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SHORT COMMUNICATION

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Anisotropic constitutive equations and experimental tensile behavior of brain tissue

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Abstract The present study deals with the experimental analysis and mechanical modeling of tensile behavior of brain soft tissue. A transversely isotropic hyperelastic model recently proposed by Meaney (2003) is adopted and mathematically studied under uniaxial loading conditions. Material parameter estimates are obtained through tensile tests on porcine brain materials accounting for regional and directional differences. Attention is focused on the short-term response. An extrapolation of tensile test data to the compression range is performed theoretically, to study the effect of the heterogeneity in the tensile/compressive response on the material parameters. Experimental and numerical results highlight the sensitivity of the adopted model to the test direction.

1 Introduction

Biomechanical modeling of the human head is a task of great interest for both medical and engineering reasons, which are mainly related to the development of computer simulations of traumatic brain injuries under impact loads (focal and diffuse injuries); virtual reality and robotic techniques in neurosurgery; design and efficiency assessment of helmets and other protective tools.

This topic involves several research aspects, including: formulation of constitutive equations for biological brain materials and particularly for soft brain tissue, accounting for directional properties, age effects, time-dependent behavior, and regional heterogeneities (see, e.g., Miller and Chinzei 1997, 2002; Arbogast and Margulies 1998, 1999; Miller et al. 2000; Miller 2001; Bilston et al. 2001;Prange and Margulies 2002; Gefen and Margulies 2004); definition of automatic procedures for brain topology reconstruction from image data (cf., Bartesaghi and Sapiro 2001; Ramon et al. 2004); and formulation of detailed finite element models of the human head (see Huang et al. 1999, 2000; Zhang et al. 2001; Kleiven 2002; Mota et al. 2003).

Brain matter consists of a base matrix (neurons and extracellular components: *gray matter*) crossed by a network of neural tracts (or axonal fibers) in the so-called *white matter*. The fibers are highly uniaxially oriented in the *corpus callosum* (where they pass from one to the opposite brain hemisphere), and arranged in a more disordered pattern, having always a preferential axis, in the *corona radiata*.

Mechanical properties of human brain tissue have been measured by several authors, both in vitro and in vivo. Concerning in vitro experiments, in recent years researchers have focused their attention on uniaxial and shear testing (Miller 2001; Miller and Chinzei 1997, 2002; Arbogast et al. 1997; Arbogast and Margulies 1998; Bilston et al. 2001; Prange and Margulies 2002). In vivo indentation tests have also been carried out (Miller et al. 2000; Gefen and Margulies 2004) to study the effects of blood pressure in vasculature on the mechanical response of brain. Commonly, experiments are conducted on porcine brain tissues, which have been found to have some similarities with human brain material.

A wide dispersion of results between different authors has been found, with material properties varying up to an order of magnitude, in relation to testing conditions, preparation of samples, and differences in regional, directional, age, and post-mortem conditions of brain tissues. In most cases, experimental results have been correlated with rubber-like hyperelastic constitutive models, obtaining material parameter estimates for elastic formulations of *isotropic* Ogden-type models (Ogden 1984).

The present paper deals with the experimental verification of a *transversely isotropic* model, which appeared recently in the literature for brain tissue (Merodio and Ogden 2003).

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Several tensile tests on porcine samples are presented, considering tissues coming from various brain regions and with different axonal fiber orientations. Attention is focused on short- or middle-term tissue response under impact/acceleration loading, disregarding viscous effects. Indeed, such effects have been found to have a limited influence on the short-term response of brain tissue under impact actions (cf., e.g., Aida 2000). A two-level procedure for fitting experimental data is presented and used in order to obtain Meaney's model parameter estimates. The given results are in good agreement with those obtained by Miller and Chinzei (2002) through uniaxial tests on cylindrical samples (isotropic modeling). A central topic of the paper is the discussion about the difference of the tissue behavior in tension and in compression (cf., e.g., Miller and Chinzei 2002). We found remarkably different parameter estimates by considering only tensile and combined tensile-compressive behaviors, with different signs of stretch exponents in the two cases.

2 Tensile tests on porcine brain tissue

In order to obtain quantitative and qualitative information about regional and directional properties of brain tissue material, several tensile tests were carried out on tissue samples, using porcine brain matter.

One of the practical difficulties in conducting uniaxial tension tests on brain tissue is placing the samples in the testing machine in a reliable and repeatable way. Miller and Chinzei (1997, 2002) solved the problem by extracting short cylindrical samples and gluing them to the plates of the tensile testing machine. The main shortcoming of their method is the identification of material parameters by relating experimental data to an analytic solution of finite elasticity that refers to the extension of a short cylinder (Miller 2001).

Instead we dealt with standard tensile tests on prismatic samples that were accurately excised from porcine brains through surgical techniques. In this section, we describe the procedures we adopted to overcome inherent difficulties connected with tensile testing of soft biological tissues. We chose quite long samples (4–6 cm) in order to realize uniaxial loading conditions in the specimen central region, and also to accurately locate the direction of fibers within the sample. An analogous result cannot be obtained through cylindrical samples, in which gray and white matter are mixed.

2.1 Specimen preparation

Brain characteristics A total of six swine brains (Fig. 1a), extracted from adult animals (age between 1 and 2 years), were collected from a slaughter house in three different lots (2–2–2). A pig head was also taken and subjected to magnetic resonance (Fig. 1c, d).

