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Regional mechanical properties of human brain tissue for computational models of traumatic brain injury

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ABSTRACT

To determine viscoelastic shear moduli, stress relaxation indentation tests were performed on samples of human brain tissue resected in the course of epilepsy surgery. Through the use of a 500 μm diameter indenter, regional mechanical properties were measured in cortical grey and white matter and subregions of the hippocampus. All regions were highly viscoelastic. Cortical grey matter was significantly more compliant than the white matter or hippocampus which were similar in modulus. Although shear modulus was not correlated with the age of the donor, cortex from male donors was significantly stiffer than from female donors. The presented material properties will help to populate finite element models of the brain as they become more anatomically detailed.

Statement of Significance

We present the first mechanical characterization of fresh, post-operative human brain tissue using an indentation loading mode. Indentation generates highly localized data, allowing structure-specific mechanical properties to be determined from small tissue samples resected during surgery. It also avoids pitfalls of cadaveric tissue and allows data to be collected before degenerative processes alter mechanical properties. To correctly predict traumatic brain injury, finite element models must calculate intracranial deformation during head impact. The functional consequences of injury depend on the anatomical structures injured. Therefore, morbidity depends on the distribution of deformation across structures. Accurate prediction of structure-specific deformation requires structure-specific mechanical properties. This data will facilitate deeper understanding of the physical mechanisms that lead to traumatic brain injury.

1. Introduction

Traumatic brain injury (TBI) causes 52,000 deaths and 275,000 hospitalizations every year in the United States, where it is the leading cause of death among young people [1]. It is also increasingly recognized as a key environmental determinant of neurodegeneration [2,3]. The significance of this problem has stimulated vigorous efforts to computationally model brain deformation during head impact to understand TBI pathology and equally vigorous efforts to measure the constitutive properties required to realistically populate these models. Biomechanical investigations of the brain must overcome experimental challenges intrinsic to the nature of brain tissue. It is extremely soft, creating small force measurements and associated signal to noise ratio issues. In addition, brain tissue degrades quickly *ex vivo* [4] and is encased in the bony cranial vault so it is difficult to precisely control and measure load and deformation on fresh tissue samples.

Recently, a need for greater spatial resolution in the measurement of brain biomechanical properties has emerged. Mathematical models have become more sophisticated and the computational resources required to solve them are more readily available. Modern models have the capacity to explicitly represent individual anatomical structures within the brain [5]. These tools offer more nuanced representations of the pathologies that arise from injury to these structures, but the constitutive properties

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necessary to populate these models are lacking. Also, there has been a recent surge in attention to chronic traumatic encephalopathy (CTE), a form of neurodegeneration triggered by repetitive mild TBI. The recently presented consensus neuropathological criteria for CTE distinguish the disorder from other tauopathies based on the spatial distribution of pathology [6]. It is hypothesized that this distribution arises from stress concentrations during head impact [7], but this hypothesis cannot be tested until reliable mathematical models with sufficiently high levels of spatial resolution with corresponding material parameters become available. The relative stiffness of cortical grey and white matter influences important physiological and pathological processes including, but not limited to, TBI pathology. For example, the buckling events that form the gyri and sulci during development depend on this ratio [8]. Jin et al. recently tested human grey and white matter using conventional homogeneous loading modes (tension, compression and shear) [9]. However, these techniques lack the spatial resolution of microindentation so it is difficult to apply them to small samples resected during surgery.

Indentation testing can be used to increase spatial resolution in the measurement of brain biomechanical properties because the relationship between load and displacement during indentation depends primarily on the small domain of material adjacent to the tip [10]. In light of these advantages, microindentation has been used to measure constitutive properties of brain in rat [11,12] and pig [13,14] by our group and others. In this study, we sought to measure the constitutive properties of grey and white matter using microindentation in fresh, unfixed human tissue samples resected during neurosurgical procedures to treat intractable epilepsy.

