# **Beyond The Brain:**

# Exploring the Systems Affected by TBI

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# Conflicts of Interest

The speakers for this presentation have no relevant financial relationships or conflicts of interest to disclose. The content presented is for educational purposes only and does not represent any product endorsements or recommendations.

# TBI is a whole body injury

- A brain injury is a whole body injury
- Each TBI adds to the prior
- System failures can take days, weeks, months, years before symptoms occur

- Metabolic shifts in the brain occur ***within hours*** of injury.

- TBI leads to rapid changes in synaptic proteins and reduction in synaptic density within ***six hours*** post injury.

- Within ***hours*** of injury a flux of the amino acid and neurotransmitter glutamate allows escalation of cell damage and cell death.

Post-concussion metabolic shifts occur that impair brain function, allow spread of damage, and prolong recovery:

a. Glucose utilization is impaired, creating an “energy crisis”
b. Neuroinflammation escalates
c. Impaired toxin removal results as glymphatic function falters

# TBI Pathology Transcends The CNS

- Gastrointestinal
- Musculoskeletal
- Visual
- Cardiac
- Cognitive-Behavioral
- Hormonal
- Circadian Rhythm/Sleep Disruption
- Immune
- Reduced Integrity of the Blood-Brain Barrier

# TBI & THE GASTROINTESTINAL SYSTEM

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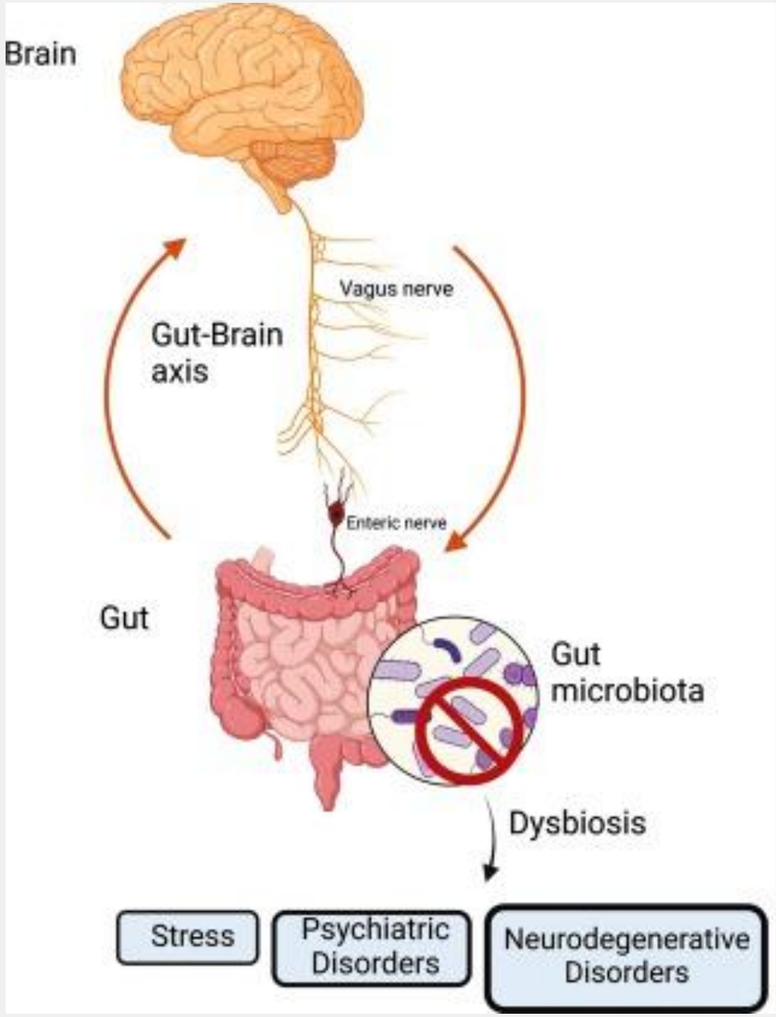
# TBI Alters the Gut Microbiome

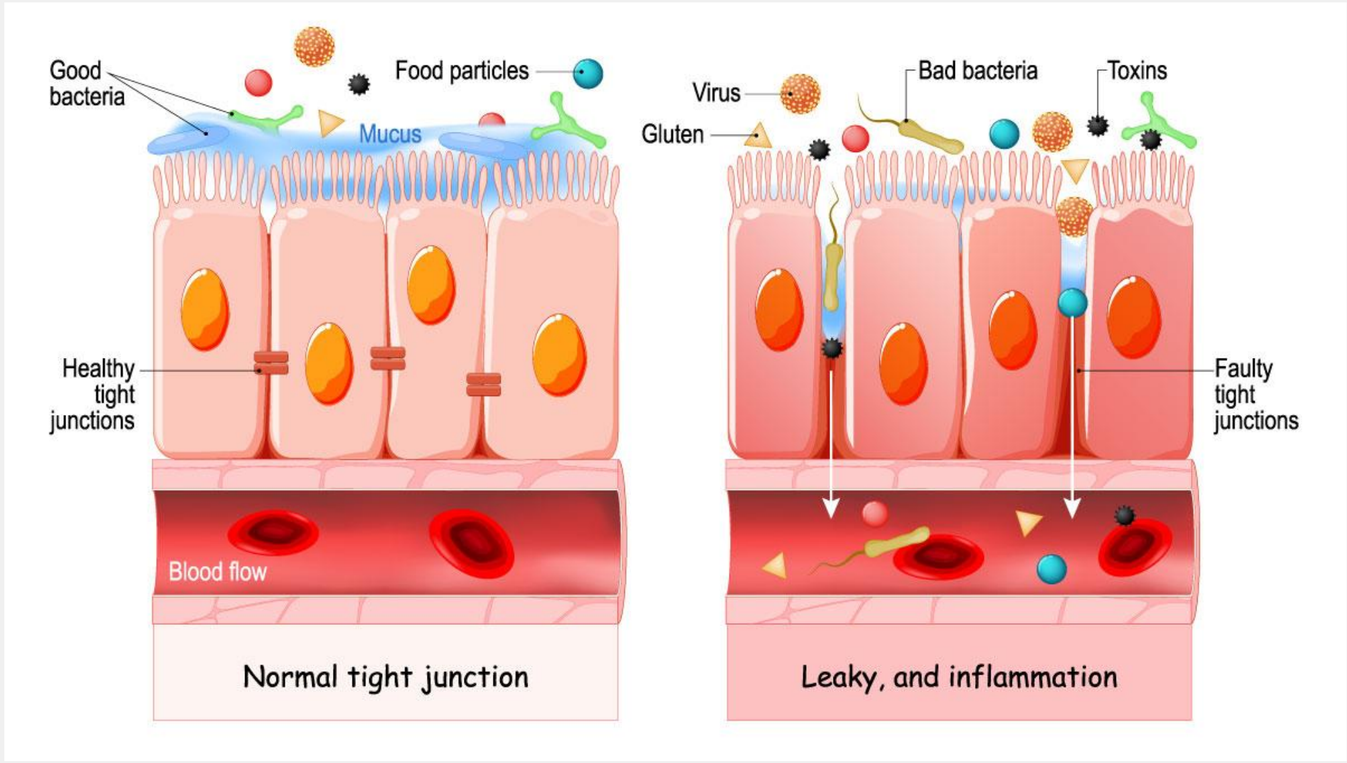
- Traumatic brain injury (TBI) disrupts gut microbiota balance, leading to **dysbiosis**.
- Changes in gut bacteria can increase **inflammation**, affecting both digestion and brain function.
- **Gut-brain axis dysfunction** may worsen post-TBI symptoms.




1.Cannon, A. R., Anderson, L. J., Galicia, K., Murray, M. G., Kamran, A. S., Li, X., Gonzalez, R. P., & Choudhry, M. A. (2023). Traumatic brain injury induced inflammation and GI motility dysfunction. *Shock*. https://doi.org/10.1097/shk.0000000000002082

2.Hanscom, M., Loane, D. J., & Shea-Donohue, T. (2021). Brain-gut axis dysfunction in the pathogenesis of Traumatic Brain Injury. *Journal of Clinical Investigation*, *131*(12). https://doi.org/10.1172/jci143777

- **TBI increases intestinal permeability**, allowing harmful substances to enter the bloodstream.
- **Leaky gut contributes to neuroinflammation**, worsening brain recovery.
- Strong links between **gut permeability, autoimmunity, and chronic inflammation**.




1.Hang, C.-H. (2003a). Alterations of intestinal mucosa structure and barrier function following traumatic brain injury in rats. *World Journal of Gastroenterology*, *9*(12), 2776. https://doi.org/10.3748/wjg.v9.i12.2776

- **80-95% of serotonin** is produced in the gut; gut dysfunction impacts mood and cognition.
- **Imbalances in gut bacteria affect dopamine and GABA**, influencing mental health.
- Restoring gut health is essential for **cognitive recovery and emotional regulation** after TBI.

1. Faries, P. L., Simon, R. J., Martella, A. T., Lee, M. J., & Machiedo, G. W. (1998). Intestinal permeability correlates with severity of injury in trauma patients. *The Journal of Trauma: Injury, Infection, and Critical Care*, *44*(6), 1031–1036. https://doi.org/10.1097/00005373-199806000-00016

2.Appleton J. (2018). The Gut-Brain Axis: Influence of Microbiota on Mood and Mental Health. Integrative medicine (Encinitas, Calif.), 17(4), 28–32.

