Acta Biomaterialia 48 (2017) 319–340

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Full length article

Mechanical characterization of human brain tissue

S. Budday[a], G. Sommer[b], C. Birkl[c], C. Langkammer[c], J. Haybaeck[d], J. Kohnert[a], M. Bauer[a], F. Paulsen[e], P. Steinmann[a], E. Kuhl[f], G.A. Holzapfel[b,g,*]

[a] *Department of Mechanical Engineering, University of Erlangen-Nürnberg, 91058 Erlangen, Germany*
[b] *Institute of Biomechanics, Graz University of Technology, 8010 Graz, Austria*
[c] *Department of Neurology, Medical University of Graz, 8036 Graz, Austria*
[d] *Department of Neuropathology, Institute of Pathology, Medical University of Graz, 8036 Graz, Austria*
[e] *Chair of Anatomy II, University of Erlangen-Nürnberg, 91054 Erlangen, Germany*
[f] *Departments of Mechanical Engineering & Bioengineering, Stanford University, CA 94305, USA*
[g] *Norwegian University of Science and Technology (NTNU), Faculty of Engineering Science and Technology, 7491 Trondheim, Norway*

ARTICLE INFO

Article history:
Received 26 July 2016
Received in revised form 24 October 2016
Accepted 25 October 2016
Available online 27 October 2016

Keywords:
Human brain
Mechanical testing
Hyperelastic modeling
Mooney Rivlin model
Ogden model

ABSTRACT

Mechanics are increasingly recognized to play an important role in modulating brain form and function. Computational simulations are a powerful tool to predict the mechanical behavior of the human brain in health and disease. The success of these simulations depends critically on the underlying constitutive model and on the reliable identification of its material parameters. Thus, there is an urgent need to thoroughly characterize the mechanical behavior of brain tissue and to identify mathematical models that capture the tissue response under arbitrary loading conditions. However, most constitutive models have only been calibrated for a single loading mode. Here, we perform a sequence of multiple loading modes on the same human brain specimen – simple shear in two orthogonal directions, compression, and tension – and characterize the loading-mode specific regional and directional behavior. We complement these three individual tests by combined multiaxial compression/tension-shear tests and discuss effects of conditioning and hysteresis. To explore to which extent the macrostructural response is a result of the underlying microstructural architecture, we supplement our biomechanical tests with diffusion tensor imaging and histology. We show that the heterogeneous microstructure leads to a regional but not directional dependence of the mechanical properties. Our experiments confirm that human brain tissue is nonlinear and viscoelastic, with a pronounced compression-tension asymmetry. Using our measurements, we compare the performance of five common constitutive models, neo-Hookean, Mooney-Rivlin, Demiray, Gent, and Ogden, and show that only the isotropic modified one-term Ogden model is capable of representing the hyperelastic behavior under combined shear, compression, and tension loadings: with a shear modulus of 0.4–1.4 kPa and a negative nonlinearity parameter it captures the compression-tension asymmetry and the increase in shear stress under superimposed compression but not tension. Our results demonstrate that material parameters identified for a single loading mode fail to predict the response under arbitrary loading conditions. Our systematic characterization of human brain tissue will lead to more accurate computational simulations, which will allow us to determine criteria for injury, to develop smart protection systems, and to predict brain development and disease progression.

Statement of Significance

There is a pressing need to characterize the mechanical behavior of human brain tissue under multiple loading conditions, and to identify constitutive models that are able to capture the tissue response under these conditions. We perform a sequence of experimental tests on the same brain specimen to characterize the regional and directional behavior, and we supplement our tests with DTI and histology to explore to which extent the macrostructural response is a result of the underlying microstructure. Results demonstrate that human brain tissue is nonlinear and viscoelastic, with a pronounced compression-tension asymmetry, and we show that the multiaxial data can best be captured by a modified version of the one-term Ogden model.

---

* Corresponding author at: Institute of Biomechanics, Graz University of Technology, 8010 Graz, Austria.
E-mail address: holzapfel@tugraz.at (G.A. Holzapfel).

http://dx.doi.org/10.1016/j.actbio.2016.10.036
1742-7061/

1. Introduction

Mechanical modeling is a promising tool to understand and predict the behavior of human brain tissue in health and disease [1]. The mechanics of the brain play not only an important role in injury such as traumatic brain injury [2] or shaken baby syndrome [3], but also in tumor growth [4] or during brain development [5–7]. Computational simulations enable us to determine criteria for injury [8], to develop smart protection systems such as helmets [9], or to predict brain development and disease progression [10,11]. However, such models require the development of constitutive laws calibrated with adequate experimental data to accurately relate tissue deformation to tissue stress.

Due to the ultrasoft and complex nature of brain tissue, biomechanical testing is challenging and former studies have reported controversial results. Shear moduli reported in the literature vary by an order of magnitude or more [12]. Recently, with enhanced sensitivity of the used testing devices, stiffness values now seem to converge in the range of 1 kPa [13]. Still, we are left with the controversy that different research groups find contrary results towards direction- [14–18], age- [13,19–22], and region-dependent properties [15,16,18,23–29] and towards the influence of post-mortem time [28,30–32]. Overall, the mechanical response of brain tissue is still far from being fully understood.

