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Brain Correlates of Stress-Induced Peripheral Vasoconstriction in Patients with Cardiovascular Disease

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Abstract

The influence of acute psychological stress on cardiovascular disease is an emerging public health concern. Identification of brain mechanisms underlying this may aid in the discovery of possible treatments. Acute psychological stress may induce arteriolar vasoconstriction and reduce blood flow to vital organs. We hypothesized that functional changes in brain regions involved with memory and autonomic/emotional regulation are implicated in the vasoconstrictive stress response, including the medial prefrontal cortex (anterior cingulate), insula, and dorsolateral prefrontal cortex. Subjects with a history of coronary artery disease (CAD) ($N=59$) underwent measurement of microvascular vasomotor tone with the EndoPAT device and O-15 positron emission tomography (PET) imaging of the brain during exposure to mental stress and control conditions. The peripheral arterial tonometry (PAT) ratio was calculated as the mean peripheral vasomotor tone during stress divided by the mean tone during rest. Whole brain contrasts were performed between groups above and below the median PAT ratio, and significant contrasts were

defined with cutoff $p < 0.005$. Stress-induced peripheral vasoconstriction (below median PAT ratio) was associated with increased stress activation in insula and parietal cortex, and decreased activation in the medial prefrontal cortex with stress tasks compared to control tasks. These findings demonstrate that stress-induced vasoreactivity is associated with changes in brain responses to stress in areas involved in emotion, and autonomic regulation. These findings have important implications on possible treatments for mental stress-induced vascular toxicity.

1. Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality world-wide, and despite decades of research, its incidence is difficult to predict (Roth et al., 2015). Traditional risk factors such as smoking, age, diabetes, serum cholesterol, serum hypercholesterolemia and systemic hypertension, do not account for all of the risk for CAD (DeFilippis, Young, Carrubba, & et al., 2015). The influence of acute psychological stress on cardiovascular disease is an emerging public health concern (Rosengren et al., 2004; Steptoe & Kivimaki, 2013; Strike & Steptoe, 2005; Vaccarino & Bremner, 2017). The population attributable risk of CAD due to chronic stress has been suggested to be 33%, which suggests a major contributory role (Rosengren et al., 2004). A recent meta-analysis showed that greater stress reactivity was significantly associated with increased incidence of cardiovascular events (Chida & Steptoe, 2010). Thus understanding the mechanisms by which mental stress reactivity increases cardiovascular disease risk is of potential utility in reducing cardiovascular disease risk beyond modification of traditional risk factors alone.

Coronary microvascular constriction during acute mental stress is hypothesized to represent an important mechanism behind mental stress-induced myocardial ischemia (MSI) (Vaccarino, 2016), which is associated with an over 2-fold increase of adverse cardiovascular events (Wei et al., 2014). Peripheral arterial tonometry (PAT) is a method that uses a noninvasive plethysmographic finger-mounted device that can continuously measure the arterial pulse volume in the finger. Stress-induced peripheral vasoconstriction measured with PAT is a strong predictor of MSI, and thus represents a useful marker of MSI (Chenzbraun et al., 2001; Goor et al., 2004; Hassan et al., 2009; Schnall, Shlitner, Sheffy, Kedar, & Lavie, 1999). Although the mechanisms are not certain, it is likely that vasoconstriction due to stress is caused at least partly by increased sympathetic nervous system activity.

No studies, to the best of our knowledge, have examined the brain mechanisms through which acute emotional stress leads to peripheral vasoconstriction; such a study may provide insight on possible treatments for stress-induced vasoconstriction (Lazar et al., 2005). Brain areas involved in the regulation of mental stress-related changes in heart rate variability include the prefrontal cortex, anterior cingulate, insula, and amygdala (Thayer, Hansen, Saus-Rose, & Johnsen, 2009). These brain areas are also involved in emotional regulation and have direct and indirect pathways that regulate peripheral cardiovascular and neurohormonal responses to stress (Campanella & Bremner, 2016; Vaccarino & Bremner, 2017). We hypothesized that patients with greater stress-induced peripheral vasoconstriction will have greater stress-induced changes in brain areas involved in the regulation of emotion,

and peripheral cardiovascular responses to stress, including the medial prefrontal cortex (anterior cingulate), prefrontal cortex, and insula. Understanding the relationship between brain perfusion and vasoconstriction during mental stress may ultimately help guide therapies for patients with abnormal stress reactivity (Lazar et al., 2005).

2. Method

2.1 Population

We studied 59 patients with a history of coronary artery disease (CAD) who were part of the Mental Stress Ischemia Prognosis Study (M. Hammadah et al., 2016). All patients were recruited from Emory University Hospital, Grady Memorial Hospital and the Atlanta VA Medical Center. Baseline demographic information, risk factors for CAD and medication status are presented in Table 1. There were a larger number of men ($N = 44$) than women ($N = 15$).

CAD was defined based on chart review, and included: a previous cardiac catheterization showing any degree of stenosis, history of prior myocardial infarction, a history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) at least one year prior to the study, or a positive nuclear stress test. Patients were excluded if they had had a recent acute coronary syndrome, 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 (SCID) (First, Spitzer, Gibbon, & Williams, 1997) of a severe mental disorder other than depression, including schizophrenia, psychotic depression, bipolar disorder, or alcohol or substance dependence in the past year, history of loss of consciousness of more than one minute, history of neurological disorder, such as dementia, stroke, or Parkinson's Disease, or contraindications to regadenoson administration. Beta-adrenergic antagonists were withheld for 24 hours and calcium channel blockers and nitrates for at least 12 hours prior to the stress test. Left ventricular ejection fraction was evaluated from myocardial perfusion imaging during the first baseline visit for the patients as previously described (M. Hammadah et al., 2016). 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 (IRB).

2.2 Measurement of Vasoconstriction using Peripheral Arterial Tonometry

The EndoPAT™ Peripheral Arterial Tonometry (PAT) device (Itamar-Medical, Israel) was used to measure peripheral vascular reactivity. 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 (Hassan et al., 2009). Pressure changes accompanying peripheral volume changes are fed to a personal computer by which the signal is bandpass filtered (0.3 to 30 Hz), amplified, displayed and stored. After eliminating areas of artifact through identification and exclusion of noisy PAT signal (high amplitude or nonphysiologic waveform), microvascular

vasoconstriction was measured by pulse wave amplitude at stress (mean during 4 stress tasks) compared to baseline rest (mean during 4 control tasks). Median PAT values for baseline-corrected response to stress were used to divide subjects into high and low vasoconstrictors based on PAT response to stress. The high vasoconstrictors were those with PAT values less than the median value the low vasoconstrictors were those with PAT at or above the median.

