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Medial temporal lobe viscoelasticity and relational memory performance

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Abstract

Structural and functional imaging studies have been among converging lines of evidence demonstrating the importance of the hippocampus in successful memory performance. The advent of a novel neuroimaging technique – magnetic resonance elastography (MRE) – now makes it possible for us to investigate the relationship between the microstructural integrity of hippocampal tissue and successful memory processing. Mechanical properties of brain tissue estimated with MRE provide a measure of the integrity of the underlying tissue microstructure and have proven to be sensitive measures of tissue health in neurodegeneration. However, until recently, MRE methods lacked sufficient resolution necessary to accurately examine specific neuroanatomical structures in the brain, and thus could not contribute to examination of specific structure-function relationships. In this study, we took advantage of recent developments in MRE spatial resolution and mechanical inversion techniques to measure the viscoelastic properties of the human hippocampus *in vivo*, and investigated how these properties reflect hippocampal function. Our data reveal a strong relationship between relative elastic/viscous behavior of the hippocampus and relational memory performance (N = 20). This is the first report linking the mechanical properties of brain tissue with functional performance.

Graphical abstract

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elastography; hippocampus; memory; viscoelasticity

Investigation of the structure-function relationship between hippocampus and memory has a long and rich history. Early work in patients with amnesia following hippocampal damage was pivotal in the initial development of our basic understanding of multiple memory systems and the role of the hippocampus in human declarative memory (Cohen and Eichenbaum, 1993; Cohen and Squire, 1980; Eichenbaum and Cohen, 2001; Scoville and Milner, 1957). The advent of structural magnetic resonance imaging (MRI) afforded researchers the opportunity to further define this relationship in both patient and neurologically healthy populations. The resulting data emphasize the critical association between the structural integrity of the hippocampus and declarative, or relational, memory performance in healthy older adults (Raz et al., 2005), patients with Alzheimer's disease (Dickerson et al., 2009) or multiple sclerosis (Sicotte et al., 2008), low-fit vs. high-fit children and adults (Chaddock et al., 2010; Erickson et al., 2011), and London taxi drivers (Maguire et al., 2000). Together these data provide evidence for the hippocampus' central role in relational memory; the binding of arbitrary relational information into a single mnemonic representation (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001).

Structural neuroimaging has largely focused on measures of hippocampal volume as a surrogate for atrophy and thus structural integrity. Measures of volume alone, however, do not reflect the nature of cytoarchitectural organization in the hippocampus. Tissue microstructure, including the integrity of axonal connections between hippocampal subfields (Hyman et al., 1986), both influences cognitive function and precedes overall volume change in disease states (Raz et al., 2014). Imaging techniques sensitive to the microscale characteristics of neural tissue are critically needed to better understand how the structural reorganization underlying volume change manifests functionally in memory performance. Such methods may prove invaluable in the development of an informed structure-function framework in healthy populations not subject to volume loss.

Diffusion tensor imaging (DTI) has proven effective for measuring tissue microstructure, particularly for white matter tracts. DTI measures the restricted diffusion of water in tissue reflecting axonal organization and integrity. While DTI has largely been used to assess white matter structural integrity, recent work has demonstrated its potential for microstructural assessment of predominantly gray-matter structures (Fellgiebel et al., 2004). Furthermore, DTI derived measures of hippocampal integrity proved more sensitive markers of amnesic mild cognitive impairment than volume (Müller et al., 2007). It has also been demonstrated that differences in DTI measures in the hippocampus are related to variability in verbal memory performance in older adults who do not yet show volumetric atrophy (van Norden et al., 2012). Still, it remains unclear if DTI measures have the sensitivity to adequately probe extra-axonal microstructure presumed to have a significant role in the functional health of gray matter structures. Thus, additional complementary techniques to identify the structural integrity of the underlying tissue are essential to get a more nuanced understanding of gray matter microstructural organization and its contribution to behavior.

