The Moderating Role of Exercise on Stress-Related Effects on the Hippocampus and Memory in Later Adulthood

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Objective: Chronic stress has well-documented negative effects on hippocampal structure and function, and has been suggested to contribute to age-related declines. In contrast, there is evidence that exercise has beneficial effects in older adults. The current investigation examined effects of lifetime stress on hippocampal volume and memory, the moderating role of stress on age effects, and the moderating role of exercise on stress-related effects. *Method:* Measures of lifetime stress, exercise engagement, magnetic-resonance-imaging-based volumes, and cognitive performance were obtained in a sample of healthy middle-aged and older adults. *Results:* There was a significant negative influence of stress on hippocampal volume. In addition, exercise engagement moderated effects of lifetime stress on both hippocampal volume and memory. Specifically, lower exercise engagement individuals evidenced greater stress-related declines compared with high exercise engagement individuals. *Conclusions:* These novel findings suggest that benefits of exercise in later adulthood may extend to minimizing detrimental effects of stress on the hippocampus and memory.

Keywords: chronic stress, medial temporal, episodic memory, aerobic exercise, aging

Cognitive and brain aging are characterized by considerable individual differences (Hertzog, 2008; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010), which have prompted investigations into factors that may serve to contribute to decline or promote successful aging (Hertzog, Kramer, Wilson, & Lindenberger, 2008; Raz, Rodrigue, Kennedy, & Land, 2009). Stress has long been suggested as a factor that contributes to cognitive and brain decline in aging (Landfield, Blalock, Chen, & Porter, 2007; Sapolsky, Krey, & McEwen, 1986; Sapolsky, 1999). Consistent with this hypothesis, stress targets similar brain structures and cognitive functions (e.g., memory) as advancing age (Balota, Dolan, & Duchek, 2000; Raz & Rodrigue, 2006). Stress-related effects on the hippocampus have been emphasized, as this structure is a target of stress hormones released by the hypothalamic-pituitary-adrenocortical (HPA) axis. The HPA axis is an integral component of brain regulation of the stress response, and the hippocampus has regulatory and feedback interactions with the HPA axis (Jankord & Herman, 2008). Both nonhuman animal and human evidence support an influence of stress on the hippocampus.

The nonhuman animal literature indicates that protracted elevations of glucocorticoids, as a result of stress, induce synaptic loss, reduced dendrite spines, decreased long-term potentiation, and reduced neurogenesis in the hippocampus (McEwen, 2008; Radley & Morrison, 2005). Similarly, in the human literature, which has primarily examined stress-related conditions such as depression and posttraumatic stress disorder, there is evidence of reduced hippocampal volumes (Karl et al., 2006; Lorenzetti, Allen, Fornito, & Yucel, 2009). Lastly, both stress and stress hormones have been associated with declines in memory performance in nonhuman animal and human investigations (Sauro, Jorgensen, & Pedlow, 2003).

In support of the conceptualization that these stress-related effects on the hippocampus and memory may play a role in brain and cognitive aging, associations between stress hormones, hippocampal damage, and/or memory impairment have been observed in aged rats (Issa, Rowe, Gauthier, & Meaney, 1990; Landfield, Waymire, & Lynch, 1978; Landfield et al., 2007; Sapolsky et al., 1986; Sapolsky, 1999). Furthermore, elevated cortisol, one stress hormone, has been consistently associated with poorer memory functioning (e.g., Carlson & Sherwin, 1999; Lupien et al., 1994, 1998; Seeman, McEwen, Singer, Albert, & Rowe, 1997) and reduced hippocampal volume (Lupien et al., 1998) in older adult humans. Importantly, these relationships have also been observed for self-report measures of stress in older adults. For example, perceived stress and reports of recent stressful life events are negatively related to memory performance (Neupert, Almeida, Mroczek, & Spiro, 2006; Peavy et al., 2007; VonDras, Powless, Olson, Wheeler, & Snudden, 2005) and hippocampal volume (Gianaros et al., 2007). These findings converge on the possibility

that chronic or repeated stress may lead to increased vulnerability to other toxic events, such as those that may occur with aging (Sapolsky et al., 1986), thereby exacerbating the effects of aging for stressed individuals.

In comparison with the detrimental effects of stress, exercise engagement promotes benefits to brain structure and memory function, including increased brain-derived neurotrophic factor levels, neurogenesis and angiogenesis in the hippocampus, and improved learning and memory in nonhuman animals (Hillman, Erickson, & Kramer, 2008; Greenwood, Strong, Foley, & Fleshner, 2009; van Praag, 2008). Beneficial effects of exercise on medial temporal structures, including the hippocampus, and memory functioning have also been observed in aged nonhuman animals and humans (Bugg & Head, 2011; Erickson et al., 2009; Gordon et al., 2008; Pereira et al., 2007; van Praag, 2008; van Praag, Shubert, Zhao, & Gage, 2005; but see Madden, Blumenthal, Allen, & Emery, 1989; van Boxtel et al., 1997). Relatively few studies have examined the possibility that exercise may confer benefits by buffering against the influence of stress. Consistent with this possibility, some studies have demonstrated that exercise attenuates or reverses the negative effects of stress on hippocampal cell proliferation (Kannangara, Webber, Gil-Mohapel, & Christie, 2009; Mello, Benetti, Cammarota, & Izquierdo, 2009; Nakajima, Ohsawa, Ohta, Ohno, & Mikami, 2010), even in aged animals (Kannangara et al., 2011). However, others have observed that stress attenuates or delays exercise-related neurogenesis in the hippocampus (Leasure & Decker, 2009; Stranahan, Khalil, & Gould, 2006). Thus, further study is needed to assess whether exercise moderates the effects of lifetime stress on hippocampal structure and memory in adult humans.