2.3 Brain Imaging

Patients underwent positron emission tomography (PET) imaging of the brain with the High Resolution Research Tomograph (HRRT) (Siemens, Inc.) (Schmand et al., 1999). This device has 2 mm spatial resolution. Subjects underwent eight PET scans of the brain (separated by 10 minutes) in conjunction with control and stressful tasks. During each scan, radiolabeled water ($\text{H}_2\text{O}[\text{O}^{15}]$), produced in an on-site cyclotron, was injected for measurement of brain blood flow.

The mental stress test was performed by experienced staff using mental arithmetic and public speaking. By having two types of stress tasks, we were able to minimize habituation and extinction of the stress reaction, and therefore maximize the stress effect. Each scan session was repeated to improve precision and reduce random error. The first four scans were control scans, followed by four stress scans. They were matched by type of task in order to remove any effects related to the task itself. For the first two control scans, participants were requested to count out loud (arithmetic control); next, they read a paragraph aloud for two scans (public speaking control). The next four scans were stress scans that were similar in theme to the neutral scans. The first two stress scans were mental arithmetic stress (compared to counting out loud); they were asked to perform a series of increasingly complicated mathematical calculations under time pressure, including addition, subtraction, multiplication and division. They also received negative feedback from a staff member who was wearing a white lab coat. The last two scans were public speaking stressors (compared to reading out loud), in which patients responded to scripted instructions to describe two situations; one involved a long-term house guest who had overstayed her welcome. The other involved an uncomfortable situation in which an elderly sister was unfairly hit while driving in a parking lot. In both scenarios, they were asked to prepare and give a speech for two minutes. They were told the speech would be evaluated for content.

All scanning sessions lasted for 2 minutes and 20mCi of radiolabeled water were injected 10 seconds after each task started to ensure that radioactive isotope uptake was maximal during peak stress at 2 minutes into stress (Muhammad Hammadah et al., 2017; Kanno, Iida, Miura, & Murakami, 1991).

2.4 Statistical Analysis

Gender-based analyses were performed due to the known relationship of PAT ratio and gender (higher in women), and therefore a separate median cut-point was used for each gender to define high and low vasoconstrictors (Vaccarino et al., 2018). We first compared baseline characteristics between case and control groups. High and low vasoconstrictors were compared for demographic variables using Chi-square tests or Fisher's exact tests for

categorical variables, and two-sample t-tests for continuous variables. The distribution of continuous variables was examined for normality as a requirement for parametric testing; if not normal, the Wilcoxon rank-sum test was used.

As an added step to evaluate for potential confounding due to independent effects on PAT ratio, we performed a multivariable linear regression model to evaluate for potential independent baseline demographic variables or risk factors for CAD that may independently associate with PAT. Data were analyzed using SAS 9.4 and statistical significance was evaluated using an $\alpha = 0.05$ cut-point.

Reconstructed PET images were realigned, smoothed (using a spatially stationary Gaussian filter), and transformed into a common anatomical space for analysis using statistical parametric mapping (SPM8) (Penny, Friston, Ashburner, Kiebel, & Nichols, 2011). Analysis of variance was used to compare brain perfusion by voxel, with minimum voxel clusters of 11 voxels and an alpha level of < 0.005 used to define statistical significance. This statistic minimizes risk of both Type 1 and Type 2 error (Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; Reiman et al., 1997).

Six whole-brain contrasts were performed to compare brain perfusion between various contexts; 1) Stress minus rest (stress-induced activation) in the high vasoconstrictor group, 2) Rest minus stress (stress-induced deactivation) in the high vasoconstrictor group, 3) Stress minus rest in the low vasoconstrictor group, 4) Rest minus stress in the low vasoconstrictor group, 5) Difference in stress activations in high minus low vasoconstrictor groups, and 6) Difference in stress deactivations in high minus low vasoconstrictor groups. For the last 2 contrasts, the clusters which showed significant relationships were then evaluated for a dose-response relationship with PAT ratio by calculating the spearman correlation adjusted for gender. Areas in which differences in brain blood flow were found between groups were identified by coordinates from a standard neuroanatomical atlas (Talairach & Tournoux, 1988).

3. Results

The sample consisted of 59 subjects. The mean (standard deviation) age was 61 (9) years, 25% were women, 41% were African American, 39% had history of myocardial infarction, and the mean ejection fraction was 71% (11%). There were no differences between CAD patients with and without stress-induced peripheral vasoconstriction in men or women in demographic variables (including age or race) or risk factors for CAD (including smoking, hypertension and diabetes (Table 1)). As per table 2, although gender was associated with higher PAT ratio with 0.25 units higher ratio in women than men ($p = 0.04$) (table 2a), when using gender-specific cutpoints for PAT, no significant associations were found between baseline factors and vasoconstriction. INSERT TABLE 1 ABOUT HERE

Mental stress was associated with increased activation in the inferior frontal gyrus and parietal cortex in both groups (Table 3–6). INSERT TABLES 3–6 ABOUT HERE Decreases were seen in the precentral and postcentral gyrus, lingual and fusiform gyrus, and medial occipital gyrus. In the high vasoconstrictor group, mental stress was additionally associated

with increased activation in the dorsolateral prefrontal cortex (superior and middle frontal gyrus), cuneus, medial prefrontal cortex (anterior cingulate, medial frontal gyrus, and medial orbital gyrus), insula, and superior occipital gyrus (Table 5 and Figure 1). INSERT TABLE 5 AND FIGURE 1 ABOUT HERE Furthermore, the high vasoconstrictors had additional decreases in paracentral lobule and inferior occipital gyrus (Table 6). INSERT TABLE 6 ABOUT HERE Low vasoconstrictors had additional decreases in insula, precuneus, cingulum and putamen (Table 4).

When high vasoconstricting patients were compared to low vasoconstricting patients (tables 7 and 8), there were greater increases in activation with stress in insula, superior frontal cortex, parietal cortex (angular and supramarginal gyrus), superior and middle temporal gyrus, and putamen. INSERT TABLES 7 AND 8 ABOUT HERE Mental stress was also associated with greater decreased activation in medial frontal gyrus, cuneus, and middle frontal gyrus in high vs. low vasoconstrictors. Other differences in parts of inferior frontal gyrus, precuneus and inferior parietal lobule were also found. Mild to moderate correlations were found for all regions.

4. Discussion

We found that CAD patients with high stress-induced peripheral vasoconstriction showed a unique pattern of brain activation, involving brain areas implicated in stress and regulation of peripheral cardiovascular function in response to stress compared to low vasoconstrictors (Campanella & Bremner, 2016). Most notably, we found that high vasoconstrictors showed increased activation with stress (vs. low vasoconstrictors) in the insula and parietal cortex, and decreased activation in medial prefrontal cortex. The inferior frontal gyrus showed both increases and decreases in different parts of this region.