Magnetic resonance elastography (MRE) (Muthupillai et al., 1995) has emerged as a powerful technique for probing neural tissue architecture through its mechanical properties (Sack et al., 2013). Specifically, MRE measures tissue viscoelasticity that reflects the underlying microstructural integrity of the neuronal-glial matrix (Riek et al., 2012; Schregel et al., 2012). The sensitivity of viscoelasticity to alterations in the cerebral microstructure has been demonstrated through studies of a number of neurodegenerative disease states in humans including Alzheimer's disease (Murphy et al., 2011), multiple sclerosis (Streitberger et al., 2012), amyotrophic lateral sclerosis (Romano et al., 2014), and Parkinson's disease (Lipp et al., 2013). These studies reported a common trend of decreasing viscoelasticity as disease progresses and neural tissue degrades, as described by viscoelastic shear stiffness and damping ratio, generally considered to reflect brain tissue composition and organization, respectively (Sack et al., 2013). The brain also softens during normal aging (Arani et al., 2015; Sack et al., 2011), a trend that appears to mirror functional decline across the lifespan (Light, 1991). These findings underscore the value of viscoelasticity measures in capturing the microstructural health of neural tissue that potentially defines cognitive status and behavioral performance.

To the best of our knowledge, however, researchers have not yet investigated the relationships between MRE structural measures and functional status as measured by task performance. One barrier in this pursuit has been the lack of sufficient spatial resolution to accurately probe sub-regions of the brain (Johnson et al., 2013b). However, recent advances in MRE methodology now make it possible to reliably measure the viscoelastic properties of unique neuroanatomical features, including white matter tracts (Johnson et al., 2013a; Romano et al., 2014) and subcortical gray matter structures (Guo et al., 2013; Johnson et al., 2015; Lipp et al., 2013). This advancement affords us the opportunity, for the first time, to investigate the relationship between hippocampal MRE measures and memory function. This is an optimal target for assessing the MRE structure-function relationship given the vast literature linking hippocampal function to relational memory success in both healthy and impaired populations (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001), as well as the existence of highly sensitive behavioral measures of relational memory processing (Monti et al., 2015).

We hypothesized that probing the integrity of hippocampal tissue structure through viscoelasticity measures could inform us about variation in hippocampal function in a healthy population. By pairing MRE, a sensitive and direct assessment of the health of the neural tissue, with sensitive behavioral measures of hippocampal function, specifically relational memory, we endeavored to advance our understanding of the structural role of hippocampus in human relational memory. In this study, we demonstrate that hippocampal viscoelastic properties are, in fact, tightly coupled with relational memory performance in healthy young adults. We chose to study a largely homogeneous population not expected to exhibit significant differences hippocampal volume so as to best investigate the sensitivity of MRE measures and their independent contribution to characterizing the structure-function relationship in the hippocampus.

2. Materials and Methods

Twenty healthy young adults between the ages of 18 and 33 participated in the study. Participants were all cognitively normal, right-handed, and male, with 12 to 23 years of education. Each provided informed, written consent approved by our Institutional Review Board. All volunteers underwent a single MRI scanning session using a Siemens 3T whole-body MRI scanner with a 32-channel head receive coil (Siemens Medical Solutions; Erlangen, Germany). The imaging protocol included high-resolution T_1 -weighted, MRE, and DTI image series. Following imaging, each volunteer participated in a performance testing session. Only males were included in this study because of known differences in the mechanical properties of the brain between men and women (Arani et al., 2015; Sack et al., 2009). In this first investigation of the structure-function relationship, we sought to reduce general noise by including only male participants.

2.1 Volumetric Analysis

We acquired the T_1 -weighted images using an MPRAGE sequence (magnetization-prepared rapid gradient echo; $0.9 \times 0.9 \times 0.9$ mm³ voxel size; 1900/900/2.32 ms repetition/inversion/echo times) for extraction of subcortical volumes using FreeSurfer v. 5.3 (Fischl et al., 2002). Automatic segmentation of the hippocampus, parahippocampus, and entorhinal cortex as well as automated measures of intracranial volume (ICV) were calculated (see (Buckner et al., 2004) for detailed method). ICV was used to normalize each region of interest for head size (Erickson et al., 2009; Raz et al., 2005).

2.2 MRE of the Hippocampus

Figure 1.A provides an overview of the hippocampal elastography procedure and output from imaged shear wave displacement to viscoelastic properties (Johnson et al., 2015). The MRE acquisition employed a 3D multislabs, multishot spiral sequence for capturing high-resolution displacement data to reduce partial volume effects and improve quantitative mechanical property estimation (Johnson et al., 2014). Imaging parameters included: 1800/75 ms repetition/echo times; 240 mm square field-of-view; 150×150 imaging matrix; and sixty 1.6 mm thick slices acquired in ten overlapping slabs. Sampling within a slab used a stack-of-spirals, with two in-plane constant-density spiral readouts (Glover, 1999) and $R=2$ SENSE parallel imaging factor (Pruessmann et al., 2001). The resulting image volume had a

$1.6 \times 1.6 \times 1.6 \text{ mm}^3$ isotropic voxel size with 96 mm of coverage in the slab direction, which was aligned approximately AC-PC and included the medial temporal lobe (MTL).

