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Brain Mechanisms of Stress and Depression in Coronary Artery Disease

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Abstract

Introduction: Major depression is associated with an increased risk for and mortality from coronary artery disease (CAD), however the mechanisms by which this occurs are not clear. Depression, which is linked to stress, is associated with changes in brain areas involved in memory and the stress response, and it is likely that these regions play an important role in this increased risk. This study assessed the effects of stress on brain and cardiac function in patients with CAD with and without depression.

Methods: CAD patients with (N=17) and without (N=21) major depression based on the Structured Clinical Interview for DSM-IV (DSM-IV) and/or a Hamilton Depression Scale score of nine or greater underwent imaging of the brain with high resolution positron emission tomography (HR-PET) and [O-15] water and imaging of the heart with single photon emission tomography (SPECT) and [Tc-99m] sestamibi during mental stress (mental arithmetic) and control conditions.

Results: Patients with CAD and major depression showed increased parietal cortex activation and a relative failure of medial prefrontal/anterior cingulate activation during mental stress compared to CAD patients without depression. Depressed CAD patients with stress-induced

myocardial ischemia, however, when compared to depressed CAD patients without showed increased activation in rostral portions of the anterior cingulate.

Conclusions: These findings are consistent with a role for brain areas implicated in stress and depression in the mechanism of increased risk for CAD morbidity and mortality in CAD patients with the diagnosis of major depression.

Introduction

The relationship between major depression and coronary artery disease (CAD) is well established (Carney and Freedland, 2017; Gan et al., 2014; Meijer et al., 2011; Vaccarino and Bremner, 2014; Vaccarino et al., 2009). Depression is associated with an increased risk of mortality which is primarily related to increased cardiovascular death (Anstey and Luszcz, 2002; Wulsin et al., 1999). The presence of depression also worsens outcomes in CAD patients regardless of whether the symptoms were present at the time of hospitalization for cardiac events or developed later (Mallik et al., 2006; Parashar et al., 2006). The mechanism by which depression increases CAD risk, however, is unclear.

Depression is associated with stress (Kendler et al., 2000), and patients with major depression show alterations in stress responsive neurohormonal systems, including cortisol and norepinephrine (Bremner, J.D. et al., 2003a; Carroll, 1982; Carroll et al., 1976; Charney et al., 1982; Delgado and Moreno, 2000; Lake et al., 1982; Nemeroff et al., 1984; Ordway et al., 1994; Roy et al., 1988; Traskman et al., 1980; Young et al., 1994). In some cases these changes are reversible with treatment (Charney et al., 1981; Golden et al., 1988). Increased sympathetic tone and other alterations in neurohormonal function in patients with depression (Carney et al., 1999; Veith et al., 1994) may contribute to the increase in mortality from CAD (Kannel et al., 1987; Vaccarino and Bremner, 2014; Vaccarino and Bremner, 2017). Central changes in the brain, including responses to stress, likely underlie these alterations in peripheral autonomic and neurohormonal function.

Brain imaging studies have shown alterations in several brain regions involved in stress and memory in patients with major depression, including the amygdala, hippocampus, and medial prefrontal cortex/anterior cingulate (Bremner, 2005; Cheng et al., 2016; Kumar et al., 2004; Sheline, 2003; Smith and Eyler, 2006). Structural magnetic resonance imaging (MRI) studies in patients with major depression showed smaller volumes of the hippocampus (Bremner et al., 2000; Bremner et al., 2004; Caetano et al., 2004; Campbell et al., 2004; Cole et al., 2011; Frodl et al., 2004; Hickie et al., 2005; Janssen et al., 2004; Krishnan et al., 1991; Lloyd et al., 2004; Mervaala et al., 2000; Opel et al., 2014; Posener et al., 2003; Sala et al., 2004; Sheline et al., 2003; Sheline et al., 1999; Sheline et al., 1996; Steffens et al., 2000; Vakili et al., 2000; Videbech and Ravnkilde, 2004; Vythilingam et al., 2002), orbitofrontal cortex and anterior cingulate (Ballmaier et al., 2004; Brambilla et al., 2002; Bremner, 2002; Bremner et al., 2002; Kumar et al., 2000; Lacerda et al., 2004; Lai et al., 2000; Lee et al., 2003; Smith and Eyler, 2006; Steffens and Krishnan, 1998). Patients with late-life depression showed an increase in “unidentified bright object” (UBO) lesions in the white matter and peri-ventricular areas on T2-weighted MRI (Greenwald et al., 1998; Hickie et al., 1997; Kumar et al., 1997; Kumar et al., 1998; Lenze et al., 1999; Narayan et al., 1999;

Steffens and Krishnan, 1998) felt to represent small infarcts that disrupt neural circuits mediating mood (Steffens and Krishnan, 1998). Functional neuroimaging studies using functional MRI (fMRI), positron emission tomography (PET) and single photon emission tomography (SPECT) have also shown altered function in these regions as well as the amygdala (Abercrombie et al., 1998; Austin et al., 1992; Baxter et al., 1989; Bench et al., 1992; Biver et al., 1994; Bremner, 2005; Bremner et al., 1997a, b; Bremner, J.D. et al., 2003a; Bremner, J. D. et al., 2003; Bremner et al., 2007; Bremner et al., 2004; Buchsbaum et al., 1984; Cheng et al., 2016; de Asis et al., 2001; Drevets et al., 2002; Drevets et al., 1997; Ebert et al., 1991; George et al., 1997; George et al., 1994; Grant et al., 2011; Hurwitz et al., 1990; Kennedy et al., 2001; Kumar et al., 2004; Lacerda et al., 2004; Martinot et al., 1990; Mayberg, 1994; Mayberg et al., 1997; Mayberg et al., 1994; Mayberg et al., 1999; Mayberg et al., 1992; Mayberg et al., 1990; Ring et al., 1994; Smith and Eyler, 2006; Smith, G.S. et al., 2002). These alterations reversed with treatment (Baxter et al., 1989; Bremner et al., 2007; Brody et al., 2001; Goodwin et al., 1993; Kennedy et al., 2001; Martinot et al., 1990; Mayberg et al., 2000; Smith, G. et al., 2002; Smith, G.S. et al., 2002).

Studies have also shown that stress, which is linked to depression, can induce myocardial ischemia in CAD patients using a standardized mental stress protocol (Arri et al., 2016; Ramadan et al., 2013; Vaccarino et al., 2014; Wei et al., 2014a; Wei et al., 2014b) {Hammadah, 2017 #9649}. Mental stress-induced myocardial ischemia (MSI) often occurs without pain, does not require diseased coronary arteries, and has been hypothesized to be related to coronary vasospasm (Deanfield et al., 1984; Lacy et al., 1995) and/or peripheral vasoconstriction during stress (Arri et al., 2016; Ramadan et al., 2013; Sullivan et al., 2018; Vaccarino et al., 2018). MSI occurs at lower heart rates than those required for physical stress-induced ischemia, and often occurs in patients without physical stress-induced myocardial ischemia (Krantz et al., 1991; LaVeau et al., 1989; Ramachandruni et al., 2006; Rozanski et al., 1988; Schang and Pepine, 1977). Similar to depression, MSI is more common than women than in men and is associated with worse outcomes .{Vaccarino, 2016 #9664}{Vaccarino, 2009 #9134}{Sullivan, 2018 #9648}

MSI may represent the mechanism by which depression increases the risk for CAD (Wei et al., 2014a). Brain areas involved in memory and the stress response that have been implicated in depression, including the medial prefrontal cortex/anterior cingulate/ orbitofrontal cortex (Bremner et al., 1997b; Bremner, J. D. et al., 2003; Cheng et al., 2016; Drevets et al., 1997; Mayberg et al., 1997), likely play a role in MSI. This region has been shown to modulate peripheral cardiovascular function, including heart rate variability (Thayer et al., 2009), and peripheral cardiovascular and neurohormonal responses to stress (Campanella and Bremner, 2016; Vaccarino and Bremner, 2017). In a recent study in a general CAD population not selected for psychiatric disorders we found increased activation with public speaking and arithmetic mental stress in rostral anterior cingulate, inferior frontal gyrus, and parietal cortex, and additional insula activation with mental arithmetic, in MSI compared to non-MSI CAD patients CAD (Bremner et al., 2018). This prior study involved a general CAD population. In the current study we studied a non-overlapping sample of CAD patients who were selected based on the presence or absence of depression in order to assess brain correlates of stress in patients with CAD with and without depression. Base on prior studies of depression and our studies of MSI we hypothesized that

patients with CAD and depression would show a relatively blunted response response to stress in the medial prefrontal/anterior cingulate area compared to CAD patients without depression, but that MSI would be associated with increased activation in this area.