Storage The brains were stored in a physiological solution and kept at a temperature of 3–7°C. Transportation to the laboratory took half an hour. Experiments were completed within 5–6 h post-mortem.

Shape of samples Samples were taken from different regions of the brain to assess regional and directional properties of the brain tissue (see below). The samples were cut with a lancet into strip shapes, approximately 4–6 cm long, 1 cm wide, and 0.2–0.5 cm thick. Obtaining an exact strip shape is difficult since the brain material is very soft and adheres, upon contacting, to any body. Therefore, the areas of the sample cross sections we used to convert load into stress must be understood as averages.

Nature of tissues To assess regional and directional properties of the brain tissue, the following different brain materials were tested:

(1) pure gray matter from *motor strip* (number of samples: $n_s = 12$);
(2) white matter from the corpus callosum with axonal fibers along the longitudinal direction (aligned with load; $n_s = 6$);
(3) white matter from the corona radiata with fibers in the longitudinal direction ($n_s = 12$);
(4) white matter from the corona radiata with fibers in the transverse direction ($n_s = 12$).

Mass density was slightly greater in white matter than in gray matter (1,039 g/cm^3 in white matter and 1,036 g/cm^3 in gray matter).

2.2 Experimental setup

Testing machine The machine employed for testing was an INSTRON 4301. The mounted load cell allowed measurement of axial force in the range 0.02–5 N, with an error of less than 0.1% of the maximum load.

Recording The experiments were documented by taking CCD camera images to ensure that during loading samples did not slip between the platens. Tests were conducted in displacement control, and load–displacement plots were automatically produced.

Placing of the samples To prevent slip of samples from the grips (cf., Fig. 1b) and to preserve integrity of brain material, we operated as follows:

- strips were continuously moistened with a physiological solution before the placing in the testing machine, and during the whole test;
- the strips were wrapped in tissue paper at the ends before insertion into the grips;
- grips were tightened manually;
- the no-slip condition was checked by visual inspection during testing and also on inspecting the CCD recording.

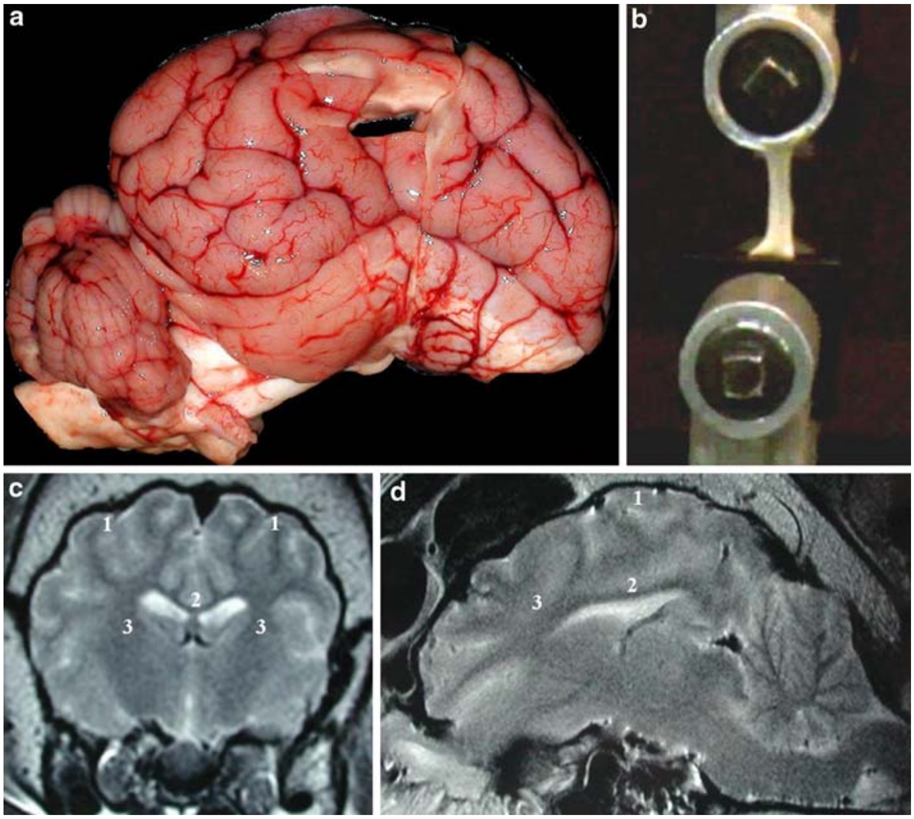

Fig. 1 View of one of the porcine brains tested, where the removal of a strip of gray matter from the motor strip is visible (**a**); image of a strip under testing (**b**); magnetic resonance images (3 T) of a swine head (**c**, **d**): **c** coronal; **d** sagittal. Regional flags: *1*=motor strip; *2*=corpus callosum; *3*=corona radiata

Temperature Tests were conducted at room temperature (20–25°C).

Loading history A displacement rate of 0.5 mm/s, corresponding to a strain rate of about 0.01/s, was fixed for all tests. This rate was low enough to minimize inertia effects. Tests were continued until failure or slipping of the samples from the grips. Only one load cycle was allowed. No preconditioning was performed due to the extreme delicacy and adhesiveness of brain tissue (cf., Miller and Chinzei 2002).

2.3 Test results

The load–displacement plots were converted into nominal stress S versus longitudinal stretch λ curves, by dividing the applied force by the (averaged) initial cross-sectional area, and the relative displacement between the platens by the initial length of the samples, respectively.