The current cross-sectional investigation of the effects of stress in middle-aged and older adults had several goals. One goal was to examine the effects of lifetime stress on memory and hippocampal volume, with the expectation that a higher occurrence of stressful events would be associated with lower memory performance and smaller hippocampal volumes. A second goal was to examine whether stress moderates the effects of age with the hypothesis that greater stress would be associated with steeper cross-sectional age-related decline in memory performance and hippocampal volume. Lastly, the current study assessed whether exercise engagement moderates the effects of lifetime stress, with the hypothesis that greater exercise engagement would be associated with an attenuation of the negative effects of stress on memory performance and hippocampal volume. A novel component of the current study is that we examined the frequency of potential stressors over the life span, which represents an extension of past reports that examined self-reported stressful life events over a shorter time span (Neupert et al., 2006; Peavy et al., 2007; VonDras et al., 2005) or assessed self-reported perceived stress (Gianaros et al., 2007). In addition, we included the primary visual cortex as a control brain region and vocabulary as a control cognitive domain to assess for the selectivity of the effects of stress and/or exercise engagement.

Method

Participants

There were 59 older adult participants from a prior unpublished study in the lab, with these individuals originally recruited from the St. Louis community through advertisements in local media (community sample). For the community sample, 51 of the 59 participants had a magnetic resonance imaging (MRI) scan. There were also 40 participants recruited from the Washington University Alzheimer's Disease Research Center (ADRC sample). All 40 of these participants had an MRI scan as part of their participation in the ADRC. For the MRI analyses, the data for the 91 participants from the ADRC and community samples were combined. Demographic information for the participants whose data contributed to the MRI analyses is presented in Table 1. Table 2 presents demographic information for participants whose data contributed to the cognitive analyses; all of these participants were from the community sample.

The ADRC sample was screened for dementia based on the Clinical Dementia Rating scale (Clinical Dementia Rating = 0; Morris, 1993). The community sample was screened for gross

Table 1
Descriptive Statistics for the MRI Analyses

	Low exercise	High exercise
N	44	44
Age, years (*M* [*SD*])	74 (9)	71 (7)
Gender (F/M)	19/25	24/20
Education, years (*M* [*SD*])	15.0 (2.8)	15.7 (2.8)
History of depression (−/+)	38/6	43/1
Geriatric Depression scale	.96 (1.07)	.60 (.83)
Beck Depression Inventory-II	2.8 (2.2)	1.7 (2.3)
Hypertension (−/+)	21/23	28/16
Stress frequency	13.2 (9.4)	13.7 (9.2)
Exercise engagement, MET hr/wk (*M* [*SD*])	.63 (.91)	9.96 (6.97)**
Strenuous sports engagement, years (*M* [*SD*])	2.55 (4.03)	2.95 (4.07)
Hippocampus, cm² (*M* [*SD*])	7.3 (.69)	7.3 (.72)
Primary visual cortex, cm² (*M* [*SD*])	3.5 (.73)	3.5 (.69)

Note. The MRI sample consists of participants combined across the ADRC and community samples. The GDS was administered to the ADRC sample; the BDI-II was administered to the Community Sample. See text for details.
* $p < .05$.   ** $p < .001$.

Table 2
Descriptive Statistics for the Cognitive Analyses

	Low exercise	High exercise
N	25	32
Age, years (M ([SD])	73 (8)	72 (8)
Gender (F/M)	22/3	23/9
Education, years (M [SD])	14.7 (3.1)	15.3 (2.7)
History of depression (−/+)	25/0	32/0
Beck Depression Inventory-II	3.0 (2.6)	2.32 (2.8)
Hypertension (−/+)	11/14	18/14
Stress frequency	17.4 (10.7)	17.7 (10.5)
Exercise engagement, MET hr/wk (M [SD])	.63 (.93)	10.76 (7.8)*
Strenuous sports engagement, years (M [SD])	2.7 (4.2)	2.6 (3.9)
WASI vocabulary	66.2 (6.5)	64.8 (7.1)
California Verbal Learning Test-II	45.9 (8.5)	44.4 (10.9)
Building memory	4.4 (2.1)	3.7 (2.0)
Standardized memory composite	.05 (.77)	−.21 (.61)

Note. All of these participants were from the community sample only. See text for details.
* $p < .001$.

cognitive functioning with the Short Blessed Test using a cutoff of 5 (Katzman et al., 1983; Morris et al., 1989). All participants were additionally screened for neurological (e.g., Parkinson's disease, head injury, stroke) and major medical conditions (e.g., diabetes). Screening of the ADRC sample was conducted at or near the time of each assessment (see the Timing of Assessments section for details), and screening of the community sample was conducted at the time of the cognitive/MRI session. Participants consented to participation in accordance with guidelines of the Washington University Human Research Protection Office.

Lifetime Stress

Lifetime stress was estimated using the 32-item Cumulative Trauma Scale (CTS) (Kira et al., 2008). The CTS is based on a taxonomy of stressors, including lifetime stress (e.g., repeated hassles), internal stressors (e.g., major medical conditions, pain), nature-made events (e.g., natural disasters), and man-made events, which includes person-made (e.g., motor vehicle accident, sexual abuse, racial discrimination) and socially made (e.g., poverty) events. Thus, a wide range of potential stressors from across the life span is assessed in the measure (e.g., divorce, sexual assault, job loss, natural disasters, discrimination, illness).

