

# Brain Correlates of Mental Stress-Induced Myocardial Ischemia

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## ABSTRACT

**Objective:** Coronary artery disease (CAD) is a major cause of morbidity and mortality, and despite important advances in our understanding of this disorder, the underlying mechanisms remain under investigation. Recently, increased attention has been placed on the role of behavioral factors such as emotional stress on CAD risk. Brain areas involved in memory and the stress response, including medial prefrontal cortex, insula, and parietal cortex, also have outputs to the peripheral cardiovascular system. The purpose of this study was to assess the effects of mental stress on brain and cardiac function in patients with CAD.

**Methods:** CAD patients ( $N = 170$ ) underwent cardiac imaging with [Tc-99m] sestamibi single-photon emission tomography at rest and during a public speaking mental stress task. On another day, they underwent imaging of the brain with [O-15] water positron emission tomography (PET) during mental stress (arithmetic and public speaking) and control conditions.

**Results:** Patients with mental stress-induced myocardial ischemia showed increased activation with stress in anterior cingulate, inferior frontal gyrus, and parietal cortex ( $p < .005$ ). This was seen with both arithmetic stress and public speaking stress. Arithmetic stress was additionally associated with left insula activation, and public speaking with right pre/postcentral gyrus and middle temporal gyrus activation ( $p < .005$ ).

**Conclusions:** These findings suggest that mental stress-induced myocardial ischemia is associated with activation in brain areas involved in the stress response and autonomic regulation of the cardiovascular system. Altered brain reactivity to stress could possibly represent a mechanism through which stress leads to increased risk of CAD-related morbidity and mortality.

**Key words:** cardiovascular disease, depressive disorders, PTSD, stress.

## INTRODUCTION

Coronary artery disease (CAD) is associated with considerable morbidity and represents the leading cause of mortality worldwide (1). Traditional risk factors, such as smoking, diabetes, and hypertension, have only been able to explain a portion of the risk for CAD. In an effort to reduce the prevalence of this disorder, other potentially modifiable risk factors have been examined, including behavioral factors.

Emotional factors, such as anger and stress sensitivity, are increasingly recognized as potential contributors to CAD (2–10). For example, anger can trigger acute episodes of acute coronary syndrome (ACS) secondary to increased hemodynamic responses (11–14). Other factors may play a role in the mechanism of anger-provoked ACS, including effects on platelet function and cardiac conductivity (4,15–17). These effects are likely mediated by brain areas involved in both emotion and cardiovascular regulation, such as the anterior cingulate (18).

A number of studies showed that acute psychological stress can induce myocardial ischemia (MSI) in patients with CAD (19–34). An increase in CAD is seen in patients with stress-related mental disorders, including major depression (35–37) and posttraumatic stress disorder (PTSD) (4,38). Negative affect, which is commonly seen in depression, is associated with an increased perception of anginal chest pain (39). Many CAD patients experience asymptomatic episodes of stress-induced myocardial ischemia on a daily basis (40–43). Mental stress-induced myocardial ischemia can occur in patients without exercise-induced myocardial ischemia and is not consistently related to atherosclerotic CAD (22,25,26,28–30,33,44–48). MSI

AA = African American, ACS = acute coronary syndrome, BMI = body mass index, CAD = coronary artery disease, MSI = mental stress ischemia, PET = positron emission tomography, PTSD = posttraumatic stress disorder, SPECT = single photon emission tomography

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is twice as common in women younger than 50 years than similar aged men (28), is more common in patients with depression (49), and is associated with increased long-term risk for adverse cardiac events with similar effect size as exercise-induced myocardial ischemia (30,50–56).

Mechanisms of MSI remain unclear. One idea is that an increase in stress-induced vasoconstriction mediates MSI. Stress also activates inflammatory pathways, and an increase in inflammation has been associated with coronary artery vasoconstriction, as seen in Kounis syndrome (57). Mental stress must, however, act through the brain to induce myocardial ischemia, whether it is mediated by inflammatory, sympathetic, or other responses (17,23,58,59); however, the mechanisms by which this occurs are not known. Brain areas involved in memory, emotion, and peripheral cardiovascular regulation include the medial prefrontal cortex, insula, and parietal cortex (17,60,61). We hypothesized that patients with MSI would show stress-induced changes in brain areas involved in the regulation of memory, emotion, and/or peripheral cardiovascular responses to stress, including medial prefrontal cortex, insula, dorsolateral prefrontal cortex, and parietal cortex. Understanding brain mechanisms in MSI may lead to new treatment interventions in CAD.

