ASSOCIATIONS BETWEEN CARDIORESPIRATORY FITNESS AND WORKING MEMORY FMRI BRAIN ACTIVITY

by

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Working memory (WM) and associated brain areas show deficits with increasing age. However, higher cardiorespiratory fitness (CRF) has been associated with better WM across the lifespan. The mechanisms by which CRF impacts WM are poorly understood. One possible mechanism is that CRF influences the integrity and function of brain regions that are involved in supporting WM function, and that this, in turn, influences accuracy rates on tasks that measure WM. Very few studies have tested whether the association between CRF and WM is statistically mediated by measures of brain function. This study addressed this gap in knowledge by examining the relationship between CRF, brain activation, and WM. We tested whether brain activation during a WM task statistically mediated the relationship between CRF and WM.

Baseline data of 125 adults (M=44.34 ± 8.60 years) were included in this study. CRF was assessed via a submaximal graded exercise test. Magnetic resonance images were collected during the n-back task to examine neural responses to WM. FMRIB's Software Library was used for fMRI data preprocessing and analysis. Regions-of-interest were defined by conducting a conjunction analysis to identify brain regions sensitive to both CRF and performance on the n-back task. Linear regression models examined the association of CRF with WM and brain activation in the left anterior cingulate cortex, left insula, and right insula.

After controlling for age, gender, race, and years of education, CRF was not significantly related to accuracy on the WM task (all $p>.15$). However, consistent with our hypotheses, higher CRF was significantly related to greater brain activation in the left insula ($p<.028$) during the 2-

back WM condition. Heightened brain activation in the left insula was not associated with WM accuracy (p=.12) after correction for variation due to age, gender, race, and education. Thus, statistical mediation could not be tested.

Although higher CRF was associated with greater brain activation in the left insula, neither CRF nor heightened left insula activation were associated with variations in WM performance after adjusting for several confounding variables. These results suggest that there are other mediators that explain the relationship between CRF and WM performance in midlife.

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1.0 INTRODUCTION

The study of the relationship between exercise and cognition dates back several decades to the pioneering work of Spirduso and colleagues, who found that older athletes had faster reaction times compared to their sedentary counterparts (1975). Since then, many studies have replicated these findings and extended them to other cognitive processes. Meta-analyses of randomized exercise interventions have concluded that exercise training improves cognitive function across the lifespan, with the most robust benefits observed in executive control processes (Colcombe & Kramer, 2003; P. J. Smith, Blumenthal, Babyak, et al., 2010). Executive-control processes include shifting mental sets, updating task demands, planning, inhibition of predominant responses, monitoring and regulating responses, goal maintenance, cognitive flexibility, and working memory (McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010). As such, the term “executive function” is an umbrella term that includes numerous cognitive functions including working memory (Zillmer & Spiers, 2001). Although there are several different definitions of working memory, it has classically been considered to be defined as a cognitive domain that includes the maintenance and manipulation of both verbal and visual information over a short period of time (Baddeley, 1992). Working memory and associated brain areas show deficits among many different patient populations, including older adults, Alzheimer’s disease, and stroke (Kirova, Bays, & Lagalwar, 2015; Nyberg & Bäckman, 2011; van Geldorp, Kessels, & Hendriks, 2013). This suggests that exercise might be an effective approach for improving executive function, including working memory, in many different populations. Yet, the mechanisms by which exercise impacts working memory remain poorly understood.

Midlife cardiovascular risk factors are associated with an increased risk of cognitive decline later in life, suggesting that healthy lifestyle factors in midlife might be critical for healthy cognitive aging (Huntley et al., 2018; Kroll et al., 2016; Meng et al., 2014). However, the impact of exercise on cognitive function in midlife, a sensitive period for detecting early changes in cognition, has not been thoroughly investigated. This study aims to address these gaps by studying a sample of middle-aged adults and examining a potential mechanism by which healthy lifestyle factors are related to working memory through associated brain areas.

1.1 Cardiorespiratory Fitness & Working Memory

Higher levels of aerobic activity have been linked to greater cardiorespiratory fitness at any age (Fleg et al., 2005). Cardiorespiratory fitness, as assessed via a graded exercise treadmill test (VO_{2max}), is a measure used to describe how well an individual's cardiovascular system is utilizing oxygen. Among older adults, higher cardiorespiratory fitness has been associated with better performance on measures of working memory (Erickson et al., 2009; Voss et al., 2010). One study examined performance on a spatial working memory task, during which participants (N=165, 51-81 years old) determined whether a dot appeared in the same location as the target dots presented three seconds earlier (Erickson et al., 2009). Here, higher VO_{2max} levels were associated with higher accuracy rates for the most difficult task condition, accounting for 5% of the variance in spatial working memory performance (Erickson et al., 2009). Similar results were found in another study (N=120, mean age=66.5) using the same task, such that higher VO_{2max} levels were associated with higher accuracy and faster response times across all levels of the task (Voss et al., 2010). This study also found higher VO_{2max} levels to be associated with fewer errors on the Wisconsin Card Sorting Task, another commonly used measure of executive function that measures the ability to flexibly adapt to a changing rule set (Voss et al., 2010). In sum, studies of older adults have unequivocally found that higher cardiorespiratory fitness is associated with better executive function, including tests that measure working memory.

Several studies have examined the relationship between cardiorespiratory fitness and working memory among younger populations. One study of young adults (N=93, mean age=23.01) examined performance on a Delayed-Matched-to-Sample working memory task, which required participants to determine which of the two uniquely patterned grids of yellow and red squares was identical to the sample display (Chudasama, 2010). They found higher VO_{2max} levels to be associated with shorter retrieval latency and better working memory performance (Hwang & Castelli, 2015). In a study of children (N=79, 9-11 years old), higher VO_{2max} levels and higher muscular fitness, as assessed using a full-body battery of strength exercises, was associated with better working memory performance (Kao, Westfall, Parks, Pontifex, & Hillman, 2017). Further, the association between muscular fitness and working memory was independent of cardiorespiratory fitness suggesting that components of fitness might impact executive function differently (Kao et al., 2017). In addition, increases in VO_{2max} levels among preadolescent children over a three year period were associated with better working memory performance on the most difficult task condition of the n-back paradigm (Scudder et al., 2016). These studies suggest that cardiorespiratory fitness may also be important for optimal working memory performance in younger populations.