A pneumatic actuator (Resoundant; Rochester, MN) vibrated the brain at 50 Hz through a soft pad placed below the head. The resulting tissue deformation was encoded using motion-sensitive gradients embedded in the MRE sequence, which was repeated to capture motion along three separate axes and with opposite gradient polarities. We sampled the displacement fields at four points across one period of vibration, and the total acquisition time was 12 minutes.

Nonlinear inversion (NLI) estimated tissue viscoelasticity from MRE displacement data (McGarry et al., 2012). To improve property estimates in subcortical regions, soft prior regularization (McGarry et al., 2013) promoted homogeneity in properties within the volume masks of the hippocampus, parahippocampus, and entorhinal cortex. These masks were applied in native space by registration of the T_2 -weighted images to the MRE magnitude using FLIRT in FSL v. 5.0.7 (Jenkinson et al., 2002; 2012). NLI estimates the complex shear modulus, $G = G' + iG''$, from which we determined the shear stiffness, μ , and damping ratio, ξ . Shear stiffness determines the wavelength in a viscoelastic solid (Manduca et al., 2001) and is defined as $\mu = 2|G|^2/(G' + |G|)$. This property is commonly reported in many recent brain MRE studies (Arani et al., 2015; Huston et al., 2015; Murphy et al., 2015). Damping ratio is a dimensionless quantity describing the relative attenuation level in the material (Cook, 2007), defined as $\xi = G''/2G'$, and is similar to the viscoelastic phase angle often calculated in brain MRE (Guo et al., 2013; Lipp et al., 2013). $\xi = 1$ is known as critical damping, where transient displacements will decay without oscillation. Here we report adjusted damping ratio, $\xi' = 1 - \xi$, to describe the relative elastic and viscous contributions to material behavior. Higher ξ' values indicate a more elastic solid, while lower ξ' values indicate a more viscous solid. As such, higher ξ' measures are indicative of greater tissue integrity.

2.3 DTI Acquisition and Analysis

DTI data was acquired using a similar 3D multislab, multishot sequence (Holtrop et al., 2012) using an identical 1.6 mm isotropic resolution and imaging volume as the MRE data. Other DTI imaging parameters included: 30 non-colinear directions, $b = 1000 \text{ s/mm}^2$; TR/TE = 1875/82 ms. Following image reconstruction, voxel-wise diffusion tensors were fit using FMRIB Diffusion Toolbox (FDT) in FSL (Behrens et al., 2003; Jenkinson et al., 2012). Diffusion metrics mean diffusivity (MD) and fractional anisotropy (FA) were extracted from the fitted diffusion tensors. Hippocampal masks for DTI data were generated in the same fashion as for the MRE data, and hippocampal FA and MD were calculated as the mean of these values across the mask.

2.4 Performance Testing

Participants also completed a battery of behavioral tasks designed to measure relational memory (Spatial Reconstruction task), declarative memory (delayed word recall and logical memory tasks from the Weschler Memory Scale), and executive function (Stroop).

Relational memory was measured using a computerized Spatial Reconstruction task (Monti et al., 2015; Watson et al., 2013), which is illustrated in Figure 1.B. On each trial, participants studied the locations of five novel line drawings for 20s. After a 4s blank delay period, the line drawings appeared again aligned at the top of the screen. Participants used the mouse to drag each stimulus back to its studied location. Reconstruction time was self-paced and there were a total of 20 trials. Four separate dependent measures were calculated. Distance measures included misplacement errors (the distance (in pixels) between each item's studied location and where that item was placed in the reconstruction; summed for all five items) and edge resizing errors (the length of the vector (in pixels) between each pair of items in the reconstruction compared to the original studied configurations; summed across all relationships on each trial). Arrangement measures included rearrangement errors (the change in overall configuration of the stimuli defined by a sign change in either the x- or y-dimension at any vertex) and swap errors (calculation of the mis-assignment of particular items to particular locations such that the correct locations were identified, but the wrong items were placed in those locations; the number of swaps per pairwise relation was calculated for each trial.). The computation of these individual measures are described in detail elsewhere (Watson et al., 2013). These measures were then combined into composite measures of displacement performance, SRd (the average of standardized misplacement and edge resizing errors), and relative alignment performance, SRa (the average of standardized rearrangement and swap errors). SRd and SRa measures were then converted such that higher numbers indicate better performance on the spatial reconstruction task.

