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Chapter 4 Pathophysiology of Mild TBI

Implications for Altered Signaling Pathways

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4.1. INTRODUCTION

Concussions and mild traumatic brain injury (TBI) represent a substantial portion of the annual incidence of TBI aided by the increased reporting of concussions in youth sports, and the increased exposure of soldiers to blast injuries in the war theater. The pathophysiology of concussions and mild TBI consist predominantly of axonal injury at the cellular level and working memory deficits at the behavioral level. Importantly, studies in humans and in animals are making it clear that concussions and mild TBI are not merely a milder form of moderate-severe TBI but represent a separate disease/injury state. Therefore, acute and chronic treatment strategies, both behavioral and pharmacological, need to be implemented based on thorough pre-clinical assessment. The review in this chapter focuses on two under-studied components of the pathophysiology of mild TBI—the role of the c-Jun N-terminal kinase pathway in axonal injury, and the role of the dopaminergic system in working memory deficits.

The growing awareness of the incidence of concussion in contact sports, coupled with the emergence of blast-related injuries in combat fighting, has heightened the urgency to understand the underlying mechanisms of mild brain trauma and devise potential therapeutic interventions. TBI in general, and mild TBI in particular, is considered a “silent epidemic” because many of the acute and enduring alterations in cognitive, motor, and somatosensory functions may not be readily apparent to external observers. Moderate to severe TBI is a major cause of injury-induced death and disability with an annual incidence of approximately 500 in 100,000 people affected in the United States (Sosin et al., 1989; Kraus and McArthur, 1996; Rutland-Brown et al., 2006). However, approximately 80% of all TBI cases are categorized as mild head injuries (Bazarian et al., 2005; Langlois et al., 2006). It is important to note that these approximations are underestimates because they do not account for incidents of TBI in which the person does not seek medical care (Faul et al., 2010). Recent estimates to correct for this underreporting have placed the annual incidence at approximately 3.8 million (Bazarian et al., 2005; Ropper and Gorson, 2007; Halstead and Walter, 2010). The Glasgow Coma Scale (GCS) score, which measures level of consciousness, has been the primary clinical tool for assessing initial brain injury severity in mild (GCS 13–15), moderate (GCS 9–12), or severe (GCS < 8) cases (Teasdale and Jennett, 1974). Although this scoring system serves as a reliable predictor of patient survival (Steyerberg et al., 2008), particularly in the acute phase of trauma and for those patients with more severe head injury (Saatman et al., 2008), it does not necessarily reflect the underlying cerebral pathology because different structural abnormalities can produce a similar clinical picture.

Concussions are a frequent occurrence in contact sports such as football, hockey, lacrosse, and soccer, and increasing evidence suggests that athletes may sustain multiple concussions throughout their career (Bakhos et al., 2010; Bazarian et al., 2005; Grady, 2010; McCrory et al., 2009). Another significant population is soldiers suffering from blast-related injuries, with one in six soldiers returning from combat deployment in Iraq meeting the criteria for concussion (Wilk et al., 2010). Gender factors may also play a role in the epidemiology of concussion. Comparisons of similar sports have yielded the observation that females have nearly twice the rate of concussion compared with males (Dick, 2009; Lincoln et al., 2011). It is important to note that concussed high school males and females self-report different symptoms, with females more often complaining of drowsiness and noise sensitivity, whereas males complain of cognitive deficits and amnesia (Frommer et al., 2011). Furthermore, females also have a higher postconcussion symptom score 3 months postinjury (Bazarian et al., 2010). Two primary complications of concussion are the postconcussion syndrome and second impact syndrome. The postconcussion syndrome is the persistence of concussion-induced symptomatology for greater than 3 months postinjury, presumably because of both neurophysiological and neuropathological processes secondary to the initial concussion (Silverberg and Iverson, 2011).

Second impact syndrome is a condition in which a second head impact is sustained during a "vulnerable period" before the complete symptomatic resolution of the initial impact leading to profound engorgement, massive edema, and increased intracranial pressure within minutes of the impact and resulting in brain herniation, followed by coma and death (Cantu, 1998; Field et al., 2003). It is believed that this vulnerable period is the duration of an injury-induced failure of cerebral blood flow autoregulation (Lam et al., 1997), which can leave the patient highly vulnerable to drastic fluxes and extremes of blood pressure. Second impact syndrome has a morbidity rate of 100% and a mortality rate of 50%, and it is important to note that as of 2001, all reported cases of second impact syndrome had occurred in athletes younger than 20 years of age (McCrory, 2001).

Neurobehavioral symptoms, which often correlate with severity of the TBI, vary in type and duration and are manifested as somatic and/or neuropsychiatric symptoms (reviewed in Riggio and Wong, 2009). Somatic symptoms refer to the physical changes associated with TBI and include headache, dizziness/nausea, fatigue or lethargy, and changes in sleep pattern. Headache is the most commonly reported somatic symptom after mild TBI and is considered acute if resolved within 2 months or chronic if headaches persist for longer than 2 months. Dizziness is another commonly reported symptom of TBI and generally resolves within 2 months but may continue in patients with moderate or severe TBI. Another particularly debilitating symptom is fatigue, likely due to difficulty in initiating or maintaining sleep. Neuropsychiatric sequelae after TBI comprise cognitive deficits and behavioral disorders and are identified in almost all TBI patients for up to 3 months, with a small percentage exhibiting persistent (months—years) symptoms. Cognitive deficits are characterized by impaired attention, memory, and/or executive function and may cause the patient to become irritable, anxious, or depressed. Cognitive deficits in cases of mild TBI generally resolve within days and do not have to be associated with loss of consciousness and posttraumatic amnesia. Behavioral manifestations after TBI include personality changes, depression, and anxiety. Personality changes describe aggression, impulsivity, irritability, emotional lability, and apathy. Major depression is one of the most frequently reported behavioral sequelae of TBI, accounting for approximately 25% to 40% of cases of moderate-to-severe TBI (Riggio and Wong, 2009).