There have been only a handful of studies examining these associations in midlife. One study of middle-aged breast cancer survivors and age-matched controls (N=62, mean age=55.4) suggests that cardiorespiratory fitness may also be important for working memory in midlife. Specifically, higher VO_{2max} levels were associated with better performance on the n-back working memory task regardless of disease status (Mackenzie et al., 2016). Although this study provides a basis for studying the association between cardiorespiratory fitness and working memory in midlife, it does not provide an explanation for the underlying mechanism for the better performance. This study aims to extend these findings in a larger sample of midlife adults and examine the mechanisms by which this relationship manifests.

1.2 Cardiorespiratory Fitness & Working Memory fMRI Brain Activation

Since increased exercise positively influences cardiorespiratory fitness, a closer examination of the exercise literature in rodents may provide information regarding the neurobiological mechanisms in humans. Data collected from animal models suggest that there might be several explanations for the relationship between cardiorespiratory fitness and working memory. Rodent studies have demonstrated that aerobic exercise influences the production of neurotrophic factors, such as brain-derived neurotrophic factor, vascular endothelial growth factor, and insulin-like growth factor 1 (Neeper, Gómez-Pinilla, Choi, & Cotman, 1995). The upregulation of neurotrophic factors, in turn, increases neuronal survival (Barde, 1994), synaptic development and plasticity (Lu & Chow, 1999), and the development of new neurons (van Praag, Christie, Sejnowski, & Gage, 1999). It is thought that, as a result, the brain has more plasticity, efficiency and adaptivity, allowing for better memory performance (van Praag et al., 1999).

Functional magnetic resonance imaging (fMRI) studies of human populations reveal that these cellular and molecular benefits of exercise in rodents may extend to humans. fMRI allows us to examine alterations in blood flow patterns, or metabolic activity, as a function of changes in neuronal activity. Variations in cardiorespiratory fitness are associated with differences in task-induced brain activity, as assessed by the blood oxygen level dependent (BOLD) response (Colcombe et al., 2004; Prakash et al., 2011). In one study of older adults (N=41, mean age=67.0), higher VO_{2max} levels were associated with differences in brain activation during a flanker executive-function task (Colcombe et al., 2004). The flanker paradigm is a commonly employed task used to investigate attentional and inhibitory functioning, as it requires the filtering of misleading information to perform accurately (Stoffels, Van der Molen, & Keuss, 1985). In particular, they found enhanced brain activation in regions of the prefrontal and parietal cortices, particularly the middle frontal gyrus, superior frontal gyrus and superior parietal lobes, as well as reduced brain activation in the anterior cingulate cortex (Colcombe et al., 2004). These results are consistent with literature demonstrating that the prefrontal and parietal cortices are involved in supporting processes related to attentional control and selective attention (Casey et al., 2000; Postle, 2006). Furthermore, since the anterior cingulate cortex supports conflict resolution and control processes, less activity in this area as a function of higher fitness suggested that there was less need for conflict resolution processes in higher fit older adults (Botvinick, Braver, Barch, Carter, & Cohen, 2001). The authors also concluded that higher cardiorespiratory fitness was associated with a greater ability of the frontal attentional circuitry to inhibit task-irrelevant information (Colcombe et al., 2004). While this study used an inhibitory control paradigm and did not study working memory, previous research using a factor analytic approach found that tests of working memory and tests of specific executive functions other than working memory (e.g., set shifting, response selection, inhibition) share common variance (McCabe et al., 2010). Specifically, working memory performance and executive function performance were correlated at $r=.97$, with a shared underlying component of executive attention. Thus, the Colcombe et al. study offers insight into the brain areas involved in inhibitory control that might also be supporting aspects of working memory.

In another study of older adults (N=70, mean age=65), higher VO_{2max} levels were associated with greater recruitment of prefrontal and parietal cortices in response to an increase in task demand during the Stroop paradigm (Prakash et al., 2011). The Stroop paradigm is a task used to investigate attentional and inhibitory control processes, as it requires the inhibition of overlearned responses when pairs of conflicting stimuli are presented (Stroop, 1935). In particular, they found greater activation in the bilateral middle and inferior frontal gyri, as well as the left superior parietal lobe, for the most challenging task conditions (Prakash et al., 2011). These results are consistent with literature demonstrating that the inferior frontal gyrus plays an important role in sustained attention (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010), the middle frontal gyrus is important for retrieving contextually rich details (Rajah, Languay, & Grady, 2011), and the superior parietal lobe is implicated in the manipulation of information in working memory (Koenigs, Barbey, Postle, & Grafman, 2009). The authors argued that cardiorespiratory fitness was not associated with widespread increases in recruitment of processing regions, but, rather, was associated with greater activation in selective regions in response to increasing task demand (Prakash et al., 2011). Taken together, these studies suggest that cardiorespiratory fitness may provide the brain with flexibility and plasticity, allowing for greater neuronal recruitment and enhanced BOLD brain activity. However, similar to Colcombe et al. (2004), this study was limited to older adults and made use of an inhibitory control task. Thus, although these studies provide insight into the brain areas involved in inhibitory control, a domain of executive control that is often correlated with working memory, we cannot necessarily extrapolate these results to midlife adults or to all brain activity related to working memory.

