Traumatic Brain Injury (TBI)

- An alteration in brain function, or other evidence of brain pathology, caused by an external force
- TBI is associated with significant adverse mental health outcomes in 1/3 of survivors
- Severity based on:
  - Extent of injury to the brain
  - Level of altered consciousness
  - Glasgow Coma Scale
    - Severe: <9
    - Moderate: 9-12
    - Mild: ≥13

Glasgow Coma Scale for Head Injury

Glasgow Coma Scale, Eye opening	
Spontaneous	4
To loud voice	3
To pain	2
None	1
Verbal response	
Oriented	5
Confused, disoriented	4
Inappropriate words	3
Incomprehensible sounds	2
None	1
Best motor response	
Obeys	6
Localizes	5
Withdraws (flexion)	4
Abnormal flexion posturing	3
Extension posturing	2
None	1

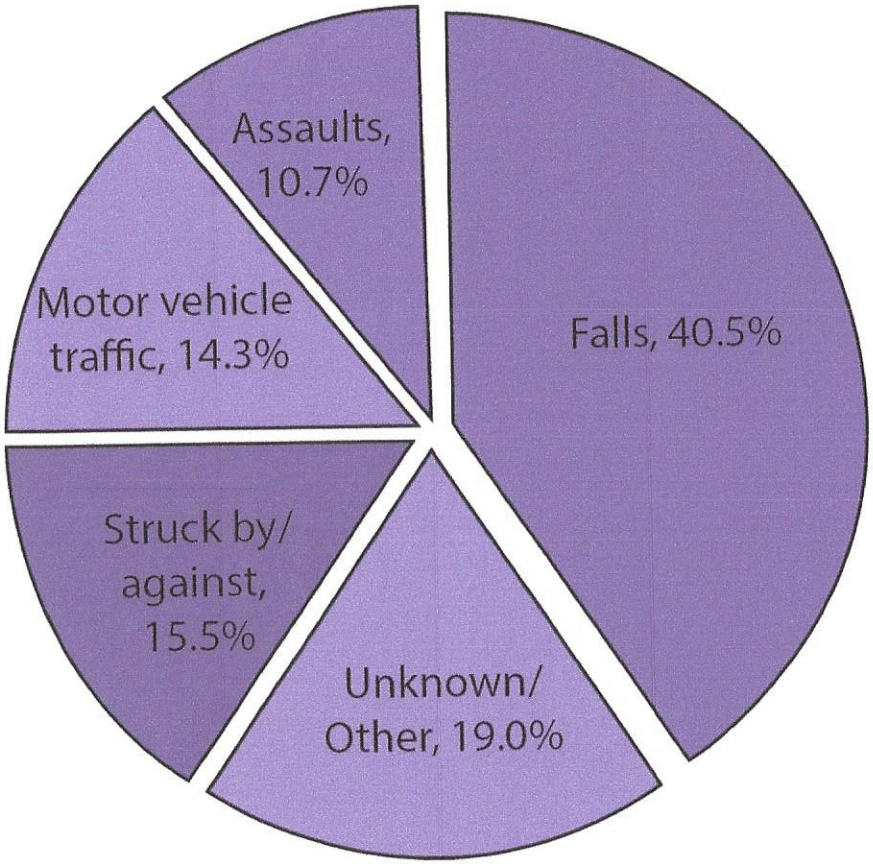
Brenner LA. Dialogues Clin Neurosci 2011;13:311-23; Brain Injury Association of America.

Epidemiology of Traumatic Brain Injury

- A TBI occurs every 7 seconds
- 1.7 million TBIs/year in the U.S.
- 22% of all wounded soldiers have suffered a TBI
  - Mild TBI (mTBI) is the "signature injury" of the current military conflicts
- Athletes: 300,000 cases of mild TBI/year
- Other (motor vehicle, violence, etc.)
- Underestimated?
  - Many mild injuries are likely to be overlooked
  - 25–42% of concussions (possibly more) go unreported

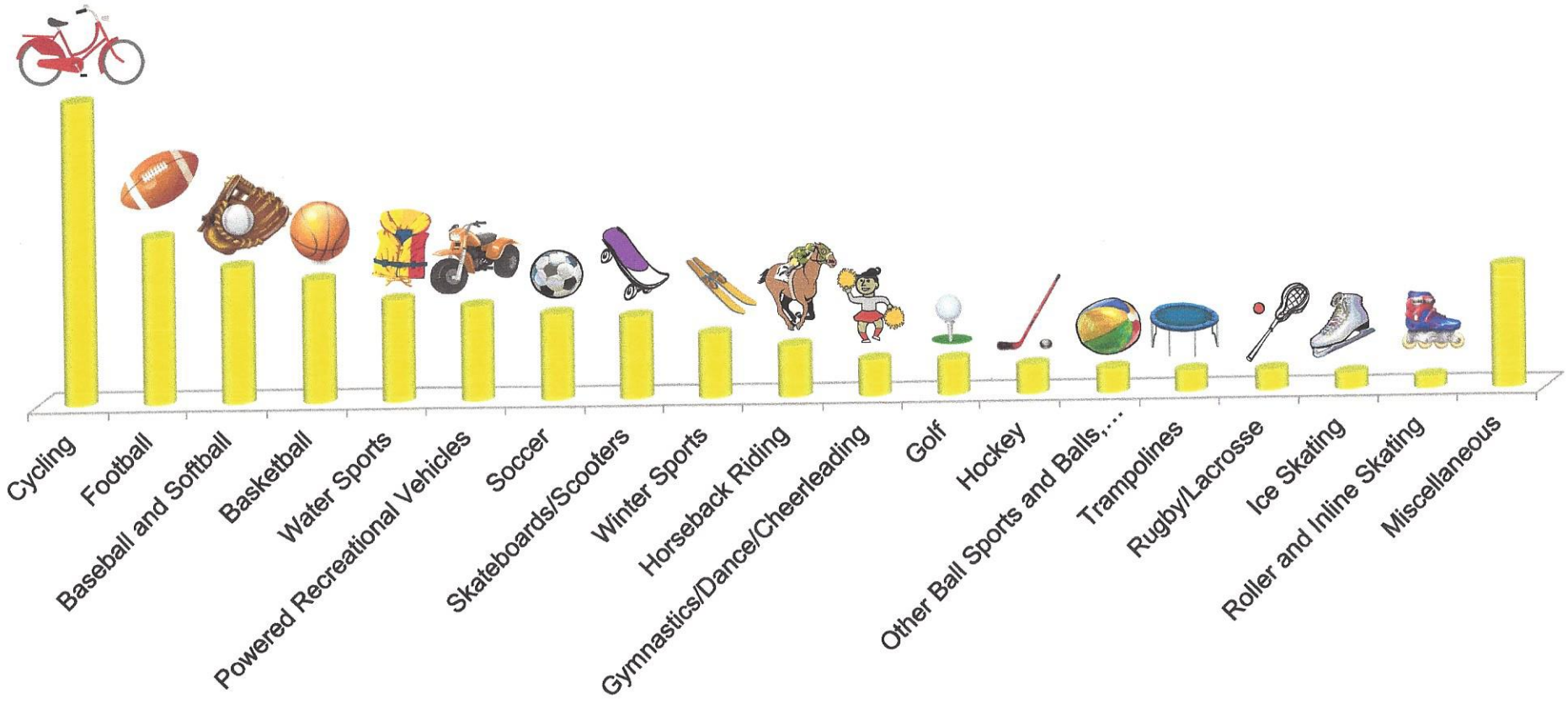
Almasi SJ, Wilson JJ. WMJ 2012;111(1):21-7; DeCuypere M, Klimo P Jr. Surg Clin North Am 2012;92:939-57; Nelson DV, Esty ML. J Neuropsychiatry Clin Neurosci 2012;24(2):237-40; Ponsford et al. J Neurol Neurosurg Psychiatry 2002;73:330-2; Sayer NA. Annu Rev Med 2012;63:405-19; Helmick KM et al. Brain Imaging Behav 2015; 9(3)358-66.

