A Knowledge Map Analysis of Brain Biomechanics:
Current Evidence and Future Directions

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Abstract

Although brain, one of the most complex organs in the mammalian body, has been subjected to many studies from physiological and pathological points of view, there remain significant gaps in the available knowledge regarding its biomechanics. This article reviews the research trends in brain biomechanics with a focus on injury. We used published scientific articles indexed by Web of Science database over the past 40 years and tried to address the gaps that still exist in this field. We analyzed the data using VOSviewer, which is a software tool designed for scientometric studies.

The results of this study showed that the response of brain tissue to external forces has been one of the significant research topics among biomechanicians. These studies have addressed the effects of mechanical forces on the brain and mechanisms of traumatic brain injury, as well as characterized changes in tissue behavior under trauma and other neurological diseases to provide new diagnostic and monitoring methods. In this study, some challenges in the field of brain injury biomechanics have been identified and new directions toward understanding the gaps in this field are suggested.

Key terms: Brain Biomechanics; Mechanical Properties; Neurological Diseases; Traumatic Injuries; Research Trends
1. Introduction

Although brain function is directly linked to its biochemical and electrophysiological activities, increasing evidence recognizes biomechanics to play an essential role in modulating the form and function of the brain. In particular, recent studies have shown that neurological diseases and traumatic injuries significantly alter brain’s material properties (Budday et al., 2019). An increasing number of studies have shown the significant role of mechanical properties of brain tissue during a multitude of events such as fetal development (Budday et al., 2014), neurological diseases such as multiple sclerosis (MS) (Streitberger et al., 2012; Weickenmeier et al., 2016) and Alzheimer’s disease (AD) (Murphy et al., 2011), and trauma caused by road traffic crashes (Sahoo et al., 2016; Yang, 2011), sports (Elkin et al., 2018; Ji et al., 2014; Laksari et al., 2018), high-pressure blasts (Laksari et al., 2015a, 2014; Sarvghad-Moghaddam et al., 2017; Sawyer et al., 2018; Tan et al., 2017) and ground-level falls (Raul et al., 2006).

In addition to developing basic science, biomechanical studies on the brain could help develop new diagnostic methods (Chaze et al., 2019; Lipp et al., 2013; Murphy et al., 2011; Streitberger et al., 2012), improve surgeon training systems and assistant surgeon robots (Kyriacou et al., 2002; Miller et al., 2010), and design head protective equipment (Kurt et al., 2017; Levadnyi et al., 2018; Vanden Bosche et al., 2017; Zhou et al., 2015). Computational models have become indispensable tools in achieving these goals (Ferrant et al., 2001; Ghajari et al., 2017; Zhao and Ji, 2018). Developing such models of brain tissue under mechanical loading heavily depends on proper geometrical estimations and fundamental material properties. With recent advancements in medical imaging, the
precise geometry of the brain can be accurately captured, but there are still uncertainties about the material properties (Brands et al., 2004).