1.3 Working Memory fMRI Brain Activation & Performance

In this proposal, we are examining whether variation in brain activity that is related to cardiorespiratory fitness could be mediating working memory performance. This question is predicated on an assumption that brain activity patterns are related to working memory performance outside of any association with cardiorespiratory fitness. In a fMRI study of young adults (N=9, 22-36 years old), participants determined whether eight bars randomly displayed on the screen were identical to a sample displayed six seconds earlier, where the orientation of one of the bars was changed for the nonmatch trials. Better performance on this visual working memory task was associated with enhanced brain activation in regions of the frontal and parietal cortices, including the superior parietal lobe, intraparietal sulcus, dorsolateral prefrontal cortex, presupplementary motor area, and frontal eye field (Pessoa, Gutierrez, Bandettini, & Ungerleider, 2002). Specifically, a 1% increase in amplitude of fMRI signal increased the probability of being correct on that trial from 50% to 70% for the right intraparietal sulcus and right frontal eye field, and from 50% to 65% for the left dorsolateral prefrontal cortex (Pessoa et al., 2002). These results are consistent with literature demonstrating that the intraparietal sulcus is important for perceptual-motor coordination and visuospatial attention (Connolly, Kentridge, & Cavina-Pratesi, 2016), the frontal eye field in orienting attention (Vernet, Quentin, Chanes, Mitsumasu, & Valero-Cabré, 2014), and the dorsolateral prefrontal cortex in the manipulation and monitoring of relational information (Blumenfeld, Parks, Yonelinas, & Ranganath, 2011). These results suggest that greater BOLD activity is linked with behavioral performance and provides a basis for predicting that the link between cardiorespiratory fitness and working memory performance is mediated by brain activation in certain circuits.

While the aforementioned study provides support for the link between brain activation and working memory performance in young adults, it remains to be tested whether this relationship exists in midlife. In addition, although the visual working memory task in the aforementioned study requires the active maintenance of relevant information, it has minimal working memory demands since it mostly consists of matching stimuli rather than updating or manipulation of information. In contrast, our study used the n-back paradigm, a reliable and valid measure of working memory in which multiple task conditions are used with increasing task demand. The n-back task involves a broad network of cortical and subcortical regions and has high reliability (Plichta et al., 2012). A meta-analytic review found that the most difficult task condition in various versions of the n-back working memory paradigm to consistently activate frontal and parietal cortical regions, including the medial posterior parietal cortex, premotor cortex, dorsal cingulate/medial premotor cortex, rostral prefrontal cortex, dorsolateral prefrontal cortex, and mid-ventrolateral prefrontal cortex (Owen, McMillan, Laird, & Bullmore, 2005).

Although previous research suggests that differences in BOLD brain activity may be one potential mechanism by which cardiorespiratory fitness is linked to working memory performance, no studies have formally tested this using a statistical mediation approach. Furthermore, these prior studies consist of younger or older adults, with a noticeable gap in midlife years. As mentioned above, midlife is now regarded as a highly sensitive period in which an inflection can be detected for early decline in cognitive function that is related to increased cardiometabolic load. This study will test for the first time whether working memory fMRI brain activation statistically mediates the relationship between cardiorespiratory fitness and working memory performance in middle-aged adults. Based on prior literature, we predict that higher cardiorespiratory fitness will be related to heightened activation in frontal cortical regions during the most demanding task condition, and that this incremental increase in activity may be further correlated with improved working memory performance. Although previous research has found cardiorespiratory fitness related activity in other cortical regions besides the frontal cortex, such as the parietal cortex, these regions may be involved in stimulus processing and may not be related to differences in working memory performance. A better understanding of the mechanisms of cardiorespiratory fitness on the brain could have major clinical and scientific implications for modifying working memory with exercise.

1.4 Aims and Hypotheses

The primary aim of the study is to examine whether higher cardiorespiratory fitness is associated with better working memory performance within a midlife sample. The second aim is to examine whether higher cardiorespiratory fitness is associated with heightened brain activation in frontal cortical regions during the working memory task. The third aim of the study is to examine whether brain activation during the working memory task is associated with working memory performance. Since prior literature has found differences in frontal cortical activity as a function of cardiorespiratory fitness, we hypothesize that variations in brain activation in these regions during the working memory task will explain differences in working memory performance. Thus, the fourth aim will test if brain activation during the working memory task statistically mediates the relationship between cardiorespiratory fitness and working memory performance. We hypothesize that brain activation during the working memory task will statistically mediate this relationship, such that participants with higher cardiorespiratory fitness will show heightened brain activation in frontal cortical regions during the working memory task, and in turn, perform better on the working memory task. These results would implicate brain activation as an important pathway by which higher cardiorespiratory fitness is associated with better working memory.

2.0 METHODS

2.1 Participants

To test my aims, I will utilize baseline data from a 12-month diet and exercise intervention. The current study will analyze the baseline data of the 125 individuals who had brain imaging data collected. Participants were eligible if they were between 18-55 years of age, had a Body Mass Index (BMI) in the overweight or obese range (BMI=25.0-39.9 kg/m^2), and were able to provide informed consent. Participants were excluded if they met any of the following criteria: current medical condition that could affect body weight; current symptoms indicative of an increased risk for a cardiovascular event; hypertension, characterized by a resting systolic blood pressure of ≥160 mmHg or a diastolic blood pressure of ≥90 mmHg; eating disorder; alcohol or substance abuse; current treatment for a psychological disorder; any form of traumatic brain injury; prior diagnosis of a neurological disorder, including dementia, Parkinson's disease, multiple sclerosis, schizophrenia or schizotypal disorder, epilepsy, autism spectrum disorder, and narcolepsy; engagement in exercise more than 2 days a week for 20 minutes or more; and MRI contraindications.

2.2 Procedures

2.2.1 Cardiorespiratory Fitness

Cardiorespiratory fitness ($VO_{2submax}$) was determined using a graded submaximal exercise test using a motor-driven treadmill. $VO_{2submax}$ was defined as a submaximal level of aerobic capacity once 85% of the maximal heart rate based on the Karvonen method had been achieved. A submaximum level was reached when two of the following occurred: 1) oxygen consumption remained at a steady state despite increasing physical exertion, 2) the respiratory exchange ratio was greater than 1.00, or 3) the age-predicted maximum heart rate was reached. Inhaled and exhaled air was measured for oxygen and carbon dioxide concentrations, expressed as a relative rate in milliliters of oxygen per kilogram of body mass per minute (ml/kg/min).

