Heightened Functional Neural Activation to Psychological Stress Covaries With Exaggerated Blood Pressure Reactivity

Peter J. Gianaros, J. Richard Jennings, Lei K. Sheu, Stuart W.G. Derbyshire, Karen A. Matthews

Abstract—Individuals who show exaggerated blood pressure reactions to psychological stressors are at increased risk for hypertension, atherosclerosis, and stroke. We tested whether individuals who show exaggerated stressor-induced blood pressure reactivity also show heightened stressor-induced neural activation in brain areas involved in controlling the cardiovascular system. In a functional MRI study, 46 postmenopausal women (mean age: 68.04; SD: 1.35 years) performed a standardized Stroop color-word interference task that served as a stressor to increase blood pressure. Across individuals, a larger task-induced rise in blood pressure covaried with heightened and correlated patterns of activation in brain areas implicated previously in stress-related cardiovascular control: the perigenual and posterior cingulate cortex, bilateral prefrontal cortex, anterior insula, and cerebellum. Entered as a set in hierarchical regression analyses, activation values in these brain areas uniquely predicted the magnitude of task-induced changes in systolic ($\Delta R^2=0.54$; $P<0.001$) and diastolic ($\Delta R^2=0.27$; $P<0.05$) blood pressure after statistical control for task accuracy and subjective reports of task stress. Heightened stressor-induced activation of cingulate, prefrontal, insular, and cerebellar brain areas may represent a functional neural phenotype that characterizes individuals who are prone to show exaggerated cardiovascular reactivity. (*Hypertension*. 2007;49:134-140.)

Key Words: blood pressure ■ cardiovascular reactivity ■ cerebellum ■ cingulate ■ insula ■ orbitofrontal cortex ■ psychological stress

Acute psychological stress raises blood pressure in most individuals. A stress-induced rise in blood pressure results from autonomic- and neuroendocrine-mediated changes in cardiac contractility and peripheral vascular resistance.[1] These stressor-induced physiological changes are thought to provide metabolic support for adaptive behavior (eg, the "fight-or-flight" response).[2] Some individuals, however, have a tendency to show exaggerated rises in blood pressure that exceed the metabolic demands of psychological stressors.[3] Such exaggerated stressor-induced blood pressure reactions predict increased risk for hypertension,[4] stroke,[5] and preclinical atherosclerosis.[6,7]

Blood pressure reactions to psychological stress are centrally controlled by brain systems that both cognitively process psychological stressors and coordinate autonomic, neuroendocrine, and cardiovascular activity with adaptive behavior.[8,9] Key among these brain systems are subdivisions of the cingulate, orbitofrontal, and insular cortices.[8–15] Anatomically, subdivisions of the cingulate, orbitofrontal, and insular cortices can control peripheral physiology by reciprocal neural connections with cell groups in subcortical and brain stem areas that regulate autonomic, neuroendocrine, and cardiovascular activity.[8–15] To date, however, it has not yet been established whether individuals who show exagger-

ated stressor-induced blood pressure reactivity also show greater stressor-induced neural activation in cingulate, orbitofrontal, insular, or other brain areas that directly or indirectly control peripheral physiology. If so, then this would provide evidence for a functional neural phenotype that characterizes individuals who are prone toward exaggerated cardiovascular reactivity and possibly stressor-related risk for cardiovascular disease.

In a preliminary study of 16 middle-aged adults, we reported that individuals with a stable tendency to show exaggerated blood pressure reactivity to a psychological stressor also showed greater stressor-induced activation of the posterior cingulate cortex, an area implicated in the self-relevant processing of emotionally salient information.[16] In this larger functional MRI (fMRI) study of 46 individuals, we extended our preliminary work by testing whether stressor-induced activation of the cingulate cortex or other brain areas involved in peripheral physiological and cardiovascular control directly predicts individual differences in blood pressure reactivity to a Stroop color-word interference task (a standardized stressor used in epidemiological studies of cardiovascular reactivity and risk for preclinical atherosclerosis[6,16–18]), apart from the influences of task performance and subjective ratings of task stress.

TABLE 1. Characteristics of 46 Postmenopausal Women

Characteristics	Mean	SD
Age, y	68.04	1.35
No. of school years completed	15.46	1.59
No. of years since menopause	15.66	2.32
Alcoholic beverages consumed per week	2.46	3.77
Height, in	63.26	3.09
Weight, lb	154.12	22.33
BMI, kg/m^2	27.17	4.24
Resting SBP, mm Hg	125.35	11.74
Resting DBP, mm Hg	74.52	6.80

Methods

Participants

Fifty postmenopausal women from the Pittsburgh Healthy Women Study were tested. Details regarding sampling, exclusion criteria, and demographics for the cohort of 541 women who began the study in 1983–1984 are reported elsewhere.[19] Women were ineligible for the present study if they had any of the following: (1) history of cardiovascular or cerebrovascular disease (including hypertension, coronary artery disease, angina, transient ischemic attacks, blood clotting, a myocardial infarction, and congestive heart failure); (2) a previous stroke or cerebrovascular incident involving loss of consciousness; (3) claustrophobia; (4) type I or II diabetes; (5) cancer; (6) a current or previous diagnosis of a neuropsychiatric disorder (including a mood disorder, dementia, or suspected Alzheimer's disease); (7) used psychotropic, blood pressure, or glucoregulatory medications currently or in the past; or (8) a metallic implant.