Over the past half-century, many studies have aimed to extract the material properties of different regions of the brain tissue both ex vivo and in vivo (Chatelin et al., 2010). Some have used human specimens (Budday et al., 2017; Franceschini et al., 2006), but because of the ethical issues and the unavailability of fresh human brain tissue, animal specimens such as porcine (Destrade et al., 2015; Feng et al., 2017b; Kaster et al., 2011; Li et al., 2016, 2020; Yue et al., 2016), bovine (Budday et al., 2015; Laksari et al., 2012; Pervin and Chen, 2009; Samadi-Dooki et al., 2017; Weickenmeier et al., 2016), ovine (Feng et al., 2013; Labus and Puttlitz, 2016a, 2016b; Lippert et al., 2004), murine (Feng et al., 2017a; Gefen et al., 2003; Haslach et al., 2017; MacManus et al., 2016, 2015; Shafieian et al., 2009), canine (Zhang et al., 2016a, 2016b), leporine (Liu et al., 2018), and cebine (Galford and McElhaney, 1970) have been widely used (Table 1). Different modeling approaches and constitutive models including elastic (Falland-Cheung et al., 2018; Weickenmeier et al., 2016), hyperelactic (Rashid et al., 2014), viscoelastic (Chatelin et al., 2012; Li et al., 2020; Samadi-Dooki et al., 2018; Weickenmeier et al., 2018a), visco-hyperelastic (Giordano and Kleiven, 2014; Prevost et al., 2011a; Rashid et al., 2013; Sahoo et al., 2016), and poroelastic (Kyriacou et al., 2002) have been used to represent the behavior of brain tissue. Many studies have used assumptions that oversimplify the characteristics of the brain; however, even complex models could not fully express the complicated behavior of brain tissue in terms of nonlinearity, anisotropy, and heterogeneity.
Table 1. Different loading modes and conditions investigated on various species.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Loading mode</th>
<th>Loading condition</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow</td>
<td>C</td>
<td>QS &amp; D</td>
<td>(Cheng and Bilston, 2007; Laksari et al., 2012; Pervin and Chen, 2009)</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>QS &amp; D</td>
<td>(Bilston et al., 2001, 1997; Darvish and Crandall, 2001)</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>QS &amp; D</td>
<td>(Budday et al., 2015; Samadi-Dooki et al., 2017; Weickenmeier et al., 2016)</td>
</tr>
<tr>
<td>Dog</td>
<td>T</td>
<td>QS</td>
<td>(Zhang et al., 2016b)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>QS</td>
<td>(Zhang et al., 2016a)</td>
</tr>
<tr>
<td>Monkey</td>
<td>C</td>
<td>D</td>
<td>(Galford and McElhaney, 1970)</td>
</tr>
<tr>
<td>Mouse</td>
<td>I</td>
<td>QS &amp; D</td>
<td>(Feng et al., 2017a; MacManus et al., 2017)</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>QS &amp; D</td>
<td>(Miller and Chinzei, 2002; Rashid et al., 2014; Velardi et al., 2006)</td>
</tr>
<tr>
<td>Pig</td>
<td>S</td>
<td>QS &amp; D</td>
<td>(Begonia et al., 2010; Hrapko et al., 2008; Miller, K., Chinzei, 1997; Prevost et al., 2011a; Rashid et al., 2014; Yue et al., 2016)</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>QS &amp; D</td>
<td>(Coats and Margulies, 2006; Garo et al., 2007; Hrapko et al., 2006; Rashid et al., 2013; Thibault and Margulies, 1998)</td>
</tr>
<tr>
<td>Rat</td>
<td>S</td>
<td>D</td>
<td>(Haslach et al., 2017)</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>QS &amp; D</td>
<td>(Christ et al., 2010; Gefen et al., 2003; Shafieian et al., 2009)</td>
</tr>
<tr>
<td>Sheep</td>
<td>T</td>
<td>QS</td>
<td>(Labus and Puttilitz, 2016b, 2016a)</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>D</td>
<td>(Feng et al., 2013)</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>QS</td>
<td>(Feng et al., 2013)</td>
</tr>
</tbody>
</table>

T: tension, C: compression, S: shear, I: indentation, QS: quasi-static, D: dynamic
The current paper aims to review the research trends of brain biomechanics based on the published papers indexed by Web of Science over the past 40 years to inform and guide future studies in the areas that need further investigations.

2. Methods

One of the significant efforts to review past trends and identify the future directions in the field of brain biomechanics is to observe the pattern of the publications that could determine the perspective of the research in this field. In order to get a clear view, an analysis of the publications in the past 40 years was performed using Web of Science database and VOSviewer (version 1.6.11) as free software for scientometry that can create and visualize different types of maps according to the network data (van Eck and Waltman, 2013). We used four groups of keywords – Soft AND Tissue AND Biomechanics (Group 1), Brain AND Biomechanics (Group 2), Brain AND Injury AND Biomechanics (Group 3), and Brain Injury AND Challenges (Group 4) – to search on Web of Science platform from 1979 to 2019 (Table 2).

The visual results of the analysis by VOSviewer show the connections (referred to as links) between the most frequent words (referred to as terms) in each group of publications. The text mining algorithm of VOSviewer groups all terms with the minimum number of occurrences into clusters (defined as non-overlapping sets of terms) indicated by different colors (Waltman et al., 2010). In the network visualization, the size of the circles shows the number of publications that included the term, and the distance between
every two terms indicates the relatedness of terms, i.e., a stronger relationship between the terms is represented by a smaller distance (Hofmann, 2016).

