The Neurometabolic Cascade and Implications of mTBI: Mitigating Risk to the SOF Community

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Abstract

Over the last decade, our understanding of biochemical changes that occur in the brain following an injury has increased dramatically. Although we have been able to discern and image severe injury and traumatic changes using techniques like computed tomography (CT) and magnetic resonance imaging (MRI) for decades, we have only recently begun to understand the physiologic changes that occur following a mild traumatic brain injury. Understanding the pathophysiology of a disease process enables healthcare providers to treat their patients better, but military healthcare providers shoulder the additional burden of conserving the fighting force. Neurocognitive testing in concert with clinical acumen and conservative profiling enables providers to protect their patients from further injury; while educating the patient and the chain of command will prevent additional injury and long-term cognitive sequelae, ultimately preserving the fighting force.

Over the last decade, our understanding of biochemical changes that occur in the brain following an injury has increased dramatically. Although we have been able to discern and image severe injury and traumatic changes using techniques like CT and MRI for decades, we have only recently begun to understand the physiologic changes that occur following a mild traumatic brain injury (mTBI). It's incumbent on healthcare providers to understand the implications of these changes, the difficulty diagnosing mTBI, the sequelae, and potential risks to the patient during recovery.

Since 11 September 2001 mTBI risk to Special Operations Forces (SOF) has increased significantly due to continuous deployment cycles around the globe. Traumatic brain injury (TBI), mTBI, and concussion seem to be the signature injuries of the Global War on Terrorism. Though Soldiers on today's battlefields have the most advanced protective ensemble of any force fielded in America's history, modern ballistic helmets were designed to protect against penetrating trauma but are poor barriers against explosive pressure and blast effect.

The Neurometabolic Cascade

Immediate and widespread cellular chemical changes occur within the brain following injury. The force required to initiate this cascade may be insufficient to cause physically evident changes on CT or MRI. However, the speed with which these changes occur and the self-perpetuating nature of cellular demise is usually sufficient to cause changes in mentation, memory, motor function, and postural stability. A 80g force of translational acceleration may be sufficient to initiate biochemical change.[1] To put this in perspective, Brolinson et. al., demonstrated an average linear acceleration force of 20.1g in over 11,000 non-injury producing collegiate football impacts.[2]

Upon impact, glutamate and other excitatory neurotransmitters attach to N-methyl-D-aspartate (NMDA) receptors leading to a rapid ion shift across the cell membrane. Rapid loss of intercellular potassium and influx of calcium forces up-regulation of the sodium-potassium pumps in an attempt to restore normal resting membrane potential. As sodium-potassium pumps deplete cerebral stores of adenosine triphosphate (ATP) compensatory hyperglycolysis occurs. Furthermore, as extracellular potassium levels rise, neuronal depolarization continues, and excitatory neurotransmitters are released propagating widespread neurotransmission and cellular glucose consumption. This excitatory cycle of NMDA receptor activation, potassium release, and signal propagation is rapid and widespread.[3] Furthermore, glucose deficit and widespread neuronal activity result in decreased cerebral blood flow at a time when supply and demand are already critically mismatched.[4]

In the uninjured state, cerebral oxidative metabolism typically runs near maximum potential. During this post-injury cellular energy crisis, oxidative metabolism falters as calcium accumulates within the

mitochondria. Additionally, decreased oxidative metabolism leads to decreased ATP production, further exacerbating the energy deficit. This additional energy deficit serves as a secondary stimulus for increased glycolysis.[1] Increased cellular effort yields lactic acid which the cell is incapable of metabolizing in its weakened state. As lactic acid levels rise, cellular pH decreases. Cellular acidosis results in cell membrane damage and blood-brain-barrier permeability with resultant cerebral edema.[3]

Intercellular magnesium levels are also affected almost immediately following a head injury. Magnesium is necessary for ATP production, cellular membrane potential, protein synthesis, and regulation of NMDA receptors. As magnesium stores wane, ATP production decreases and NMDA receptors are activated more readily. As protein synthesis fails, the cell membrane is further weakened and calcium accumulates within the mitochondria. This hypermetabolic state and ensuing energy crisis is a precursor for widespread cellular demise and potential cellular death.