Several regions in which differences between vasoconstrictor groups were found also have plausible biological mechanisms. The insula, which was more active with stress in the high vasoconstrictors, plays a key role in regulation of peripheral cardiovascular responses to stress (de Morree, Szabo, Rutten, & Kop, 2013; K. Nagai, S. Hoshide, & K. Kario, 2010; Nagai, Kishi, & Kato, 2007), and has been found to consistently activate with psychological stress (Kogler et al., 2015). Increased insula activity leads to sympathetic activation and parasympathetic deactivation. Furthermore, the insula has connections with the anterior cingulate cortex, amygdala, prefrontal cortex, superior temporal gyrus, hippocampus and many other brain areas that modulate emotional and physiological responses to stress (Nagai et al., 2007). Previous research has shown that the insular cortex is involved in stress-related psychiatric disorders (Nagai et al., 2007) including panic disorder (Javanmard et al., 1999), anxiety disorders (Stein, Simmons, Feinstein, & Paulus, 2007), and posttraumatic stress disorder (PTSD) (Chen, Li, Xu, & Liu, 2009; Chen et al., 2006; Lanius R.A., 2015; Rauch et al., 1996; Simmons, Strigo, Matthews, Paulus, & Stein, 2009; Teicher, Anderson, Ohashi, & Polcari, 2014). The anterior insula is particularly important for the purposes of interoception, performance monitoring, and predictive coding; this can have an important influence on action states and link together peripheral vasomotor tone with afferent cardiac signals (Marshall, Gentsch, & Schütz-Bosbach, 2018).

High vasoconstrictors also showed greater activation of the parietal cortex during stress. The parietal lobe plays an important role in perception of the self in space and time, contextual cues, and visuospatial memory (Bremner, Krystal, Southwick, & Charney, 1995; Jonides et al., 1993; Pardo, Fox, & Raichle, 1991; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Zandbelt, Bloemendaal, Neggens, Kahn, & Vink, 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 also implicated this region in stress-related psychiatric disorders (van Rooij, Geuze, Kennis, Rademaker, & Vink, 2015). Individuals at increased risk for cardiovascular disease 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 studies support our findings of increased parietal cortical response to stress in high vs. low vasoconstrictors.

The inferior frontal gyrus showed both increases and decreases in different parts of this region during stress in the peripheral vasoconstricting patients. This area has connections to the parietal lobe and together these brain areas could mediate a heightening of activity in brain areas involved in perception and cognition during stress. The frontal cortex also regulates insula function, and via this connection also peripheral autonomic activity (Napadow et al., 2008). These regions form the central autonomic network, which along with the amygdala and anterior cingulate gyrus, and regulate both arms of the autonomic nervous system (M. Nagai, S. Hoshida, & K. Kario, 2010).

Brain areas that showed relative deactivation in peripheral vasoconstrictors included the medial prefrontal cortex (anterior cingulate) and cuneus. The medial prefrontal cortex, which consists of several related areas including the orbitofrontal cortex, anterior cingulate and subcallosal gyrus, and anterior prefrontal cortex (Devinsky, Morrell, & Vogt, 1995; Vogt, Finch, & Olson, 1992), have inhibitory inputs to the amygdala, which mediates fear memories (Morgan & LeDoux, 1995; G.J. Quirk, 2002; G.J. Quirk, Russo, Barron, & Lebron, 2000). Inhibition of the amygdala by the medial prefrontal cortex represents the mechanism of extinction of fear memories, and a failure in function in this area could lead to increased amygdala function with associated increases in fear and stress reactions (G.J. Quirk et al., 2000). 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 via direct outputs from this area to the periphery (Devinsky et al., 1995; G.J. Quirk, 2002; G. J. Quirk, Garcia, & Gonzalez-Lima, 2006; G.J. Quirk et al., 2000; Vogt et al., 1992). Studies have consistently linked hypofunction in the medial prefrontal cortex to PTSD and other stress-related psychiatric disorders (Bremner, 2011; Bremner, Narayan, et al., 1999; Bremner, Staib, et al., 1999a, 1999b; Campanella & Bremner, 2016; Etkin & Wager, 2007). The amygdala, like the insula, plays a critical role in regulation of peripheral cardiovascular responses to stress, via indirect sympathetic pathways through the hypothalamus to the periphery. This could therefore represent a mechanism for peripheral vasoconstriction in susceptible patients.

This research has several limitations. First, our findings are not generalizable beyond subjects with CAD. Nonetheless, this is an important population to study because of their

high morbidity and mortality. Second, stress challenges in the laboratory may not reflect real-life stress. However, laboratory studies offer a controlled environment where specific effects can be tested with greater precision. Additionally, we are assuming that higher acute stress reactivity leads to greater adverse outcomes, but must also allow for the possibility that blunted reactivity may also be pathological (Phillips, Ginty, & Hughes, 2013). This may therefore limit the accuracy and prognostic implications of these findings. The statistical threshold of $p < 0.005$ is less conservative than other approaches such as Bonferroni, and therefore the possibility of type I error must be considered. Despite this our findings are supported by biological plausibility as discussed. Additionally, our whole-brain analysis with PAT as a dichotomous exposure may limit the statistical power (increasing changes of type II error) and ability to find a dose-response relationship, which would be more robust. Despite this, several highly significant findings were noted.

These findings potentially have implications for clinical practice, as they shift the evaluation of peripheral stress reactivity away from vascular biology and towards neurobiology. Currently for most vascular diseases, stress reduction is not a mainstay of clinical practice. Understanding brain mechanisms may help target more effective treatments for these patients than has been available up to now with the focus on modification of traditional risk factors of cardiovascular disease. For instance, for some patients interventions aimed at brain and behavior, like relaxation or mindfulness training, could be useful in reducing stress-induced cardiovascular morbidity and mortality (Holzel et al., 2011; Lazar et al., 2005). Such interventions would represent a major change in cardiovascular prevention efforts from the current focus of traditional risk factors (hypertension, cigarette smoking, diabetes, and dyslipidemia).

In conclusion, we found that peripheral vasoconstriction during mental stress in CAD patients was associated with increased activation in several brain areas involved in the stress response systems, including the insular and parietal cortex, with decreased function in medial frontal cortex. These findings suggest a mechanism by which brain areas involved in fear inhibition, and visuospatial processing of threat could be involved in stress-related vascular function. Future studies should evaluate the effects of interventions such as meditation that may alter stress-induced changes in the brain as well as improve cardiovascular reactivity.