# TBI & THE VISUAL SYSTEM

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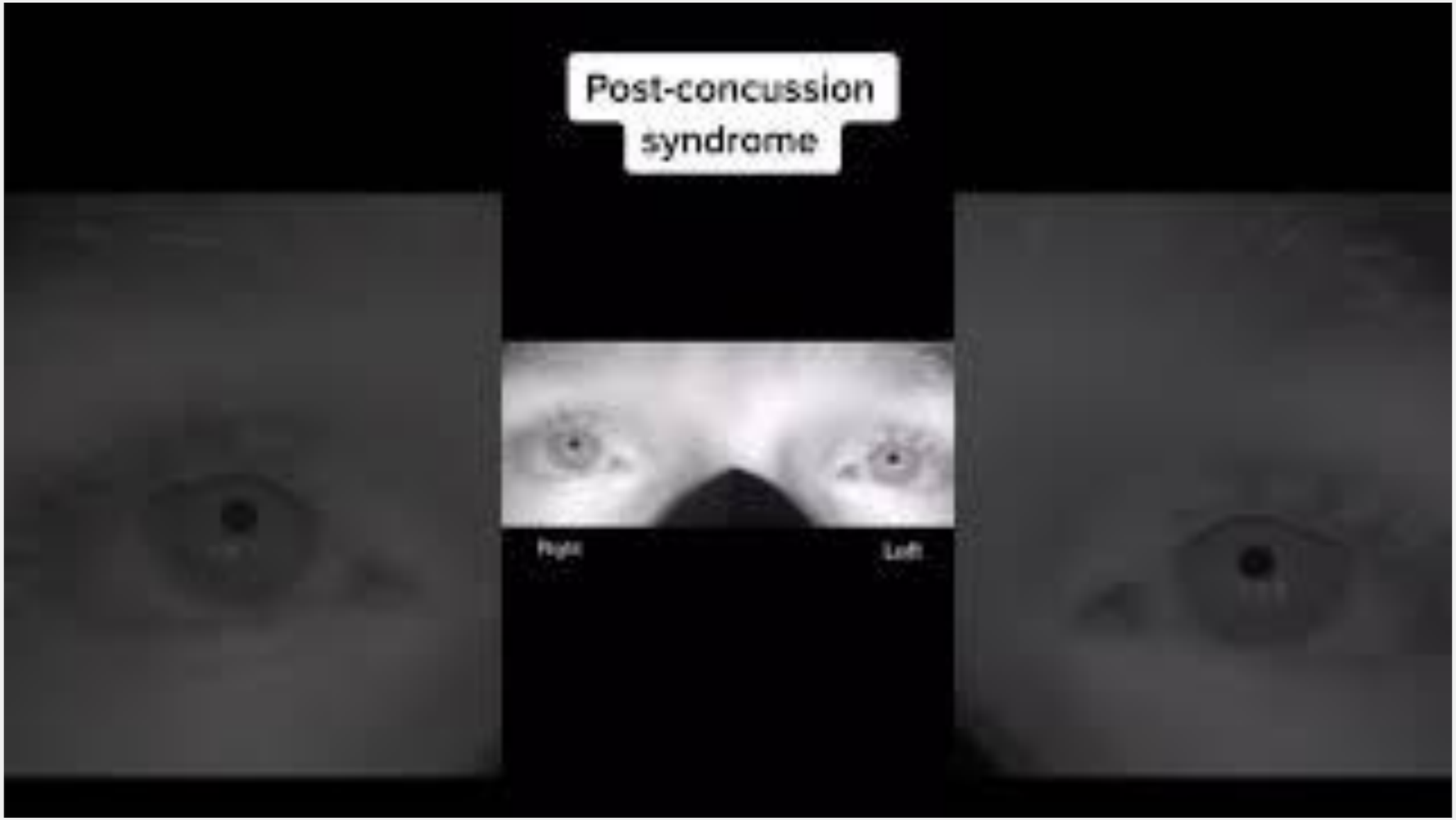
- Visual processing is highly dependent on brain function.
- TBI can disrupt:
  - **Convergence:** Difficulty bringing eyes together for near vision.
  - **Fixations:** Trouble keeping eyes still on a target.
  - **Smooth Pursuits:** Impaired ability to track moving objects.
  - **Saccades:** Rapid eye movements between objects are affected.

1.Richman, E. A. (2016, May 4). Traumatic brain injury and visual disorders: What every ophthalmologist should know. American Academy of Ophthalmology. https://www.aao.org/eyenet/article/traumatic-brain-injury-visual-disorders-what-every-2

2.Hunfalvay, M., Roberts, C.-M., Murray, N., Tyagi, A., Kelly, H., & Bolte, T. (2019). Horizontal and vertical self-paced saccades as a diagnostic marker of traumatic brain injury. Concussion, 4(1). https://doi.org/10.2217/cnc-2019-0001

3.Heitger, M. H., Jones, R. D., Macleod, A. D., Snell, D. L., Frampton, C. M., & Anderson, T. J. (2009b). Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability. Brain, 132(10), 2850–2870. https://doi.org/10.1093/brain/awp181


Post-concussion
syndrome

- **Common post-TBI visual symptoms:**
  - Dizziness and motion sickness.
  - Headaches and difficulty reading.
  - Slower reaction times and cognitive fatigue.

- Studies show **a strong correlation between visual dysfunction and prolonged concussion symptoms**.

1.Richman, E. A. (2016, May 4). Traumatic brain injury and visual disorders: What every ophthalmologist should know. American Academy of Ophthalmology. https://www.aao.org/eyenet/article/traumatic-brain-injury-visual-disorders-what-every-2

2.Armstrong, R. A. (2018). Visual problems associated with traumatic brain injury. Clinical and Experimental Optometry, 101(6), 716–726. https://doi.org/10.1111/cxo.12670

# TBI & THE CARDIOVASCULAR SYSTEM

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- TBI triggers a surge in **catecholamines** (stress hormones), leading to increased heart rate and blood pressure.

- Excess catecholamines cause cardiac dysfunction, increasing stress on the heart.

- Inflammation and oxidative stress further damage heart tissue.

1.Christensen, T. (2020, November 11). Traumatic brain injury, PTSD boost heart attack risk in veterans. www.heart.org. https://www.heart.org/en/news/2020/11/11/traumatic-brain-injury-ptsd-boost-heart-attack-risk-in-veterans

2.Coppalini, G., Salvagno, M., Peluso, L. et al. Cardiac Injury After Traumatic Brain Injury: Clinical Consequences and Management. Neurocrit Care 40, 477–485 (2024). https://doi.org/10.1007/s12028-023-01777-3

- **25–35% of TBI patients experience cardiac injury**, including irregular heartbeats and myocardial damage.

- **Higher risk for cardiovascular disease, arrhythmias, and heart failure**.

- **TBI survivors are 5–10 times more likely to develop chronic heart conditions**.

1.Coppalini, G., Salvagno, M., Peluso, L. et al. Cardiac Injury After Traumatic Brain Injury: Clinical Consequences and Management. Neurocrit Care 40, 477–485 (2024). https://doi.org/10.1007/s12028-023-01777-3

2.Izzy, S., Grashow, R., Radmanesh, F., Chen, P., Taylor, H., Formisano, R., Wilson, F., Wasfy, M., Baggish, A., & Zafonte, R. (2023). Long-term risk of cardiovascular disease after traumatic brain injury: Screening and prevention. The Lancet Neurology, 22(10), 959–970. https://doi.org/10.1016/s1474-4422(23)00241-7

# TBI & THE MUSCULOSKELETAL SYSTEM

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- **Higher risk of subsequent injuries after a concussion**.
- **Impaired coordination and balance** increase the likelihood of falls.
- **Delayed reaction times** contribute to musculoskeletal strain and joint injuries.
- **Higher chance of sustaining another concussion** or musculoskeletal injury post TBI.

1. Smulligan, K. L., Wilson, J. C., & Howell, D. R. (2022). Increased risk of musculoskeletal injuries after concussion. Operative Techniques in Sports Medicine, 30(1), 150896. https://doi.org/10.1016/j.otsm.2022.150896

- **TBI disrupts bone metabolism and remodeling**
- **Endocrine and vascular disruptions** lead to abnormal bone formation.
- **Higher risk of osteoporosis and delayed fracture healing**.
- **Muscle atrophy and joint instability** contribute to chronic pain and mobility issues.

