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

A cute 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. These stressor-induced physiological changes are thought to provide metabolic support for adaptive behavior (eg, the “fight-or-flight” response). Some individuals, however, have a tendency to show exaggerated rises in blood pressure that exceed the metabolic demands of psychological stressors. Such exaggerated stressor-induced blood pressure reactions predict increased risk for hypertension, stroke, and preclinical atherosclerosis. 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. 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), apart from the influences of task performance and subjective ratings of task stress.
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. 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) or excessive fMRI movement artifacts (n=2). 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, 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 Reference16 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, In Vivo 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 Sigma 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 T1*-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). 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). For preprocessing, T1*-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 T1*-weighted images were coregistered to the

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.04</td>
<td>1.35</td>
</tr>
<tr>
<td>No. of school years completed</td>
<td>15.46</td>
<td>1.59</td>
</tr>
<tr>
<td>No. of years since menopause</td>
<td>15.66</td>
<td>2.32</td>
</tr>
<tr>
<td>Alcoholic beverages consumed per week</td>
<td>2.46</td>
<td>3.77</td>
</tr>
<tr>
<td>Height, in</td>
<td>63.26</td>
<td>0.09</td>
</tr>
<tr>
<td>Weight, lb</td>
<td>154.12</td>
<td>22.33</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.17</td>
<td>4.24</td>
</tr>
<tr>
<td>Resting SBP, mm Hg</td>
<td>125.35</td>
<td>11.74</td>
</tr>
<tr>
<td>Resting DBP, mm Hg</td>
<td>74.52</td>
<td>6.80</td>
</tr>
</tbody>
</table>
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 T2*-weighted images were then smoothed with a 10-mm full-width-at-half-maximum isotropic Gaussian kernel. Before analysis, T2*-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 outside the criteria 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 analysis, 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 R² in step 2.
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±16.12 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 (ΔSBPbaseline-MRI \( r = 0.49 \), \( P < 0.001 \); ΔDBPbaseline-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 \( \approx 60\% \) 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 (\( P \text{false-discovery-rate corrected}<0.001 \)). Panels A and C of the Figure show 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 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
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. In step 2, higher standardized BOLD activation in other areas that covaried with SBP 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. 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. 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. 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.\textsuperscript{8,10–13,15,24,30–32} Together with our preliminary results,\textsuperscript{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.\textsuperscript{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\textsuperscript{15}); coordinate autonomic activity with somatic motor responses (cerebellum\textsuperscript{14}); and support the cognitive and emotional processing of psychological stressors (lateral prefrontal cortex\textsuperscript{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.\textsuperscript{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).\textsuperscript{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 foregoing 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\textsuperscript{8,17,18} and by greater calcification in the coronary arteries.\textsuperscript{36} Exaggerated blood pressure reactivity also predicts incident hypertension\textsuperscript{4} and stroke.\textsuperscript{5} Exaggerated blood pressure reactivity is thought to mediate the relationship among several environmental, genetic, and psychosocial factors and risk for cardiovascular disease.\textsuperscript{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.

**Acknowledgments**

We thank Michael Eddy for his technical assistance and Leslie A. Mitrik for testing participants. Dr Richard Lane provided constructive comments on a draft of this article.

**Sources of Funding**

Research support was provided by the Pittsburgh Mind-Body Center (National Institutes of Health grant HL 076852/076858), by National Institutes of Health grant MH K01 070616-03, and by National Institutes of Health grant HL 28266.

**Disclosures**

None.

**References**


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

Hypertension. 2007;49:134-140; originally published online November 13, 2006; doi: 10.1161/01.HYP.0000250984.14992.64

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/