Methods

Patient Population

Sixty patients with coronary artery disease (CAD) were recruited from the Emory University Hospital and Clinics and by advertisement. CAD diagnosis was based on a prior diagnosis of myocardial ischemia, previous cardiac catheterization showing any degree of stenosis, or coronary revascularization. Subjects with depression met DSM-IV-TR criteria for major depression as measured by the Structured Clinical Interview for DSMIV (SCID) interview (First et al., 1995) and/or had a score on the Hamilton Depression Scale (Hamilton, 1960) of nine or greater. Patients were excluded with a history of unstable angina, myocardial infarction, or decompensated heart failure in the past week. Patients were also excluded with a history of meningitis, traumatic brain injury, neurological disorder, organic mental disorder, dyslexia, history of loss of consciousness of greater than one minute, history of current alcohol abuse or substance abuse or dependence (past year) based on the SCID, history of schizophrenia, schizoaffective disorder, psychotic depression, mania/hypomania, anorexia/bulimia, based on the SCID, history of serious medical disorder other than cardiovascular disease, e.g. cancer, renal failure, or evidence of a major abnormality based on laboratory studies that contraindicated participation, active suicidal ideation, history of oral or inhaled steroid usage (past year), current use of exogenous estrogens or progesterone (“hormone replacement therapy”) in the past 3 months, or current antipsychotic medication treatment (past one month).

Patients on cardiac medications including beta blockers or statins were not excluded. Medications were held the morning of the imaging tests. Subjects treated with stable doses of antidepressants were included, but subjects undergoing active changes in antidepressant medications during the study period were excluded. This protocol was approved by the Emory University Investigation Review Board (IRB). All patients provided written informed consent for participation.

Of the 60 original CAD patients, 11 were excluded based on study criteria, and six dropped out before completing the study assessments. An additional five subjects completed the study but did not have a PET scan of the brain either for technical reasons or in one case due to claustrophobia in the scanner. A total of 38 patients completed all study procedures and had a usable PET scan, including 17 patients with depression and 21 patients without depression.

Assessments

All patients were evaluated for psychiatric diagnosis with the Structured Clinical Interview for DSMIV (SCID) interview (First et al., 1995). Depression symptoms were evaluated with the Hamilton Depression Scale, a reliable and valid measure of depressive symptoms based on clinician interview (Hamilton, 1960). The Addiction Severity Index (ASI) interview was

used to assess lifetime alcohol abuse (McClellan et al., 1985). The Subjective Units of Distress Scale (SUDS) is a measure of subjective distress widely used in cognitive behavioral therapy. Subjects are asked to rate current subjective distress on a linear scale of 0 to 100 with 100 being the highest level of distress. The SUDS was used to assess the level of stress attained in the cognitive challenge to verify that the procedure was stressful for the subjects. Analogue ratings of fear, nervousness, high, and anger (scale of 0–4, with 4 being extreme) were also performed to assess emotional state at the time of each of the scans, as previously described (Bremner et al., 2009; Bremner et al., 1999).

Medication history and socio-demographic factors were assessed with a structured questionnaire. Subjects were assessed for past history of psychotropic usage and usage of antidepressant, mood stabilizer and antipsychotic medication treatment in the past. Medical information including previous CHD events and procedures, age of onset of CHD, current medications, and CHD risk factors (blood pressure, lipid and glucose levels, history of diabetes, current and past smoking, and body mass index), were also assessed.

Imaging Methods

Subjects underwent single photon emission computed tomography (SPECT) cardiac imaging on a dedicated research cardiac imaging scanner (Philips Cardio MD) and high resolution positron emission tomography (HR-PET) imaging of the brain with the High Resolution Research Tomograph (HRRT, CTI, Knoxville TN, 2 mm resolution) (Schmand et al., 1999; Weinhard et al., 2000).

For cardiac imaging each patient underwent SPECT imaging of the heart at rest on a separate day from the mental stress day. After confirmation of proper positioning, resting myocardial perfusion images were acquired for 10 minutes after the injection of 8 mCi ^{99m}Tc-sestamibi.

For the mental stress day, subjects underwent scanning of the brain with HR-PET and SPECT scanning of the heart. The mental stress day consisted of an arithmetic mental stress task and a counting control using methods we have previously described and that have been shown to increase stress as measured by subjective ratings, heart rate, blood pressure and cortisol response (Bremner et al., 2009; Bremner, J.D. et al., 2003b; Hammadah et al., 2016; Vaccarino et al., 2014). Patients underwent four HR-PET scans of the brain, two while counting out loud (“counting controls”) and two during mental arithmetic, with a SPECT scan of the heart following the second mental arithmetic task. Each task lasted for two minutes. At the beginning of the study a physician wearing a white laboratory coat entered the room. The testing physician was blind to the diagnosis and clinical care of the patient. The mental arithmetic cognitive challenge battery included arithmetic (serial subtraction, addition, multiplication and division) cognitive tasks performed under time pressure and with negative feedback regarding the performance and the time spent in the task given. The level of difficulty was increased until subjects were unable to successfully complete three consecutive tasks. The purpose of calibrating difficulty to individual performance is to have a similar level of stress for all subjects regardless of ability. Subjective ratings of distress were obtained at baseline and after the cognitive challenge as assessed with the Subjective

Units of Distress Scale (SUDS) as well as analogue ratings of fear, nervousness, high, and anger.

Ten seconds after the beginning of each task patients received an intravenous injection of 20 mCi radiolabeled water followed immediately by HR-PET imaging of the brain for 80 seconds. One minute after the onset of the second mental stress condition subjects received an intravenous injected dose of 8 mCi ^{99m}Tc-sestamibi followed 45 minutes later by a SPECT scan of myocardial perfusion with mental stress. Gated images were also obtained for measurement of ejection fraction and evaluation of regional wall motion abnormalities. Myocardial images from baseline and mental stress were reconstructed in short axis, vertical long axis and horizontal long axis views.

Data Analysis

A Chi-square test was used to test the association between categorical risk factors and depression status. The distribution of continuous variables was examined for normality as a requirement for parametric testing. Data were analyzed using SAS 9.4 and statistical significance was evaluated using an alpha=0.05 cut-point.

Cardiac data were analyzed using the Emory Toolbox, a validated instrument for display and quantitation of cardiac SPECT imaging data (Garcia et al., 2007; Van Train et al., 1994), and were additionally scored by a Nuclear Medicine physician blinded to subject diagnosis using a 20-segment bull's eye diagram of the heart. This diagram is used to rate perfusion abnormalities at rest and stress on a scale of 0 (normal) to 4 (absent perfusion) for each of 20 segments of the heart and to develop a quantitative index of perfusion with rest and stress. The myocardial perfusion score represented the stress score subtracted from the rest score. Ischemia was defined as a myocardial perfusion score of 3 or greater with at least one segment representing a moderate stress-induced perfusion defect (score of 2 in that segment).

PET brain images were realigned to the first image in the scanning session using statistical parametric mapping (spm). Images were then transformed into a common neuroanatomical space, smoothed, and subjected to statistical analysis using methods previously described by us in detail (Bremner et al., 1999; Fani et al., 2011). Analysis of variance was used to compare brain perfusion by voxel within hypothesized regions (anterior cingulate, medial prefrontal cortex) in CAD patients with and without depression during mental stress. Hypothesized regions as reviewed above were defined as the stereotactical coordinates of medial prefrontal cortex and anterior cingulate as defined by a common stereotactical atlas of the brain (Talairach and Tournoux, 1988). Significance was defined as a minimal cluster of 11 voxels with a $p<0.005$ in hypothesized areas (medial prefrontal cortex and anterior cingulate). This method minimizes Type I and Type II error (Lane et al., 1997; Reiman et al., 1997). Exploratory analyses of other brain areas were also performed and are displayed in the tables. with minimum voxel clusters of 11 voxels.

Results

Depressed patients (N=17) compared to non-depressed (N=21) patients with CAD had higher body mass index, fewer years of education, and more symptoms of depression (Table 1). There were no differences between groups in other factors including age, race, gender, rates of diabetes, smoking history, high cholesterol history, or hypertension. Depressed patients took more antidepressants, anxiolytics, and diuretics, but depressed and non-depressed CAD patients showed similar use of beta-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, statins, and vasodilators. Forty one percent of CAD patients with depression and 32% of CAD patients without depression had mental stress-induced myocardial ischemia, a difference that was not statistically significant.

In the group as a whole, stress resulted in increased activation in superior, frontal gyrus, anterior cingulate, orbital and rectal gyrus, parietal cortex (superior and inferior parietal lobules), superior temporal gyrus, amygdala / parahippocampal gyrus, and midbrain (Tables 2–7). When non-depressed and depressed patients were examined separately, only the non-depressed patients showed stress-induced activation in medial prefrontal cortex, which includes anterior cingulate, orbitofrontal cortex (orbital and rectal gyrus), and subcallosal gyrus (Table 2). Depressed patients additionally showed increased activation with stress in parietal cortex (angular gyrus) (Table 4), and direct comparison showed that depressed patients activated this area to a greater degree with stress than non-depressed patients (Table 6).

Stress in the group as a whole resulted in decreased activation in insula, postcentral and precentral gyrus, subcallosal gyrus, posterior cingulate, lingual gyrus, cuneus, and uncus (Tables 3 and 5). Depressed patients alone additionally showed decreases in precuneus, fusiform gyrus, thalamus, paracentral lobule, and lateral geniculate body (Table 5). When depressed patients were compared to nondepressed patients there were significantly greater stress-induced decreases in insula, post and precentral gyrus, anterior cingulate, subcallosal gyrus, posterior cingulate, lingual gyrus, cuneus, precuneus, middle occipital gyrus, thalamus, and paracentral lobule (Table 7).

