Defence Research and Development Canada
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Blast-induced mild traumatic brain injuries

Loading mechanisms, diagnostic tools, research efforts and emerging technologies

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Technical Report
DRDC Valcartier TR 2013-236
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Abstract

Blast-induced mild traumatic brain injuries (mTBI) can induce significant cognitive deficits and, lead to neurodegeneration. It often remains undiagnosed in a military context because emergency medical attention is directed towards more severe and life-threatening injuries. Recent studies have shown that mTBI may be responsible for a variety of effects on the central nervous system (CNS) and might play a role in some aspects of post-traumatic stress disorder (PTSD). Since soldiers routinely use ammunitions and dangerous explosives, they are under the constant risk of blast exposure in their operational duty. Military personnel protective equipment (PPE) being increasingly efficient against fragmentation and shrapnel penetration, there has been a decrease in the number of fatalities due to explosions and care providers are now dealing with various forms of TBI. Blast-induced neurotrauma injury mechanisms are challenging to define since the sensitivity of brain tissue to various levels of stresses and strains have yet to be determined. Traumatic brain injuries, whether caused by Improvised Explosive Devices (IED) or repeated exposure to lower intensity explosions, can result in a subset of physiological and pathological changes such as neuroinflammation, neuronal death and diffuse axonal injuries (DAI). The extent of these injuries can vary and clinical data indicate that there may be a difference between blast-induced TBI and TBI related to deceleration or impact. There is little information available on threshold levels and injury criteria for blast exposures. Brain damage after a blast has been established both clinically and experimentally, but the comprehension of the cellular response would require more extensive characterization to ascertain the injury mechanisms. Therefore, it is of great importance to identify the pathways responsible for mTBI in order to provide adequate care and protect adequately military personnel against overpressure. Thus, there is a need to determine a mechanistic injury tolerance level through the use of experimental models, biofidelic surrogates, computer simulations or a combination of these methodologies. Defining these physiological thresholds will allow the implementation of protection equipment to better assess the risk of mTBI occurrence in a military context.

This report presents the findings of a literature review carried out in 2011. More specifically, the review sought to capture new theories on blast injury mechanisms, injury criteria and material properties. This effort was undertaken under the bilateral collaborative research agreement "Development of a Novel Biofidelic Headform for Blast-induced Brain Trauma Assessment" between Defence Research and Development Canada Valcartier (DRDC) and the Combating Terrorism Technical Support Office (CTTSO) Technical Support Working Group (TSWG), Personnel protection soup-group.

Résumé

Les lésions traumatiques légères au cerveau résultant de l'effet du souffle peuvent induire des déficits cognitifs importants et même conduire à une neurodégénérescence. Dans un contexte militaire, ces lésions sont souvent non diagnostiquées parce que l'attention médicale est souvent dirigée vers des blessures les plus graves qui menacent la vie du soldat. Des études récentes ont montré que les blessures crâniennes induites par l'effet du souffle peuvent être responsables d'une variété de conséquence sur le système nerveux central et peuvent jouer un rôle dans certains aspects du syndrome de stress post-traumatique. Puisque les soldats utilisent régulièrement des munitions et des explosifs, ils sont souvent à risque d'être exposé à un effet de souffle de plus ou moins grande intensité. L'équipement de protection du personnel militaire étant de plus en plus efficace contre la fragmentation, il y a eu une diminution du nombre de décès suivant une explosion et les prestataires de soins doivent maintenant faire face à diverses formes de traumas affectant le cerveau. Les mécanismes de blessures liés aux traumatismes neurologiques crâniens sont difficiles à identifier puisque la sensibilité des tissus du cerveau à différents niveaux de stress et de déformation n'a pas encore été bien déterminée. Les lésions traumatiques cérébrales, qu'elles soient causées par des engins d'explosifs improvisés ou l'exposition répétée à des explosions de moindre intensité, peuvent donner lieu à un sous-ensemble de changements physiologiques et pathologiques tels que la neuro-inflammation, les blessures de type DAI et la mort neuronale. L'étendue de ces lésions peut varier et les données cliniques semble indiquer qu'il peut y avoir une différence entre les traumas crâniens liés à un effet du souffle et ceux liés à une décélération ou à un impact direct. Malheureusement, il y'a peu d'informations disponibles sur les seuils et les critères de blessures pour les expositions à l'effet du souffle. Des lésions cérébrales suivant une explosion ont été constatées cliniquement et expérimentalement, toutefois la compréhension de la réponse cellulaire reste à explorer. Par conséquent, il est d'une grande importance d'identifier les causes de ce type de trauma afin de fournir des soins adéquats et s'assurer du niveau de protection offert au personnel militaire. Ainsi, il est nécessaire de déterminer des seuils de tolérance aux effets de souffle et se basant sur le développement de modèles expérimentaux et numériques. La définition de ces seuils permettra la mise en place d'équipements de protection afin de mieux évaluer le risque d'apparition de ce type de lésions.

Ce rapport est le résultat d'une revue de la littérature qui a été entreprise entre en 2011 pour mettre à jour les connaissances scientifiques dans ce domaine. Plus précisément, la revue visait à connaître les nouvelles théories sur les mécanismes de blessure, les critères de blessures et les mécanismes de détection. Cet effort a été fait sous une collaboration bilatéral entre Recherche et développement pour la Défense Canada – Valcartier (RDDC) et le CTTSO/TSWG/PP (*Combating Terrorism Technical Support Office / Technical Support Working Group / Personnel protection*).

Executive summary

Blast-induced mild traumatic brain injuries: Loading mechanisms, diagnostic tools, research efforts and emerging technologies

Robert Gauvin, Amal Bouamoul, Simon Ouellet; DRDC Valcartier TR 2013-236; Defence R&D Canada – Valcartier; December 2013.

Introduction: Brain injuries have become more prevalent in current military conflicts. While it remains unclear whether overpressure plays a significant role in this pathology, a multi-phase research program was undertaken in 2006 to develop a head surrogate enabling the ranking of headgear performance in blast environment (The Blast-Induced Brain Injury Protection Evaluation (BI^2PED)).

This report is the outcome of a second literature review that was undertaken between in 2011 to update the knowledge documented in the field of blast-induced mild traumatic brain injuries (mTBI). Specifically, the review sought to capture new theories on primary blast injury mechanisms and identify injury criteria that may be useful for the development of the BI^2PED headform. A deeper understanding of both the physical and cellular mechanisms involved in the pathophysiology of brain injury is required to determine whether or not improvements in the performance of military helmets against overpressure are necessary.

Results: There has been much research into understanding the effects of blast waves on cerebral tissue and the propensity for brain injury to occur in a blast environment. Following exposure to blast waves, brain cells become activated and initiate a signaling cascade leading to the degeneration of neurons and glial cells resulting in impaired normal brain function. Generally, the latest research suggests that blast wave interaction with the head is still not well understood and that the exact mechanism by which the brain is injured is unclear. Nevertheless, the literature review did identify potential medical pathways, biosensors and living material and numerical methods that can be used in the developments of a biofidelic headform surrogate.

Significance: The findings of this literature review might provide guidance for the design of the BI^2PED headform surrogate and enable to better focus research efforts.

Future plans: The objectives of further studies could be to develop a precisely controlled surrogate model comprised of biosensors and living material. By controlling the physical parameters occurring around the model during blast exposure (i.e. using different charges and distances) this model would allow establishing the parameters necessary to reproduce mild, moderate and severe TBI. Another area where research is essential is the ability to reduce and reverse the degenerative effects of blast-induced TBI.

Sommaire

Blast-induced mild traumatic brain injuries: Loading mechanisms, diagnostic tools, research efforts and emerging technologies

Robert Gauvin, Amal Bouamoul, Simon Ouellet ; DRDC Valcartier TR 2013- 236; R & D pour la défense Canada – Valcartier; décembre 2013.

Introduction : Un programme de recherche s'échelonnant sur plusieurs phases dans la section protection et effets d'armes de DRDC Valcartier a été entrepris en 2006 pour développer un prototype expérimental de tête instrumentée ((The Blast-Induced Brain Injury Protection Evaluation (BI^2PED)) permettant d'évaluer et de classer la performance des casques militaires vis-à-vis les effets de souffle. Ce rapport est le résultat d'une deuxième revue de littérature qui a été entrepris en 2011 afin de mettre à jour les connaissances publiées dans ce domaine. Plus précisément, l'étude visait à connaître les nouvelles théories sur les mécanismes et les critères de blessures pouvant être utilisés dans le développement de la tête instrumentée. Une meilleure compréhension des mécanismes physiques et cellulaires impliqués dans la physiopathologie des lésions cérébrales sont nécessaire afin d'évaluer le nécessité d'améliorer les équipements de protection pour réduire le nombre de blessures lié aux effets du souffle.

Résultats : Plusieurs recherches ont été effectuées sur la compréhension des conséquences de l'effet du souffle sur le tissu cérébral et comment la lésion cérébrale se produit et se propage. Après une exposition au souffle, les cellules du cerveau sont activées et déclenchent une cascade de signalisation conduisant à la dégénérescence des neurones ce qui résulte en un affaiblissement des fonctions cérébrales. Les plus récentes recherches suggèrent que l'interaction d'ondes avec la tête n'est toujours pas bien comprise et que le mécanisme exact par lequel le cerveau est blessé n'est pas bien documenté. Néanmoins, la revue de la littérature a identifié quelques voies médicales prometteuses, des biocapteurs, des cultures biologiques et des méthodes numériques qui peuvent être utilisés dans les développements d'un prototype de test biofidèle.

Importance : Les résultats de cette revue seront utilisés comme référence pour guider la conception du la tête instrumentée ainsi que dans l'orientation générale du programmes de recherche.

Perspectives : Les objectifs de nouvelles études pourraient être de mettre au point une tête instrumentée composée de biocapteurs et de cultures biologiques. En contrôlant les conditions physiques qui agissent sur la tête lors de l'exposition à l'effet du souffle (par exemple différente charges explosives à différente distances), ce modèle permettrait d'établir les paramètres nécessaires à la reproduction légère, modérée et sévère du traumatisme. Un autre domaine de recherche essentielle est la capacité de réduire et d'inverser les effets dégénératifs de l'effet du souffle.

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Acknowledgements

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1 Introduction

The first description of blast effects on human subjects originated from WWI, when the term shell shock emerged as a new terminology to define exposure to an explosion [1]. Since then, it has not been determined if the symptoms associated with this exposure were due to a physical or a psychological condition. However, it did spark an interest for military research in this area [2-4]. Soldiers routinely train with munitions and dangerous explosives and travel in tactical vehicles, aircrafts and ships depending on fuel for mobility. Thus, they are under the constant risk of exposure to blast waves in their operational duty, both during exercise and operations in armed conflicts. According to recent statistics, explosive blasts accounted for over 60% of combat casualties in Operation Iraqi Freedom and Operation Enduring Freedom [5, 6]. Moreover, of all soldiers returning from Iraq and Afghanistan, 44% have shown post-traumatic stress disorder (PTSD) symptoms [7]. These numbers can be explained by the fact that soldiers are being equipped with more efficient protective equipment against fragmentation and shrapnel penetration, reducing the number of fatalities and increasing their survival rate. Consequently, neurotrauma has emerged as the signature wound of recent armed conflicts, following a significant increase for this type of injuries compared to previous wars [8, 9]. Since more soldiers are now surviving exposure to an explosion, care providers must deal with various forms of TBI, caused by fragments, blunt impact or perhaps the shock waves, the latter being referred to herein as blast-induced TBI. The last ten years have led to a considerable augmentation in the amount of literature and work performed on blast-induced TBI. Large amounts of funding have also been attributed for research by multiple agencies, clearly indicating a will to tackle this pathology and optimize soldier protection against all potential threats.

According to the Committee of the American Congress of Rehabilitation Medicine, a diagnosis of blast-induced mild traumatic brain injury (mTBI) is provided when an explosion results into a short duration (< 5 minutes) loss of consciousness, a loss of memory, an alteration in mental status and focal neurological deficit following the injury [10]. Multiple studies have confirmed the presence of cognitive, behavioral and emotional post-concussion symptoms in service members who reported having sustained injuries consistent with mTBI [7, 11, 12]. However, mTBI does not represent a critical problem when compared to close proximity blast exposure leading to physical damage such as multiple fractures and penetrating head wounds [13]. Thus, patients suffering from mild traumatic blast injuries are often classified as lightly injured with the incidence of these traumas being greatly underestimated. Although mild and moderate blast injuries often go undiagnosed or untreated because emergency medical attention is directed towards more severe injuries, mild traumatic brain injuries can produce significant deficit and lead to neurodegeneration [10]. Previous results have shown that blast injury can be responsible for a variety of effects on the central nervous system (CNS) and some aspects of PTSD, suggesting that blast injury should be treated as a more severe injury than is nowadays stated [14]. Since PTSD complicates the outcomes for a high proportion of deployed soldiers reporting blast-related TBI symptoms [15], there is an urgent need for a tool that would allow discriminating physical injuries from psycho-cognitive disorders [14]. There is little information available on either brain injury threshold levels or brain injury criteria for blast exposures. The potential for brain damage after a blast has been reported both clinically and experimentally, but the cellular pathophysiology of the brain response would require more extensive characterization to improve our knowledge of the injury mechanisms.