Reliability and validity. Reliability and validity of a short form (22 items) of the CTS measuring frequency of experiences were established in a sample of 499 individuals aged 12–79 years (Kira et al., 2008). The scale demonstrated adequate internal consistency (Cronbach's alpha = .85) and adequate convergent (i.e., positive associations with other trauma scales), divergent (negative associations with measures of adjustment and futuristic orientation), and predictive (i.e., positive associations with posttraumatic stress disorder, lifetime stress disorders, and poor health) validity.

Procedure

The CTS was administered by telephone and participants indicated the frequency and impact of a list of 32 stressors. First, frequency with which a particular stressor was experienced was rated as never (0), once (1), twice (2), 3 times (3), or many times (4). Next, the stressor's impact in terms of the degree to which it subsequently had a positive or negative influence on the participant's life was rated on a 7-point Likert-type scale (i.e., extremely positive, very positive, somewhat positive, negative, somewhat negative, very negative, extremely negative). The current report focused on lifetime stress events, and thus the independent variable used in analyses was the sum of the number of events across stressors (range = 0–128), with higher values indicating greater frequency of stress events.

Exercise Engagement

Validity. A validated questionnaire assessing history of walking, running, and jogging activity for the past 10 years was used to estimate exercise engagement (Bowles, FitzGerald, Morrow, Jackson, & Blairal, 2004). The measure was significantly correlated with cardiorespiratory fitness, measured via treadmill test in a sample of 5,063 individuals aged 18–80 years. Stable correlations were observed between retrospective self-report of activity for a particular year and aerobic fitness for that year across the 10 1-year assessment periods, suggesting participants across the examined age range were capable of relatively accurate self-report over this extended time span. Although reliability was not directly assessed, validity is limited by reliability, and thus the demonstrated validity can be considered indicative of adequate reliability (Bowles et al., 2004).

Procedure. The questionnaire was administered by telephone, and participants reported number of months per year, number of workouts per week, average number of miles per workout, and average time per mile for each year in which they engaged in an exercise program involving walking, running, or jogging over the preceding 10 years. A physical exercise engagement score was derived by estimating metabolic equivalent (MET) values, using the compendium of physical activities, as described previously. The index of exercise engagement was average MET hr per week over the past 10 years. As a reference, an individual who followed the American Heart Association's physical exercise recommendation for older adults (30 minutes of moderate exercise,

5 days per week) would score 7.5 MET hr per week. Participants were categorized into low-exercise and high-exercise engagement groups based on the median value of 3.15 MET hr per week for the sample.

Participants also reported the number of years, within the last 10 years, during which they participated in strenuous sports other than running, walking, or jogging at least twice a week for 6 consecutive months. Examples included racquet sports, cycling, swimming, aerobic dance, and strenuous sports involving running, such as basketball and soccer.

MR Acquisition

For all scans, cushions reduced head movement during scanning, and a scout image was acquired first in order to center the field of view on the brain. For the ADRC sample ($n = 40$), imaging was performed using a Siemens Vision 1.5T scanner and two to four T1-weighted sagittal MP-RAGE scans (TR = 9.7 ms, TE = 4 ms, flip angle = 10°, TI = 20 ms, $1 \times 1 \times 1.25$ mm resolution) were acquired for each subject. For the community sample ($n = 51$), images were acquired using a Siemens 1.5T Sonata Scanner (Erlangen, Germany) and two T1-weighted sagittal MP-RAGE scans (TR = 1900ms, TE = 3.93 ms, flip angle = 7°, TI = 1100, $1 \times 1 \times 1.25$ mm resolution) were acquired for each subject.

Regional Volumetry

Hippocampal volume was obtained using Freesurfer software (Desikan et al., 2006; Fischl et al., 2002). During processing, each voxel is assigned a neuroanatomical label based on probabilistic information derived from a manually labeled training set, which included healthy young and older adults. Previous work indicates that this technique generates volumes with a high correspondence to manually generated volumes (Desikan et al., 2006; Fischl et al., 2002). As there were no hypotheses regarding laterality effects, volumes were summed across hemispheres. Total intracranial volume (ICV) was used to adjust hippocampal volumes for body size differences. The adjustment was performed via a formula based on the analyses of covariance approach: adjusted volume = raw volume − ($b \times$ [ICV minus mean ICV]), where b is the slope of the regression of volume on ICV (Jack et al., 1989; Mathalon, Sullivan, Rawles, & Pfefferbaum, 1993). Adjusted hippocampal volume was used as the dependent variable in analysis.

Although there may be concerns with regard to biases in cross-scanner aggregation, there is evidence of reliability of Freesurfer-derived estimates of cortical thickness and volumes across scanner upgrades, different manufacturers, and number of MP-RAGE acquisitions, particularly when scanners have the same field strength (e.g., Fennema-Notestine et al., 2007; Han et al., 2006; Jovicich et al., 2009), and cross-scanner aggregation has been successfully used previously (e.g., Desikan et al., 2009; McEvoy et al., 2009; Storandt, Mintun, Head, & Morris, 2009). An in-house comparison between the Sonata 1.5T and Vision 1.5T scanners in Freesurfer-derived hippocampal and primary visual cortex volumes yielded an average intraclass correlation of .80, indicating a strong correspondence between volumes derived from the two scanners.