## METHODS

### Study Sample

Patients between the ages of 30 and 79 years with known CAD ( $N = 186$ ) from the Mental Stress Ischemia Prognosis Study were included in the study. Mental Stress Ischemia and Prognosis Study patients were recruited from Emory University Hospital, Grady Memorial Hospital, and the Atlanta Veterans Administration Medical Center from September 2010 to September 2016 (56). CAD was defined based on a previous cardiac catheterization, showing atherosclerosis, history of prior myocardial infarction, a history of percutaneous coronary intervention or coronary artery bypass grafting at least 1 year before the study, or a positive nuclear stress test. Patients were excluded if they had had a recent ACS or decompensated congestive heart failure within 1 week of the enrollment visit, pregnancy based on pregnancy testing, systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg on the day of the test, a history based on the Structured Clinical Interview for the Diagnostic and Statistical Manual IV of a severe mental disorder including schizophrenia, psychotic depression, bipolar disorder, or alcohol or substance dependence in the past year, history of loss of consciousness of more than 1 minute, history of neurological disorder, such as dementia, stroke, or Parkinson disease, or contraindications to regadenoson administration. Beta-adrenergic antagonists were held for 24 hours and calcium channel blockers and nitrates for at least 12 hours before the stress test. Patients for whom withholding medications was considered unsafe were excluded. All patients provided written informed consent, and the study was approved by the Emory University Investigational Review Board.

### Psychometric Assessment

All patients were assessed with a number of psychometric instruments, including the Beck Depression Inventory (BDI), a reliable and validated self-report measure of depressive symptoms (62). Information about medications and other clinical data was obtained through questionnaires and medical chart review. The Subjective Units of Distress Scale was used to assess stress before and after the stress procedures. Psychiatric diagnosis was assessed using the Structured Interview for the Diagnostic and Statistical Manual IV (63).

## Measurement of Vasoconstriction Using Peripheral Arterial Tonometry

The EndoPAT Peripheral Arterial Tonometry (PAT) device (Itamar-Medical, Israel) was used to measure peripheral vascular reactivity to stress. The device measured finger pulse wave amplitude with a probe using a robust modified form of volume plethysmography as a means of estimating pulsatile arterial volume changes independently of venous pulsations/pooling (64). Pressure changes accompanying peripheral volume changes are fed to a personal computer by which the signal is bandpass filtered (0.3–30 Hz), amplified, displayed, and stored. After eliminating areas of artifact, microvascular vasoconstriction was measured by pulse wave amplitude at stress (mean during 4 stress tasks) compared with baseline rest (mean during 4 control tasks). We have found PAT measurement of stress-induced vasoconstriction to be highly reproducible in our laboratory (65).

## Mental Stress Testing

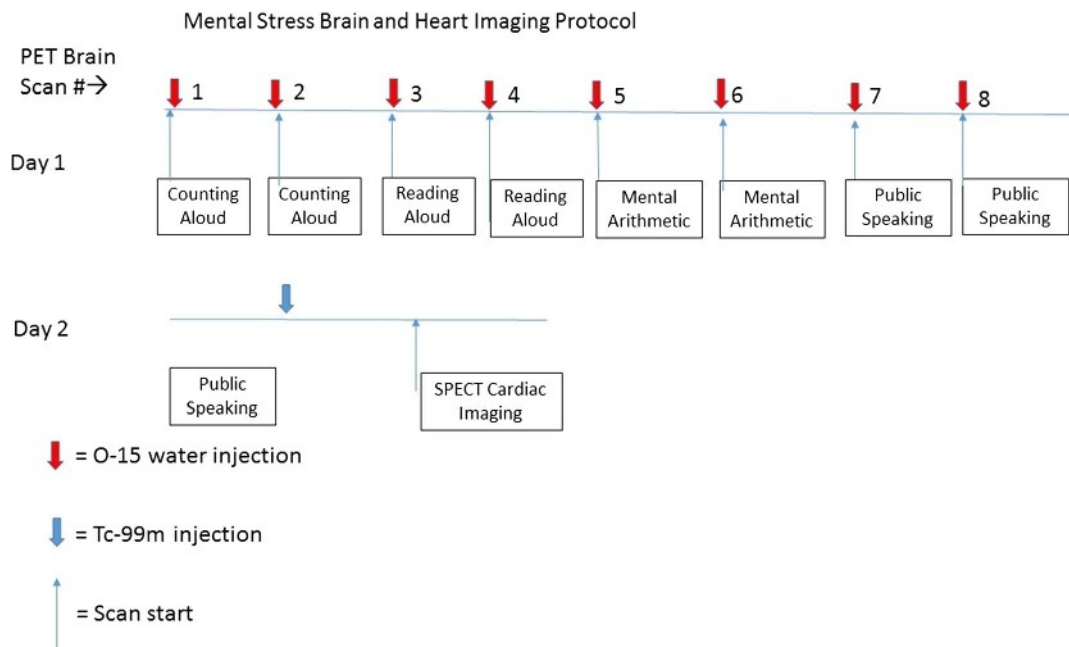
Participants underwent mental stress testing in conjunction with imaging of the heart and brain. Participants initially underwent cardiac imaging of the heart (described hereinafter) at rest and during a public speaking task. On a separate day, participants returned for imaging of the brain during two mental stress tasks. There were four conditions, two control and two stress conditions (mental arithmetic and public speaking), and participants underwent scanning of the brain twice for each condition, for a total of eight brain scans (Fig. 1). Mental stress testing was performed by trained staff using mental arithmetic and public speaking. First, participants were asked to count out loud for the mental arithmetic control condition for two scans and then to read a paragraph out loud for the public speaking control for two scans. For the mental arithmetic stress condition, they were asked to perform a series of increasingly complicated mathematical calculations under time pressure, including addition, subtraction, multiplication, and division, whereas they received negative feedback on their performance from a staff member performing the test who was wearing a white coat. For the public speaking mental stress task, patients listened to a scripted message with instructions for the mental stress task. For the cardiac imaging day (which occurred first), participants were given a situation where an elderly relative was being mistreated in a nursing home, and they had to meet with the administrator to try and rectify the situation. For the brain imaging day, participants were given two stressful situations, one involving a long-term house guest who had overstayed her welcome and the other an uncomfortable situation in which an elderly sister was unfairly hit while driving in a parking lot. They were then asked to prepare and give a speech for each situation that was 2 minutes in duration. They were told the speech would be evaluated for content.

