Aerobic fitness, hippocampal viscoelasticity, and relational memory performance

Hillary Schwarb\textsuperscript{a,\ast}, Curtis L. Johnson\textsuperscript{b}, Ana M. Daugherty\textsuperscript{a}, Charles H. Hillman\textsuperscript{c}, Arthur F. Kramer\textsuperscript{a,c}, Neal J. Cohen\textsuperscript{a}, Aron K. Barbey\textsuperscript{a,d,e,f,g,h,\ast}

\textsuperscript{a}Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, 405 N. Mathews Ave, Urbana, IL 61081, USA

\textsuperscript{b}Department of Biomedical Engineering, University of Delaware, 150 Academy Street, 161 Colburn Lab, Newark, DE 19716, USA

\textsuperscript{c}Department of Psychology, Northeastern University, 125 Nightingale Hall, 360 Huntington Ave., Boston, MA 02115, USA

\textsuperscript{d}Department of Psychology, University of Illinois at Urbana-Champaign, 603 E. Daniel St, Champaign, IL 61820, USA

\textsuperscript{e}Neuroscience Program, University of Illinois at Urbana-Champaign, 405 N. Mathews Ave, Urbana, IL 61081, USA

\textsuperscript{f}Department of Internal Medicine, University of Illinois at Urbana-Champaign, 506 S. Mathews Ave, Urbana, IL 61801, USA

\textsuperscript{g}Department of Bioengineering, University of Illinois at Urbana-Champaign, 1304 W. Springfield Ave, Urbana, IL 61801, USA

\textsuperscript{h}Carle R. Woese Institute for Genomic Biology, University of Illinois at Urbana-Champaign, 1206 W. Gregory Dr, Urbana, IL 61801, USA

Abstract

The positive relationship between hippocampal structure, aerobic fitness, and memory performance is often observed among children and older adults; but evidence of this relationship among young adults, for whom the hippocampus is neither developing nor atrophying, is less consistent. Studies have typically relied on hippocampal volumetry (a gross proxy of tissue composition) to assess individual differences in hippocampal structure. While volume is not specific to microstructural tissue characteristics, microstructural differences in hippocampal integrity may exist even among healthy young adults when volumetric differences are not diagnostic of tissue health or cognitive function. Magnetic resonance elastography (MRE) is an emerging noninvasive imaging technique for measuring viscoelastic tissue properties and provides quantitative measures of tissue integrity. We have previously demonstrated that individual differences in hippocampal viscoelasticity are related to performance on a relational memory task; however, little is known about health correlates to this novel measure. In the current study,
we investigated the relationship between hippocampal viscoelasticity and cardiovascular health, and their mutual effect on relational memory in a group of healthy young adults (N=51). We replicated our previous finding that hippocampal viscoelasticity correlates with relational memory performance. We extend this work by demonstrating that better aerobic fitness, as measured by VO2max, was associated with hippocampal viscoelasticity that mediated the benefits of fitness on memory function. Hippocampal volume, however, did not account for individual differences in memory. Therefore, these data suggest that hippocampal viscoelasticity may provide a more sensitive measure to microstructural tissue organization and its consequences to cognition among healthy young adults.

Keywords
Elastography; Hippocampus; Memory; Aerobic fitness; Viscoelasticity

Introduction

The adverse health outcomes accompanying a sedentary lifestyle have recently garnered considerable attention both in popular culture and the scientific community. While the clinical health consequences of reduced aerobic capacity are well understood (e.g., increased risk of cardiovascular disease, stroke, cancer, etc.), the influence of decreased cardiovascular health on cognition is an emerging area of investigation that has received particular attention in studies of childhood development and aging (Hillman et al., 2008; Raz et al., 2006; Voss et al., 2016; Warsch and Wright, 2010). Indeed, frequent physical activity and higher levels of aerobic fitness have been linked to better performance on tasks of memory and executive control, (for reviews see Etnier et al., 2006; Hillman et al., 2008), and exercise interventions generally result in improved cognitive function (for reviews see Colcombe and Kramer, 2003; Kramer et al., 2003). The benefits of aerobic fitness on cognitive function appear to be at least partially expressed by larger hippocampal volume (e.g., Chaddock et al., 2010; Erickson et al., 2009; Erickson et al., 2011) and better functional MRI activation (e.g., Colcombe et al., 2004) of relevant neural substrates, as well as higher white matter integrity (e.g., Burzynska et al., 2014; Chaddock-Heyman et al., 2014) and cerebral blood flow (e.g., Alfini et al., 2016; Chaddock-Heyman et al., 2016; Chapman et al., 2013; Thomas et al., 2013) that may deliver more global benefits.

Brain regions are differentially vulnerable to deviations in vascular health (Raz and Rodrigue, 2006) and the hippocampus appears to be selectively sensitive. The hippocampus plays a necessary and critical role in declarative, or relational, memory, as demonstrated by decades of neuropsychological research with amnestic patients (e.g., Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001; Scoville and Milner, 1957) as well as more recent work using structural and functional MRI (e.g., Davachi, 2006; Hannula and Ranganath, 2008; Kirwan and Stark, 2004; Monti et al., 2015). Relational memory is the ability to flexibly bind together elements of an experience (Konkel and Cohen, 2009) and hippocampal integrity is requisite for binding all manners of relations (e.g., spatial information, temporal information, associative information; Konkel et al., 2008; Warren et al., 2011; Watson et al., Cohen, 2013). There is growing evidence that physical
activity improves both hippocampal integrity and relational memory performance (for a recent review see Kandola et al., 2016). Higher levels of aerobic fitness are associated with larger hippocampal volume among children (e.g., Chaddock et al., 2010; Herting and Nagel, 2012) and older adults (e.g., Erickson et al., 2009) as well as improved relational memory performance among children (e.g., Chaddock et al., 2011; Monti et al., 2015) and older adults (e.g., Erickson et al., 2011). In murine models, aerobic exercise promotes synaptic plasticity (for reviews see van Praag, 2008; Voss et al., 2013), increases the rate of hippocampal neurogenesis (Clark et al., 2011; Pereira et al., 2007; van Praag et al., 1999, 1999, 2005), and bolsters memory function (i.e., spatial memory; for review see van Praag, 2008).

Whereas studies of aerobic fitness effects on brain structure and function in child development and aging continue to accumulate, lesser attention has been paid to samples of healthy young adults. The early and late years of the lifespan are marked by considerable variability in both hippocampal volume and hippocampal-dependent memory function, thereby maximizing the opportunity to observe fitness effects (Voss et al., 2011). The contribution of aerobic fitness to brain health is expected to be consistent across the entire human lifespan, but several studies have failed to show such a relationship among healthy young adults (for a review see Hillman et al., 2008). There are a few notable exceptions. Baym et al. (2014) reported a significant positive relationship between relational memory performance and aerobic fitness levels among young adults, while (Stroth et al., 2009) showed improvement in visuospatial memory, but not verbal memory, following a six-week running intervention compared to a control group. Pereira et al. (2007) also showed increases in an in vivo correlate of neurogenesis (i.e., cerebral blood volume) in the dentate gyrus following a fitness intervention. However, no single study to date has identified the complex relation between aerobic fitness, hippocampal structure, and relational memory in young adults.

Given the robust effects reported in other age groups, the failure to find evidence of fitness-structure-function relationships in young adults suggests a lack of sensitivity in the assessment of hippocampal structure and not the absence of the mechanism per se. Studies have typically relied on hippocampal volumetry to assess individual differences in hippocampal structure, which is a gross proxy of tissue composition that is not specific to microstructural characteristics. Thus, it is plausible that variability in hippocampal microstructure that informs cognitive function can go undetected by measures of volume in young, healthy brains. As such, alternative imaging tools may be necessary to illuminate the relationship between aerobic fitness, hippocampal integrity, and memory performance in this segment of the lifespan.

