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Invited review

The neurophysiology of brain injury

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Abstract

Objective: This article reviews the mechanisms and pathophysiology of traumatic brain injury (TBI).

Methods: Research on the pathophysiology of diffuse and focal TBI is reviewed with an emphasis on damage that occurs at the cellular level. The mechanisms of injury are discussed in detail including the factors and time course associated with mild to severe diffuse injury as well as the pathophysiology of focal injuries. Examples of electrophysiologic procedures consistent with recent theory and research evidence are presented.

Results: Acceleration/deceleration (A/D) forces rarely cause shearing of nervous tissue, but instead, initiate a pathophysiologic process with a well defined temporal progression. The injury foci are considered to be diffuse trauma to white matter with damage occurring at the superficial layers of the brain, and extending inward as A/D forces increase. Focal injuries result in primary injuries to neurons and the surrounding cerebrovasculature, with secondary damage occurring due to ischemia and a cytotoxic cascade. A subset of electrophysiologic procedures consistent with current TBI research is briefly reviewed.

Conclusions: The pathophysiology of TBI occurs over time, in a pattern consistent with the physics of injury. The development of electrophysiologic procedures designed to detect specific patterns of change related to TBI may be of most use to the neurophysiologist.

Significance: This article provides an up-to-date review of the mechanisms and pathophysiology of TBI and attempts to address misconceptions in the existing literature.

Keywords: Acceleration; Brain hemorrhage; Traumatic; Deceleration; Diffuse axonal injury; Electrophysiology; Neurophysiology

1. Introduction

Over the past decade, scientific information on traumatic brain injury (TBI) has increased exponentially. For example, using the search engine PubMed (National Library of Medicine) and the term "axonal injury", there were 1993 articles available between the years 1994 and 2003, compared to only 932 for the years 1966–1993. Today, more is known about the pathophysiology of TBI spanning a range from molecular change, to changes in gross brain structure or function. Dramatic advances have been made regarding how injuries occur at the cellular level, where they occur in the brain, and the permanence of these injuries. In addition, significant advances have been made regarding the ability to accurately detect and classify various forms of neurotrauma. An anticipated by-product of rapid growth in knowledge is that previous outdated knowledge persists, potentially misguiding clinicians and researchers. The purpose of this review is to update neurophysiologists on these recent advances. In addition, a brief and current review of electrophysiologic procedures will be described in areas of TBI assessment that are not well suited to standard clinical procedures. It is believed that an accurate depiction of current research in this area will be beneficial to those interested in the development and use of novel assessment procedures.

2. Acceleration/deceleration forces and "diffuse" axonal injury

Acceleration/deceleration (A/D) forces are considered to be an important factor in the genesis of TBI. This was discovered relatively early in the history of modern head injury research by Denny-Brown and Russell (1941) who wrote that concussion with loss of consciousness (LOC) was

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difficult to inflict when the head was in a restricted position. At approximately the same time, a physicist, Holbourn (1943) examined the effects of A/D forces on a gelatin model of the human brain. Holbourn described how sheer strains occurred in the brain, suggesting that rotational acceleration forces are the primary cause of injury producing predictable damage to the brain. Strich, a pathologist, built upon Holbourn's work and described the pathology observed in the brains of patients who experienced lethal A/D forces sustained during "road accidents". Initially, Strich (1956) examined 5 subjects with common clinical and pathologic findings including mode of injury and immediate and persistent LOC. The primary microscopic feature observed in neural tissue was diffuse degeneration of white matter without obvious damage to cortex. Later, Strich (1961) expanded this work, once again describing widespread diffuse degeneration of white matter that occurred in the midst of normal nerve fibers. At that time, it was noted that in cases with shorter survival times (up to 6 weeks), large numbers of nerve fibers with retraction balls (the appearance of severed axons with axoplasm extruded from the proximal and distal segments) were observed. Based on this observation, it was concluded that the nerve fibers were torn or stretched at the time of injury. The work of Holbourn and Strich continues to be very influential today (e.g. Hammoud and Wasserman, 2002).

In addition, dominant theories of TBI considered the brainstem to be the focus of injury since even mild A/D forces could cause LOC. Ward (1958, 1966), Hayes et al. (1984) and others (see review by Shaw, 2002) implicated the reticular nuclei and pontine cholinergic neurons in brainstem as the primary site of damage and dysfunction related to TBI. Often cited studies by Pilz (1983) and Jane et al. (1985) demonstrated that a proportionately larger number of cells were damaged in the brainstem in primates and humans who sustained TBI related to A/D forces.[1] Taken together, these studies have led numerous clinicians and researchers to conclude that A/D injuries result in sheer strains within the cranial vault, and these in turn lead to sheering of neurons and blood vessels occurring principally in the brainstem.

2.1. Ommaya–Gennarelli model of TBI

A significant theoretical contribution regarding the mechanisms of TBI was proposed by Ommaya and Gennarelli (1974) who suggested that A/D forces (also termed impulsive loading) cause mechanical strains that operate in a "centripetal sequence". Injuries of this nature can occur when the head is propelled through space and is abruptly stopped by a solid object, such as the ground, or when the head is set into motion, for example, when a boxer is struck. With mild forces, the sequence begins at the surface of the brain and progressively affects deeper structures as forces become more severe. A classification system was developed to identify the progressive grades of cerebral injury ranging from minor to severe disruptions of consciousness. Briefly, grades I and II involved cortical–subcortical disconnection, grades II and III involved cortical–subcortical and diencephalic disconnection, with grades IV and V involving cortical–subcortical, diencephalic, and mesencephalic disconnection. According to their system, a grade I to II concussion may involve memory disturbance without loss of motor control and partially impaired awareness. In this case they suggested that significant mechanical strains *did not* reach the reticular system. On the other hand, severe cases typically demonstrated greater degrees of diffuse irreversible damage and when diffuse damage reached a critical point, a grade V coma occurred (Ommaya and Gennarelli, 1974).

Based on their original classification system, the authors postulated 3 critical predictions. (1) When the degree of trauma is sufficient to produce LOC, cortex and subcortical systems will be primarily affected, with damage being more severe than that found in the rostral brainstem. (2) That damage to the rostral brainstem will not occur without more severe damage occurring in the cortex and subcortical structures, since the mesencephalon is the last area to suffer trauma. And (3), cognitive symptoms such as confusion and disturbance of memory can occur without LOC, however, the reverse cannot occur (Ommaya and Gennarelli, 1974).

In addition to these critical predictions, the theory reinforced 3 important aspects of how TBI occurs and the potential effects different A/D forces have on the brain. First, it reinforced the principle that the *direction* of force can determine severity of injury. Specifically, rotational forces were believed to cause the most severe injuries (Holbourn, 1943; Ommaya and Gennarelli, 1974). In addition, the direction of rotation was found to affect the severity of injury and recovery (Gennarelli et al., 1982) with sagittal (front-to-back) injuries resulting in good recovery, lateral injuries (side-to-side) resulting in persistent coma or severe disability, and oblique injuries falling in between. Another point reinforced by the Ommaya–Gennarelli model was the notion of a continuum of injury. Succinctly stated, mild, moderate, and severe brain injuries caused by A/D forces are not discrete entities but occur on a continuum ranging from the surface of the brain inward with increasing amounts of damage occurring at each level of depth as forces increase (Peerless and Rewcastle, 1967; Povlishock et al., 1994). This concept has been supported recently in an animal model where mild to moderate forces caused traumatic axonal injury (TAI) in corpus callosum, with animals exposed to the most impact energy showing the greatest number of abnormalities (Kallakuri et al., 2003). In another study, mild forces produced no loss of delayed microtubule-associated protein-2 (MAP-2) within

[1] In the Pilz study, the distribution of axonal injury could not be assessed in every case since this was a retrospective study and only limited material was available in a proportion of the cases. This may explain the higher incidence of damage that occurred in deeper structures.

the ipsilateral dentate hilus, while moderately injured animals exhibited immunoreactive shrunken neurons and with MAP-2 changes observed in multiple areas of hippocampus (Saatman et al., 1998). Finally, research supporting the Ommaya–Gennarelli model demonstrates that A/D forces alone are sufficient to cause severe TBI. In other words, severe injuries do not always involve actual trauma to the head. For example, the Penn II device used by Gennarelli et al. (1982) delivered a well-calibrated A/D pulse that moved a primate's head through space rapidly without impact, and when performed in the lateral plane, severe injuries resulted. Examples of significant non-impact brain trauma in humans have been described in relation to motor vehicle accidents (Gieron et al., 1998; Henry et al., 2000; Varney and Varney, 1995) and in infants with "shaken baby syndrome" (Duhaime et al., 1998). In addition, significant frontocentral slowing and spike activity have been associated with non-impact A/D forces (Gieron et al., 1998; Henry et al., 2000).

2.1.1. Location of brain injury associated with varying amounts of force

Early studies suggested that the brainstem was the primary site of injury associated with transient disruptions in consciousness and behavioral suppression (Denny-Brown and Russell, 1941; Foltz and Schmidt, 1956). More recently, studies by Jane et al. (1985) and Pilz (1983) have been cited in support of this position (Dacey et al., 1993). Nonetheless, numerous studies point to cellular injury that does not specifically involve brainstem, especially with injuries produced by mild to moderate forces. In these studies, various characteristics of neurons themselves appear to make them more susceptible to diffuse injury. For example, when axons change direction to accommodate a blood vessel's presence, to enter target nuclei, or when decussation within the brain parenchyma occurs, they can be more easily damaged (Adams et al., 1977; Grady et al., 1993; Oppenheimer, 1968; Povlishock, 1993; Yaghmai and Povlishock, 1992). Large caliber neurons are often injured more than smaller neurons that surround them (Yaghmai and Povlishock, 1992). Of particular importance, injured axons are observed more often where a change in tissue density occurs, such as at the grey–white matter interface near cerebral cortex (Gentry et al., 1988; Grady et al., 1993; Peerless and Rewcastle, 1967; Povlishock, 1993).

