



Original Article

Structural Anisotropy vs. Mechanical Anisotropy: The Contribution of Axonal Fibers to the Material Properties of Brain White Matter

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Abstract—Brain's micro-structure plays a critical role in its macro-structure material properties. Since the structural anisotropy in the brain white matter has been introduced due to axonal fibers, considering the direction of axons in the continuum models has been mediated to improve the results of computational simulations. The aim of the current study was to investigate the role of fiber direction in the material properties of brain white matter and compare the mechanical behavior of the anisotropic white matter and the isotropic gray matter. Diffusion tensor imaging (DTI) was employed to detect the direction of axons in white matter samples, and tensile stress-relaxation loads up to 20% strains were applied on bovine gray and white matter samples. In order to calculate the nonlinear and time-dependent properties of white matter and gray matter, a visco-hyperelastic model was used. The results indicated that the mechanical behavior of white matter in two orthogonal directions, parallel and perpendicular to axonal fibers, are significantly different. This difference indicates that brain white matter could be assumed as an anisotropic material and axons have contribution in the mechanical properties. Also, up to 15% strain, white matter samples with axons parallel to the force direction are significantly stiffer than both the gray matter samples and white matter samples with axons perpendicular to the force direction. Moreover, the elastic moduli of white matter samples with axons both parallel and perpendicular to the loading direction and gray matter samples at 15–20% strain are not significantly different. According to these observations, it is suggested that axons have negligible roles in the material properties of white matter when it is loaded in the direction perpendicular to the axon direction. Finally, this observation showed that the anisotropy of brain tissue not only has effects on the elastic behavior, but also has effects on the viscoelastic behavior.

Keywords—Brain tissue, White matter, Diffusion tensor imaging, Anisotropic structure.

INTRODUCTION

Traumatic brain injury is one of the primary causes of disability and death in the world.³⁸ In order to reliably predict the mechanical response of brain tissue in different injury conditions such as car crashes^{46,51} sport,^{17,33} and blast,^{34,48} finite element (FE) models including accurate geometry and material properties of brain tissue are needed.¹⁸

The advent of new neuroimaging techniques such as diffusion tensor imaging (DTI) has provided anatomical details of brain microstructure. DTI is a magnetic resonance imaging (MRI) technique based on the motion of water molecules. In conventional MRI, the white and gray matter of brain tissue appear relatively homogeneous, while in DTI, white matter tracts are visualized. There is an analogy between the shape of an ink drop spreading on a paper and the motion of water molecules in a tissue. If the ink distribution is circular, it is an isotropic diffusion, and if it is spread in an elliptical shape with significant preference to one direction, the diffusion is considered anisotropic. In DTI, this anisotropic diffusion is attributed to the fibrous structure.⁴⁰ Since the introduction of DTI in the mid-1990s,⁶ many studies have aimed to extract the axonal fiber orientation of brain tissue from both fresh and formalin-fixed specimens,^{4,8,12,31,49} and have shown that DTI of live and fixed brain tissue displays similar results.⁴⁰

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Many studies have attempted to determine the material properties of different brain regions through *in-vivo* and *ex-vivo* experiments.^{3,27,39,44} While most of these studies have shown that the gray matter of brain tissue has an isotropic structure,^{23,43,54} there is not a clear consensus about brain white matter.^{10,12,13,43,52} Arbogast and Margulies measured viscoelastic properties of the swine brainstem under shear loading in three axonal fiber directions and showed the brainstem displays transversely isotropic behavior.² Feng *et al.* investigated the stiffness of the porcine corpus callosum in two orientations, parallel and perpendicular to the axons, using an indentation method. The results exhibited that the corpus callosum is a transversely isotropic material and the stiffness in the perpendicular direction is significantly higher than the parallel direction.²² Samadi-Dooki *et al.* showed that the stiffness of bovine white matter varies in the horizontal, sagittal, and coronal planes through indentation loading.⁴⁷ Shuck and Advani studied the mechanical properties of human brain tissue under shear, and showed that white matter may be considered as an isotropic material.⁵² Budday *et al.* studied the effect of fiber direction on the mechanical behavior of human white matter under compression and tension up to 10% strain. The results revealed no significant direction-dependent responses,¹² and suggested that although white matter is an anisotropic structure due to the presence of axons, this anisotropy did not present itself mechanically.¹⁰ However, this observation may be justified by the assumption proposed by Murphy that at infinitesimal strains, anisotropic materials could be considered as an isotropic material.⁴¹ As Bayly *et al.* using a tagged MRI method showed that human brain under impact condition could experience strains higher than 20%,⁷ it seems that investigating the effect of axonal fiber direction on the mechanical properties of brain tissue for strains higher than 10% is necessary.