Collectively, these observations underscore the need to develop age-, sex-, and injury severity—appropriate animal models of mild TBI and concussions. The following review describes the current state of knowledge of the pathophysiology of mild TBI/concussions, with particular attention to axonal injury and cognitive deficits.

4.2. EXPERIMENTAL APPROACHES TO STUDYING CONCUSSIONS

The symptomatology associated with concussion appears to be primarily functional in nature because standard neuroimaging studies reveal no structural abnormalities; however, postmortem analyses of brains from patients who had sustained a recent mild TBI, but had died from nontraumatic causes, showed evidence of axonal injury (Blumbergs et al., 1994, 1995). Specialized functional magnetic resonance imaging has revealed decreases in cortical blood flow to the mid-dorsolateral prefrontal cortex during the acute postconcussive period in athletes challenged in a working memory task as well as activation patterns that correlate with symptom severity and recovery (Chen et al., 2004), whereas diffusion tensor imaging has also detected evidence of microstructural white matter and axonal injuries in some cases of prolonged deficits (Arfanakis et al., 2002; Niogi et al., 2008; Smits et al., 2010; Wilde et al., 2008). Furthermore, electroencephalography and transcranial magnetic stimulation studies have determined that acute and long-term electrophysiological changes in brain activity can occur in the absence of overt neuropsychological impairment (De Beaumont et al., 2007a, 2007b; Gosselin et al., 2006).

A concussion may be caused by either a direct blow to the head (contact forces, Figure 4.1a) or by a blow to elsewhere on the body with the forces being subsequently transmitted to the brain (inertial forces, Figure 4.1b) (McLean, 1996; Teasdale and Matthew, 1996). Rotational forces around a defined axis are thought to be responsible for damage to deep white matter tracts, resulting in a diffuse axonal injury as well as causing damage to deep gray matter nuclei (McLean, 1996; Thibault and Gennarelli, 1990). A third possible force, the presumable basis of blast trauma, is based on the stereotactile theory, which posits that as a result of the interplay between the spherical shape of the skull and the fact that brain tissue has the same density on concentric planes, the pressure waves created by skull—brain interactions or skull vibrations may propagate through brain tissue as a spherical wave front, resulting in a more focused and direct energy reaching deeper brain structures (Willinger et al., 1996).

Animal models of TBI have been developed in the ferret, cat, pig, and monkey but the most common and developed model is the rodent (Gennarelli, 1994). Two models predominate to elucidate mechanisms of diffuse or concussive brain injury—the midline fluid-percussion model (Dixon et al., 1987) and the impact-acceleration model (Marmarou et al., 1994). Both models were originally characterized in the rat and demonstrate characteristics of human TBI such as cognitive dysfunction (Beaumont et al., 1999; Lyeth et al., 1990) and axonal injury (reviewed in Buki and Povlishock, 2006). More recently, concussive brain injury has been modeled in mice (Laurer et al., 2001; Longhi et al., 2005; Spain et al., 2010; Tang et al., 1997a, 1997b; Zohar et al., 2003). Injury induced by a weight drop, fluid percussion, or a modified cortical impact device resulted in diffuse neurodegeneration in the cortex and hippocampus and βAPP(+) intraaxonal swellings in the thalamus, corpus callosum, and external capsule (Longhi et al., 2005; Spain et al., 2010; Tang et al., 1997b; Tashlykov et al., 2007). Closed-head injury in mice resulted in long-term behavioral dysfunction characterized by learning deficits, depressive behavior, and increased passive avoidance (Milman et al., 2005; Tang et al., 1997a; Spain et al., 2010; Zohar et al., 2003). In contrast, impact to the intact skull using a silicone-tipped indenter only resulted in a transient deficit in motor function with no effect on spatial learning ability (Laurer et al., 2001, 2005). Although these animal models reflect the acute neurochemical, microscopic, and anatomical pathophysiology of concussive brain trauma, they do not appear to model the hallmark of concussion—transient neurologic (cognitive) dysfunction. Impact to the intact skull of mice over the midline suture resulted in spatial learning and working memory deficits only in the first 3 days after trauma (Creed et al., 2011). Traumatic axonal injury was observed up to 3 days postinjury and degenerating axons at 14 days postinjury. These structural alterations in injured axons were accompanied by functional deficits that manifested as reductions in compound action potential and decreased retrograde transport, which were present up to 2 weeks postinjury. Further evidence of diffuse brain injury arose from the observation of cortical edema over the first 24 hours postinjury and neuronal degeneration in the cortex and hippocampus up to 3 days postinjury.

4.3. AXONAL INJURY AFTER MILD TBI

Traumatic axonal injury is triggered by the inertial forces of trauma to the brain, resulting in subsequent structural and subcellular changes within the axon cylinder (Buki and Povlishock, 2006). One of the initial changes is altered axolemmal permeability because of focal microscopic mechanoporation of the axolemma and was first observed as influx of the normally excluded protein, horseradish peroxidase, after head injury (Pettus et al., 1994; Pettus and Povlishock, 1996). These microscopic holes may provide a route for intraaxonal calcium influx, leading to calpain activation (Buki et al., 1999; Saatman et al., 1996). Calpain activation may effect structural alterations to the axonal cytoskeleton leading to disruption of both anterograde and retrograde transport and eventual swellings in contiguous axons and finally secondary axotomy (Buki and Povlishock, 2006; Creed et al., 2011; Shojo and Kibayashi, 2006). Direct evidence of retrograde transport impairment using Fluoro-Gold transport in the brain after a traumatic injury was recently demonstrated (Creed et al., 2011). In part, disruption of axonal transport may be mediated by neurofilament compaction, which occurs as a result of dephosphorylation and has been recognized as another prominent characteristic of axonal injury after TBI (Chen et al., 1999; Christman et al., 1994; Creed et al., 2011; Povlishock et al., 1997).