Cognitive Assessment

All 59 participants in the community sample completed the cognitive measures of memory and vocabulary. We did not have equivalent cognitive data for the ADRC sample.

Memory. For the California Verbal Learning Test-II (Delis, Kramer, Kaplan, & Ober, 2000) participants were orally presented with a list of 16 categorizable grocery items, five times. The number of items correctly recalled across the five trials was the index of performance. The estimated test–retest reliability is .92 (Delis et al., 2000). For the Building Memory Test (Ekstrom, French, Harman, & Dermen, 1976), participants first studied a map of a fictitious urban location with landmark buildings. During the test phase, participants were shown a blank map and tested, in a multiple-choice format, on their memory of landmark locations. The index of performance is number correct minus .25 points for false-positives. The estimated reliability is .80 (Ekstrom et al., 1976). A composite measure of memory was created by standardizing scores for each task and summing the standardized scores.

Vocabulary. The Vocabulary subtest from the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) was administered and scored according to standard protocol. The raw score was the index of performance. The estimated split-half reliability is .94 (Wechsler, 1999).

Depression Symptoms

Depression symptoms were measured with the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) in the community Sample, and with the Geriatric Depression Scale (GDS; Yesavage et al., 1983) in the ADRC sample. The BDI-II has an estimated reliability of .92 (Beck et al., 1996), and the GDS has an estimated reliability of .94 (Yesavage et al., 1983). BDI-II scores range from 0 to 63, whereas scores on the GDS range from 0 to 15. While the specific item content and format differ between these two measures, they are strongly correlated (rs = .71 to .77; e.g., McCabe et al., 2006; von Hippel, Vasey, Gonda, & Stern, 2008), show similar associations with cognitive measures (von Hippel et al., 2008), and show similar sensitivity to reductions in symptoms following cognitive–behavioral therapy (Laidlaw et al., 2008). Thus, there are indications that the two measures similarly estimate the underlying construct of depression symptomatology. In order to have an estimate of depressive symptoms for the MRI analyses (which were based on combined data from the ADRC and community samples), scores on the respective depressive symptoms measured within each sample were standardized using a z transformation to obtain an estimate of each individual's relative ranking.

Timing of Assessments

The MRI scan was conducted, on average, 1.62 years ($SD =$ .85) prior to the exercise engagement assessment and 3.52 years ($SD = 1.26$) prior to the lifetime stress assessment. Thus, the exercise assessment captured exercise behavior preceding and during the time of the scan for all individuals. Similarly, the lifetime stress assessment captured stressful events preceding and during the time of the scan for all individuals. The lifetime stress assessment was subsequent to the exercise engagement assessment

for 90% of the sample ($M = 1.86$ years; $SD = .45$). For the other nine individuals, stress assessment preceded exercise assessment by an average of just 5.5 months ($SD = .13$). Thus, any reported exercise behavior would have occurred almost exclusively during a time period for which stressful experiences were also captured.

The cognitive assessment was conducted, on average, 1.60 years ($SD = .84$) prior to the exercise engagement assessment and 2.65 years ($SD = .32$) prior to the lifetime stress assessment. Thus, the exercise assessment captured exercise behavior preceding and during the time of the cognitive assessment for all individuals. Similarly, the lifetime stress assessment captured stressful events preceding and during the time of the cognitive assessment for all individuals. The lifetime stress assessment was subsequent to the exercise engagement assessment for 83% of the sample ($M = 1.41$ years; $SD = .17$). For the other 10 individuals, lifetime stress assessment preceded exercise assessment by an average of just 5.6 months ($SD = .12$). Thus, any reported exercise behavior would have occurred almost exclusively during a time period for which stressful experiences were also captured.

Data Analyses

Outliers and missing data. Univariate outliers were defined as values 3 standard deviations from the mean. Three individuals in the MRI analyses and two individuals in the cognitive analyses had outlier data points. These outliers were removed from analyses to meet assumptions of regression analyses. Thus, the final sample was 88 for the MRI analyses and 57 for the cognitive analyses (see Tables 1 and 2, respectively). Exercise engagement data were missing for four individuals, California Verbal Learning Test data were missing for four individuals, Building Memory Test data were missing for three individuals, and vocabulary data were missing for one individual, representing .03% of the total data points. Missing data were replaced using a regression substitution imputation approach, which uses regression to predict the missing data point, based on other variables. All other variables included in the regression model were used for the imputation.

Covariates. Gender (coded as $0 = $ male and $1 = $ female), education (years), history of hypertension, and standardized depression scores (combined across GDS and BDI-II for the MRI analyses; BDI-II only for the cognitive analyses) were included as covariates in all analyses. As there were individuals with a history of depression in the MRI analyses (but not the cognitive analyses), history of depression was an additional covariate in analyses of regional brain volumes.

Statistical analyses. Four hierarchical regressions were conducted to address our primary questions regarding the main effects of lifetime stress, the moderating role of stress on age effects, and the moderating role of exercise on stress effects. The approach to investigating moderation followed the steps outlined by Baron and Kenny (1986). These steps included a hierarchical regression approach to examine the unique variance accounted for by the hypothesized two-way interactions, above and beyond the hypothesized main effects. The dependent variables were hippocampal volume, primary visual cortex volume, memory performance, *or* vocabulary performance. Exercise engagement status was coded as 0 or 1. The continuous age and lifetime stress predictors were standardized using a z transformation in order to minimize multi-

collinearity with the interaction terms in the model. Interaction terms were created by multiplying the relevant variables.