Explosive detonations produce a high peak pressure followed by a transient shockwave, resulting in a considerable impulse of energy transmitted through the surroundings. The kinetic energy from the blast wave propagates through the body and initiates a large spectrum of frequencies and stress concentration at multiple sites, including the air-containing organs as well as other tissues such as the brain. This energy transfer has been shown in animal studies to initiate damage to the CNS and result into indirect neurotrauma (Figure 1).

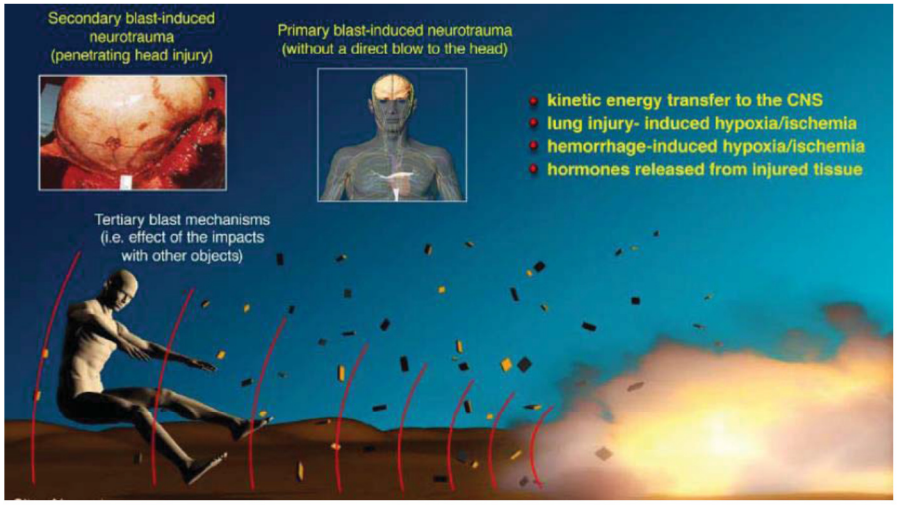

Figure 1: An explosive detonation creates a considerable impulse of energy transmitted through the body, leading to various types of injuries. [74]

Traumatic brain injury, whether it is caused by rapid acceleration-deceleration or by blast caused by Improvised Explosive Devices (IED), results in a subset of physiological and pathological changes such as neuroinflammation, neuronal death and diffuse axonal injuries (DAI). The extent of these injuries can vary from one type to another and clinical data indicate that the intensity and severity of these pathologies may differ between blast-induced TBI versus TBI related to deceleration or impact. Mild traumatic brain injury and blast-induced neurotrauma injury mechanisms are challenging to define since the sensitivity of brain tissue to various levels of stresses and strains have yet to be determined. Despite the importance of understanding and mitigating blast-induced TBI, little is known about shockwave propagation through the head and brain tissue and about the effects of wearing personal protective equipment (PPE).

A number of studies on impact-related TBI have established injury tolerance criteria and have linked head kinematics to relevant quantitative mechanical and biological metrics in collision sports and motorized vehicle accidents [16-20]. On the other hand, the incomplete understanding of blast-induced traumatic brain injury does not allow for the representation of a rigorous temporal sequence of events that would cover the whole mechanism leading to brain injury [21]. Accumulating experimental and clinical evidences suggest that a blast wave can cause brain injury as symptoms have been observed in the absence of either penetrating wounds to the head (secondary blast effects) or acceleration/deceleration or coup/countercoup effects (tertiary blast effects) [22]. Thus, peak pressure, duration or impulse might represent appropriate mechanical variables to determine relevant injury tolerance criteria. However precise indicators for neurotrauma initiation still remain to be established. Some recent numerical simulation and computational work has suggested that the load developed inside the brain during blast exposure

could be due to the flexure of the skull [23]. However, experimental data are still needed to validate this injury mechanism hypothesis. Repeated concussions and repeated exposure to low intensity shocks can also lead to a sub-cellular form of TBI that not only impairs day-to-day function, but also increases the long-term risk of developing neurodegenerative diseases [24-30]. Therefore, it is of great importance to identify the mechanisms responsible for mTBI in order to provide adequate care and improve the protection of military personnel against this type of threat.

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2 Loading and injury mechanisms in mTBI

Explosive devices can be divided into many categories: those that can be projected to a target, those exploding passively when a target sets off a trigger, those detonated from a remote location and those transported and detonated at a specifically chosen site to induce a maximum degree of trauma. During a detonation, the explosive charge is rapidly converted into a gas, creating a pulse of increased air pressure lasting only milliseconds [31-33]. The pressure wave travels faster than the speed of sound and is followed closely by a blast wind generated by the massive air displacement caused by the expanding gases. Depending on the type and quantity of explosive, the velocity and impulse of the blast wave can vary. When this wave impacts on the body, part of the wave is deflected or reflected, but most of it is absorbed and propagated through the continuum [33, 34]. These high frequency stress waves are believed to injure human tissues through multiple mechanisms including spallation, implosion and inertial effects [35]. Spallation results from a pressure wave traveling through media of different densities, where a portion of the denser medium displaces into the space originally occupied by the less dense medium. Implosion occurs when gases within the tissues are suddenly compressed by a blast wave. In both spallation and implosion cases, organs can be damaged by collapsing on themselves or by expanding at high rates, which releases kinetic energy that may disrupt cells and tissue. Inertial effects are occurring when tissues are propelled at different speeds as the overpressure wave passes through the body. These forces result in similar effects to those seen in impact related TBI, damaging the tissue structure and components. Factors that influence the injury level include the charge of explosive, the location of the subject from the detonation (standoff distance and height), the orientation of the body to the blast wave and the environmental factors surrounding the blast event [34]. From a personnel protection point of view, there is a need to determine a mechanistic injury tolerance level through the use of experimental models, biofidelic surrogates, computer simulations or a combination of these technologies. Defining this physiologic threshold will allow the implementation of protection equipment and better assessment of the risk of mTBI occurrence in a military context.

2.1 Loading mechanisms during blast exposure

In general, blast injuries are divided in 4 four distinct categories. Injuries caused by a direct interaction with the blast wave are called primary blast injuries. Injuries caused by objects that are set in motion by the blast and that are striking the subject are classed as secondary blast injuries. Injuries caused by the dynamic force of the blast blowing a subject against another object are termed tertiary blast injuries. Finally, injuries caused by the exposition of the subject to smoke, debris and other environmental factors causing harm or discomfort are termed quaternary blast injuries [31, 36]. These mechanisms are summarized in Table 1.

A blast wave has a finite amplitude and duration, which releases a large amount of energy in a short period of time (Figure 2). An idealized free-field blast can be described by the biphasic Friedlander curve, presenting an instantaneous rise to peak pressure followed by an exponential decay of the pressure as a function of time.

Table 1: Summary of the body injury mechanisms caused by blast and explosions.

Immediate effects of blasts and explosions
Primary - Direct effects, overpressurization/underpressurization of body and organs Rupture of tympanic membranes Pulmonary damage Rupture of hollow viscera
Secondary - Indirect effects, consequence of the detonation Penetrating trauma Fragmentation injuries
Tertiary - Effects of structural collapse and body motion, consequence of the blast wind Crush injuries and blunt trauma Penetrating injuries Fractures and traumatic amputations Open or close wounds
Quaternary - Environental effects following the blast event Burns Asphyxia Exposure to toxic hazards (chemical, biological, radioactive)

Adapted from DePalma et al. 2005.

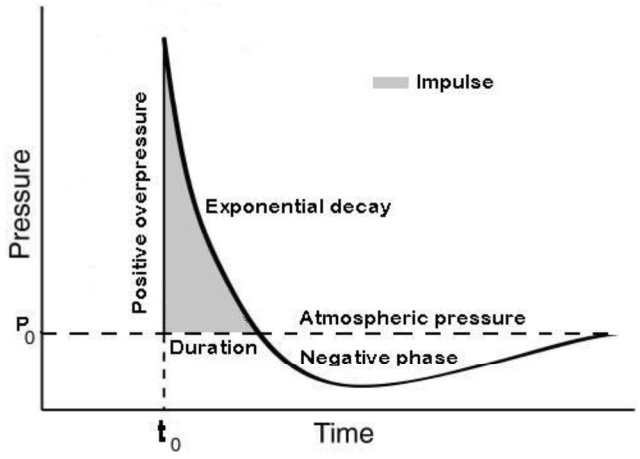


Figure 2: Pressure profile of a free-field blast wave described by the biphasic Friedlander equation. One can observe the instantaneous rise to the peak pressure, the exponential decay leading to the negative pressure phase and the return to atmospheric pressure after the passage of the blast wave. The impulse, in grey, represents the energy released by the explosion and is defined as the area under the curve of the pressure-time relationship. Note that these events are all taking place within the few milliseconds following the detonation.

Due to the short rise time between ambient and peak pressure, the shock front is considered to be an instantaneous step on the timescale of approximately one microsecond. This rapid loading and traveling shockwave will cause the excitation of high frequency modes of vibration in the system

being exposed. It is important to be aware that blast-induced stresses occur on a shorter timescale than those associated with intracranial accelerations linked to impact-related TBI. The wave profile can be modified by various factors encountered during the blast scenario. Reflection, reverberation and amplification effects can augment the complexity of the wave and increase the duration of the event, depending on its interaction with the surrounding environment. Thus, a blast wave might not always consist of a single wave front followed by intense blast winds coming from a single orientation and loading tissues in a preferential direction [32]. It is also necessary to understand that an explosion is a non-linear and complex fluid flow influenced by various environmental factors. The propagation of the shockwave within the air and its interaction with anatomic structures such as the skin, skull, intracranial tissues and body fluids result into longitudinal and transverse shear forces, as well as tension and compression loadings. The distance from the site of detonation is of the utmost importance regarding these loading conditions, since the intensity of the pressure wave declines with the cube root of this distance. Previous work has shown that solid abdominal organs such as the liver and kidneys have higher injury thresholds than gas-containing organs such as lungs and ears and that injuries in different organs can be induced by various mechanisms [26].

A blast wave generates shear and stress waves interacting with the body. A significant fraction is absorbed by the skull and propagated through the brain as a stress wave [33]. Part of the incident shockwave is reflected against the skull surface, which is a solid structure that can resist compression loading, while another fraction is deflected. Thus, this structure plays a protective role against deformation or flexure against the blast wave. It has been demonstrated that skull bone reflects a fraction of the shockwave at approximately 580 m/s, whereas the portion transmitted to the brain travels at speed near 3000 m/s despite the impedance mismatch between the skull and brain tissue [1, 4]. At this interface, density changes along with material sound speed variations result in different impedances. When the shockwave encounters this interface of mismatched impedance, different degrees of transmission and reflection occur, causing complex interaction between the wave and the two materials. These impedance mismatches can lead to significant pressure changes at the interface, potentially focusing and amplifying the pressure and energy transfer [37]. The definition of this energy transfer process, which deforms the tissues in a non-linear fashion due to their viscoelastic and anisotropic properties [38], remains challenging since the stress and strain involved during a blast event occur at high rate and are applied during a short period of time. Since the brain's mechanical behavior is dependent upon strain and loading parameters, it is likely that the response of brain cells subjected to two different strain rates will also differ [39]. This parameter has a considerable importance since cellular injury and brain viscoelasticity are more impacted by the stress rate than the total stress applied on the system. Given the short duration of an explosive blast shock, the force and pressurization effects on the head will also vary at different points within and along the head, and might result into localized brain injuries.

The proposed mechanisms by which blast waves result in brain damage includes brain contusion caused by a movement against the rough interior of the skull, indirect hit of the brain opposite the location of the impact, as well as shearing and stretching of brain tissue due to a relative motion of brain structures to each other. These results are mostly emerging from post-traumatic TBI studies, where it has been noted that most brain injuries occurring in car crash tests and/or following impacts or direct blows to the head were observed in the frontal, temporal and cingulated regions of the brain [40]. Animal studies have shown a relationship between the orientation of the blast wave and different types and localization of brain damage such as diffuse

axonal injuries (DAI) [41]. DAI can result from loadings that cause shearing or stretching of axons, leading to impaired axonal transport and focal swelling. Most commonly, DAI affects gray and white matter junction, mainly in the frontal and temporal region (Figure 3).

