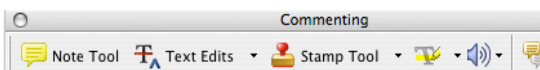
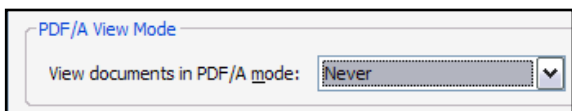
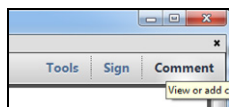
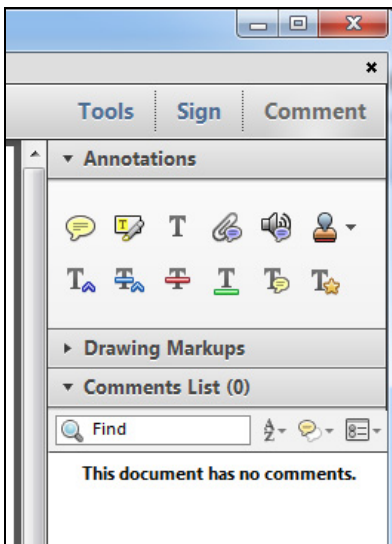
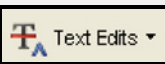




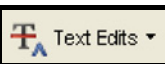





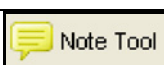



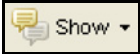
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Frequency of Mentally Stimulating Activities Modifies the Relationship Between Cardiovascular Reactivity and Executive Function in Old Age

Feng Lin, Ph.D., Kathi Heffner, Ph.D., Mark Mapstone, Ph.D.,
Ding-Geng (Din) Chen, Ph.D., Anton Porsteinsson, M.D.

Objectives: Recent evidence suggests that younger and middle-age adults who show greater cardiovascular reactivity (CVR) to acute mental stress demonstrate better reasoning and memory skills. The purpose of this study was to examine whether older adults would exhibit a similar positive association between CVR and executive function and whether regular engagement in mentally stimulating activities (MSA) would moderate this association. **Design:** Secondary cross-sectional analysis. **Setting:** Three general clinical research centers located in the Midwest and on the West Coast and East Coast. **Participants:** A total of 487 older adults participating in an ongoing national survey. **Measurements:** Heart rate (HR) and low-frequency (LF) and high-frequency (HF) domains of heart rate variability (HRV) were measured at baseline and in response to standard mental stress tasks (Stroop color word task and mental arithmetic). Executive function was measured separately from the stress tasks by using five neuropsychological tests. MSA was measured by self-reported frequency of six common MSA. **Results:** Higher HR reactivity was associated with better executive function after controlling for demographic characteristics and health variables and baseline HR activity, and the interaction between HR reactivity and MSA was significant for executive function. Higher LF-HRV reactivity was also associated with executive function, but subsequent analyses indicated that frequency of MSA was the strongest predictor of executive function in models that included LF-HRV or HF-HRV. **Conclusions:** Higher HR reactivity to acute psychological stress is related to better executive function in older adults. For those with lower HR reactivity, engaging frequently in MSA produced significant compensatory benefits for executive function. (Am J Geriatr Psychiatry 2013; ■:■—■)

Key Words: Acute stress, aging, cardiovascular reactivity, heart rate variability, executive function, mentally stimulating activities

Received December 5, 2012; revised March 22, 2013; accepted April 6, 2013. From the School of Nursing (FL, DC), University of Rochester Medical Center, Rochester, NY; Department of Psychiatry (KH, AP), School of Medicine and Dentistry, University of Rochester Medical Center, Rochester, NY; Department of Neurology (MM), School of Medicine and Dentistry, University of Rochester Medical Center, Rochester, NY; and the Department of Biostatistics and Computational Science (DC), School of Medicine and Dentistry, University of Rochester Medical Center, Rochester, NY. Send correspondence and reprint requests to Feng Lin, Ph.D., 601 Elmwood Ave, HWH 2w128, Rochester, NY 14642. e-mail: vankee_lin@urmc.rochester.edu

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CVR, Cognition, and Mental Activity

The notion that the mind (central nervous system) and body (peripheral systems) interact to contribute to both mental and physical health has become increasingly evident.¹ For instance, both the sympathetic and parasympathetic branches of the autonomic nervous system regulate cardiovascular activity at rest and also in response to environmental challenges, measured as cardiovascular reactivity (CVR) from rest. Higher CVR to short-term (acute) stressors is implicated in cardiovascular health risk, such as increased incident coronary heart disease in patients with heart disease history, or elevated blood pressure,^{2,3} but is also associated with positive health outcomes, including better self-perceived health and lower incident depression and obesity.⁴ More recent evidence suggests that both cognitive function and CVR to acute stressors are regulated by similar neural pathways, suggesting a new avenue to explore the neurobiological underpinnings of a health outcome that is critical for older adults: age-related cognitive decline.⁵

A few recently published cross-sectional studies have found that greater CVR to acute stress is associated with enhanced cognitive performance (in particular, attention, memory, and reasoning) in younger or middle-age adults.^{6–8} Similarly, in a prospective cohort study in Scotland, lower CVR was a risk factor predicting future decline in reasoning and reaction time, and the relationship was stronger in old age relative to young and middle-age groups.⁹ Reasoning, attention, and reaction time are components of executive function, which is a higher-order cognitive system controlling multiple cognitive processes that regulate goal-directed behaviors and information organization.¹⁰ Executive function declines early in the aging trajectory.¹¹ It is unclear whether the relationship between CVR and overall executive function remains at older ages. Furthermore, the positive association between increased CVR to acute stress and better cognitive function, as well as the other positive health outcomes observed in previous studies, may reflect a more adaptive central nervous system.⁵ For instance, the prefrontal cortex (PFC), which regulates executive function, also regulates the autonomic nervous system during acute stress.⁴ Thus, examining the direct relationships between executive function and CVR may shed light on links between cognitive and autonomic regulation.