Leading Causes of TBI



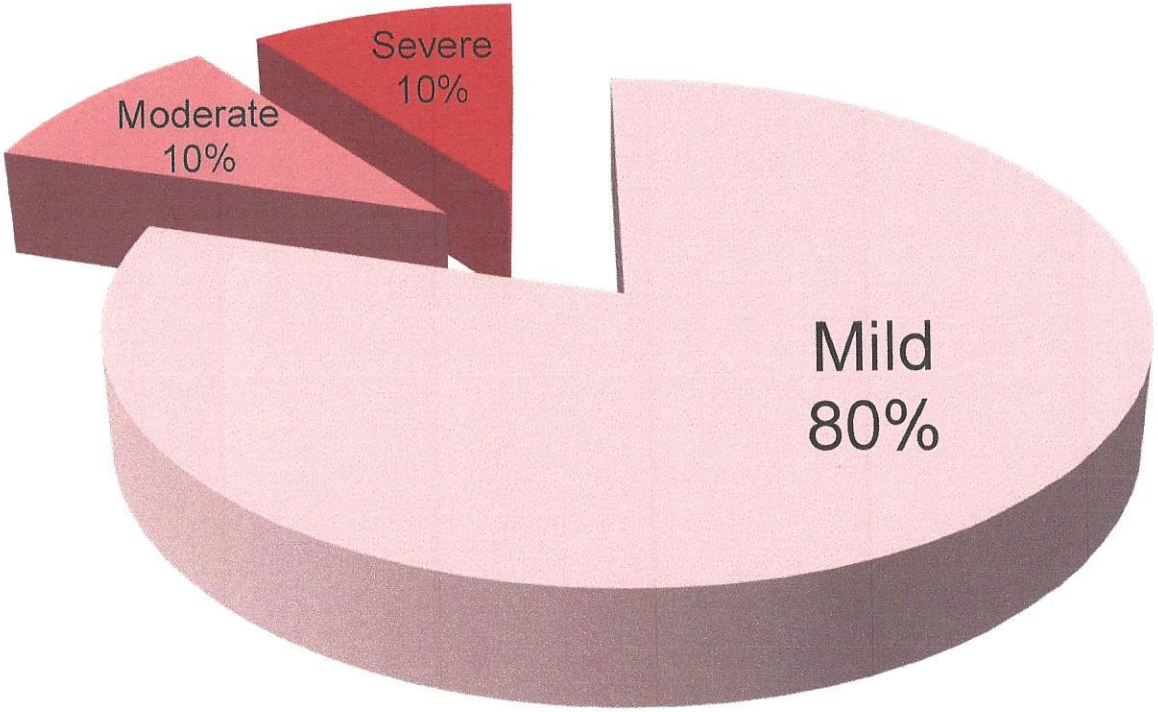
Segal SK. Beyond the Impact, 2017.

Incidence of Sports-Related TBI



gForce Tracker. http://www.gforcetracker.com/why-its-important.php.

Mild TBI (mTBI)



DeCuypere M, Klimo P Jr. Surg Clin North Am 2012;92:939-57.

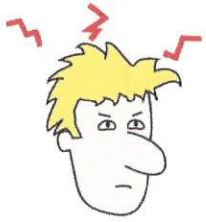
Even Mild Injury Can Cause Major Problems

- Any concussion, no matter how mild, may result in permanent neurological impairment
- Subconcussive head injuries may cause pathophysiological brain changes, including cortical dysfunction, without clinical presentation of concussion
- Conversely, some individuals with apparently severe injuries have good functional outcomes

Broglio SP et al. Exerc Sport Sci Rev 2012;40(3):138-44; Kelly JC et al. Rehabil Res Pract 2012;2012:371970; Maller LL et al. Brain Res 2010;64:213-40; Hou R et al. J Neurol Nerosurg Psychiatry 2012;83:217-23.

Post-concussive Syndrome (PCS)

- Constellation of ongoing physical, cognitive, and emotional symptoms associated with TBI
- Persist beyond the expected time-frame (1-6 weeks)



Headaches

Dizziness

Short-term memory problems

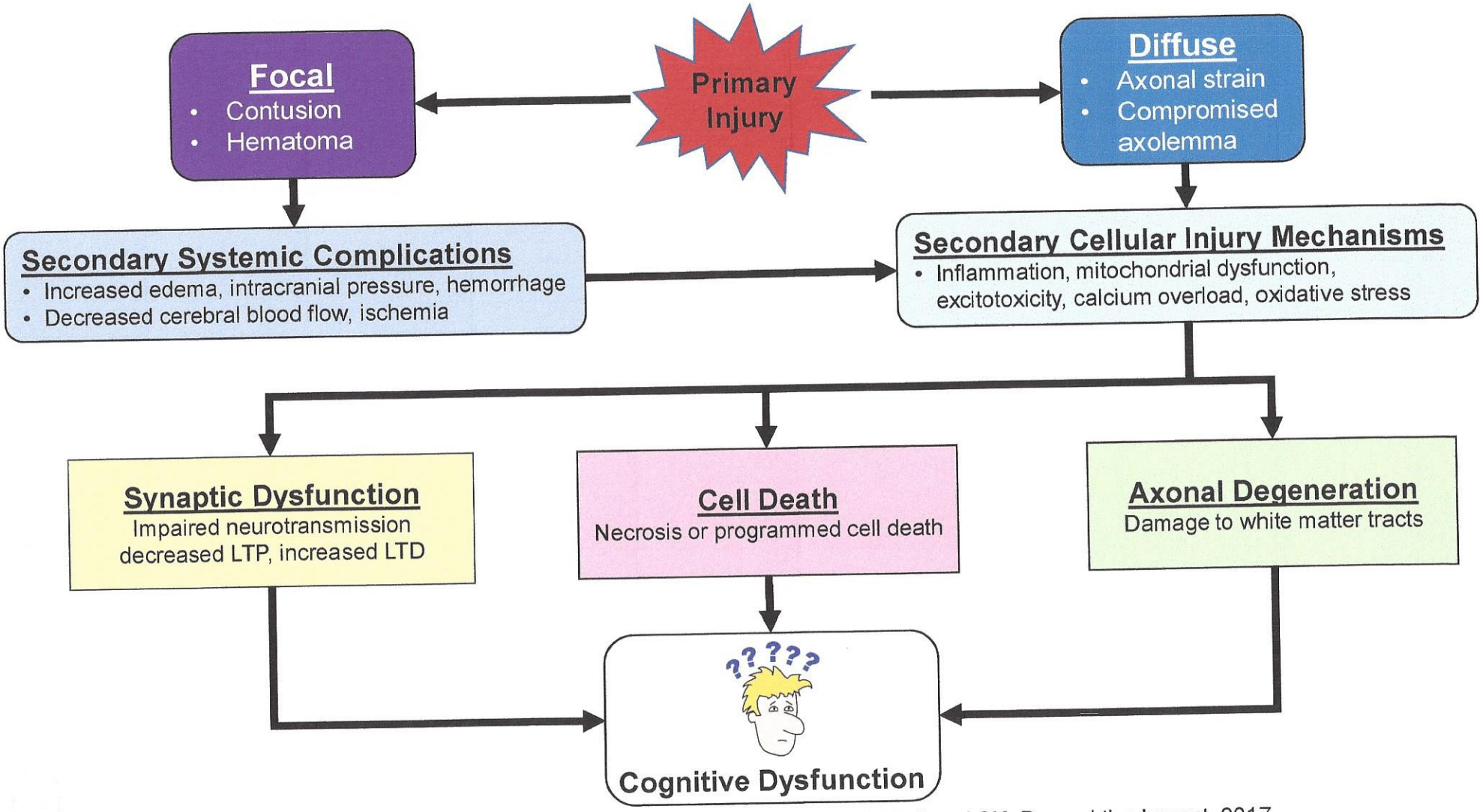
Noise sensitivity

Light sensitivity

Segal SK. Beyond the Impact, 2017.