In all analyses, the nuisance covariates were entered in the first step. Age was entered in the second step so that we could examine effects of the other predictors independent of age. The primary variable of interest, lifetime stress, was entered in the next step, and exercise engagement was entered in the fourth step. The two primary interactions of interest (Age $\times$ Lifetime Stress; Lifetime Stress $\times$ Exercise Engagement) were entered in the next steps. The Age $\times$ Exercise Engagement interaction was entered in the seventh step, and the 3-way interaction was entered in the last step. Cohen's f^2 was calculated as a measure of effect size.

Results

Regression Assumptions

Age, hippocampal volume, primary visual cortex volume, lifetime stress, memory, and vocabulary were all normally distributed (all $ps \geq .09$; Kolmogorov–Smirnov test). For all models, error was normally distributed (all $ps \geq .21$; Kolmogorov–Smirnov test). Examination of the plots of standardized residuals against standardized predicted values indicated that there was no homoscedasticity for any of the models (e.g., no systematic associations across the range of values). Homogeneity of variances was observed for the exercise groups in terms of the outcome variables (i.e., hippocampal volume, primary visual cortex volume, memory, and vocabulary; all $ps \geq .44$; Levene's Test for Equality of Variances). Based on the Durbin–Watson test, there were independent observations (Durbin–Watson between 1.5 and 2.05 for all models). Lastly, there was not a problematic level of multicollinearity in any of the models (Variance Inflation Factor scores <4, with highest values for three-way interaction).

Hippocampus

Age accounted for a significant amount of variance in hippocampal volume, $\Delta R^2 = .32$, $F(1, 81) = 42.20$, $\beta = -.59$, $p < .001$, $f^2 = .52$, with increasing age associated with smaller volumes. Lifetime stress also accounted for a significant amount of variance, $\Delta R^2 = .04$, $F(1, 80) = 5.01$, $\beta = -.22$, $p < .05$, $f^2 = .06$. Exercise engagement did not account for a significant amount of variance, $\Delta R^2 = .01$, $F(1, 79) = .703$, $\beta = -.09$, ns, $f^2 = .01$. However, the Lifetime Stress $\times$ Exercise Engagement interaction did account for a significant amount of variance, $\Delta R^2 = .05$, $F(1, 77) = 7.83$, $\beta = .36$, $p < .01$, $f^2 = .06$, reflecting greater decline in hippocampal volume with increasing stress for the low exercise group, $r(42) = -.29$, $p = .05$, compared with the high exercise group, $r(42) = .16$, ns (see Figure 1). Neither the two-way interactions involving age (Age $\times$ Lifetime Stress: $\Delta R^2 = .01$, $F[1, 78] = .70$, $\beta = .08$, ns, $f^2 = .01$; Age $\times$ Exercise Engagement: $\Delta R^2 = .02$, $F[1, 76] = 3.63$, $\beta = -.21$, ns, $f^2 = .01$) nor the Age $\times$ Lifetime Stress $\times$ Exercise Engagement interaction, $\Delta R^2 = .00$, $F(1, 75) = .00$, $\beta = -.01$, ns, $f^2 = .01$, accounted for a significant amount of variance.

Additional models were tested to examine any potential influences of scanner type or the delays between assessments. Due to the strong correlations among the delay variables, it was not possible to enter all of the delays (i.e., scan–exercise; scan–stress;
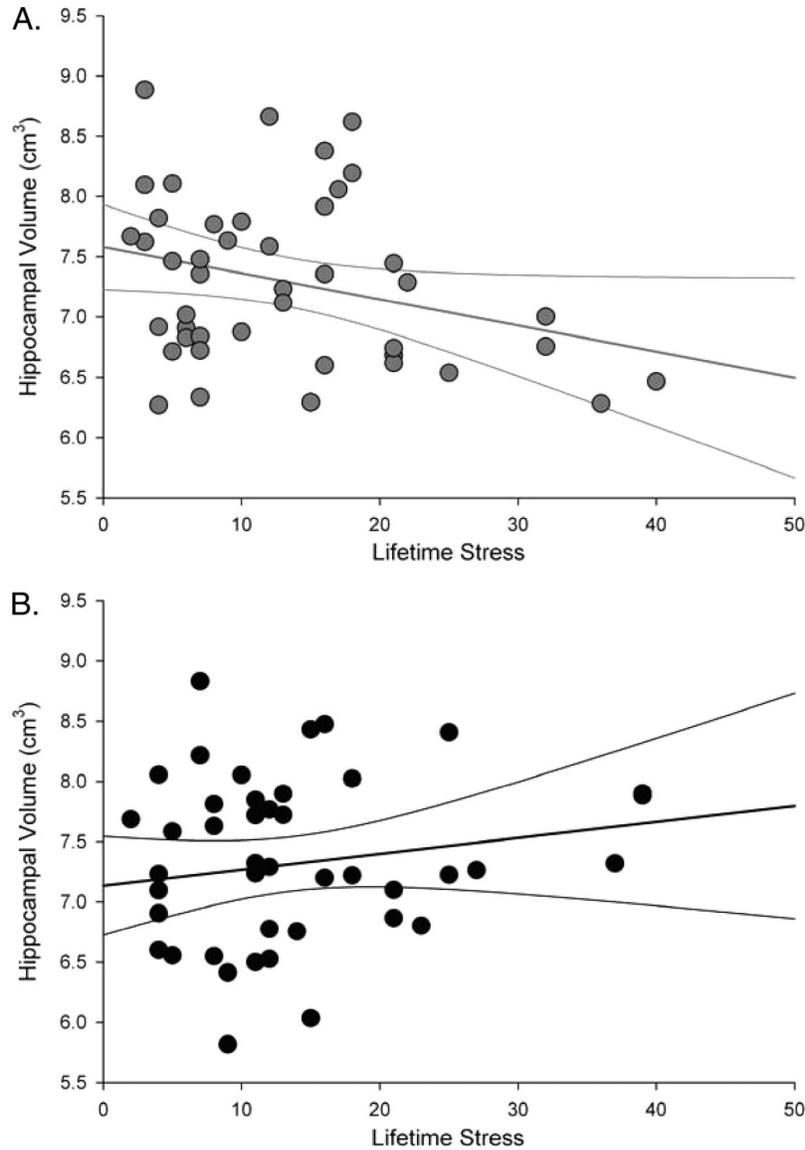
Figure 1. Exercise engagement moderates stress effects on hippocampal volume. (A) Low exercise group; (B) high exercise group. Lines represent the regression line (middle) with the 95% confidence interval.

