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Mechanosensation in Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is distinct from other neurological disorders because it is induced by a discrete event that applies extreme mechanical forces to the brain. This review describes how the brain senses, integrates, and responds to forces under both normal conditions and during injury. The response to forces is influenced by the unique mechanical properties of brain tissue, which differ by region, cell type, and subcellular structure. Elements such as the extracellular matrix, plasma membrane, transmembrane receptors, and cytoskeleton influences its properties. These same components also act as force-sensors, allowing neurons and glia to respond to their physical environment and maintain homeostasis. However, when applied forces become too large, as in TBI, these components may respond in an aberrant manner or structurally fail, resulting in unique pathological sequelae. This so-called “pathological mechanosensation” represents a spectrum of cellular responses, which vary depending on the overall biomechanical parameters of the injury and may be compounded by repetitive injuries. Such aberrant physical responses and/or damage to cells along with the resulting secondary injury cascades can ultimately lead to long-term cellular dysfunction and degeneration, often resulting in persistent deficits. Indeed, pathological mechanosensation not only directly initiates secondary injury cascades, but this post-physical damage environment provides the context in which these cascades unfold. Collectively, these points underscore the need to use experimental models that accurately replicate the biomechanics of TBI in humans. Understanding cellular responses in context with injury biomechanics may uncover therapeutic targets addressing various facets of trauma-specific sequelae.

Keywords

traumatic brain injury; biomechanics; force; mechanosensation; mechanotransduction; mechanobiology; acute; repetitive; extracellular matrix; plasma membrane; cytoskeleton

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1. Epidemiology and Clinical Classifications

Traumatic brain injury (TBI) is unique from other neurological disorders or diseases in that it is caused by a mechanical insult—such as a blow or jolt to the head, or an object penetrating the skull—that results in brain dysfunction. Falls are the most common source of injury, though motor vehicle accidents, being struck by or against an object, and assault are also causes of harm (Centers for Disease Control and Prevention, 2019). The incidence of TBI varies with age and sex, with children ages 0–4 years of age, adolescents 15–19 years of age, adults over 75 years of age, and particularly males, comprising the most likely groups to experience a TBI-related hospital visit (Faul & Coronado, 2015). The likelihood of TBI exposure is also increased in athletes and military service members (Centers for Disease Control and Prevention et al., 2013; Theadom et al., 2014). TBI is a major cause of death and disability; in the United States alone there were approximately 2.87 million TBI-related emergency department visits, hospitalizations, and deaths in 2014, with global estimates of 27.08 million new cases in 2016 (Centers for Disease Control and Prevention, 2019; GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators, 2019). These numbers likely do not reflect the true incidence of TBI, as many mild injuries go unreported (Bell et al., 2017). In addition to the health burden, there is a significant economic burden as well, with estimated lifetime costs including direct costs like hospital care and indirect costs like lost productivity totaling $60.4 billion in US 2000 dollars (Finkelstein et al., 2006). With no effective therapeutic interventions, it is evident that further research on the mechanisms of injury are required.

Because there are numerous ways forces can be applied to the head to produce injury, TBI is a heterogeneous disorder. Symptoms can range from temporary, mild cognitive deficits to permanent, severely debilitating changes in motor function, emotion, and cognition (K. J. Dixon, 2017). Clinically, TBI is divided into three categories: mild, moderate, and severe (Table 1). These classifications are based in part on the Glasgow Coma Scale (GCS), which uses a numerical scale to quickly assess motor responsiveness, verbal performance, and eye opening as they relate to the depth and duration of impaired consciousness or coma (Teasdale & Jennett, 1974). GCS scores of 13–15 indicate a mild injury, scores of 9–12 indicate a moderate injury, and scores less than 9 indicate a severe injury. In addition to GCS scores shortly after injury, other symptoms are also used to classify injury severity. Mild injuries involve loss of consciousness for 0–30 minutes, altered consciousness or mental state for less than 24 hours, and posttraumatic amnesia of 0–1 days. Moderate injuries involve loss of consciousness for 30 minutes to 24 hours, altered consciousness or mental state for greater than 24 hours, and posttraumatic amnesia for 1–7 days. Severe injuries involve loss of consciousness and altered consciousness or mental state for greater than 24 hours, and posttraumatic amnesia for greater than 7 days (Department of Veterans Affairs & Department of Defense, 2016). Of note, these classifications are based on symptoms rather than the cause of injury or underlying pathology, although moderate and severe injuries can sometimes produce abnormalities on structural imaging scans (Department of Veterans Affairs & Department of Defense, 2016).

Injury outcomes depend on both the type and severity of the initial event, termed the "primary injury," as well as the multifaceted pathophysiological cascades—including inflammation, edema, hypoxia, metabolic deficits, reactive oxygen species activity, and excitotoxicity (K. J. Dixon, 2017; McIntosh et al., 1998)—that occur subsequently, termed the "secondary injury." Collectively, damage from the primary insult and its evolving secondary injuries may initiate a continuum of developing neurodegenerative changes progressing for weeks, months, or even many years following injury, producing a wide range of outcomes (L. Wilson et al., 2017). Although the heterogeneity of TBI is gaining increased recognition (Saatman et al., 2008), its wide range of symptomatic outcomes, evolving pathology, and progressive degeneration remain poorly understood. This review will focus on damage caused by the primary injury, particularly how exactly outside forces are translated to the brain and its cells.

2. Brain Mechanics and Neural Mechanosensation

2.1. Basic Mechanics of Biological Materials

Because TBI is a physical injury, it is important to understand the mechanical properties of the brain as well as forces that act on it. Tissue mechanics of the central nervous system have recently been reviewed (Ayad et al., 2019; Meaney & Cullen, 2016). Briefly, mechanical properties encompass the physical attributes of a material as well as the behaviors that materials exhibit upon the application of forces. In engineering, the application of force is expressed in terms of *stress*, which is defined as the force applied over a cross-sectional area. There are five different types of stress: compression, tension, shear, torsion, and bending (Fig. 1). In response to stress, a material can change shape, or deform. The amount of deformation is measured as *strain*, which is a ratio of the dimensions of an object after the application of forces relative to the dimensions prior to the application of forces. The tendency of a material to deform in response to a force is termed Young's modulus (E, also called the elastic modulus). Young's modulus describes material under compression and tension (forces acting towards or away from a material surface, respectively), while the shear modulus (G) describes the response to shear stress (forces acting parallel to a material surface). However, most biological work uses the terms E, G, and stiffness interchangeably. The higher the elastic modulus, the stiffer the material and the greater the resistance to deformation. The amount of deformation (strain), together with stress, form a relationship that determine how a material behaves. For instance, many materials exhibit *elastic* behavior, meaning that when a force is applied it immediately deforms, and when that force is removed it instantly reverts back to its original shape. Other materials, including most biological materials, exhibit deformation and gradual recovery (*hysteresis*), with energy lost in this process. In addition, the behavior of most biological materials depends not only on the amount of stress, but also on the rate at which it is applied, where faster rates of loading elicit stiffer behavior and slower rates of loading elicit softer - or flowing - behavior. Because they display both the elastic properties of a solid which dominate the response upon high rate loading, and the viscous (resistance to flow) properties of a fluid which dominate the response for slow loading, these materials are termed *viscoelastic*.

2.2. Mechanical Properties of the Brain

The brain is a viscoelastic material and one of the softest tissues in the body (Moore et al., 2010). Although nearly incompressible, it is highly susceptible to tensile and shear forces (S. Cheng et al., 2008; Jin et al., 2013; Libertiaux et al., 2011). However, brain properties are not homogenous. At the macro scale, the brain displays differences in white matter and gray matter. White matter is stiffer than gray matter although it shows larger regional variation, is more viscous, responds less rapidly to stress, and its anisotropy means its response is highly dependent on the direction the stress is applied (Braun et al., 2014; Budday et al., 2015; Kruse et al., 2008; Prange & Margulies, 2002; van Dommelen et al., 2010). The stiffness of different brain regions is also heterogeneous; for example, the brainstem and other subcortical gray matter are stiffer than the cortex, while the cerebellum is much softer (C. L. Johnson et al., 2016; Murphy et al., 2013; J. Zhang et al., 2011). Age and disease also impact the mechanical properties, with the human brain softening in age and in many neurological diseases (Murphy et al., 2019; Sack et al., 2011). However, in addition to age and region, the species may also affect the mechanical properties (Elkin et al., 2011; MacManus et al., 2017b; Prange & Margulies, 2002). At the micro scale, different cell types exhibit diverse stiffness, and even within a cell different regions such as the soma and axon have varying stiffness and respond differently to mechanical stimulation (Gaub et al., 2020; Grevesse et al., 2015; Lu et al., 2006).

At the cellular level, several components confer the brain with its unique mechanical properties (Tyler, 2012). The plasma membranes surrounding all cells give rise to many of the viscoelastic properties of the brain as they are viscoelastic materials themselves (Crawford & Earnshaw, 1987). The phospholipid bilayer is sensitive to bending and compressive forces (Evans & Hochmuth, 1978). The integrity, stability, and elasticity of the plasma membrane are in part maintained by the cytoskeleton. Actin and spectrin, in addition to generating their own forces, are important for counteracting plasma membrane tension, particularly in the axon (Dubey et al., 2020; Galkin et al., 2012; Y. Zhang et al., 2017). Periodic actin-spectrin rings forming a lattice have been described in the axon and some dendrites, where they may stabilize or be stabilized by microtubules, as reviewed by Leite & Sousa (Leite & Sousa, 2016). Microtubules and neurofilaments provide key structural support to protect cells from compression forces (Ofek et al., 2009; Ouyang et al., 2013). Mechanical support is also provided by the extracellular matrix (ECM). In adults, the ECM occupies an estimated 20% of the brain and its composition is unique compared to the ECM of most other soft tissues (Nicholson & Syková, 1998). While the ECM of other organs is primarily made up of fibrous proteins like fibrillar collagens, brain ECM is almost entirely composed of non-fibrillar elements like glycosaminoglycans (e.g., hyaluronic acid), proteoglycans (e.g., lecticans), and glycoproteins (e.g., tenascins) (Ruoslahti, 1996; Zimmermann & Dours-Zimmermann, 2008). This relative lack of fibrillar proteins contributes to the low stiffness of the brain.

2.3. Physiological Mechanosensation in Neurons

Many of the components that give the brain its viscoelastic properties can also act as sensors of mechanical forces (Fig. 2A–E). Cells detect forces and convert them into biochemical signals in a process called mechanotransduction. It is important to note that brain cells are

continuously subjected to forces even under physiological conditions. For instance, during development neural stem cell migration and differentiation is dependent on sensing ECM architecture and rigidity (Engler et al., 2006; Franco & Muller, 2011; Segel et al., 2019). In mature neurons, action potential propagation in axons is accompanied by membrane deformation (G. H. Kim et al., 2007), and dendritic spines “twitch” and rapidly contract in response to synaptic activity (Crick, 1982). The pulsing flow of blood through capillaries deforms the environment (Wagshul et al., 2011). Neurons must be able to detect, integrate, and respond to these signals.

The first mechanosensitive molecules to be described were stretch-activated ion channels (Guharay & Sachs, 1984; Hudspeth, 1986; Martinac et al., 1987). Since then, a wide variety of mechanosensitive receptors have been found in both the peripheral and central nervous system, including members of the transient receptor potential (TRP) ion channel family, degenerin/epithelial sodium channel (DEG/ENaC) family including acid-sensing ion channels, two-pore potassium channel family, and Piezo family of cation channels (Bagriantsev et al., 2014; Ben-Shahar, 2011; Y.-R. Cheng et al., 2018; Choi et al., 2015; Dedman et al., 2009; Moran et al., 2004; Qiu et al., 2019). Other channels not classically thought of as mechanotransducers can also be affected by mechanical forces. For instance, it has long been known that the voltage-sensing mechanisms of many voltage-gated channels are sensitive to changes in the plasma membrane or other forms of mechanical disruption (Ben-Tabou et al., 1994; Boland & Drzewiecki, 2008; Piao et al., 2006; Shcherbatko et al., 1999).