### Table 2. Parameters and statistics for the searched keywords.

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Keywords</th>
<th>No. of pub.</th>
<th>No. of terms</th>
<th>Min no. of occurrence</th>
<th>No. of pub. meet the threshold</th>
<th>No. of selected terms</th>
<th>No. of clusters</th>
<th>No. of links</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Soft AND Tissue AND Biomechanics</td>
<td>1,766</td>
<td>42,214</td>
<td>30</td>
<td>370</td>
<td>222</td>
<td>4</td>
<td>18,066</td>
</tr>
<tr>
<td>2</td>
<td>Brain AND Biomechanics</td>
<td>1,101</td>
<td>24,528</td>
<td>20</td>
<td>342</td>
<td>205</td>
<td>4</td>
<td>13,556</td>
</tr>
<tr>
<td>3</td>
<td>Brain AND Injury AND Biomechanics</td>
<td>718</td>
<td>17,071</td>
<td>20</td>
<td>244</td>
<td>146</td>
<td>3</td>
<td>7,858</td>
</tr>
<tr>
<td>4</td>
<td>Brain Injury AND Challenges</td>
<td>1,397</td>
<td>12,991</td>
<td>30</td>
<td>104</td>
<td>62</td>
<td>5</td>
<td>1,706</td>
</tr>
</tbody>
</table>

### 3. Results

The results from the keyword search are summarized in Table 2, where the number of selected publications successively decreases from 370 to 104. As shown in Figure 1, “injury” was one of the most frequent words among 1,766 publications with keywords of Group 1. The links between this word (injury) and frequent words of other clusters displayed that injury of the brain, ligament, and articular cartilage due to “motion” during activities such as sport are of the most frequently used topics in the field of soft tissue biomechanics. These results showed the interests associated with the injury mechanisms in this research area.
The search results with the keywords in Group 2 (1,101 publications) showed that in the field of brain biomechanics, “impact” and “model” were the most frequent keywords that would accompany “brain” and “biomechanics”. The frequency of the word “impact”, which is known as the main mechanism of brain injury, showed that injury investigation was not only one of the prevailing topics in the field of soft tissue biomechanics, but also a research priority in brain tissue studies. The other frequent word in this group, “model”, indicated the importance of modeling in brain injury studies (Figure 2).

To have a closer look at the brain injury studies, the word “injury” was added to the keywords of Group 2 to create Group 3. The results of the search using this group showed that more than 65% of publications on brain biomechanics were related to brain injury biomechanics. The most frequent words in this group displayed that “concussion” caused by head impacts during athletic events or falls has been the subject of huge attention. “Model”, another highly repeated word, showed the importance of modeling approach in studies associated with brain injuries, most prominently finite element (FE) modeling, as a powerful tool for prediction of the mechanical behavior of brain tissue under different types of loading (Figure 3).

The results of searching keywords in Group 4 showed that the current challenges in this field were to detect changes in the cellular behavior during TBI and find diagnostic biomarkers for brain disorders (e.g., AD and stroke). Investigating the effect of age on the mechanical properties of brain tissue and the development of the computational age-dependent models, especially in children, showed growing interests. Furthermore, the frequency of the word “rehabilitation” indicated the importance of the physical and
cognitive issues after TBI which was in a close relationship with the quality of life of people facing brain injury (Figure 4).

Figure 1. The network visualization of most frequent terms in Group 1 (Soft AND tissue AND Biomechanics).
Figure 2. The network visualization of most frequent terms in Group 2 (Brain AND Biomechanics).

Figure 3. The network visualization of most frequent terms in Group 3 (Brain AND injury AND Biomechanics).
Figure 4. The network visualization of most frequent terms in Group 4 (“Brain Injury” AND “Challenges”).

4. Discussion

As shown above, insights into the biomechanics of the brain could help to understand the underlying mechanisms of injury and proposing new methods for the diagnosis and treatment of central nervous system (CNS) diseases. As a result, in the following section we focus on providing a summarizing overview of the previously published material properties of brain tissue under different conditions such as aging and disease.

Recently, elastography methods as minimally invasive imaging methods have been used to determine the local stiffness of tissue based on the displacement field which is created by applied mechanical waves to the tissue (Muthupillai et al., 1995). Two main modalities i.e. magnetic resonance elastography (MRE) (Atay et al., 2008; Green et al., 2008;
Guertler et al., 2018; Hiscox et al., 2016; Kruse et al., 2008; Kurt et al., 2019; Testu et al., 2017; Vappou et al., 2008; Weickenmeier et al., 2018b, 2018a) and ultrasound elastography (deCampo and Hwang, 2018; Liu et al., 2018, 2017) have been used.

