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The Moderating Role of Exercise in Stress-related Effects on the Aging Brain

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Tara Singh graduated in 2009 as a Psychology and Environmental Studies major, and is deeply interested in understanding how an individual’s lifestyle and environment impacts his or her health. Witnessing the lifestyles of aging individuals in Dharavi, one of Asia’s largest slums, has exposed her to a spectrum of stressful conditions that people throughout the world face. She is particularly interested in the process of aging, and the role of one’s environment on health-related choices. Currently, Tara is helping to conduct a variety of research and hopes to continue her education in the field of Public Health, ultimately applying what she learns on an international scale.

ABSTRACT
Stress over the lifetime has been shown to negatively impact brain structure and cognition in animal models. In addition, advancing age has been observed to have negative effects on brain structure and function. Lifetime stress may contribute to the observed detrimental effects of aging. Aerobic exercise has been shown to be beneficial for brain structure and cognition. Thus, the primary goals of the current study were to assess the effects of lifetime stress in older adult humans and to examine possible moderation of these effects on brain structure and function in older adults through exercise engagement. MRI-based volumes of the prefrontal cortex, orbitofrontal cortex, hippocampus, and amygdala were obtained for 60 healthy adults aged 55 to 87. Cognitive function was measured through a battery of cognitive tasks measuring immediate memory, working memory, executive functions, and processing speed. Data were also obtained through retrospective questionnaires on lifetime stress and exercise engagement. Smaller brain volumes associated with stress were demonstrated for the orbitofrontal cortex and amygdala. Lower capacity for cognitive functions of executive functions and processing speed with a non-significant trend for the hippocampus were also demonstrated. In addition, there was a non-significant trend for participants with higher levels of lifetime stress to demonstrate steeper age-related decline in immediate memory. There were non-significant trends for exercise engagement to moderate the effects of stress on orbitofrontal cortex and immediate memory: for individuals with lower amounts of stress those who exercised more evidenced less age effects. The potential impact of exercise in moderating the impacts of stress on brain structure and function clearly warrant further research as well as exploration of such factors as amount of exercise, a threshold for beneficial exercise effects and personality factors.

KEY TERMS
- Brain Aging
- Brain Structure
- Cognition
- Executive Function
- Processing Speed
- Immediate Memory
- Working Memory

FACULTY MENTOR: DENISE HEAD, PH.D., ASSISTANT PROFESSOR OF PSYCHOLOGY AND AFRICAN AND AFRICAN AMERICAN STUDIES
Professor Head conducts research on the neural basis of cognitive aging using behavioral testing and both structural and functional neuroimaging in healthy and pathological aging (e.g. dementia of the Alzheimer type) populations. A particular focus is on executive control processes including working memory, inhibition, temporal processing and task switching.

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INTRODUCTION AND BACKGROUND

Accumulated effects of lifetime stress can have a deleterious impact and may be particularly evident for the aging brain structure and cognition. Through the normal process of aging, and its expected effects on brain structure and cognition, older individuals tend to exhibit heightened vulnerability to the effects of lifetime stress on the brain’s structure and function. The positive impact of exercise on general health, as well as on brain structure and cognition has become a popular subject of research. The current study attempts to combine these factors and explore relationships between them. This paper begins with presentation of the concept of brain aging in terms of structure and function, followed by the additional influence of stress, and that of exercise.

Brain aging, defined as the cumulative effects of age on the brain’s structure and function, is marked by great individual variability. The structure of the hippocampus plays an important role in spatial, episodic, and contextual memory, while the prefrontal cortex is responsible for executive function and integration of cognition and emotion through neurotransmitters.1 Aging has broadly been associated with decline in brain size, loss of myelin (the protective sheath covering axons of neurons), region-specific loss of neuronal bodies, and reduced synaptic density.2 It is important to note that in terms of cognitive function, executive functions, such as planning, scheduling, and working memory may be particularly affected by age. In addition, while fluid intelligence and processing speed are targets of age, crystallized intelligence is intact, and in some cases, improves.3

According to Radley and Morrison, “Stress may be defined as any type of threat, either real or perceived, that requires compensatory responses for maintenance of homeostasis” (p. 271).1 Normally, a stressful event activates the amygdala, the emotion-processing structure, which in turn activates the HPA system or axis which releases glucocorticoids to activate the hippocampus, and terminates the stress response.1 When this system is deregulated by too much glucocorticoid release, neuronal communication is damaged by reduced neurogenesis in the dentate gyrus, dendrite growth in the amygdala, and dendrite and synapse loss in the hippocampus and prefrontal cortex.1 Subsequent effects of such deregulation result in increased likelihood of depression associated with hippocampus-atrophy, increased sense of fear due to higher density of dendrites in the amygdala, and a disrupted ability to integrate cognition and emotional stress due to damage of the prefrontal cortex.1