Following the exhaustion of glucose stores and consumption of available ATP, the cell membrane is weakened and begins to leak. In this weakened state, the resulting cerebral edema makes the brain vulnerable to additional insult or overstimulation. Should additional trauma occur during this depressed state, the brain has little reserve to compensate. Even if no further physical injury occurs, studies have shown that overstimulation of the brain during this vulnerable recovery period may increase the size of the lesion and prolong the recovery period.[5] This cascade of effects at cell level is shown in Figure 1.

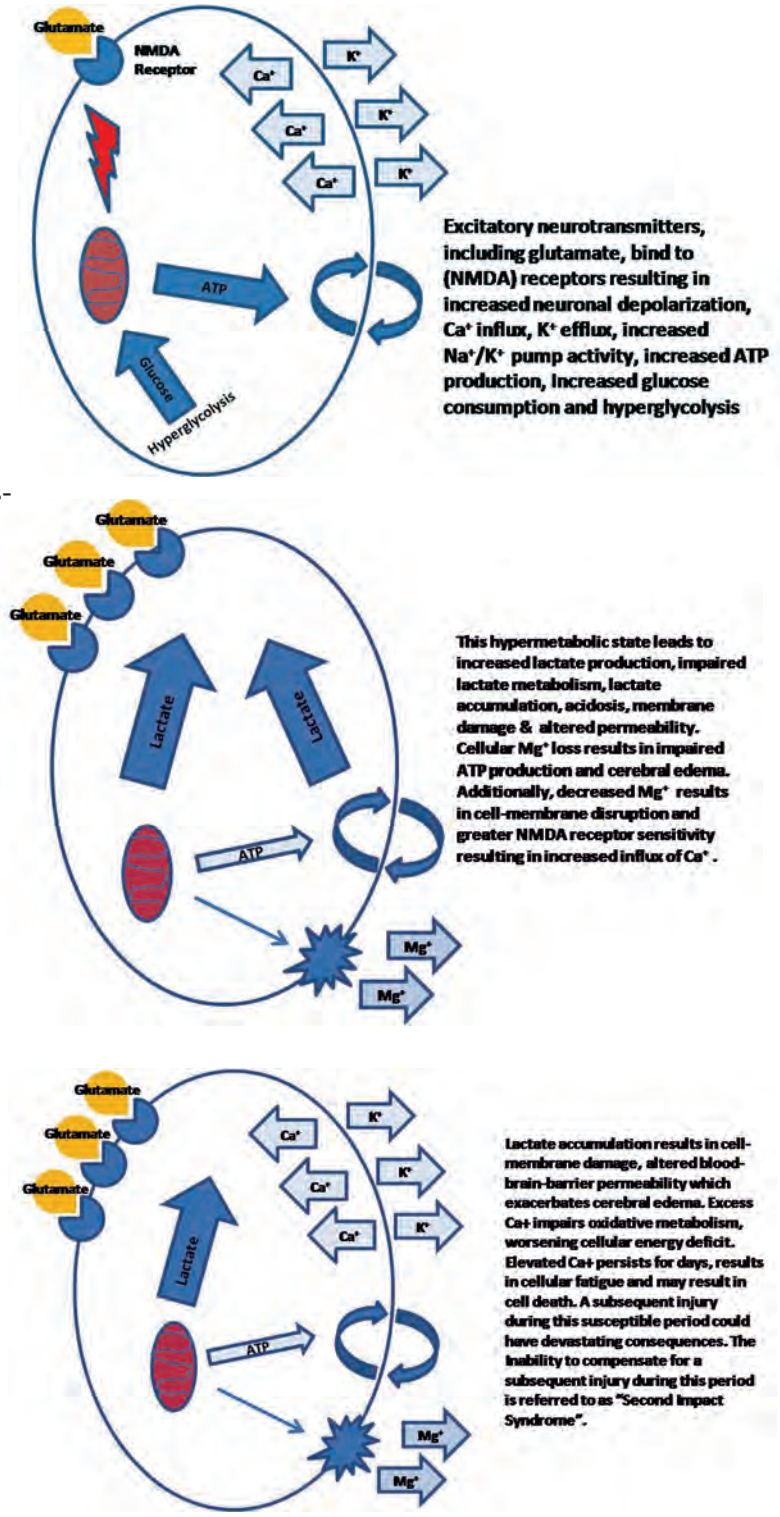


Figure 1

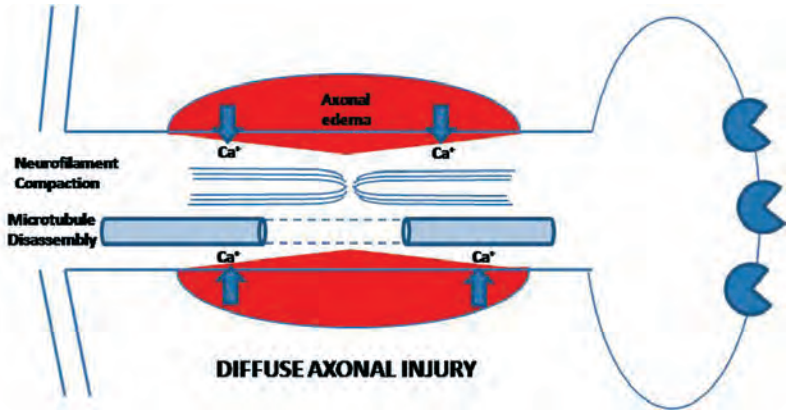
Diffuse Axonal Injury

Stretching and shearing of white matter and axons following even mild head trauma is referred to as diffuse axonal injury (DAI). The majority of mTBIs result in changes in parenchymal cytoarchitecture sufficient to cause changes in neurocognitive affect, but are usually not significant enough to manifest as changes on CT or MRI. Rarely, axonal shearing injury, or DAI, may result in hemorrhage identifiable with standard imaging techniques. The axolemma is the portion of the cell membrane surrounding the axon of a neuron and is responsible for maintaining the membrane potential of the neuron. Axolemmal permeability results in additional influx of calcium and mitochondrial swelling. Axonal stretching further alters membrane potential and depolarization.

Stretching or tearing of the normally elastic axons leads to disruption of cytoskeletal structures. Axonal transport continues up to the point of disruption, then stops abruptly. Build-up of transport organelles at the site of disruption accumulates and causes edema. Neurofilament compaction occurs in the center of axonal swelling, resulting in secondary axotomy. The detached ends of neurofilaments retract and form axonal bulbs or "retraction balls".