FATIGUE FOLLOWING BRAIN INJURY

Author: Jennie Ponsford

Introduction
A significant proportion of people with brain injury (32-73%) reportedly experience fatigue (1, 2). Whereas fatigue resolves within days or weeks for most people with mild injuries, it can persist over many years following moderate to severe injuries and impact negatively on participation in numerous activities, including work, study, leisure and social pursuits. Despite its common occurrence, causes of fatigue are not well understood and there are no established treatments.

Defining fatigue
Fatigue is subjective and is experienced by everyone. There are no established methods of measuring it. Aaronson and colleagues (3) define fatigue as “The awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity” (p. 46). Resources
may be physiological or psychological. At a physiological level, fatigue may be caused by loss of energy, hormones, neurotransmitters or neural connections, due to brain injury. This type of fatigue results directly from the injury. Fatigue may also be associated with muscle weakness or injuries in the peripheral nervous system. This type of fatigue may be assessed using motor tasks, such as grip strength, thumb pressing or speed of finger tapping. However, these are not sensitive to fatigue originating in the central nervous system, such as occurs with a brain injury. Psychological fatigue is defined as, “A state of weariness related to reduced motivation, prolonged mental activity, or boredom that occurs in situations such as chronic stress, anxiety or depression.”(4) (p.291). As depression and anxiety are commonly associated with TBI, it is important to consider this aspect of fatigue.

**Causes of fatigue**

Fatigue is commonly associated with neuronal injury or dysfunction in conditions such as TBI and multiple sclerosis (MS). Fatigue caused by injury or disease is termed **Primary fatigue** (5). Various factors may exacerbate fatigue, including pain, sleep disturbance or stress. Fatigue due to these factors is termed **Secondary fatigue** (5). Fatigue may be a symptom of depression and depression may result in early morning wakening. Anxiety may also disturb sleep, more commonly resulting in difficulty falling asleep. Emotional distress may thereby contribute to sleep disturbances and exacerbate fatigue. Fatigue following brain injury is most probably caused by any or all of these influences.

**Measuring fatigue**

There is no single valid and reliable fatigue assessment measure. Scales have been developed for assessment of fatigue in particular health conditions, including cancer and Multiple Sclerosis. These scales assess fatigue from a number of perspectives: its severity, its impact on lifestyle and associated emotional effects. Aaronson et al. (3) have recommended that each of these aspects of fatigue be assessed, as well as associated secondary factors such as sleep or depression and biological parameters. Most measures of fatigue are self-report measures. Measures used in studies of people with TBI have included: the **Visual Analogue Scale for Fatigue (VAS-F)** (4) which subjectively quantifies of fatigue and energy levels on a likert scale at one point in time; The **Fatigue Severity Scale (FSS)** (6), a 9-item general fatigue scale used to assess the consequences of fatigue and its impact on daily functioning on a 7-point scale; the **Barrow Neurological Institute Fatigue Scale (BNI Fatigue Scale)** (7), which comprises 10 items, relating to daily levels of energy and alertness and the **Global Fatigue Index (GFI)** (8), derived from 15 of 16 items of the Multidimensional Assessment of fatigue (MAF). No studies have succeeded in identifying an objective measure of fatigue. Physical tests, such as a thumb pressing task, have not been shown to be sensitive to fatigue in people with brain injuries (9). Other studies examining performance on complex cognitive tasks over time have found that whilst level of performance may be lowered by presence of subjective fatigue, performance did not decline over time more in people with brain injury than healthy controls (10, 11). Whilst
such group findings may mask individual differences, the search for an “objective”
measure of fatigue continues.

**What causes fatigue?**

Whilst severity of self-reported fatigue following brain injury has not been closely
associated with the age of the person, it has been related to higher education and some
research has suggested females may report greater impact of fatigue on their lifestyle,
perhaps related to their tendency to show lower mood (2, 12).

Fatigue is thought to be caused by diffuse axonal injury, and particularly injury in brain
regions which regulate arousal, attention and speed of response, including the ascending
reticular activating system, limbic system, anterior cingulate, middle frontal and basal
ganglia areas (13). Due to the presence of impairments of speed of information
processing, attention, memory and executive function performance of mentally demanding
tasks is more effortful for many people with brain injury, which find most cognitively
demanding tasks more effortful.

It has been suggested that fatigue results from the increased effort needed to keep up with
complex everyday demands in the presence of impaired attention, processing speed and
other cognitive functions. Fatigue levels are related to severity of attentional problems.
Moreover whilst people with brain injury may be able to maintain task performance over
time, this is associated with a disproportional increase in blood pressure, consistent with
greater effort, and this is associated with fatigue levels, and subsequent emotional distress
(11).

Self-reported fatigue has not been shown to be related to severity of injury (2, 12) or
general cognitive impairment. Fatigue levels may decline somewhat in the first 6-12
months post-injury but thereafter plateau out or rise further over time (2, 14). There
is variability in the patterns and time-course of fatigue over time. Whilst it would be
reasonable to assume that increasing fatigue over time may be associated with increased
activity levels, there is no demonstrated association of fatigue with employment status (2,
12) or other major life activities (1). However, the most impaired individuals are also least
likely to be employed, and there have been no studies systematically examining the impact
of increased lifestyle demands on fatigue. Increasing fatigue may also reflect growing
emotional distress, with increasing experience of functional limitations over time.
Therefore, fatigue levels are likely to be determined by a combination of functional
impairment and disability, lifestyle demands and emotional distress.

It has also been suggested that neuroendocrine abnormalities, such as Growth Hormone
deficiency (GHD), present in many people with brain injury, may underpin fatigue.
However, there has been no evidence to support this (15). Baumann and colleagues (16)
have argued that fatigue is caused by lower levels of the wake-promoting neurotransmitter
CSF Hypocretin-1, caused by loss of hypocretin neurons. This may cause daytime
sleepiness.
Secondary causes of fatigue

There is has been no established relationship between fatigue and the presence of orthopaedic injuries. Moreover whilst the taking of medication is not related to greater the impact of fatigue on daily lifestyle, there is a modest association between the experience of fatigue levels at a given point in time and the taking of analgesic medication (2). Pain levels are significantly related to subjective fatigue (1, 2, 15). Depression and anxiety are also strongly associated with self-reported fatigue in individuals with brain injury (1, 2, 15). The direction of this association remains somewhat unclear. Fatigue is known to be a symptom of depression, but it may also be that the experience of fatigue over an extended period of time may result in the development of depression and anxiety. We (17) found that presence of fatigue was significantly associated with presence of depression six months later, whereas depression was not associated with the subsequent reporting of fatigue. Cantor and colleagues (1) also found that secondary factors accounted for a higher proportion of variance in fatigue in healthy controls than in individuals with brain injury, suggesting that the injury itself may make a unique contribution to fatigue.

Increased levels of self-reported fatigue have also been associated with poor sleep quality or sleep disturbances in a number of studies (1, 2). This suggests that sleep problems, which are reported by 30 to 80 percent of individuals with TBI (18) may contribute to fatigue. Reported sleep complaints following TBI include insomnia, hypersomnia and excessive daytime sleepiness. Excessive daytime sleepiness (EDS) is manifested as tiredness or drowsiness during the daytime after insufficient sleep or sleep disruption. People with EDS commonly feel the need to nap when they want to be awake. There is a theoretical distinction between EDS and fatigue, although in practice individuals with brain injury may not differentiate between the symptoms.

Treating fatigue

In assessing patients with brain injury who report fatigue, clinicians should investigate all potential contributing factors, including cognitive factors such as attention and processing speed, sedating effects of medications, pain, emotional state, and sleep disturbances, and apply necessary treatments. Adjustments may be made to the individual’s lifestyle to allow for cognitive and physical limitations. This may involve reducing work hours, modifying the pace or demands of activities, reducing distraction and need for multi-tasking, and/or taking frequent rest breaks. Addressing psychological issues related to such lifestyle changes may be necessary. Where there is sufficient self-awareness, strategies may be developed to manage information overload and associated social difficulties in a range of situations. Physical conditioning programs can reduce physical fatigue and promote well-being, although they are not likely to alleviate fatigue arising from central nervous system injury. Where sleep disturbance is reported it is important to have this objectively evaluated, as subjective reports may not accurately identify the source of the problem. Potential causes of sleep problems, such as pain, anxiety or depression need to assessed and treated as necessary. Instruction in sleep hygiene techniques, including avoidance of naps if this interferes with nighttime sleep, adhering to a regular
schedule of time spent in bed, and avoiding time spent in bed awake may be provided along the lines described by Ouellet and Morin (19), who have demonstrated in a case series that such techniques can be effective in individuals with TBI.

Modafinil is a wake-promoting drug approved in the United States for treating excessive sleepiness associated with narcolepsy, obstructive sleep apnoea and shift work disorder. It has been used in the treatment of fatigue in individuals with multiple sclerosis and TBI. Randomized controlled trials have shown no impact on subjective fatigue in individuals with TBI, but some evidence of reduced daytime sleepiness (20) (21).

Bright Light Therapy also presents a potential treatment for fatigue and daytime sleepiness. Light exerts non-visual effects on many biological functions. In healthy and patient populations light exposure results in reduced sleepiness, has arousing effects on a number of biological parameters, increases vigilance performance, and can improve mood. A pilot trial by our research group found a reduction in subjective fatigue and sleepiness during daily exposure to short wavelength light (22). This research is continuing.

Conclusions
Fatigue and sleep disturbance are common and persistent problems following brain injury. Fatigue and its impact on daily lifestyle may be assessed using a number of measures. Studies suggest that fatigue may be associated with impaired attention and information processing speed, necessitating greater effort in performing tasks. Thus assessment of these aspects of cognitive function is important. It may also be associated with depression, anxiety, and pain, which also require assessment, although the directions of these associations remain unclear. Sleep disturbances are also commonly reported and these contribute to fatigue. It is important to assess for and treat anxiety, depression, pain and sleep disturbances. The injured person may be supported in making modifications to their lifestyle and daily activities to enable them to more effectively live within their cognitive and physical limitations. Sleep hygiene techniques may assist in minimising sleep disturbance. There is some preliminary evidence that Modafinil may reduce daytime sleepiness. Of non-pharmacological interventions light therapy holds promise as a means of increasing daytime alertness, as well as enhancing vigilance and mood. Further controlled trials of all of these interventions are needed.