The initial cross-sectional area was determined by averaging two measurements carried out in correspondence with the central region of the specimen.

Figure 2a–d shows the S–λ curves obtained by averaging experimental data for each of the conducted test (see above). The graphs include standard deviation bars. The ratio between standard deviation and mean value of S (coefficient of variation), for any fixed value of λ, ranged between 0.2 and 0.4 between the different tests, with lower values for small stretches. The ranges of λ in Fig. 2 correspond to the stretch intervals for which all the tests for a given material were carried out successfully until material failure or sample slipping from machine grips occurred.

3 Meaney's model for brain tissue

Due to its peculiar nature, the mechanical behavior of brain tissue is expected to be sufficiently well described through an unidirectional fiber reinforced composite model, and, in particular, by means of a transversely isotropic hyperelastic model.

Recently, Merodio and Ogden (2003) has proposed a transversely isotropic model which consists of a first-order Ogden model augmented by a I_4-type reinforcing term (cf., Spencer 1984; Holzapfel 2000; Ogden 2003). It deals with the following strain-energy function

$$W = \frac{2\mu}{\alpha^2}\left(\lambda_1^\alpha + \lambda_2^\alpha + \lambda_3^\alpha - 3\right) + \frac{2k\mu}{\beta^2}\left(I_4^{\beta/2} + 2I_4^{-\beta/4} - 3\right), \quad \lambda_1\lambda_2\lambda_3 = 1, \tag{1}$$

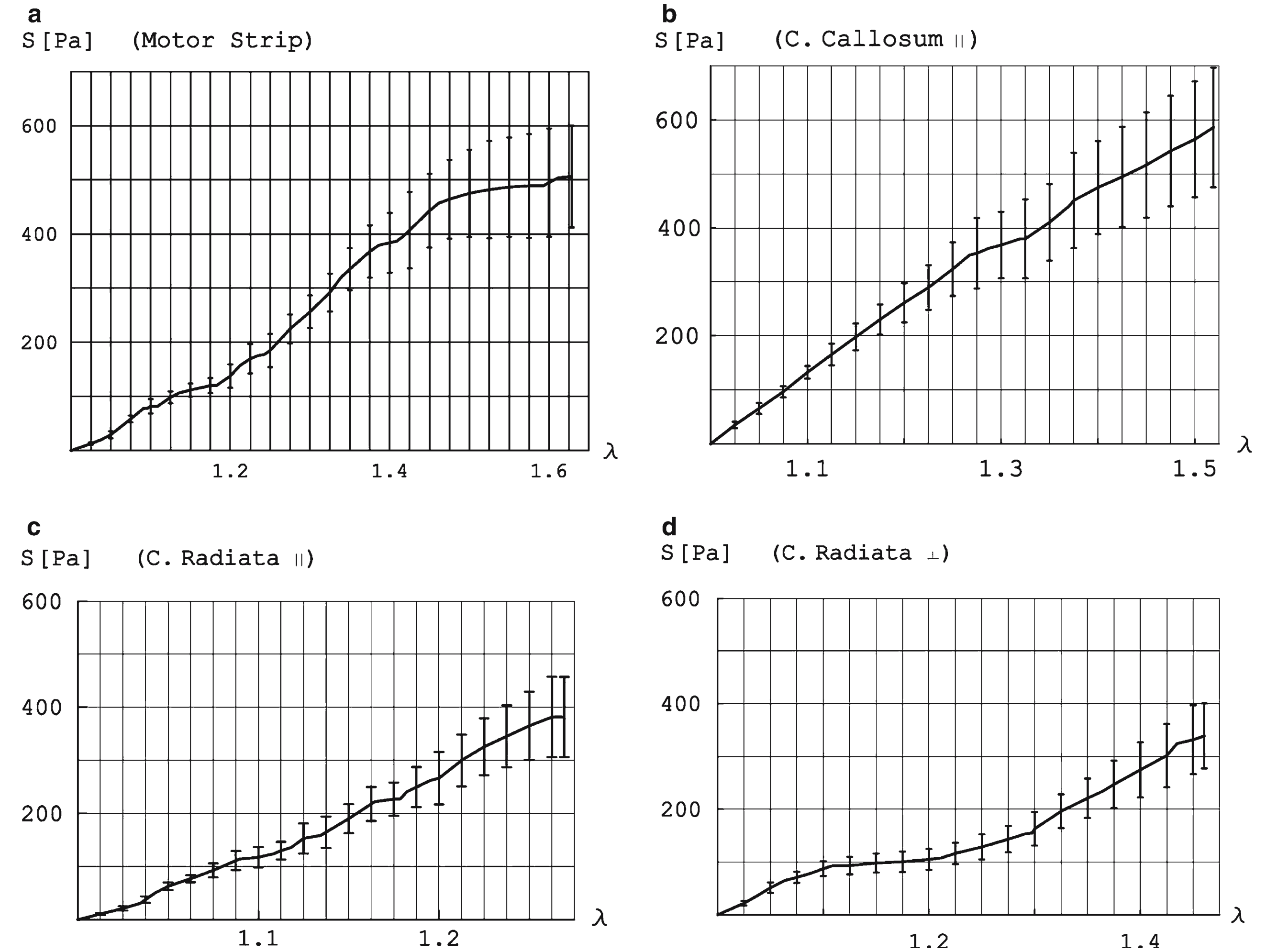

Fig. 2 Averaged nominal stress against longitudinal stretch in simple tension tests on different brain porcine samples. *Error bars* indicate standard deviation

where $\lambda_1, \lambda_2, \lambda_3$ are the principal stretches of the (incompressible) material, and I_4 coincides with the square of material stretch in the fiber direction.