In fact, the overwhelming majority of studies indicate that damage to cortex and subcortical white matter occurs when the brain is exposed to A/D forces. Magnetic resonance imaging (MRI) has been particularly useful in demonstrating that in accordance with the Ommaya–Gennarelli model, the depth of lesion is positively correlated with the effect on consciousness. Jenkins et al. (1986) clearly showed that impaired consciousness and coma were associated with a greater number of lesions located at superficial structures with less damage to deep structures. In this study, 6 of 8 subjects with intact consciousness had lesions restricted to cortex (Jenkins et al., 1986). Others have shown that in subjects diagnosed with mild TBI, all lesions were located at the grey–white interface and associated white matter with none located in the brainstem or corpus callosum (Mittl et al., 1994). In addition, depth of lesion observed on MRI was associated with the duration of impaired consciousness with deep central grey matter and brainstem lesions resulting in the longest periods of LOC (Levin et al., 1992; Wilson et al., 1988). Finally, a direct test of the Ommaya–Gennarelli model using an MRI assessment of 251 children with TBI demonstrated that depth of lesion increases with increased force and thereby produces a more severe disturbance of consciousness (Levin et al., 1997).

Electrophysiologic procedures used to assess TBI are also consistent with the Ommaya–Gennarelli model. For example, a review by Gaetz and Bernstein (2001) stated that compared to cognitive event-related potentials (ERPs), fewer studies show changes in brainstem auditory evoked potentials (BAEP) and somatosensory evoked potentials (SEP) following mild TBI. BAEPs on the other hand have been used to assess outcome associated with severe TBI (Facco and Munari, 2000). However, they are less sensitive than other evoked potentials (EPs) such as SEPs for assessing positive and negative outcome (Anderson et al., 1984; Cant et al., 1986; Facco and Munari, 2000; Rosenberg et al., 1984; Soldner et al., 2000). Conversely, cognitive ERPs appear to be more sensitive to changes in brain function associated with these injuries. This pattern of results is consistent with studies that show ERPs originate from multiple distributed neural generators that include multiple cortical areas (Halgren et al., 1995; Lamarche et al., 1995).

It is interesting that given the substantial research support the Ommaya–Gennarelli model has received, it continues to have a lack of general acceptance. For example, some have considered it contradictory since it attempts to resolve "a primary site of action or impact at the cortex with a mechanism of action responsible for the LOC buried deep within the brain" (Shaw, 2002, p. 314). Shaw's (2002) statement implies that the mechanisms responsible for LOC are solely based in brainstem. However, while the reticular system has long been considered an important component in human consciousness it is only one element in a system that generates arousal and attention. Cognitive processes such as arousal and awareness are functionally related to the reticular system that begins in the brainstem as the reticular core (Stewart-Amidei, 1991). The reticular core has vast influence on multiple brain areas and receives sensory information from the cortex via thalamus (Stewart-Amidei, 1991), leading some to suggest that the neural basis for consciousness is distributed (Picton and Stuss, 1994; Turner and Knapp, 1995; Sieb, 1990).

Of particular importance is the influence of cortex and subcortical white matter on the reticular system (Picton and Stuss, 1994). One role of the neocortex in attention is that it

drives or activates the reticular system. It may be the case that cortical influences on brainstem are responsible for certain patterns of brain activation such as the internal generation of arousal in the absence of sensory stimuli (van Zomeren and Brower, 1994). Therefore, if cortex is believed to play a substantial role in maintaining a distributed consciousness, then trauma involving cortex and subcortical white matter will affect consciousness since brainstem reticular cells will be suppressed due to a lack of input. This position was postulated early on by Foltz and Schmidt (1956) who hypothesized that the immediate loss of function in the reticular formation was caused by traumatic neuronal depression or loss of afferent activity from sensory systems (i.e. the cerebral cortex and its associated white matter).

3. Cellular neurophysiology of traumatic axonal injury

The work of Holbourn (1943) and Strich (1956, 1961) provided evidence that A/D injuries resulted in sheer strains within the cranial vault causing stretching and sheering of neurons and blood vessels. There are numerous studies that cite this early work as evidence for shearing injuries to neurons and blood vessels (Adams et al., 1977, 1991; Gennarelli, 1993; Hammoud and Wasserman, 2002; Pilz, 1983; Maxwell et al., 1988). A more recent modification of this perspective was the suggestion of a distinction between shearing of axons or "primary axotomy" and secondary axotomy that causes damage to axons in the hours and days following injury (Maxwell et al., 1993). Others have suggested that the majority of diffuse or TAI occurs as a pathophysiologic process whereby small ion species enter the axons at or near the nodes of Ranvier, causing damage to the cytoskeleton and microtubules (Christman et al., 1994; Erb and Povlishock, 1991; Grady et al., 1993; Pettus et al., 1994; Povlishock et al., 1983; Povlishock and Becker, 1985; Yaghmai and Povlishock, 1992). Axons contain numerous microscopic elements including microtubules and neurofilaments. Microtubules are thick cytoskeletal fibers and consist of long polar polymers constructed of protofilaments packed in a long tubular array. They are oriented longitudinally in relation to the axon and are associated with fast axonal transport (Schwartz, 1991). Neurofilaments are essentially the "bones" or cytoskeleton of the axon and are the most abundant fibrillar group in axons (Schwartz, 1991).

3.1. The temporal progression of TAI

A variety of in vivo and in vitro methods have been used to explore the time course and pathophysiology of TAI,[2] which was correctly described by Gennarelli and Graham (1998, p. 163) as "a process, not an event". Prominent examples include the fluid-percussion model (e.g. Povlishock et al., 1994), acceleration injury devices such as the Penn II (Gennarelli et al., 1982), optic nerve stretch injury models (Gennarelli et al., 1989), weight drop models (Marmarou et al., 1994), and in vitro axonal stretch models (Smith et al., 1999a). These models were designed to replicate the effects of A/D forces on the brain resulting in damage to axons similar to that observed in humans. They have been used in conjunction with a variety of tracers such as horseradish peroxidase (HRP) and immunolabeling methods. These methods allow for the identification of damaged axons, and can be used to determine whether axolemmal disruption had occurred immediately following trauma and to identify TBI-related changes to the cytoskeleton and microtubules. Following injury, TAI is typically observed at various time points to document changes as they occur over time.

Using these methods, changes in traumatically injured axons have been reported within minutes of injury. For example, at 5 min following a moderate injury, an HRP tracer was observed within the axoplasm at nodal, paranodal, and internodal regions (Pettus et al., 1994). For neurons with HRP within the axon, the neurofilament network appeared dense or more tightly packed, and local mitochondrial abnormalities such as swelling with disruption of the cristae were observed without any overt disruption of the overlying axolemma (Maxwell et al., 1988; Pettus et al., 1994). Within 30 min of a mild traumatic insult, scattered axons showed focal increases of labeled 68 kD neurofilament immunoreactivity and slight swelling, sometimes accompanied by blebbing (multiple axonal swellings) or infolding of the axolemma, or both. In this group, there was focal neurofilament disarray, misalignment of the axon with local axolemmal infolding, with no HRP entering the intracellular milieu (Pettus et al., 1994). Therefore an early distinction between mild and moderate injury was that moderate injury produced a perturbation of the axolemma large enough for the HRP tracer to enter the cell, while mild injuries disrupted the axolemma enough to allow entry of small molecular ion species. Nonetheless, both mild and moderate injuries resulted in densely packed neurofilaments and subsequent cellular pathology (Pettus et al., 1994).

In the hours following injury, a gradual progression of axonal pathology occurred without related petechial haemorrhage or parenchymal damage in the surrounding tissue. At approximately 1 h post-injury, swollen axons contained HRP as well as focal aggregations of organelles including mitochondria, neurotubules, and tubular and ventricular profiles of smooth endoplasmic reticulum. Once again, the axolemma and myelin sheath appeared to be intact with no physical tearing or shearing of the axon cylinder (Povlishock et al., 1983). At 1–2 h post-injury there were multiple axonal injury profiles. Some axons demonstrated

[2] The term traumatic axonal injury has supplanted diffuse axonal injury since damage was believed to occur primarily at the axons, and while trauma can occur to individual axons among many non-injured cells, damaged axons tend to group in various areas of the brain and are therefore not considered truly "diffuse".

focal swelling while others were lobulated and in the process of disconnection. At this point, intense 68 kD immunoreactivity was observed with most neurofilaments paralleling the long axis of the axon. However, some neurofilaments appeared to be oblique to the axon's long axis, indicating a disruption of axoplasmic transport. The isolated segments undergoing the most advanced stages of disconnection demonstrated organelles migrating around the 68 kD immunoreactive neurofilament cores contributing to cellular expansion (Yaghmai and Povlishock, 1992).

At 2–3 h following mild injury, similar abnormalities were noted, however, swelling continued and was associated with an intact axolemma surrounded by organelles within an expanded irregular axoplasmic core. In some cases, no labeling was observed in the distal segment suggesting either a total blockage of HRP transport or focal axonal discontinuity (Pettus et al., 1994; Povlishock et al., 1983). At 3 h post-injury a more advanced axonal change was observed including disconnection of the axon with continued expansion to form a mature reactive swelling. With prolonged survival, the affected axons demonstrated a loss of axonal blebbing or infolding observed at earlier post-injury times. Some reactive axons displayed a proximal stump undergoing continued swelling due to increased accumulation of organelles capping an expanding neurofilamentous core (Pettus et al., 1994).