Depressed patients without mental stress-induced myocardial ischemia (MSI) showed increased activation with stress in the parietal cortex (Table 8) and decreased activation in cingulate, lingual gyrus, cuneus, inferior temporal gyrus, middle and inferior occipital gyrus, thalamus and paracentral lobule (Table 9)

Depressed patients with MSI had increased activation in middle frontal gyrus and rostral anterior cingulate with stress (Table 10) and decreased function in caudal anterior cingulate, putamen, and superior occipital gyrus (Table 11).

Comparison of ischemic to non-ischemic showed they had greater activations with stress in the rostral anterior cingulate (Table 12, Figure 2) and greater decreases with stress in dorsal anterior cingulate (Table 13).

Discussion

This study showed that CAD patients with depression demonstrated altered functional responses to stress compared to CAD patients without depression in brain regions involved in memory, emotion, and the fear response. Specifically, depressed patients compared to non-depressed showed increased activation with stress in parietal cortex (angular gyrus) and a failure of activation in medial prefrontal cortex (anterior cingulate, orbitofrontal cortex, and subcallosal gyrus). Depressed patients with stress-induced myocardial ischemia showed greater activation in rostral anterior cingulate during stress than depressed non-ischemic patients, with deactivations in more posterior portions of the cingulate. These brain areas are all involved in stress, memory, and regulation of peripheral cardiovascular function (Campanella and Bremner, 2016).

The medial prefrontal cortex, including anterior cingulate, orbitofrontal cortex, and subcallosal gyrus, plays an important role in emotional regulation (Devinsky et al., 1995; Vogt et al., 1992). Multiple studies have implicated this region in the symptomatology of depression (Bremner et al., 1997b; Bremner et al., 2005; Bremner, J. D. et al., 2003; Drevets et al., 1997; George et al., 1994; Mayberg, 1994). The anterior cingulate also regulates the peripheral neurohormonal and autonomic systems involved in cardiovascular responses to stress (Diorio et al., 1993; Nagai et al., 2010; Napadow et al., 2008). It sends inhibitory inputs to the amygdala, which mediates fear memories (Morgan and LeDoux, 1995; Quirk et al., 2006). Lesions of the medial prefrontal cortex result in a failure to extinguish fear reactions, as well as failure to mount peripheral cortisol and sympathetic response to stress (Devinsky et al., 1995; Vogt et al., 1992). Decreased medial prefrontal activation with stress in depressed CAD patients is consistent with prior studies of depression. Altered function of this area likely plays a role in the increase in cardiovascular events in patients with depression (Vaccarino and Bremner, 2014; Vaccarino and Bremner, 2017; Vaccarino et al., 2016).

CAD patients with stress-induced myocardial ischemia demonstrated altered brain responses to stress compared to those without, including increased activation in rostral anterior cingulate. We recently published a study of brain correlates of MSI in a larger sample of CAD patients. This sample, unlike the current study, was not not selected for psychiatric disorders, and there was no overlap between subjects in the two studies. In that study we found increased activation with public speaking and arithmetic mental stress in rostral anterior cingulate, inferior frontal gyrus, and parietal cortex, and additional insula activation with mental arithmetic, in MSI compared to non-MSI CAD patients (Bremner et al., 2018). The current study replicated the finding of increased rostral anterior cingulate activation with stress in MSI. The smaller sample size in the current study may explain the lack of activation in areas seen in the prior study, including parietal cortex and inferior frontal gyrus. As noted elsewhere, increased anterior cingulate activation with stress may drive increased peripheral cardiovascular and neurohormonal responses that lead to myocardial ischemia. Since this was only seen in MSI patients, however, it suggests that there is a subsample of CAD patients with depression who are susceptible to MSI through this brain region. It does not provide an explanation, however, for the link between depression and CAD, since in the CAD depressed patients as a whole there was blunted rostral anterior cingulate activation

compared to non-depressed CAD patients. Evidence from other studies, including the lack of an association between early trauma and MSI, suggests that MSI may not be completely attributable to psychiatric disorders. The relationship between depression and CAD is likely more complex, and may involve common genetic or other factors {Vaccarino, 2008 #8315}.

This prior study involved a general CAD population. In the current study we studied a non-overlapping sample of CAD patients who were selected based on the presence or absence of depression in order to assess brain correlates of stress in patients with CAD with and without depression. Base on prior studies of depression and our studies of MSI we hypothesized that patients with CAD and depression would show a relatively blunted response response to stress in the medial prefrontal/anterior cingulate area compared to CAD patients without depression, but that MSI would be associated with increased activation in this area.

This is consistent with a prior study of MSI in patients with CAD not selected for history of depression (Bremner et al., 2018), and suggests a mechanism by which the brain mediates MSI. This is logical since appraisal of threat by brain regions involved in fear, memory, and emotion, is an important part of the stress response (LeDoux, 1996; Phillips and LeDoux, 1992). Patients with depression and stress-induced myocardial ischemia showed increased activation in more anterior parts of cingulate involved in emotion and decreases in more posterior portions involved in assessment of threat in context, time and space (Devinsky et al., 1995; Vogt et al., 1992). One possibility is that increased anterior cingulate function leads to exaggerated peripheral sympathetic and neurohormonal responses to stress in some vulnerable patients, leading to increased stress-induced myocardial ischemia.

Stress was associated with an increase in parietal function in the depressed compared to the nondepressed CAD patients, specifically angular gyrus. The parietal lobe plays an important role in perception of the self in space and time and contextual cues as well as visuospatial memory (Bremner et al., 1995; Jonides et al., 1993; Pardo et al., 1991; Petersen et al., 1988; Zandbelt et al., 2013). It has been hypothesized that increased parietal lobe function with stress could be a neural correlate of heightened awareness or a hypervigilant response to stress (Bremner, 2003; Bremner et al., 1995). Studies have implicated this region in stress-related psychiatric disorders (van Rooij et al., 2015). Individuals at increased risk for cardiovascular disease in prior studies were found to have an increased task-related activation in the parietal cortex (Chuang et al., 2014). This area has also been shown to modulate peripheral cardiovascular responses to stress (de Morree et al., 2013). These findings suggest that increased parietal cortical response to stress could play a role in increased cardiovascular events in patients with depression.

This research is subject to several limitations. Findings from the current study are limited to patients with CAD and are not generalizable to e.g. patients with depression without CAD. Laboratory-induced stress may not be relevant to the types of stressors CAD patients with depression encounter in daily life. Nevertheless, we have used this paradigm in a number of studies and have found that it has a certain amount of ecological validity. The sample size of the current study was limited, and this was particularly relevant to comparison of depressed CAD patients with and without myocardial ischemia. The results should be therefore be

considered preliminary, and future studies should focus on CAD patients with depression comparing those with and without stress-induced myocardial ischemia.

In summary, the current study found that patients with CAD and depression showed altered brain responses to mental stress compared to CAD patients without depression in brain areas involved in fear, memory, and peripheral modulation of neurophysiological responses to stress. Specific findings included an increase in parietal cortex activation and decreased anterior cingulate/medial prefrontal cortex response to stress in the CAD patients with depression relative to CAD patients without depression. CAD patients with depression who also developed stress-induced myocardial ischemia, however, had increased rostral anterior cingulate activation with stress compared to CAD patients with depression who did not have stress-induced myocardial ischemia. These findings suggest a pathway by which the brain may mediate the increased cardiovascular morbidity and mortality in some patients with CAD and depression implicating brain areas involved in emotion and autonomic regulation by which stress in certain vulnerable individuals could mediate this effect. Although research in this area is limited, the findings suggest that interventions like mindfulness training or biofeedback that have been shown to affect brain function and reduce stress and anxiety may be useful in the prevention of morbidity and mortality in some vulnerable patients with CAD. This is particularly true for those vulnerable to stress-induced myocardial ischemia, and is not necessarily limited to CAD patients with depression.