The choice between material isotropy and anisotropy could lead to significantly different predictions by computational models. As some recent studies have used DTI results to implement fiber orientation of brain tissue into FE models,^{26,28,29,60} there is a growing interest in finding the effect of axonal fibers on the mechanical behavior of brain tissue. The present study aimed to investigate the mechanical anisotropy of brain white matter using a continuum approach, compare the mechanical behavior of white matter with that of gray matter, and suggest a microstructural explanation for the existing diversity about white matter anisotropy.

MATERIALS AND METHODS

Diffusion Tensor Imaging

Three bovine brains were acquired from a local slaughterhouse and all the experimental tests took place within 5 h post-mortem. MRI including T1-weighted imaging and DTI was performed on fresh bovine brains to explore the orientations of axonal fibers. During imaging process, all brains were immersed in 0.01 M phosphate buffer saline (PBS) solution while kept in polypropylene (PP) containers to reduce noise artifacts. Images were obtained with a 3T scanner (Magnetom PRISMA, Siemens Healthcare, Erlangen, Germany) using a head coil array with 32 elements in 12 directions at National Brain Mapping Lab (NBML) in Iran, and the setting was similar to Budday *et al.*¹² The results of DTI were processed and visualized using ExploreDTI software package,³⁶ and orientation distribution of axons in brainstem was characterized by OrientationJ plugin (ImageJ, National Institute of Health, MD).

Sample Preparation for Mechanical Testing

Based on the results of DTI, brainstem samples were extracted in two orthogonal directions, with axons parallel ($\theta = 0^\circ$) and perpendicular ($\theta = 90^\circ$) to the loading direction (Fig. 1a). Fifteen cylindrical bovine brain samples, with diameter of 12.73 ± 1.04 mm and height of 10.23 ± 1.41 mm, were extracted using a metal punch from fresh brain specimens from cerebral cortex (gray matter) and brainstem (white matter), respectively. The samples were extracted in such an order that there was at least one sample from each brain specimen in each group. The samples were kept in PBS solution at room temperature ($\sim 23^\circ\text{C}$).

Experimental Setup

Each excised sample has gone under uniaxial tensile stress-relaxation loading using a uniaxial universal testing machine (Instron 5566, Instron Co., Norwood, MA, USA) up to 20% strain with loading rate of 150 mm/min and 30 s hold time (Fig. 1b). The samples were attached to the upper and lower plates of the test device using cyanoacrylate adhesive (Fig. 1c). This would ensure the confined boundary conditions during the loading period.

Constitutive Modeling

The mechanical behavior of gray matter and white matter was modeled using quasi-linear viscoelastic (QLV) theory defined as²⁵:

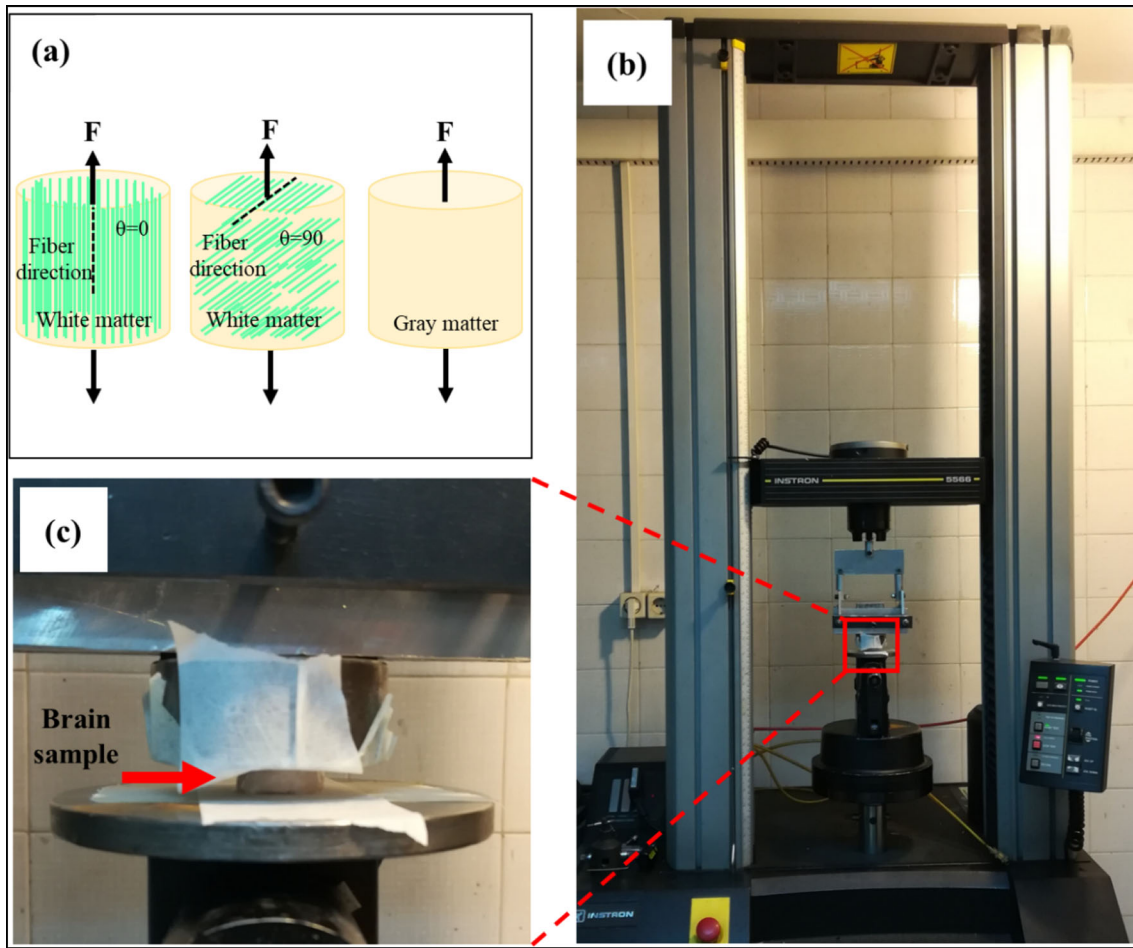


FIGURE 1. (a) Schematic figure of tension direction in white matter and gray matter samples, (b) Testing machine, (c) brain sample glued to the upper and lower plates of the testing device.

$$P(\lambda_1, t) = \int_0^t G(t-\tau) \frac{\partial P^e(\lambda_1)}{\partial \lambda_1} \frac{\partial \lambda_1}{\partial \tau} d\tau \quad (1)$$

where $P^e(\lambda_1)$ is the instantaneous elastic function, λ_1 is the stretch ratio, and $G(t)$ is the reduced relaxation function in the form of a Prony series:

$$G(t) = G_\infty + \sum_{i=1}^3 G_i e^{-\eta_i t} \quad (2)$$

where η_i is the decay rate and three decay rates of 0.1, 1, and 10 s^{-1} were chosen with respect to ramp and relaxation time.³⁵ The instantaneous elastic function for $P^e(\lambda_1)$ in Eq. (1) was calculated using an Ogden-type hyperelastic model including isotropic and anisotropic parts for describing the mechanical behavior of extra-fibrillar matrix and fibers, respectively³⁷:

$$\Psi = \frac{2\mu}{\alpha^2} (\lambda_1^\alpha + \lambda_2^\alpha + \lambda_3^\alpha - 3) + \frac{2k\mu}{\beta^2} (I_4^{\beta/2} + 2I_4^{-(\beta/2)} - 3) \quad (3)$$