At 4–6 h following mild injury, HRP laden swellings were further enlarged, more complex, and were often separated by a thin strand of protein linking the two segments (Povlishock et al., 1983). The majority of neurofilament laden 68 kD immunoreactive axonal swellings were detached from their distal segments with some axonal swellings undergoing complete lobulation. The 68 kD positive neurofilaments were now confined to the core of an expanding organelle mass, produced via anterograde axoplasmic transport (Yaghmai and Povlishock, 1992). Following fatal motor vehicle accidents in humans (Grady et al., 1993), 68 kD antibodies were observed near discrete focal swellings that occurred without disconnection, indicating the early stages of cytoskeletal disorganization (a process that may be slower in humans) (Povlishock et al., 1997). In a different human study, observations following injury were consistent with those observed in animal models. Specifically, there was infolding of the axon associated with immunoreactive neurofilaments that were misaligned and fragmented, moving in planes both oblique and transverse to the length of the axon in the presence of parenchyma showing no evidence of trauma (Christman et al., 1994).

At 12–24 h post-injury, Povlishock et al. (1983) reported that swellings had progressed to resemble enlarged peroxidase-laden ball-like expansions. No continuity could be identified between these swellings and their distal axonal segments, suggesting an abrupt separation of the axon cylinder. In addition to these peroxidase labeled swellings, other proximal swellings terminated in enlarged, thickened club-like endings (Povlishock et al., 1983; Yaghmai and Povlishock, 1992). At 12 h post-injury in humans, swellings were again identified with some disconnection of immunoreactive axons, embedded in fields with numerous unaltered axonal profiles (Grady et al., 1993).

In animals at 24–72 h, a further enlargement of cleanly separated axons was observed, with some showing what was assumed to be a regenerative attempt in the form of growth cones that protruded from reactive axonal swellings (Yaghmai and Povlishock, 1992). At 24 h in humans, the reactive swellings exhibited further change in their appearance with a non-immunoreactive cap of axoplasm now encompassing an expanded 68 kD immunoreactive neurofilament core. In some cases, lobulation of the axon was evident. From 30 h to 1 week, grossly swollen axonal segments were now commonly disconnected in humans (Christman et al., 1994; Grady et al., 1993). Typically, the swollen reactive segment was surrounded by a lucent cavity, which was in turn surrounded by a myelin sheath (Christman et al., 1994).

At 3–4 days following injury, Povlishock and Becker (1985) noted that the injury profiles differed from axon to axon. Some axons exhibited an intact axolemma that was separated from the overlying distended myelin sheath by a cavity with no evidence of electron dense products. Some axons appeared to consist of multiple segmented swellings. The swellings had no myelin covering with interspersed organelle and neurofilaments and neurotubules in their dilated portions. The constricted segments, on the other hand, contained only neurofilaments and neurotubules. The distal axonal segments demonstrated Wallerian degeneration with macrophages encompassing the degenerating axon cylinder identified within the myelin sheath (Povlishock and Becker, 1985). By 88 h in humans, further progression of the reactive swellings had occurred. Similar to injured animal profiles, heterogeneity was observed among the population of reactive axons (Christman et al., 1994).

At 5–7 days, various forms of reactive change were identified (Povlishock and Becker, 1985). Some axons were comparable to those observed at the 3–4 days. A second group of axons that were initially similar to those at days 3 and 4 now revealed a disruption of the axolemma with increasingly lucent axoplasm as well as mitochondrial disruption. A third group showed evidence of regenerative change reflected in the presence of reactive sprouting (Povlishock and Becker, 1985). At 9–14 days, Povlishock and Becker (1985) observed that two conditions were predominant. In one group, the degenerative response continued, displaying several retrogressive changes such as lobulation, increased electron density and axolemmal/axoplasmic disruption, all of which were accompanied by focal macrophage accumulation. In another group, a regenerative response progressed in a similar manner as days 5–7, with the exception that sprouting was more heterogeneous and differentiated (Povlishock and Becker,

1985). At 17–30 days, regenerative or degenerative axonal changes were predominant. Macrophages were observed in the presence of degenerating profiles that were actively phagocytosing the damaged swellings. The reactive sprout containing swellings were prominent and were similar to those recognised in the previous time period (Povlishock and Becker, 1985). At 59 days post-injury in humans, comparable distended and disconnected reactive swellings were observed (Grady et al., 1993).

The progressive changes observed in animal models and humans are consistent with a progressive series of neurophysiologic events initiated by A/D forces on the axon, and ending in some cases with a frank separation of proximal and distal axon segments. As Povlishock and Becker (1985) stated, it had been long assumed that axonal shear or tensile force caused a physical disruption of the axon into a proximal and distal segment. It was believed that following immediate physical disruption, large amounts of axoplasm were discharged from the axon forming a large reactive swelling classically termed a "retraction ball". These studies provide evidence contrary to the shearing hypothesis, and instead, suggest that even low-intensity mechanical brain injury produces axonal change that is more subtle than that suggested previously (i.e., direct tearing of the axon). Interesting differences were described between species in that reactive axonal change occurs more slowly in humans (Povlishock et al., 1992). It has been known for some time that retraction balls in humans are not found unless the individual survives for several hours post-injury. Another important conclusion was that axonal change showed heterogeneity that became more distinct over time with the distal portions of some cells undergoing Wallerian degeneration and others undergoing a regenerative attempt (Povlishock and Becker, 1985). Importantly, recent studies have demonstrated a functional link between the pathophysiology associated with TAI and deficits observed using visual EPs (Bain et al., 2001).

3.1.1. Contributions of amyloid precursor protein studies

Amyloid precursor protein (APP) has recently been shown to be a sensitive marker for axonal damage commonly observed following TAI (Leclercq et al., 2001) and is an accurate marker for impaired axonal transport (Stone et al., 2001). APP studies often demonstrate similar findings as those using neurofilament immunoreactivity and HRP. Specifically, they are able to detect infolding of the axolemma (Stone et al., 2001) with progressive immunoreactive swellings at nodal and paranodal regions (Stone et al., 1999). In addition to confirming previous findings, they have been useful in the discovery of novel information regarding the pathophysiology of TAI. First, most of the early studies described TAI in large caliber axons. In a recent study, similar pathology was observed in a population of *small* caliber axons that demonstrated immunoreactive punctate spheroidal or multilobulated profiles 30 min post-injury with a time course that paralleled large caliber axons. The swelling contained immunoreactive profiles, some of which were APP positive, and occurred at nodal and paranodal regions. These cellular profiles showed smaller axons undergoing increased swelling and organelle accumulation. At 3 h post-injury, both large and small caliber axons were observed and showed a progression of APP immunoreactivity and number (Stone et al., 1999). Second, using an immunocytochemical marker for neurofilament compaction and APP coupled with the antibody RM014 (a marker for impaired axonal transport), Stone et al. (2001) discovered that labeling of trauma induced axonal transport and neurofilament compaction did not always occur in the same location. Specifically, there were distinct classes of TAI. One class was RM014 immunoreactivity observed between 30 and 60 min following severe injury within thin elongate axons in medial lemniscus and pyramidal tract without the presence of APP and without the development of axonal swellings. In a completely different set of injured axons, APP was associated with highly focal swollen profiles within both the pyramidal tracts at 30 min and medial lemnisci at 1 h that underwent continual swelling (Stone et al., 2001). APP immunoreactivity has also been used to demonstrate areas of the brain that are uniquely susceptible to injury, such as posterior versus anterior corpus callosum (Leclercq et al., 2001) and that diffuse TAI, often attributed exclusively to A/D forces, may occur following death associated with intoxication and especially, chronic opiate abuse (Niess et al., 2002). In addition, it has been used to understand the potential relationship between TBI and Alzheimer's disease (Blumberg et al., 1994; Emmerling et al., 2002; Raghupathi and Margulies, 2002; Smith et al., 1999b; Stone et al., 2002).

3.2. Factors initiating immunoreactive swellings

Several hypotheses exist regarding the potential causes of reactive axonal swellings that occur following TBI. Among the earliest explanations was Strich's (1961) assertion that shear stresses and tearing of neurons were responsible for their generation. Others have argued that the presence of reactive swelling is an injury secondary to ischemia, edema, or increased intracranial pressure (e.g. Onaya, 2002). Gennarelli et al. (1982), Povlishock et al. (1992), and others tended to agree that there is little evidence consistent with this position. For example, Povlishock observed that following injury, reduced regional blood flow was recorded using [^{14}C] iodioantipyrine blood flow analysis, however ischemic levels were never reached. Additionally, in anatomical foci displaying axonal injury there was no evidence of damage due to ischemia (Povlishock et al., 1992). While initially controversial, the hypothesis suggesting that calcium (Ca^{2+}) is the primary factor responsible for reactive axonal change has gained general acceptance. Specifically, there appears to be an intricate cascade that begins with axonal stretch, followed

by Ca^{2+} influx, resulting in an oxygen dependent axonal and dendritic neurofilament sidearm compaction.

3.2.1. A/D forces cause axonal stretch

It is now generally accepted that mechanical strain is the primary mediator of axonal injury (Bain et al., 2001). Gennarelli (1996) has recently proposed 4 stages of TAI, two that are primarily reversible, and two that cause primary and secondary damage to axons. Stage I damage causes transient ionic imbalances following stress to the nodal and paranodal regions of the axon. This in turn allows for an influx of sodium (Na^+), Ca^{2+} and chloride (Cl^-) and the efflux of potassium (K^+). This ionic imbalance causes a failure to generate and propagate action potentials with the normal ionic balance restored in a matter of minutes. Stage II injury results from an axonal stretch in the 5–10% range and exaggerates the ionic imbalances described in Stage I injury, causing impaired axoplasmic flow in approximately 17% of cells examined. It was suggested that very few of these axons undergo secondary axotomy, however, this stage marks the initiation of minimal cell death. Stage III damage is associated with 15–20% strain, resulting in ionic imbalances and Ca^{2+} influx that is not reversible. Finally, Stage IV stretch causes primary axotomy associated with strains of over 20% (Gennarelli, 1996).

