PPCS?

Factors to consider when **evaluating treatment options** in concussion and post-concussion syndrome

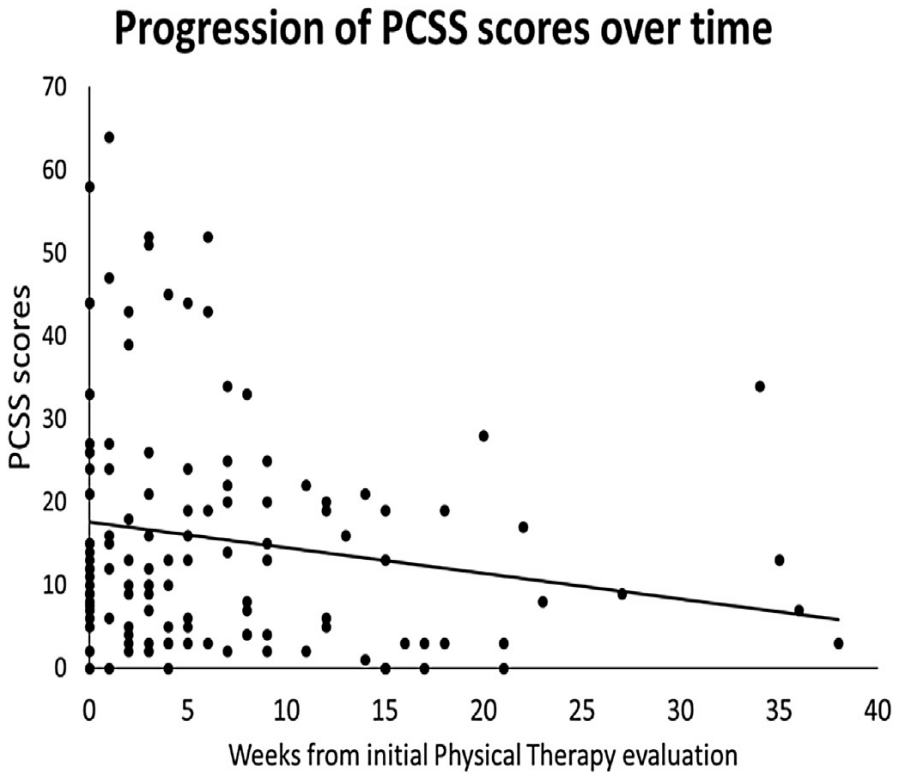
- Target population
  - ED population
  - Sport-specific population
- Timing of intervention
  - Early
    - **Sample size**
    - Biological targets
  - Later
    - Greater influence of pre-injury and environmental factors
    - Biological targets

- Phenotype
  - Post-concussion syndrome
  - Predominant headaches
    - Migraine
    - Exercise induced
    - Cervicogenic
  - Mood disturbance
  - Sleep disturbance
  - Cognitive disturbance
    - Associated with anxiety
    - Associated with ADHD/LD
- Type of intervention
  - Pharmacological
  - Non-pharmacological
  - Neutraceutical
  - Control group

Interventions

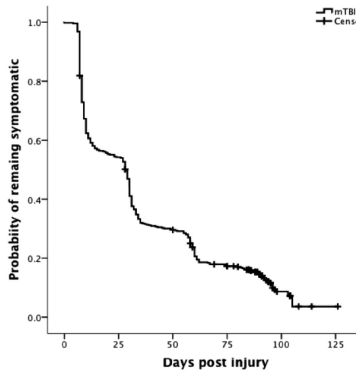


Multimodal therapy
exercise, vestibular/oculomotor and cervical spine rehabilitation



- 25 participants between 1 and 8 months post injury
- PT led

- Decreasing trend of PCS symptoms statistically significant
- No control group and ?natural decay of symptoms



Grabowski 2017 Physical Therapy in Sport 23 (2017) 22e30
Barlow et al, 2015 Pediatric Neurology 53: 491-7

CRICOS code 00025B

Collaborative care model for PCS:
Care management, CBT, and possible pharmacotherapy