1. Bajwa, N. M., Kesavan, C., & Mohan, S. (2018). Long-term consequences of traumatic brain injury in Bone metabolism. Frontiers in Neurology, 9. https://doi.org/10.3389/fneur.2018.00115

# TBI & COGNITIVE-BEHAVIORAL EFFECTS

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# TBI & THE MUSCULOSKELETAL SYSTEM

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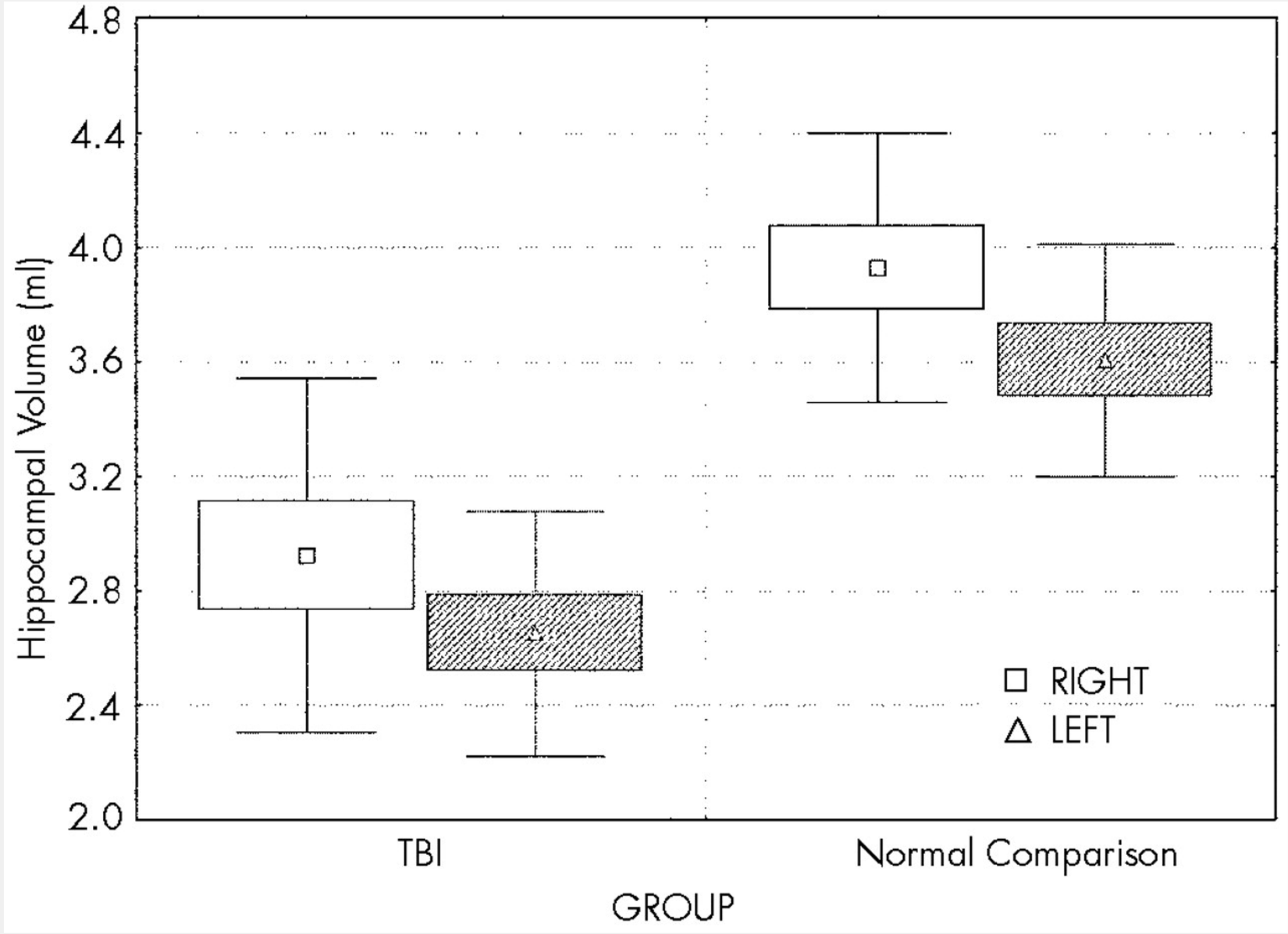
- **Higher risk of developing ADHD and learning disabilities** post-TBI.
- Slower **processing speed, problem-solving difficulties, and reduced attention span**.
- **Memory impairment due to hippocampal damage** – difficulty forming and recalling new memories.


1. Nelson, L. D., Guskiewicz, K. M., Marshall, S. W., Hammeke, T., Barr, W., Randolph, C., & McCrea, M. A. (2016). Multiple self-reported concussions are more prevalent in athletes with ADHD and learning disability. Clinical Journal of Sport Medicine, 26(2), 120–127. https://doi.org/10.1097/jsm.0000000000000207

2. Jorge, R. E., Robinson, R. G., Moser, D., Tateno, A., Crespo-Facorro, B., & Arndt, S. (2004). Major depression following traumatic brain injury. Archives of General Psychiatry, 61(1), 42. https://doi.org/10.1001/archpsyc.61.1.42

3. Jorge, R. E., Acion, L., Starkstein, S. E., & Magnotta, V. (2007). Hippocampal volume and mood disorders after traumatic brain injury. Biological Psychiatry, 62(4), 332–338. https://doi.org/10.1016/j.biopsych.2006.07.024




Arciniegas DB, Topkoff JL, Rojas DC, Sheeder J, Teale P, Young DA, Sandberg E, Reite ML, Adler LE. Reduced hippocampal volume in association with p50 nonsuppression following traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2001 Spring;13(2):213-21. doi: 10.1176/jnp.13.2.213. PMID: 11449028.

Right and left hippocampal volumes, TBI vs normal comparison groups (two-way analysis of covariance with total brain volume as the covariate; $F$=11.9, df=1,17, $P$ < 0.003).

- **TBI increases the risk of mood disorders**, including:
  - **Depression and anxiety** due to neurotransmitter imbalances.
  - **Post-traumatic stress disorder (PTSD)**, especially in severe or repeated injuries.
  - **Emotional dysregulation** – increased irritability and mood swings.
  - **Suicide Risk**
- **Reduced empathy and social withdrawal** can strain personal relationships.


1. de Sousa, A., McDonald, S., & Rushby, J. (2012). Changes in emotional empathy, affective responsivity, and behavior following severe traumatic brain injury. Journal of Clinical and Experimental Neuropsychology, 34(6), 606–623. https://doi.org/10.1080/13803395.2012.667067

2. Verhaeghe, S., Defloor, T., & Grypdonck, M. (2005). Stress and coping among families of patients with traumatic brain injury: A review of the literature. Journal of Clinical Nursing, 14(8), 1004–1012. https://doi.org/10.1111/j.1365-2702.2005.01126.x

- **Behavioral changes** post-TBI can cause frustration and emotional strain for family members.

- **Caregivers report increased stress, burnout, and financial burdens**.

- Importance of **mental health support, therapy, and structured rehabilitation**.

# TBI &
# HORMONAL DISRUPTIONS

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# TBI & THE MUSCULOSKELETAL SYSTEM

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- **TBI disrupts multiple endocrine pathways**

- Key hormonal imbalances impact:
  - **Energy levels, metabolism, mood, and cognition**.
  - **Hypothalamus, pituitary, thyroid, and adrenal glands**.

- **Cortisol dysregulation** and **pituitary dysfunction** are most common.

1. Bollerslev, J., Klibanski, A., & Tritos, N. (2013). Traumatic brain injury: effects on the endocrine system. The Journal of clinical endocrinology and metabolism, 98(3), 27A–8A. https://doi.org/10.1210/jcem.98.3.zeg27a

- **Cortisol Dysregulation**
  - **Initial spike post-TBI** worsens inflammation and **blood-brain barrier (BBB) dysfunction**.
  - Long-term = **fatigue, anxiety, depression, and immune suppression.**

- **Pituitary Dysfunction**
  - Reduced estrogen, progesterone, testosterone, and thyroid hormones.
  - **36–100% of males with severe TBI have low testosterone.**
  - **Linked to cognitive decline, memory loss, and metabolic disorders.**


1. Hohl, A., Zanela, F. A., Ghisi, G., Ronsoni, M. F., Diaz, A. P., Schwarzbold, M. L., Dafre, A. L., Reddi, B., Lin, K., Pizzol, F. D., & Walz, R. (2018). Luteinizing hormone and testosterone levels during acute phase of severe traumatic brain injury: Prognostic implications for adult ma le patients. Frontiers inEndocrinology, 9. https://doi.org/10.3389/fendo.2018.00029

2. Gilis-Januszewska, A., Kluczyński, Ł., & Hubalewska-Dydejczyk, A. (2020b). Traumatic brain injuries induced pituitary dysfunction: A call for algorithms. Endocrine Connections, 9(5). https://doi.org/10.1530/ec-20-0117

# TBI and hypopituitarism

- Spectrum of signs and symptoms of hypopituitarism is broad, non- specific, overlapping with PTSD, leading to misdiagnosis
  - Fatigue
  - Mood symptoms
  - Concentration/Neurocognitive difficulties
  - Circadian shifts/sleep disruption
  - Menstrual irregularities
  - Abnormal body composition: weight gain, visceral fat,
  - Adverse metabolic shifts

**Aimaretti et al. Clinical picture and the treatment of TBI-induced hypopituitarism. Pituitary (2019) 22:261-269**

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# TBI and hypopituitarism

- Anti-pituitary and anti-hypothalamic antibodies have been demonstrated in a significant number of subjects exposed to head trauma, suggesting autoimmunity as a factor post TBI hypopituitarism

Guaraldi F et al. Hypothalamic-Pituitary Autoimmunity and Traumatic Brain Injury. J Clin Med. 2015 May 19;4(5):1025-35

# TBI and hypopituitarism

- Most common hormones affected:
  - Human growth hormone
  - Adrenocorticotropic hormone [ACTH] deficiency
  - Gonadotropin deficiency [LH/FSH]

**Aimaretti et al. Clinical picture and the treatment of TBI-induced hypopituitarism. Pituitary (2019) 22:261-269**

# TBI and hypopituitarism

- TBI is a leading cause of secondary hypopituitarism in children and adults, with hormonal disruption creating disability, impaired QOL, compromised development
- The prevalence of hypopituitarism after TBI is about 30%
- GH is the most common hormone lost
- TBI-induced pituitary dysfunction remains undiagnosed and therefore untreated in most patients because of the nonspecific and subtle clinical manifestations of hypopituitarism.