However, evidence has recently surfaced suggesting that axons are far more resistant to stretch than previous studies indicated. For example, Smith et al. (1999a) reported a remarkable threshold for primary axotomy following a deformation of axons in vitro. It was discovered that (1) axons from human neuronal cultures demonstrated a remarkably high tolerance to tensile strain with no primary axotomy occurring at strains below 65% of their original length, and (2) axons exhibited delayed elasticity after dynamic deformation, from a straight orientation prior to stretch, to an undulating course following injury, to a gradual recovery of their original shape. At 2 h following stretch, multiple swellings could be seen along the length of many axons similar to the swollen axons described in human brain studies (Smith et al., 1999a).

3.2.2. Ca^{2+} influx occurs during stretch

One of the more recent perspectives regarding how Ca^{2+} enters the cell following stretch was a process labeled "mechanoporation" (Gennarelli, 1996). Mechanoporation was defined as the "development of transient defects in the cell membrane that are due to its mechanical deformation" (Gennarelli, 1996, p. 511). The mechanically induced pores were considered to be either transient or stable, the latter associated with long-term membrane leakage. According to Gennarelli (1996), ions were driven by diffusion through the pores and into cells with Ca^{2+} entering due to the large extracellular gradient. Choi (1988) suggested that the influx of extracellular Ca^{2+}, combined with any Ca^{2+} release triggered from intracellular stores, would elevate cytosolic free Ca^{2+} and would be cytotoxic if Ca^{2+} levels were sustained for at least 4 reasons. First, Ca^{2+} mediated activation of catabolic enzymes such as calpain I can result in the degradation of several structural neuronal proteins such as tubulin, microtubule-associated proteins, neurofilament polypeptides, and spectrin. Second, elevated cytosolic Ca^{2+} activates phospholipases that can break down the cell membrane, resulting in the release of arachidonic acid. This could in turn lead to the production of oxygen free radicals and enzyme generated superoxide radicals. Third, heightened cytosolic Ca^{2+} combines with diacylglycerol and activates protein kinase C leading to alterations of Ca^{2+} channels further enhancing Ca^{2+} influx. Finally, Ca^{2+} influx initiates glutamate neurotoxicity in a positive feedback manner by further stimulating the release of the transmitter glutamate (Choi, 1988).

However, the proposed mechanism by which Ca^{2+} enters the cell has recently been challenged (Wolf et al., 2001). Using an in vitro procedure of cultured human cells, Ca^{2+} influx was observed following a stretch injury using a Ca^{2+} sensitive dye coupled with pharmacological manipulation of existing ion channels. Following a series of experiments, it was discovered that strain on the axonal membrane causes it to stretch, allowing for the abnormal influx of Na^+ through mechanosensitive channels. This in turn causes a reversal of the Na^+–Ca^{2+} exchanger and activation of voltage gated Ca^{2+} channels, resulting in a net influx of Ca^{2+}. The authors of this study concluded that their results do not support the concept of mechanoporation or primary axotomy (Wolf et al., 2001).

3.2.3. Ca^{2+} influx causes neurofilament compaction

Ca^{2+} has long been considered a primary factor in axonal neurofilament compaction caused by damage to the associated sidearms (Christman et al., 1994; Grady et al., 1993; Pettus et al., 1994; Povlishock, 1993; Yaghmai and Povlishock, 1992). However, recent studies have shown that damage to neurofilaments depends on a variety of factors and may not occur as previously thought. First, the degree of neurofilament damage varies with the severity of force applied to the cell. For example, mild TBI is associated with misalignment of the cytoskeleton while severe injuries cause rapid neurofilament compaction. Second, it was believed that influx of Ca^{2+} dependent neural proteases such as μM calpain "cleave" the neurofilament sidearms leading to compaction (Povlishock et al., 1997). Recent studies have altered this perspective somewhat adding that neurofilament compaction is not accompanied by a complete loss of the neurofilament sidearms. Instead, there appears to be a change in overall height of sidearms that does not involve cleavage or loss as previously proposed (Okonkwo et al., 1998). Third, damage to neurofilaments may not be restricted to axons. Following a focal injury in rats, confocal microscopy revealed neurofilament immunoreactivity in apical dendrites with widespread

loss of normal neurofilament morphology (Postmanur et al., 2000).

4. Neurophysiology of focal brain injury

4.1. Primary focal brain injury

The basic pathophysiology of focal brain injury is somewhat less complex than the progression of diffuse injury to axons and dendrites. Focal brain injuries occur in the form of contusions or frank disruptions of brain tissue and also include haemorrhage and haematoma formation in the extradural, subarachnoid, subdural and intracerebral areas (Gennarelli, 1993). Contusions typically occur at the apex of gyri and appear as either multiple punctate haemorrhages or streaks of haemorrhage with an eventual progression of bleeding into adjacent white matter (Gennarelli and Graham, 1998). According to Gennarelli and Graham (1998), contusions are typically observed at the frontal poles, orbital frontal lobes, temporal poles, the lateral and inferior surfaces of temporal lobes, and cortex above the Sylvian fissure. There are numerous subdivisions of contusions including contusions that occur directly beneath fractures, coup contusions that occur under the site of impact, contrecoup contusions that occur in regions distant to (but not always opposite of) the impact site, herniation contusions, and gliding contusions, the latter associated with diffuse injuries. There are also several categories of haemorrhage including intracranial haematoma associated with a direct rupture of a blood vessel, extradural haematoma associated with skull fracture, and acute subdural haematoma caused by a rupture of the bridging veins of the dura or possibly cortical arteries. Following a contusion or haemorrhage, blood extends into adjacent cortex where neurons undergo secondary necrosis due to ischemia (Gennarelli and Graham, 1998).

Another related example of focal injury is stroke and can be classified as either occlusive or haemorrhagic (Brust, 1991). Haemorrhagic stroke is an ischemic event that occurs in neural tissue deprived of blood due to bleeding from the supply vessel. This form of stroke occurs as a secondary injury that can follow contusion and haemorrhage associated TBI. On the other hand, occlusive stroke is caused by a blockage of blood supply by atherosclerosis or thrombosis (Brust, 1991). Finally, missile or puncture wounds of the brain cause primary injuries to neural and vascular tissue, as well as secondary ischemic injury (Cooper, 1993). Focal injuries are believed to cause secondary progressive concentric zones of similar cellular physiology (Gennarelli, 1993). Zones that progressively extend outward from the primary injury include structural disruption, primary traumatic damage without destruction of the brain tissue, and a tertiary zone of potential delayed insult associated with ischemia and edema. Inflammatory or cytotoxic mechanisms may or may not develop in a more delayed fashion (Gennarelli, 1993).

4.2. Secondary effects of focal trauma

Inflammatory and cytotoxic mechanisms of injury are often the product of ischemia. Ischemia may be considered the most significant factor related to secondary damage that occurs following brain injury (Gennarelli, 1993; Lindenberg et al., 1955). Focal injuries produce zones of profoundly reduced regional cerebral blood flow that may be a factor in ischemic neuronal necrosis (Bullock et al., 1991). In adjacent zones where ischemia may not reach critical levels, another process may occur that eventually leads to tissue damage and death. Specifically, glutamate neurotoxicity may play a role in secondary ischemic damage. Hypoxia-related neuronal depolarisation has been shown to increase extracellular levels of glutamate via increased release and decreased uptake (Choi, 1988). Abnormally high levels of extracellular glutamate activate a wide variety of receptors that can cause depolarisation of the cell membrane, allowing for the activation of voltage dependent Ca^{2+} channels (Gennarelli, 1993). An influx of Ca^{2+} can propagate glutamate neurotoxicity in a positive feedback fashion by further stimulating the release of the transmitter glutamate (Choi, 1988). Other amino acid neurotransmitters such as glycine may also be involved in seizure activity and toxicity induced secondary damage (Nilsson et al., 1994). Increased levels of extracellular excitatory amino acids such as glutamate and aspartate are released from hippocampal regions immediately after moderate to severe injury (Faden et al., 1989; Hayes and Dixon, 1994). In humans, increases as large as 10–15 times normal levels occur for glutamate and aspartate lasting up to 4 days in the extracellular fluid adjacent to focal contusions. Glutamate antagonists have been shown to lower intracranial pressure caused by edema (Schroder et al., 1995).

Edema is also an important factor related to secondary brain injury, and in extreme cases, death related to pressure and swelling within the cranial vault that produces herniation of structures in the brainstem. Unlike ischemia, edema can be caused by numerous factors, and is the end point of several pathological processes that occur following injury. According to Fishman (1975), there are two primary types of edema: vasogenic and cytotoxic. One form of vasogenic edema occurs at the tight junctions of endothelial cells that limit the transfer of macromolecules across the blood brain barrier (BBB). Moderate to severe injuries can result in hypertensive responses that can disrupt the BBB. Factors related to the post-traumatic hypertensive response are the peak magnitude of blood pressure and the abruptness of the hypertensive onset (Hayes and Dixon, 1994). Another form of vasogenic edema is related to the presence of arachidonic acid that causes minor vasomotor change, but more importantly causes increased endothelial cell permeability for small and large tracers and induces edema (Wahl and Schilling, 1993).

Cytotoxic edema, on the other hand, does not strictly involve the BBB, but involves all of the cellular elements of

the brain. One form of cytotoxic edema occurs during hypoxic conditions where cells swell within a period of seconds after a hypoxic episode due to failure of the adenosine triphosphate (ATP) dependent Na^+ K^+ pump. As a result, Na^+ rapidly accumulates within cells, as does water due to osmotic pressure (Bullock et al., 1991; Fishman, 1975). A second cause of cytotoxic edema involves increased amounts of extracellular excitatory amino acid neurotransmitters such as glutamate and glycine that can cause acute swelling in dendrites and cell bodies. The presence of high extracellular glutamate levels causes membrane channels to open, which in turn leads to Na^+ influx, membrane depolarisation, and secondary influx of Cl^- and water resulting in excitotoxic swelling. This type of pathology, and the Ca^{2+} dependent late degeneration induced by glutamate, can act in isolation to produce irreversible neuronal injury. However, the latter is more important at lower levels of toxic exposure and may predominate under many pathological conditions (Choi, 1988). Yet another cause of cytotoxic edema results directly from mechanical trauma and a deformation of the neuronal membrane. This causes massive K^+ efflux into the extracellular fluid with consequent astrocytic swelling as the astrocytes attempt to maintain cellular homeostasis (Schroder et al., 1995). Following fatal injuries in humans, extreme swelling was reported in grey and white matter and in astrocytes. Astrocytes with the most damage demonstrated cytoplasmic disruption and altered cell membranes, with the majority of swelling observed in the astrocytic feet (Bullock et al., 1991). Free radical production and associated damage has also been linked with both forms of edema (Ellis et al., 1991; Kontos et al., 1992; Nelson et al., 1992; Povlishock and Kontos, 1992; Sutton et al., 1993). Giza and Hovda (2001) have provided a detailed review of the neurometabolic cascade that occurs following TBI.

