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Aerobic fitness, hippocampal viscoelasticity, and relational memory performance

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A B S T R A C T

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_2max, 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 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_2max), 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-