A potentially important contributor to individual differences in cognitive function is lifestyle behaviors.^{5,12} Routine engagement in mentally stimulating activities (MSA), such as playing puzzles, Sudoku, or computer games that rely on sustained attention and information processing, is a lifestyle behavior considered to protect against cognitive decline in the aging process; accumulated evidence supports a positive causal relationship between routinely engaging in MSA and improving cognitive function or slowing cognitive decline.^{13,14} Whether MSA are related to acute stress responses is unknown but plausible. Active engagement in MSA seems to improve executive function by enhancing neuroplasticity in cortical networks,¹⁵ including networks of the PFC,¹⁶ which, as mentioned, also contribute to regulation of the autonomic nervous system and CVR.^{17,18} Thus, MSA may be related indirectly to CVR via their effects on central physiologic stress regulation. This finding would suggest concurrent associations among MSA, CVR, and executive function. Furthermore, MSA may serve to protect cognitive function in the context of neurobiological alterations that are typically associated with impaired cognitive performance. For example, mental activities compensated for high white matter lesions in protecting processing speed in the aging process.¹⁹ Likewise, autonomic regulation may show less covariation with cognitive function, when cognitive function is being protected by MSA. As such, we examined whether regularly engaging in MSA would diminish the association between CVR and executive function in older adults.

In this cross-sectional study, we examined the association between CVR and cognitive function by measuring cardiac activity during acute stressors (i.e., stressful mental tasks) and executive function in older adults, as well as the possible moderating effect of regular engagement in MSA. Cardiac activity at rest and in response to acute stressors was indexed according to both time and frequency domain indices derived from electrocardiogram (ECG) readings. The time domain index was heart rate (HR). Heart rate variability (HRV), a measure of the variation in the time interval between heart contractions, was derived from spectral analysis of the ECG signal to provide frequency domain indices. The high-frequency domain of HRV (HF-HRV; 0.15–0.5 Hz) indexed

primarily parasympathetic (vagal) control of HR. Thus, this index provided information about whether HR increases (or decreases) were due primarily to withdrawal of (or increased input by) the parasympathetic nervous system. The low-frequency domain of HRV (LF-HRV; 0.04–0.15 Hz) provided an index of both parasympathetic and sympathetic cardiac control.²⁰ The acute stressors used in the study were a series of acute laboratory-based mental stress tasks including a mental arithmetic task (Math) and a Stroop word-color task (Stroop). Executive function was assessed by using five cognitive tests sharing different executive components and, independent of the acute mental stress tasks, allowing for a more comprehensive assessment of executive function.⁹ We tested the following hypotheses: 1) greater CVR to the acute mental stress tasks is associated with better executive function; and 2) the association between CVR and executive function is moderated by the frequency of engagement in MSA.

METHODS

Participants

The Survey of Midlife Development in the United States (MIDUS), an ongoing nationally representative longitudinal survey data set, was the primary source for this study. The baseline data (MIDUS I) collected between 1995 and 1996 focused on sociodemographic and psychobehavioral assessments from >7,000 noninstitutionalized respondents. These assessments were repeated at a 10-year follow-up as MIDUS II Project 1 (survey assessment). Four new categories of assessments were added in MIDUS II: daily diaries (Project 2), cognitive function (Project 3), biomarkers (Project 4), and neuroscience (Project 5). All participants who participated in Projects 2–5 must have completed Project 1 first. The average lag of data collection was 24 months between Project 1 and Project 4, and 22 months between Project 3 and Project 4. More details describing information between MIDUS I and MIDUS II can be found elsewhere.²¹

The current study used data from MIDUS II Projects 1, 3, and 4. There were a total of 1,015 participants who participated in these three projects. We excluded those with flagged problems

(i.e., problematic testing procedure due to test disruption, interview equipment failures, other problems) in cognitive tests ($n = 11$), those did not attend the acute stress protocol ($n = 33$), and those aged 54 years or younger ($n = 486$). The final sample for the current study included 487 participants aged 55–84 years (Appendix).

