Chapter 4
Brain Tissue Mechanical Properties

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4.1 Introduction

The human brain is a soft highly metabolically active tissue, floating in cerebrospinal fluid (CSF) within the rigid cranium. This environment acts to isolate the brain from the majority of external mechanical loads experienced by the head during normal daily life. The brain does experience a range of mechanical loads directly, as a result of blood and CSF flow and to some extent, body posture. The dynamic balance of pulsatile hydrodynamic forces in the skull is maintained by blood and CSF flow into and out of the skull throughout the cardiac cycle (the Monro-Kellie hypothesis), since the internal volume of the skull is constant. Reflex responses maintain blood flow during changes in posture and activity, so as to stabilise the mechanical and biochemical environment of the brain.

Brain tissue consists of white and grey matter, and different regions of the brain are made up of different proportions of white and grey matter. White matter is largely composed of myelinated axons of nerve fibres, while the grey matter is dominated by unmyelinated axons and cell bodies.

Since the brain is so well insulated from mechanical perturbations under normal circumstances, one might ask why it is important to understand the mechanical properties of brain tissue. While mechanical factors are thought to play a role in a range of conditions, including brain development [1], brain mechanics have been most commonly studied in an attempt to understand conditions where loads are applied either directly or indirectly to the brain. Much of the early work on brain mechanics was focused on understanding the biomechanics of traumatic brain injury, where high loading rate motion of, or impacts to, the skull results

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K. Miller (ed.), *Biomechanics of the Brain*, Biological and Medical Physics, Biomedical Engineering, https://doi.org/10.1007/978-3-030-04996-6_4

in internal damage to the brain. At the other end of the loading rate spectrum lie neurostructural conditions such as hydrocephalus, where very slow dilatation of the ventricles deep within the brain, often due to obstruction of a CSF outflow pathway, compresses the surrounding brain tissue. Either slow or fast loading can lead to neural injury and neurological and/or cognitive dysfunction. Brain tissue mechanical behaviour has also been suggested to vary in some disease conditions [2–5], and noninvasive methods of measuring tissue properties in vivo could potentially be useful for discriminating between conditions that have similar symptoms and imaging appearance, but different treatment outcomes. An example of this is discriminating between normal pressure hydrocephalus, which responds well to surgical shunt placement, and cerebral atrophy due to other neurological disorders which does not [6, 7].

Another key driver for research aimed at understanding the fundamental biomechanical response of brain tissue is to provide high-quality experimental data to allow for development of mathematical and computational models of brain behaviour. This includes development of accurate constitutive models of brain tissue behaviour, relevant to the problem being studied, and also to allow finite element and other computational models to accurately simulate the brain response to complex loading conditions. Such simulations might include analysis of traumatic brain injury mechanisms and tissue injury thresholds, simulation of brain diseases that have a mechanical component (e.g. hydrocephalus), and simulation of surgical procedures for surgical planning or surgical training systems.

Brain tissue mechanics have become an increasing focus of research in the last couple of decades, in part due to emerging methods for measuring in vivo brain properties and associations between changes in brain mechanics and a variety of neurological disorders.

In this chapter, the fundamental viscoelastic properties of brain tissue will be critically reviewed, and limitations of the current state of knowledge and directions for future research will be identified.

4.2 Shear Properties of Brain Tissue

Interest in the shear response of brain tissue arose from early studies by Holbourn [8] who hypothesised that diffuse axonal damage seen in the brain parenchyma after traumatic brain injury occurred as a result of rotational shear within the brain. This was further substantiated in the 1980s by Thibault and Gennarelli's experimental work with non-human primates [9].

Methodological issues have played a major role in the apparently disparate shear properties reported for brain tissue in the literature, and only in the late 1990s did the rigour of rheology begin to be applied to measurement of shear properties of brain tissue. Much of the large disparity between the previously reported data can be explained in the light of more rigorous approaches to control of sample preparation, test conditions, and the use of standard rheological test

procedures. However, there is also considerable intra-study variability in reported brain mechanical properties data, to which biological variation is likely to be at least a substantial contributor. A key flaw of many early studies of shear properties in the literature was the (sometimes unstated) assumption of linear viscoelastic behaviour and therefore flawed interpretation of large amplitude oscillatory data. The appropriate approach is to first identify the linear viscoelastic limit for a tissue, conduct tests to characterise the linear viscoelastic response, and then conduct appropriate large-amplitude (nonlinear) tests with appropriate analysis methods.

Shear response of a viscoelastic material is characterised in terms of the shear modulus, usually denoted by the symbol G. This quantity represents the unit stress response to a unit shear strain and is constant for a given frequency in linear viscoelastic materials. The relaxation shear modulus represents the temporal stress response to a unit shear strain and is typically denoted $G(t)$. The storage and loss moduli represent the elastic (G') and viscous (G'') components of the linear viscoelastic shear modulus, respectively, and are a function of loading rate, often reported as frequency.

4.2.1 Linear Viscoelastic Properties

The traditional rheological approach to measuring viscoelastic properties of complex materials is to first establish the linear viscoelastic limit and characterise the material behaviour at or below this limit. In the linear viscoelastic region, the stress generated is proportional to the strain applied, so that the shear modulus is constant.

4.2.1.1 Oscillatory Loading

Oscillatory testing of tissues is most often carried out using parallel plate geometries, where one plate is fixed, while the other is moved sinusoidally parallel to the fixed plate, while torque is recorded. Parallel plates are used because of the difficulty of cutting brain tissue samples to fit the cone-and-plate setup that is often used for viscoelastic fluids. The moving plate is typically either rotated about an axis perpendicular to the plates, as in traditional rotational rheometers, or moved linearly parallel to the fixed plate. Other methods have been used, including an eccentrically loaded sample in a rotational rheometry setup [10], and shear wave propagation methods such as magnetic resonance elastography [11].

Oscillatory loading results are typically reported as the storage (G') and loss (G'') moduli, which represent the elastic and viscous components of the dynamic shear modulus ($G^* = G' + iG''$). This complex notation is used for the shear modulus to indicate that the stress associated with the viscous response is temporally out of phase with the elastic response and the input sinusoidal displacement (by $\pi/2$).