2.2.2 Working Memory

Working memory was assessed in the scanner using the n-back paradigm, which included two components: 1-back and 2-back. In this classic test of working memory, participants were required to monitor a series of lowercase letters presented one at a time and determine whether the current letter matches the letter presented one or two items back. The 2-back condition is compared to the 1-back condition (2-back – 1-back), as the former requires working memory whereas the latter consists of minimal working memory demands. Three blocks of both 1-back and 2-back conditions were presented for 47 seconds each, with a 30-second fixation cross presented between each block. Two runs of the n-back were presented in counterbalanced order (i.e., 1-back, 2-back; 2-back, 1-back), during which the rate of stimulus presentation was identical.

Participants were given a button box for each hand and instructed to press with their right index finger if the current stimulus was a match and with their left index finger if it was not a match. Participants were asked to respond as quickly and as accurately as possible. Task related accuracy will serve as a metric of working memory performance in this study. All participants practiced the task prior to entering the scanner to ensure that they understood the instructions and to avoid the confounding influence of practice effects.

2.2.3 MRI Data Acquisition

Magnetic resonance images were collected on a Siemens 3T Verio MRI scanner with a 32-channel phased-array head coil. High-resolution anatomical MPRAGE (1 x 0.97 x 0.77 mm voxels, 256 slices, TE=2.93ms, TR=1,900ms) images will be used for anatomical reference.

During the n-back paradigm, functional images were acquired using a T2*-weighted whole brain echo-planer imaging sequence with BOLD contrast (64 x 64 x 34 matrix, 3.5 x 3.5 x 3.2 mm slice thickness, TR=2,000ms, TE= 30ms, flip angle=70). A total of 204 volumes were collected per participant. N-back stimuli were visually displayed from a computer running E-prime software to a rear-projecting mirror mounted on the head coil via a projector. The presentation of stimulus was synchronized with scanning time using a trigger signal. Accuracy rate was collected for all task conditions.

2.3 Statistical Analyses

2.3.1 Descriptive Statistics

Correlations between age, gender, years of education, race, weight, and the variables of interest were examined to assess the need for covariates. All variables related to working memory performance and brain activation were tested for normality of distribution. Working memory performance (response times and accuracy) on the n-back paradigm was analyzed using paired t-tests to verify the more challenging working memory load for the 2-back condition.

2.3.2 Neuroimaging

FMRIB's Software Library 5.0.8 (FSL) fMRI Expert Analysis Tool 6.0 (FEAT) was used for fMRI data preprocessing (Woolrich et al., 2009; Woolrich, Ripley, Brady, & Smith, 2001). Within the FEAT analysis, the following preprocessing steps were conducted: removal of non-brain structures using Brain Extraction Tool (BET) (S. M. Smith, 2002), motion correction using Motion Correction FMRIB's Linear Registration Tool (MCFLIRT) (Jenkinson, Bannister, Brady, & Smith, 2002), temporal filtering, and spatial smoothing using an isotropic 7-mm Gaussian kernel (full width at half maximum, FWHM). A 7mm kernel was used to optimally reduce the influence of anatomical variability among the individual maps in generating group maps and improve the signal to noise ratio by reducing the noise across voxels. A two-step registration process was used for each participant in order to put functional data into a standard space. First, each participant's low-resolution T2*-weighted image was registered to their high-resolution T1-weighted structural image. Then, the participant's high-resolution T1-weighted structural image was registered to standard space of the 152T1 Montreal Neurological Institute (MNI) template.

The data were then entered into individual lower-level FEAT analyses to measure brain activation during the working memory task. Three linear contrasts were produced: 1) 1-back greater than baseline, 2) 2-back greater than baseline, and 3) 2-back greater than 1-back. Each contrast generated a lower-level statistical parametric map thresholded with a z-score of 2.3 and a cluster threshold of $p<.05$. The individual lower-level statistical parametric maps were used as inputs for higher-level mixed-effects whole-brain group analyses using FMRIB's Local Analysis of Mixed Effects (FLAME) (Beckmann, Jenkinson, & Smith, 2003). To examine the association between cardiorespiratory fitness and neural activation during the working memory task, demeaned cardiorespiratory fitness was entered as a variable of interest. In addition, three separate analyses were conducting using demeaned n-back accuracy (i.e., 1-back, 2-back, or 2-back greater than 1-back) as a variable of interest to examine the association between working memory performance and neural activation during the working memory task. These higher-level analyses resulted in three voxel-wise parameter estimate maps of interest for each contrast: 1) group mean, 2) positive association with the variable of interest, and 3) negative association with the variable of interest. A conjunction analysis was then performed using the whole-brain maps that identified brain regions sensitive to both cardiorespiratory fitness and performance on the n-back task to identify where associations overlapped. Thus, these maps identified voxels that independently showed both an association with cardiorespiratory fitness and working memory performance. The peak signal within these conjunction masks were then extracted by creating a 10-mm sphere around the peak. Based on *a priori* hypotheses, we focused our reported results on the middle frontal gyrus (MFG), superior frontal gyrus (SFG), anterior cingulate cortex (ACC), insula, and inferior frontal gyrus pars triangularis. To test Aim 2, 3, and 4, fMRI brain activation was defined as a mean percent signal change for the regions of interest (ROI) for each subject and thresholded at a $p<.05$. The statistical images for all group-level analyses were thresholded with a z-score of 2.3 and a cluster threshold of $p<.05$.

2.3.3 Testing Aim 1

To test Aim 1, we conducted linear regression models to examine the association between cardiorespiratory fitness and performance on the working memory task for the 1-back, 2-back, and 2-back greater than 1-back task conditions, while controlling for age, gender, race, and years of education.