## Cardiac Imaging at Rest and With Mental Stress

Participants underwent cardiac single-photon emission computed tomography (SPECT) imaging of the heart on a separate day for assessment of myocardial perfusion at rest and with mental stress. For the rest image, they received 10–14 mCi of [Tc-99m] sestamibi intravenously. Thirty to 40 minutes later resting SPECT images of the heart were obtained at rest. Participants then underwent a public speaking task (nursing home scenario) after which they were injected with 10–14 mCi [Tc-99m] sestamibi at the time of peak stress followed in 30–40 minutes by SPECT imaging of the heart with mental stress. We have found these methods of measuring mental stress-induced myocardial ischemia to be highly reproducible (65).

## Brain Imaging With Mental Stress

Patients underwent high-resolution positron emission tomography imaging of the brain in conjunction with control and mental stress tasks. High-resolution positron emission tomography imaging of the brain was performed with the high-resolution research tomograph (Siemens, Inc, Erlangen, Germany) (66). This device has 2-mm spatial resolution and significantly higher sensitivity than conventional PET cameras (66,67).



**FIGURE 1.** Brain and cardiac imaging with mental stress protocol. Participants underwent 8 brain scans after injection of radio-labeled water in conjunction with exposure to control and mental stress conditions. Control conditions involving counting out loud for 2 scans, then reading a neutral paragraph out loud for 2 scans. Mental stress conditions included performing a series of increasingly complicated mathematical calculations under time pressure for 2 scans, followed by a public speaking task in which patients were given 2 stressful situations and then asked to prepare and give a speech for each situation that was 2 minutes in duration. Color image is available only in online version ([www.psychosomaticmedicine.org](http://www.psychosomaticmedicine.org)).

Blood pressure and heart rate were recorded at 5-minute intervals during the resting phase and at 1-minute intervals during the stress phases using an automatic oscillometric device.

Participants underwent eight PET scans of the brain in conjunction with control and stressful tasks. During each scan, radio-labeled water ( $\text{H}_2^{15}\text{O}$ ), produced in an on-site cyclotron, was injected for measurement of brain blood flow. During the first four scans, patients were asked to count out loud (2 scans) and talk about a neutral event (2 scans). The last four scans were performed during an acute mental stress challenge involving mental arithmetic (2 scans) and public speaking (2 scans). All sessions lasted for 2 minutes and 20 mCi of O-15 water were injected 10 seconds after each task started. A physician was present during the study, and electrocardiogram and vital signs were continuously monitored.

Of the 186 patients who started the study, 170 were able to finish the protocol with usable data. Reasons for noncompletion included failure to complete the PET imaging procedure due to elevated blood pressure during the procedure ( $n = 1$ ), claustrophobia in the scanner ( $n = 3$ ), failure to obtain venous access ( $n = 3$ ), inability to lie flat or remain on the scanner table due to pain or physical limitations ( $n = 4$ ), and failure of image acquisition or lost or corrupted image data ( $n = 5$ ).

### Image Analysis

Myocardial perfusion images were interpreted by two experienced readers blinded to the condition and without prior knowledge of the medical history or angiographic data. Discrepancies in interpretation of SPECT images were resolved by consensus. Rest and stress images were visually compared for the number and severity of perfusion defects using a 17-segment model (68). Each segment was scored from 0 to 4, with 0 being normal uptake, 1 possibly normal perfusion, 2 definitely abnormal perfusions, 3 severe perfusion defects, and 4 no perfusions. A sum rest score was calculated by adding up the perfusion scores across the 17 myocardial segments. Sum stress scores were calculated by adding up the perfusion

scores across segments during stress and subtracting out sum rest scores. Ischemia was defined as a new myocardial perfusion defect with a score of 2 or higher in any segment, or worsening of a pre-existing impairment of at least 2 points in a single segment, or worsening of at least 1 point in 2 or more contiguous segments (68).