Figure 4.1 summarises the data reported in the literature within the linear viscoelastic region [10, 12–15]. From this, it can be seen that brain tissue is a very

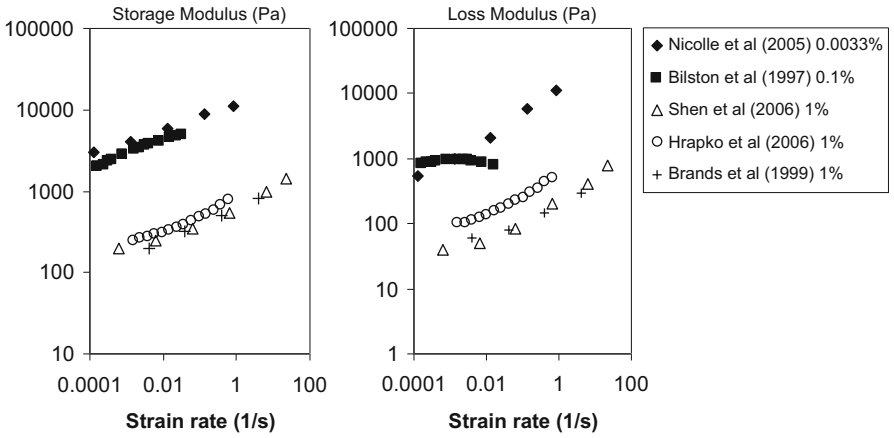

Fig. 4.1 Linear viscoelastic shear moduli for brain tissue from ex vivo brain samples

soft solid, with a shear modulus of the order of a few kilopascals at physiological loading rates. The shear modulus increases in a power-law fashion with loading rate. This figure also shows reasonable consistency for both G' and G" measurements made at similar strains, but the studies who reported the linear viscoelastic regime to be at higher strains (e.g. 1%) report the brain to be softer than those who made measurements at lower strains. Since the brain exhibits shear thinning once the linear viscoelastic limit is exceeded, resulting in lower apparent shear moduli, it seems likely that the measurements made at larger strains are not, in fact, made within the linear viscoelastic regime, and this explains the discrepancy. The strain sweep data presented by Bilston et al. [12] indicates that between 0.1% and 1% strain, the apparent storage modulus drops by approximately 40%, supporting this contention, and thus the data collected at 1% strain is likely not to be truly within the linear viscoelastic limit. The values reported by Bilston et al. [12] are also consistent with more recent in vivo elastography methods discussed below. The data of Shen et al. [15] was collected at long post-mortem times and is thus less likely to be reliable (see discussion below on methodological issues).

Interestingly, the trend in strain-rate sensitivity is very similar for all test data, with a power-law increase of storage moduli with strain rate, where stress increases by an order of magnitude over approximately five decades of loading rate.

4.2.1.2 Relaxation

The linear viscoelastic relaxation modulus for brain tissue has been measured less frequently than the oscillatory properties, at least partly because of the technical challenges in measuring these properties at very low strains. It is, however, quite important, since the most commonly used nonlinear models used to describe brain

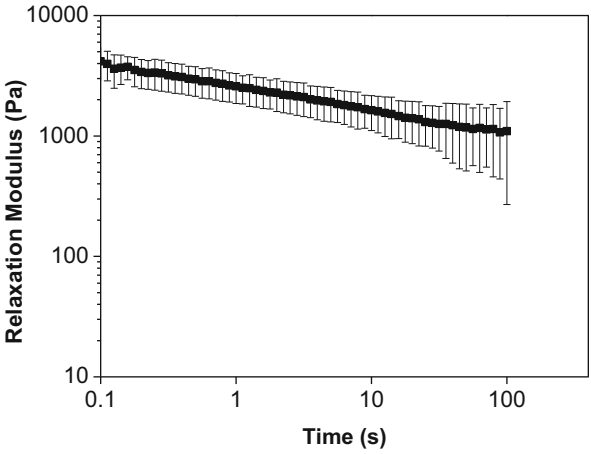

Fig. 4.2 Linear viscoelastic relaxation modulus for brain tissue measured ex vivo. (Adapted from Bilston et al., 1997)

tissue rely on quasilinear viscoelastic theory (QLV, [16]), which has as a key requirement that the shape of the relaxation modulus be independent of strain. The only data set that is convincingly within the linear viscoelastic region is that of Bilston et al. [12], and the relaxation modulus is shown in Fig. 4.2. Indeed, this data has been shown to be consistent with the small amplitude oscillatory data, since using it to predict the linear viscoelastic response gives results similar to the oscillatory data at 0.1% shown in Fig. 4.1 (see [12] for further details).

4.2.1.3 Other Measurements

In recent years, researchers have attempted to use novel techniques to measure brain tissue properties, with a particular focus on those testing situations that are difficult to measure using traditional rheometry, such as very high loading rates and in vivo measurements.

4.2.1.4 Elastography Measurements

One technique that has received significant recent attention is magnetic resonance elastography (MRE), which relies on the relationship between the amplitude, wavelength, and velocity of propagating mechanical waves to extract linear viscoelastic properties of soft tissues. The MR scanner is used to image small amplitude vibration within the brain parenchyma, which is usually created by transmitting mechanical vibration (of frequency typically 30–100 Hz) to the skull and into the brain parenchyma. Mathematical analysis, involving localised inversion of the wave equation at each pixel in the image plane, allows estimation of the local shear

modulus. In the simplest implementation, the local wavelength is used to estimate the 'elastic' shear modulus of the tissue, according to Muthupillai et al. [17]:

$$G = \nu^2 \lambda^2 \rho,$$

where ν = frequency, λ = the local wavelength, and ρ = density.

More advanced implementations solve the full wave equation over the three-dimensional image domain. Some of these techniques use a correspondence principle approach, whereby the shear modulus is considered to be a complex quantity in the wave equation, allowing both the elastic and viscous components (*G'* and *G"*, respectively) of the shear modulus to be extracted, if a sufficiently high signal to noise ratio is present in the image data. This relies on the attenuation of the propagating wave as it penetrates the brain parenchyma to estimate the viscous damping.

The estimated shear moduli for healthy brain tissue that has been gathered using MRE, while not as widely varying as some of the early ex vivo brain data, are nevertheless somewhat variable, due in large part to the different analytical approaches taken to estimating the elastic and/or viscoelastic properties and data quality. Although there is still considerable debate about the best methods of both wave induction in brain elastography and data analysis, numerous studies have used MRE to examine both healthy populations and also several clinical populations. Selected data from a selection of brain MRE studies in healthy adults is shown in Fig. 4.3.