Type of Injury	Neurological Damage
Blow to the head with an object	Damage to underlying tissue/vessels
Thrown against a wall or solid surface	Focal and diffuse damage
Punched in the face or head	Contusions, bruising/bleeding
Violent shaking of the body	Diffuse axonal injuries/torn nerve tissue
Falling and hitting your head	Focal and diffuse damage
Being strangled	Diffuse damage (hypoxia)
Near drowning	Diffuse damage (hypoxia)
Being shot in the face or head	Disintegration of brain tissue

Brain Injury Association of America, 2012.



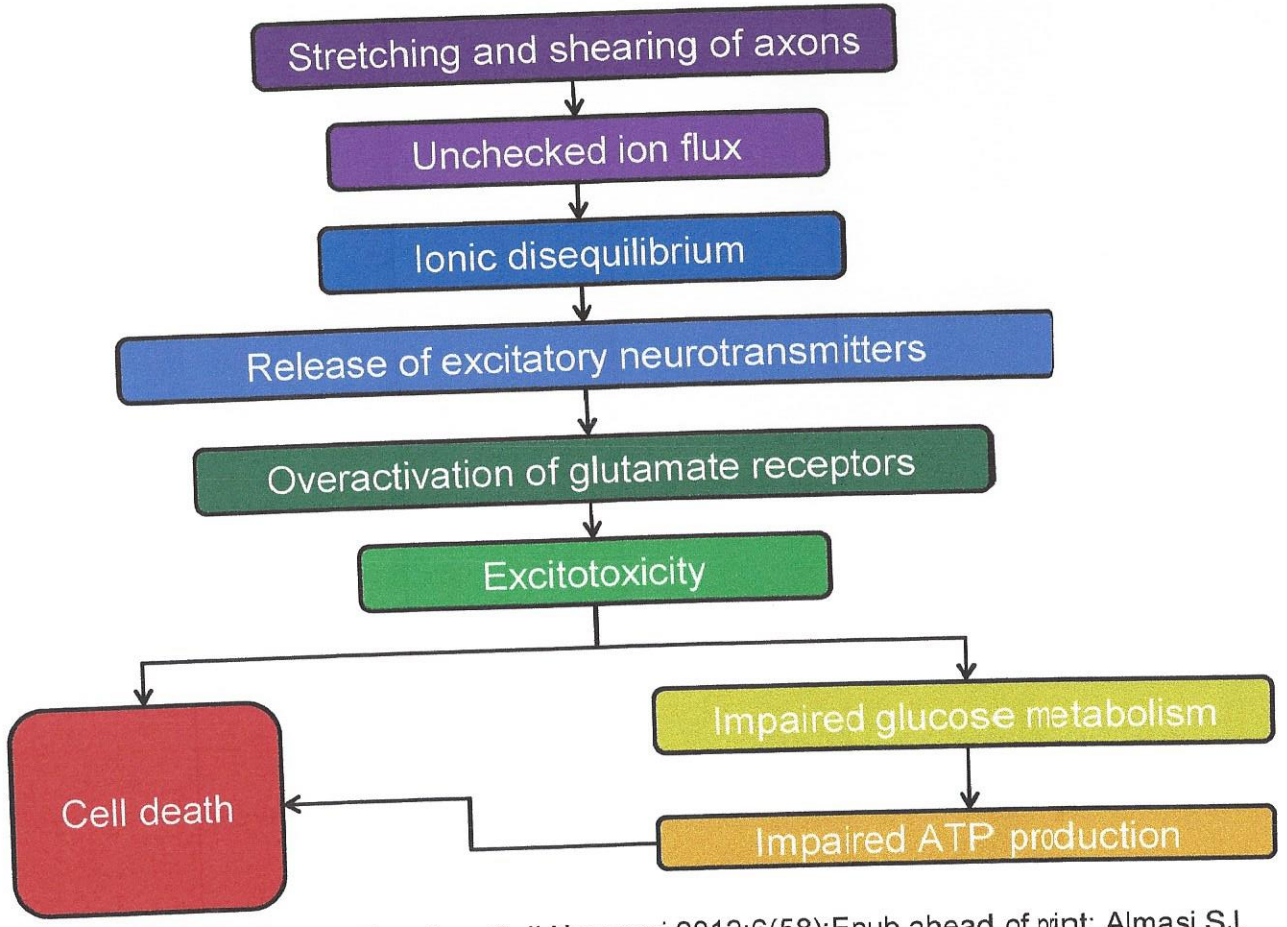
Walker KR, Tesco G. Frontiers Aging Neurosci Rev 2013;5(29):1-25; Segal SK. Beyond the Impact, 2017.

Diffuse Axonal Injury

- Multifocal involvement of myelinated tracts
- Related to primary injury or secondary cascades
- Directly disrupts neuronal circuitry
- Degeneration and disconnection of axons may occur over several months post-injury
- Noradrenergic, dopaminergic, serotonergic, and cholinergic neurotransmitter systems may be effected
- Subsequent neuroplastic changes can lead to either favorable or maladaptive repair

Van Reekum R et al. J Neuropsychiatry Clin Neurosci 2000;12(3):316-27; Brenner LA. Dialogues Clin Neurosci 2011;13:311-23; Kaplan GB et al. Behav Pharmacol 2010;21:427-37; Kaplan GB et al. Behav Pharmacol 2010;21:427-37.

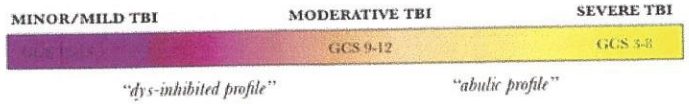
Neuropathology of mTBI: Secondary Injury Cascades

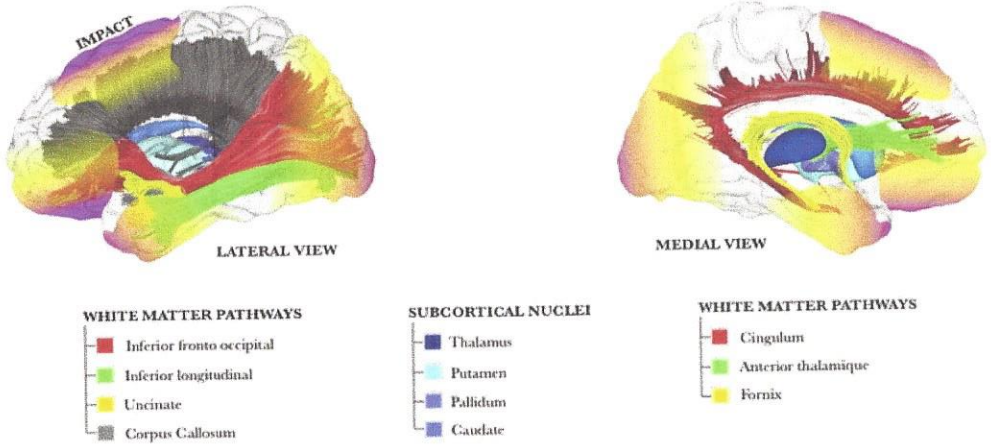


Patterson ZR, Holahan MR. Frontiers Cell Neurosci 2012;6(58);Epub ahead of print; Almasi SJ, Wilson JJ. WMJ 2012;111(1):21-7; Kaplan GB et al. Behav Pharmacol 2010;21:427-37.

