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Neural responses during acute mental stress are associated with angina pectoris

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Abstract

Angina pectoris is associated with increased risk of adverse cardiovascular events in coronary artery disease (CAD) patients, an effect not entirely attributable to the severity of CAD.

Objective: Examine brain correlates of mental stress in patients with CAD with and without a history of angina.

Methods: Participants (n = 170) with stable CAD completed the Seattle Angina Questionnaire along with other psychometric assessments. In this cross-sectional study, participants underwent laboratory-based mental stress testing using mental arithmetic and public speaking tasks along with control conditions in conjunction with positron emission tomography brain imaging using radiolabeled water. Brain activity during mental stress was compared between participants who did or did not report chest pain/angina in the previous month. A factor analysis was coupled with dominance analysis to identify brain regions associated with angina.

Results: Participants reporting angina in the past month experienced greater (p < .005) activations within the left: frontal lobe (z = 4.01), temporal gyrus (z = 3.32), parahippocampal gyrus (z = 3.16), precentral gyrus (z = 3.14), right fusiform gyrus (z = 3.07), and bilateral cerebellum (z = 3.50) and deactivations within the right frontal gyrus (z = 3.67), left precuneus (z = 3.19), and left superior temporal gyrus (z = 3.11) during mental stress. A factor containing the left motor areas, inferior frontal lobe, and operculum (average McFadden’s number addition =

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2020.110110.
in addition to depression severity (0.10) and adulthood trauma exposure (0.064) correlated with angina history.

**Conclusions:** Self-reported angina in patients with stable CAD is associated with increased neural responses to stress in a network including the inferior frontal lobe, motor areas, and operculum, potentially indicating an upregulated pain perception response.

**Keywords**
Angina; Coronary artery disease; Mental stress; Frontal lobe; Cardiovascular

### 1. Introduction

The mechanisms of cardiovascular disease are complex, and likely include many factors including visceromotor, autonomic, immune, inflammatory, and neuroendocrine components, and modulation by behavioral and lifestyle factors [1]. Behavioral factors shown to increase cardiovascular disease include acute mental stress [2], depression [3–6], and posttraumatic stress disorder (PTSD) [7,8]. Biological and behavioral risk factors share common potential neuroendocrine pathways involved in the stress response, including increased activity within central autonomic areas [9] or structural changes within areas such as the hippocampus or prefrontal cortex resulting from altered glucocorticoid and hypothalamic-pituitary-adrenal axis regulation [10–12], likely providing a link for increased risk for cardiovascular disease.

One condition which intimately features brain-heart connections is angina pectoris (referred hereinafter as angina). Angina is traditionally thought to occur following an oxygen supply and demand mismatch within the coronary arteries and manifests as chest pain for > 30 s [13]. The presence and severity of angina appears to increase risk of cardiovascular events [14] and may increase morbidity [13,15] independent of vascular disease severity [16] and often is not associated with traditional coronary artery disease (CAD) risk factors [17]. Severity of angina does not appear to be correlated with CAD severity or revascularization [18,19] but instead is most strongly associated with psychological variables, such as pre-existing health beliefs, depression, and anxiety [6,20–22]. In coronary artery disease (CAD) patients, we have previously observed a positive relationship between frequency of angina symptoms within the previous four weeks and degree of myocardial ischemia during acute mental stress [23]; this effect appears to occur more in women compared to men [19]. However, the relationship between neural responses during acute mental stress and the presence of angina is currently unknown.

The neural correlates of angina and cardiac chest pain have been detailed previously [24,25]. Dobutamine-induced angina [26,27] increases regional cerebral blood flow within the hypothalamus, hippocampus, periaqueductal grey, thalamus, prefrontal cortex, and anterior cingulate. Cerebral blood flow within the thalamus persisted following cessation of dobutamine infusion, leading the authors to suggest this area gates pain signaling within the cortex [24,26,27] These upregulated brain areas were hypothesized to represent the neural signature of pain perception originating at the heart [27] which is consistent with angina acting through general interoception and pain perception networks [28,29]. Subsequent
investigations have implicated the insula in cardiac pain perception as it controls peripheral cardiovascular responses [30,31].

Despite the known psychological component of angina, the neural correlates during events with the potential to elicit angina have not been thoroughly examined. Angina can increase psychological distress including a higher perceived risk of myocardial ischemia and increased rates of anxiety, depression, and neuroticism [32]. Other latent factors, such as previously-experienced trauma, which can alter psychological well-being, can increase brain activations during acute mental stress [33]. Therefore, previous angina may increase neural responses to mental stress, although the mechanism is not currently understood. The purpose of this study was twofold: i) examine differences in neural activity following acute mental stress between CAD patients with and without previous angina and ii) determine the relative strength of these brain activity differences as correlates of angina. We hypothesized that CAD patients reporting angina within the four weeks, compared to those reporting no angina, would exhibit increased brain activity during mental stress in brain areas involved in stress and emotion that mediate directly or indirectly peripheral cardiovascular responses, including thalamus, prefrontal cortex, hippocampus, amygdala, insula, and inferior and medial frontal lobe. Secondly, we hypothesized that these neural differences would be stronger correlates of angina presence in the previous month compared to traditional risk factors.