Of the 464 active Healthy Women Study participants in September 2005, 209 met ≥1 exclusion, 71 were not interested in participating, and 134 could not be contacted or conveniently tested. Brain imaging data for 4 women were excluded because of a noncompletion of the protocol (n=2) or excessive fMRI movement artifacts (n=2; see below). Results reported herein are for N=46 participants who did not differ in age (t=0.15; P=0.89) or years of educational attainment (t=0.69; P=0.49) from nonparticipants. The University of Pittsburgh Institutional Review Board granted study approval. Participants provided informed consent after receiving a study description. See Table 1 for participant characteristics.

Study Protocol and Covariate Assessment

Participants completed a 2-part protocol consisting of a laboratory and MRI session, which were separated by a mean of 9.6 (± SD=15.1) days. At the laboratory, we obtained a medical history and anthropometric and demographic information. At the laboratory and MRI sessions, we also recorded 3 auscultatory measures of resting blood pressure following the protocol of the Multiple Risk Factor Intervention Trial,[20] with resting blood pressure defined as the average of the final 2 readings combined across the sessions. Body mass index (BMI) was computed as weight (in kilograms)/height (in meters squared). In the laboratory and MRI sessions, participants completed a battery of cognitive and motor tasks. Embedded in the battery was the Stroop color-word interference task. The laboratory session served to familiarize participants with the tasks and to estimate blood pressure reactivity before the MRI session.

Stroop Color-Word Interference Task

In the laboratory and MRI sessions, participants rested quietly for an 8-minute baseline period before completing 2 repetitions of the Stroop color-word interference task. The task had 2 conditions, an incongruent condition and a congruent condition, each lasting 2 minutes. In both conditions, participants identified the color of target words by selecting 1 of 4 identifier words that named the color of the target word. Participants made their selections in the laboratory and MRI sessions with a 4-button response device. For incongruent condition trials, the target word was displayed in a color that was incongruent with the color that the target word named, and all of the identifier words were displayed in colors that were incongruent with the colors that the identifier words named. For congruent condition trials, the target word was displayed in a color that was congruent with the target word, and all of the identifier words were displayed in the same color as the target word. Feedback about accuracy was provided on each trial of both conditions by outlining the participant's choice and highlighting the correct answer. In the incongruent condition, accuracy at target word identification was titrated to ≈60% by varying response time windows (see Reference[16] for further detail). To control for motor response differences between conditions, the number of trials presented in the congruent condition was matched to the total number of trials completed in the incongruent condition (for example trials, please see Figure I, available at http://hyper.ahajournals.org).

Task Accuracy and Stress

Task accuracy for each condition was computed as the percentage of total trials that were correctly completed. After task completion, participants rated their level of stress for each condition on a 0 (not at all) to 3 (extreme) scale.

Blood Pressure Measurement

In both the laboratory and MRI testing sessions, blood pressure was measured during the baseline and task periods from the brachial artery of the left arm (not used for task responding). In the laboratory session, participants were seated upright with their feet flat on the floor; in the MRI session, participants were supine while inside the bore of the scanner. Blood pressure was measured with an automated device in the laboratory (auscultatory-Korotkoff method: IBS Model SD-700A; IBS Corp., Waltham, MA) and MRI (oscillometric method: Omega Model 1400, InVivo Research, Orlando, FL) sessions. In both sessions, blood pressure was measured once every 2 minutes during the 8-minute baseline and once during each repetition of the Stroop task conditions. To compute baseline blood pressure, the 4 measurements from the baseline period were averaged. To compute task-related blood pressure, the 2 measurements from the demanding incongruent condition were averaged. The task–baseline blood pressure difference was used as an indicator of blood pressure reactivity following the procedures of our preliminary study.[16]

MRI

Image Acquisition

Brain images were acquired with a 3-T Signa scanner (GE Medical Systems) and a radiofrequency head coil. Structural images were obtained with a spoiled gradient recalled acquisition pulse sequence ([SPGR] time to echo/time to repetition=5000/25 ms; flip angle=40°). The SPGR sequence yielded 124 axial slices (1.5-mm slice thickness; 0-mm spacing between slices), covering a whole-brain volume of 256×192 mm with a 24×18 cm field of view. Functional T$_2$*-weighted blood–oxygen level-dependent (BOLD) images were obtained with a reverse-spiral pulse sequence (time to echo/time to repetition=25/1500 ms; 60° flip angle).[21] The first 5 functional images were discarded to allow the BOLD signal to stabilize; remaining functional images consisted of 34 axial and contiguous slices, which were parallel to the plane of the anterior and posterior commissures (3.2-mm slice thickness; 20-cm field of view).