As noted by Radley and Morrison, exercise may present a potential method for reversing or preventing the detrimental impacts of stress on brain structure and function, particularly important for older individuals who are more vulnerable to the effects because of the “the interactive effects of stress and aging” (p.281)1 One study conducted by Larson et al.,4 assessed adults above the age of 65 in terms of their self-reported performance of physical activity per week, and found a significantly higher rate of Alzheimer’s disease development in those individuals who exercised less than three times per week after 6.2 years. Similar effects have been seen in randomized clinical trials like that of Colcombe et al.,5 which demonstrate better attention and focus for people who were aerobically trained compared to those who were trained in stretching and toning.6
The current correlational study aimed to examine the negative effects of aging and stress on brain structure and function, and the moderating role of exercise. Originally, the study sought to examine a potential moderating role of internal locus of control and high self efficacy on the relationship between exercise, stress, aging, and brain structure and function; however, though data was collected for these variables, they were not included in final analyses. Hypotheses for the study include that higher levels of stress would be associated with smaller regional brain volumes (particularly in the hippocampus) and lower cognitive performance (particularly in memory) in older adults. Additionally, based on prior research, it was predicted that aerobic exercise would moderate the effects of stress on regional brain volumes and cognition. Specifically, older individuals who had dealt with comparable levels of stress, but who exercised, would demonstrate larger brain volumes and higher cognitive performance than those who did not exercise.

METHOD

Participants
Participants include 60 healthy adults aged 55 to 87 (mean age = 74; SD = 8) all of whom have participated in a previous study conducted by Dr. Denise Head, Department of Psychology, Washington University in St. Louis. Participants were screened for any gross signs of cognitive dysfunction with the Mini-Mental State Exam. Participants were also screened for neurological (e.g., Parkinson's disease, head injury, stroke) and psychiatric illnesses (e.g., major depression). All participants were right-handed, native English speakers. The current sample consists of 47 females and 13 males, and there are 37 Caucasian-Americans and 23 African-Americans of varying socio-economic status. The mean education level was 15.1 years (SD = 2.9). Participation in the past study by Dr. Head is critical because relevant data concerning brain structure, cognition, and lifetime involvement in exercise were already obtained on the current participant pool.

Measures
Lifetime Stress. The Cumulative Trauma Scale is a recently developed measure of lifetime stress proposed and validated by Kira which utilizes the definition employed by the APA (American Psychological Association) Trauma Group, “A process that leads to the disorganization of a core sense of self and world and leaves an indelible mark on one’s world views…” (p.63). The CTS lists a series of chronic stressors throughout one's life and measures the stress based on an objective and a subjective scale. Participants first respond by stating the number of times a particular stressor was experienced, responding with once, twice, three times, or many times. The participant then ranks the stressor’s affects in terms of how positively or negatively the event has impacted their life. Frequency and intensity of stressful events combine to measure a cumulative load of stress across life span. The scale was found to have adequate internal consistency for the whole sample, as well as for the specific gender and age groups, convergent validity, divergent validity, and predictive validity.
MRI Acquisition and Processing. Up to four repetitions of a high resolution 3D-MPRAGE sequences were acquired. The study specifically investigates structural changes in the amygdala, hippocampus, prefrontal cortex and orbitofrontal cortex. Images were analyzed using the Freesurfer software suite, determined to be a valid and reliable automated labeling system for dividing human cerebral cortex on MRI scans. By assessing the degree of mismatch between manual (the gold standard) and automated labeling, the automated labeling system was found to be highly accurate, valid and reliable.9

Cognitive Performance. Cognition was measured through a battery of tasks, focusing on multiple domains of cognition to account for a number of different changes that might occur. The study aimed to account for changes in memory, processing speed, executive function, working memory, fluid intelligence, and crystallized intelligence. The ultimate aim is to see if people with comparable levels of stress show differences in cognitive ability and in what areas these deficiencies emerge. Composites estimates for each domain were created by standardizing and summing the scores for tasks within a domain.