[6] These microscopic structural changes in neurofilaments occur in as little as five minutes, with resultant secondary axotomy beginning as early as four hours post-injury.[7] Influx of calcium into axons may adversely affect axonal microtubules as well. Though not all microtubules are affected, those closest to nodes of Ranvier seem to be the most calcium sensitive. In the presence of excess calcium, and under pressure from local edema, microtubules rapidly break down and undergo disassembly.

Diffuse axonal injury (DAI) characteristically occur in the brain stem, corpus callosum, and frontal hemispheres. Lesions also typically occur in the frontal and temporal lobes and may occur in the cerebral cortex, superior cerebral peduncles, basal ganglia, thalamus, and deep hemispheric nuclei. The majority of lesions occur where the grey and white matter meet, likely due to the differing densities of adjoining tissues.[8-11] Typically in mTBI only the cytoskeleton is disrupted. However, in some cases proteolytic disruption of the cytoskeleton and cell membrane lead to apoptosis and cell death. In mTBI the mitochondria, dendrites, and damaged cytoskeletal components have limited ability to regenerate and heal, typically occurring in about two weeks.

Diffuse axonal injury is typically classified by severity. Grade I is characterized by widespread axonal damage without focal neurologic abnormalities. Grade II is characterized by widespread axonal damage with focal deficit, typically in the corpus callosum. Grade III is characterized by widespread axonal damage, focal deficit and rostral brain stem injury which may include tears of the tissue.[12] There are no specific treatment modalities for DAI beyond stabilization and palliative care. Managing intracranial pressure is essential in minimizing sequelae of DAI.



