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ORIGINAL RESEARCH

Blood Pressure Reactivity to Psychological Stress in Young Adults and Cognition in Midlife: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

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***Background*—**The classic view of blood pressure (BP) reactivity to psychological stress in relation to cardiovascular risks assumes that excess reactivity is worse and lower reactivity is better. Evidence addressing how stress-induced BP reactivity in young adults is associated with midlife cognitive function is sparse.

***Methods and Results*—**We assessed BP reactivity during a star tracing task and a video game in adults aged 20 to 32 years. Twenty-three years later, cognitive function was assessed with use of the Digit Symbol Substitution Test (a psychomotor speed test), the Rey Auditory Verbal Learning Test (a verbal memory test), and the modified Stroop test (an executive function test). At the time of follow-up, participants (n=3021) had a mean age of 50.2 years; 56% were women, and 44% were black. In linear regression models adjusted for demographic and clinical characteristics including baseline and follow-up resting BP, lower systolic BP (SBP) reactivity during the star tracing and video game was associated with worse Digit Symbol Substitution Test scores (β [SE]: 0.11 [0.02] and 0.05 [0.02], respectively) and worse performance on the Stroop test (β [SE]: −0.06 [0.02] and −0.05 [0.02]; all $P<0.01$). SBP reactivity was more consistently associated than diastolic BP reactivity with cognitive function scores. The associations between SBP reactivity and cognitive function were mostly similar between blacks and whites.

***Conclusions*—**Lower psychological stress-induced SBP reactivity in younger adults was associated with lower cognitive function in midlife. BP reactivity to psychological stressors may have different associations with target organs in hypertension. **(*J Am Heart Assoc*. 2016;5:e002718 doi: 10.1161/JAHA.115.002718)**

Key Words: blood pressure • blood pressure monitoring • cognition • stress test • young

The classic view of blood pressure (BP) reactivity to psychological stress in relation to cardiovascular risks assumes that excess reactivity is worse and lower reactivity is better.[1,2] Cardiovascular reactivity to psychological stress in younger and middle-aged adults, reflecting the functioning of the peripheral vessels and the autonomic nervous system (α- and β-adrenergic responses),[1] has been shown to correlate with future cardiovascular outcomes, such as incident hypertension, subclinical target organ damage (eg, carotid artery remodeling, left ventricular hypertrophy, and coronary artery calcium), and incident cardiovascular disease.[2–7] Evidence addressing whether BP reactivity to psychological stress in younger adults is associated with future cognitive function is sparse. The association is complex because lower stress-induced BP reactivity has been shown to correlate with structural and functional alterations in the brain.[8–12]

Emerging neuroimaging research indicates that individual differences in BP reactivity to psychological stress are

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Accompanying Data S1, Tables S1 through S8, and Figures S1 through S3 are available at http://jaha.ahajournals.org/content/5/1/e002718/suppl/DC1

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associated with regional brain activity; less BP reactivity correlates with less neuron activity.[9–12] Prior studies of associations between stressor-induced BP reactivity and cognitive function (not measured as part of a stress protocol) show inconsistent results.[13–17]Most of the studies were small and cross-sectional analyses in middle-aged/older persons, raising the possibility that comorbidities (eg, cerebrovascular diseases and advanced arterial stiffness) could have affected both participants' BP reactivity and cognition. We hypothesized that, if the associations are tested among young adults with few comorbidities, lower stress-induced BP reactivity may be associated with lower cognitive function.

Using the Coronary Artery Risk Development in Young Adults (CARDIA) Study data on young adults (aged 20–32 years) with few comorbidities, we assessed whether higher or lower BP reactivity to psychological stress (mirror star tracing that produces an α-adrenergic response, and a video game, eliciting a β-adrenergic response)[1] was associated with measures of cognitive function 23 years later, including psychomotor speed, verbal memory, and executive function.

Methods

Study Population

The CARDIA Study is a multicenter longitudinal study of 5115 young adults aged 18 to 30 years (mean age 25 years) in 1985–1986 (see Data S1). The participants underwent baseline (year 0: Y_0) and follow-up examinations at Y_2, Y_5, Y_7, Y_{10}, Y_{15}, Y_{20}, and Y_{25}; the retention rates across examinations were 91%, 86%, 81%, 79%, 74%, 72%, and 72%, respectively (Figure S1). At the Y_2 follow-up examination, BP reactivity testing was conducted. All participants provided written informed consent at each examination, and institutional review boards from each field center and the coordinating center approved the study annually.

Among 5115 participants, we excluded 701 participants who declined to participate in the star tracing and video game stress tasks, 1217 participants who did not attend the follow-up examination at Y_{25}, 142 participants with missing data on cognitive function at Y_{25}, and 34 participants with any missing covariates. As a result, we included 3021 participants who attended the Y_2 and Y_{25} examinations and completed cognitive testing at Y_{25}.