Neuropsychological tests included the Word List and Logical Memory tasks from the Wechsler Memory Scale (Wechsler and Stone, 1973). The Word List task included the first five learning trials (free recall after each) followed by a delayed free recall approximately 20 minutes later. Total number of recalled words following the delay served as the dependent measure. For the Logical Memory task, Story A was read followed by Story B twice (free recall after each). After an approximately 30 minute delay, participants recalled as much of Story A and then Story B as they could remember, and the total number of story units remembered after the delay served as the dependent measure. All performance measures were then standardized (*z*-scores) and then averaged into a single delayed-memory composite measure.

Executive function (EF) was assessed using the Stroop task (Stroop, 1935). The color-word Stroop task included 120 trials (50% congruency, three colors: red, blue, and green). Stimuli were presented centrally and sequentially on a computer monitor and all stimuli remained on the screen until a response was made. Reaction times were measured separately for congruent and incongruent trials and difference scores were calculated for each participant and served as the dependent measure.

2.5 Statistical Analyses

Pearson partial correlation coefficients, *r*, with age and education as control variables were calculated to investigate how each structural measure correlated with the different functional measures included in this study. Significance of correlations was determined at $p < 0.05$ and indicated throughout the text and figures with a *. Correction for multiple comparisons was

performed using the Bonferroni method for each family of q comparisons: measures of hippocampal structure compared with SR task performance ($q = 6$) and MRE measures of the MTL compared with SR task performance ($q = 6$).

3. Results and Discussion

The ability to probe the viscoelasticity of the human hippocampus *in vivo* was dependent on the development of an MRE method capable of generating reliable property measures in subcortical gray matter structures (Johnson et al., 2015). This method was designed to reduce the influence of nearby tissue and cerebrospinal fluid (CSF) by coupling high-resolution MRE imaging (Johnson et al., 2014) with an inversion procedure designed to promote material homogeneity within the pre-defined hippocampal volume mask (McGarry et al., 2013; 2012). This inversion scheme serves a similar purpose as the approach described by Murphy et al. for estimating the mechanical properties of individual lobes of the brain in the presence of atrophy and thus larger CSF boundaries (Murphy et al., 2013). It should be noted that the final, effective resolution of the resultant viscoelastic property maps is somewhat diminished from the acquired imaging resolution. This is due to regularization necessary to stabilize solution of the ill-posed mechanical inverse problem. Based on previous work using the same inversion, we estimated through line-width and edge transfer functions that the final effective resolution is approximately half that of the imaging resolution (McGarry, 2013). This further highlights the importance of both using the highest possible MRE imaging resolution and adopting an inversion strategy to best isolate the region of interest.

In a previous work, we took repeated measurements using this technique to estimate the uncertainty of the hippocampal MRE measurements, and found the coefficient of variation (CV) of hippocampal damping ratio, ξ , to be 5.1% (Johnson et al., 2015), which is well below the population variation of 15.8% found in this work. Further, we demonstrated that variations in the hippocampal masks used in this procedure contributed negligibly to the measurement variance. From these findings we conclude that the MRE measurements reported here are reliable and free from undue influence of mask creation and how they were incorporated in the inversion. In particular, the use of FreeSurfer for segmentation may result in small volume differences as opposed to manual tracing (Morey et al., 2009), though we do not expect this to affect our MRE measures.

3.1 Structural Relationships with SR Task Performance

Figure 2 illustrates the correlations between hippocampal ξ' and SR task performance, where ξ' correlated significantly with both SRd ($r = 0.72$, $p = 0.001^*$) and SRa ($r = 0.64$, $p = 0.004^*$) such that the relative elastic behavior of the hippocampus is associated with greater relational memory performance. In our sample, the relationships between volume and SRd ($r = 0.31$, $p = 0.215$) and SRa ($r = 0.40$, $p = 0.104$) were non-significant, as were the relationships with hippocampal stiffness, μ (SRd: $r = 0.26$, $p = 0.303$; SRa: $r = 0.37$, $p = 0.135$). Figure 3 presents volume and stiffness data for the population and the relationships with the SR task. In addition to being not significant in our sample, the functional relationships with volume and μ exhibited effect sizes much smaller than with ξ' .