By reason of availability, only a few studies have actually tested human brain tissue [14,15,18,21,33–37]. Alternatively, researchers consulted porcine [13,15,16,38–42] or bovine brain tissue [26,28,30,43] due to their structural similarities with the human brain. Others tested the properties of rat [20,22,25] or mouse brains [44]. Most of those studies have focused on a specific type of loading. For example, human brain tissue has been tested *in vitro* under shear [14,18,21,33,36], compression [18,34,35,38], tension [18], and cyclic tension–compression [37] loadings, or *in vivo* using magnetic resonance elastography [23,24,27]. While these studies have significantly contributed to a better understanding of the material properties of the tissue, they remain insufficient to accurately describe its constitutive behavior under arbitrary loading conditions required for computational modeling. Systematic investigations of multiple loading modes remain sparse and have used different samples for each loading mode [18], which could influence the results, given the high regional, inter-specimen variation reported for brain tissue. In the present study, we sequentially test each specimen under multiple loading modes: shear in two orthogonal directions, compression, and tension.

The profound microstructural heterogeneity of brain tissue further raises the question to what extent constitutive models should account for regional and directional properties. It seems impractical to determine one set of material parameters valid for brain tissue as a whole. It is rather essential to understand how microstructural variations and anisotropy translate into the macroscopic mechanical response of the tissue and to systematically study regional and directional dependencies. Macroscopically, we can separate brain tissue into gray and white matter. Gray matter mostly consists of neurons responsible for data processing, and white matter of myelinated nerve fibers allowing a rapid signal transduction. However, our brain's microstructure varies significantly even within those two tissue types. For our study on the regional properties, we differentiate between tissue from the corpus callosum, the inner white matter mainly composed of highly aligned nerve fibers connecting both hemispheres; the corona radiata, the outer white matter composed of less aligned nerve fibers and glial cells; the basal ganglia, the deep gray matter; and the cortex. A similar distinction has previously been used to assess regional dependencies in porcine [15] and human [18] brain tissue. Regional variations in tissue stiffness can be of great interest for neurosurgeons or helmet designers as more compliant regions are most likely more susceptible to injury. To find possible correlations between the macroscopic mechanical response and the underlying microstructure, we fix each specimen for histological staining upon completion of biomechanical testing. Furthermore, we compare histological images of tested and virgin specimens to ensure that the performed tests did not distort the tissue microstructure.

Another question that has not yet been satisfactorily answered is whether microstructural anisotropy due to the alignment of nerve fibers in white matter results in an anisotropic mechanical response, similar to the effect of collagen fibers in arterial tissue [45]. Previous studies on the directional properties have estimated fiber orientation from anatomical knowledge [15–18]. Here, for the first time, we combine biomechanical testing with diffusion tensor imaging and determine the orientation of nerve fibers prior to specimen extraction to guarantee a uniform fiber distribution throughout the tested sample. We test each sample under simple shear in two orthogonal directions, under unconfined compression and tension loadings to genuinely detect the contribution of nerve fibers for different loading modes. With the design of the current experimental study, we aimed to minimize the effects of nonuniform fiber distribution, nonuniform specimen dimensions, and inter-specimen variation, to unravel the controversy over both regional and directional properties.

Once we have understood the mechanical characteristics of brain tissue, the development of realistic finite element models is highly dependent on both the formulation of appropriate constitutive laws and the accurate identification of the corresponding material parameters. Generally, we face the problem of lacking experimental data suitable for detailed parameter estimation [46]. Constitutive parameters proposed in the literature have mostly been calibrated with experimental data from a single loading mode [40–42,47], but do not necessarily hold for arbitrary loading cases [38,48]. In the current study, we focus on the accurate characterization of the hyperelastic component of the mechanical response of brain tissue. We compare the applicability of five different constitutive models [49–52] to predict the behavior of brain tissue under multiple uniaxial loading modes and multiaxial loading cases. We simultaneously consider three loading modes, shear, compression, and tension, and test the validity of those constitutive models for combined compression/tension-shear loading [44,53].

Furthermore, we make use of calibrating constitutive models to make the experimental nonlinear stress–strain curves amenable to statistical analyses. Thus, we additionally calibrate the model that performed best, the one-term Ogden model, with each experimental curve separately to obtain one value for the shear modulus per specimen and loading mode. We emphasize that the purpose of those shear modulus calculations and their systematic comparison was to detect loading mode specific regional- and directional-dependencies such as the contribution of nerve fibers in compression versus tension, but not to determine material parameters appropriate for computational modeling of the brain.

The current experimental study provides not only novel insights into regional and directional dependencies but also yields essential information to construct realistic constitutive models capable of capturing the mechanics of the brain under multiaxial loading cases.

2. Materials and methods

2.1. Brain specimen

We obtained brain tissue from ten human cadavers during autopsy requested by the local health authorities with a post mortem interval of less than 24 h. The study was approved by the