Visit BP and BP Reactivity Testing

At each examination, research staff measured right-arm brachial artery BP 3 times after the participant had been sitting in a quiet room for 5 minutes. Three measurements were taken at 1-minute intervals, and the average of the second and third measurements was defined as the visit BP (see Data S1).

BP reactivity task[3,4] included an 8-minute baseline period followed by the presentation of a video game (Atari Breakout) and star tracing task (with a mirror image) in randomized order for 3 minutes each. BP was recorded with an automated BP monitor (2600B Vita-Stat; Spacelabs Medical, Inc) throughout the tasks and the last 4 minutes of the baseline period. Automated BP monitors were calibrated weekly. BP reactivity was calculated by subtracting the average of the final 3 baseline readings (ie, resting BP before task) from the average levels measured during each of the 2 tasks (mean 2.95±0.24 readings in each task).[3,4] Standardization of the stress protocol was accomplished by centralized training of technicians, quality assurance site visits, and use of audiotaped instructions to participants.

Data on other factors including drinking status, education, physical activity, laboratory values, and a history of diabetes were collected by using standardized protocols and quality control across study centers and examinations (see Data S1).

Cognitive Function Assessment

A battery of standardized tests to measure cognitive function were performed at the Y_{25} examination.[18] The details are described in Data S1. The Digit Symbol Substitution Test (DSST), a subtest of the Wechsler Adult Intelligence Scale (third edition), assesses psychomotor speed, as well as attention, executive function, and working memory. The range of scores is 0 to 133, with increasing scores indicating better performance. The Rey Auditory Verbal Learning Test (RAVLT) assesses the ability to memorize and to retrieve words (verbal memory) after several presentations of the word list immediately one after another and then after a delay of 10 minutes. Results from the long-delay (10 minutes) free recall were used in analyses. The range of scores is 0 to 15, with increasing scores indicating better performance. The Stroop test evaluates the ability to view complex visual stimuli and to respond to one stimulus dimension while suppressing the response to another dimension, an executive skill largely attributed to frontal lobe function. The test was scored by counting the seconds it took participants to read words printed in a different color ink, plus the number of errors (therefore, the unit is seconds plus errors). A higher interference score indicates worse performance on the task (range 1–160). Each trial was scored by summing the number of errors and the time required to complete each trial. An interference score was calculated by subtracting the score on the incongruent trial from the second congruent trial.

Statistical Analysis

Statistical analyses were performed by using SAS software version 9.3 (SAS Institute Inc). To show the distribution of BP

reactivity over all participants, the range of BP reactivity during each task was calculated by decile. Differences in cognitive function scores among the decile groups were assessed using analysis of covariance with adjustment for age, sex, race, and educational attainment. Unadjusted and multivariable-adjusted linear regression models were used to assess the association of BP reactivity with cognitive function (both the variables were used as a continuous variable). We verified the model assumptions of linearity, normality of residuals, homoscedasticity, and absence of collinearity.[19] In the first step, we carried out unadjusted analyses (Model 1). In the second step, we added age at baseline (Y_2), sex, race, and educational attainment (years) as adjustment covariates (Model 2). In the last step, we further adjusted for clinical characteristics at Y_{25} (ie, body mass index, smoking, alcohol, physical activity, glucose and lipid parameters, use of antihypertensive drugs, and incidence of stroke) plus resting BP before the task (Model 3) or visit BP at Y_{25} (Model 4). As a sensitivity analysis, we conducted the following: (1) sex, (2) race, (3) smoking and drinking status at baseline, (4) the presence or absence of obesity (body mass index $\geq$30 kg/m^2) at follow-up, (5) excluding those with diabetes during follow-up, and (6) excluding those who had antihypertensive drugs at Y_{25} or incident stroke during follow-up. Statistical significance was defined by a P value of <0.05 on 2-sided tests.

Table 1. Clinical Characteristics of Study Cohort (n=3021)

Descriptive Variable	Baseline (Y_2)	Follow-up Time (Y_{25})
Age, y	27.1±3.6	50.2±3.6
Men, %	43.8	—
Blacks, %	44.1	—
Education, y	14.1±2.2	—
Body mass index, kg/m^2	25.0±5.0	30.0±7.0
Current smoker, %	25.7	15.6
Current drinker, %	71.6	55.4
Physical activity, exercise units	384.6±282.3	341.8±274.6
Antihypertensive medication, %	2.2	25.8
Visit SBP, mm Hg	107.4±10.5	119.3±15.9
Visit DBP, mm Hg	67.3±9.1	74.5±11.1
Fasting glucose, mg/dL	81.9±10.8	99.5±29.0
Total cholesterol, mg/dL	183.7±34.4	192.4±36.4
High-density lipoprotein, mg/dL	54.9±13.9	57.9±17.8

Data are expressed as the mean±SD or percentage. In the CARDA study, BP reactivity testing was conducted at the first follow-up examination at year 2 (Y_2), and cognitive testing was conducted at the follow-up examination at Y_{25}. DBP indicates diastolic blood pressure; SBP systolic blood pressure.