Procedures

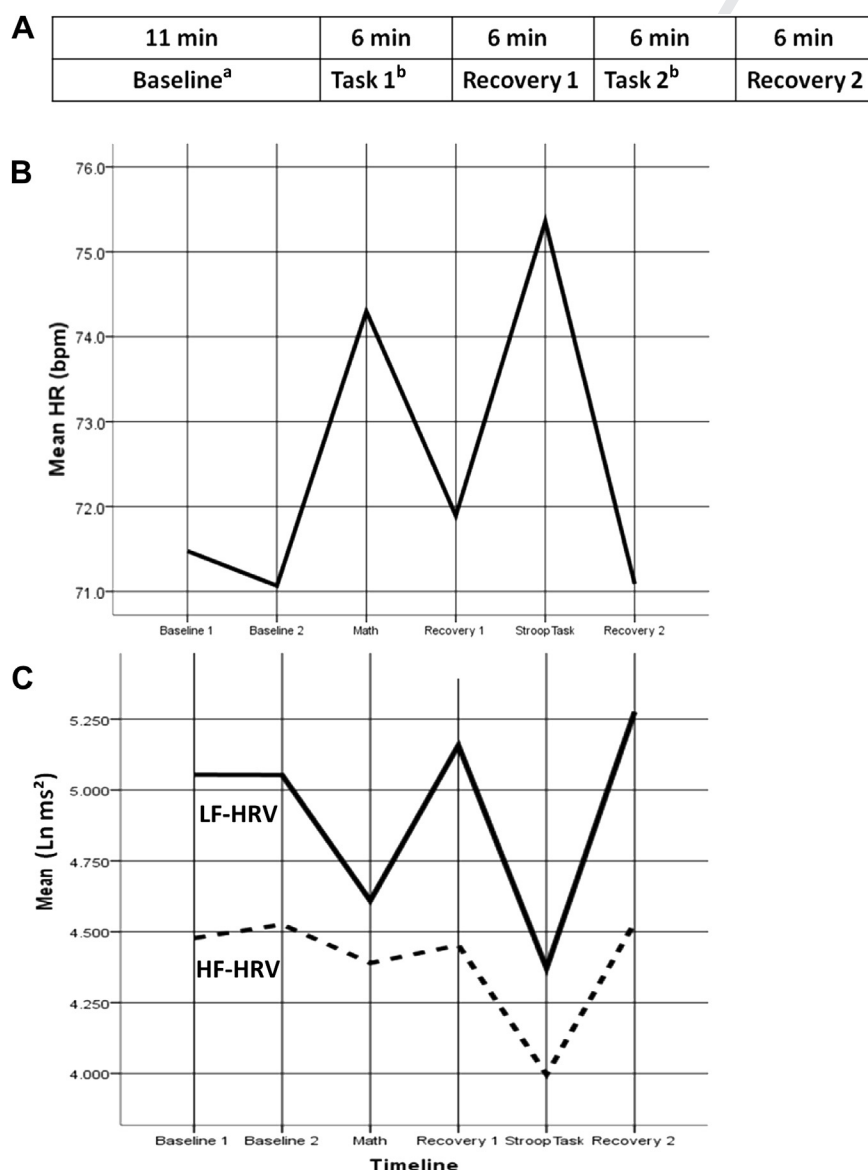
Project 1 was administered over the telephone and by mail-in survey and included sociodemographic and psychobehavioral assessments. Project 3, including a series of cognitive tests, was administered over the telephone. Project 4 included 2-day visits to one of three participating general clinical research centers located in the Midwest and on the West Coast and East Coast. Institutional review board approval was obtained at each center, and written informed consent was obtained from all participants. More details on the protocol of Project 4 can be found elsewhere.²¹

Of relevance to the current study, on Day 1, participants completed a detailed medical history interview with general clinical research center clinicians as well as self-administrated questionnaires. On Day 2, medication use was assessed and participants then engaged in the acute stress protocol while cardiovascular measures were recorded. The protocol order (Figure 1A) was: resting status baseline (11 minutes, including two 5-minute epochs, Baseline 1 and Baseline 2), mental stress task 1 (randomly assigned to Math or Stroop task, 6 minutes), recovery 1 (6 minutes), mental stress task 2 (assigned to the other unfinished task: Math or Stroop task, 6 minutes), and recovery 2 (6 minutes). Participants were instructed to sit quietly during the baseline and recovery phases of the protocol. Among participants who attended the acute stress protocol, 61 had missing data for some epochs of interest (i.e., missing HR data for one of the tasks, for recovery). A comparison of demographic information between this group and participants with complete data was conducted.

Measures

Cardiac measures. HR and HRV were derived from the ECG readings, which were collected at rest and during the acute mental tasks in Project 4. To collect ECG data, standard ECG electrodes were placed using a standard lead-II electrode configuration

FIGURE 1. Cardiac measurement over the psychophysiology experimental protocol. ^aThere were two sets of baseline variables (Baseline 1 and Baseline 2) within 11 minutes, each representing a 5-minute epoch. ^bTask 1 and Task 2 could be a mental arithmetic task (Math) or a Stroop word-color task (Stroop). The sequence of the two mental stress tasks was varied by participants. Regardless, there was a recovery period (6 minutes) between the two tasks to avoid the influence of Task 1 on Task 2. In addition, there were 26 participants performing the Paced Auditory Serial Addition Task instead of Math task (data not shown). For the purpose of illustration, we recoded data and displayed the graphs (B and C) on heart rate (HR), low-frequency domain of heart rate variability (LF-HRV), and high-frequency domain of heart rate variability (HF-HRV) based on the type of mental stress task (Math or Stroop task) instead of the order of the task (Task 1 or 2).



(electrodes placed on the participant's left and right shoulders, and in the left lower quadrant). ECG was continuously monitored during the acute stress protocol (Figure 1A). The beat-to-beat ECG waveforms (in particular, the series of intervals between

consecutive R waves) were analyzed to calculate HR and frequency domain of HRV by using proprietary event detection software (Cmark by Delano McFarlane). All data were analyzed with a 300-second epoch duration (for "resting status baseline" data,

two 300-second epochs were analyzed). If any unscorable data (due to noisy signal) precluded a full 300-section segment, epoch duration was decreased by 60-section segments (i.e., 240 seconds or 180 seconds). The minimum epoch length analyzed was 180 seconds. For the 61 participants whose epoch length was <180 seconds, their ECG data were not analyzed. (A comparison of their background characteristics with the rest of the sample is provided in the Results section.) HR was determined as an average of all valid RR intervals for the specified length of time described and converted to beats-per-minute units. The frequency domain of HRV (i.e., LF and HF) was calculated by the spectra of RR interval series by using an interval method for computing Fourier transformations.²² Because LF-HRV and HF-HRV were skewed, natural log transformation was applied before any analysis. More information about the standard procedure has been reported previously.²³

Baseline HR, LF-HRV, and HF-HRV were computed as the average HR or LF-HRV or HF-HRV across Baselines 1 and 2. HR, LF-HRV, and HF-HRV during the Math and Stroop tasks were each calculated as the average measure across each task. HR, HF-HRV, and LF-HRV reactivity scores were calculated as the task average minus the baseline average. Preliminary analyses indicated that the Stroop task elicited greater cardiac reactivity across participants; as such, we used HR, LF-HRV, and HF-HRV reactivity during the Stroop task in these analyses.

