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Evaluation the Neurobiological Correlates of Vasoconstriction during Emotional Stress

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B.S., East China Normal University, 2012

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Abstract

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By Chuqing Chen

The influence of acute psychological stress on cardiovascular disease is an emerging public health concern. The brain mechanisms through which acute emotional stress leads to peripheral vasoconstriction are not clear. Understanding the relationship between brain perfusion and vasoconstriction during mental stress may ultimately help guide therapies for patients with abnormal stress reactivity. We hypothesize that patients who vasoconstrict more will have less blood flow in prefrontal cortex and cingulate cortex, as well as increased blood flow in insula during stress compared to rest. A retrospective case control study was performed. A group of 59 patients with a history of coronary artery disease (CAD) from Emory University Hospital, Grady Memorial Hospital and Atlanta VA Medical Center was selected. Microvascular vasoconstriction was measured with EndoPAT^{TM} device. All patients underwent 8 positron emission tomography (PET) scans of the brain, including 4 at control scans and 4 with mental stress scans. The results of our findings are that vasoconstriction during acute mental stress is associated with increased activation in several brain areas, including the left parietal lobe, left temporal lobe, left occipital lobe, left frontal lobe and left insula. Additionally, it is associated with deactivations in the right parietal lobe, right temporal lobe, and right frontal lobe. More research should be done to understand the significance of these findings in clinical practice to decrease stress-induced microvascular dysfunction.

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Introduction

World Health Organization (WHO) reported that there was an estimated 17.5 million people died from cardiovascular disease (CVD) in 2012, representing 31% of all global deaths.[1] Traditional risk factors such as smoking, age, diabetes, cholesterol and hypertension, only account for approximately 50% of the preventable risk.[2] The influence of acute psychological stress on cardiovascular disease is an emerging public health concern.[3] Yoichi Chida and Andrew Steptoe found, in a recent meta-analysis, that greater stress reactivity was significantly associated with increased incidence of cardiovascular events.[4] Thus understanding the mechanisms by which mental stress reactivity increases cardiovascular disease risk is of potential utility in reducing cardiovascular disease risk beyond traditional risk factors alone.

Microvascular vasoconstriction during acute mental stress may signify increased risk of stress-induced myocardial ischemia. Peripheral arterial tonometry (PAT) is a noninvasive plethysmographic finger-mounted device that can continuously measure the arterial pulse volume in the finger, and detect changes during mental stress that correlate with mental stress ischemia.[5-8] Although the mechanisms are not certain, it is likely that vasoconstriction due to stress is caused by increased sympathetic nervous system activity.

The brain mechanisms through which acute emotional stress leads to peripheral vasoconstriction are not clear. Current research shows that a networked brain area has been noted to regulate the relation between mental stress response and HRV.[9] The areas include prefrontal cortex, cingulate cortex, insular, and amygdala; together,

they influence the sympathetic system [Figure 1]. Those parts of brain area also play a role in regulating the vasoconstriction, and relative hyper- or hypo-perfusion during mental stress in these areas may lead to more pathological mental stress responses. We hypothesize that patients who vasoconstrict more will have less blood flow in prefrontal cortex and cingulate cortex, as well as increased blood flow in insula during stress compared to rest. Understanding the relationship between brain perfusion and vasoconstriction during mental stress may ultimately help guide therapies for patients with abnormal stress reactivity.

Methods

Population

We studied a select group of 59 patients with a history of coronary artery disease (CAD) from Emory University Hospital, Grady Memorial Hospital and Atlanta VA Medical Center. CAD was defined based on a prior diagnosis of myocardial ischemia (MI), previous cardiac catheterization showing any degree of stenosis, or history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Patients were excluded if they had acute coronary syndrome within 1 week of enrollment visit, life expectancy of less than 5 years, pregnancy, critical angina intolerant of holding medications within 48 hours, psychosis, alcoholism, or stage IIIHTN. All patients provided written informed consent, which was approved by Emory IRB.