References


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EXAMINATION OF BRAIN INJURY THRESHOLDS IN TERMS OF THE SEVERITY
OF HEAD MOTION AND THE BRAIN STRESSES

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Introduction

Human head injuries occur due to many causes including falls, car accidents, sports, and physical assaults. According to the Center for Disease Control and Prevention (CDCP), each year in the United States (US), as many as 300,000 mild traumatic brain injuries (mTBI) occur due to sports.1 Although clinical data from such incidents is usually considered to be the prime source of information regarding the injury, biomechanical simulations for such incidents can reproduce data for injury protection. The brain injury thresholds in a biomechanical analysis are set in terms of the severity index (SI), or head impact criteria (HIC), which, in turn, are measured in terms of the linear accelerations of the head under an assault. The severity of the motion, including its acceleration, can be a good indicator of the cause of any failure or injury. The size of the inflicted stresses/strains is, however, a step further in the detection of any failure or injury. Thresholds, in terms of intracranial pressure (ICP) and shear stresses (the external force that acts on an object parallel to the plane in which it lies) and strains (over twisting and stretching), have also been documented in the literature.2

Although such criteria cannot be tested, or set at a unique value due to many uncompromised parameters, the severity of each threshold can be challenged in biomedical simulations of a human head model. Researchers have carried out various experiments of simulating assaults on surrogated heads to relate the injury to head kinematics (movement analysis) of the motion. While such efforts are always valuable, more concentration needs to be placed on brain stresses and strains as primary causes of injury. Nahum et al.,3 Hardy et al.,4 Troseille et al.7 carried out several impact scenarios on human cadaver heads to measured ICP of the brain, as well as acceleration of the head. Numerical methods and, in particular, finite element (FE) simulations, have been successful techniques for biomechanical analysis of the brain under various types of loading and they give remarkable insight into what happens to the brain in those situations. Several studies that have determined the mechanical responses of brain tissue under impact and blast loading conditions can be referenced.8–10

Injury criterion is necessary for safety, training, protection, and design of safety equipment. The definition of various injury criteria, highlighting the injury thresholds, has had positive effects on reducing the severity of injuries and mortalities. The Wayne State Tolerance Curve (WSTC) was introduced by Gurdjian et al.11 as a human head tolerance limit indicator. The WSTC assumes that the fracture tolerance of the skull is equivalent to the tolerance of the brain injury. Gadd12 introduced the Severity Index (SI), based on the WSTC, by integrating the linear acceleration raised to the power of 2.5. The HIC was then introduced by the US National Highway Traffic Safety Administration (NHTSA) as an alternative formulation of the SI.13 The HIC is often used in the diagnoses of traumatic brain injuries (TBIs). The major limitation of both the HIC and the SI is that they do not take the rotational acceleration/angular acceleration (quantitative expression of the angular velocity change that occurs to a spinning object per unit time) into account. The Abbreviated Injury Scale (AIS) was introduced by the Association for the Advancement of Automotive Medicine (AAAM) as an anatomically-based coding system to classify, and describe, the severity of specific individual injuries. AIS codes range from 0 (no injury) to 6 (fatal injury).11 There are also a number of criteria that include the effect of rotational/angular accelerations.14–16 The injury thresholds, in terms of stresses/strains and ICPs, have not
ICP causes volume change while shear stress distorts and deforms the brain tissue. Some suggested values for brain injury threshold strains and stresses are given as: ICP > 235 kPa = severe or fatal injury and ICP < 173 kPa = minor or no injury; strain > 0.2 injury; and shear stress 11 to 16.6 kPa = injury. In this paper, comparisons have been made between SI, the resultant head acceleration, brain ICP, and shear stresses when a human head falls and strikes with a rigid wall from the occipital side at different speeds. It is concluded that these thresholds are correlated.

Table 1. Correlations between accelerations and AIS levels

<table>
<thead>
<tr>
<th>Max linear acceleration</th>
<th>AIS level</th>
<th>Injury description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50g</td>
<td>0</td>
<td>No injury</td>
</tr>
<tr>
<td>50-100g</td>
<td>1</td>
<td>Minor</td>
</tr>
<tr>
<td>100-150g</td>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>150-200g</td>
<td>3</td>
<td>Serious</td>
</tr>
<tr>
<td>200-250g</td>
<td>4</td>
<td>Severe</td>
</tr>
<tr>
<td>250-300</td>
<td>5</td>
<td>Critical</td>
</tr>
<tr>
<td>&gt;300g</td>
<td>6</td>
<td>Non-survivable</td>
</tr>
</tbody>
</table>

FE Modeling of the Human Head

The size and geometry of a 50th percentile deformable finite element head model (FEHM) (a FEHM is a model being discretized into several simple-shaped elements so that their related mathematical equations can be easily and accurately solved and implemented for the whole complex structure). The FEHM is derived from a Magnetic Resonance Tomography (MRT) method adapted from Horgan and Gilchrist. While the FEHM is clinically simplistic, it consists of the essential parts of the head anatomy including the scalp, skull, pia mater, dura mater, cerebral spinal fluid (CSF), tentorium, falk, and brain that can all act, mechanically, as a real human brain (Figure 1(a)). Materially, the brain of the FEHM is assumed to be a viscoelastic substance—a substance that displays elasticity and viscosity, or resistance of the fluid to flow, and that resists applied forces in a time-dependent manner—and its constants have been obtained by Ruan et al. The mechanical properties for CSF of the FEHM is derived from the research of Kleiven and Hardy. The rest of the components are assumed to have linear elastic response. To properly, and accurately, model the interactions of the different parts, when the head experiences different types of loading conditions, or kinematical motions, appropriate contact conditions are defined between different elements of the head and brain.

Figure 1. (a) Human head model and its components; (b) computational ICP which is justified by the experimental data
Validation of Human Head Impact

In all computational simulations, validation is of great importance because it indicates the credibility of the results. The FEHM in this study has been validated, several times, under impact loads. Originally Horgan and Gilchrist\(^1\) verified it against different commonly referenced cadaveric experiments.\(^2\)–\(^4\) In the modeling process, the authors of this paper examined and validated the FEHM with an experiment of Nahum et al.\(^2\) In the experiment, a cylindrical mass, with a weight of 5.59 kg and a speed of 9.94 m/s, impacted the head which was inclined 45 degrees from the brain Frankfort plane. The results of computational replication of the impact scenario that monitor ICP are shown in Figure 1(b). The close agreement of the results against the cadaver experiment meets the requirements for the simulation.

Figure 2. (a) Resultant accelerations of the head; (b) Variation of ICPs; and (c) Shear stress on the brain, at four impact speeds
Biomechanical Data due to Impact

In the study presented here, the head was assumed to hit the wall with the velocities of 1, 2, 3 and 5 m/s. In Figure 2(a), the accelerations of the head were monitored and illustrated for different impact scenarios. When the speed was increased, the acceleration increased dramatically. At the speed of 1 m/s, the acceleration of the head was less than 50g. Table 1 shows the comparisons and correlations of the linear acceleration with AIS levels. When the speed increased to 2 m/s, the head was under an acceleration of about 140g which is the vicinity of moderate injury. This can also be supported by previous studies that have found the acceleration of 98g is the risk of mild concussion in football players. At the speed of 3 m/s, the acceleration went beyond 220g, causing severe head injury (AIS 4+). HIC values can be better representatives of the injury than acceleration as they include the size, as well as the duration of acceleration. The corresponding HIC values for the three scenarios were calculated as 196.4, 363.8, 705.3, and 1939, all in terms of g, respectively. As indicated, the impact at 3 m/s created HIC of more than 700 which is in the region of high risk and severe brain injury. At 5 m/s, the maximum acceleration and the corresponding HIC value confirmed that fatal injury would occur.

At the tissue level, ICP rapidly changes over time due to the relative motion of the brain, with respect to the skull. This relative motion creates positive and negative pressures in the coup and contrecoup sites of the brain. In this study, the variations of ICPs were collected from an area of the occipital lobe and are demonstrated in Figure 2(b). Likewise, the acceleration changed and the value of the ICP increased as the velocity of the head increased. The duration of the ICP elevation, however, became shorter. For these specific case studies, the ICPs changed from 47 to 276 kPa when the impact velocity of the head varied from 1 to 5 m/s. This correlation indicates that when the ICP goes up to about 191 kPa, the HIC is almost 700, which is the threshold of brain injury. The value of 191 kPa is in between the ICP range proposed by Ward et al. and this verifies the accuracy of the computational studies. At the maximum speed of 5 m/s, the ICP threshold clearly indicated a non-survivable injury. The collected results of accelerations, ICPs, and HICs are shown in Table 2 and can be compared, and correlated, to each other.

<table>
<thead>
<tr>
<th>Speed of impact (m/s)</th>
<th>Acceleration (g)</th>
<th>ICP (kPa)</th>
<th>Shear stress (kPa)</th>
<th>HIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62.1</td>
<td>47.4</td>
<td>3.71</td>
<td>196.1</td>
</tr>
<tr>
<td>2</td>
<td>140.3</td>
<td>137.3</td>
<td>9.31</td>
<td>363.8</td>
</tr>
<tr>
<td>3</td>
<td>222.3</td>
<td>191.1</td>
<td>14.05</td>
<td>705.3</td>
</tr>
<tr>
<td>5</td>
<td>317.07</td>
<td>276.14</td>
<td>25.64</td>
<td>1939</td>
</tr>
</tbody>
</table>

A similar response and correlation can be seen in the behavior of brain tissue shear stress as depicted in Figure 2(c): At 1 m/s no injury is expected. Based on the thresholds proposed by Kang et al. at speeds of 2 and 3 m/s, however, the shear stresses are 9.3 and 14.05 kPa, respectively, estimating the probabilities of mild and severe injuries. At speed of 5 m/s, the shear stress is considerably larger than 16 kPa (brain tolerance) and fatal injury occurs. The data of shear stress can clearly predict the occurrence of injury.

Conclusion
In this paper, a computational study of a head impact with a rigid surface has been presented. Kinematical and biomechanical data from a validated head model were collected for several head impact scenarios. With the velocity of impact ranging from 1 to 5 m/s, the acceleration of the head changed from 62g to 317g, respectively. The HIC scores of the impact indicated the risk of severe injury for velocities higher than 3 m/s. ICP variations were also measured as important injury-related parameters and were compared and correlated with acceleration and HICs. The ICP varied from 47 to 276 kPa and, acceptably, explained the level of injuries. The response of the brain in terms of shear stress also showed similar correlations. The study showed correlations of the injury thresholds.