where Ψ is the strain energy density functions (SEDF), $\lambda_1, \lambda_2, \lambda_3$ are the principal stretch ratios, μ is the shear modulus of isotropic material, k is a coefficient which indicates the increase of material stiffness in the fiber direction, and α and β are material parameters associated with the material nonlinearity. Previous publications suggested that the nonlinear behavior of the material is not sensitive to the direction, therefore we can assume $\alpha = \beta$.³⁷ I_4 is a pseudo-invariant that is related to fiber direction (θ)³²:

$$I_4 = \lambda_1^2 \cos^2 \theta + \frac{\sin^2 \theta}{\lambda_1} \quad (4)$$

Under uniaxial tension in one direction (λ_1), deformation gradient tensor can be described as:

$$F = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_2 \end{bmatrix} \quad (5)$$

Assuming white matter as an incompressible material and due to symmetry ($\lambda_2 = \lambda_3$), the determinant of tensor F is equal to 1:

$$J = \lambda_1 \lambda_2^2 \quad (6)$$

Based on the SEDF, first Piola–Kirchhoff stress tensor P was derived from⁵⁴:

$$P^e = \sum_{i=1}^3 \left(\frac{\partial \Psi}{\partial \lambda_i} - p \lambda_i^{-1} \right) v^{(i)} \otimes u^{(i)} \quad (7)$$

where $u^{(i)}$ and $v^{(i)}$ are eigenvectors of the right and left stretch tensors, respectively.⁵⁴

The visco-hyperelastic model contains eight material parameters, of which the fiber directions (θ) in white matter samples were determined using the DTI. According to the range of $-5 < \alpha < 5$ proposed by Velardi *et al.* for brain tissue,⁵⁴ α can be determined using trial-and-error approach.⁶¹ The remaining parameters, i.e., μ , k , and G 's can be obtained by curve fitting. To obtain the best fit to the experimental data, the least-squares method as a minimization algorithm was used. This method minimized the sum of squared errors (SSE):

$$\text{SSE} = \sum_{i=1}^n (P^{\text{Exp.}} - P^{\text{Model}})_i^2 \quad (8)$$

where n is the number of sets of pairs i.e. the total number of measurements in the corresponding time series.

RESULTS

Figure 2 is the Red–Green–Blue (RGB) color-coded fractional anisotropy (FA) image of a bovine brain tissue. Green color shows nerve fiber tracts running in the anterior–posterior direction, red color shows fiber tracts running in the left–right direction, and blue color shows the superior–inferior direction. The analysis of the DTI scans showed that most of axonal fibers in the sagittal plane of brainstem are aligned with the angle of 0.5° , and the median of the axonal direction is 0° (Fig. 2).

The results of the mechanical testing showed that all white matter and gray matter samples displayed strain-softening behavior, shown in Fig. 3. In the range of 0–15% strains, the incremental elastic moduli (E1, E2, and E3) of white matter samples with axons parallel (WM0) to the loading direction are significantly more than gray matter (GM) and white matter samples with axons perpendicular (WM90) to the loading direction. Figure 3 also reveals that the incremental elastic moduli from 15 to 20% strains (E4) did not show

significant differences between gray and white matter samples.

A representative experimental stress time history and the fitted model to the white matter samples with axons parallel and perpendicular to the loading direction and gray matter samples are shown in Fig. 4. The corresponding parameters of the Ogden-type visco-hyperelastic constitutive model are reported in Table 1. The results showed that the shear moduli of isotropic material (μ) for white matter samples with axons parallel and perpendicular to the loading direction and gray matter samples are not significantly different ($p < 0.05$). The value of parameter k is significantly higher for samples with axonal fibers parallel to the loading direction compared with those perpendicular to the loading direction ($p < 0.05$), which means axonal fibers in parallel direction are stiffer than in perpendicular direction ($k\mu_{\text{WM0}} > k\mu_{\text{WM90}}$). Also, the nonlinearity (α) of white matter samples with axons parallel and perpendicular to the loading direction is less than that of the gray matter samples (Table 1).