More recently, in cultured rat cortical neurons, blocking extracellular calcium, voltage-gated sodium or calcium channels, or TRPV channels decreased or abolished the response to sub-traumatic forces (Gaub et al., 2020). The gating of NMDA receptors (NMDAR) is also mechanosensitive, possibly via interactions with the cytoskeleton and/or membrane lipids (L. R. Johnson et al., 2019; Maneshi et al., 2017). As for the mechanism of this mechanosensitivity, some ion channels are modulated by forces directly causing conformation changes to the protein. Others are activated indirectly by pressure, tension, stress, or stretch deformations at the plasma membrane that lead to conformational changes, as recently reviewed by Lim et al. (Lim et al., 2018). For instance, plasma membrane fatty acid composition fine-tunes the Piezo1 mechanical response, with saturated and unsaturated fatty acids differentially modulating channel activation or inactivation in the N2A neuronal cell line (Romero et al., 2019).

Transmembrane receptors that couple neurons to other cells (e.g., cadherins) or to the ECM (e.g., integrins) are also able to relay physical changes in the environment to the cell. Integrins, for example, link the actin cytoskeleton to ECM proteins like fibronectin. When integrins connected to actin experience a sufficient force, other integrins are recruited to form an integrin adhesion complex that grows into a signaling hub. Downstream signaling can control actin cytoskeletal dynamics which in turn can affect the localization of mechanosensitive transcription factors in addition to other downstream effectors, as recently reviewed by Chighizola et al. (Chighizola et al., 2019). While neurons do not have true focal adhesions, they do have adhesions termed focal points that contain molecules such as dispersed integrin and focal adhesion kinase (Armendáriz et al., 2014). Although much of

the work on integrins has been performed on non-neuronal cells, there is evidence in both the peripheral and central nervous system that their signaling is important for neurite outgrowth, myelination, synaptic plasticity, and disease (Jaudon et al., 2020; Lin et al., 2012; Previtali et al., 2001; Y. Wang et al., 2019; X. Wu et al., 2016).

Physical changes in the environment do not only rely on signal transduction cascades from transmembrane receptors to alter gene expression. Gene expression can also be impacted by changes to nuclear architecture. The cytoskeleton is connected to the nucleus through the linker of the nucleoskeleton and cytoskeleton (LINC) complex, which transmits force to the nucleus and can result in spatial chromosome reorganization and subsequent transcriptional changes (Tajik et al., 2016). LINC-independent processes exist as well that directly deform the nucleus (Jahed & Mofrad, 2019). For instance, gating of the nuclear pore complex can be directly regulated by forces applied to the nucleus (Elosegui-Artola et al., 2017). Once again, although these studies were performed in non-neuronal cells, it is known that the nuclei of neurons can deform and move within cells, particularly during migration (Nakazawa & Kengaku, 2020), suggesting that these mechanisms may be at play in neurons as well.

2.4. Physiological Mechanosensation in Glia

Neurons are not the only mechanosensitive cells in the brain. Astrocytes can act as soft, compliant structures that surround neurons and may act to cushion them (Lu et al., 2006). These cells may act as a force-sensing scaffold across the brain as suggested by Ostrow & Sachs, as *in vitro* experiments have shown that mechanically stimulating one astrocyte produced calcium signaling in the entire interconnected network of astrocytes (Ostrow & Sachs, 2005). These cells have long been known to express stretch-activated and curvature-sensitive mechanotransducing ion channels, and more recent studies have shown that Piezo1 can regulate calcium oscillations and cytokine release (Bowman et al., 1992; Velasco-Estevez et al., 2020). Proteins involved with integrin adhesion complexes have been found to regulate glutamate transporter expression and astrocyte morphology (Avalos et al., 2004; Cho et al., 2018; Leyton et al., 2001). The cytoskeleton, including intermediate filaments like glial fibrillary acidic protein (GFAP), also plays a role in mechanotransduction in astrocytes. During migration, the astrocyte intermediate filament network of GFAP, vimentin, and nestin, together with the cytoskeletal linker plectin, promote the actin-driven treadmilling of adherens junctions (De Pascalis et al., 2018). This cytoskeletal remodeling during migration is also associated with changes in cell stiffness (Curry et al., 2017). Stiffness also increases with age and correlates with the complexity of actin, microtubules, and intermediate filaments (S.-M. Lee et al., 2015).

Cytoskeletal changes are also implicated in mechanosensitive oligodendrocyte differentiation and maturation. Mechanostimulation acting through the actin cytoskeleton and LINC complex mediate nuclear and epigenetic changes in oligodendrocyte progenitor cells that favor differentiation (M. Hernandez et al., 2016; Jagielska et al., 2017). Differentiation, maturation, and morphology are also associated with increased production of the microtubule network and are regulated by part of the focal adhesion complex, the mechanosensor p130Cas (Makhija et al., 2018; Shimizu et al., 2019). Once mature,

myelination itself appears to be dependent on axon stiffness, among other properties (Espinosa-Hoyos et al., 2018).

Stiffness is an important property for microglia as well. When cultured on compliant substrates, microglia adapt their spread area, morphology, and actin cytoskeleton to the stiffness of their environment. When cultured on stiffness gradients, microglia migrate towards the stiffer regions in a process called durotaxis, which is amplified when the cells are activated (Bollmann et al., 2015). Furthermore, microglia (and astrocytes) respond to increasing stiffness with changes in morphology and upregulation of inflammatory genes and proteins (Moshayedi et al., 2014), demonstrating that cells not only sense but also react to mechanical properties.

2.5. Physiological Mechanosensation in Blood Vessels

In addition to neurons and glia, cells comprising the vasculature coursing through and around the brain can also detect changes in mechanical forces. As this topic has been reviewed elsewhere (Baeyens et al., 2016; Fang et al., 2020; Monson et al., 2019), a few major points are summarized here. Cerebral blood vessels are unique from the vasculature in other organs due in part to the meninges surrounding the brain. Within the subarachnoid space, the internal carotid and vertebral arteries gain a layer of pia-arachnoid tissue that remains with the arteries when they enter the brain parenchyma, forming the Virchow-Robin spaces. While in the subarachnoid space, the arteries are intermittently tethered to the pia and arachnoid by collagenous trabeculae that attach to an outer vascular coat (Monson et al., 2019). This tethering likely influences the stress-strain fields experienced across these regions.

The mechanical characteristics of blood vessels have been investigated for many years, but the properties of cerebral blood vessels specifically have received limited focus. Studies on large arteries leaving the Circle of Willis and their branches on the brain surface have shown that these cerebral arteries display nonlinear and anisotropic properties that are direction-dependent, similar to vessels elsewhere in the body. However, unlike other vessels, arteries from the brain are stiff in both the axial and circumferential directions. Unfortunately, the mechanical properties of smaller arteries and veins have not been characterized (Monson et al., 2019). On a cellular level, the mechanosensing abilities of endothelial cells lining the inside of vessels to detect and react to forces such as fluid shear stress from blood flow and circumferential cyclic expansion from heart propulsions has been covered extensively elsewhere, and the reader is pointed to recent reviews (Baeyens et al., 2016; Fang et al., 2020). Notably, many of the mechanosensors described for neurons and glia—ion channels, cell-cell and cell-ECM proteins, cytoskeleton, mitochondria, and nucleus—are also involved in endothelial cell mechanosensation.

By these numerous mechanisms, neurons and non-neuronal cells are able to detect and respond to physiological mechanical forces within their environment. Collectively, these capabilities allow the cells to sense, integrate, and respond to mechanical features in their environment across a micro- to macro- scale. These force-sensing and responding capabilities are not only necessary for homeostasis, but also for the brain - at a cellular level

- to adapt and respond to changes in its physical environment. But how do individual cells and the brain as a whole respond when larger, non-homeostatic forces are applied?

3. Injury Biomechanics and Pathological Mechanosensation

3.1. Injury Biomechanics

Forces can be exerted, or *loaded*, on the head in several different ways, as described in detail by Meaney & Cullen (Meaney & Cullen, 2016). Forces applied relatively slowly (typically over timespans greater than 200 milliseconds) are termed static or quasi-static, while forces applied more rapidly (typically over less than 50 ms) are termed dynamic. Dynamic loading is the most common cause of injury, and can be divided into three types relevant to TBI: impact, impulsive, and blast overpressure (Fig. 3). In impact loading, the head strikes or is struck by an object. In contrast, the head does not strike an object during impulsive loading, and instead is set in motion due to another part of the body moving. In blast overpressure or shock wave loading, rapidly moving, very short (less than 5 ms) pressure waves travel through the brain. Shockwave propagation linked with blast exposure may induce complex, multi-faceted injury mechanisms associated with transmission of shear strain and stress waves through the brain (primary blast injury), impact loading (e.g., from shrapnel or hitting a larger object; termed secondary blast injury), and impulsive loading (head acceleration due to the body being thrown; termed tertiary blast injury). Further description of blast injury mechanisms and sequelae are beyond the scope of this article, but have recently been reviewed elsewhere (Chandra & Sundaramurthy, 2015; Magnuson et al., 2012). However, blast overpressure illustrates an important point: the physical injury event can initiate multiple loading mechanisms. For instance, an object striking the head often sets the head in motion, resulting in both impact and impulsive loading. Conversely, head motion initiated by rapid body movement often results in the head striking an object, leading to both impulsive and impact loading. Purely impulsive loading where the head does not strike an object after being set in motion, or purely impact loading to an immobilized head, are rare events.

Injuries resulting from dynamic loading can be further categorized as open- or closed-head. Open-head injuries occur when an object penetrates the brain. These relatively infrequent injuries can be devastating, but the majority of damage may be due to physical transection of tissue or cells from penetration of a foreign object and/or skull fragments, though shock wave forces and damage may also be generated from high-velocity projectiles (de Lanerolle et al., 2015). In contrast, non-penetrating closed-head injuries make up 88–97.5% of cases (Demetriades et al., 2004; Gennarelli et al., 1994; Maegele et al., 2007, 2019), and this review will focus on the mechanisms of this type of injury.

Within closed-head injuries, two broad categories of forces are at play: inertial and contact (Meaney & Cullen, 2016). Inertial forces are caused by impulsive loading due to head acceleration, while contact forces are caused by impact loading to the head. Although these forces may occur in isolation, as with impulsive loading in which only inertial forces are present, they are commonly seen in combination. For instance, in impact loading a blow to the head may cause a sudden head movement resulting in a secondary impulsive loading event, together generating both contact and inertial forces. Contact forces can have local effects at or near the impact site, and can have effects far from the impact area due to

complex skull distortion or stress wave propagation. In either case, contact forces cause focal injuries as opposed to diffuse brain injury. Diffuse brain injury can be produced from inertial loading, which generally induces head acceleration. Head acceleration can produce differential movement of the skull and brain that can cause strain at the brain surface, and can also produce strain within the brain that can cause widespread damage. There are three types of head acceleration: translational, rotational, and angular (Fig. 4). Translational or linear acceleration occurs when the center of gravity of the brain moves in a straight line without rotation. This type of acceleration rarely occurs in isolation, and can produce focal injuries but not diffuse brain injuries. When the center of gravity of the brain (which is around the pineal region) does not move but the brain rotates around this region, rotational acceleration occurs. Again, this type of acceleration rarely occurs in isolation, but is capable of producing high levels of strain within the brain. When components of translational and rotational acceleration are combined so that the center of gravity of the brain moves in an angular manner, angular acceleration occurs. This type of acceleration is most common clinically and can produce almost every type of TBI. Because translational velocity increases farther outward from the axis of rotation, rotation produces differential displacements of tissue within the brain, resulting in tissue shearing (Ommaya et al., 2002; Ommaya & Gennarelli, 1974). In all cases, when loading deforms or strains the tissue beyond its functional or structural tolerance, injury occurs.