2. Methods

2.1. Participant population

Participants (n = 170) included in this study were a subsample of the Mental Stress Ischemia Prognosis Study (MIPS) [34] between 30 and 79 y and with confirmed CAD. Recruitment occurred between September 2010–2016 at Emory University Hospital, Grady Memorial Hospital, and Atlanta VA Medical Center. For the brain sub-study of MIPS, participants with mental stress ischemia and depression were oversampled. CAD was defined by a positive nuclear stress test or history of coronary artery bypass grafting, myocardial infarction, or percutaneous coronary intervention at least one year prior to enrollment. Participants were excluded if they were pregnant, had high blood pressure (systolic ≥180 or diastolic ≥100 mmHg), recent acute coronary syndrome, recent (within one year) severe mental disorder (i.e., schizophrenia, psychosis, bipolar disorder, substance dependence), previous loss of consciousness > 1 min, previous neurological disorder (i.e., stroke, dementia, Parkinson’s disease), or contraindications to regadenoson. Prior to participation, calcium channel blockers and nitrates were withheld for 12 h and beta-adrenergic antagonists were withheld for 24 h; participants were excluded if withholding medication was considered harmful. All participants provided written consent and the study was approved by the Emory University Institutional Review Board (IRB).

2.2. Study design

Participants (Table 1) reported to the laboratory for a preliminary screening visit where baseline measures and psychological assessment was completed. Participants returned two more times for: (i) a cardiac imaging session to determine physical and mental-stress
induced myocardial ischemia as detailed elsewhere [9] and (ii) another mental stress session but with brain imaging. Mental stress consisted of two tasks, public speaking and mental arithmetic, along with control conditions of talking about a neutral event and counting out loud. Participants were scanned during all conditions. Control tasks were completed first and with the stressful task order counterbalanced across all participants. Each mental stress condition was completed twice in succession, resulting in eight position emission tomography (PET) images per participant. Mental arithmetic required participants to answer increasingly difficult addition, subtraction, multiplication, or division problems with negative feedback being provided by an administrator in a white lab coat similar to previous research [10]. Mental math difficulty increased until participants answered three successive problems incorrectly. Public speaking required participants to prepare (for 2 min) and present a two-minute speech in response to two stressful interpersonal situations [9] in front of a white coat clad audience and video camera; participants were also informed the content and duration of the speech would be evaluated. Previous reports have been published regarding the overall activation and deactivation patterns during mental stress [9,33].

2.3. Angina assessment

Previous angina/chest pain assessment was completed using the Seattle Angina Questionnaire’s angina frequency sub-scale [35,36] similar to previously published methods in this cohort [19]. The angina frequency subscale assesses the frequency at which participants had chest pain, chest tightness, or angina and/or medicated with nitrroglycerin within the past four weeks [35]. Similar to previous work [19], angina frequency score was coded as either no angina (score = 100) or angina (score <100) within the previous four weeks. A measure of angiographic coronary artery disease burden, the GENsini score, was also assessed [37].

2.4. Psychometric assessment

In addition to previous angina determination, participants completed multiple psychometric scales. Participants completed the short form of the Early Trauma Inventory-Self Report (ETI-SR-SF) questionnaire which has been validated to measure general, physical, emotional, and sexual trauma exposure before the age of 18 [38,39]. Total item endorsement from the ETI-SR-SF (out of 27) was used in the current study. In addition, participants also completed a complementary scale, the Adulthood Trauma Inventory (ATI) [40] which collects trauma exposures after the age of 18; the total score (out of 33) was recorded. Participants also completed the Beck Depression Inventory (BDI) to measure self-reported depressive symptoms [41] with the total score being used. Participants also completed the full Structured Clinical Interview for DSM-IV (SCID) to determine whether participants had a history of or current post-traumatic stress disorder (PTSD) [42]. The SCID global function score was also calculated.

2.5. Neuroimaging

Brain imaging was completed using a High Resolution Research Tomograph (HR-PET) (CTI, Knoxville, TN) with a 2 mm spatial resolution [43]. For each scan, 20 mCi of radio-labeled water (H$_2$(O$^{15}$)), produced in an on-site cyclotron, was injected into the participant 10 s following initialization to measure blood perfusion within the brain. Each scan had a
duration of 2 min with concomitant electrocardiogram and vital sign monitoring by a physician. Participants completed two HR-PET scans for each of the four mental stress conditions.