Many studies have used these to investigate the effect of different parameters on the changes in the mechanical properties of brain tissue and have contributed greatly to our current understanding. Sack et al. (2011) investigated the brain material properties in human subjects aged 18-72 years using the MRE technique and showed that as the age increases, the shear modulus of the brain tissue decreases. Also, Arani et al., (2015) used MRE to study the correlation between age and the brain stiffness in healthy older adults (56-89 years). They observed that aging could lead to brain softening, and the changes in stiffness are regional dependent. Using the same method, Yeung et al. (2019) showed that the stiffness values of white and gray matters of brain tissue for children (7-12 years) and adults (>18 years) are not significantly different.

While the lack of in vivo studies of neonatal human brain stiffness does not indicate a significant correlation between age and brain stiffness, animal studies may fill this gap. Pong et al. (2016) used MRE to study the effect of age on the mechanical properties of rat brain tissue in the first six weeks after birth. The results showed that brain shear modulus increased in the first two weeks (corresponding to early childhood), remained constant from week two to week four, and decreased in week six (adolescence). According to these studies, it could be hypothesized that brain’s stiffness rises from birth to the first year of life, remains constant from childhood to adulthood, and decreases during old age that may be related to the physiological aging of cells, during which the amount of water and tissue protein contents changes (Shulyakov et al., 2011).
Some studies have used the relationship between mechanical properties and cell function as a clinical parameter in diagnosis of certain neurological disease such as MS (Streitberger et al., 2012), AD (Murphy et al., 2011), normal pressure hydrocephalus (NPH) (Fattahi et al., 2016; Freimann et al., 2012; Streitberger et al., 2011), meningioma (Murphy et al., 2013), Parkinson’s disease (PD) (Lipp et al., 2013), amyotrophic lateral sclerosis (ALS) (Romano et al., 2014), and cerebral palsy (CP) (Chaze et al., 2019).

Streitberger et al. (2012) examined the in vivo viscoelastic properties of human brain tissue with MS using MRE and showed that MS significantly reduces the shear modulus of patients’ brain tissue (Figure 5). It should be mentioned that myelin, a fatty white substance surrounding axons of neurons, degrades in MS, a process known as demyelination. Interestingly, Weickenmeier et al. (2017, 2016) combined nanoindentations and histological staining to examine the effects of myelination on the variation of stiffness of bovine tissue. They found a strong correlation between white matter stiffness and myelin content. This observation proves the correlation between tissue contents and disease progression.

These pieces of evidence of the relationship between neurological diseases and the material properties of brain tissue are not the only available hints. Murphy et al. (2011) investigated the effects of AD on brain’s mechanical properties using MRE and observed that AD could also lead to a decrease in tissue stiffness. NPH is a disease whose cause is still unknown, but studies show that this abnormality leads to a change in the mechanical properties of the brain tissue. Streitberger et al. (2011) reported that brain’s shear modulus in patients with NPH decreases about 20% in comparison to healthy subjects (Figure 5). Meningioma is the most common primary intracranial tumor, which is
typically categorized as either soft or fibrous. Since procedures for removing soft tumors are less complicated than fibrous tumors, detailed information about the mechanical properties of the tumor could reduce the risk of complications in surgeries. For this specific reason, Murphy et al. (2013) used MRE for measuring the mechanical properties of the tumor and surrounding healthy tissue and showed that this method could well differentiate the tumor from healthy tissue. Lipp et al. (2013) used MRE as an image-based marker for differentiating between patients with Parkinson's disease and healthy subjects. Although the shear modulus of brain tissue in patients with Parkinson's disease was higher than healthy subjects (Figure 5), this difference was not statistically significant (P>0.05). Chaze et al. (2019) measured the viscoelastic properties of brain tissue in children with cerebral palsy (CP). The results showed that the stiffness of gray matter in children with CP is significantly lower than the control group (Figure 5).
Figure 5. In vivo quantification of the shear modulus of human full brain in neurological diseases (data were collected from the following studies: multiple sclerosis (MS) (Streitberger et al., 2012), Alzheimer’s disease (AD) (Murphy et al., 2011), normal pressure hydrocephalus (NPH) (Streitberger et al., 2011), meningioma (Murphy et al., 2013), Parkinson’s disease (PD) (Lipp et al., 2013), and cerebral palsy (CP) (Chaze et al., 2019)).