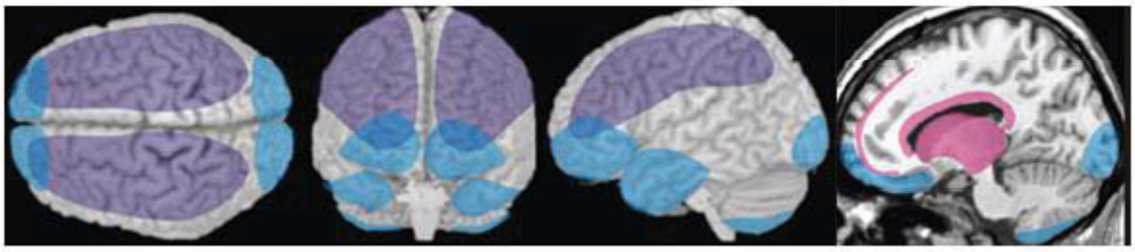


Figure 3: The most common types of non-penetrating traumatic brain injuries are diffuse axonal injury, contusion, and subdural hemorrhage. Preferential locations for diffuse axonal injury (pink) are the cortico-medullary (gray matter/white matter) junction (particularly fronto-temporal), internal capsule, deep gray matter, upper brainstem, and corpus callosum. The most common locations for contusions (blue) are the superficial gray matter of the inferior, lateral and anterior aspects of the frontal and temporal lobes, while the most common locations for subdural hemorrhage (purple) are the frontal and parietal convexities. [42].

It has been suggested that the sulci, the network of folds that covers the surface of the brain and has an intricate geometry, could protect internal structures from various loading conditions [43]. However, it is likely that the exposure to high frequencies could cause severe damage to the brain [30], although the transfer of mechanical energy from the blast to the brain at the macro- and microscale remains misunderstood (Figure 4) [44].

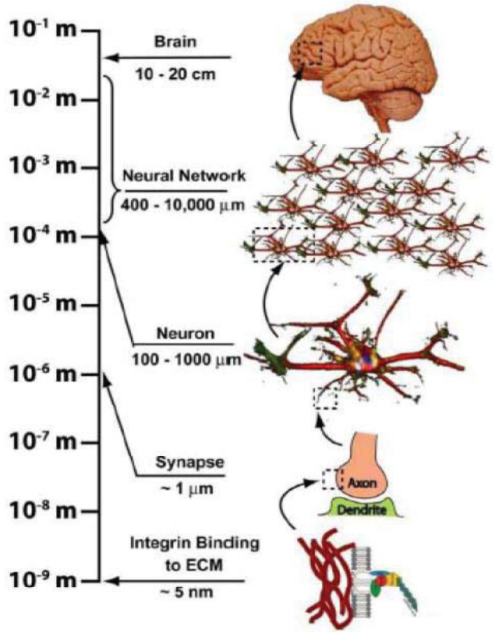


Figure 4: The energy released from a blast transmits macroscopically to the brain. However, it is unclear if axonal injuries occur due to the overpressure, the impulse, or if it is due to delayed secondary mechanisms, damaging brain structures via cellular and molecular pathways.

There is currently a lack of consensus about the physics of shockwaves used in mTBI research, since most studies published in medical and physiological journals do not describe extensively their experimental setups and parameters. The pressure terminology remains confusing and the exact location of a subject from the charge is often missing, making it hard to distinguish if the desired waveform and its reflection do not result in a more complex phenomenon than a simple Friedlander waveform. Various other hypotheses have been considered to explain how the blast energy could be transferred to the brain and create traumatic injuries. For example, it has been hypothesized that blast forces could be focused by the orbital sockets into brain structures [45]. A thoracic mechanism has also been proposed for blast-induced brain injury [46, 47]. This theory relies on the fact that a high pressure wave hitting the body could compresses the abdomen and chest, transmitting the pressure loading to the vasculature of the brain via the systemic circulation. Animal studies have provided mitigated results regarding the thoracic hypothesis. This mechanism still requires more investigation in order to be accepted as a plausible mechanism for mTBI [50]. Lastly, a recent study also suggested that a bone piezoelectricity phenomenon could produce a short range electric field in response to an applied mechanical stress, and potentially be a source of intense electric fields that might affect neurological function [51]. These electric fields were estimated to be on the order of 10 V/m over millisecond duration pulses, exceeding Institute of Electrical and Electronics Engineers safety standards by an order of magnitude and comparable to electric fields known to have neurological effects [52]. In spite of these findings, lots of work remains to be done in these areas to demonstrate that those mechanisms represent a significant percentage of the occurrences for mTBI.

Computer simulations models have also predicted various potential mechanisms of injury, including high strain effects in coup and countercoup regions, high shear stress in white matter resulting in diffuse axonal injuries, blast pressure magnification caused by the reflection of the blast wave into the skull and potential skull flexure inducing damages to brain tissue [23, 53-57]. The development of sensors measuring the level of load and deformation into these structures would be a useful tool to experimentally confirm these models and design efficient head protective equipment [58]. Along those lines, military helmet liners have evolved from leather to plastic suspensions to sophisticated energy-absorbing padded liners, significantly increasing the capacity of this equipment to resist to impacts. Additional modifications might be necessary in order to make these helmets resistant to the passage of a shockwave.

2.2 Injury mechanisms following blast exposure

It is unclear whether the blast-induced brain injuries mechanisms are similar to impact-related TBI like those seen in sports or automotive crashes, or if blast injury mechanisms produce physiologically distinct changes. However, both these loadings generate similar symptoms and cognitive outcomes (Figure 5).

Brain damage following traumatic injury is a result of direct (mechanical disruption, primary injury) and indirect (secondary or delayed) mechanisms, but blast-induced mTBI does not involve the breakage of the blood-brain-barrier and does not lead to an acute inflammatory response [59]. Brain tissue, like most other connective tissues and biological materials, is a non-linear viscoelastic material. Recent evidence suggests that the biological response of single living cells mimics the mechanical behavior of the tissue, i.e., the response of the cells is strongly influenced by the magnitude and rate of the mechanical stimulus [60]. It has been shown that externally applied loadings on adherent cells in culture can produce changes in cell dynamics, in cytoskeletal and membrane rearrangement and can influence the cell physiological response such as intracellular signaling and apoptosis [61-64]. Cellular responses play an important role in brain injury after blast exposure. Cell morphology provides evidence of degenerative processes in neurons, featured by their darkened atrophic dendrites and accumulation of heavy subunits of neurofilament proteins [25]. When neural axons are stretched beyond a critical threshold, normal biochemical processes in the cells are disrupted, leading to functional impairment of the neurons or in worse cases, cell death (Figure 6).

It has been estimated that TBI is likely to occur *in vivo* for brain deformations larger than 10% and occurring at a strain rate greater than 1/10 of a second [65]. More recent *in vitro* studies have determined that stress over 20% is likely to induce neuronal damage [66], but strains of approximately 10% are not injurious at strain rates lower than 1/50 of a second [67]. Studies have identified various brain tissue pathologic features and outcomes following exposure to blast (Figure 7), ranging from cell death [68-70], increases in intracellular calcium [70, 71] and changes in gene expression [72]. It has been demonstrated that calcium elevation in brain cells following a mechanical insult can result into axonal injury [73] and recent work showed that mechanical stress can lead to the release of proteins that can further exacerbate the initial injury [74].

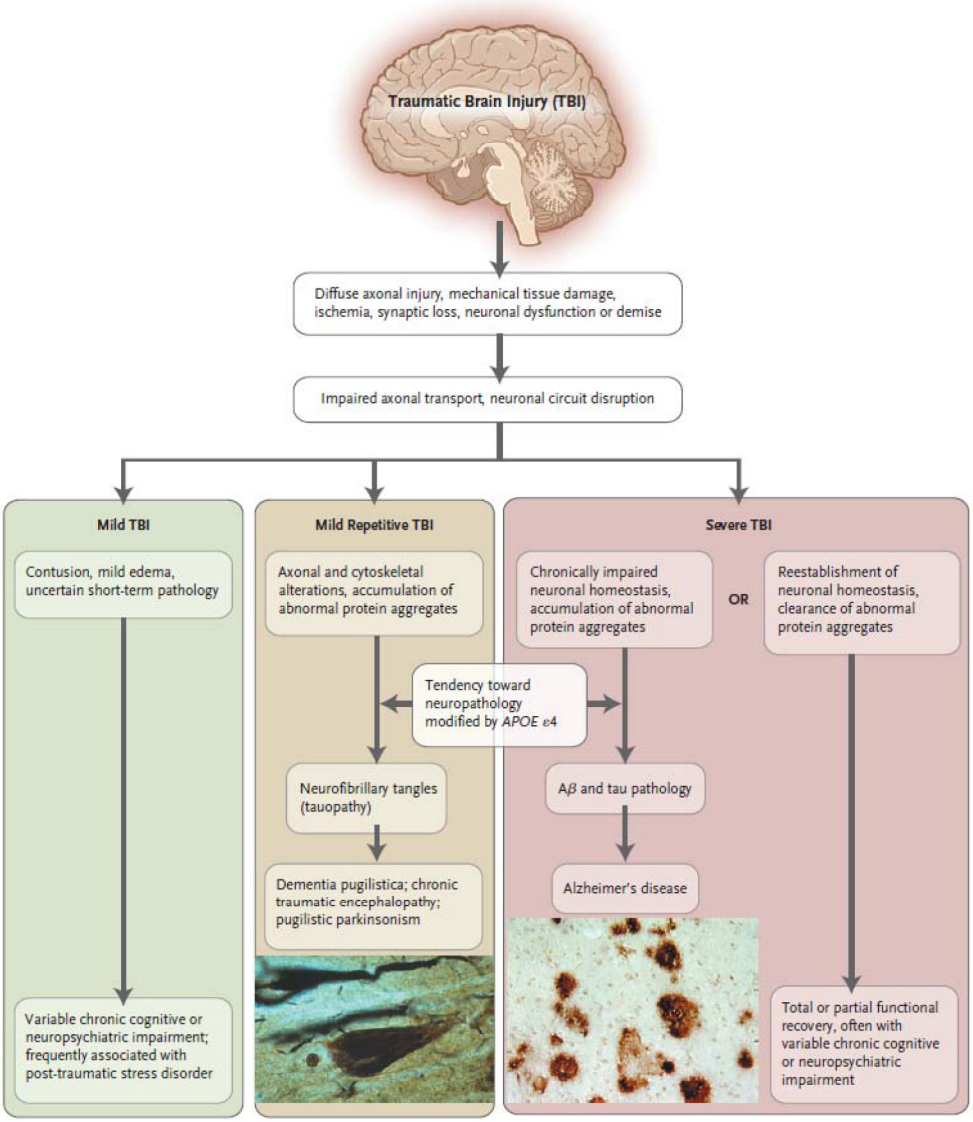


Figure 5: Spectrum of pathologic features and outcomes of traumatic brain injury, regardless of the injury mechanism. [21].

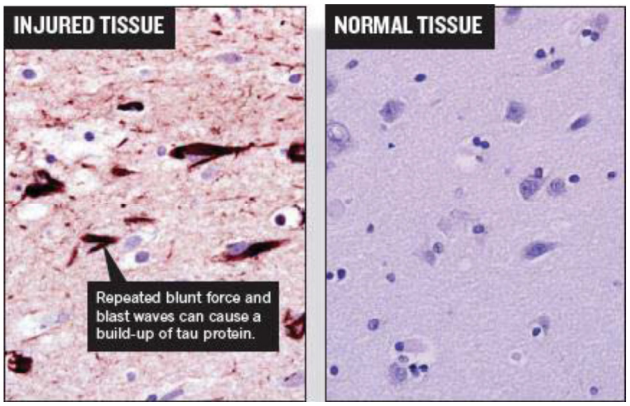


Figure 6: Brain tissue affected by a blast wave can show few outwards signs of injury. However, microscopic examination can reveal neurological abnormalities similar to those found in Alzheimer disease [24].