5. Combined focal and diffuse injuries

The spectrum of brain injuries ranging from purely focal to diffuse can be viewed as a clinical syndrome resulting from a combination of principally neural or vascular events brought about by the mechanical distortion of the head (Gennarelli and Graham, 1998). When the human brain undergoes moderate to severe A/D forces, it is often the case that a combined pattern of diffuse and focal injury results. The relative degree to which diffuse and focal trauma develops is largely dependent upon the circumstances of injury. Mild injuries typically result in axonal damage found within brain parenchyma showing no other signs of neuronal or vascular change. In this case, vascular disruption does not appear to influence the overall pathogenesis of axonal swelling and disconnection (Povlishock, 1993). Moderate to severe injuries on the other hand frequently result in vasculature damage. For example, severe deceleration forces associated with a high speed motor vehicle accident and no head impact may result in a pattern of predominantly diffuse injury, with several small traumatic foci related to petechial haemorrhage or tearing of small blood vessels. At the opposite end of the continuum, a gunshot wound will cause an obvious primary focal deficit, with concentric zones of ischemic and neurometabolic injury occurring in a secondary manner, with some diffuse trauma associated with stretching of axons and dendrites that occurred as a consequence of tissue deformation. Combined injuries such as fluid-percussion and focal entorhinal cortex lesions in rats resulted in worse behavioral outcome, producing a more profound pathophysiologic response to brain injury (Phillips et al., 1994). In addition, hypoxia has been shown to exacerbate damage observed in the ipsilateral CA1 middle and medial areas of rats following a moderate parasagittal fluid-percussion injury (Bramlett et al., 1999). Therefore, there appears to be an interaction between the pathophysiology of traumatic axonal and dendritic injury and ischemia and edema that occurs following focal injury that when combined, worsens outcome.

6. Current electrophysiologic methods for the assessment of brain injury

The electroencephalogram (EEG) is one of an increasingly large number of structural and functional procedures used to assess TBI. The EEG has a history of use as a research and clinical tool and has been applied to a variety of clinical/diagnostic problems with varying amounts of success. Currently, structural imaging techniques and neurobehavioral procedures dominate the assessment and rehabilitation process following TBI. Computed tomography (CT) and MRI are useful for the detection of potentially life threatening focal trauma such as intracranial haemorrhage or haematoma (Young and Destian, 2002). Neuropsychologic assessment is used to determine the severity and range of functional deficits and is used to plan appropriate rehabilitation strategies (Dacey et al., 1993; Levin, 1993). The use of EEG has been limited in the majority of medical centres to the detection of focal slow wave or seizure activity following trauma and is not typically used for the assessment of diffuse TAI (Hammoud and Wasserman, 2002). Regarding mild TBI, some have concluded that EEG is "generally useless" as an assessment tool (LeBlanc, 1999). While some may concede that electrophysiologic procedures are of little use for TBI assessment, there are examples indicating "niches" where these procedures may be particularly useful. One example is the use of EPs as indicators of outcome following TBI. Another example is for the assessment of patients who are unable or unwilling to respond during a standard neuropsychologic assessment (Gaetz, 2002).

6.1. Assessment of outcome in patients who are unable to respond

6.1.1. Patients with disturbance of consciousness or coma

The BAEP has been used to assess changes in brainstem function associated with disturbed consciousness and coma following TBI. While there is limited evidence suggesting the BAEP is useful to predict outcome (Kane et al., 1996), the majority of studies do not support this position. For example, patients with unfavourable outcomes almost always had abnormal BAEPs while only a portion of patients with normal BAEPs had favourable outcomes (Cant et al., 1986). When combined with other procedures, such as the Glasgow coma scale (GCS), brainstem trigeminal responses (Soustiel et al., 1993), or long or middle latency EPs (Rosenberg et al., 1984), the diagnostic accuracy of the BAEP increased. Pattern visual checkerboard reversal evoked potentials (PVEPs) have also been used to assess moderate to severe injury, however, this procedure cannot be used regularly since it is difficult to administer when the patient is comatose. When it could be used, it was useful in revealing residual dysfunction of visual pathways associated with TBI (Gupta et al., 1986). Like the BAEP, the combined use of PVEPs with BAEPs, and SEPs, increases prognostic accuracy (Greenberg et al., 1977a,b).

Several studies have provided support for the position that SEPs are useful indicators of outcome following TBI and that they are superior to other EPs regarding sensitivity and specificity. SEPs have been shown to be better predictors of outcome compared to BAEPs and VEPs (Anderson et al., 1984; Cant et al., 1986). In a recent study by Soldner et al. (2000), 30 mild to severe TBI patients were assessed using median and tibial nerve SEPs and BAEPs. When correlated with the Glasgow outcome scale (GOS), there was no significant relationship to clinical scoring of the BAEPs. However, the relationship between the GOS and median and posterior tibial nerve SEPs was significant for all patients. The authors concluded that the BAEP is useful in the detection of functional damage while SEPs are useful for prognostic estimation (Soldner et al., 2000). Others have demonstrated that lower limb SEPs were of most use in the prediction of coma duration and were significantly correlated with the GOS. On the other hand, no relationship was observed between clinical and neuroradiologic variables and motor evoked potentials (MEPs). The authors concluded that lower limb SEPs accurately reflect the stage of functional recovery as demonstrated by the high correlations with other clinical prognostic indicators and rating scales (Mazzini et al., 1999). In a recent review, Facco and Munari (2000) discuss these findings in detail and make the point that these are flexible procedures that allow for successful assessment of function when other techniques cannot be used (i.e. when a patient is intubated or at the bedside of a comatose patient).

6.1.2. Patients with TBI associated communication deficits

The assessment of language comprehension in patients who also have deficits in language production and motor dysfunction presents a significant problem. Specifically, the question can be asked: what is the best method to assess a patient whose very condition prevents adequate testing (Connolly et al., 1999a)? One potential solution proposed by Connolly (2000) was to use computerized neuropsychologic tests of language comprehension to elicit ERPs in patients who could not respond otherwise. For example, auditory and visual N400 responses were elicited using incongruous versus congruous words in a patient who had sustained severe left hemisphere TBI. Despite morphologic abnormalities, the patient's ERPs to the terminal words of spoken sentences showed clear differential responses in the 300–500 ms range that guided subsequent treatment and rehabilitation of the injury (Connolly et al., 1999b). The Peabody Picture Vocabulary Test (PPVT) has also been adapted to record N400 ERPs and has been used in normative studies of children (Byrne et al., 1999) and in adults with TBI (Marchand et al., 2002). In the latter study, excellent agreement was reported between the PPVT and ERP measures. In addition, computer adaptations of the vocabulary subtests of the Wechsler Intelligence Scale for Children-III (WISC-III) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) were used to elicit N2/P3 responses in 22 subjects. Large amplitude N2 responses were recorded to incorrect answers and large amplitude P3 responses were recorded to correct answers (Connolly et al., 1999a). The authors contended that while useful for the assessment of language comprehension, these methods may also be useful for the assessment of any cognitive function currently measured with neuropsychologic measures including attention, memory, perception, and level of consciousness (Connolly, 2000).

6.2. Assessment of patients who may be unwilling to respond

Assessment of those who experience mild TBI is problematic for a number of reasons. First, the standard protocol used to assess TBI severity and plan rehabilitation is dominated by CT, MRI, and neurobehavioral procedures. While these procedures may be effective for moderate to severe injury, they may be less useful for the assessment of mild TBI. For example, CT is advocated for determining whether life threatening cognitive decline related to a vascular injury will occur following discharge from a medical centre (Dunham et al., 1996; Ingebrigtsen and Romner, 1996; Livingston et al., 1991, 2000; Shackford et al., 1992; Stein and Ross, 1990), However, negative CT findings are often interpreted by physicians that no significant neural trauma has occurred. The distinction in sensitivity of CT relative to MRI for the detection of trauma following mild TBI has been effectively demonstrated (Levin et al., 1992; Mittl et al., 1994). Although MRI has been shown to be more sensitive than CT, it may not be able

to detect damage to multiple individual axons that occurs among several normally functioning cells. Other factors that complicate assessment of mild TBI include the relative contribution of chronic pain, anxiety, litigation stress, and depression to the post-injury symptom profile, prompting some to consider whether there are any cognitive symptoms attributable to mild TBI alone (Satz et al., 1999). At a minimum, there is significant overlap in the symptoms of post-concussion syndrome (PCS) and those of major depression, making a distinction between the two difficult (DSM-IV-TR, 2000).

In a recent review of electrophysiologic procedures for the assessment of mild TBI, Gaetz and Bernstein (2001) suggested that several procedures were categorized as either "promising" or "good" prospects for assessment of these injuries. Specifically, changes in the latency and amplitude of the visual ERPs were considered potentially useful methods for mild TBI assessment (Ford and Khalil, 1996; Gaetz et al., 2000; Gaetz and Weinberg, 2000; Sangal and Sangal, 1996). In addition, non-standard EEG procedures such as coherence and frequency analysis were also considered promising (Cudmore et al., 2000; Parsons et al., 1997; Tebano et al., 1988; Thatcher et al., 1989, 1998a,b; Thornton, 1999; Watson et al., 1995). This work has been supported by more recent studies that show novel EEG procedures can be used to assess outcome (Slewa-Younan et al., 2002; Thatcher et al., 2001a,b; Vespa et al., 2002). As an adjunct to mild TBI assessment, some have devised potential strategies to use ERPs for the assessment of post-traumatic stress disorder (PTSD) (Granovsky et al., 1998) and malingering (Ellwanger et al., 1997).

