Concussion Pathophysiology 2:
Management, Recovery and Long-term Consequences

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45min
Credit where credit deserved!

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Outline

1. Neurometabolic Cascade of Concussion
2. Pathophysiology meets Risk Factors
3. Subacute Pathophysiology
4. Recovery
5. Acute-to-Subacute-to-Chronic Pathophysiology
6. Summary
Pathophysiology of TBI

Blood flow

Ionic flux

Cell Death

Protease activation

Energy Crisis

Ca²⁺

Axonal injury

Glutamate

Inflammation

Giza & Hovda, Neurosurg 2014
Barkhoudarian et al, PMR Clin NA 2016
Neurometabolic Cascade Following Traumatic Brain Injury

- Calcium
- Potassium
- Glutamate
- Glucose
- Cerebral Blood Flow
- Inflammation
- Demyelination

Adapted from Giza & Hovda, Neurosurg 2014
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Neurometabolic Cascade of mTBI: Pathophysiology Meets Risk Factors

- Prior TBI
- Protease activation
- Ca^{2+}
- Migraine?
- Pre-existing cognitive impairment
- Younger age
- Less myelination
- Glutamate
- Prior TBI
- ADP
- Pump
- K^+
- Mito
- K^+
- Ca^{2+}
- Migraine?
PCS Comorbid Diagnoses or Contributing Factors

Prior concussion

Headache (migraine, tension, CDH)

Fogginess

Prior headaches

Younger (teen)age

On-field AMS

Dizziness

Depression

Anxiety

Learning disability / ADHD

Adapted from Giza, Kutcher, et al., Neurol 2013
Sex Differences in Axons

- Female axons show more injury-induced changes than males.
- Female axons show more undulations & greater calcium flux post-stretch than males.

♀ worse than ♂

Dolle’ JP, et al., Exp Neurol 2018
Age Differences in Axons

N1 = myelinated shows recovery

Unmyelinated axons are more vulnerable than myelinated

N2 = unmyelinated does not show recovery

Reeves TM, et al. Exp Neurol, 2005
Fear Learning: Anxiety

TBI causes enhanced fear-based learning associated with excitatory-inhibitory imbalance.

1. Neurometabolic Cascade of Concussion
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3. **Subacute Pathophysiology**
4. Recovery
5. Acute-to-Subacute-to-Chronic Pathophysiology
6. Summary
Neurometabolic Cascade: Inflammation & Axonal Injury

- Blood flow
- Ionic flux
- Inflammation
- Synaptic dysfunction
- Glutamate
- Axonal injury

Giza & Hovda, Neurosurg 2014
Barkhoudarian et al, PMR Clin NA 2016
Repeat juvenile TBI results in greater axonal injury and memory impairment.

Prins ML, et al., Dev Nsci 2010
Neurometabolic Cascade: Neurovascular changes

- Neurovascular changes
- Axonal injury
- Ca$^{2+}$
- Ionic flux
- Glutamate
- Synaptic dysfunction
- Blood flow
- Inflammation

Giza & Hovda, Neurosurg 2014
Barkhoudarian et al, PMR Clin NA 2016
Mild TBI patients with post-contrast FLAIR meningeal enhancement showed increase inflammatory gene expression in peripheral blood.

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene name</th>
<th>Fold change</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOC100134822</td>
<td>Uncharacterized LOC100134822</td>
<td>1.62426</td>
<td>5.05E-05</td>
</tr>
<tr>
<td>Fc2R</td>
<td>Fc fragment of IgA, receptor for</td>
<td>1.58147</td>
<td>4.81E-08</td>
</tr>
<tr>
<td>MCTP2</td>
<td>Multiple C2 domains, transmembrane 2</td>
<td>1.54058</td>
<td>1.85E-05</td>
</tr>
<tr>
<td>GPR27</td>
<td>G-protein-coupled receptor 27</td>
<td>1.52042</td>
<td>5.88E-05</td>
</tr>
</tbody>
</table>
Neurometabolic Cascade: Network & Synaptic Dysfunction

- Blood flow
- Ionic flux (Ca^{2+})
- Inflammation
- Axonal injury
- Axonal degeneration
- Glutamate
- Synaptic dysfunction

Giza & Hovda, Neurosurg 2014
Barkhoudarian et al, PMR Clin NA 2016
Translation: Network Dysfunction

N1 = myelinated shows recovery
N2 = unmyelinated does not show recovery

Unmyelinated axons are more vulnerable to TBI

White matter changes seen after pediatric mTBI subacutely (2 wks) and chronically (4 mos).