The c-Jun N-terminal kinases (JNKs) are a subfamily of mitogen-activated protein kinases that play important roles in the central nervous system, in both physiological (neurite outgrowth and extension, brain development and neuronal repair) and pathological conditions (apoptosis, axonal injury) (Herdegen and Waetzig, 2001; Kuan et al., 2003; Waetzig and Herdegen, 2003; Yang et al., 1997). JNK activation has been observed in experimental models of TBI in both neurons (Raghupathi et al., 2003; Ortolano et al., 2009; Otani et al., 2002) and axons (Raghupathi et al., 2003) and in humans (Ortolano et al., 2009).

Their ability to participate in and also be activated by cytoskeletal changes allows JNK to play an important role in dynamic neurite outgrowth and elongation during brain development (Waetzig and Herdegen, 2005). Importantly, JNK activation has been implicated in axonal injury after trauma in vivo (Broude et al., 1997; Raghupathi et al., 2003; Raivich et al., 2004) and in vitro (Cavalli et al., 2005; Verhey et al., 2001). Direct phosphorylation of the kinesin-1 heavy chain subunit by activated JNK in the squid axoplasm led to the inhibition of binding between kinesin-1 and axonal microtubules and subsequent fast axonal transport (Morfini et al., 2006). Interestingly, this disruption in axonal

transport appeared to be mediated by the neuron-specific JNK3 isoform (Morfini et al., 2009), which may explain the observed protective effect of genetic deletion of the JNK3 isoform after axotomy of dopaminergic neurons (Brecht et al., 2005).

4.4. WORKING MEMORY DEFICITS AND DOPAMINERGIC SIGNALING IN MILD TBI

Working memory deficits are a major complaint of patients suffering from TBI with transient deficits after mild TBI/concussions and permanent morbidity from severe TBI (Mayers et al., 2011; Gorman et al., 2012; McAllister et al., 2001; Slovarp et al., 2012; Theriault et al., 2011). In rats and mice, working memory deficits have been documented and appear not to be dependent on the location of the impact or the type of model used. Thus, contusive trauma or fluid-percussion injury either over the frontal cortices or the parietal cortex (Hamm et al., 1996; Hoane et al., 2006; Hoskison et al., 2009; Vonder Haar et al., 2011) all resulted in significant long-term working memory deficits in the adult rat. Conversely, closed-head midline cortical contusion injury that impacts the skull midway between Bregma and Lambda is capable of producing a working memory deficit in adult male mice tested on days 1–3 postinjury, but that has resolved by days 7–9 postinjury (Creed et al., 2011).

Working memory is an organism's ability to transiently maintain information in an active and available form over a time delay. It is the mental chalkboard that allows for successful interactions within an ever-changing environment by permitting one to manipulate and actively use the stored information to apply it to a current situation for goal-directed or problem-solving purposes. Working memory relies on the appropriate interactions of a distributed network of brain regions, though the primary region of integration appears to be the prefrontal cortex (PFC). The cellular activity underlying working memory is based on the activity of neurons after the withdrawal of a prior stimulus or event. Neurons within the prefrontal cortex have "memory fields" or the representation of a target stimulus to which a neuron fires maximally (Funahashi et al., 1989). Working memory requires a finely tuned balance of excitatory and inhibitory inputs into and within the PFC. In animals, mild TBI induces a hypoexcitable brain state in which the evoked population excitatory postsynaptic potential is significantly decreased compared with uninjured animals followed by a period of hyperexcitability (Ding et al., 2011). Sanders and colleagues (2001) noted that an fluid-percussion-induced mild TBI over the right parietal cortex of male rats caused reductions of the slope and increases in the latency of vibrissa-evoked potentials 3 days postinjury, whereas alterations in presynaptic neuronal function have also been observed as early as 1 hour postinjury in adult male rats (Reeves et al., 2000).

Pyramidal, excitatory neurons act in concert with inhibitory interneurons; this system is modulated by dopaminergic afferents to the prefrontal cortex from the ventral tegmental area (Durstewitz and Seamans, 2002). These dopamine afferents form symmetric synapses on the dendritic spines of pyramidal neurons, which in turn contain the D1 dopamine receptor subtype (Charuchinda et al., 1987; Lidow et al., 1991; Smiley et al., 1994). Expression of the D1 receptor increased in the PFC as early as 3 hours and remained elevated up to 3 days after contusive brain trauma (Kobori and Dash, 2006). In contrast, in the striatum, the binding properties of the D1 receptor decreased in the acute posttraumatic period but increased in the subacute period, with no concomitant change in the level of expression (Henry et al., 1997; Wagner et al., 2009). Nonspecific dopamine agonists such as methylphenidate (Newsome et al., 2009; Wagner et al., 2007) and amantadine (Dixon et al., 1999; Meythaler et al., 2002) have ameliorated TBI-induced cognitive deficits. In a model of moderate brain trauma, the D1 receptor antagonist SCH23390 attenuated working memory deficits (Kobori and Dash, 2009), whereas after concussive TBI, the efficacy of SCH23390 was augmented by a coadministration of the D2 receptor antagonist sulpiride (Tang et al., 1997a, 1997b). In contrast, in a model of concussion in adolescent rats, we observed that a partial agonist of the D1 receptor (SKF38393) almost completely restored working memory function in brain-injured rats (unpublished observations). These data, while implicating the dopamine system in posttraumatic working memory deficits, underscore the complicated nature of the response of the brain to differing severities of injury.