These results indicate that ξ' is a highly sensitive predictor of hippocampal function, as measured by the SR task, while the volumetric measure was not. A previous study found that SR performance, and particularly SRa performance, significantly correlated with volume (Monti et al., 2015). However, that work incorporated subjects across a broad age range expected to have substantial variations in volume, whereas in the current population, with a much narrower age range (18–33 yo), we found a very small distribution of bilateral hippocampal volumes ($9.27 \text{ cm}^3 \pm 7.7\%$). In contrast with the volumetric findings, we found that the distribution in the original, non-adjusted ξ was nearly twice as wide ($0.17 \pm 15.8\%$). Table 1 describes the variation in each measure across our population. In our sample, ξ , and thus ξ' , is more variable than traditional volume measures and seem to provide additional opportunity for detecting structural differences in the hippocampus, and their relationships to function, in the absence of the gross volume changes that can stem from neurodegenerative processes.

Previous work has emphasized the relationship between hippocampal volume and cognitive decline in aging (Raz et al., 2005) and various disease states (Dickerson et al., 2009; Sicotte et al., 2008). The relationship between hippocampal atrophy and declining memory performance is thus well established. Volume, however, is a fairly gross measure of tissue degradation and the precise nature and mechanisms of hippocampal atrophy are not well understood (Raz et al., 2014). We expect that the increased sensitivity of ξ' and its relation to functional performance is due to the microstructural basis of the measure; and that is why, in our sample, it outperforms hippocampal volume in relating to performance on relational memory test performance.

ξ' illustrates the contribution of elastic and viscous effects to the tissue behavior, or how much the kinematic response to a shear loading is like that of an elastic solid (higher ξ') as opposed to a viscous fluid (lower ξ'). Given the unique structure of the hippocampus, we believe that the ξ' measure is a reflection of the organization and integrity of axonal pathways that connect the hippocampal subfields and the hippocampal formation, which are critical for memory function (Hyman et al., 1986; Yassa et al., 2011). These pathways may mechanically couple the layers of the hippocampus, effectively reducing the sliding and frictional losses between layers, and thus lead to a greater ξ' . In this case, lower ξ' would reflect fewer connections or reduced axonal integrity that would allow the hippocampal layers to move independently, ultimately increasing motion attenuation due to energy dissipation.

One interesting finding here is that, unlike hippocampal viscosity, hippocampal stiffness did not significantly correlate with any of the relational memory performance measures. Like viscosity, stiffness is often considered a measure of structural integrity in brain tissue (Sack et al., 2013), though it could reflect composition as well as microstructural organization. In fact, there is strong evidence to suggest that stiffness is more dependent on composition, such as the infiltration of immune cells (Riek et al., 2012) or number of neurons (Freimann et al., 2013; Klein et al., 2014), while viscosity is most sensitive to the organization of these components (Johnson et al., 2013a; Sack et al., 2013; Schregel et al., 2012). Previous studies have shown that neurons and glia of the hippocampus exhibit different stiffness values (Lu et al., 2006), as do the various subfields of the hippocampus (Elkin et al., 2007); thus,

differences in composition on both the micro- and meso-scale may be driving hippocampal stiffness in our population, but do not have a significant bearing on relational memory performance measures. Despite the absence of significant effects of stiffness here, it is unlikely that hippocampal stiffness has no relationship with function in all populations, and future studies may find that aging and neurodegenerative effects are differentially manifested in stiffness and viscosity, and correlate with similarly different forms of functional decline.

3.2 Relationships with Other Functional Measures

We also explored the relationship between hippocampal ξ' and the delayed-memory composite measure. Successful performance on these tasks also depends on relational memory processes, as they involve binding words or story details to the temporal-spatial context. Recent work has shown that these tasks share considerable variance with the SR task in a principal components analysis (PCA) of performance and regional volumetrics from a population of older adults (Monti et al., 2015), making these tests an appropriate comparator with the SR task here. However, despite the ξ' measure being strongly correlated with relational memory performance on the SR task, the ξ' measure was not correlated with delayed-memory performance ($r = 0.14$, $p = 0.592$; Figure 4). This result was obtained even though delayed-memory task performance correlated significantly with SR task performance in the current sample (SRd: $r = 0.59$, $p = 0.010^*$; SRa: $r = 0.58$, $p = 0.012^*$). We note that in our recent study comparing hippocampal volume in older adults to multiple measures of memory performance (Monti et al., 2015), correlations of hippocampal volume were weaker with delayed recall performance than with SR task performance, suggesting that perhaps these standard neuropsychological tests may be less sensitive to differences in hippocampal integrity than the SR task performance measures used here. Moreover, performance on both delayed-memory tasks exhibited less variation (words: 24.2% and stories: 23.2%) than did the SR (SRd and SRa) performance measures here (28.2% and 46.5%), consistent with the idea that the SR task is more sensitive to functional differences within a normal, homogeneous population than are the more standard neuropsychological measures used here.