PET images of the brain were realigned and analyzed using statistical parametric mapping (SPM8) (69) and methods previously described (70). Images were realigned to the first scan of the study session. The mean concentration of radioactivity in each scan was obtained as an area-weighted sum of the concentration of each slice and was adjusted to a nominal value of 50 ml/min per 100 g. The data underwent transformation into a common anatomical space and were smoothed with a three-dimensional Gaussian filter to 8-mm full width half max. A post hoc analysis involved placement of circular regions of interest over brain areas implicated in the statistical parametric mapping analysis to assess relationship between brain activation with stress and myocardial perfusion.

### Statistical Analysis

Analysis of variance was used to compare baseline demographic and risk factors and sum rest and stress scores obtained from cardiac SPECT images between CAD patients with and without MSI. Brain regional blood flow was compared for mental stress and neutral conditions. Statistical analyses yielded image data sets in which the values assigned to individual voxels correspond to the  $t$  statistic of the difference in brain blood flow between conditions. Statistical images were displayed with values of  $z$  score units. A threshold  $z$  score of 2.68 ( $p < .005$ , uncorrected) was used to define significant activation within voxels. This value has been shown to minimize the possibility of both type 1 and type 2 errors in brain imaging studies (71,72). In addition, a minimum cluster of 11 voxels was used to define areas of significant activation within hypothesized areas (medial prefrontal, inferior frontal, and parietal cortex and insula). Location of areas of activation was identified as the distance from the anterior commissure in

**TABLE 1.** Demographic and Risk Factors for CAD Patients With and Without Mental Stress Ischemia

	MSI- (n = 125, 74%)	MSI+ (n = 45, 26%)
Age	62 (8 SD)	63 (9 SD)
Sex	45 F/80 M	9 F/36 M
Race	38% AA/59% white/3% Asian	31% AA/65% white/2% Asian/2% NA
BMI, kg/m <sup>2</sup>	30 (6 SD)	30 (6 SD)
BDI score	13 (11 SD)	11 (11 SD)
Hypertension	76%	76%
Dyslipidemia	81%	87%
Diabetes	34%	33%
Smoking (current)	13%	7%
Smoking (lifetime)	63%	67%
Percentage of patients taking:		
Antidepressants	36%	22%
ACE inhibitors	42%	47%
Angiotensin receptor inhibitors	14%	18%
Diuretics	31%	29%
Vasodilators	12%	7%
Anxiolytics	6%	7%
$\beta$ -Blockers	77%	73%
Statins	89%	83%

MSI = mental stress ischemia; F = female; M = male; AA = African American; NA = Native American; BMI = body mass index; BDI = Beck Depression Inventory; ACE = angiotensin converting enzyme.

millimeters, with *x*, *y*, and *z* coordinates, transformed from Montreal Neurological Institute coordinates to those of the Talairach stereotaxic atlas, a commonly used atlas for the expression of stereotaxic coordinates (73).

## RESULTS

There were no significant differences between patients with CAD with and without mental stress ischemia (MSI) for any demographic or risk factors, including age, sex, race, depressive symptoms, body

mass index (BMI), or history of smoking, diabetes, hypertension, or dyslipidemia (Table 1). The groups also showed similar patterns for use of medications including vasodilators, angiotensin receptor blocker, angiotensin converting enzyme inhibitors, diuretics and  $\beta$ -blockers (Table 1).

Participants showed increased heart rate, blood pressure, and subjective distress during the cardiac imaging stress compared with the brain imaging stress. As measured by the delta of increase

**TABLE 2.** Areas of Increased Activation During Mental Arithmetic Stress in Patients With Mental Stress-Induced Myocardial Ischemia Compared With Non-MSI Patients

Z Score	Voxel Number	Talairach Coordinates			Brain Region	Brodmann's Area
		<i>x</i>	<i>y</i>	<i>z</i>		
6.43	8112	-6	16	43	L. Medial frontal gyrus	6
6.10		48	30	24	R. Middle frontal gyrus	46
6.08		-4	40	20	L. Anterior cingulate	32
5.31	208	50	-41	41	R. Inferior parietal lobule	40
4.26		61	-49	28	R. Supramarginal gyrus	40
3.49		57	-45	35	R. Supramarginal gyrus	40
5.28	481	-32	21	-5	L. Inferior frontal gyrus	47
4.38		-36	17	-12	L. Inferior frontal gyrus	47
4.04		-40	16	7	L. Insula	13
4.03	50	-57	-33	-4	L. Middle temporal gyrus	
3.67	27	-48	-47	36	L. Inferior parietal lobule	40
3.45	72	0	43	3	Anterior cingulate	
2.91		8	50	-3	R. Anterior cingulate	10
3.16	15	34	-83	-23	R. Middle temporal gyrus	22

$z > 2.68$ ,  $p < .005$ .

over baseline, there was an increase in heart rate (11 (9 SD) versus 3 (4 SD),  $p < .001$ ), systolic blood pressure (25 (17 SD) versus 8 (9 SD),  $p < .001$ ), and subjective distress as measured with the Subjective Units of Distress Scale (10 (20 SD) versus 2 (29 SD),  $p < .001$ ), on the cardiac day compared with the brain imaging day. There was no difference in peripheral vasoconstriction, however, as measured with PAT for the cardiac versus brain imaging day (0.72 (0.35 SD) versus 0.74 (0.45 SD),  $p = .78$ ).