Reeves TM, et al. Exp Neurol, 2005
Mayer AR et al., J Neurosci 2012
Translation: Synaptic Dysfunction

N-methyl-D-aspartate (NMDA) Receptor = IQ Gene?????
Different types: NR2A, NR2B

NR2A protein (IQ gene) is selectively reduced after developmental TBI.

Giza, Santa Maria & Hovda, J. Neurotrauma 2006
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Physiological Recovery: Profile

Window for physiological recovery may outlast clinical recovery.

- Pre-injury baseline
- Clinical recovery
  - Acute
    - Symptomatic
    - Clinical dysfx
    - Physiol dysfx
  - Subacute
    - Asymptomatic
    - Clinical normal
    - Physiol dysfx
- Clinical & Physiological recovery
- Physiological recovery
- Full recovery
  - Asymptomatic
  - Clinical normal
  - Physiol normal

“Buffer Zone”

Forced exercise induces a sustained stress response, loss of BDNF & impaired autonomic response to exercise.

Griesbach et al., J Neurotrauma, 2012 & 2014

BDNF = brain derived neurotrophic factor

Following TBI, Early ↑ Running ↔ BDNF

Early after mTBI, exercise may be bad; but delayed exercise increases BDNF & is beneficial

Griesbach, et. al. Neurosci 2004
Initiation of exercise

Reducing the Time Interval Between Concussion and Voluntary Exercise Restores Motor Impairment, Short-term Memory, and Alterations to Gene Expression

Running Title: The Benefits of Post-Concussion Exercise

Authors: Richelle Mychasiuk¹, Harleen Hehar¹, Irene Ma¹, Sydney Candy², and Michael J Esser²

In rats used to running, early running improved motor function & cognition.

Delayed running or social isolation enhanced dysfunction.

When, How much, What type of Exercise?

<table>
<thead>
<tr>
<th>Time to initiate exercise</th>
<th>Day1</th>
<th>Day3</th>
<th>Day7</th>
<th>Day14</th>
<th>Day30</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild TBI couch potato</td>
<td></td>
<td></td>
<td>↑</td>
<td>↑</td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Mod TBI couch potato</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Mild TBI couch potato</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>forced exercise postTBI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild TBI rat-thlete</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In sedentary rats, early running or stressful running was deleterious and delayed running beneficial. In rats used to running…“rat-thletes”, beneficial effects of running occurred earlier.
Treatment: Activity & Exercise

- Forced rest prolongs recovery
- Active rehab is beneficial
- Exercise + cognitive behavioral therapy improves recovery & reduces anxiety

Benefits of Strict Rest After Acute Concussion: A Randomized Controlled Trial

Danny George Thomas, MD, MPH; Jennifer N. Apps, PhD; Raymond G. Hoffmann, PhD; Michael McCrea, PhD; Thomas Hammeke, PhD

A pilot study of active rehabilitation for adolescents who are slow to recover from sport-related concussion

L. Gagnon, L. Grilli, D. Friedman, G. L. Iverson


Giza CC, et al., JAMA Neurol 2018
Exercise as Treatment?

- Active exercise improves symptoms
- Athletes may improve more rapidly
- Exercise tolerance improves with training


Leddy JJ, et al., Clin J Sport Med 2010
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Neurometabolic Cascade Chronic Cumulative Hypotheses?

Blood flow

Cell Death

Altered Proteolysis

Protein Aggregate

Protein

Energy Crisis

Abnormal Protein

Toxic Accumulation: Intra- or Extracellular

Axonal injury

Inflammation

Glutamate

Altered neurotransmission

Giza & Hovda, Neurosurg 2014
Subacute Tau Accumulation

Sham

Injured

Tau subacutely after blast injury

Long Term Potentiation

Spatial learning, memory

Subacute Amyloid Accumulation

APP blebs early after in vitro stretch

APP blebs early after human TBI

Model of microtubule damage, impaired axonal transport & accumulation of APP blebs after traumatic injury

**Science News**

**Hits, not concussions, cause chronic traumatic encephalopathy**

New insights into the disease show head impact, not concussion, triggers CTE and pave way for early detection, prevention and treatment.