Many of the early brain MRE studies used small sample sizes, but more recently, larger studies have been performed, giving greater confidence in their findings. Such studies have suggested that brain shear modulus may decline slightly with age and that females may have very slightly stiffer brains than males [21, 23]. The practical significance of these small differences is not yet clear. Some research groups have

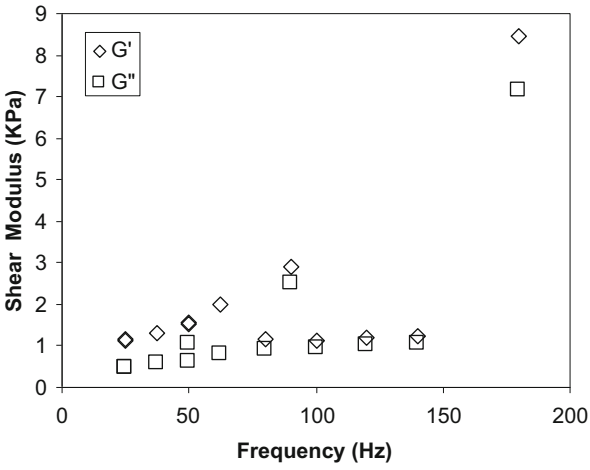

Fig. 4.3 Brain shear modulus measurements made using MR elastography. (Data from [11, 18–22])

attempted to create 'maps' of regional brain properties in healthy adults using MRE [24, 25], although the regional differences are not large and regions and values reported vary between groups. The most consistent finding is that the cerebellum is considerably less stiff than the cerebral hemispheres [25, 26], possibly due to its finer structure [26]. There has also been progress towards estimating differences in white and grey matter and also in methods to estimate anisotropy of white matter tracts. Although consensus remains to be reached on the precise quantitative differences, it is reasonably clear that the differences in white and grey matter shear moduli are likely fairly small and that the degree of mechanical anisotropy is also modest in most brain regions.

Vappou et al. [27] have published a direct comparison of rheometry data on ex vivo brain tissue with MRE measurements, but it is difficult to draw direct conclusions about the validity of MRE on the basis of their work, since their testing frequencies did not overlap for the two methods, their MRE shear moduli were estimated from a simple wavelength-based formula rather than full inversion of the wave equation, and their rheometry testing was conducted at a shear strain of 0.5%, which the above discussion suggests may have been beyond the linear viscoelastic limit, and thus have slightly underestimated the shear modulus. Further rigorous validation of MRE is required before the absolute values estimated from this technique can be considered quantitatively reliable or results from different analytical techniques can be compared. Studies performed using different MRE techniques still tend to report differing shear modulus values at similar frequencies [28], although general trends towards higher moduli at higher frequencies are consistent with rheometry studies.

Brain MRE has recently begun to be used in research studies in clinical populations, including demyelination [29, 30], dementia [31, 32], cerebrospinal fluid flow disorders such as hydrocephalus [33–35], and brain cancers [36–38]. These studies, while intriguing, remain to be repeated in independent cohorts, and typically show substantial overlap between patient and control groups, and occasionally have contradictory results, which may indicate that they are limited in their diagnostic power using current methods.

Despite these issues, MRE has great promise as a relatively noninvasive method of measuring in vivo human tissue properties, which is impossible using other more traditional techniques.

Ultrasound has also been used to estimate brain tissue properties, in the linear viscoelastic (small amplitude) range ex vivo. Lippert et al. (2004) used the 'wave in a tube' technique, where a sample is placed in a tube and an ultrasonic (100 kHz–10 MHz) waves passed through the sample. By measuring this wave propagation, the wave speed in the tube is estimated and the linear viscoelastic shear modulus (G*) extracted. Lippert et al. [39] estimated the shear modulus for juvenile ovine brain tissue samples to be in the range of 140–400 MPa, where the larger values are associated with the higher frequencies. These values are orders of magnitude larger than values from lower frequencies, and somewhat higher than simple extrapolation of the power-law behaviour measured at lower frequencies (e.g. the data shown in Fig. 4.1) would predict. Atay et al. [40] measured mouse brain shear modulus

using MR elastography at an intermediate frequency of 1 kHz, obtaining values of approximately 10–15 kPa, still well below the values obtained by high-frequency ultrasound. Ultrasound shear wave elastography has also recently been applied to brain tissue in vivo in human subjects [41] and ex vivo porcine samples [42], yielding tissue shear modulus estimates more in keeping with MRE measures.

In summary, the linear viscoelastic properties of brain tissue, while a fundamental stepping stone for understanding the more complex nonlinear properties, have been measured using reliable techniques in only a small number of studies, and methodologically flawed data sets are common. There is still room for more robust characterisation of these properties under a wider range of loading conditions, including further cross-validation of data from one testing mode against another (e.g. oscillation vs relaxation or tension vs compression). The former has rarely been done (e.g. see Bilston et al. [12]) and would create greater confidence in the quality and reliability of the data.

4.2.2 Nonlinear Viscoelastic Properties

Most soft biological tissues are thought to be nonlinearly viscoelastic at moderate to large amplitudes of loading [16]. Nonlinear viscoelastic materials require more complex mechanical testing protocols in order to characterise the behaviour of the material, in order to ascertain how the properties change with loading type, loading amplitude, and loading rate. Brain tissue has a very low linear viscoelastic limit, rendering it nonlinearly viscoelastic at most strains of practical interest.