Reference
SIMULATION AND CLINICAL ASSESSMENT OF BLAST-INDUCED TRAUMATIC BRAIN INJURY

Authors: Paul A. Taylor, John S. Ludwigsen, Andrei A. Vakhtin, Corey C. Ford

Introduction
Recent combat statistics report that over 267,000 US soldiers deployed in Iraq and Afghanistan have sustained traumatic brain injury (TBI), with over 48,000 of those categorized at the moderate-to-severe level, 69% caused by blast exposure [1–3]. The principal source of these brain injuries was one or more encounters with the blast wave produced by a detonated improvised explosive device (IED). Primary blast injury is associated with direct exposure of the head and body to the blast wave without other blunt injury mechanisms [4]. The role of direct or primary blast exposure in the development of TBI is not well understood and has been the focus of our research.
Modeling and simulation-based investigations into the causal relationship between explosive blast and TBI have recently begun to appear in the literature [5–7]. In an earlier study [6], we identified the presence of blast-induced, early-time stress waves that occur within the brain well before the onset of any head motion. These studies also revealed the need for a more complete head model to better define the important structures of the brain.

In response, we developed a high resolution, head-neck model and simulated the effects of blast direction on intracranial stress waves and the deposition of wave energy [8]. We also investigated a group of veterans with mild TBI (mTBI), whose injury scenarios were primarily limited to blast exposure [9]. Our goal was to establish correlations between simulation predictions of intracranial wave energy deposition and the brain injury observed in these subjects. The next step would be to construct a brain injury threshold criterion to define the limits of wave physics variables (e.g., stress or energy maxima) that would lead to brain injury. A modeling and simulation (M&S) approach, in conjunction with a brain injury threshold criterion, would facilitate investigations of the mechanisms of blast-induced brain injury and provide the means to assess helmet design effectiveness and strategies to protect against blast induced brain injury.

Modeling and Simulation

We constructed a virtual head-neck model based on the National Library of Medicine’s Visible Human dataset [10]. The model possesses anatomically correct distributions of bone, white and gray brain matter, falx and tentorium, cerebral spinal fluid (CSF), and muscle-scalp (see Figure 1). Anatomical details of the model are defined at a 1 mm resolution. Constituent material properties are defined for bone, white and gray matter, membranes, cerebral spinal fluid, and muscle-scalp. All constitutive model descriptions for our bio-materials have been reported in detail in a separate article [8]. We assigned a non-linear equation-of-state representation for dry air, specifically designed for shock wave simulations [11].

![Image of head-neck model](image)

Figure 1

*Figure 1. Head-neck model. Top row: front, rear, and left side views. Bottom row: coronal, axial, and mid-sagittal cuts displaying internal structure.*

We use two simulation methods, each chosen for its ability to capture the relevant physics of the injury scenario under investigation. Blast simulations are performed using the shock wave physics code CTH [12], and for blunt impact, we employ the transient dynamics code PRESTO [13]. PRESTO was also used to validate the head-neck model by simulating the magnetic resonance tagging experiments of Sabet et al. [14] and Feng et al. [15].
Simulations of direct blast exposure to the unprotected head were performed to study the effects of both the blast magnitude and direction (Figure 2). Localized brain injury may correlate with one or more of three possible stress wave energy quantities: isotropic compressive energy (ICE), isotropic tensile energy (ITE), and deviatoric shear energy (DSE).

![Figure 2](image)

Figure 2. Stop-action plots of blast-generated pressure waves propagating through the head model from the front (left image), rear (center image), and lateral (right image) directions.

Brain tissue is infused with a significant amount of fluid and therefore is essentially incompressible; however, ITE could result in cavitation if local fluid pressure is reduced to partial vacuum levels. Fluid could undergo a phase transformation from liquid to vapor initiating bubble formation. When these bubbles collapse they could generate micro-shock wavelets that are thought to cause tissue damage in the vicinity of the collapse [16–18]. DSE is thought to cause tissue damage as a result of axonal membrane tearing and cytoskeletal disruption [19,20]. Figure 3 displays maximum predicted levels of these energy terms for a 360 KPa blast wave directed at the head from the rear. Although ICE has, thus far, not been associated with brain injury, it is plotted in Figure 3 for completeness.
A significant unexpected finding in the simulations was the prediction of independence of ITE and DSE deposition on blast direction [8]. Deposition of these two energy quantities occurred in the same regions of the brain with the same magnitudes regardless of the blast direction (front, rear, or side). This result suggests that it is not necessary to take blast direction into account, an important result for the designers of protective headgear.

**Clinical Assessment of TBI**

We conducted functional magnetic resonance image (fMRI) studies on 13 combat veterans, who were diagnosed with mTBI. These veterans were given a battery of 12 neuropsychological tests. Their averaged t-scores defined a Gaussian distribution with a mean of 44, 6 points below normal controls [9]. The mTBI subjects demonstrated statistically significant deficits in tasks measuring attention and processing speed.
We then applied independent component analysis (ICA) to resting state fMRI data, which has shown potential to be more sensitive to small individual differences than conventional fMRI analyses [21–23]. Using ICA, temporal correlations between multiple brain regions can be examined [21]. These techniques allow detection of brain networks associated with attention, vision, motion, hearing, and other functions.

We compared our mTBI group and a cohort of normal controls taken from an extensive dataset of normal controls presented by Calhoun et al. [24] and Erhardt et al. [25]. A large fMRI study was presented by Allen et al. [26], who identified 28 independent resting state networks in a large sample of over 600 normal subjects. These 28 independent components were categorized into 7 resting state network groups: sensory-motor, attentional, visual, frontal, auditory, basal ganglia, and default mode, all of which were identified in our mTBI subjects.

Three main aspects of the ICA components can be tested [27]. A time course spectra analysis allows examination of differences in the power of specific blood oxygenation level-dependent (BOLD) signal frequencies between groups. This has the potential to identify abnormalities in specific brain networks. Cross correlation between component time courses defines functional network connectivity (FNC) between specific brain regions that may be functionally disrupted by injury. Abnormal FNC has the potential to explain cognitive impairments observed in TBI subjects and suggests where investigations of specific white matter tracts connecting these regions should be focused using techniques such as diffusion tensor imaging (DTI).

The details of this approach are reported elsewhere [9] and briefly summarized here. ICA identified significant spatial map differences in the mTBI group’s frontal and visual networks. The mTBI group displayed higher activity in bilateral temporoparietal junctions (visual network) and lower activity in the left inferior temporal lobe (frontal network) relative to controls (Figure 4). Time course spectra between mTBI and control groups were significantly different in the attentional, frontal, and default mode networks. Lastly, FNC in the mTBI group was impaired in 6 network pairs relative to controls. FNC differences were detected between attentional-sensorimotor, attentional-frontal, frontal-default mode, default mode-basal ganglia, and sensorimotor-sensorimotor network pairs.
Although these studies involved a small subject group, our interpretation of the results is that healthy hyperactive regions of the brain may be working overtime to compensate for functionally disconnected or damaged regions. The two regions that appear to be involved include the ventral and dorsal streams of visual processing. This fits with neuropsychological results showing impairments in attention and processing speed in mTBI subjects.

**Correlation of Simulation Prediction and Clinical Outcomes**

A major goal in our work is to establish a correlation between simulation predictions of selected wave physics variables, and the presence of localized brain injury. We were able to qualitatively compare simulation predictions with clinical results to see what spatial overlap may exist between regions of predicted wave energy deposition and spatial maps of altered functional network activity.

Figure 5 shows locations of hyper- and hypo-active regions, identified by our analysis of the mTBI group, overlaid on our prediction of blast-induced deviatoric shear energy deposition. Figures 5(a)-(c) show the hyperactive brain regions of our mTBI group residing in areas predicted to receive low levels of deviatoric shear energy. It is possible that hyperactive regions could be compensating for other regions to which they are connected. Conversely, Figures 5(d)-(f) show the hypactive region to reside in a region of the brain that sustained elevated levels of deviatoric shear energy. This suggests that deviatoric shear energy deposition may be associated with local brain injury.
Conclusion
We have established a viable modeling and simulation capability with which to investigate traumatic brain injury from blast and blunt force impact. Our results predict that for blast-induced TBI, important metrics of intracranial wave motion may be independent of blast direction. This result should reduce the complexities of correlating simulation results with clinical measures of TBI and of creating new designs of head protection gear.

We have attempted to correlate simulation predictions of brain injury with clinical measures of blast-induced mTBI. Although our results are encouraging, we do not suggest that any definitive correlation exists at this point in time. Although this is a goal that we strive to achieve, there is much more work to perform before such an accomplishment can be realized.

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MILD TRAUMATIC BRAIN INJURIES WERE PREVIOUSLY UNDIAGNOSABLE, AND THEREFORE TREATMENT UNCERTAIN, AND DAMAGES SPECULATIVE

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Introduction

Every year, an estimated 1.5 million individuals sustain a traumatic brain injury (TBI), and approximately 75% of these are classified as a mild TBI [1,2]. The American Congress of Rehabilitation Medicine defines a
mild traumatic brain injury as a patient “who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following:

1. any period of loss of consciousness;
2. any loss of memory for events immediately before or after the accident;
3. any alteration in mental state at the time of the accident (eg, feeling dazed, disoriented, or confused); and
4. focal neurological deficit(s) that may or may not be transient;

but where the severity of the injury does not exceed the following:

- loss of consciousness approximately 30 minutes or less;
- after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13-15; and
- post-traumatic amnesia (PTA) not greater than 24 hours.’[3]

Mild TBI has been termed a “silent epidemic,” [4] because many patients do not have visible physical signs. Rather, many patients possess disabling cognitive, psychological, and/or behavioral impairments and employment disabilities that are often unnoticed or misdiagnosed. Individuals seeking medical attention generally receive a standard history and physical exam. Further imaging such as a head Computerized Tomography (CT) or possibly Magnetic Resonance Imaging (MRI) will usually be obtained if the patient has loss of consciousness, posttraumatic amnesia, focal neurological deficits, physical signs of a skull fracture, or was involved in a dangerous mechanism of injury, or are older than the age of 65 [5]. The current diagnostic tests are neither sensitive nor specific enough to identify individuals who have sustained a mild TBI [6-8]. Individuals therefore may not be receiving the proper diagnosis, and without a diagnosis, it is difficult to provide precise and appropriate clinical management. Accurate diagnosis would also be of immense assistance in distinguishing those that truly suffer from mild TBI sequelae as opposed to those with malingering symptoms [9].