Besides using MRE as a diagnostic method, some studies have used MRE for treatment monitoring. Freimann et al. (2012) used MRE to assess the effect of surgery for draining excess cerebrospinal fluid (CSF) from the NPH brain. The results showed that MRE could indicate the difference between the viscoelastic properties of brain tissue before and after the surgery. Pepin et al. (2014) studied the feasibility of MRE for investigating chemotherapy responses in mice. The results showed that tumor stiffness decreased after chemotherapy, and this change could be used as a marker for the early assessment of the tumor treatment. Feng et al. (2016) used MRE to study the effect of radiotherapy on the mechanical properties of murine brain tumors. The findings of this study indicated that radiation treatment did not affect the brain stiffness, while the difference observed in mechanical properties of the brain tumor and healthy tissue could potentially be used as a biomarker for tumor diagnosis. These studies have established the grounds that measuring the in vivo mechanical properties of brain tissue can be considered as a new clinical tool for the diagnosis and treatment monitoring of CNS diseases. Future studies can extend the application of this technique to a broader range of neurological diseases with higher precision and accuracy.
There are also reports in the literature that observed changes in the material properties of brain tissue due to head impacts. Badachhape et al. (2018) used MRE and accelerometers to measure soft tissue motion and skull motion, respectively. There is some evidence that the rotational movement of the skull leads to the relative motion of the brain (Laksari et al., 2015b). This relative motion and the difference between the stiffness of the white and gray matter in different regions could contribute to the development of local stress concentration that causes damage (Bayly et al., 2005; Laksari et al., 2018). Using tagged-MRI, it has been shown that during the movement of the head, different regions of the brain experience a complex deformation (Badachhape et al., 2017; Bayly et al., 2005). Since the brain experiences different loading conditions in scenarios leading to traumatic brain injuries (Labus and Puttlitz, 2016a; Miller et al., 2000), it is crucial to study the material properties under different loading modes, rates, and conditions. There are reports that have characterized the brain tissue under either small/large deformation, low/high loading rates, and different loading modes such as tension, compression, and shear (Bilston et al., 2001; Destrade et al., 2015; Finan et al., 2017; Haslach et al., 2017; Labus and Puttlitz, 2016b; Miller and Chinzei, 2002; Velardi et al., 2006; Yue et al., 2016).

Shafieian et al. (2009) used an impact acceleration model to induce traumatic axonal injury (TAI) in rats. They characterized the viscoelastic properties of brain tissue using the indentation technique before and after the injury, and showed that the injury changes the viscoelastic properties of the tissue (Figure 6). Alfasi et al. (2013) and Feng et al. (2017a) applied a similar technique on rats and mice brain samples, respectively. Through biological staining of the injured tissue, they observed that the changes in the mechanical
properties of the tissue have a close relationship with the amount of glial fibrillary acidic protein (GFAP) (Figure 7). Boulet et al. (2013) induced brain injury in a mouse model using a controlled cortical impact (CCI) method and quantified the in vivo changes in the brain stiffness using MRE. This study showed that brain’s stiffness significantly decreases with injury severity, and 28 days after the impact, tissue stiffness increases to match the primary value that indicates the recovery from injury. Qiu et al. (2020) used a similar method to study the effect of different impact angles and velocities on the induced injury and measured the viscoelastic properties of brain tissue using indentation tests. The results showed that the instantaneous and long-term shear moduli of injured brain tissue are lower than non-injured tissue.

These findings provide a hint that as large deformations cause injuries to the tissue, and the amount of injury correlates to the level of deformation, an accurate constitutive equation must include a damage function. This idea has been previously introduced and practiced for other tissues such as tendon (Natali et al., 2005), ligament (Guo and De Vita, 2009; Liao and Belkoff, 1999), blood vessel (Alastrué et al., 2007; Li et al., 2014; Peña et al., 2010), skin (Li and Luo, 2016), and mesentery (Chu and Blatz, 1972).

Budday et al. (2017) studied the effects of cyclic tension, compression, and shear loading conditions on human brain samples. While their results showed a significant difference between the first and the two proceeding cycles, they concluded that the preconditioning for brain tissue is recoverable. However, it should be mentioned that the reversibility of the tissue behavior was only investigated at strains below 10%, and as histological staining indicates, the tissue microstructure remained unchanged. In other words, to
grasp the effects of cyclic loading on the brain tissue injuries, larger deformations are required.

Franceschini et al. (2006) carried out the only study to date that has used a damage function for brain tissue. They examined the human brain tissue under cyclic tension-compression tests and consequently observed that this loading could cause permanent deformation in the tissue. While Franceschini et al. (2006) used a strain energy density function based on the Ogden hyperelastic model with an additional damage term to describe the behavior of injured brain tissue, they did not investigate the pathology of the tissue after loading. It should be noted that this constitutive model introduces damage as a function of deformation, hence its main shortcoming is that changes in the tissue microstructure are not considered, while it has been shown that tissue damage leads to changes in the physiological contents of the tissue (Kallakuri et al., 2003; Kane et al., 2012; Raghupathi et al., 2004).