Another group that is challenging to assess are athletes. They are typically highly motivated to perform well on examinations, tend to minimize symptoms, and are often willing to return to active participation in their sport well before the cognitive effects of their injury have subsided. Recent studie's employing electrophysiologic procedures have demonstrated significant changes in brain function following mild TBI in athletes. For example, Dupuis et al. (2000) reported a reduction in P3 amplitude immediately following injury that resolved over time. In another study, differences in gamma activity and readiness potential amplitude were reported for athletes who performed forceful movements of graded difficulty (Slobounov et al., 2002). Finally, cumulative changes in visual P3 latency have been demonstrated in athletes who have experienced a significant number of concussions (Gaetz et al., 2000). The studies on athletes are important for two primary reasons. First, they have practical implications for assessment in athletes and can be used to determine when it is safe to resume participation in a sport. Second, they demonstrate that changes in brain function that occur following mild TBI are not always related to depression, PTSD, or malingering since these individuals are highly compliant and motivated to return to their sport.

7. Integration of cellular and clinical neurophysiology

The electrophysiologic procedures described in this review provide an overview of techniques that share at least two primary features. The first is that they allow for the assessment of brain function in patients who otherwise are difficult to assess. Two procedures were described for patients who are unable to respond due to their injuries. For patients with significant disturbances of consciousness resulting from severe TBI, EPs such as SEPs allow for an assessment of function in brainstem, thalamic, and cortical areas and can be used to assess outcome. In patients who cannot communicate verbally or behaviorally following focal deficits to language or motor areas, an assessment of subcortical and cortical systems involved in language processing can be performed using computerized neuropsychologic tests combined with ERPs such as the N400. A subset of patients with mild TBI may fall into a category for those who are unwilling to respond to standardized testing. Mild TBI patients who are in litigation related to their injuries, or who are experiencing symptoms that can be attributed to brain injury, depression, or PTSD provide a significant challenge to clinicians. Athletes are also difficult to assess since the effects of mild TBI have been historically downplayed and considered transient injuries with no long-term cognitive sequelae. Standardized assessment procedures using EPs, ERPs, or novel EEG techniques may prove beneficial for the assessment of cognitive problems with a physiologic basis as well as associated circumstances such as PTSD or malingering.

The electrophysiologic procedures described also capitalize on current theory of brain injury and are consistent with the Ommaya–Gennarelli model. Outcome in patients with profound deficits of consciousness is effectively assessed using procedures that are robust to variations in consciousness and are generated from known sources in thalamus and cortex. When present, they suggested an intact pathway with a good prognosis for recovery. When absent, they indicated damage to the ascending pathway and a poor prognosis for recovery. In addition, patients who have sustained a mild TBI may be effectively assessed using cognitive ERPs that are generated from multiple cortical and subcortical areas, reflecting the diffuse nature of these injuries that occur primarily in white matter near the surface of the brain.

An abundance of scientific information has been recently provided regarding the pathophysiology of TBI. Previous notions of shearing of nerve tissue and a brainstem injury foci have been replaced with the current descriptions of focal and diffuse damage occurring as "a process, not an event" (Gennarelli and Graham, 1998). It is important for the neurophysiologist to understand the pathophysiology of TBI, and to understand features of injury including the fact that impact is not required for significant damage to occur and that mild A/D forces can cause injury to axons and dendrites in the presence of non-injured neural tissue

and cerebrovasculature. Finally, it is important for the neurophysiologist to understand that there are no procedures available for the assessment of "brain injury". As described in this review, TBI comes in a variety of forms, ranging from diffuse injuries to white matter, to highly localized injuries. It is likely that most moderate to severe injuries consist of a combination of focal and diffuse injuries. When attempting to develop or use electrophysiologic procedures for the assessment of TBI, it will be beneficial for the neurophysiologist to understand the mechanisms involved in the production of injury, as well as the short and long-term pathophysiologic sequelae that endure following the injury.

References

Adams JH, Mitchell DE, Graham DI, Doyle D. Diffuse brain damage of the immediate impact type: its relationship to "primary brain-stem damage" in head injury. Brain 1977;100:489–502.

Adams JH, Graham DI, Gennarelli TA, Maxwell WL. Diffuse axonal injury in non-missile head injury. J Neurol Neurosurg Psychiatry 1991;54: 481–3.

Anderson DC, Bundlie S, Rockswold GL. Multimodal evoked potentials in closed head trauma. Arch Neurol 1984;41:369–74.

Bain AC, Raghupathi R, Meaney DF. Dynamic stretch correlates to both morphological abnormalities and electrophysiological impairment in a model of traumatic axonal injury. J Neurotrauma 2001;18:499–511.

Blumberg PC, Scott G, Manavis J, Wainwright H, Simpson DA, McLean AJ. Staining of amyloid precursor protein to study axonal damage in mild head injury. Lancet 1994;344:1055–6.

Bramlett HM, Green EJ, Dietrich WD. Exacerbation of cortical and hippocampal CA1 damage due to posttraumatic hypoxia following moderate fluid-percussion brain injury to rats. J Neurosurg 1999;91: 653–9.

Brust JCM. Cerebral circulation: stroke. In: Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science, 3rd ed. New York, NY: Elsevier; 1991. p. 1041–9.

Bullock R, Maxwell W, Graham D, Teasdale G, Adams J. Glial swelling following human cerebral contusion: an ultrastructural study. J Neurol Neurosurg Psychiatry 1991;54:427–34.

Byrne JM, Connolly JF, MacLean SE, Gordon KE, Beattie TL. Brain activity and language assessment using event-related potentials: development of a clinical protocol. Dev Med Child Neurol 1999;41: 740–7.

Cant BR, Hume AL, Judson JA, Shaw NA. The assessment of severe head injury by short-latency somatosensory and brain-stem auditory evoked potentials. Electroenceph clin Neurophysiol 1986;65:188–95.

Choi D. Glutamate neurotoxicity and diseases of the nervous system. Neuron 1988;1:623–34.

Christman C, Grady S, Walker S, Holloway K, Povlishock J. Ultrastructural studies of diffuse axonal injury in humans. J Neurotrauma 1994;11: 173–86.

Connolly JF. Applying cognitive research in the twenty-first century: event-related potentials in assessment. Brain Cogn 2000;2:99–101.

Connolly JF, Major A, Allen S, D'Arcy RC. Performance on WISC-III and WAIS-R NI vocabulary subtests assessed with event-related brain potentials: an innovative method of assessment. J Clin Exp Neuropsychol 1999a;21:444–64.

Connolly JF, Mate-Kole CC, Joyce BM. Global aphasia: an innovative assessment approach. Arch Phys Med Rehabil 1999b;80:1309–15.

Cooper PR. Gunshot wounds of the brain. In: Cooper PR, editor. Head injury, 3rd ed. Philadelphia, PA: Williams and Wilkins; 1993. p. 355–71.

Cudmore LJ, Segalowitz SJ, Dywan J. EEG coherence shows altered frontal-parietal communication in mild TBI during a dual-task. Brain Cogn 2000;44:86–90.

Dacey RG, Vollmer D, Dikmen SS. Mild head injury. In: Cooper PR, editor. Head injury, 3rd ed. Philadelphia, PA: Williams and Wilkins; 1993. p. 159–82.

Denny-Brown D, Russell W. Experimental cerebral concussion. Brain 1941;64:93–164.

Diagnostic and statistical manual of mental disorders. 4th ed. Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.

Duhaime AC, Christian CW, Rorke LB, Zimmerman RA. Nonaccidental head injury in infants—the "shaken baby syndrome". N Engl J Med 1998;338:1822–9.

Dunham CM, Coates S, Cooper C. Compelling evidence for discretionary brain computed tomographic imaging in those patients with mild cognitive impairment after blunt trauma. J Trauma 1996; 41:679–86.

Dupuis F, Johnston KM, Lavoie M, Lepore F, Lassonde M. Concussions in athletes produce brain dysfunction as revealed by event-related potentials. NeuroReport 2000;11:4087–92.

Ellis E, Dodson L, Police R. Restoration of cerebrovascular responsiveness to hyperventilation by the oxygen radical scavenger *n*-acetylcystine following experimental traumatic brain injury. J Neurosurg 1991;75: 774–9.

Ellwanger J, Rosenfeld JP, Sweet JJ. P300 event-related brain potential as an index of recognition response to autobiographical and recently learned information in closed head injury patients. Clin Neuropsychol 1997;11:428–32.

Emmerling MR, Morganti-Kossmann MC, Kossmann T, Stahel PF, Watson MD, Evans LM, et al. Traumatic brain injury elevates the Alzheimer's amyloid peptide $A\beta_{42}$ in human CSF. Ann N Y Acad Sci 2002;903: 118–22.

Erb DE, Povlishock JT. Neuroplasticity following traumatic brain injury: a study of GABAergic terminal loss and recovery in the cat lateral vestibular nucleus. Exp Brain Res 1991;83:253–67.

Facco E, Munari M. The role of evoked potentials in severe head injury. Intensive Care Med 2000;26:998–1005.

Faden A, Demediuk P, Panter S, Vink R. The role of excitatory amino acids and NMDA receptors in traumatic brain injury. Science 1989;244: 798–800.

Fishman R. Brain edema. N Engl J Med 1975;293:706–11.

Foltz E, Schmidt R. The role of the reticular formation in the coma of head injury. J Neurosurg 1956;13:145–54.

Ford MR, Khalil M. Evoked potential findings in mild traumatic brain injury 1: middle latency component augmentation and cognitive component attenuation. J Head Trauma Rehabil 1996;11:1–15.