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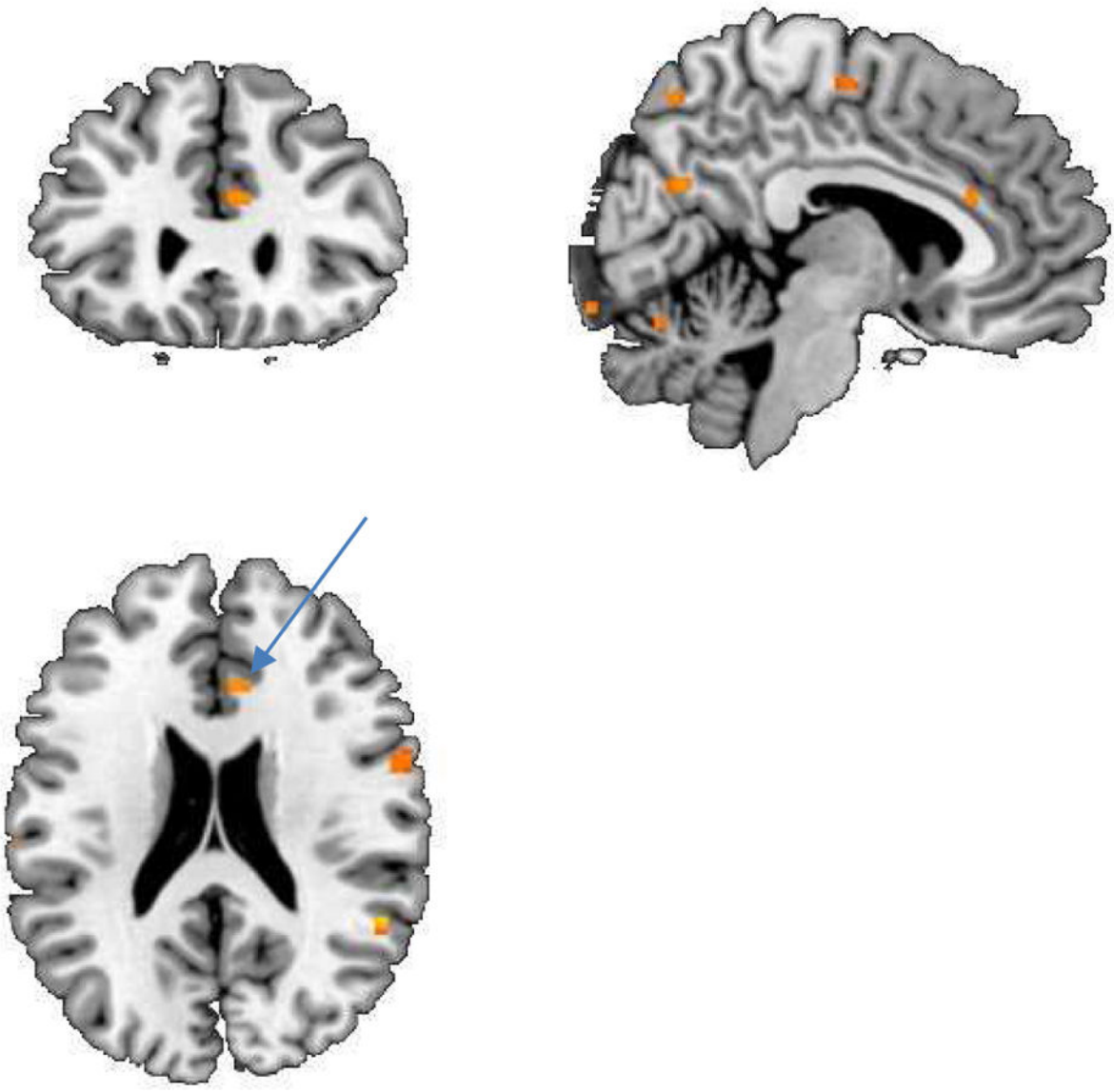

Figure 1.

SPM maps of brain function measured with PET in CHD patients with and without depression. There was a greater anterior cingulate (arrow) response to mental stress in the CHD patients without depression compared to CHD patients with depression during mental stress (i.e. failure of anterior cingulate/medial prefrontal activation with mental stress in heart disease and depression, yellow area).

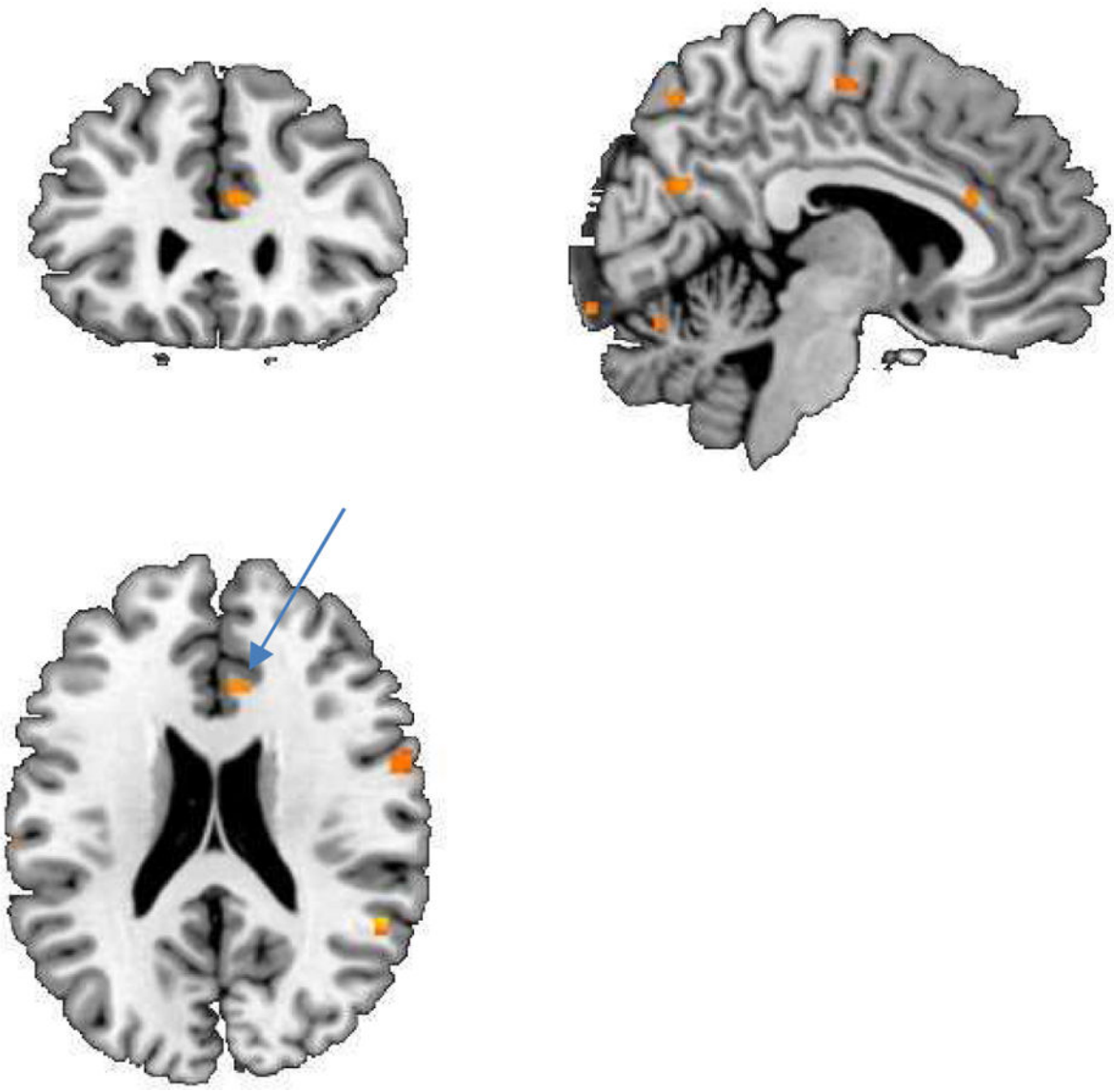

Figure 2.

SPM maps of brain function measured with PET in CHD patients with depression and stress-induced myocardial ischemia compared to those without stress-induced myocardial ischemia showing increased activation with stress in the anterior cingulate (yellow area, arrow).

Table 1.

Demographic and Risk Factors for CAD Patients with and without Depression[1]

	Non-Depressed (N=21)	Depressed (N=17)
Age	58 (10 SD)	61 (6 SD)
Gender	4 F/17 M	5 F/12 M
Race	38% AA/62%	29% AA/65%
	Cauc/3% Asian	Cauc/6% NA
Years of Education	16 (3 SD)	14 (2 SD) *
BMI	30 (5 SD)	36 (8 SD) *
Ham-D Score	14 (4 SD)	2 (2 SD) *
Hypertension	60%	88%
Dyslipidemia	65%	75%
Diabetes	25%	50%
Smoking (current)	10%	13%
Smoking (lifetime)	65%	38%
Percentage of patients taking:		
Antidepressants	14%	41%
ACE Inhibitors	29%	47%
Angiotensin Receptor Inhibitors	10%	18%
Diuretics	5%	41%
Vasodilators	10%	29%
Anxiolytics	5%	29%
Beta Blockers	57%	59%
Statins	62%	71%

[1] CAD=coronary artery disease; F=female; M=male; AA=African American; Cauc=Caucasian; NA=Native American; BMI=body mass index; Ham-D=Hamilton Depression Scale; ACE=angiotensin converting enzyme.

* $p<.05$

Table 2.