Seattle

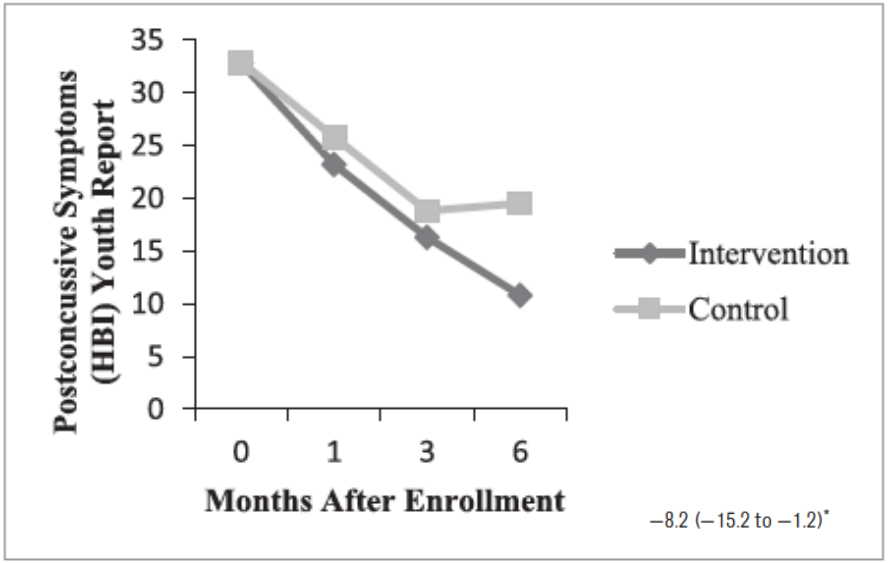
RCT

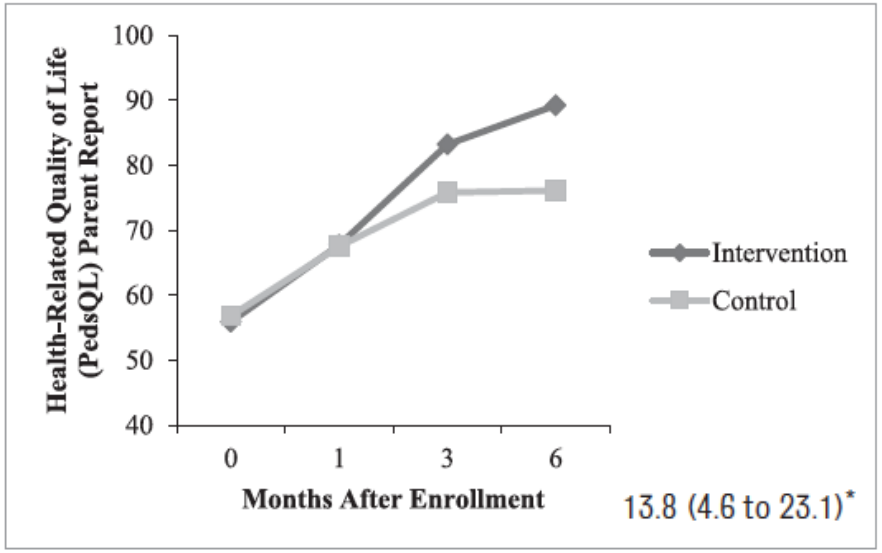
- Collaborative care (n=25)
- Standard care (n=23)
- 1 to 6 months post injury
- 11 – 17 year olds

- Stratified for symptom load

- Unblinded

A





McCarty et al, PEDIATRICS Volume 1 38, number 4 , October 2016

CRICOS code 00025B

*p<0.05

Case

13 year old hockey player

Checked from behind at the neck, fell to ice, no LOC, gradual onset of headache over next day

Occipital headache, dizziness (vertigo), off balance

PMHx migraine with aura

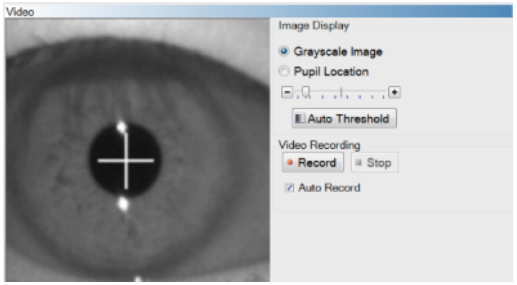
Exam: Bedside exam normal at 1 week post injury other than mildly abnormal BESS (score of 11) and discomfort when moving neck

Thoughts?