Alterations in neurotransmission

Long-term alterations in excitatory as well as inhibitory neurotransmissions are possible following even mild TBI. Studies have shown that adrenergic,[13] cholinergic,[14] and glutamatergic[15] transmissions are all potentially affected. Down regulation of excitatory neurotransmission has been implicated in impaired memory, shortened attention span, and learning deficits. Down regulation of inhibitory neurotransmission has been implicated in compromised inhibition and development of seizures.[16] Furthermore, plasticity, as measured by NMDA-dependent long-term potentiation, may be persistently impaired.[17]

Post traumatic amnesia and anterograde memory impairment are clinical manifestations of a disrupted cholinergic neurotransmission system. In the acute phase of TBI, disruption of the cholinergic system manifests as an altered level of consciousness, unrelated to dysfunction of the reticular activating system. New learning and memory impairment are manifestations of other conditions associated with deficient cholinergic transmission, such as Alzheimer's disease. Theoretically, therefore, disruption of cholinergic neurotransmission would likewise be responsible for learning and memory deficit following TBI.[1]

Diffuse amyloid plaques form in over one-third of individuals who survived at least six days following a TBI of apparently any severity.[18] Deposition of beta-amyloid (Aβ) throughout the brain occurs following cerebral ischemia, increased intracranial pressure, cerebral contusions, DAI, or cerebral edema. Graham et al. has suggested that the deposition of Aβ is the result of acute traumatic stress in nerve cells.[19] Amyloid precursor protein (APP), up-regulated acutely following TBI, is the source of the Aβ. While APP may be neuroprotective, by protecting against hypoglycemia by reducing calcium and glutamate neurotoxicity within the cell, abnormal processing of APP results in Aβ deposition.

There is debate in the literature about the primacy of Aβ deposition or neurofibrillary tangles in dementia. Neurofibrillary tangles correlate more closely with cognitive impairment in Alzheimer's disease and some suggest it precedes formation of extracellular amyloid deposits.[20] Nevertheless, it is generally accepted that neurofibrillary tangles are the proximate cause of dementia and have at least some relationship with amyloid deposits. Monniere et al. demonstrated in-vitro neuronal dystrophy, gliosis, and reactive astrocytosis when astrocytes were plated on Aβ. These characteristic findings are consistent with dystrophic neurites observed in the presence of in-vivo Aβ in Alzheimer's disease.[21] Considering the results of Morrerie and colleagues' findings, it is

reasonable to deduce that Aβ may be contributory to cognitive impairment in TBI.

Implications of mTBI to the patient and the force

Post-Concussive Syndrome

Post-concussive syndrome (PCS) is the presence of concussive symptoms for weeks or months after a concussion, and is marked by four dominant symptoms: 1) brief alteration in consciousness or neurological function with acute changes in mentation and speed of processing, 2) physical symptoms such as headaches, dizziness, vertigo, and fatigue, 3) cognitive deficits in short term memory, attention, and concentration, and 4) an increased vulnerability for changes in mood and emotional functioning.[22] The literature suggests that these post-concussive symptoms typically resolve within tendays to three months, although about 15% may continue to experience symptoms up to a year after the concussion.

Persistent post-concussive syndrome (PPCS) is typically defined as symptoms that last for more than three months. There are a number of modifying factors that may influence recovery, to include: 1) symptom number and severity, 2) the presence of post-traumatic amnesia, 3) prolonged loss of consciousness (>1 min), 4) the recency, timing, and frequency of prior concussions, and 5) a history of migraines, psychiatric conditions, or ADHD/learning disabilities. While there is debate about the relative primacy of these factors, most acknowledge that a patient's outcome is based on a complex interaction of neurological, physical, and psychological factors, and that one's premorbid personality, available coping resources, environmental demands, recovery expectations, external support, and PCS education may significantly influence these factors. It is also important to remember that PCS symptoms may be mirrored by post-traumatic stress disorder (PTSD) symptoms, and that PTSD can exacerbate the cognitive symptoms of PCS.[23] In particular, noise sensitivity, fatigue, anxiety, insomnia, decreased concentration, decreased memory, anger, irritability, and depression may overlap.