2. Methods

2.1. Tissue

Blocks of healthy human nonepileptic neocortex were collected as surgical waste from procedures to resect underlying epileptic foci. Specimens of nonsclerotic hippocampus were also collected during these procedures. All patients provided informed consent, and protocols were approved by the Institutional Review Board of Columbia University Medical Center (January 20, 2010). 1 mm thick slices of tissue were cut using a vibratome, transported in Gey's solution containing 4.5 mg/mL glucose, and tested within 6 h of resection. This time limit was based on a detailed investigation of the evolution of biomechanical properties of resected brain tissue, which found that properties remained constant for 6 h after excision [4]. For testing, slices were adhered to the bottom of a 35 mm petri dish using a thin layer of cyanoacrylate glue and bathed in warmed CO_2 independent media (Gibco 18045) containing 4.5 mg/ml glucose (Sigma). The indentation location was selected to be at least 2 indenter diameters away from the nearest interface between white and grey matter. This precaution was required by the assumption of a homogenous continuum contained in the mathematical model. It also eliminated the risk of the indenter tip slipping into a cleavage plane formed by white matter separating from grey matter.

2.2. Indentation testing

Microindentation was performed at room temperature as previously described [12,15,16] to extract mechanical parameters from the white and grey matter of the cortex as well as the three main subregions within the hippocampus, cornu ammonis 1 (CA1), CA3, and dentate gyrus (DG). A petri dish was mounted on a 10 g capacity load cell (GSO-10, Transducer Techniques), offset and scaled to provide a dynamic range of 1 g above the weight of the sample. Since the load cell was mounted underneath the tissue, it was stationary throughout the experiment so inertial compensation was unnecessary. A flat ended cylindrical punch 500 μm in diameter (National Jet Company) was used to indent the tissue. The punch was mounted on a linear actuator (M-227.10, Physik Instrumente), and its displacement was monitored using a capacitive transducer (capaNCDT 6100, Micro-Epsilon). The indenter tip was lowered incrementally towards the surface of the tissue until a tare load of 1–2 mg was achieved. Then the tip was advanced into the tissue to a depth of 39.3 μm in a period of approximately 70 ms and held at that position for 20 s. The signal from the load cell was amplified with a 20 kHz low-pass signal conditioner (OM-19, Load Cell Central) and filtered with a 2 kHz Bessel low-pass filter before transmission to the data acquisition card (NI-USB 6210 DAQ, National Instruments). Since the most rapid step of the indentation requires approximately 70 ms, the cutoff frequency of 2 kHz was unlikely to eliminate relevant frequency components of the indentation load. Both displacement and load data were acquired with a custom written LabVIEW code (LabVIEW 8.6, National Instruments) at 10 kHz.

2.3. Mathematical modeling

Data was de-noised using the automated wavelet de-noising tools in the Matlab Wavelet Toolbox (Mathworks) to suppress noise without suppressing transient elements of the signal. Similar to strategies of data reduction employed previously, the filtered data was down-sampled to a set of 100 points for fitting, 50 points linearly distributed over the first 100 ms of the experiment and another 50 logarithmically distributed over the remaining 19.9 s [12,15,16]. This weighting scheme was intended to emphasize the initial, highly dynamic period of the load history since our goal was to determine properties appropriate for use in computational models of TBI.

The maximum speed of the indenter was approximately 1 mm/s, which is 3 orders of magnitude slower than the speed of distortional waves in brain tissue so inertial effects were neglected and a quasi-static analysis was applied. Indentation with a flat cylindrical punch creates a heterogeneous strain field that asymptotes towards infinity at the edge of the cylinder so it is impossible to motivate a small strain analysis by considering the peak strain in the material. In practice, the peak strain does not approach infinity because the edge of the cylindrical indenter is not perfectly 90°, but has a finite radius. Parametric finite element modeling predicted that a fillet radius equal to 1% of the indenter radius is sufficient to eliminate infinite strains at the corner of the contact but the associated deviation of the indentation load from that associated with a perfect cylinder is negligible [10]. Moreover, as we have shown previously, numerical analysis of the strain field under an indenter indicates that the median strain in the material is an order of magnitude less than the peak strain [10]. Therefore, choosing analytical assumptions based on peak strain is excessively conservative. Instead, the effective strain under the indenter was calculated using Eq. (1) [11]:

$$\varepsilon = \frac{2\delta}{\pi R} \tag{1}$$

where ε is the effective strain, δ is the indentation depth and R is the indenter radius. This equation predicts an effective strain of 10% for our chosen indentation depth and indenter radius, justifying a small strain analysis.