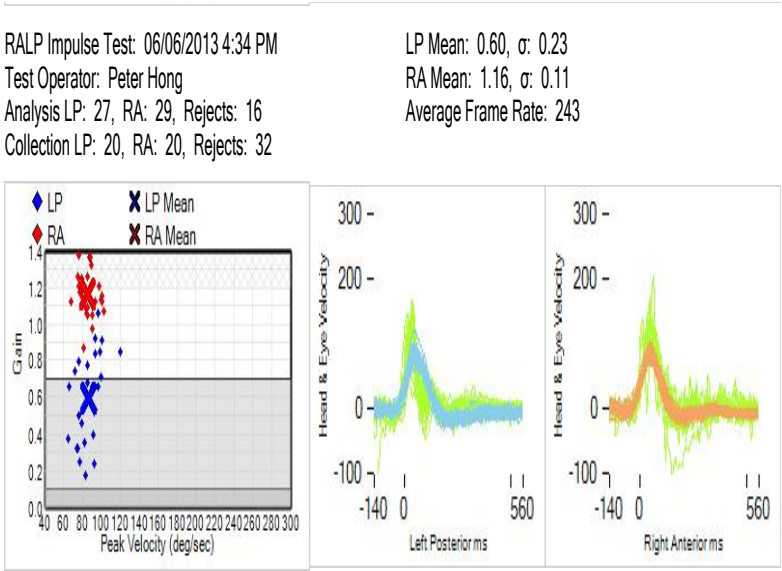
Rule out neck pathology – usually just clinical examination

How to treat?

Computerized assessment of vestibular function: vestibular injury is found in 10% acutely



- 10% of acute mTBI
- < 5% of persistent PCS in children
- Important for management of mTBI



Huang, Giesbrecht, Crowe, Schneider, Barlow, IBIA 2014

Original Research—Pediatric Otolaryngology

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–Head and Neck Surgery
2015, Vol. 152(6) 1133–1139

DOI: 10.1177/0194599815576720
http://otojournal.org
SAGE

Objective Vestibular Testing of Children with Dizziness and Balance Complaints Following Sports-Related Concussions

Guangwei Zhou, MD, ScD[1,2], and Jacob R. Brodsky, MD[1,2]

Retrospective study – **42 children with persistent dizziness and balance problems over 3 years**

Comprehensive assessment balance, semicircular canal and otoliths – including sensory orientation test, rotation test, dynamic visual acuity, video nystagmography, and cVEMP