Memory. The Wechsler Memory Scale-III (WMS-III) (Logical Memory Subtest)10 Participants must recall two paragraphs immediately after presentation and again after a 30-40 minute delay. The California Verbal Learning Test-III is a measure of list learning. Participants must learn a list of 16 categorizable words and recall the list after a 30-minute delay. For the Building Memory task, participants are asked to study a map for four minutes and are then given a new map, on which they must recall the locations of the buildings.

Processing Speed. For the Wechsler Adult Intelligence Scale-III (WAIS-III) (Symbol Search Subtest)11, participants must search a set of symbols and indicate which symbols match up as quickly as possible. For the Letter Comparison and Pattern Comparison tasks participants are given two series of letters and patterns (respectively) and must indicate whether these sequences are the same or different as quickly as possible.

Executive Functions. For the Trail Making Test, Part A, participants must draw a line from point 1 to 25 as quickly as possible. A second level, Part B, requires participants to incorporate ordering based on letters as well. The Wisconsin Card Sorting Test (WCST) requires the participant to sort cards that display geometric designs into categories by the shape, color, or number of the designs that appear on the cards. The WCST provides an estimate of perseveration (i.e., continuing to respond based on an incorrect, previous sorting rule) (Neuroscan Corp., Herndon, VA). For the Stroop Color-Word test, participants must read the word, the color of the ink used for the word, and finally the color of the ink of a word which spells another color as fast as possible for 45 sec.

Working Memory. In the Listening Span task, participants hear a series of sentences (ranging from two to seven). The participant must answer a question about the sentences and recall the last word of each sentence. For the WMS III Letter-Number sequencing task participants hear an intermixed series of numbers and letters and are then asked to repeat the sequence in order with numbers first and then letters.

Exercise Engagement. Participants were asked to complete a Walking, Running, & Jogging Questionnaire12, which assesses engagement in these activities over the past
ten years, and considers frequency, duration and distance traveled separately. Responses were converted to Metabolic Equivalent (MET) values reflecting the energy cost of an activity. (e.g., walking at a slow pace (2.0 mph) = 2.5 MET; running at a 6 mph pace = 10 MET). Findings of construct validity have been reinforced by past research which has validated self-reported historical fitness against treadmill tests.

**Self-Efficacy.** The General Perceived Self-Efficacy Scale used to assess whether a person has a low or high self-efficacy based on participants’ ratings of validity of 10 statements about the self. An example items is “I am confident that I could deal efficiently with unexpected events.” The rating scale ranges from not at all true, barely true, moderately true and exactly true.

**Locus of Control.** The Rotter’s Locus of Control Scale was used to determine whether the participant demonstrated an internal or external locus of control through their selection of one of two versions of 32 statements. An example item is: a) many of the unhappy things in people's lives are partly due to bad luck; b) people’s misfortunes result from the mistakes they make.

**General Procedure**
Following acquisition of verbal assent to participation in this study, Rotter’s Locus of Control Scale was administered over the phone. The Cumulative Trauma Scale was completed next, and finally, the scale for General Perceived Self-Efficacy was administered. The participants were asked to write down the scales for response so that they could recall them more easily. The participants were debriefed after completion of each questionnaire, and told that any question could be repeated if needed. Following completion of the three questionnaires, participants were asked a series of questions for the processing of their payment for participation, $15. Completion of the questionnaires took approximately 30 to 45 minutes, and participants were informed that their payment would not be contingent on their completion of the questionnaires, and that they should feel free to skip any question. Additionally, during the final debriefing, participants were offered a list of referrals for psychological services, should there have been any concerns that they wanted to discuss with a professional.

**Data Analyses**
Following acquisition of data on the variables of locus of control, lifetime stress, and self-efficacy, all data, including already obtained data on lifetime exercise, brain structure and function, were analyzed with a series of hierarchical regressions. The dependent variable was either regional brain volume (e.g., hippocampus) or cognitive performance (e.g., memory). The first stage of analysis was to examine the effects of lifetime stress. In these analyses, age was entered first in the model, followed by lifetime stress and then the interaction between age and stress. A main effect of stress would support the hypothesis that stress has an impact on brain structure/cognition. A significant interaction would suggest that lifetime stress moderates age effects on brain structure/cognition. In the second stage of analysis, the potentially moderating role of exercise engagement on the effects of stress was examined only for those brain regions/cognitive domains that showed an effect of stress. The independent variables for the analysis of exercise were age, lifetime stress, exercise engagement and all interactions between age, stress and exercise with the 3-way interaction entered last. A significant interaction
would support the hypothesis that exercise moderates the impact of stress on brain volume/cognition.