These results indicate that the relative elastic/viscous behavior of the hippocampus is a sensitive measure specific to behavioral tasks known to strongly depend on the hippocampus. We would also expect that hippocampal MRE measures do not correlate with behavioral tasks that depend on extra-hippocampal structures. To test this, we compared our measures with EF performance, which is believed to depend on frontal structures (Botvinick et al., 2001) and not the hippocampus. As anticipated, the hippocampal ξ' measure did not correlate significantly with EF performance ($r = 0.02$, $p = 0.933$; Figure 4).

3.3 DTI of the Hippocampus

The power of MRE lies in the nature of how mechanical properties relate to the tissue microstructure. Viscoelasticity measures describe how tissue behaves as an integrated structure, and thus are directly related not only to microscale composition but also to the cellular and extracellular interactions driven by tissue organization. Intuitively, MRE measures should reflect function that depends on system-level integration of connected networks. In that sense, MRE may have an advantage over other microstructural imaging

techniques, including DTI, which are sensitive to axonal microstructure within each voxel only. Indeed, in our sample, DTI metrics of the hippocampus were not significantly correlated with SR task performance: MD (SRd: $r = 0.23$, $p = 0.356$; SRa: $r = 0.13$, $p = 0.620$) and FA (SRd: $r = -0.29$, $p = 0.247$; SRa: $r = -0.35$, $p = 0.152$).

Here, we present DTI metrics averaged across the entire hippocampal volume. This approach has found success in characterizing mild cognitive impairment (Müller et al., 2007; 2005) and temporal lobe epilepsy (Salmenpera et al., 2006). And while previous research revealed a relationship between hippocampal MD and verbal memory performance (van Norden et al., 2012), these measures may lack the sensitivity to reflect relational memory performance in our largely homogeneous cohort. DTI can also probe the white matter pathways in the hippocampus, and have revealed a loss of integrity with age (Yassa et al., 2011; 2010), but this requires acquisitions with ultra-high spatial resolution (Augustinack et al., 2010; Yassa et al., 2010) that are challenging for *in vivo* human imaging. Additional work is needed to directly assess the independent contributions of MRE and DTI to understanding the organization of hippocampal tissue, along with other factors, such as hippocampal blood flow assessed with arterial spin labeling techniques that has also shown a relationship with memory performance (Heo et al., 2010).

3.4 MRE of Other MTL Regions

We also explored whether the structure-function relationships reported in this study are unique to the hippocampus within the MTL. We tested MRE properties from entorhinal cortex and the parahippocampus, calculated using the same procedure as for the hippocampus described above. Both the parahippocampal gyrus and the entorhinal cortex are gray matter regions of the MTL that provide input to the hippocampus and have been shown to play a role in memory performance as part of the hippocampal memory system (Eichenbaum and Cohen, 2001; Eichenbaum et al., 1994). It has been suggested that the parahippocampus holds specific representations in a “buffer” for a short period (i.e., minutes) and the hippocampus extracts critical relations among items held in the buffer (Eichenbaum et al., 1994; Eichenbaum and Cohen, 2001). The entorhinal cortex serves as an interface between the hippocampus and the neocortex (Morrissey and Takehara-Nishiuchi, 2014) and disambiguates overlapping representations isolating distinct representations (Lipton and Eichenbaum, 2008). Therefore, compared to the hippocampus, neither the parahippocampus nor entorhinal cortex were expected to play a prominent role in binding arbitrary relations as in the SR task. Consistent with these expectations, we found that ξ' of both the entorhinal cortex did not correlate significantly with either of the two SR performance measures after Bonferroni correction (SRd: $r = 0.28$, $p = 0.270$; SRa: $r = 0.29$, $p = 0.243$) and the parahippocampus (SRd: $r = 0.52$, $p = 0.029$; SRa: $r = 0.41$, $p = 0.091$), and that the correlation effect sizes were smaller than those of the hippocampus ξ' with SRd and SRa.