Post-concussive syndrome has been a much debated topic in the literature, particularly when it comes to definitions and nomenclature. Despite this, there is general consensus that even concussions without a loss of consciousness can result in the above noted neurometabolic cascade and white matter abnormalities, particularly in the corpus callosum, hippocampus, and fornix.[22] In fact, the literature has begun to demonstrate the presence of pathological changes in the brain in some samples even in the absence of a concussion. For example, Zhang et al.[24] and Chappell et al.[25] have demonstrated white matter pathology in a sample of young healthy boxers with no neurological impairment using diffusion tensor imaging. Similarly, Zetterberg at al.[26] demonstrated the presence of CSF markers for neuronal and astroglial injury seven to ten days after a bout in 14 amateur boxers that was positively associated with the number of hits during the bout. Of note, none of these amateur boxers received a knock-out punch, or met behavioral criteria for a concussion. Together, these studies highlight that pathological changes do take place in the brain, even when neurobehavioral symptoms may not be readily apparent.

Baseline neuropsychological testing

Recent research and clinical experience suggests that an exclusive reliance on an individual's self-report of symptoms may be an inadequate benchmark for the disposition of those with PCS or TBI. Concussion management in sports at the professional, collegiate, and high school levels now frequently includes neuropsychological baseline and post-injury testing for return-to-play decisions. McCrory et al.[27] recently published the consensus statement on concussion in sport, in which the clinical value of neuropsychological assessment is reinforced. While in most cases the cognitive sequelae largely resolve during the time course of other symptoms, it has been shown that cognitive recovery commonly follows the other PCS symptoms.[28,29] Moreover, Van Kampen et al.[30] found that the inclusion of neurocognitive testing improved the identification of athletes who still had PCS symptoms from 64% (self-reported symptoms only) to 83% (cognitive data only) to 93% (self-report and/or cognitive data).

A premorbid baseline measure of the cognitive domains most susceptible to decline following a brain insult is largely considered the gold standard in clinical neuropsychology. In the absence of an individual's premorbid baseline, normative data must be used to determine if someone's performance falls within the "normal" range. One limitation with using normative data, particularly for the SOF community, is that most normative datasets are predominantly derived from samples with average levels of intelligence. In contrast, SOF members go through rigorous selection criteria that have resulted in a community with largely above average intelligence. As such, the application of "average" norms to someone with a recent concussion, and who is premorbidly "above average" may suggest the absence of cognitive sequelae when in fact there has been a decrement. Returning these individuals to duty would put them at greater risk for additional mTBIs, and possible even second impact syndrome.

To mitigate these risks and facilitate individualized comparisons as opposed to the use of normative data, we undertook the task of collecting baseline neurocognitive data from nearly every member of an elite Special Operations unit. The Immediate Post-concussion Assessment and Cognitive Testing (ImPACT) was chosen as the baseline and post-injury measure because of its relative psychometric strengths (strong reliabil-

ity and validity), the ready availability of alternate forms for repeat testing, and ease of use in both garrison and deployed environments. From our experience, the vast majority of PCS cases returned to baseline within 10 days, with consultation by a clinical neuropsychologist facilitating test interpretation as needed. After seven to ten days, the sensitivity/specificity of computerized neurocognitive testing declines, so a comprehensive neuropsychological evaluation is recommended should recovery time exceed ten days. In our experience, roughly one in ten cases required a comprehensive neuropsychological evaluation, and in these cases significant moderator variables likely delayed each individual's recovery time (prior concussions, psychiatric symptoms).

While the neuropsychological presentation following mTBI can be highly individualized, impaired attention (slower reaction time, increased distractibility, and difficulty multitasking), memory (verbal or nonverbal), executive functioning, and emotional dysregulation tend to be common cognitive symptoms. Even after a patient returns to baseline on neuropsychological testing, and is otherwise asymptomatic at rest, the literature suggests there may be continued cognitive vulnerabilities to physiological or psychological stress. For example, Ewing, McCarthy, Gronwall, and Wrightson[31] demonstrated that those with mTBIs who have returned to baseline on tasks of vigilance and auditory memory at ground level may still demonstrate residual cognitive difficulties at altitude due to the physiological stress of hypoxia (altitude of 12,467ft).