RESULTS
Data collected about the personality factors of locus of control and self-efficacy were ultimately excluded from analysis due to insufficient power for multiple analyses. Instead, analyses focused on examination of the adverse effects of lifetime stress on brain structure and cognitive function and the potentially moderating role of exercise.

Stress, Exercise, and Regional Brain Structure
We hypothesized that along with the adverse effects of normal aging on brain structure, high levels of cumulative stress would be associated with smaller regional brain volume, particularly in the hippocampus and amygdala. Exercise was thought to potentially moderate these adverse effects on brain volume. The following analysis examines the prefrontal cortex, orbitofrontal cortex, hippocampus, and amygdala.

As expected, age accounted for a significant amount of variance in the prefrontal cortex (ΔR²=.225, F(1,53)=15.413, p<.0001). There was not an effect of lifetime stress on prefrontal cortex volume (ΔR²=.021, F(1,52)=1.442, p=.24). The age x lifetime stress interaction was also not significant (ΔR²=.007, F<1).

Similarly, age accounted for a significant amount of variance in the orbitofrontal cortex (ΔR²=.069, F(1,53)=3.903, p=.05). Stress also accounted for a significant amount of variance in orbitofrontal cortex with higher frequency of stress events associated with smaller orbitofrontal cortex volume (ΔR²=.085, F(1,52)=5.244, p=.05) (see Figure 1A). The interaction between age x stress did not have a significant effect on orbitofrontal cortex volume (ΔR²=.016, F(1,51)=.999, n.s.). There was a non-significant lifetime stress x exercise interaction (ΔR²=.044, F(1,50)=2.722, p=.11); however, it reflected a greater effect of stress on orbitofrontal cortex for those with greater exercise engagement. There was a non-significant trend for the age x lifetime stress x exercise engagement interaction to account for a significant amount of variance in orbitofrontal cortex volumes (ΔR²=.045, F(1,47)=2.799, p=.10). However, the interaction was not entirely consistent with hypotheses as there were trends for high lifetime stress and high engagement in exercise to be associated with the greatest age-related declines (see Figure 4A). In the lower stress individuals there was a trend for those who exercised more to evidence less age-related decline than those who exercised less.

Age also predictably had a significant effect on hippocampal volume (ΔR²=.151, F(1,53)=9.408, p<.01). There was a non-significant trend for stress to account for a significant amount of variance in hippocampal volume (ΔR²=.053, F(1,52)=3.473, p=.07) with stress associated with smaller hippocampal volume at higher levels (see Figure 1B). However, there was no significant effect on hippocampal volume from the age x lifetime stress interaction (ΔR²=.000, F<1). The lifetime stress x exercise engagement interaction was not significant (ΔR²=.002, F<1). Additionally, the age x lifetime stress x exercise engagement interaction did not account for a significant amount of variance in hippocampal volume (ΔR²=.000, F<1).

Age also predictably had a significant effect on amygdala volume (ΔR²=.100, F(1,
53)=5.891, p<.05). Stress had a significant impact on this region's volume as well, coinciding with smaller volumes at higher levels ($\Delta R^2=.083, F(1, 52)=5.290, p<.05$) (see Figure 1C). However, the age x lifetime stress interaction failed to have a significant impact on amygdala volume ($\Delta R^2=.001, F<1$). The lifetime stress x exercise engagement interaction was not significant ($\Delta R^2=.023, F(1, 50)=1.502, n.s.$). Additionally, the age x lifetime stress x lifetime exercise interaction did not account for a significant amount of variance in amygdala volume ($\Delta R^2=.001, F<1$).

**Stress, Exercise, and Cognition**

We hypothesized that stress would have a detrimental effect on cognitive function, particularly in memory. Additionally, we predicted that higher levels of exercise engagement would potentially moderate the impact of aging and stress.

There was a non-significant trend for an effect of age on immediate memory ($\Delta R^2=.040, F(1, 58)=2.407, p=.12$). There was not a main effect of stress ($\Delta R^2=.028, F(1,57)=1.698, p=.20$). Additionally, there was a non-significant trend for the age x lifetime stress interaction in immediate memory ($\Delta R^2=.042, F(1,56)=2.652, p=.11$) with individuals with lower stress demonstrating a shallower slope (more gradual decline) in age-related decline than higher stress individuals (see Figure 2A). There was with greater stress having a negative impact on immediate memory in the low exercise individuals (see Figure 3). For high stress individuals, there was a trend for those who exercised more to evidence steeper age-related declines (see Figure 4B). For low stress individuals, there were trends for those who exercised less to evidence a negative relationship between immediate memory capacity and age, but for those who exercised more to evidence a positive relationship between immediate memory and age.