2.6. **Image analysis**

HR-PET images were processed similar to previous research [9,33] using statistical parametrical mapping (SPM12; www.fil.ion.ucl.ac.uk/spm). Each individual scan (n = 8) was spatially normalized to a participant-specific mean intensity image before being transformed into a common anatomical space (SPM8 PET Template). The individual scan was further smoothed with a three-dimensional Gaussian filter to 5-mm full width half maximum and normalized to whole brain activity. For each participant, a first level (individual) model including all mental stress conditions was created. The model was grand mean scaled to 50 ml/dl/min, estimated, and included contrasts for areas of activation (all mental stress – all control) and deactivation (all control – all mental stress). Negative values were then removed from the contrast images to isolate areas of activation and deactivation. Second level (between-participant) analyses were then computed using the participant-specific grand mean scaled difference images with data grouped by angina status. Contrasts were calculated to include areas of greater activation/deactivation in participants with angina compared to without. The second level analyses also included covariates of age, gender, whether participant was African American, years of education, previous heart failure, Beck Depression Inventory total score, ETI total score, ATI total score, diagnosis of PTSD, and body mass index.

2.7. **Statistical analysis**

Brain blood perfusion analysis utilized t-contrasts and included all model covariates coded according to previous guidelines [44]. The contrast of interest, greater areas of activation and deactivation for participants with angina compared to without was calculated and an image was produced with individual voxels corresponding to between-group mean differences. Significant voxel clusters for the second-level contrast image were identified using a threshold of p < .005 (uncorrected) which minimizes both Type I and Type II error rates in brain imaging research [45,46]. A minimum voxel cluster size of ≥11 was also employed. Cluster locations were identified using the distance (in millimeters) from the anterior commissure with x, y, and z coordinates transformed from Montreal Neurological Institute (MNI) coordinates to the Talairach stereotaxic atlas [47].

The main neuroimaging analysis contrast images were utilized to complete a factor analysis across brain areas with significantly greater activation and deactivation in participants with angina. The employed factor analysis followed the three faced construct validation method to evaluate factor structure [48]. First, all participants were randomly separated into a training (20% of sample, or n = 34), tuning (40% of sample, n = 68), and test (40% of sample, n = 68) datasets. To achieve homogeneity of angina status across datasets, a stratified random sampling technique was used based on angina score, with binning occurring at the upper 25% (75–100) and lower 75% (0–74) of scores due to a majority of participants not experiencing previous angina. Supplementary Fig. 1 presents the density plots for each dataset and angina score.
The factor analysis also required additional processing for the brain activation maps (Supplementary Fig. 2). Factor analysis requires normally distributed data which was not present with the raw data. Therefore, the contrast maps from the second-level analysis were smoothed using a 3-D Gaussian filter with a sigma of two in MATLAB. This resulted in an expanded cluster to minimize the effect of individual variances in localization of brain activity. The filtered map was overlaid onto the AAL atlas [49] to identify specific brain regions for the cluster. Using these cluster location indices, a custom MATLAB script looped over all first level participant contrast maps to find the median level of blood flow located within each brain area but constrained to the previously identified cluster. The median activation values for each AAL area were then square root normalized. Secondly, previous research has identified appropriate ratios of variables to sample size [50] to limit incorrect factor structure rates, factor loading errors, and misclassification of factors. To more closely adhere to these ratios (5:1 for exploratory factor analysis and 10:1 for confirmatory factor analysis), aggregated brain areas were required to decrease variables going into the analysis (Supplementary Table 1, Supplementary Fig. 3).

In accordance with the three faced construct validation method, three independent factor analyses were performed. The first, an exploratory factor analysis (EFA), was completed using the training data set (n = 34). The number of factors was determined with a screen plot (psych package in R; cran.r-project.org/web/packages/psych). An EFA was completed with the ‘fa’ function (psych package in R), a varimax rotation, and previously determined number of factors. With the EFA factor loadings, an initial confirmatory factor analysis (CFA) was completed on the tuning dataset (n = 68). The CFA model was determined from EFA loadings > 0.3 and manually specified using the lavaan package in R (cran.r-project.org/web/packages/lavaan). The CFA model was created with a maximum likelihood estimator and standardized latent variable variances, tested, and adjusted by removing poor loading areas until the model yielded better performance compared to a base model (p > .05) and also exhibited adequate Tucker-Lewis Index (TLI; > 0.90), root mean squared error adjustment (RMSEA; < 0.10), and chi-square to degrees of freedom ratio less than three [48]. A second CFA with a maximum likelihood estimation with robust standard errors and a Satorra-Bentler scaled test statistic was completed on the test data set (n = 68) using the previously determined factor structure. Low-loading areas were again removed to satisfy TLI, RMSEA, and chi-square:degrees of freedom. Next, using the lavPredict function from lavaan with maximum likelihood, a calculated value was determined for each factor across the entire sample (n = 170). These values were combined with the subject demographic variables exhibiting significant differences between angina groups for inclusion in a dominance analysis.