Table 2. Range of Stress-Induced SBP/DBP Reactivity Divided by Deciles

Variables	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	Ninth	Tenth	Mean±SD
Star tracing	n=302	n=300	n=298	n=297	n=319	n=292	n=303	n=305	n=304	n=301	
SBP change, mm Hg	−220.3 to 1.3	1.3 to 5.0	5.0 to 7.3	7.3 to 9.3	9.3 to 11.3	11.3 to 13.2	13.3 to 15.3	15.3 to 18.0	18.0 to 21.7	21.7 to 54.5	11.5±8.5
Star tracing	n=307	n=274	n=308	n=304	n=322	n=297	n=301	n=305	n=301	n=302	
DBP change, mm Hg	−29.0 to 2.0	2.2 to 5.0	5.0 to 7.0	7.0 to 8.7	8.7 to 10.3	10.3 to 12.3	12.3 to 14.2	14.3 to 16.7	17.0 to 20.3	20.7 to 42.0	10.8±7.6
Video game	n=303	n=303	n=304	n=312	n=299	n=282	n=311	n=294	n=311	n=302	
SBP change, mm Hg	−28.5 to 0.3	0.3 to 3.3	3.5 to 5.7	5.7 to 7.3	7.5 to 9.3	9.3 to 11.2	11.3 to 13.3	13.3 to 15.7	15.7 to 19.7	19.7 to 80.0	9.8±7.9
Video game	n=319	n=293	n=315	n=276	n=305	n=306	n=290	n=312	n=305	n=300	
DBP change, mm Hg	−33.3 to 0.0	0.2 to 3.0	3.0 to 5.0	5.0 to 7.0	7.0 to 8.7	8.7 to 10.0	10.2 to 12.0	12.3 to 14.3	14.7 to 18.0	18.0 to 52.3	8.8±7.3

Mean±SD of each stress-induced SBP/DBP reactivity in all participants (n=3021) is shown for the rightmost line. DBP indicates diastolic blood pressure; SBP, systolic blood pressure.

Results

At baseline, the included participants showed a lower percentage of men (43.8% versus 48.0%), blacks (44.1% versus 62.4%), and current smokers (25.7% versus 36.8%); higher educational attainment (14.1 versus 13.3 years); and lower visit systolic BP (SBP) (107.4 versus 108.7 mm Hg; all $P<0.01$) compared with those not included in this study (n=2094; Table S1).

Table 1 provides the demographic and clinical characteristics at Y_2 and Y_{25} of the included participants. For the 3021 participants, mean resting SBP and diastolic BP (DBP) before BP reactivity task were 111.5±11.0 mm Hg and 64.6±10.5 mm Hg, respectively. The mean and range of visit SBP and DBP at Y_2 were 107.4 (range 78–158) mm Hg and 67.3 (range 31–109) mm Hg, respectively, and 119.3 (77–207) mm Hg and 74.5 (range 40–127) mm Hg at Y_{25}, respectively (Figure S2).

The mean and range of stress-induced BP reactivity stratified by deciles are shown in Table 2. BP reactivity between the star tracing and the video game was correlated (Pearson's r correlation=0.622 in SBP reactivity and r=0.616 in DBP reactivity; both $P<0.0001$). Tables 3 through 6 show the associations between BP reactivity during each task and clinical characteristics adjusted for age, sex, and race. Female sex, lower educational attainment, and current smoking were associated with lower SBP reactivity during the star tracing and video game.

Among participants, mean scores on the DSST, RAVLT, and Stroop test were 70.5±16.0 symbols (range=8.0–125.0), 8.4±3.3 words (range=0–15.0), and 22.6±10.7 seconds plus errors (range=21.0–127.0), respectively. Mean (95% CI) scores of cognitive function with adjustment for age, sex, race, and education in deciles of SBP reactivity (Figure) and DBP reactivity (Figure S3) during each task were calculated. Lower SBP reactivity during the star tracing and the video game (particularly the first and second deciles of SBP reactivity [≤5 mm Hg]) was associated with worse DSST and Stroop test scores (Figure).