Not only do the properties of the applied force, such as the direction, magnitude, and duration, influence the amount of damage that occurs, but so do the mechanical properties of the tissue itself. Though brain tissue is nearly incompressible, it is highly susceptible to tensile and shear forces (S. Cheng et al., 2008; Jin et al., 2013; Libertiaux et al., 2011). Measures of brain deformation in healthy human volunteers undergoing mild angular head acceleration have demonstrated patterns of radial-circumferential shear strain that are modified by internal membranes (such as the dura, flax cerebri, and tentorium) as well as brain region (Sabet et al., 2008). More specifically, shear strains are different among cortical gray matter, white matter, and deep gray matter (Chan et al., 2018). Compression in frontal regions and stretching in posterior regions has also been observed (Bayly et al., 2005). Injury can also change the mechanical properties of the tissue: a cortical impact study in mice showed a major decrease in shear stiffness of the impacted brain region immediately following injury that lasted for several days (Boulet et al., 2013). Studies in mice have also confirmed regional differences in mechanical responses to large-deformation dynamic micro-indentation, suggesting that distinct brain regions dissipate different amounts of energy for a given applied force, which may explain why some regions or cells are more vulnerable than others (MacManus et al., 2017a). Not surprisingly, at a cellular level, analyses of the biomechanics of single cortical neurons subjected to strains relevant to TBI found that the cell response exhibited hysteresis and time and rate dependencies emblematic of viscoelastic materials like the brain as a whole (Bernick et al., 2011). But how do these characteristics influence how cells respond to forces applied to the entire brain?

3.2. Modeling Injury Biomechanics Experimentally

Before examining the response of cells to injurious loading, it is important to first consider how to apply these forces in experimental models. Both the type of injury applied, as well as

the characteristics of the substrate onto which it is applied, will influence the response. Therefore, the specific features of TBI that can be examined may not be generalizable to all cases, but rather will depend on the model used.

3.2.1. *In Vitro* Models—*In vitro*** models of TBI typically involve growing neurons with or without additional cell types in a 2- or 3-dimensional matrix, and applying tensile, shear, or compressive forces to whole cells or specific cellular compartments. The most common 2D model is stretch injury, in which neurons are grown on elastic silicone membranes that are stretched by a rapid pressure pulse, resulting in two-dimensional strain applied to randomly oriented planar cultures non-uniformly (Cargill & Thibault, 1996; Tavalin et al., 1995) or equally in two directions (Geddes & Cargill, 2001). Stretch can be applied in one direction to isolated axonal projections in order to imitate injury in white matter tracts termed diffuse axonal injury, described further in the next section (Smith et al., 1999). In addition to tensile injuries, shear stress can also be applied to neurons grown in 2D by using fluid motion to deform cells (LaPlaca & Thibault, 1997). Of note, the type of injury applied influences the mechanical responses at both acute and delayed time points, emphasizing the need for caution in extrapolating specific injury mechanisms and responses to other scenarios (Geddes-Klein et al., 2006).

In addition to 2D configurations, 3D cultures and injury paradigms have also been created. These models may better represent loading mechanisms, thresholds, and consequences of injury than their 2D counterparts, as all strain fields in the brain are applied across three dimensions—an inescapable consequence of the 3D architecture of brain tissue. Neurons can be grown in 3D scaffolds with or without additional cells such as astrocytes. The presence of multiple cell types, increased complexity of neural cell morphology, and the increased cell-cell and cell-ECM contacts affect the transfer of strain to cells and better reflect the actual brain environment (Cullen & LaPlaca, 2006; LaPlaca et al., 2005). These 3D constructs can be subjected to shear or compressive forces, with rapid shear loading most closely replicating the inertial forces experienced in the nearly incompressible brain tissue (Cullen et al., 2011; LaPlaca et al., 2005).

Compared to animal models, the reduced complexity of these *in vitro* systems confers greater control over experimental conditions such as cell types, matrix constituents, and applied forces. It is also easy to measure responses immediately in real time or repeatedly in order to obtain cellular-level detail on injury mechanisms and outcomes. However, these models do not recapitulate the complexity of the intact brain, and their relevance to functional outcomes at the tissue and organism level such as behavior are unclear.

3.2.2. *In Vivo* Models—There are a variety of injury paradigms used to model TBI *in vivo*. Most methods have components of both focal and diffuse injury. The contribution of each element exists on a continuum, with some models incorporating more than one over the other.

One model that applies pure impact loading on an immobilized head to produce contact forces that result in mostly focal injuries is called controlled cortical impact (CCI), and was first developed in ferrets and later adapted for use in rats, mice, pigs, and primates (C. E.

Dixon et al., 1991; King et al., 2010; Lighthall, 1988; Manley et al., 2006; Smith et al., 1995). In this method, a craniectomy is performed to expose the dura, after which a pneumatic impactor is used to rapidly drive a rod a precise depth into the brain tissue. Newer modifications to this protocol have used an impactor over a closed skull to produce a milder injury that can be administered repetitively (M L Prins et al., 2010).

In contrast, the fluid percussion injury (FPI) model produces mostly diffuse injuries along with a focal element. Initially developed in rabbits and cats, it was later adapted to rats and mice (Carbonell et al., 1998; C. E. Dixon et al., 1987; Lindgren & Rinder, 1966; McIntosh et al., 1989; Rinder, 1969; Sullivan et al., 1976). Instead of applying impact or impulse loading as would occur during TBI, FPI applies a sharp increase in intracranial pressure surrounding the brain. FPI involves using a pendulum to strike a tube of saline, creating a fluid pressure impulse that is delivered to the exposed dura of an animal attached to the other end of the tube. The dura can be exposed at the midline (central), lateral, or somewhere in between (parasagittal), and the position of this craniectomy affects injury outcomes (Floyd et al., 2002). Of note, work using a cut skull gel model to assess regional strain distribution revealed that the maximum site of strain was located in the lower brainstem while deformations were minor in other regions of the brain (Thibault et al., 1992). Although this model produces diffuse strain fields, they are not produced by the same forces that produce diffuse strain fields in inertial injuries experienced by humans. As such, though there may be some similarities in resulting pathologies, the mechanisms underlying those pathologies may vary depending on how forces are administered.

A third commonly used paradigm, the weight-drop model, can be mostly focal or mostly diffuse depending on how it is executed. Typically implemented as a closed-head injury in rats and mice, it involves dropping a weight from a defined distance onto the skull (Chen et al., 1996; Shapira et al., 1988). The severity of injury can be modulated by altering the weight or height from which it is dropped. When the head of the animal is fixed, a focal injury is produced. When the head is protected by a helmet or shield and allowed to rotate in response to injury in a version also called the impact-acceleration model, no focal contusion is observed and a diffuse injury is produced (Marmarou et al., 1994). However, for reasons explained below, it is not possible to reproduce the necessary acceleration to achieve a purely diffuse *inertial* injury in rodents. The diffuse injury produced in this model is due to impact loading and resultant contact forces.

To truly investigate diffuse injury caused by inertial forces, the head needs to rotate. Recent methods such as Closed-Head Impact Model of Engineered Rotational Acceleration (CHIMERA) have tried to incorporate head rotation into rodent models with more control than that achieved in weight-drop models (Namjoshi et al., 2014). However, measures of angular acceleration and velocity, which are responsible for producing high levels of shear strain, indicate that these levels do not reach scaled thresholds to produce concussion. Additionally, while there was diffuse pathology, the gradient emanated from the site of impact, suggesting that impact is likely the primary source behind observed pathology (Sauerbeck et al., 2018). The reason rodent brains cannot be used to mimic the inertial forces seen in TBI is that they are simply too small. Brain mass, in addition to rotational/angular acceleration, determines the amount of shearing force experienced. The smaller the

brain mass, the greater the rotational acceleration needed to produce the same deformation fields observed in a larger brain. In rodents, the acceleration necessary to generate the forces seen in human injuries is unachievable (V. E. Johnson et al., 2015).

It is possible to scale the rotational/angular loading experienced by humans to animals with larger brains such as pigs and non-human primates (Cullen et al., 2016; Ommaya et al., 1967). Early work on non-human primates established that angular, not linear, acceleration was required to produce concussion and also recapitulated many pathologies seen in human injury (Adams et al., 1981; Gennarelli et al., 1982; Ommaya et al., 1966; Ommaya & Gennarelli, 1974; Yarnell & Ommaya, 1969). While research has moved away from using non-human primates, whose brains most closely resemble our own, pig brains also share many features with humans. In addition to both being gyrencephalic, pig and human brains have similar white matter to gray matter ratios (about 60:40); unlike lissencephalic rodent brains with a paucity of white matter (14:86 in rats and 10:90 in mice) (Bailey et al., 2009; Howells et al., 2010; K. Zhang & Sejnowski, 2000). These characteristics allow for pathology to develop in patterns and extents seen in humans (Cullen et al., 2016; McKee et al., 2009; Meaney et al., 1995).

This swine paradigm of angular head acceleration is the only model in use today capable of mechanistically recreating the biomechanical etiology of closed-head diffuse TBI. However, procuring and caring for pigs is expensive, and executing rotational injuries requires highly specialized equipment and personnel. While it is unwise to use rodents alone to study diffuse injuries, their ready availability and potential for transgenic manipulation make them vital for investigating other aspects of the heterogeneous injury spectrum characteristic of TBI, including but not limited to mechanisms of secondary injury such as cell death, neuroplasticity, inflammation, neurodegeneration, and accumulation of proteins such as amyloid beta and tau (W. H. Cheng et al., 2019; Edwards et al., 2020; Ertürk et al., 2016; Gold et al., 2018; Kokiko-Cochran et al., 2018; Muza et al., 2019; Schoch et al., 2012).

3.3. Pathological Mechanosensation in Neurons

Both *in vivo* and *in vitro* models have been used to explore how cells sense and react to injurious forces. This review will focus on the acute responses to supra-threshold loading, particularly those arising from diffuse strain fields (Fig. 2F–J, Fig. 5). For information on secondary injury cascades and longer-term responses, the reader is directed to a number of other review papers referenced at the end of this section.