The load associated with the recorded displacement history for a given set of constitutive properties was predicted using the solution provided by Hayes for indentation of an elastic layer of finite thickness with a cylindrical punch [17], which is given by Eq. (2)

$$P = \frac{4\kappa G R \delta}{(1-\nu)} \tag{2}$$

where P is load, κ is the correction factor for finite thickness effects, G is the shear modulus, R is the indenter radius, δ is the indentation depth and ν is the Poisson's ratio. This expression assumes purely elastic behavior. Since brain tissue is highly viscoelastic, load, indentation depth and stiffness were expressed as functions of time, and Eq. (2) was reformulated as a hereditary integral relating these functions.

$$P(t) = \frac{4R\kappa}{1-\nu}\int_0^t G(t-\tau)\left(\frac{d\delta}{d\tau}\right)d\tau \tag{4}$$

The relaxation function G(t) was expressed as follows:

$$G(t) = G_\infty + \sum_i G_i e^{-\frac{t}{\tau_i}} \tag{5}$$

The number of optimal terms was determined statistically with the F-statistic [18,19]:

$$F = \frac{(SSE_R - SSE_F)/(K_F - K_R)}{SSE_F/(N - K_F - 1)} \tag{6}$$

where SSE_F is the sum of the squared error of the larger Prony fit (full model), SSE_R is the sum of squared error of the smaller Prony fit with one fewer term (reduced model), k_F is the number of parameters in the full model, k_R is the number of parameters in the reduced model, and N is the number of data points analyzed for each fit.

The hereditary integral was implemented in Matlab as a convolution of the experimentally-measured velocity history and an estimate of the relaxation function. The resulting prediction of the load history was optimized to match the experimentally measured load history by varying the estimates of the relaxation coefficients using lsqcurvefit in Matlab (Mathworks). The resulting relaxation function coefficients were used to calculate the shear modulus at 10 ms, 50 ms and 20 s (G_{10ms}, G_{50ms}, and G_{20s}, respectively). The first two time points are relevant to the simulation of impact TBI, and the last is the best estimate of the quasi-static properties of the tissue available from our data set.

2.4. Statistics

The statistical significance of observed differences was determined by analysis of variance (ANOVA) followed by Bonferroni-corrected *post hoc* testing with the threshold for significance set at $p < 0.05$.

Table 1
Gender and age of sample donors.

Sample Number	Gender	Age	Region[a]
1	Male	4	C, H
2	Male	31	C
3	Male	43	C
4	Female	7	C, H
5	Male	50	H
6	Female	27	C
7	Male	12	H
8	Female	19	C
9	Unknown	Unknown	C
10	Male	58	C, H
11	Female	35	H

[a] C cortex, H hippocampus.

3. Results

Tissue from 11 donors was tested. The gender and age of the donors are given in Table 1. All samples were visually inspected for evidence of permanent deformation after indentation and none was observed.

Within the hippocampus, the subregion (CA1, CA3, DG) did not significantly affect the time dependent moduli ($p > 0.05$, data not shown), allowing for the regional data in the hippocampus to be combined for subsequent analysis. The time dependent moduli, G_{10ms}, G_{50ms}, and G_{20s}, for the white and grey matter of the cortex and the hippocampus are presented in Fig. 1. As determined by a two-way ANOVA, both region and time point significantly affected the modulus ($p < 0.05$). Cortical grey matter was significantly more compliant than the other structures as determined by Bonferroni *post hoc* tests ($p < 0.05$). The time dependent modulus for all regions declined in a statistically significant manner at later times as determined by repeated measures ANOVA ($p < 0.05$.), indicating the viscoelastic nature of brain tissue.

To render the data useful for computational modeling, all the force displacement curves within each region were averaged and used to fit a relaxation function for that region (Fig. 2). A Prony series with two terms optimally fit the data for cortical white matter whereas a series with three terms optimally fit the cortical grey matter and hippocampus data. The parameters and their 95% confidence intervals are presented in Table 2.

With a sufficient sample number, the dependence of mechanical properties on available patient information was further explored for the cortical data. There was no significant correlation between age and modulus for either cortical white or grey matter at any of the time points considered ($p > 0.2$, linear regression, Fig. 3).