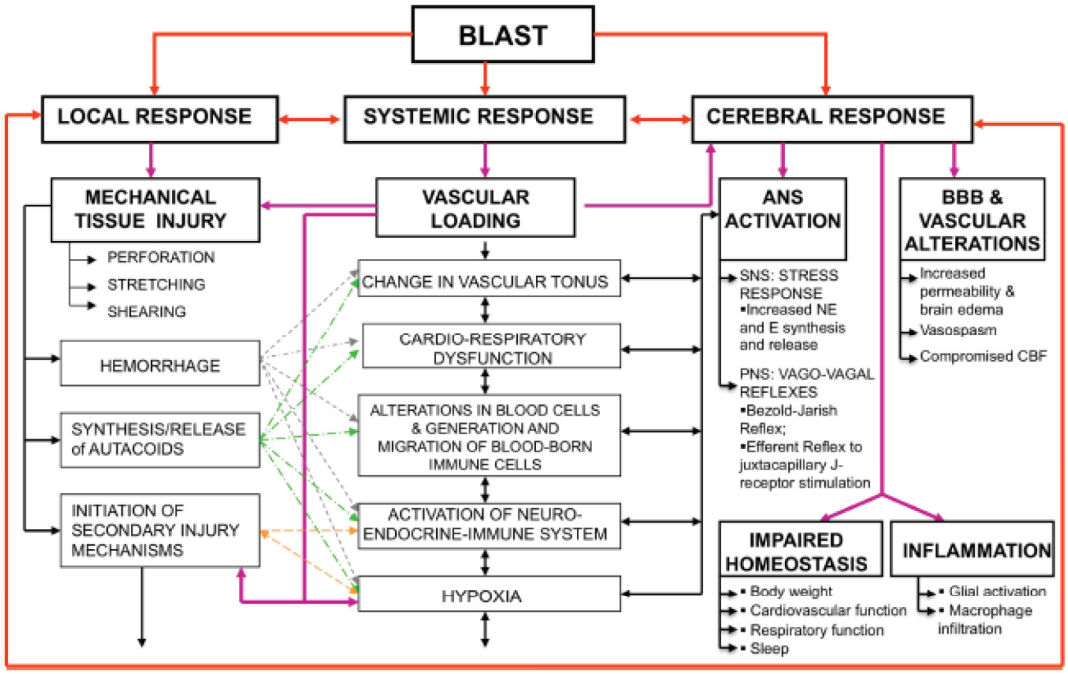


Figure 7: Activation of systemic, local and cerebral response to blast exposure, and interactive mechanisms causing or contributing to blast-induced neurotrauma. (Abbreviations: ANS, autonomous nervous system; BBB, blood brain barrier; BINT, blast-induced neurotrauma; CBF, cerebral blood flow; E, epinephrine; NE, norepinephrine; SNS, sympathetic nervous system; PNS, parasympathetic nervous system) *[74].*

The physical deformation of neuron cells can result in transient calcium influx activating mechanotransduction pathways, causing deleterious effects to astrocytes [75, 76]. Plasma membrane disruption may be the earliest cellular outcome of a mechanical trauma. The increase in cell permeability plays an important role in the initiation of cascades following brain injury. The integrity of the plasma membrane is critical in maintaining ionic gradients that are used by neurons to perform neurotransmission [77]. Immediately after a mechanical insult, the membrane becomes non-specifically disrupted, which permits uncontrolled ionic flux in and out of the cell. For example, the release of glutamate from neurons and glial cells can initiate a cascade resulting in impaired neuronal function [78-82]. Glutamate is considered to be the major mediator of excitatory signals in the CNS. It is involved in most aspects of normal brain function including cognition and memory. It is also known to regulate brain development, cell proliferation and differentiation and is responsible for the formation of synapses in brain tissue [83, 84]. Disruption of the cell membrane allow the intracellular glutamate to be released in toxic quantities outside the cytoplasm, therefore resulting in the activation of apoptotic cascades via the glutamate receptors and leading to the death of the surrounding cells [85-87]. Such mechanisms and other molecular pathways are well-known in the pathophysiology of TBI (Figure 8).

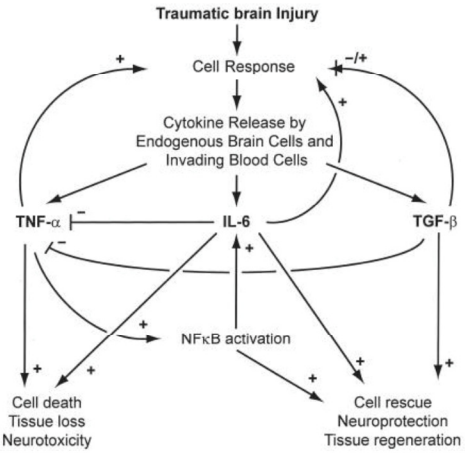


Figure 8: Relationship between biomolecules and cytokines following traumatic brain injury. TBI leads to multiple cellular responses accompanied with the release of various mediators directing cell behavior. These mediators, for example interleukin (IL), Tumor growth Factor(TGF)-beta and Tumor Necrosis Factor (TNF)-alpha can lead to various mechanisms depending on the load and strain rate applied on the cells [59].

Other possible neuronal injury mechanisms include voltage-sensitive sodium and calcium channels malfunction induced by cell depolarization [27, 88-90], nitric oxide synthase and reactive oxygen species release causing protein, DNA and lipid damage as well as the activation of mechanically sensitive mitogen-activated protein kinases. These kinases, such as ERK, JNK and p38, are all known to be activated by mechanical cues and leading to apoptotic cell death [75, 91-94]. Changes in gene and protein expression under mechanical stimulations have been demonstrated for numerous cell types. Thus, mechanical injury of brain tissue could lead to abnormal activation of the molecular pathways responsible for mechanotransduction. An extensive review of these cellular mechanisms is beyond the scope of this manuscript, but the current knowledge regarding these injury pathways and the management of their outcomes can be found elsewhere [95-97].

The mechanical events that cause injury to brain cells initiate an extended cascade, which may develop over minutes to hours following the blast. It has been shown that axons are not typically torn or stretched upon blast exposure, but rather secondary neuronal damage is responsible for axons disruption [59, 98, 99]. Clinical research now shows that the development of neurological injuries is not limited to the time of the blast event and is likely to evolve for hours following the trauma via delayed inflammatory events (Figure 9).

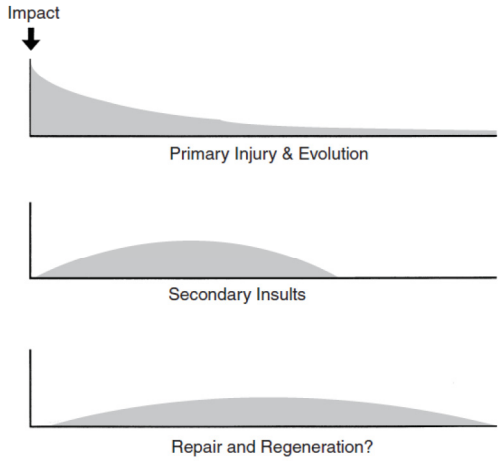


Figure 9: The blast event triggers a biological reaction leading to delayed cellular responses. This response can result into various outcomes such as neuroprotection, reversible neuronal damage, neurodegeneration or even cell death [99].

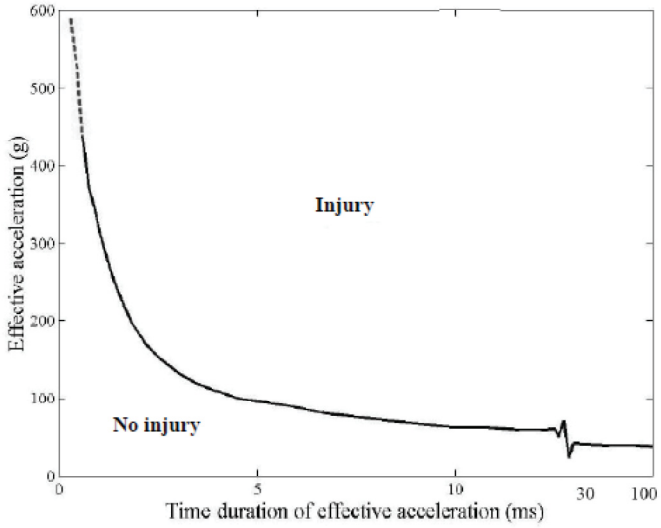
Mild TBI causes focal impairment of the axonal cytoskeleton through mechanical and biochemical alterations, leading to axonal swelling and disconnection of downstream axonal segments [100]. For example, a transient disruption of calcium homeostasis may be an early event that initiates a series of aberrant signaling cascades that ultimately leads to cell dysfunction. Abnormal calcium homeostasis is a critical component of the progression of secondary injury in both gray and white matter. In neuronal cell injury, a calcium imbalance is associated with post-synaptic receptor modification and cell death [88]. Following secondary injuries, axonal membranes become disrupted, allowing the massive influx of extracellular calcium to enter the cells constituting the white matter. This increased calcium concentration can initiate a cascade of events, in which enzymes degrade the key structural proteins responsible for the maintenance and transport of solutes, resulting in axonal disconnection and loss of functionality [101]. These diffuse axonal injuries are characterized by the separation and extension in white matter tracts. Genes associated with apoptosis such as c-jun, c-myc and c-fos were also found to be expressed throughout the layers of the laminar structure of the cerebral cortex 2 hours after exposure to short-lasting impulse noise [29]. Another mechanism that has been established to play a role in mTBI is the oxidative stress (overproduction of reactive oxygen species) [102]. These delayed and active molecular processes, involving white matter deterioration and neuronal cell death, give hope that therapeutic options will be developed to inhibit these mechanisms and protect brain cells against delayed injuries.

Gene and protein expression appears to be modified by mechanical trauma in brain cells when exposed to a highly dynamic environment. Recent clinical data have shown that repetitive low-intensity blast exposure can cause mild traumatic brain injury, translating into persistent post-concussive symptoms and permanent brain damage [103]. It is likely that the repeated effect of lower intensity blast exposure might induce brain injury. An example of this is weapons that are commonly used in training and combat exceeding the threshold noise level of occupational safety standards [104]. Brain injury may depend on the degree of attenuation and synergy of the blast wave with the helmet, skin, skull and its transmission to the brain. It was shown that transmission of the shockwave is similar between a bazooka and a howitzer, whereas an automatic rifle has higher frequency spectra which suggest a lower transmission [29]. It is possible to think that a sum of small blast events might change the mechano-transduction cascade and impact on the downstream phenomenon as a molecular switch or trigger leading to brain damage.

2.3 Injury criteria and metrics for mTBI evaluation

One of the main challenges in blast-induced neurotrauma is relating the data measured to the level of injury. There must be a threshold below which no loss of function or concussion symptoms occur and a maximum beyond which irreversible changes in brain function occur [16]. Although brain injury is widely recognized as an important area of research, only a few injury criteria are used to quantify this metric, most of them pertaining to injuries caused by impact or head acceleration/deceleration related to car crash or contact sports [16]. $HIC = \left[\frac{1}{\tau_2-\tau_1}\int_{\tau_1}^{\tau_2}\alpha(t)dt\right]^{2.5}(t_2-t_1)$. $$HIC = \left[\frac{1}{\tau_{2-}\tau_1}\int_{\tau_1}^{\tau_2}\alpha(t)dt\right]^{2.5}(t_2-t_1)$$

The head injury criterion (HIC), based on the Wayne State Tolerance Curve, was developed through extensive research on post-mortem human subjects and is one of the most commonly used metric for safety testing in the automotive industry [105] (Figure 10).



$$HIC = \left[\frac{1}{\tau_2-\tau_1}\int_{\tau_1}^{\tau_2} \alpha(t)dt\right]^{2.5}(t_2 - t_1).$$

Figure 10: The head injury criterion (HIC) developed by Wayne State University. This tolerance curve is the current gold standard for head injury in the automotive industry [105].

Other criteria such as the head impact power (HIP) and the generalized acceleration model for brain injury (GAMBIT) may also be used, but a proof of the relevance of these criteria for blast-induced mTBI situations has not been published. Based on recent studies, it is now believed that mTBI can occur without macroscopic damage and without large translational and rotational motions. The shock wave interaction with the brain can solely result in focal injury to axons and trigger a cascade of events leading to neurological and functional disabilities [14]. Blast-induced brain injury and neurotrauma thresholds are therefore likely to be different from existing automotive-based head response corridors, since the energy absorbed during a collision is quite different from an impulse resulting from blast overpressure. Thus, a completely new set of biomechanical and physiological standards of blast exposure must be established.

The mechanisms that regulate the response of the brain networks have been investigated in numerous studies. However, less attention has been dedicated to the mechanical thresholds triggering these changes. These thresholds can be evaluated from various angles: which regions of the brain are most likely to be affected by the mechanical level of loading, what will initiate neuronal damage, what will trigger functional or cognitive deficit, etc. Biomechanical responses, such as pressure, stress and strain, could be correlated with biologic data to determine a tissue level injury threshold. At the systemic scale, it has been documented that the mean intracranial pressure is usually between 0-0.2 psi, the upper limit being 0.4 psi. However, intracranial pressure (ICP) of 0.4 psi can result in brain damage if prolonged for extended periods of time and ICP rising beyond 0.8 psi is usually fatal [14]. For a highly transient event such as blast, the peak pressure vs. systemic response correlation has also been determined approximately based on prospective studies [106]. For example, it has been established that personnel knock-down occurs

at peak pressure ranging from 1-1.5 psi, eardrum damage occurs from 5-15 psi, lung damage occurs from 30-75 psi and peak pressure above 100 psi often results in fatalities.