While we did not find significant relationships between MRE measure of the parahippocampus and entorhinal cortex and the SR task, reliably localizing MRE measures to these structures is more challenging. We performed the repeatability analysis previously described for the hippocampus and found much poorer performance for ξ of the entorhinal

cortex (12.7% CV) and parahippocampus (21.7% CV). This is likely due in part to each structure being approximately 15% the size of the hippocampus, further highlighting the critical importance of spatial resolution in MRE for characterizing small structures in the brain. However, we do not believe the relative size of the hippocampus compared to either the parahippocampus or entorhinal cortex is responsible for its significant relationship with performance on the SR task alone; but rather the hippocampus' pivotal role in the rapid and obligatory binding of arbitrary item-location pairs (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001). Critically, we would also like to highlight that we are currently capable of reliably measuring the viscoelasticity of the hippocampus (Johnson et al., 2015) and in this work have demonstrated its relationship with memory function. We believe that these findings may serve as a basis for future investigations into the structure-function relationship of specific structures through MRE.

Finally, we also compared SR performance with a non-specific measure of whole-brain ξ' . Whole-brain measures have, until recently, been the standard method for reporting brain MRE measures (Murphy et al., 2011; Sack et al., 2011; Streitberger et al., 2012), and such a comparison provides context regarding the spatial localization of the hippocampal MRE measures reported in this study. We did not find any significant correlations with whole-brain measures, as expected (SRd: $r = 0.39$, $p = 0.105$ SRa: $r = 0.33$, $p = 0.183$; Figure 5.B). Again, the whole-brain relationships exhibited smaller effect sizes than the hippocampal relationships.

4. Conclusions

In this study we investigated the structure-function relationship between hippocampal microstructural integrity, using MRE measures, and relational memory performance. Taking advantage of highly sensitive imaging and behavioral techniques made it possible to understand this relationship in a group of healthy young adult males. The resulting data demonstrate, for the first time, that measures of viscoelasticity in the hippocampus assessed with MRE are related to functional measures of relational memory performance. Specifically, the measure of relative elastic/viscous behavior, ξ' , showed a strongly significant relationship with performance on measures of relational memory (SRd and SRa) in healthy young adults, such that a more elastic hippocampal mechanical response (i.e., higher ξ') correlated with better performance and fewer errors on the spatial reconstruction (SR) task. ξ' did not significantly correlate with more traditional neuropsychological measures of declarative memory (i.e., delayed word and story recall). These data lend further support for the previously proposed idea that our SR measures are more sensitive to structural decline in the hippocampus compared to these delayed-memory measures (Monti et al., 2015). Finally, there was no relationship between ξ' on a standard measure of executive function (Stroop task) that typically engages frontal processes (Botvinick et al., 2001) rather than hippocampal processes. These data indicate that this sensitive measure of the structural integrity of the hippocampus relates strongly to sensitive measures of hippocampal function and provide novel information about how variability in hippocampal tissue relates to memory performance, even in healthy young adults.

While the specificity of these elastography findings requires further investigation, early evidence suggests that MRE and DTI, both sensitive measures of microstructural integrity, provide overlapping, but not identical, information regarding the microstructural integrity of the predominately gray-matter hippocampus as it relates to behavior. As such, DTI measures exhibited trends consistent with the MRE findings, though these trends did not reach significance in our current sample; furthermore the sensitivity of these measures was clearly less than those from MRE in this data set. Future work is also necessary to understand the specificity of hippocampal MRE to behavioral measures. We report that hippocampal MRE is more sensitive to SR task performance than either whole-brain MRE or MRE of other medial temporal lobe structures (i.e., parahippocampus and entorhinal cortex) that play a role in memory processing, but whose function is not specific to relational memory processing required of the SR task. Finally, these data demonstrate that the structure-function relationship of hippocampal viscoelasticity seems specific to relational memory (i.e., a key function of the hippocampus; (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001)) as hippocampal viscoelastic measures did not significantly correlate with behavioral measures of executive function.

Taken altogether, this study provides the first evidence that MRE measures can be directly related to behavioral performance and, more specifically, that relative elastic/viscous behavior of the hippocampus correlates with performance on sensitive measures of relational memory. This correlation exists even in a relatively homogenous sample of highly-educated, healthy young males, thereby suggesting that this method holds great promise for expanding our understanding of structure-function interactions as they relate to memory within and across populations in which the variance in structural and functional integrity are likely to be even higher than observed here. While further work is certainly necessary to explore the boundaries of hippocampal viscoelasticity and memory performance across the life span in various populations, the general significance of combining sensitive measures of microstructural organization of brain tissue with sensitive behavioral measures of cognitive performance is far reaching. Combining MRE and behavior may prove particularly useful in early diagnosis and treatment of memory-specific disorders such as mild cognitive impairment and Alzheimer's disease. Alternatively, this technique could provide information about variations in tissue health that are susceptible to specific trauma; this line of research would likely be particularly relevant to the study of chronic traumatic encephalopathy. The data presented here provide an initial, promising picture of the utility of MRE as a noninvasive measure of microstructural neural organization that is tightly coupled with behavior.