Tables 7 through 9 shows linear regression models examining the associations between BP reactivity during each task and cognitive function. Lower SBP reactivity during the star tracing was associated with worse DSST, RAVLT, and Stroop test scores (Model 1 in Tables 7 through 9). SBP reactivity during the star tracing remained significantly associated with the DSST and Stroop test scores, even after adjustment for demographic variables, clinical characteristics

Table 3. Age-, Sex-, and Race-Adjusted Correlation of SBP Reactivity During Each Task With the Demographic Variables and Clinical Characteristics (n=3021)

Variables	SBP Reactivity During Task, mm Hg	
	Star Tracing	Video Game
Clinical characteristics at Y_2 (baseline)		
Body mass index, kg/m^2	−0.036*	−0.070‡
Physical activity, exercise units	0.044*	0.025
Education, y	0.078§	0.070‡
Clinical characteristics at Y_{25} (follow-up)		
Body mass index, kg/m^2	−0.031	−0.052†
Physical activity, exercise units	0.005	−0.005
Fasting glucose, mg/dL	−0.029	−0.047*
Total cholesterol, mg/dL	0.023	0.010
High-density lipoprotein, mg/dL	0.024	0.040*
Blood pressure parameters		
Resting SBP during task, mm Hg	−0.127§	−0.125§
Visit SBP at Y_2, mm Hg	0.011	0.023
Visit SBP at Y_{25}, mm Hg	0.013	0.015
Change of visit SBP (Y_{25}–Y_2), mm Hg	0.005	−0.0002

Pearson's correlation coefficients adjusted by age, sex, and race are shown. SBP indicates systolic blood pressure.
Statistical significance was defined as $P<0.05$. *$P<0.05$, †$P<0.01$, ‡$P<0.001$, §$P<0.0001$.

Table 4. Age-, Sex-, and Race-Adjusted Correlation of DBP Reactivity During Each Task With the Demographic Variables and Clinical Characteristics (n=3021)

Variables	DBP Reactivity During Task, mm Hg	
	Star Tracing	Video Game
Clinical characteristics at Y_2 (baseline)		
Body mass index, kg/m^2	−0.019	−0.050†
Physical activity, exercise units	0.030	0.003
Education, y	0.041*	0.026
Clinical characteristics at Y_{25} (follow-up)		
Body mass index, kg/m^2	−0.016	−0.014
Physical activity, exercise units	0.029	0.015
Fasting glucose, mg/dL	−0.031	−0.037*
Total cholesterol, mg/dL	0.013	0.017
High-density lipoprotein, mg/dL	0.011	0.031
Blood pressure parameters		
Resting DBP during task, mm Hg	−0.300§	−0.267§
Visit DBP at Y_2, mm Hg	0.004	0.047†
Visit DBP at Y_{25}, mm Hg	0.029	0.059†
Change of visit DBP (Y_{25}–Y_2), mm Hg	0.023	0.018

Pearson's correlation coefficients adjusted by age, sex, and race are shown. DBP indicates diastolic blood pressure.
Statistical significance was defined as $P<0.05$. *$P<0.05$, †$P<0.01$, $P<0.001$, §$P<0.0001$.

Table 5. Differences of SBP Reactivity During Individual Task by Clinical Characteristics (n=3021)

	SBP Reactivity During Task, mm Hg			
	Star Tracing	*P* Values	Video Game	*P* Values
Sex				
Men, 43.8%	12.4±8.8	<0.0001	10.6±8.0	<0.0001
Women, 56.2%	10.8±8.2		9.1±7.8	
Race				
Whites, 55.9%	12.7±8.2	<0.0001	9.8±7.4	0.68
Blacks, 44.1%	10.0±8.6		9.7±8.5	
Current smoking at Y_2 (baseline)				
Yes, 25.7%	9.0±7.9	<0.0001	8.1±7.4	<0.0001
No, 74.3%	12.3±8.5		10.3±8.0	
Daily drinking at Y_2 (baseline)				
Yes, 71.6%	11.6±8.6	0.60	9.8±7.7	0.86
No, 28.4%	11.4±8.3		9.8±8.5	
Antihypertensive medication use at Y_2 (baseline)				
Yes, 2.2%	11.8±10.0	0.77	10.5±10.2	0.42
No, 97.8%	11.5±8.5		9.7±7.9	
Current smoking at Y_{25} (follow-up)				
Yes, 15.6%	9.0±8.1	<0.0001	8.6±7.9	0.0005
No, 84.4%	11.9±8.5		10.0±7.9	
Daily drinking at Y_{25} (follow-up)				
Yes, 55.3%	11.8±8.6	0.009	9.9±7.6	0.28
No, 44.7%	11.0±8.4		9.6±8.3	
Antihypertensive medication use at Y_{25} (follow-up)				
Yes, 25.8%	11.4±8.9	0.79	10.5±8.8	0.005
No, 74.2%	11.5±8.4		9.5±7.6	

P values were obtained with the unpaired t test. Statistical significance was defined as $P<0.05$. SBP indicates systolic blood pressure.