Measurement of Vasoconstriction using Peripheral Arterial Tonometry

The EndoPAT™ device (Itamar-Medical, Israel) was used to measure finger pulse wave amplitudes 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.[8] This device includes a proximal probe component with application of a constant counter pressure of 7 mm of mercury within the whole probe to keep venous transmural pressure deliberately negative. The probe components are connected via thin flexible tubing to isolated volume reservoirs to buffer pressure changes within the probe. An additional volume reservoir not connected to the probe serves as a pressure reference. 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, microvascular vasoconstriction was measured by pulse wave amplitude at stress (mean during 4 stress tasks) compared to baseline rest (mean during 4 control tasks).[15, 16]

Brain Imaging

All patients underwent 8 positron emission tomography (PET) scans of the brain. During the first 4 scans, patients were asked to count out loud (2 scans) and talk about a neutral event (2 scans). The last 4 scans were performed during an acute metal stress challenge. The stress tasks included doing mental arithmetic under negative time pressure (2 scans) and making a speech involving the recall of a stressful situation

(2 scans). A physician wearing a white laboratory coat provided negative feedback and time pressure. All sessions lasted for 2 minutes and 20mCi of O-15 water was injected 10 seconds after each task started. PET images were realigned and analyzed by using statistical parametric mapping (SPM8).

Areas in which differences were found between stress and rest brain perfusion were identified via coordinates from Montreal Neurological Institute (MNI). We then used a non-linear algorithm transformation to convert MNI to Talairach with following equation: (1) if Z was above or equal to 0, then X'= 0.9900X, Y'= 0.9688Y +0.0460Z and Z'= -0.0485Y +0.9189Z; (2) if Z was below 0, then X'= 0.9900X, Y'= 0.9688Y +0.0420Z and Z'= -0.0485Y +0.8390Z.

Statistical Analysis

A retrospective case control study was performed; cases were defined as PAT values less than the median value, and a separate median value was calculated for each sex. We first compared the baseline differences between the cases and controls to evaluate for significant imbalances as a means of possible confounding. A Chi-square test was used to test the association between categorical risk factors and case vs. control status. If expected value in each cell was less than 5, or total number less than 50, Fisher’s exact test was used. The distribution of continuous variables was examined for normality as a requirement for parametric testing. The beck depression inventory (BDI) score was not normally distributed, and therefore log-transformed. The PAT ratio and age were normally distributed. Two sample t-test were used for those

continuous variables. Data were analyzed using SAS 9.4 and statistical significance was evaluated using an alpha=0.05 cut-point.

Analysis of variance was used to compare brain perfusion by voxel, with minimum voxel clusters of 11 voxels. Because of multiple comparisons, statistical significance was calculated with alpha=0.005.

Results

No significant differences between cases and controls were found due to race, history of coronary bypass surgery, marriage status, heart failure history, diabetes, smoking history, high cholesterol history, hypertension, log BDI score, and age. The cases and controls were well-balanced within each gender group. There was a significant difference of PAT ratio between case and control groups within both male and female group ($p<0.0001$ & $p =0.0012$) [Table 1].

A linear model was performed to test whether specific baseline covariates independently associated with PAT as another means of testing the balance between groups and possible confounding. The results, which yielded no significant statistical findings except sex, are listed in Table 2(a). All predicted values together could account for 15.79% variability of PAT ratio.

Also, a logistic model was performed to evaluate the relationship between baseline covariates and gender-specific cases of vasoconstriction based on low PAT. No covariates were significantly predicted sex-specific low PAT, although one trend was observed; the odds ratio of having low PAT among diabetes patients was 0.22 (95%

CI: 0.047,1.023) vs. without diabetes, controlling for age history of coronary bypass surgery, marriage status, race, heart failure history, smoking history, high cholesterol, high cholesterol, hypertension and log of new beck depression inventory [Table 2(b)].

Mental stress in low PAT patients associated with increased activation in several brain, including the left parietal lobe [precuneus, superior parietal lobule (Broadmann 7), supramarginalgyrus (Broadmann 40), angular gyrus], left temporal lobe [superior temporal gyrus (Broadmann 22), middle temporal gyrus, middle temporal gyrus, supramarginal gyrus],left occipital lobe, middle temporal gyrus [(Broadmann 19)], left frontal lobe [inferior frontal gyrus(Broadmann 47)] and left sub-lobar[Insula] [Table 3].