In Eq. 1, μ is the infinitesimal shear modulus of the unreinforced material (no fibers); α and β are parameters; $k(> 0)$ is a coefficient which measures the increase of stiffness of the material in the fiber direction. The case with $k = 0$ corresponds to the gray matter tissue.

Meaney suggests to set $\beta = \alpha$, which is motivated by the fact that experimental results on white matter tissues show small changes of α with the test direction (cf., Prange and Margulies 2002).

Subsequently, we briefly examine the mathematical properties of the Meaney model under uniaxial loading, following the approach adopted in (Merodio and Ogden 2005). We deal with the strain-energy function ($\alpha = \beta$)

$$W = \frac{2\mu}{\alpha^2}\left(\lambda_1^\alpha + \lambda_2^\alpha + \lambda_3^\alpha - 3\right) + \frac{2k\mu}{\alpha^2}\left(I_4^{\alpha/2} + 2I_4^{-\alpha/4} - 3\right), \quad \lambda_1\lambda_2\lambda_3 = 1, \tag{2}$$

assuming that the load is applied along the X_2-axis of a given Cartesian frame X_1, X_2, X_3 and that fibers can be aligned along either X_2 or X_1.

We use the short-hand notation λ for the stretch in the loading direction ($\lambda \equiv \lambda_2$), and the symbols $\mathbf{S}$ and $\mathbf{T}$ for the first Piola-Kirchoff stress tensor and the Cauchy stress tensor, respectively. Such tensor fields are derived from the strain-energy function through (see, e.g.,Ogden 1984)

$$\mathbf{S} = \sum_{i=1}^{3}\left(\frac{\partial W}{\partial \lambda_i} - p\lambda_i^{-1}\right)\mathbf{v}^{(i)} \otimes \mathbf{u}^{(i)};$$
$$\mathbf{T} = \sum_{i=1}^{3}\left(\lambda_i\frac{\partial W}{\partial \lambda_i} - p\right)\mathbf{v}^{(i)} \otimes \mathbf{v}^{(i)}, \tag{3}$$

$\mathbf{u}^{(i)}$ and $\mathbf{v}^{(i)}$ being the eigenvalues of the right and left stretch tensors $\mathbf{U}$ and $\mathbf{V}$, respectively.

Obviously, under uniaxial loading along the X_2-axis, the unique nonzero components of $\mathbf{S}$ and $\mathbf{T}$ are $S(\equiv S_{22})$ and $T(\equiv T_{22})$, respectively.

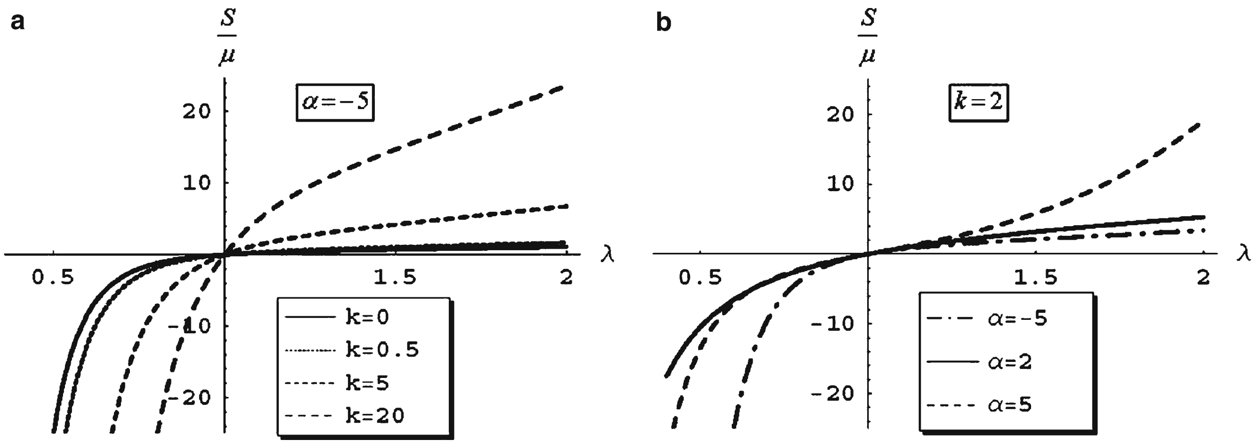

Fig. 3 Plots S/μ against stretch λ in the fiber direction for $\alpha = -5$ and $k = 0, 0.5, 5, 20$ (**a**); $k = 2$ and $\alpha = -5, 2, 5$ (**b**)