Table 6. Differences of DBP Reactivity During Individual Task by Clinical Characteristics (n=3021)

	DBP Reactivity During Task, mm Hg			
	Star Tracing	*P* Values	Video Game	*P* Values
Sex				
Men, 43.8%	11.3±7.8	0.0008	8.7±7.5	0.27
Women, 56.2%	10.4±7.4		9.0±7.2	
Race				
Whites, 55.9%	10.8±7.0	0.73	8.2±6.8	<0.0001
Blacks, 44.1%	10.7±8.2		9.6±7.9	
Current smoking at Y_2 (baseline)				
Yes, 25.7%	10.0±7.3	0.0004	8.2±7.1	0.01
No, 74.3%	11.1±7.6		9.0±7.4	
Daily drinking at Y_2 (baseline)				
Yes, 71.6%	10.9±7.4	0.14	8.8±7.2	0.62
No, 28.4%	10.4±7.9		8.7±7.4	
Antihypertensive medication use at Y_2 (baseline)				
Yes, 2.2%	10.9±8.3	0.89	10.9±8.7	0.02
No, 97.8%	10.8±7.6		8.8±7.3	
Current smoking at Y_{25} (follow-up)				
Yes, 15.6%	10.5±7.7	0.35	8.6±7.2	0.49
No, 84.4%	10.9±7.5		8.9±7.4	
Daily drinking at Y_{25} (follow-up)				
Yes, 55.3%	10.9±7.5	0.32	8.8±7.3	0.58
No, 44.7%	10.7±7.7		8.9±7.4	
Antihypertensive medication use at Y_{25} (follow-up)				
Yes, 25.8%	11.0±8.0	0.36	9.6±7.8	0.0002
No, 74.2%	10.7±7.4		8.5±7.2	

P values were obtained with the unpaired t test. Statistical significance was defined as $P<0.05$. DBP indicates diastolic blood pressure.

at Y_{25}, and resting BP before the task (Model 3) or visit BP at Y_{25} (Model 4 in Tables 7 and 9). Lower SBP reactivity during the video game was associated with worse DSST and Stroop test scores in the adjusted models (Models 2–4 in Tables 7 and 9). In Model 4, the unstandardized β values for a 1-year increase of age ranged between −0.130 and −0.135 for the DSST (all $P<0.001$), between −0.051 and −0.049 for the RAVLT (all $P<0.05$), and between 0.097 and 0.098 for the Stroop test (all $P<0.0001$).

Overall patterns in the associations between measures of BP reactivity and cognitive function were similar between blacks and whites (Table S2). Sensitivity analyses by sex, smoking and drinking status at baseline, and the presence of obesity (body mass index ≥30 kg/m^2) at follow-up showed relatively similar results (Tables S3–S6). There was no statistical interaction between these parameters and measures of stress-induced BP reactivity in association with cognitive function (all *P*=NS). When participants with diabetes during follow-up (n=467) or those who had antihypertensive drugs at Y_{25} or incident stroke during follow-up (n=789) were excluded, the significant association of BP reactivity during each task with cognitive function remained similar (Tables S7 and S8).

Discussion

In this 23-year follow-up study, we first demonstrated that lower SBP reactivity during the star tracing and the video game in young adulthood (mean age 27 years) is associated with worse psychomotor speed (as measured with the DSST) and executive function (as measured with the Stroop