90% had an abnormality on one of the tests

- < 10% hearing problem

Important implications for therapy

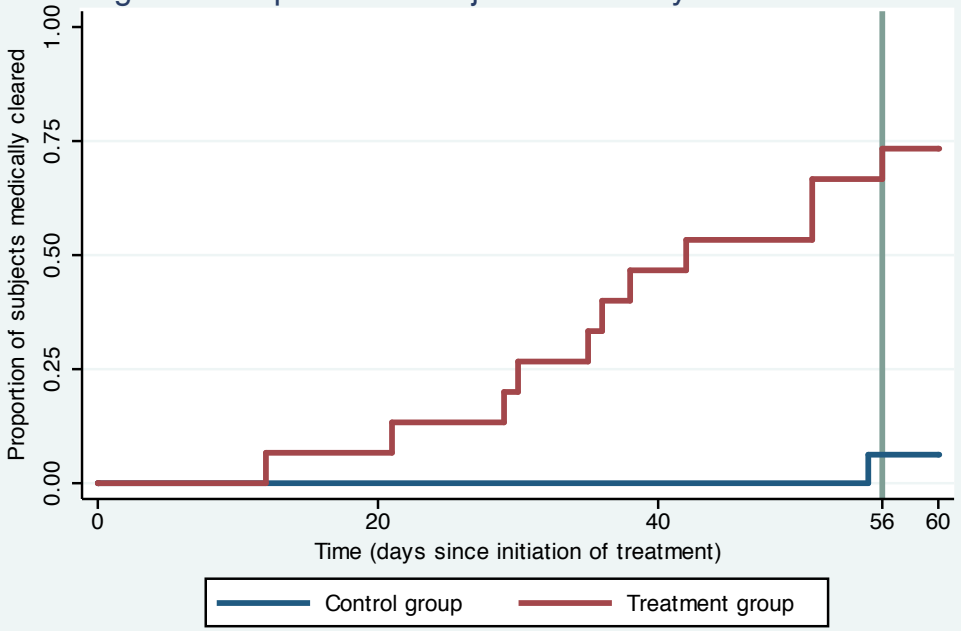
Specialized physiotherapy may help children with **neck pain**, **dizziness** and/or headaches

Cervicovestibular rehabilitation in sport-related concussion: a randomised controlled trial

Kathryn J Schneider,[1,2] Willem H Meeuwisse,[1,3] Alberto Nettel-Aguirre,[2,3,4] Karen Barlow,[2] Lara Boyd,[5] Jian Kang,[1] Carolyn A Emery[1,2,3]

	Control Group	Treatment Group	Total
Not Cleared	13	4	17
Cleared*	3	11	14
	16	15	31