Magnetic resonance elastography (MRE) provides an alternative method for quantitatively assessing hippocampal integrity. MRE is an imaging technique for noninvasively measuring viscoelastic tissue properties (Manduca et al., 2001; Muthupillai et al., 1995), which relate to the microstructure and health of brain tissue (Sack et al., 2013). The sensitivity of MRE measures is reflected in the observation of tissue softening in many neurological conditions (Arani et al., 2015; Murphy et al., 2016; Romano et al., 2014; Streitberger et al., 2012); in animal studies, this softening has been linked to demyelination (Schregel et al., 2012)
and inflammation (Riek et al., 2012) in white matter structures. Recently, we demonstrated
the feasibility of performing MRE of the human hippocampus in vivo (Johnson et al.,
2016) and identified a strong correlation between hippocampal viscoelasticity and relational
memory performance in healthy young adults (Schwarb et al., 2016) such that individuals
with higher viscoelastic measures (i.e., adjusted damping ratio; see method) indicative of
a more organized/intact microstructure performed better on the relational memory task.
These data suggest that MRE measures reflect the functional health of normal tissue even
in the absence of disease, and hippocampal viscoelasticity may be a more sensitive measure
to microstructural differences than gross volumetry via MRI. In light of this finding, we
hypothesized that the sensitive MRE measures may reveal novel aspects of the fitness-
memory relationship in young adults.

In the current work, we investigated the relationship between aerobic fitness, hippocampal
integrity, and relational memory performance in healthy young adults. Maximum oxygen
consumption (VO\textsubscript{2}max), the gold standard for assessing aerobic fitness, was measured with
a graded treadmill test; MRE was used to measure hippocampal viscoelasticity, a measure
of microstructural integrity in the hippocampus (Johnson et al., 2016); and a hippocampal-
dependent spatial reconstruction task (Monti et al., 2015; Schwarb et al., 2016; Watson et
al., 2013) was used to measure relational memory performance. In combining these sensitive
techniques, we investigated the hypothesis that aerobic fitness, hippocampal viscoelasticity,
and memory performance are related to each other and that, in fact, the relationship between
fitness and memory performance is mediated by hippocampal viscoelasticity.

**Methods**

**Participants**

Participants were recruited from the Urbana-Champaign community as part of a larger
cognitive training intervention study designed to assess the efficacy of different intervention
modalities on cognitive performance in healthy adults (N=384). A small number
of participants (N=63) volunteered to complete an optional additional MRI session that
included an MRE scan. The University of Illinois Urbana-Champaign Institutional Review
Board approved all aspects of the study and participants provided informed consent at
enrollment. All participants were right-handed with normal or corrected-to-normal vision
without color blindness reported no previous neurological disorders, or surgeries, were on no
medications affecting central nervous function, and were not pregnant. Participants received
monetary compensation for their participation. Only those participants who completed MRE
scans are included in this report.

As such, data were collected from 63 participants ages 18–35 (mean age=22.9) and included
32 males and 31 females. Five participants were excluded for failing to complete the
hippocampal-dependent spatial reconstruction memory task. Due to significant skewedness
in some of our variables of interest, Median Absolute Deviation (MAD) methods were used
to detect statistical outliers (Hampel, 1974; Leys et al., 2013). As such, six participants were
removed based on their memory performance measures and an additional participant was
excluded due to hippocampal MRE viscoelasticity measures. The resulting sample included
51 participants ages 18–35 (mean age=23.1) and included 25 men and 26 women.
MRI scanning

MRI and MRE data were collected using a Siemens 3T Trio whole-body MRI scanner with a 32-channel head RF receive coil (Siemens Medical Solutions; Erlangen, Germany). The imaging protocol included high-resolution $T_1$-weighted and MRE image series. $T_1$-weighted images were acquired using an MPRAGE sequence (magnetization-prepared, rapidly-acquired gradient echo; $0.9 \times 0.9 \times 0.9 \text{ mm}^3$ voxel size; $1900/900/2.32 \text{ ms}$ repetition/inversion/echo times).

The MRE acquisition used a 3D multislab, multishot spiral sequence (Johnson et al., 2014) to capture MRE images at $1.6 \times 1.6 \times 1.6 \text{ mm}^3$ spatial resolution. Imaging parameters included: $1800/73 \text{ ms}$ repetition/echo times; $240 \text{ mm}$ field-of-view; $150 \times 150$ matrix; $60$ slices at $1.6 \text{ mm}$ thickness. A pneumatic actuator (Resoundant; Rochester, MN, USA) generated $50 \text{ Hz}$ vibrations in the brain via a soft pillow driver placed below the head. We sampled the resulting displacement fields in three directions and at four time points across one period of vibration. Complex, full vector displacement fields were generated in a total acquisition time of 12 min.

Volumetric analysis

$T_1$-weighted images were used for extraction of hippocampal volume using FreeSurfer v. 5.3 (Fischl et al., 2002). Automatic segmentation of both the hippocampus and intracranial volume (ICV) were calculated (as in Schwarb et al., 2016; see Buckner, 2004 for detailed method); all segmentations were visually inspected for accuracy and manual corrections were made when necessary. Hippocampal volume was corrected for sexual dimorphism in ICV via the ANCOVA method (Erickson et al., 2009; Jack et al., 1989; Raz et al., 2005).

MRE analysis

Mechanical properties of the hippocampus and caudate were calculated from MRE displacement images using our hippocampal elastography procedure (Johnson et al., 2016; Schwarb et al., 2016), which is outlined briefly in this section (Fig. 1a). The nonlinear inversion (NLI) algorithm (McGarry et al., 2012) computed tissue shear modulus, $G=G'+iG''$ from MRE displacement data. We supplemented the NLI approach with subject-specific hippocampal and caudate volumes in MRE data-space created by registering the FreeSurfer segmentation using FLIRT in FSL (Jenkinson et al., 2002; Jenkinson et al., 2012). These masks were used in soft prior regularization (SPR) (McGarry et al., 2013) to promote local homogeneity of mechanical properties in the hippocampal and caudate regions during NLI. As described in our previous study (Johnson et al., 2016), this method returns reliable measures of shear stiffness, $\mu=2|G|^2/(|G|+G')$ (Manduca et al., 2001), and damping ratio, $\xi=G''/(2G')$ (McGarry and Van Houten, 2008). In this work, we report adjusted damping ratio, $\xi' = 1-\xi$, to describe the relative elastic-viscous behavior of the hippocampus. We reported a strong relationship between this parameter and behavior in our previous study (Schwarb et al., 2016). For both the hippocampus and caudate, bilateral structural properties were determined by averaging over the bilateral mask.
Aerobic fitness

A graded exercise test designed to measure maximal oxygen consumption (VO$_2$max; Fig. 1b) was used to assess aerobic fitness. VO$_2$max is considered the “gold standard” for measuring aerobic fitness (American College of Sports Medicine, 2014) and was measured using a computerized indirect calorimetry system (ParvoMedics True Max 2400) and a modified Balke protocol (American College of Sports Medicine, 2014). The test included a warm-up period in which participants walked on a motor-driven treadmill while speed was gradually increased. After the warm-up period, treadmill speed remained constant and the incline was increased 2–3% every 2 min. Throughout the test, heart rate was constantly monitored using a Polar heart rate monitor (Polar WearLink +31, Polar Electro, Finland) and participants provided subjective rate of perceived exertion every 2 minutes using the Borg scales of perceived exertion (American College of Sports Medicine, 2014). Averages for oxygen uptake (VO$_2$) and respiratory exchange ratio (RER) were assessed every 15 s. The test ended at maximum effort which was defined using two or more of the following criteria: (1) age-defined maximum heart rate norms (i.e., heart rate > 85% of predicted maximum heart rate), (2) respiratory exchange ratio (CO$_2$/O$_2$) greater than 1.1, (3) subjective rate of perceived exertion greater than 17 of 20, and (4) leveling of VO$_2$ despite increasing aerobic demand. Maximum oxygen consumption (VO$_2$max) is reported relative to body weight (relative VO$_2$max) and was calculated as milliliters of oxygen per kilogram per minute (ml/kg/min). VO$_2$max scores were also standardized according to age- and gender-based norms and a VO$_2$max percentile measure was calculated for each participant.