2.3.4 Testing Aim 2

To test Aim 2, linear regression models were conducted to examine the association between cardiorespiratory fitness and percent signal change in the ROIs that were identified in the voxel-based analysis in regions that overlapped with activation patterns identified for each contrast (i.e., group mean, positive association with n-back performance, negative association with n-back performance).

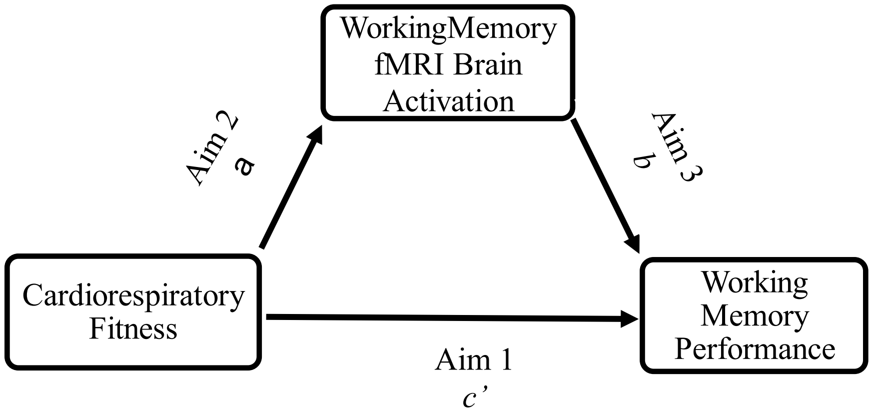
2.3.5 Testing Aim 3

Aim 3 was tested with linear regression to examine the association between percent signal change and performance on the n-back task. To reduce the number of statistical comparisons, we focused only on the regions that were found to be associated with cardiorespiratory fitness in Aim 2.

2.3.6 Testing Aim 4

To test Aim 4, we first examined the results of Aims 2 and 3 (i.e., the a and *b* paths, respectively, as depicted in Figure 1) and confirmed that the assumptions of statistical mediation were met. If they were met, we used PROCESS to test whether activation during the n-back task statistically mediated the relationship between cardiorespiratory fitness and performance (Hayes, 2013).

Figure 1. Aim 4 Conceptual Model



3.0 RESULTS

3.1 Participants

Means and standard deviations of cardiorespiratory fitness, demographic variables, and performance on the n-back task are presented in Table 1. The 125 participants were on average 44.34 years old (± 8.60) with 16.47 years (± 2.67) of education. Females made up 78.4% of the sample. Average BMI was in the obese range (32.43 ± 3.93 kg/m$_2$), consisting of 40 participants with overweight (BMI = 25.0-29.9 kg/m$_2$) and 85 participants with obesity (BMI ≥ 30.0 kg/m$_2$). Participants responded more slowly (1-back = 600.8-1,326.0 ms; 2-back = 522.0-1,554.4 ms; t=14.40, p<.001) and less accurately (1-back = 31-100% correct; 2-back = 24-100% correct; t=9.68, p<.001) on the most difficult task condition.

Table 1: Sample Characteristics (N=125)

Variable	**Mean (± SD)**
Age (years)	44.34 (±8.60)
Gender (% female)	78.4
Education (years)	16.47 (±2.67)
Race (% Caucasian)	76.8
Body Mass Index (kg/m$_2$)	32.43 (±3.93)
Cardiorespiratory Fitness (ml/kg/min)	22.92 (±4.36)
1-back Accuracy (% correct)	90.4 (±12.8)
2-back Accuracy (% correct)	80.2 (±15.9)
1-back Response Time (ms)	875.04 (± 157.71)
2-back Response Time (ms)	1040.40 (±170.38)

Correlations between age, gender, years of education, race, weight, and the variables of interest are presented in Table 2. Weight was not significantly correlated with any variables of interest and, thus, was not included as a covariate in any models. Age and race were significantly correlated with 1-back and 2-back accuracy (ranging between r=-.25, p<.01 and r=.21, p<.05), such that younger age and Caucasian race were associated with better performance. Education was significantly correlated with 2-back accuracy (r=.23, p<.01) and 2-back greater than 1-back accuracy (r=.22, p<.01), such that more years of education was associated with better performance. Gender (r=.52, p<.01) and race (r=.26, p<.01) were significantly correlated with cardiorespiratory fitness, such that male gender and Caucasian race were associated with higher cardiorespiratory fitness. Thus age, gender, race, and years of education were included as covariates in all models.

Table 2: Pearson's Correlations For All Variables of Interest (N=125)

	1	2	3	4	5	6	7	8	9
1. Age	-	r=-.09	r=-.09	r=-.01	r=-.08	r=-.07	r=-.25**	r=-.24**	r=-.06
2. Gender		-	r=-.06	r=-.15	r=-.39**	r=-.52**	r=-.03	r=-.05	r=-.09
3. Education			-	r=-.01	r=-.04	r=-.03	r=.10	r=.23**	r=.22*
4. Race				-	r=-.01	r=.26**	r=.20*	r=.21*	r=.07
5. Weight (kg)					-	r=.02	r=.04	r=.04	r=.02
6. CRF						-	r=.17	r=.12	r=-.03
7. 1-back ACC							-	r=.69**	r=-.16
8. 2-back ACC								-	r=.61**
9. 2>1 ACC									-

*Correlation is significant at the p<.05 level
**Correlation is significant at the p<.01 level
Notes: Gender = male: 1, female: 2; CRF = cardiorespiratory fitness; ACC = accuracy

3.2 Aim 1

Linear regression models examined the association between cardiorespiratory fitness and performance on the working memory task for the 1-back, 2-back, and 2-back greater than 1-back task conditions, as depicted in Table 3. Inconsistent with our hypothesis, the regression analyses revealed that after controlling for age, gender, race, and years of education, cardiorespiratory fitness was not significantly related to accuracy for the 1-back (zero-order correlation($r_{1,2}$)=.18, β=.15, p=.15), 2-back ($r_{1,2}$=.12, β=.06, p=.60), or 2-back greater than 1-back ($r_{1,2}$=-.03, β=-.09, p=.42) task conditions.