Developing a mTBI injury criterion is likely to require an understanding of mechanisms at the cellular level. So far, the indications of TBI pathogenesis suggest an interplay between excitotoxicity, oxidative stress and proteolytic mechanisms that can lead to various cellular dysfunctions [96]. Moreover, the complex cellular signaling initiated by the mechanical injury is often prolonged sometime after the blast event and induces evolutive brain system damage. A relevant blast-induced head injury criterion will have to rely on a combination of tissue loadings as well as cellular injury thresholds based on the initiation of cellular cascades resulting into neuronal alterations. For example, it has been demonstrated that the threshold for astrocyte reactivity to mechanical stimuli is well below the level of stretch that will affect its viability [108]. Axonal strain has also been shown to lead to functional damage of the neurons. However, this metric has never been used as a measure of injury for blast induced mTBI [25, 98, 109]. This method could provide a coupling between the cellular mechanisms of damage at the microscale and the mechanical loading at the macroscale [67, 110]. A valid injury criteria for personnel protection systems must be a biomechanical and physiological index of exposure, whose magnitude indicates a probable level of injury [111]. In the case of mTBI, there is no currently available clear injury criteria linked to peak pressure, impulse or duration since the understanding of the mechanisms of injury remains unclear.

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3 Current diagnostic tools for mTBI

The occupational standards of blast overpressure for military personnel have historically been based on injury data from lungs and ears, which have been considered more sensitive to blast exposure than the brain [45]. More recently, physicians at the Walter Reed Army Medical Center categorized the severity of traumatic brain injury according to the duration of loss of consciousness and post-traumatic amnesia [36]. Mild TBI has been defined as an injury that causes a loss of consciousness for less than an hour or amnesia for less than 24 hours. Moderate TBI causes a loss of consciousness between 1 and 24 hours and post-traumatic amnesia for 1 to 7 days. Severe TBI causes loss of consciousness for more than 24 hours or post-traumatic amnesia for more than a week. However, the consensus regarding what would be a gold standard for the medical assessment of mTBI remains the Holy Grail. Patients suffering from mTBI do not have visible abnormalities on brain imaging, while patients with moderate and severe TBI may show evidences of hemorrhage as well as swelling of brain tissue [112].

The mTBI Diagnostic workshop, held in August 2010 in St. Pete Beach (Florida, USA), regrouped several investigators working in the field of mTBI [113]. The premise of this meeting was to define a few focused research projects that would be completed over the next 2-3 years and used to validate an optimal method or combination of tests accurate and reliable enough for the diagnosis of mTBI within 2-3 hours of injury in theatre of military operations. As a first step, the panel summarized and highlighted the currently available mTBI diagnostic evaluation methods, as shown in Table 2.

Table 2: Currently available evaluation methods for traumatic brain injury diagnostic.

Physiological domain	Evaluation method
Electrophysiology	Brainscope ®Ahead M-100 electroencephalogram
Cognitive assessment	MACE, ANAM and imPACT tests
Systemic function	Pupillometry; Heart rate variability
Vestibular activity	Balance error scoring; Rhomberg test; Vestibular-ocular reflex
Attention/awareness	Smooth pursuit eye tracking (Eye track)
Biomarkers	Blood/serum analysis; Saliva; Urine
Vascular integrity	Transcranial Doppler; Hemodynamics
Structural imaging	Transcranial ultrasounds; MRI; CT-scan
Cranial Nerve function	Olfaction; Oculomotor reflex
Physical examination	Neurological signs; Clinical interview

Adapted from Marion et al. 2011.

To date, this panel has suggested that an ideal diagnostic tool would include a structural interview, a detailed neurological evaluation and a physiological test provided by an adequate biomarker confirming the occurrence of TBI. The panel stated that magnetic resonance imaging, more specifically diffusion tensor imaging, currently remains the method with the most potential to identify presence of mTBI sequelae in a patient, but remains an emerging an exploratory technology [114]. Blood and body fluids constituents, protein levels and electrophysiological

evaluation methods have also been put forward as potential standard tools for an accurate mTBI diagnostic, but none were close to clinical trials or military application at the moment of writing the current report.

3.1 Cognitive and psychological assessments

The symptoms of post-concussive injuries usually correspond to malfunction of the specific area linked with the portion of the brain that sustained damage. Physical and cognitive symptoms associated with mTBI include headache, dizziness, fatigue, impaired balance and coordination, sensitivity to light and sounds, lack of focus and concentration, memory deficit, as well as disrupted executive functions and decision making [12, 94, 115, 116]. These symptoms are qualitatively similar for most patients diagnosed with mTBI regardless of the mechanism of injury [11], but greatly differ in the case of acute traumatic brain injury, where more life-threatening events are taking place [13, 45, 117]. These changes are likely to be multifactorial and caused by the combination and succession of events taking place during blast exposure, such as the presence of post-traumatic stress syndrome and damage to other body tissues. The extensive description of persistent sequelae following blast-induced mTBI is beyond the scope of this review, but this topic has been extensively reviewed by Schultz and colleagues [118].It is worth mentioning that the fact that moderate brain injury increases by 2.3 fold the risk of developing Alzheimer's disease, while a severe head injury can quadruple the risk [119], adds the magnitude of the importance of mitigation.

It has been proposed that repeated exposure to non-injurious blast shockwaves causes impairments in day-to-day function, increased risk of developing neurodegenerative diseases and might induce long-term effects such as memory impairment and abnormal cognitive disorders in soldiers [24, 42, 120]. While this remains to be demonstrated, the performance of PPE exposed to different types of blast should nevertheless be taken into consideration in order to limit the brain damage that soldiers might sustain in their active duty. It has been suggested that it could be possible to link the cellular mechanisms leading to post-traumatic cellular dysfunction to the observed behavioral impairments. However, the difficulty of this approach resides in the design of behavioral testing, which has to be easy to administer and interpret while maintaining its clinical relevance [121].

3.2 Imaging techniques

Traumatic brain injuries can be visualized by various non-invasive imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT), transcranial Doppler and diffusion tensor imaging (DTI) [108, 114, 122]. CT is mainly used to detect head traumas such as skull fracture, herniation or subfalcine shifts, as well as brain parenchymal hematoma. MRI provides similar information, but is more sensitive and can detect smaller lesions such as diffuse axonal injuries (DAI). On the other hand, Doppler imaging measures the physiological condition of the cerebrovasculature and identifies damaged blood vessels of fluid leaks into the cranial cavity due to the injured state.

Conventional imaging techniques such as MRI and CT are capable of rapid identification of hemorrhages, contusions and edema in the dural, cerebral and parenchymal spaces. However, they often result in negative findings when screening for mTBI. Since the absence of visible

damage on structural scans does not necessarily mean that there is no injury at the microscale, it remains important to generate new solutions to adequately determine the source of damage caused by mTBI. DTI is an advanced form of magnetic resonance imaging that is sensitive to DAI [108, 114]. It is based on the understanding that water molecules diffuse more rapidly in a direction parallel to long axonal fibers and has the potential to detect white matter damage. By measuring diffusion in multiple directions, DTI enables calculation of fractional anisotropy and evaluates the integrity of white matter tracts, typically undetectable with conventional MRI and CT imaging (Figure 11).

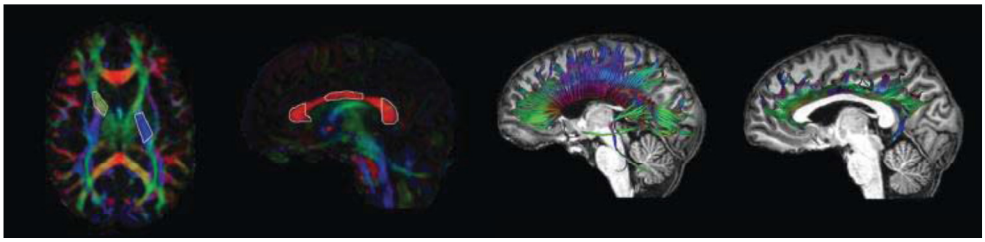

Figure 11: Axial diffusion tensor imaging (DTI) and fractional anisotropy (FA) color map of a subject with blast-induced mTBI, demonstrating the quality of DTI data acquisition. The DTI and FA color map for the same individual is portrayed in the sagittal plane. A sagittal view of the tractography of the total corpus callosum is overlaid on the same subject weighted image, again illustrating the excellent quality of the results [108].

Researchers are currently exploring the relationship between DTI, cognitive outcomes and neurophysiological functions [108]. It has been suggested that a database of images characteristic of mTBI could be used as a tool to categorize the location, nature and degree of damage to the central nervous system sustained by patients suffering mTBI. DTI currently represents the most sensitive tool to identify small tissue damage caused by a blast shock and could be used in a consistent way for clinical research and diagnostic purposes. Although promising, the conclusions regarding DTI analysis remain controversial in terms of the interpretation of the results and the correlation with the extent of axonal damage [123].

3.3 Distinction between PTSD and mTBI

Studies indicate that approximately 80% of patients suffering from TBI develop chronic PTSD, which is an ensemble of anxiety-related symptoms following traumatic events [35, 124]. However, mild TBI and PTSD frequently go undetected as they may occur without a direct blow to the head and in absence of any external injuries. Since the events causing TBI are also responsible for severe combat stress, the two conditions are inevitably linked. Recent studies suggest that soldiers suffering from mTBI have a greater risk of developing PTSD than those having severe brain injuries and who sustained longer periods of unconsciousness [120]. However, no clear conclusion has been made regarding which of these phenomena may precede or be the causal effect of the other.

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4 R&D efforts in blast-induced mTBI

Mild traumatic brain injury is initiated by an insult that surpasses the structural strength of the weakest component of the brain, triggering many interdependent physiological events. The early blast exposure studies date back to the 1950's in Sweden, when Clemedson and colleagues used rabbits to evaluate the effects of blast waves on living subjects in a cylindrical detonation chamber [2]. Since this pioneering work, various approaches have been developed to study these injury mechanisms. However, the cellular and molecular mechanisms regulating the systemic response and the timeframe at which these events are taking place remain to be elucidated in order to completely understand their effects.

4.1 Animals models

Animal models have been widely used to study biomechanical responses as well as physiological and neurological consequences of blast exposure on living systems [49, 125-128]. The majority of blast-injury related work has been done on animals submitted to total body blasts [22, 45, 126, 129, 130]. Others have been exposed to multiple forms of loading ranging from direct exposure to explosives to controlled blast waves produced in shock tubes [49, 125]. Although live explosives and free field blast testing remain the ideal experimental setup to reproduce the characteristics of a detonation, the use of shock tubes has proven to be an efficient method to precisely control the physical characteristics of a blast wave. However, shock tubes lack the capability to model a realistic blast wave which is often non-ideal, non-uniform and possess multiple shocks and expansion fronts. Most of this *in vivo* work has been performed on rats, rabbits, pigs and non-human primates.

The effects of blast waves on animals have been reported in terms of cognitive effects, tissue function and damage as well as cell signaling and systemic responses (Table 3). The transmission of the primary blast wave transmitted through the skull and brain usually resulted into neuronal and CNS damage, demonstrated by decreased electroencephalographic activity and neural degeneration. These blast exposures also led to impaired behavioral and cognitive performance in animals [49, 94, 125]. Several of these studies report patterns of injuries to the lungs and DAI. Axonal and glial abnormalities were also observed and correlated with impaired performance of an active avoidance task [94, 125, 128].

Table 3: Summary of animal studies investigating the effects of blast exposure on the central nervous system.