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Figure 1.

A) Overview of hippocampal elastography procedure. T_1 -weighted images are segmented to generate masks of hippocampal volume. These are combined with three-dimensional, full vector, complex displacement fields captured with high spatial resolution (1.6 mm isotropic voxels) in the MRE acquisition for mechanical property estimation with nonlinear inversion (NLI). The hippocampus masks are used to promote regional homogeneity during the estimation process through SPR, which further reduces partial volume effects. The procedure returns tissue viscoelastic properties: shear stiffness, μ , and damping ratio, ξ ,

which describes the relative tissue viscosity. Stiffness and damping ratio maps include outlines of the bilateral hippocampal region-of-interest where properties were reported. B) Illustration of spatial reconstruction task and its performance metrics. Participants are shown a random arrangement of five objects and, after a brief delay, are asked to reposition objects as they remember them. Performance is characterized by displacement (SRd) and relative arrangement (SRa) of objects.

Figure 2.

A) Adjusted hippocampal damping ratio (ξ') measures plotted against standardized spatial reconstruction task performance measures (SRd and SRa). Positive values indicate better performance on the spatial reconstruction task. Pearson correlation coefficients, r , demonstrate significant correlations only for ξ' with both SRd and SRa ($p < 0.005$). We found a positive relationship between ξ' and behavioral measures, suggesting that the more the hippocampus behaves like an elastic solid, the better an individual's memory performance. B) Average damping ratio in the hippocampus across the entire population in standard space.

Figure 3.

Measures of hippocampal structure (volume, stiffness, mean diffusivity, and fractional anisotropy) plotted against behavioral spatial reconstruction task measures (SRd and SRa). Pearson correlation coefficients, r , reveal that none of these measures significantly correlate with SR behavioral measures suggesting that more sensitive structural measures are required to understand the structure-function relationship between hippocampal integrity and relational memory performance in this population.

Figure 4.

Measures of hippocampal ξ' plotted against traditional neuropsychological measures of hippocampal memory (i.e., delayed-memory measures) and executive function. These correlations are not significant, despite NP tests of declarative memory being dependent on hippocampal function. These data hint at the importance of combining sensitive structural measures with sensitive behavioral measures to understand the complexity of the hippocampus' relationship with memory.

Figure 5.

Normalized adjusted damping ratio, ξ' , measured in the entorhinal and parahippocampal cortices (both subcortical gray matter structures in the medial temporal lobes), as well as across the entire brain does not significantly correlate with SR task performance following multiple comparisons correction. For comparison, ξ' measured in the hippocampus are shown (as in Figure 2). These findings demonstrate the specificity of our hippocampal MRE measurements relative to similar structures and the unique information gained from localizing MRE measures to neuroanatomical regions of interest.

Table 1

Sensitivity of measures and correlation with age and education

	Population Mean (SD%)	Age Correlation, <i>r</i> (<i>p</i> -value)	Education Correlation, <i>r</i> (<i>p</i> -value)
Volume [cm ³]	9.27 (7.7%)	−0.45 (0.049)	−0.42 (0.063)
μ [kPa]	3.39 (10.5%)	0.20 (0.396)	0.22 (0.345)
ξ	0.17 (15.8%)	0.01 (0.955)	−0.17 (0.483)
<i>FA</i>	0.25 (3.6%)	0.19 (0.416)	−0.02 (0.931)
<i>MD</i>	0.92 (7.6%)	−0.07 (0.783)	−0.23 (0.332)
SRd	120.96 (28.2%)	0.19 (0.430)	−0.11 (0.632)
SRa	0.052 (46.5%)	0.15 (0.543)	−0.09 (0.711)
Word List	9.05 (24.2%)	0.08 (0.747)	0.42 (0.068)
Logical Memory	15.55 (23.2%)	−0.04 (0.881)	0.10 (0.684)
Stroop	74.5 (49.5%)	0.19 (0.424)	0.11 (0.654)

Measures are reported as the mean across the population and standard deviation as a percent of the mean. Volume, μ, ξ, *FA*, and *MD* measures are from the hippocampus. Pearson correlation coefficients, *r*, and associated *p*-values are reported relating each measure with age and education