Image Processing

Brain images were preprocessed and analyzed with statistical parametric mapping software (SPM2, Wellcome Trust Centre for the Study of Cognitive Neurology).[22] For preprocessing, T$_2$*-weighted images were realigned to the first image of each functional imaging series to correct for image distortions because of head movements. Parameters for image realignment were retained and used as covariates in all of the single-subject analyses of task-related activation (see below). Realigned T$_2$*-weighted images were coregistered to the

Perigenual Cingulate (pACC) Activation and Blood Pressure Reactivity
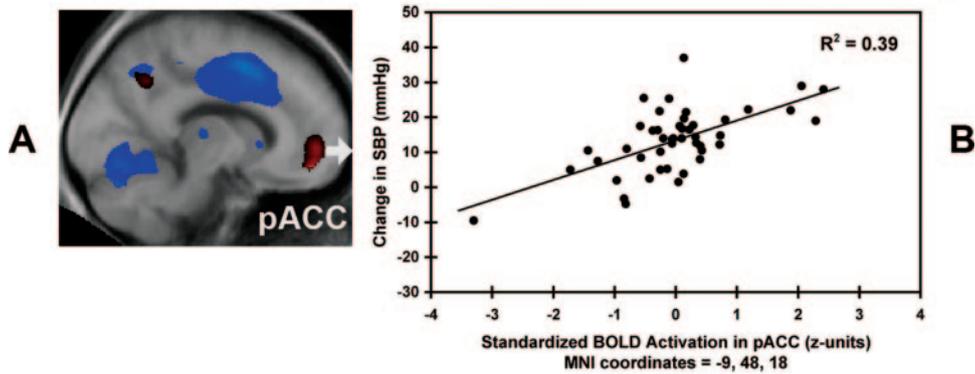
Insula Activation and Blood Pressure Reactivity
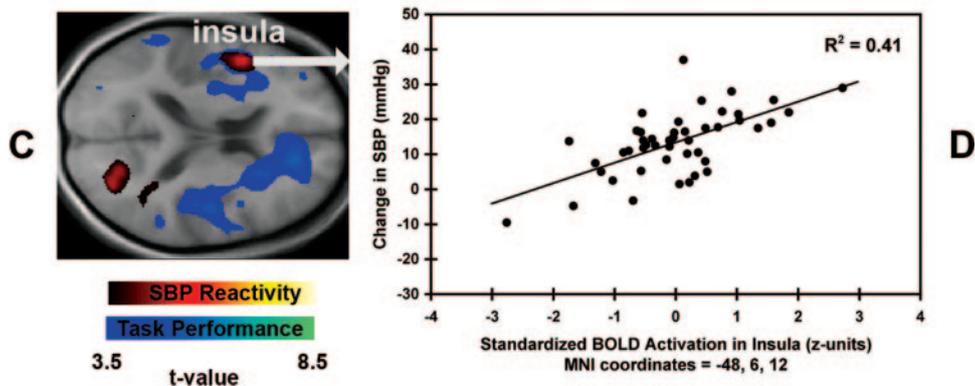
Profiled in A (sagittal view) and C (axial view) are (1) brain areas that were engaged by performing a Stroop color-word interference task (in blue-green) and (2) areas where a greater task-induced activation predicted increased SBP reactivity (red-yellow). Color profiling in A and C is based on statistical parametric maps derived from mixed-effects analyses of regional brain activity (see Methods section). Parametric t values from these analyses are scaled to the color bars at bottom, and they are superimposed on an average structural MRI of our participants' brains. Arrows in A and C point to scatter plots in B and D illustrating the change in SBP from baseline to the incongruent condition of the Stroop task (reflecting SBP reactivity) as a function of the standardized task-induced change in fMRI BOLD activity in the perigenual cingulate cortex (B) and left anterior insula (D). MNI indicates Montreal Neurological Institute.

native anatomic space of each woman's structural SPGR image. Realigned and coregistered images were then spatially normalized to the anatomic space of the International Consortium for Brain Mapping 152 template (Montreal Neurological Institute). Normalized T_2*-weighted images were then smoothed with a 10-mm full-width-at-half-maximum isotropic Gaussian kernel. Before analysis, T_2*-weighted images were high-pass filtered (cutoff: 512 s) to remove linear drifts in BOLD signal intensity.