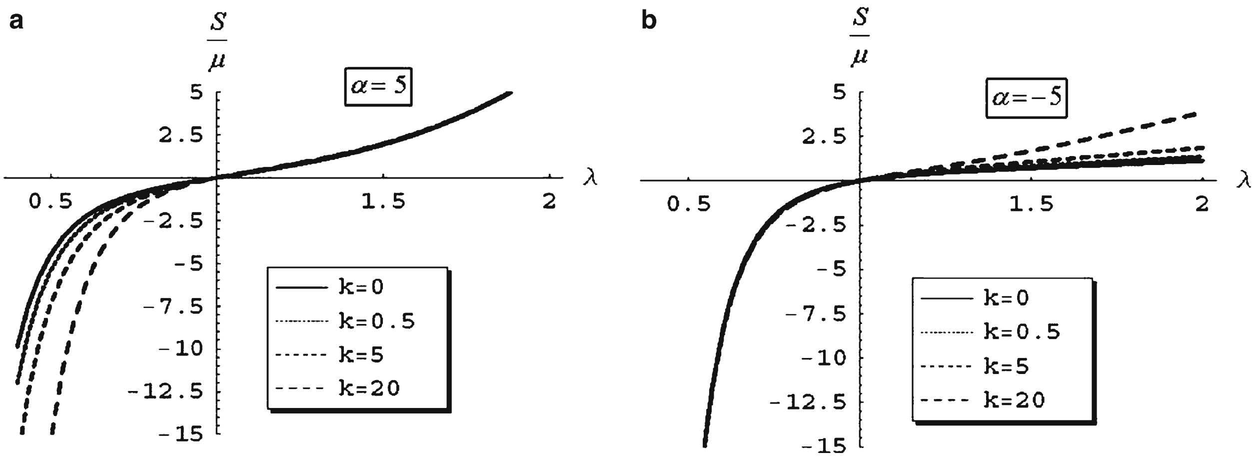

Fig. 4 Plots of S/μ against stretch λ in the direction orthogonal to the fibers for $k = 0, 0.5, 5, 20$ and $\alpha = 5$ (**a**); $\alpha = -5$ (**b**)

For *uniaxial load in the fiber direction*, upon imposing $S_{ij} = 0$ for $(i, j) \neq (2, 2)$ and enforcing the incompressibility constraint ($J = 1$), it is easy to obtain

$$\lambda_1 = \lambda_3 = \lambda^{-1/2}, \quad p = \frac{2\mu\lambda^{-\alpha/2}}{\alpha}, \quad I_4 = \lambda^2; \tag{4}$$

$$W = \frac{2\mu(1+k)}{\alpha^2}\left(\lambda^{\alpha} + 2\lambda^{-\alpha/2} - 3\right),$$
$$S = \frac{2\mu(1+k)\lambda^{-1-\alpha/2}\left(\lambda^{3\alpha/2} - 1\right)}{\alpha},$$
$$T = \lambda S = \frac{2\mu(1+k)\lambda^{-\alpha/2}\left(\lambda^{3\alpha/2} - 1\right)}{\alpha}. \tag{5}$$

It is not difficult to verify that S (as well as T) is a monotonic function of λ, for any value of k, approaching $-\infty$ for $\lambda \to 0$ and $+\infty$ for $\lambda \to \infty$.

The response of the material is illustrated in Fig. 3, which shows plots of S/μ against λ for several values of k and α.

Let us now consider the case of *uniaxial load orthogonal to the fibers* (fibers aligned along X_1). Differently from the previous case, here we have $\lambda_1 = \lambda_3 = \lambda^{-1/2}$ if and only if $k = 0$ (excluding the meaningless case α=0).

By writing $\lambda_3 = 1/\lambda_1\lambda$ (due to incompressibility) and imposing $S_{ij} = 0$ for $(i, j) \neq (2, 2)$, we get the following relation between λ_1 and λ

$$\lambda_1\left[\lambda_1^{\alpha} + k\left(\lambda_1^{\alpha} - \lambda_1^{-\alpha/2}\right)\right]^{1/\alpha} = \lambda^{-1} \tag{6}$$

which cannot be solved analytically for λ_1 except for special values of α. It is instead possible to numerically determine λ_1 as a function of λ, once α and k are given and inadmissible roots of Eq. 6 ($\lambda_1 < 0$) are discarded. Under uniaxial loading orthogonal to the fibers, it can then be shown that the stretch in the fiber direction exhibits a limiting nonzero minimum value (limiting contractive stretch) for $\alpha > 0$ and $k \neq 0$. Differently, the same stretch exhibits a finite maximum value (limiting extensional stretch) for $\alpha < 0$ and $k \neq 0$.

Once $\lambda_1 = \lambda_1(\lambda)$ has been numerically determined for given α and k, it is possible to express p, I_4, W, S, and T as functions of λ. The dependence of S/μ on λ is shown in Fig. 4 for several values of α and k. As can be seen S is rather insensitive to k in the tensile range for $\alpha > 0$ (cf., Fig. 4a), or in the compressive range for $\alpha < 0$ (Fig. 4b). In each case, the effects of the transverse reinforcement are very weak for

Table 1 Uniaxial response in the direction of the fibers (a) and orthogonal to the fibers (b) using the model by Meaney (2003), i.e. eq. (2). Different values for α, k and λ are displayed, while $\Delta\%$ denotes the normalized difference in percent (see the text)

(a)	S/μ (load ∥ fibers)						
	$k=0$		$k=2$		$k=10$		
λ	$\alpha=-5$	$\alpha=5$	$\alpha=-5$	$\alpha=5$	$\alpha=-5$	$\alpha=5$	$\Delta\%$
0.80	−1.239	−0.709	−7.438	−4.258	−26.033	−14.902	+74.7
0.90	−0.411	−0.316	−2.467	−1.896	−8.634	−6.635	+30.1
1.20	+0.392	+0.618	+2.351	+3.709	+8.229	+12.981	−36.6
1.30	+0.510	+0.983	+3.060	+5.897	+10.710	+20.638	−48.1