stress–exercise) in one model. The main effect of stress and the Stress × Exercise interaction remained significant when scanner type or delays between assessments were additionally controlled (all *ps* < .05). When individuals with missing data points were excluded, the main effect of stress was a nonsignificant trend (*p* = .056) and the Stress × Exercise interaction remained significant (*p* < .05).

Primary Visual Cortex

The main effects of age, lifetime stress, or exercise (all *ps* ≥.42) nor any interactions (all *ps* ≥.10) were significant for the primary visual cortex volumes. Results were similar with missing data excluded.

Memory Performance

Neither age, $\Delta R^2 = .04$, $F(1, 51) = 2.37$, $\beta = -.22$, *ns*, $f^2 = .05$, lifetime stress, $\Delta R^2 = .01$, $F(1, 50) = .80$, $\beta = -.15$, *ns*, $f^2 = .02$, nor exercise engagement, $\Delta R^2 = .05$, $F(1, 49) = 3.33$, $\beta = -.25$, *ns*, $f^2 = .07$, accounted for a significant amount of variance. However, the Lifetime Stress × Exercise Engagement interaction accounted for a significant amount of variance, $\Delta R^2 = .16$, $F(1, 47) = 11.51$, $\beta = .67$, $p < .01$, $f^2 = .13$, which reflected a greater effect of stress on memory performance for those in the low exercise group, $r(23) = -.46$, $p < .05$, compared with those in the high exercise group, $r(30) = .24$, *ns* (see Figure 2). Neither the two-way interactions involving age (Age × Lifetime Stress: $\Delta R^2 = .02$, $F[1, 48] = .94$, $\beta = .15$, *ns*, $f^2 = .01$; Age × Exercise Engage-
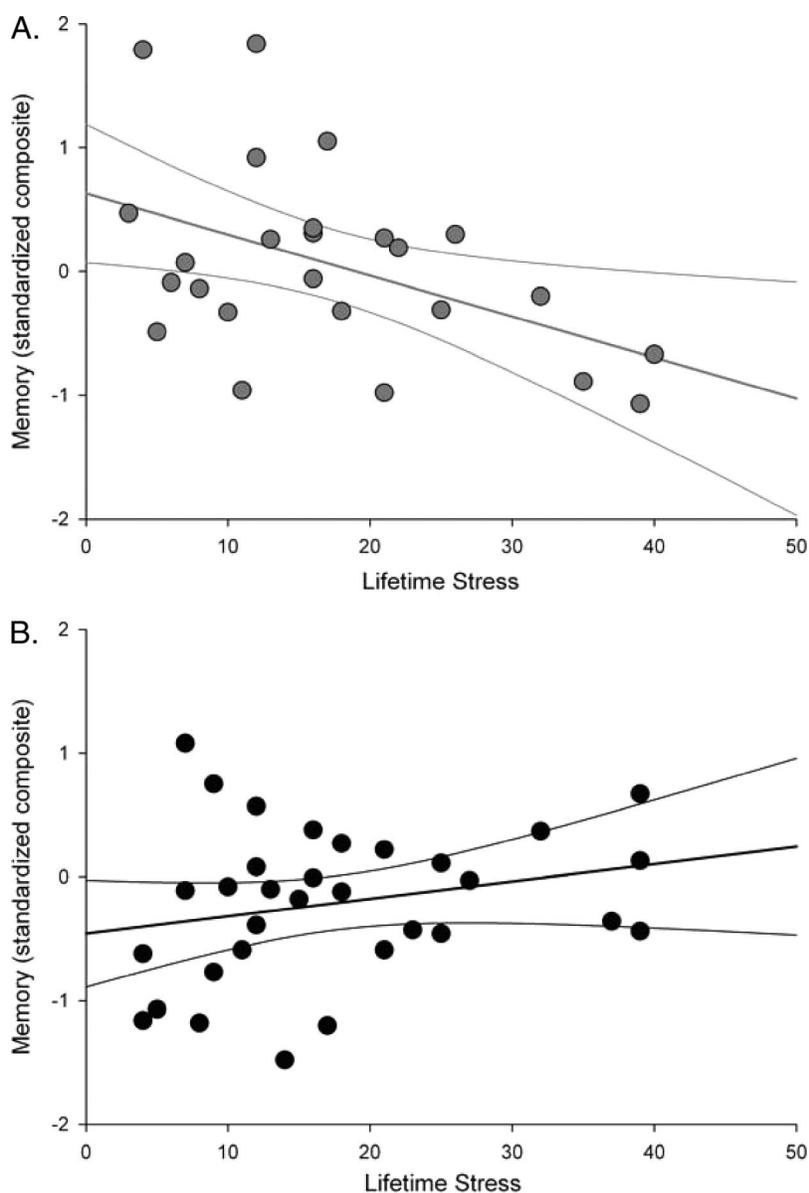
Figure 2. Exercise engagement moderates stress effects on memory performance. (A) Low exercise group; (B) high exercise group. Lines represent the regression line (middle) with the 95% confidence interval.