**Date:** January 18, 2018  
**Source:** Boston University School of Medicine  
**Summary:** Researchers have identified evidence of early Chronic Traumatic Encephalopathy (CTE) brain pathology after head impact -- even in the absence of signs of concussion. Early indicators of CTE pathology not only persisted long after injury but also spread through the brain, providing the best evidence to date that head impact, not concussion, causes CTE.

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**Redefining CTE?**

- **Mouse model**
- **Single impact**
- **≤2 wks post-TBI**
  - N=20; sham N=8
- **5.5 mo post-TBI**
  - N=3; sham N=1

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**Mouse neuropath is mostly <2 weeks after single TBI**

**Be careful making broad conclusions**

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Tagge et al., Brain 2018
Cumulative repeat mTBI: Acute-to-chronic linkage

Using 3xTg AD rat model to address effects of RmTBI on amyloid deposition

Repeat mTBI with 24 hr (vs 72 hr) impact interval results in greater cortical amyloid deposition late in life

Grant D, et al. J Neurotrauma 2017
Cumulative repeat mTBI: Acute-to-chronic linkage

Repeat mTBI in youth worsens chronic hippocampal amyloidosis. Impact Interval Matters.

Grant D, et al. J Neurotrauma 2017
Induction of a transmissible tau pathology by traumatic brain injury

Elisa R. Zanier,1 Ilaria Bertani,1 Eliana Sammali,1,2 Francesca Pisciutta,1 Maria Antonietta Chiaravalloti,1 Gloria Vegliante,1 Antonio Masone,1 Alessandro Corbelli,2 Douglas H. Smith,4 David K. Menon,3 Nino Stocchetti,6,7 Fabio Fiordaliso,3 Maria-Grazia De Simonis,1 William Stewart6,9 and Roberto Chiesa1

See Sastre et al. (doi:10.1093/brain/awy225) for a scientific commentary on this article.

Traumatic brain injury is a risk factor for subsequent neurodegenerative disease, including chronic traumatic encephalopathy, a tauopathy mostly associated with repetitive concussion and blast, but not well recognized as a consequence of severe traumatic brain injury. Here we show that a single severe brain trauma is associated with the emergence of widespread hyperphosphorylated tau pathology in a proportion of humans surviving late after injury. In parallel experimental studies, in a model of severe traumatic brain injury in wild-type mice, we found progressive and widespread tau pathology, replicating the findings in humans. Brain homogenates from these mice, when inoculated into the hippocampus and overlying cerebral cortex of naïve mice, induced widespread tau pathology, synaptic loss, and persistent memory deficits. These data provide evidence that experimental brain trauma induces a self-propagating tau pathology, which can be transmitted between mice, and call for future studies aimed at investigating the potential transmissibility of trauma associated tau pathology in humans.

p-tau detected chronically after single severe TBI in humans

Zanier ER, et al., Brain 2018
Transmissible tau after 1 TBI

P-tau is detected chronically after experimental TBI in wild type mice.

Inoculation of TBI homogenates into uninjured mice caused p-tau accumulation and working memory deficits.

Zanier ER, et al., Brain 2018
In vivo detection of chronic inflammation

TSPO-PET showed higher signal in retired football players compared to controls.

Former National Football League (NFL) Players Demonstrate Higher Binding of $[^{11}C]DPA-713$ Across Many Brain Regions Compared with the Brains of Age-, Sex-, Education-, and Body Mass Index-Matched Control Individuals.

Coughlin JM, et al. JAMA Neurol 2017
Imaging Tau in vivo

FDDNP-PET binds both amyloid & tau; but signal in mesial temporal structures is more likely to be tau & differs from pattern seen in Alzheimer's.

Increased $F^{18}$-T807 but not $F^{18}$-Florbetapir was detected in vivo in a symptomatic retired NFL player.

Barrio J., et al., PNAS 2015

Mitsis EM, et al., Transl Psychiatry 2014
Neuropathology: Chronic Traumatic Encephalopathy (CTE)

3/6 (50%) CTE + other neurodegeneration, 0/6 (0%) CTE only

Damage consistent with CTE reported in 68/85 (80%) brains of athletes and military personnel

Hazrati, et al., Front Human Nsci 2013

Damage consistent with CTE reported in 21/66 (32%) athlete brains in neurodegenerative brain bank

Bieneck, et al., Acta Neuropathologica 2015

Incidence / Risk is unknown!