DISCUSSION

The mechanical anisotropy of brain white matter has been subjected to discussion for a long time and several studies. The aim of the present study was to investigate the effect of axons directions on the mechanical behavior of brain white matter, and define a correlation between the structural anisotropy and mechanical anisotropy. Also, this study aimed to shed light on the existent variations about the mechanical properties of white and gray matters, and propose a new description for the relationship between material properties and the microstructure of white matter and gray matter.

While many previous studies have observed that white matter shows anisotropic behavior,^{2,22,54} there has been suggestions that the axons orientation has no significant contribution in the mechanical behavior of the white matter.^{10,12,52} In this study, the analysis of DTI scans showed that most of axonal fibers in brainstem are aligned in one direction (Fig. 2). Therefore, the brainstem was considered as a transversely isotropic material and tested in parallel and perpendicular directions to the axonal fibers.

The results showed that up to 15% strain, the stiffness values of white matter samples with axons parallel to the loading direction are more than samples perpendicular to the fibers (Fig. 3), which is in agreement with the study of Yousefsani *et al.*⁵⁸ On the other hand, Dennerll *et al.* showed that the lateral stiffness of axons is less than the axial stiffness by applying lateral and axial tensile displacement using a needle to mea-

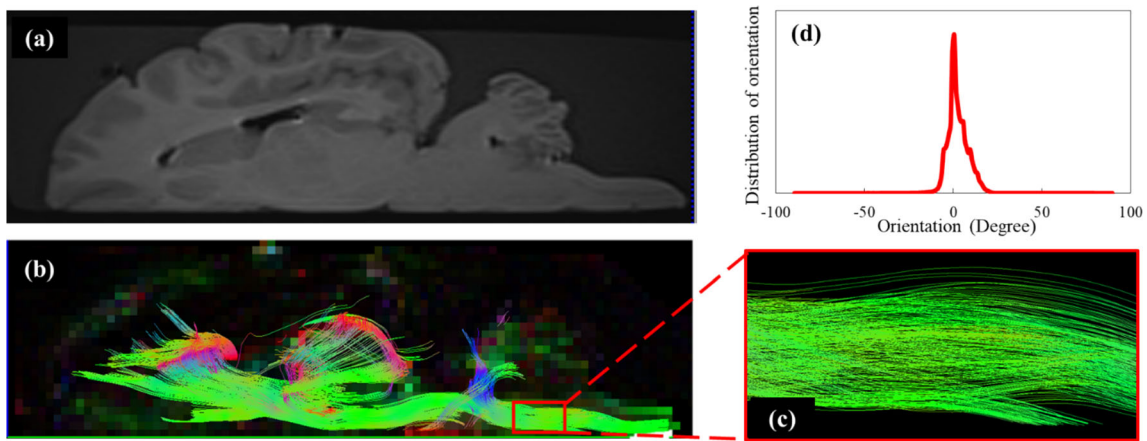


FIGURE 2. (a) Sagittal view of a bovine brain sample from T1-weighted MRI, (b) DTI, (c) axons orientation in brainstem, (d) distribution of orientation obtained after analysis with OrientationJ.