4.2.2.1 Oscillatory Response

While there are several reports of oscillatory response of brain tissue in the literature [13, 43–45], most of these have interpreted data without proper analysis of the nonlinear viscoelastic effects and are thus of questionable validity. The key problem is that in the nonlinear viscoelastic regime, the shear modulus is a function of strain and not independent of strain as it is within the linear viscoelastic regime. In the case of brain tissue, there is substantial shear thinning at strains beyond the linear viscoelastic regime, and the shear modulus estimated from larger amplitude test data can be significantly underestimated (as discussed above). In this context, shear thinning is observed as a decreasing shear modulus with increasing applied shear strain. Oscillatory tests at large amplitude require analysis of the full loading and unloading cycle, which is non-sinusoidal at large amplitudes, and thus the simple calculation of G' and G'' from the phase difference between the peak torque and the peak shear strain is no longer valid. In addition, the decomposition of the complex modulus into the storage and loss modulus is typically based on the phase difference between the peak input shear strain and the peak torque generated. If the torque signal is non-sinusoidal, decomposition of the shear modulus based on this method will give erroneous values. Newer rheometers have the capacity to measure the full

loading cycle, and thus more rheologically rigorous methodologies can, and should, be applied to study oscillatory loading of brain tissue, to better characterise not only the fully nonlinear behaviour but also the transition regime between 0.1% and 1% strain just above the linear viscoelastic limit. Newer methods such as applying large amplitude oscillatory shear and using shear in combination with other loading conditions [46] in which inertial effects are properly considered, may also be useful for brain tissue.

4.2.2.2 Relaxation

Beyond the linear viscoelastic regime, the relaxation modulus for brain tissue decreases with applied shear strain (see data from the literature [12, 13, 15, 43, 47, 48] summarised in Fig. 4.4). This is consistent with the shear thinning seen in the oscillatory data noted above. Relaxation in brain tissue ex vivo appears to continue over the whole time period that has been measured to date, and while there are some minor differences in the shape of the relaxation curve at the early and later parts of the curves, there is moderate consistency of the approximate shape across much of the data. Note that the shape of the early part of the relaxation curve can be affected by the loading rate used for the initial 'step', which can never be instantaneous in practice [49]. At longer times, tests may be affected by post-mortem tissue changes, including degradation and/or dehydration. This is more marked at low strains where the torques are near the resolution of the test instrument and may explain some of the differences in shape in the relaxation curves at long times.

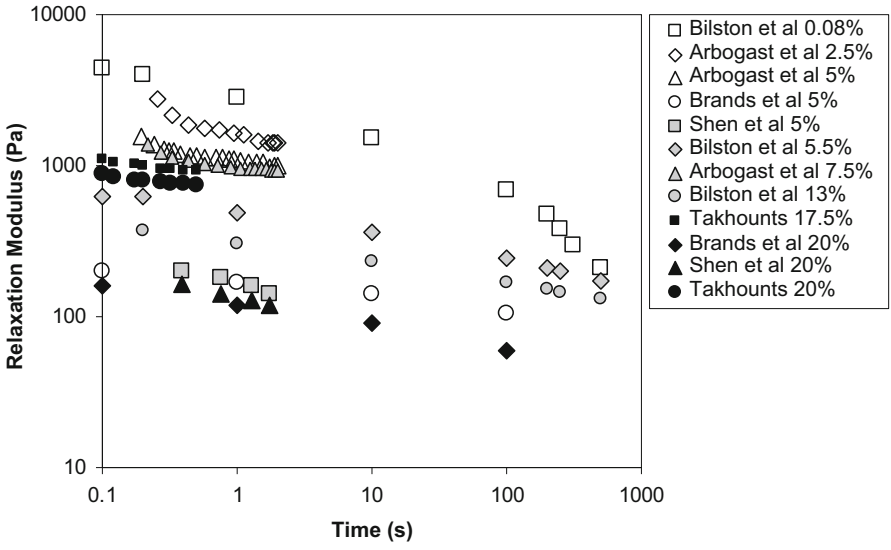

Fig. 4.4 Relaxation modulus for brain tissue in shear

4.2.2.3 Constant Loading Rate

Shear tests, analogous to the traditional engineering tensile tests, aimed at constructing a stress-strain curve have also been conducted by several researchers over a wide range of loading rates. These tests demonstrate the nonlinear response of brain tissue, and almost all test series have shown a clear increase in apparent stiffness with increasing loading rate. Failure or tissue yield in shear appears to begin at approximately 100–200% strain at low to moderate loading rates, according to Bilston et al. [47]. This is significantly a higher strain than the brain can withstand in tension and compression. Few constant shear rate tests in the literature have had inertia corrections applied to the data, and at high loading rates, the sample inertia may contribute to the recorded load. Data from the literature [10, 47, 50] are summarised in Fig. 4.5.

4.2.2.4 Other Test Types

In rheological studies of polymers, it is standard practice to further characterise complex fluids and soft solids using combination and multistep loading histories, such as multiple steps, including those in opposite directions. This has rarely been done in the study of brain tissue and would likely provide significant

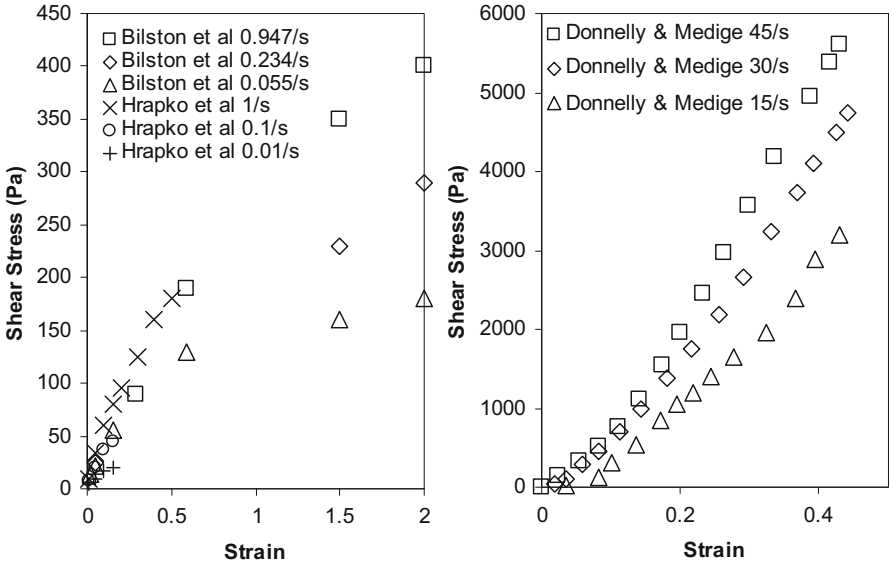

Fig. 4.5 Constant shear rate test data for brain tissue at low to moderate loading rates (left) and high (right) loading rates

new information that would help in developing and establishing the validity of constitutive models for brain tissue.