McKee A, et al., Brain 2012
1. Cohort study; n=2692 subjects; 834 played football; 1858 no football
2. Primary outcomes: depression & composite cognitive score
3. Matched for demographics, IQ, education, etc.
4. No difference in cognition, lower depression scores
5. Football was different in 1950s
6. Unable to control for prior mTBI; subgroups

Deshpande et al., JAMA Neurol 2017
### Chronic Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Post-concussion syndrome (PCS)</th>
<th>Chronic Traumatic Encephalopathy (CTE)</th>
<th>Persistent post-concussive symptoms (PPCS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial TBI</strong></td>
<td>LOC, PTA, altered mentation, post-traumatic seizures</td>
<td>Repetitive mTBI/blast injuries</td>
<td>Diagnosed concussion +/- LOC, PTA, etc</td>
</tr>
<tr>
<td><strong>Onset of symptoms</strong></td>
<td>Unspecified to within 4 weeks of TBI event</td>
<td>Months to years after exposure to repeat impacts</td>
<td>Concussion sx &lt;24-48 hrs; PPCS &gt;3-6 weeks</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>3/8 from headache, dizziness, fatigue, irritability, problems with sleep, concentration, memory or stress/emotions</td>
<td>Broad range of symptoms: cognitive dysfunction, emotional, motor impairment</td>
<td>Multiple symptoms from 21-22 item validated checklists</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Unspecified to a minimum of 3 months</td>
<td>Unspecified to minimum of 2 years</td>
<td>Symptoms lasting longer than expected (&gt;3-6 weeks)</td>
</tr>
<tr>
<td><strong>Other terminology</strong></td>
<td>Neurocognitive disorder, mild</td>
<td>Dementia pugilistica, “punch-drunk”</td>
<td>PPCS</td>
</tr>
<tr>
<td><strong>Diagnostic criteria</strong></td>
<td>Nonspecific, see above</td>
<td>Phosphorylated-tau on brain autopsy</td>
<td>Specific for each symptom complex</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Unspecified, rest, waiting</td>
<td>None</td>
<td>Diagnosis specific</td>
</tr>
<tr>
<td><strong>Implication</strong></td>
<td>Non-specific intervention, chronic disability</td>
<td>Progressive neurodegeneration &amp; death</td>
<td>Treatment focused on each diagnosis</td>
</tr>
</tbody>
</table>
PPCS Diagnostic Approach

1. **Neuropsychological evaluation** - ADHD, anxiety, depression, learning problems, MCI
2. **MRI** (include SWI) – usually normal – evidence of prior TBI, chronic SDH, ventriculomegaly, atrophy, low pressure headache
3. **Sleep study** – sleep issues frequently comorbid
4. **Cervical/musculoskeletal examination** – cervicogenic headache, occipital neuralgia, dizziness
5. **Autonomic testing/orthostatics** – dysautonomia, POTS
6. **Vestibular/oculomotor testing** – BPPV, vestibular dz, migraine
7. **Laboratory/blood tests** – endocrine, metabolic, vascular
8. **Other** – deconditioning, migraine, other chronic pain

Not all chronic problems are “PCS” or CTE!
**Post-Concussion Symptom Pie**

**Deconditioning**
- Aerobic exercise
- Nutrition
- Hydration

**Sleep disturbance**
- Sleep hygiene
- Melatonin
- Sleep study?

**Headache**
- Abortive meds
- Preventive meds
- PT/cervical
- Injections
- Avoid med overuse

**Anxiety/Depression**
- Neuropsych assessment
- Psychotherapy
- CBT
- Medications

**Dizziness**
- Vestibular tx
- Hydration
- Autonomic eval
- Migraine

**Cognitive**
- Neuropsych assessment/premorbid
- Treat comorbidities
- CBT
- Medications
Science vs Clinical Care vs Policy

**Clinical care** can be based on evidence but ultimately is individualized & anecdotal – know your evidence & use your clinical judgment

**Research** quality matters – prospective, longitudinal, proper controls, objective measures, consistent definitions

**Policies** built on evidence, not anecdote, are essential

Giza CC, Stewart W, Prins ML, JAMA Peds 2018
Sum Up

1. The Neurometabolic Cascade may have subacute & chronic components
2. Pathophysiology is related to comorbidities & risk factors for persistent post-concussion symptoms
3. Physiological recovery is associated with, but does not match exactly with, clinical recovery
4. Exercise or other physiological activation may promote recovery
5. Mechanisms linking acute-to-chronic pathophysiology are being discovered
6. Advanced molecular imaging may provide some view of chronic pathophysiology
7. Make a differential diagnosis for persistent post-concussion symptoms & treat the cause!