Emerging research in imaging tests and serum biomarkers appear to assist with a more accurate diagnosis of mild TBI [6-8]. These imaging tests are better at identifying microstructural damage like diffuse axonal injury (DAI) and small hemorrhages that occurs in mild TBI [10]. The biomarkers are specific proteins released after injury [11]; which include: S100B, Neuron Specific Enolase (NSE), and Cleaved -Tau Protein (CTP) [8]. S100B has the most promising research at this time and could be a potential screening tool with its increased sensitivity for identifying mild TBI [5,12].

Considering the number of individuals that sustain a mild TBI, and the cost of lost productivity associated with this problem, it is important to establish a diagnosis of mild TBI in order to appropriately treat those most affected by the injury. We propose individuals that are medically evaluated for mild TBI receive a standard history and physical exam combined with newer imaging tests, along with serum biomarkers to provide a precise and timely diagnosis of mild TBI. These measures will help ensure appropriate treatment to be initiated and payors be identified.

**Imaging**

The current difficulty in the definitive diagnosis of mild TBI can be partly attributed to the fact that when patients are evaluated with imaging tests, it is done with CT or MRI, which are mainly aimed at identifying macroscopic lesions. However, these conventional imaging tests are limited in their capacity to assess microscopic white matter injury associated with DAI. DAI is caused by acceleration and deceleration forces or rotation forces acting on the head, leading to shearing of the brain tissue [13]. Only a small percentage of patients with mild TBI demonstrate visible pathology such as fractures, contusions, and hemorrhages on head CT. In a review study that examined 4000 patients, 5-10% of mild TBI patients with a GCS score of 15 had an
abnormal head CT [7]. In a similar study by Harad et al. only 20-30% of patients with initial GCS score of 13 had an abnormal head CT. [14]. Standard MRI has improved detection of small hemorrhages, herniation, midline shift and brain edema compared to the use of CT for screening of these problems [10]. Despite these improvements over CT, standard MRI is not suited to identify diffuse axonal injury. Furthermore, abnormal findings on CT and MRI do not correlate with decreased neuropsychological outcomes acutely at 1 month or at one year follow up [15]. These findings suggest conventional head CT and MRI are unable to accurately diagnose or prognosticate recovery in mild TBI patients.

Fortunately, newer imaging tests and their incorporated software provide improved detection and localization of injured tissues or altered function associated with mild TBI. However, these new tests are mainly employed for research at this time. Susceptibility Weighted Imaging (SWI) has improved localization of hemorrhage [16]. Magnetic resonance spectroscopy (MRS) uses metabolite measurements associated with brain injury to determine dysfunctional regions [16]. Functional MRI has been used for localization of altered cortical activation while performing certain tasks [16]. Diffusion Weight imaging (DWI), Diffusion Tensor Imaging (DTI) and Diffusion Kurtosis Imaging (DKI) provide improved edema and axonal injury detection [17]. DKI is a newer imaging modality that is superior to DTI in examining tissue complexity. DTI measures tissue organization through measurements of random translation of water molecules of Gaussian or bell curve distribution. DTI measures diffusivity under the assumption of unimpeded water diffusion in a homogenous environment [17]. Biological tissues display increased heterogeneity of microstructure; which is taken into account by various measurements in DKI [18]. DKI has the potential for increased precision with the diagnosis of mild TBI compared to DTI, but at this time there are few studies of its use in the evaluation of mild TBI. This paper will mainly focus on DTI and SWI because they have a significant data supporting the diagnosis of mild TBI. Other imaging tests are discussed as supportive evidence of specific areas in the brain that are affected by mild TBI and correlated with deficits in various cognitive domains.

**Diffusion Tensor Imaging (DTI)**

DTI studies have become the preferred imaging modality to evaluate DAI associated with TBI in mild TBI research. DTI has four times improved sensitivity over CT for detecting non-hemorrhagic DAI and can evaluate for other intracranial pathology as it twice as sensitive as CT for detecting contusion [15]. DTI permits the evaluation of white matter, nerve fibers and can assess myelin sheaths and nerve cell membranes [19]. DWI and DTI detect changes in diffusion between different groups of H2O molecules, while DTI has the additional capability of assessing the direction of the water diffusion [20]. Compared to most imaging tests, DTI can identify microscopic tissue damage and examine white matter tracts. The parameters assessed in DTI are: fractional anisotropy (FA), apparent diffusion coefficient (ADC), and mean diffusivity (MD). DTI uses FA as an index of local coherence of fibers [21]. Normally, water molecules in white matter tracts align along the direction of the tract and move faster along an axon, and are therefore termed anisotropic. Decreased structural integrity of brain tissue leads to increased random motion of water molecules in all directions or otherwise described as a reduction in FA [17]. FA is measured on a scale from 0 to 1. In areas of highly restricted diffusion, such as corpus callosum, the FA is high. The FA is moderate in the gray matter because it moderately restricted to the diffusion of fluids through the tissue. The FA approaches 0 in areas of low restriction such as cerebral spinal fluid [19]. ADC is the average of the diffusion of water measured in 3 planes x,y,z [22]. Mean diffusivity is similar to ADC as it measures average diffusion [22].
**Diffusion Tensor Imaging in the Evaluation of Mild TBI at the Acute, Subacute, and Chronic Stages**

DTI studies have shown that even one mild TBI can show damage to the white matter tracts in the acute, subacute and chronic phases post-injury. These studies will be discussed below, with the main areas significantly correlated with mild TBI being the: internal capsule, corpus callosum and subcortical white matter; although other areas have also been shown to be impaired by mild TBI.

**Acute and Subacute Changes in Mild TBI**

Contrasting findings have been reported on DTI studies with some studies reporting increased FA while others report decreased FA in areas affected by mild TBI. To study the acute phase of injury, Bazarian et al. [23] compared mild TBI patients to matched orthopedic patients that did not sustain head injuries within 72 hours of injury. They demonstrated that the mild TBI group had significantly increased FA in the posterior corpus callosum as compared to orthopedic controls. Mayer et al. [24] also found at less than 3 weeks post-injury, mild TBI participants had increased FA in the corpus callosum and various left hemispheric tracts, with normalization of FA after 3-5 months. In contrast to these two studies [23, 24], Arfanakis et al. [25] found decreased FA predominantly in the internal capsule and corpus callosum of mild TBI participants sustaining an injury within 24 hours with a tendency towards normalization of FA in 2 of the 5 patients at 30 days. Rutgers et al. [26] examined those with mild, moderate, and severe TBI and found that at less than 3 months, patients with mild TBI had lower FA and significantly higher ADC in the genu of the corpus callosum compared with control subjects [26]. At 3 months post-injury, no significant difference was found between the groups. Although FA was different, the areas affected by mild TBI were similar between the studies. The differing FA values may represent different pathophysiological processes. Increased FA may represent axonal swelling or cytotoxic edema, while decreased FA may represent axonal degradation and discontinuity with water between the spaces Mayer et al. [24]. In the future, serial DTI studies may provide a way to monitor the resolution of various deficits in mild TBI patients.

**Chronic Changes in Mild TBI**

DTI studies have documented persistent chronic changes in the white matter following one mild TBI episode. DTI studies performed after 3 months continue to reveal pathology in areas similar to those found in the acute and subacute phases of mild TBI. In a study that examined military personnel that sustained blast injuries resulting in mild TBI, participants were examined within 90 days of injuries with follow up after 6-12 months [27]. The investigators found mild TBI patients had decreased relative anisotropy in the middle cerebellar peduncles, cingulum bundles and right orbito-frontal cortex with persistent changes on follow up [27]. A study of civilian participants by Inglese et al. [17] found increased MD and lower FA in corpus callosum, centrum semiovale also known as the cerebral white matter, and internal capsule significant changes in the mild TBI group that was evaluated an average of 4.05 days and 5.7 years post-injury compared to healthy controls. Lipton et al. [28] examined those with continued post-concussive symptoms including: “difficulty with attention, concentration, memory and poor job performance”. Mild TBI participants had significantly decreased FA in the corpus callosum, subcortical white matter, and internal capsules bilaterally compared to the control group [28]. Kraus et al. [29] found decreased fractional anisotropy in the corticospinal tract, sagittal stratum and superior longitudinal fasciculus of individuals with chronic mild TBI. These findings show long-term alterations in white matter can be found even years post-injury. The areas most commonly affected are the cerebral lobar white matter and the corpus callosum and internal capsule. Military personnel that sustained blast injuries were different than civilian populations in that they were more affected in the cerebellar peduncles and not the corpus callosum or internal capsule.
Rutgers et al. [30] wanted to further investigate sites that had a predilection for injury in 21 mild TBI participants that were on average 5.5 months post-injury at subacute (<3 months) and chronic (> 3 months) stages of injury compared to controls. They observed significantly reduced FA in cerebral lobar white matter, corpus callosum, and cingulum [30]. Of all the regions with deficits, changes in the cerebral lobar white matter were seen in 61.8% of mild TBI and most prominently in the frontal lobe of 42% of patients [30]. The cingulum or corpus callosum is affected in 23.6% of the individuals with mild TBI. Finally, the internal capsule, mesencephalon, brain stem and cerebellum had changes in 5.7% to 2.1% of the mild TBI participants [30]. Rutgers et al. [30] also utilized fiber tracking and found discontinuity of the white fiber tracts such as supratentorial projection fiber bundles and corpus callosum fibers. 19.3% of mild TBI participants had discontinuity of the fronto-temporo-occipital fiber bundles[30]. These findings also support chronic visible changes demonstrated in the same areas as the subacute and acute stage of mild TBI.

**Mild TBI patients assessed with neuropsychological testing and structural correlates established on DTI**

The studies in the previous section utilized DTI in the evaluation of areas affected by mild TBI. Other studies have gone further to corroborate areas of altered function seen on advanced imaging with deficits in cognitive function seen on neuropsychological testing [18, 31-36]. The correlation between neuropsychological testing and advanced imaging has improved the precision with which various cognitive deficits can be diagnosed [18, 31-36].

Neuropsychological evaluations are important in assessing how mild TBIs have affected cognitive function. The domains examined are: attention, speech and language, memory or orientation, visual-spatial or constructional ability, executive function, affect and mood, and thought processing. Research utilizing DTI has improved the recognition of specific areas associated with cognitive processes in normal and abnormal populations. Sasson et al. [31] studied the variance in cognitive domains as assessed by computerized neuropsychological testing and examined different regions with diffusion tensor imaging in a healthy population consisting of a large array of ages. DTI parameters measured demonstrated an association of executive function with the frontal white matter and the superior longitudinal fasciculus. Information processing corresponded with the cingulum, corona radiata, inferior longitudinal fasciculus, parietal white matter, and thalamus [31]. Memory was localized to changes in the temporal, frontal, cingulate and parahippocampal regions [31]. Similarly, mild TBI assessed with neuropsychological testing in conjunction with DTI as well other advanced diagnostic imaging tests, have found some similar correspondences. Evidence of correlation between neuropsychological testing and regions of altered function demonstrated on advanced diagnostic imaging in patients following mild TBI are: frontal cortex [32], corpus callosum [34, 35], uncinate fasciculus [33-35], superior longitudinal fasciculus [34], anterior corona radiata, thalamus [18,36]and cerebellum [39]. Establishing structure-function associations may be used to predict persistent cognitive deficits as well as distinguish malingerers from those with legitimate impairments.