4.3 Compressive Properties of Brain Tissue

The earliest data for compressive properties of brain tissue are those of Estes and McElhaney [51], who compressed rhesus and human brain tissue to large strains over a broad range of loading rates. They found that brain tissue was notably strain-rate sensitive, with increasing stiffness at higher loading rates, and increasing stiffness with applied strain, resulting in a concave upward nonlinear stress-strain curve (see Fig. 4.6). Miller and Chinzei [52] conducted compressive tests at lower strain rates and obtained similar qualitative results, although their data showed lower stresses for similar strains and strain rates. Cheng and Bilston [53] recently conducted compression tests of brain at very low strain rates, with similar stress-strain responses to those of Chinzei and Miller. Data from these tests are shown in Fig. 4.6. Tamura et al. [54] conducted moderate to high rate compression tests, and their data lies somewhat below that of Estes and McElhaney, suggesting the long post-mortem time used for Estes and McElhaney's work may have affected their results. Most recently, Pervin and Chen [55] conducted both quasistatic and high loading rate tests of brain tissue in compression, using a modified Hopkinson split bar technique, again confirming the brain's strong strain-rate sensitivity. Their data, collected at 1000–3000/s from very fresh samples, lies well above that of Estes and

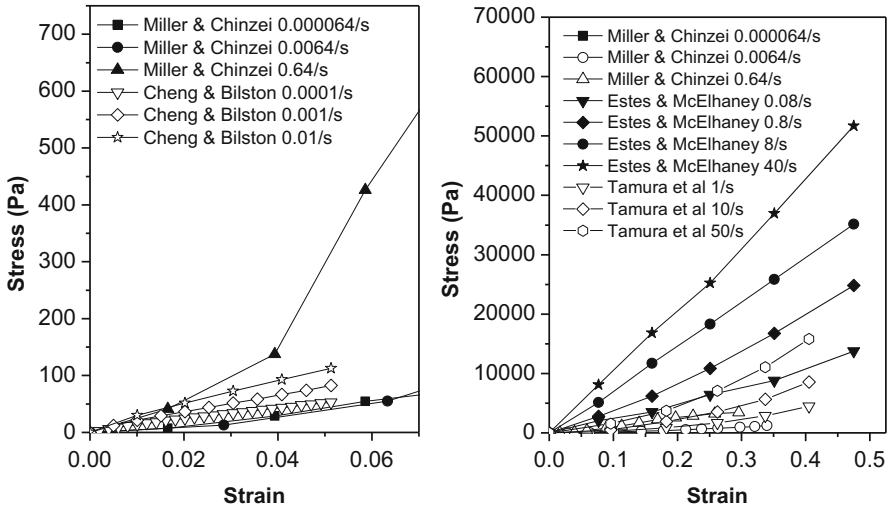

Fig. 4.6 Selected compressive properties of brain tissue at low to moderate loading rates (left) and moderate to high loading rates (right)

McElhaney (an order of magnitude higher at 1000/s, not shown), which suggests that the strain-rate sensitivity does not disappear, even at very high loading rates. Data is reported for peak strains up to 30–50% in compression, suggesting this is the onset of failure. Rashid et al. [56] observed strain-rate effects at compressive strain rates of 30–90/s also. None of these studies explicitly considered inertial effects, which can be expected to be significant.

Traditional rheological test protocols have rarely been applied to compression testing, and thus the linear viscoelastic properties of brain in compression have not been ascertained. Fallenstein et al. used sinusoidal indentation tests in the live macaque brain and showed that for very small indentations (25 μm) the force response was sinusoidal, suggesting linear response, but for larger indentations (300 μm) the responses were non-sinusoidal. The linear limit may lie between these two, but the local strain field is difficult to estimate, especially since the pia mater was intact underneath the probe, and thus these data do not give a clear value for the compressive linear viscoelastic strain limit, although it is likely to be quite low. Miller et al. [57] indented porcine brain in vivo, using a finite element model to extract parameters for a hyper-viscoelastic constitutive model.

Relaxation moduli in compression at large strains have been reported in a small number of studies [53, 54]. Cheng and Bilston [53] found that the relaxation response was relatively independent of loading rate, after the short period after the initial ramp (see Fig. 4.7). Tamura et al. [54] found a consistent reduced relaxation modulus over a range of large strains (20–70%). Rashid et al. [56] reported relaxation force after high strain tests (10–50% unconfined compression), observing rapid relaxation in the first few milliseconds of relaxation, slowing thereafter but continuing until measurement ceased after half a second.

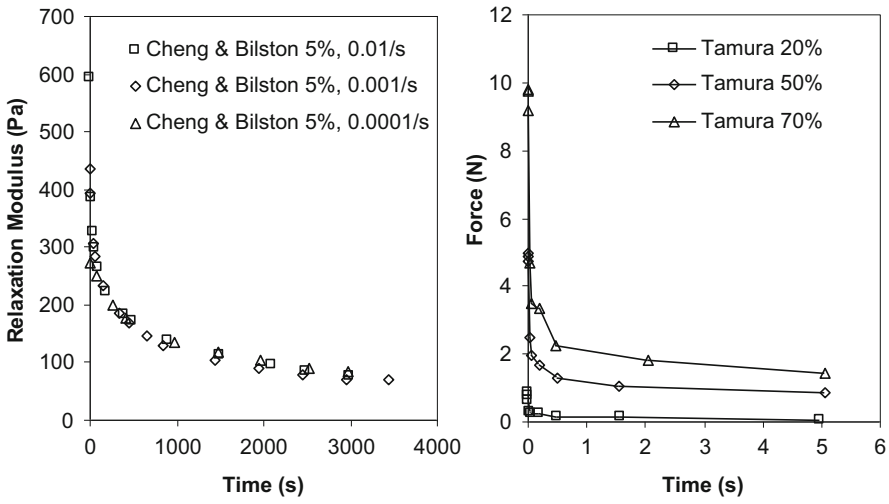

Fig. 4.7 Compressive relaxation data for brain tissue

Compressive properties have also been considered in the context of brain tissue being a fluid-saturated two-phase material. The main application of this type of modelling has been in the study of hydrocephalus. The simpler biphasic or poroelastic models, similar to those developed for modelling soils, assume a linear elastic tissue matrix saturated with an inviscid (or alternatively a Newtonian) fluid. This gives rise to flow through the interstitial spaces of the tissue according to Darcy's Law, coupled to linear elastic deformation.