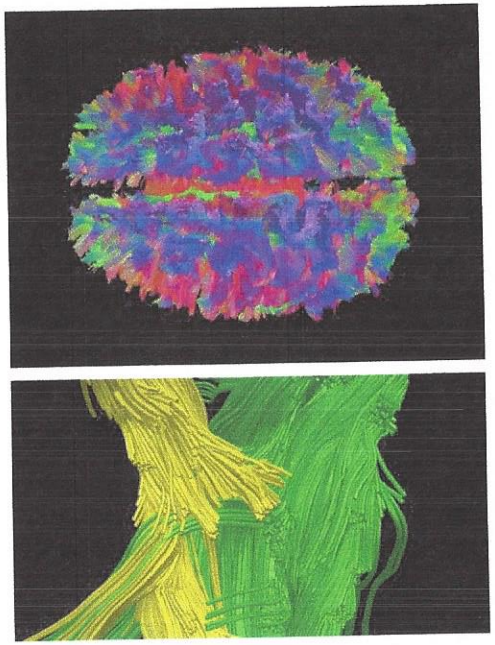
Imaging for TBI

- Diffusion Tensor Imaging (DTI)
  - Advanced form of MRI that outlines axonal tracts
  - Allows detection of microstructural axonal injury



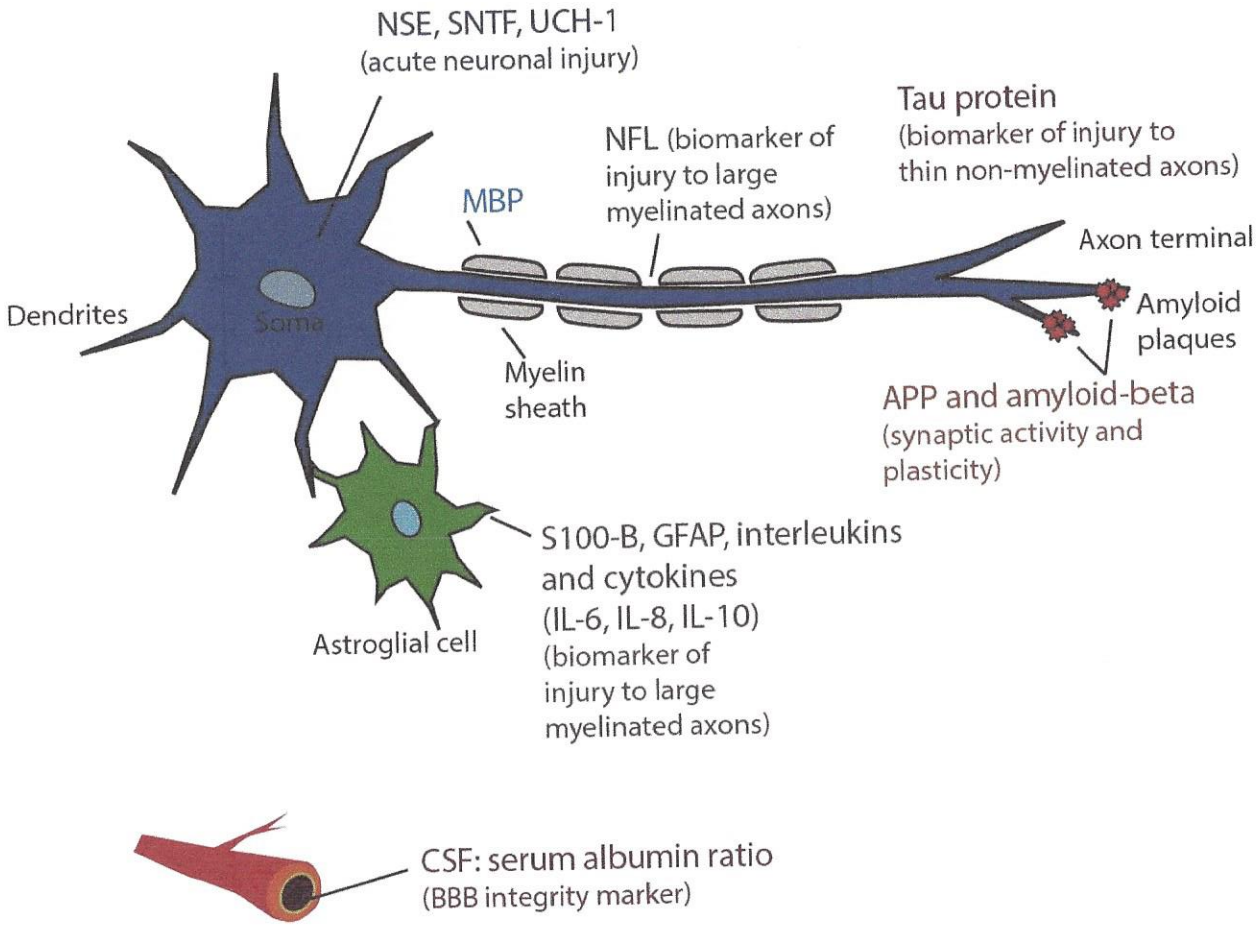


- High Definition Fiber Tracking (HDFT)



DeCuypere M, Klimo P Jr. Surg Clin North Am 2012;92:939-57; Sayer NA. Annu Rev Med 2012;63:405-19; Zappalà G et al. Cortex 2012:48(2):156-65; Presson et al. Milit Med 2015;180(suppl 3):109-21; Chmura et al. Milit Med 2015;180(suppl 3):122-34; Presson et al. Brain Imaging Behav 2015;9(3):484-99; http://discovermagazine.com/2015/sept/16-broken-cables.

Biomarkers for TBI



Segal SK. Beyond the Impact, 2017.

Long-term Consequences

- 48.3% of patients with TBI have an incident Axis I psychiatric disorder when assessed 30 years post-injury
- As many as 33% of individuals with mTBI report persistent problems
  - Cognitive dysfunction is the most commonly reported problem
- 1.1% of the U.S. population (~3.2 million people) has long-term disability secondary to mTBI
- Neurocognitive, psychiatric, and behavioral disturbances may not be immediately evident

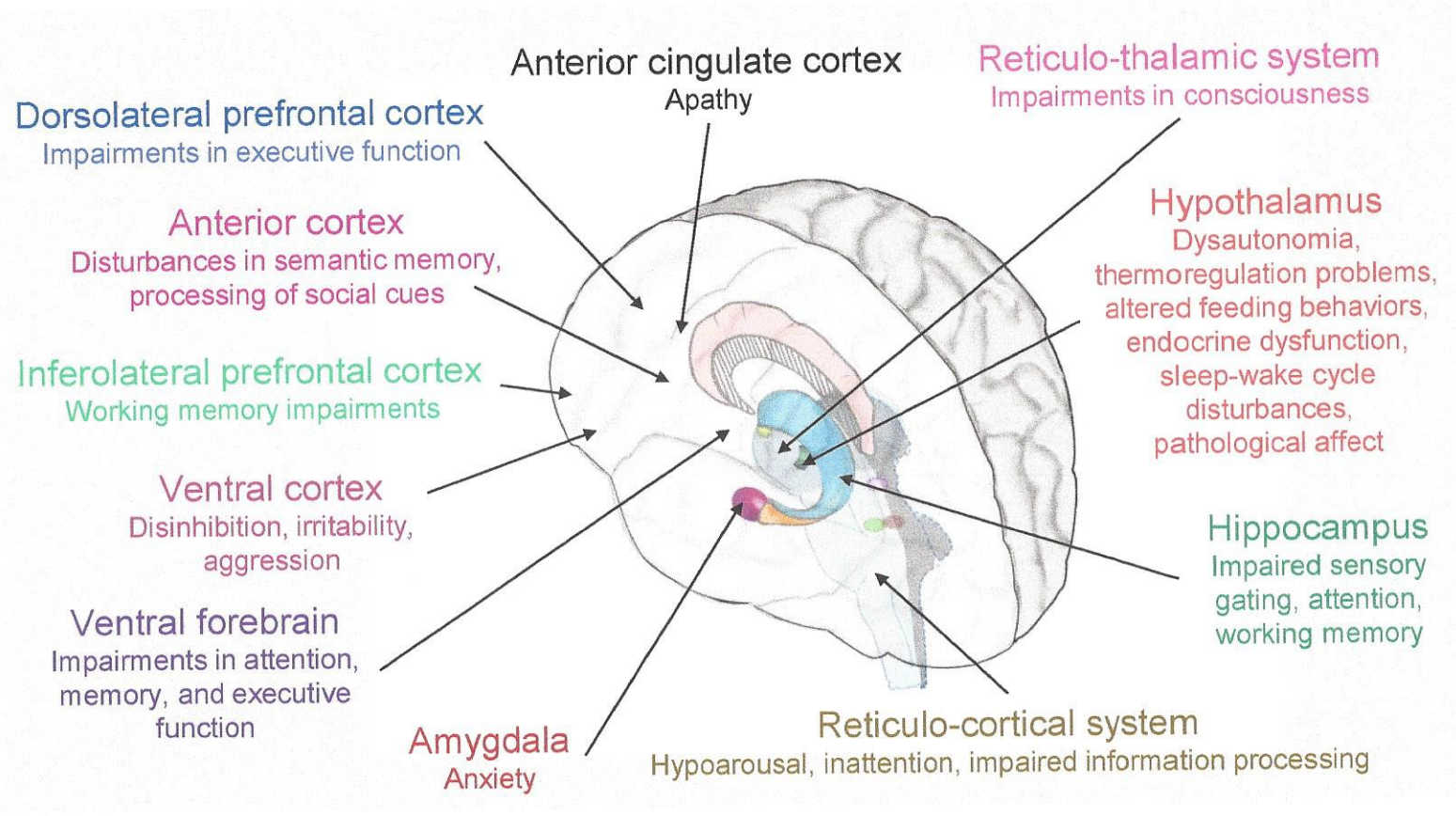
Brenner LA. Dialogues Clin Neurosci 2011;13:311-23; Collen J et al. Chest 2012;142(3):622-30; Fann JR et al. J Neurotrauma 2009;26(12):2383-402; Rapoport MJ. CNS Drugs 2012;26(2):111-21.