Areas of Increased Activation During Mental Arithmetic Stress in CAD Patients Without Depression

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
4.34	141	−32	19	−6	L. Inferior Frontal Gyrus	47
2.82		−30	17	−16	L. Inferior Frontal Gyrus	47
4.85	102	32	13	−16	R. Inferior Frontal Gyrus	47
4.80	1392	10	19	60	R. Precentral Gyrus	6
4.68		−6	46	31	L. Superior Frontal Gyrus	9
4.57		14	14	49	R. Superior Frontal Gyrus	6
4.33	183	48	27	4	R. Inferior Frontal Gyrus	45
3.10		53	12	9	R. Precentral Gyrus	44
4.17	86	34	22	45	R. Middle Frontal Gyrus	8
2.74		28	14	47	R. Middle Frontal Gyrus	6
3.93	31	48	21	27	R. Middle Frontal Gyrus	46
3.59	80	−18	60	−10	L. Superior Frontal Gyrus	10
3.10		−14	54	−4	L. Superior Frontal Gyrus	10
2.80		−14	47	−2	L. Anterior Cingulate	32
3.70	78	22	44	29	R. Superior Frontal Gyrus	9
3.20		22	45	40	R. Superior Frontal Gyrus	8
3.53	74	46	1	52	R. Middle Frontal Gyrus	6
3.52	27	−38	13	27	L. Middle Frontal Gyrus	9
3.49	24	40	21	−3	R. Inferior Frontal Gyrus	47
3.47	55	42	38	−15	R. Middle Frontal Gyrus	11
2.72		40	35	−8	R. Middle Frontal Gyrus	47
3.19	32	4	−26	71	R. Medial Frontal Gyrus	6
3.01		14	−30	66	R. Precentral Gyrus	4
3.19	20	−34	30	26	L. Middle Frontal Gyrus	9
3.10	24	12	65	12	R. Superior Frontal Gyrus	10
3.09	10	10	59	−20	R. Superior Frontal Gyrus	11
3.08	12	−16	38	−20	L. Inferior Frontal Gyrus	11
3.07	19	36	51	9	R. Middle Frontal Gyrus	10
3.18	22	12	42	−17	R. Middle Frontal Gyrus	11
3.13	27	40	2	37	R. Middle Frontal Gyrus	6
2.96		40	3	26	R. Precentral Gyrus	6
3.32	15	−42	−23	55	L. Postcentral Gyrus	3
3.26	11	−14	41	7	L. Anterior Cingulate	32
3.20	14	0	37	9	L. Anterior Cingulate	24
3.18	19	4	38	−25	R. Rectal Gyrus	11
3.88	22	10	26	−20	R. Rectal Gyrus	11
3.45	52	−12	25	41	L. Sub-Gyral	8
3.49	43	57	−10	−11	R. Sub-Gyral	21

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
3.54	68	−8	57	12	L. Medial Frontal Gyrus	10
2.93	10	−4	−26	62	L. Medial Frontal Gyrus	6
2.83	14	−12	49	16	L. Medial Frontal Gyrus	10
3.25	15	44	−41	37	R. Supramarginal Gyrus	40
3.66	76	40	−64	47	R. Inferior Parietal Lobule	7
4.01	49	−38	−63	53	L. Superior Parietal Lobule	7
4.00	135	48	−48	47	R. Inferior Parietal Lobule	40
3.05		32	−50	43	R. Inferior Parietal Lobule	40
3.00		38	−56	54	R. Superior Parietal Lobule	7
3.97	26	55	−43	30	R. Inferior Parietal Lobule	40
3.68		63	−39	−5	R. Middle Temporal Gyrus	21
3.61		53	−26	−7	R. Middle Temporal Gyrus	21
3.56	41	48	9	−24	R. Superior Temporal Gyrus	38
3.13		51	3	−27	R. Middle Temporal Gyrus	21
3.82	56	−46	−22	−7	L. Superior Temporal Gyrus	22
3.46	13	51	−15	−30	R. Inferior Temporal Gyrus	20
2.99	12	55	−51	−6	R. Middle Temporal Gyrus	37
4.39	268	59	−21	−1	R. Superior Temporal Gyrus	21
3.53	26	12	2	−3	R. Lentiform Nucleus (Globus Pallidus)	
3.22		16	6	2	R. Lentiform Nucleus (Putamen)	
4.21	40	−14	8	3	L. Putamen	
3.41	11	−18	−9	−2	L. Parahippocampal Gyrus	27
3.01	19	16	−93	−2	R. Lingual Gyrus	17
3.55	17	18	−85	3	R. Lingual Gyrus	17
3.31	10	10	−82	−4	R. Lingual Gyrus	18
3.31	19	26	−84	−8	R. Middle Occiptal Gyrus	18
3.28	13	−4	−18	−11	L. Red Nucleus	
5.17	1047	−26	−83	−23	L. Cerebellum	
4.29		−30	−77	−31	L. Cerebellum	
4.18		−18	−80	−36	L. Cerebellum	
3.87	62	−2	−34	−25	L. Cerebellum	
3.39		0	−37	−32	L. Cerebellum	
3.94	31	12	−52	−21	R. Cerebellum	
3.75	40	−14	−53	−14	L. Cerebellum	
3.68	136	10	−77	−21	R. Cerebellum	
3.63		4	−71	−18	R. Cerebellum	
3.38		18	−75	−28	R. Cerebellum	
3.57	109	−6	−52	−39	L. Cerebellum	
3.55		−4	−64	−29	L. Cerebellum	
3.38		0	−54	−23	L. Cerebellum	

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
3.43	60	30	−75	−27	R. Cerebellum	
3.19		40	−75	−21	R. Cerebellum	
3.27	22	−12	−40	−20	L. Cerebellum	

Table 3.

Areas of Decreased Activation During Mental Arithmetic Stress in CAD Patients Without Depression

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
4.51	927	−42	−6	4	L. Insula	13
4.03		−59	−22	18	L. Postcentral Gyrus	40
3.89		−51	−20	19	L. Insula	40
3.68	17	42	−18	−6	R. Insula	13
3.86	41	44	−1	−12	R. Superior Temporal Gyrus	38
2.68		44	7	−7	R. Insula	13
3.68	17	42	−18	−6	R. Insula	13
4.40	721	65	−1	28	R. Precentral Gyrus	6
4.03		65	−22	23	R. Postcentral Gyrus	40
3.73		61	−8	26	R. Precentral Gyrus	4
4.09	22	10	−74	2	R. Lingual Gyrus	18
3.87	17	12	13	29	R. Cingulate Gyrus	24
3.54	51	−51	−4	41	L. Precentral Gyrus	6
3.47	32	−65	−16	23	L. Postcentral Gyrus	1
3.69	145	−51	−36	24	L. Inferior Parietal Lobule	40
3.46		−59	−32	29	L. Inferior Parietal Lobule	40
3.08		−63	−39	30	L. Inferior Parietal Lobule	40
3.69	60	−50	−62	−2	L. Inferior Temporal Gyrus	19
3.57		−57	−60	3	L. Middle Temporal Gyrus	21
3.07	16	−61	−52	14	L. Superior Temporal Gyrus	22
3.07	11	−46	−19	5	L. Superior Temporal Gyrus	22
2.82	11	−26	−89	15	L. Middle Occipital Gyrus	18
3.47	20	53	−68	9	R. Middle Occipital Gyrus	19
2.81		50	−70	2	R. Middle Occipital Gyrus	37
3.40	38	−18	7	−19	L. Uncus	34
3.39	15	28	8	1	R. Lentiform Nucleus (Putamen)	
3.37	24	−14	−17	56	L. Medial Frontal Gyrus	6
3.34	28	−6	−64	31	L. Cuneus	7
3.33	11	−20	−64	31	L. Precuneus	7
3.18	13	−8	−56	40	L. Precuneus	7

Table 4.

Areas of Increased Activation During Mental Arithmetic Stress in CAD Patients With Depression

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
4.02	196	51	24	17	R. Inferior Frontal Gyrus	45
3.43		42	15	23	R. Inferior Frontal Gyrus	46
2.87		59	24	10	R. Inferior Frontal Gyrus	45
3.61	87	24	27	10	L. Inferior Frontal Gyrus	47
3.54		30	20	18	L. Inferior Frontal Gyrus	47
3.06		18	28	15	L. Inferior Frontal Gyrus	47
3.39	25	28	17	16	R. Inferior Frontal Gyrus	47
3.25	22	32	25	−3	R. Inferior Frontal Gyrus	47
2.85		28	29	−8	R. Inferior Frontal Gyrus	47
3.10	15	53	19	1	R. Inferior Frontal Gyrus	47
3.06	19	40	33	−5	R. Inferior Frontal Gyrus	47
3.89	23	51	36	15	R. Inferior Frontal Gyrus	47
2.77		46	42	12	R. Middle Frontal Gyrus	11
3.74	30	32	23	36	R. Middle Frontal Gyrus	9
3.63	55	44	33	6	R. Interior Frontal Gyrus	46
2.86		48	36	13	R. Middle Frontal Gyrus	46
3.25	13	24	11	60	R. Middle Frontal Gyrus	6
3.10	15	28	5	53	R. Middle Frontal Gyrus	6
2.92	14	42	32	19	R. Middle Frontal Gyrus	46
2.85	29	30	10	40	R. Middle Frontal Gyrus	6
2.78		30	14	47	R. Middle Frontal Gyrus	6
3.53	84	46	12	38	R. Middle Frontal Gyrus	8
3.43		46	4	42	R. Middle Frontal Gyrus	6
3.29	23	32	18	53	R. Middle Frontal Gyrus	6
2.80		34	11	55	R. Middle Frontal Gyrus	6
3.64	34	8	65	17	R. Superior Frontal Gyrus	10
3.29	32	10	34	52	L. Superior Frontal Gyrus	6
3.04		14	26	47	L. Superior Frontal Gyrus	8
4.00	182	8	18	58	R. Superior Frontal Gyrus	6
3.71		12	26	56	R. Superior Frontal Gyrus	6
3.04		10	31	43	R. Superior Frontal Gyrus	8
3.31	107	34	61	53	R. Superior Parietal Lobule	7
3.30		38	54	56	R. Superior Parietal Lobule	7
2.98		44	52	45	R. Inferior Parietal Lobule	40
3.30	25	55	39	39	R. Interior Parietal Lobule	40
3.31	14	46	62	49	L. Inferior Parietal Lobule	40
3.48	18	51	66	33	L. Angular Gyrus	39
3.61	30	−2	42	15	L. Medial Frontal Gyrus	9