Figure 1. Proportion of subjects medically cleared over time

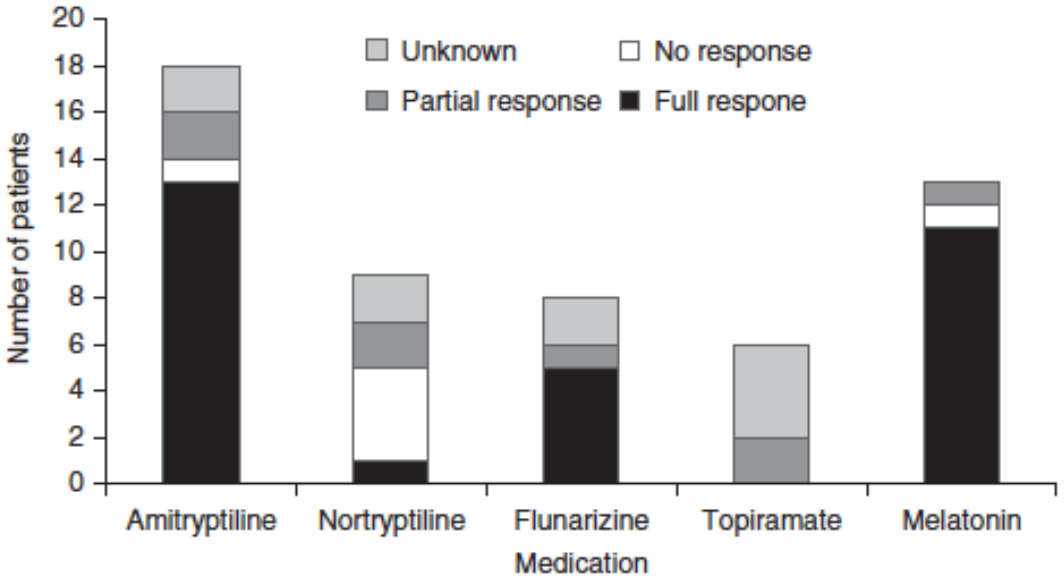


https://www.physiotherapyalberta.ca

Schneider KJ, *Br J Sports Med. 2014 (June 13th)*

Persistent post traumatic headaches seem to respond to medical therapy

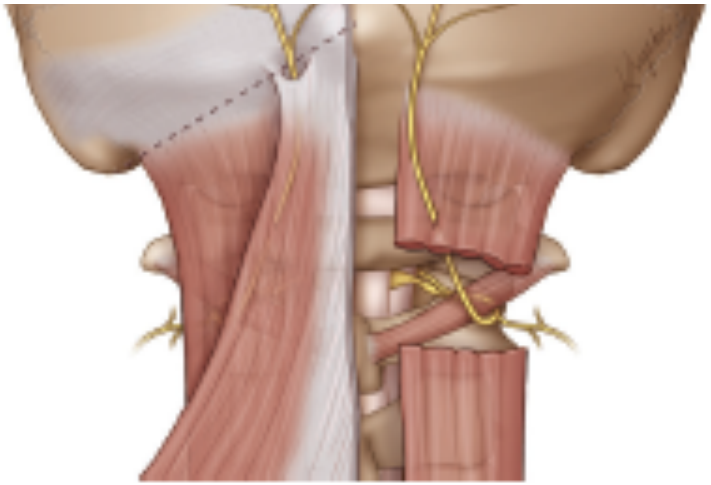
	N=83
Migraine (with or without aura)	46%
Tension type	7%
Occipital neuralgia	3%
Vestibular disorder	4%
Cervicogenic	4%
Headache associated with mood disorder	10%
Primary exercise headache	3%
Medication Overuse headache	5%
Unclassifiable	30%

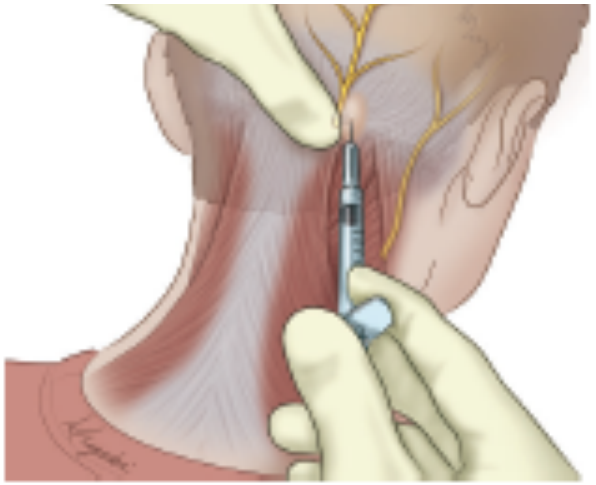


- Treatment chosen according headache phenotype
- PTH had been present for a mean of 7 months
  - 64% response overall
  - 50% complete resolution
- Other tx included
  - Botox
  - Psychotherapy/Physiotherapy

Kuczynski A, Dev Med Child Neurol. 2013

Occipital nerve blocks – cervicogenic PTH





Occipital neuralgia, tenderness over GON and occipital headaches

64% response rate using greater occipital nerve blocks

- 2% lidocaine (50 mg) injected subcutaneously with or without methylprednisolone (20mg) injection