Before and After TBI

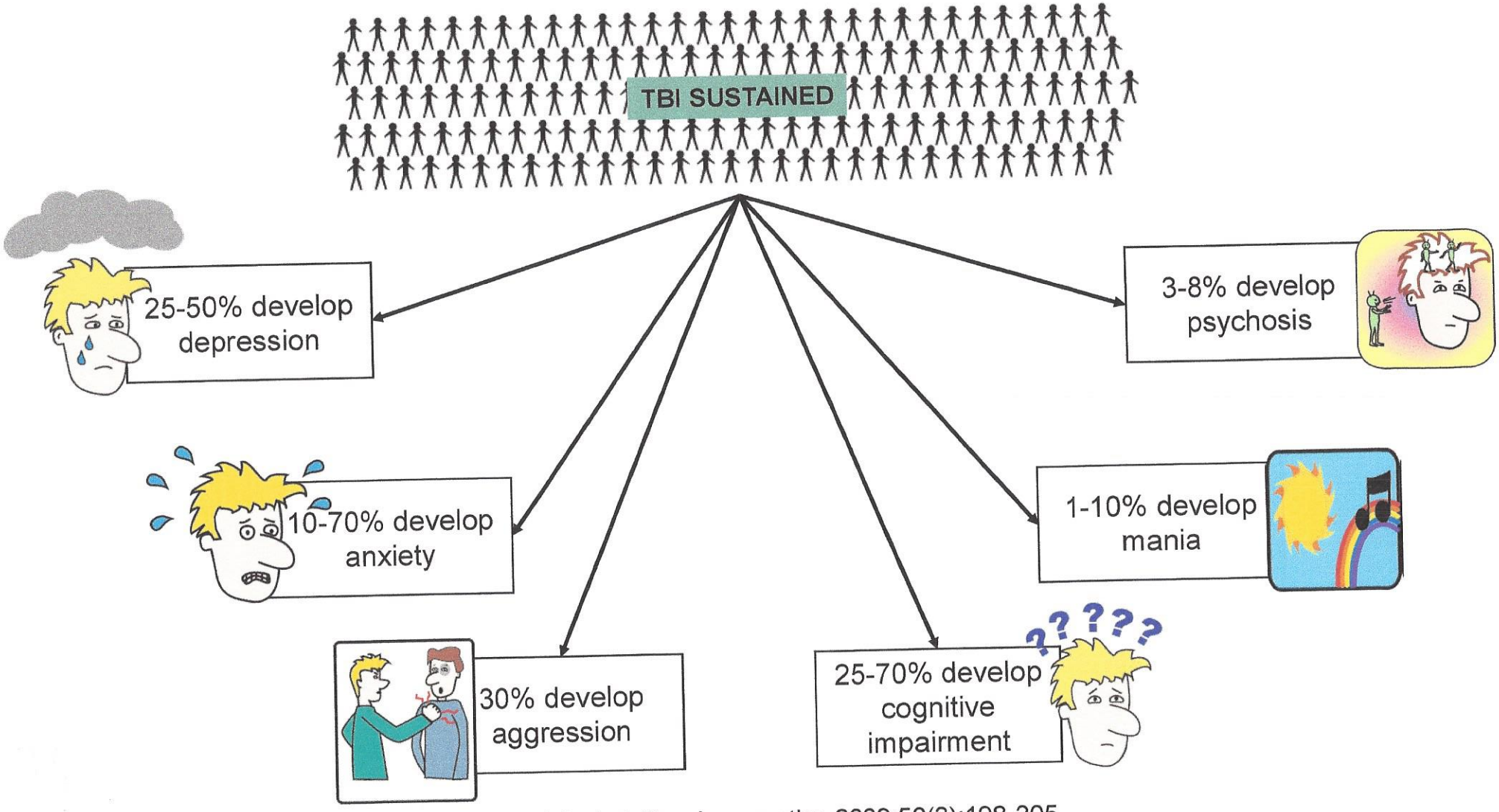
- Pre-injury psychiatric disorders may increase the risk of developing post-injury psychiatric disorders
  - Not all studies show a correlation between pre-injury mental health and post-injury outcome
- Measures of emotional factors taken 3–7 days following injury are the best behavioral predictors of post-concussive syndrome at 3 months
- 41% of individuals with TBI develop a new psychiatric condition in the 3 years post-injury
- 2/3 of cases of depression and anxiety develop for the first time post-injury

McAllister TW. Dialogues Clin Neurosci 2011;13:287-300; Mooney G, Speed J. Brain Inj 2001;15(10):865-77; Rockhill CM et al. J Neurotrauma 2012;29:1038-46; Whelan-Goodinson R et al. J Rehabil Med 2008;40:850-7; King NS. J Neurol Neurosurg Psychiatry 1996;61:75-81.

Neuroanatomy of Neuropsychiatric Symptoms Following TBI



Silver JM et al. Am J Psychiatry 2009;166(6):653-61;
Stahl SM. Stahl's essential psychopharmacology. 4th ed. 2013.



Vaishnavi S et al. Psychosomatics 2009;50(3):198-205.

Anxiety Disorders in Patients With TBI

- TBI increases risk of:
  - Generalized anxiety disorder by 2.3X
  - Panic disorder by 5.8X
- Prevalence rate 15 years following TBI: 44%
- Over 2/3 of anxiety disorders have onset following TBI
- In most cases, panic disorder manifests over 10 years following TBI
  - Suggests a slowly evolving reaction to injury
- Anxiety in the acute stage is a significant predictor of post-concussive syndrome

Alway Y et al. Neuropsychological Rehabil 2012;22(3):374-90; Hou R et al. J Neurol Neurosurg Psychiatry 2012;83:217-23; Rapoport MJ. CNS Drugs 2012;26(2):111-21; Rogers JM, Read CA. Brain Inj 2007;21(13-14):1321-33; Hoofien D et al. Brain Inj 2001;15(3):189-209.