Dominance analysis allows for the ranking of independent variables in the prediction of a dependent variable [51,52]. Although typically used with continuous dependent variables, recent adaptations [52] have allowed for the extension of this analysis to logistic regression models. Dominance analysis is preferred over previous methods for determining relative importance (e.g., dividing coefficient by standard error) given the ability to average across all possible combinations of desired independent variables [53]. In doing so, dominance analysis eliminates potential issues regarding ordering effect where the first variable accounts for a large percentage of the variance [53]. For the dominance analysis, a logistic
regression model was fit to the data specifying angina status as the dependent variable using a glm function in R (www.r-project.org). A dominance analysis model was fit to the logistic regression model using the dominanceanalysis package in R (cran.r-project.org/web/packages/dominanceanalysis) which employs previously published methods [51,52]. The dominance analysis compares the relative contribution (measured using $R^2$) for each independent variable to every model combination. Model fit was measured using McFadden’s number ($R^2_M = \frac{\ln(L_0) - \ln(L_M)}{\ln(L_0)}$, where $L_M$ is the likelihood of the model and $L_0$ is the likelihood of the null model) [54] given the close parallels to the more traditional $R^2$. Dominance, in this context, refers to one independent variable compared to another using the following descriptors [52]: complete dominance was considered as exhibiting a larger $R^2$ contribution across all models not containing the independent variables of interest, conditional dominance was considered if the average $R^2$ contribution for each model size ($n = \text{number of independent variables}$) was greater, general dominance was considered if the overall average $R^2$ contribution was greater, and no dominance was the absence of any greater $R^2$ contribution.

Normality of demographic data was determined using the Shapiro-Wilk test within R. Descriptive comparisons between angina and no angina groups were completed using a two-sample t-test or Mann-Whitney-Wilcoxon test for continuous variables or chi-square test for discrete variables. The a priori $\alpha$ level for non-brain imaging data was chosen at 0.05.

3. Results

3.1. Demographic data

Demographic data are presented in Table 1. Participants with angina ($n = 59, 35\%$) were younger, were more likely female and African American, had a greater body mass index, completed less years of school, and more likely to have a history of heart failure. In addition, participants with angina had greater Beck Depression Inventory scores and rate of lifetime and current depression, greater levels of previous early and lifetime trauma, worse SCID global functioning score, and greater rates of current and lifetime PTSD ($p < .05$). Participants with angina did not have a greater lifetime GENSINI score or mental or physical stress-induced myocardial ischemia ($p > .13$). Supplementary Tables 2 and 3 present the lifetime and current SCID disorder prevalence, respectively.

3.2. Neuroimaging data

Fig. 1 and Table 2 present the brain areas with greater ($p < .005$) mental stress-induced activation and deactivation in participants with angina compared to those without. During acute mental stress, participants with angina experienced greater activations ($p < .005$) compared to participants without angina within the left inferior and medial frontal lobe (Brodmann Area (BA) 11), left middle temporal gyrus (BA 21), left superior temporal gyrus (BA 22), left parahippocampal gyrus (BA 36), left precentral gyrus (BA 4), right fusiform gyrus (BA 36), and bilateral cerebellum. During mental stress, participants with angina experienced greater deactivations ($p < .005$) compared to those without within the right superior frontal gyrus (BA 10), right middle frontal gyrus (BA 9), left precuneus and
superior parietal lobule (BA 7), and left superior temporal gyrus (BA 38). Controlling for income, which was significant between angina classifications but not included within the dominance analysis, did not drastically alter neural responses (Supplementary Fig. 4).

3.3. Factor analysis

The scree plot indicated that four factors were appropriate for the dataset. The EFA indicated four factors that explained 61.8% of the variance. The EFA TLI was 1.13 and the RMSEA was 0.014 (90% CI: 0.00–0.099) with a mean item complexity of 1.4. The CFA within the tuning dataset resulted in a model test statistic of 44.30 with 46 degrees of freedom (p value of being similar to the baseline model = 0.54), a TLI of 1.026, and RMSEA of 0.00 (90% CI: 0.00–0.075; p value of being > 0.05 = 0.80) indicating close fit. Fig. 2A presents the loadings for the first through fourth factors. Two factors (F2, F4) included only areas of activation, one factor (F1) included only areas of deactivation, and one factor (F3) combined activation and deactivation. Only the right cerebellum loaded onto more than one factor (F2, F4). The final factor analysis (test dataset) resulted in a model with a test statistic of 27.5 with 20 degrees of freedom (p value of being similar to the baseline model = 0.12), a TLI of 0.93, RMSEA of 0.08 (90% CI: 0.00–0.14, p value of being > 0.05 = 0.25) indicating a close fit. Fig. 2B presents factor loadings for the final factor analysis. Three factors included areas of activation (F2-F4) with one factor (F1) including only areas of deactivation. Only the right cerebellum loaded onto two factors, with the loading on F4 being negative.

3.4. Dominance analysis

Fig. 3 presents results of the dominance analysis. BDI (0.10) and ATI total score (0.065) contributed most, on average, to the angina status model accuracy (Fig. 3A). Factor 3 (left motor areas, inferior frontal lobe, and left operculum activation; average $R^2_A$ = 0.057) was third highest contributor to the angina model accuracy across all variables. Factor 2 (left and right cerebellum, cerebellum vermis activation; 0.028) was the seventh best correlate. Factors 1 (right frontal lobe deactivation) and 4 (parahippocampal activation) performed worse, however, contributing 0.013 and 0.007 on average to the McFadden’s number. Fig. 3B presents a matrix describing comparisons across all levels and perturbations of the dominance analysis. Factor 3 presented with at least general dominance (greater overall average contribution) compared to all variables except BDI and ATI total score with conditional (greater at every individual level) or complete dominance compared to ETI total score, all other brain factors, dyslipidemia, diabetes, education level, gender, heart failure, and hypertension. Factor 2 also exhibited conditional dominance over dyslipidemia, Factors 1 and 4, and hypertension. Factor 1 exhibited conditional dominance over Factor 4 and hypertension, while Factor 4 was only conditionally dominant over hypertension.