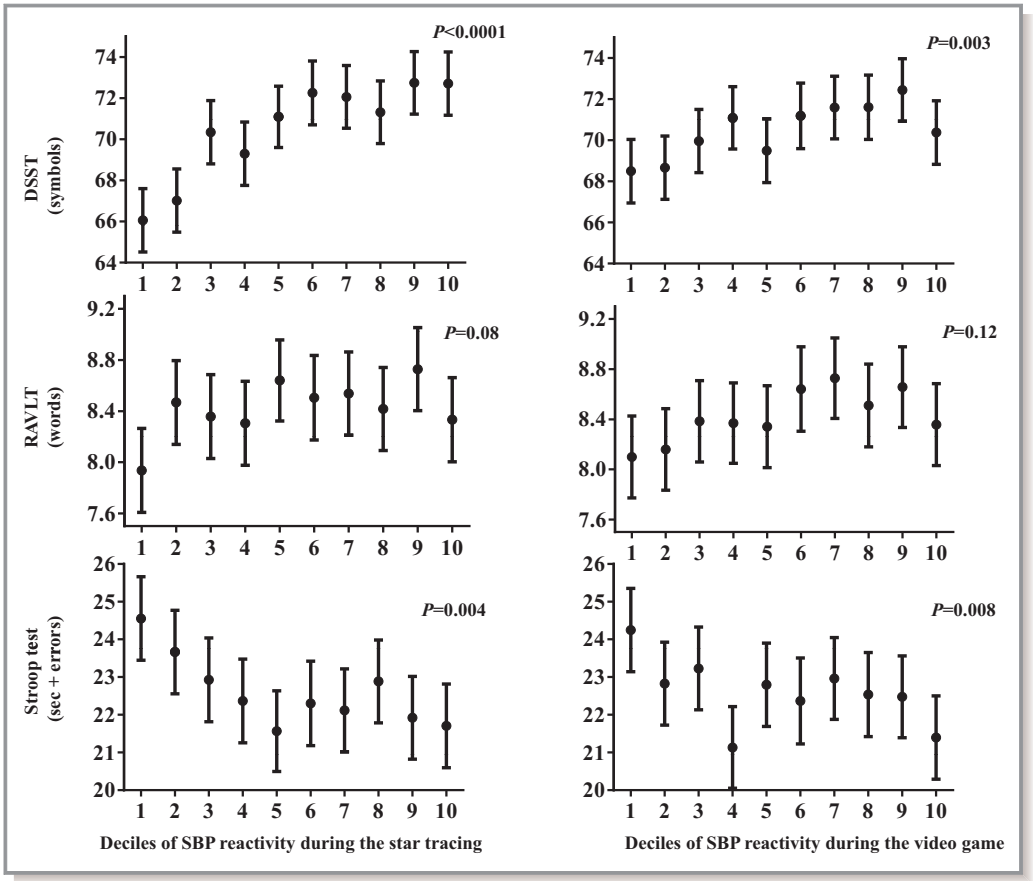

Figure. Scores of cognitive function test in deciles of systolic blood pressure (SBP) reactivity during each task. Bars represent means (95% CIs) with adjustment for age, sex, race, and education. *P* values were calculated by analysis of covariance.

test) in midlife. These associations were independent of cardiovascular risk factors including resting BP measured at both baseline and follow-up. Our results bring into question the classic view of stress-induced BP reactivity and disease—that larger responses are worse and smaller responses are better. BP reactivity to psychological stressors may have different associations with target organs in hypertension.

The mechanisms of the cardiovascular reactivity to psychological stress remain to be determined, but have been speculated as (1) cognitive emotional reactions, determined by consciousness and adaptive behaviors; (2) autonomic and endocrine outputs from the hypothalamus and brain stem; and (3) peripheral tissue function.[1,8] The first process contributes to cognitive function but less so to the cardiovascular system. The third process reflects an individual's cardiovascular system. For example, excess BP reactivity is associated with altered α- and β-adrenoreceptor sensitivity, endothelial dysfunction, higher vascular resistance, and vascular remodeling.[1,2] This may be a reason higher BP reactivity has been shown to be associated with incident hypertension, greater carotid artery intima-media thickness, and incident cardiovascular disease.[2–5,7] In contrast, the first process may influence cognitive function. The hypoactivated brain areas (eg, the anterior cingulate, the amygdala, and the insular cortex), seen in those with a lower cardiovascular reaction to stress, can contribute to evaluating and processing motivational and emotional information when psychological stress is imposed and then coordinate appropriate motivated behavioral responses.[8,12,20–22] Therefore, lower BP reactivity may be a marker of emotion and motivational dysregulation (impairing the first process)[1,8] and, consequently, lower cognitive function. Although BP reactivity was evaluated 23 years before the cognitive function tests in this study, such central motivational dysregulation may persist across adulthood. It has been shown, however, that the correlations between psychological stress-induced BP reactivity and individual task-related unpleasantness, distress, and negative emotion are modest[10,11,23] and the associations of stress-induced BP reactivity with cognitive function are independent of individual task appraisal.[16,17] It may be unlikely that individual trait differences could largely explain

Table 7. Unadjusted and Multivariable-Adjusted Linear Regression Models to Examine the Associations of BP Reactivity During Each Task in Young Adults With Midlife DSST Scores (n=3021)