Other research has suggested that high levels of stress can decrease information processing speed and increase subtle memory deficits during mentally challenging tasks.[32] Together, these studies suggest a continued vulnerability that may exist when more stressful conditions are encountered than the highly standardized and optimal environment of a clinical neuropsychological evaluation. As such, even with a return to baseline on neurocognitive testing, a specific job-performance evaluation may be prudent to ensure the absence of more subtle inefficiencies that may manifest under the more extreme conditions in which SOF personnel may find themselves (i.e. HALO/HAHO, etc.).

PROFILING, RETURN TO DUTY, AND FORCE PROTECTION

Most of the management guidelines for combat and military duty related mTBI are based on the ever evolving management of sports related concussion. Much can be gained from applying elite level sports medicine practices into our community of Special Operations "Warrior-Athletes". However, it is incumbent upon military healthcare providers to understand the significant differences in returning a symptomatic athlete to play early verses returning a symptomatic special operator to duty early. Returning to unrestricted duty, both in combat and in training, while still symptomatic not only puts the individual at much greater risk but also puts every person around and associated with them at much greater risk due to the nature of their work. Therefore, it is recommended that healthcare providers conservatively apply return to play/duty guidelines and use a multi-disciplinary team approach when making final return to duty decisions.

Currently, the mainstays of mTBI treatment are physical and cognitive rest and protecting the brain from further insults while it is recovering.[33,34] It is postulated that the previously discussed metabolic dysfunction may lead to significantly increased neurological vulnerability if even minor trauma is sustained while the brain is still healing.[35] Preventing a subsequent mTBI while the brain is still recovering may potentially minimize the risk of catastrophic neurologic sequelae as well as long term lingering post-concussive symptoms, mental health issues (depression), and behavioral health issues (ADHD/ADD).

Profiles are typically looked upon with distain in the SOF community. In mTBI cases, clearly written duty restrictions that are understood by the patient and the chain of command are essential to the long term health of the individual and their successful return to duty. The mTBI profile is unique in that it should limit both physical and cognitive activities. It is vital to the patients' recovery that the uniqueness of each profile be explained to both the patient and their chain of command in order to maximize compliance. The physical limitations are typically the easiest to write and should limit physical training (both cardiovascular and weight lifting activities), airborne operations (both static line and military free fall), close quarters battle, marksmanship or demolitions training, operating military vehicles, and/or other high risk training.

Cognitive activities that require concentration and attention to detail (TOC battle captain duties, LNO duties, video gaming, and even pleasure reading) may exacerbate symptoms and prolong recovery and should be prohibited.[33] The duration of each profile will vary from patient to patient and will depend on how each individual responds to their injury. Individual Services may have mandatory periods of duty restriction based solely on the diagnosis of an mTBI. Providers should be cognizant of the requisite challenges affecting specific occupations (i.e. aviation personnel) when prescribing duty restrictions.

It is recommended that the patient follow up with their healthcare provider at short intervals to allow for individual recovery patterns with a subsequent gradual increase in physical and mental activity. Furthermore, computerized cognitive testing at regular intervals will reveal cognitive improvement, stagnation, or decline. Self-reported symptom scales typically return to normal before patients return to baseline on cog-

nitive evaluations. Therefore, neuropsychological test results are equally important in determining duration and limitations of the profile.

Once the patient is completely asymptomatic at rest (meaning not requiring any medications that may mask or modify the symptoms of a mTBI) they may begin a graduated return to duty program.[33] The Defense and Veteran's Brain Injury Clinic (DVBIC) recommends an exertional testing program in its Consensus Statement on the acute management of mTBI/concussion in the deployed setting. However, due to the typical fitness level of SOF, exertional challenges may not identify many Special Operations patients who are still impaired.[36]

The breadth of mission-requirements within SOF will preclude the development of a SOF specific gradual return to duty program. Therefore, unit-medical personnel should consider each patient's duty requirements and develop individualized return-to-duty plans in concert with the patient and their chain of command. Regardless of the patient's job, the key non-negotiable tenant of every return-to-duty program is that the patient should not proceed to the next level if they develop symptoms while exercising, or anytime after exercising.

It is recommended that the return-to-duty program follow a crawl-walk-run type of progression, starting with light aerobic exercise with the gradual addition of military mission-specific requirements. Special Operations missions require a high degree of mental dexterity along with physical prowess. Due to this fact it is vital that the gradual return to duty program include a combination of mental and physical tasks, performed simultaneously, to better reflect real life mission requirements.