**Frontal Cortex/Dorsolateral Prefrontal Cortex (DLPFC)**

Using DTI, Rutgers et al. determined that 42% of patients sustaining a mild TBI were identified to have altered white matter changes in the frontal lobe [30]. Lipton et al. [28] found individuals with mild TBI exhibited impaired performance in neuropsychological tests of executive functions correlated with decreased fractional anisotropy in the DLPFC at 2 weeks post injury. In the McAllister et al. [32] study, many patients with mild TBI complained of poor memory, inability to concentrate and thinking slower. These complaints
are descriptions of impairment in working memory [32]. McAllister and his colleagues [32] utilized fMRI to examine healthy controls vs. mild TBI patients 1 month following injury. They found mild TBI patients had decreased overall activation of the frontal cortex compared to controls in performing the attention/vigilance task and then the memory task [32]. They also had increased activation of right parietal and DLPFC compared to controls when they performed the second memory task compared to the first memory task [32]. These findings offer evidence that impairment seen on neuropsychological tests of executive function and memory can also be demonstrated in mild TBI populations.

**Corpus Callosum**

Rutgers et al. [30] found that 26% of mild TBI participants had decreased FA in the corpus callosum. The corpus callosum connects with various regions in the brain as well as directly connects the two hemispheres of the brain. The genu of the corpus callosum connects to the frontal cortex, while the body and splenium connect to the temporal, parietal and occipital portion [19]. The extent to which the corpus callosum is damaged appears to correlate with total IQ. Matsushita et al. [19] examined 9 adults with mild TBI and 11 subjects with moderate TBI 0-20 days post TBI (average 3.5 days) and compared them to 27 matched healthy controls. Significantly decreased FA in the genu, stem and splenium of the corpus callosum was seen in moderate TBI group compared to controls, while the mild TBI group was only different from the control group with decreased fractional anisotropy in the splenium of the corpus callosum [19]. 11 of the 20 TBI participants underwent neuropsychological testing with a mean of 560 days post-injury and a positive correlation was noted between FA in splenium of the corpus callosum and total IQ [19].

**Uncinate Fasciculus, Superior Longitudinal Fasciculus, and Anterior Corona Radiata**

The uncinate fasciculus is a white matter tract that connects the orbitofrontal cortex to the temporal pole [33]. Its proposed function has been related to emotion and memory, although recent research reveals that it is involved in language, and specifically naming deficits [33]. The superior longitudinal fasciculus has a role in “visual awareness, maintenance of attention, initiation of complex motor behavior, phonemic and articulatory aspects of language, and lexical decision making” Geary et al. [34] found mild TBI subjects with deficits in uncinate fasciculus and superior longitudinal fasciculus correlated with impairment in verbal learning. Niogi et al. [35] found decreases in FA values in anterior corona radiata was correlated with deficits in attention while deficits in the uncinate fasciculus correlated with deficits in memory and attention.

**Thalamus**

The thalamus acts as a relay station as it has reciprocal projections to the entire cerebral cortex and is involved in processing and transmitting cognitive, sensory and motor function information [18,36, 37]. The role of the thalamus is related to attention, concentration, and processing speed [18,36, 37]. Little et al. [36] found that thalamic changes accounted for variance in executive function, attention and memory. Grossman et al. [18] utilized DKI to compare healthy controls to individuals that had sustained a mild TBI within one year. They found mild TBI patients had deficits in attention and processing speed as well as executive functions that correlated with white matter changes in the thalamus [18].
**Cerebellum**

The cerebellum appears to be affected in 5.7% to 2.1% of participants in the Rutgers et al. study [30] of a civilian population, but may have higher incidence in military personnel sustaining a mild TBI [27]. The cerebellum has a role in cognitional and perception as it projects to prefrontal cortex [38]. It also has circuits to the temporal, posterior parietal, and limbic cortices [38]. Alteration in pathways to frontal cortex lead to decreased working memory [38,39].

Hattori et al. [39] recruited mild TBI individuals from a treatment-seeking population that presented with cognitive fatigue as major limiting factor in returning to work despite near normal neuropsychological testing. Healthy controls were compared to subjects who had sustained mild TBI at 6 least months prior to the study with average of 28.6 months post-injury [39]. 6 of 15 subjects were involved in litigation, but none had disability claims [39]. They utilized Single-Photon Emission of Computerized Tomography (SPECT) to measure active areas of the brain during a test for attentional processing entitled Paced Auditory Serial Addition Test (PASAT) [39]. SPECT evaluates brain function through the detection of radiotracers that light up in areas associated with increased blood flow [20]. Subjects with mild TBI had significantly lower PASAT scores than controls in the first of four sessions performed [39]. Another interesting finding in the study was that mild TBI subjects had greater activation seen in DLPFC, which corresponds with working memory and executive function [39]. Differing regions of activation may represent compensation for deficits in the frontocerebellar circuit [39]. Additionally, increased activation in the cerebellar cortex correlated with PASAT performance in the healthy control group [39]. These findings suggest the use of neuropsychological testing in combination with advanced imaging has improved correlation of area of cognitive deficits with regions/white matter tracts altered by the mild TBI.

**Susceptibility Weighted Imaging (SWI)**

SWI has enhanced recognition of microhemorrhages that may not be picked up on CT, T1 or T2 weighted MRIs, or GRE MRI at this time [10]. SWI detects blood at the level of iron and blood products [10]. In one study that utilized SWI in mild TBI patients, the locations of microhemorrhages were related to patient complaints [40]. Visual complaints correlated with microhemorrhages in occipital regions whereas hearing deficits correlated with temporal hemorrhages [40]. The microhemorrhages were not detected in 76% of patients on conventional MRI in this study [40]. Tong et al. [41] examined children and adolescents who suffered mild to severe TBIs and found a significant inverse relationship between the GCS, and the number and size of hemorrhagic DAI lesions seen on SWI. Participants who suffered a mild TBI had the lowest quantity and smallest volume of hemorrhagic lesions while those with severe TBI (lower GCS) had the highest quantity and largest volume of hemorrhagic lesions [41]. Finally, the authors noted a direct relationship between degree of disability and number and size of hemorrhagic lesions found on 6 and 12-month follow-up, suggesting worse prognosis in those with greater number and size of hemorrhagic lesions [41].

**Biomarkers**

There are emerging advances in the use of biomarkers for the diagnosis of mild TBI [8]. These new advances in biomarkers show that neurons and supporting cells are damaged during head trauma. This damage leads to the release of specific proteins into the cerebrospinal fluids [11]. Furthermore, if the blood brain barrier is affected, these proteins may be released and found in the peripheral circulation [42]. Many proteins are
New research is attempting to measure the serum or cerebrospinal fluid concentration of biomarkers released after brain injury [8]. This is an attempt to correlate outcomes and sequelae of symptoms following a mild TBI. This will assist with a more accurate diagnosis of mild TBI. The biomarkers with the most hopeful research are the following: S100B, Neuron-Specific Enolase (NSE), and cleaved tau protein (CTP) [8,43].

**S100B**

In the current discussions and studies surrounding biomarkers, S100 B is viewed as the most promising marker for diagnosing mild TBI [8,44-47]. S100B is a protein released from astrocytes. It is found in brain tissue and may be measured in the cerebrospinal fluid and serum following an injury. However, S100B is not specific to brain injury [8,48]. Studies have also shown elevated levels of S100B in bone fractures, thoracic contusions without fractures, burns, and minor traumas [48]. It is released into the CSF and serum and has been detected as early as 30 minutes after a brain injury. The half-life is approximately 97 minutes [49].

S100B is very sensitive for mild TBI, however not very specific. In one study designed to evaluate if S100B was a predictor of CT findings after mild brain injury, S100B was found to have a high sensitivity of 0.95 and low specificity of 0.31 when measured within 12 hours of initial injury [50]. In an additional study where S100B was used as a predictor of findings of CT within 3 hours, the sensitivity was improved. It was found to be 0.99 and specificity found to be .30 [12]. This high sensitivity has prompted a number of studies to evaluate if it could be used as a screening tool and possibly decrease the need for obtaining a head CT on all individuals who sustain a minor head injury [12, 50, 51].

A prospective multicenter study by Biberthaler et al. [12] specifically studied if S100B measurements could affect the need for an initial head CT. Every patient had serum S100B measured an average of 60 minutes within trauma and had a head CT to determine if they had any intracranial pathology relevant to head trauma. They found that patients with positive head CT findings had the highest S100B concentrations with a GCS of 13, less with a GCS of 14, and lowest S100B concentrations with GCS of 15. They also found that patients with negative head CT had S100B concentrations equally low as the concentration in GCS of 15. The researchers discovered that in defining the cutoff level for S100B at 0.10 ug/L, they were able to have 99% sensitivity for ruling out intra-cerebral lesions. However, S100B only had a specificity of 30%. The authors believed this could be improved if they were using an MRI for imaging instead of CT because of the MRI’s ability to detect smaller lesions. And finally, the researchers determined that screening with S100B levels in patients sustaining mild brain injuries, might allow for a decrease in 30% of head CTs. [12] This reallocation of resources might be best for the appropriate uses of newer imaging when indicated.