(b)	S/μ (load ⊥ fibers)					
	$k=2$			$k=10$		
λ	$\alpha=-5$	$\alpha=5$	$\Delta\%$	$\alpha=-5$	$\alpha=5$	$\Delta\%$
0.80	−1.333	−0.977	+36.4	−1.355	−1.209	+12.1
0.90	−0.465	−0.405	+14.8	−0.484	−0.462	+4.8
1.20	+0.527	+0.675	−21.9	+0.632	+0.690	−8.4
1.30	+0.718	+1.043	−31.2	+0.915	+1.056	−13.3

low values of $k(0 < k \leqslant 5)$ and moderately large values of $\lambda(0.8 \leqslant \lambda \leqslant 2)$.

In Tables 1a and b, we examined the effects of the sign of the stretch exponent α on the material response, both in the direction of the fibers (Table 1) and in the direction orthogonal to the fibers (Table 2). We considered two values of α (-5 and 5), and recorded S/μ for selected values of λ, in compression ($\lambda = 0.8, 0.9$) and in tension ($\lambda = 1.2, 1.3$).

For loading parallel to the fibers, the normalized difference $\Delta = (S|_{\alpha=-5} - S|_{\alpha=+5})/\, S|_{\alpha=+5}$ between the two examined responses is independent of the value of the strengthening parameter k (cf., Eq. 5_2). Such a difference ranges from about $+75\%$ for $\lambda = 0.80$ to about -48% for $\lambda = 1.30$ (see also Fig. 3b). Differently, for loading orthogonal to the fibers, Δ depends on k and decreases as k increases (cf., Fig. 4).

Miller and Chinzei (2002) and Prange and Margulies (2002) have experimentally validated a first order, isotropic ($k = 0$), and viscoelastic formulation of model 2. It is known that *policonvexity* of the isotropic model holds if $|\alpha| > 1$ (cf., Ball 1977; Ciarlet, 1998). Miller and Chinzei estimated $\mu_0 = 842$ Pa (instantaneous value of μ) and $\alpha \approx -4.7$ (constant in time) for porcine brain tissue using uniaxial tests. Instead Prange and Margulies obtained several different estimates for μ_0 and α through shear tests on swine tissues obtained from various brain regions. For adult porcine samples, they found μ_0-values varying between 180 and 290 Pa and α-values varying between 0.03 and 0.075, in relation to the different nature of the tissues (gray or white matter), regional origin (thalamus, corona radiata, corpus callosum) and relative position of axonal fibers with respect to test direction (in white matter and mixed white/gray matter samples).

4 Material parameter estimation

In the case of uniaxial (tensile and/or compressive) loading parallel to fibers, it is possible to fit test data (nominal stress vs. fiber stretch) to model 5_2 and estimate $(1 + k)\,\mu$ and α. Successively, it is possible to estimate μ, and thus also k, through uniaxial tests transverse to the fiber direction, taking $(1 + k)\mu$ and α as fixed. In this second phase, due to the impossibility of obtaining an analytic expression for the Meaney model, one could fit data to the Ogden model. This can be acceptable for moderately large stretches (see Section 3). Alternatively, one could use the fitting procedures proposed by Ogden et al. (2004) for multiple data sets.

For gray matter (from motor strip), we fitted the isotropic formulation of model $5_2(k = 0)$ to the tensile test data in Fig. 2a (mean S–λ curve), employing the Levenberg–Marquardt optimization algorithm (see, e.g., Twizell and Ogden 1983), which is available under the add-on package <Statistics—“NonlinearFit”> of Mathematica® (Wolfram 1999). We obtained the following estimates for the material parameters: $\mu = 319.28$ Pa, $\alpha = 3.50$ (cf., Fig. 5a). For white matter from the corpus callosum under uniaxial load aligned with fibers, we fitted the Meaney model to data in Fig. 2b, obtaining $(1 + k)\mu = 502.12$ Pa, $\alpha = 2.38$ (cf., Fig. 5b). Since we did not test brain material from this region under load transverse to the fibers, we were not able to estimate μ and k separately in this case. Finally, for white matter from the corona radiata, we employed the two-level fitting procedure as described above, to estimate the complete set of material parameters μ, α, and k. In detail, first we fitted model 5_2 to the data in Fig. 2c, obtaining $(1+k)\mu = 378.55$ Pa, $\alpha = 6.84$ (Fig. 5c). Then, we fitted the isotropic model with $\alpha = 6.84$ to the data in Fig. 2d, obtaining $\mu = 136.82$ Pa, which implies $k = 1.77$ (Fig. 5d).