	Star Tracing				Video Game			
	SBP Change, mm Hg		DBP Change, mm Hg		SBP Change, mm Hg		DBP Change, mm Hg	
Variables	β (SE)	R^2, %	β (SE)	R^2, %	β (SE)	R^2, %	β (SE)	R^2, %
DSST (symbols)								
Model 1 (unadjusted)	0.148 (0.018)§	2.1	0.047 (0.018)†	0.2	0.040 (0.018)*	0.1	−0.007 (0.018)	0.00
Model 2	0.115 (0.016)§	28.3	0.056 (0.016)‡	27.3	0.051 (0.016)†	27.3	0.015 (0.016)	27.0
Model 3	0.106 (0.016)§	30.5	0.056 (0.016)‡	29.7	0.048 (0.016)†	29.7	0.011 (0.016)	29.4
Model 4	0.105 (0.016)§	30.6	0.054 (0.015)‡	29.8	0.049 (0.016)†	29.7	0.014 (0.015)	29.5

β indicates unstandardized regression coefficient, and R^2 means a measure for the model prediction. In each linear model, DSST scores were used as the dependent variable and BP reactivity during the star tracing or the video game served as the independent variable modeled continuously. As adjustment factors: Model 2 included demographic variables (age at baseline, sex, race, and education), Model 3 included demographic variables plus clinical characteristics at Y_{25} (body mass index, smoking, alcohol, physical activity, fasting glucose, total cholesterol/high-density lipoprotein, use of antihypertensive drugs, incidence of stroke) plus resting BP before BP reactivity test, Model 4 included demographic variables plus clinical characteristics at Y_{25} plus visit BP at Y_{25}. BP indicates blood pressure; DBP, diastolic blood pressure; DSST, Digit Symbol Substitution Test; SBP, systolic blood pressure.
Statistical significance was defined as *P<0.05, †P<0.01, ‡P<0.001, §P<0.0001.

the lower cognitive function in those with lower stress-induced BP reactivity.

Other potential mechanisms exist underlying the association between lower BP reactivity and lower cognitive function. First, according to functional neuroimaging studies, those who exhibit lower BP reactivity to psychological stress showed less neuron activity in the anterior cingulate and amygdala, the posterior cingulate, and the insular cortex.[9–12] These brain regions are involved not only in autonomic nervous and cardiovascular regulation but also in cognitive function, particularly executive functions.[12,20,21] In the current study, stress-induced SBP reactivity was associated with DSST and Stroop test scores. Both reflect executive function[22,24] but not RAVLT scores, which reflect hippocampus (memory) function.[25]

Second, less stress-induced BP reactivity is observed in those with low socioeconomic status and a number of poor health conditions, including smoking, obesity, and perceived health and psychological disorders (eg, depression, substance abuse, and antisocial personality).[1,8,26–28] Therefore, lower stress-induced BP reactivity may merely be an epiphenomenon of certain pathophysiological conditions.[1,8] We found less SBP/DBP reactivity during the star tracing and video game was observed in those currently smoking, with

Table 8. Unadjusted and Multivariable-Adjusted Linear Regression Models to Examine the Associations of BP Reactivity During Each Task in Young Adults With Midlife RAVLT Scores (n=3021)

	Star Tracing				Video Game			
	SBP Change, mm Hg		DBP Change, mm Hg		SBP Change, mm Hg		DBP Change, mm Hg	
Variables	β (SE)	R^2, %	β (SE)	R^2, %	β (SE)	R^2, %	β (SE)	R^2, %
RAVLT (words)								
Model 1 (unadjusted)	0.066 (0.018)‡	0.4	0.013 (0.018)	0.02	0.022 (0.018)	0.02	0.014 (0.018)	0.02
Model 2	0.028 (0.016)	21.6	0.022 (0.016)	21.6	0.033 (0.016)*	21.6	0.035 (0.016)*	21.7
Model 3	0.020 (0.017)	22.4	0.021 (0.017)	22.4	0.029 (0.016)	22.4	0.034 (0.017)*	22.5
Model 4	0.023 (0.017)	22.6	0.024 (0.016)	22.7	0.031 (0.016)	22.6	0.040 (0.016)*	22.8

β indicates unstandardized regression coefficient, and R^2 means a measure for the model prediction. In each linear model, Digit Symbol Substitution Test scores were used as the dependent variable and BP reactivity during the star tracing or the video game served as the independent variable modeled continuously. As adjustment factors: Model 2 included demographic variables (age at baseline, sex, race, and education), Model 3 included demographic variables plus clinical characteristics at Y_{25} (body mass index, smoking, alcohol, physical activity, fasting glucose, total cholesterol/high-density lipoprotein, use of antihypertensive drugs, incidence of stroke) plus resting BP before BP reactivity test, Model 4 included demographic variables plus clinical characteristics at Y_{25} plus visit BP at Y_{25}. BP indicates blood pressure; DBP, diastolic blood pressure; RAVLT, Rey Auditory Verbal Learning Test; SBP, systolic blood pressure.
Statistical significance was defined as *P<0.05, P<0.01, ‡P<0.001, P<0.0001.