Although there is no convergence among the results of limited studies that examine the behavior of the injured brain tissue, the differences are justifiable because of the difference in the type and amount of applied load and the time elapsed from injury. The overall assessment of these studies indicates the need for a more thorough investigation of the changes in the mechanical properties of damaged tissue overtime. Also needed is the inclusion of damage functions in constitutive models for predicting the effect of injury on the mechanical properties of brain tissue under large deformations. Brain, as a viscoelastic material, exhibits strain-rate-dependent mechanical properties. Many studies have shown that brain tissue under both quasi-static and dynamic loadings exhibits stiffer response with increase in strain rate (Begonia et al., 2010; Haslach et al., 2017; Li et al.,
and therefore, failure strain and toughness increase (Zhang et al., 2016b). Therefore, developing a viscoelastic damage function, which includes the rate-dependence effects, instead of the commonly used elastic damage functions could help more accurately predict the mechanical behavior of brain tissue.

Figure 6. (A) The setup used for inducing brain injury, (B) the indentation method for testing the mechanical properties of the injured tissue, (C) the assessment of the glial cells’ activities in the injured region using histological staining.
Figure 7. The effect of injury on the mechanical and biochemical properties of rat brain tissue; (A) Decrease in the shear modulus of injured brain tissue compared with uninjured tissue (3 hours after injury) (Shafieian et al., 2009), (B) increase in the elastic modulus of injured brain tissue compared with uninjured tissue (2 hours after injury) (Alfasi et al., 2013), (C) changes in the elastic modulus and the amount of GFAP in the injured tissue over a period of 7 days (Feng et al., 2017a), (D) crystal structure of rat GFAP (from https://swissmodel.expasy.org).
5. Conclusion and Future directions

The current study on the trends of brain biomechanics researches showed that “injury” and “modeling” were two major topics in this field. As the mechanical properties of injured and uninjured brain tissues are different, considering a damage function in the constitutive models to improve the predicted behavior is essential. It should be noted that considering the effect of the tissue regeneration process along with the damage is important in studying the changes in material properties of the tissue after injury. To our knowledge, the regeneration rate of brain tissue and its relationship with changes in tissue stiffness have not yet deeply studied.

The results of our mapping analysis revealed that brain injury biomechanics is not entirely understood and requires multidisciplinary approaches to demonstrate the complex behavior of the brain tissue during injury and recovery. According to the results of this study, several important issues require more attention in future studies:

- A clear description of brain tissue injury in terms of length scale has not yet been proposed. Understanding the role of different tissue components in the brain mechanical properties could help to propose such a description for brain injury. Identifying the contribution of different subcellular components such as cytoskeletal proteins, cell-extracellular matrix (ECM) interactions, and the interfaces between different cells (e.g., myelin-axon unit) in the mechanical properties of the brain tissue are suggested to clear this issue (Figure 8).

- As previous studies have shown, cells are mechanosensitive, and injury conditions may affect the expression of cellular proteins such as GFAP. Therefore, the
discovery of the biomarkers characterizing tissue injury process could help to improve the diagnostic and therapeutic methods.

- Limited studies have been done to identify the injury threshold of the brain tissue based on the strain and strain rate. As mechanical properties of brain tissue are nonlinear, anisotropic, and regional dependent, finding the injury threshold for different conditions has a high priority.

- In addition to the developing head protective devices such as helmets, the development of new biomaterials to promote the healing and regeneration process in the damaged tissues should be given special attention.

Figure 8. A schematic of injuries in sub-cellular components such as (A) cell-ECM junctions, (B) cytoskeletal proteins, and (C) myelin-axon interface.
This study provides a closer objective look at the pattern of the studies in the field of brain biomechanics and showed that the response of brain tissue to external forces has been one of the significant topics among biomechanicians. These studies have focused on creating scientific grounds to address the effects of mechanical forces on the brain, the mechanisms of TBI, as well as characterizing tissue behaviors in different neurological diseases with the aim of providing new diagnostic and therapeutic methods. Although an immense effort has been directed toward these goals, there are still several fundamental questions that need to be addressed. Through categorizing the mentioned points and questions, this study aimed to provide more information and help direct future research.
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