Executive function. Two sets of neuropsychological tests were conducted over the telephone at Project 3: the Brief Test of Adult Cognition by Telephone (BTACT) and the Stop and Go Switch Task (SGST). Details on the rationale for, and psychometric properties of, the BTACT and SGST and the composite scores have been published previously.^{24,25} Of relevance to this report, we used a previously validated composite index of executive function derived from reported exploratory and confirmatory factor analyses of the subtests from the BTACT and SGST,¹² as used in previous studies of MIDUS participants.^{26,27} The executive function factor comprises five standard cognitive measures of multiple cognitive components regulated by executive function,¹⁰ including working memory (Digits Backward), verbal fluency (Category Fluency), inductive reasoning (Number Series), and processing speed (Backward Counting) from BTACT and

attention switching and inhibitory control from the SGST. An average of z scores for all executive function measures was used in the data analysis, with higher scores indicating better executive function.

Engagement in MSA. Participants were asked about their current frequency of engagement in six mental activities as part of Project 1, including reading, doing word games, playing cards, attending lectures, writing, and using a computer. Each participant indicated the frequency of engaging in these activities by using a 6-point ordinal scale ranging from 1 (daily) to 6 (never). The mean score of all items was calculated, with lower scores indicating more frequent mental activities. This scale was used in a previous study to examine the association of education and cognitive function¹² as well as cardiovascular risk factors and cognitive function.²⁸ All participants completed Project 1 before participating in Projects 3 and 4, which ensured that their self-report on the engagement in MSA occurred before the assessments of CVR and executive function.

Demographic and health information/covariates. Demographic information, collected from Project 1, included age, gender, education (from “no education” to “doctoral degree,” grouped into three categories: “high school graduate, GED or less,” “some college,” and “college graduate”), and race (white versus other racial/ethnic groups).

The following data were collected from Project 4. Depressive symptoms were measured by using the Depressive Symptoms subscale from the Mood and Symptom Questionnaire.²⁹ Twelve items of depressive symptoms were assessed by using the question “How much have you felt or experienced things this way during the past week?” Participants responded with the use of a Likert scale, with scores ranging from 1 (“not at all”) to 5 (“extremely”). A sum score was computed, with higher scores indicating more depressive symptoms. Internal consistency of the subscale was 0.90 in MIDUS II.

Perceived control was measured by using a 19-item Self-Control Scale.³⁰ Participants responded by using a Likert scale, with scores ranging from 1 (“strongly disagree”) to 7 (“strongly agree”). A mean score was computed, with higher scores indicating higher ability of self-control. The internal consistency of the subscale was 0.71 in MIDUS II.

Data on smoking were collected by using a single question: “Have you ever smoked regularly?” Data on alcohol intake were assessed by using a single

TABLE 1. Characteristics of Demographic Information and Health History

	Total Sample (N = 487)	Engagement in MSA ^{a,b}				p
		High (n = 214)	Low (n = 266)	t or χ^2 test	df	
Age, mean (SD), y	65.06 (7.61)	65.14 (7.31)	64.95 (7.73)	0.27	478	0.790
Male, no. (%)	226 (46.4)	84 (39.3)	138 (51.9)	7.61	1	0.006
White, no. (%)	449 (92.2)	200 (93.5)	244 (91.7)	0.51	1	0.475
Education, no. (%)				25.99	2	<0.001
High school graduate, GED, or less	138 (28.3)	38 (17.8)	99 (37.2)			
Some college	238 (48.9)	111 (51.9)	122 (45.9)			
College graduate	111 (22.8)	65 (30.4)	45 (16.9)			
Depressive symptoms, mean (SD)	17.21 (5.35)	17.01 (4.85)	17.37 (5.78)	-0.72	477	0.467
Perceived control, mean (SD)	4.96 (0.53)	4.95 (0.51)	4.98 (0.55)	-0.62	478	0.532
Regularly smoking, n (%)	241 (49.5)	98 (45.8)	139 (52.3)	1.98	1	0.259
Alcohol intake, n (%)	204 (41.9)	98 (45.8)	103 (38.7)	2.44	1	0.118
Use of beta-blockers, n (%)	108 (22.2)	43 (20.1)	64 (24.1)	1.02	1	0.312
Hypertension, n (%)	322 (66.1)	143 (66.8)	177 (66.5)	0.03	1	0.863
Diabetes, n (%)	68 (14.0)	32 (15.0)	34 (12.8)	0.47	1	0.492
Heart attack, n (%)	16 (3.3)	8 (3.7)	8 (3.0)	2.79	1	0.248
MSA, mean (SD) ^c	3.74 (0.86)	2.97 (0.48)	4.36 (0.53)	-30.02	472	<0.001
Executive function, mean (SD) of z scores	-0.09 (0.85)	0.11 (0.79)	-0.26 (0.85)	4.86	478	<0.001

Notes: Bold indicates a significant p value. GED: General Educational Development; MSA: mentally stimulating activities; SD: standard deviation.

^aSeven cases were not available.

^bMedian score of 3.50 was used as the cutoff score.