4.5. CONCLUSION

Concussions and mild TBI represent a significant component of the spectrum of TBI-associated syndromes. Accumulating evidence suggests that the pathophysiology of mild TBI may pose questions not addressed over the years in models of moderate-to-severe TBI. Although the cellular manifestation of axonal injury may be transient in

mild TBI, deficits in axonal function may be present over a longer period postinjury. Similarly, alterations in dopaminergic signaling may follow a different trajectory than what has been reported in more severe cases and treatment with dopaminergic agents may have to take into account the severity of the injury. These observations underscore the importance of continued studies in mild TBI.

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REFERENCES

1. Arfanakis K, Haughton V. M, Carew J, Rogers B, Dempsey R, Meyerand M. Diffusion tensor MR imaging in diffuse axonal injury. AJNR Am J Neuroradiol. 2002;23:794–802. [PubMed: 12006280]
2. Bakhos L. L, Lockhart G. R, Myers R, Linakis J. G. Emergency department visits for concussion in young child athletes. Pediatrics. 2010;126:e550–556. [PubMed: 20805145]
3. Bazarian J. J, McClung J, Shah M. N, Cheng Y. T, Flesher W, Kraus J. Mild traumatic brain injury in the United States, 1998–2000. Brain Inj. 2005;19:85–91. [PubMed: 15841752]
4. Bazarian J. J, Blyth B, Mookerjee S, He H, McDermott M. P. Sex differences in outcome after mild traumatic brain injury. J Neurotrauma. 2010;27:527–539. [PMC free article: PMC2867588] [PubMed: 19938945]
5. Beaumont A, Marmarou A, Czigner A, Yamamoto M, Demetriadou K, Shirotani et al. The impact-acceleration model of head injury: Injury severity predicts motor and cognitive performance after trauma. Neurol Res. 1999;21:742–754. [PubMed: 10596383]
6. Blumbergs P. C, Scott G, Manavis J, Wainwright H, Simpson D. A, McLean A. J. Topography of axonal injury as defined by amyloid precursor protein and the sector scoring method in mild and severe closed head injury. J Neurotrauma. 1995;12:565–572. [PubMed: 8683607]
7. Blumbergs P. C, Scott G, Manavis J, Wainwright H, Simpson D. A, McLean A. J. Staining of amyloid precursor protein to study axonal damage in mild head injury. Lancet. 1994;344:1055–1056. [PubMed: 7523810]
8. Brecht S, Kirchhof R, Chromik A, Willesen M, Nicolaus T, Raivich G. et al. Specific pathophysiological functions of JNK isoforms in the brain. Eur J Neurosci. 2005;21:363–377. [PubMed: 15673436]
9. Broude E, McAtee M, Kelley M. S, Bregman B. S. c-Jun expression in adult rat dorsal root ganglion neurons: Differential response after central or peripheral axotomy. Exp Neurol. 1997;148:367–377. [PubMed: 9398479]
10. Buki A, Povlishock J. T. All roads lead to disconnection? Traumatic axonal injury revisited. Acta Neurochir (Wien) 2006;148:181–93. discussion 193–4. [PubMed: 16362181]
11. Buki A, Siman R, Trojanowski J. Q, Povlishock J. T. The role of calpain-mediated spectrin proteolysis in traumatically induced axonal injury. J Neuropathol Exp Neurol. 1999;58:365–375. [PubMed: 10218632]
12. Cantu R. C. Second-impact syndrome. Clin Sports Med. 1998;17:37–44. [PubMed: 9475969]
13. Cavalli V, Kujala P, Klumperman J, Goldstein L. S. Sunday Driver links axonal transport to damage signaling. J Cell Biol. 2005;168:775–787. [PMC free article: PMC2171809] [PubMed: 15738268]
14. Charuchinda C, Supavilai P, Karobath M, Palacios J. M. Dopamine D2 receptors in the rat brain: Autoradiographic visualization using high-affinity selective agonist ligand. J Neurosci. 1987;7:1352–1360. [PubMed: 2437261]
15. Chen J.-K, Johnston K, Frey S, Petrides M, Worsley K, Ptitp A. Functional abnormalities in symptomatic concussed athletes: An fMRI study. NeuroImage. 2004;22:68–82. [PubMed: 15109998]
16. Chen X. H, Meaney D. F, Xu B. N, Nonaka M, McIntosh T. K, Wolf J. A, Saatman K. E, Smith D. H. Evolution of neurofilament subtype accumulation in axons following diffuse brain injury in the pig. J Neuropathol Exp Neurol. 1999;58:588–596. [PubMed: 10374749]
17. Christman C. W, Grady M. S, Walker S. A, Holloway K. L, Povlishock J. T. Ultrastructural studies of diffuse axonal injury in humans. J Neurotrauma. 1994;11:173–186. [PubMed: 7523685]
18. Creed J. A, DiLeonardi A. M, Fox D. P, Tessler A. R, Raghupathi R. Concussive brain trauma in the mouse results in acute cognitive deficits and sustained impairment of axonal function. J Neurotrauma. 2011;28:547–563. [PMC free article: PMC3070143] [PubMed: 21299360]