Table 3: Linear Regression Models of Cardiorespiratory Fitness and Working Memory Performance

Model	β	t	p-value
1-back Accuracy			
Age	-.22	-2.54	.01*
Gender	.07	.71	.48
Race	.19	2.12	.04*
Education	.09	1.02	.31
CRF	.15	1.44	.15
2-back Accuracy			
Age	-.21	-2.43	.02*
Gender	-.004	-.04	.97
Race	.20	2.28	.03*
Education	.22	2.50	.02*
CRF	.06	.52	.60
2-back > 1-back Accuracy			
Age	-.06	-.60	.55
Gender	-.09	-.78	.43
Race	.08	.83	.41
Education	.21	2.26	.03*
CRF	-.09	-.81	.42

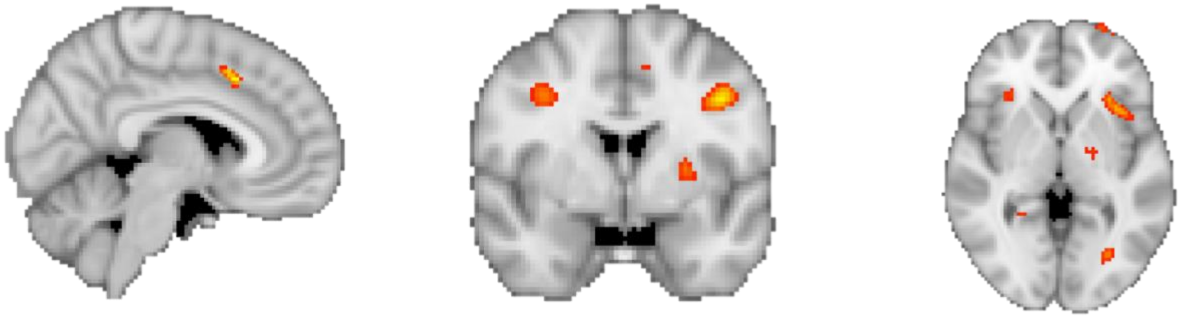
*Significant at the p<.05 level

Notes: Gender = male: 1, female: 2; CRF = cardiorespiratory fitness

3.3 Aim 2

The voxel-based analysis identified a series of brain regions that were positively associated with cardiorespiratory fitness including the right and left ACC, right and left MFG, and right and left insula, as illustrated in Figure 2. As explained earlier, we used these maps in a conjunction analysis with the higher-level task conditions to identify ROIs that overlapped with activation associated with n-back performance and extracted peaks from these maps. We then conducted further linear regression models to examine the association between cardiorespiratory fitness and mean percent signal change in these ROIs after correcting for relevant covariates, as depicted in Table 4. The regression analyses revealed that after controlling for age, gender, race, and years of education, higher cardiorespiratory fitness remained significantly related to greater BOLD activation in the left insula (β=.23, p=.028).

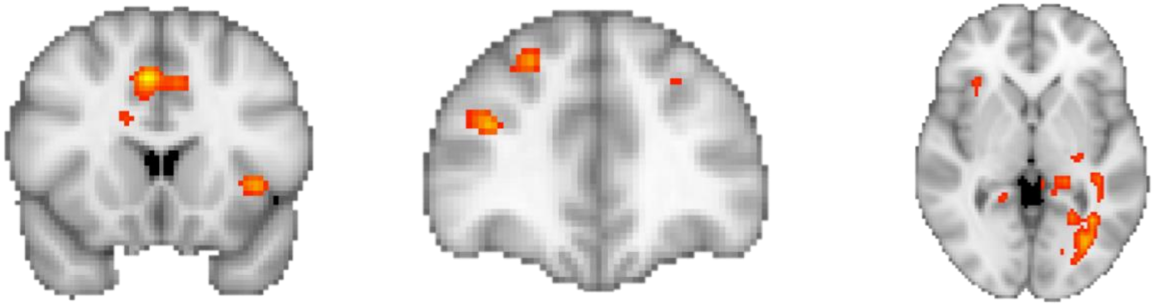
Figure 2. Voxel-Based Analysis of Positive Associations with Cardiorespiratory Fitness in the Anterior Cingulate Cortex, Middle Frontal Gyrus, and Insula



1-Back Right ACC

2-Back Right & Left MFG

2-Back Right & Left Insula



2-Back Right & Left ACC

2-Back>1-Back Right MFG

2-Back>1-Back Right Insula

Figure 3. Left Anterior Cingulate Cortex (Yellow), Right Insula (Blue), and Left Insula (Red) Regions-of-Interest

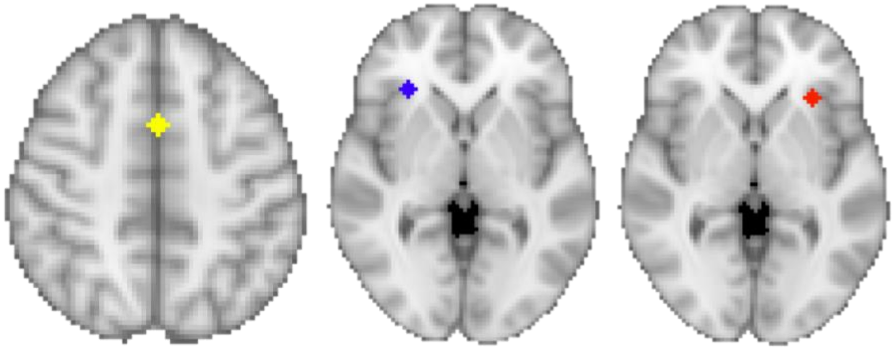


Table 4: Linear Regression Models of Cardiorespiratory Fitness and Mean Percent Signal Change in the Left ACC, Left and Right Insula During the 2-back After Adjusting for Covariates