Elevated S100B levels following mild TBI are associated with a number of unfavorable outcomes. According to a review by Lomas and Dunning [52], these elevated S100B levels could be used as a predictor for poorer long-term outcomes. Stranjalis et al. [53] found that patients with mild head injury and elevated S100B had worse short-term outcome measured by decreased return to work. These patients with an increased S100B had a failure to return to work rate of 37% compared to 4.9% in patients who had did not have an elevated S100B levels. In another study, elevated S100B levels were associated with neuropsychological abnormalities [54]. Waterloo et al. [54] defined patients with minor head injury as having the following: positive loss of consciousness secondary to a head injury, a GCS of 14 or 15, no focal neurological deficits, and no abnormal intracranial pathology found on CT. The researchers performed neuropsychological testing on patients with and without elevated S100B. Although elevated S100B levels in patients with minor head injury did not affect cognition, the researchers did find differences in sequential reaction time and selective attention. Specifically, the patients with increased S100B levels appeared to have decreased attention and limitations in speed of processing information [54].
Although S100B appears to have the most promising research related to mild TBI, the studies have not been wholly consistent. Many studies use variable serum cut off levels and have not reached a consensus on the accuracy of the data. However, S100B has been proven to have a strong association with severe TBI, but mild TBI is still in the incipient phase of research [55]. Another reason S100B does not have consistent research data is that many studies have shown extra-cranial injuries from the trauma could be associated with the elevated S100B [48,56]. One way to correct for this extra-cranial release has been proposed by Bazarian et al. [44]. They studied the use of a correction factor—creatinine kinase (CK)—with the extra-cranial release of S100B. The researchers measured S100B and CK levels in 96 mild TBI patients. They compared the S100B corrected with CK and the uncorrected S100B levels to test their ability to predict initial head CT, headache present at three months, and symptoms associated with post-concussive syndrome at three months. The corrected S100B had a statistically significant improvement in the ability to predict headache at three months. However, there was no significance of correlation with initial head CT or three month post-concussive syndrome. The study concluded that S100B itself was poorly predictive of outcome, but that CK is valid as a correction factor of S100B [44]. Possibly, this research will encourage additional studies of S100B using CK as a correction factor.

**Neuron Specific Enolase (NSE)**

NSE is a protein found in the glycolytic pathways of neurons and neuroendocrine cells. It is another common biomarker that has been studied in its relationship to brain injury [5, 8]. It can be detected as early as six hours from injury and has a half-life of 24 hours. It has been found to be associated with poor short-term and long-term outcomes from brain injury [45]. De kruijk et al. [57] found that elevated NSE following a mild TBI was associated with an increase in headaches and dizziness six months after initial injury.

Unlike S100B, NSE has been found to have high specificity in relation to certain aspects of brain injury. One recent prospective study in particular studied the correlation between NSE, severity of brain injury as measured by the Glasgow Coma Scale (GCS), and prognosis as measured by the Glasgow Outcome Score (GOS). Although there was no significance in mild brain injury in particular; they did find that NSE of all patients studied including: mild, moderate, and severe brain injury, was 87% sensitive and 82.1% specific for predicting a poor neurological outcome according to the GOS [58]. However, this is inconsistent when predicting intracranial lesions in pediatric patients following brain injury, NSE has a 77% sensitivity and 52% specificity [45].

**Cleaved-Tau Protein (CTP)**

CTP is a breakdown product of microtubule-associated tau protein. This protein is associated with axons in brain tissue [8]. In a rat-model study by Gabbita et al. [59], CTP was found to be elevated after TBI. The increase was found to be severity dependent, with severe TBI having more of an increase than mild TBI. The researchers also found that the levels were significantly elevated within six hours and peaked within 168 hours. The researchers felt CTP was a potential marker of brain injury in the rat-model and it would be beneficial to see if the same applies to humans [59].

However, a recent pilot study was performed by Bazarian et al. [60] to evaluate if there was a relationship between elevated CTP levels and S100B levels and symptoms associated with mild TBI at 3 months. Unfortunately, the researchers did not find significant a relationship between neither CTP nor S100B and symptoms associated with these patients who sustained a mild TBI at three months.
Using serum biomarkers as a tool for diagnosing mild TBI is still evolving. Begaz et al. [46] performed a review of prospective cohort studies of the relationship between serum biomarkers S100 proteins, NSE, CTP and mild TBI. They found that none of the biomarkers had a consistently reliable correlation with persistent symptoms, known as post-concussion syndrome, following mild TBI. However, they did feel it was necessary to combine a number of clinical factors along with the biomarkers to predict the development of post-concussion syndrome after sustaining a mild TBI [46].

S100B has the most research supporting it as a diagnostic marker for mild TBI [5,8,46]. Although studies have shown there is an elevation in S100B after a person has sustained a mild TBI, it is inconsistently correlated with neuropsychological testing [54,61]. The most consistent research has shown the positive correlation between S100B predicting head CT outcomes. This may possibly decrease the number and expense of CT scans in the future [1,52].

Using S100B as a screening tool for performing a head CT is a level C recommendation in the “Clinical Policy: Neuroimaging and Decisionmaking in Adult Mild Traumatic Brain Injury In the Acute Setting” in 2008. The recommendation states, “In mild TBI patients without significant extra-cranial injuries and a serum S-100B level less than 0.1 g/L measured within 4 hours of injury, consideration can be given to not performing a CT” [5]. However, they did note that the Food and Drug Administration has not yet approved S100B [5]. The clinical policy does believe there is a potential for biomarkers, to be utilized for the detection of abnormal head CT [5] but continued research is still needed. Some have suggested the possibility of combining these biomarkers in a panel with a history and a physical examination. [5,46]. Others have suggested this along with a correction factor of CK for extra-cranial sources [44]. Combining the panel and correcting for extra-cranial sources, along with a history and physical exam, health care providers will be able to diagnose mild TBI more precisely and accurately and allow the appropriate allocation of resources for diagnostic studies.

**Long Term Sequalae of Mild TBI**

*Unfavorable Outcome*

Individuals who sustain a mild TBI may encounter a number of complications including emotional, physical, and cognitive symptoms [1, 62, 63, 64]. Patients who sustain mild TBI exhibit functional disability such as difficulty with finding or sustaining jobs, individual relationships, and the ability to return to school [63,64]. Vanderploeg et al. [63] found that individuals with mild TBI had increased self-reporting depression, post-concussive symptoms, disability, underemployment, low income, and marital problems. Individuals who sustained mild TBIs were also found to have “unfavorable short-term outcomes” [65]. These include failure to return to work or activities. These unfavorable outcomes have even been correlated with elevated S100B levels. Although there is some discourse surrounding symptoms following a mild TBI, post concussive symptoms, and post concussive syndrome, researchers believe having this positive correlation between elevated S100B and mild TBI and “unfavorable short term outcome” would assist with supporting true post-concussive symptoms [65]. As Deutsch et al. [64] point out, an individual’s sense of self is tied to his/her type of work. Returning to work is a crucial component of the patient’s rehabilitation. In general, the more severe the injury, the more likely patients will have poor return to work outcome [66]. Return to work outcome is also related to non-modifiable risk factors such as age, marital status and pre-injury educational level. These factors—elder [67], unmarried, and less education [68] —negatively influence a patient’s return to work outcome.

Improved prognostication and being able to determine those who might be more susceptible to poorer outcome would more efficiently allocate resources to appropriate individuals to improve their recovery. The
standard imaging studies in mild TBI patients generally do not distinguish between individuals who will have favorable outcomes compared to those with unfavorable outcomes. Messe et al. [69] compared imaging of mild TBI patients with good outcomes, imaging of mild TBI patients with poor outcomes, and imaging of mild TBI with healthy controls. Patients with mild TBI who had poor outcomes had a significantly increased mean diffusivity on DTI compared to the good outcome group [69]. Changes on DTI that may be predictive of poor outcome would be useful in the establishment of appropriate follow-up and rehabilitative care.

With brain injuries in general, the combination of the loss of income and the cost of disability has been estimated to cost society $56 billion a year [70]. Mild TBI are estimated to account for over a quarter of this at $16.7 billion [70]. However, many believe this number underestimates the number of mild TBIs due to diagnosis in the emergency department and released, treatment in a non-hospital setting, undiagnosed patients who never received any treatment. [2,70].

Persistence of Symptoms

It has been estimated that 80 to 90% of patients who sustain mild TBI fully recover from their injury within three months [9]. When followed with serial imaging, the recovery correlates with the normalization of FA in various injured areas seen on DTI [24, 25, 26]. This leaves 10 to 20% of patients who sustain mild TBIs who continue to have persistent symptoms and may have what is referred to as post-concussive syndrome (PCS) [62, 71, 72] or “post-concussive disorder” [9]. The ICD-10 characterizes post-concussive syndrome as one that occurs after a head injury with loss of consciousness with symptoms in 3 or more categories that begin no later than 4 weeks post injury. The categories are as follows: “(1) headache, dizziness, malaise, fatigue, noise intolerance (2) irritability, depression, anxiety, emotional lability (3) subjective concentration, memory, or intellectual difficulties without neuropsychological evidence of marked impairment (4) insomnia (5) reduced alcohol tolerance (6) preoccupation with the above symptoms and fear of brain damage with hypochondriacal concern and adoption of sick role” [73].

The DSM-IV criteria for PCS are similar to ICD-10 with a requirement of head trauma with concussion as manifested by loss of consciousness, post-traumatic amnesia, and, less commonly, onset of seizures. Neuropsychological testing would demonstrate difficulty with attention or memory. Patients need to have three or more symptoms that last at least three months and begin shortly after the injury or worsening of previous symptoms. Diagnosis also requires disturbance in social and occupational functioning [72].

Carroll et al. [71] have summarized that patients exhibit deficits in regards to cognitive, emotional, and physical effects from mild traumatic brain injury, but the majority of these patients recover within 3 to 12 months. They report that many symptoms continue to persist, but if this is the case, then there are a number of contributing factors such as psychosocial stressors, co-morbid conditions, and situational [71]. Long-term sequelae of mild TBI has been controversial as the symptoms tend to be vague and can be found in non-TBI populations. Furthermore, individuals involved in litigation or have pre-existing social or psychological issues generally report increased symptoms or deficits [74-76]. Through meta-analyses, it has also been found that patients with mild, uncomplicated TBI can recover and reach normal cognitive function within one to three months [77]. However, there is confusion over the use of the term “postconcussive syndrome”. It can be used to describe any combination of symptoms following mild TBI and has been documented to be present in individuals following trauma [78], including college students and individuals with depression or chronic pain [79]. These studies demonstrate a lack of consensus among chronic symptoms or the resolution of mild TBI symptoms.
Treatment

It is difficult to identify continued deficits and, in turn, the treatment of mild TBI. Although there has been consistent evidence for deficits and treatment of moderate and severe TBI, mild TBI lacks consistent evidence. For instance, there is sufficient evidence to show that there is a relationship between patients with a moderate or severe brain injury and impaired social functioning, unprovoked seizures, dementia, Parkinson’s Disease, endocrine deficiencies [62]; however, the committee consisting of Bazarian et al. did find that “there is limited/suggestive evidence of an association between sustaining a mild TBI resulting in loss of consciousness or amnesia” [62] in relation to seizures following a brain injury, parkinsonism, “ocular/visual motor deterioration” [62]. This committee also found that “there is sufficient evidence of an association between sustaining a TBI and development of post-concussive symptoms (such as memory problems, dizziness, and irritability).”[62] They believed this applied to patients who sustained all severities, from mild to severe, of brain injuries [62].