Often get immediate relief

Repeat treatments sometimes required

Injected therapies often have a large placebo effect

Dubrovsky A, 2014

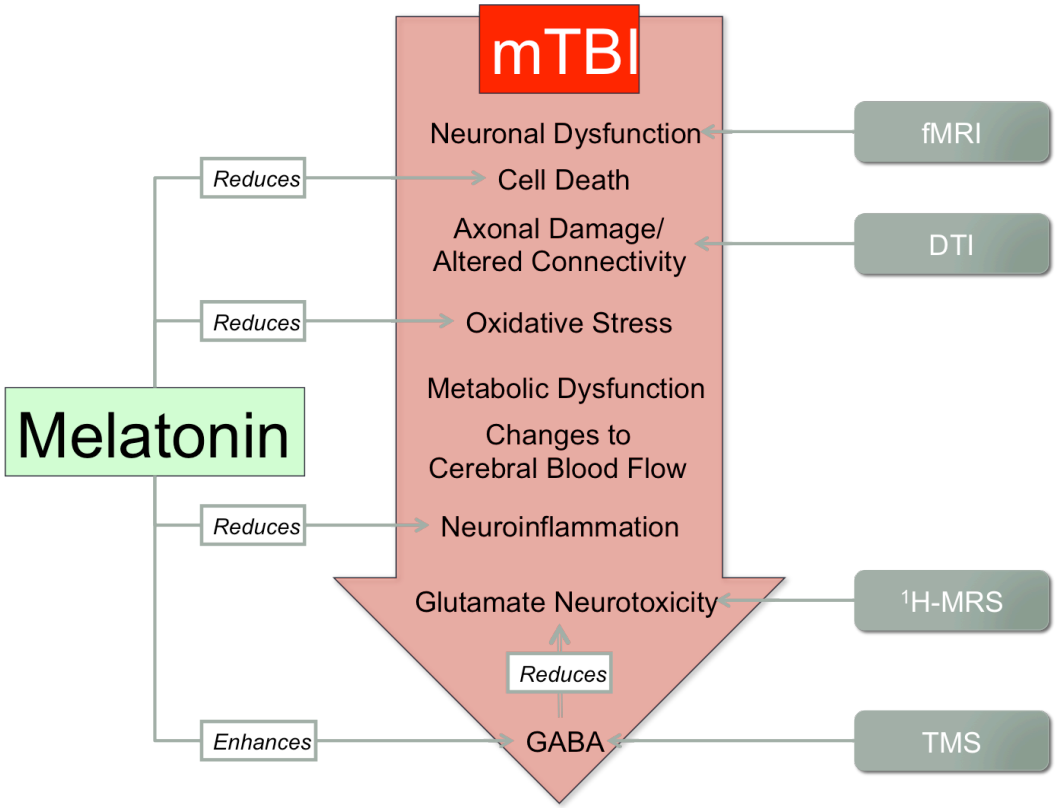
Seeger et al, J Chil Neurol 2014

Melatonin
as a therapeutic agent in mTBI?

