Aerobic Fitness Predicts Relational Memory but Not Item Memory Performance in Healthy Young Adults

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Abstract

■ Health factors such as an active lifestyle and aerobic fitness have long been linked to decreased risk of cardiovascular disease, stroke, and other adverse health outcomes. Only more recently have researchers begun to investigate the relationship between aerobic fitness and memory function. Based on recent findings in behavioral and cognitive neuroscience showing that the hippocampus might be especially sensitive to the effects of exercise and fitness, the current study assessed hippocampal-dependent relational memory and non-hippocampal-dependent item memory in young adults across a range of aerobic fitness levels. Aerobic fitness was assessed using a graded exercise test to measure oxygen consumption during maximal exercise (VO_2max), and relational and item memory were assessed using behavioral and eye movement measures. Behavioral results indicated that aerobic fitness was positively correlated with relational memory performance but not item memory performance, suggesting that the beneficial effects of aerobic fitness selectively affect hippocampal function and not that of the surrounding medial temporal lobe cortex. Eye movement results further supported the specificity of this fitness effect to hippocampal function, in that aerobic fitness predicted disproportionate preferential viewing of previously studied relational associations but not of previously viewed items. Potential mechanisms underlying this pattern of results, including neurogenesis, are discussed. ■

INTRODUCTION

The decline of cardiovascular health in the United States has become of increasing concern over the past two decades in large part because of marked decrease in physical activity and fitness. Indeed, the top two causes of death in the United States, cardiovascular disease and cancer, can be in many cases linked to poor lifestyle choices. Although sedentary lifestyle and corresponding low aerobic capacity have well understood physical consequences, their influence on cognition has only recently gained attention.

Seminal work in animal models has linked aerobic exercise to the structure and function of the hippocampus (Voss, Vivar, Kramer, & van Praag, 2013). In rodents, aerobic exercise increases angiogenesis and synaptogenesis in the whole brain and additionally increases neurogenesis in the hippocampus (Wu, Ying, & Gomez-Pinilla, 2008; van Praag et al., 2002; van Praag, Christie, Sejnowski, & Gage, 1999; van Praag, Kempermann, & Gage, 1999). Aerobic exercise also increases production and secretion of brain-derived neurotrophic factor, a marker of neurogenesis in the hippocampus that has been linked to decreases in inflammation in the brain (Wu et al., 2008; Cotman, Berchtold, & Christie, 2007). On the behavioral side, rodent models have shown improvements in learning and memory following physical activity (van Praag,

Shubert, Zhao, & Gage, 2005). As in animal models, human aerobic exercise has been shown to increase cerebral blood volume in the hippocampus, which has been linked to neurogenesis (Pereira et al., 2007).

Converging evidence from human and animal lesion data has demonstrated that the hippocampus is critically involved in relational memory, a form of memory necessary for flexibly binding together individual elements of experience into memory (Konkel & Cohen, 2009; Ryan, Althoff, Whitlow, & Cohen, 2000; Bunsey & Eichenbaum, 1996). In contrast, memory for individual items can be demonstrated independent of the hippocampus and is thought to instead rely on the perirhinal cortex surrounding the hippocampus (Davachi, Mitchell, & Wagner, 2003). To the extent that the hippocampus seems to be a particularly favorable target of fitness effects on the adult brain, the effects of fitness on memory function might be expected, likewise, to affect relational memory disproportionately.

Previous research has linked aerobic fitness to hippocampal function at both ends of the human lifespan (Erickson et al., 2011; Chaddock et al., 2010; Hillman, Motl, et al., 2006). Markers of exercise-related neurogenesis have been shown to be associated with improved memory performance in older adults (Erickson et al., 2011). One reason for this preferential focus on the ends of the developmental spectrum concerns variability, in that children and older adults show more cognitive and neuroarchitectural

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variability than young adults, maximizing opportunity to observe strong fitness effects (Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011).