19. De Beaumont L, Brisson B, Lassonde M, Jolicoeur P. Long-term electrophysiological changes in athletes with a history of multiple concussions. Brain Inj. 2007a;21:631–644. [PubMed: 17577714]
20. De Beaumont L, Lassonde M, Leclerc S, Theoret H. Long-term and cumulative effects of sports concussions on motor cortex inhibition. Neurosurgery. 2007b;61:329–337. [PubMed: 17762745]
21. Dick R. W. Is there a gender difference in concussion incidence and outcomes? Br J Sports Med. 2009;43:i46–50. [PubMed: 19433425]
22. Ding M. C, Wang Q, Lo E. H, Stanley G. B. Cortical excitation and inhibition following focal traumatic brain injury. J Neurosci. 2011;31:14085–14094. [PMC free article: PMC3444158] [PubMed: 21976493]
23. Dixon C. E, Lyeth B. G, Povlishock J. T, Findling R. L, Hamm R. J, Marmarou A. et al. A fluid percussion model of experimental brain injury in the rat. J Neurosurg. 1987;67:110–119. [PubMed: 3598659]
24. Dixon C. E, Kraus M. F, Kline A. E, Ma X, Yan H. Q, Griffith R. G. et al. Amantadine improves water maze performance without affecting motor behavior following traumatic brain injury in rats. Restor Neurol Neurosci. 1999;14:285–294. [PubMed: 12671249]
25. Durstewitz D, Seamans J. K. The computational role of dopamine D1 receptors in working memory. Neural Netw. 2002;15:561–572. [PubMed: 12371512]
26. Faul M, Xu L, Wald M. M, Coronado V. G. Atlanta, GA: 2010. Traumatic brain injury in the United States: Emergency department visits, hospitalizations and deaths 2002–2006. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.
27. Field M, Collins M. W, Lovell M. R, Maroon J. Does age play a role in recovery from sports-related concussion? A comparison of high school and collegiate athletes. J Pediatr. 2003;142:546–553. [PubMed: 12756388]
28. Frommer L. J, Gurka K. K, Cross K. M, Ingersoll C. D, Comstock R. D, Saliba S. A. Sex differences in concussion symptoms of high school athletes. J Athl Train. 2011;46:76–84. [PMC free article: PMC3017493] [PubMed: 21214354]
29. Funahashi S, Bruce C. J, Goldman-Rakic P. S. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J Neurophysiol. 1989;61:331–349. [PubMed: 2918358]
30. Gennarelli T. A. Animate models of human head injury. J Neurotrauma. 1994;11:357–368. [PubMed: 7837277]
31. Gorman S, Barnes M. A, Swank P. R, Prasad M, Ewing-Cobbs L. The effects of pediatric traumatic brain injury on verbal and visual-spatial working memory. J Int Neuropsychol Soc. 2012;18:29–38. [PMC free article: PMC3707395] [PubMed: 22014162]
32. Gosselin N, Theriault M, Leclerc S, Montplaisir J, Lassonde M. Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. Neurosurgery. 2006;58:1151–1161. [PubMed: 16723894]
33. Grady M. W. Concussion in the adolescent athlete. Curr Probl Pediatr Adolesc Health Care. 2010;40:154–169. [PubMed: 20705248]
34. Halstead M. E, Walter K. D. Clinical report—Sport-related concussion in chlidren and adolescents. Pediatrics. 2010;126:597–615. [PubMed: 20805152]
35. Hamm R. J, Temple M. D, Pike B. R., O, Dell D. M, Buck D. L, Lyeth B. G. Working memory deficits following traumatic brain injury in the rat. J Neurotrauma. 1996;13:317–323. [PubMed: 8835799]
36. Henry J. M, Talukder N. K, Lee A. B, Walker M. L. Cerebral trauma-induced changes in corpus striatal dopamine receptor subtypes. J Invest Surg. 1997;10:281–286. [PubMed: 9361992]
37. Herdegen T, Waetzig V. The JNK and p38 signal transduction following axotomy. Restor Neurol Neurosci. 2001;19:29–39. [PubMed: 12082227]
38. Hoane M. R, Tan A. A, Pierce J. L, Anderson G. D, Smith D. C. Nicotinamide treatment reduces behavioral impairments and provides cortical protection after fluid percussion injury in the rat. J Neurotrauma. 2006;23:1535–1548. [PubMed: 17020488]
39. Hoskison M. M, Moore A. N, Hu B, Orsi S, Kobori N, Dash P. K. Persistent working memory dysfunction following traumatic brain injury: Evidence for a time-dependent mechanism. Neuroscience. 2009;159:483–491. [PMC free article: PMC4264540] [PubMed: 19167462]
40. Kobori N, Dash P. K. Reversal of brain injury-induced prefrontal glutamic acid decarboxylase expression and working memory deficits by D1 receptor antagonism. J Neurosci. 2006;26:4236–4246. [PubMed: 16624944]