**Kelestimur, F Antibodies against the pituitary and hypothalamus in boxer. Handb Clin Neurol. 2021:181:187-91**
**Guaraldi F et al. Hypothalamic-Pituitary Autoimmunity and TBI. J clin Med. 2015 May 19;4(5):1025-35**

# TBI and hypopituitarism

- While panhypopituitarism is always permanent, partial hypopituitarism/isolated hormone deficiencies are dynamic
- Hormonal shifts of partial hypopituitarism can occur from a few days to decades after TBI
- Hormonal shifts of partial hypopituitarism wax and wane over time, THE HALLMARK OF AUTOIMMUNITY

Guaraldi F et al. Hypothalamic-Pituitary Autoimmunity and Traumatic Brain Injury. J Clin Med. 2015 May 19;4(5):1025-35

# TBI &
# SLEEP DYSREGULATION

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# TBI Disrupts Circadian Rhythms

- **Traumatic brain injury (TBI) disrupts the body's natural sleep-wake cycle.**

- Common post-TBI sleep disturbances
  - **Insomnia** – difficulty falling or staying asleep.
  - **Hypersomnia** – excessive daytime sleepiness.
  - **Fatigue** – persistent tiredness, affecting daily function.
  - **Cognitive impairments** – slower processing speed, memory issues.

- **30–70% of individuals experience sleep disturbances post-TBI**


1. Lim, M. M., Elkind, J., Xiong, G., Galante, R., Zhu, J., Zhang, L., Lian, J., Rodin, J., Kuzma, N. N., Pack, A. I., & Cohen, A. S. (2013). Dietary therapy mitigates persistent wake deficits caused by mild traumatic brain injury. *Science Translational Medicine*, *5*(215). https://doi.org/10.1126/scitranslmed.3007092

2. Jorge, R. E., Robinson, R. G., Moser, D., Tateno, A., Crespo-Facorro, B., & Arndt, S. (2004). Major depression following traumatic brain injury. *Archives of General Psychiatry*, *61*(1), 42.


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# The Impact of Poor Sleep on Recovery

- **Sleep disorders increase hospitalization duration and rehabilitation costs.**

- **Poor sleep is linked to:**
  - **Higher rates of depression and anxiety** *(49)*.
  - **Chronic fatigue syndrome** – long-term exhaustion affecting recovery.
  - **Weakened immune function**, leading to slower healing.

- Sleep disturbances **worsen neuroinflammation**, delaying brain healing.

REF 62,63

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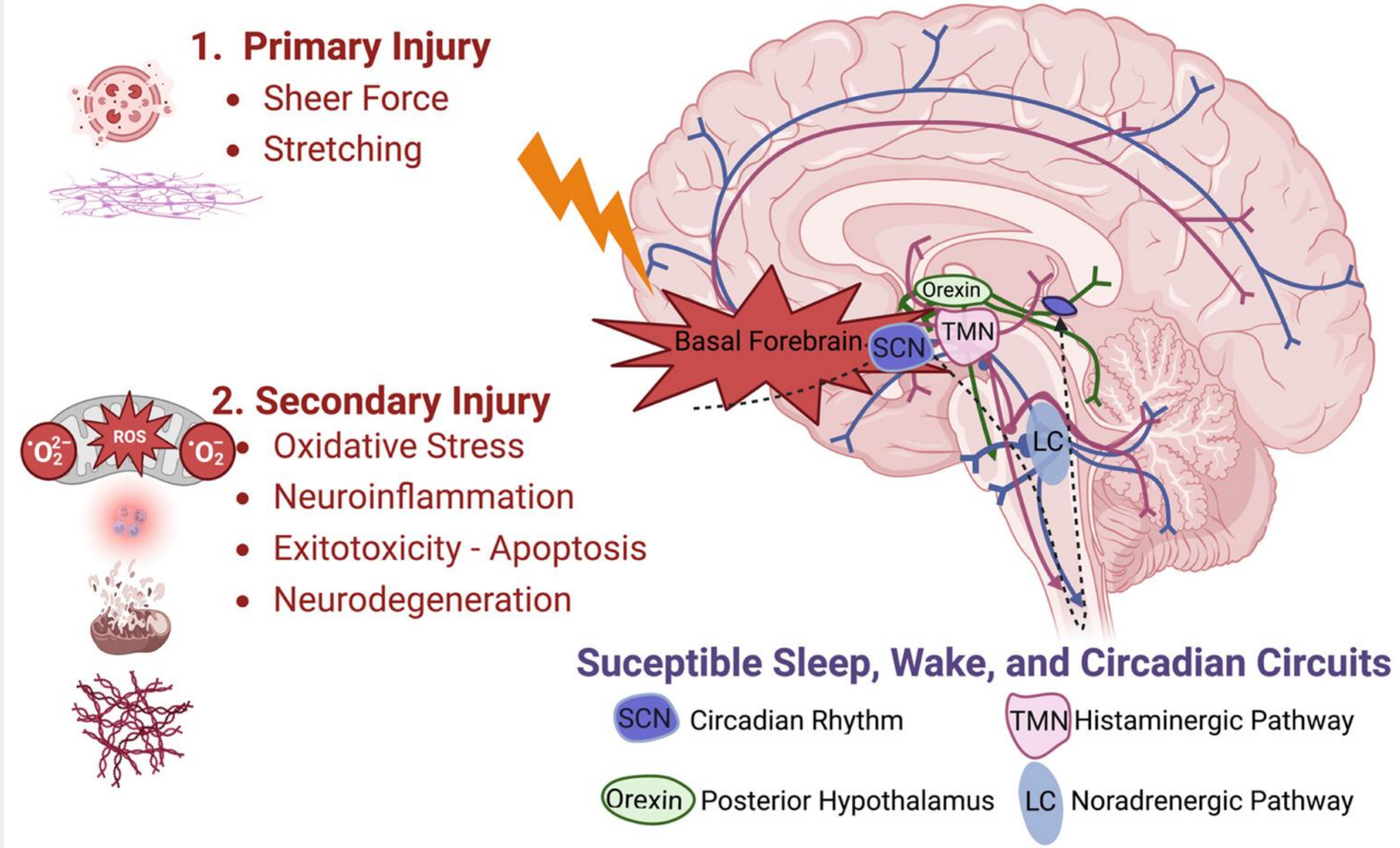
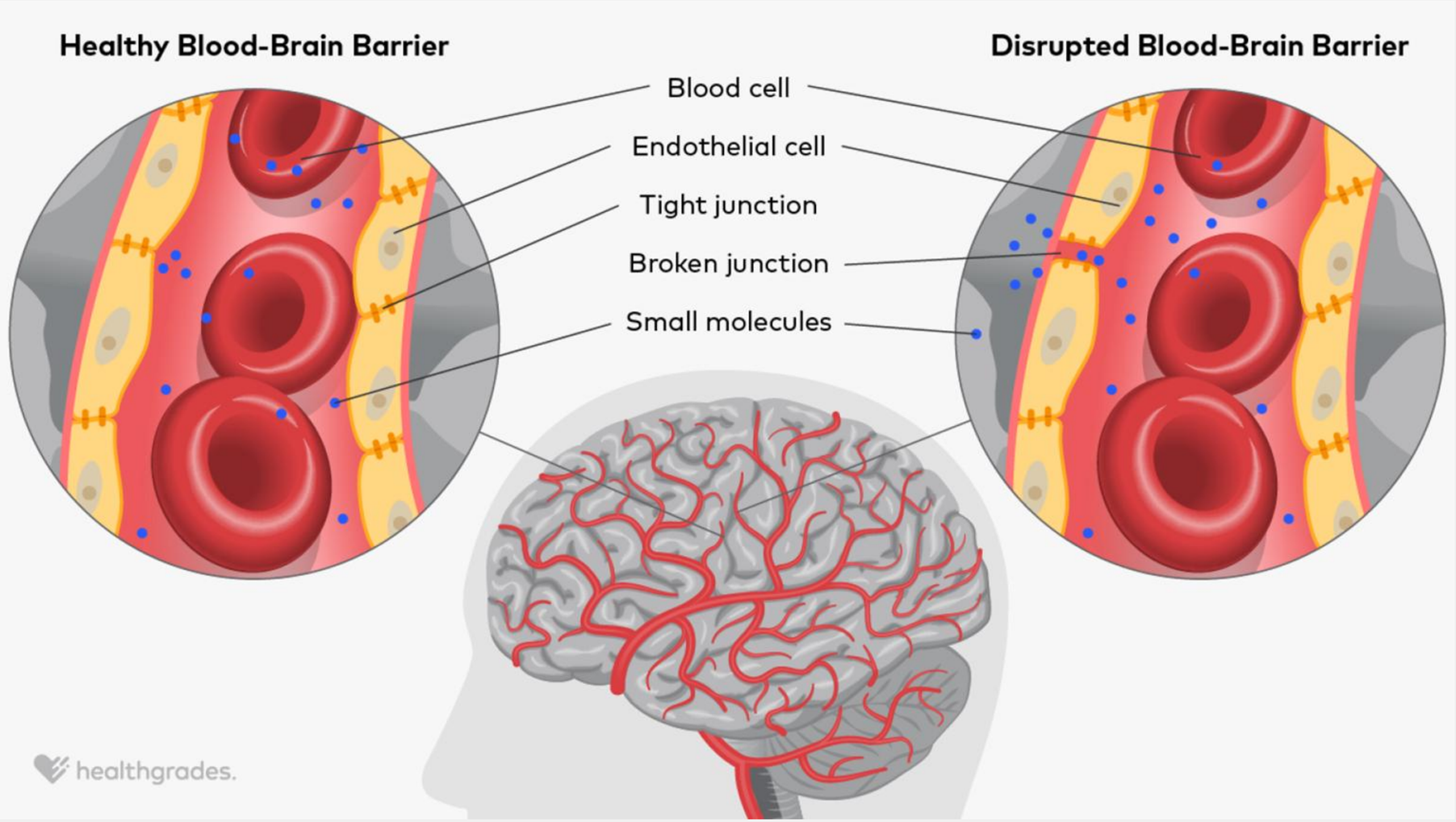
# Pathophysiology of Post-TBI Sleep Dysfunction