Data Analyses

Functional imaging data were analyzed using the framework of the general linear model in SPM2.[22] First, BOLD activity in each condition (congruent or incongruent) was modeled for each individual with a delayed box car function that was convolved with the standard SPM2 hemodynamic response function while entering the 6 translation and rotation motion parameters from image realignment (in x, y, and z dimensions) as covariates. As stated above, 2 women with motion parameters >3 mm in ≥1 dimension were excluded from further analysis. Second, to estimate task-induced activation, we contrasted BOLD activity in the incongruent condition with activity in the congruent condition for each individual, which generated voxel-wise contrast coefficients reflecting areas of BOLD activation during the incongruent condition (incongruent > congruent). Third, individual contrast coefficients were aggregated across individuals to perform a mixed-effects t test, which yielded a voxel-wise map of t values reflecting common areas of BOLD activation to the incongruent condition. Finally, estimates of BOLD

activation to the incongruent condition were correlated with the change in systolic blood pressure (SBP) from baseline to the incongruent condition in the MRI session, which yielded a voxel-wise map of t values reflecting brain areas where heightened BOLD activation covaried with SBP reactivity across individuals. The false-discovery rate procedure and a voxel-extent threshold of 20 voxels were used to correct voxel-wise P values across the entire brain volume.[23] Results are illustrated as color-scaled maps of t values in the Figure.

After initial brain imaging data analysis, we used 2-step hierarchical regressions to test whether the relationships between task-induced BOLD activation and blood pressure reactivity were independent of individual differences in task accuracy (percentage of correctly identified target words in the incongruent condition) and subjective ratings of task stress during the incongruent condition. The dependent variable for the 2-step regressions was either the SBP or diastolic blood pressure (DBP) change from baseline to the incongruent condition. The independent variables entered in step 1 were estimates of task accuracy and subjective ratings of stress for the incongruent condition. The independent variables in step 2 were the standardized BOLD activation values from all of the brain areas in which BOLD activation to the incongruent task condition correlated with blood pressure reactivity. These areas were defined in the correlation analyses described above; the specific peak voxel coordinates and spatial extents for all of the areas are in Table 2. The unique percentage of variance in blood pressure reactivity explained by the standardized BOLD activation values was evaluated by the ΔR^2 in step 2.

TABLE 2.   Brain Regions Where Heightened fMRI BOLD Activation Covaried With Greater SBP Reactivity to a Stroop Color-Word Interference Stressor

Side	Region	BA	MNI Coordinates			Voxels	*t* value
			x	y	z		
L	Insula		−48	6	12	347	5.50
L	Perigenual cingulate cortex	32	−9	48	−18	411	5.26
R	Posterior cingulate cortex/precuneus	31	30	−75	15	588	4.86
R	Lateral prefrontal cortex	9/10	30	42	27	29	3.97
L	Lateral prefrontal cortex	8/9	−33	30	36	50	3.70
L	Cerebellum		−18	−63	−15	63	3.99

Reported are left (L) and right (R) brain regions followed by their approximate Brodmann areas (BA) and peak-voxel coordinates in Montreal Neurological Institute (MNI) anatomical space; after MNI coordinates at right are the number of voxels defining the spatial extent of each region and associated *t* values for each peak voxel. Coordinates (x, y, and z) are in millimeters, where x=left (−) to right (+); y=anterior (+) to posterior (−); and z=superior (+) to inferior (−). All of the results met a whole-brain corrected statistical threshold of $P<0.05$ using the false-discovery error rate and an extent threshold of 20 voxels.

Results

Blood Pressure Reactivity

In the MRI session, SBP increased by an average of 13.41 mm Hg from baseline to the incongruent condition of the Stroop task (mean±SD: 129.94±14.58 versus 143.35±15.60 mm Hg; 95% CI of the increase: 10.70 to 16.12 mm Hg). DBP also increased by an average of 5.89 mm Hg (68.04±8.84 versus 73.92±8.57 mm Hg; 95% CI of the increase: 4.27 to 7.51 mm Hg). Despite postural and recording differences, the changes in blood pressure from baseline to the incongruent condition correlated across the laboratory and MRI sessions, suggesting that the Stroop task elicited moderately reliable individual differences in blood pressure reactivity (ΔSBP$_{Laboratory·MRI}$ $r=0.49$, $P<0.001$; ΔDBP$_{Laboratory·MRI}$ $r=0.58$, $P<0.001$).