41. Kraus J. F, McArthur D. L. Epidemiologic aspects of brain injury. Neurol Clin. 1996;14:435–450. [PubMed: 8827181]
42. Kuan C. Y, Whitmarsh A. J, Yang D. D, Liao G, Schloemer A. J, Dong C. et al. A critical role of neural-specific JNK3 for ischemic apoptosis. Proc Natl Acad Sci U S A. 100. 2003:15184–15189. [PMC free article: PMC299947] [PubMed: 14657393]
43. Lam J. M, Hsiang J. N, Poon W. S. Monitoring of autoregulation using Doppler flowmetry in patients with head injury. J Neurosurg. 1997;86:438–445. [PubMed: 9046300]
44. Laurer H. L, Bareyre F. M, Lee V. M, Trojanowski J. Q, Longhi L, Hoover R. et al. Mild head injury increasing the brain's vulnerability to a second concussive impact. J Neurosurg. 2001;95:859–870. [PubMed: 11702878]
45. Lidow M. S, Goldman-Rakic P. S, Gallager D. W, Rakic P. Distribution of dopaminergic receptors in the primate cerebral cortex: Quantitative autoradiographic analysis using [3H]spiperone and [3H]SCH23390. Neuroscience. 1991;40:657–671. [PubMed: 2062437]
46. Lincoln A. E, Caswell S. V, Almquist J. L, Dunn R. E, Norris J. B, Hinton R. Y. Trends in concussion incidence in high school sports: A prospective 11-year study. Am J Sports Med. 2011;39:958–963. [PubMed: 21278427]
47. Longhi L, Saatman K. E, Fujimoto S, Raghupathi R, Meaney D. F, Davis J. et al. Temporal window of vulnerability to repetitive experimental concussive brain injury. Neurosurgery. 2005;56:364–74. discussion 364–74. [PubMed: 15670384]
48. Lyeth B. G, Jenkins L. W, Hamm R. J, Dixon C. E, Phillips L. L, Clifton G. L. et al. Prolonged memory impairment in the absence of hippocampal cell death following traumatic brain injury in the rat. Brain Res. 1990;526:249–258. [PubMed: 2257484]
49. Marmarou A, Foda M. A, van den Brink W, Campbell J, Kita H, Demetriadou K. A new model of diffuse brain injury in rats. Part I: Pathophysiology and biomechanics. J Neurosurg. 1994;80:291–300. [PubMed: 8283269]
50. Mayers L. B, Redick T. S, Chiffriller S. H, Simone A. N, Terraforte K. R. Working memory capacity among collegiate student athletes: Effects of sport-related head contacts, concussions, and working memory demands. J Clin Exp Neuropsychol. 2011;33:532–537. [PubMed: 21218317]
51. McAllister T. W, Sparling M. B, Flashman L. A, Guerin S. J, Mamourian A. C, Saykin A. J. Differential working memory load effects after mild traumatic brain injury. Neuroimage. 2001;14:1004–1012. [PubMed: 11697932]
52. McCrory P. Does second impact syndrome exist? J Clin Sport Med. 2001;11:144–149. [PubMed: 11495318]
53. McCrory P, Meeuwisse W, Johnston K, Dvorak J, Aubry M, Molloy M. et al. Consensus statement on Concussion in Sport: The 3rd International Conference on Concussion in Sport held in Zurich, November 2008. Clin J Sport Med. 2009;19:185–200. [PubMed: 19423971]
54. McLean A. Traumatic Brain Injury: Bioscience and Mechanics. Bandak A, Eppinger R, Ommaya A, editors. Mary Ann Liebert; Larchmont, NY: 1996. Brain injury without head impact.
55. Meythaler J. M, Brunner R. C, Johnson A, Novack T. A. Amantadine to improve neurorecovery in traumatic brain injury-associated diffuse axonal injury: A pilot double-blind randomized trial. J Head Trauma Rehabil. 2002;17:300–313. [PubMed: 12105999]
56. Milman A, Rosenberg A, Weizman R, Pick C. G. Mild traumatic brain injury induces persistent cognitive deficits and behavioral disturbances in mice. J Neurotrauma. 2005;22:1003–1010. [PubMed: 16156715]
57. Morfini G. A, You Y. M, Pollema S. L, Kaminska A, Liu K, Yoshioka K. et al. Pathogenic huntingtin inhibits fast axonal transport by activating JNK3 and phosphorylating kinesin. Nat Neurosci. 2009;12:864–871. [PMC free article: PMC2739046] [PubMed: 19525941]
58. Morfini G, Pigino G, Szebenyi G, You Y, Pollema S, Brady S. T. JNK mediates pathogenic effects of polyglutamine-expanded androgen receptor on fast axonal transport. Nat Neurosci. 2006;9:907–916. [PubMed: 16751763]
59. Newsome M. R, Scheibel R. S, Seignourel P. J, Steinberg J. L, Troyanskaya M, Li X, Levin H. S. Effects of methylphenidate on working memory in traumatic brain injury: A preliminary FMRI investigation. Brain Imaging Behav. 2009;3:298–305. [PubMed: 22005992]
60. Niogi S. N, Mukherjee P, Ghajar J, Johnson C, Kolster R. A, Sarkar R. et al. Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: A 3T diffusion