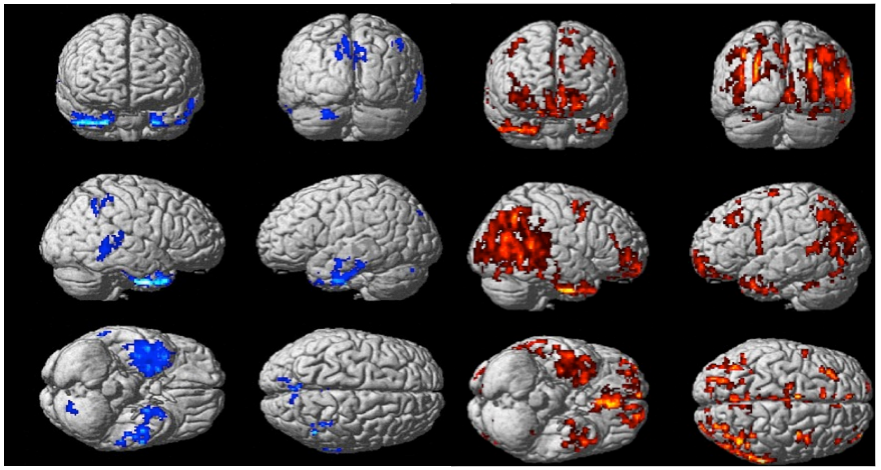
Pre-clinical models in TBI

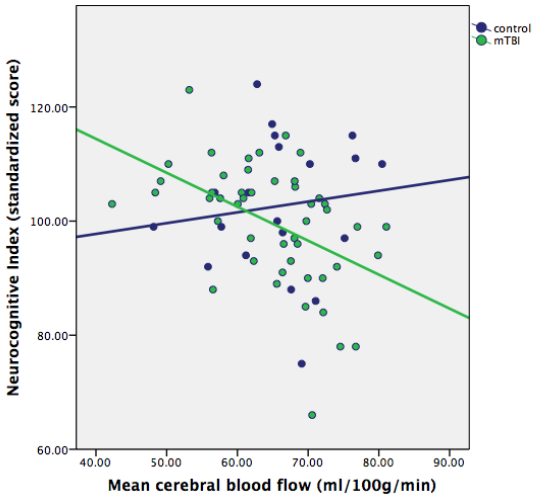
Safe

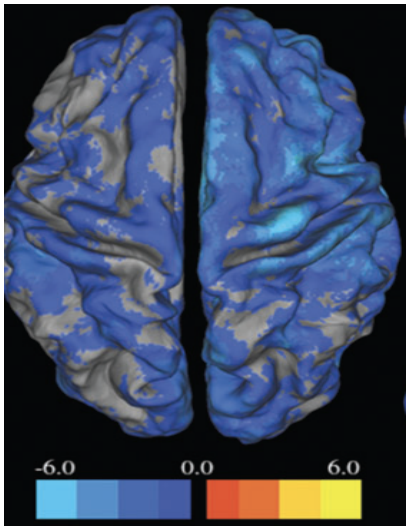
Therapeutic benefits
- Pain
- Anxiety
- Sleep dysfunction
- Neuroprotective effects
- Anti-inflammatory



Cerebral Blood Flow







CBF progressively decreases after mTBI

In PCS, CBF remains elevated relative to normal controls and those who have recovered from mTBI

Cerebrovascular reactivity is impaired

- After exercise stress (acute/subacute)
- With CO2 inhalation (chronic PCS)

Therapies to target NVU

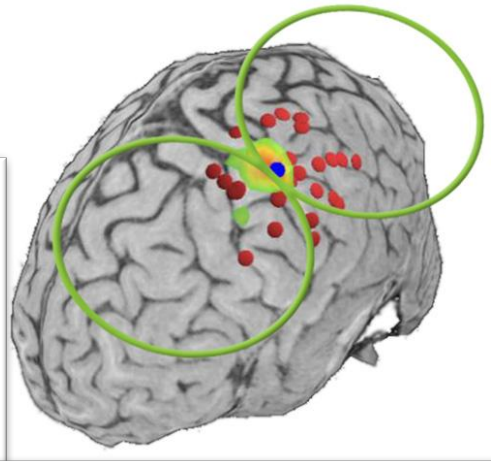
- **Exercise (Gagnon, 2009; Leddy 2019)**
- **Sildenafil**
- **Others++**

Len 2011, Mutch 2016,
Wang et al J Neurotrauma, 2016
Barlow et al, J Neurotrauma 2016

Neuronavigation-guided TMS

Role for TMS to help explore connectivity and neuroplasticity after mild TBI

Symptom-network profiles



Iverson, Frontiers Neurol, 2019

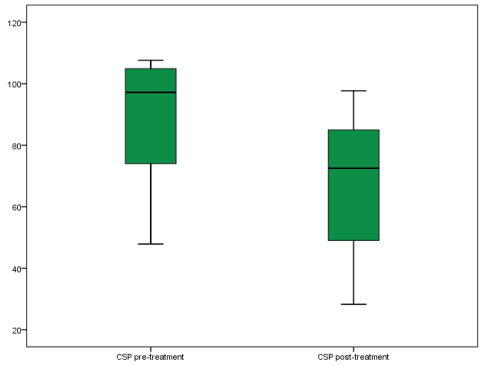
Pilot data using rTMS in Adolescent PPCS
Prospective open label cohort study

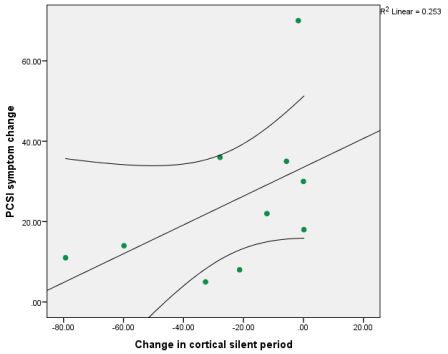
Population	Enrolment	Treatment	Baseline	Results
Adolescents with PPCS (age 12-18 y) for > 6 months N=14	9 females 5 males Age 15 (SD 2.4) yrs	20 sessions (10Hz; 110% RMT)	Pre-treatment PCSI score = 58 (SD 29)	77% improved **PCSI change 29** (95% CIs: 13.7, 44.0) t=4.2; p=0.001