Conducting the traditional soil consolidation tests on brain tissue samples has been said to be technically challenging [53], and thus unconfined compression data is often used to estimate the properties. Chinzei and Miller [58, 59] showed that a simple poroelastic model is not able to simulate the strain-rate sensitivity observed in brain tissue. That group have also published information on methodological issues with such multiphase models and for specific applications such as hydrocephalus [58, 60]. Cheng and Bilston [53] used a poroviscoelastic model for brain tissue to model their compressive data at low loading rates. There is a wide range of values (approximately 3–4 orders of magnitude reported for the hydraulic conductivity of brain tissue in the literature (2×10^{-10}–4×10^{-7} m/s) [53, 61, 62], of which very few are based on definitive experimental work (e.g. [53]. who reported 4.0×10^{-7} m/s), and further research is needed to accurately characterise these parameters. Chapter 6 contains additional discussion of the application of multiphase models in surgical simulation.

4.4 Tensile Properties of Brain Tissue

Brain tissue properties in tension are less well characterised than in other loading modes, with only a few studies reporting tensile properties. This is at least in part due to the difficulties of conducting these tests, particularly in gripping samples effectively. General observations of the behaviour of brain tissue in tension are that it appears to soften with increasing strain and exhibits a strain-rate sensitivity that is consistent with the response in other loading modes, that is, increasing apparent stiffness with increasing loading rate. Figure 4.8 shows some of the data from the literature [63, 64]. At higher loading rates, Rashid et al. [65] also observed strong rate dependence in ex vivo porcine brain specimens, with stresses approximately doubling for a given strain between 30/s and 90/s strain rates. Failure limits in tension are not well characterised, but appear to be in the range of 20–60% strain.

More recently, Schiavone et al. [66] have used an aspiration method to measure in vivo brain deformation with tensile loading at the surface intra-operatively on a human patient. They used a simplified finite element model to estimate hyperelastic parameters for that patient.

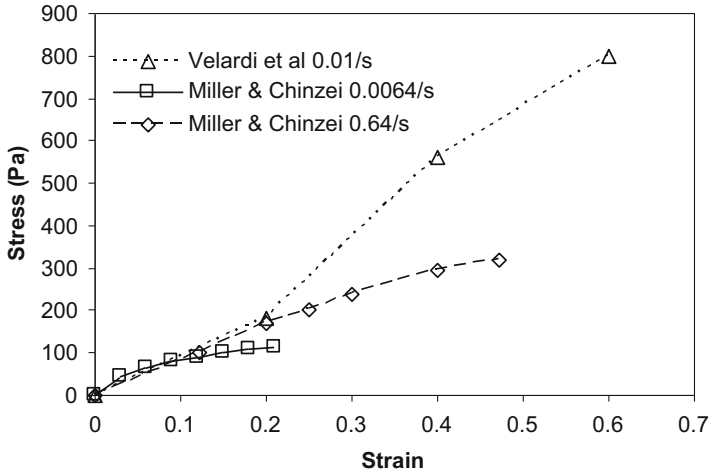

Fig. 4.8 Tensile properties of brain tissue

4.5 Constitutive Models for Brain Tissue

As can be seen from the previous sections on brain tissue mechanical response, capturing the mechanical response of brain tissue in three dimensions over a broad range of loading types and loading rates is a very challenging task. The ideal constitutive equation would be able to model the shear, compressive, and tensile response of brain tissue, within the loading rate regime of interest for a particular study. There have been many studies that have developed constitutive equations for specific aspects of brain mechanical response, but few that have been widely used beyond the original description of test data. To date, there is no widely accepted constitutive model for brain tissue that is able to match the full spectrum of the strongly strain-rate sensitive, nonlinearly viscoelastic behaviour of brain tissue. Recently, researchers have focused attention on modelling multiple loading types (compression, tension, shear, etc.) with a single constitutive law. The nonlinear elastic behaviour of ex vivo human brain tissue in multiple loading modes was able to be reconciled with a single-term Ogden model [67], and a more complex viscoelastic model had some success in capturing viscoelastic behaviour [68]. However, a good fit was only obtained by using all the test data, and while this is a major step forward, the predictive capacity of the model needs testing. Moreover, the test data modelled was from samples tested a long time post mortem, and attempts to model fresh tissue, in vivo data, or viscoelastic behaviour in multiple loading conditions remain an area of active research.

The most commonly used constitutive models used for computational calculations are based on quasilinear viscoelastic (QLV) theory (see [16] for full discussion of this theory). These typically use a hyperelastic model to describe the nonlinear elasticity, combined with a linear viscoelastic relaxation modulus to describe the time-dependent behaviour.

Hyperelastic models were originally developed to describe the nonlinear elastic behaviour of rubbers. They use the concept of a strain energy potential function, from which the relationship between stress and strain tensors is derived. The strain energy function, W, is usually defined in terms of the invariants (I_1, I_2, I_3) of the strain tensor, $\boldsymbol{S}$, which is itself defined by the deformation gradient tensor, $\boldsymbol{F}$. If a material is incompressible, then the third strain invariant is unity, and the strain energy function is only a function of the first two invariants. The stress-strain relationship is then obtained from a partial derivative of the strain energy potential with respect to $\boldsymbol{F}$. Depending on the choice of the strain energy potential, the particular stress and strain tensors used, and the invariants that the definition uses, this derivation can become algebraically complex, and the reader is referred to solid mechanics texts for further details. Common hyperelastic models include those that use strain energy functions that are polynomial functions of the invariants, such as the Mooney-Rivlin model, and the Ogden model, which uses a strain energy function defined in terms of the principal stretch ratios occurring in a material. The Mooney-Rivlin model [69, 70] for an incompressible material defines the strain energy potential in terms of the material parameters, μ_i, as

$$W = \frac{\mu_1}{2}(I_1 - 3) + \frac{\mu_2}{2}(I_2 - 3) \tag{4.1}$$

The Ogden model [71] defines the strain energy potential in terms of the material parameters, μ_i and α_i, and the principal stretch ratios, λ_i, as

$$W = \sum_N \frac{2\mu_i}{{\alpha_i}^2}\left({\lambda_1}^{\alpha_i} + {\lambda_2}^{\alpha_i} + {\lambda_3}^{\alpha_i} - 3\right) \tag{4.2}$$