In order to evaluate the influence of the different brain material responses under tensile and compressive loadings on parameter estimation, we also addressed an extrapolation of the data presented in Fig. 2 in the compression range $\lambda \in (0.8, 1.0)$. To this end, we adopted the model in Table 2 for the response of the brain material in compression, which was deduced from Fig. 4 of Miller and Chinzei (2002). In

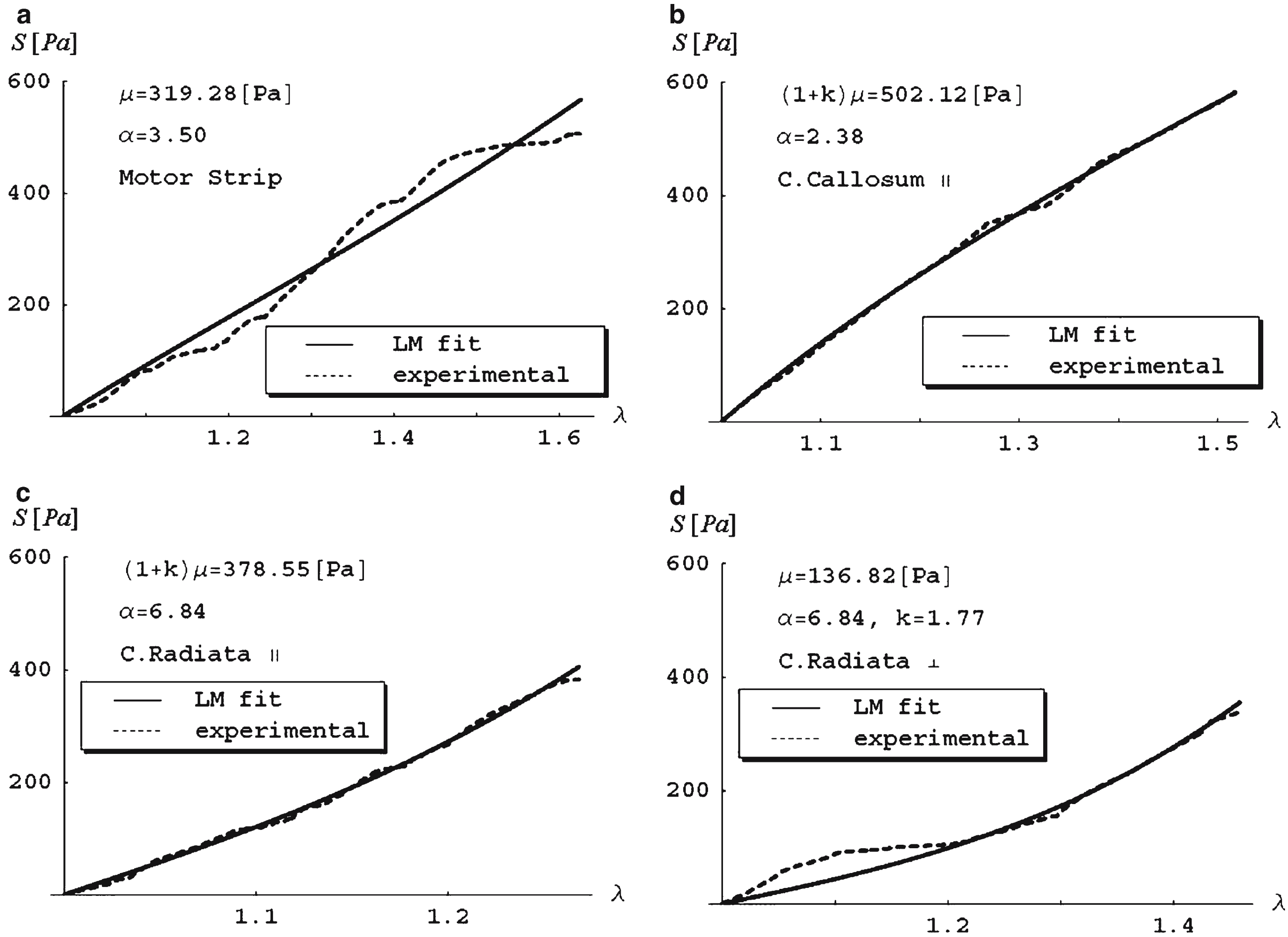

Fig. 5 Fits of the augmented Ogden model to simple tension tests (Levenberg–Marquardt nonlinear fit method)

Table 2 Theoretical model used to extrapolate tensile data to the compression range $\left(\bar{S} = S|_{\lambda=1.2}\right)$

λ	S_{22} / $\bar{S}_{22}$
0.80	−4.20
0.85	−2.60
0.90	−1.30
0.95	−0.67

Table 2, $\bar{S}$ denotes the value of S at $\lambda = 1.2$. The fitting of the extended test data to the Meaney model, conducted as described above, leads us to new estimates of the material parameters, which are displayed in Fig. 6.

As can be seen quite different estimates of μ, α, and k may be obtained with respect to pure tension data (cf., Figs. 5, 6), and negative values of α may be found. The results in Fig. 6 agree well with those given by Miller and Chinzei (2002). The values of α obtained in pure tension are not very far from $+5.0$, while those corresponding to the complete uniaxial response are not far from -5.0. Hence, data given in Tables 1 and 2 are useful to predict the (remarkable) error that would occur in a finite element model by using tensile material constants for the computation of the complete (tensile and compressive) brain response due to impact/acceleration loading.

5 Concluding remarks

In this work we have discussed the mechanical behavior of soft brain tissues. We have focused our attention on transversely isotropic constitutive equations, regional differences, directional properties, and tensile testing. Fitting procedures for material parameter estimation have been proposed and employed in practice, obtaining estimates for porcine brain materials under pure uniaxial tension and combined uniaxial compression-tension. In the latter case, tensile test data were associated to a theoretical model of the compressive response, deduced by other available experimental studies (Miller and Chinzei 2002).

