



## Aerobic fitness, hippocampal viscoelasticity, and relational memory performance

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### 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 VO<sub>2</sub>max, 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.

### 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

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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 amnesic 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, 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 ( $\text{VO}_2\text{max}$ ), 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 skewness 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 ms repetition/inversion/echo times).

The MRE acquisition used a 3D multislabs, 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 ms repetition/echo times; 240 mm field-of-view;  $150 \times 150$  matrix; 60 slices at 1.6 mm thickness. A pneumatic actuator (Resoundant; Rochester, MN, USA) generated 50 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 ( $\text{VO}_2\text{max}$ ; Fig. 1b) was used to assess aerobic fitness.  $\text{VO}_2\text{max}$  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 ( $\text{VO}_2$ ) 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 ( $\text{CO}_2/\text{O}_2$ ) greater than 1.1, (3) subjective rate of perceived exertion greater than 17 of 20, and (4) leveling of  $\text{VO}_2$  despite increasing aerobic demand. Maximum oxygen consumption ( $\text{VO}_2\text{max}$ ) is reported relative to body weight (relative  $\text{VO}_2\text{max}$ ) and was calculated as milliliters of oxygen per kilogram per minute (ml/kg/min).  $\text{VO}_2\text{max}$  scores were also standardized according to age- and gender-based norms and a  $\text{VO}_2\text{max}$  percentile measure was calculated for each participant.

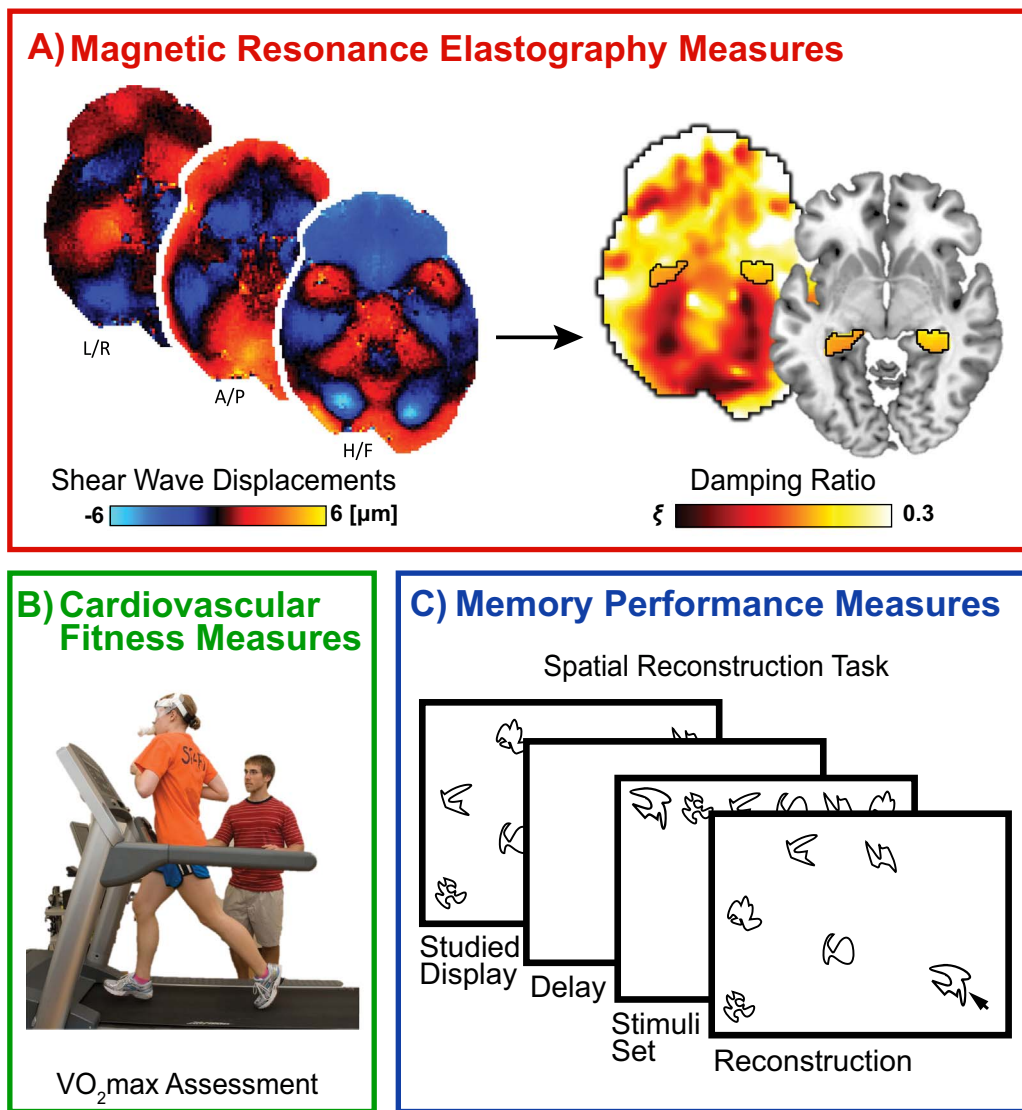
### Memory performance assessment

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 ( $\text{CFI} > 0.90$ ); root mean square error of approximation ( $\text{RMSEA} < 0.05$ ); standardized root mean residual ( $\text{SRMR} < 0.08$ ). Mediation was tested as statistical significance of an indirect effect (James and Brett, 1984). To avoid