Nonetheless, studies have begun to examine the cognitive effects of aerobic fitness or physical activity in young adults. One cohort study of over 1 million men found that aerobic fitness at age of 18 significantly predicted full-scale intelligence quotient as well as specific subscales of intelligence (Åberg et al., 2009). Demonstrating that aerobic fitness can be linked to specific cognitive abilities with known neural substrates, positive relationships have been reported between physical activity and aerobic fitness with measures of inhibitory control (Hillman, Motl, et al., 2006), task-switching abilities (Hillman, Kramer, Belopolsky, & Smith, 2006), and ability to flexibly employ cognitive control in a task requiring inhibition and action monitoring (Themanson, Pontifex, & Hillman, 2008). Moving into the broad realm of memory, one cohort study indicated that physical activity in a middle-aged sample predicted rate of verbal memory decline in later adulthood (Richards, Hardy, & Wadsworth, 2003). In the current study, we sought to investigate the degree to which aerobic fitness may differentially predict hippocampal-dependent relational memory and non-hippocampal-dependent item memory in healthy young adults. We aimed to investigate (1) whether aerobic fitness is broadly related to memory function in young adults and (2) the specificity of the relationship between aerobic fitness and hippocampal function relative to the function of surrounding medial temporal lobe (MTL) cortex. This allowed an investigation of the selectivity of the relationship between aerobic fitness and memory in the brain, testing whether effects are specific to hippocampal function or are more globally related to memory function.

In addition to measuring overt behavioral response, we assessed relational and item memory using eye movement measures (Hannula, Baym, Warren, & Cohen, 2012). We measured aerobic fitness using VO_2max and hypothesized that aerobic fitness would be positively correlated with relational, but not item, memory, demonstrated by improved accuracy and greater proportion of time spent viewing correctly selected relational associations.

METHODS

Participants

Sixty-eight neurologically intact young adults aged 18–34 years (21.79 ± 0.4; 32 men) from the University of Illinois community participated in this study. One additional participant was excluded for failure to reach two or more maximum effort criteria on the aerobic fitness assessment. Two participants were excluded from eye movement analyses because of data file corruption or watering eyes, leaving 66 participants in those analyses. All participants provided written informed consent in accor-

dance with the regulations of the University of Illinois institutional review board, and all procedures were in accordance with the regulations of the University of Illinois institutional review board.

Aerobic Fitness Assessment

Aerobic fitness was evaluated using a graded exercise test designed to measure maximal oxygen consumption (VO_2-max) during physical activity. VO_2 max is considered the "gold standard" for measuring aerobic fitness, and higher scores on this test indicate increased aerobic capacity (American College of Sports Medicine, 2014). VO_2max scores were assessed using an indirect computerized calorimetry system (ParvoMedics True Max 2400, Sandy, UT) during a modified Balke treadmill test (American College of Sports Medicine, 2014). During the test, participants' heart rate was constantly monitored using a Polar heart rate monitor (Polar WearLink +31, Polar Electro, Oulu, Finland) and individual subjective rate of perceived exertion was assessed every 2 min using the Borg scales of perceived exertion (American College of Sports Medicine, 2014).

The VO_2max test included an initial warm-up period in which the treadmill gradually increased in speed while the participant walked on it. After this warm-up period, treadmill speed remained constant whereas incline was increased 2–3% every 2 min. Average oxygen consumption and respiratory exchange ratio were sampled every 20 sec during the test using a mouthpiece. Maximum oxygen consumption (VO_2max) is reported relative to body weight (relative VO_2max) and was calculated as milliliters of oxygen per kilogram of bodyweight per minute (ml/kg/min). Maximum effort 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 (American College of Sports Medicine, 2014).

Memory Task

Several days following fitness testing (3.15 ± 0.29), participants completed a memory task designed to measure both relational and item memory that had both behavioral and eye movement measures (Monti, Hillman, & Cohen, 2012). This task was divided into four study–test blocks each designed to measure either relational memory or item memory.