Memory performance assessment

Relational memory performance was tested using a computerized Spatial Reconstruction (SR) task (Monti et al., 2015; Schwarb et al., 2016) illustrated in Fig. 1c. On each trial, participants studied the location of six novel line drawings randomly distributed on the screen for 20 s. The line drawings then disappeared for 4 s and then reappeared in a straight line across the top of the screen. Participants used the mouse to put each line drawing back in its original studied location thus reconstructing the original studied display. Reconstruction time was self-paced and there were a total of 20 trials.

As in our previous work (Schwarb et al., 2016), four separate dependent measures were calculated. Misplacement errors: The distance (in pixels) between each item's studied location and where that item was placed in the reconstruction; summed for all six items. Edge resizing errors (in pixels): 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. Rearrangement errors (proportion): 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 (proportion): Calculation of the misassignment 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). Due to potential acute exercise effects on memory performance, SR task performance and fitness performance were assessed on separate days.
**Statistical analyses**

Preliminary data evaluations were conducted with Pearson partial correlation coefficients, \( r \), including age and sex as control variables. The significance of correlations was determined at \( p < 0.05 \) and indicated throughout the text and figures with an asterisk (*). To further examine these relationships, we tested the dependency of relational memory on aerobic fitness mediated by hippocampal properties in a path model in Mplus 7.0 (Muthén and Muthén, 1998–2012). The path model included age and sex as covariates to each measure and non-significant paths were constrained in the final model. Two path models were tested, first a model that only included hippocampal viscoelasticity as a mediator, and second, a model that additionally included hippocampal volume as a possible second mediator. Model fit was determined by several accepted indices (Hu and Bentler, 1999; Raykov and Marcoulides, 2006): normal theory weighted chi-square (\( \chi^2 \)) non-significance; comparative fit index (CFI > 0.90); root mean square error of approximation (RMSEA < 0.05); standardized root mean residual (SRMR < 0.08). Mediation was tested as statistical significance of an indirect effect (James and Brett, 1984). To avoid spurious results related to smaller sample size, all coefficients were bootstrapped with bias-correction (5000 draws; Hayes and Scharkow, 2013) to produce 95% confidence intervals (BS 95% CI) of unstandardized effects, which, if not including zero, are evidence for an effect at \( p < 0.05 \). All other reported effects are standardized.

**Results**

**Study variables**

Table 1 presents descriptive statistics (mean, standard deviation, minimum/maximum values, and skewedness) for all study variables. While aerobic fitness measures fell along a normal distribution, behavioral measures of relational memory and structural measures of regional integrity (both adjusted DR and volume) were significantly skewed. While outlier detection methods vary considerably in the literature and there is no standard practice (Miller, 1991; Simmons et al., 2011), MAD methods are touted as the most appropriate tool for unbiased outlier detection with skewed datasets (Hampel, 1974; Leys et al., 2013). MAD identified seven statistical outliers, six due to memory performance and one due to hippocampal viscoelastic measures; there were no aerobic fitness outliers.

The four dependent measures from the SR task (i.e., misplacement errors, edge resizing errors, rearrangement errors, and swap errors) were all highly and significantly correlated with each other (\( p < .001 \) in all cases; Table 2). Therefore, these measures were combined into a single composite measure created by normalizing each measure via \( z \)-score, and averaging across measures for each participant. The sign was then reversed on these composite score error values so that higher memory measures indicate better SR task performance. We refer to this composite measure generally as SR performance, a measure of relational memory.

**Relationships between hippocampal structure and memory performance**

Fig. 2a illustrates the correlations between both hippocampal adjusted damping ratio \( (\xi') \) and hippocampal volume with SR task performance. Hippocampal \( \xi' \) significantly

*Neuroimage. Author manuscript; available in PMC 2017 October 12.*
correlated with SR performance ($r=0.38^*, p=0.007$), whereas hippocampal volume did not ($r=0.04, p=0.800$; Fig. 2b). This replicates our previous finding (with an independent sample) of a significant relationship between SR task performance and hippocampal $\xi'$, but not hippocampal volume, in a more homogeneous population of young men (Schwarb et al., 2016). The current work extends this finding by replicating this relationship with a larger, more heterogeneous sample of young men and women. As in the previous work, we did not find a significant relationship between SR performance and hippocampal stiffness ($\mu$; $r=-0.09, p=0.542$).

To assess the specificity of this finding to the hippocampus, we performed a similar analysis comparing memory performance to viscoelastic measures in a control region, the caudate. The caudate is an optimal control region because it is not generally believed to be involved in episodic memory (for a review see Packard and Knowlton, 2002) nor is it typically influenced by aerobic fitness (Chaddock et al., 2012; Erickson et al., 2011; but see Verstynen et al., 2012). Indeed, in our sample, caudate $\xi'$ was not significantly correlated with relational memory performance, $r=0.10, p=0.486$. Furthermore, Steiger’s $z$-test revealed that this correlation was significantly smaller than the correlation between hippocampal $\xi'$ and relational memory, $z=2.2, p < .05$.

Relationships between hippocampal structure and aerobic fitness

Fig. 3a illustrates the correlations between both hippocampal $\xi'$ and hippocampal volume with aerobic fitness. Again, $\xi'$ significantly correlated with measures of aerobic fitness ($r=0.32^*, p=0.026$), while volume did not ($r=-0.02, p=0.871$; Fig. 3b). To the best of our knowledge, this is the first report of viscoelastic brain measures showing a relationship with aerobic fitness. The relationship between aerobic fitness and hippocampal volume was not significant suggesting that $\xi'$ may provide a complementary sensitive measure of hippocampal integrity for populations without significant volumetric differences. The relationship between aerobic fitness and hippocampal $\mu$ ($r=0.09, p=0.549$) was also not significant.

As before, caudate $\xi'$ was not significantly correlated with aerobic fitness, $r=0.10, p=0.515$. Again, Steiger’s $z$-test revealed that this correlation was significantly smaller than the correlation between hippocampal $\xi'$ and aerobic fitness, $z=1.7, p < .05$.

Relationships between aerobic fitness and memory performance

The correlation between SR task performance and aerobic fitness was also significant ($r=0.29^*, p=0.041$) consistent with previous work showing a significant relationship between relational memory performance and aerobic fitness in healthy young adults (Baym et al., 2014). Together these findings indicate that the relationship between aerobic fitness and relational memory performance may, in fact, be mediated by hippocampal structural measures (i.e., $\xi'$). We investigated this empirical question using a mediation model.