Patients with MSI compared with CAD patients without MSI had an increase in mean myocardial perfusion defects at rest as measured by the summed rest scores (8 (5 SD) versus 6 (5 SD),  $p = .016$ ) and an increase in mental stress-induced myocardial ischemia as measured with the summed stress scores (4 (3 SD) versus 2 (2 SD),  $p < .001$ ).

When the group of CAD patients was looked at as a whole, there was increased activation with stress in the inferior frontal gyrus and parietal cortex (inferior and superior parietal lobules). Decreased activation was seen in all patients in the pre- and postcentral gyrus, cerebellum, fusiform gyrus, and lingual gyrus. Both activations and deactivations were seen in different parts of the medial frontal gyrus and superior temporal gyrus in the group as a whole.

When MSI+ patients were compared with MSI-, the former had increased activations during stress in the parietal cortex (inferior parietal lobule and supramarginal gyrus), middle temporal gyrus and anterior cingulate (Tables 2, 5), and decreased activation in the cerebellum, cingulate, and medial frontal gyrus (Tables 3, 4). In addition to the brain areas listed previously, during arithmetic stress, MSI+ patients also had increased activation in the left insula, medial frontal, inferior, and middle frontal gyrus (Fig. 2, Table 2). During speech stress, there was additional activation in right pre- and postcentral gyrus and posterior cingulate (Table 5, Fig. 3). There were no significant correlations between resting myocardial perfusion and brain activation with stress in anterior cingulate, parietal cortex, amygdala, hippocampus, orbitofrontal, medial prefrontal, lingual, or fusiform gyrus in the MSI+ patients.

## DISCUSSION

This study showed that CAD patients with mental stress-induced ischemia (MSI) compared with those without MSI had increased activation in the medial frontal gyrus, anterior cingulate, inferior frontal gyrus, and parietal cortex (including inferior parietal lobule and supramarginal gyrus), brain areas involved in memory, emotion, and perception of the self in time and space. Activation in these areas was seen with both mental arithmetic and public speaking stress. Mental arithmetic additionally activated the insula, an important output to regulation of peripheral cardiovascular responses to stress (61). Public speaking, on the other hand, further activated pre- and postcentral gyrus (motor function and sensation) and middle temporal gyrus (auditory function). MSI was also associated with decreased activation in cerebellum, cingulate, and medial frontal gyrus. Consistent with previous reports of increased resting and mental stress-induced myocardial perfusion defects (74) and increased cardiovascular reactivity to mental stress (40) in MSI+ patients, in the current study CAD patients with MSI had an increase in both resting and stress-induced myocardial perfusion defects compared with CAD patients without MSI, and we have previously reported an increase in mental stress-induced heart rate and blood pressure in this sample in the MSI+ versus MSI- patients (75). There was no relationship, however, between baseline myocardial perfusion defects in MSI+ patients and brain activation with stress in any of these regions.

In patients with MSI, mental stress was associated with increased activation in the parietal lobe, including both supramarginal gyrus and inferior parietal lobule. The parietal lobe modulates perception of the self in space and time, perception of contextual cues, and visuospatial memory (76–80) in addition to modulation of peripheral cardiovascular responses to stress (81). This brain area plays a key role in increased awareness and hypervigilance during threat or attack (76,82). Studies have also implicated this region in stress-related psychiatric disorders (83) and risk for cardiovascular disease (84). Our findings suggest increased parietal cortical response to stress could underlie MSI.

**TABLE 3.** Areas of Decreased Activation During Mental Arithmetic Stress in Patients With Mental Stress-Induced Myocardial Ischemia Versus Non-MSI Patients

Z Score	Voxel Number	Talairach Coordinates			Brain Region	Brodmann's Area
		x	y	z		
4.02	33	-22	-71	-19	Cerebellum	
3.57	31	-44	26	6	Inferior frontal gyrus	13
3.51	20	24	-69	-20	Cerebellum	
3.44	16	-12	14	38	Cingulate gyrus	32
3.23	16	-16	39	37	Superior frontal gyrus	9
3.21	11	10	6	42	Cingulate gyrus	24
3.19	19	0	23	30	Cingulate gyrus	32
3.16	13	-10	32	24	Cingulate gyrus	32
3.12	15	2	42	29	Medial frontal gyrus	9
2.96	25	-36	45	0	R. inferior frontal gyrus	10
2.91	13	-50	9	24	L. inferior frontal gyrus	44

$z > 2.68$ ,  $p < .005$ .



