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Curr Cardiol Rep. Author manuscript; available in PMC 2013 July 29.

Published in final edited form as:
Curr Cardiol Rep. 2009 March ; 11(2): 133–140.

Heart-Brain Interactions in Mental Stress Induced Myocardial Ischemia

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Abstract

Myocardial ischemia, which results from emotional provocation, occurs in as many as 30–50% of patients with CAD during the discourse of their daily lives. This emotionally provoked or mental stress ischemia is associated with the poor prognosis, with emerging treatment strategies. This chapter will outline the conceptual constructs which support the pathophysiologic underpinnings, and biobehavioral aspects associated with this mental stress ischemia. We will review a biobehavioral model where cognitive stress is transduced in the brain. The response of the brain to psychosocial stress is a highly sophisticated and integrated process by which sensory inputs are evaluated and appraised for its importance in relation to previous experience and current goals. The biologic consequences of such stress transduced in the CNS has its effect upon the cardiovascular flow and function through changes in autonomic balance, which result in various biologic processes that culminate in the perturbation of flow and function of the heart.

Introduction

The stress during the discourse of our daily lives with attendant emotional provocation has been associated with angina and has been a consistent part of the human historical narrative. The impact of the cartesian duality of mind-body has had profound impact on western thought and has served to minimize the impact of cognitive processes upon biologic outcomes.[1] The advent of sophisticated neuroimaging technology and modern bio-behavioral constructs have allowed an empiric approach which has guided recent advances reviewed in this chapter. Specifically, we outline testable hypotheses which address mechanisms that support conceptual constructs of how cognition impacts cardiovascular performance.

Epidemiologic studies have shown that acute coronary events can occur in individuals that lack the traditional high-risk profile for coronary artery disease (CAD),[2] highlighting the importance of factors such as psychological and biobehavioral factors we all confront during the course of our daily lives.[3] Cardiac manifestations of mental stress induced ischemia can include left ventricular dysfunction,[4,5] acute coronary events,[6] and cardiac arrhythmias.[7,8] Studies have shown that as many as 30 to 50% of CAD patients exhibit transient, symptomless myocardial ischemia during mental stress.[9,10,11] Furthermore, up to 2/3 of ischemic episodes detected by ambulatory electrocardiographic monitoring in patients with chronic CAD are asymptomatic, noted at very low workloads, and related to factors like

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mental stress.[12,13] Mental stress ischemia (MSI) has been linked to a three-fold increase in adverse clinical outcomes in patients with CAD.[14,15,16,17,18,19]

These observations, taken in concert with the high frequency of myocardial infarction during catastrophic environmental events,[20,21,22] suggests that the identification of patients who are vulnerable to MSI is highly relevant, especially given current global geopolitical concerns.

In this review, we will discuss the current understanding of the pathophysiology of MSI, a phenomenon that is more complex than the demand and supply paradigm observed with exercise stress testing. We will also discuss recent advances that have led to an enhanced understanding of the brain-heart interactions that occur during MSI.

Physiological correlates of mental stress ischemia

Although there are some shared pathophysiologic commonalities, MSI has distinct physiologic correlates compared to demand-induced ischemia as suggested by differences in hemodynamic, vascular, and neuroendocrine responses (Table 1).[23,24] For example, exercise produces a substantially greater increase in heart rate and a more modest elevation in systolic blood pressure,[25] which parallels the increased metabolic demand and supply gap created by physical activity. In contrast, diastolic blood pressure and systemic vascular resistance rise during mental stress, but are the same or decreased in response to exercise.[24,26] Angina is the usual manifestation of myocardial ischemia triggered by physical exertion, but is noticeably absent in most cases of MSI.[27] Electrocardiographic changes are also less apparent with MSI when compared to pharmacological stress.

The brain-heart interaction

Given that stress and emotional factors are cognitive in nature, we approached this injury by understanding how stress is transduced by the CNS and how this transduction results in ischemic syndromes. We then analyzed if there were specific brain activation patterns associated with emotional provocation and associated physiologic effectors which may perturb the cardiovascular flow/function relationship. Then we compared these brain activation patterns to those associated with ischemic, which results from a traditional demand (exercise) stimulus.

Recent research focusing on the detection of CNS activity accompanying stress and emotional processing has identified multiple areas of the brain that appear to be intimately involved in the awareness of, and response to, stressful circumstances.[28] These areas include both cortical and subcortical regions that have been implicated in processing the emotions provoked by external stimuli, and in mediating executive responses to those same emotions and stimuli.