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5. References

- Bremner JD (2003). Functional neuroanatomical correlates of traumatic stress revisited 7 years later, this time with data. *Psychopharmacology Bulletin*, 37(2), 6–25. 0894-9867D5/1000-0527507.50/NO DOI

- Bremner JD (2011). Stress and human neuroimaging studies. In Conrad CD(Ed.), *The Handbook of Stress: Neuropsychological Effects on the Brain*. West Sussex, United Kingdom: Blackwell Press 10.1002/9781118083222.ch22
- Bremner JD, Krystal JH, Southwick SM, & Charney DS (1995). Functional neuroanatomical correlates of the effects of stress on memory. *Journal of Traumatic Stress*, 8, 527–554. 10.1002/jts.2490080403 [PubMed: 8564272]
- Bremner JD, Narayan M, Staib LH, Southwick SM, McGlashan T, & Charney DS (1999). Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *American Journal of Psychiatry*, 156(11), 1787–1795. 10.1176/ajp.156.11.1787 (INCORRECT IN PUBMED) [PubMed: 10553744]
- Bremner JD, Staib L, Kaloupek D, Southwick SM, Soufer R, & Charney DS (1999a). Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: A positron emission tomography study. *Biology Psychiatry*, 45, 806–816. 10.1016/S0006-3223(98)00297-2
- Campanella C, & Bremner JD (2016). Neuroimaging of PTSD. In Bremner JD(Ed.), *Posttraumatic Stress Disorder: From Neurobiology to Treatment* (pp. 291–320). Hoboken, New Jersey: Wiley 10.1002/9781118356142.ch12
- Chen S, Li L, Xu B, & Liu J (2009). Insular cortex involvement in declarative memory deficits in patients with post-traumatic stress disorder. *BMC Psychiatry*, 9, 39 10.1186/1471-244X-9-39 [PubMed: 19538748]
- Chen S, Xia W, Li L, Liu J, He Z, Zhang Z, ... Hu D (2006). Gray matter density reduction in the insula in fire survivors with posttraumatic stress disorder: a voxel-based morphometric study. *Psychiatry Research: Neuroimaging*, 146(1), 65–72. 10.1016/j.psychres.2005.09.006
- Chen Zbraun A, Levin G, Scheffy J, Keren A, Stern S, & Goor D (2001). The peripheral vascular response to exercise is impaired in patients with risk factors for coronary artery disease. *Cardiology*, 95(3), 126–130. 10.1159/000047358 [PubMed: 11474157]
- Chida Y, & Steptoe A (2010). Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: a meta-analysis of prospective evidence. *Hypertension*, 55(4), 1026–1032. 10.1161/HYPERTENSIONAHA.109.146621 [PubMed: 20194301]
- Chuang Y-F, Eldreth D, Erickson KI, Varma V, Harris G, Fried LP, ... Carlson MC (2014). Cardiovascular risks and brain function: a functional magnetic resonance imaging study of executive function in older adults. *Neurobiology of Aging*, 35(6), 1396–1403. 10.1016/j.neurobiolaging.2013.12.008 [PubMed: 24439485]
- de Morree HM, Szabo BM, Rutten G-J, & Kop WJ (2013). Central nervous system involvement in the autonomic responses to psychological distress. *Netherlands Heart Journal*, 21, 64–69. 10.1007/s12471-012-0351-1 [PubMed: 23184602]
- DeFilippis AP, Young R, Carrubba CJ, & et al. (2015). An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Annals of Internal Medicine*, 162(4), 266–275. 10.7326/M14-1281 [PubMed: 25686167]
- Devinsky O, Morrell MJ, & Vogt BA (1995). Contributions of anterior cingulate to behavior. *Brain*, 118(1), 279–306. <https://doi-org.proxy.library.emory.edu/10.1093/brain/118.1.279> [PubMed: 7895011]
- Etkin A, & Wager TD (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry*, 164(10), 1476–1488. 10.1176/appi.ajp.2007.07030504 [PubMed: 17898336]
- First MB, Spitzer RL, Gibbon M, & Williams JBW (1997). *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version*: American Psychiatric Press.
- Goor DA, Sheffy J, Schnall RP, Arditti A, Caspi A, Bragdon EE, & Sheps DS (2004). Peripheral arterial tonometry: a diagnostic method for detection of myocardial ischemia induced during mental stress tests: a pilot study. *Clinical Cardiology*, 27(3), 137–141. 10.1002/clc.4960270307 [PubMed: 15049379]
- Hammadah M, Al Mheid I, Wilmot K, Ramadan R, Shah AJ, Sun Y, ... Quyyumi AA (2017). The Mental Stress Ischemia Prognosis Study (MIPS): Objectives, study design, and prevalence of

inducible ischemia. *Psychosomatic Medicine*, 79(3), 311–317. 10.1097/PSY.0000000000000442 [PubMed: 28002382]