Age also accounted for a significant amount of variance in working memory ($\Delta R^2=.102, F(1,58)=6.609, p<.05$). Stress, however, did not demonstrate a significant impact on working memory ($\Delta R^2=.002, F<1$). Nor did the age x lifetime stress interaction account for a significant amount of variance in working memory ($\Delta R^2=.000, F<1$).

For high stress individuals, there was a trend for those who exercised more to evidence steeper age-related declines (see Figure 2B). The lifetime stress x exercise engagement interaction was not significant ($\Delta R^2=.006, F<1$). Additionally, the age x lifetime stress interaction did not account for significant variance in executive function ($\Delta R^2=.014, F<1$).

Finally, age accounted for a significant amount of variance in processing speed ($\Delta R^2=.169, F(1, 58)=11.812, p<.01$). Additionally, there was a non-significant trend for lifetime stress ($\Delta R^2=.000, F(1, 57)=2.448, p=.12$) with greater stress associated with slower processing speed (see Figure 2C). However, the age x lifetime stress interaction did not account for a significant amount of variance in processing speed ($\Delta R^2=.000, F<1$). Also, the age x lifetime stress x lifetime exercise interaction did not account for a significant amount of variance in processing speed ($\Delta R^2=.007, F<1$).
Figure 1. Stress effects on brain regions.
Lifetime stress and volumes are residuals controlling for age.

Figure 1A. Orbitofrontal volume

Figure 1B. Hippocampal volume
Figure 1C. Amygdala volume

Figure 2. Stress effects on cognition. A) Immediate memory. B) Executive functions. C) Processing speed. Lifetime stress and cognitive scores are residuals controlling for age.

Figure 2A. Immediate memory
Figure 2B. Executive functions

Figure 2C. Processing speed
Figure 3. Interactive effects of stress and exercise on immediate memory. Lifetime stress and memory scores are residuals controlling for age.

Figure 4. Interactive effects of age, stress, and exercise. A) Orbitofrontal volume. B) Immediate memory. Data points are derived from the regression equation. See text for details on the regression analyses.

Figure 4A. Orbitofrontal volume
DISCUSSION

Our initial hypotheses, as well as findings in past research and literature have been supported in a variety of ways. We expected that brain aging would place older individuals at higher risk in terms of the effect of stress on brain structure and function. Due to the abundant literature supporting exercise’s beneficial impact on brain structure and function, we further predicted that exercise engagement might moderate the effects of stress. Thus, our first task was to replicate findings supporting the impact of age.

In congruence with literature on this subject, age-related brain shrinkage was found in each region of interest including the prefrontal cortex, orbitofrontal cortex, hippocampus, and amygdala. Importantly, we demonstrated that lifetime stress had a significant negative effect on brain volume in orbitofrontal and amygdalar regions with a non-significant trend for the hippocampus. This unique result extends findings from the animal literature to psychologically healthy non-demented older adult humans. According to past research in animals, chronic or high levels of stress result in damage of the hippocampus, ventromedial prefrontal cortex (including orbitofrontal), and amygdala. These regions are involved in the brain’s stress response, emotional processing and memory. In order to examine interactions between age and stress, such that high levels of lifetime stress intensify the impact of aging on brain structure, we conducted regressions examining for an age x lifetime stress interaction with each region of interest. Surprisingly, we found no significant interactions between age and stress. Thus, it appears that although stress has a negative impact on brain structure it did not exacerbate age-related cross-sectional declines.
Interestingly, a three-way interaction between age, lifetime stress, and exercise engagement approached significance in relation to volume of the orbitofrontal cortex. There were trends for the orbitofrontal cortex volume to demonstrate the sharpest cross-sectional rate of decline for those participants who reported high levels of stress and high levels of exercise. One possible explanation of such an effect is that participants with already high levels of stress, who exercised with relatively greater frequency over their lifetimes, had additional stress concerning fitness and body image (issues which were not considered stressors by the Cumulative Trauma Scale). Additionally, in congruence with our predictions about exercise moderating the negative impacts of age and stress on brain structure, orbitofrontal cortex volume of participants with low levels of stress who reported relatively lower amounts of exercise engagement demonstrate a trend for a sharper rate of decline than those who reported relatively higher levels of exercise over the last ten years. It is possible that for a certain level of lifetime stress, exercise can benefit brain volume by moderating effects of age and stress; however, beyond a certain threshold of cumulative stress, exercise may no longer provide this function and may in fact become a negative factor itself. It is unclear why such an interaction is not exhibited in the remaining regions of interest where stress had some effect (i.e., hippocampus and amygdala) and exercise has been shown to have a positive effect.13