^cLower scores indicate higher frequency.

question that asked about the frequency of drinking. Active alcohol intake was defined as drinking ≥ 1 days per week. Hypertension was measured based on sitting systolic blood pressure ≥ 130 mm Hg, sitting diastolic blood pressure ≥ 85 mm Hg, or currently taking antihypertensive treatment. Diabetes was defined as glycosylated hemoglobin levels $\geq 7\%$ or self-reported history in past 12 months.³¹ Data on heart attack were collected based on a single question of relevant health history. Use of beta-blockers was recorded by using the information from the participant's medication list. The interval (i.e., lag in months) between Projects 3 and 4 was collected and controlled in the analysis.

Data Analysis

Analyses were conducted by using SPSS version 19.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). All analyses were conducted separately for the three reactivity indices. The differences of each variable according to the frequency of engagement in MSA were examined by using independent *t* tests for continuous variables and χ^2 tests for categorical variables. The cardiac activities in response to mental stress tasks or baseline status were examined by using repeated measures analysis of variance with

pair-wise comparison with Bonferroni adjustment for multiple comparisons. The associations between CVR measures and executive function, and the moderating effect of engagement in MSA on this association, were examined by using multiple linear regression. Scores on HR, HF-HRV, and LF-HRV and engagement in MSA were centered. Models were adjusted for demographic and health characteristics along with the corresponding baseline value for HR or HRV; covariates were chosen based on previously reported associations between these variables and cardiovascular activity or cognitive function.^{6,9,32,33}

To further explore the subgroup differences in executive function if there were any interactions of CVR measure \times MSA, multiple linear regression and analysis of covariance were applied. Statistical significance for Bonferroni adjustment was set at an alpha level of 0.018; other analyses were conducted by using an overall alpha level of 0.05 (two-sided).

RESULTS

Sample Characteristics

Table 1 displays the sample characteristics. The mean age of the sample was 65.06 years. Participants

TABLE 2. Descriptive Data of Cardiac Measurement

Descriptive (Mean and SD)	Repeated ANOVA ^b				
	Bonferroni-Adjusted Pairwise t Test (df = 424)				
	Mean (SE) Difference				
	Baseline ^a	Math Task	Stroop Task	Math–Baseline	Math–Stroop
HR	71.29 (11.11)	74.30 (10.83)	75.36 (11.43)	2.94 (0.16) ^d	–1.06 (0.14) ^d
LF-HRV	5.10 (1.12)	4.61 (1.12)	4.37 (1.16)	–0.50 (0.04) ^d	0.22 (0.04) ^d
HF-HRV	4.53 (1.25)	4.39 (1.18)	4.00 (1.28)	–0.16 (0.03) ^d	0.38 (0.03) ^d
				4.00 (0.19) ^d	313.29 ^d
				–0.72 (0.04) ^d	172.30 ^d
				–0.53 (0.04) ^d	124.41 ^d
					2.60 (0.27) ^e
					–0.73 (0.87)
					–0.52 (0.79)

Notes: ANOVA: analysis of variance; HF-HRV: high-frequency domain of heart rate variability; HR: heart rate; LF-HRV: low-frequency domain of heart rate variability; SD: standard deviation; SE: standard error.

^aAverage score of baseline assessment at two time points.

^bSixty-one cases were missing.

^cReactivity = cardiac Stroop task activity – cardiac baseline activity, given that the Stroop task induced significantly greater reactivity than the Math task.

^dp < 0.001.

^eThe distribution of raw scores was skewed and some scores were negative; thus, natural log transformation was performed as $\ln(\text{Stroop} - \text{baseline} + 10)$.

engaged in MSA, on average, “several times a month.” The median point 3.50 was used as the cutoff score to categorize the engagement in MSA into high- versus low- frequency groups. Those participants engaging in more mental activities tended to be female and have higher education and better executive function.

Baseline HR and HRV and Reactivity to Stressors

Figure 1A displays the protocol order of the psychophysiological experiment. Figures 1B and 1C display the HR, LF-HRV, and HF-HRV throughout the protocol. Baseline HR, LF-HRV, and HF-HRV were calculated by using the relevant average scores of Baselines 1 and 2. HR and HRV measures were significantly different from baseline in response to the mental stress tasks (Table 2; repeated analysis of variance, Math–Baseline and Stroop–Baseline, all $p < 0.001$): HR significantly increased in response to mental stress tasks (baseline—mean [SD]: 71.29 [11.11]; Math: 74.30 [10.83]; Stroop: 75.36 [11.43]; $F_{[2, 424]} = 313.29$), whereas LF-HRV (baseline—mean [SD]: 5.10 [1.12]; Math: 4.61 [1.12]; Stroop: 4.37 [1.16]; $F_{[2, 424]} = 172.30$) and HF-HRV (baseline—mean [SD]: 4.53 [1.25]; Math: 4.39 [1.18]; Stroop: 4.00 [1.28]; $F_{[2, 424]} = 124.41$) significantly decreased in response to the tasks. The Stroop task induced a significantly larger increase in HR (mean [SE] difference = -1.06 [0.14]; $t_{[424]} = 7.57$) and a larger decrease in LF-HRV (mean difference: 0.22 [0.04]; $t_{[424]} = 5.50$) and HF-HRV (mean difference: 0.38 [0.03]; $t_{[424]} = 12.67$) compared with the Math task (Table 2, pairwise t test, Math–Stroop, all $p < 0.001$). Thus, HR, LF-HRV, and HF-HRV reactivity during the Stroop task were used in all subsequent analyses of associations between HR and HRV and executive function.