Task Performance and Stress Ratings

In the MRI session, participants' mean accuracy at identifying the color of target words was 62.53% (SD: 16.38%) during the incongruent condition and 95.33% (SD: 5.33%) during the congruent condition of the Stroop task. Participants completed a comparable number of trials during the incongruent condition (mean: 62.30±13.71) as they did during the congruent condition (mean: 62.89±13.91). These findings confirm that the performance titration procedure for the incongruent condition successfully maintained accuracy at ≈60% and that both incongruent and congruent task conditions had comparable motor response demands. Using a 0 to 3 scale, participants rated the incongruent condition as more stressful than the congruent condition (mean: 2.39±0.65 versus 0.48±0.62; 95% CI of the difference: 1.69 to 2.14).

Task-Induced Regional Brain Activation

Compared with the congruent condition, the incongruent condition of the Stroop task increased the activity of the dorsolateral prefrontal cortex, anterior cingulate cortex, supplementary motor area, parietal cortex, occipital cortex, caudate, and cerebellum. For each of these areas, BOLD activity during the incongruent condition was greater than that of the congruent condition (Ps $_{false-discovery-rate\ corrected}<0.001$). Panels A and C of the Figure illustrate areas (coded in blue-green) in which the incongruent condition increased BOLD activity.

Relationships Between Task-Induced Brain Activation and Blood Pressure Reactivity

A larger increase in SBP from baseline to the incongruent condition of the Stroop task covaried with heightened activation in Brodmann area 24/32 of the perigenual cingulate cortex, extending spatially into area 10 of the orbital prefrontal cortex. A larger increase from baseline in SBP also covaried with heightened activation of the left anterior insula, the posterior cingulate cortex (extending from area 31 into the precuneus), the left and right lateral prefrontal cortex (spatially encompassing areas 8, 9, and 10), and the left cerebellum. Table 2 lists the Montreal Neurological Institute coordinates for the voxels within each region where there was a peak association between heightened activation and SBP reactivity.

The perigenual area in which heightened activation covaried with greater SBP reactivity was distinct from areas that were engaged by behavioral task performance of the incongruent Stroop task condition. Exceptions to this pattern of results were found for the left anterior insula and the remaining areas, where activation overlapped with both SBP reactivity and task performance. To illustrate, panels A and C of the Figure show (in red-yellow) brain areas where heightened BOLD activation covaried with an increase in SBP from baseline to the incongruent condition (defined herein as reactivity); adjacent panels B and D illustrate the strength of between-person covariation between activation of the perigenual cingulate cortex and anterior insula and SBP reactivity. A supplementary table and anatomical illustration of brain regions activated by the task and related to blood pressure reactivity at subthreshold levels is available at http://hyper.ahajournals.org.

Heightened BOLD activation of the perigenual and posterior cingulate cortex and anterior insula also covaried with a

TABLE 3.　Correlations Among fMRI BOLD Activation Values, Stroop Task Performance, Task Stress Ratings, and the Task-Induced Change (Δ) in SBP and DBP

Variables and Regions	1	2	3	4	5	6	7	8	9	10
1. ΔSBP										
2. ΔDBP	0.60*									
3. Task performance (% accuracy)	0.37†	0.26								
4. Task stress rating (0–3 scale)	−0.07	−0.12	−0.06							
5. Insula	0.64*	0.48*	0.40*	−0.12						
6. Perigenual cingulate cortex	0.62*	0.44*	0.27	−0.01	0.65*					
7. Posterior cingulate/precuneus	0.59*	0.33†	0.12	−0.03	0.50*	0.55*				
8. Right prefrontal cortex	0.51*	0.26	0.10	−0.17	0.37†	0.06	0.28			
9. Left prefrontal cortex	0.49*	0.15	0.13	−0.26	0.39*	0.36†	0.52*	0.37†		
10. Left cerebellum	0.52*	0.22	0.08	−0.10	0.59*	0.55*	0.36†	0.38*	0.35†	

Voxel coordinates for numbered brain regions (5 to 10) are provided in Table 2.

*$P<0.01$; †$P<0.05$.

larger increase in DBP from baseline to the incongruent condition of the Stroop task ($P<0.05$; Table 3). However, as indicated by the univariate correlations shown in Table 3, BOLD activation in other areas that covaried with SBP reactivity did not covary with DBP reactivity at a conventional level of statistical significance ($P<0.05$). Table 3 further shows that there were moderate and positive correlations in BOLD activation values across the perigenual and posterior cingulate cortex, bilateral prefrontal cortex, anterior insula, and cerebellum.