Path analysis of structure-function-fitness relationship

We tested the effect of aerobic fitness on relational memory mediated by hippocampal $\xi'$ and hippocampal volume in two path models. The first model that only included $\xi'$ as a
mediator had excellent fit: $\chi^2 (5) = 1.70, p=0.89$; CFI=1.00; RMSEA=0.00; SRMR=0.09. Similar to the pattern of correlations reported, better aerobic fitness predicted greater hippocampal $\xi'$ (0.47, $p < 0.001$; BS 95% CI: 0.001/0.002) that in turn accounted for greater SR task performance (0.37, $p=0.003$; BS 95% CI: 3.89/12.57). Critically, $\xi'$ mediated the effects of aerobic fitness on relational memory (indirect effect=0.17, $p=0.02$; BS 95% CI: 0.01/0.02). See Fig. 4a for a diagram of the final model. Men demonstrated greater aerobic fitness than women (−0.66, $p < 0.001$; BS 95% CI: −13.13/−7.54). This partially accounted for greater hippocampal viscoelasticity of male brains (−0.31, $p < 0.001$; BS 95% CI: −0.03/−0.01) and, in turn, greater SR task performance (−0.11, $p=0.03$; BS 95% CI: −0.24/−0.05).

In a secondary analysis, we tested hippocampal volume as a correlate of $\xi'$ and potential second mediator of the aerobic fitness-memory relationship (Fig. 5). As shown with Pearson partial correlations, hippocampal volume was unrelated to aerobic fitness and relational memory performance. The final model that constrained these effects replicated the observed data well: $\chi^2(9)=2.04, p=0.99$; CFI=1.00; RMSEA=0.00; SRMR=0.08. Hippocampal viscoelasticity and volume were statistically unrelated (0.11, $p=0.43$; BS 95% CI: −1.61/4.59) and when accounting for volume, $\xi'$ still significantly mediated the effect of fitness on relational memory ($p=0.02$).

**Discussion**

Hippocampal structure and function are sensitive to individual differences in aerobic fitness and, as shown here, this is associated with variability in microstructural tissue properties even in healthy, young adults. MRE measures of hippocampal microstructure proved to be a powerful tool for investigating the hippocampal structure-function relationship: $\xi'$, an index of both the elastic and viscous behavior of tissue, was more sensitive to the effects of aerobic fitness than gross volume in young adults. Indeed, higher aerobic fitness was associated with better hippocampal viscoelasticity, which in turn predicted better relational memory recall. Thus, microstructural differences in hippocampal tissue appear to convey the benefits of aerobic fitness on memory function.

Aerobic fitness bolstering the hippocampal structure-function relationship has been consistently demonstrated with volumetry derived from MRI among children (Chaddock, 2012; Chaddock et al., 2011), adolescents (Herting and Nagel, 2012), and older adults (Erickson et al., 2009; Erickson et al., 2011). Moreover, aerobic fitness is related to better hippocampal-dependent memory function. Higher fit children perform better on relational memory tasks compared to lower fit children (Chaddock et al., 2011), which is in part explained by differences in hippocampal volume (Chaddock et al., 2010), and a similar relationship has been observed in older adults (Erickson et al., 2009; Herting and Nagel, 2012). Indeed, aerobic activity appears to mitigate the typical decrease in hippocampal volume in normal aging (Bugg and Head, 2011; Bugg et al., 2012; Kramer et al., 1985), and fitness interventions improve relational memory performance in older adults (Erickson et al., 2011; Monti et al., 2012).
The mechanism of aerobic fitness benefits to hippocampal structure and function is likely due to microstructural changes, for which MRE is a more specific measure as compared to volumetry as a gross proxy. In rodents, frequent aerobic exercise is accompanied by increases in synaptic plasticity, gliogenisis, neurotrophin levels, and neuronal spine density (for reviews see van Praag, 2008; Voss et al., 1985). There is also some evidence for increased neurotrophin levels with better aerobic fitness in human studies (Wagner et al., 2015). The hippocampus, specifically, also shows increased neurogenesis (Clark et al., 2011; Pereira et al., 2007; van Praag, et al., 1999a, 1999b, 2005), which is a strong candidate mechanism by which physical activity leads to changes in hippocampal structure detectable via MRI and memory ability (Baym et al., 2014).

Given the robust evidence of aerobic fitness benefits via volumetry among children and older adults that plausibly share this common mechanism, the inconsistent evidence in young adults for a fitness-hippocampal volume-function relationship is surprising. Whereas hippocampal volumes have reduced variability among young adults as compared to periods of development and aging, young adults display notable individual differences in hippocampal-dependent memory function (Baym et al., 2014). Thus, gross volumetry may be insufficient to detect the functionally-relevant microstructural variability in this segment of the lifespan. Here, we demonstrate that MRE derived $\xi'$, as an index of tissue viscoelasticity, is a more sensitive measure, replicating our recent report in an independent sample of young adults (Schwarb et al., 2016). We previously suggested that our success in showing that individual differences in hippocampal structural integrity correlate with differences in relational memory performance stem from the use of highly sensitive measurement tools (Ofen and Shing, 2013; van Petten, 2004); this includes both MRE measures of brain viscoelasticity (Schwarb et al., 2016) and reconstruction measures of relational memory (Monti et al., 2015).

$\xi'$ provides an in vivo measure of tissue properties by indicating how much the kinematic response to a shear loading is like that of an elastic solid (higher $\xi'$) versus a viscous fluid (lower $\xi'$). Since its translation to human brain imaging, MRE investigations have consistently reported decreases in viscosity and elasticity accompanying various neurodegenerative disorders including multiple sclerosis (Monti et al., 2015), Alzheimer’s disease (Streitberger et al., 2012; Wuerfel et al., 2010), and Parkinson’s disease (Murphy et al., 2011, 2016). As such, MRE measures have proven sensitive to demyelination (Lipp et al., 2013), inflammation (Schregel et al., 2012), and neuronal loss (Millward et al., 2015; Riek et al., 2012). Recently, however, evidence has emerged that MRE measures are also sensitive to neurogenesis. Klein and colleagues (Freimann et al., 2013; Hain et al., 2016) demonstrated increased neuronal density in the mouse dentate gyrus that was also accompanied by an increase in elasticity in that region as measured by MRE.

Based upon this understanding, $\xi'$ may be an approximation of human tissue properties including neurogenesis, which is a strong candidate mechanism by which physical activity leads to changes in hippocampal structure and memory ability (Baym et al., 2014). Numerous rodent studies have reported increased hippocampal neurogenesis accompanying frequent aerobic exercise (Clark et al., 2011; Creer et al., 2010; van Praag, et al., 1999a, 1999b, 2005) and increased hippocampal cerebral blood volume, as a distant proxy marker for increased perfusion and oxygen availability.
of neurogenesis, correlates with better memory outcomes in human adults (Pereira et al. 2007). We previously hypothesized that MRE $\xi'$ may measure the organization and integrity of the axonal pathways that connect, and mechanically couple, the various layers and subfields and the hippocampal formation (Schwarb et al., 2016). In light of the findings in this work, it is likely that microstructural elements related to neurogenesis in adults are either the dominant factor in $\xi'$ or at least complementary to our theory of the integrity of intra-hippocampal axons. MRE measures currently lack sufficient resolution to directly assess neurogenesis in humans and we can only speculate about its contribution to the results reported here. Nonetheless, as an approximation of cytoarchitecture and the evidence from MRE presented here is in line with theoretical mechanisms of systemic aerobic fitness on hippocampal structure and function. Furthermore, developments in MRE technology provide an opportunity to investigate this mechanism in humans in vivo with greater specificity to tissue properties than is otherwise feasible with alternative neuroimaging methods.