There was a significant effect of gender and time point on the time-dependent shear modulus of both cortical grey and white matter (two-way ANOVA, $p < 0.05$, Fig. 4 (a) and (b)). There was a significant interaction between these effects in the cortical grey matter but not in the cortical white matter. The gender-dependence was greater for cortical white matter, whereas for the cortical grey matter, the effect was confined to short time points only. The force displacement curves were averaged and used to fit a relaxation function for each gender within each region (Fig. 4 (c) and (d)). A two term Prony series was used to fit male and female cortex grey matter while a three term Prony series was used to fit male and female cortex white matter. The parameters and their 95% confidence intervals are displayed in Table 3.

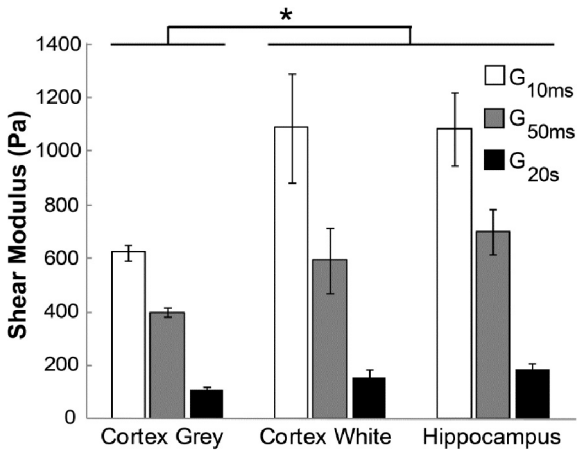

Fig. 1. Time-dependent moduli for human cortex and hippocampus under indentation loading (error bars = 1 standard error, n = 6–8, *$p < 0.05$).

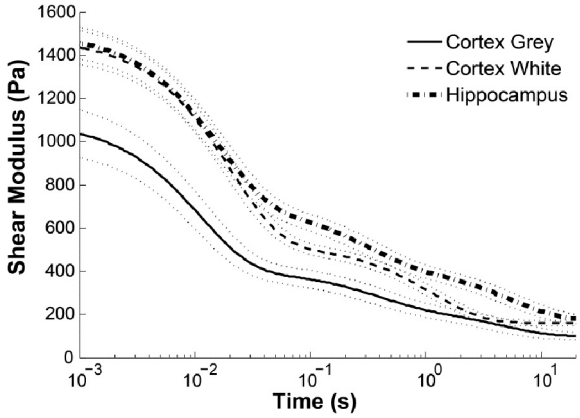

Fig. 2. Relaxation functions for human cortex and hippocampus (dotted lines represent 95% confidence intervals).

4. Discussion

The goal of this study was to generate local mechanical properties of individual anatomical structures within freshly resected, human brain tissue. Microindentation was used to generate highly localized measurements of the stress strain response within human cortical grey and white matter and hippocampus. We found both structures were highly viscoelastic, in agreement with previous studies [20–24]. We found that cortical white matter was stiffer than cortical grey matter. This agrees with recent reports that human corona radiata is stiffer than grey matter [9]. Note that white matter properties appear to vary throughout the brain so that the properties of the corona radiata should not be assumed to match the properties of, for example, the corpus callosum [25]. Our data are the first directly measured mechanical properties for human hippocampus.

The primary intended application of this research is for mathematical modeling of head impacts. The results are presented as average, regional, viscoelastic properties for cortical white and grey matter and hippocampus in Table 2 to facilitate this application. The fitting function was weighted to emphasize the first 100 ms of the test (see Section 2), which is the time period most relevant to head injury events. We chose to model the relaxation as a Prony series with the number of terms determined statistically. One of the most challenging aspects of TBI biomechanics is modeling large strains that can arise during head impact. These experiments were designed to obtain data with strains of around 0.1 and strains rates in the 0.005–5 s^{-1} range (see Section 2). These strains are small enough to be modeled with the applied small strain analysis given the scale of the observed differences. The rates are lower than those thought to arise during severe impact TBI but they are larger than those applied in some other studies of brain material properties [26]. Caution is recommended when applying our data in simulations that exceed the strains and strain rates of our experiments. For example, the data reported herein may be more relevant to mild closed head TBI than to severe or penetrating TBI. Our methods could be extended to larger strains by using a deeper experimental indentation and replacing the current closed form mathematical analysis, which relies on the assumption of small strain, with an inverse finite element analysis, which does not rely on this assumption. However, creating and validating a computationally efficient inverse finite element modeling scheme for indentation events is a non-trivial challenge in the case of a cylindrical indenter. This challenge would be mitigated by the use of a spherical indenter. On a related note, these experiments were performed at room temperature, and principles of time temperature superposition could be used to adjust the properties to body temperature [27].