Gaetz M. An emerging role for event-related potentials in the assessment of brain injury. Clin Neurophysiol 2002;113:1665–6.

Gaetz M, Bernstein D. The current status of electrophysiologic procedures for the assessment of mild traumatic brain injury. J Head Trauma Rehabil 2001;16:386–405.

Gaetz M, Weinberg H. Electrophysiological indices of persistent post-concussion symptoms. Brain Inj 2000;14:815–32.

Gaetz M, Goodman D, Weinberg H. Electrophysiological evidence for the cumulative effects of concussion. Brain Inj 2000;14:1077–88.

Gennarelli TA. Mechanisms of brain injury. J Emerg Med 1993;11:5–11.

Gennarelli TA. The spectrum of traumatic injury. Neuropathol Appl Neurobiol 1996;22:509–13.

Gennarelli TA, Graham DI. Neuropathology of head injuries. Semin Clin Neuropsychiatry 1998;3:160–75.

Gennarelli TA, Thibault LE, Adams JH, Graham DI, Thompson CJ, Marcincin RP. Diffuse axonal injury and traumatic coma in the primate. Ann Neurol 1982;12:564–74.

Gennarelli TA, Thibault LE, Tipperman R, Tomei G, Sergot R, Brown M, et al. Axonal injury in the optic nerve: a model simulating diffuse axonal injury in the brain. J Neurosurg 1989;71:244–53.

Gentry L, Godersky J, Thompson B, Dunn V. Prospective comparative study of intermediate-field MR and CT in the evaluation of closed head trauma. Am J Radiol 1988;150:673–82.

Gieron MA, Korthals JK, Riggs CD. Diffuse axonal injury without direct head trauma and with delayed onset of coma. Pediatr Neurol 1998;19: 382–4.

Giza CC, Hovda DA. The neurometabolic cascade of concussion. J Athletic Training 2001;36:228–35.

Grady MS, McLaughlin MR, Christman CW, Valadka AB, Flinger CL, Povlishock JT. The use of antibodies targeted against the neurofilament subunits for the detection of diffuse axonal injury in humans. J Neuropathol Exp Neurol 1993;52:143–52.

Granovsky Y, Sprecher E, Hemli J, Yarnitsky D. P300 and stress in mild head injury patients. Electroenceph clin Neurophysiol 1998;108: 554–9.

Greenberg RP, Mayer JD, Becker DP, Miller JD. Evaluation of brain function in severe human head trauma with multimodality evoked potentials. Part 1: evoked brain injury potentials, methods and analysis. J Neurosurg 1977a;47:150–62.

Greenberg RP, Becker DP, Miller JD, Mayer DJ. Evaluation of brain function in severe human head trauma with multimodality evoked potentials. Part 2: localization of brain dysfunction and correlation with posttraumatic neurological conditions. J Neurosurg 1977b;47:163–77.

Gupta NK, Verma NP, Guidice MA, Kooi KA. Visual evoked response in head trauma: pattern shift stimulus. Neurology 1986;36:578–81.

Halgren E, Marinkovic K, Chauvel P. Generators of the late cognitive potentials in auditory and visual oddball tasks. Electroenceph clin Neurophysiol 1995;94:156–64.

Hammoud DA, Wasserman BA. Diffuse axonal injuries: pathophysiology and imaging. Neuroimaging Clin N Am 2002;12:205–16.

Hayes R, Dixon C. Neurochemical changes in mild head injury. Semin Neurol 1994;14:25–31.

Hayes RL, Pechura CM, Katayama Y, Povlishock JT, Giebel ML, Becker DP. Activation of pontine cholinergic sites implicated in unconsciousness following cerebral concussion in the cat. Science 1984; 223:301–3.

Henry GK, Gross HS, Herndon CA, Furst CJ. Nonimpact brain injury: neurobehavioral correlates with consideration of physiological findings. Appl Neuropsychol 2000;7:65–75.

Holbourn AHS. Mechanics of head injury. Lancet 1943;2:438–41.

Ingebrigtsen T, Romner B. Routine early CT-scan is cost saving after minor head injury. Acta Neurol Scand 1996;93:207–10.

Jane J, Steward O, Gennarelli T. Axonal degeneration induced by experimental noninvasive minor head injury. J Neurosurg 1985;62: 96–100.

Jenkins A, Teasdale G, Hadley M, MacPherson P, Rowan J. Brain lesions detected by magnetic resonance imaging in mild and severe head injuries. Lancet 1986;2:445–6.

Kallakuri S, Cavanaugh JM, Özaktay AC, Takebayashi T. The effect of varying impact energy on diffuse axonal injury in the rat brain: a preliminary study. Exp Brain Res 2003;148:419–24.

Kane NM, Curry SH, Rowlands CA, Manara AR, Lewis T, Moss T, et al. Event-related potentials—neurophysiological tools for predicting emergence and early outcome from traumatic coma. Intensive Care Med 1996;22:39–46.

Kontos C, Wei E, Williams J, Kontos H, Povlishock J. Cytochemical detection of superoxide in cerebral inflammation and ischemia in vivo. Am J Physiol 1992;263:H1234–42.

Lamarche M, Louvel J, Buser P, Rektor I. Intracerebral recordings of slow potentials in a contingent negative variation paradigm: an exploration in epileptic patients. Electroenceph clin Neurophysiol 1995;95:268–76.

LeBlanc KE. Concussion in sport: diagnosis, management, return to competition. Comp Ther 1999;25:39–44.

Leclercq PD, McKenzie JE, Graham DI, Gentleman SM. Axonal injury is accentuated in the caudal corpus callosum of head-injured patients. J Neurotrauma 2001;18:1–9.

Levin H, Williams D, Eisenberg H, High W, Guinto F. Serial MRI and neurobehavioral findings after mild to moderate closed head injury. J Neurol Neurosurg Psychiatry 1992;55:255–62.

Levin HS. Neurobehavioral sequalae of closed head injury. In: Cooper PR, editor. Head injury, 3rd ed. Philadelphia, PA: Williams and Wilkins; 1993. p. 525–51.

Levin HS, Mendelsohn D, Lilly MA, Yeakley J, Song J, Scheibel RS, et al. Magnetic resonance imaging in relation to functional outcome of pediatric closed head injury: a test of the Ommaya–Gennarelli model. Neurosurgery 1997;40:432–41.

Lindenberg R, Fisher R, Durlacher S, Lovitt W, Freytag E. Lesions of the corpus callosum following blunt mechanical trauma to the head. Am J Pathol 1955;31:297–318.

Livingston DH, Loder PA, Koziol J, Hunt CD. The use of CT scanning to triage patients requiring admission following minimal head injury. J Trauma 1991;31:483–9.

Livingston DH, Lavery RF, Passannante MR, Skurnick JH, Baker S, Fry DE, et al. Emergency department discharge of patients with a negative cranial computed tomography scan after minimal head injury. Ann Surg 2000;1:126–32.

Marchand Y, D'Arcy RCN, Connolly JF. Linking neurophysiological and neuropsychological measures for aphasia assessment. Clin Neurophysiol 2002;113:1715–22.

Marmarou A, Adb-Elfattah Foda MA, Brink WVD, Campbell J, Demetriadou K. A new model of diffuse brain injury in rats: Part I: pathophysiology and biomechanics. J Neurosurg 1994;80:291–300.

Maxwell W, Kansayra A, Graham D, Adams J, Gennarelli T. Freeze-fracture studies of reactive myelinated nerve fibres after diffuse axonal injury. Acta Neuropathol 1988;76:395–406.

Maxwell WL, Watt C, Graham DI, Gennarelli TA. Ultrastructural evidence of axonal shearing as a result of lateral acceleration of the head in non-human primates. Acta Neuropathol 1993;86:136–44.

Mazzini L, Pisano F, Zaccala M, Miscio G, Gareri F, Galante M. Somatosensory and motor evoked potentials at different stages of recovery from severe traumatic brain injury. Arch Phys Med Rehabil 1999;80:33–9.

Mittl R, Grossman R, Hiehle J, Hurst R, Kauder D, Gennarelli T, et al. Prevalence of MR evidence of diffuse axonal injury in patients with mild head injury and normal head CT findings. Am J Neuroradiol 1994; 15:1583–9.

Nelson C, Wei E, Povlishock J, Kontos H, Moskowitz M. Oxygen radicals in cerebral ischemia. Am J Physiol 1992;263:H1356–62.

Niess C, Grauel U, Toennes SW, Bratzke H. Incidence of axonal injury in human brain tissue. Acta Neuropathol 2002;104:79–84.

Nilsson P, Ronne-Engstrom E, Flink R, Ungerstedt U, Carlson H, Hillered L. Epileptic seizure activity in the acute phase following cortical impact trauma. Brain Res 1994;637:227–32.

Okonkwo DO, Pettus EH, Moroi J, Povlishock JT. Alteration of the neurofilament sidearm and its relation to neurofilament compaction occurring with traumatic axonal injury. Brain Res 1998;784:1–6.

Ommaya A, Gennarelli T. Cerebral concussion and traumatic unconsciousness: correlation of experimental and clinical observations on blunt head injuries. Brain 1974;97:633–54.

Onaya M. Neuropathological investigation of cerebral white matter lesions caused by closed head injury. Neuropathology 2002;22:243–51.

Oppenheimer D. Microscopic lesions of the brain following head injury. J Neurol Neurosurg Psychiatry 1968;31:299–306.

Parsons LC, Crosby LJ, Perlis M, Britt T, Jones P. Longitudinal sleep EEG power spectral analysis studies in adolescent with minor head injury. J Neurotrauma 1997;14:549–59.

Peerless S, Rewcastle N. Shear injuries of the brain. CMAJ 1967;96: 577–82.

Pettus E, Christman C, Giebel M, Povlishock J. Traumatically induced altered membrane permeability: its relationship to traumatically induced reactive axonal change. J Neurotrauma 1994;5:507–22.