As in our previous study, we did not observe a significant relationship between hippocampal stiffness, $\mu$, and relational memory (Schwarb et al., 2016), nor between $\mu$ and fitness, despite stiffness being the most commonly reported parameter affected in neurological conditions. The two MRE parameters, $\mu$ and $\xi'$, describe independent measures of tissue behavior, and may be differentially related to microstructural composition and organization (Hiscox et al., 2016); however, we have previously observed some correlation between the parameters in the hippocampus (Sack et al., 2013) likely owing to common dependence on some aspects of microstructure. The interrelatedness of hippocampal $\mu$ and $\xi'$ complicate our understanding of the observed structure-function-fitness relationship in healthy young adults reported here, though we expect that a cognitive relationship with $\mu$ may be observed with other structures and functions, or in developmental or pathologic populations. This is highlighted by an observed improvement in both hippocampal $\mu$ and $\xi'$ with exercise training in adults with multiple sclerosis (Johnson et al., 2016). Further research is certainly necessary to parse out the shared and independent influences of $\mu$ and $\xi'$ in the study of neurocognitive mechanisms across the brain contributing to behavior.

In addition to limitations of the neuroimaging method, the cross-sectional evidence presented here cannot definitively test causality between aerobic fitness and hippocampal structure-function. Future fitness intervention studies have the potential to speak more directly to this relationship. Still, the current work provides a necessary foundation for such future investigations. The findings from this work are threefold. First, MRE provides a sensitive measure of microstructural tissue structure in the hippocampus and individual differences in hippocampal viscoelasticity are related to memory outcomes; thus providing an important replication of this previously reported novel finding (Sandroff et al., 2017). Second, individual differences in aerobic fitness are related to variability in hippocampal viscoelasticity. And finally, the relationship of aerobic fitness on relational memory performance was mediated by hippocampal $\xi'$. These data support the promise and utility of MRE as a noninvasive tool for investigation microstructural organization of neural tissue and its relationship with cognition.
Acknowledgments

The research is based upon work supported by the Office of the Director of National Intelligence (ODNI), Intelligence Advanced Research Projects Activity (IARPA), via Contract 2014-13121700004 to the University of Illinois at Urbana-Champaign. The views and conclusions contained herein are those of the authors and should not be interpreted as necessarily representing the official policies or endorsements, either expressed or implied, of the ODNI, IARPA, or the U.S. Government. The U.S. Government is authorized to reproduce and distribute reprints for Governmental purposes notwithstanding any copyright annotation thereon. This research is additionally part of the Blue Waters sustained-petascale computing project, which is supported by the National Science Foundation (awards OCI-0725070 and ACI-1238993) and the state of Illinois. Blue Waters is a joint effort of the University of Illinois at Urbana-Champaign and its National Center for Supercomputing Applications. MRE data acquisition and analysis was further supported by NIH/NIBIB grants R01-EB018320 and R01-001981. We would also like to thank Patricia Jones (project manager), Courtney Allen (project coordinator), Ginger Reeser (project coordinator), and the entire INSIGHT staff for their commitment and dedication to the success of this work.

References

Alfini AJ, Weiss LR, Leitner BP, Smith TJ, Hagberg JM, Smith JC. 2016; Hippocampal and cerebral blood flow after exercise cessation in master athletes. Front. Aging Neurosci. 8:184. doi: 10.3389/fnagi.2016.00184 [PubMed: 27547184]

American College of Sports Medicine. ACSM’s Guidelines for Exercise Testing and Prescription 9 ed. Wolters Kluwer/Lippincott, Williams, & Wilkins Health; Philadelphia, PA: 2014.

Arani A, Murphy MC, Glaser KJ, Manduca A, Lake DS, Kruse SA, Huston J 3rd. 2015; Measuring the effects of aging and sex on regional brain stiffness with MR elastography in healthy older adults. Neuroimage. 111:59–64. DOI: 10.1016/j.neuroimage.2015.02.016 [PubMed: 25698157]

Baym CL, Khan NA, Pence A, Raine LB, Hillman CH, Cohen NJ. 2014; Aerobic fitness predicts relational memory but not item memory performance in healthy young adults. J. Cogn. Neurosci. 26 (11):2645–2652. DOI: 10.1162/jocn_a_00667 [PubMed: 24893739]

Buckner RL. 2004; Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuro. 44 (1):195–208. [PubMed: 15450170]

Bugg JM, Head D. 2011; Exercise moderates age-related atrophy of the medial temporal lobe. Neurobiol. Aging. 32 (3):506–514. DOI: 10.1016/j.neurobiolaging.2009.03.008 [PubMed: 19386382]

Bugg JM, Shah K, Villareal DT, Head D. 2012; Cognitive and neural correlates of aerobic fitness in obese older adults. Exp. Aging Res. 38 (2):131–145. DOI: 10.1080/0361073X.2012.659995 [PubMed: 22404537]

Burzynska AZ, Chaddock-Heyman L, Voss MW, Wong CN, Gothe NP, Olson EA, Kramer AF. 2014; Physical activity and cardiorespiratory fitness are beneficial for white matter in low-fit older adults. PLoS One. 9 (9):e107413. doi: 10.1371/journal.pone.0107413 [PubMed: 25229455]

Chaddock, L. The Effects of Physical Activity Onthe Brain and Cognition during Childhood (Ph.D.). University of Illinois at Urbana-Champaign; Urbana, IL: 2012.

Chaddock L, Erickson KI, Prakash RS, Kim JS, Voss MW, Vanpatter M, Kramer AF. 2010; A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. Brain Res. 1358:172–183. DOI: 10.1016/j.brainres.2010.08.049 [PubMed: 20735996]

Chaddock L, Hillman CH, Buck SM, Cohen NJ. 2011; Aerobic fitness and executive control of relational memory in preadolescent children. Med. Sci. Sport Exerc. 43 (2):344–349. DOI: 10.1249/MSS.0b013e3181e9af48

Chaddock L, Hillman CH, Pontifex MB, Johnson CR, Raine LB, Kramer AF. 2012; Childhood aerobic fitness predicts cognitive performance one year later. J. Sport Sci. 30 (5):421–430. DOI: 10.1080/02640414.2011.647706

Chaddock-Heyman L, Erickson KI, Chappell MA, Johnson CL, Kienzler C, Knecht A, Kramer AF. 2016; Aerobic fitness is associated with greater hippocampal cerebral blood flow in children. Dev. Cogn. Neurosci. 20:52–58. DOI: 10.1016/j.dcn.2016.07.001 [PubMed: 27419884]
Chaddock-Heyman L, Erickson KI, Holtrop JL, Voss MW, Pontifex MB, Raine LB, Kramer AF. 2014; Aerobic fitness is associated with greater white matter integrity in children. Front. Hum. Neurosci. 8 :584. doi: 10.3389/fnhum.2014.00584 [PubMed: 25191243]

Chapman SB, Aslan S, Spence JS, Defina LF, Keebler MW, Didehbani N, Lu H. 2013; Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. Front. Aging Neurosci. 5 :75. doi: 10.3389/fnagi.2013.00075 [PubMed: 24282403]

Clark PJ, Kohman RA, Miller DS, Bhattacharya TK, Brzezinska WJ, Rhodes JS. 2011; Genetic influences on exercise-induced adult hippocampal neurogenesis across 12 divergent mouse strains. Genes Brain Behav. 10 (3) :345–353. DOI: 10.1111/j.1601-183X.2010.00674.x [PubMed: 21223504]

Cohen, NJ, Eichenbaum, H. Memory, Amnesia and the Hippocampal System. MIT Press; Cambridge: 1993.