In terms of cognitive function, we predicted that the negative effects of stress on brain function would particularly damage memory. Our analysis included examination of immediate memory, working memory, executive function and processing speed. Age, as expected, significantly affected working memory and processing speed with non-significant trends for immediate memory and executive functions in congruence with existing literature. Stress however, significantly affected executive functions with a non-significant trend for processing speed, whereas working memory was unaffected. Additionally, a non-significant trend for an interaction between age and stress was only observed in the immediate memory domain. We found that the participants who reported relatively higher levels of lifetime stress exhibited a sharper slope of age-related decline in immediate memory capacity. This finding supports our predictions of stress exacerbating the negative effect of age in terms of brain function. Once again, it is unclear why such an interaction was not exhibited for other areas of cognitive function like working memory, executive function, or processing speed.

While a three-way interaction between age, lifetime stress, and lifetime exercise was not observed for working memory, executive function, or processing speed, there was a non-significant trend for immediate memory. Participants who reported high stress levels and high levels of exercise demonstrated a trend for the steepest rate of decline in immediate memory function. As noted previously, one hypothesis is that beyond a certain threshold for stress, exercise no longer serves its beneficial functions and may become harmful rather than helpful in terms of brain structure and function. A notable observation of the study is within the low stress level group, between participants who reported high levels of exercise and those who reported low levels of exercise. Those with low levels of lifetime exercise exhibited a trend for general decline in immediate memory whereas those with high levels of lifetime exercise exhibited a trend for maintained immediate memory! Such a dramatic benefit of exercise on cognitive function has great implications for the potential plasticity of cognitive function.
for older individuals. However, it is important to note again that the three-way interaction did not reach significance in the current sample.

Potential limitations of the current study include the self-report nature of measures of lifetime stress and exercise engagement. Participants of an average age of 69 years were asked to recall different stressful events in their lives over the telephone, making the responses subject to boredom, or forgetfulness. The same potential flaw exists in the measure of exercise engagement. A retrospective questionnaire concerning frequency and intensity of activity level throughout one’s life is subject to limits in validity and reliability, though the questionnaire was validated previously. The 60 participants who completed this questionnaire for the current study may have incorrectly recalled their levels of activity. In terms of lifetime activity levels, the potential gender bias in this study involving 47 older women and 13 older men has implications also. Activity levels and stress experiences of women and men of this generation may differ. Thus, responses for activity levels may have been skewed from the beginning. Such disparities in gender composition and the use of self-report based measures may in part contribute to the some of the lack of expected findings noted above. Certainly, a longitudinal study that examined exercise activity and stress levels from an early age into older adulthood in a large sample of healthy individuals would be a great design to address methodological limitations. In addition, the sample is relatively small and clearly, replication of the significant results is necessary. Furthermore, the relatively small sample likely limited the power to detect differences across conditions. It would be interesting to replicate the study and see if results differ.

Along this line, in addition to replication of the study to confirm findings with a larger, more gender-balanced sample, I would like to further explore the possibility of there being a certain threshold level of stress, beyond which point exercise is no longer helpful. Further research is also necessary to elucidate how much, and what kind of exercise is most beneficial and why. Considering that exercise has the potential to impact brain structures and functions that are so critical to daily life, further research into this area is warranted. More importantly, the trends for interactive effects of age, lifetime stress, and exercise engagement on orbitofrontal cortex and immediate memory suggest that exercise can have extremely beneficial effects in geriatric life, demanding further research.

Overall, the finding of negative effects of stress on brain structure and cognition in older adult humans is an important extension of the animal literature, particularly as the individuals did not report any history of psychological disorders. In addition, the finding of trends for moderating effects of exercise on the negative impact of stress and age on the orbitofrontal cortex and immediate memory are extremely promising. However, further research is necessary to confirm these results as well as clarify why activity levels appear to benefit certain areas of structure and function, but not others.
Notes


5 Colcombe et al 2004