Animal Model	Experimental Setup	Peak Pressure	Monitored Effects	References
Monkey	Air shock tube	200-345 kPa	Transient auditory and visual impairment	Bogo et al., 1971
Rabbit	Air shock tube	300 kPa	Presence of increased energy consumption markers in the medulla (brain stem)	Cernak et al., 1996
Pig	RDX/TNT	200-300 kPa	Reduction of electroencephalography amplitude, apnea	Axelson et al., 2000
Pig	Ammo detonation	10-30 kPa	Intracerebral hemorrhage	Saljo et al., 2008
Pig	Explosive shock tube	60-180 kPa	Vasospasm in the brain, impairment of motor coordination, fiber degeneration, GFAP positive astrocytes, increased neuron-specific enolase in serum	Bauman et al., 2009
Rat	Air shock tube	100-200 kPa	Axonal degeneration of the optic nerve	Petras et al., 1997
Rat	Air shock tube	340 kPa	Swollen neurons, glial reaction, myelin debris, increased nitrate concentration	Cernak et al., 2001
Rat	110kg TNT	N/A	Transient microglial response, darkened dendrites, disruption of the choroid plexus	Kaur et al., 1995-1997
Rat	Explosive shock tube	150-250 kPa	Redistribution of phosporylated neurofilament H in axons, induction of terminal kinases, neuronal apoptosis, GFAP positive astrocytes	Saljo et al., 2000-2002
Rat	Explosive shock tube	20 kPa	Decreased grip strength, apoptosis cells in cerebral cortex. Effects reversed by aminoguanidine	Moochala et al., 2004
Rat	Air shock tube	40 kPa	N/A, technical achivement of measuring intracranial pressure in a live animal model	Chavko et al., 2007
Rat	Air shock tube	120-150 kPa	Hemorrhage, brain tissue necrosis, less fiber degeneration in animals wearing a Kevlar vest	Long et al., 2009
Rat	Air shock tube	repetitive 10-60 kPa	Increased intracranial pressure after blast, returned to normal by D7.	Saljo et al., 2010
Whale	Percutaneous grenade	N/A	Macroscopic and microscopic intracerebral hemmorhage, severity related to proximity	Knudsen et al., 2003

Adaptation from Elder et al., 2010

Cernak and colleagues reported microscopic evidences (SEM) of vacuole formation in both nerve terminals and myelin chains in rats brain 24 hours and 5 days after a whole body blast exposure in a shock tube, for a peak pressure of approximately 50psi [74, 94]. Saljo and colleagues exposed rats to peak pressures of 35 psi in a shock tube and identified enhanced expression of phosphorylated neurofilament in the temporal, cingulated and piriform cortices using immunohistochemistry, 48 hours and 7 days following the exposure [104]. More recently, Long *et al*. reported that the use of Kevlar body armor reduced the mortality in a rat model exposed to a 20 psi overpressure. A recent study published by Garman *et al.* exposed rats to a 35 psi peak pressure in a shock tube with and without using a shield to protect the animal [131]. These investigators used an array of techniques such as hematoxilin and eosin and amino cupric silver stains as well as a variety of immunohistochemical markers for amyloid precursor protein, glial fibrillary acidic protein, ionized calcium binding adapter molecule 1 , ED1 and rat immunoglobin G to identify the exact injury mechanism [131]. The results showed multifocal axonal and dendritic degeneration for all subjects 24 hours and 72 hours following the exposure. Recent studies also demonstrated that for similar overpressure, waveform distributions in the brain were dependent on the orientation of the animal during the blast exposure [41, 130]. Although major differences can be observed between rat and human brain in terms of dimensions and physiology, these findings demonstrate that there is a geometrical dependence influencing the fraction of the blast that will affect brain tissue. Bauman and associates carried out extensive blast studies in a pig model. In moderate and severe blast exposure, the predominant pathological feature two weeks following the injury was fiber tract degeneration in the white matter of the cerebellum, revealed by silver staining [127]. Glial fibrillary acidic protein immunostaining was also prominent versus the non-exposed control, suggesting secondary astrocytosis. From a practical point of view, rodents are less expensive to obtain, easier to manage and requires less sophisticated facilities. However, anatomical and physiological features of their skull and brain

makes them a far from ideal model to study their reaction to blast exposure. Species such as pigs and primates offer the advantage of having more similarities with human brain, but are costly and require specialized care in a laboratory environment.

The group of Pamela VandeVord (Wayne State University) has recently developed a method to measure the intracranial pressure (ICP) in a rat model [132]. This study investigated the potential of the shock wave to enter the skull and reach the brain through the eye orbits. However, it was shown that protecting the eyes of the animal did not influence the ICP measured inside the rat brain and demonstrated that reliable and accurate ICP measurement is only possible if a proper sealing of the interface between the sensors and their passage through the skull is achieved. Cernak *et al.* have developed a model capable of reproducing structural damage and functional impairment dependent on the intensity of the insult for both mild and moderate TBI [22]. It has been suggested that the mechanical perturbation of integrins, a transmembrane protein that couples the cytoskeleton to the extracellular space, could be responsible for the disruption of neuronal membrane, resulting into DAI. The transfer of mechanical forces to the cytoskeleton could activate signal transduction pathways, alter ion channel currents and initiate pathological cascades [98]. However, this model has yet to translate into any correlation regarding human mTBI levels. Collectively, these studies might indicate that the passage of a shockwave through the head has an effect on the CNS even at modest blast pressures.

Although animal studies are helping to better understand the interaction between a blast shockwave and brain structure, it is of the utmost importance that the structure of human brain and cranium be taken into account in the study of shockwave propagation and its role in human neurotrauma. Animal models are unable to provide an adequate representation of the scale, geometry and properties of a human head. Another problem is that physiological and biological responses to external injurious stimuli are significantly different for various species. Thus, physical scaling based on animal size and using pressure-duration factors could give misleading information about a causal relationship between the intensity and the nature of functional deficit. Moreover, carrying out animal experiments is expensive, time-consuming, requires a great deal of knowledge and expertise and must be performed in approved facilities. The effort invested in animal studies is often diminished by the outcome of the work, which is very dependent on the magnitude of the microscopic analysis of histological sections. Typically, only a few selected regions of interest in the brain can be investigated, leaving a large quantity of experimental data unexamined.

4.2 *In vitro* models

A deeper understanding of both the physiological and cellular mechanisms involved in the physiopathology of brain injury is necessary to effectively provide care to the population suffering from mTBI. Although *in vitro* models cannot replace *in vivo* experiments, they allow the discrimination between injury mechanisms. By using specifically designed models, it is possible to study a specific mechanical insult precisely controlled and directly measured [67]. One possible consequence of injury to the brain could be the aberrant activation of molecular pathways responsible for mechanotransduction. This activation could in turn be responsible for triggering secondary damage associated with TBI, resulting into cell death and tissue necrosis. An *in vitro* model could allow gaining insight into more complex mechanisms associated with the mTBI sequelae and could improve the establishment of tissue tolerance and injury criteria.

A great deal of effort has been invested in the development of clinically relevant *in vitro* models of brain injury. The utility of these models resides in reproducing the sequence of events occurring *in vivo* to understand the complex nature of tissue damage initiated by exposure of brain tissue to blast loading. These models can also lead to novel therapeutics that could potentially inhibit the deleterious effects following these events. *In vitro* models offer several advantages over animal models, including the precise specification of loading parameters (e.g., strain, stress and rate), control of the extracellular environment (e.g., temperature, humidity, and pressure), easy and repeated access to samples and simplified administration of the various components. By controlling the loading conditions, the quantitative relationship between prescribed injury severity and injury response can be precisely examined. Most *in vitro* TBI studies involve the use of systems reproducing some features of the central nervous system. These include tissue explants and organotypic cultures, primary cell cultures and immortalized cell lines. The use of a specific *in vitro* model is generally dictated by its applicability and relevance depending on the situation it is aiming to reproduce. *In vivo*, the cellular and molecular mechanisms of defense are highly complex and interrelated. Therefore it is challenging to identify a single pathway in response to a stimulus in a whole organ or tissue. The isolation of cells comprised in a tissue of interest present a simple and relevant system for which input and output parameters can be controlled and used to characterize the cell response to various blast loadings (Figure 12).

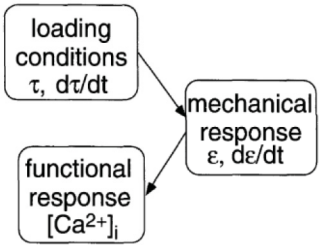

Figure 12: The experimental variables of an in vitro *model can be precisely controlled, allowing for straightforward interpretation of the results obtained using the system [71].*

In vitro models are useful for determining the sequence and chronology of cellular events following a mechanical injury applied experimentally. Using tightly controlled biomechanical parameters, injurious stimulus and outcome measures can be tailored to answer a set of specific questions. Explants of CNS tissues require access to freshly isolated brains and rely on a limited timeframe to perform the experiments [95]. This approach has the advantage of preserving the anatomical structure [72], the physical properties [133] and the neuronal systems found *in vivo* [72, 134]. Moreover, the presence of heterogeneous cell populations, bioactive molecules (extracellular matrix proteins, lipids, soluble factors) as well as functional axonal connections greatly improves the relevance of these models [135]. Similarly, organotypic cultures consist of using *ex vivo* brain tissue samples, usually from rodents, to perform *in vitro* TBI experiments while maintaining the morphological organization of the tissue as well as the interconnections between cell types in a 3D environment [136-138]. The main difference resides in sample preparation, requiring the tissue to be cut into thin sections (250-400 µm) that can be maintained in culture for extended periods of time. This model allows for the recapitulation of a quiescent state by clearing dead cells and repopulating denuded dendritic fields induced by the cutting process [139]. Another well accepted model for *in vitro* tissue study is the use of primary cell lines isolated from their tissue of origin [76, 98, 110, 140, 141]. Primary cell cultures allow examining the effect of injury on a single cell type or on a combination of known cell populations

in well-defined and controlled proportions. The limitation of that approach is that cells are cultured in monolayers and often behave differently in comparison to being cultured in a tridimensional environment [142, 143].

The use of brain culture preparation offers several advantages over dissociated cell cultures. Typically, cellular studies rely on dissociated cells of homogeneous or heterogeneous populations. During the harvesting procedure, cells are enzymatically or mechanically dissociated. These processes severe the connections between cells and disrupt their spatial arrangement. Organotypic brain culture preparations present an attractive alternative that maintains the morphological organization of the tissue as well as the local interconnections between cell types in a 3D extracellular matrix. This population of neurons, astrocytes and other brain cells allows for realistic interactions between the different cell types. Maintaining a high level of biological complexity in culture in conjunction with blast testing contributes to reproducing the *in vivo* setting of TBI both biologically and mechanically. Although *in vitro* models can unlock mechanistic understandings, their effectiveness is dependent on their ability to reproduce the *in vivo* injury or related sequelae. They have the unique advantage of providing a platform that can be used to perform experiments in a reproducible and controlled environment [95]. They can be designed to study specific regions of the brain submitted to mechanical stimuli, without having to account for systemic and inflammatory responses. However, this lack of circulatory and immune system is also considered a limitation of *in vitro* models since it can oversimplify the realistic physiological situation and can only give access to a certain amount of information regarding a phenomena [144]. Thus, *in vitro* models require to be validated against *in vivo* models since their preparation may induce significant changes to cell and tissue function. Cultured cells may adopt a different phenotype or behavior and tissue biopsies might be affected by the isolation or cutting process, which is an injury itself. Multiple injury models are required to cover the full spectrum of mechanical insults that could trigger mTBI. Once the loading conditions will be determined, the monitoring of cell response under mechanical stimulation will provide valuable information in understanding cell injury mechanisms. Finite elements and physical models have provided a number of studies predicting the transfer of loads into tissues [65, 145], these results being critical to implement the *in vitro* systems reproducing realistic TBI parameters [67, 76, 135, 140, 144].

4.3 Head surrogates

Designing equipment for blast mitigation requires an in-depth understanding of the underlying injury mechanisms. In the absence of adequate knowledge, it becomes problematic to evaluate and validate the effectiveness of blast protective equipment. The relevance and performance of a surrogate headform for mTBI investigation requires biofidelic features and materials, as well as a human-like biomechanical response in the range of loads and dynamic solicitations designated for study. The human head is comprised of numerous tissues and structures such as the grey and white matter, the sulci, as well as the falx and tentorium membranes (Figure 13). All these components play a role in the transmission of a blast wave through brain tissue and into the biomechanical response of the head during blast exposure.