Table 3 displays the comparison of baseline cardiac measures and CVR (mean [standard deviation]) according to the frequency of engaging in MSA. Baseline LF-HRV (high MSA: 5.24 [1.15]; low MSA: 4.97 [1.09]; $t_{[418]} = 2.51$, $p = 0.012$), LF-HRV reactivity (high MSA: -0.84 [0.87]; low MSA: -0.62 [0.84]; $t_{[418]} = -2.58$, $p = 0.010$), and HF-HRV reactivity (high MSA: -0.61 [0.80]; low MSA: -0.44 [0.77]; $t_{[418]} = -2.24$, $p = 0.026$) were significantly different according to the frequency of engaging in MSA. Thus, engaging in high MSA was significantly related

TABLE 3. Comparison of Cardiac Measurement According to the Frequency of Engagement in MSA

	Baseline			Reactivity		
	HR	LF-HRV	HF-HRV	HR	LF-HRV	HF-HRV
High, mean (SD)	71.49 (10.76)	5.24 (1.15)	4.65 (1.28)	2.61 (0.27)	−0.84 (0.87)	−0.61 (0.80)
Low, mean (SD)	71.26 (11.40)	4.97 (1.09)	4.42 (1.21)	2.59 (0.28)	−0.62 (0.84)	−0.44 (0.77)
<i>t</i> test (<i>p</i>) ^a	0.21 (0.944)	2.51 (0.012)	1.88 (0.061)	0.72 (0.473)	−2.58 (0.010)	−2.24 (0.026)

Notes: Bold indicates a significant *p* value. Seven cases were missing mentally stimulating activities (MSA) data, and 61 cases were missing. HF-HRV: high-frequency domain of heart rate variability; HR: heart rate; LF-HRV: low-frequency domain of heart rate variability.

^a*df* = 418.

TABLE 4. Regression Models of Cardiac Measurement and Engagement in MSA on Executive Function (N = 419)

	Model 1			Model 2			Model 3		
	B (SE)	<i>t</i> ₍₄₀₆₎	<i>p</i>	B (SE)	<i>t</i> ₍₄₀₅₎	<i>p</i>	B (SE)	<i>t</i> ₍₄₀₄₎	<i>p</i>
Baseline cardiac activity	0.002 (0.01)	0.46	0.646	0.003 (0.01)	0.74	0.391	0.003 (0.01)	0.90	0.369
HR	0.27 (0.14)	2.00	0.047	0.29 (0.13)	2.24	0.026	0.29 (0.13)	2.23	0.026
MSA				−0.32 (0.04)	−7.21	<0.001	−0.32 (0.04)	−7.19	<0.001
MSA × HR							0.33 (0.14)	2.33	0.020
	$R^2 = 0.23$, $F_{(13, 406)} = 9.40$, $p < 0.001$			$R^2 = 0.32$, $F_{(14, 405)} = 13.53$, $p < 0.001$			$R^2 = 0.33$, $F_{(15, 404)} = 13.13$, $p < 0.001$		
	Model 1			Model 2			Model 3		
	B (SE)	<i>t</i> ₍₄₀₆₎	<i>p</i>	B (SE)	<i>t</i> ₍₄₀₅₎	<i>p</i>	B (SE)	<i>t</i> ₍₄₀₄₎	<i>p</i>
Baseline cardiac activity	−0.002 (0.04)	−0.04	0.965	−0.01 (0.04)	−0.36	0.717	−0.01 (0.04)	−0.36	0.717
LF-HRV	−0.09 (0.05)	−2.00	0.046	−0.06 (0.04)	−1.37	0.173	−0.06 (0.04)	−1.35	0.177
MSA				−0.31 (0.05)	−6.89	<0.001	−0.31 (0.05)	−6.88	<0.001
MSA × LF-HRV							0.004 (0.09)	0.10	0.926
	$R^2 = 0.23$, $F_{(13, 406)} = 5.35$, $p < 0.001$			$R^2 = 0.31$, $F_{(14, 405)} = 6.69$, $p < 0.001$			$R^2 = 0.31$, $F_{(15, 404)} = 6.25$, $p < 0.001$		
	Model 1			Model 2			Model 3		
	B (SE)	<i>t</i> ₍₄₀₆₎	<i>p</i>	B (SE)	<i>t</i> ₍₄₀₅₎	<i>p</i>	B (SE)	<i>t</i> ₍₄₀₄₎	<i>p</i>
Baseline cardiac activity	−0.02 (0.03)	−0.59	0.555	−0.02 (0.03)	−0.72	0.469	−0.02 (0.03)	−0.74	0.457
HF-HRV	−0.05 (0.05)	−1.08	0.281	−0.03 (0.05)	−0.73	0.463	−0.04 (0.05)	−0.78	0.438
MSA				−0.31 (0.04)	−7.05	<0.001	−0.32 (0.05)	−7.15	<0.001
MSA × HF-HRV							−0.07 (0.05)	−1.32	0.187
	$R^2 = 0.23$, $F_{(13, 406)} = 5.21$, $p < 0.001$			$R^2 = 0.31$, $F_{(14, 405)} = 6.66$, $p < 0.001$			$R^2 = 0.31$, $F_{(15, 404)} = 6.27$, $p < 0.001$		

Notes: Controlled for age, gender, education, hypertension, diabetes, heart attack, regularly smoking, alcohol intake, perceived control, depressive symptoms, and interval between Projects 3 and 4. Seven cases with missing mentally stimulating activities (MSA) data and 61 cases with missing cardiac data were excluded from the analysis. HF-HRV: high-frequency domain of heart rate variability; HR: heart rate; LF-HRV: low-frequency domain of heart rate variability; SE: standard error.

to higher baseline LF-HRV and greater decreases in LF-HRV and HF-HRV reactivity.