The viscous or time-dependent behaviour is often modelled as the sum of a series of Maxwell elements, so that the relaxation modulus is given by

$$G(t) = \sum_N G_i e^{-t/\tau_i} \tag{4.3}$$

One example of a model in this class is that of Miller and Chinzei [63], which is often used for neurosurgical modelling. This is based on the combination of an Ogden-like hyperelastic model and a Prony series relaxation modulus, defined by Eqs. 4.4 and 4.5:

$$W = \frac{2}{\alpha^2}\int_0^t \left[\mu(t-\tau)\frac{d}{d\tau}\left(\lambda_1^\alpha + \lambda_2^\alpha + \lambda_3^\alpha - 3\right)\right] d\tau \tag{4.4}$$

$$\mu = \mu_0\left[1 - \sum_{k=1}^{n} g_k\left(1 - e^{-\frac{t}{\tau_k}}\right)\right] \tag{4.5}$$

Values for the material constants, α, and the Prony series coefficients suitable for modelling of surgical procedures are given in [63]. The model has been based on tension and compression data from animals, and it has not yet been validated for human brain or for shear loading.

Other models use rate-dependent viscosity, such as the Carreau model (e.g. [47]) or Ellis model [10]. The stress is then given by

$$\mathbf{S}(t) = \int_{-\infty}^{t} G\,(t-s)\,\frac{\partial \mathbf{T}}{\partial s} ds, \tag{4.6}$$

where $\mathbf{T}$ is the elastic stress-strain function derived from the strain energy potential.

The use of this class of model assumes that the time-dependent behaviour can be separated from the nonlinear elastic behaviour, an assumption that is not universally supported by experimental data (e.g. [47]). Nevertheless, the errors introduced by deviation from such assumptions are probably less than the variation seen in the reported experimental data, as noted above.

Other researchers have developed, and implemented into finite element simulation software, more complex rheological models, including fully nonlinear models in which strain-time separability is not assumed, and that capture some of the yield behaviour at large strains [15, 47].

The most appropriate constitutive model used to describe brain tissue will depend heavily on the application of interest. Neurosurgical simulation not including cutting procedures has been shown to require a suitable large deformation framework, but is not sensitive to the specific constitutive model used [72]. Modelling of hydrocephalus may be done with a single-phase model if the fluid distribution in the brain is not of particular interest (e.g. [73]) but also with suitable poroviscoelastic models with appropriate large deformation formulation [53, 74]. Injury simulations are often done with simpler constitutive models due to the high computational demands of large 3D explicit simulations, despite their limitations. These include linear viscoelastic models (e.g. [75, 76]) as well as hyperelastic models, with or without the viscous component (e.g. [77, 78]). A more detailed comparison of brain tissue constitutive models has recently been published [79].

4.6 Discussion

4.6.1 Mechanical Characteristics of Brain Tissue

Decades of research on brain tissue mechanics has established that brain tissue is a very soft, nonlinearly viscoelastic solid material, with a very low linear viscoelastic strain limit, of the order of 0.1–0.3%. Brain tissue is strain-rate sensitive, with increasing stiffness with increasing strain rate. Failure occurs at moderate strains, of the order of 25–100%, depending on the loading type.

However, there is still much that is either not yet known about brain tissue mechanics or the subject of debate, due to inconsistent or contradictory data in the literature. Some of the reasons for these inconsistencies are discussed below.

Despite the well-defined structural anisotropy of white matter arising from the axonal fibre bundles, mechanical anisotropy has not been comprehensively established. Some studies suggest that there is moderate mechanical anisotropy in white matter under shear, with the axonal fibre direction up to twice as stiff as the perpendicular direction [43, 80] and in tension [64], while others have not found significant mechanical anisotropy in compression [55]. The strains used to estimate properties are likely to have an influence, as increasing stretch of axons may stiffen the tissue, as occurs in other fibrous soft tissues.

Regional variations in tissue properties across the brain have been suggested by some studies [43, 80, 81], although the differences are not large, and some of these studies suffer from methodological problems. A recent post-mortem human brain study indicated some indication of small variations across different regions [82]. This modest, at best, regional variation is consistent with more recent MRE studies, with the exception of the softer cerebellum [26].

Like most very soft hydrated tissues, brain tissue is usually assumed to be incompressible, or nearly incompressible, due to its very high water content (e.g. [52, 83]). There have been only a few studies that have directly examined this assumption, and its validity almost certainly depends on the mechanical process of interest. In very slow processes involving displacement of interstitial fluid within the brain parenchyma, such as hydrocephalus or mass lesions in the brain involving brain oedema, this assumption may not be valid, as there is time for fluid to move within the brain tissue, and regions could locally appear compressible due to fluid transfer. For processes at shorter time scales, there is no evidence that brain tissue is significantly compressible, at least at macroscopic length scales. Indeed, Franceschini et al. [61] report that the undrained (i.e. whole tissue) Poisson's ratio for brain tissue is 0.5, while the 'drained' compressibility is 0.496, lending credence to the incompressibility assumption. A recent study used image correlation methods to confirm that incompressibility holds, at least at slow loading rates [84].

Age dependence of brain tissue properties has also been described in a small number of studies. Prange and Margulies [80] suggested neonatal brain tissue is stiffer than in adults, as did Gefen and Margulies [85]. On the other hand, Thibault and Margulies [86] found that shear modulus of the brain was significantly greater for adult brain tissue than neonatal tissue. It is fair to say that this issue is not yet settled and methodologically robust studies are required. As noted on p. 76 of this Chapter, Sack et al. [21] found that brain tissue shear modulus decreases with age from early adulthood to old age, using MR elastography in vivo, which has been confirmed by other studies, which suggest such changes vary by brain region, e.g. [23]. These studies also observed a small difference between females and males, with female brain tissue being marginally stiffer [86].