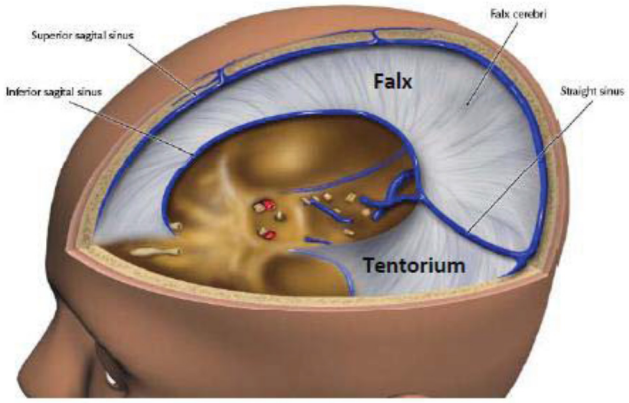

Figure 13: Section of a human head showing numerous tissues and structures. [167]

The current standardized mechanical surrogates were mainly developed for assessing the safety designs of automotive vehicles. Models such as the Hybrid III have been used worldwide for studying head acceleration and deceleration in car crash simulations [8]. This surrogate has body mass as well as dimensional and inertial properties that resemble those of an average human. However, the Hybrid III does not reproduce the tissue properties and internal physiological structures and it does not take into account the internal mechanical response of the various components [146]

Differences in morphology, brain topography, geometry as well as constituent ratio and distribution are important considerations when designing a clinically relevant surrogate for mTBI studies. Similar to most biological tissues, brain tissue possesses anisotropic properties [109, 147-149]. The properties of the skull [150] and brain tissue [38, 151-154] have been studied by numerous groups at various strain and loading rates. The results obtained often depend on the method used to establish these parameters. Gray and white matter behave differently, gray matter being a mixture of cellular bodies and white matter being a more fibrous tissue surrounded by blood vessels [147]. Experimental studies have shown that the material stiffness of the white matter is direction-dependent at high-strain rates [38, 155]. It was also shown that no structural changes occur in brain tissue for strains below 50% and that damage evolution was initiated for strains greater than 50% when brain tissue was loaded under uniaxial tension [156]. The influence of a fluid layer surrounding the brain and the effect of friction between the brain and skull plays an important role in compression loading [38]. The irregular shape and roughness of the skull base, the intricate sulci and the presence of the falx and tentorium membranes also allow for a complex interaction between the brain and skull. The sulci are a network of folds that cover the surface of the brain, providing a larger surface area for the brain to create a complex network of neurons and allowing the pia mater to envelop the brain in a stiffer matrix, thus influencing the mechanical behavior of the brain under dynamic loading [157]. The constitutive response of brain tissue incorporates a variety of mechanisms such as non-linear viscoelasticity, anisotropy and strain rate dependent behaviors [38, 39, 150, 158]. Several studies have investigated this response experimentally [72, 134, 156, 159] and others have produced a variety of constitutive models to capture the behavior of brain tissue under various loading conditions [127, 160-162]. Considering the inherent variability associated with the mechanical properties of biological tissues, there is a significant uncertainty in quantifying tissue response to mechanical loading [54]. Ongoing work

is establishing material properties of the brain across a large strain rate going from low strain rates seen in impact injury to intermediate and higher strain rates seen in ballistic injuries, therefore improving their relevance for a blast injury scenario [16, 153, 163].

Head surrogates have been used to assess the performance of protective equipment in free-field testing. It is a significant challenge to generate the experimental conditions required to test at a strain rate similar to those occurring during blast wave propagation. While the head injury criteria (HIC) and head impact power (HIP) have been used to correlate the response of the surrogate to the potential damage, these criteria are not necessarily adequate to conclusively establish if the loading conditions could lead to mTBI [164]. These surrogates are often simplified and do not account for important parameters such as the headform properties and geometry as well as blast waveform [165, 166].

More recently, new head surrogates have been designed to investigate the effects of blast. The Applied Mechanisms and Design Research Lab of Dr. Carl Nelson at the University of Nebraska-Lincoln, has developed a Realistic Explosive Dummy Head (RED Head, Figure 14) aiming at understanding the passage of pressure waves through the brain and the flexure of the skull during a blast exposure. The RED Head has a polydimethylsiloxane silicone-based organic polymer skin averaging a thickness of 7mm. This skin surrogate is painted with dots, thus allowing for particle tracking and displacement measurement used for strain measurements during blast exposure. The skull is prepared from dense urethane foam and has an inlet port to insert the cerebrospinal fluid stimulant in the head surrogate. It has a stainless steel base plate bolted at the bottom of the skull, allowing for the connection of the surrogate to a flexible neck structure. An undisclosed silicone rubber is used as the brain stimulant in this headform. This brain surrogate is instrumented with fiber optic pressure sensors, strain gauges and accelerometers. Although this experimental model seems promising, no published literature is available on the use of this surrogate for blast or other testing purposes. The Naval Research Laboratories have also developed an instrumented GelMan skull-brain surrogate with an instrumented helmet to collect experimental data under blast loading. A helmet mounted sensor capable of monitoring real-time exposure of warfighters subjected to dynamic events during a blast or a ballistic impact has also been developed by in Allen-Vanguard [58]. The device were purchased and deployed by the US Marines; however there is no report of these data so far.

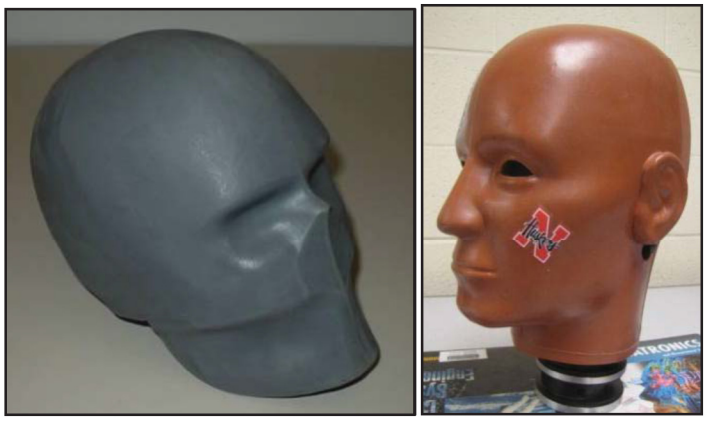

Figure 14: Realistic Explosive Dummy Head (RED Head) from the University of Nebraska-Lincoln

Since 2006, DRDC Valcartier has embarked on an extensive research project aimed at developing a biofidelic Blast-Induced Brain Injury Protection Evaluation device (BI^{2}PED Headform, Figure 15, [197]). Through several iterations, the appropriate materials and geometries required to engineer a biofidelic scalp, skull, brain and falx/tentorium membrane simulant have been determined [167,197]. Based on several other studies, Dow Corning Sylguard 527 silicone gel was selected for the brain matter [133, 160, 165-170]. Although some finite element studies of brain injury account for the difference in stiffness between the white and gray matter, the directional dependence of the white matter is often assumed to be negligible [16, 55, 152, 166]. Therefore, the use of a single homogeneous silicone part with biofidelic geometry, separated by physiological-like membranes and surrounded by a fluid layer was considered precise enough for this purpose. Based on published literature detailing the dynamic properties of brain, skull, and soft tissues, the values obtained for the materials used for the BI^{2}PED Headform are within the target ranges and indicated their general suitability as tissue simulants in the headform design.

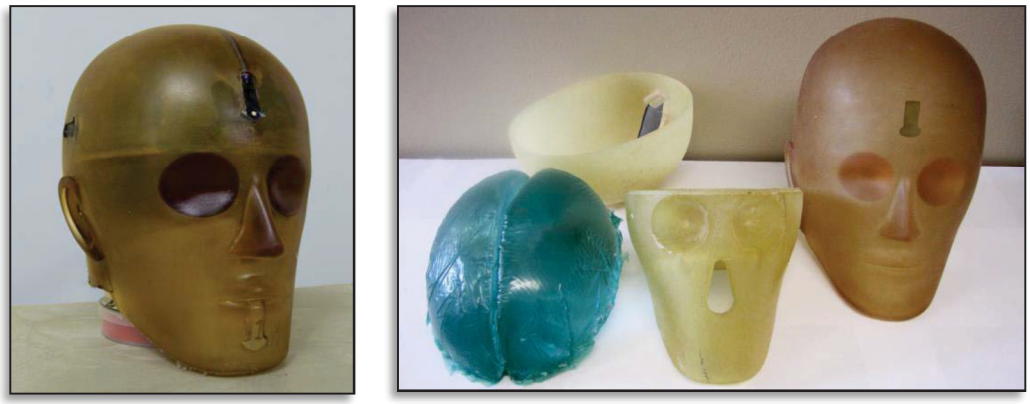

Figure 15: Blast-Induced Brain Injury Protection Evaluation device (BI^{2}PED Headform)

By comparing the weight of the various components of the BI^{2}PED Headform, it was noted that the current mass of the headform, which is approximately 3.5 kg, was within the standard deviation obtained for the average human head mass. Based on the dimensions of the 25-75th percentile, an average head weighs 4.1+/-0.6 kg, with a lower value of 2.8 kg and a maximum value of 4.7 kg (n=8) [171]. These variations found in the literature regarding head mass could be attributed to differences in the methods used for preserving and processing the heads used in these studies [153, 171]. For example, depending on the number of vertebrae left on the head after cutting and the fluid used for tissue preservation, a broad range of head mass can be obtained (Figure 16).

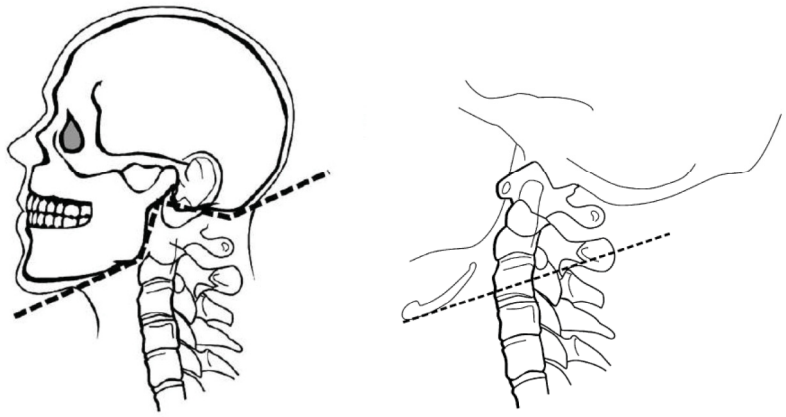

Figure 16: Based on previous studies, the exact location on the neck where the separation between the head and the body was performed had a considerable impact on head mass. Significant differences where observed when no vertebrae were left and where the head was separated from the body at the base of the skull [171] .

The instrumentation of the BI^{2}PED Headform also went through multiple design phases in order to determine the appropriate pressure, acceleration, force and strain gauges required to record the dynamic sequence of event. Although there are no validated or standard models for the specific study of blast effects on the human head, the current effort aims to design a model equipped with external and internal pressure sensors able to capture the maximum amount of data and accurately document the complex 3D pressure distribution occurring during blast exposure. Currently, the BI^{2}PED headform relies on piezoresistive pressure gauges (Kulite, Leonia, NJ, USA), precisely positioned within the brain tissue simulant and outside the skull to allow for the measurement of the peak pressure experienced outside and inside the headform. Other groups have experimented with multiple sensor types and configurations, but there has been no consensus regarding a standard configuration or data acquisition protocol [37, 165].

It is important that a head surrogate allows for repeatability, reproducibility, sensitivity, and reliability. The development of an optimal biofidelic surrogate will lead to more accurate mathematical models allowing numerical simulations to be made of various blast exposure scenarios. The combination of accurate experimental and numerical models will result in rational design and the improvement of personal protection equipment against blast loading. For that purpose, the biomechanical response of post-mortem human subjects during simulated blast wave interaction was recently been investigated in a shock tube [172]. Strain gauges and fiber optic pressure sensors were used to measure the structural dynamics of the skull and the intracranial pressure gradients [172]. However, this study requires further analysis in order to correlate the responses obtained with injury levels into humans.

4.4 Computer Simulations

It is important to make a clear distinction between functional and mechanical tissue damage, especially for brain tissue. Most current approaches only apply to mechanical damage. However, an absence of mechanical damage does not necessarily mean that no functional damage is present. Thus, currently available injury criteria for mTBI are far from ideal. In order to determine the probability of occurrence of head injury, finite elements models are being developed to allow for a distinction between the different injury mechanisms. However, the difficulty in interpreting numerical simulations that do not incorporate experimental data validating the modeling results resides in the lack of precision regarding the localization of the charge, the blast parameters and the approximations of the physical properties of the model. Without an accurate representation of the constitutive behavior of the various tissue components of the head, the predictive capabilities of a numerical model are limited. It is known that the mechanical properties of the brain tissue are complex due to the assembly of components and their intricate geometry. For example, the main components of the brain tissue, that is, the gray and white matter, are inhomogeneous, anisotropic and viscoelastic [147, 149]. Moreover, white matter is a fibrous tissue with preferential orientations and a density that may vary from one region of the brain to another. The cerebrospinal fluid, the surface properties of the skull as well as the structures surrounding the brain such as the vasculature and ventricles also contribute to the mechanical behavior of brain tissue. Moreover, it is essential for the model to be validated by experimental work that will confirm the reliability and robustness of the constitutive equations. The precision of a numerical model depends on the relevance of both constitutive equations, regulating the response of the system to various srimuli, as well as the precision of the external inputs driving the dynamic environment to be reproduced.