The results obtained highlight the sensitivity of material parameters to test conditions. In particular, the exponent α of the principal stretches appearing in the strain-energy function changed the sign passing from simple tension ($\alpha > 0$) to compression-tension loads ($\alpha < 0$). All the estimates obtained for α fall within the range $|\alpha| > 1$.White matter was

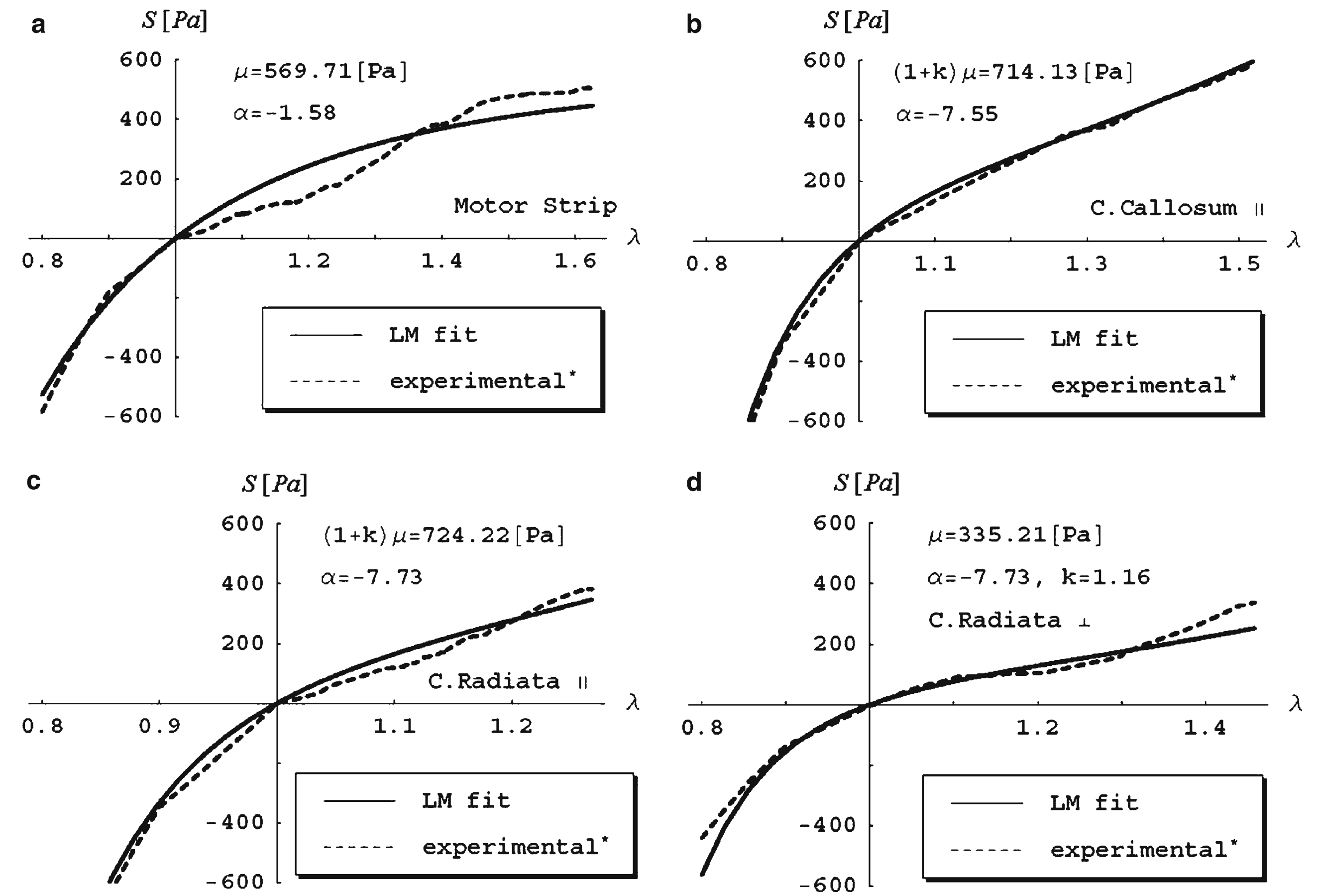

Fig. 6 Fits of the augmented Ogden model to complete uniaxial load data (*: tensile experimental data extrapolated in compression, see Table 2)

found to be stiffer than gray matter, and, within the former, the corpus callosum showed higher shear modulus than the corona radiata.

It is evidently necessary to adopt models with at least two terms for the isotropic part, one describing the response of the brain matrix tissue in tension and the other the response in compression, and at least one term for the fiber reinforcing part. Refinements of the Meaney model are obtained by dealing with strain energies of the form

$$W = \sum_{n=1}^{N} \frac{\mu_n}{\alpha_n}\left(\lambda_1^{\alpha_n} + \lambda_2^{\alpha_n} + \lambda_3^{\alpha_n} - 3\right) + \sum_{r=1}^{R}\left(\nu_r I_4^{\beta_r} + \xi_r I_4^{\gamma_r} - \nu_r - \xi_r\right), \quad \lambda_1\lambda_2\lambda_3 = 1, \tag{7}$$

where N and R are positive integers and $\mu_n, \alpha_n, \nu_r, \xi_r, \beta_r, \gamma_r$ are material parameters.

Significant developments are expected in future studies, with reference to a mathematical analysis of model 7 under general loading conditions (cf., Merodio and Ogden 2002, 2003, 2005); fitting of multiple experimental data relative to indentation, uniaxial, and shear tests; time-dependent behavior; tissue damage; and large-scale assessment of material models through finite element modeling of the human head.

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