Stimuli included 216 novel creatures created in Spore Creature Creator (Electronic Arts, Inc., Redwood City, CA; see Figure 1 for examples) and were presented using Presentation software (Neurobehavioral Systems, nbs.neuro-bs.com) on a 21-in. color monitor. Creatures were presented on black backgrounds and resized to
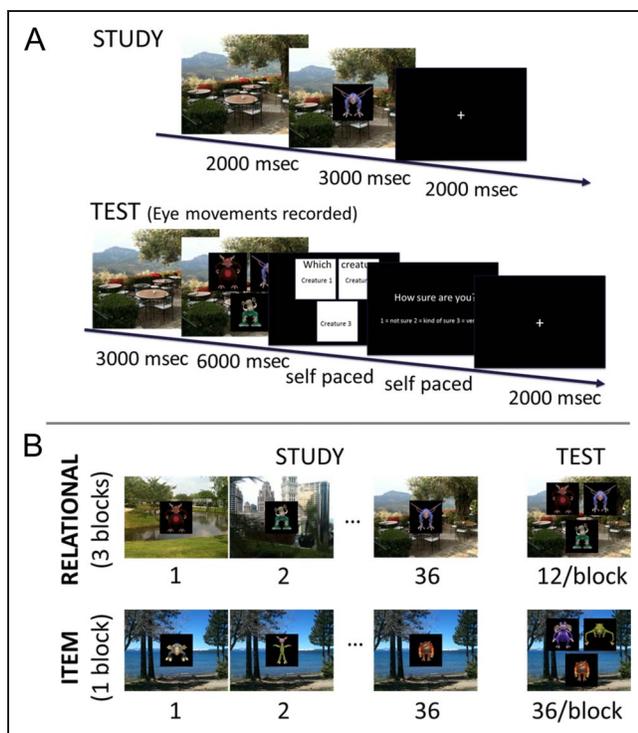
Figure 1. Example stimuli and displays from the memory task. (A) The task progression of study and test phases of the task. (B) The Relational condition in the top row and the Item block in the bottom row.

480×480 pixels (16.4° visual angle at a distance of 46 cm). One hundred ten color images of real-world scenes measuring 1280×1280 pixels (42.5° visual angle at a distance of 46 cm) and taken by Brand X photography were used as scene backgrounds.

An Eyelink 1000 eye tracker (SR Research, Mississauga, Ontario, Canada) was used to remotely record eye movements. The eye tracker was calibrated immediately before the start of the test phase of each block. A desk-mounted gel-padded chin rest was used to minimize head movement during data collection.

Trials in each block of the task (both Relational and Item conditions) followed the same format (see Figure 1). During the study phase, participants studied 36 creature–scene pairings in which a scene preview was presented for 2000 msec at which time a creature was superimposed in the center of the scene. The creature–scene pairing remained on the screen for 3000 msec. A fixation cross was then presented for 2000 msec before the onset of the next scene preview. Following the study trials, a test phase used behavioral response and eye movement measures to assess encoding success. During each trial, a 3000-msec scene preview was shown after which three creatures were superimposed atop the scene for 6000 msec (see Figure 1). To minimize eye movement away from the test display during behavioral response, participants were instructed to press a single button when

they saw the creature that was originally paired with that scene (Relational condition) or that had been studied (Item condition). Following the probe, the test array was replaced with a black screen with three white boxes where the creatures had been. Each box was numbered, and participants were told to voice to the experimenter which number corresponded to the creature they had selected. Confidence in that decision was then assessed using a three-point scale (1 = *not sure*, 2 = *kind of sure*, and 3 = *very sure*).

In each block of the Relational condition, participants were explicitly encouraged to encode the relations between unique creature–scene pairings (Hannula, Ryan, Tranel, & Cohen, 2007) by pressing one of two buttons to indicate whether they supposed each creature "lived" in the paired habitat "alone" or "with others." Following each study block, participants were tested on 12 probe trials in which one of the scenes from the study phase was previewed, then superimposed with three creatures that had been studied in that block, only one of which had been studied with that scene. Familiarity across probe creatures was thus matched necessitating the use of hippocampal-dependent relational memory. Participants were instructed to make a single button press when they felt they knew which creature had been studied with that scene.