Colcombe SJ, Kramer AF. 2003; Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol. Sci. 14 (2) :125–130. [PubMed: 12661673]

Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, Elavsky S. 2004; Cardiovascular fitness, cortical plasticity, and aging. Proc. Natl. Acad. Sci. USA. 101 (9) :3316–3321. DOI: 10.1073/pnas.0400266101 [PubMed: 14978288]

Creer DJ, Romberg C, Saksida LM, van Praag H, Bussey TJ. 2010; Running enhances spatial pattern separation in mice. Proc. Natl. Acad. Sci. USA. 107 (5) :2367–2372. DOI: 10.1073/pnas.0911725107 [PubMed: 20133882]

Davachi L. 2006; Item, context and relational episodic encoding in humans. Curr. Opin. Neurobiol. 16 (6) :693–700. DOI: 10.1016/j.conb.2006.10.012 [PubMed: 17097284]

Eichenbaum, H, Cohen, NJ. From Conditioning to Conscious Recollection: Multiple Memory Systems in the Brain. Oxford University Press; New York: 2001.

Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, Kramer AF. 2009; Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus. 19 (10) :1030–1039. DOI: 10.1002/hipo.20547 [PubMed: 19123237]

Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kramer AF. 2011; Exercise training increases size of hippocampus and improves memory. Proc. Natl. Acad. Sci. USA. 108 (7) :3017–3022. DOI: 10.1073/pnas.1015950108 [PubMed: 21282661]

Etnier JL, Nowell PM, Landers DM, Sibley BA. 2006; A meta-regression to examine the relationship between aerobic fitness and cognitive performance. Brain Res. Rev. 52 (1) :119–130. DOI: 10.1016/j.brainresrev.2006.01.002 [PubMed: 16490256]

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, Dale AM. 2002; Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 33 (3) :341–355. [PubMed: 11832223]

Freimann FB, Muller S, Streitberger KJ, Guo J, Rot S, Ghoroi A, Braun J. 2013; MR elastography in a murine stroke model reveals correlation of macroscopic viscoelastic properties of the brain with neuronal density. NMR Biomed. 26 (11) :1534–1539. DOI: 10.1002/nbm.2987 [PubMed: 23784982]

Hain EG, Klein C, Munder T, Braun J, Riek K, Mueller S, Steiner B. 2016; Dopaminergic neurodegeneration in the mouse is associated with decrease of viscoelasticity of substantia nigra tissue. PLoS One. 11 (8) :e0161179. doi: 10.1371/journal.pone.0161179 [PubMed: 27526042]

Hampel FR. 1974; Influence curve and its role in robust estimation. J. Am. Stat. Assoc. 69 (346) :383–393. doi: 10.2307/2285666

Hannula DE, Ranganath C. 2008; Medial temporal lobe activity predicts successful relational memory binding. J Neurosci. 28 (1) :116–124. DOI: 10.1523/JNEUROSCI.3086-07.2008 [PubMed: 18171929]

Hayes AF, Scharkow M. 2013; The relative trustworthiness of inferential tests of the indirect effect in statistical mediation analysis: does method really matter? Psychol. Sci. 24 (10) :1918–1927. DOI: 10.1177/0956797613480187 [PubMed: 23953556]

Herting MM, Nagel BJ. 2012; Aerobic fitness relates to learning on a virtual Morris Water Task and hippocampal volume in adolescents. Behav. Brain Res. 233 (2) :517–525. DOI: 10.1016/j.bbr.2012.05.012 [PubMed: 22610054]

Neuroimage. Author manuscript; available in PMC 2017 October 12.
Hillman CH, Erickson KI, Kramer AF. 2008; Be smart, exercise your heart: exercise effects on brain and cognition. Nat. Rev. Neurosci. 9 (1) :58–65. DOI: 10.1038/nrn2298 [PubMed: 18094706]

Hiscox LV, Johnson CL, Barnhill E, McGarry MD, Huston J 3rd, van Beek EJR, Roberts N. 2016 Magnetic resonance imaging (MRE) of the human brain: technique, findings and clinical applications. Phys. Med. Biol.

Hu L, Bentler PM. 1999: Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct. Equ. Model.: Multidiscip. J. 6 (1) :1–55.

Jack CR Jr, Twomey CK, Zinsmeister AR, Sharbrough FW, Petersen RC, Cascino GD. 1989; Anterior temporal lobes and hippocampal formations: normative volumetric measurements from MR images in young adults. Radiology. 172 (2) :549–554. DOI: 10.1148/radiology.172.2.2748838 [PubMed: 2748838]

James LR, Brett JM. 1984; Mediators, moderators, and tests for mediation. Appl. Psychol. 69 (2) :307–321.

Jenkinson M, Bannister P, Brady M, Smith S. 2002; Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage. 17 (2) :825–841. [PubMed: 12377157]

Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. 2012; FSL. Neuroimage. 62 (2) :782–790. DOI: 10.1016/j.neuroimage.2011.09.015 [PubMed: 21979382]

Johnson CL, Holtrop JL, McGarry MD, Weaver JB, Paulsen KD, Georgiadis JG, Sutton BP. 2014; 3D multislab, multislab acquisition for fast, whole-brain MR elastography with high signal-to-noise efficiency. Magn. Reson. Med. 71 (2) :477–485. DOI: 10.1002/mrm.25065 [PubMed: 24347237]

Johnson, CL; Schwarb, H; M, DJM; Anderson, AT; Huesmann, GR; Sutton, BP; Cohen, NJ. Viscoelasticity of subcortical gray matter structures. Hum. Brain Mapp. 2016.

Kandola A, Hendrikse J, Lucassen PJ, Yucel M. 2016; Aerobic exercise as a tool to improve hippocampal plasticity and function in humans: practical implications for mental health treatment. Front. Hum. Neurosci. 10 :373. doi: 10.3389/fnhum.2016.00373 [PubMed: 27524962]

Kirwan CB, Stark CE. 2004; Medial temporal lobe activation during encoding and retrieval of novel face-name pairs. Hippocampus. 14 (7) :919–930. DOI: 10.1002/hipo.20014 [PubMed: 15382260]

Konkel A, Cohen NJ. 2009; Relational memory and the hippocampus: representations and methods. Front. Neurosci. 3 (2) :166–174. DOI: 10.3389/neuro.01.023.2009 [PubMed: 20011138]

Konkel A, Warren DE, Duff MC, Tranel DN, Cohen NJ. 2008; Hippocampal amnesia impairs all manner of relational memory. Front. Hum. Neurosci. 2 :15. doi: 10.3389/neuro.09.015.2008 [PubMed: 18989388]

Kramer AF, Colcombe SJ, McAuley E, Eriksen KI, Scafe P, Jerome GJ, Webb AG. 2003; Enhancing brain and cognitive function of older adults through fitness training. J. Mol. Neurosci. 20 (3) :213–221. DOI: 10.1385/JMN:20:3:213 [PubMed: 14501000]

Kramer AF, Erickson KI, Colcombe SJ. 2006; Exercise, cognition, and the aging brain. J. Appl. Physiol. 101 (4) :1237–1242. DOI: 10.1152/japplphysiol.00500.2006 [PubMed: 16778001]

Leys C, Ley C, Klein O, Bernard P, Licata L. 2013; Detecting outliers: do not use standard deviation around the mean, use absolute deviation around the median. J. Exp. Soc. Psychol. 49 (4) :764–766. DOI: 10.1016/j.jsp.2013.03.013

Lipp A, Trbojevic R, Paul F, Fehlner A, Hirsch S, Scheel M, Sack I. 2013; Cerebral magnetic resonance elastography in supranuclear palsy and idiopathic Parkinson's disease. Neuroimage Clin. 3 :381–387. DOI: 10.1016/j.nicl.2013.09.006 [PubMed: 24273721]

Manhuta A, Oliphant TE, Dresner MA, Mahowald JL, Kruse SA, Amromin E, Elman RL. 2001; Magnetic resonance elastography: non-invasive mapping of tissue elasticity. Med. Image Anal. 5 (4) :237–254. [PubMed: 11731304]