CVR, Engagement in MSA, and Executive Function

Table 4 displays the regression on executive function. Collinearity tolerance of predictors and covariates was >0.95 across all analyses, indicating there was little redundant information between these

predictors and covariates; thus, multicollinearity was not a concern in the analysis. Controlling for all covariates (i.e., age, gender, education, hypertension, diabetes, heart attack, regularly smoking, alcohol intake, perceived control, depressive symptoms, interval between Projects 3 and 4), none of the baseline cardiac measures was associated with executive function. HR (B [SE] = 0.27 [0.14], $t_{[406]} = 2.00$, $p = 0.047$) and LF-HRV reactivity (B [SE] = −0.09 [0.05],

$t_{[406]} = -2.00$, $p = 0.046$), but not HF-HRV reactivity ($B [SE] = -0.05 [0.05]$, $t_{[406]} = -1.08$, $p = 0.281$), were significant predictors of executive function (Model 1s). HR and LF-HRV explained 1% of the variance in executive function, respectively. When considering the engagement in MSA in the model, MSA significantly predicted executive function in all models (HR: $B [SE] = -0.32 [0.04]$, $t_{[405]} = -7.21$, $p < 0.001$; LF-HRV: $B [SE] = -0.31 [0.05]$, $t_{[405]} = -6.89$, $p < 0.001$; HF-HRV: $B [SE] = -0.31 [0.04]$, $t_{[405]} = -7.05$, $p < 0.001$) (Model 2s). MSA explained approximately 9% of the variance in executive function. HR reactivity had a significant interaction with the engagement in MSA in predicting executive function ($B [SE] = 0.33 [0.14]$, $t_{[404]} = 2.33$, $p = 0.020$) (Model 3s). Such interaction explained another 1% of the variance in executive function.

Given the interaction between HR reactivity and the engagement in MSA in predicting executive function, the association of HR reactivity and executive function was further examined according to two subgroups of MSA. After controlling for all covariates, the significant relationship between HR reactivity and executive function remained for the low ($B [SE] = 0.43 [0.19]$, $t_{[406]} = 2.25$, $p = 0.030$) but not high ($B [SE] = 0.06 [0.18]$, $t_{[406]} = 0.33$, $p = 0.750$) MSA group. Figure 2 further illustrates the interaction. HR reactivity was categorized by the median score (2.60) to high versus low HR reactivity. Among the four subgroups (high MSA/high HR reactivity, high MSA/low HR reactivity, low MSA/high HR reactivity, and low MSA/low HR reactivity), the high MSA/high HR reactivity subgroup had the highest adjusted mean for executive function, whereas the low MSA/low HR reactivity group had the lowest adjusted mean for executive function.

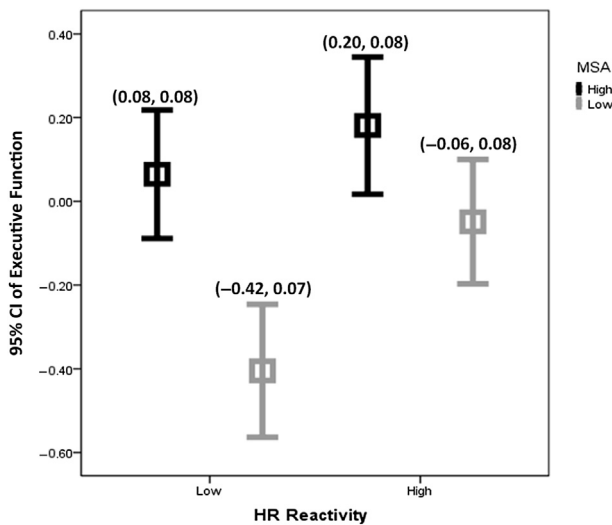
Analysis of Missing Data

Although all participants included in the analysis attended the acute stress protocol, the data on cardiac activities in 61 participants were not recordable. This subset of participants were significantly older than those who completed the Stroop task (mean age: 68.21 versus 64.61 years; $t_{[60]} = -3.50$, $p = 0.001$). Other demographic and health characteristics and executive function were similar.

CONCLUSIONS

The current study examined cross-sectional associations between CVR to acute stress and executive function in older adults, and the role of engagement in MSA in these associations. Similar to previous studies of younger and middle-aged adults, we found that higher HR reactivity was associated with better executive function after controlling for demographic and health variables and baseline HR. The direction of the relationship between HR reactivity and cognitive function in the current study is consistent with two recently published cross-sectional or prospective studies showing greater HR reactivity associated with better memory⁶ and reasoning.⁹ The current study extends these findings to executive function, a broad cognitive construct consisting of a set of complex, partially overlapping cognitive abilities including reasoning but also extending to working memory, attention, processing speed, response inhibition, and problem-solving that, together, guide self-regulation or goal-oriented behaviors. One strength of this study is that we derived a composite score from a number of comprehensive executive tasks tapping these abilities rather than relying on one dimension exclusively, and these tasks were independent from the acute mental stress task (Stroop) that also relies on some aspects of executive function (e.g., attention and inhibition). To our knowledge, this is the first study to comprehensively examine executive function and identify significant associations between HR reactivity and executive function. Our data are cross-sectional and therefore cannot clarify causality, but they support investment in future work to identify directional links between executive function and CVR. The top-down role of PFC in regulating both the CVR and executive function is well recognized, which may somewhat explain the link between CVR and executive function.³⁴ However, a bottom-up mechanism is also plausible. Greater CVR may reflect more adaptive endothelial function and metabolic balance, and may promote adequate blood pressure, which are all important for maintaining healthy cerebrovascular function, especially in the frontal lobe.^{2,35} The contribution of the cardiovascular system to brain function and, ultimately,

FIGURE 2. Illustration of interaction between heart rate (HR) reactivity and the engagement in mentally stimulating activities (MSA) in predicting executive function. For the purpose of illustration, HR reactivity was categorized according to the median score (2.60) to high versus low HR reactivity. Adjusted mean and standard error of executive function were reported for each subgroup controlling for age, gender, education, hypertension, diabetes, heart attack, regularly smoking, alcohol intake, perceived control, depressive symptoms, interval between Projects 3 and 4, and baseline HR. CI: confidence interval.



executive function, is less recognized and worthwhile of further exploration.