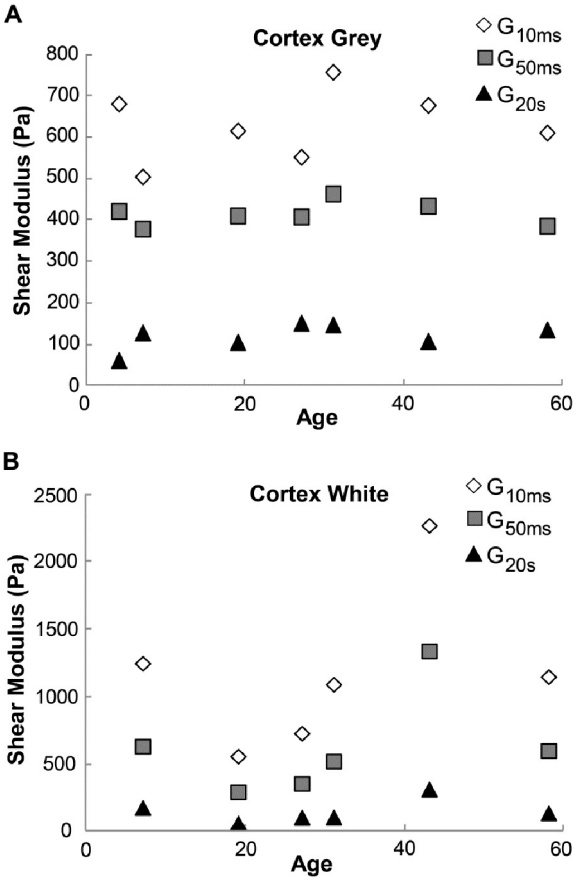

Fig. 3. Variation of shear modulus, G, as a function of age at each of the time points considered for (A) cortical grey matter and (B) cortical white matter. Note the different scales between (A) and (B).

Demographic information for the tissue donors was used to study the effect of age and gender on the stiffness of the cortex. One advantage of testing samples resected during surgery is that tissue donors are distributed in age across the range of normal human life span whereas post mortem subjects are typically elderly at the time of death. The ages of tissue donors ranged from 4 to 58 years in this sample (see Table 1), creating a valuable opportunity to test for evolution of mechanical properties with maturation. However, no correlation between age and stiffness was apparent in this study (see Fig. 3). This agrees with previous reports from humans [9] but not with previous reports regarding

Table 2
Relaxation function parameters for each region of the cortex with 95% confidence intervals.

Region	G_∞ (Pa)	G_1 (Pa)	τ_1 (s)	G_2 (Pa)	τ_2 (s)	G_3 (Pa)	τ_3 (s)
Cortex Grey	98.46 ± 16.4	138.6 ± 27.8	4.46 ± 2.24	168.8 ± 30.1	0.358 ± 0.14	689.4 ± 109	0.011 ± 0.0027
Cortex White	160.5 ± 12.8	363.8 ± 22.7	1.17 ± 0.19	957.9 ± 76.7	0.020 ± 0.003		
Hippocampus	172.4 ± 20.7	258.3 ± 22.0	5.53 ± 1.52	273.0 ± 28.8	0.302 ± 0.076	801.7 ± 63.7	0.0159 ± 0.0027