Differences between measured properties of brain tissue in vivo and ex vivo have been debated for decades. Some studies show significant drops in situ immediately after death [45, 87, 88]. Weaver et al. attributed this change to drops in interstitial

and cerebral perfusion pressure. A recent study comparing in vivo and ex vivo brain properties using MRE indicates that brain stiffness declines after death, but also that frequency dependence is different in vivo compared to ex vivo [89], further emphasising the difficulties of extrapolating from ex vivo data to in vivo brain properties. Others show an increase in shear modulus beyond 6 hours for samples tested ex vivo [90], while indentation tests have shown no effect on overall stiffness when comparing in vivo to in situ but decreases in shear modulus ex vivo (within 6 hours of death) compared to in vivo and in situ [91]. It seems likely on the basis of this data that there are drops in apparent tissue stiffness immediately after death, and possibly increases at longer times post mortem. Since the ex vivo studies in the literature have used a range of times after death up to days, this may be a significant factor in differences in reported data, and such data should be viewed with caution. A recent MRE study suggested that venous pressure, as manipulated by constriction of jugular outflow from the head, can also influence brain mechanical properties [92].

Few studies have directly compared different species under the same testing protocols. The studies that have been done show that properties are similar, at least between human and porcine brains and human [86] and human and rhesus monkey [51].

4.6.2 Methodological Considerations

As mentioned throughout the above sections, characterisation of brain tissue properties has been plagued by differences in results arising from differences in test methods. These differences fall into three main categories – sample preparation, post-mortem time, and testing conditions.

The issue of post-mortem time is discussed in the previous sections above, but it is likely that much of the data in the literature conducted at long times after death is of limited value due to significant changes in tissue properties post mortem.

Sample preparation has received less attention, but it is also of importance. Delicate brain tissue is easily dehydrated and is also subject to osmotic swelling if bathed in fluids with inappropriate osmotic content [47]. Despite this, a range of bathing fluids have been used, including PBS [90], simple saline [50], and silicon oil [15] in addition to artificial CSF [47], which has a similar osmotic content to CSF. Ensuring that the sample has suitable dimensions to minimise the influence of edge effects, slip at gripping surfaces or test platens, and sample inertial effects at high loading rates is also essential. These issues are often not fully considered in published studies. Liu [93] showed that sample thickness affects measured shear moduli in a parallel plate configuration, and similar results were observed by Garo et al. [90]. Recently, storage temperature has also been suggested to affect the measured properties [94].

Sample preconditioning processes have not been studied in detail in brain tissue, although several studies have noted the effects of previous strain loading cycles

on subsequent measured data. Gefen and Margulies discuss this in some detail [91]. A recent study in spinal cord tissue suggests that the amplitude of the preconditioning has a strong effect on the subsequently measured properties [95], and more recent data from our laboratory also suggests preconditioning strain rate can alter subsequently measured properties.

It must be remembered here that the properties of prime interest are the in vivo properties of human brain tissue. It is only very recently that it has been possible to measure human brain properties in vivo, using MR elastography, and then only at very small deformations, corresponding to the linear viscoelastic regime. Response of brain tissue in vivo at larger deformations must be inferred from a combination of ex vivo tests and animal in vivo tests. This brings with it much uncertainty about how to extrapolate the available ex vivo data and animal in vivo results to the in vivo human brain.

4.7 Future Directions

It is clear from the discussion above that while we have made great strides in characterising the mechanical properties of brain tissue, there is still much to be done. Consistent data sets for different loading regimes, such as shear, compression, and tension, are still not readily available. Data for complex loading histories, such as multiple step loading and step reversals, which have been found to be useful in developing and testing accurate constitutive models for other complex nonlinearly viscoelastic materials are highly desirable. It is essential that such data be collected with full consideration of the methodological issues noted above.

The use of more rigorous rheological testing protocols in compression and testing may allow for more definitive determination of the true linear viscoelastic limit for brain tissue. The collection of data through the full loading and unloading cycle in oscillatory testing may also assist in all test modes.

The other key gap in the body of knowledge regarding brain tissue is integration of data from different loading types – particularly reconciling shear, compression, and tensile loading data. To date, this is not possible because data that has been collected in different testing modes comes from different species and has been subject to different loading regimes (strains, strain rates), been subject to different preparation methods, and been tested at different post-mortem times. There is a clear need for multimodal data (shear, compression, tension, and combination loading) to be collected using robust rheological techniques so that reliable constitutive models can be developed and validated across all loading types. One recent ex vivo human brain rheological study has begun this endeavour by testing tension, compression, and shear loading in a single study [82].

Definitive conclusions about the effect of tissue perfusion pressure on the properties of brain tissue would be valuable in determining what corrections (if any) are required to adapt ex vivo data to predict in vivo brain response. Further in vivo measurements, of both linear viscoelastic (e.g. using MR elastography or similar

methods) and large deformation measurements (e.g. by indentation, aspiration, or other methods), are needed.

Brain mechanics at high loading rates still requires more study, including separating out tissue inertial effects from inherent tissue viscoelasticity. At low loading rates, high-quality quantitative data on interstitial fluid flow in the brain, as is thought to be relevant for diseases such as hydrocephalus, is still lacking.

The use of easily interpretable constitutive models may also assist the field of brain tissue mechanics. While some mechanical properties have intrinsic definitions that are interpretable without reference to a constitutive model, such as the linear viscoelastic moduli, other parameters that are widely reported, often incorrectly, to describe tissue properties beyond this linear range are parameters within constitutive models, with their own inherent assumptions. Given the complexity and strong nonlinearity of brain tissue mechanical response, it is unrealistic to expect that one constitutive model will fit all circumstances, and those who wish to describe brain tissue properties in a given context will need to select and use a model that can capture the features of brain tissue mechanics within the relevant loading regime. A model that works for quasistatic brain deformation during surgery will likely not be suitable for high-velocity impact loading, for example.

4.8 Conclusions

While interest in brain tissue mechanics is enjoying a resurgence of late, and much data has been collected to characterise the response of brain tissue to mechanical loading, there is still much to be done to rigorously characterise this complex material. New developments in measuring techniques, including MRE, however, have great potential for noninvasively measuring tissue properties in vivo, which may allow these properties to be used for diagnostic purposes, as well as shedding light on how this complex organ responds to loads, be they due to dynamic processes that lead to traumatic brain injury or slow processes involved in neurological diseases such as brain tumours or hydrocephalus.

Acknowledgements Lynne Bilston is supported by an NHMRC Senior Research Fellowship.

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