- Hammadah M, Alkhoder A, Al Mheid I, Wilmot K, Isakadze N, Abdulhadi N, ... Quyyumi AA (2017). Hemodynamic, catecholamine, vasomotor and vascular responses: Determinants of myocardial ischemia during mental stress. *International Journal of Cardiology*, 243, 47–53. 10.1016/j.ijcard.2017.05.093 [PubMed: 28571621]
- Hassan M, York KM, Li H, Li Q, Lucey DG, Fillingim RB, & Sheps DS (2009). Usefulness of peripheral arterial tonometry in the detection of mental stress-induced myocardial ischemia. *Clinical Cardiology*, 32(9), E1–6. 10.1002/clc.20515
- Holzel BK, Carmody J, Vangel M, Congleton C, Yerramsetti SM, Gard T, & Lazar SW (2011). Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Research: Neuroimaging*, 191(1), 36–43. 10.1016/j.pscychresns.2010.08.006 [PubMed: 21071182]
- Javanmard M, Shlik J, Kennedy SH, Vaccarino FJ, Houle S, & Bradwejn J (1999). Neuroanatomic correlates of CCK-4-induced panic attacks in healthy humans: a comparison of two time points. *Biology Psychiatry*, 45(7), 872–882. 10.1016/S0006-3223(98)00348-5
- Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S, & Mintun MA (1993). Spatial working memory in humans as revealed by PET. *Nature*, 363(6430), 623–625. 10.1038/363623a0 [PubMed: 8510752]
- Kanno I, Iida H, Miura S, & Murakami M (1991). Optimal scan time of oxygen-15-labeled water injection method for measurement of cerebral blood flow. *Journal of Nuclear Medicine*, 32(10), 1931–1934. [PubMed: 1919735]
- Kogler L, Mueller VI, Chang A, Eickhoff SB, Fox PT, Gur RC, & Dernti B (2015). Psychosocial versus physiological stress - Meta analyses on deactivations and activations of the neural correlates of stress reactions. *Neuroimage*, 119, 235–251. 10.1016/j.neuroimage.2015.06.059 [PubMed: 26123376]
- Lane RD, Reiman EM, Ahern CE, Schwartz GE, & Davidson RJ (1997). Neuroanatomical correlates of happiness, sadness, and disgust. *American Journal of Psychiatry*, 154(7), 926–933. 10.1176/ajp.154.7.926 [PubMed: 9210742]
- Lanius RAF.P.A, Tursich M, Jetly R, McKinnon MC (2015). Restoring large-scale brain networks in PTSD and related disorders: A proposal for neuroscientifically-informed treatment interventions. *European Journal of Psychotraumatology*, 6 10.3402/ejpt.v6.27313
- Lazar SW, Kerr CE, Wasserman RH, Gray JR, Greve DN, Treadway MT, ... Fischl B(2005). Meditation experience is associated with increased cortical thickness. *Neuroreport*, 16(17), 1893–1897. 10.1097/01.wnr.0000186598.66243.19 [PubMed: 16272874]
- Marshall AC, Gentsch A, & Schütz-Bosbach S (2018). The Interaction between Interoceptive and Action States within a Framework of Predictive Coding. *Frontiers in Psychology*, 9, 180 10.3389/fpsyg.2018.00180 [PubMed: 29515495]
- Morgan CA, & LeDoux JE (1995). Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Behavioral Neuroscience*, 109(4), 681–688. <http://dx.doi.org.proxy.library.emory.edu/10.1037/0735-7044.109.4.681> [PubMed: 7576212]
- Nagai K, Hoshida S, & Kario K (2010). The insular cortex and cardiovascular system: a new insight into the brain-heart axis. *Journal of the American Society of Hypertension*, 4(4), 174–182. 10.1016/j.jash.2010.05.001 [PubMed: 20655502]
- Nagai M, Kishi K, & Kato S (2007). Insular cortex and neuropsychiatric disorders: a review of recent literature. *European Psychiatry*, 22(6), 387–394. 10.1016/j.eurpsy.2007.02.006 [PubMed: 17416488]
- Napadow V, Dhond R, Conti G, Makris N, Brown EN, & Barbieri R (2008). Brain correlates of autonomic modulation: combining heart rate variability with fMRI. *Neuroimage*, 42(1), 169–<https://dx.doi.org/10.1016%2Fj.neuroimage.2008.04.238> [PubMed: 18524629]
- Pardo JV, Fox PT, & Raichle ME (1991). Localization of a human system for sustained attention by positron emission tomography. *Nature*, 349(6304), 61–64. 10.1038/349061a0 [PubMed: 1985266]
- Penny WD, Friston KJ, Ashburner JT, Kiebel SJ, & Nichols TE (2011). *Statistical parametric mapping: the analysis of functional brain images*: Elsevier.

- Petersen SE, Fox PT, Posner MI, Mintun MA, & Raichle ME (1988). Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature*, 331(6157), 585–589. 10.1038/331585a0 [PubMed: 3277066]
- Phillips AC, Ginty AT, & Hughes BM (2013). The other side of the coin: blunted cardiovascular and cortisol reactivity are associated with negative health outcomes. *International Journal of Psychophysiology*, 90(1), 1–7. 10.1016/j.ijpsycho.2013.02.002 [PubMed: 23454029]
- Quirk GJ (2002). Memory for extinction of conditioned fear is long-lasting and persists following spontaneous recovery. *Learning & Memory*, 9(6), 402–407. 10.1101/lm.49602
- Quirk GJ, Garcia R, & Gonzalez-Lima F (2006). Prefrontal mechanisms in extinction of conditioned fear. *Biology Psychiatry*, 60(4), 337–343. 10.1016/j.biopsych.2006.03.010
- Quirk GJ, Russo GK, Barron JL, & Lebron K (2000). The role of ventromedial prefrontal cortex in the recovery of extinguished fear. *The Journal of Neuroscience*, 20(16), 6225–6231. 10.1523/JNEUROSCI.20-16-06225.2000 [PubMed: 10934272]
- Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, ... Pitman RK (1996). A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Archives of General Psychiatry*, 53(5), 380–387. 10.1001/archpsyc.1996.01830050014003 [PubMed: 8624181]
- Reiman EM, Lane RD, Ahern GL, Schwartz GE, Davidson RJ, Friston KJ, ... Chen K (1997). Neuroanatomical correlates of externally and internally generated human emotion. *American Journal of Psychiatry*, 154(7), 918–925. 10.1176/ajp.154.7.918 [PubMed: 9210741]
- Rosengren A, Hawken S, Ôunpuu S, Sliwa K, Zubaid M, Almahmeed WA, ... Yusuf S (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. *The Lancet*, 364(9438), 953–962. 10.1016/S0140-6736(04)17019-0
- Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, & Murray CJ (2015). Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation*, 132(17), 1667–1678. 10.1161/CIRCULATIONAHA.114.008720 [PubMed: 26503749]
- Schmand M, Weinhard K, Casey ME, Eriksson L, Jones WF, Reed JH, ... Nutt R (1999). Performance evaluation of a new LSO High Resolution Research Tomograph-HRRT. *IEEE Transactions on Medical Imaging*, 2(October Nuclear Medicine Science), 1067–1071. 10.1109/NSSMIC.1999.845845
- Schnall RP, Shlitner A, Sheffy J, Kedar R, & Lavie P (1999). Periodic, profound peripheral vasoconstriction--a new marker of obstructive sleep apnea. *Sleep*, 22(7), 939–946. <https://doi-org.proxy.library.emory.edu/10.1093/sleep/22.7.939> [PubMed: 10566912]
- Simmons A, Strigo IA, Matthews SC, Paulus MP, & Stein MB (2009). Initial evidence of a failure to activate right anterior insula during affective set shifting in posttraumatic stress disorder. *Psychosomatic Medicine*, 71(4), 373–377. 10.1097/PSY.0b013e3181a56ed8 [PubMed: 19398499]
- Stein MB, Simmons AN, Feinstein JS, & Paulus MP (2007). Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *American Journal of Psychiatry*, 164(2), 318–327. 10.1176/ajp.2007.164.2.318 [PubMed: 17267796]
- Steptoe A, & Kivimäki M (2013). Stress and cardiovascular disease: an update on current knowledge. *Annual Review of Public Health*, 34, 337–354. 10.1146/annurev-publhealth-031912-114452
- Strike PC, & Steptoe A (2005). Behavioral and emotional triggers of acute coronary syndromes: a systematic review and critique. *Psychosomatic Medicine*, 67(2), 179–186. 10.1097/01.psy.0000155663.93160.d2 [PubMed: 15784781]
- Talairach J, & Tournoux P (1988). Co-planar stereotaxic atlas of the human brain: Three-dimensional proportional system. Stuttgart, Germany: Georg Thieme.
- Teicher MH, Anderson CM, Ohashi K, & Polcari A (2014). Childhood maltreatment: Altered network centrality of cingulate, precuneus, temporal pole and insula. *Biology Psychiatry*, 76(4), 297–305. 10.1016/j.biopsych.2013.09.016
- Thayer JF, Hansen AL, Saus-Rose E, & Johnsen BH (2009). Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Annals of Behavior Medicine*, 37(2), 141–153. 10.1007/s12160-009-9101-z