tensor imaging study of mild traumatic brain injury. AJNR Am J Neuroradiol. 2008;29:967–973. [PubMed: 18272556]
61. Ortolano F, Colombo A, Zanier E. R, Sclip A, Longhi L, Perego C. et al. c-Jun N-terminal kinase pathway activation in human and experimental cerebral contusion. J Neuropathol Exp Neurol. 2009;68:964–971. [PubMed: 19680147]
62. Otani N, Nawashiro H, Fukui S, Nomura N, Shima K. Temporal and spatial profile of phosphorylated mitogen-activated protein kinase pathways after lateral fluid percussion injury in the cortex of the rat brain. J Neurotrauma. 2002;19:1596. [PubMed: 12542859]
63. Pettus E. H, Povlishock J. T. Characterization of a distinct set of intra-axonal ultrastructural changes associated with traumatically induced alteration in axolemmal permeability. Brain Res. 1996;722:1–11. [PubMed: 8813344]
64. Pettus E. H, Christman C. W, Giebel M. L, Povlishock J. T. Traumatically induced altered membrane permeability: Its relationship to traumatically induced reactive axonal change. J Neurotrauma. 1994;11:507–522. [PubMed: 7861444]
65. Povlishock J. T, Marmarou A, McIntosh T, Trojanowski J. Q, Moroi J. Impact acceleration injury in the rat: Evidence for focal axolemmal change and related neurofilament sidearm alteration. J Neuropathol Exp Neurol. 1997;56:347–359. [PubMed: 9100665]
66. Raghupathi R, Muir J. K, Fulp C. T, Pittman R. N, McIntosh T. K. Acute activation of mitogen-activated protein kinases following traumatic brain injury in the rat: Implications for posttraumatic cell death. Exp Neurol. 2003a;183:438–448. [PubMed: 14552884]
67. Raivich G, Bohatschek M, Da Costa C, Iwata O, Galiano M, Hristova M. et al. The AP-1 transcription factor c-Jun is required for efficient axonal regeneration. Neuron. 2004;43:57–67. [PubMed: 15233917]
68. Reeves T. M, Kao C. Q, Phillips L. L, Bullock M. R, Povlishock J. T. Presynaptic excitability changes following traumatic brain injury in the rat. J Neurosci Res. 2000;60:370–379. [PubMed: 10797540]
69. Riggio S, Wong M. Neurobehavioral sequelae of traumatic brain injury Mt Sinai J Med. 2009;76:163–172. [PubMed: 19306386]
70. Ropper A. H, Gorson K. C. Clinical practice. Concussion. N Engl J Med. 2007;356:166–172. [PubMed: 17215534]
71. Rutland-Brown W, Langlois J. A, Thomas K. E, Xi Y. L. Incidence of traumatic brain injury in the United States, 2003. J Head Trauma Rehabil. 2006;21:544–548. [PubMed: 17122685]
72. Saatman K. E, Bozyczko-Coyne D, Marcy V, Siman R, McIntosh T. K. Prolonged calpain-mediated spectrin breakdown occurs regionally following experimental brain injury in the rat. J Neuropathol Exp Neurol. 1996;55:850–860. [PubMed: 8965100]
73. Saatman K. E, Duhaime A. C, Bullock R, Maas A. I, Valadka A, Manley G. T. Classification of traumatic brain injury for targeted therapies. J Neurotrauma. 2008;25:719–738. Workshop Scientific Team and Advisory Panel Members. [PMC free article: PMC2721779] [PubMed: 18627252]
74. Sanders M. J, Dietrich W. D, Green E. J. Behavioral, electrophysiological, and histopathological consequences of mild fluid-percussion injury in the rat. Brain Res. 2001;904:141–144. [PubMed: 11516420]
75. Shojo H, Kibayashi K. Changes in localization of synaptophysin following fluid percussion injury in the rat brain. Brain Res. 2006;1078:198–211. [PubMed: 16497279]
76. Silverberg N. D, Iverson G. L. Etiology of the post-concussion syndrome: Physiogenesis and psychogenesis revisited. NeuroRehabilitation. 2011;29:317–329. [PubMed: 22207058]
77. Slovarp L, Azuma T, Lapointe L. The effect of traumatic brain injury on sustained attention and working memory. Brain Inj. 2012;26:48–57. [PubMed: 22149444]
78. Smiley J. F, Levey A. I, Ciliax B. J, Goldman-Rakic P. S. D1 dopamine receptor immunoreactivity in human and monkey cerebral cortex: Predominant and extrasynaptic localization in dendritic spines. Proc Natl Acad Sci USA. 1994;91:5720–5724. [PMC free article: PMC44068] [PubMed: 7911245]
79. Smits M, Houston G. C, Dippel D. W, Wielopolski P. A, Vernooij M. W, Koudstaal P. J. et al. Microstructural brain injury in post-concussion syndrome after minor head injury. Neuroradiology. 2011;53:553–563. [PMC free article: PMC3139069] [PubMed: 20924757]