Posttraumatic Stress Disorder (PTSD) in Patients With TBI

- mTBI increases risk for development of PTSD by 5.8X
- 16.5% of patients with TBI meet diagnostic criteria for PTSD
- Of 2234 OEF/OIF veterans:
  - 12% have mTBI
  - 11% have PTSD

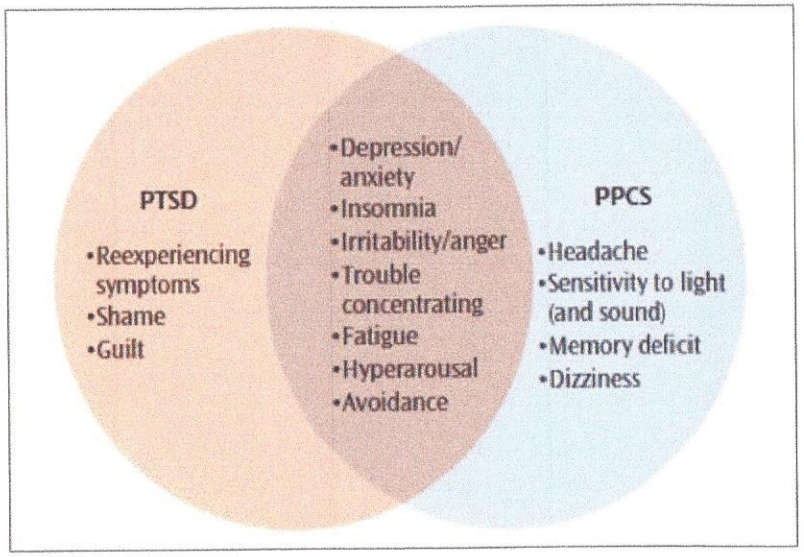
  } Significant overlap between groups

  - 44% of those with loss of consciousness have PTSD
- Conversely, the combat environment may independently increase the risk for both TBI and PTSD
- 56% of women who experience interpersonal violence (IPV) have PTSD
- IPV: women with TBI reported to have greater levels of PTSD symptomology than women without TBI

Sayer NA. Annu Rev Med 2012;63:405-19; Brenner LA. Dialogues Clin Neurosci 2011;13:311-23; Kaplan GB et al. Behav Pharmacol 2010;21:427-37; Nelson DV, Etsy ML. J Neuropsychiatry Clin Neurosci 2012;14(2):237-40.

PTSD in Patients With TBI

- Combat-related or abuse-related TBI may be associated with damage that predisposes an individual to PTSD
  - Common brain areas are implicated in both PTSD and post-concussive syndrome
  - Inadequate frontal inhibition of limbic structures
- **Only sertraline and paroxetine are FDA-approved to treat PTSD**

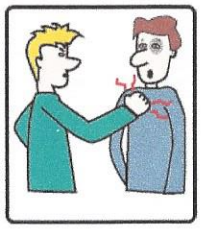


Summerall EL, McAllister TW. Psychiatr Ann 2010;40(11):563-80; Sayer NA. Annu Rev Med 2012;63:405-19; Brenner LA. Dialogues Clin Neurosci 2011;13:311-23; Kaplan GB et al. Behav Pharmacol 2010;21:427-37; Nelson DV, Esty ML. J Neuropsychiatry Clin Neurosci 2012;14(2):237-40.

Personality Changes in Patients With TBI

- Affect 1/3 of patients with TBI
- Often a primary source of concern for family members, though often unrecognized by patients
- Personality changes can persist for years post-injury
- Changes include:
  - Apathy: damage to reward circuitry
  - Emotional lability: damage to frontal cortex/limbic connections
  - Impaired judgment: damage to prefrontal cortex
  - Increased impulsivity: damage to frontal cortex
  - Irritability: damage to orbitofrontal cortex

Hoofien D et al. Brain Inj 2001;15(3):189-209; Chahine LM, Chemali Z. Epilepsy Behav 2006;8:610-5; Diaz AP et al. J Neurotrauma 2012;29:1029-37; McAllister TW. Dialogues Clin Neurosci 2011;13:287-300.



Aggression and Agitation in Patients With TBI

- 34% of patients with TBI exhibit aggressive behavior
- Hostility, temper outbursts, and poor self-control may be present for decades following TBI
- Risk factors for aggression following TBI
  - Frontal lobe injury
  - Premorbid affective disorder
  - Personality disorder
  - Alcohol or substance abuse
- Presence of agitation during acute recovery predicts poorer psychological adjustment and long-term outcomes

Bogner JA et al. Am J Phys Med Rehabil 2001;80:636-44; Hoofien D et al. Brain Inj 2001;15(3):189-209; Riggio S. Psychiatr Clin North Am 2010;33:807-19; Vaishnavi S et al. Psychosomatics 2009;50(3):198-205.

Pseudobulbar Affect (PBA) in Patients With TBI

- Occurs in the context of brain injury, including TBI, stroke, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS)
- PBA is characterized by uncontrollable, inappropriate laughing and/or crying incongruent with mood
- Only 40% of individuals who discuss PBA symptoms with a clinician are diagnosed (often mistaken for depression)
- Patients with PBA often have:
  - Increased risk of depression and anxiety
  - Decreased quality of life
  - Impaired social interaction (due to embarrassment)
- Both serotonergic and dopaminergic pathways seem to be involved
- Glutamatergic and sigma-1 receptors may also be involved

mmings JL et al. CNS Spectrums 2006;11(6):1-7; Garnock-Jones KP. CNS Drugs 2011;25(5):435-45; Miller A et al. 2011;11(7):1077-88; Pioro EP. Drugs 2011;71(9):1193-207; Work SS et al. Adv Ther 2011;28(7):586-601; Chahine LM, Chemali Z. Epilepsy Behav 2006;8:610-15; Miller A et al. Expert Rev Neurother 2011;11(7):1077-88.