Model	β	t	p-value
Left ACC (x=0, y=6, z=48)			
CRF	.09	.86	.39
Left Insula (x=-30, y=24, z=0)			
CRF	.23	2.23	.028*
Right Insula (x=29, y=28, z=0)			
CRF	.19	1.76	.081

*Significant at the p<.05 level
Notes: x, y, and z are coordinates from Montreal Neurological Institute; ACC = anterior cingulate cortex, CRF = cardiorespiratory fitness

3.4 Aim 3

Using the left insula ROI that was significant in Aim 2, a linear regression model was conducted to examine the association between mean percent signal change in this ROI and 2-back accuracy. The regression analysis revealed that after controlling for age, gender, race, and years of education, greater BOLD activation in the left insula was not significantly related to performance (β=.14, p=.115).

3.5 Aim 4

Aim 4 tested whether BOLD activation statistically mediated the relationship between cardiorespiratory fitness and working memory performance (see Figure 1). Testing for statistical mediation requires that the relationship between the independent variable and the mediator (path a), and the relationship between the mediator and the dependent variable (path *b*) are statistically significant (Hayes, 2013). Aim 2 tested path a and showed that there was a significant relationship between cardiorespiratory fitness and activation in the left insula for the 2-back condition. Aim 3 tested path *b* and did not show a significant relationship between activation in the left insula and 2-back performance. Thus, the assumptions necessary for statistical mediation were not met and those analyses were not conducted.

4.0 DISCUSSION

Previous research has found higher cardiorespiratory fitness and greater prefrontal brain activation to be associated with better working memory performance (Erickson et al., 2009; Hwang & Castelli, 2015; Kao et al., 2017; Mackenzie et al., 2016; Owen et al., 2005; Pessoa et al., 2002; Scudder et al., 2016; Voss et al., 2010). However, it is unknown whether frontal brain activation during a working memory task statistically mediates the relationship between cardiorespiratory fitness and performance. This hypothesis was tested by examining the relationship of cardiorespiratory fitness and brain activation with working memory performance in a sample of midlife adults. Based on previous literature, we predicted that higher cardiorespiratory fitness would be associated with greater frontal brain activation and better working memory performance, and that frontal brain activation would statistically mediate the relationship between cardiorespiratory fitness and working memory performance. Inconsistent with our hypotheses, higher cardiorespiratory fitness was not significantly correlated or associated with better working memory performance after adjusting for several confounding variables, including age, gender, race, and years of education. Although we found evidence that higher cardiorespiratory fitness was associated with greater brain activation in the left insula independent of our covariates, this heightened activation was not related to better working memory performance, and, therefore statistical mediation could not be tested. Our results suggest that midlife demographics may have a more important role in working memory performance than cardiorespiratory fitness. Furthermore, cardiorespiratory fitness in midlife may not have a significant impact on working memory performance through variations in frontal brain activity, but instead may be mediated by other factors.

Although previous research has found midlife cardiovascular risk factors to be associated with an increased risk of cognitive decline later in life (Huntley et al., 2018; Kroll et al., 2016; Meng et al., 2014), we failed to find an association between cardiorespiratory fitness and working memory in this study. One potential explanation for these findings is that subtle changes in cognition may not be discernable in midlife. In particular, a longitudinal study following individuals from midlife into old age found subtle, detectable differences in working memory performance beginning at age 60 (Hughes, Agrigoroaei, Jeon, Bruzzese, & Lachman, 2018). Although the aforementioned study by Mackenzie et al. found a significant association between cardiorespiratory fitness and working memory, their sample included individuals aged 18-70 years with a mean age of 55.4 years (2016). As our study included individuals aged 18-55 years with a mean age of 44.34 years, future studies would benefit from examining this association in a slightly older sample with a narrower age range in order to more precisely estimate the association of cardiorespiratory fitness with the trajectory of working memory changes. Furthermore, although meta-analyses of randomized exercise interventions have concluded that exercise training improves cognitive function across the lifespan (Colcombe & Kramer, 2003; P. J. Smith, Blumenthal, Babyak, et al., 2010), it is possible that the improvements in cognitive function associated with exercise may not be due to increases in cardiorespiratory fitness. It is also possible that cardiorespiratory fitness may have a limited effect on working memory in this age range. In particular, a meta-analysis of randomized exercise interventions found a significant association between age and improvements in working memory, such that older samples demonstrated greater improvements than younger samples (P. J. Smith, Blumenthal, Hoffman, et al., 2010). Future examination of this question in a midlife randomized exercise intervention may help elucidate these findings.

Although heightened activation in the left ACC, left insula and right insula were associated with higher cardiorespiratory fitness, only the left insula remained significant after adjusting for several confounding variables. The insula, located within the Sylvian sulcus connecting the frontal and temporal lobes, is involved in initiating signals across large-scale networks to mediate cognitive processes, such as perception, cognition, emotion, and interoception (Menon & Uddin, 2010). Our results are consistent with prior literature demonstrating that the insular cortex is a key region involved in the n-back task (Ragland et al., 2002; Z. A. Yaple, Stevens, & Arsalidou, 2019; Z. Yaple & Arsalidou, 2018). Our results were specific to the left insula, although the explanation for this laterality difference is unclear. It has been suggested that the structure of the insula plays a critical role in the laterality of brain function, such that leftward asymmetry predicts left-hemispheric language organization (Biduła & Króliczak, 2015). Since the n-back task used in this study consisted of lower-case letters, a left hemispheric dominance may have emerged among participants who were more likely to rely on verbal cognitive strategies. However, this is only speculative, highlighting the need for future research to examine laterality differences in the context of verbal working memory tasks. Nonetheless, these results may have implications for patient populations, such as schizophrenia, Alzheimer's disease and stroke, as structural and functional changes in the insula have been demonstrated in these populations (Lin et al., 2017; Palaniyappan & Liddle, 2012; Sander, Winbeck, Klingelhöfer, Etgen, & Conrad, 2001). Our results indicate that higher cardiorespiratory fitness may be protective against functional insula changes typical of schizophrenia, Alzheimer's disease, and stroke.