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
3.82	108	−4	33	41	L. Medial Frontal Gyrus	8
3.19		12	34	26	L. Medial Frontal Gyrus	9
4.19	318	16	39	11	R. Anterior Cingulate	32
3.97		12	45	5	R. Frontal Medial Gyrus	10
3.93		14	47	12	R. Frontal Medial Gyrus	10
4.13	28	6	9	14	R. Subcallosal Gyrus	25
4.33	375	57	55	11	R. Inferior Temporal Gyrus	20
4.20		59	29	−2	R. Middle Temporal Gyrus	21
3.59		61	22	11	R. Middle Temporal Gyrus	21
4.21	23	48	6	27	R. Middle Temporal Gyrus	21
4.08	46	61	43	10	L. Middle Temporal Gyrus	21
2.78		55	31	−2	L. Middle Temporal Gyrus	21
2.98	14	34	22	21	R. Superior Temporal Gyrus	38
3.06	13	44	60	39	R. Cerebellum	
3.55	72	36	83	23	L. Cerebellum	
3.17		26	79	21	L. Cerebellum	
2.96		18	79	28	L. Cerebellum	

Table 5.

Areas of Decreased Activation During Mental Arithmetic Stress in CAD Patients With Depression

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
5.69	3555	−40	2	−3	L. Insula	13
5.60		−44	−32	18	L. Superior Temporal Gyrus	41
5.28		−61	−22	18	L. Postcentral Gyrus	40
5.51	2202	61	−3	15	R. Middle Temporal Gyrus	21
4.94		40	−8	−1	R. Insula	
4.87		61	2	7	R. Precentral Gyrus	6
3.22	13	−28	−14	67	L. Precentral Gyrus	6
3.02	11	22	−12	67	R. Precentral Gyrus	6
3.01	17	−10	−31	70	L. Postcentral Gyrus	3
3.40	57	55	−34	22	R. Insula	13
3.09		53	−26	18	R. Postcentral Gyrus	40
2.64		59	−26	25	R. Inferior Parietal Lobule	40
3.01	15	−40	−25	36	L. Postcentral Gyrus	2
4.36	69	−32	−84	24	L. Superior Occipital Gyrus	19
3.38	44	−40	−79	11	L. Middle Occipital Gyrus	19
3.23	23	42	−79	11	R. Middle Occipital Gyrus	19
3.21	15	−26	−87	6	L. Middle Occipital Gyrus	19
4.18	96	4	−78	28	R. Cuneus	18
3.92		6	−80	35	R. Cuneus	19
3.69		−2	−86	26	L. Cuneus	19
3.31	26	−16	−79	22	L. Cuneus	18
3.21	43	−12	−82	34	L. Cuneus	19
3.40	26	20	−93	14	R. Cuneus	18
3.01	11	12	−81	21	R. Cuneus	18
3.20	48	10	−68	38	R. Precuneus	7
2.93		12	−67	27	R. Precuneus	31
3.20	14	18	−52	50	R. Precuneus	7
4.34	306	−6	−64	42	L. Precuneus	7
3.88		−2	−68	29	L. Precuneus	31
3.42		4	−57	21	R. Posterior Cingulate	23
4.06	177	−2	−43	26	L. Cingulate Gyrus	31
3.58		4	−39	37	R. Cingulate Gyrus	31
3.24		4	−47	30	R. Precuneus	31
3.37	11	4	26	17	R. Anterior Cingulate	24
3.95	87	0	13	29	L. Cingulate Gyrus	24
3.16		−4	8	36	L. Cingulate Gyrus	24
3.08		2	4	31	R. Cingulate Gyrus	24
3.91	61	−8	−15	3	L. Thalamus	

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
3.85	44	−8	−15	41	L. Cingulate Gyrus	24
2.88		−4	−12	36	L. Cingulate Gyrus	24
3.63	68	−8	−29	44	L. Paracentral Lobule	31
3.32		−14	−37	41	L. Cingulate Gyrus	31
3.43	16	10	8	40	R. Cingulate Gyrus	32
2.95	12	8	−25	34	R. Cingulate Gyrus	31
2.94		16	−6	43	R. Cingulate Gyrus	24
3.15	92	−10	−63	14	L. Posterior Cingulate	30
3.15		−4	−54	12	L. Posterior Cingulate	29
3.50	18	−16	−58	7	L. Posterior Cingulate	30
3.71	38	−6	1	59	L. Medial Frontal Gyrus	6
3.70	54	4	27	−13	R. Medial Frontal Gyrus	11
3.07		0	34	−13	L. Medial Frontal Gyrus	11
3.41	37	8	−5	50	R. Medial Frontal Gyrus	6
3.52	42	26	3	−10	R. Subcallosal Gyrus	34
2.99	22	24	−21	−1	R. Lateral Geniculum Body	
2.98	13	18	−40	48	R. Paracentral Lobule	5
3.05	24	10	−11	43	R. Paracentral Lobule	31
3.50	44	50	−58	8	R. Middle Temporal Gyrus	39
3.13		55	−64	3	R. Middle Temporal Gyrus	37
4.02	148	−44	−62	7	L. Middle Temporal Gyrus	37
3.39		−50	−68	9	L. Middle Occipital Gyrus	19
2.93		−50	−58	14	L. Superior Temporal Gyrus	22
2.91	21	50	−67	16	R. Middle Temporal Gyrus	39
5.47	759	42	−61	−14	R. Fusiform Gyrus	37
3.35	24	−40	−71	−12	L. Fusiform Gyrus	19
3.45	29	−18	5	−20	L. Uncus	34
4.12	113	16	−68	2	R. Lingual Gyrus	18
2.84		22	−74	0	R. Lingual Gyrus	18
3.29	22	−12	−74	−3	R. Lingual Gyrus	18
3.16	13	12	−80	−6	R. Lingual Gyrus	18
2.89	13	−2	−80	2	L. Lingual Gyrus	18
5.41	265	−20	−63	−17	L. Cerebellum	
3.83		−10	−55	−17	L. Cerebellum	
3.52		−26	−70	−8	L. Lingual Gyrus	18
4.04	64	−22	−45	−16	L. Cerebellum	
3.11	14	−18	−54	−36	L. Cerebellum	
3.73	98	24	−42	−21	R. Cerebellum	
2.83		34	−46	−30	R. Cerebellum	
3.63	22	−42	−49	−18	L. Cerebellum	

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
3.69	37	−10	−62	−36	L. Cerebellum	
3.65	26	26	−52	−31	R. Cerebellum	
4.90		22	−61	−20	R. Cerebellum	
4.49		30	−57	−12	R. Cerebellum	

Table 6.

Areas of Greater Increased Activation During Mental Arithmetic Stress in CAD Patients With Depression compared to CAD Patients without Depression

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
3.62	29	−51	−66	33	L. Angular Gyrus	39
3.53	24	59	−41	39	R. Inferior Parietal Lobule	40
3.41	16	8	9	−12	R. Subcallosal Gyrus	
3.12	24	16	39	11	R. Anterior Cingulate	32
2.89	12	18	44	54	Left Precuneus	

Table 7.