Task Performance, Stress Ratings, and Blood Pressure Reactivity

Two-step hierarchical regression analyses showed that heightened BOLD activation in the perigenual and posterior cingulate cortex, bilateral prefrontal cortex, anterior insula, and cerebellum during the incongruent condition covaried with both SBP and DBP reactivity, apart from individual differences in task accuracy and subjective ratings of task stress. In step 1, task accuracy and subjective stress ratings together accounted for 13.8% of the variance in SBP reactivity ($P=0.05$) and 8.8% of the variance in DBP reactivity ($P=0.15$). In step 2, higher standardized BOLD activation values from the perigenual and posterior cingulate cortex, bilateral prefrontal cortex, anterior insula, and cerebellum entered as a set uniquely accounted for additional variance in both SBP ($\Delta R^2=0.54$; $P<0.001$) and DBP ($\Delta R^2=0.27$; $P<0.05$) reactivity.

Supplementary univariate correlation analyses showed that BOLD activation values from the perigenual and posterior cingulate cortex, bilateral prefrontal cortex, anterior insula, and cerebellum did not correlate with resting SBP or DBP ($P>0.11$). Furthermore, neither SBP nor DBP reactivity correlated with other study variables, including BMI, number of years since menopause, and use of hormone replacement therapy (yes or no; $P>0.30$).

Discussion

Individuals who showed greater blood pressure reactivity to a standardized psychological stress task also showed heightened stressor-induced functional neural activation in areas of the perigenual and posterior cingulate, lateral prefrontal, and insular cortices, along with an area of the cerebellum. Moreover, the perigenual area in which heightened activation covaried with blood pressure reactivity was distinct from areas that were engaged by task performance. These findings suggest that there is some spatial dissociation between brain areas involved in supporting task-related performance and those mediating individual differences in blood pressure reactivity in this sample. Furthermore, the relationships between heightened functional neural activation and greater blood pressure reactivity persisted after accounting for the influences of task accuracy and subjective ratings of task stress, indicating a unique relationship between functional neural reactivity and blood pressure reactivity. Collectively, the present findings indicate that heightened stressor-induced activation of brain areas involved in peripheral cardiovascular control may partly account in for an individual's tendency to show exaggerated blood pressure reactivity.

We and others have demonstrated that acute psychological stressors evoke patterns of functional neural activation in cingulate, orbital prefrontal, insular, and even cerebellar areas that correlate with concurrent changes in autonomic and cardiovascular reactivity.[24–28] In previous neuroimaging studies, however, indicators of neural activation and concurrent changes in peripheral physiology have been examined largely on a within-person basis. As a result, the functional neural correlates of individual differences in cardiovascular reactivity to psychological stress have not yet been clearly defined.

In a preliminary study, we found that 8 individuals who were classified as high blood pressure reactors on 2 testing occasions showed heightened activation in the posterior cingulate cortex to a Stroop stressor as compared with 8 low reactors.[16] Replicating our preliminary findings, the present study of 46 separate individuals showed that heightened posterior cingulate activation covaried in a continuous fashion with greater blood pressure reactivity. The posterior cingulate may play a role in evaluating or monitoring the environment for self-relevant information that is appraised as emotionally salient.[29] The posterior cingulate may influence cardiovascular reactivity via reciprocal connections with areas of the anterior cingulate cortex, which are networked

with cell groups in the amygdala, thalamus, hypothalamus, midbrain periaqueductal gray, and brain stem.[8,10–13,15,24,30–32] Together with our preliminary results,[16] the present findings suggest that heightened stressor-induced posterior cingulate activation represents a functional neural correlate of exaggerated cardiovascular reactivity.

In addition to the posterior cingulate, heightened stressor-induced activation in other brain areas also covaried with greater blood pressure reactivity across individuals, including an area of the perigenual cingulate cortex that extended spatially into an adjacent area of the orbital medial prefrontal cortex (Brodmann area 10). This finding agrees with previous neuroimaging studies showing that stressor-induced changes in cardiovascular activity correlate within individuals with activation of the medial prefrontal cortex, particularly in the perigenual cingulate cortex.[26,27,33] Further extending previous results, stressor-induced activation of the perigenual cingulate and adjacent medial prefrontal cortex correlated with patterns of activation in other brain regions that also predicted greater blood pressure reactivity. These regions included those that may initiate and represent autonomic, neuroendocrine, and cardiovascular activity (anterior insula[15]); coordinate autonomic activity with somatic motor responses (cerebellum[34]); and support the cognitive and emotional processing of psychological stressors (lateral prefrontal cortex[10,30]). In line with previous speculations, it is possible the correlated patterns of heightened stressor-induced activation across these brain regions (summarized in Table 3) could account for greater blood pressure reactivity via functional interactions with subcortical and brain stem cell groups involved in cardiovascular control.[14,35]

We note, however, that we did not find associations between individual differences in blood pressure reactivity and stressor-induced neural activation in other brain regions known to be involved in stress-related physiological control, including medial temporal areas (eg, amygdala), medial forebrain areas (eg, hypothalamus), and midbrain and brain stem areas (eg, periaqueductal gray and medulla).[8] These null findings may be because of the methodologic difficulty of using fMRI to image activity in these relatively smaller areas, which are susceptible to even slight movement artifacts and magnetic field distortions because of their close proximity to air–tissue interfaces. Another possibility that should be tested in future work is that the forgoing brain areas may not be as strongly related to individual differences in stressor-induced blood pressure reactivity as are the cingulate, prefrontal, insular, and cerebellar areas identified in the present study.