Though previous studies have found differences in ACC activation as a function of cardiorespiratory fitness (Colcombe et al., 2004; Prakash et al., 2011), there was no indication of a significant association in this study after correction for variation due to age, gender, race, and years of education. In particular, age, gender, race and years of education explained 17.1% of the 17.6% total variance accounted for in ACC activation. Thus, the association of ACC activation with age (β=.12, p=.15), gender (β=-.24, p=.019), race (β=.21, p=.018), and years of education (β=.03, p=.72) hinders our ability to determine whether the ACC activation related to cardiorespiratory fitness is uniquely associated with cardiorespiratory fitness or is due to associations with these other factors. The discrepancy in findings between this study and previous research may be due to differences in tasks, as the previous studies utilized inhibitory control tasks (Colcombe et al., 2004; Prakash et al., 2011). Future exploration is needed to elucidate the unique contribution of cardiorespiratory fitness to variations in ACC activation during the n-back task.

While previous studies have found a positive relationship between cardiorespiratory fitness and working memory performance (Erickson et al., 2009; Hwang & Castelli, 2015; Kao et al., 2017; Mackenzie et al., 2016; Scudder et al., 2016; Voss et al., 2010), there was no indication of a significant correlation or association in this study. Since many participants performed at ceiling on both the 1-back (n=24) and the 2-back (n=7), an exploratory analysis with response time was conducted to assess whether there was more meaningful variation in response time. However, we failed to find an association of response time with cardiorespiratory fitness (ranging between r=-.05, p=.55 and r=.01, p=.93) or left insula brain activation (r=-.05, p=.57). Prior studies that utilized n-back tasks consisted of monitoring the location or identity of nonverbal content whereas this study's task consisted of verbal content (Kao et al., 2017; Mackenzie et al., 2016; Scudder et al., 2016). Different versions of the n-back task have been found to vary in difficulty, such that verbal n-back tasks elicit greater accuracy than spatial n-back tasks (Nagel, Ohannessian, & Cummins, 2007). Furthermore, Kao et al. used a maximal exercise test (2017), Scudder et al. used a PACER test (2016), and Mackenzie et al. used an estimated VO_{2peak} from a submaximal exercise test (2016). Thus, these differences in task designs and study protocols may have given rise to the discrepancy in findings.

Although brain activation in frontal and parietal cortical regions has been linked with working memory performance in previous studies (Owen et al., 2005; Pessoa et al., 2002), there was no indication of a significant association in this study. In particular, meta-analyses of working memory tasks have found regions such as the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex to be consistently activated across studies (Owen et al., 2005; Rottschy et al., 2012), and these regions are unequivocally associated with performance (Anderson et al., 2018; Bor, Cumming, Scott, & Owen, 2004; Pessoa et al., 2002; Veltman, Rombouts, & Dolan, 2003). When examining the association between frontal brain activation and working memory performance, we may have limited our ability to detect a performance effect by only selecting regions that had a significant association with cardiorespiratory fitness. Since cardiorespiratory fitness was not associated with working memory performance in our study, the ROIs selected may not have overlapped with frontal cortical regions preferentially associated with performance. However, in an exploratory voxel-based analysis, we failed to find any brain areas associated with accuracy for the 1-back and 2-back task conditions that met cluster threshold. Thus, the importance and relevance of variations in the magnitude of activation with performance metrics on the n-back task remain a critical avenue for research, as it influences the interpretation of activation patterns and differences in activation as a function of age, disease, or lifestyle factors.

Since brain activation in frontal cortical regions and working memory performance were not related in this study, we were not able to statistically test whether frontal brain activation mediates the relationship between cardiorespiratory fitness and working memory performance. It is possible that other mediators may better explain this relationship. Other studies report that brain volume (Erickson et al., 2009), resting state functional connectivity (Voss et al., 2010), neuronal metabolites (Erickson et al., 2012), and white matter microstructure (Oberlin et al., 2016) mediate the relationship between cardiorespiratory fitness and working memory performance. Future exploration of which neural metrics are most sensitive to cardiorespiratory fitness may help clarify the potential neuroprotective effects of cardiorespiratory fitness on working memory performance.

The results of the current study should be interpreted in the context of several limitations. As with all cross-sectional studies, it is not possible to draw causal relationships from these findings. Furthermore, fMRI is an indirect measure of neural activation. The use of a block design task rather than an event-related design task may have limited our ability to estimate effects and adjust for errors. Given that our sample was restricted to individuals with an overweight or obese BMI, we may have limited the variability we could see in our results and reduced our sensitivity to detect effects. In addition, other biological risk factors of obesity (e.g., insulin sensitivity, inflammation) may have been at play in our sample and influenced the results. Lastly, the sample consisted of a small portion of men and had limited ethnic and racial diversity, limiting the generalizability to other demographic characteristics.

Despite these limitations, we used a sensitive measure of cardiorespiratory fitness and advanced neuroimaging techniques to examine the importance of cardiorespiratory fitness and brain activation in the context of working memory. For the first time, we test whether brain activation statistically mediates the relationship between cardiorespiratory fitness and working memory. Our findings suggest that left insula brain activation during a working memory task is associated with individual differences in cardiorespiratory fitness among midlife adults. In particular, we report that higher cardiorespiratory fitness is associated with greater left insula brain activation during the n-back task. However, given that left insula brain activation did not mediate the relationship between cardiorespiratory fitness and working memory performance, many other environmental and neurobiological factors are likely influencing working memory. Future research would benefit from following a sample with a wider range of BMI and cardiorespiratory fitness across time to assess the relationship between changes in activation and changes in performance.

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