ment: $\Delta R^2 = .01$, $F[1, 76] = .37$, $\beta = .13$, *ns*, $f^2 = .01$) nor the Age × Lifetime Stress × Exercise Engagement interaction, $\Delta R^2 = .01$, $F(1, 45) = .87$, $\beta = -.22$, *ns*, $f^2 = .01$, accounted for a significant amount of variance. The Stress × Exercise interaction remained significant when delays between assessments were additionally controlled and when individuals with missing data were excluded (all *ps* <.05).

Vocabulary

Neither the main effects of age, lifetime stress, or exercise (all *ps* ≥.28) nor any interactions (all *ps* ≥.15) were significant for vocabulary scores. Results were similar with missing data excluded.

Discussion

The present investigation examined the negative effects of lifetime stress and the moderating influence of exercise engagement on hippocampal volume and memory performance in healthy middle-aged and older adults. Considering the literature supporting exercise-related benefits on these variables, it was predicted that exercise engagement would moderate the effects of stress. In addition, it was expected that greater lifetime stress would be associated with greater cross-sectional age-related declines in these variables.

A significant negative influence of self-reported lifetime stress on hippocampal, but not primary visual cortex volume, was observed. A negative effect of stress on the hippocampus is consis-

tent with the extensive literature on nonhuman animals (McEwen, 2008; Radley & Morrison, 2005) and stress-related psychiatric conditions (Karl et al., 2006; Lorenzetti et al., 2009), demonstrating the effects of chronic stress on the hippocampus. This finding also represents an extension of two past reports that observed associations of hippocampal volume with cortisol levels (Lupien et al., 1998) and with self-reported perceived stress (Gianaros et al., 2007) in psychiatrically normal older adult humans. Importantly, the effect of lifetime stress on the hippocampus (but not the primary visual cortex) was moderated by exercise engagement. Specifically, stress-related declines in hippocampal volume were greater for the low-exercise group than for the high-exercise group. This is a novel observation in humans, and the pattern coincides with reports that exercise may attenuate or reverse the negative effects of stress on hippocampal cell proliferation in nonhuman animals (Kannangara et al., 2009; Nakajima et al., 2010), including aged mice (Kannangara et al., 2011). Our findings do, however, contrast with two additional nonhuman animal studies that observed stress-related attenuation of exercise-related neurogenesis in rats (Leasure & Decker, 2009; Stranahan et al., 2006). Discrepant findings across nonhuman animal studies may relate to the type of stressor, level of stress, species-related differences in perceptions of a particular stressor (e.g., social isolation), and/or animal care management protocols (Kannangara et al., 2009).

As expected, there was no association between lifetime stress and vocabulary. Although the influence of lifetime stress on memory performance was in the expected negative direction, a significant main effect was not observed. The absence of a main effect of stress on memory is inconsistent with previous reports of associations between cortisol (Carlson & Sherwin, 1999; Lupien et al., 1994, 1998; Seeman et al., 1997) or self-reported stress during briefer intervals (Neupert et al., 2006; Peavy et al., 2007; VonDras et al., 2005) and memory in older adults. However, the absence of a main effect was observed in the context of a significant interaction between lifetime stress and exercise engagement for memory performance but not vocabulary. This interaction reflected that stress-related reductions in memory were apparent, but only for the low-exercise group and not the high-exercise group. This pattern is consistent with recent reports of exercise attenuating stress effects on memory in nonhuman animals (Mello et al., 2009; Nakajima et al., 2010).

Collectively, the novel pattern of findings for both hippocampal volume and memory provide support for a buffering influence of exercise in the context of lifetime stress. In addition, current results are consistent with memory being, in part, a hippocampally dependent function, and post hoc analysis revealed a significant association between hippocampal volume and memory performance in the subsample of the community sample that had both measures ($n = 49$; age-partialed $r[42] = .30$, $p < .05$). While the current report does not address mechanisms, exercise has been demonstrated to have multiple positive effects, including enhanced neurogenesis and angiogenesis, reduced levels of stress hormones, reduced HPA axis response to mild psychological stressors, and reversal of corticosterone-induced HPA dysregulation (Hillman et al., 2008; Greenwood et al., 2009; Kannangara et al., 2009; van Praag, 2008; Droste, Chandramohan, Hill, Linthorst, & Reul, 2007; Kim et al., 2008), which may serve to protect hippocampal structure and memory functioning against the potentially detrimental effects of stress.