Although there is not a standardized treatment for mild TBI, a number of interventions have been shown to be helpful. Ruff [9] has found that cognitive therapy tailored to the individual patient, education of available resources, and recognition of symptoms can assist recovery. The Clinical Practice Guideline: Occupational and Physical Therapy for Mild Traumatic Brain Injury [80] recommends a number of interventions physical and occupational therapists can provide in relation to temporomandibular disorders, attention, balance dysfunction, vestibular dysfunction, and several other deficits. It is likely best to continue to treat these patients utilizing a team approach with an early recognition of symptoms, prevention of further immediate injury, education of symptoms and prevention, cognitive, physical, occupational, and if necessary, vocational therapy, neuropsychological testing, necessary medications, and continued monitoring by specialists. In terms of rehabilitation and facilitating the patients’ return to work, the importance of continued cognitive therapy and behavioral re-evaluation to understand the changing needs of the patient is stressed [9, 66]. Treatment is critical, because the lack of treatment can lead to decreased productivity [70] and increased healthcare costs.

Conclusion

A growing number of individuals are sustaining mild TBI each year. Many of these patients are not receiving the appropriate evaluation and diagnosis [2, 81]. The current tests do not provide a true objective diagnosis and may not identify individuals who have sustained a mild TBI [2, 81]. This current standard of diagnosis, which only utilizes imaging such as CT or MRI to rule out acute brain injury, is not sufficient to make a precise diagnosis of mild TBI. Bazarian suggested this is similar to addressing a patient with acute cardiac symptoms with only a Chest X-Ray and EKG [82]. A Chest X-Ray and EKG alone do not provide enough data to make a precise and timely diagnosis. Other tests such as: echocardiograms, angiograms; and blood biomarkers such as: troponin, CK-MB, and LDH are also utilized to make a specific diagnosis in relation to cardiac disease [82]. Without sufficient evidence to support a diagnosis, treatment of mild TBI will likely be found to be speculative, as was the case in Scognamillo v. Herrick, (2003) 106 Cal. App. 4th 1139.

It is vital these individuals who sustain a mild head injury receive a diagnosis. Without determining a precise diagnosis, patients may not receive medically necessary treatment. In most jurisdictions, including California, all health plans are required to provide medically necessary care. This includes care for diagnosis, as well as treatment. [83, 84]. It would be hard to argue that medically necessary care for headache, dizziness, cognitive deficits in mild head trauma [1,62] differ markedly from the same symptoms caused by migraine or tension
headaches alone. However, there is emerging research in innovative technology and biomarkers that may assist with an objective, precise, and timely diagnosis of mild TBI [8, 10, 16, 81, 82]. Using new diagnostic tests discussed, it would be possible to identify patients who would have a poorer outcome after sustaining a mild TBI [69]. Treatment for these patients would emphasize closer observation. Continued monitoring and constant reevaluation of these patients is vital to address the changing needs of the patient in regards to treatment and rehabilitation [9]. We advocate that individuals who present on standard history and physical exam as possibly having a mild TBI be evaluated with DTI imaging and biomarkers as these diagnostic tests will assist with the precision and timeliness of diagnosing mild TBI.

The precision and timeliness of an accurate diagnosis is critical not only if the patient will require medically necessary treatment to return to being a vital functioning member of society, but it will also establish the responsible party for such treatment. The diagnostic tests recommended have the ability of establishing the causal link between injury, the responsible person, and the damages sustained. In the past, an individual having a mild TBI could not establish the causation required to impose liability or fault on the person or entity properly to bear the responsibility for the medically necessary treatment required.

The tests advocated in this article can now provide what in the past was not possible, which is (1) precision and timeliness of an accurate diagnosis, and (2) a legal basis for establishing causation between the act or omission causing injury and the medically necessary care to treat the injuries proximately resulting therefrom. Precision and timeliness of an accurate diagnosis is critical and necessary to establish a responsible party and if the patient will require medically necessary treatment to return to being a vital and functioning member of society.

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“AS YOU ARE NOW, SO ONCE WAS I”:
A reflection on empathy when working with persons with acquired brain injury

Author: Carrie Hartwell, PhD, MA, LCSW

Imagine. For the next few moments, set aside the pressing issues of the day – your schedule, meetings, and the patients or projects before you today – and simply relax, giving yourself the next few minutes to focus completely on the images and thoughts that follow. Try to quiet the usual hum of sounds and movement that surrounds you, clear your mind, and imagine...
Picture yourself in your home this morning. Go back there in your mind – step into the front door and look around you, noticing what is to the right, left, and in front of you. Notice the colors, the temperature, the smells... what sounds do you hear in your home this morning? Fill in the picture in your mind with the things and the people inside your home. Who is home today? Imagine your loved ones there with you, perhaps those you live with or those very close to you who have come to visit. Imagine each of their faces, what they are doing, where they are in the house. Bring to mind how you feel when you are there at home with them. What are the things and memories that surround you – your favorite spaces in the home, favorite photographs and memories, important life events that have happened here, and furnishings or objects in your home that you value? Spend a few moments walking through the home in your mind... go from room to room, noticing what’s in each room, the colors and items you see, favorite things, favorite memories in each space. Picture the details that matter most to you – the people and things that truly make this your “home” – as vividly as you can.

Now think about your past, and the many experiences and choices that have led you to be in this space now, in this home, at this time in your life. Think back through your work history, the jobs you have had that have helped you to come to the place of living in this home and having these things, and the ways that your career has grown and changed over the years, impacting your life as well as touching the lives of others. Bring to mind the people and relationships that have shaped and supported you over the years, helping to make you who you are today. As you consider your life as a whole, think about what has been most important to you, how your identity has developed and changed over the years, and how you feel about yourself and the life you have built. Picture the most satisfying aspects of your life, the things that bring you the most joy, the things you are proud of, the things you have accomplished or been recognized for, and the people you love most and are closest to – family, friends, loved ones, colleagues. Imagine the entire story of your life, including your past and the road you have traveled, your present, and all your hopes and plans for the future.

Now imagine that this morning, you leave for work as usual, leaving your home and loved ones to go do the important work you do each day. Imagine what you have ahead of you today, remembering for a moment the value you place on your career, as well as the ways that others are impacted by the work you do. As you are driving on your way to work thinking about the day ahead, suddenly you realize that you have taken a wrong turn and are on a road you do not recognize. You try to turn around and find your way back to your usual route, but with each turn, you find yourself becoming increasingly disoriented. You continue driving, certain that you will see something you recognize eventually, but the road becomes increasingly desolate until you realize that you are the only person traveling on it. Starting to feel a bit anxious, it occurs to you that you are in a completely unfamiliar place and have no idea how to find your way back. You pull over to look for a map, and you find that you do not have one. You check your cell phone and GPS, and you find that none of the technology you have with you works here. A sense of vulnerability begins to creep in as you realize that you are truly lost and have no way to get back, and no way to get help. You are overcome with utter disbelief – what could have happened? You just left your home minutes ago, as you do everyday... how did you end up in this place? You try to retrace your steps, trying to imagine what went wrong. You think about the home you just left this morning, the people you love and are not able to contact, the places you’re supposed to be today, and how you have no way of getting back or getting a message to anyone... today or indeed maybe ever. You try to open your car door and find that all the doors and windows are locked. You begin to panic.

You remain in your car and things begin to go dark. You become disoriented. The next thing you realize, people you have never seen before emerge from all directions, surrounding you and pulling you from your car in spite of your efforts to explain your situation and insist that you just need to get back home. They put you in a vehicle and drive you to an unfamiliar place. You continue to try to explain to them who you are and what has happened to you, but they look at you strangely and ignore your requests. You realize, to your horror, that they speak a different language than you and do not understand who you are or what has
happened to you. You become terrified, feeling completely at their mercy, as you realize that you are powerless to get away from them or to return home. You have no idea what’s happening to you or why, and no ability to free yourself or to get in touch with your family, or indeed anyone. You are truly and utterly alone in a way that you have never been at any time in your life. You think about your spouse or partner. Your children. The people at work who are expecting you. How will you get back to them? You get up and try to leave, but you find that your legs aren’t working properly and that you can no longer walk. Even if you could, the doors are locked and you have no idea where you are or how to leave this place. Terrified, you begin to realize that other parts of your body are also impaired. You cry for help, but your voice wavers. You lose control of your limbs and bodily functions; even your mind seems to be failing you as you simply cannot believe what surrounds you. This cannot be real. It doesn’t make sense. You are smart and capable and have important things to do with your life, and people who love you and depend on you. You think about the life you left this morning… the places you’re supposed to be today, at work and with your family, the important events coming up on your calendar. You simply have to get back. But you can’t.

Horrifying realities begin to set in. In this new place, you are quite literally trapped, in a body and mind that feel foreign to you. The body you have known so well for your entire life no longer feels like “you” – it responds differently and can no longer do the same things, and you find yourself doing things that embarrass you. Your skills, strengths, and even the intelligence you have always relied on now seem absent or inaccessible to you. The people around you in this new place don’t know the “old” you; your identity, and your status in relation to others, is forever changed. From this moment on, you will not be going back to your career, you no longer live with your loved ones, and all your friendships will fade. There is no opportunity to say goodbye to the world and people you left behind, no packing your home or office and taking the things that mattered to you – it’s all gone immediately, without explanation or time to prepare. From now on, people will be dressing you, wiping your bottom, and treating you differently, being unable to see the “real” you because of the way you now look and communicate. You are not beautiful or attractive in this place, and you may never again kiss or caress a lover… your masculinity or femininity, and your sexuality, have been stripped from you. In short, you may never be returning to the world you just left this morning. Your home, your relationships and family, your career, your memories, the things you are proud of, your abilities – all of them, your entire life as you knew it, and all the hopes and plans you had for your future, are now likely to be forever changed...

Empathy is defined as the capacity or action of understanding and vicariously experiencing the feelings, thoughts, and perceptions of another, from his or her perspective rather than one’s own (see Banja, 2006; Merriam-Webster, 2013). Empathy is a construct that can be found in the training curriculums and textbooks of a wide variety of professions, including the diverse fields of providers who serve individuals with acquired brain injury. At first glance, this ability to “put oneself in another’s shoes” may sound deceptively rudimentary and routine, but in reality, empathy can be both as critical and challenging as many other professional skills of brain injury service providers.