3.3.1. Cytoskeleton Abnormalities in Axons and Dendrites—Diffuse axonal injury (DAI) is one of the most common types of damage produced by TBI, and has been reviewed extensively elsewhere (V. E. Johnson, Stewart, & Smith, 2013; Smith & Meaney, 2000). Briefly, it occurs when inertial forces deform white matter, resulting in multifocal regions of swollen and disconnected axons. In severe cases, DAI is accompanied by tears in the white matter (primary axotomy) and intracranial hemorrhage, usually resulting in prolonged unconsciousness (coma) and poor outcomes (Gennarelli et al., 1982; Mata-Mbemba et al., 2015, 2018; O'Donnell et al., 2018; Smith et al., 2000). Whether severe or mild, DAI is the result of damage to the axonal cytoskeleton. *In vitro* stretch models have

shown that breaks in microtubules along the axon produce discrete or periodic swellings called varicosities, leading to interruption of transport along the axon (Tang-Schomer et al., 2010, 2012). Whether or not microtubules break seems to depend on the microtubule-associated protein tau, as mathematical models show that the viscoelastic properties of the protein as well as binding interactions combine with strain rate to influence microtubule rupture (Ahmadzadeh et al., 2014, 2015). The involvement of the microtubules in DAI has also been confirmed in studies in guinea pig optic nerve, cat fluid percussion, and post-mortem human tissue, which show disruptions in neurofilaments as well (Christman et al., 1994; Maxwell & Graham, 1997; Pettus et al., 1994). While this secondary pathology can develop over the course of hours to days, there is also a more immediate response. Within minutes of injury from a variety of *in vivo* models, nodes of Ranvier and paranodal regions were noted to be particularly vulnerable to swelling (Greer et al., 2013; Maxwell, 1996; Maxwell et al., 1991). Within seconds of *in vitro* stretch injury, axons become undulated and misaligned before gradually returning to their pre-stretch orientation, indicative of loss of elasticity (Smith et al., 1999). Other *in vitro* work has demonstrated that acute mechanical perturbation of the neuronal integrin adhesion complexes that link the cytoskeleton to the ECM can induce focal swellings in neurites minutes after injury (although it should be noted that neuronal focal adhesion complexes are an *in vitro* epiphenomenon and do not exist in the brain, though perturbations to integrin likely do occur *in vivo*) (Hemphill et al., 2011).

Interestingly, injury to axons can result in dendritic alterations in the same neurons. Following *in vitro* axonal stretch, dendritic beading formed within minutes (Monnerie et al., 2010). Beading and dendritic spine loss seem to be dependent on sodium influx and NMDARs (Monnerie et al., 2010; Nagendran & Taylor, 2019). Even in acute hippocampal slices not subjected to mechanical injury but instead exposed transiently to NMDA, dendritic swelling and loss of microtubule associated protein 2 (MAP2) were observed immediately (Hoskison et al., 2007). Indeed, glutamate is known to modulate the dendritic cytoskeleton, as 8 hours of exposure caused a decrease in the number of microtubules in the distal region of retracting dendrites of cultured hippocampal neurons, and caused an increase in microtubule number in the dendritic shaft of both retracting and growing dendrites (M. T. Wilson & Keith, 1998). This cytoskeleton remodeling is likely to occur acutely after TBI, as neurotransmitter and ionic imbalances are an immediate consequence of injury (see below). In fact, in various rodent models of TBI, alterations in MAP2, neurofilaments, and/or dendritic morphology have been observed at time scales ranging from 10 minutes to 1 week after injury (Campbell et al., 2012; Gao et al., 2011; Hicks et al., 1995; Posmantur et al., 1996; Taft et al., 1992; Winston et al., 2013). The effects on dendritic spines also appear to be dependent on matrix metalloprotease 9, suggesting the involvement of the ECM as well (Pijet et al., 2019).

3.3.2. Mechanosensitive Ion Channels—Besides cytoskeletal disruptions, axonal injury has also been associated with increased levels of intracellular calcium. This increase is mediated by sodium influx through mechanosensitive sodium channels, which subsequently triggers the opening of voltage-gated calcium channels, as revealed in an *in vitro* stretch injury model (Wolf et al., 2001). The elevated calcium can lead to the proteolysis of the sodium channel α subunit 5–20 minutes after injury, resulting in persistent

elevations in intracellular calcium (Iwata et al., 2004). Further work showed that stretch or bleb-inducing membrane damage caused leaking from voltage-gated sodium channel 1.6 (Nav1.6), which is present at axonal nodes of Ranvier (J. A. Wang et al., 2009).

Outside the context of DAI, other ion channels have been reported to respond to mechanical trauma. *In vitro* mechanical injuries have long been known to induce a persistent loss in the voltage-dependent magnesium block of NMDARs and potentiate their currents (LaPlaca & Thibault, 1998; L. Zhang et al., 1996). The immediate action on NMDAR initiates secondary signaling cascades that result in the enhancement of AMPA and $GABA_A$ currents, the former of which can last for days (Goforth et al., 2004; Kao et al., 2004; Spaethling et al., 2012). Outside of *in vitro* experiments, neocortical and hippocampal pyramidal cells in mouse brain slices express stretch-activated mechanically-gated channels capable of triggering action potentials (Nikolaev et al., 2015). In contrast, cerebellar Purkinje cells and locus coeruleus cells did not have any mechanically-gated currents and their robust rhythmic spike activity was resistant to mechanical modulation, suggesting they may be less vulnerable to TBI. Furthermore, rat FPI experiments have demonstrated that neuronal depolarization immediately after injury results in huge increases of extracellular potassium, which cause the release of neurotransmitters such as glutamate that result in further potassium flux (Katayama et al., 1990).

3.3.3. Plasma Membrane Permeability—Supra-threshold mechanical loading can alter ion homeostasis not only through changes in ion channels, but also by the temporary formation of micro- or nano-tears in neuronal plasma membrane. Acute increases in cytosolic calcium and efflux of lactate dehydrogenase dependent on loading rate have been reported since studies in the 1990s using *in vitro* membrane deformation by fluid shear stress (LaPlaca et al., 1997). Since then, other 2D or 3D *in vitro* models of stretch or shear injury have used variously sized cell-impermeable molecules to demonstrate that mechanical injury results in transient increases in plasma membrane permeability, also termed mechanoporation, that depend on strain rate and magnitude (Cullen et al., 2011; Geddes, Cargill, et al., 2003; Geddes, LaPlaca, et al., 2003; LaPlaca et al., 2006, 2009). Curiously, plasma membrane permeability has not been observed in unidirectional strain fields (Smith et al., 1999), suggesting that the complexity of the strain field is a major driver in inducing this mechanism of injury. The type of strain is also important, as compressive forces produce less or no permeability (Bar-Kochba et al., 2016; Cullen et al., 2011). The time course of these breaches in membrane integrity and subsequent repair can vary, as demonstrated by studies showing that neurons remain permeable to small molecules up to 5 minutes after severe stretch, but are only permeable to large molecules seconds after injury (Geddes, Cargill, et al., 2003). Additionally, neurons may undergo an initial round of membrane damage and repair, followed by a phase of secondary membrane degradation (Cullen et al., 2011). Although high strain rates and the ensuing structural compromise may lead to cell death in some cases (Cullen et al., 2011), in others the cells survive with functional deficits, such as electrophysiological disturbances (LaPlaca et al., 2006). The extent of the dysfunction may depend on the cell type, as cortical neurons were shown to exhibit longer increases in permeability than hippocampal neurons, but injury of hippocampal neurons produced larger increases in intracellular calcium and sustained ATP deficits, suggesting that

secondary cascades and not primary membrane damage may underlie selective vulnerability of some neuron populations over others (Geddes, LaPlaca, et al., 2003).

Consistent with *in vitro* studies examining the relationship between strain and extent of permeability, comparing *in vivo* CCI injury in rats to stress/strain tissue patterns in a 3D finite elements simulation revealed that brain areas predicted to have the most stress/strain positively correlated with the number of cells with membrane damage (LaPlaca et al., 2019). Also similar to *in vitro* studies, weight drop injury in rats demonstrated that permeabilized neurons may experience membrane resealing, delayed permeability, or enduring membrane leakage (Farkas et al., 2006). Interestingly, central FPI in rats produced scattered somatic neuronal permeability that did not overlap with other markers of neuronal injury such as degeneration, stress, and axonal injury, indicating distinct injury phenotypes (Singleton & Povlishock, 2004). Some of these permeabilized neurons displayed signs of necrosis, while others looked ultrastructurally normal. This range of outcomes for permeabilized cells was also seen in a mouse CCI model (Whalen et al., 2008). On top of these primarily impact injuries, it has also been shown that neuronal permeability is produced in cortical and subcortical regions following diffuse head rotational (inertial) injuries in the pig, which more accurately reflect the biomechanics seen in most human injuries (Keating et al., 2020; Wofford et al., 2017).

In addition to somatic permeability, mechanoporation is also observed in axons and was actually first described in this compartment (Pettus et al., 1994). It has been debated whether axonal permeability triggers the disconnected axons that are a hallmark of DAI, with a rat impact acceleration model reporting axons with membrane damage and axons with impaired transport as distinct populations (Stone et al., 2004), while an *in vitro* fluid shear stress injury-induced mechanoporation did lead to axonal bead formation (Kilinc et al., 2008). Recently, studies using finite element simulations with or without molecule dynamics simulations showed that in a typical injury scenario, axons sustain deformations large enough to enable pore formation in the membrane bilayer, and support this mechanoporation as a more likely injury trigger than microtubule failure (Montanino et al., 2020; Montanino & Kleiven, 2018).

These simulations also illustrate that changes in permeability can be expected even below the threshold for pore formation (Montanino et al., 2020). This finding is not surprising, as many factors influence membrane permeability, including lipid composition. For instance, membrane permeability increases as the number of unsaturated fatty acids, either free or present in the hydrophobic tails of phospholipid molecules, increases (Ehringer et al., 1990). In contrast, sphingomyelin is suggested to increase resistance to water penetration in molecular dynamics simulations at equilibrium and under deformation, as well as increase bilayer stiffness (Saeedimasine et al., 2019). Cholesterol was also long thought to increase membrane bending rigidity, but recent evidence suggests that its effects are not universal but instead depend on the lipid composition of the membrane, as reviewed by Dimova (Dimova, 2014). Conversely, polyunsaturated fatty acids cause membranes to be more flexible, and are necessary for mechanosensation in peripheral touch receptor neurons (Vásquez et al., 2014). The ability of membrane lipid composition to alter properties such as bending rigidity may influence whether cells experience tears in response to mechanical loading.

3.3.4. Extracellular Matrix and Adhesions—The stiffness of a cell is also influenced by the local ECM composition (Viji Babu et al., 2019). The levels and distribution of different ECM components change in response to injury, as recently described in detail by George & Geller (George & Geller, 2018). To summarize, injury leads to the degradation of hyaluronic acid, accompanied by an increase in proteoglycans and fibrous ECM proteins. Although these changes are not acute, long-lasting alterations in ECM properties may influence how a neuron reacts to subsequent mechanical loading in the case of repetitive injuries. Furthermore, ECM composition is just part of the story: the number, density, and nature of cell-matrix adhesions (e.g., integrins) is also important. For instance, cortical neurons plated in a 3D matrix of varying concentrations of collagen demonstrated that neuronal viability after high-rate shear deformation decreased as the level of collagen increased, implicating ECM mechanical properties as well as cell-matrix adhesions in acute mechanotransduction events (Cullen, Lessing, et al., 2007). The number, density, and nature of cell-matrix and cell-cell (e.g., cadherins) adhesions likely contribute to the fidelity of strain transfer from the environment to the neuron and by extension affect the associated intracellular signaling cascades. They may also serve as fixed points preventing sliding between adjacent surfaces, which could concentrate stress and precipitate localized receptor or membrane failure. Clearly, the effects of supra-threshold forces on ECM, adhesions, plasma membrane, ion channels, and cytoskeleton are all interrelated and contribute to pathological mechanosensation in neurons.