80. Sosin D. M, Sacks J. J, Smith S. M. Head injury-associated deaths in the United States from 1979 to 1986. JAMA. 1989;262:2251–2255. [PubMed: 2795806]
81. Spain A, Daumas S, Lifshitz J, Rhodes J, Andrews P. J, Horsburgh K, Fowler J. H. Mild fluid percussion injury in mice produces evolving selective axonal pathology and cognitive deficits relevant to human brain injury. J Neurotrauma. 2010;27:1429–1438. [PubMed: 20528171]
82. Steyerberg E. W, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh G. S. et al. Predicting outcome after traumatic brain injury: Development and international validation of prognostic scores based on admission characteristics. PLoS Med. 2008;5 e165; discussion e165. [PMC free article: PMC2494563] [PubMed: 18684008]
83. Tang Y. P, Noda Y, Hasegawa T, Nabeshima T. A concussive-like brain injury model in mice (I): Impairment in learning and memory. J Neurotrauma. 1997a;14:851–862. [PubMed: 9421456]
84. Tang Y. P, Noda Y, Hasegawa T, Nabeshima T. A concussive-like brain injury model in mice (II): Selective neuronal loss in the cortex and hippocampus. J Neurotrauma. 1997b;14:863–873. [PubMed: 9421457]
85. Tashlykov V, Katz Y, Gazit V, Zohar O, Schreiber S, Pick C. G. Apoptotic changes in the cortex and hippocampus following minimal brain trauma in mice. Brain Res. 2007;1130:197–205. [PubMed: 17174280]
86. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2:81–84. [PubMed: 4136544]
87. Teasdale G, Matthew P. Neurological Surgery. 4th. Youmans J. R, editor. WB Saunders; New York: 1996. Mechanisms of cerebral concussion, contusion, and other effects of head injury.
88. Theriault M, De Beaumont L, Tremblay S, Lassonde M, Jolicoeur P. Cumulative effects of concussions in athletes revealed by electrophysiological abnormalities on visual working memory. J Clin Exp Neuropsychol. 2011;33:30–41. [PubMed: 20480425]
89. Thibault L, Gennarelli T. Des Plaines, IL: 1990. Brain injury: An analysis of neural and neurovascular trauma in the nonhuman primate. Paper presented at: 34th annual proceedings of the Association for the Advancement of Automotive Medicine.
90. Verhey K. J, Meyer D, Deehan R, Blenis J, Schnapp B. J, Rapoport T. A. et al. Cargo of kinesin identified as JIP scaffolding proteins and associated signaling molecules. J Cell Biol. 2001;152:959–970. [PMC free article: PMC2198804] [PubMed: 11238452]
91. Vonder Haar C, Anderson G. D, Hoane M. R. Continuous nicotinamide administration improves behavioral recovery and reduces lesion size following bilateral frontal controlled cortical impact injury. Behav Brain Res. 2011;224:311–317. [PMC free article: PMC3159802] [PubMed: 21704653]
92. Waetzig V, Herdegen T. Context-specific inhibition of JNKs: Overcoming the dilemma of protection and damage. Trends Pharmacol Sci. 2005;26:455–461. [PubMed: 16054242]
93. Wagner A. K, Kline A. E, Ren D, Willard L. A, Wenger M. K, Zafonte R. D. et al. Gender associations with chronic methylphenidate treatment and behavioral performance following experimental traumatic brain injury. Behav Brain Res. 2007;181:200–209. [PMC free article: PMC1974874] [PubMed: 17517440]
94. Wilde E, McCauley S, Hunter J, Bigler E, Chu Z, Wang Z. et al. Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. Neurology. 2008;70:948–955. [PubMed: 18347317]
95. Wilk J. E, Thomas J. L, McGurk D. M, Riviere L. A, Castro C. A, Hoge C. W. Mild traumatic brain injury (concussion) during combat: Lack of association of blast mechanism with persistent postconcussive symptoms. J Head Trauma Rehabil. 2010;25:9–14. [PubMed: 20051900]
96. Willinger R, Taleb L, Kopp C. Traumatic Brain Injury: Bioscience and Mechanics. Bandak A, Eppinger R, Ommaya A, editors. Mary Ann Liebert; Larchmont, NY: 1996. Modal and temporal analysis of head mathematical models.
97. Yang D. D, Kuan C. Y, Whitmarsh A. J, Rincon M, Zheng T. S, Davis R. J. et al. Absence of excitotoxicity-induced apoptosis in the hippocampus of mice lacking the Jnk3 gene. Nature. 1997;389:865–870. [PubMed: 9349820]
98. Zohar O, Schreiber S, Getslev V, Schwartz J. P, Mullins P. G, Pick C. G. Closed-head minimal traumatic brain injury produces long-term cognitive deficits in mice. Neuroscience. 2003;118:949–955. [PubMed: 12732240]

Figures

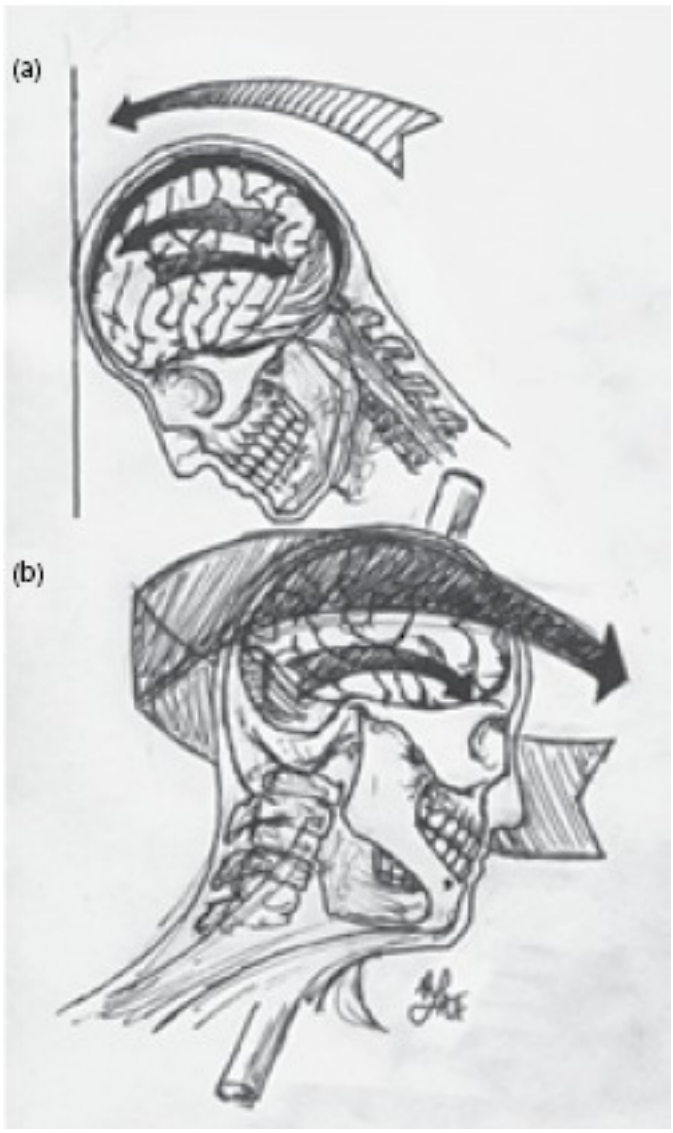

FIGURE 4.1

Representation of contact (a) and rotational forces (b) associated with traumatic brain injury.

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