Increases in blood flow of cases vs. controls were also found in right cerebrum including right parietal lobe [precuneus (Broadmann7), inferior parietal lobule (Broadmann 40)], right temporal Lobe [superior temporal gyrus], right parietal lobe [inferior parietal lobule], right frontal lobe [precentral gyrus, superior frontal gyrus (Broadmann 9)], and right sub-lobar region [lentiform nucleus (putamen)].

There was more activation in left cerebrum than right cerebrum in general. The increases of blood flow in precuneus (Broadmann 7) was the most significant in both left and right cerebrum ($p<0.0001$& $p=0.0006$). The supramarginal gyrus (Broadmann 40) and precuneus (Broadmann 7) were the largest brain areas which had increases of blood flow in left and right cerebrum, respectively (voxel=116&34) (Figure 2).

Cases (vs. controls) also demonstrated stress deactivations in the brain during stress compared to rest. There were significant decreases of blood flow in brain areas in left cerebrum including frontal lobe [middle frontal gyrus (Broadmann 46), inferior

frontal gyrus and medial frontal gyrus (Broadmann6)], left occipital lobe [cuneus(Broadmann17)] and left frontal lobe [precuneus] [Table4]. Blood flow in middle frontal gyrus (Broadmann 8) in right frontal lobe and postcentral gyrus in parietal lobe also decreased.

The middle frontal gyrus (Broadmann 46) in left cerebrum and middle frontal gyrus (Broadmann 8) in right cerebrum had the most significant decrease of blood flow in left and right cerebrum, respectively($p=0.0005$ & $p<0.0001$) and was the largest brain area in left and right cerebrum, respectively (47 and 59 voxels, respectively) (Figure 3) .

Discussion

In this study, we evaluated stress-induced brain perfusion changes in CAD patients who had relative vasoconstriction during mental stress tasks, and found that mental stress responses were different in several brain regions between patients who vasoconstricted during stress and had PAT ratios below the gender-specific median value. Most notably, we found decreased stress perfusion in the left and right medial frontal lobes [left middle frontal gyrus (Broadmann 46), left inferior frontal gyrus, left medial frontal gyrus (Broadmann6) and right middle frontal gyrus (Broadmann8)]. Additionally, we found an increase of blood flow in left sub-lobar region (Insula).

While many regions were identified, in general these findings are consistent with our hypothesis. The insula, which is located centrally, influences autonomic function; increases in its activity leads to sympathetic activation and parasympathetic deactivation. It has connections with anterior cingulated cortex, amygdala, prefrontal cortex, superior temporal gyrus, hippocampus and many other brain areas.[10] Previous

research has shown that the insular cortex is involved in panic disorder[11] and PTSD.[12]

The frontal cortex inhibits the insula, and therefore a decrease of blood flow in frontal cortex may result in a net increased activity in the insula. The frontal lobe plays an important role in problem solving, selecting attention and a variety of higher cognitive function. Previous research has demonstrated relationships amongst the insula, prefrontal cortex and autonomic activity.[13] These regions form the central autonomic network, which along with the amygdala and anterior cingulate gyrus, regulate both arms of the autonomic nervous system.[14]

We also found increased stress activation of the left and right temporal lobe in cases vs. controls; specifically, this included the left inferior frontal gyrus (Broadmann 47) and right superior frontal gyrus (Broadmann 9). This may be because the temporal lobe plays an important role in auditory function and recognition, which occurs during the mental stress tasks of mental arithmetic and speech-making under negative time pressure. Those tasks require patients to deal with auditory information, and perhaps patients with more vasoconstriction (low PAT ratio) gave more effort than controls during the stress tasks.

This research is subject to several limitations. First, our findings have limited generalizability to CAD patients. Nonetheless, this is an important population to study because of their high morbidity and mortality. Second, stress challenges in the lab may not reflect real-life stress. Although lab studies can offer better control of stressors, they are unable to reflect multiple and various naturally occurring real-life stressors. Third, some patients may have demonstrated more efforts than others. That might be

a confounder and have an influence on our findings.

In conclusion, we found that vasoconstriction during mental stress in CAD patients associated with increased activation in several brain areas, including the left parietal lobe, left temporal lobe, left occipital lobe, left frontal lobe and insula. There were also significant stress deactivations found in the left frontal lobe, left occipital lobe, and right parietal lobe. Generally speaking, there were more stress activations in left cerebrum than right cerebrum in vasoconstrictor cases vs. controls. These findings may help to inform our general understanding of neurocardiology and the role of the brain in stress reactivity, but more research on stress interventions and brain effects are needed to assess the clinical relevance of these findings.