Empathy is not easy or innate. It requires of providers greater levels of personal openness, investment, and vulnerability well beyond basic “active listening” or sympathy (see Banja, 2006), and when working with brain injury survivors, it exposes us to significant pain and suffering. Who would readily elect to imagine having life totally, irrevocably changed in an instant, or to realize how vulnerable our own treasured, hard-earned skills, knowledge, and relationships are – things we consider “certainties” and constants in our lives and upon which we define ourselves and depend? Research from the field of social psychology has consistently shown that we are not automatically inclined to empathize with others who have experienced negative outcomes, and in fact, we tend to misattribute others’ negative experiences to internal characteristics of those individuals (while perceiving our own negative outcomes as the result of...
environmental factors) (see, for example, Jones and Nisbett’s classic study (1971) on the “actor/observer effect”) – a tendency that helps preserve our own egos and sense of safety in the world.

Empathy is an essential component of care for persons with acquired brain injury. As Banja (2006) notes, provider empathy is an approach to treatment that is fundamentally ethical, respectful, and empowering to patients and is, in itself, a healing clinical intervention. An empathic approach strengthens the provider-patient relationship, and research from a variety of health disciplines has consistently shown that the quality of this relationship or alliance is a highly influential factor impacting patient satisfaction, compliance, and outcomes (see, for example, Banja, 2006; Banja, 2008; Fuertes, Mislowack, Bennett, Paul, Gilbert, Fontan, & Boylan, 2007). Studies with brain injury survivors and their providers from multiple fields including psychology, medicine, physical and occupational therapy, and other professions have produced similar results, demonstrating the critical impact of patient-centered, empathic care on a wide variety of patient health, psychosocial, and functional outcomes following brain injury (Coetzer, 2010; Darragh, Sample, & Krieger, 2001; Judd & Wilson, 2005; Klonoff, 2010; Schonberger, Humle, & Teasdale, 2006; Schonberger, Humle, Zeeman, & Teasdale, 2006; Sherer, Evans, Leverenz, Stouter, Irby, Lee, & Yablon, 2007).

It is easy to forget sometimes that it is often a single experience on a single day – perhaps even a single instant – that ultimately separates a life like mine from those of the individuals with whom I work. They, as I, had homes, careers, places to be, and people depending on them. Traumatic brain injury, tragically, has no regard for history, status, dreams, or responsibilities, however vital. As a clinician working with survivors of traumatic brain injury, I am often reminded of a Latin phrase I first encountered many years ago while traveling in Europe: “Eram quod es; eris quod sum,” which roughly translates into English, “As you are now, so once was I; as I am now, so will you be.” Generally attributed to Horace, poet of ancient Rome, the saying has been used in art and epitaphs across continents and centuries, inviting viewers to reflect on their own mortality. In the context of my everyday work, far removed from the tombs of Europe, it is not the shared fate of death that the saying evokes, but rather the common humanity of the living. “As you are now, so once was I; as I am now, so… [could] you be.” As providers, it would be easy to lose sight at times, in a sea of assistive devices and deficits and diagnoses and indignities, of the wholeness and complexity of the human beings before us, with lives only some moments ago just like ours. And yet it is this critical awareness, of our shared vulnerability and relatedness, upon which our ability to provide quality care fundamentally depends.

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**TBI PHARMACEUTICALS — THE LONG ODYSSEY OF CYCLOSPORINE IS ALMOST OVER**

**NeuroVive Pharma updates on cyclosporine’s progress toward approval as a pharmaceutical for treating moderate to severe traumatic brain injury**

**Part 2: Addendum**
Patient No. 1: German Boy Recovers After Severe Head Injury

Sometime in the 1990s, an anonymous 14-year-old German liver transplant recipient — regularly using cyclosporine to prevent tissue rejection — was hit by a car and suffered head injuries. By chance, an anaesthesiologist was at the scene when the accident occurred. He immediately examined the boy and suspected severe brain damage, later confirmed by an early Glasgow Coma Scale (GCS) score of three.

Although the worst was feared — children under 14 with a GCS below eight have a 28% mortality rate or have significant brain disability if they do survive — the patient not only survived but proceeded to make an amazing recovery. He was discharged from hospital five weeks later and was able to return to school after two months. He recovered unexpectedly well and is now an adult with a young son living in a town in northern Germany. The neuroprotective properties of cyclosporine were suspected in the recovery and the case was reported in a detailed case study published in the *Journal of Neurosurgical Anesthesiology* in 1998. The study concluded: “We conclude that neuroprotective properties of cyclosporine A [sic] may have been involved in the good recovery after severe brain injury in this 14-year-old patient.”

Reference


Cyclosporine Mitigates Heart Attacks in Proof-of-Concept Study

Mitochondria are present and producing effective energy in almost all cells in the body. It turns out that mitochondrial collapse and dysfunction may be associated with a variety of acute injuries, such as myocardial infarctions and also chronic diseases such as ALS, MS and other neurological disorders. In myocardial infarctions, reperfusion (re-opening) of the blocked artery can cause what’s called reperfusion injury, and extra damage and disability to the heart muscle, as well as increased mortality. The mechanism of action and process underpinning this additional damage to the heart muscle is the same as that affecting brain cells during traumatic brain injury. Mitochondrial protection in heart muscle tissue is one answer to moderating the long-term impact of heart attacks on health and lifestyle.

Every year, an estimated 500,000 people in the United States have a myocardial infarction. Infarct size is a major determinant of mortality. During myocardial reperfusion, the abruptness of the reperfusion can cause additional damage — a phenomenon called *myocardial reperfusion injury*. Studies indicate that this form of injury can account for up to 50% of the final size of the infarct. Focusing on reducing the additional infarct resulting from reperfusion would protect heart muscle and allow the patient to live longer and in better health after the initial attack.

Interestingly, a number of proposed interventions, e.g., ischemic post-conditioning, have been claimed to deliver cardioprotective benefits by acting on the opening of the mitochondrial permeability transition pore (the opening of which is directly inhibited by cyclosporine). CsA has been studied for its cardioprotective capabilities and found to be a potentially significant pharmaceutical for ameliorating long-term damage from heart attacks. As Gerczuk and Kloner noted in their recent (2012) review of the latest therapies to limit infarct size: “To date, cyclosporine is the most promising pharmacological post-conditioning mimetic.”

A small proof-of-concept clinical study by Piot and his colleagues, published in the *New England Journal of Medicine* in 2008, found that the administration of CsA with the aim of inhibiting the induction of the mPT...
was associated with a 40% reduction in infarct size. An editorial in the same issue of the journal called for large, multi-centre studies to determine if this new treatment option can positively influence clinical outcomes. In addition, targeting the mPT “may also offer protection in other clinical contexts, such as stroke, cardiac surgery, and organ transplantation.”

Following that lead, in April 2011, a European investigator-initiated, multi-centre phase III study of NeuroVive’s cyclosporine-based cardioprotection pharmaceutical (called CicloMulsion but it is the exact same product formulation as NeuroSTAT for TBI) in myocardial infarctions enrolled the first of 1,000 patients. With more than 700 patients enrolled (as of July 1, 2013) this study is expected to report results in early 2015.

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Crossing the Blood–Brain Barrier

It is difficult for many drugs, including cyclosporine, to cross the blood–brain barrier. However, traumatic brain injury often causes the blood–brain barrier to open, permitting cyclosporine to reach those areas of the brain in which the need is greatest. However, in other conditions, such as stroke, the barrier does not open in the same way as in TBI. NeuroVive is conducting research to identify variants of cyclosporine that can penetrate the blood–brain barrier, with a view to being able to provide the brain with neuronal protection under conditions other than TBI. NeuroVive is also evaluating the possibility of administering cyclosporine directly to the brain fluid (e.g., through lumbar puncture).

In pre-clinical pilot studies, NeuroVive’s researchers demonstrated, in collaboration with scientists in the Army, that cyclosporine crosses the blood–brain barrier in prolonged seizures due to hyperactivity in the brain. In cases of stroke, scheduled cardiac surgery and cardiac arrest, the brain cannot yet be reached satisfactorily through intravenous therapy, since a method of increasing the passage of cyclosporine through the blood–brain barrier in these conditions has not yet been found. To this effect, in 2010 NeuroVive and the Dutch brain drug delivery company to-BBB entered into a joint program to develop therapies for stroke and other acute neurodegenerative diseases by combining their technologies.

NeuroVive is also conducting research to develop advanced cyclosporins, cyclophilin inhibitors, formulations, new chemical compounds, or small molecules that allow improved or free passage across the blood–brain barrier. The company is also researching and developing cyclosporine analogue molecules without immunosuppressive effects (called NICAMS for Non Immunosuppressive Cyclosporine Analogue Molecules) that can be combined with new formulations and technologies.
Pharmaceutical Approaches to TBI:

There are a number of TBI pharmaceuticals in a variety of stages of development. The most promising of these approaches are “multipotential,” targeting at least two or more secondary-stage injury mechanisms, including excitotoxicity, apoptosis, inflammation, edema, blood-brain barrier disruption, oxidative stress, mitochondrial disruption, calpain activation, and cathepsin activation.\(^1\)

The value of multipotential agents is that they have potential to modulate one or more of these multiple secondary injury factors, providing a great chance of achieving clinical value. Previously, more than 30 phase III clinical studies for single-factor targeted TBI pharmaceuticals failed to find significance. Multipotentials may have a greater chance of delivering a successful therapeutic result for TBI patients and ultimately recouping the costs of development and trials.\(^2\)

Promising pharmacological multi-potential agents fall under two categories: those that have been studied clinically and those that constitute emerging pre-clinical strategies. Clinically studied pharmaceuticals include the statins (targeting excitotoxicity, apoptosis, inflammation, edema), progesterone (excitotoxicity, apoptosis, inflammation, edema, oxidative stress), and cyclosporine (mitochondrial disruption, calpain activation, apoptosis, oxidative stress).\(^3\)

Emerging multi-potential neuroprotective agents showing promise in pre-clinical studies include diketopiperazines (apoptosis, calpain activation, cathepsin activation, inflammation), substance P antagonists (inflammation, blood-brain barrier, edema), SUR1-regulated NC channel inhibitors (apoptosis, edema, secondary hemorrhage, inflammation), cell-cycle inhibitors (apoptosis, inflammation), and PARP inhibitors (apoptosis, inflammation).\(^4,5\)

McConeghy and et al’s review of neuroprotection pharmacologies in CNS Drugs\(^5\) provides an excellent survey of the current state of pharmaceutical development strategies in TBI.

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