**TABLE 4.** Areas of Decreased Activation During Speech Mental Stress in Patients With Mental Stress–Induced Myocardial Ischemia Versus Non-MSI Patients

Z Score	Voxel Number	Talairach Coordinates			Brain Region	Brodmann's Area
		x	y	z		
7.14	107	22	−65	−13	Cerebellum	
6.82	395	−55	0	4	Superior temporal gyrus	22
5.83		−51	−20	18	Insula	40
5.68		−46	−8	−11	L. sup. temporal gyrus	21
6.71	165	40	−4	−2	Insula	
6.42		51	−5	11	Precentral gyrus	43
5.35		57	1	11	Precentral gyrus	6
5.66	26	−42	−16	−5	Insula	13
5.33	34	50	−73	9	Middle temporal gyrus	39
4.49		42	−79	11	Middle occipital gyrus	19
3.04		48	−69	22	Middle temporal gyrus	39
5.09	21	46	−10	−5	Insula	22
4.87	142	−20	−59	−21	Cerebellum	
4.42		−20	−73	−15	Cerebellum	
4.33		−12	−62	−26	Cerebellum	
4.32	19	−51	−29	12	Superior temporal gyrus	41
3.04		−51	−23	7	Superior temporal gyrus	41
3.84	30	4	44	−17	Medial frontal gyrus	11
2.60		−4	46	−13	Medial frontal gyrus	11
3.84	13	57	−35	29	Inferior parietal lobule	40
3.37		65	−30	29	Inferior parietal lobule	40
3.63	35	65	−6	26	Precentral gyrus	6
3.50		65	−16	28	Postcentral gyrus	1
3.48	23	−6	−23	45	Paracentral lobule	31
3.24	23	−4	−2	41	Cingulate gyrus	24

$z > 2.68, p < .005$ .

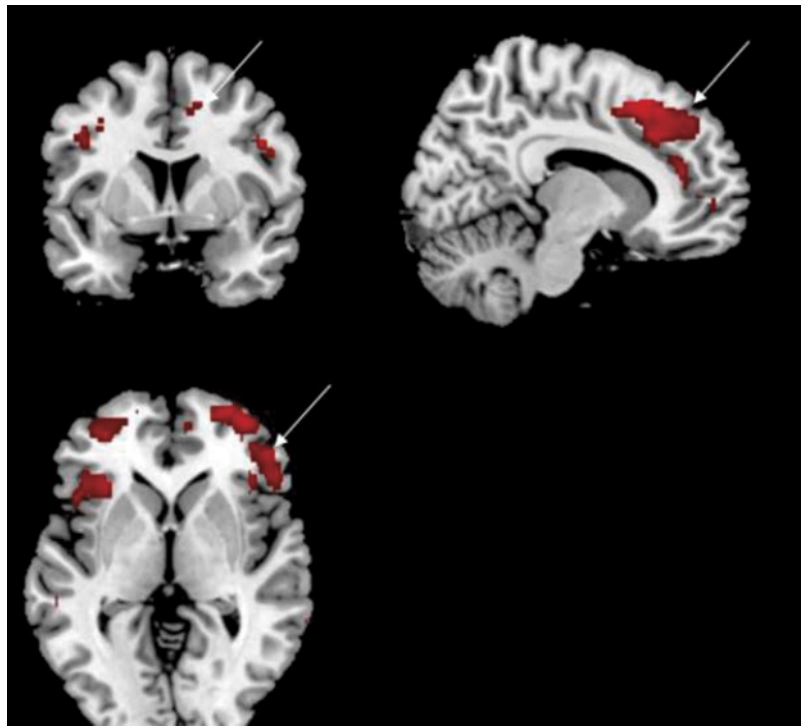
The inferior frontal gyrus, which was also activated with stress in the MSI+ patients, is involved in processes that are relevant to stress, including regulation of attention and outcome expectancies (80). A recent meta-analysis of brain imaging studies in humans showed that the inferior frontal gyrus and anterior insula were the only two brain areas that consistently activate with both physiological and psychological stressors (85). The inferior frontal gyrus, which has connections to the parietal lobe, in conjunction with parietal lobule could mediate a heightening of activity in brain areas involved in perception and cognition during stress.

The medial prefrontal cortex (anterior cingulate) was activated with stress in MSI patients. This area is involved in the modulation of emotion, problem solving, selective attention, and other higher cognitive functions (86–89). It also works in tandem with the insula to regulate peripheral autonomic activity (90,91) and is responsible for activation of peripheral cortisol and sympathetic responses to stress (86,92). Previous studies have implicated this area in symptoms of depression (93,94) and PTSD (61).

MSI patients showed increased activation of the left insula during mental arithmetic stress. The insula is a key brain area with output to peripheral cardiovascular systems that respond to stress (81,91) including activation of sympathetic systems and

deactivation of parasympathetic function. It also has important connections to brain areas involved in the stress response (95), and altered function and structure in this region have been linked to several psychiatric disorders related to stress, including PTSD (95–103), which have also been linked to increased morbidity and mortality related to CAD (104). Increased stress reactivity in susceptible CAD patients may lead to greater insula activation with stress, and this may represent a mechanism for increased MSI in vulnerable patients.