Appendices

Table 1. Descriptive analysis for predictor and controlled variables

		Female(N=15)			Male(N=44)		
		Case N(%)	Control N(%)	P value	Case N(%)	Control N(%)	P value
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)	
Divorced	Yes	3 (50.00)	3 (50.00)	1.0000	3 (50.00)	3 (50.00)	1.0000
	No	4 (44.44)	5 (55.56)		19 (50.00)	19 (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	0		6	6	

	(100)			(50.00)	(50.00)	
		Mean(Std)			Mean(Std)	
age	62.71 (8.12)	58.63 (9.10)	0.3783	62.41 (10.85)	61.73 (7.46)	0.8093
Log (bdi_sum)	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)	<.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	T value	P value	Adjusted R square
Intercept	0.69	0.46	1.5	0.1411	0.1579
Female	0.42	0.13	3.3	0.0019	
African American	0.03	0.11	0.23	0.8157	
History of coronary bypass surgery	0.02	0.10	0.23	0.8185	
Divorced	0.05	0.13	0.43	0.6697	
Heart Failure	-0.13	0.19	-0.68	0.4997	
Diabetes	0.08	0.11	0.74	0.4635	
Past smoker	-0.05	0.10	-0.55	0.5858	
Current smoker	0.07	0.18	0.41	0.6805	
High Cholesterol	0.01	0.12	0.05	0.9633	
Hypertension	0.10	0.11	0.87	0.39	
Log(bdi_sum)	-0.03	0.05	-0.66	0.5155	
Age	0.00	0.01	-0.22	0.8254	

b) Logistic Regression Model of Determinants of Gender-Specific Low PAT Category

Variable	Parameter Estimate	Standard Error	Wald Chi-Square	P value
Intercept	-1.49	3.16	0.22	0.6369
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(bdi_sum)	-0.25	0.32	0.60	0.4396
age	0.04	0.04	1.06	0.304

Table3. Increased Blood Flow with Stress Compared to Rest in Cases vs. Controls

Size (Voxels)	X	Y	Z	P value	Laterality	Region		BA[a]
46	-20	-68	33	<0.0001	Left	Parietal Lobe	Precuneus	
86	-53	-8	-3	0.0002	Left	Temporal Lobe	Superior Temporal Gyrus	
	-55	-14	-9	0.0008	Left	Temporal Lobe	Middle Temporal Gyrus	
	-59	-14	-1	0.0025	Left	Temporal Lobe	Superior Temporal Gyrus	
48	-24	22	-18	0.0002	Left	Frontal Lobe	Inferior Frontal Gyrus	47
	-28	19	-13	0.0004	Left	Frontal Lobe	Inferior Frontal Gyrus	
40	-24	-70	44	0.0002	Left	Parietal Lobe	Superior Parietal Lobule	7
82	-61	-25	-2	0.0003	Left	Temporal Lobe	Middle Temporal Gyrus	
	-53	-23	1	0.0010	Left	Temporal Lobe	Superior Temporal Gyrus	
	-61	-23	5	0.0014	Left	Temporal Lobe	Superior Temporal Gyrus	
58	-48	4	3	0.0005	Left	Sub-lobar	Insula	
	-50	9	-6	0.0010	Left	Temporal Lobe	Superior Temporal Gyrus	22
34	-57	-50	15	0.0005	Left	Temporal Lobe	Superior Temporal Gyrus	
116	-59	-43	35	0.0006	Left	Parietal Lobe	Supramarginal Gyrus	40
	-50	-53	27	0.0007	Left	Temporal Lobe	Supramarginal Gyrus	

