Mean arterial pressure, fitness, and executive function in middle age and older adults

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ABSTRACT

Previous literature suggests that higher fitness is related to better executive function in older adulthood, but the mechanisms underlying this association are poorly understood. While many studies have focused on these associations in older adulthood, recent evidence suggests the importance of cardiorespiratory fitness (CRF) and long-term blood pressure control on cognitive functioning. The purpose of the current study was to examine whether mean arterial pressure (MAP) mediated the association between CRF and executive function in middle age and older adults. Participants were adults (age 40–+) without any self-reported psychiatric and neurological disorders or cognitive impairment from the Nathan Kline Institute Rockland Sample (N = 224, M age = 56). CRF was defined by VO2max estimated via a bike test, neuropsychological testing was used to examine executive functioning, and MAP was calculated from systolic and diastolic blood pressure recordings. Mediation models were analyzed controlling for age, sex, and education. Results indicated that higher CRF was associated with better inhibition (B = -0.0048, t = -2.16, p = 0.03) and there was a significant indirect effect of greater CRF on better inhibition through lower MAP (B = -0.0011; CI [-0.0026, -0.0002]). There were additional significant indirect effects of greater CRF and better fluency (B = 0.0028; CI [0.0009, 0.0053]) and planning (B = 0.0037; CI [.0014, 0.0074]) through lower MAP. This suggests that MAP may be an underlying physiological mechanism by which CRF influences executive function in mid- and older adulthood.

Introduction

Physical activity and associated gains in fitness have been shown to be neuroprotective for older adults, with evidence suggesting preserved brain structure [7,8], function [53], and better cognitive functioning [38]. Many recent meta-analyses suggest that exercise interventions and subsequent gains in fitness may have a selective effect on cognition in older adulthood, with the greatest impact on executive functioning [10,28,47]. Executive functioning is an important set of higher-order cognitive skills that include inhibition, planning, fluency, and switching between tasks [14]. Not only are these skills especially important for maintaining independence in older adulthood [22], but some evidence suggests that changes in executive function may be occurring earlier in middle age [20] and may be predictive of future cognitive decline [29]. Therefore, there is a need to examine how fitness may be related to executive function across a younger adult sample.

Cardiorespiratory fitness (CRF) is a measure of the ability of the circulatory and respiratory systems to deliver oxygen, and the peak rate at which oxygen can be consumed, during sustained physical activity at a maximal effort [45]. As a consequence of genetic makeup, overall vascular health, and engagement in vigorous or sustained physical activity, CRF has emerged as an important measure of physical health [25,43]. Higher CRF has been shown to be related to greater brain volume [41], particularly in gray matter regions like the prefrontal cortex [17]. Higher CRF has also been associated with preserved white matter integrity [24], and functional connectivity [6,52], as well as better cognitive functioning [51] in older adults. However, the mechanisms underlying these positive effects are not fully understood. Several studies suggest that increased cerebral blood flow may be the mechanism by which greater CRF is associated with better cognitive outcomes in aging [1,9]. Cerebral perfusion can be impacted by many factors, notably blood pressure. Moreover, exercise and greater CRF are among the most potent non-pharmacological interventions to reduce hypertension and maintain healthy blood pressure in across the adult lifespan.
Mean arterial pressure (MAP) reflects both systolic and diastolic blood pressure during each cardiac cycle and provides an estimate of perfusion [36]. Even subclinical cerebral hemodynamics in older adulthood have been shown to impact brain structure and function [33]. In particular, frontal-subcortical networks appear to be particularly impacted by vascular dysfunction [11], and dysfunction in cerebral autoregulation can negatively impact executive function [50]. Thus, executive dysfunction often occurs as a result of vascular damage [39]. A recent systematic review examined the components of executive function most impacted by systemic arterial hypertension and found that inhibition and shifting were most impacted [34]. While this is well-documented in older adulthood, less evidence exists examining this relationship in middle age and younger older adults. Some evidence suggests that vascular health during middle adulthood is a critical time for intervention [32]. Therefore, it is important to understand factors that might mitigate vascular dysfunction on brain health and cognition.

The purpose of the current study was to examine whether MAP mediated the associations between CRF and several aspects of executive function (i.e., inhibition, fluency, planning, switching) in a large sample of participants ranging from middle age to older adulthood. This study contributes to the current literature by utilizing a sample with greater diversity in age than is typically examined and by examining the mechanisms by which CRF may be neuroprotective. We hypothesize that greater CRF will be associated with better executive function in all domains. We also hypothesize that MAP will mediate the association between CRF and executive function, particularly in inhibition and switching models [34].