Bell, A., Hewins, B., Bishop, C., Fortin, A., Wang, J., Creamer, J. L., Collen, J., & Werner, J. K., Jr. (2023). Traumatic Brain Injury, Sleep, and Melatonin—Intrinsic Changes with Therapeutic Potential. *Clocks & Sleep*, *5*(2), 177-203. https://doi.org/10.3390/clockssleep5020016

# dr merediths slides

# Blood Brain Barrier Disruption and TBI



# Blood Brain Barrier Disruption and TBI

- Increased paracellular transport  caused by reduced expression of tight junction proteins, allowing passage of molecules usually restricted
- Increased transcytosis across the endothelial cell, allowing transport of usually restricted larger molecules (albumin etc) into the brain
- Increased water accumulation in the brain = cerebral edema

Cash A, Theus MH Mechanisms of Blood-Brain Barrier Dysfunction in Traumatic Brain Injury Int J Mol Sci. 2020 May 8:21(9):3344

# Blood Brain Barrier Disruption and TBI

- BBB disruption occurs within minutes following injury and can persist for years
- BBB disruption is considered a major risk factor of high mortality/morbidity
  - **Primary** injury disrupts structure/integrity of blood vessels
  - **Secondary** injury to BBB occurs as a result of:
    - Excess glutamate disrupting BBB via activation of NMDA receptors
    - Intravascular coagulation leading to microvascular ischemia
    - Increased levels ROS, TGF-beta, VEG-F, MMP further damage BBB

Cash A, Theus MH Mechanisms of Blood-Brain Barrier Dysfunction in Traumatic Brain Injury Int J Mol Sci. 2020 May 8:21(9):3344

# Markers of BBB disruption

- Glial fibrillary acidic protein (GFAP), an intracellular type III intermediate filament protein, provides structural support and maintains the mechanical integrity of astrocytes
- GFAP levels in serum and CSF are both elevated post TBI
- FDA has approved a rapid blood test to aid the diagnosis of mild TBI

Zheng X et al. Prediction of clinical progression in nervous system disease: plasma glial fibrillary acidic protein (GFAP) Eur J Med Res. 2024 Jan 12;29:51.
Papa L et al. time course and Diagnostic Accuracy of glial and neuronal Blood biomarkers GFAP and UCH-L1 in a Large Cohort of Trauma Patients With and Without Mild TBI. Jama Neuol. 2016 May 1;73(5):551-560.

# Markers of BBB disruption

- GAFP
- Fragmented tight junction proteins: occluding, claudin-5
- Ubiquitin caarobxyl-terminal hydrolase isozyme L1 [UCH-L1]
- S100 calcium- binding protein B

Zheng X et al. Prediction of clinical progression in nervous system disease: plasma glial fibrillary acidic protein (GFAP) Eur J Med Res. 2024 Jan 12;29:51.
Papa L et al. time course and Diagnostic Accuracy of glial and neuronal Blood biomarkers GFAP and UCH-L1 in a Large Cohort of Trauma Patients With and Without Mild TBI. Jama Neuol. 2016 May 1;73(5):551-560.

# Blood Brain Barrier Disruption and TBI

- Paradoxically many of the molecules that initially destroy the BBB after TBI later play a role in the repair process
- Blocking their action in the acute phase could lead to later problems

Cash A, Theus MH Mechanisms of Blood-Brain Barrier Dysfunction in Traumatic Brain Injury Int J Mol Sci. 2020 May 8:21(9):3344

# Aquaporin channels

- AQP4, a water selective channel protein, is expressed at junction of endothelial cells and astrocyte end feet which cover microvascular surface of BBB
- AQP4 channels maintain ion concentrations and fluid homeostasis
- AQP4 expression is increased at 1,4,24 hours post TBI in rat studies

Cash A, Their MH Mechanisms of Blood-Brain Barrier Dysfunction in Traumatic Brain Injury Int J Mol Sci. 2020 May 8;21(9):3344

# Aquaporin-4 [AQP4]

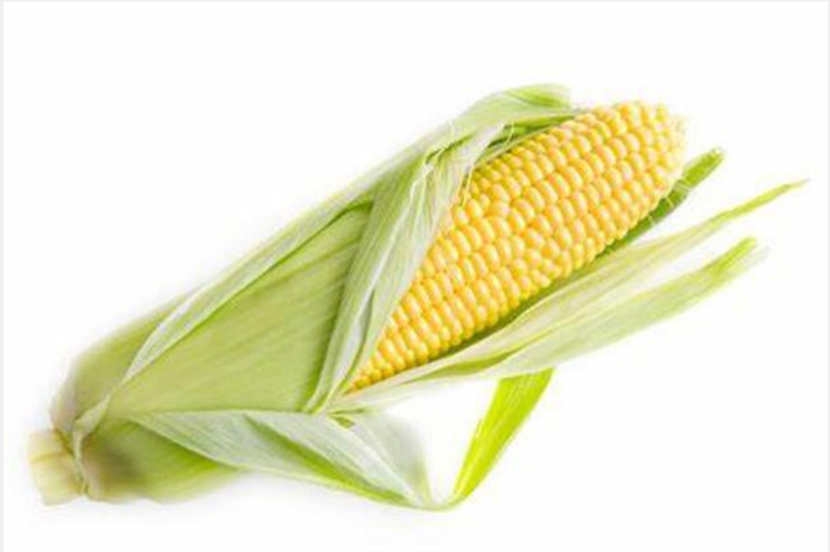
- AQP4 involved with  glymphatic function of elimination of toxins and metabolites from brain tissue
- Antibodies to AQP4 underlie Neuromyelitis Optica, analogous to MG and other autoimmune channelopathies

AQP4 is the target of multiple current studies in acute/chronic management of BBB disruption

Sven J et al. Mechanisms of disease; aquaporin-4 antibodies in neuromyelitis optica. Nat clin Pract Neurol. 2008 Apr;4(4):202-14

| | | | | |
|---|---|---|---|---|
| Lentil Lectin + Pea Lectin | | | 1.24 | 0.4-1.2 |
| Tuna, Canned | 0.49 | | | 0.0-1.0 |
| Hazelnut Vicilin + Cashew Vicilin | 0.74 | | | 0.5-2.1 |
| Scallops + Squid | 0.74 | | | 0.2-2.0 |
| Caseins | 1.15 | | | 0.0-3.0 |
| Alpha-Gliadin + Gliadin Toxic Peptide | 1.21 | | | 0.3-2.1 |
| Non-Gluten Wheat Proteins | 1.25 | | | 0.3-1.6 |
| **Blood Brain Barrier and Neurofilaments** | | | | |
| Blood-Brain Barrier Protein + Claudin-5 | | | 1.59 | 0.2-1.4 |
| Aquaporins | | | 1.67 | 0.2-1.0 |
| Neurofilament Proteins | 1.67 | | | 0.4-2.1 |