	-51	-51	34	0.0009	Left	Parietal Lobe	SupramarginalGyrus	
34	22	-64	47	0.0006	Right	Parietal Lobe	Precuneus	7
15	-4	-60	49	0.0007	Left	Parietal Lobe	Precuneus	7
17	63	-21	3	0.0007	Right	Temporal Lobe	Superior Temporal Gyrus	
21	20	7	-9	0.0010	Right	Sub-lobar	Lentiform Nucleus	Putamen
24	-40	-62	36	0.0013	Left	Parietal Lobe	Angular Gyrus	
15	42	-64	44	0.0013	Right	Parietal Lobe	Inferior Parietal Lobule	
14	-50	-61	16	0.0014	Left	Occipital Lobe	Middle Temporal Gyrus	19
13	57	2	7	0.0015	Right	Frontal Lobe	Precentral Gyrus	
11	28	44	33	0.0019	Right	Frontal Lobe	Superior Frontal Gyrus	9
11	51	-58	40	0.0024	Right	Parietal Lobe	Inferior Parietal Lobule	40

Abbreviations: a. Broadmann Area

Table 4. Reduced Blood Flow with Stress compared to Rest in Cases vs. Controls

Size (Voxels)	X	Y	Z	P value	Laterality	Region		BA[a]
59	26	23	39	<0.0001	Right	Frontal Lobe	Middle Frontal Gyrus	8
32	44	-30	51	0.0002	Right	Parietal Lobe	Postcentral Gyrus	
47	-48	28	21	0.0005	Left	Frontal Lobe	Middle Frontal Gyrus	46
11	-42	17	-8	0.0008	Left	Frontal Lobe	Inferior Frontal Gyrus	
13	-4	-3	52	0.0010	Left	Frontal Lobe	Medial Frontal Gyrus	6
17	-8	-97	0	0.0013	Left	Occipital Lobe	Cuneus	17
12	-18	-44	54	0.0019	Left	Frontal Lobe	Precuneus	

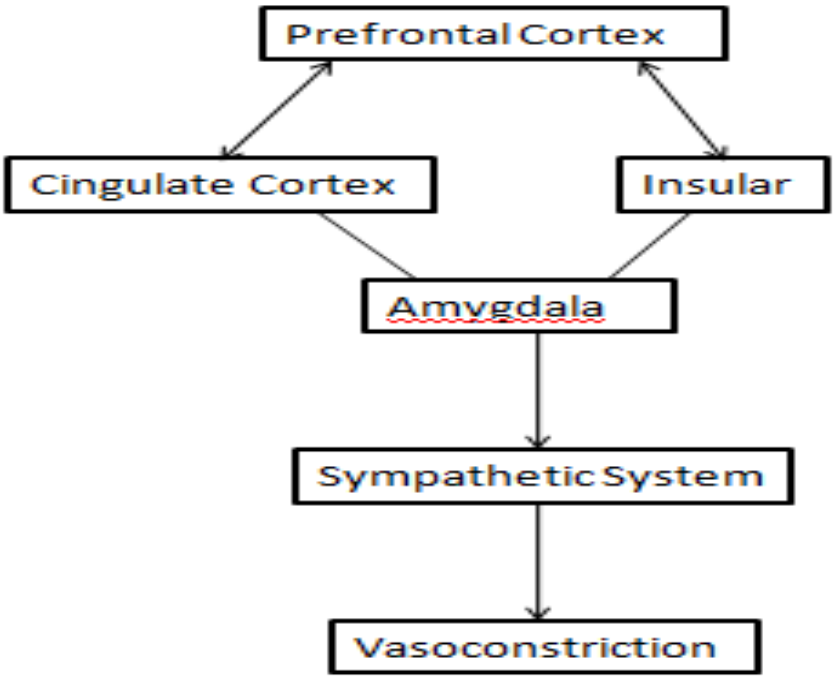

Figure1. A diagram showing the pathway by which the brain area might influence the vasoconstriction