In the Item condition, participants studied creature–scene pairings with unique creatures each paired with the same scene. To encourage encoding of individual items (i.e., individual creatures), participants were instructed to press one of two buttons to indicate whether they judged that creature to look more like a "boy" or a "girl." During the test phase, probe displays showed one studied creature and two novel creatures paired with the originally studied scene for that block. Participants were instructed to make a single button press when they felt they knew which creature had been studied. Given that two creatures were novel and one studied, the Item condition could be solved using familiarity alone, an ability that has been shown to be independent of the hippocampus (Davachi & Wagner, 2002).

The order of blocks was counterbalanced such that half of participants completed the Item condition first and the other half the Relational condition first. To familiarize participants with the task demands and to ensure that the participants were aware of the memory demands of the task, an abbreviated practice study–test block was provided before the start of each condition. Finally, lists of stimuli presented in the Item or Relational conditions and target locations on test trials were counterbalanced across participants.

To exclude the possibility that the current effects may be because of acute exercise effects (Hillman, Snook, & Jerome, 2003), participants were asked to refrain from moderate-to-vigorous exercise or physical activity on the day of cognitive testing, including walking or biking to the session.

Data Preprocessing and Analysis

Behavioral Data

Pearson's correlations were performed to assess bivariate relationships between VO_2max and memory outcomes. Next, to determine which covariates were associated with VO_2max and therefore may have influenced our outcome of interest, we performed bivariate correlations between VO_2max and age, sex, and body mass index (BMI). Partial correlations included sex and BMI as control variables as these were correlated with VO_2max. Statistics were performed using SPSS 19 (IBM, Somers, NY).

Eye Movement Data

Eye movement analyses were performed on ROIs in the three-creature test arrays. Each test array contained three ROIs that corresponded to the locations of each of the three creatures. Time courses of viewing elicited during trials in which the participant correctly selected the studied creature (Item condition) or relation (Relational condition) were compared with viewing elicited during trials in which the participant selected an incorrect creature. Time courses were plotted both time-locked to the onset of the three-creature display and time-locked to behavioral response (see Figure 2). Onset-locked time courses were calculated in 500-msec time bins for the first 3500 msec following onset of the three-creature array. Response-locked time courses were calculated in 500-msec time bins from 2500 msec before behavioral response to 2500 msec following behavioral response. Response-locked time courses were then quantified using preferential disproportionate viewing (PDV), which was defined within participant as the difference in proportion of time spent viewing correctly selected matching creatures relative to proportion of time spent viewing incorrectly selected creatures before behavioral response (including time bins: 2500–2000, 2000–1500, 1500–1000,
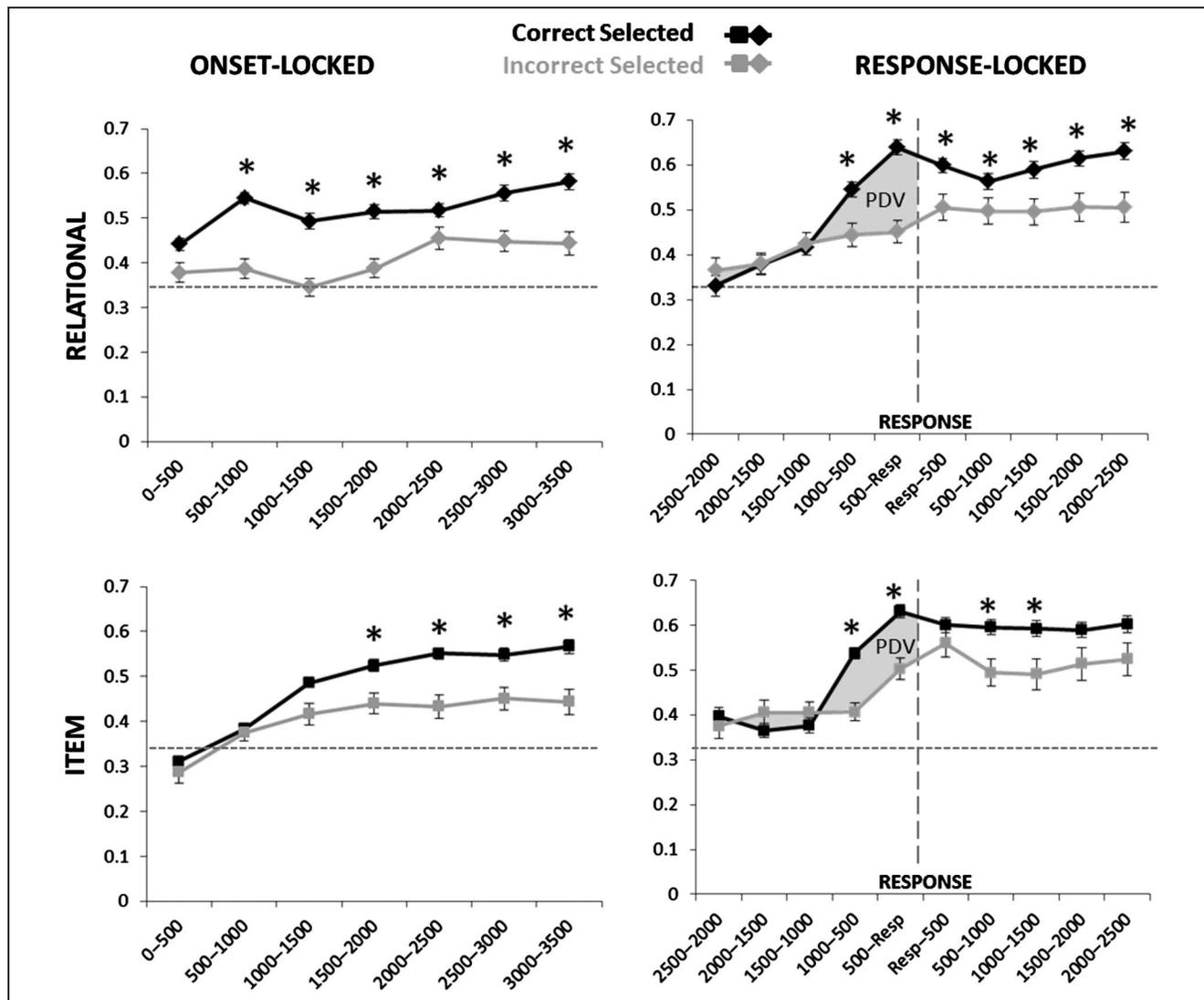