4. Discussion

In patients with CAD and angina or chest pain within the previous four weeks compared to those without angina, we show altered brain responses to acute mental stress. Novel findings of our study are that patients with angina/chest pain history had mental stress-induced increased brain activations within the left inferior frontal lobe (BA 11), bilateral cerebellum, left temporal lobe (BA 21 and 22), left para-hippocampus gyrus, and left precentral gyrus.
(BA 4), and deactivations within the right superior frontal lobe (BA 10, 9), left parietal lobe (BA 7), and left temporal lobe (BA 38). Within these areas, the factor analysis revealed a network of brain areas with similar activation patterns involving the left motor areas (BA 4), left operculum (BA 22, 44), and left orbitofrontal cortex (BA 11). Together with adulthood trauma exposure and severity of depressive symptoms, brain activation was an independent correlate of angina/chest pain.

An important finding of this study is that brain activity during acute mental stress was a strong correlate of angina/chest pain, even after adjustment for traditional CAD risk factors shown in previous studies to be associated with angina [6,13,55]. As expected, many of these risk factors were significantly different in our angina/chest pain group. However, within the dominance analysis model, traditional risk factors were weaker correlates of angina/chest pain compared to some activated brain networks during acute mental stress. Interestingly, the brain activity factors were clustered in areas with strong—ranked 3rd and 7th—or weak—ranked 12th and 15th—performance as correlates of angina/chest pain. However, even the lower ranked clusters (frontal lobe deactivation and parahippocampal gyrus activation) performed better than known risk factors such as BMI, current PTSD, and congestive heart failure as correlates of angina [13,56,57]. These results, therefore, provide strong evidence that stress-induced reactivity within these network of brain areas is associated with, and therefore may be a mechanism of, angina/chest pain in patients with stable CAD.

The second major finding of this study is that a network consisting of the left motor areas, inferior frontal lobe, and left operculum (inferior frontal and superior temporal lobes) was the strongest neuroimaging correlate of angina/chest pain. We hypothesize these areas represent a multi-faceted network—integrating visceral information and reactivity to mental stress—which is more active in CAD patients with angina/chest pain. The inferior frontal lobe (BA 11) is activated by negative stimuli [58] pertaining to decision-making, social behavior, fear, and episodic contexts [59,60] along with working memory and executive control [59]. Our previous studies have also identified that patients with CAD and mental stress-induced myocardial ischemia (MSIMI) exhibit greater left inferior frontal lobe (BA 47) activations during acute mental stress [9]. Women with MSIMI also exhibit greater right inferior frontal lobe (BA 44) activation during active mental stress compared to men with MSIMI [61]. Additionally, the inferior frontal lobe also has functional connections to many areas which comprise the pain-perception network such as the amygdala, insula, hypothalamus, and somatosensory cortex [24,58,59,62]. However, while some reports observe increased inferior frontal lobe activity during myocardial ischemia [27], the inferior frontal lobe appears to respond to cutaneous [63] but not visceral pain [64,65]. Therefore, the inferior frontal lobe activations likely result from either greater negative responses or increased cognitive (working memory, executive control) demand during the mental stress with angina.

In contrast, the primary motor cortex and operculum aggregated areas appear to respond to visceral, but not cutaneous, pain [64]. Activation of the motor cortex may alleviate visceral pain as evidenced by high-frequency repeated transcranial magnetic stimulation in this area reducing pain levels in patients with irritable bowel syndrome [66]. Excitatory motor cortex
activity can increase activation within the thalamus, the hypothesized neural gate for pain perception [24], and other networks involved in the neural representation of angina [67]. The left operculum has not always been identified within models of angina despite studies finding this area important within bodily self-consciousness and heart beat detection [68]. Furthermore, patients with Syndrome X (angina-like chest pain without CAD) experienced greater Rolandic operculum activation with dobutamine-induced chest pain compared to controls [57]. It should be noted, however, that instances of Rolandic and frontal operculum activations occasionally overlap with activations in the insula but that did not occur in the present study.