Table 9. Unadjusted and Multivariable-Adjusted Linear Regression Models to Examine the Associations of BP Reactivity During Each Task in Young Adults With Midlife Stroop Test Scores (n=3021)

	Star Tracing				Video Game			
	SBP Change, mm Hg		DBP Change, mm Hg		SBP Change, mm Hg		DBP Change, mm Hg	
Variables	β (SE)	R^2, %	β (SE)	R^2, %	β (SE)	R^2, %	β (SE)	R^2, %
Stroop test (s+errors)								
Model 1 (unadjusted)	−0.12.0 (0.018)§	1.4	−0.029 (0.018)	0.1	−0.057 (0.018)†	0.3	0.022 (0.018)	0.01
Model 2	−0.064 (0.017)‡	17.5	−0.026 (0.017)	17.2	−0.052 (0.017)†	17.4	−0.009 (0.017)	17.1
Model 3	−0.059 (0.017)‡	18.4	−0.019 (0.017)	18.2	−0.053 (0.017)†	18.3	−0.003 (0.017)	18.1
Model 4	−0.059 (0.017)‡	18.5	−0.025 (0.017)	18.1	−0.053 (0.017)†	18.4	−0.009 (0.017)	18.1

β indicates unstandardized regression coefficient, and R^2 means a measure for the model prediction. Blood pressure (BP) reactivity during each task was used as a continuous variable. In each linear model, Stroop test scores were used as a dependent variable, and BP reactivity during the star tracing or the video game was used as an independent variable. As adjustment factors: Model 2 included demographic variables (age at baseline, sex, race, and education), Model 3 included demographic variables+clinical characteristics at Y_{25} (body mass index, smoking, alcohol, physical activity, fasting glucose, total cholesterol/high-density lipoprotein, use of antihypertensive drugs, incidence of stroke)+resting BP before BP reactivity test, Model 4 included demographic variables+clinical characteristics at Y_{25}+visit BP at Y_{25}. DBP indicates diastolic blood pressure; SBP, systolic blood pressure.
Statistical significance was defined as $P<0.05$, †$P<0.01$, ‡$P<0.001$, §$P<0.0001$.

less educational attainment and higher body mass index. Although we adjusted for these factors, several factors remain uncontrolled, including early life adversity, racial/ethnical discrimination, psychological factors, and quality of sleep.[1,8,28,29]

Strengths and Limitations

The major strengths of this study include the study cohort of well-characterized participants from young adulthood to middle age, application of a comprehensive standardized cognitive test battery, and a standardized reactivity protocol that used well-characterized laboratory stressors. However, there are limitations. First, we could not assess change in cognitive function from baseline to follow-up, and we cannot conclude whether low cognitive function scores reflect cognitive decline per se. Second, a number of people from the original cohort were not included in the present analysis (41%). Those who were not included were more likely to be African American and to have lower educational attainment. In addition, the follow-up BP in this population (119/75 mm Hg) was lower than that in the US general population of the same age.[30] This might result from research participation effects (ie, the Hawthorne effect),[31] and participants in the CARDIA study might not be representative of the US general population. Third, the methods used in the different steps of the study (eg, BP measures) might not be homogeneous. These factors, if anything, may have led us to underestimate the true association between BP reactivity and cognitive function. Fourth, the associations between BP reactivity and cognitive function were significant, but the effect sizes were small. However, the effect sizes were relatively similar to those associated with an increase in 1 year of aging. Fifth, BP reactivity tasks were conducted after 8 minutes of seated rest, while a majority of prior studies[7,13,14,27,29] conducted BP reactivity tasks after 5 to 15 minutes of seated rest. The resting BP before a task may or may not be hemodynamically stabilized. Sixth, the results might depend on how often participants have played video games on a daily basis. Given that new technologies (eg, smartphones) are diffusing into daily life swiftly and people can play a game easily, our results may not be generalized to the current generation. Finally, our sample consisted of blacks and whites in young adulthood with few comorbidities. Extrapolation of our findings to older individuals and to other race/ethnicity groups should be done with caution.

Conclusion

The present study suggests that lower psychological stress-induced BP reactivity in younger adults is associated with lower cognitive function in midlife. Elevated levels of midlife BP have been shown to be associated with a range of changes in the brain that have been associated with late-life cognitive impairment.[32,33] The results of our study suggest not only is "level" important to consider when aiming to identify those at younger age who may be at risk for cognitive impairment in later life but also variability per se in BP levels should be investigated. Replication in different studies and further etiopathophysiological studies to understand biological mechanisms behind the association of lower stress-induced BP reactivity with lower cognitive function are warranted. Additional follow-up in the CARDIA study will help to determine the significance of BP reactivity in young adulthood on aging-related cognitive decline and dementia through older age.

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