The Brain Heart Laterality Hypothesis states that asymmetric activation of sympathetic inputs to the heart during stress can be the cause of arrhythmias. The greatest risk of potentially life-threatening ventricular arrhythmias is felt to occur from left lateral brain activation with ipsilateral activation of sympathetic pathways to the left side of the heart (105). Studies have shown that asymmetric brain responses to stress result in proarrhythmic asymmetric sympathetic inputs to the heart (106). Previous studies have shown a correlation between increased blood pressure and heart rate during mental stress and activation in the right insula and cerebellum and with heart rate in the anterior cingulate, whereas cardiovascular reactivity was associated with decreased prefrontal and temporal activation (107). Studies have also

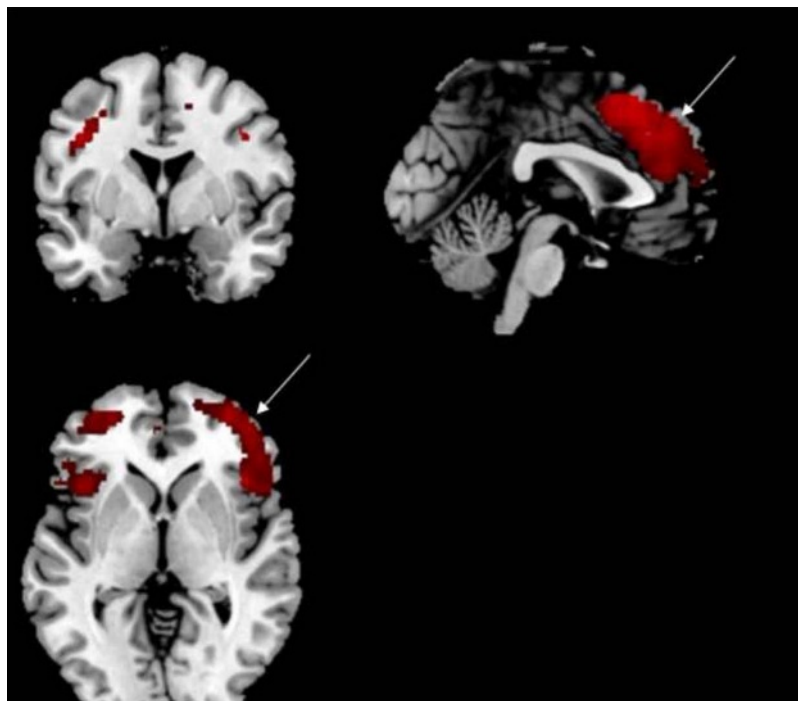


**FIGURE 2.** Areas of increased activation with mental arithmetic stress in CAD patients with mental stress-induced myocardial ischemia versus CAD patients without MSI. Increases are seen in anterior cingulate and inferior frontal gyrus (in addition to parietal cortex). Color image is available only in online version ([www.psychosomaticmedicine.org](http://www.psychosomaticmedicine.org)).

**TABLE 5.** Areas of Increased Activation During Speech Mental Stress in Patients With Mental Stress-Induced Myocardial Ischemia Versus Non-MSI Patients

Z Score	Voxel Number	Talairach Coordinates			Brain Region	Brodmann's Area
		x	y	z		
7.82	15715	-4	18	41	Cingulate gyrus	32
7.82		-6	27	34	Cingulate gyrus	32
7.82		-6	30	24	Anterior cingulate	32
7.82	241	42	-52	43	Inferior parietal lobule	40
6.31		50	-41	41	Inferior parietal lobule	40
4.34		55	-29	40	Postcentral gyrus	2
5.51	72	-40	-48	41	Inferior parietal lobule	40
5.44		-46	-43	39	Inferior parietal lobule	40
5.05	48	61	-47	26	Supramarginal gyrus	40
4.06	35	-59	-37	-9	Middle temporal gyrus	21
3.84		-57	-43	-3	Middle temporal gyrus	21
3.93	93	-32	-69	-26	Cerebellum	
3.90	15	40	-26	53	Postcentral gyrus	3
2.88		46	-19	51	Postcentral gyrus	3
3.68	53	59	-10	-7	Middle temporal gyrus	21
3.38		57	-20	-5	Middle temporal gyrus	21
3.49	44	30	-64	-30	Cerebellum	
3.04	14	12	-20	-67	R. precentral gyrus	6

$z > 2.68, p < .005$ .



**FIGURE 3.** Areas of increased activation with public speaking stress in CAD patients with mental stress-induced myocardial ischemia versus CAD patients without MSI. Increases are seen in anterior cingulate and inferior frontal gyrus (and also parietal cortex). Color image is available only in online version ([www.psychosomaticmedicine.org](http://www.psychosomaticmedicine.org)).

implicated insula and somatosensory cortex in representation of peripheral autonomic function (108). The current study found increased left insula and increased right somatosensory activation and decreased medial prefrontal activation, with stress in MSI+ patients. Interpreted in conjunction with previous studies, these results suggest that unique brain activation and deactivation patterns in MSI+ patients may be associated with increased risk for sudden cardiac death. This may explain in part the increase in morbidity and mortality in these patients compared with those with exercise-induced myocardial ischemia (28,109,110).