3.3.5. Other Potential Mechanisms of Pathological Mechanosensation in Neurons—In addition to these known responses to the supra-threshold loading seen in TBI, there are likely other mechanisms of mechanotransduction. For instance, forces may affect receptor-ligand interactions. When two molecules are being pulled apart by tensile forces, greater force increases the likelihood that they separate in situations known as slip-bonds. In contrast, greater shear stress can actually promote adhesion in situations called catch-bonds (Sokurenko et al., 2008). Integrin, cadherin, and actin have all been shown to be capable of producing catch-bonds (Kong et al., 2009; C. Lee et al., 2013; Rakshit et al., 2012). However, above the optimum force for catch-bond formation, a receptor and ligand can be pulled apart like a slip-bond (C. Lee et al., 2013; Sokurenko et al., 2008). The high loading experienced during TBI could therefore disrupt receptor-ligand interactions, altering the cell-cell, cell-matrix, or cytoskeleton interactions.

While the cytoskeleton can transmit forces to mitochondria (Bartolák-Suki et al., 2017), the organelles may be able to directly sense forces themselves. In non-neuronal cells, mechanically deforming mitochondrial membranes led to mitochondrial fission that was not dependent on actin polymerization, but instead appeared to depend on the integral mitochondrial membrane adapter protein mitochondrial fission factor (MFF), which can detect and has a preference for mitochondrial tubules of smaller diameter. Deforming and constricting mitochondrial membranes reduces their diameter, causing MMF accumulation and recruitment of fission machinery like DRP1. Through fission, mitochondria may be able to resolve mechanical strain and avoid shearing or tearing (Carsten et al., 2017). Those outcomes may not be avoidable after supra-threshold forces such as those experienced during TBI. Indeed, in neurons mitochondria appear to be damaged acutely after injury.

Within minutes of fluid percussion injury in cats, axonal mitochondria exhibited swelling and disruption of cristae that persisted for hours (Pettus et al., 1994). In cultures of neurons and astrocytes, stretch injury decreased neuronal mitochondria membrane potential 15 minutes after injury, which appeared to be at least partially linked to intracellular calcium elevation through NMDAR (Ahmed et al., 2000, 2002). This damage can have dire consequences for the cell (see section 3.5 Physiological and Functional Consequences of Pathological Loading). Given the effect of forces on mitochondria, it is likely that other organelles are affected by supra-threshold loading as well.

3.4. Pathological Mechanosensation in Glia

In addition to neurons, astrocytes also respond to biomechanical loading, though they seem to be less susceptible to strain-induced death than neurons (Cullen, Simon, et al., 2007). Mechanical injury causes astrocytes to release ATP extracellularly (Ahmed et al., 2000; Neary et al., 2003, 2005). Shortly after *in vitro* stretch injury, extracellular ATP can activate P2 purinergic receptors, which along with increases in intracellular calcium, resulted in ERK and Akt activation, which play a role in astrogliosis (Neary et al., 2003, 2005). While not necessarily an acute response to injury, ATP signaling through P2 receptors also resulted in an increase in astrocytic N-cadherin expression and cell surface localization 24 hours after stretch injury (Tran et al., 2008), suggesting that altered glia-glia or glia-axon adhesions may influence subsequent responses during repetitive injuries. Though extracellular ATP may increase, intracellular ATP concentrations decreased 15 minutes after stretch injury, which appeared to be caused by dysfunctional mitochondria with decreased membrane potentials (Ahmed et al., 2000). Interestingly, this injury in astrocytes seemed to influence mitochondrial function in neurons (Ahmed et al., 2000). Similar to neurons, mechanical injury resulted in an increase in intracellular sodium that was dependent on the severity of injury, and activated NMDAR (Floyd et al., 2005; Maneshi et al., 2017). Intracellular calcium also rises in response to shear stress. These increases occurred at areas of the cytoskeleton exhibiting the most strain, as shearing produced non-uniform distribution of forces across the cytoskeleton, particularly in cells having fewer stress fibers and lower tension before injury (Maneshi et al., 2018). Other proteins that comprise or interact with the cytoskeleton change as well, though these changes are not quite immediate. For instance, increased GFAP reactivity was seen at 48 hours in shear strain 3D culture system, along with hypertrophic process density, increased secretion of the ECM molecule chondroitin sulfate proteoglycan, and increased astrocyte density, depending on the strain rate (Cullen, Simon, et al., 2007). An increase in GFAP was correlated with a general softening in non-nuclear regions of astrocytes at the site of stretch injury and in the surrounding area (Miller et al., 2009). In fact, and contrary to long-held assumptions, *in vivo* the astrocytic glial scar is actually softer than surrounding tissue, and correlated with expression levels of cytoskeletal components GFAP and vimentin, as well as extracellular matrix components laminin and collagen IV (Moeendarbary et al., 2017). Even in injuries that do not produce a glial scar, astrocyte reactivity is a hallmark of TBI and impacts numerous processes over a variety of time scales (Burda et al., 2015).

While the biomechanical responses of astrocytes have received much attention, pathological mechanotransduction in other glial cells is less studied. It is clear that microglia can respond

rapidly to injury, as in an intact living mouse brain, their processes have been observed to rapidly converge on the site of laser ablation injury without cell body movement in an ATP-dependent manner (Davalos et al., 2005). Microglia processes were also observed to contact diffusely injured axons 6 hours after a central FPI in pigs (Lafrenaye et al., 2015). The cell bodies themselves can also migrate rapidly, as illustrated by microglial localization to permeabilized neurons within 15 minutes of swine diffuse rotational injury (Wofford et al., 2017). As major players in the complex neuroinflammatory response, microglia impact many processes from secondary injury to repair across acute and chronic time points (Loane & Kumar, 2016).

Since axonal injury is a hallmark of diffuse brain injury, and as white matter damage has been detected with diffusion tensor imaging within hours to days after even mild injury (Bazarian et al., 2007; Herrera et al., 2017; Soni et al., 2020; Wilde et al., 2008; T. C. Wu et al., 2010), there has been interest in the mechanical responses of myelin and oligodendrocytes. Though the role of mechanical forces on immature oligodendrocyte differentiation and migration have been investigated (Makhija et al., 2020), only recently has the response of mature oligodendrocytes to supra-threshold forces been examined. High-magnitude tensile strain applied to cultured matured oligodendrocytes produced damage to cell morphology, partial cell loss, and decreased myelin protein expression (Chierto et al., 2019). This stretch-induced myelin protein loss was shown to be transient and reversible, and caused by calcium-dependent MAP-ERK1/2 activation (J. Kim et al., 2020). Interruption of the myelin sheath not only has implications for action potential conduction, but also for the mechanical response of the axon to loading. Spinal cord studies revealed that myelinated and demyelinated spinal cords displayed differences in stiffness and tensile stress, suggesting that myelin and axoglial junctions play a large role in determining the tensile response of the tissue (Shreiber et al., 2009). Indeed, unmyelinated axons are more susceptible to fluid percussion or *in vitro* stretch injury than their myelinated counterparts (Reeves et al., 2005, 2012; Staal & Vickers, 2011). Even in myelinated neurons, the mechanical response of the axon is dependent in part on the thickness of the myelin sheath (g-ratio) and the cholesterol concentration of the myelin (Zhu et al., 2016). In particular, the unmyelinated nodes of Ranvier experience larger strains that the rest of the axon (Zhu et al., 2016), and secondary injury abnormalities in paranodal myelin organization and adhesion have been observed days to weeks after injury (Marion et al., 2018; Reeves et al., 2010). Together, it is clear that the mechanical properties and responses of myelin and oligodendrocytes have significant roles in the progression of white matter pathology (Armstrong et al., 2016).

3.5. Pathological Mechanosensation in Blood Vessels

The biomechanics of cerebral blood vessels during TBI has recently been reviewed (Monson et al., 2019). To briefly summarize, blood vessels in the brain often tear and bleed as an immediate biophysical consequence of TBI. It is also possible that mechanical forces below the threshold for hemorrhage could contribute to vascular dysfunction including alterations in contractility through microstructural damage to vascular cells and ECM. However, little is known about the local loading conditions that blood vessels in the brain experience during TBI or how the vessels respond to these forces. It is likely that loading conditions vary

depending on where the vessel is located in the brain (e.g., epidural, subarachnoid, parenchymal, etc.). Furthermore, the brain's response to loading in a particular region may be influenced by the degree of vascularization. It is noteworthy that gray matter is more vascularized than white matter, and cerebral arteries are considerably stiffer than the surrounding tissue. Interestingly, branching segments of vessels appear to be more susceptible to mechanical failure than straight segments, suggesting that the resultant stress concentrations may be relevant to vessels experiencing uneven shear, such as the bridging veins extending from the surface of the brain to the relatively stiff sinuses. At the level of capillaries, the blood brain barrier is known to experience an immediate and biphasic (and in some cases, multiphasic) increase in permeability. Across vessel sizes, it is evident that application of mechanical forces during injury has an important role in vascular pathology, and further studies are needed to investigate the precise effects of different loading conditions.

3.6. Physiological and Functional Consequences of Pathological Loading

The failure of the cytoskeleton and plasma membrane, along with alterations in ion channels, ECM, and adhesions, in response to supra-threshold mechanical loading can lead to a wide range of consequences for the cell and the tissue (Loane et al., 2015). Deformation of various subcellular compartments may affect the diffusion of particles. Diffusion of substances in the cytoplasm is very complex, and depends on spatial restrictions due to the cytoskeleton, organelles, the physical geometry of the area or compartment, as well as other considerations (Luby-Phelps, 2000). The presence and concentration gradients of biomolecules and other signaling factors are often tightly regulated *within* subcellular compartments of the cytoplasm. In dendrites in particular, the regulation of calcium diffusion has been shown to depend on the presence of buffering proteins and crowding from large structures, as well as spine geometry (Biess et al., 2007, 2011; Cugno et al., 2019; Korkotian & Segal, 2006; Straube & Ridgway, 2009). When these compartments are deformed, diffusion rates can be expected to change.

Whether from altered diffusion or changes in ion channels and membrane permeability, acute loss of ionic homeostasis at the point of mechanical injury kicks off a variety of signaling cascades that contribute to secondary injury, including excitotoxicity and changes in energy metabolism (Giza & Hovda, 2001; McGinn & Povlishock, 2015). Mitochondrial dysfunction not only results in metabolic alterations, but also leads to increased reactive oxygen species (ROS), which further damage the cell (Hiebert et al., 2015). ROS, along with factors released by primary or secondary plasma membrane disruption and excitotoxic neuronal injury, drive early neuroinflammation, which can contribute to further secondary injury and persist chronically (Simon et al., 2017). These factors contribute to a variety of delayed cell death mechanisms in neurons that did not die as from the primary injury (Raghupathi, 2004; Stoica & Faden, 2010). Even neurons that survive all of these insults may display altered electrophysiological and network properties (Cohen et al., 2007; Goforth et al., 2011; Magou et al., 2015; Patel et al., 2012; Prado et al., 2005; Sharp et al., 2014; Wolf et al., 2017). Ultimately, long-term dysfunction and death may contribute to chronic neurodegenerative diseases (Smith et al., 2013).

4. Repetitive Brain Injuries

Although forces may only be transduced acutely, they can have lasting effects that can influence how the brain responds to a subsequent injury. At the macro level for instance, CCI in mice can alter the stiffness of the impacted brain region for several days (Boulet et al., 2013), which would change the response to loading if another injury were to occur within that time frame. At the micro level, changes to ECM composition or cell adhesions may also alter how subsequent forces are transferred to cells. Alterations to the cellular mechanosensation machinery can impact its ability to transduce signals, which along with an environment shaped by physical damage and secondary injury cascades, can make the cell more susceptible to further insults during windows of biomechanical vulnerability.