**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 (VO<sub>2</sub>max) treadmill test used to assess aerobic fitness. VO<sub>2</sub>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.

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

**Table 1**

Descriptive statistics of the study variables.

|                                 | Mean(SD)    | Min/Max    | Skewness |
|---------------------------------|-------------|------------|----------|
| <b>Memory measures</b>          |             |            |          |
| 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     |
| <b>Aerobic fitness measures</b> |             |            |          |
| Relative VO <sub>2</sub> max    | 42.1(8.2)   | 27.7/59.7  | 0.21     |
| VO <sub>2</sub> percentual (%)  | 42.0(30.7)  | 3/97       | 0.47     |
| <b>Hippocampal measures</b>     |             |            |          |
| Adjusted DR                     | .85(.03)    | .75/.91    | -1.02    |
| Volume (mm <sup>3</sup> )       | 8964(810)   | 4629/10313 | -2.67    |
| <b>Caudate measures</b>         |             |            |          |
| Adjusted DR                     | .80(.03)    | .71/.83    | -0.9     |

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.



**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  $p < .001$ .

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 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,  $r=-.10$ ,  $p=.486$ . 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.

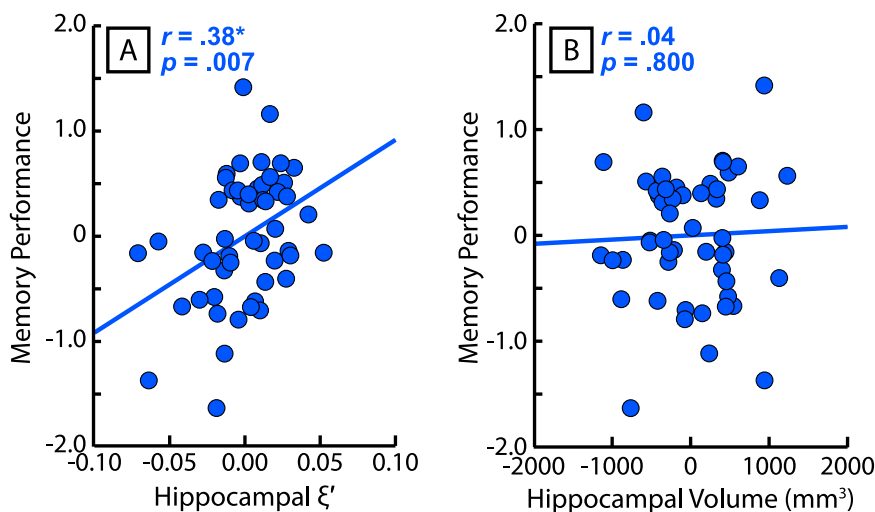
As before, caudate  $\xi'$  was not significantly correlated with aerobic fitness,  $r=.10$ ,  $p=.515$ . Again, Steiger's z-test revealed that this correlation was significantly smaller than the correlation between hippocampal  $\xi'$  and aerobic fitness,  $z=1.7$ ,  $p < .05$ .

*Relationships between aerobic fitness and memory performance*

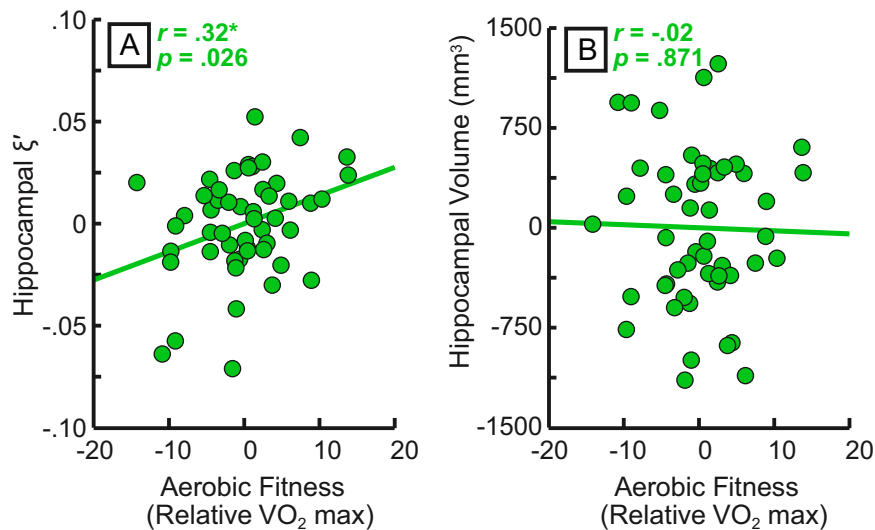
The correlation between SR task performance and aerobic fitness was also significant ( $r=.29^*$ ,  $p=.041$ ) consistent with previous work showing a significant relationship between relational memory performance and aerobic fitness in healthy young adults (Baym et al., 2014). Together these findings 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*