# AQP4 Food Cross Reactors



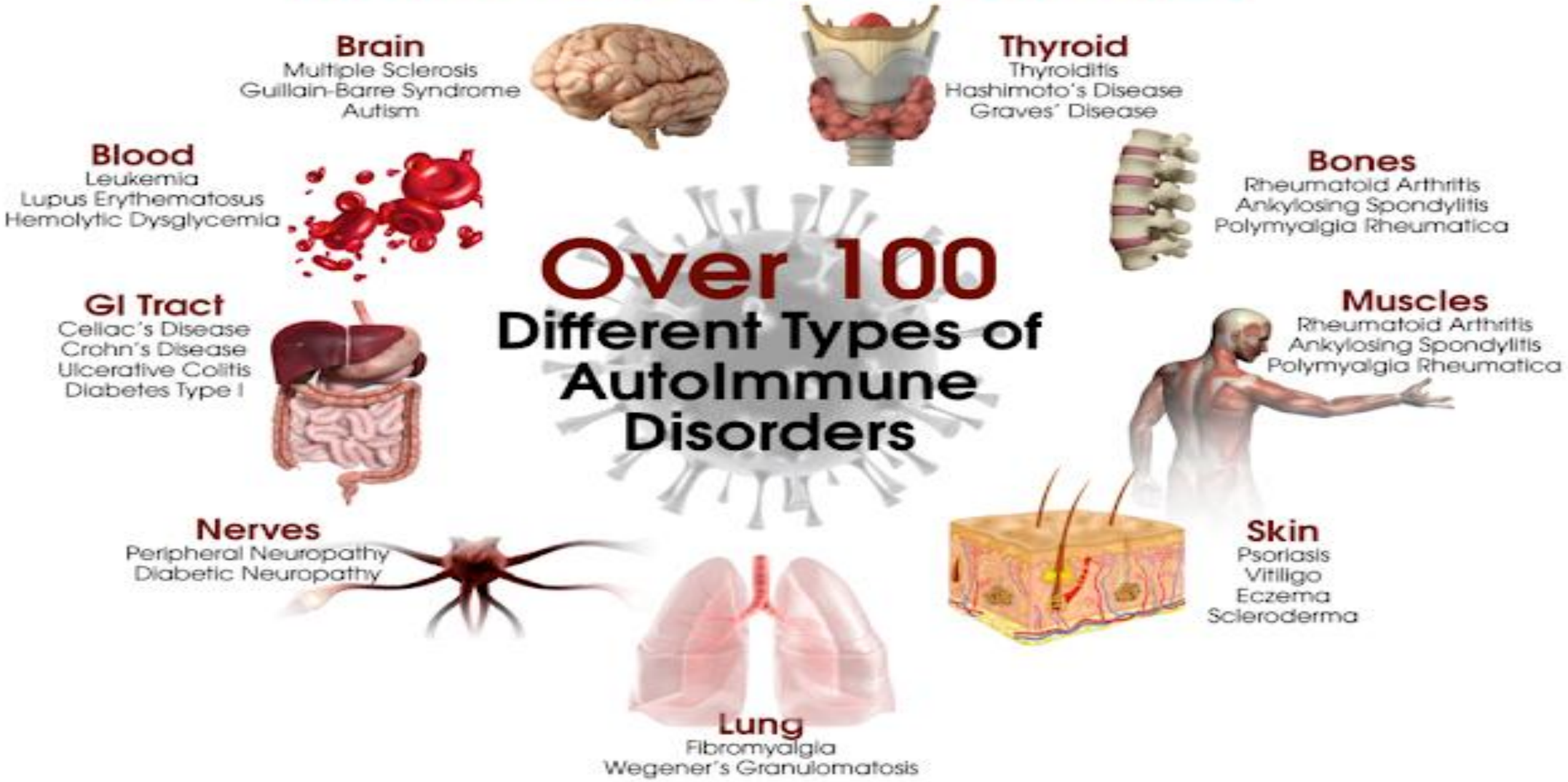
| | | | | |
|---|---|---|---|---|
| Lentil Lectin + Pea Lectin | 0.68 | | | 0.4-1.2 |
| Tuna, Canned | 0.67 | | | 0.0-1.0 |
| Hazelnut Vicilin + Cashew Vicilin | 1.05 | | | 0.5-2.1 |
| Scallops + Squid | 0.74 | | | 0.2-2.0 |
| Caseins | 0.71 | | | 0.0-3.0 |
| Alpha-Gliadin + Gliadin Toxic Peptide | 0.65 | | | 0.3-2.1 |
| Non-Gluten Wheat Proteins | 0.63 | | | 0.3-1.6 |
| **Blood Brain Barrier and Neurofilaments** | | | | |
| Blood-Brain Barrier Protein + Claudin-5 | 0.55 | | | 0.2-1.4 |
| Aquaporins | 0.76 | | | 0.2-1.0 |
| Neurofilament Proteins | 1.02 | | | 0.4-2.1 |

# Aquaporin-4

- Is there an autoimmune component to Parkinson's disease [PD]?
- AQP4 is a potential link from TBI to Neurodegenerative disease
- Neuroinflammation found to be important pathogenetic characteristic of PD
- PD characterized by Microglial activation, elevated proinflammatory cytokines, reactive oxygen species and mitochondrial dysfunction
- AQP4 dysfunction now felt to be a factor in development of Parkinson's and other neurodegenerative diseases

Lapshina, KV, Ekimova IV. Aquaporin-4 and Parkinson's Disease. Int J Mol Sci. 2024 Jan 30;25(3):1672
Yang C et al. Aquaporin-4 and Alzheimer's Disease. J Alzheimer's Dis. 2016 Mar 25;52(2):391-402
Arighi A et al. Cerebrospinal Fluid Level of AQP4: A New Window on Glymphatic System Involvement in Neurodegenerative Disease? J Alzheimer's Dis. 2019;69(3):663-669

# AUTOIMMUNE DISEASES



# Autoimmunity: Upward Trajectory

- A 2023 UK study examined the incidence and prevalence of 19 of the most common autoimmune diseases in the UK 2000 to 2019
- Together the 19 diseases affected 10.2 % of the population with largest increases seen in Celiac, Graves, and Sjogrens.
- Female to male distribution was  @ 2:1
- Crohn's is a notable exception to female predominance

Conrad et al. Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. Lancet. 2023 Jun 3;401(10391):1878-1890.

# Recognizing the many faces of autoimmunity

- Osteoarthritis
- Osteoporosis
- Meniere's disease
- Narcolepsy
- Epilepsy
- Autism Spectrum Disorders
- Infertility
- Obsessive Compulsive Syndrome
- Leukemia [STAT3 gain of function mutations]
- ASIA syndrome
-

Food Antigens

Brain Injury/TBI

Toxins

- Chemicals
- Smoke
- Breast implant illness
- Vaccines
- Mold Toxins

Psychic Trauma

- Chronic high stress
- Acute trauma
- PTSD
- Family of origin trauma

Infections

- Dental inflammation
- Chronic viruses
- Tick borne
- COVID
- Strep

Sleep Apnea

# Patient with Hashimoto's and Fibromyalgia

- 45 yo Mom with prior diagnoses of Hashimoto's thyroiditis and Fibromyalgia

Episodic flares of fatigue, brain fog, joint discomfort, body pain, tachycardia, dizziness

Fatigue with episodic "in bed days" preceded by "dizzy but energetic, I know the crash is coming"

Flares frequently preceded by "doing too much" either physically or psychically, sugar

# Patient with Hashimoto's and Fibromyalgia

- Removed food triggers: always feels better on Whole 30
- Repaired and prioritized sleep
- SIBO diagnosed and treated: fewer flares
- Intestinal Permeability (leaky gut) resolved
- Chronic active Epstein Barr diagnosed: fewer flares with more self care, meditation coaching, better sleep, less sugar
- CD 57 cells low consistent with environmentally acquired illness/mold illness
- Mycotoxins detected, improved after Detox; CD57 normalized
- FLARES MUCH LESS FREQUENT BUT STILL EPISODIC!

What Were We Missing?

# “I was fine until_____”

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# 23 year old after concussion


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| | | | | |
|---|---|---|---|---|
| **GLUTEN-CONTAINING/GLUTEN-CONTAMINATED** | | | | |
| Rye, Barley, Spelt, Polish Wheat | 0.69 | | | 0.0-1.1 |
| Instant Coffee | | 1.13 | | 0.0-1.5 |
| **GLIADIN CROSS-REACTIVE FOODS** | | | | |
| Cow's Milk | 1.18 | | | 0.0-2.0 |
| Alpha-Casein + Beta-Casein | 0.41 | | | 0.1-1.7 |
| Casomorphin | 0.23 | | | 0.0-1.8 |
| Milk Butyrophilin | 0.37 | | | 0.0-1.4 |
| Whey Protein | 0.39 | | | 0.1-1.3 |
| Milk Chocolate | 0.35 | | | 0.0-1.2 |
| Yeast | 0.86 | | | 0.0-1.5 |
| Oats | | 1.23 | | 0.0-1.4 |
| Millet | | 1.27 | | 0.3-1.5 |
| Rice | | | 1.35 | 0.0-1.2 |
| Corn | 1.34 | | | 0.0-2.7 |
| **NEWLY-INTRODUCED AND/OR OVER-CONSUMED ON GLUTEN-FREE DIET** | | | | |
| Buckwheat | 0.29 | | | 0.0-0.8 |
| Sorghum | | | 1.22 | 0.3-1.2 |
| Hemp | | | 3.40 | 0.0-2.3 |
| Sesame | | | 1.40 | 0.1-1.3 |
| Amaranth | | | 3.08 | 0.0-1.8 |
| Quinoa | | | 1.60 | 0.5-1.5 |
| Tapioca | | 1.16 | | 0.0-1.4 |
| Teff | | | 1.36 | 0.0-1.3 |
| Potato | 1.21 | | | 0.7-1.8 |
| **COMMON ANTIGENIC FOODS** | | | | |
| Egg, Raw | | | 0.87 | 0.0-0.6 |
| Soy | 0.53 | | | 0.2-1.2 |