4.1. Temporal Windows of Biomechanical Vulnerability

The timing of repetitive injuries influences cellular vulnerability to further harm from another injury. Some studies suggest that a mild injury may actually be protective against a second injury by a process called preconditioning, which has been extensively studied as it relates to hypoxia and ischemia (Li et al., 2017). In TBI models, hippocampal cultures subjected to a low-level stretch administered 24 hours before a mild stretch resulted in less release of a common marker of damage (S100β) than mild injury alone (Slemmer & Weber, 2005). *In vivo*, rat weight drop models demonstrated that repetitive mild injuries prevented motor deficits that were seen in animals that received the single injuries (Allen et al., 2000; Mychasiuk et al., 2015). Weight-drop in adolescent mice produced changes in skull bone structure and integrity that reduced the percentage of animals experiencing skull fracture after another injury at the adult age compared to animals receiving adult injuries alone (McColl et al., 2018). These studies suggest that mild preconditioning injuries may strengthen the brain's defenses under very specific conditions.

However, many studies support the notion that the brain is most vulnerable to increased damage during the first several days after the initial injury, after which time a second injury produces no more damage than a single injury. In mice, repetitive closed-skull CCI led to increased cognitive deficits and/or axonal injury only in animals injured 3 or 5 days apart, not 7 days apart (Longhi et al., 2005). Similarly, repetitive mild CCI in rats showed that the brain was most vulnerable to damage when injuries were delivered at 1 and 3, but not 7, day intervals (Huang et al., 2013). In pig models of diffuse rotational injury as well, repetitive injuries occurring within 3 days resulted in increased damage such as neuronal plasma membrane permeability, axonal damage, and cognitive dysfunction (Friess et al., 2009; Keating et al., 2020). Though Friess and colleagues also reported damage when injuries were separated by 7 days in pediatric animals, Keating *et al.* did not observe damage in adult animals receiving repetitive injuries separated by 7 days (Friess et al., 2009; Keating et al., 2020). Together these studies suggest that the brain is most vulnerable to a second injury within several days of receiving the first insult. It is important to note, however, that this increased vulnerability clearly depends on the severity of the injuries and likely the type of injury as well, both of which are related to the nature of the injury biomechanics. But how are cells sensitized to increased damage from repetitive injuries?

4.2. Mechanisms of Increased Vulnerability

4.2.1. Cytoskeleton Abnormalities in Neurites—An injury may not cause overt pathological changes in axons and dendrites initially, but can cause damage when administered repetitively. For instance, mice receiving a single closed-skull CCI displayed only small areas of axonal injury, while animals receiving another injury 24 hours later exhibited much greater axonal injury along with a loss of dendritic MAP2 staining (Laurer et al., 2001). Damaged dendrites with loss of MAP2 have also been observed in *in vitro* stretch injuries of organotypic hippocampal cultures injured 24 hours apart (Effgen & Morrison, 2017). Damage to the cytoskeleton itself during the first injury may prime further damage during a second injury, as cytoskeletal mislocalization has been observed in axonal growth cones after in vitro stretch injuries (Yap et al., 2017). Alternatively, the effects on neurites may be indirect. For instance, *in vitro* stretch injury of axons at strains of less than 5% did not cause DAI, but when a second identical insult was delivered 24 hours later, intracellular calcium concentrations increased to levels seen after a single high stretch of 20%, and the axons exhibited minor undulations and swellings (Yuen et al., 2009). Although no degeneration was observed after the first injury, it did lead to increased sodium channel expression after 24 hours, which was indirectly responsible for the increase in calcium. This channelopathy was suggested to lower the injury strain threshold and provide a mechanistic basis for increased vulnerability to a second injury (Yuen et al., 2009). Increases in intracellular calcium immediately activate the cytoskeleton-cleaving enzyme calpain whose levels remains elevated for several days, weakening the mechanical stability of the axon in particular (Büki et al., 1999; Ma, 2013; McGinn et al., 2009).

4.2.2. Plasma Membrane Permeability—Altered ion homeostasis can also result from plasma membrane disruptions. In addition to immediate tears, the plasma membrane can exhibit delayed permeability (Cullen et al., 2011; Farkas et al., 2006; M. L. Hernandez et al., 2019), which may impact the response to a repetitive injury. A first injury may prime cells for further damage. For instance, repetitive injuries separated by 15 minutes or 3 days resulted in increased plasma membrane permeability in subcortical oculomotor regions compared to single injuries or repetitive injuries separated by 7 days in a pig model of diffuse, closed-head acceleration (Keating et al., 2020).

Underlying this heightened susceptibility to damage from repetitive injuries could be alterations in plasma membrane composition. Evidence of lipid peroxidation, which damages membranes, occurs as early as 1 hour post-injury in a moderately severe mouse weight drop model (Hall et al., 2004). Mild CCI in rats results in hydrolysis of polyunsaturated free fatty acids and diacylglycerols by 30 minutes after injury (Homayoun et al., 2000). Mass spectrometry brain imaging after CCI or FPI revealed changes in most classes of lipids 3 days after injury, with some classes like ceramides or docosahexaenoic acid (DHA) exhibiting an increase as early as 1 day (Barbacci et al., 2017; Guo et al., 2017; Mallah et al., 2018; Roux et al., 2016). CCI also resulted in lipid dysregulation detectable in serum during the first week post-injury (Hogan et al., 2018). Altered lipid composition could change membrane properties such as stiffness, which would impact how cells respond to subsequent forces. Importantly, these lipid alterations can persist months to years after injury in animals and humans (Abdullah et al., 2014; Emmerich, Abdullah, Crynen, et al., 2016;

Emmerich, Abdullah, Ojo, et al., 2016), highlighting the increased susceptibility and chronic effects of these injuries.

Another explanation for increased vulnerability to plasma membrane poration could involve faulty membrane repair mechanisms. Studies investigating plasma membrane permeability involve trapping a dye within a cell, indicating that mechanisms to repair the plasma membrane are rapidly deployed within minutes. These reparative mechanisms appear to include calcium-dependent vesicle exocytosis and cytoskeleton remodeling (Hendricks & Shi, 2014). However, repair may be energetically taxing for the neuron (Togo et al., 2000), and may be occurring at a time of metabolic dysfunction, as detailed below. Additionally, these mechanisms may be limited or unavailable as the secondary injury unfolds and calcium activates enzymes that digest the cytoskeleton and damage membranes (Deng et al., 2007; Homayoun et al., 1997, 2000; Mustafa et al., 2011). Together, these conditions may prevent the neuron from fully repairing its plasma membrane, resulting in secondary poration or increasing the vulnerability to damage from a second injury.

4.2.3. Mitochondria and Metabolic Changes—Mitochondria damage and subsequent alterations in cellular metabolism are acute responses to injury that may increase vulnerability to another insult. In a closed-skull impact model in mice, a second impact delivered 48 hours after the first resulted in cortical mitochondrial dysfunction 4 days after the final injury and increased markers of oxidative stress (Hubbard et al., 2019). A similar injury in rats caused decreases in cerebral glucose usage 24 hours after the first injury that recover by 3 days post injury, and administration of a second injury within this window caused the cerebral metabolic rate of glucose to become even more depressed and remained low for 3 days post-injury (Mayumi L. Prins et al., 2013). This pattern has also been observed in a rat FPI study (Selwyn et al., 2016). In a rat diffuse weight drop model, injuries repeated at 1, 2, 3, or 4, but not 5 days resulted in altered mitochondrial-related metabolism 48 hours after the last impact (Vagnozzi et al., 2007). A loss of mitochondrial function may inhibit the cell from having enough energy to adequately repair damage from primary and secondary injuries, rendering it more susceptible to subsequent damage. Mitochondrial dysfunction also results in ROS production and impaired calcium buffering capabilities, which together damage the plasma membrane, cytoskeleton, and other proteins (Hill et al., 2017) to potentially further lower the threshold for later injury.

4.2.4. Other Potential Mechanisms of Increased Vulnerability—Vessel disruption (hemorrhage) can expose neurons and glia to relatively unregulated whole blood, which can disrupt brain homeostasis. Even without an actual vessel tear, nervous system homeostasis may not be able to be maintained by vasculature that has been impaired by either mechanical forces directly or the biochemical environment of the injured brain. Similarly, the biphasic increase in BBB permeability may predispose the brain to damage from a subsequent injury (Monson et al., 2019). In addition, a single injury may prime cell death pathways that become fully activated upon a second injury. The expression or activation of pro-death proteins such as Bax and proteases such as calpains and caspases increase minutes to days after injury, while pro-survival proteins like Bcl-2 and Bcl-xL decrease (Raghupathi, 2004). Calpain-independent pathways involving overactive poly (ADP-ribose) polymerase

(PARP-1) responding to DNA damage induced by oxidative stress can deplete the cell's energy, also resulting in cell death (Barr & Conley, 2007). A subsequent injury resulting in more mitochondrial dysfunction and/or increases in intracellular calcium may trigger death in neurons that survived the first insult. And death is not just limited to neurons; oligodendrocytes also undergo apoptosis following TBI, leading to white matter loss (Flygt et al., 2013).

Cell death may be exacerbated by inflammation. Inflammatory cytokines are increased after rat FPI, followed by upregulation of apoptosis-related genes (Shojo et al., 2010). Inflammatory stimuli are also able to induce caspase activation, subtypes of which in addition to promoting apoptosis, can also mediate axonal degeneration (Kaushal et al., 2015). Furthermore, inflammatory mediators interact with various components of glutamate signaling to produce changes in receptors, transporters, and inflammatory genes (Simon et al., 2017). These interactions can trigger ROS generation and damage, which contribute to dendritic retraction, synaptic injury, damage to microtubules, and mitochondrial dysfunction in a process termed immunoexcitotoxicity (Blaylock & Maroon, 2011). Of note, inflammation has been observed a year after a single injury (V. E. Johnson, Stewart, Begbie, et al., 2013). Together, the inflammation, priming of cell death pathways, mitochondrial and metabolic changes, plasma membrane alterations, and cytoskeleton abnormalities initiated by a single injury can shift the vulnerability curve for pathological mechanosensation to render cells more susceptible to a second injury.

4.3. Consequences of Repetitive Injuries

Besides cell death, mechanically-induced changes in ion channels and ion homeostasis can impact the electrophysiological properties of neurons. Uniaxial stretching of squid giant axons at increasing rates depolarized the axonal membrane and the time needed to recover to baseline was nonlinear, with stretches of over 20% resulting incomplete recovery to the resting potential (Galbraith et al., 1993). Similarly, stretch injury in organotypic hippocampal slices resulted in altered electrophysiological function dependent on strain and strain rate in a complex manner (Kang & Morrison, 2015). When these organotypic cultures were stretched repetitively 24 or 72 hours apart, long term potentiation was lost (Effgen & Morrison, 2017). Thus, by altering ion homeostasis, repetitive injuries can have a long-term impact on the neuronal function. For instance, repetitive diffuse injuries have been shown to induce posttraumatic epilepsy, though this response can also be caused by single severe injuries (Reid et al., 2016; Shandra et al., 2019). Repetitive mild injuries in particular have been linked to chronic neurodegenerative diseases (Gardner et al., 2015; Gardner & Yaffe, 2015; McKee et al., 2009; Smith et al., 2013). Mechanisms involving excitotoxicity, increases in intracellular calcium, mitochondrial dysfunction, ROS-induced damage, and inflammation, may all contribute to the development of diseases such as chronic traumatic encephalitis (CTE), Alzheimer's disease, Parkinson's disease, and other dementias (Faden & Loane, 2015; Kulbe & Hall, 2017). It is clear that repetitive mechanical loading can cause primary and secondary damage with dire consequences.