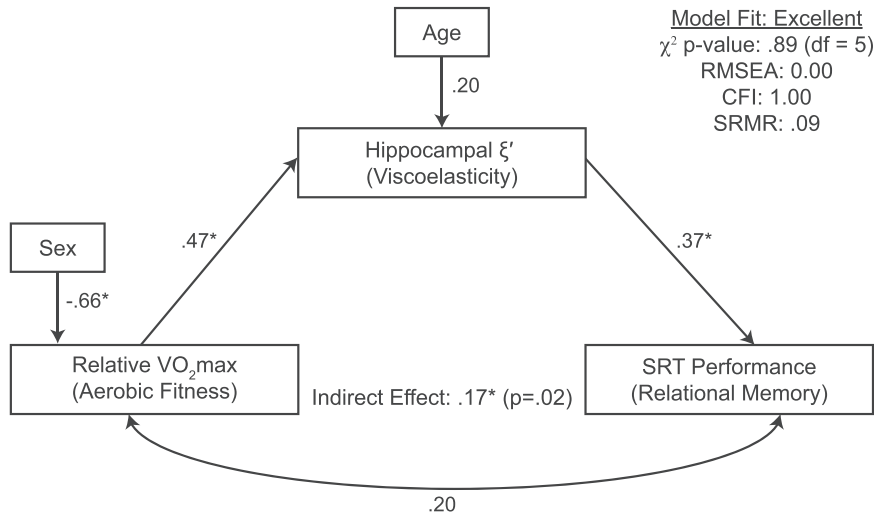
We tested the effect of aerobic fitness on relational memory mediated by hippocampal  $\xi'$  and hippocampal volume in two path models. The first model that only included  $\xi'$  as a mediator had excellent fit:  $\chi^2(5) = 1.70$ ,  $p=0.89$ ; CFI=1.00; RMSEA=0.00;



**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  $VO_{2max}$  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  $VO_{2max}$  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 ( $p < .05$ ).

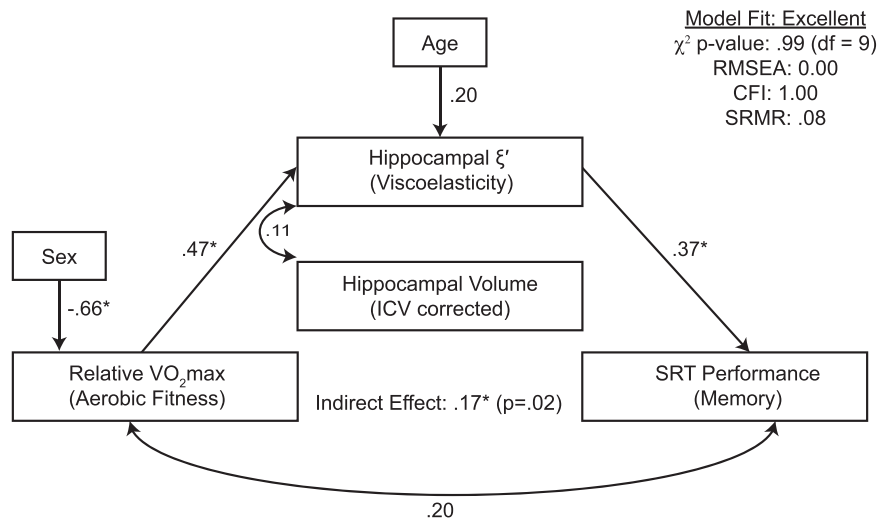
SRMR=0.09. Similar to the pattern of correlations reported, better aerobic fitness predicted greater hippocampal  $\xi'$  ( $0.47, p < 0.001$ ; BS 95% CI: 0.001/0.002) that in turn accounted for greater SR task performance ( $0.37, p=0.003$ ; BS 95% CI: 3.89/12.57). Critically,  $\xi'$  mediated the 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



**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 ( $p < .05$ ).

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, gliogenesis, 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 consis-

tently 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 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 intrahippocampal 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 inter-relatedness 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.

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