- Vaccarino V (2016). Mental Stress-Induced Myocardial Ischemia. In Baune BT & Tully PJ (Eds.), *Cardiovascular Diseases and Depression - Treatment and Prevention in Psychocardiology*: Springer.
- Vaccarino V, & Bremner JD (2017). Behavioral, emotional and neurobiological determinants of coronary heart disease risk in women. *Neuroscience & Biobehavioral Reviews*, 74(Pt B), 297–309. 10.1016/j.neubiorev.2016.04.023 [PubMed: 27496672]
- Vaccarino V, Sullivan S, Hammadah M, Wilmot K, Al Mheid I, Ramadan R, ... Raggi P (2018). Mental Stress-Induced-Myocardial Ischemia in Young Patients With Recent Myocardial Infarction: Sex Differences and Mechanisms. *Circulation*, 137(8), 794–805. 10.1161/circulationaha.117.030849 [PubMed: 29459465]
- van Rooij SJH, Geuze E, Kennis M, Rademaker AR, & Vink M (2015). Neural correlates of inhibition and contextual cue processing related to treatment response in PTSD. *Neuropsychopharmacology*, 40, 667–675. 10.1038/npp.2014.220 [PubMed: 25154707]
- Vogt BA, Finch DM, & Olson CR (1992). Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cerebral Cortex*, 2(6), 435–443. <https://doi-org.proxy.library.emory.edu/10.1093/cercor/2.6.435-a> [PubMed: 1477524]
- Wei J, Rooks C, Ramadan R, Shah AJ, Bremner JD, Quyyumi AA, ... Vaccarino V (2014). Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. *The American Journal of Cardiology*, 114(2), 187–192. 10.1016/j.amjcard.2014.04.022 [PubMed: 24856319]
- Zandbelt BB, Bloemendaal M, Neggers SFW, Kahn RS, & Vink M (2013). Expectations and violations: delineating the neural network of proactive inhibitory control. *Human Brain Mapping*, 34(9), 2015–2024. 10.1002/hbm.22047 [PubMed: 22359406]

Figure 1.
Areas of greater increases in activation with mental stress in CAD patients with stress-induced peripheral vasoconstriction (left) compared to those without peripheral vasoconstriction (right) demonstrating increased activation in parietal cortex and inferior frontal gyrus.

Table 1.

Descriptive analysis for predictor and controlled variables. Case = High vasoconstrictor, and control = low vasoconstrictor

		Female (<i>n</i> = 15)			Male (<i>n</i> = 44)		
		Case N(%)	Control N(%)	<i>p</i> value	Case N(%)	Control N(%)	<i>p</i> value
age		62.71 (8.12)	58.63 (9.10)	0.3783	62.41 (10.85)	61.73 (7.46)	0.8093
African American	Yes	6 (54.55)	5 (45.45)	0.5692	8 (53.33)	7 (46.67)	0.7505
	No	1 (25.00)	3 (75.00)		14 (48.28)	15 (51.72)	
History of coronary bypass surgery	Yes	2 (50.00)	2 (50.00)	1.0000	8 (50.00)	8 (50.00)	1.0000
	No	5 (45.45)	6 (54.55)		14 (50.00)	14 (50.00)	
Heart Failure	Yes	2 (66.67)	1 (33.33)	0.5692	1 (100.00)	0 (0.00)	1.0000
	No	5 (41.67)	7 (58.33)		21 (48.84)	22 (51.16)	
Diabetes	Yes	1 (20.00)	4 (80.00)	0.2821	3 (30.00)	7 (70.00)	0.1502
	No	6 (60.00)	4 (40.00)		19 (55.88)	15 (44.12)	
Past smoker	Yes	5 (55.56)	4 (44.44)	0.6084	10 (43.48)	13 (56.52)	0.3652
	No	2 (33.33)	4 (66.67)		12 (57.14)	9 (42.86)	
Current smoker	Yes	0	0		3 (42.86)	4 (57.14)	1.0000
	No	7 (46.67)	8 (53.33)		19(51.35)	18 (48.65)	
High Cholesterol	Yes	6 (50.00)	6 (50.00)	1.0000	17 (45.95)	20 (54.05)	0.4121
	No	1 (33.33)	2 (66.67)		5 (71.43)	2 (28.57)	
Hypertension	Yes	6 (42.86)	8 (57.14)	0.4667	16 (50.00)	16 (50.00)	1.0000
	No	1 (100)	0		6 (50.00)	6 (50.00)	
		Mean(Std)			Mean(Std)		
Log Beck Depression Score		2.14 (0.79)	2.29 (0.62)	0.6971	1.74 (1.14)	2.03 (1.05)	0.3797
PAT ratio ^a		0.80 (0.23)	1.30 (0.24)	0.0012	0.49 (0.09)	0.84 (0.28)	< 0.0001

Abbreviations: a. Peripheral arterial tonometry

Table 2.

Multivariate Model of Predictors of Microvascular Function

a) Linear Regression Model of Determinants of PAT ratio				
Variable	Parameter Estimate	Standard Error	P value	Adjusted R square
Age	0.00	0.01	0.83	
Female	0.42	0.13	0.0019	
African American	0.03	0.11	0.82	
History of coronary bypass surgery	0.02	0.10	0.82	
Divorced	0.05	0.13	0.67	
Heart Failure	−0.13	0.19	0.50	
Diabetes	0.08	0.11	0.46	
Past smoker	−0.05	0.10	0.59	
Current smoker	0.07	0.18	0.68	
High Cholesterol	0.01	0.12	0.96	
Hypertension	0.10	0.11	0.39	
Log of BDI	−0.03	0.05	0.52	
b) Multivariable Logistic Regression Model of High Vasoconstrictor Status using Gender-Specific Cutpoints				
Variable	Parameter Estimate	Standard Error	Wald Chi-Square	p value
Age	0.04	0.04	1.06	0.304
Female	−0.29	0.85	0.12	0.7296
African American	0.67	0.74	0.83	0.363
History of coronary bypass surgery	0.43	0.66	0.44	0.5085
Divorced	0.31	0.83	0.14	0.7116
Heart Failure	1.63	1.39	1.37	0.2412
Diabetes	−1.52	0.79	3.73	0.0536
Past smoker	−0.51	0.67	0.59	0.4437
Current smoker	0.39	1.10	0.12	0.7245
High Cholesterol	−0.39	0.82	0.23	0.6301
Hypertension	−0.38	0.75	0.25	0.6168
Log of BDI	−0.25	0.32	0.60	0.4396

Table 3.