We also recognize that we studied older postmenopausal women who were in good cardiovascular health. Additional work should attempt to replicate the present findings in more heterogeneous samples that include men. We do note, however, that in the present sample, stressor-induced neural activation and blood pressure reactivity were independent of other potential confounders, including BMI, number of years since menopause onset, and use of hormone therapy. Furthermore, the Stroop color-word task used in the present study elicited reliable individual differences in blood pressure reactivity across 2 testing contexts (laboratory and MRI environments) that differed in a number of ways (eg, in

posture and blood pressure monitoring methods). As such, this particular Stroop task may prove useful for testing whether stressor-related neural activation not only covaries with individual differences in blood pressure reactivity but also associated cardiovascular risk factors.

Perspectives

Exaggerated blood pressure reactivity to psychological stress is associated with preclinical atherosclerosis, as indicated by greater intima–media thickness and plaque in the carotid arteries[6,17,18] and by greater calcification in the coronary arteries.[36] Exaggerated blood pressure reactivity also predicts incident hypertension[4] and stroke.[5] Exaggerated blood pressure reactivity is thought to mediate the relationship among several environmental, genetic, and psychosocial factors and risk for cardiovascular disease.[3,37] Here, we provide novel evidence that heightened stressor-induced neural activation in a delimited set of brain systems is uniquely associated with exaggerated blood pressure reactivity. Our current work is testing whether this form of heightened activation is a neural phenotype by which psychological stress and other factors associated with exaggerated blood pressure reactivity may increase risk for atherosclerosis and other precursors to cardiovascular disease.

Disclosures

None.

References

1. Herd JA. Cardiovascular response to stress. *Physiol Rev*. 1991;71:305–330.
2. Folkow B. Physiological organization of neurohormonal responses to psychological stimuli: implications for health and disease. *Ann Beh Med*. 1993;15:236–244.
3. Krantz DS, Manuck SB. Acute psychophysiologic reactivity and risk of cardiovascular disease: a review and methodologic critique. *Psychol Bull*. 1984;96:435–464.
4. Matthews KA, Katholi CR, McCreath H, Whooley MA, Williams DR, Zhu S, Markovitz JH. Blood pressure reactivity to psychological stress predicts hypertension in the CARDIA study. *Circulation*. 2004;110:74–78.
5. Everson SA, Lynch JW, Kaplan GA, Lakka TA, Sivenius J, Salonen JT. Stress-induced blood pressure reactivity and incident stroke in middle-aged men. *Stroke*. 2001;32:1263–1270.
6. Jennings JR, Kamarck TW, Everson-Rose SA, Kaplan GA, Manuck SB, Salonen JT. Exaggerated blood pressure responses during mental stress are prospectively related to enhanced carotid atherosclerosis in middle-aged Finnish men. *Circulation*. 2004;110:2198–2203.
7. Treiber FA, Kamarck T, Schneiderman N, Sheffield D, Kapuku G, Taylor T. Cardiovascular reactivity and development of preclinical and clinical disease states. *Psychosom Med*. 2003;65:46–62.
8. Benarroch EE. *Central Autonomic Network: Functional Organization and Clinical Correlations*. Armonk, NY: Futura Publishing Company; 1997.

9. Spyer KM. Central nervous control of the cardiovascular system. In: Mathias CJ, Bannister R, eds. *Autonomic Failure: A Textbook of Clinical Disorders in The Autonomic Nervous System*. Oxford, United Kingdom: Oxford University Press; 1999:45–55.

10. Barbas H, Saha S, Rempel-Clower N, Ghashghaei T. Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. *BMC Neurosci*. 2003;4:25.

11. Buchanan SL, Powell DA. Cingulothalamic and prefrontal control of autonomic function. In: Vogt BA, Gabriel M, eds. *Neurobiology of the Cingulate Cortex and Limbic Thalamus: A Comprehensive Handbook*. Boston, MA: *Birkhauser*; 1993:381–414.

12. Loewy AD, Spyer KM. *Central Regulation of Autonomic Functions*. Oxford, United Kingdom: Oxford University Press; 1990.

13. Neafsey EJ. Prefrontal cortical control of the autonomic nervous system: anatomical and physiological observations. *Prog Brain Res*. 1990;85: 147–165.

14. Soufer R, Arrighi JA, Burg MM. Brain, behavior, mental stress, and the neurocardiac interaction. *J Nucl Cardiol*. 2002;9:650.