5. Application of Biomechanics to Advance the Investigation and Treatment of TBI

The impacts of specific types of force application and of immediate physical damage itself are currently underappreciated in neurotrauma research. However, these acute mechanical responses either predispose or directly initiate mechanisms of secondary cellular dysfunction and/or death. Although these secondary mechanisms of damage are not unique to TBI, primary physical damage from force loading, along with the physically damaged environment in which secondary injury cascades unfold, is unique to trauma. Since this post-physical damage environment is the context in which the well-documented secondary processes dominate, there is a need to accurately represent the tissue- and cellular-level injury biomechanics in the development and application of reduced models of TBI.

Clearly, to fully describe the physical causation and physiological consequences of TBI, it is vital to establish relationships between defined cell- and tissue-level biomechanical inputs and acute structural or biophysical alterations. Understanding this relationship is important as the relative contributions of primary (physical) and secondary (pathophysiological) damage may vary according to the particular type of forces experienced or severity of injury. Therefore, consideration of injury biomechanics is critically important in utilizing pre-clinical models to accurately identify pathophysiology and develop targeted treatments specific to the types of forces producing injury. Ideally, animal models of TBI should reflect human injury with respect to biomechanical inputs (with appropriate scaling if necessary), immediate cellular/tissue biophysical responses, and neuropathology distribution and types. Moving forward, animal models should be vetted based on their ability to address all three of these areas, which will enable the opportunity to define and integrate the physical causation of injury as well as the biological consequences.

Information gained from pre-clinical work will be critical for the development of mechanistically based, targeted therapeutics for neuroprotection following TBI. It is evident that the response of the brain to supra-threshold loading depends on the types of forces that are applied. For example, pure impulse (inertial) loading produces different kinds of damage than pure impact (contact) loading. Likewise, the failure of certain structures but not others may differentially alter homeostasis. As such, different therapies might be expected to be more efficacious at treating one form of injury and its specific type of damage over another. Thus, pre-clinical studies of treatments that utilize biomechanically-relevant injury paradigms to target injury type- or causation-specific processes may result in useful therapies unique to a particular kind of loading. Similarly, clinical trials that include specific injury types or biomechanical causations as inclusion criteria for enrollment or subgroup analyses may demonstrate success in certain injury populations. Although determining the precise forces experienced by any given individual during TBI is likely not possible, in certain high-risk groups such as athletes or war fighters, wearable force sensors can provide this type of information (Rowson et al., 2018). Ultimately, clinical guidelines for treatment based on the type of injury and its biomechanical causation would be valuable

While more information is needed to know exactly how applying biomechanics would be implemented, one can envision an instance where a wearable force sensor on the helmet or

in the mouth guard of an injured football player can be accessed by a doctor so the physician has a general sense of the loading experienced. Either the knowledge of the doctor or software could inform the physician which pathologies the athlete is (or is not) at risk for. This information could guide initial diagnostics—as well as compliment biomarker-based measurements—and potentially enable pre-symptomatic treatments for patients before actual pathology has blossomed. Patient-specific biomechanical loading could also influence guidelines for return to play, sub-specialists for follow-up care, and the time course and duration of monitoring. In this way, each patient could receive specialized care tailored to the type of damage likely to occur based on the particular biomechanical loading experienced.

6. Conclusions

Because TBI is a physical injury, it is important to recognize the mechanical properties of the brain and the forces that act on it in order to understand the brain's response to injury. The brain's properties vary at both the macro and micro scales, with various subcellular components including the extracellular matrix, plasma membrane, transmembrane receptors, and cytoskeleton all contributing to its properties and force-sensing abilities. Under physiological conditions, these elements are able to adequately transduce forces and allow neurons and glia to detect, integrate, and react to changes in their physical environment. However, when loading becomes too great, as in TBI, these mechanosensors break down, damaging the cell. Even if these components do not fail completely in response to an initial injury, the threshold for damage may be lowered and secondary injury cascades and/or repetitive injuries can induce failure.

The concept of immediate structural damage should be considered in context with evolving, secondary pathophysiology, and potential interrelationships should be addressed. Understanding cell and tissue injury biomechanics is important for establishing links between physical and physiological consequences, including how different types of supra-threshold loading affect specific mechanotransducers or brain regions. Proper consideration of TBI biomechanics is critical to moving the field forward, as injury models not representative of human injury will fail to replicate mechanisms of primary damage, acute reparative processes, and the underlying environment in which secondary damage ensues; thus having little or no hope of determining accurate mechanisms of pathology or establishing effective treatments capable of translating clinically. Models with sufficient biomechanical fidelity to human TBI are critical to advance our understanding of the cellular, tissue, and whole-organism responses to neurotrauma. Replicating the causes and consequences of human injury will facilitate the development of targeted therapeutics to address the damage inflicted upon cells by specific mechanisms of injury.

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Highlights

- TBI is caused by extreme mechanical forces acting on the brain
- Cytoskeleton, plasma membrane, and transmembrane proteins sense forces in the brain
- Such biological force-sensors affect brain homeostasis and influence TBI responses
- These components can structurally fail due to mechanical forces produced during TBI
- Considering biomechanical parameters will advance the study and treatment of TBI

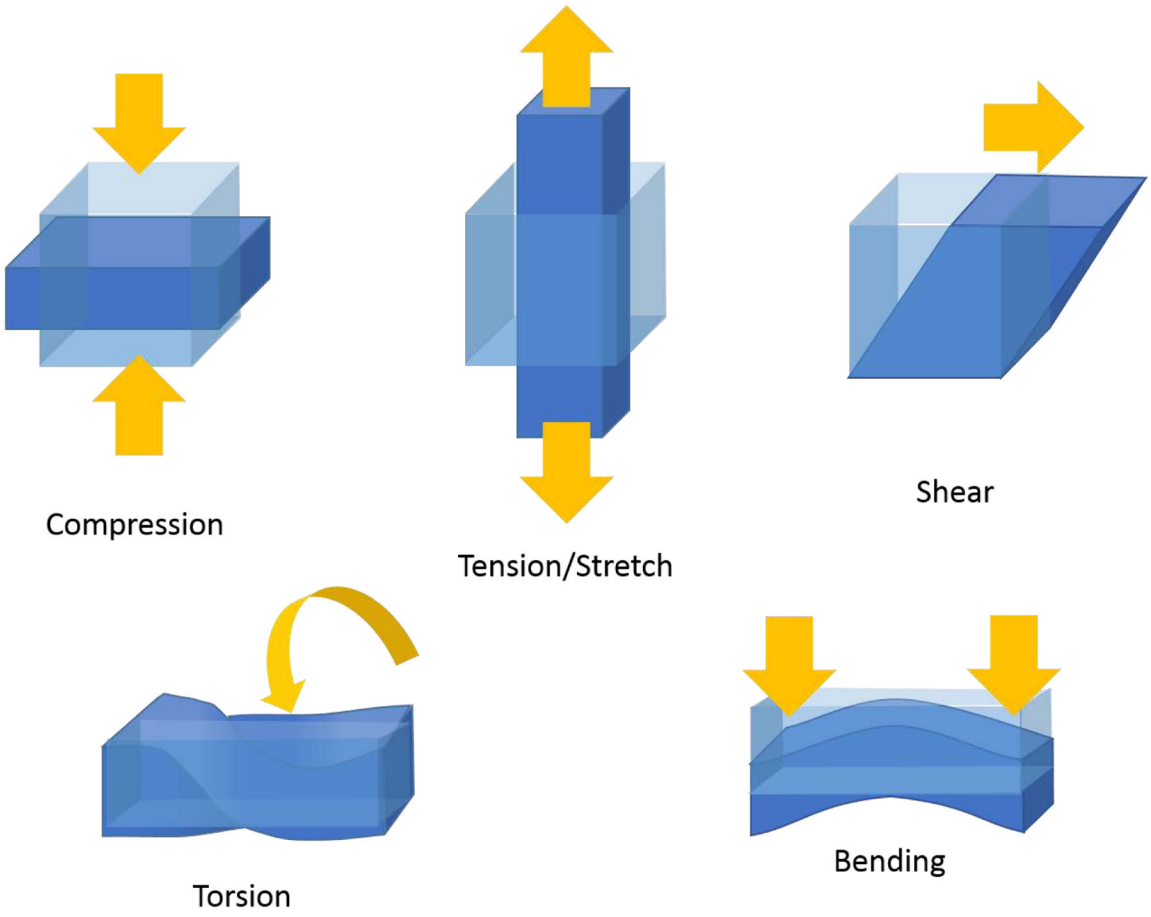

Figure 1:
Types of stress. The five types of stress that deform materials.

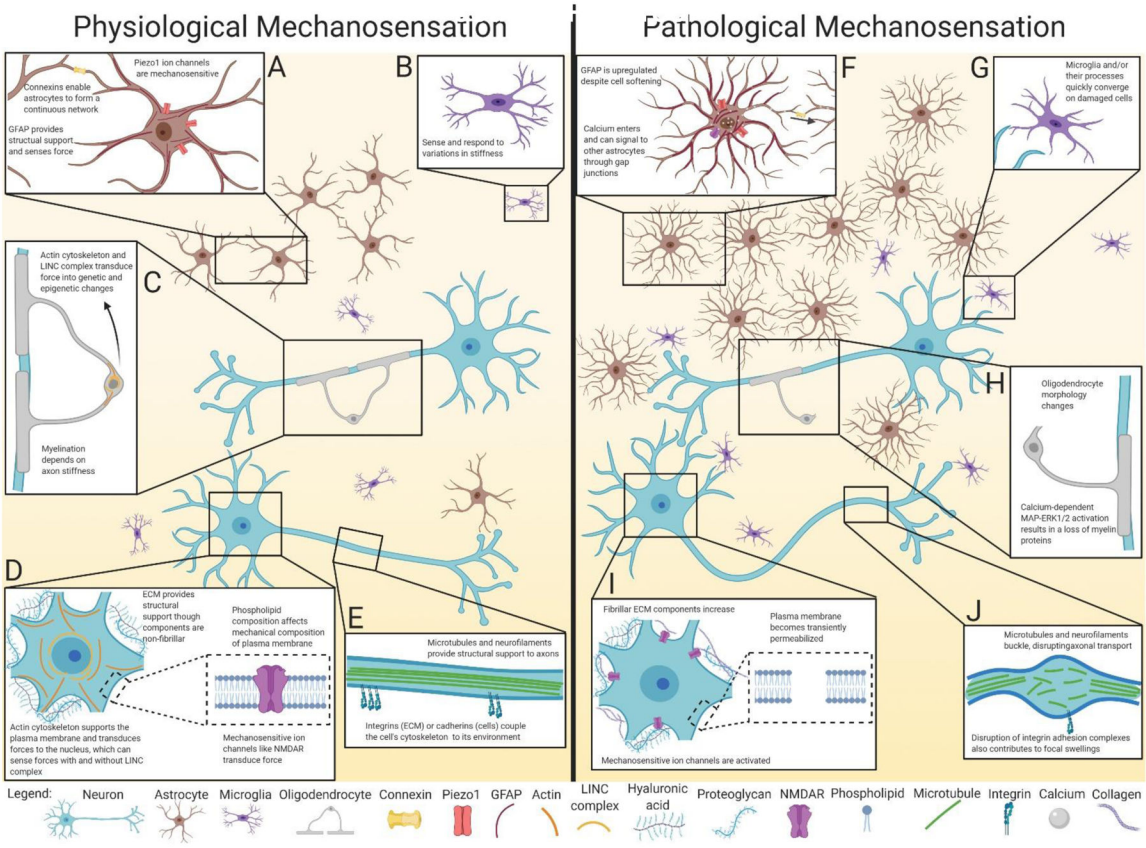

Figure 2:

Physiological and pathological mechanosensation in neurons and glia. A: Astrocytes are linked together in a continuous network of gap junctions formed from connexins. This network may act as a scaffold to sense forces throughout the brain via mechanosensitive Piezo1 channels, along with cytoskeletal elements such as GFAP. B: Microglia can adapt their spread area, morphology, and cytoskeleton to changes in environmental stiffness. C: Oligodendrocytes sense force through their cytoskeleton and LINC complex, resulting in transcriptional changes to promote differentiation and maturation. Once mature, myelination itself depends on the ability to sense the stiffness and diameter of axons. D: Neuronal mechanical properties are affected by the composition of the ECM and plasma membrane. Applied forces are transduced through mechanosensitive components such as ion channels, cytoskeletal proteins, and the nucleus. E: In the axon, cytoskeletal proteins such as microtubules and neurofilaments provide structural support. The cytoskeleton is coupled to the environment via transmembrane proteins such as integrins and cadherins that transduce mechanical forces. F: In response to supra-threshold forces, astrocytes proliferate and become hypertrophic, upregulating components of the cytoskeleton like GFAP, despite becoming softer. The opening of mechanosensitive ion channels such as Piezo1 and NMDAR allow cations including calcium to enter the cell, which may signal to other connected astrocytes through gap junctions. G: Activated microglia and their processes converge on damaged cells and areas of increasing stiffness. H: Oligodendrocytes experiencing high strain display altered morphology and decreased myelin protein expression. Myelin organization can become disrupted, particularly in paranodal regions. I:

Neuronal plasma membranes experience small tears, which along with activation of mechanosensitive ion channels, disrupt ion homeostasis. Supra-threshold forces also result in altered ECM composition, with a shift to stiffer substrates. J: Diffuse axonal injury results from the breakage of cytoskeletal components such as microtubules and neurofilaments, which along with disruption of adhesion complexes, results in focal swellings. Although beyond the scope of this graphic, note that mechanosensation pathways are also critical to brain vasculature homeostasis and pathophysiology, as reviewed in Monson et al. (2019), Baeyens et al. (2016), and Fang et al. (2020).

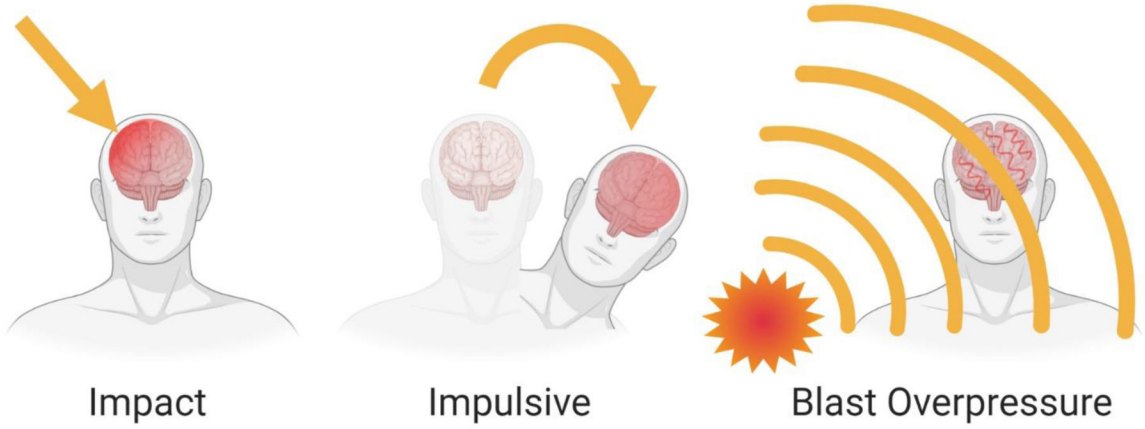

Figure 3:

Types of dynamic loading in TBI. A: In impact loading, the head strikes or is struck by an object, producing contact forces at the site. B: In impulsive loading, the head is set in motion without direct impact to the head, for instance if an object strikes another part of the body or if inertial forces act on the body (e.g., a restrained occupant in a motor vehicle collision). This loading accelerates the head and causes rotation about the base of the neck and the craniocervical junction. C: In blast overpressure or shock wave loading, rapidly moving, very short pressure waves travel through the brain, producing a complex injury involving stress waves, with potential head impact and/or head acceleration.

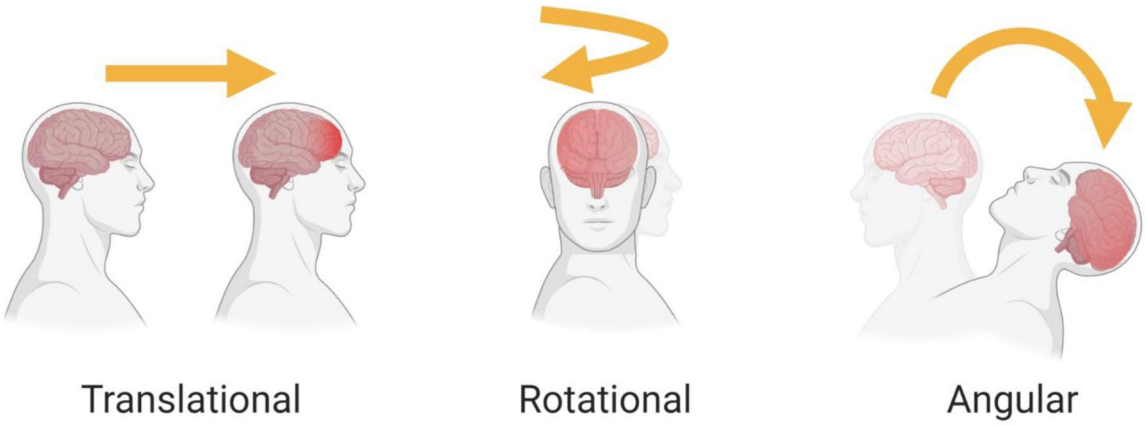

Figure 4:

Types of head acceleration. A: Translational or linear acceleration occurs when the center of mass of the brain moves in the straight line without rotation, potentially producing a focal injury. B: Rotational acceleration occurs when the center of mass of the brain does not move while the head rotates around it, producing high levels of diffuse strain. C: Angular acceleration occurs when the center of mass of the brain moves in an angular manner, combining elements of translational and rotational acceleration.

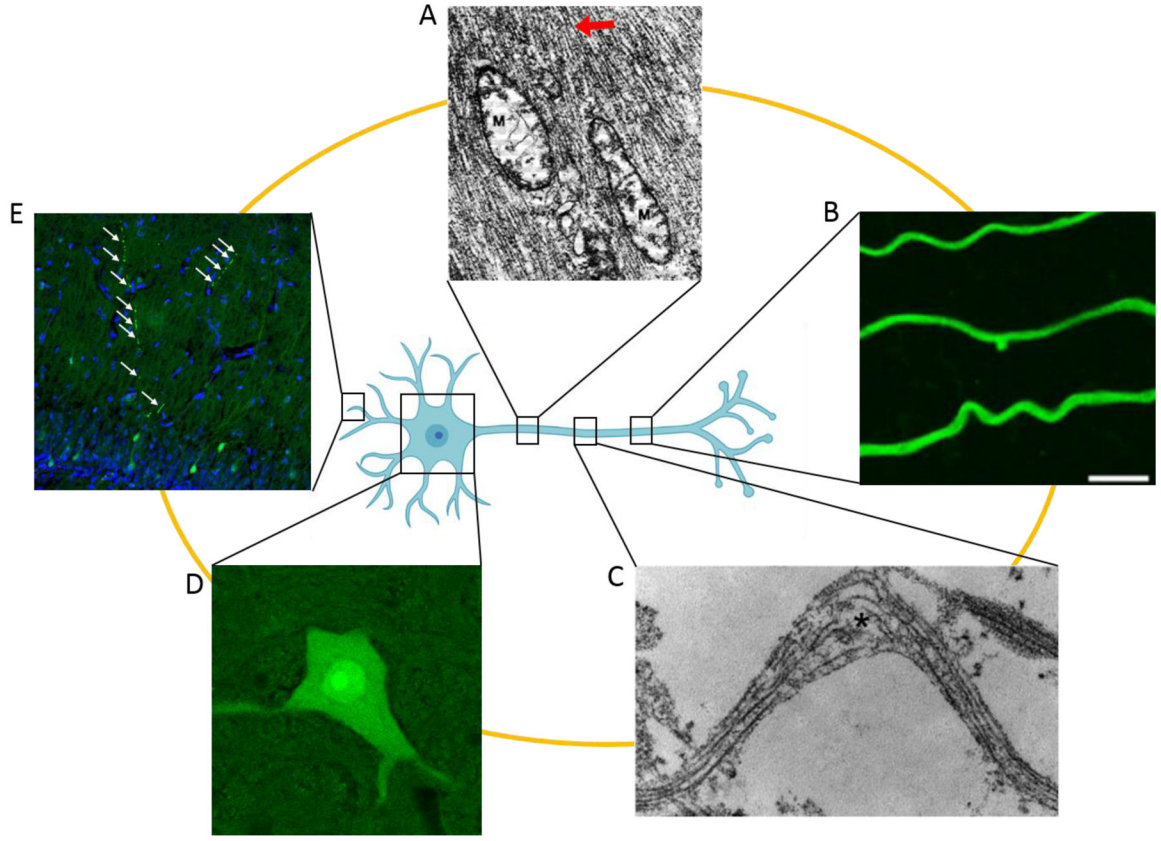

Figure 5:

Examples of acute neuronal pathologies. A: Electron micrograph of permeabilized axon revealing dilated mitochondria with disrupted cristae (M) and abnormally tightly packed neurofilaments (arrow) within minutes after fluid percussion injury in cats (adapted with permission from Pettus, 1994). B: Fluorescence image of undulating axons labelled with βIII-tubulin 2 minutes after in vitro axonal stretch injury, scale bar 5 μm (reprinted with permission from Tang-Schomer 2012). C: Electron micrograph showing compaction and misalignment of axon microtubules, along with frayed broken ends (asterisk) minutes after in vitro axonal stretch injury (reprinted with permission from Tang-Schomer 2010). D: Fluorescence image of a permeabilized neuronal cell body in the superior colliculus flooded with a cell-impermeable dye 15 minutes after swine diffuse head acceleration injury. E: Fluorescence image of dendritic beading (arrows) in mechanoporated hippocampal dentate granule neurons labeled by a cell-impermeable dye 15 minutes after swine diffuse head acceleration injury. Cell-impermeable dye (Lucifer Yellow), green; nuclei (Hoechst), blue.

Table 1:

Classification of TBI severity

(If a patient meets criteria in more than one category of severity, the higher severity level is assigned)			
Criteria	**Mild**	**Moderate**	**Severe**
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of consciousness (LOC)	0–30 min	>30 min and <24 hours	>24 hours
Alterations of consciousness / mental state (AOC) *	Up to 24 hours	>24 hours; severity based on other criteria	
Posttraumatic amnesia (PTA)	0–1 day	>1 day and <7 days	>7 days
Glasgow Coma Scale (GCS) (best available score in first 24 hours) **	13–15	9–12	<9

* Alteration of mental status must be immediately related to the trauma to the head. Typical symptoms would be looking and feeling dazed and uncertain of what is happening, confusion, and difficulty thinking clearly or responding appropriately to mental status questions, and being unable to describe events immediately before or after the trauma event.

** In April 2015, the DoD released a memorandum recommending against the use of GCS scores to diagnose TBI. See the memorandum for additional information.

Table reproduced from VA/DoD Clinical Practice Guideline for the Management of Concussion-Mild Traumatic Brain Injury.