Areas of Greater Decreased Activation During Mental Arithmetic Stress in CAD Patients With Depression versus Without Depression

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
3.55	31	−44	−34	19	L. Insula	13
3.45	55	40	−8	−1	R. Insula	13
4.11	45	−40	2	−2	L. Insula	13
2.71		−42	−1	−11	L. Superior Temporal Gyrus	13
3.63	23	−51	−6	−11	L. Superior Temporal Gyrus	21
	14	−50	−35	5	L. Middle Temporal Gyrus	22
3.46	33	50	−60	5	R. Middle Temporal Gyrus	37
2.93		53	−64	0	R. Inferior Temporal Gyrus	19
3.23	12	−59	−39	5	L. Middle Temporal Gyrus	22
3.17	12	46	7	−19	R. Superior Temporal Gyrus	38
3.63	45	−46	−20	−6	L. Superior Temporal Gyrus	22
3.92	131	4	−49	26	R. Cingulate Gyrus	31
3.46		8	−35	34	R. Cingulate Gyrus	31
3.16	24	−8	−27	40	L. Cingulate Gyrus	31
2.91		−10	−35	39	L. Cingulate Gyrus	31
2.94	17	8	4	47	R. Cingulate Gyrus	24
3.26		−2	−43	24	L. Posterior Cingulate	23
3.12	15	2	−59	23	R. Posterior Cingulate	31
3.26		20	−64	8	R. Posterior Cingulate	30
3.06	13	10	44	−15	R. Orbital Gyrus	11
3.92	59	12	−82	−5	R. Lingual Gyrus	18
3.28		18	−83	2	R. Lingual Gyrus	17
3.83	23	−18	−29	−4	L. Parahippocampal Gyrus	27
3.43	16	6	−80	33	R. Cuneus	19
3.58	20	12	−83	19	R. Cuneus	18
3.06	13	18	−52	45	R. Precuneus	7
3.00	12	0	−71	27	L. Precuneus	31
2.81		4	−67	22	R. Precuneus	31
3.52	34	−4	−62	38	L. Precuneus	7
3.17	16	40	−78	−5	R. Inferior Occipital Gyrus	19
3.31	21	−51	−68	8	L. Middle Occipital Gyrus	19
3.48	19	42	21	−5	R. Inferior Frontal Gyrus	47
3.19	15	28	7	−13	R. Inferior Frontal Gyrus	47
3.71	28	0	34	−18	L. Medial Frontal Gyrus	11
3.12	16	−10	18	50	L. Superior Frontal Gyrus	6
3.59	70	−4	−28	57	L. Paracentral Lobule	6
3.44		−10	−37	66	L. Paracentral Lobule	4

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
3.29	13	55	−43	27	R. Inferior Parietal Lobule	40
3.27	39	51	−1	17	R. Precentral Gyrus	6
3.25	18	−42	−23	50	L. Postcentral Gyrus	3
3.16	19	−8	−17	6	L. Thalamus	
5.06	183	42	−61	−15	R. Cerebellum	
3.35		32	−59	−14	R. Cerebellum	
4.81	85	−20	−63	−21	L. Cerebellum	
3.31		−16	−67	−28	L. Cerebellum	
4.36	196	−14	−53	−16	L. Cerebellum	
3.47		−12	−40	−20	L. Cerebellum	
3.44		−4	−49	−18	L. Cerebellum	
3.01	15	−26	−85	−25	L. Cerebellum	
2.97	28	34	−58	−41	R. Cerebellum	
3.20	13	−40	−71	−15	L. Cerebellum	
3.41	10	−20	−88	−18	L. Cerebellum	
3.28	13	−42	−50	−21	L. Cerebellum	
4.02	123	−10	−62	−39	L. Cerebellum	
3.24		−4	−51	−44	L. Cerebellum	
2.97		−2	−72	−37	L. Cerebellum	
3.92	93	24	−52	−34	R. Cerebellum	
3.77		22	−62	−28	R. Cerebellum	
3.79	40	6	−73	−15	R. Cerebellum	

Table 8.

Areas of Increased Activation During Mental Arithmetic Stress in CAD Patients With Depression Without Stress-Induced Myocardial Ischemia

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
4.39	203	18	41	13	R. Medial Frontal Gyrus	10
3.67		18	49	9	R. Medial Frontal Gyrus	10
3.30	14	8	29	34	R. Medial Frontal Gyrus	6
3.78	80	10	44	29	R. Medial Frontal Gyrus	9
3.37		10	43	40	R. Superior Frontal Gyrus	8
3.11	15	8	63	17	R. Medial Frontal Gyrus	10
4.05	208	46	33	2	R. Inferior Frontal Gyrus	46
3.83		51	24	19	R. Inferior Frontal Gyrus	45
3.45		44	36	20	R. Middle Frontal Gyrus	46
3.84	52	51	36	−15	R. Inferior Frontal Gyrus	47
2.97		55	36	−9	R. Inferior Frontal Gyrus	47
3.95	94	59	−22	−11	R. Middle Temporal Gyrus	21
3.87		63	−12	−4	R. Middle Temporal Gyrus	21
3.88	21	−42	4	−42	L. Middle Temporal Gyrus	38
3.18	18	50	4	−27	R. Middle Temporal Gyrus	21
3.69	15	−55	−16	−9	L. Middle Temporal Gyrus	21
3.25	13	10	18	58	R. Superior Frontal Gyrus	6
3.20	16	−2	31	44	L. Superior Frontal Gyrus	8
3.65	32	20	50	−11	R. Middle Frontal Gyrus	11
3.53	66	59	−31	−7	R. Middle Temporal Gyrus	21
3.09		59	−29	3	R. Superior Frontal Gyrus	22
3.47	72	48	10	47	R. Middle Frontal Gyrus	6
2.90		46	4	40	R. Middle Frontal Gyrus	6
2.77		46	12	38	R. Middle Frontal Gyrus	8
3.44	34	55	29	−5	R. Inferior Frontal Gyrus	47
3.20	17	−30	19	−18	L. Inferior Frontal Gyrus	47
3.12	16	−50	34	−15	L. Inferior Frontal Gyrus	47
3.40	11	18	17	36	R. Cingulate Gyrus	32
3.00	12	46	−70	37	R. Precuneus	39
2.94	16	−28	−75	44	L. Superior Parietal Lobule	7
2.86	24	18	24	49	R. Superior Frontal Gyrus	8
3.38	53	34	−63	53	R. Superior Parietal Lobule	7
3.16	13	44	−52	45	R. Inferior Parietal Lobule	40
4.25	94	−12	−79	−35	L. Cerebellum	
2.77		−26	−79	−35	L. Cerebellum	
3.07	20	12	−81	−20	R. Cerebellum	
2.69		10	−83	−26	R. Cerebellum	

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
3.90	43	−26	−79	−21	L. Cerebellum	
3.98	66	20	−77	−30	R. Cerebellum	

Table 9.

Areas of Decreased Activation During Mental Arithmetic Stress in CAD Patients With Depression Without Stress-Induced Myocardial Ischemia

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
4.83	2360	−40	2	−2	L. Insula	13
4.81		−48	−12	28	L. Precentral Gyrus	6
4.71		−40	2	7	L. Insula	13
4.80	1266	40	−12	2	R. Insula	13
4.20		42	−15	15	R. Insula	13
4.18		59	−1	22	R. Precentral Gyrus	6
3.04	18	−34	−17	12	L Insula	13
2.83		53	−26	16	R Postcentral Gyrus	43,40
3.25	15	67	−32	16	R Postcentral Gyrus	43,40
3.23	46	−4	−56	12	L Posterior Cingulate	30,23
2.95		2	−55	19	Posterior Cingulate	23,30
3.39	28	65	−18	19	R Postcentral Gyrus	43,40
2.90	16	24	−14	67	R Precentral Gyrus	6
2.98	18	−14	−32	68	L Paracentral Lobule	4
3.28	23	20	−40	46	R Cingulate Gyrus	31
4.01	107	−2	−45	26	L. Cingulate Gyrus	31
3.76	131	12	−10	43	R. Cingulate Gyrus	31
3.61		−8	−15	41	L. Cingulate Gyrus	24
3.28		10	−5	50	R. Cingulate Gyrus	24
3.42	46	10	−28	33	R. Cingulate Gyrus	23
2.59		8	−37	31	R. Cingulate Gyrus	31
3.51	43	0	28	−13	L. Medial Frontal Gyrus	11
3.63	29	−6	−25	53	L. Medial Frontal Gyrus	6
2.73		−8	−27	44	L. Cingulate Gyrus	31
3.08	27	−2	11	29	L Anterior Cingulate	24
3.25	33	−6	2	42	R Anterior Cingulate	32,24
3.83	32	26	3	−10	R. Subcallosal Gyrus	34
3.28	14	−16	−37	41	L Posterior Cingulate	31
3.16	20	6	−37	39	L Posterior Cingulate	31
3.77	26	−40	39	−4	L. Middle Frontal Gyrus	47
3.31	42	−40	−3	55	L Middle Frontal Gyrus	6
2.94	20	34	−74	−11	R Fusiform Gyrus	19
4.00	13	−20	−88	−14	L. Fusiform Gyrus	18
3.36	13	−28	−85	6	L Middle Occipital Gyrus	19
3.27	13	24	−92	−11	R Inf. Occipital Gyrus	18
3.75	29	40	−80	−3	R. Inf. Occipital Gyrus	19
3.66	36	−30	−84	26	L. Sup. Occipital Gyrus	19

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
3.21	12	−50	−46	8	L Sup. Temporal Gyrus	22
3.19	22	36	−81	10	R Middle Occipital Gyrus	19
3.15	12	−28	−71	−12	L Middle Occipital Gyrus	19
2.90	23	−36	−79	13	L Middle Occipital Gyrus	18
2.74		−40	−79	6	L Middle Occipital Gyrus	18
2.98	11	−2	−78	4	Lingual Gyrus	18
3.63	57	14	−68	5	L. Lingual Gyrus	18
2.70		20	−74	2	R. Lingual Gyrus	18
3.60	31	22	−72	28	R. Precuneus	31
3.06	18	14	−68	33	R. Precuneus	7
3.30	21	−16	−79	22	L Cuneus	18
3.46	29	−2	−68	33	L. Cuneus	7
3.56	42	−10	−80	35	L. Cuneus	19
4.42	52	−6	−16	1	L. Thalamus	
4.24	200	−46	−60	10	L. Mid. Temporal Gyrus	39
3.94		−51	−64	−2	L. Inf. Temporal Gyrus	19
3.35	56	50	−25	9	R Sup. Temporal Gyrus	22
4.16	480	20	−59	−22	R. Cerebellum	
4.12		22	−42	−21	R. Cerebellum	
3.93		24	−57	−14	R. Cerebellum	
3.56	153	−20	−61	−19	L. Cerebellum	
3.27		−10	−51	−16	L. Cerebellum	
3.18		−10	−61	−14	L. Cerebellum	

Table 10.