15. Verberne AJ, Owens NC. Cortical modulation of the cardiovascular system. *Prog Neurobiol*. 1998;54:149–168.

16. Gianaros PJ, May JC, Siegle GJ, Jennings JR. Is there a functional neural correlate of individual differences in cardiovascular reactivity? *Psychosom Med*. 2005;67:31–39.

17. Gianaros PJ, Bleil ME, Muldoon MF, Jennings JR, Sutton-Tyrrell K, McCaffery JM, Manuck SB. Is cardiovascular reactivity associated with atherosclerosis among hypertensives? *Hypertension*. 2002;40:742–747.

18. Kamarck TW, Everson SA, Kaplan GA, Manuck SB, Jennings JR, Salonen R, Salonen JT. Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men: findings from the Kuopio Ischemic Heart Disease Study. *Circulation*. 1997;96:3842–3848.

19. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. *N Engl J Med*. 1989;321:641–646.

20. Dischinger P, DuChene AG. Quality control aspects of blood pressure measurements in the Multiple Risk Factor Intervention Trial. *Control Clin Trials*. 1986;7:137S–157S.

21. Stenger VA, Boada FE, Noll DC. Three-dimensional tailored RF pulses for the reduction of susceptibility artifacts in T2*-weighted functional MRI. *Magn Reson Med*. 2000;44:525–531.

22. Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: A general approach. *Hum Brain Mapp*. 1995;2:189–210.

23. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage*. 2002;15:870–878.

24. Critchley HD. Neural mechanisms of autonomic, affective, and cognitive integration. *J Comp Neurol*. 2005;493:154–166.

25. Critchley HD, Mathias CJ, Josephs O, O'Doherty J, Zanini S, Dewar BK, Cipolotti L, Shallice T, Dolan RJ. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain*. 2003; 126:2139–2152.

26. Gianaros PJ, Derbyshire SW, May JC, Siegle GJ, Gamalo MA, Jennings JR. Anterior cingulate activity correlates with blood pressure during stress. *Psychophysiology*. 2005;42:627–635.

27. Gianaros PJ, Van Der Veen FM, Jennings JR. Regional cerebral blood flow correlates with heart period and high-frequency heart period variability during working-memory tasks: implications for the cortical and subcortical regulation of cardiac autonomic activity. *Psychophysiology*. 2004;41:521–530.

28. Soufer R, Bremner JD, Arrighi JA, Cohen I, Zaret BL, Burg MM, Goldman-Rakic P. Cerebral cortical hyperactivation in response to mental stress in patients with coronary artery disease. *Proc Natl Acad Sci U S A*. 1998;95:6454–6459.

29. Maddock RJ. The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain. *Trends Neurosci*. 1999;22: 310–316.

30. Ongur D, Ferry AT, Price JL. Architectonic subdivision of the human orbital and medial prefrontal cortex. *J Comp Neurol*. 2003;460:425–449.

31. Vogt BA, Laureys S. Posterior cingulate, precuneal and retrosplenial cortices: cytology and components of the neural network correlates of consciousness. *Prog Brain Res*. 2005;150:205–217.

32. Vogt BA, Vogt L, Laureys S. Cytology and functionally correlated circuits of human posterior cingulate areas. *NeuroImage*. 2006;29: 452–466.

33. Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ. Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. *J Physiol*. 2000;523:259–270.

34. Cavdar S, San T, Aker R, Sehirli U, Onat F. Cerebellar connections to the dorsomedial and posterior nuclei of the hypothalamus in the rat. *J Anat*. 2001;198:37–45.

35. Lovallo WR, Gerin W. Psychophysiological reactivity: mechanisms and pathways to cardiovascular disease. *Psychosom Med*. 2003;65:36–45.

36. Matthews KA, Zhu S, Tucker DC, Whooley MA. Blood pressure reactivity to psychological stress and coronary calcification in the Coronary Artery Risk Development in Young Adults Study. *Hypertension*. 2006; 47:391–395.

37. Williams RB, Marchuk DA, Gadde KM, Barefoot JC, Grichnik K, Helms MJ, Kuhn CM, Lewis JG, Schanberg SM, Stafford-Smith M, Suarez EC, Clary GL, Svenson IK, Siegler IC. Central nervous system serotonin function and cardiovascular responses to stress. *Psychosom Med*. 2001; 63:300–305.

Hypertension

American Heart Association®

Heightened Functional Neural Activation to Psychological Stress Covaries With Exaggerated Blood Pressure Reactivity

Peter J. Gianaros, J. Richard Jennings, Lei K. Sheu, Stuart W.G. Derbyshire and Karen A. Matthews

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/49/1/134

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2006/11/13/01.HYP.0000250984.14992.64.DC3