Educating the patient and the chain of command is an integral part of the process and starts with the diagnosis and continues until the patient is medically cleared for duty. Mild TBIs are unique from many other medical conditions in that typically, the severity of the diagnosis cannot be determined until the patient recovers or fails to recover. Investing the time to explain the uniqueness of each individual's injury and our inability to accurately predict a timeline, for disease progression and recovery, is paramount to controlling the expectations of both the patient and the chain of command.

Acknowledgement

A special thanks to Dr. Andre M. Pennardt, Dr. Jonathen C. Taylor, and Marc Selby for their insightful contributions, editorial assistance, and enthusiastic support.

References

1. McCrea MA. (2008). Mild Traumatic Brain Injury and Post-concussion Syndrome. New York: Oxford University Press, Inc.
2. Brolinson PG, Manoogian S, McNeely D, Goforth M, Greenwald R, Duma S. (2006). Analysis of linear head accelerations from collegiate football impacts. *Curr Sports Med Re*; 5:23-28
3. Giza CC, Hovda DA. (2001). The neurometabolic cascade of concussion. *J Athletic Training*; 36(3):228-235.
4. Doberstein C, Velarde F, Badie H, Hovda DA. (1992). Changes in local cerebral blood flow following concussive brain injury. *Society of Neuroscience*; January 1, Anaheim, CA. Abstract 18,175.
5. Humm JL, Kozlowski DA, James DC, Gotts JE, Schallert T. (1998). Use-dependent exacerbation of brain damage occurs during an early post-lesion vulnerable period. *Brain Res*; 783:286-292.
6. Blumbergs PC, Jones NR, North JB. (1989). Diffuse axonal injury in head trauma. *J Neurology, Neurosurgery, and Psychiatry*; 52:838-841.
7. Lovell MR, Echemendia RJ, Barth JT, Collins MW. (2004). Traumatic brain injury in sports. The Netherlands: Swets and Zeitlinger B.V., Lisse; 45-70.
8. Wasserman J, Koenigsberg RA. (2007). Diffuse axonal injury. *Emedicine.com*. Retrieved 2009-05-25.
9. Smith D, Greenwald B. (2003). Management and staging of traumatic brain injury. *Emedicine.com*. Retrieved through web archive on 2009-05-25.
10. Boon R, de Montfor GJ. (2002). Brain Injury. Learning Discoveries Psychological Services. Retrieved through web archive on 2009-05-25.
11. Singh J, Stock A (2006). Head Trauma. *Emedicine.com*. Re trieved 2009-05-25.
12. Bigler ED. (2000). The Lesion(s) in Traumatic brain injury: Implications for clinical neuropsychology. Retrieved through web archive on 2009-05-25.
13. Pappius HM. (1988). Significance of biogenic amines in functional disturbances resulting from brain injury. *Metabolic Brain Disease*; 3(4), 303-230.
14. Gorman LK, Fu K, Hovda DA, Murray M, Traystman RJ. (1996). Effects of traumatic brain injury on the cholinergic system in the rat. *Journal of Neurotraum*; 13(8), 457-463.
15. Miller LP, Lyeth BG, Jenkins LW, Oleniak L, Panchision D, Hamm RJ et al. (1990). Excitatory amino acid receptor subtype binding following traumatic brain injury. *Brain Research*; 526(1), 103-107.
16. Lee SM, Smith ML, Hovda DA, Becker DP. (1995). Concussive brain injury results in chronic vulnerability of post-traumatic seizures, Society for Neuroscience; November 8-11; San Diego, CA. Abstract 21,762.
17. D'Ambrosio R, Maris DO, Grady MS, Winn HR, Janigro D. (1998). Selective loss of hippocampal long-term potentiation, but not depression, following fluid percussion injury. *Brain Res*; 786:64-79.
18. Roberts GW, Gentlemen SM, Lynch A, et al. (1991). βA4 amyloid protein deposition in brain after head trauma. *Lancet*; 338, 1422-1423.
19. Graham DI, Gentlemen SM, Lynch A. et al. (1995). Distribution of β-amyloid protein in the brain following severe head injury. *Neuropathology and Applied Neurobiology*; 21, 27-34.