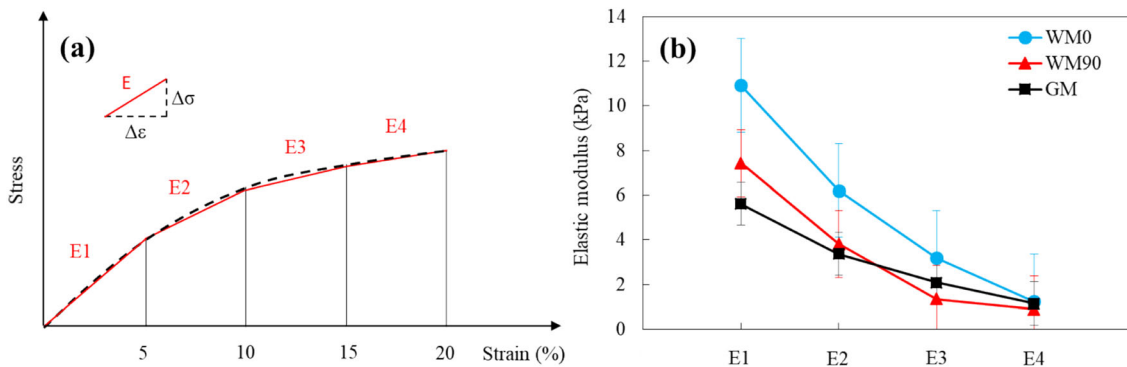


FIGURE 3. (a) Schematic representation of the apparent elastic moduli determined from the stress-strain curves, (b) the calculated elastic moduli of four strain spans for gray matter and white matter samples.

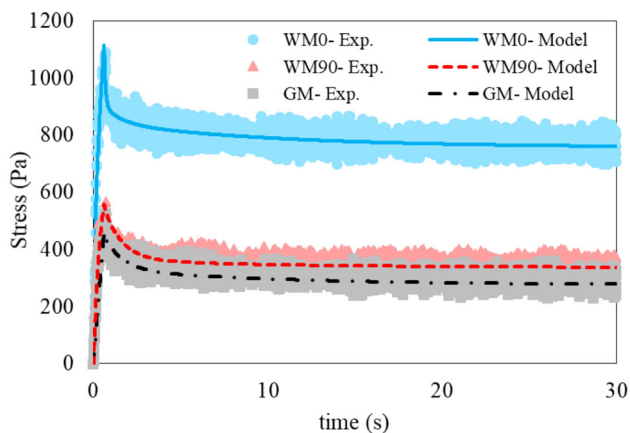


FIGURE 4. Experimental results vs. fitted visco-hyperelastic model to stress relaxation data at 20% strain.

sure mechanical properties of a single axon (Fig. 5).¹⁶ Therefore, the higher stiffness of white matter tissue parallel to axonal fibers in comparison to the samples

perpendicular to the axons could be attributed to the differences between lateral and axial stiffness of the axonal fibers (Fig. 6). In future studies, multiscale assessments should be followed by more multiscale modeling to improve our knowledge about the contribution of axonal fibers in the mechanical behavior of nervous tissue.

Also, our results showed that up to 15% strain, the stiffness values of gray matter samples and white matter samples perpendicular to the axons are not significantly different. Wu *et al.* have expressed that the material properties of the isotropic ground substrate of white matter are the same as gray matter.⁵⁷ Therefore, it could be suggested that axons in perpendicular direction have negligible roles in the material properties of white matter. On the other hand, brain tissue in comparison to collagenous tissues has an insignificant amount of extracellular matrix (ECM), and most of the volume of brain tissue is composed of different cell types (glial cells and neurons).¹¹ As white matter has a high cell-to-ECM volume ratio⁴² and the vast majority

TABLE 1. Constitutive parameters obtained from the Ogden-type visco-hyperelastic model.

| | μ (kPa) | α ($= \beta$) | k | θ ($^\circ$) | G_∞ | G_1 | G_2 | G_3 |
|------|-----------------|------------------------|-------------------|-----------------------|-------------------|-----------------------------|-----------------------------|-----------------------------|
| WM0 | 2.18 ± 0.11 | - 2 | $1.02 \pm 0.00^*$ | 0 | $0.29 \pm 0.02^*$ | $0.02 \pm 0.00^{*,\dagger}$ | $0.01 \pm 0.00^{*,\dagger}$ | $0.68 \pm 0.02^{*,\dagger}$ |
| WM90 | 2.23 ± 0.08 | - 2 | $1.00 \pm 0.00^*$ | 90 | $0.43 \pm 0.07^*$ | $0.04 \pm 0.01^*$ | $0.34 \pm 0.06^*$ | $0.17 \pm 0.12^*$ |
| GM | 2.52 ± 1.00 | 4 | 0 | - | 0.38 ± 0.12 | $0.08 \pm 0.02^\dagger$ | $0.25 \pm 0.09^\dagger$ | $0.27 \pm 0.21^\dagger$ |

*Indicates significant difference ($p < 0.05$) between WM0 and WM90 (comparison is between values in the same column).