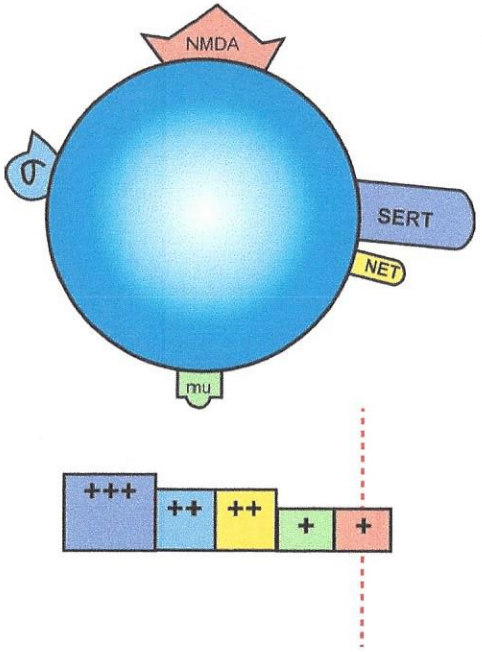
PBA in Patients With TBI: Treatment

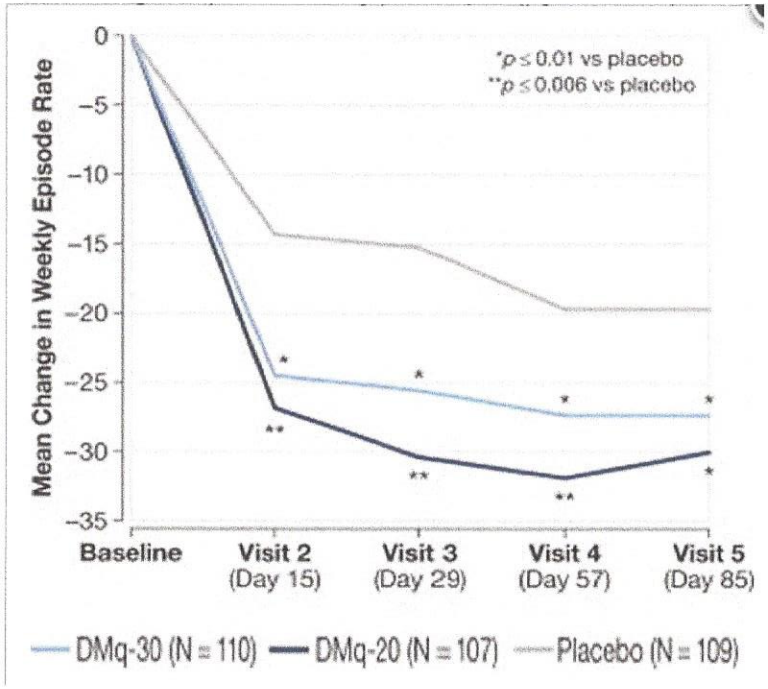
- Dextromethorphan
  - Coadministered with quinidine (CYP450 2D6 inhibitor)
  - Potent sigma-1 receptor agonist
    - Sigma-1 receptors: expressed in cerebellum and brain stem
    - Modulates NMDA signaling, inhibiting presynaptic release of glutamate in cortex
    - Modulates postsynaptic intracellular Ca^{2+} mobilization
  - Uncompetitive NMDA receptor antagonist
    - Limits glutamatergic signaling and potentiates dopaminergic signaling
  - Serotonin reuptake transporter (SERT) inhibitor

Garnock-Jones KP. CNS Drugs 2011;25(5):435-45;
Miller A et al. Expert Rev Neurother 2011;11(7):1077-88.

Dextromethorphan

- Antidepressants, amantadine, and L-dopa are also used off-label; limited evidence





Stahl's essential psychopharmacology. 4th ed. 2013; Pioro EP et al. Ann Neurol 2010;68(5):693-702; Wortzel HS et al. CNS Drugs 2008;22(7):531-45.

Cognitive Deficits in Patients With TBI

- Most common complaint following TBI
- Cognitive deficits persist for decades following injury
- Deficits may include decreased ability to:
  - Maintain attention
  - Inhibit incorrect responses
  - Recognize mistakes
- Attentional deficits in young adults with a history of concussion mimic those seen in older patients who are transitioning from mild cognitive impairment (MCI) to Alzheimer's disease (AD)

Brenner LA. Dialogues Clin Neurosci 2011;13:311-23;
Broglio SP et al. Exerc Sport Sci Rev 2012;40(3):138-44.

Alzheimer's Disease (AD) in Patients With TBI

- TBI may initiate the molecular cascades involved in Alzheimer's disease pathology
- Damage to axons leads to impaired protein transport
  - Buildup of amyloid-beta and tau
- Apolipoprotein E epsilon 4 (APOEε4)
  - Genetic risk factor for AD
  - Individuals who are APOE4 positive and sustain a TBI are at 10X greater risk of developing AD
- Diminished cognitive reserve associated with TBI may facilitate development of AD in susceptible individuals

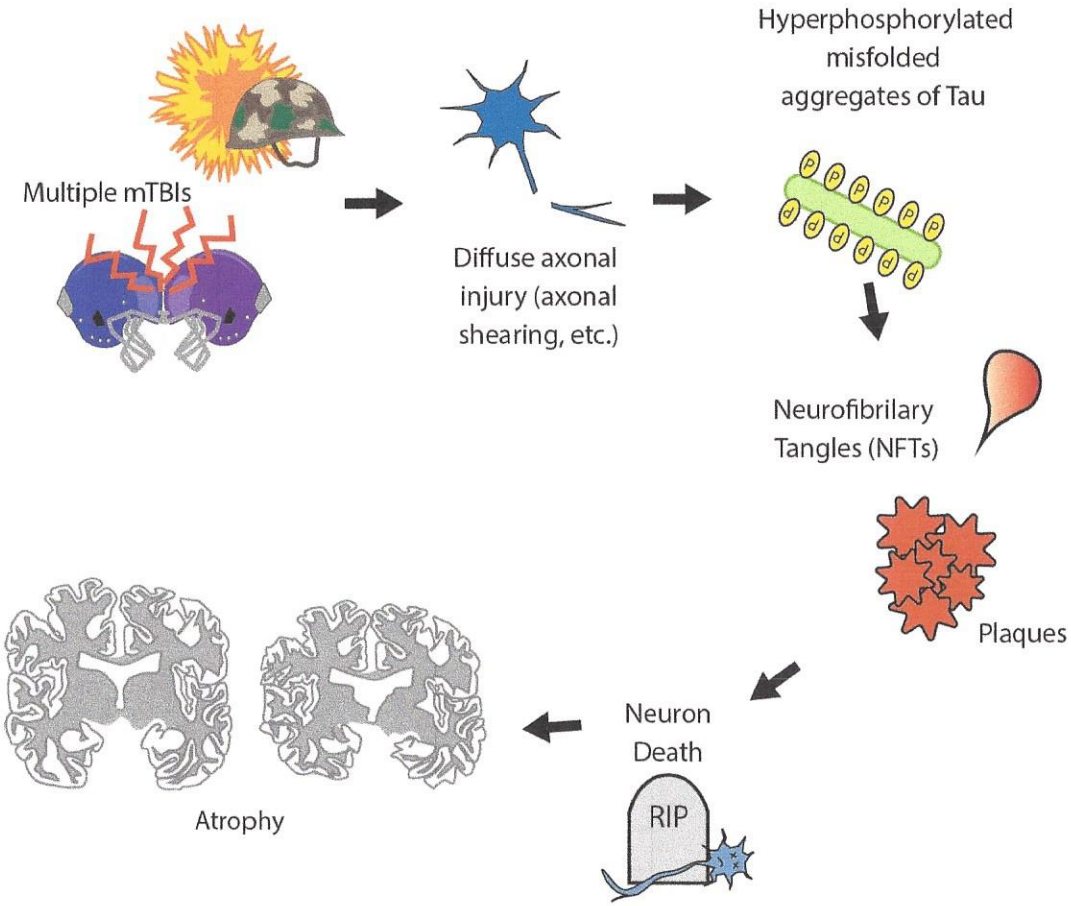
Sivanandam TM, Thakur MK. Neurosci Biobehav Rev 2012;36(5):1376-81.

Chronic Traumatic Encephalopathy (CTE)

- CTE is a progressive degenerative disease that results from repetitive head trauma
- In cases of repetitive mTBIs, at least 17% develop CTE
- Characterized by neurofibrillary tangles in frontal and temporal cortices
- Amyloid deposits may or may not be present
- Atrophy of cerebral hemispheres, medial temporal lobe, thalamus, mammillary bodies, and brain stem, with ventricular dilation and a fenestrated cavum septum pellucidum