| TEST | RESULT | | | |
|---|---|---|---|---|
| **Array 5 – Multiple Autoimmune Reactivity Screen **** | **IN RANGE (Normal)** | **EQUIVOCAL*** | **OUT OF RANGE** | **REFERENCE** (ELISA Index) |
| Parietal Cell + ATPase | 0.71 | | | 0.0-2.2 |
| Intrinsic Factor | 0.62 | | | 0.0-2.5 |
| ASCA + ANCA | 0.59 | | | 0.4-1.6 |
| Tropomyosin | 2.38 | | | 0.0-3.0 |
| 21-Hydroxylase (Adrenal Cortex) | 0.81 | | | 0.6-1.9 |
| Myocardial Peptide | 0.67 | | | 0.0-1.9 |
| Alpha-Myosin | 0.59 | | | 0.6-2.0 |
| Phospholipid | 0.57 | | | 0.4-1.7 |
| Platelet Glycoprotein | 0.47 | | | 0.6-1.8 |
| Ovary/Testis *** | 0.69 | | | 0.6-1.8 |
| Fibulin | 0.63 | | | 0.4-1.3 |
| Collagen Complex | 0.74 | | | 0.2-1.5 |
| Arthritic Peptide | | | 1.71 | 0.0-1.7 |
| Osteocyte | 1.16 | | | 0.7-2.0 |
| Cytochrome P450 (Hepatocyte) | 1.49 | | | 0.8-2.3 |
| Myelin Basic Protein | 0.42 | | | 0.6-1.7 |
| Asialoganglioside | 0.84 | | | 0.6-1.6 |
| Alpha-Tubulin + Beta-Tubulin | 1.15 | | | 0.0-2.7 |
| Cerebellar | 0.57 | | | 0.4-1.5 |
| Synapsin | | | >5.10 | 0.0-2.1 |

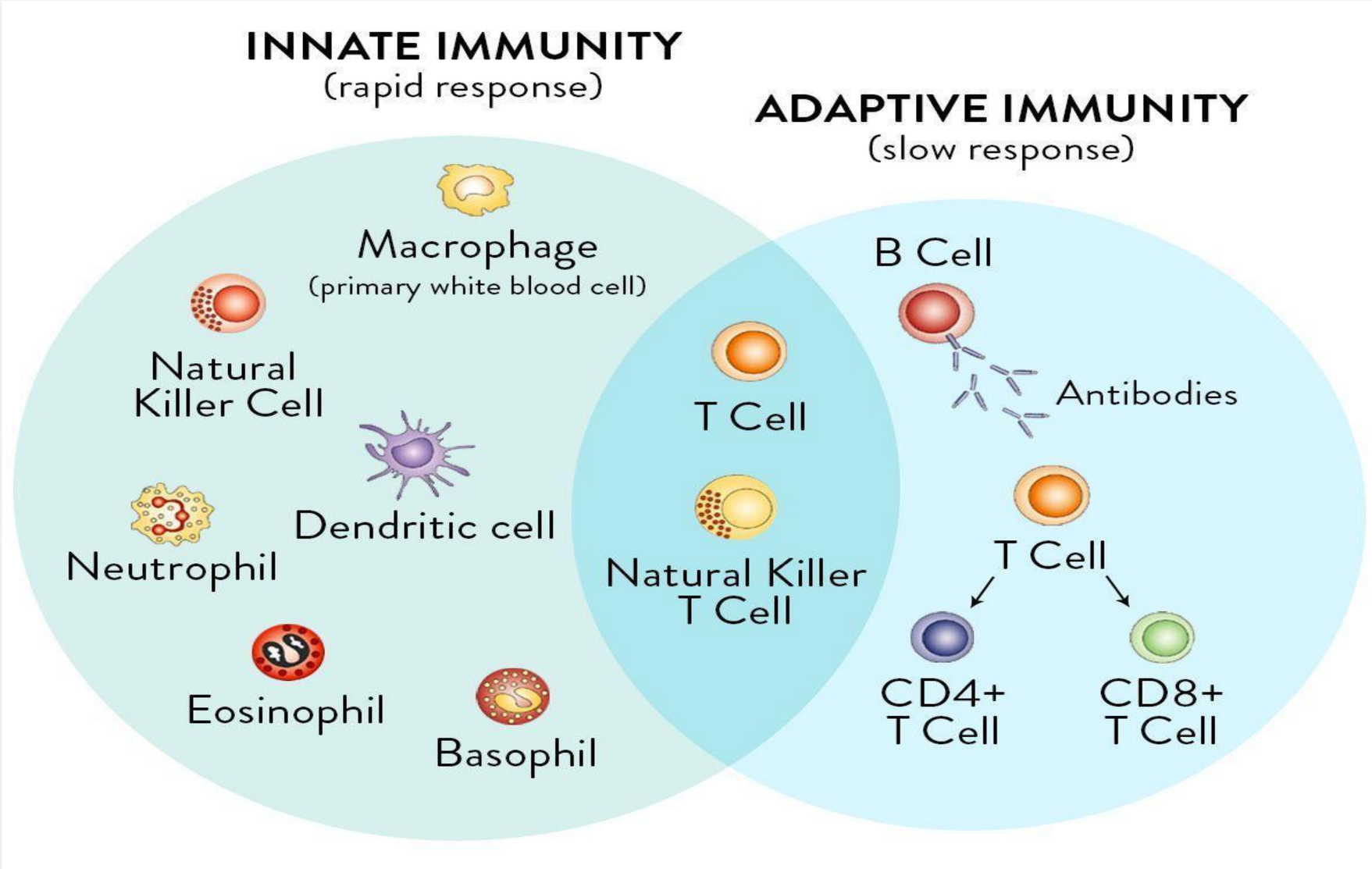
| TEST | RESULT | | | |
|---|---|---|---|---|
| **Array 11 Chemical Immune Reactivity Screen** | **IN RANGE (Normal)** | **EQUIVOCAL*** | **OUT OF RANGE** | **REFERENCE** (ELISA Index) |
| Aflatoxins IgG+IgA | 1.47 | | | 0.9-3.2 |
| Aflatoxins IgM | 1.00 | | | 0.4-2.3 |
| Formaldehyde and Glutaraldehyde IgG+IgA | 1.53 | | | 0.6-2.4 |
| Formaldehyde and Glutaraldehyde IgM | 1.55 | | | 0.4-2.7 |
| Isocyanate IgG+IgA | | | 2.40 | 0.2-1.5 |
| Isocyanate IgM | 0.90 | | | 0.2-2.1 |
| Trimellitic and Phthalic Anhydrides IgG+IgA | | | 1.82 | 0.3-1.5 |
| Trimellitic and Phthalic Anhydrides IgM | 1.89 | | | 0.4-2.6 |
| Benzene Ring Compounds IgG+IgA | 0.51 | | | 0.4-1.6 |
| Benzene Ring Compounds IgM | 1.08 | | | 0.3-2.1 |
| BPA Binding Protein IgG+IgA | 0.68 | | | 0.4-1.5 |
| BPA Binding Protein IgM | 0.60 | | | 0.2-1.2 |
| Bisphenol A IgG+IgA | 0.58 | | | 0.1-1.8 |
| Bisphenol A IgM | 1.27 | | | 0.1-2.0 |
| Tetrabromobisphenol A IgG+IgA | | 1.31 | | 0.3-1.4 |
| Tetrabromobisphenol A IgM | | 2.27 | | 0.0-2.5 |
| Tetrachloroethylene IgG+IgA | | 1.43 | | 0.1-1.5 |
| Tetrachloroethylene IgM | 0.60 | | | 0.1-2.1 |
| Parabens IgG+IgA | | | >2.20 | 0.2-1.5 |
| Parabens IgM | | 1.08 | | 0.0-1.2 |
| Mercury Compounds IgG+IgA | 0.35 | | | 0.2-1.3 |
| Mercury Compounds IgM | 1.13 | | | 0.1-2.2 |
| Mixed Heavy Metals IgG+IgA | | | 4.17 | 0.2-1.8 |
| Mixed Heavy Metals IgM | 1.11 | | | 0.0-2.1 |

# The immunological response to TBI

- Our understanding is limited as contusion, concussion, and blast injury create different patterns of inflammation
- Studies in animal models demonstrate that targeting the same inflammatory pathways in experimental contusion and concussion models can result in the opposite effect on neurological outcome

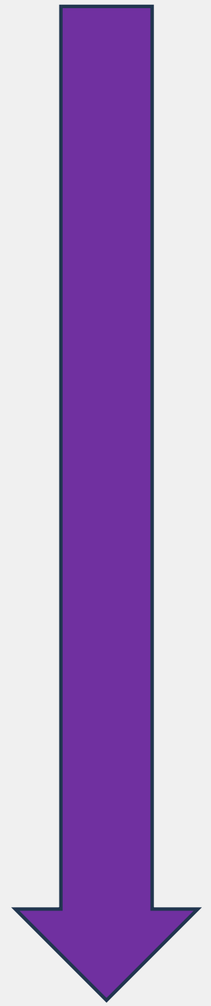
Jassam YN et al. Neuroimmunology of Traumatic Brain Injury: Time for a Paradigm Shift Neuron. 2017 Sep 13;95(6): 1246-1265

# The immunological response to TBI



# The immunological response to TBI

- Damage of CNS Barriers
- Innate Immunity: “Alarmins” from damaged tissue bind to DAMP (damage associated molecular pattern] and PAMP receptors
- Microglial activation
- Gene expression
- Complement Activation
- Neutrophil recruitment
- Peripheral immune cell recruitment
- Adaptive Immunity