Neurophysiological measures changed

cSP 25 (95% CI 3.8, 37.9) t=2.7; p=0.022

Trend to correlate with symptom improvement r=0.59; p=0.09





Investigators

www.playgametrial.ca

Canada

Deborah Dewey – Neuropsychology
Brian Brooks – Neuropsychology
Adam Kirton – TMS
Val Kirk – Sleep dysfunction
Frank MacMaster – Neuroimaging
Michael Esser – Translational models
Alberto Nettel-Aguirre – Biostatistics
Susan Crawford – Biostatistics
Jeff Buchhalter – Medical advisor
Angelo Mikrogianakis – ED medicine
Candice Cameron – Pharmacy research
David Johnson – Clinical trials
Roger Zemek – Ottawa site

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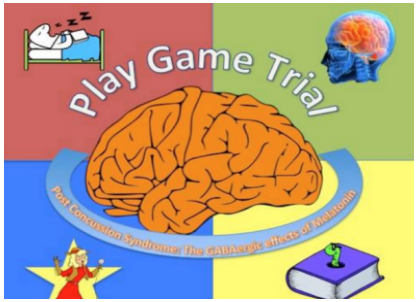
Kartik Iyer

Families



Thank you

The University Of Queensland
AUSTRALIA
CREATE CHANGE

NHMRC

Children's Hospital Foundation

THE IAN POTTER FOUNDATION

MAiC

UNIVERSITY OF CALGARY

Play Game Try!

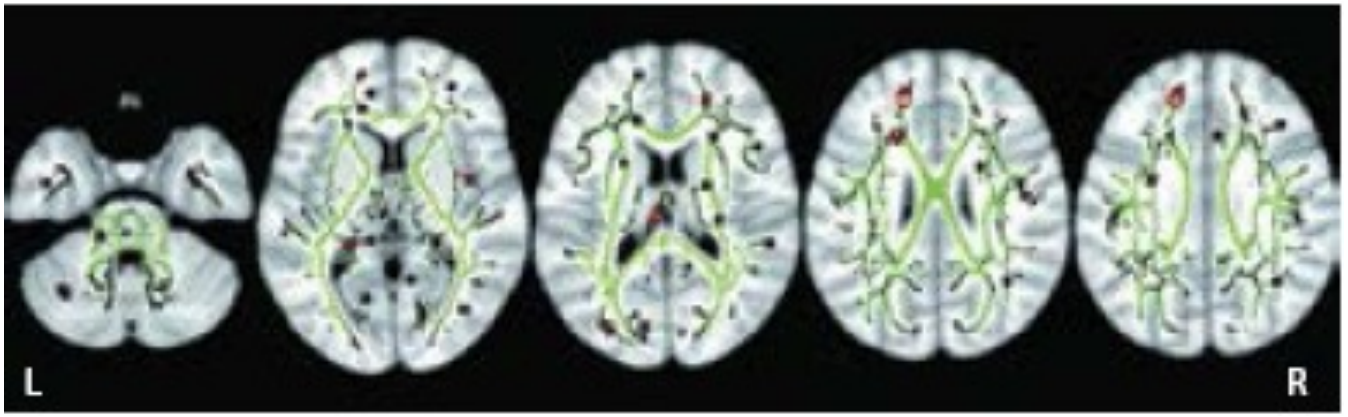
Alberta Children's HOSPITAL RESEARCH INSTITUTE

Alberta Health Services

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Hotchkiss Brain Institute

Is PPCS one disorder?



- Each person has unique pre-injury and environmental factors
  - Latent class analysis combining pre-injury and acute clinical characteristics
  - Clinical phenotypes to determine risk of PPCS at 4 and 12 weeks
- Each mTBI uniquely disrupts brain networks

Wada, T., Y. Asano, et al. American Journal of Neuroradiology 33(11):2117–2122, 2012.
Bigler, Neuropathology of Mild Traumatic Brain Injury - Brain Neurotrauma
Yestes et al, J Neurotrauma 2019: 7, e017012.