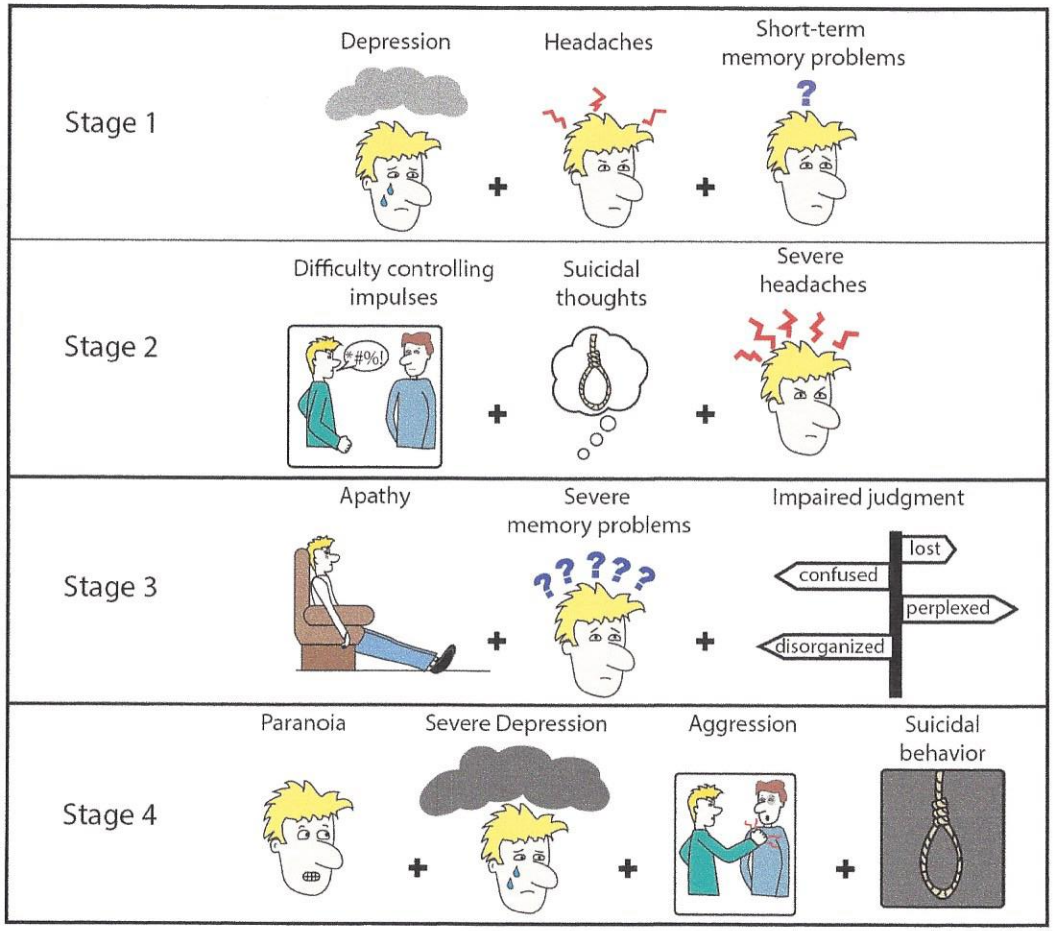
DeKosky et al. Nature 2013;9:192-200; Yaffe K. Lancet 2012;11:1020-1; Broglio SP et al. Exerc Sport Sci Rev 2012;40(3):138-44; McKee et al. J Neuropathol Exp Neurol 2009;68(7):709-35.

CTE Neuropathology



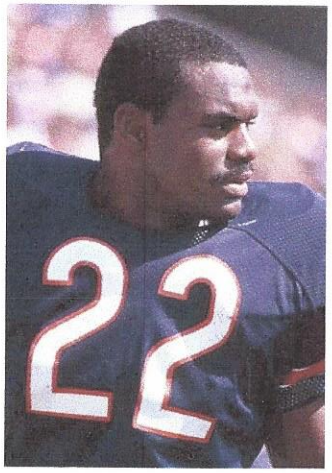
Segal SK. Beyond the Impact, 2017.

Stages of CTE

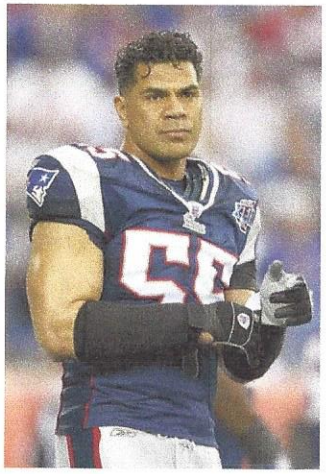


Segal SK. Beyond the Impact, 2017.

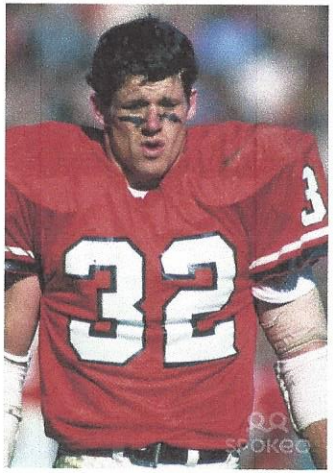
Recent NFL Suicides Attributed to CTE



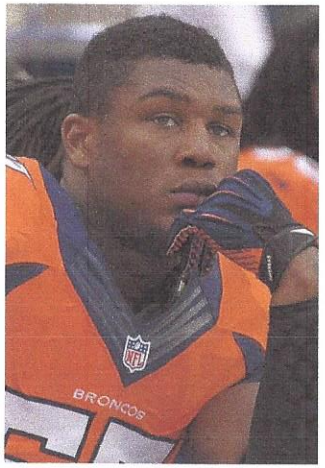
Dave Duerson
1960-2011



Junior Seau
1969-2012



Ray Easterling
1949-2012



Adrian Robinson
1989-2015

Sleep Disturbances in Patients With TBI

- 72% of patients with TBI have a sleep–wake disorder
  - Excessive daytime sleepiness and fatigue: 55%
  - Insomnia: 30%
  - Circadian rhythm disorders: 36%
  - Obstructive sleep apnea and narcolepsy are also common
- Insomnia in patients with TBI is associated with headaches, depressive symptoms, and irritability
- Unrecognized or untreated sleep disorders may worsen outcomes and increase disability from TBI

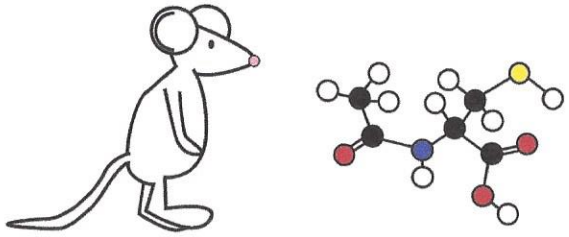
Collen J et al. Chest 2012;142(3):622-30;
Baumann CR. NeuroMol Med 2012;14:205-12.

Melatonin

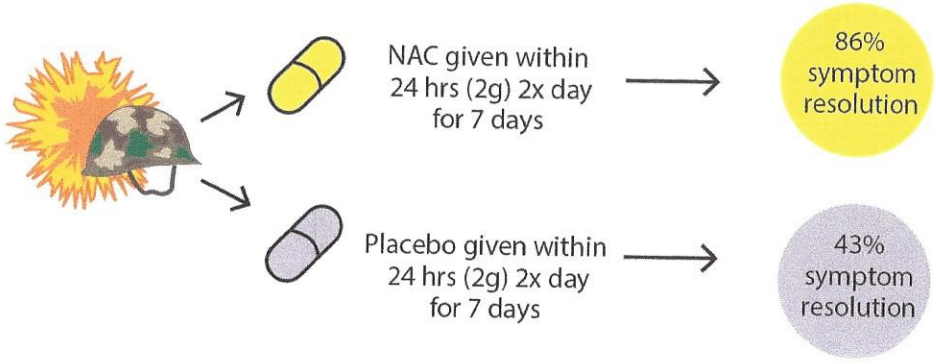
- Direct damage to the pineal gland can disrupt melatonin production
- Patients with severe TBI showed 42% less melatonin production overnight compared to controls
- Dim light melatonin onset (DLMO) delayed by 1.5 hours in TBI patients compared to controls
- In animal models of TBI, melatonin administration has resulted in reduced neuronal cortical apoptosis, decreased brain edema, and attenuated neurological deficits
- More studies in TBI patients are needed

Garfinkel D, Laudon M. Lancet 1995;346(8974):541-4; Kemp et al. Brain Inj 2004;18(9):911-9; Zhdanova et al. J Clin Endocrinol Metab 2001;86(10):4727-30; Grima et al. Neurorehabil Neural Repair 2016;1-6; Wu et al. J Pineal Res 2016; 61(2):1-10.

Alternative Novel Treatment for Post-Concussive Symptoms: N-Acetyl Cysteine (NAC)



NAC is neuroprotective
in animal models



Hoffer et al. PLOS One 2013;8(1):e54163.