Figure 2. Eye movement time courses depicting proportion of viewing time. Top: Relational condition. Bottom: Item condition. Shaded gray regions indicate PDV. Horizontal dashed lines indicate chance viewing of 33%. *$p < .05$, Bonferroni-corrected. Error bars indicate *SEM*.

Table 1. Demographic Variables and Behavioral Performance[a]

Characteristic	All Participants (n = 68)	Women (n = 36)	Men (n = 32)
Age, years	21.79 ± 0.40	21.50 ± 0.52	22.13 ± 0.63
BMI, kg/m^2	24.29 ± 0.51	23.56 ± 0.76	25.11 ± 0.64
VO$_2$max, ml/kg/min	48.66 ± 1.30	42.16 ± 1.49[b]	55.97 ± 1.31
BMI category [count (percent of sample)]			
Underweight	5 (7)	4 (11)	1 (3)
Normal weight	36 (53)	20 (56)	16 (50)
Overweight	22 (32)	9 (25)	13 (41)
Obese	5 (7)	3 (8)	2 (6)
Relational memory accuracy (%)	72.67 ± 0.02	67.21 ± 0.02	78.82 ± 0.03
Item memory accuracy (%)	79.77 ± 0.02	78.62 ± 0.02	81.08 ± 0.03
Relational memory RT, correct trials only (msec)	2503.50 ± 77.74	2225.52 ± 112.43[b]	1942.86 ± 111.38
Item memory RT, correct trials only (msec)	2093.48 ± 79.40	2547.92 ± 101.72	2471.82 ± 122.23

[a]Unless otherwise noted, values are means ± *SEM*s.

[b]Significantly different from males, $p < .05$ (*t* tests).