Areas of Increased Activation with Mental Stress in CAD Patient with Low Peripheral Vasoconstriction

Z score	Voxel number	Talairach			Brain region	Brodmann's area
		x	y	z		
6.85	14143	24	13	58	Superior temporal gyrus	6
6.27		51	24	21	Inferior frontal gyrus	45
6.26		-44	24	21	Inferior frontal gyrus	45
5.64	887	42	-50	45	Inferior parietal lobe	40
4.39		46	-32	51	Inferior parietal lobe	40
3.89		42	-23	44	Post central gyrus	2
5.24	300	-40	17	-4	Inferior frontal gyrus	47
4.89	33	10	-65	62	Superior parietal lobe	7
4.84	608	-34	-64	49	Superior parietal lobe	7
4.51		-46	-48	48	Inferior parietal lobe	40
3.82		-46	-36	50	Inferior parietal lobe	40
4.59	71	-65	-35	-9	Medial temporal gyrus	21
3.64		-61	-43	-5	Medial temporal gyrus	21
3.1		-55	-35	-2	Medial temporal gyrus	21
4.26	78	-2	-97	-4	Lingual gyrus, Primary visual cortex	17
3.71		8	-95	-4	Lingual gyrus, Primary visual cortex	17
2.87		-14	-96	-7	Lingual gyrus, Primary visual cortex	17
4.21	71	65	-39	-6	Medial temporal gyrus	21
3.91		65	-47	1	Medial temporal gyrus	21
3.74		69	-29	0	Inferior frontal gyrus	47
4.09	41	-55	21	1	Inferior frontal gyrus	47
3.78	43	16	-10	63	Medial frontal gyrus	6
3.3	31	34	-67	51	Superior parietal lobe	7
2.9		32	-60	51	Superior parietal lobe	7
3.06	16	12	57	19	Medial frontal gyrus	10
6.85	14143	24	13	58	Superior temporal gyrus	6
6.27		51	24	21	Inferior frontal gyrus	45
6.26		-44	24	21	Inferior frontal gyrus	45

 $z > 2.68, p < 0.005$

Table 4.

Areas of Decreased Activation with Mental Stress in CAD Patient with Low Peripheral Vasoconstriction

Z score	Voxel number	Talairach			Brain region	Brodmann's area
		x	y	z		
5.98	1335	-53	-4	8	Superior temporal gyrus	22
5.66		-59	-17	17	Superior temporal gyrus	40
5.12		-51	4	0	Superior temporal gyrus	22
5.71	536	57	0	7	Pre central gyrus	6
4.46		65	-5	22	Pre central gyrus, postcentral	6, 43
4.43		51	-5	11	Pre central gyrus	6, 42
5.62	82	16	-63	-19	Cerebellum	
3.52		26	-71	-15	Cerebellum	
4.91	74	40	-4	-5	Insula	21
4.57	126	-16	-71	-13	Cerebellum	
4.11		-22	-82	-9	Lingual gyrus	18
3.75		-32	-82	-10	Fusiform gyrus	18
4.48	637	-44	-75	9	Medial occipital gyrus	19, 39
4.33		-42	-74	0	Inferior temporal gyrus	37
3.87		-46	-55	27	Superior temporal gyrus	39
4.10	130	24	-86	30	Middle occipital gyrus	19
3.82		28	-82	23	Middle occipital gyrus	19
2.90		8	-86	28	Cingulum	19
4.01	11	-20	-59	-19	Cerebellum	
3.86	83	42	-73	24	Middle temporal gyrus	39
3.81	15	-2	-65	-20	Cerebellum	
3.80	25	-8	-64	31	Precuneus	7
3.63	35	36	-81	11	Middle occipital gyrus	18, 19
3.49	11	4	-63	31	Precuneus	7
3.48	13	-22	-89	-2	Cuneus	17
3.46	52	50	-10	37	Precentral gyrus	6
3.44	16	30	8	0	Putamen	
3.41	46	6	44	-16	Medial frontal gyrus	11
3.36	60	-53	-23	3	Superior temporal gyrus	22
3.13		-63	-23	1	Medial temporal gyrus	21
3.35	24	50	-73	9	Middle occipital gyrus	19

 $z > 2.68, p < 0.005$

Table 5.

Areas of Increased Activation with Mental Stress in CAD Patients with High Peripheral Vasoconstriction

Z score	Voxel Number	Talairach coordinants			Brain Region	Brodmann's Area
		x	y	z		
6.14	12859	34	3	55	Right Middle Frontal Gyrus	6
6.03		36	21	-1	Right Inferior Frontal Gyrus	47
5.98		12	29	39	R. Med Frontal Gyrus, R. Ant Cing.	8,32
		22	46	-16	Right Medial Orbital Gyrus	
		4	43	14	Right Anterior Cingulate	
		-29	49	14	L. Middle and Superior Frontal Gyrus	
		-27	20	-19	Left Inferior Frontal Gyrus	
4.20	111	26	44	31	Right Superior Frontal Gyrus	9
2.92		28	36	28	Right Middle Frontal Gyrus	46
		31	18	-19	Right Inferior Frontal Gyrus	
6.02	1180	38	-52	45	Right Inferior Parietal Lobe	40
5.32		51	-48	43	Right Inferior Parietal Lobe	40
3.93		51	-35	42	Right Inferior Parietal Lobe	40
5.59	1337	-36	-62	47	Left Superior Parietal Lobe	7
5.12		-48	-48	43	Left Inferior Parietal Lobe	40
4.45		-53	-41	43	Left Inferior Parietal Lobe	40
3.18	22	-57	-50	15	Left Superior Temporal Gyrus	22
		-19	46	-17	Left Medial Orbital Gyrus	
		-4	40	15	Left Anterior Cingulate	
		-37	18	-3	Left Insula	
		-29	49	14	Left Middle and Superior Gyrus	
4.94	423	61	-19	1	Right Superior Temporal Gyrus	21, 22
4.64		63	-43	4	Right Superior Temporal Gyrus	22
4.57		63	-10	-6	Right Middle Temporal Gyrus	21
3.61	70	-61	-35	-10	Left Middle Temporal Gyrus	21
3.43		-59	-43	-5	Left Middle Temporal Gyrus	21
3.02		-61	-45	2	Left Middle Temporal Gyrus	21
3.58	41	-55	-14	-11	Left Middle Temporal Gyrus	21
4.03	47	-20	-68	33	Left Cuneus, Left Superior Occipital Gyrus	19
3.51	131	-4	-58	49	Left Precuneus	7
3.38		10	-63	62	Right Precuneus	7
3.24		2	-67	60	Right Precuneus	7
3.16	27	22	-71	53	Right Precuneus	7
3.85	32	-24	-79	-31	Left Cerebellum	
2.62		-30	-76	-38	Left Cerebellum	
2.93	14	-16	-83	-21	Left Cerebellum	

 $z > 2.68, p < 0.005$

Table 6.