†Indicates significant difference ($p < 0.05$) between WM0 and GM (comparison is between values in the same column).

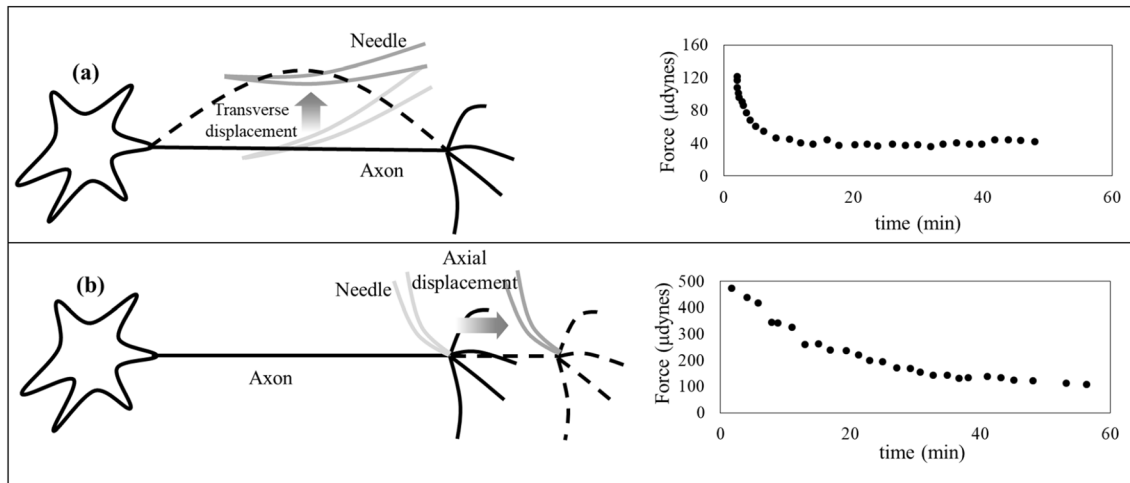


FIGURE 5. Displacement methods and viscoelastic responses of the axons to the (a) lateral and (b) axial tensions.¹⁶

of glial cells in white matter are astrocytes,⁶² it could be hypothesized that the white matter stiffness calculated in perpendicular direction is mostly affected by the stiffness of astrocytes.

The results of elastic moduli calculated using stress-strain data showed that with increasing the strain levels, the stiffness values of gray matter samples and white matter samples with axons parallel and perpendicular to the loading direction decrease (Fig. 3), which is in agreement with the results presented by previous works. They have reported that brain tissue exhibits strain-softening under tension and strain-stiffening under compression.^{19,53} Moreover, some previous studies showed that the stiffness of white matter is higher than gray matter^{9,24,55} and this difference is attributed to the contribution of axons in the mechanical properties of the tissue,^{47,59} but few studies have shown that gray matter is stiffer than white matter^{15,30} or their stiffness is equal.^{14,20}

The results of the present study indicated that white matter samples with axons parallel to the loading direction were significantly stiffer than gray matter, while the stiffness of white matter samples with axons perpendicular to the loading direction and gray matter samples was not significantly different. Most previous studies have not been determined the axonal orienta-

tions using precise methods such as DTI or histological staining, and they have tested white matter samples randomly without considering axonal fiber directions. Therefore, our findings may explain the diversity observed among the previous works.

The results of this study have also showed that the stiffness of gray matter and white matter samples decreases as the strain increases and at about 15–20% strains, the values are not significantly different (Fig. 3). As it has been shown that the injury threshold for the brain tissue is ~ 18% strain,^{5,13,56} and the injury alters the material properties of the brain tissue,^{1,21,45,50} this similarity between the stiffness of gray matter and white matter samples could be attributed to the effect of injury on the changes in the mechanical properties of the tissue. However, investigating the recoverability of this softening behavior could help to verify the suggested hypothesis. While Budday *et al.* examined the recoverability of the softening behavior for brain tissue samples under cyclic loading with 10% strain, and concluded that the mechanical behavior of brain tissue after 60 min is recoverable,¹² they did not study the recoverability of brain tissue for strains close to the injury threshold that is highly recommended for future works.