1000–500, and 500–Response; see gray-shaded region in Figure 2). PDV provides an assessment of memory that precedes conscious awareness (as indicated by behavioral response) and was designed to account for the phenomenon in which eye movements are directed toward the creature that the participants will subsequently behaviorally select (for a review of the use of eye movements to measure memory, see Hannula et al., 2010). Indeed this difference between correctly selected creatures and incorrectly selected creatures reflects the magnitude to which previous exposure to the stimuli enhances this effect (Hannula et al., 2007). Trials were excluded from further analysis if the participant failed to look at any of the three ROIs for >30% of total viewing time. Eye move-

ment preprocessing and analysis was performed using Matlab 10.0 (Mathworks, Natick, MA).

RESULTS

Behavioral Performance

Descriptive statistics regarding behavioral accuracy, RT, VO$_2$max, and demographic variables are reported in Table 1. Unadjusted bivariate correlations between behavioral accuracy and VO$_2$max yielded a significant positive correlation in the Relational condition ($r = .47$, $p < .001$) but no significant correlation in the Item condition ($r = .19$, $p < .13$; see Figure 3). Control variables
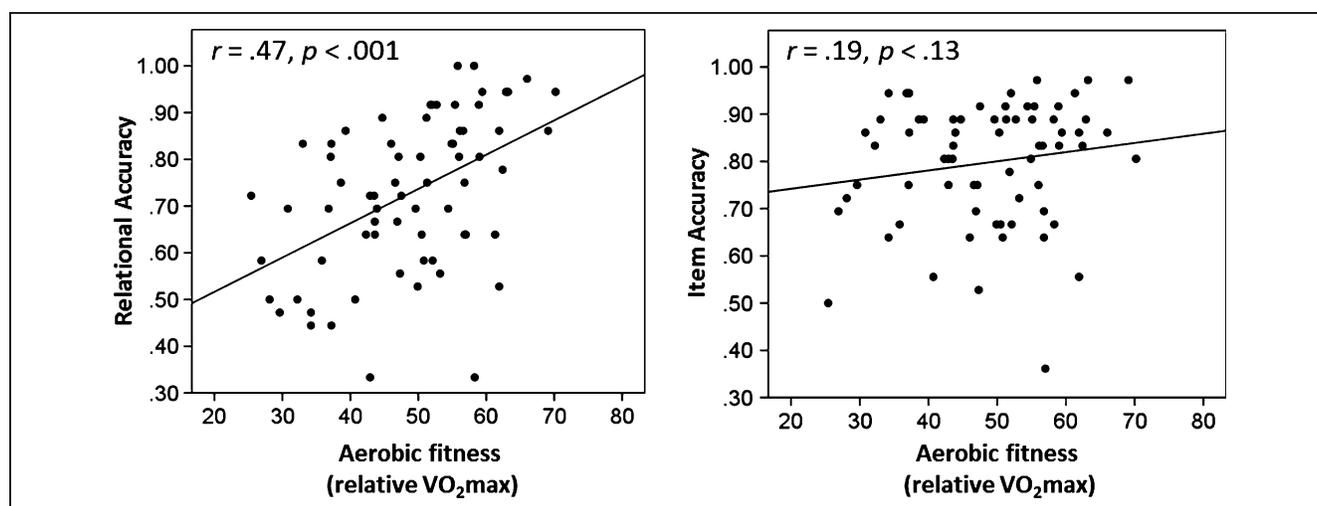