McGarry MD, Johnson CL, Sutton BP, Van Houten EE, Georgiadis JG, Weaver JB, Paulsen KD. 2013; Including spatial information in nonlinear inversion MR elastography using soft prior regularization. IEEE Trans. Med. Imaging. 32 (10) :1901–1909. DOI: 10.1109/TMI.2013.2268978 [PubMed: 23797239]

McGarry MD, Van Houten EE. 2008; Use of a Rayleigh damping model in elastography. Med. Biol. Eng. Comput. 46 (8) :759–766. DOI: 10.1007/s11517-008-0356-5 [PubMed: 18521645]

Neuroimage. Author manuscript; available in PMC 2017 October 12.
McGarry MD, Van Houten EE, Johnson CL, Georgiadis JG, Sutton BP, Weaver JB, Paulsen KD. 2012; Multiresolution MR elastography using nonlinear inversion. Med. Phys. 39 (10) :6388–6396. DOI: 10.1118/1.4754649 [PubMed: 23093674]

Miller J. 1991; Reaction time analysis with outlier exclusion: Bias varies with sample size. Q. J. Exp. Psychol. 43 (4) :907–912. DOI: 10.1080/14640749108400962

Millward JM, Guo J, Berndt D, Braun J, Sack I, Infante-Duarte C. 2015; Tissue structure and inflammatory processes shape viscoelastic properties of the mouse brain. NMR Biomed. 28 (7) :831–839. DOI: 10.1002/nbm.3319 [PubMed: 25963743]

Monti JM, Cooke GE, Watson PD, Voss MW, Kramer AF, Cohen NJ. 2015; Relating hippocampus to relational memory processing across domains and delays. J. Cogn. Neurosci. 27 (2) :234–245. DOI: 10.1162/jocn_a_00717 [PubMed: 25203273]

Monti JM, Hillman CH, Cohen NJ. 2012; Aerobic fitness enhances relational memory in preadolescent children: the FITKids randomized control trial. Hippocampus. 22 (9) :1876–1882. DOI: 10.1002/hipo.22023 [PubMed: 22522428]

Murphy MC, Huston J 3rd, Jack CR Jr, Glunduca A, Felmlee JP, Ehman RL. 2011; Decreased brain stiffness in Alzheimer’s disease determined by magnetic resonance elastography. J. Magn. Reson Imaging. 34 (3) :494–498. DOI: 10.1002/jmri.22707 [PubMed: 21751286]

Murphy MC, Jones DT, Jack CR Jr, Glunduca A, Husty J 3rd. 2016; Regional brain stiffness changes across the Alzheimer’s disease spectrum. Neuroimage Clin. 10 :283–290. DOI: 10.1016/j.nicl.2015.12.007 [PubMed: 26900568]

Muthén, LK, Muthén, BO. Mplus User’s Guide 7 ed. Los Angeles, CA: Muthén & Muthén; 1998.

Muthupillai R, Lomas DJ, Rossman PJ, Greenleaf JF, Manduca A, Ehman RL. 1995; Magnetic resonance elastography by direct visualization of propagating acoustic strain waves. Science. 269 (5232) :1854–1857. [PubMed: 7569924]

Ofen N, Shing YL. 2013; From perception to memory: changes in memory systems across the lifespan. Neurosci. Biobehav. Rev. 37 (9) :2258–2267. DOI: 10.1016/j.neubiorev.2013.04.006 [PubMed: 23623983]

Packard MG, Knowlton BJ. 2002; Learning and memory functions of the Basal Ganglia. Annu Rev. Neurosci. 25 :563–593. DOI: 10.1146/annurev.neuro.25.112701.142937 [PubMed: 12052921]

Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, Small SA. 2007; An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc. Natl. Acad. Sci. USA. 104 (13) :5638–5643. DOI: 10.1073/pnas.0611721104 [PubMed: 17374720]

Raykov, T, Marcoulides, GA. A First Course in Structural Equation Modeling 2 ed. Lawrence Erlbaum; Mahwah: 2006.

Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Acker JD. 2005; Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb. Cortex. 15 (11) :1676–1689. DOI: 10.1093/cercor/bhi044 [PubMed: 15703252]

Raz N, Rodrigue KM. 2006; Differential aging of the brain: patterns, cognitive correlates and modifiers. Neurosci. Biobehav. Rev. 30 (6) :730–748. DOI: 10.1016/j.neubiorev.2006.07.001 [PubMed: 16919333]

Riek K, Millward JM, Hamam I, Mueller S, Pfueffel CF, Paul F, Sack I. 2012; Magnetic resonance elastography reveals altered brain viscoelasticity in experimental autoimmune encephalomyelitis. Neuroimage Clin. 1 (1) :81–90. DOI: 10.1016/j.nicl.2012.09.003 [PubMed: 24179740]

Romano A, Guo J, Prokscha T, Meyer T, Hirsch S, Braun J, Scheel M. 2014; In vivo waveguide elastography: effects of neurodegeneration in patients with amyotrophic lateral sclerosis. Magn. Reson. Med. 72 (6) :1755–1761. DOI: 10.1002/mrm.25067 [PubMed: 24347290]

Sack I, Jöhrens K, Wuerfel E, Braun J. 2013; Structure-sensitive elastography: on the viscoelastic powerlaw behavior of in vivo human tissue in health and disease. Soft Matter. 9 :5672–5680. DOI: 10.1039/C3SM05552A

Sandhoff BM, Johnson CL, Motl RW. 2017; Exercise training effects on memory and hippocampal viscoelasticity in multiple sclerosis: a novel application of magnetic resonance elastography. Neuroradiology. 59 (1) :61–67. DOI: 10.1007/s00234-016-1767-x [PubMed: 27889837]

Schregel K, Wuerfel E, Garteiser P, Gemeinhardt I, Prozorovski T, Aktas O, Sinkus R. 2012; Demyelination reduces brain parenchymal stiffness quantified in vivo by magnetic resonance

Neuroimage. Author manuscript; available in PMC 2017 October 12.
elastography. Proc. Natl. Acad. Sci. USA. 109 (17) :6650–6655. DOI: 10.1073/pnas.1200151109 [PubMed: 22492966]

Schwarb H, Johnson CL, McGarry MD, Cohen NJ. 2016; Medial temporal lobe viscoelasticity and relational memory performance. Neuroimage. 132 :534–541. DOI: 10.1016/j.neuroimage.2016.02.059 [PubMed: 26931816]

Slovence WB, Milner B. 1957; Loss of recent memory after bilateral hippocampal lesions. J. Neurol. Neurosurg. Psychiatry. 20 (1) :11–21. [PubMed: 13406589]

Simmons JP, Nelson LD, Simonsohn U. 2011; False positive psychology: Undisclosed flexibility in data collection and analysis allows presenting anything as significant. Psychol. Sci. 22 (11) :1359–1366. DOI: 10.1177/0956797611417632 [PubMed: 22006061]

Streitberger KJ, Sack I, Krefting D, Pfuller C, Braun J, Paul F, Wuerfel J. 2012; Brain viscoelasticity alteration in chronic-progressive multiple sclerosis. PLoS One. 7 (1) :e29888. doi: 10.1371/journal.pone.0029888 [PubMed: 22276134]

Stroth S, Hille K, Spitzer M, Reinhardt R. 2009; Aerobic endurance exercise benefits memory and affect in young adults. Neuropsychol. Rehabil. 19 (2) :223–243. DOI: 10.1080/09602010802091183 [PubMed: 18609015]