Notably, there were no significant interactions between stress and age for hippocampal volume or for memory performance. Thus, there was no support for the hypothesis that individuals who had experienced greater stress would experience greater declines with age. Much of the work that would suggest interactive effects of stress and age has focused on specific subfields of the hippocampus (e.g., dentate gyrus, CA3; Landfield et al., 2007; Sapolsky, 1999; McEwen, 2008), and thus it is conceivable that if specific subfields of the hippocampus were examined in humans, then interactive effects of stress and aging would be observed. Moreover, as the degree to which environmental events are considered as stressful depends, in part, on an individual's perceptions, which may reflect multiple factors such as past experiences, personality characteristics, available coping resources, and social support (Lazarus & Folkman, 1984; McEwen, 2008; Monroe, 2008), future investigations might also include measurement of individual differences in cognitive appraisal processes and the factors associated with it. There is evidence of a downregulation of negative emotions and improved ability to regulate emotions with age (e.g., Phillips, Henry, Hosie, & Milne, 2008; Scheibe & Carstensen, 2010), age differences in appraisal processes and coping strategies (e.g., Diehl, Coyle, & Labouvie-Vief, 1996), an influence of social support on cognitive functioning in older adults (Hertzog et al., 2008), and personality-related differences in brain structure in aging (e.g., Jackson, Balota, & Head, 2011). These age effects may serve to mitigate the experience of distress and, thereby, stress-related effects on brain structure and cognition in older adults.

There are several potential limitations associated with the current study, including the retrospective self-report nature of the lifetime stress and exercise measurements. The measures of exercise and lifetime stress may be limited by the ability of healthy older adults to accurately recall and report their experiences over an extended time span and by the use of phone administration as opposed to in-person administration. In addition, the cognitive status of the community sample was not assessed at all time points, and some individuals may have experienced cognitive decline in between measurements. These limitations could lead to either over- or underestimation of stressful experiences or exercise behavior, thereby adding noise to our measures and reducing the likelihood of finding significant effects of interest. Furthermore, the current self-report measure of exercise engagement is significantly, but not perfectly, related to cardiorespiratory fitness. However, the expected pattern of selective effects for the hippocampus and memory does provide some additional support for the validity of the self-report measures. In addition, although the low- and high-exercise groups did not differ significantly in years of participation in strenuous sports other than running, walking, and jogging, the exercise engagement measure did not include other potentially relevant occupational and leisure time physical activities or nonstrenuous exercises. Another potential measurement limitation is that although Freesurfer provides automated estimates of hippocampal volume, with strong correspondence to manually derived estimates (Cherbuin, Anstey, Reglade-Meslin, & Sachdev, 2009; Fischl et al., 2002; Tae, Kim, Lee, Nam, & Kim, 2008), it may overestimate volume (e.g., Cherbuin et al., 2009; Tae et al., 2008). However, automated measures show similar associations as manual measures with disease and cognitive outcomes (e.g., Cherbuin et al., 2009; Tae et al., 2008).

An additional limitation relates to the timing of the multiple assessments. For all individuals, the lifetime stress and exercise measurements captured experiences and behavior during the time of the MRI scan or cognitive assessment. In addition, for the large majority of participants, the exercise assessment captured behavior during the time that stressful experiences would have been reported. For a small number of individuals, there is a period of about 6 months, on average, during which exercise could have occurred subsequent to the occurrence of stressful experiences. If these individuals substantially increased their exercise subsequent to our measurement, this may have influenced the effects of stress and we would not have captured this. However, we did have an estimate of 9.5 years of exercise behavior that overlapped with stressful events and observed a significant interaction (even after controlling for the delay between these measurements).

Another consideration is that the current study aggregated stressors that might occur across an individual's life. As stressors during development, adolescence, or old age may lead to differential effects across brain regions (Lupien, McEwen, Gunnar, & Heim, 2009; Tottenham & Sheridan, 2010), future studies might make efforts to understand the influence of the developmental timing of stressors on multiple brain structures and cognitive domains in older adults. Stressful experiences can lead to the diagnosis of a stress-related disorder, such as depression, or to increased depression symptoms. While we attempted to control for this, the aggregation of two depression measures in the MRI analyses may not have fully captured depression symptoms, leading to the potential conflation of stress experience and depression symptoms in these analyses. Lastly, interpretations of the current results are limited by the cross-sectional nature of the study, and it is conceivable that reduced hippocampal volumes or memory influenced exercise engagement or reports of lifetime stress. A recent randomized control trial observed that an aerobic exercise intervention was associated with increased hippocampal volume and improved memory (Erickson et al., 2011). Future longitudinal investigations of individual change in brain structure and function may incorporate individuals varying in stressful experiences to more directly assess interactions between stress and exercise.

Despite the limitations, the current findings of selective effects of stress on hippocampal volume, and evidence that engagement in exercise may buffer against the detrimental effects of stress for the hippocampus and memory, are suggestive that programmatic investigations of the influences of stress and exercise on cognitive and brain aging are warranted. Finally, the current findings have implications for Alzheimer's disease, as hippocampal atrophy and memory decline are integral aspects of the disease (Barnes et al., 2009; Grober et al., 2008). Increasing evidence has suggested a link between stress and the development of Alzheimer's disease (Csernansky et al., 2006; Li et al., 2010), with contrasting evidence suggesting physical exercise may have a beneficial effect on the disease (Honea et al., 2009; Liang et al., 2010; Rockwood & Middleton, 2007). Thus, examination of the interactions between stress and exercise in this population could provide important insights into approaches for prevention.

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