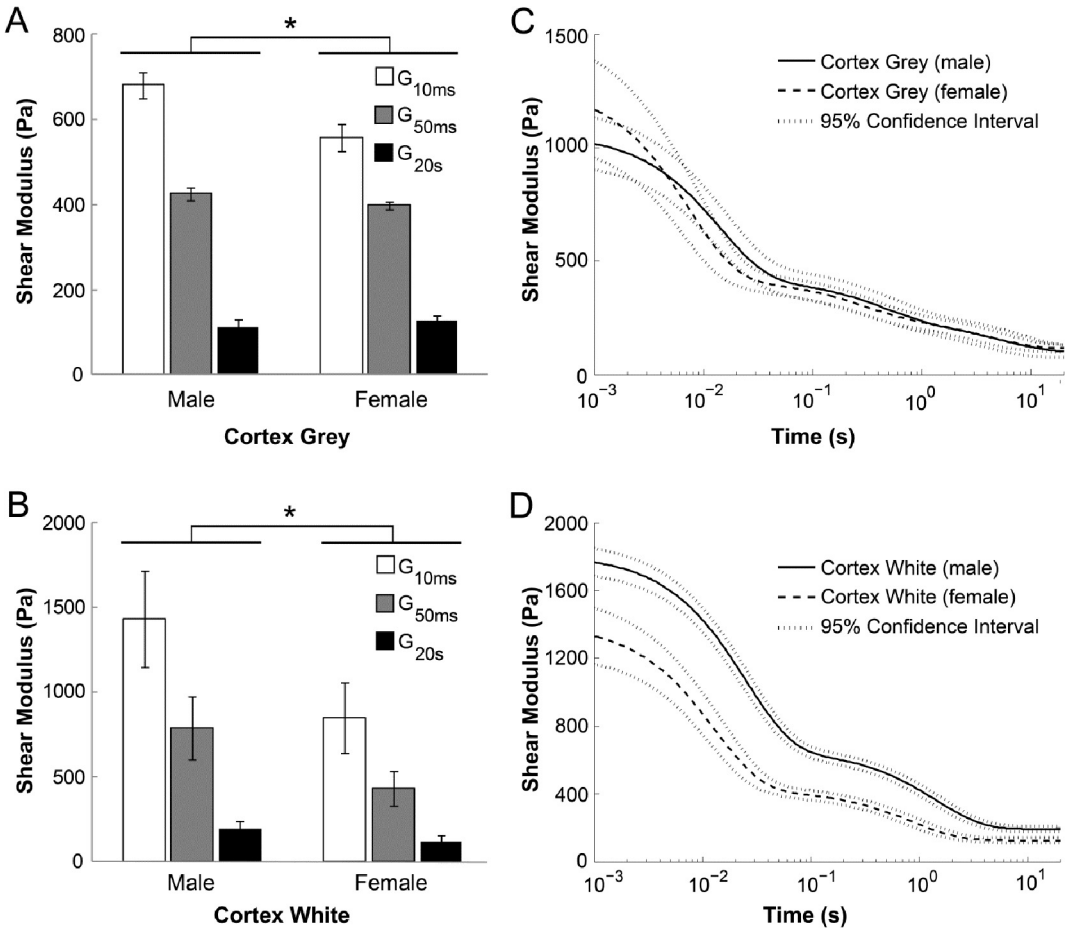

Fig. 4. The effect of time point and gender on shear modulus for (A) cortex grey matter and (B) cortex white matter (n = 4 for male, 3 for female, error bars = 1 standard error, $^{*}p < 0.05$). Relaxation functions based on gender for (C) cortex grey matter and (D) cortex white matter (dotted lines represent 95% confidence intervals). Note the different scales between (A) and (B) as well as between (C) and (D).

Table 3
Relaxation function parameters with 95% confidence intervals for each gender in the cortex grey and cortex white regions.

Region	Gender	G_∞ (Pa)	G_1 (Pa)	τ_1 (s)	G_2 (Pa)	τ_2 (s)	G_3 (Pa)	τ_3 (s)
Cortex Grey	Male	99.1 ± 26.7	144 ± 36.8	5.29 ± 3.82	640.0 ± 103	0.014 ± 0.0039	179 ± 41.6	0.425 ± 0.213
	Female	114.7 ± 16.3	142.4 ± 27.1	4.03 ± 1.94	160.2 ± 28.9	0.276 ± 0.119	861 ± 237	0.0074 ± 0.0026
Cortex White	Male	193.6 ± 17.0	464.1 ± 28.2	1.42 ± 0.23	1154 ± 77.1	0.025 ± 0.003		
	Female	126.4 ± 14.3	297.4 ± 26.2	0.875 ± 0.205	979.6 ± 173	0.013 ± 0.003		