Thomas BP, Yezhuvath US, Tseng BY, Liu P, Levine BD, Zhang R, Lu H. 2013; Life-long aerobic exercise preserved baseline cerebral blood flow but reduced vascular reactivity to CO2J. Magn. Reson Imaging. 38 (5) :1177–1183. DOI: 10.1002/mrni.24090

van Petten C. 2004; Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. Neuropsychologia. 42 (1) :1394–1413. DOI: 10.1016/j.neuropsychologia.2004.04.006 [PubMed: 15193947]

van Praag H. 2008; Neurogenesis and exercise: past and future directions. Neuromol. Med. 10 (2) :128–140. DOI: 10.1007/s12017-008-0028-z

van Praag H, Christie BR, Sejnowski TJ, Gage FH. 1999a; Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc. Natl. Acad. Sci. USA. 96 (23) :13427–13431. [PubMed: 10557337]

van Praag H, Kempermann G, Gage FH. 1999b; Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat. Neurosci. 2 (3) :266–270. DOI: 10.1038/6368 [PubMed: 10195220]

van Praag H, Shubert T, Zhao C, Gage FH. 2005; Exercise enhances learning and hippocampal neurogenesis in aged mice. J. Neurosci. 25 (38) :8680–8685. DOI: 10.1523/JNEUROSCI.1731-05.2005 [PubMed: 16177036]

Verstynen TD, Lynch B, Miller DL, Voss MW, Prakash RS, Chaddock L, Erickson KI. 2012; Caudate nucleus volume mediates the link between cardiorespiratory fitness and cognitive flexibility in older adults. J. Aging Res. 2012 :939285. doi: 10.1155/2012/939285 [PubMed: 22900181]

Voss MW, Nagamatsu LS, Liu-Ambrose T, Kramer AF. 2011; Exercise, brain, and cognition across the life span. J. Appl. Physiol. 111 (5) :1505–1513. DOI: 10.1152/japplphysiol.00210.2011 [PubMed: 21527670]

Voss MW, Vivar C, Kramer AF, van Praag H. 2013; Bridging animal and human models of exercise-induced brain plasticity. Trends Cogn. Sci. 17 (10) :525–544. DOI: 10.1016/j.tics.2013.08.001 [PubMed: 24029446]

Voss MW, Weng TB, Burzynska AZ, Wong CN, Cooke GE, Clark R, Kramer AF. 2016; Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. Neuroimage. 131 :113–125. DOI: 10.1016/j.neuroimage.2015.10.044 [PubMed: 26493108]

Wagner G, Herbsleb M, de la Cruz F, Schumann A, Brunner F, Schachtzabel C, Bar KJ. 2015; Hippocampal structure, metabolism, and inflammatory response after a 6-week intense aerobic exercise in healthy young adults: a controlled trial. J. Cereb. Blood Flow Metab. 35 (10) :1570–1578. DOI: 10.1038/jcbfm.2015.125 [PubMed: 26082010]

Warren DE, Duff MC, Tranel D, Cohen NJ. 2011; Observing degradation of visual representations over short intervals when medial temporal lobe is damaged. J. Cogn. Neurosci. 23 (12) :3862–3873. DOI: 10.1162/jocn_a_00089 [PubMed: 21736458]
Warsch JR, Wright CB. 2010; The aging mind: vascular health in normal cognitive aging. J Am. Geriatr. Soc. 58 (Suppl 2) :S319–324. DOI: 10.1111/j.1532-5415.2010.02983.x [PubMed: 21029061]

Watson PD, Voss JL, Warren DE, Tranel D, Cohen NJ. 2013; Spatial reconstruction by patients with hippocampal damage is dominated by relational memory errors. Hippocampus. 23 (7) :570–580. DOI: 10.1002/hipo.22115 [PubMed: 23418096]

Wuerfel J, Paul F, Beierbach B, Hamhaber U, Klatt D, Papazoglou S, Sack I. 2010; MR-elastography reveals degradation of tissue integrity in multiple sclerosis. Neuroimage. 49 (3) :2520–2525. DOI: 10.1016/j.neuroimage.2009.06.018 [PubMed: 19539039]
Fig. 1.
A) Overview of hippocampal elastography procedure. Three-dimensional, full vector, complex displacement fields are captured with high spatial resolution (1.6 mm isotropic voxels) in the MRE acquisition for mechanical property estimation with nonlinear inversion (NLI). Hippocampal masks are generated and used to promote regional homogeneity during the estimation process through SPR, which reduces partial volume effects. The procedure returns tissue viscoelastic properties: shear stiffness, $\mu$, and damping ratio, $\xi$. B) Depiction of the oxygen consumption ($\text{VO}_2\text{max}$) treadmill test used to assess aerobic fitness. $\text{VO}_2\text{max}$ is considered the "gold standard" for measuring aerobic fitness. C) Illustration of spatial...
reconstruction task in which 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 errors and relative arrangement errors of objects.
Fig. 2.
A) Adjusted hippocampal damping ratio ($\xi'$) measure residuals plotted against spatial reconstruction task performance residuals. Positive values indicate better task performance. Pearson correlation coefficient, $r$, demonstrates a significant correlation for $\xi'$ suggesting that the more the hippocampus behaves like an elastic solid, the better an individual's memory performance. B) Hippocampal volume residuals plotted against spatial reconstruction task performance residuals demonstrating no significant relationship between volume and task performance.
Fig. 3.
A) Adjusted hippocampal damping ratio ($\xi'$) measure residuals plotted against relative VO$_2$max aerobic fitness score residuals. Pearson correlation coefficient, $r$, demonstrates a significant correlation for $\xi'$ suggesting that the more fit an individual is, the more the hippocampus behaves like an elastic solid. B) Hippocampal volume residuals plotted against relative VO$_2$max aerobic fitness score residuals demonstrating no significant relationship between volume and aerobic fitness in this sample.
Fig. 4.
Path model testing the effect of aerobic fitness on relational memory mediated by hippocampal $\xi'$. Regression path values are standardized coefficients. Asterisks indicate significance ($p < .05$).
Fig. 5.
Path model testing the effect of aerobic fitness on relational memory mediated by hippocampal $\xi'$ accounting for hippocampal volume. Regression path values are standardized coefficients. Asterisks indicate significance ($p < .05$).
Table 1

Descriptive statistics of the study variables.

|                        | Mean(SD) | Min/Max | Skewness |
|------------------------|----------|---------|----------|
| **Memory measures**    |          |         |          |
| Misplacement error (pixels) | 174.5(72.4) | 61.1/387.5 | 1.36 |
| Edge resizing error (pixels) | 137.6(47.8) | 45.5/267.7 | .89 |
| Rearrangement error (%) | 23.8(9.4)  | 6.7/45.7 | .76 |
| Swap error (%)         | 7.1(6.7)  | 0/27.3  | 1.73 |
| **Aerobic fitness measures** |        |         |          |
| Relative VO$_2$max     | 42.1(8.2) | 27.7/59.7 | 0.21 |
| VO$_2$ percential (%)  | 42.0(30.7) | 3/97    | 0.47 |
| **Hippocampal measures** |        |         |          |
| Adjusted DR            | .85(.03) | .75/.91 | −1.02 |
| Volume (mm$^3$)        | 8964(810) | 4629/10313 | −2.67 |
| **Caudate measures**   |          |         |          |
| Adjusted DR            | .80(.03) | .71/.83 | −0.9  |
### Table 2
Correlations among SR task dependent measures.

| Error type  | Misplacement | Edge resizing | Rearrangement | Swap      |
|-------------|--------------|---------------|---------------|-----------|
| Misplacement| 1.00         |               |               |           |
| Edge Resizing| 0.928 **    | 1.00         |               |           |
| Rearrangement| 0.897 **    | 0.904 **     | 1.00         |           |
| Swap        | 0.852 **    | 0.876 **     | 0.812 **     | 1.00      |

** indicates p < .001.