The third major finding of this study was the strong correlate ranking of the factor comprised of the bilateral lateral cerebellum and vermis. This is a novel finding, as cerebellar activity is not considered within the neural pathways for chest pain perception [24,25,65] and does not suffer from hypoperfusion in patients with Syndrome X [69,70]. We hypothesize the basis for this finding occurs from one of two pathways: [1] increased brain activation required during mental stress testing or [2] processing the anticipation or presence of cardiovascular/chest pain. Bilateral cerebellum and cerebellar vermis activity has previously been observed during mental arithmetic exercise which also positively correlated with mean arterial pressure and heart rate during the task [71]; this activity was hypothesized to be an indicator of cardiovascular arousal. The lateral cerebellum is anatomically connected to the frontal lobe which facilitates assistance of cognitive processing [72]. The mental stress tasks in the current study elicit increases in frontal lobe activity [9,33,73] and therefore it is possible participants with angina/chest pain required additional processing assistance during the tasks.

Secondly, in a model of visceral pain (esophageal distension), the cerebellum was active during the anticipation and presence of pain with men appearing most susceptible [74]. Specifically, increased cerebellar activity (both lateral and vermis) may result from active inhibition of Purkinje cells in a negative feedback loop to facilitate nociception and appropriate cerebellar output [75]. The cerebellum does output information regarding the internal state [76] and therefore activation could relate to the transmitting of negative emotional state resulting from pain and/or mental stress. For example, CAD patients with MSIMI had increased brain activations during acute mental stress in a similar cerebellar area (x = −32, y = −69, z = −12) [9]; activations within this area also appear exacerbated in women compared to men with MSIMI [61]. Lastly, the cerebellum has connections to angina-involved brain regions such as the amygdala, hippocampus, hypothalamus, and insula is also known to be involved with emotional processing [76,77].

Strengths of this study include the large sample size of CAD patients, a high-resolution PET scanner with enhanced spatial resolution for location of brain activity, and implementation of a validated factor analysis pipeline. Limitations of the study include the fact that findings from the current study are not generalizable to conditions of angina-like chest pain without CAD, such as Syndrome X, as neural correlates differ from angina [24,56]. Another limitation is the cross-sectional nature of this study and the retrospective assessment of angina via the Seattle Angina Questionnaire. None of the patients reported chest pain with mental stress. Furthermore, the GENSINI score was not different between angina categories.
Although this may seem counter-intuitive, it is consistent with previous literature [78]. The Seattle Angina Questionnaire is a validated assessment of angina/chest pain within the previous four weeks which was completed before any stress testing in our study. Lastly, the factor analysis technique required the averaging of multiple brain areas. While we recognize more information could be gathered by using individual brain areas, this decision was made to limit potential Type I errors created by a low feature to data ratio [50].

Other factors not directly assessed within the study protocol also have the potential to impact the neural activation patterns. Although the current study did not measure medication adherence, other studies have observed associations between depression and poor adherence to medications [79], which may elicit greater rates of angina due to increased symptom burden and physical limitation and decreased quality of life. Similar poor adherence has also been observed in PTSD [80,81], although this may not alter cognitive functioning [82]. One argument is that a lower pain threshold, which would be elicited by poor medication adherence, contributes to angina. However, results from the Psychophysiological Investigations of Myocardial Ischemia (PIMI) study indicate individuals with a lower pain perception threshold were not significantly more likely to develop angina during acute mental/exercise stress or during daily life [83]. Angina results from a confluence of factors, including greater symptom burden [23], and therefore the potential that poor medication adherence occurs and contributes to the presence of angina within this study cannot be discounted. We were unable to identify targeted investigations examining the role of medication adherence on neural functioning within a CAD cohort, and therefore this area requires further investigation.

In summary, this study made the novel observation that neural responses to mental stress were better correlates of angina/chest pain in this population with stable CAD than many traditional risk factors for CAD or presence of conventional ischemia. This network of brain areas included the inferior frontal lobe, motor areas, and frontal and Rolandic operculum, suggesting an upregulation of cognitive and sensory brain activity during acute mental stress. Cerebellar activity following acute mental stress was also a strong correlate of angina/ chest pain and may reflect elevated cognitive and/or visceral sensing demand. Taken together, these findings suggest that neural responses to acute mental stress are important correlates of angina/chest pain which perform better than most traditional risk factors. These findings provide novel insight into the pathophysiology of angina, specifically regarding mechanisms of exacerbated neural reactivity during stress which may help explain the psychological underpinnings of perceived chest pain. Resolving whether these upregulated brain areas are predictive or a consequence of the experience of angina requires further investigation. Future studies should also investigate potential interventions which have shown to be effective in other acute-onset conditions. For example, a 12-week cognitive behavioral therapy intervention reduced functional tremor severity by 78% which was paralleled by decreased anterior cingulate activation during an emotional task [84]. Cognitive behavioral therapy has also been shown effective in reducing inferior frontal gyrus and supplementary motor area activations in panic disorder patients [85]. Whether a similar intervention is effective to reduce angina frequency is currently unknown.
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References


Fig. 1. Sagittal slices of brain areas with significantly ($p < .005$) greater activations (red) and deactivations (blue) during mental stress in participants with coronary artery disease experiencing previous angina compared to those who do not. Values below slice indicate Talairach x coordinate with negative and positive values denoting left and right hemisphere, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Fig. 2. Factor Loadings for each aggregated brain area activated or deactivated to a greater extent.
Solid lines indicate areas with activation and dashed lines indicate areas of deactivation.
Fig. 3. Dominance analysis results.
A) Ranking of the mean ± 95% Confidence Interval McFadden’s Number Addition across all study variables. B) Matrix comparing the level of dominance for two study variable combinations. Dominance is based upon study variables on the vertical axis. General dominance indicates a greater overall McFadden’s Number addition. Conditional dominance indicates a greater McFadden’s Number addition at each level of model complexity ($n = 1:17$). Complete dominance and no dominance indicate when one variable always or never had a greater McFadden’s Number addition.
Table 1
Demographic information for study participants \((n = 170)\) separated by presence of angina.