Phillips LL, Lyeth BG, Hamm RJ, Povlishock JT. Combined fluid percussion brain injury and entorhinal cortical lesion: a model for

assessing the interaction between neuroexcitation and deafferentation. J Neurotrauma 1994;11:641–56.
Picton T, Stuss D. Neurobiology of conscious experience. Curr Opin Neurobiol 1994;4:256–65.
Pilz P. Axonal injury in head injury. Acta Neurochir Suppl (Wien) 1983;32: 119–23.
Postmanur RM, Newcomb JK, Kampfl A, Hayes RL. Light and confocal microscopic studies of evolutionary change in neurofilament proteins following cortical impact injury in the rat. Exp Neurol 2000;161: 15–26.
Povlishock J, Kontos H. The role of oxygen radicals in the pathobiology of traumatic brain injury. Hum Cell 1992;5:345–53.
Povlishock J, Hayes R, Michel M, McIntosh T. Workshop on animal models of traumatic brain injury. J Neurotrauma 1994;11:723–31.
Povlishock JT. Pathobiology of traumatically induced axonal injury in animals and man. Ann Emerg Med 1993;22:980–6.
Povlishock JT, Becker DP. Fate of reactive axonal swellings induced by head injury. Lab Invest 1985;52:540–52.
Povlishock JT, Becker DP, Cheng CLY, Vaughan GW. Axonal change in minor head injury. J Neuropathol Exp Neurol 1983;42:225–42.
Povlishock JT, Erb DE, Astruc J. Axonal response to traumatic brain injury reactive axonal change, deafferentation, and neuroplasticity. J Neurotrauma Suppl 1992;9:s189–s200.
Povlishock JT, Marmarou A, McIntosh T, Trojanowski JQ, Moroi J. Impact acceleration injury in the rat: evidence for focal axolemmal change and related neurofilament sidearm alteration. J Neuropathol Exp Neurol 1997;56:347–59.
Raghupathi R, Margulies SS. Traumatic axonal injury after closed head injury in the neonatal pig. J Neurotrauma 2002;19:843–53.
Rosenberg C, Wogensen K, Starr A. Auditory brain-stem and middle- and long latency evoked potentials in coma. Arch Neurol 1984;41:835–8.
Saatman KE, Graham DI, McIntosh TK. The neuronal cytoskeleton is at risk after mild and moderate brain injury. J Neurotrama 1998;15: 1047–58.
Sangal RB, Sangal JM. Closed head injury patients with mild cognitive complaints without neurological or psychiatric findings have abnormal visual P300 latencies. Biol Psychiatry 1996;39:305–7.
Satz P, Alfano MS, Light R, Morgenstern H, Zaucha K, Asarnow RF, et al. Persistent post-concussive syndrome: a proposed methodology and literature review to determine the effects, if any, of mild head and other bodily injury. J Clin Exp Neuropsychol 1999;21:620–8.
Schroder M, Muizelaar P, Bullock R, Salvant J, Povlishock J. Focal ischemia due to traumatic contusions documented by stable xenon-CT and ultrastructural studies. J Neurosurg 1995;82:966–71.
Schwartz JH. Synthesis and trafficking of neural proteins. In: Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science, 3rd ed. New York, NY: Elsevier; 1991. p. 49–65.
Shaw N. The neurophysiology of conscussion. Prog Neurobiol 2002;67: 281–344.
Shackford SR, Wald SL, Ross SS, Cogbill TH, Hoyt DB, Morris JA, et al. The clinical utility of computed tomographic scanning examination in the management of patients with minor head injuries. J Trauma 1992; 33:385–94.
Sieb R. A brain mechanism for attention. Med Hypotheses 1990;33: 145–53.
Slewa-Younan S, Green AM, Baguley IA, Felmingham KL, Haig A, Gordan E. Is "gamma" (40 Hz) synchronous activity disturbed in patients with traumatic brain injury? Clin Neurophysiol 2002;113: 1640–6.
Slobounov S, Sebastianelli W, Simon R. Neurophysiological and behavioural concomitants of mild brain injury in collegiate athletes. Clin Neurophysiol 2002;113:185–93.
Smith DH, Wolf JA, Lusardi TA, Lee VM-Y, Meaney DF. High tolerance and delayed elastic response of cultured axons to dynamic stretch injury. J Neurosci 1999a;19:4263–9.
Smith DH, Chen X-H, Nonaka M, Trojanowski JQ, Lee VM-Y, Saatman KE, et al. Accumulation of amyloid β and tau and the formation of neurofilament inclusions following diffuse brain injury in the pig. J Neuropathol Exp Neurol 1999b;58:982–92.
Soldner F, Hölper BM, Chone L, Wallenfang T. Evoked potentials in acute head injured patients with MRI-detected intracerebral lesions. Acta Neurochir (Wien) 2000;143:873–83.
Soustiel JF, Hafner H, Guilburd JN, Zaroor M, Levi L, Feinsod M. A physiological coma scale: grading of coma by combined use of brain-stem trigeminal and auditory evoked potentials and the Glasgow coma scale. Electroenceph clin Neurophysiol 1993;87:277–83.
Stein S, Ross S. The value of computed tomographic scans in patients with low-risk head injuries. Neurosurgery 1990;26:638–40.
Stewart-Amidei C. Assessing the comatose patient in the intensive care unit. AACN Clin Issues Crit Care Nurs 1991;2:613–22.
Strich S. Diffuse degeneration of the cerebral white matter in severe dementia following head injury. J Neurol Neurosurg Psychiatry 1956; 19:163–85.
Strich S. Shearing of nerve fibres as a cause of brain damage due to head injury. Lancet 1961;2:443–8.
Stone JR, Walker SA, Povlishock JT. The visualization of a new class of traumatically injured axons through the use of a modified method of microwave antigen retrieval. Acta Neuropathol 1999;97:335–45.
Stone JR, Singleton RH, Povlishock JT. Intra-axonal neurofilament compaction does not evoke axonal swelling in all traumatically injured axons. Exp Neurol 2001;172:320–31.
Stone JR, Okonkwo DO, Singleton RH, Mutlu LK, Helm GA, Povlishock JT. Caspase-3-mediated cleavage of amyloid precursor protein and formation of amyloid β peptide in traumatic brain injury. J Neurotrauma 2002;19:601–14.
Sutton R, Lescaudron L, Stein D. Unilateral cortical contusion injury in the rat: vascular disruption and temporal development of cortical necrosis. J Neurotrauma 1993;10:135–49.
Tebano MT, Cameroni M, Gallozzi G, Loizzo A, Palazzino G, Pezzini G, et al. EEG spectral analysis after minor head injury in man. Electroenceph clin Neurophysiol 1988;70:185–9.
Thatcher RW, Walker RA, Gerson I, Geisler FH. EEG discriminant analyses of mild head trauma. Electroenceph clin Neurophysiol 1989; 73:93–106.
Thatcher RW, Biver C, McAlaster R, Camacho M, Salazar A. Biophysical linkage between MRI and EEG amplitude in closed head injury. Neuroimage 1998a;7:352–67.
Thatcher RW, Biver C, McAlaster R, Salazar A. Biophysical linkage between MRI and EEG coherence in closed head injury. Neuroimage 1998b;8:307–26.
Thatcher RW, Biver C, Gomez JF, North D, Curtin R, Walker RA, et al. Estimation of the EEG power spectrum using MRI T2 relaxation time in traumatic brain injury. Clin Neurophysiol 2001a;112:1729–45.
Thatcher RW, North DM, Curtin RT, Walker RA, Biver CJ, Gomez JF, et al. An EEG severity index of traumatic brain injury. J Neuropsychiatry Clin Neurosci 2001b;13:77–87.
Thornton KE. Exploratory analysis: mild head injury, discriminant analysis with high frequency bands (32–64 Hz) under attentional activation conditions and does time heal? J Neurother 1999;Fall/Winter:1–10.
Turner B, Knapp M. Consciousness: a neurobiological approach. Integr Physiol Behav Sci 1995;30:151–6.
van Zomeren AH, Brower WH. Clinical neuropsychology of attention. New York, NY: Oxford University Press; 1994.
Varney NR, Varney RN. Brain injury without head injury. Some physics of automobile collisions with particular reference to brain injuries occurring without physical head trauma. Appl Neuropsychol 1995;2: 47–62.
Vespa PM, Boscardin WJ, Hovda DA, McArthur DL, Nuwer MC, Martin NA, et al. Early and persistent impaired percent alpha variability on continuous electroencephalography monitoring as predictive of poor outcome after traumatic brain injury. J Neurosurg 2002;97:84–92.
Wahl M, Schilling L. Regulation of blood flow—a brief review. Acta Neurochir (Suppl) 1993;59:3–10.

Ward AA. The physiological basis of concussion. J Neurosurg 1958;15: 129–34.

Ward AA. The physiology of concussion. In: Caveness WF, Walker AE, editors. Proceedings of the Conference on Head Injury. Philadelphia, PA: Lippincott; 1966. p. 203–8.

Watson MR, Fenton GW, McClelland RJ, Lumsden J, Headley M, Rutherford WH. The post-concussional state: neurophysiological aspects. Br J Psychiatry 1995;167:514–21.

Wilson JTS, Wiedmann KD, Hadley DM, Condon B, Teasdale G, Brooks DN. Early and late magnetic resonance imaging and neuropsychological outcome after head injury. J Neurol Neurosurg Psychiatry 1988;51:391–6.

Wolf JA, Stys PK, Lusardi T, Meaney DH, Smith DH. Traumatic axonal injury induces calcium influx modulated by tetrodotoxin sodium channels. J Neurosci 2001;21:1923–30.

Yaghmai A, Povlishock J. Traumatically induced reactive change as visualized through the use of monoclonal antibodies targeted to the neurofilament subunits. J Neuropathol Exp Neurol 1992;51:158–76.

Young RJ, Destian S. Imaging of traumatic intracranial hemorrhage. Neuroimaging Clin N Am 2002;12:189–204.