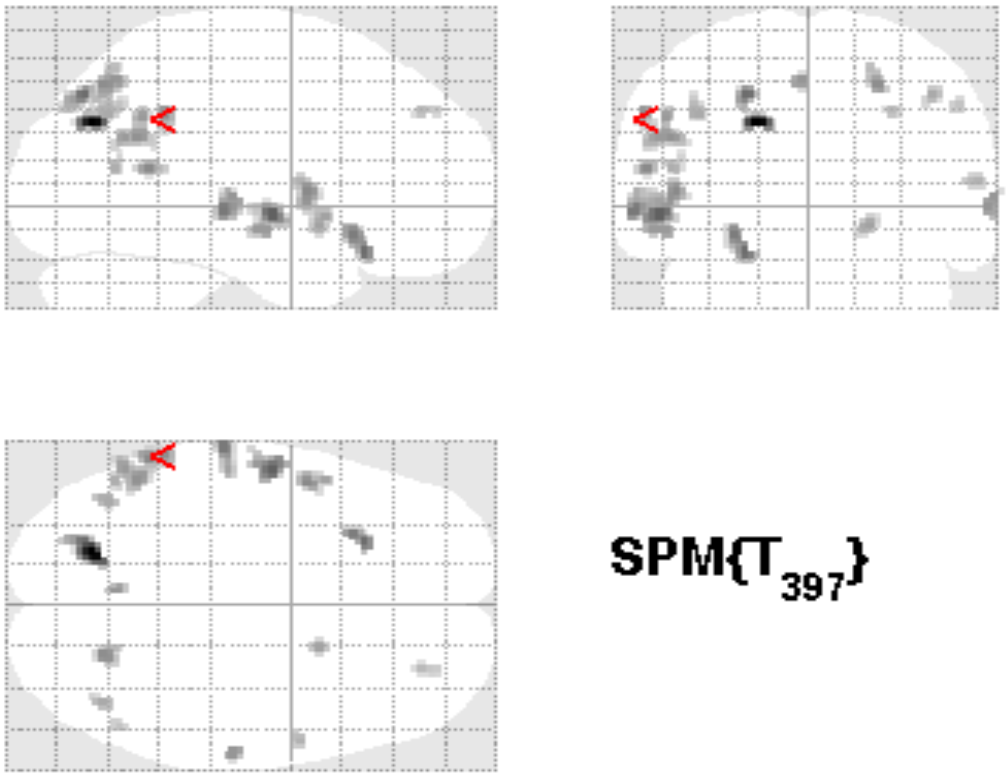

Figure 2. Stress Activations – Pointer on left temporal lobe (largest cluster)

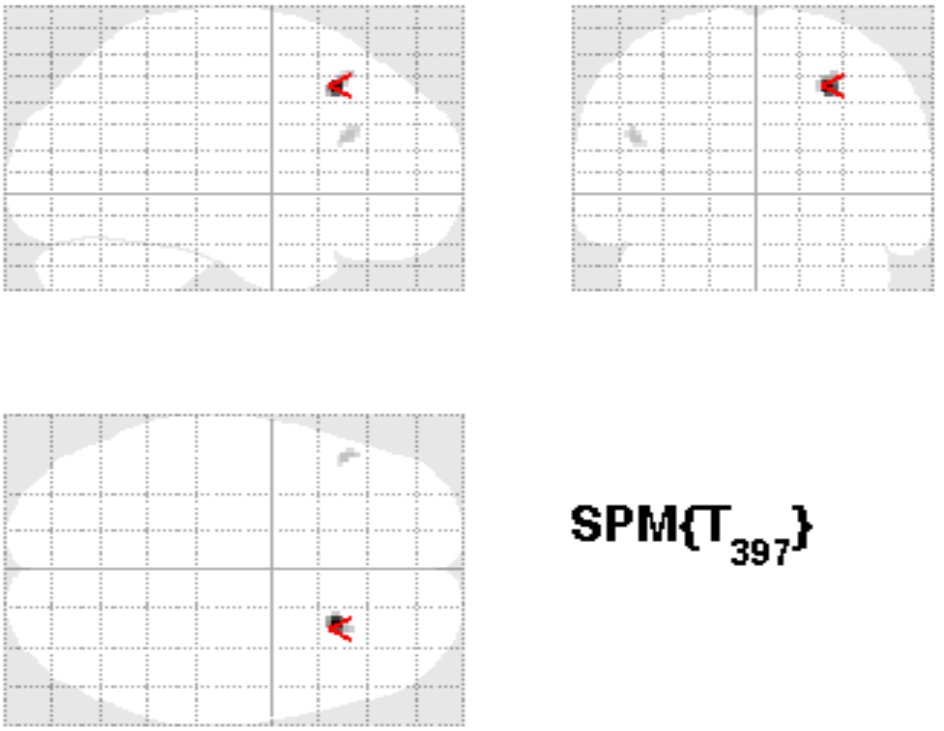

Figure 3. Stress Deactivations – Right Frontal Lobe (largest cluster, most significant)

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