<table>
<thead>
<tr>
<th></th>
<th>Angina ((n = 59))</th>
<th>No angina ((n = 111))</th>
<th>Test statistic, (p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean ± SD)</td>
<td>59.5 ± 8.8</td>
<td>63.8 ± 7.5</td>
<td>(W = 4216.5, p = .002)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>44.1</td>
<td>24.3</td>
<td>(X^2(1,170) = 7.00, p = .008)</td>
</tr>
<tr>
<td>Body Mass Index, kg·m(^{-2}) (mean ± SD)</td>
<td>31.8 ± 7.3</td>
<td>29.5 ± 4.9</td>
<td>(W = 4216.5, p = .05)</td>
</tr>
<tr>
<td>Education level, y (mean ± SD)</td>
<td>13.8 ± 3.5</td>
<td>15.5 ± 3.5</td>
<td>(W = 4278.5, p = .001)</td>
</tr>
<tr>
<td>African American (%)</td>
<td>52.5</td>
<td>27.0</td>
<td>(X^2(1,170) = 10.91, p = .0001)</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>76.3</td>
<td>84.7</td>
<td>(X^2(1,170) = 1.83, p = .18)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>79.7</td>
<td>74.8</td>
<td>(X^2(1,170) = 0.51, p = .47)</td>
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<tr>
<td>Diabetes (%)</td>
<td>44.1</td>
<td>29.7</td>
<td>(X^2(1,170) = 3.50, p = .06)</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>25.4</td>
<td>11.7</td>
<td>(X^2(1,170) = 5.26, p = .02)</td>
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<tr>
<td>Myocardial infarction (%)</td>
<td>32.8</td>
<td>38.5</td>
<td>(X^2(1,170) = 0.54, p = .46)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td>(X^2(2,170) = 3.78, p = .15)</td>
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<tr>
<td>Never smoked</td>
<td>37.3</td>
<td>34.2</td>
<td></td>
</tr>
<tr>
<td>Quit smoking</td>
<td>42.4</td>
<td>55.0</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>20.3</td>
<td>10.8</td>
<td></td>
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<tr>
<td>Medications (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant</td>
<td>39.7</td>
<td>30.6</td>
<td>(X^2(1,170) = 1.39, p = .24)</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>39.7</td>
<td>45.0</td>
<td>(X^2(1,170) = 0.45, p = .50)</td>
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<tr>
<td>Angiotensin receptor blockers</td>
<td>10.3</td>
<td>17.1</td>
<td>(X^2(1,170) = 1.39, p = .24)</td>
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<td>Diuretics</td>
<td>32.8</td>
<td>28.8</td>
<td>(X^2(1,170) = 0.28, p = .60)</td>
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<td>Vasodilators</td>
<td>8.6</td>
<td>13.5</td>
<td>(X^2(1,170) = 0.87, p = .35)</td>
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<td>Anxiolytics</td>
<td>10.3</td>
<td>4.5</td>
<td>(X^2(1,170) = 2.14, p = .14)</td>
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<tr>
<td>Beta blockers</td>
<td>72.4</td>
<td>76.6</td>
<td>(X^2(1,170) = 0.35, p = .55)</td>
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<td>Statins</td>
<td>84.5</td>
<td>89.2</td>
<td>(X^2(1,170) = 0.78, p = .38)</td>
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<tr>
<td>Annual household income (%)</td>
<td></td>
<td></td>
<td>(X^2(5,170) = 14.26, p = .01)</td>
</tr>
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<td></td>
<td>Angina (n = 59)</td>
<td>No angina (n = 111)</td>
<td>Test statistic, p value</td>
</tr>
<tr>
<td>----------------</td>
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<td>---------------------</td>
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<td>$50,000 - $99,999</td>
<td>23.7</td>
<td>22.5</td>
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<tr>
<td>&gt; $100,000</td>
<td>11.9</td>
<td>29.7</td>
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<tr>
<td>Do not know</td>
<td>11.9</td>
<td>4.5</td>
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</table>