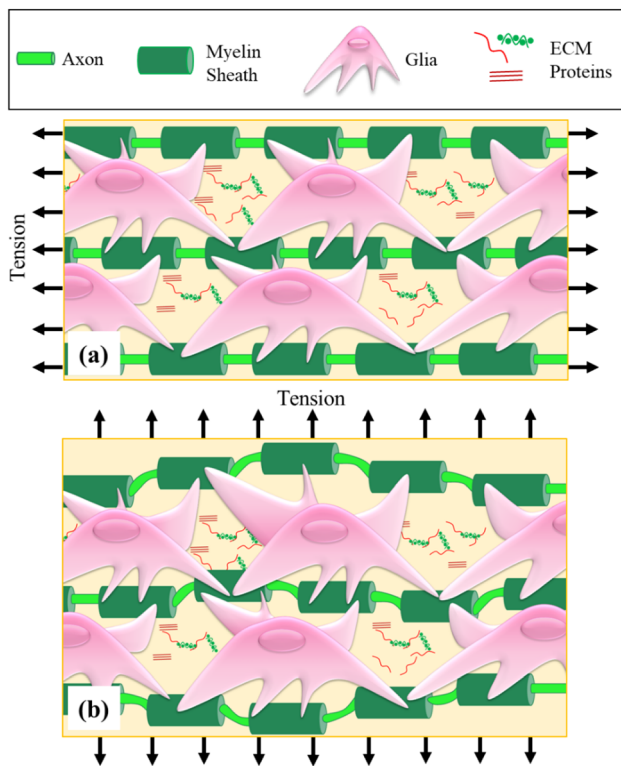


FIGURE 6. A schematic of the suggested contribution of (a) axial and (b) lateral strength of axons in mechanical properties of brain white matter (the schematic figure is for illustration purpose only and is not necessarily drawn to scale).

Moreover, the results displayed that relaxation parameters of white matter samples with axons parallel and perpendicular to the loading direction are significantly different (Table 1). This observation showed that the anisotropy of brain tissue not only has effects on the elastic behavior, but also has effects on the viscoelastic behavior. According to these results, it could be suggested that different fiber orientation may lead to different behaviors in sub-structural components such as sliding fibers on each other, and in turn alter the viscoelastic responses. However, these results are obtained at a certain strain and strain rate, and a general conclusion requires more data from different applied strain and strain rate. Also, using real-time microscopy methods to detect the changes in the microstructure caused by mechanical loading and its effect on the viscoelastic response is recommended for future researches.

In the current study, the orientation of axonal fibers in bovine white matter was determined precisely using DTI method. The uniaxial tensile stress-relaxation tests were applied to bovine white matter samples with axons parallel and perpendicular to the loading direction and gray matter samples, and the mechanical properties were examined using an Ogden-type visco-

hyperelastic model. The results showed that the mechanical properties of white matter is highly dependent to the direction of the fibers, and tissue stiffness in the parallel direction is significantly higher than perpendicular direction. Also, the results indicated that the mechanical behavior of white matter samples with axons perpendicular to the loading direction and gray matter samples are similar. According to these observations, it is suggested that structural anisotropy caused by axons is similar to other biological fibers such as collagen and elastin, and could contribute in mechanical properties of the tissue. Therefore, it could be concluded that structural anisotropy caused by axons may lead to the mechanical anisotropy, and considering brain white matter as an anisotropic tissue in future brain modeling is strongly recommended. Moreover, this study has investigated the relaxation behavior of the tissue under 20% tensile strain, therefore the changes in the value of different parameters of the visco-hyperelastic model according to the changes of strain could not be calculated. Accordingly, we propose that the variation in the visco-hyperelastic parameters with respect to the strain value should be examined in the future studies.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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