Several of the unique areas activated with speaking stress probably relate to increased demand on regions with specific functions. The precentral gyrus controls motor activity, and giving a speech under negative feedback pressure likely involves more demand on motor function. Similarly the middle temporal gyrus mediates primary auditory function, and greater demands with speech stress likely led to greater activation in this area as well. Both types of stressors resulted in decreases in function in cerebellum and parts of the posterior cingulate during MSI. Decreased function implies in the MSI+ group that could be related to the fact that MSI-patients activate these areas to a greater extent or that the control task is associated with greater activation than the stress task. These areas are involved in spatial and motor processing tasks that play a key role in the stress response (92). Recently, there has been an increased appreciation for the role of the cerebellum in social and emotional processing and regulation in addition to its role in motor control (111–114). A failure in this brain region to mount a successful response to stress may contribute to maladaptive cardiovascular responses to stress.

The current study did not find specific predictors of MSI, including medication or behavioral factors. We did not show a relationship between medications and mental stress induced ischemia in the current study. This is consistent with other studies from our group and others that did show that anti-ischemic medications affect ischemic responses to stress (31,75,115,116). The association with depression and other psychosocial factors has also been variable. We have found associations with depression and anger in a separate sample of postmyocardial infarction patients (24,117), but not in this sample of overall older patients with broadly defined CAD. The current study was not specifically designed, however, to assess the relationship between depression or other behavioral factors such as hostility, which limits our ability to make conclusions in this area.

This research is subject to several limitations. First, our findings are not generalizable outside of populations of CAD patients (118,119). Nonetheless, this is an important population to study because of their high morbidity and mortality. The results may also not be generalizable to specific CAD groups. For instance, our sample had only slightly more white than African American (AA) individuals. This is typical of the racial distribution of Georgia, but not many other areas of the country. Although AAs have an increase in hypertension (118) and oxidative stress (119), studies have not shown an increase in stress-induced blood pressure reactivity (119). Therefore, the impact on race in this group is unclear. Another limitation of the current study is that although laboratory studies can offer better control of stress exposure through a standardized experimental protocol, they may not reflect multiple and various naturally occurring real-life stressors. This limits our ability to generalize that the results are applicable to the variety of stresses existing in daily life. Future studies of



ambulatory monitoring of cardiovascular function in naturalistic daily life settings will represent an important step in addressing this need. There was an increase in heart rate, blood pressure, and subjective distress on the cardiac compared with the brain imaging day. This is likely due to several factors, including the fact that the cardiac imaging day came first so there was some adjustment to the stress challenge on the brain imaging day. In addition, participants were upright on the cardiac day versus prone on the imaging day. This allowed the testers to more fully engage with the participants, as evidenced by the fact that they reported more subjective distress on that day. We did not, however, find any differences in stress-induced peripheral vasoconstriction between the two days, however, which would be consistent with the idea that stress exerted an equivalent effect on cardiac function. We have previously reported in this sample increased cardiovascular reactivity to stress in the MSI+ patients, which could have driven the differences in brain activation between the groups, although there was no relationship with myocardial function and brain activation. In addition, there could have been differences in effort with mental stress tasks between groups, although we attempted to limit this by varying task difficulty according to ability to successfully perform the task. Another limitation is in our ability to conclude that mental stress acted through the brain to cause myocardial ischemia in susceptible participants. For one thing, cardiac and brain stress were performed on separate days (mainly due to the fact that the scanners were in different locations). Therefore, the stress episode seen in conjunction with myocardial ischemia was not the same stress episode associated with the brain activations. Even if they did occur on the same day, we would be limited in our ability to determine cause and effect. For instance, stress might affect brain regions, which drive peripheral autonomic response leading to myocardial ischemia, which in turn leads to activation in other brain regions. For those and other reasons, we can only point to associations between patterns of cardiac and brain responses to mental stress, which suggest potential models by which stress could act through the brain to induce myocardial ischemia. The fact that we did not find a relationship between myocardial perfusion and stress-induced brain activation in the MSI+ patients, however, suggests that the current findings are not entirely driven by deficiencies in myocardial function.

The study also had several strengths. We have found our methods of measurement of stress-induced myocardial ischemia and vasoconstriction to be highly reproducible in our laboratory (65). A sample of 22 participants underwent repeated measures of PAT, systolic and diastolic blood pressure, and heart rate at two time points within 8 weeks using the same mental stress protocol. Bland-Altman plots showed excellent reproducibility of PAT measurements, with only one data point falling outside the 95% limits of agreement. For systolic, diastolic blood pressure, and heart rate, Bland-Altman plots showed that more than 95% of data points were within the 95% limits of agreement (65). These findings indicate a high level of reliability of our mental stress protocol. Other strengths of the current study include the fact that this is the largest study to date to examine brain correlates of MSI and used state-of-the-art imaging instrumentation and methodology.

In conclusion, we found that MSI in CAD patients was associated with increased activation in several brain areas, including the parietal lobe, inferior frontal lobe, anterior cingulate, and insula.

The findings suggest that brain areas involved in memory, fear inhibition, and visuospatial processing of threat may mediate stress-related myocardial dysfunction.

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