The mechanical properties of brain tissue have been tested in tension [158, 173], compression [38, 149, 156, 158], shear [38, 133, 156, 174] and indentation [175, 176]. The mechanical properties of other tissues comprised in the head such as scalp, cranial bone and dura mater have also been studied [150, 177]. In consideration of biological variability regarding the mechanical behavior of brain and intracranial tissues, computational models often rely on simpler viscoelastic and isotropic estimations. However, the relaxation time constants involved for low deformation rates become almost irrelevant under blast loading, since shockwaves travel at speeds several orders of magnitude less than where viscoelastic effects may be significant. Most simulation models are modeled as a continuous and homogenous material, without any vascular structures or physiological features such as the falx and tentorium membranes. Since each experimentally determined injury criteria depends on a set of technical parameters, it is important to be aware that a numerical model based on a single data set may be applicable only to a very specific area of the brain and under very specific loading conditions [17].

To this date, a number of finite element simulations of blast-induced TBI have been reported [23, 53-55, 57, 178] and current hydrocodes have been used to evaluate blast damages to structures and buildings [179]. Most of these groups report that localized tensile and compressive stresses are due to the direct interaction between the brain and the blast wave. However, none of these studies have been validated with correlating experimental data. Therefore, there is a need for a proper validation of anatomical modeling to experimentally measure the mechanics of the passage of a blast wave through brain tissue. For example, the simulation of a 1.3 MPa blast wave resulted into increased volumetric tension at sites opposite the blast source [55]. Although the peak pressure was 1.3 MPa, the pressure recorded at the air-skull interface was over 4 MPa. This

was explained by the impedance difference between the air and skull. The propagation of this pressure through the skull-brain interface resulted in a peak pressure of 2.7 MPa, again explained by the impedance difference between the two materials. Thus, this model clearly shows that there is a pressure magnification for the pressure wave transmitted through the skull and into the brain. Recently, a very sophisticated numerical work aimed at the evaluation of the effect of an exposure to a 50% lethal lung injury peak pressure, based on a Computer-Aided Design generated by an algorithm capable of producing a volumetric mesh from images collected with a CT scan and using the standardized Bowden curves [54]. Another simulation showed that the presence of the Advanced Combat Helmet reduced the intra-cranial pressure by 15-35% and reduced the strain rate on the brain by up to 30%, depending on the standoff distance and explosive charge used [180]. Numerical models have also shown that the head remains almost still during the passage of a blast wave through the skull [55], suggesting that stress localization in early time wave interactions may contribute to the development of axonal injuries.

A detailed computational model with proper validation could be useful to inspect the entire 3D brain structure following blast-induced traumatic brain injury. This strategy could help determining regions of interest that may require more extensive histological analysis and could improve the efficiency of research efforts to help establish injury mechanisms and thresholds for mTBI. However, numerical models must be validated using experimental data to map the pressure distribution and provide accurate information for prediction of mTBI. Both the experimental and numerical approaches will be crucial and complementary in enhancing the understanding of the interactions occurring during blast events in brain tissue. The constitutive model and properties will be refined as more results using experimental models become available at blast strain rates. Precise numerical models might also shorten the engineering cycle required for the development of personal protective equipment required to perform both under impact or ballistic loading and blast mitigation [181].

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5 Future Directions

Challenges in evaluating protective equipment against blast exposure are related to the lack of understanding of the mechanisms responsible for blast-induced mTBI and neurodegeneration. The limited number of physiologically-relevant animal models or biofidelic surrogates enabling us to draw conclusions regarding human brain injury tolerance and mitigation slows the ability to integrate new concepts into current protective equipment. So far, animal models have contributed significantly to the study of mild traumatic brain injury. Since surrogates are limited in recording only physical parameters such as accelerations, pressure, load, velocity, strain and displacements, the link between these data and injuries requires the correlation with animal model experiments. However, the relevance of physiological data collected using these models in shock tube experiments are sometimes orders of magnitude from the physical set of events occurring in a blast scenario. Moreover, both these types of model lack the capability to precisely evaluate and diagnose the physiological effect of a blast wave on humans. The 3D nature of *in vitro* culture models represents an appropriate model for primary blast wave exposure study. Most brain cell types are represented and form a differentiated and stable architecture. Cell injury, as measured by proteomic activity or cell immunostaining has been shown to be dependent on strain and strain rate. However, these techniques require extensive amounts of time and rigorous expertise. Thus, it is imperative to develop new types of technologies to assess the complex interactions occurring at the cell scale when brain and other organs are exposed to blast overpressure.

A new *in vitro* system that could investigate the behavior of brain cells exposed to a blast shockwave and look at the activity of specific biological markers to correlate the physical parameters with the resultant cell damage could be of great interest. Biosensors such as antibody-based platforms and microarrays are powerful tools that can complement traditional cell biology protocols and address sensitive issues such as reproducibility and time required for analysis [182]. Combined with bioinformatics analysis and interpretation, these methods generate a new level of understanding about biological mechanisms, drawing conclusions using system biology principles. A biosensor has the characteristic that it can be objectively measured and evaluated as an indicator of normal or abnormal biological processes. Ideally, brain injury biosensors should be unique to the brain and should provide information on injury mechanisms. Various approaches can be taken for the development of biomarkers for mTBI assessment. These include identifying vascular responses such as endothelial-neural disturbances, neuroinflammation, apoptosis, and axonal damage among others [110, 183]. Although there are currently no specific brain injury biomarkers available, several candidates have shown pre-clinical potential. Thus far, those generating interest are neuron specific enolase, S-100-Beta, glial fibrillary acid protein and myelin basic protein [184]. On the other hand, some attempts to measure traditional biochemical parameters in the blood such as serum enzymes, blood urea, nitrogen level as well as leukocytes and hemoglobin concentration, have failed to result in efficient diagnostic tools for mTBI [116, 185]. After looking at a variety of signaling proteins that seem to become overexpressed in the blood stream after a brain injury, army-funded researchers have tested two of these molecules in small scale phase 2 clinical trials: ubiquitin C-terminal hydrolase [186] and glial fibrillary acidic protein [187], which will soon be tested in large-scale phase 3 trials, rising hope for rapid mTBI diagnostic [184, 188].

The increase in research funding has led to significant progress towards a diagnostic test for mTBI. Although the use of surrogates, *in vivo, in vitro* and numerical models provides important data regarding blast induced mTBI, the physical and biological synergistic effects of detonation on human brain will be better understood when relevant biosensors become available. The challenge with biomarkers is to identify the proteins that are expressed very early following the traumatic event and to develop a field deployable technology that could detect low levels of the protein of interest. However, it is unlikely that a single marker, such as the overexpression of troponin during myocardial infarction, will allow mTBI to be diagnosed, as an ensemble of factors have been used to correlate a blast event to mTBI.

6 Conclusions and recommendations

A deeper understanding of both the physical and cellular mechanisms involved in the pathophysiology of brain injury is necessary to determine the mechanism responsible for the increased incidence of mTBI among soldiers. Even though many experiments have shown that intracranial overpressures can transmit through brain structures during a blast, there is very limited information on how these pressures can affect biological function. Until recently, most injury risk studies have compared brain tissue response with the thresholds proposed for impact-induced brain injury found in the literature. However, the difference between impact-related and blast-related mTBI resides in the duration of the traumatic event, which is of longer duration for impact trauma, whereas a blast only lasts a few milliseconds. From a purely mechanical perspective, the rate at which a given load is applied to a structure plays an important role in the structure response.

Following exposure to blast waves, brain cells become activated and initiate a signaling cascade leading to the degeneration of neurons and glial cells resulting in impaired normal brain function. The transmission and reflection of blast shockwaves is likely to affect the brain while going unnoticed to clinical examination. The major challenge of prospective studies is to determine the blast parameters encountered by the victim. The relationship between diffusion tensor abnormalities (DTI) abnormalities and clinical outcomes in military personnel has yet to be determined. So far DTI has proven helpful to determine and quantify axonal injuries, but no correlation with blast event parameters have been performed. By establishing links between blast characteristics and neuronal damage, one could determine a blast-induced mTBI head injury criterion. Other monitoring approaches such as the colorimetric blast injury dosimeter, which exploits the mechanical failure of photonic crystals to detect blast exposure, has been developed. Although little is known about thresholds that induce mTBI, the idea of a wearable sensor capable of registering the severity of blast exposure in relation to the risk of TBI represent an interesting method for mTBI evaluation. It is known that exposure to blast can cause mTBI and PTSD. Since both disorders present overlapping symptoms such as impaired concentration, fatigue, memory loss and irritability, the distinction between the transient neurological function and psychological stress reaction is far from obvious. This distinction is usually done by discriminating predominant symptoms as organic or psychological. Since soldiers are highly motivated to perform, they tend to minimize the symptoms and are often willing to return to active duty well before the cognitive effects of their injury have subside. Therefore, the successful development of biochemical and biological markers for blast-induced brain injuries could help distinguish between mTBI and PTSD for low levels of blast exposure and reduce the number of soldiers returning prematurely on missions while minimizing their condition. The need for a physiological and mechanistic injury-based tolerance curve for mTBI will also be fundamental to progress in the development of adequate personal protective equipment against blast exposure. This chart should include a timeline considering the time elapsed since the incident, which would take secondary molecular response into consideration. Since neurodegenerative responses contribute to cell damage throughout an extended period of time and that military evacuation times to trauma centers can take several hours, it will be important to develop neuroprotective solutions in order to reduce these secondary effects.

Although the development of personal protective equipment to counteract overpressure will be primordial if it is determined that blast waves are at least partly responsible for mTBI, another area where research is essential is the ability to reduce and reverse the degenerative effects of blast-induced TBI. Advances in the fields of cell biology and pharmacology could help reduce these effects by inactivating the signaling cascades originating from blast exposure and resulting into mTBI symptoms. *In vitro* and *in vivo* models present certain limitations, which in turn might be their greatest assets. By using precisely designed *in vitro* models, it is possible to study specific mechanical injuries to brain cells in the absence of any other secondary source of trauma. On the other hand, animal models allow the study of the complete systemic response of an organism to a blast shockwave and the influence of various protective equipment on the pressure distribution on the animal. Both these approaches have proven helpful in some ways. The objectives of further studies could be to develop a precisely-controlled surrogate model comprised of biosensors and living material. By controlling the physical parameters occurring around the model during blast exposure (i.e., for different charges and distances) this model would allow the establishment of parameters necessary to reproduce mild, moderate and severe TBI. These data sets could then be used as a reference to develop computational models allowing the extrapolation and prediction of mTBI occurrence. More knowledge on blast injury mechanisms and injury models is required to guide the conception of such a device, but this type of technology might help to reduce the occurrence of neurotrauma and mTBI and if necessary, modify the design of PPE.

The development of advanced physical and computational biofidelic models of mTBI will lead to predictive capabilities, rather than limiting the extent of the studies to post-injury assessment. Advances in neuroimaging, biomarkers, behavioral and genetic information and systems biology will improve understanding of the intersection between physiological and cognitive disorders. Systems biology approaches will allow a network map to be constructed, of proteins and pathways involved in mTBI. Whether or not these pathways will be equally critical after blast exposure compared to direct impact to the head still remains to be elucidated. The use of combined approaches might assist in the design of protective equipment as well as in the diagnosis of mTBI and in the promotion of adequate treatment for the symptoms related to blast-induced TBI. It is important to note that the currently available head injury criteria are not valid for blast-induced trauma. Moreover, injury criteria developed to date are only valid under certain restrictions and particular conditions, being also method- and load-dependent and not accounting for blast physics parameterization.

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List of symbols/abbreviations/acronyms/initialisms

BI^2PED	Blast induced brain injury protection evaluation device
CNS	Central nervous system
CT	Computed tomography
DAI	Diffuse axonal injuries
DND	Department of National Defence
DRDC	Defence Research & Development Canada
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
HIC	Head injury criterion
HIP	Head impact power
ICP	Intracranial pressure
IED	Improvised Explosive Devices
MRI	Magnetic resonance imaging
mTBI	Mild traumatic brain injury
PPE	Personal protective equipment
PTSD	Post-traumatic stress disorder
R&D	Research & Development
SEM	Scanning Electron Microscope
TBI	Traumatic brain injuries

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This report presents the findings of a literature review carried out in 2011. More specifically, the review sought to capture new theories on blast injury mechanisms, injury criteria and material properties.

Ce rapport est le résultat d'une revue de la littérature qui a été entreprise entre en 2011 pour mettre à jour les connaissances scientifiques dans ce domaine. Plus précisément, la revue visait à connaître les nouvelles théories sur les mécanismes de blessure, les critères de blessures et les mécanismes de détection.

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Blast-induced, mild traumatic brain injuries, mTBI, blast injury mechanisms

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