Notably, higher LF-HRV reactivity was also associated with executive function, although including frequency of MSA in the model rendered this association nonsignificant. We observed no association between HF-HRV reactivity and executive function. LF-HRV is mediated by both sympathetic and vagal mechanisms, whereas HF-HRV is almost exclusively vagally mediated. In light of our discrepant LF-HRV and HF-HRV findings, the association between LF-HRV changes and executive function may reflect associations between cognitive performance and HRV that were primarily due to sympathetic nervous system control of the heart. Previous studies found a reduced influence of the parasympathetic/vagal system in the regulation of attentional resources as individuals age.³⁴ Further research is needed to characterize the components of autonomic regulation of CVR that may be linked to cognitive function.

An important caveat to the observed relationship between HR reactivity and executive function is the moderating effect of MSA. Specifically, among older adults who more frequently engaged in MSA, the association between lower HR reactivity and poorer executive function was attenuated. Conversely, among infrequent users of MSA, lower HR reactivity was associated with lower executive function. One intriguing possibility suggested by these findings is that MSA may preserve executive function even when other central regulatory processes, such as those involved in stress adaptation, are compromised. MSA in this study included activities such as learning, computer use, and playing puzzles, which may create an enriched environment for older adults. Previous studies found that these mental activities compensated for low education¹² or high white matter lesions,¹⁹ protecting episodic memory or processing speed. Importantly, in this study, MSA explained a much larger amount of variance in executive function, compared with HRV, suggesting that MSA engagement may be a potentially efficacious intervention to modify the central nervous system and relevant self-regulation or goal-oriented behaviors. As a cross-sectional study, although data on MSA were obtained before executive function and CVR, the lag between the projects in MIDUS was not extensive enough to determine MSA's causal role in modifying the CVR-executive function association. Future studies should examine the moderating effect of MSA by using a prospective design and address whether frequent engagement in MSA also compensates for changes in central networks, especially PFC, that regulate CVR and cognitive function.

In addition to the moderating effects of MSA on the relationship between HR reactivity and executive function, we observed associations between MSA and HRV indices. Participants who engaged in more MSA tended to have higher baseline LF-HRV and greater decreases in LF HRV and HF-HRV reactivity in response to mental stress tasks. The notion that MSA may influence systemic cardiac function through central stress regulation³⁶ could shed light on the role of neuroplasticity in stress adaptation. Cognitive interventions can improve the structure and function of PFC and relevant cortical networks in groups at risk for cognitive impairment.^{37,38} Future cognitive intervention studies may further explore whether such brain changes would alter cardiovascular reactivity to stressors.

In the current study, baseline cardiac activity was not associated with executive function. Some investigators have reported similar nonsignificant results,⁶ whereas others have observed a significant association between higher HRV at rest and better cognitive function.^{32,39–41} The differences in results may be explained by the type of participants (e.g., older adults versus young athletes or sailors), length of epoch time recorded (e.g., 11 minutes versus 2–24 hours), or types or presence of covariates.

Limitations of the current study should be noted. First, we did not account for the potential influence of respiration rate and tidal volume on HF-HRV. It is unclear whether respiration rate might contribute to the explanation of the nonsignificant association between HF-HRV and executive function in this study, but future studies should include these variables. Second, another index of frequency domain of HRV, very low frequency, was not collected as part of the MIDUSII study. Very low frequency HRV at rest has been related to cognitive function,³² and this variable

should also be considered when designing future studies on mental stress and CR. Finally, given the cross-sectional design of the study, the causal relationships between CVR and executive function cannot be determined. Although a previous prospective study supported such a causal relationship,⁹ there is still a possibility that baseline executive function shapes physiologic adaptation to environmental challenges given that CVR to psychological challenge is assumed to be regulated by the central nervous system.^{20,42}

Our findings contribute to the growing literature investigating the relationship between physiologic stress responses and executive function. Importantly, increasing the frequency of mental activities may hold promise not only for modifying risks of cognitive decline but could also modify stress regulation in older adults.

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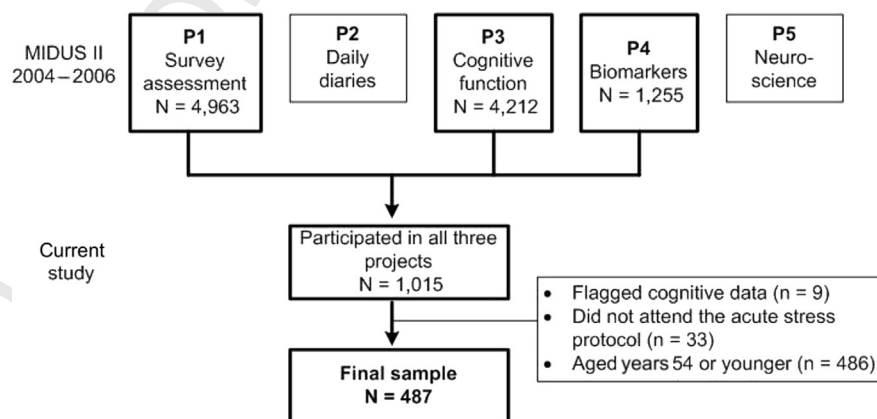
Disclosures: No disclosures to report.

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APPENDIX. Flowchart. P: Project.



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