the rat brain [12] or the pig brain [28]. Therefore, the human brain may be mechanically mature earlier in neurodevelopment than the rat and pig brain. On the other hand, gender did appear to affect the stiffness of the tissue. In our sample, male cortex was stiffer than female cortex. In the grey matter, the effect was modest and appeared to be confined to short time points. In the white matter, the effect was substantial and spanned all time points tested. These observations may be relevant to reports that female athletes experience more frequent [29] and severe [30] concussions than their male counterparts in sports played by both genders. In addition to the numerous physiological factors at play, it is possible that the female brain deforms more during impact because it is softer. However, it is important to note that these observations arise from a very small number of samples (4 males and 3 females) due to the difficulty of obtaining human tissue, and more exploration of this topic is warranted before firm conclusions are drawn. Unfortunately, there were not enough specimens for a similar analysis of the hippocampus due to the difficulty in obtaining living human brain and due to the sclerotic pathology of some hippocampal specimens as the result of the intractable epilepsy motivating the surgery.

This study is subject to several important limitations that should influence interpretation of these results. The tissue was tested *ex vivo*, which eliminates important phenomena that are captured when testing *in situ*, such as cerebral perfusion pressure, which may couple neurophysiology to mechanical stiffness [31]. However, our experimental design choice also has important advantages in that it offers access to structures that are enclosed *in situ*, such as cortical white matter and deeper structures like the hippocampus. In addition, most deformation in brain tissue is deviatoric not volumetric because the shear modulus is much lower than the bulk modulus. Therefore, any effect of hydrostatic pressure on the deformation field is likely to be modest. An indenter is a valid tool for measuring mechanical heterogeneity in material properties only if the length scale of the heterogeneity is significantly longer than the size of the indenter. Unfortunately,

in biological tissues, there is heterogeneity at every length scale. In the human brain, there is heterogeneity due to different anatomical regions at the centimeter length scale. There is heterogeneity due to fiber reorientation at the millimeter length scale. There is heterogeneity due to the distinction between cell bodies and neurites at the 100 μm length scale, and due to the distinction between nucleus and cytoplasm at the 10 μm length scale. Modern finite element models are just now achieving sufficient sophistication to represent different anatomical regions of the brain explicitly. The experiment was designed to rely on the same set of assumptions as these finite element models i.e. the 500 μm indenter diameter was selected to be small on the length scale of transitions between anatomical regions, but large relative to other scales of heterogeneity. The structures tested (white matter, grey matter, hippocampus) are several fold larger than the width of the indenter, justifying these assumptions.

While every effort was made to test tissue as quickly as possible after resection, there was an unavoidable delay of up to 6 h. A detailed study of the effect of post-mortem time on brain stiffness concluded that mechanical tests should be conducted within 6 h of resection to guarantee reproducible results [4]. Another important limitation arises from the fact that all these patients were undergoing brain surgery to treat severe epilepsy so the mechanical properties may have been affected by the pathology of the disease. This issue is inevitable with human tissue since brain tissue cannot be resected from healthy individuals for ethical reasons. However, both the neocortex specimens removed as part of the surgical approach to mesial temporal lobe epilepsy and the nonsclerotic hippocampi included within this study were normal on preoperative MR imaging and grossly normal intraoperatively. Our mathematical model employs small strain theory and is therefore not applicable to large deformations that might plausibly arise during severe head injuries. Future work will address this limitation by replacing the current analytical model with iterative finite element modeling.

In summary, measurement of local properties of human cortex and hippocampus using microindentation revealed that cortical white matter was stiffer than cortical grey matter with hippocampus being similar to cortical white matter. Also, male cortex was stiffer than female cortex in this sample but age did not significantly influence stiffness. These results demonstrate that microindentation of small tissue samples resected in the course of surgery is a practical method for obtaining local properties for anatomical structures within the brain. This approach has key advantages in comparison to harvesting larger samples from post-mortem subjects for conventional mechanical testing in homogeneous loading modes, including access to younger subjects than are typically available post-mortem and less tissue degradation before testing.

In conclusion, this data set provides mechanical properties to inform simulations of dynamic mechanical events in the human brain. Appropriate applications include simulation of mild TBI events and other events involving strains around 0.1 and strain rates of 0.005–5 s^{-1}. The data was acquired from rare samples that are difficult to obtain, specifically human tissue resected during surgery for the treatment of epilepsy. Although donors ranged in age from 4 to 58 years old, there was no evidence of a maturation effect on brain biomechanical properties in this data set. There was an effect of gender on brain biomechanics in this data set, but that finding should be interpreted as merely suggestive given the low number of samples tested.

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