Method

Participants

Participants included a sample of 224 adults (aged 40+ years) from the publicly available Nathan Kline Institute Rockland Sample (NKI-RS; http://fcon_1000.projects.nitrc.org/indi/enhanced; [37]). The NKI-RS is composed of many studies with the same core protocol. Only data from the latest baseline visit was used for each participant to ensure adequate sample size, as complete follow-up data was only available for a subset of these participants due to active data collection. Use of this data for this project was approved through the exempt review process by the University of Maryland College Park Institutional Review Board. Participants were eligible for inclusion if they were 40 years of age or older, had no self-reported neurological (e.g., Alzheimer’s, Parkinson’s) or psychiatric disorders (e.g., MDD, PTSD, OCD) and completed cardiorespiratory fitness measures, blood pressure measurements, and
neuropsychological testing. Participants were excluded if they did not complete a baseline visit, were younger than 40 years old, or had self-reported neurological or psychiatric disorders. Fig. 1 depicts a flowchart for included participants for each model. Demographic statistics are presented in Table 1.

Materials

Cardiorespiratory fitness

Cardiorespiratory fitness (CRF) was measured using a six-minute bike test using a recumbent cycle ergometer (RBK 815, Precor, Woodinville, WA) based on a modified Astrand-Ryhming submaximal cycle ergometer test [4]. The level of resistance was determined by the age and sex of each participant. Participant resting heart rate was obtained prior to the test and during the test using a pulse oximeter on the finger. The participant was instructed to pedal at 70 RPM’s for 6 min. Final heart rate was obtained when completed. If the participant failed to complete the full 6 min of pedaling at 70 RPM’s, they were not able to be included in the analyses. Estimates of VO₂max were then extrapolated using the Astrand nomogram [4,30]. Values falling outside the range of VO₂max for men and women across relevant age groups [3,26,27]. Only one participant with a very high value (>100 mL·kg-1·min-1) was excluded. Because of the known influence of age and sex on VO₂max, estimates of VO₂max were standardized and converted into a percentile rank based on age and sex using normative information [3].

Executive function

Each participant received neuropsychological testing as part of a larger cognitive battery. All participants were administered specific subtests of the Delis-Kaplan Executive Function System (DKEFS) including the Trail Making Test, Verbal Fluency, Design Fluency, Color Word Interference, and Tower Test. These tests have good psychometric properties, measure non-verbal and verbal executive function, and have relatively brief administration times [56]. To combine subtests and create composites, z-scores were calculated for each participant [49]. The switching composite category consisted of DKEFS Verbal Fluency Category Switching: Total Switching Accuracy and DKEFS Design Fluency: Switching Total Correct. The planning composite category consisted of TOWER: Total Achievement Total Score and Trails 4: Total Time to Complete. The fluency composite category consisted of Verbal Fluency: Total Letter Fluency for Three Letter Trials and Design Fluency: Total Correct Trials 1–3. The inhibition category consisted of Color Word Inhibition: Total Time to Complete.

Mean arterial pressure

The systolic and diastolic blood pressures were both taken with a mercury blood pressure gage, cuff, and stethoscope at the baseline visit. Mean Arterial Pressure (MAP) is the average arterial pressure throughout one cardiac cycle, systole, and diastole and is a good measure of perfusion [13]. Changes in perfusion pressure, along with changes in vascularity and blood viscosity, affect cerebral blood flow (CBF; [19]). MAP was calculated using Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP). This was calculated as follows: MAP = ([SBP × 2] + DBP)/3.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (IBM SPSS Version 25.0) PROCESS Macro [23]. The relation between level of CRF and executive function as mediated through MAP was examined with four separate models for each executive function category (Switching, Planning, Fluency, Inhibition) and unstandardized beta values were calculated through PROCESS. Conceptual and empirical evidence suggests that indirect effects should be examined irrespective of direct effects [46]. All indirect effects were analyzed using bootstrap analyses set at 10,000 samples and a 95% confidence interval [44]. In order to capture the unique relations between CRF, MAP, and executive function, age, sex, and years of education were controlled for in all analyses.