Figure 3. Scatterplots depicting the relationships between aerobic fitness and behavioral accuracy in the Relational and Item conditions. Aerobic fitness is reported as relative VO$_2$max, calculated as milliliters of oxygen per kilogram of bodyweight per minute (ml/kg/min).
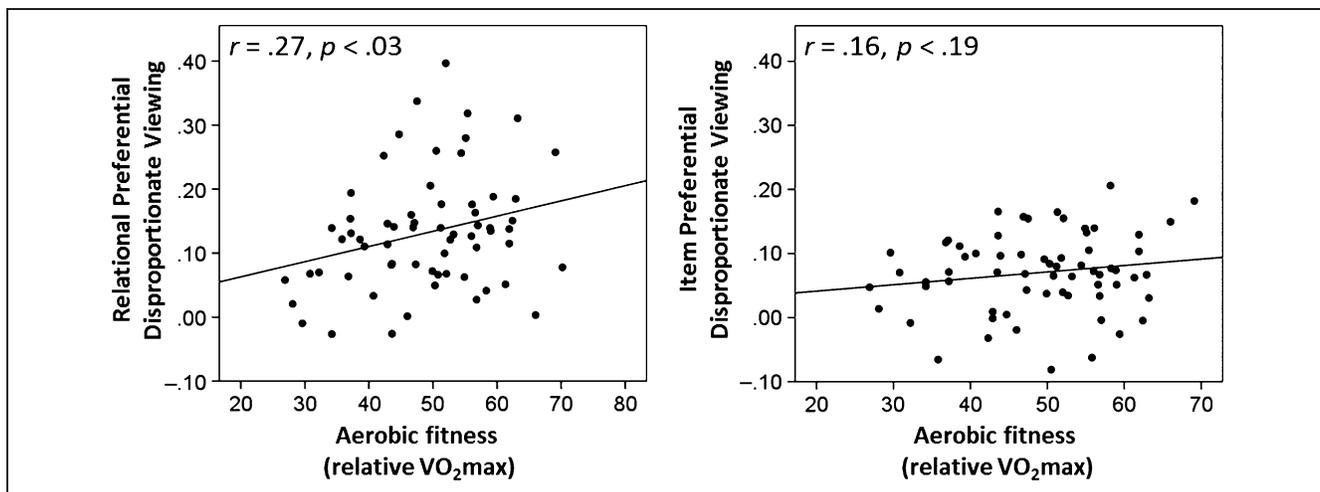
Figure 4. Scatterplots depicting the relationships between aerobic fitness and PDV of correct selections greater than incorrect selections before response in the Relational and Item conditions. As in Figure 3, aerobic fitness is reported as relative VO_2max, calculated as milliliters of oxygen per kilogram of bodyweight per minute (ml/kg/min).

sex and BMI were found to be significantly related to VO_2max ($t_{66} = 6.87$, $p < .001$, and $r = -.25$, $p < .04$, respectively), but age was not ($p > .05$). Finally, adjusting for sex and BMI, the partial correlation between VO_2max and Relational accuracy remained significant ($r = .32$, $p < .01$). Secondary analyses separating the correlations between fitness and memory performance by sex revealed a significant positive correlation between behavioral accuracy and VO_2max in the Relational condition among women ($r = .43$, $p < .009$) but not men ($r = .26$, $p < .16$), although there was a numerical trend in the positive direction for men. There were no significant correlations in the Item condition for either women ($r = .03$, $p < .86$) or men ($r = .10$, $p < .61$).

Eye Movements

Onset-locked Time Courses

Relative to the onset of the three-creature test display, PDV became significant during the first 1000 msec of viewing in the Relational condition, replicating previous studies using a similar paradigm ($t_{65} = 5.17$, $p < .001$; Hannula et al., 2007) and during the first 2000 msec in the Item condition ($t_{65} = 2.78$, $p < .01$; see Figure 2).

Response-locked Time Courses

Eye movement data again replicated previous findings in that approximately 500–1000 msec before behavioral response, participants preferentially viewed the stimulus that had been paired with that scene background in the Relational condition ($t_{65} = 4.35$, $p < .001$; Hannula et al., 2007). A similar pattern of PDV was also observed in the Item condition ($t_{65} = 5.62$, $p < .001$; see Figure 2).

Correlations with Aerobic Fitness

The bivariate correlation between VO_2max and the magnitude of PDV before response yielded a positive relationship in the Relational condition ($r = .27$, $p < .03$), but not in the Item condition ($r = .16$, $p < .19$; Figure 4), further supporting the specificity of the fitness effect to relational memory. A partial correlation including sex and BMI as control variables continued to show a marginal positive relationship between VO_2max and PDV in the Relational condition ($r = .25$, $p < .053$).