20. Masliah E, Mallory M, Hansen L, et al. (1994). Synaptic and neuritic alterations during the progression of Alzheimer's disease. *Neuroscience Letters*; 174, 67-72.
21. Monnerie H, Esquenazi S, Shashidhara S, Le Roux PD. (2005). Beta-Amyloid-induced reactive astrocytes display altered ability to support dendrite and axon growth from mouse cerebral cortical neurons in vitro. *Neurology Research*; 27(5):525-32 (ISBN: 0161-6412).
22. Bigler, E.D. (2008). Neuropsychology and clinical neuroscience of persistent post-concussive syndrome. *Journal of the International Neuropsychological Society*; 14, 1-22.
23. Lezak, M.D., Howieson, D.B., & Loring, D.W. (2004). Neuropsychological Assessment, 4th ed. New York: Oxford University Press.
24. Zhang, L, Heier, LA, Zimmerman, RD, Jordan, B, and Ulug, AM (2006). Diffusion anisotropy changes in the brains of professional boxers. *American Journal of Neuroradiology*; 27, 2000-2004.
25. Chappell, MH, Ulug, AM, Zhang, L, Heitger, MH, Jordan, BD, Zimmerman, RD, and Watts, R. (2006). Distribution of microstructural damage in the brains of professional boxers: A diffusion MRI study. *Journal of Magnetic Resonance Imaging*; 24, 537-542.
26. Zetterberg, H, Hietala, MA, Jonsson, M, Andreasen, N, Styrud, E, Karlsson, I, Edman, A, Popa, C, Rasulzada, A, Wahlund, LO, Mehta, PD, Rosengren, L, Blennow, K, and Wallin, A. (2006). Neurochemical aftermath of amateur boxing. *Archives in Neurology*; 63, 1277-1280.
27. McCrory, P, Meeuwisse, W, Johnston, K, Dvorak, J, Aubry, M, Molloy, M, and Cantu, R. (2009). Consensus statement on concussion in sport: The 3rd International Conference on Concussion in Sport held in Zurich, Nov 2008. *Journal of Athletic Training*; 44(4), 434-448.
28. Bleiberg, J, Cernich, AN, Cameron, K, Sun, W, Peck, K, Ecklund, PJ, Reeves, D, Uhorchak, J, Sparling, MB, and Warden, DL. (2004). Duration of cognitive impairment after sports concussion. *Neurosurgery*; 54(5), 1073-1078.
29. Bleiberg, J, and Warden, DL. (2005). Duration of cognitive impairment after sports concussion. *Neurosurgery*; 56(5), E1166.
30. Van Kampen, D A, Lovell, M, Pardini, JE, Collins, MW, and Fu, FH. (2006). The "value added" of neurocognitive testing after sports-related concussion. *The American Journal of Sports Medicine*; 34(10), 1630-1635.
31. Ewing, R, McCarthy, D, Gronwall, D, and Wrightson, P. (1980). Persisting effects of minor head injury observable during hypoxic stress. *Journal of Clinical Neuropsychology*; 2, 147-155.
32. Hanna-Pladdy, B, Berry, ZM, Bennett, T, Phillips, HL, and Gouvier, WD. (2001). Stress as a diagnostic challenge to postconcussive symptoms: Sequelae of mild traumatic brain injury or physiological stress response. *The Clinical Neuropsychologist*; 15(3): 289-304.
33. McCrory P, Meeuwisse W, Johnston K, et al. (2009). Consensus Statement on Concussion in Sports 3rd International Conference on Concussion in Sports, Zurich, Nov 2008. *Clin J Sport Med*; 19:3 May, 185-200.
34. Reddy CC, Collins MW. (2009). Sports concussions: Management and predictors of outcome. *Current Sports Medicine Repor*t; 8;1:10-15.
35. Lovell MR. (2009). The management of sports related concussion: Current status and future trends. *Clinics in Sports Medicine*; 28:1: Jan, 95-111.
36. Defense and Veterans Brain Injury Center Consensus Conference on the acute management of concussion/mild traumatic brain injury (mTBI) in the deployed setting. 23 July and 1 August 2008.

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