Results

Descriptive characteristics

Table 1 provides means and standard deviations for sociodemographic characteristics. The average age was 56 years old (SD = 9.05). The majority of the participants were female (72%) and White (84%). On average, participants had completed 16 years (SD = 4.16) of education. The average systolic blood pressure was 127.11 mmHg (SD = 19) and average diastolic blood pressure was 76.31 mmHg (SD = 11.68). The average mean arterial pressure was 93.24 mmHg (SD = 13.54). A small minority of the sample had diabetes (Type 1 =<1%; Type 2 = 4.7%). On average, participants were in the 40th percentile for VO₂max indicating that this sample overall had lower than expected fitness. A minority of the participants had self-reported hypertension (21%) or hypotension (11%). Overall, average sample performances on measures of executive function were comparable to normative data on these subtests.

Direct effects and mediation models

The direct effect of CRF on executive function controlling for age, sex, and education was significant for the Inhibition model only (B = -0.0048, t = -2.16 p = .03). In addition, there were significant indirect effects of CRF on Inhibition (B = -0.0011, CI = -0.0026, -0.0002),

Table 2

| Analyses               | B     | CI       | t-value | p-value |
|------------------------|-------|----------|---------|---------|
| CRF and MAP            | -0.12 | [-0.18, -0.07] | -4.43   | <0.00001|
| MAP and Inhibition     | 0.009 | [-0.021, 0.02] | 1.59    | .11     |
| MAP and Switching      | -0.009 | [-0.028, 0.0099] | -0.94   | .35     |
| MAP and Fluency        | -0.023 | [-0.042, -0.0038] | -2.37   | .02     |
| MAP and Planning       | -0.031 | [-0.049, -0.014] | -3.51   | .0006   |
| Direct Effect of CRF on Inhibition | -0.0048 | [-0.0092, -0.0004] | -2.16   | .03     |
| Direct Effect of CRF on Switching | 0.0064 | [-0.0010, 0.0136] | 1.71    | .09     |
| Direct Effect of CRF on Fluency | 0.0015 | [-0.0059, 0.009] | 0.41    | .69     |
| Direct Effect of CRF on Planning | 0.0045 | [-0.0024, 0.011] | 1.29    | .20     |
| Indirect Effect of MAP (Inhibition Model)* | -0.0011 | 0.0006 | -0.0026 | -0.0002 |
| Indirect Effect of MAP (Switching Model) | 0.0011 | 0.0011 | -0.0010 | 0.0036 |
| Indirect Effect of MAP (Fluency Model)* | 0.0028 | 0.0012 | 0.0009 | 0.0053 |
| Indirect Effect of MAP (Planning Model)* | 0.0037 | 0.0015 | 0.0014 | 0.0074 |

Significant p-values are depicted in bold. * Indicates significant indirect effect. Note. CI = Confidence Interval, LLCI = Lower Limit Confidence Interval, ULCI = Upper Limit Confidence Interval, CRF = Cardiorespiratory Fitness, MAP = Mean Arterial Pressure.
Planning ($B = 0.0037, CI = 0.0014, 0.00074$) and Fluency ($B = 0.0011, CI = −0.0010, 0.0036$) through MAP after controlling for age, sex, and education. There was not a significant indirect effect of CRF on Switching through MAP (see Table 2).

**Indirect effects**

There were significant associations in the mediation models when controlling for age, sex, and education (see Fig. 2 for mediation model schematic). Greater CRF was significantly associated with lower MAP in all models ($p < 0.00001$). Greater mean arterial pressure was related to worse fluency ($B = −0.023, t = −2.37, p = 0.02$) and planning ($B = −0.0048*, CI = −0.0011, 0.00074$).
Recent study that found that in a sample of 501 adults aged 40 examining the mechanisms underlying this association. The current design of the NKI-RS study. This sample was mostly White and highly preserve cognitive functioning. A recent study that found that in a sample of 501 adults aged 40 examining the mechanisms underlying this association. The current design of the NKI-RS study. This sample was mostly White and highly preserve cognitive functioning.

suggest the importance of both CRF and maintenance of blood pressure impacts executive function in adults [34]. Taken together, these results suggest the importance of both CRF and maintenance of blood pressure impacts executive function in adults [34]. Taken together, these results identify that greater CRF is associated with better executive functioning through MAP in a sample of middle-age and younger older adults, suggesting the importance of viewing MAP as underlying physiological mechanism in this association. Further efforts are needed to examine these associations over time and in more diverse populations.

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