DISCUSSION

The current study yielded several novel findings, including showing for the first time a positive relationship between aerobic fitness and memory function in healthy young adults. Moreover, we demonstrated for the first time in young adults (consistent with the results of a large animal literature) that this effect is specific to hippocampal-dependent relational memory, without a corresponding non-hippocampal-dependent item memory effect. Secondary analyses by sex revealed the same pattern of results for both men and women, but that these effects were statistically carried by women. Eye movement effects mirrored the behavioral findings, with the effects of aerobic fitness being specific to the Relational condition, and not the Item condition. Interestingly, these eye movement effects emerged before behavioral response.

There are several possible explanations for the observed relationship between aerobic fitness and memory function in young adults, stemming from the known effects of physical activity on angiogenesis, synaptogenesis, neurogenesis, and neural inflammation (Wu et al., 2008; Cotman et al., 2007; van Praag et al., 2002; van Praag, Christie, et al., 1999). In adjudicating between these possibilities, we note

the observed specificity of aerobic fitness on hippocampal-dependent relational memory relative to MTL cortical-dependent item memory. With convergence from the animal literature, one major factor that differentiates hippocampus from MTL cortex is the presence of neurogenesis in the hippocampus. Many rodent studies demonstrate a positive relationship between physical activity and neurogenesis in the hippocampus, which is also reflected in enhanced performance on hippocampal tasks such as spatial (relational) memory and pattern separation, the ability to discriminate between highly similar or overlapping stimuli or memory representations (Creer, Romberg, Saksida, van Praag, & Bussey, 2010; van Praag et al., 2005; van Praag, Christie, et al., 1999). Indeed, these effects have been shown to be present in hippocampal tasks but notably absent in nonhippocampal tasks such as motor tasks (Clark et al., 2008).

Next, the current study bolsters the literature regarding the utility of eye movements in assessing memory. Independent of aerobic fitness, we observed that eye movements were disproportionately directed to selected targets relative to selected lures in both the Relational and Item conditions. This finding underscores the applicability of eye movements in measuring multiple forms of memory (Hannula et al., 2010). The finding here that preferential viewing emerged before behavioral response in viewing replicates previous studies using a similar paradigm, in that preferential viewing to the previously viewed relation was apparent up to 1000 msec before behavioral response (Hannula et al., 2007). The current study extended these results, however, to show preferential viewing effects both for previously viewed items and previously viewed relations. Taken together, these findings support the idea that eye movements are a veridical index of previous experience (Hannula et al., 2010).

Additionally, replicating previous studies using a similar paradigm, time courses plotted relative to the onset of the three-creature display showed early divergence in viewing between correctly selected relations relative to incorrectly selected relations (see Figure 2; Hannula et al., 2007). Interestingly, comparing across conditions, this effect emerges earlier in the Relational condition than the Item condition: It was evident in the first 1000 msec in the Relational condition and not until the 1500–2000 msec window in the Item condition. Converging with previous work showing that removing the scene preview delays PDV by approximately 1000 msec (Hannula et al., 2007), this effect is likely because of the lack of diagnostic scene preview in the Item condition, given that each scene background is identical in that condition. In other words, the scene background in the Item condition carries no information about which set of creatures will appear with it, whereas the scene background in the Relational condition allows for reactivation of the memory for the target creature. Indeed, the rapidly emerging preferential viewing in the time course of this effect in the Relational condition suggests reactivation of the relational association during the scene preview (Walker, Low, Cohen, Fabiani, &

Gratton, 2014). This then allows preferential viewing to emerge sooner following appearance of the three-creature array, as well as allowing for faster behavioral responses than in the Item condition.

In conclusion, the current study extends the literature in several meaningful ways. First, we demonstrated a selective relationship between aerobic fitness and hippocampal-dependent relational memory measured both behaviorally and using eye movements, and no corresponding relationship with hippocampal-independent item memory. It should be noted, however, that the current study used a cross-sectional design, limiting our ability to infer a causal relationship between aerobic fitness and memory function. Second, we showed that preferential viewing is elicited before behavioral response, both for relational memory and item memory, further reinforcing the utility of eye movements as a sensitive measure of prior experience. Considering the increasingly sedentary lifestyle in the modern world, the current results highlight the importance of staying physically active to maintain aerobic capacity and maximize hippocampal function even during the cognitive peak of young adulthood.

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