Areas of Decreased Activation with Mental Stress in CAD Patient with High Peripheral Vasoconstriction

Z score	Voxel number	Talairach			Brain region	Brodmann's area
		x	y	z		
5.54	106	16	-65	-14	Cerebellum	
4.21		24	-71	-12	Cerebellum	
5.35	558	61	-1	24	Precentral gyrus	1,2,3,4,6,40
5.31		53	-9	13	Precentral gyrus	6
4.36		48	-10	34	Precentral gyrus	4, 6
4.26	643	-51	-8	26	Precentral gyrus	1,2,3,4,6,40
4.11		-51	-14	21	Postcentral gyrus	43
3.95		-59	-8	28	Precentral gyrus	4, 6
3.65	61	-4	-3	52	Medial frontal gyrus	6
3.11		-4	-19	53	Medial frontal gyrus	6
2.75		-8	-11	54	Medial frontal gyrus	6
3.61	35	-6	-38	50	Paracentral lobule	5
3.52	11	-10	-63	-24	Cerebellum	
3.52	19	53	4	-2	Superior temporal gyrus	22
3.51	17	51	-71	9	Medial occipital gyrus	19, 39
3.48	66	40	-81	13	Medial occipital gyrus	18,19
3.22		38	-89	8	Medial occipital gyrus	18,19
3.13		38	-75	22	Medial temporal gyrus	19
3.47	28	22	-84	34	Cuneus	19
3.46	14	-32	-79	15	Medial occipital gyrus	18,19
3.44	68	12	-74	-5	Lingual gyrus	18, 19
3.23		16	-82	1	Lingual gyrus	18
3.00		8	-76	2	Lingual gyrus	18
3.41	11	36	-74	-13	Fusiform gyrus	18, 19
3.39	44	-16	-96	18	Medial occipital gyrus	18
3.32	43	26	-24	64	Post central gyrus	4
3.15		20	-26	58	Post central gyrus	4
3.31	22	44	-69	26	Medial temporal gyrus	39
3.3	11	-22	-59	-21	Cerebellum	
3.27	16	-32	-90	-4	Inferior occipital gyrus	18
2.96	18	-18	-76	-13	Fusiform gyrus	18
2.92	13	10	-92	19	Medial occipital gyrus	18

 $z > 2.68, p < 0.005$

Table 7.

Areas of Greater Increases in Activation With Stress in CAD Patients, High vs. Low Vasoconstrictors

Z score	r	Voxel Number	Talairach coordinants			Brain Region	Brodmann's Area
			x	y	z		
2.98	0.10	14	-50	-61	16	Left Middle Temporal Gyrus	39
3.60		86	-53	-8	-3	Left Middle Temporal Gyrus, Left Superior Temporal Gyrus	21, 22
3.14	0.31 *		-55	-14	-9	Left Middle Temporal Gyrus	21
2.81			-59	-14	-1	Left Middle Temporal Gyrus	21
3.43	0.18	82	-61	-25	-2	Left Middle Temporal Gyrus	21
3.09			-53	-23	1	Left Superior Temporal Gyrus	22
2.99			-61	-23	5	Left Superior Temporal Gyrus	22
3.29	0.23	58	-48	4	3	Left Superior Temporal Gyrus, Left Insula	
3.09			-50	9	-6	Left Superior Temporal Gyrus	12, 38
3.27	0.08	34	-57	-50	15	Left Superior Temporal Gyrus	22
3.18	0.20	17	63	-21	3	Right Superior Temporal Gyrus	22
3.24	0.19	116	-50	-53	27	Left Superior Temporal Gyrus	39
3.20			-59	-43	35	Left Supramarginal Gyrus	40
3.13			-51	-51	34	Left Supramarginal Gyrus	40
3.51	0.41 *	48	-24	22	-18	Left Inferior Frontal Gyrus	47
3.38			-28	19	-13	Left Inferior Frontal Gyrus	47
2.89	0.10	11	28	44	33	Right Superior Frontal Gyrus	9
3.01	0.06	15	42	-64	44	Right Inferior Parietal Lobe	40
2.82	0.45	11	51	-58	40	Right Inferior Parietal Lobe	40
3.23	0.26	34	22	-64	47	Right Precuneus	7
3.19	0.21	15	-4	-60	49	Left Precuneus	7
3.51	0.24	40	-24	-70	44	Left Precuneus	7
4.43	0.38 *	46	-20	-68	33	Left Precuneus	19
3.08	0.27 *	21	20	7	-9	Right Putamen	
3.02	0.22	24	-40	-62	36	Left Angular Gyrus	39
2.96	0.15	13	57	1	7	R. Gyrus Precentralis Pars Opercularis	6

 $z > 2.68, p < 0.005$ $z > 2.68, p < 0.005,$ * $p < 0.05$

Table 8.

Areas of Greater Decreases in Activation With Stress in CAD Patients, High vs. Low Vasoconstrictors

Talairach coordinants							
Z score	r	Voxel Number	x	y	z	Brain Region	Brodman's Area
3.56	0.27 [*]	32	44	-30	51	Right Inferior Parietal Lobe	40
4.38	0.39 [*]	59	26	23	39	Right Middle Frontal Gyrus	8
3.27	0.41 [*]	47	-48	28	21	Left Inferior Frontal Gyrus	45
3.17	0.11	11	-42	17	-8	Left Inferior Frontal Gyrus	47
3.09	0.23	13	-4	-3	52	Left Medial Frontal Gyrus	6
3.01	0.36 [*]	17	-8	-97	0	Left Cuneus	17
2.89	0.21	12	-18	-44	54	Left Precuneus	7

 $z > 2.68, p < 0.005,$ ^{*}
 $p < 0.05$