**Psychometric scores**

- **Beck depression inventory (mean ± SD)**: 19.3 ± 12.8 vs. 8.3 ± 8.1, $W = 1487, p < .001$
- **SCID major depression (%)**: 61.0 vs. 27.9, $X^2(1,170) = 17.66, p < .001$
- **Current depression (%)**: 42.4 vs. 12.6, $X^2(1,170) = 19.30, p < .001$
- **PTSD diagnosis (%)**: 30.5 vs. 9.0, $X^2(1,170) = 12.94, p = .0003$
- **Current PTSD (%)**: 16.9 vs. 4.5, $X^2(1,170) = 7.42, p = .006$
- **ETI total score (mean ± SD)**: 9.7 ± 6.2 vs. 6.5 ± 4.5, $W = 2284, p = .001$
- **ATI total score (mean ± SD)**: 23.8 ± 12.1 vs. 17.2 ± 9.0, $W = 2194, p = .0007$
- **SCID global function (mean ± SD)**: 75.0 ± 15.1 vs. 84.0 ± 11.9, $W = 4325.5, p = .0003$
- **GENSINI score**: 35.2 ± 6.2 vs. 41.2 ± 4.5, $W = 2605, p = .29$
- **Mental stress induced MI (%)**: 28.8 vs. 22.5, $X^2(1,170) = 0.82, p = .37$
- **Physical stress induced MI (%)**: 47.5 vs. 35.5, $X^2(1,170) = 2.31, p = .13$

PTSD = Posttraumatic Stress Disorder, ETI = Early Childhood Trauma Inventory, ATI = Adulthood Trauma Inventory, SCID = Structured Clinical Interview for DSM-IV, ACE = Angiotensin converting enzyme, MI = myocardial ischemia.
Brain areas with significantly (p < .005) greater activation and deactivation in participants with coronary artery disease with angina (n = 59) compared to no angina (n = 111) during mental stress (mental arithmetic, public speaking) as determined with positron emission tomography.

<table>
<thead>
<tr>
<th>Voxel number</th>
<th>Brain region</th>
<th>Brodmann’s area</th>
<th>Talairach X</th>
<th>Y</th>
<th>Z</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Greater activations in Angina vs. No Angina</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>82</td>
<td>L Frontal Lobe, Inferior Gyrus</td>
<td>11</td>
<td>−22</td>
<td>32</td>
<td>−20</td>
<td>4.01</td>
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<tr>
<td>180</td>
<td>L Frontal Lobe, Middle Gyrus</td>
<td>11</td>
<td>−30</td>
<td>40</td>
<td>−17</td>
<td>3.23</td>
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<tr>
<td>78</td>
<td>L Cerebellum</td>
<td>−48</td>
<td>−56</td>
<td>−26</td>
<td>3.50</td>
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<tr>
<td>78</td>
<td>L Cerebellum</td>
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<td>−46</td>
<td>−33</td>
<td>3.31</td>
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<td>78</td>
<td>R Cerebellum</td>
<td>10</td>
<td>−61</td>
<td>−15</td>
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<tr>
<td>78</td>
<td>R Cerebellum</td>
<td>2</td>
<td>−67</td>
<td>−20</td>
<td>3.38</td>
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<tr>
<td>42</td>
<td>R Cerebellum</td>
<td>−8</td>
<td>−77</td>
<td>−25</td>
<td>3.37</td>
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<tr>
<td>44</td>
<td>R Cerebellum</td>
<td>−20</td>
<td>−70</td>
<td>−35</td>
<td>3.33</td>
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<tr>
<td>13</td>
<td>R Temporal Lobe, Middle Gyrus</td>
<td>21</td>
<td>−61</td>
<td>−30</td>
<td>−12</td>
<td>3.32</td>
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<tr>
<td>24</td>
<td>L Parahippocampal Gyrus</td>
<td>22</td>
<td>−51</td>
<td>4</td>
<td>7</td>
<td>3.18</td>
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<td>18</td>
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<td>36</td>
<td>−32</td>
<td>−28</td>
<td>−22</td>
<td>3.16</td>
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<tr>
<td>17</td>
<td>L Cerebellum</td>
<td>−18</td>
<td>−50</td>
<td>−34</td>
<td>3.15</td>
<td></td>
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<tr>
<td>24</td>
<td>L Frontal Lobe, Precentral Gyrus</td>
<td>4</td>
<td>−32</td>
<td>−17</td>
<td>44</td>
<td>3.14</td>
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<td>30</td>
<td>R Temporal Lobe, Fusiform Gyrus</td>
<td>36</td>
<td>46</td>
<td>−40</td>
<td>−20</td>
<td>3.07</td>
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<tr>
<td><strong>Greater deactivations in Angina vs. No Angina</strong></td>
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<tr>
<td>67</td>
<td>R Frontal Lobe, Superior Gyrus</td>
<td>24</td>
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<td>2</td>
<td>3.67</td>
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<tr>
<td>14</td>
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<td>25</td>
<td>29</td>
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<td>−66</td>
<td>47</td>
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<tr>
<td>12</td>
<td>L Temporal Lobe, Superior Gyrus</td>
<td>38</td>
<td>−53</td>
<td>16</td>
<td>−24</td>
<td>3.11</td>
</tr>
</tbody>
</table>

Significant clusters are presented by size (number of voxels) and location (Brodmann area, cluster peak Talairach coordinates).