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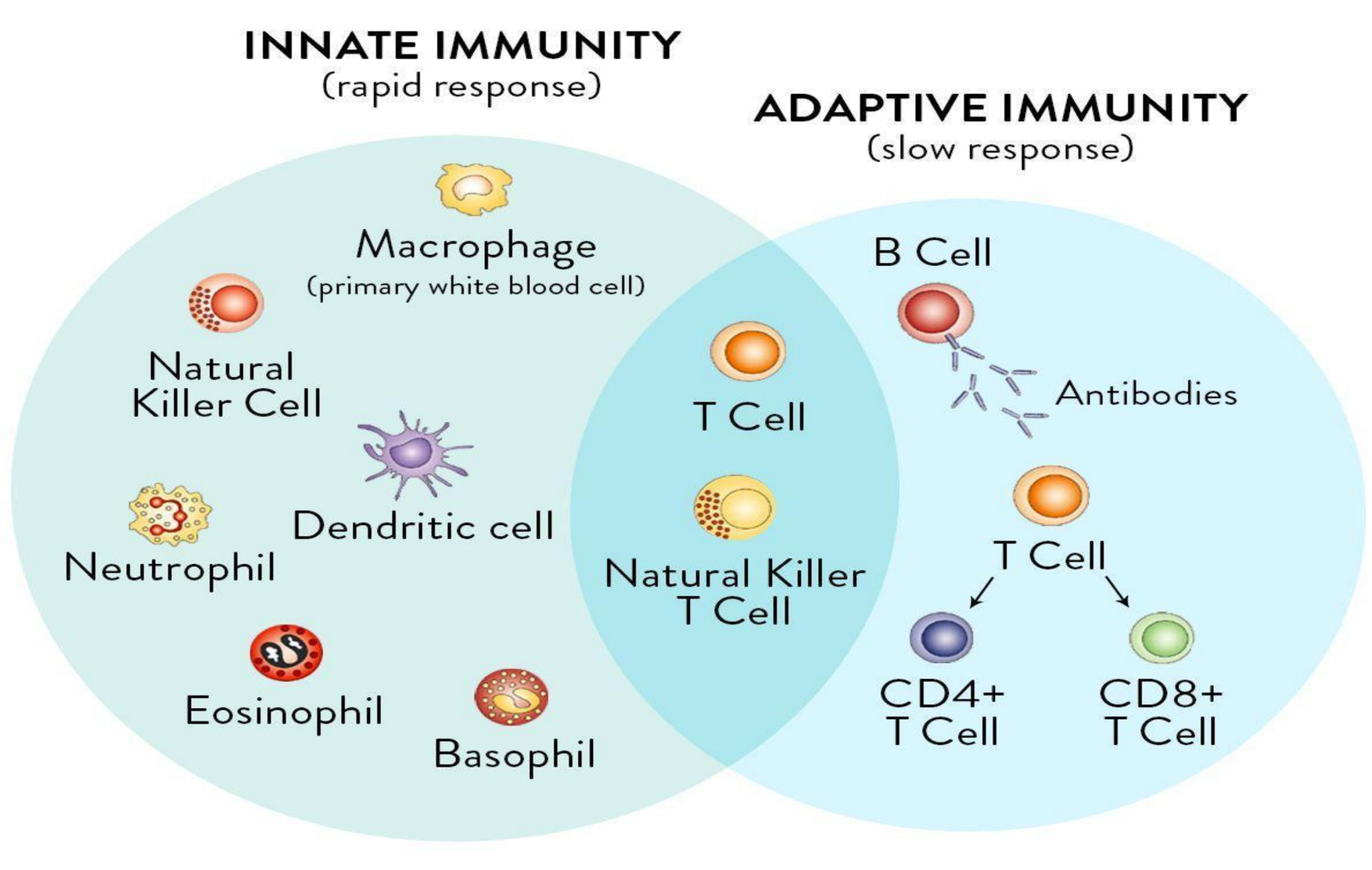
# The immunological response to TBI



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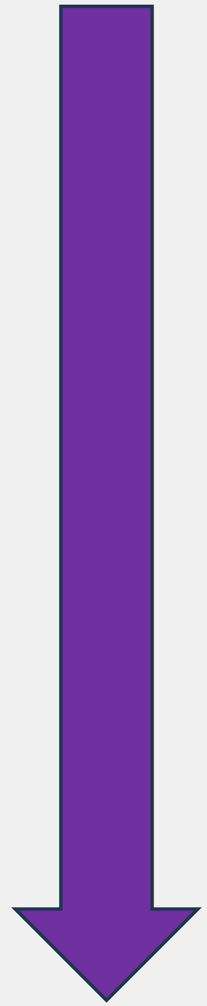

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# The immunological response to TBI

- Phase I: Innate Immune System Activation
  - Responds in a non-specific manner with limited capacity to remember the antigens it encounters
    - Phagocytes: neutrophils, macrophages, microglia, dendritic cells
    - Granulocytes: eosinophils, basophils, mast cells, neutrophils
    - Natural Killer NK cells
    - Unconventional T lymphocytes

Jassam YN et al. Neuroimmunology of Traumatic Brain Injury: Time for a Paradigm Shift Neuron. 2017 Sep 13;95(6): 1246-1265

# The immunological response to TBI

- Phase I: Innate Immune System Activation
  - Utilizes pattern recognition molecules [TLRs, NOD-like receptors] to sense
  - Releases chemokines and cytokines that amplify immune response
  - Triggers expression of NFkB, increasing IL-6 , TNF alpha levels
  - Promotes inter-cellular signaling at site of injury
  - Activates complement system

Jassam YN et al. Neuroimmunology of Traumatic Brain Injury: Time for a Paradigm Shift Neuron. 2017 Sep 13;95(6): 1246-1265

# The immunological response to TBI

- Phase II: Adaptive Immune System Activation
  - Antigen specific w ability to remember previously encountered antigens
  - Activation/Expansion of T and/or B lymphocytes
  - T lymphocytes recognize peptide antigens displayed on MHC or APCs
  - B lymphocytes produce antibodies, activate T cells

Jassam YN et al. Neuroimmunology of Traumatic Brain Injury: Time for a Paradigm Shift Neuron. 2017 Sep 13;95(6): 1246-1265

# The immunological response to TBI

- Adaptive Immune System is critical in defense against pathogens, but can also be directed against self-antigens = Autoimmunity

Jassam YN et al. Neuroimmunology of Traumatic Brain Injury: Time for a Paradigm Shift Neuron. 2017 Sep 13;95(6): 1246-1265

# TBI and Brain AutoAntibodies

- In TBI, levels of brain antigens and brain-reactive antibodies correlates with the frequency of head impacts and severity of stroke in most studies.
- The presence of brain-reactive autoantibodies does not necessarily correlate with active disease, rather indicates “silent autoimmunity” or “autoimmune potential”
- Are these brain-reactive antibodies pathogenic?

Javidi E, Magnus T. AutoImmunity After Ischemic Stroke and Brain Injury. Front Immunol. 2019 Apr 2;10:686

# TBI and Brain AutoAntibodies

- Anti pituitary
- Anti hypothalamus
- Anti cardiolipin
- Anti GFAP [Glial fibrillary acidic protein]
- Anti AQP-4 [Aquaporin 4]
- Anti NMDA receptor IgG
- ANCA
- Anti ds DNA

Javidi E, Magnus T. AutoImmunity After Ischemic Stroke and Brain Injury. Front Immunol. 2019 Apr 2;10:686

# TBI and autoimmune astrocytopathy

- Autoimmune GFAP astrocytopathy is an inflammatory disease of the CNS
- Autoimmune GFAP may coexist with other antibodies including AQP-4, NMDA receptor IgG, ANCA, anti ds DNA, anti cardiolipin

Zheng X et al. Prediction of clinical progression in nervous system disease: plasma glial fibrillary acidic protein (GFAP) Eur J Med Res. 2024 Jan 12;29:51.

# The immunological response to TBI

- Inflammation is a necessary and beneficial response to injury or infection, though can become pathologic
- Targeting a single molecule or pathway may negate the beneficial roles of inflammation
- Targeting a single molecule or pathway is unlikely to address the complexity of the immune process
- A broad approach to optimization of all necessary factors for optimal immune function appears to be warranted, rather than a targeted approach with unknown immune consequences

# TBI impact on neurogenesis: A link to neurodegenerative disease?

- Multiple studies indicate the critical role of neurogenesis in cognitive dysfunction, Alzheimer's disease, Parkinson's disease
- Any insult or injury to the CNS, including TBI or infectious disease, can provoke an inflammatory response
- CNS inflammation can either promote or inhibit neurogenesis via glial activation, cytokines, chemokines, reactive oxygen species
- These mechanisms regulate every step of adult neurogenesis

Amanollahi M et al. Mol Neurobiol. 2023 Feb;60(2):923-959

# KEY POINTS

- TBI has far-reaching effects beyond the brain, impacting multiple systems.
- Addressing systemic dysfunction is essential for comprehensive recovery.
- Future interventions should include targeted metabolic, inflammatory, and detoxification support.
- A multidisciplinary approach is key to improving post-TBI outcomes.

- Lacking robust studies in this arena, experts in the field advocate for “a logical application of science to the problem of concussion or a TBI”.

- A “TBI First Aid Kit” should include essential nutrients to support brain recovery, be put to use **within the first 24 hours post-injury** and continued for at least 7-21 days.