Areas of Increased Activation During Mental Arithmetic Stress in CAD Patients With Depression and Stress-Induced Myocardial Ischemia

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
4.43	109	57	−53	−11	R. Middle Temporal Gyrus	37
3.91	25	40	6	−37	R. Middle Temporal Gyrus	38
3.36		38	14	−38	R. Middle Temporal Gyrus	38
3.40	12	48	−2	−40	R. Middle Temporal Gyrus	38
3.24	18	−61	−45	−10	L. Middle Temporal Gyrus	21
2.92	11	20	−78	−8	R. Cuneus	17
3.57	12	36	−80	41	R. Precuneus	19
3.97	64	10	22	47	R. Medial Frontal Gyrus	8
3.13	14	−2	35	41	L. Medial Frontal Gyrus	8
3.58	104	16	46	23	R. Superior Frontal Gyrus	9
3.51		12	40	16	R. Medial Frontal Gyrus	9
2.94	13	20	66	8	R. Superior Frontal Gyrus	10
3.35	24	38	37	−7	R. Middle Frontal Gyrus	47
3.52	32	36	−44	43	R. Inferior Parietal Lobule	40
3.29	69	57	33	6	R. Inferior Parietal Lobule	46
3.11		51	36	13	R. Middle Frontal Gyrus	46
3.01		44	33	4	R. Inferior Frontal Gyrus	46
2.97	15	−48	25	26	L. Middle Frontal Gyrus	46
2.98	14	12	34	−10	R. Anterior Cingulate	10
3.26	20	8	45	−2	R. Anterior Cingulate	32
3.29	23	−28	20	3	L. Claustrum	
3.11	12	14	47	−23	R. Orbital Gyrus	11
3.08	16	4	−54	−28	R. Cerebellum	
2.90	24	−28	−62	−36	L. Cerebellum	
2.84		−28	−60	−27	L. Cerebellum	
2.68		−34	−64	−30	L. Cerebellum	

Table 11.

Areas of Decreased Activation During Mental Arithmetic Stress in CAD Patients With Depression and Stress-Induced Myocardial Ischemia

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
5.34	451	−10	−64	36	L. Precuneus	7
3.82		2	−63	23	R. Precuneus	31
3.33		−16	−55	30	L. Cingulate Gyrus	31
3.71	128	16	−53	32	R. Precuneus	31
3.52		14	−65	27	R. Precuneus	31
2.94		18	−63	20	R. Precuneus	31
3.21	28	14	−54	54	R. Precuneus	7
2.74		8	−48	48	R. Precuneus	7
3.18	23	−18	−86	37	L. Cuneus	19
2.93	18	10	−84	34	R. Cuneus	19
2.63		2	−82	39	R. Cuneus	19
3.67	24	24	−86	28	R. Cuneus	19
4.31	209	−42	−23	12	L. Transv. Temporal Gyrus	41
4.09		−46	−32	18	L. Insula	13
3.53	61	34	4	−5	R. Claustrum	
3.28		36	−8	−6	R. Claustrum	
2.85		42	−6	−1	R. Insula	13
3.09	19	−34	−86	25	L. Superior Occipital Gyrus	19
4.04	51	−50	−35	29	L. Inferior Parietal Lobule	40
4.04	89	−53	−61	16	L. Middle Temporal Gyrus	19
4.00		−59	−55	21	L. Superior Temporal Gyrus	22
3.96	20	50	−54	8	R. Superior Temporal Gyrus	39
3.15	18	44	−16	−8	L. Superior Temporal Gyrus	22
3.92	59	51	−67	16	R. Middle Temporal Gyrus	39
3.53	35	−30	−7	6	L. Putamen	
3.71	61	0	−41	26	L. Cingulate Gyrus	31
2.65		−4	−45	34	L. Cingulate Gyrus	31
3.41	18	−6	8	38	L. Cingulate Gyrus	32
3.53	89	−6	−41	44	L. Cingulate Gyrus	31
3.26		−6	−27	38	L. Cingulate Gyrus	31
2.77		−14	−31	42	L. Cingulate Gyrus	31
3.52	23	−14	−63	12	L. Posterior Cingulate	30
3.45	17	18	50	−6	R. Medial Frontal Gyrus	10
3.44	37	−40	−10	11	L. Sub Gyral	21
3.30	25	26	40	18	R. Middle Frontal Gyrus	10
3.24	24	16	−33	3	R. Thalamus	
3.05	19	36	−36	55	R. Postcentral Gyrus	40

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
3.73	27	−63	−22	18	L. Postcentral Gyrus	40
3.71	99	−63	−9	19	L. Postcentral Gyrus	43
3.55		−57	3	13	L. Precentral Gyrus	6
3.56	31	55	−6	37	R. Precentral Gyrus	6
3.30	21	61	−14	32	R. Precentral Gyrus	4
3.19	14	51	−1	26	R. Precentral Gyrus	6
3.19	14	42	−7	45	R. Precentral Gyrus	6
2.69		42	−10	36	R. Precentral Gyrus	6
3.11	28	61	−5	13	R. Precentral Gyrus	43
3.17	12	−40	−6	41	L. Precentral Gyrus	6
2.99	22	34	−80	11	R. Fusiform Gyrus	19
3.88	22	22	−77	28	R. Cerebellum	
3.14	18	26	−46	21	R. Cerebellum	
3.30	19	−24	−61	15	L. Cerebellum	

Table 12.

Areas of Greater Increases in Activation During Mental Arithmetic Stress in CAD Patients With Depression With Compared to Those Without Stress-Induced Myocardial Ischemia

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
4.18	52	−57	−33	44	L. Inferior Parietal Lobule	40
2.82	12	63	−31	42	R. Inferior Parietal Lobule	40
3.00	12	61	−49	26	R. Supramarginal Gyrus	40
3.84	72	8	45	−2	R. Anterior Cingulate	32
3.13		10	36	10	R. Medial Frontal Gyrus	10
3.31	16	10	22	47	R. Medial Frontal Gyrus	8
3.45	25	−8	47	16	L. Medial Frontal Gyrus	9
2.89	11	−2	42	29	L. Medial Frontal Gyrus	9
3.03	29	2	34	24	R. Rectal Gyrus	11
3.63	19	−32	19	40	L. Middle Frontal Gyrus	8
3.51	38	20	−90	−11	R. Fusiform Gyrus	18
3.42	13	32	−12	13	R. Hippocampus	
3.32	16	20	−74	−8	R. Lingual Gyrus	18
3.14	29	34	2	9	R. Claustrum	
3.10	19	−40	6	13	L. Insula	13
2.99	18	51	−8	2	R. Superior Temporal Gyrus	22
2.93	11	−48	−57	30	L. Superior Temporal Gyrus	39
3.40	13	38	14	38	R. Middle Temporal Gyrus	38
3.38	16	−50	−49	−4	R. Middle Temporal Gyrus	37
2.85	11	59	−53	−11	R. Inferior Temporal Gyrus	20
3.35	28	−6	−69	25	L. Cerebellum	

Table 13.

Areas of Greater Decreases in Activation During Mental Arithmetic Stress in CAD Patients With Depression With v Those Without Stress-Induced Myocardial Ischemia

Z score	Voxel Number	Talairach Coordinates x	y	z	Brain region	BA
4.42	139	−10	−64	36	L. Precuneus	7
2.97		−8	−67	29	L. Cuneus	7
4.04	36	16	−53	32	R. Precuneus	31
3.58	31	−53	−63	14	L. Middle Temporal Gyrus	19
3.35	24	−42	−23	14	L. Transverse Temp. Gyrus	41
3.52	30	20	50	−8	R. Medial Frontal Gyrus	10
3.23	46	24	42	18	R. Medial Frontal Gyrus	9
2.72		22	47	11	R. Medial Frontal Gyrus	10
3.44	32	−6	−39	44	L. Cingulate Gyrus	31
3.22	12	36	58	1	R. Middle Frontal Gyrus	10
3.41	27	53	29	−5	R. Inferior Frontal Gyrus	47
3.21	19	16	−35	4	R. Thalamus	
3.13	14	14	−12	−16	R. Parahippocampal Gyrus	34
2.98	14	32	−73	−26	R. Cerebellum	
4.99	67	22	−77	−28	R. Cerebellum	