The “central autonomic network” (CAN) is a label affixed by some to describe the flexible network of dynamically interconnected areas of the brain that are thought to regulate the physiological effects of mediated emotions through autonomic neurohormonal outputs. The neural pathways involved in these processes modulate the autonomic nervous system in an integrative fashion.[29] These regions include the medial prefrontal cortex, amygdala, and anterior cingulate gyrus. The medial prefrontal cortex has a general role in emotional processing and specific roles for emotional/evaluative processing and self regulation. The amygdala has been posited as critical to fear related processing,[30] and also corresponds to dispositional affective style. The anterior cingulate has a cognitive dorsal segment mediating response inhibition[31] and an affective ventral subdivision involved in processing and integrating emotional information.[32]

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The physiologic consequences of stress initiated CNS activation include increases in heart rate and blood pressure, which define hemodynamic reactivity. The prefrontal cortex-limbic system that controls this response has direct and indirect throughputs to neurohormonal systems which act through norepinephrine and cortisol. Additionally, the amygdala has effectors to the lateral hypothalamus that activate sympathetic and cortisol pathways in the periphery.[33] Norepinephrine secreted by the locus coeruleus, the major source of norepinephrine-producing neurons, also has direct pathways to the amygdala and the hippocampus. Below the cortex are several neuronal networks in the brainstem, such as C1 cells in the rostral medulla. These networks send afferent signals to the locus coeruleus, which re-amplifies the cortical process via projection to the hypothalamus.

Significantly, the areas of activation that make up the CAN and the stressors that provoke its activation indicate that the CAN is strongly associated with the limbic system and is involved in the negative feedback circuit between the limbic system and the prefrontal cortex. This circuit appears essential to the regulation of autonomic responses to stressful stimuli. A situational imbalance in the activity between these two, or a fixed inability of the prefrontal cortex to attenuate limbic responses, may be linked with autonomic dysregulation which, during mental stress, can result in a net shift towards increased sympathetic tone and/or withdrawal of parasympathetic tone. If chronic, this imbalance can increase risk for cardiovascular disease by promoting processes that lead to vascular inflammation and intimal perturbation.[24,34,35] In addition to the acute responses of hemodynamic reactivity, chronic stress with activation of these autonomic systems leads to changes in the endothelium over time, with an increase in atherosclerotic burden, an increase in risk for arrhythmias, and an increase in platelet aggregation and other factors known to enhance the risk for cardiovascular morbidity and mortality.[8]

Brain activation patterns during mental stress

Our group has previously reported the brain activation response to mental stress in subjects with and without CAD utilizing O_{15} Positron Emission Tomography (PET) imaging of the brain.[28] Patients with CAD demonstrated significantly increased blood flow to the left anterior cingulate, the left parietal cortex, and the left parahippocampus, brain regions involved with emotion, memory, attention, and neurohormonal and autonomic regulation. There was also greater limbic to prefrontal activity, suggesting that the limbic regions associated with fear and anxiety possess an enhanced effect on cardiovascular function. In comparison, patients without CAD exhibited brain activation patterns referable to the cognitive effort of the mental task. Among the CAD group, those who became ischemic to mental stress compared to those who did not had even greater activation in the aforementioned sub cortical limbic structures (parahippocampus and related cingulate areas) (Figure 1).

We have also shown that the patterns of brain activation differ significantly between patients with MSI versus those with demand-related ischemia.[36] 58 patients with CAD underwent simultaneous O_{15} PET brain activation imaging and evaluation for myocardial ischemia during a laboratory arithmetic mental stress and infusion of dobutamine, a surrogate for demand stimulus ischemia. 8 patients had ischemia to both mental and dobutamine stress, while 13 had myocardial ischemia to mental stress alone. In comparison to patients with dobutamine-induced ischemia, patients with MSI again demonstrated hyperactivation in frontolimbic circuits associated with neurohormonal and autonomic regulation, emotion, memory, fear, and anxiety. These findings suggest that MSI has a distinct cerebral activation pattern referable to the cognitive nature of mental stress in comparison to demand-induced ischemia where activations occurred in the peripheral sensorimotor areas (Figure 2).

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Gender Interaction and the Brain during Mental Stress

Our group also demonstrated gender differences in the patterns of brain activation during mental stress.[37] Women with CAD have greater bilateral and medial temporal activation (amygdala and hippocampus) during mental stress than do men with CAD. Women with CAD also have greater activation in the prefrontal cortex (middle frontal gyrus and inferior frontal gyrus) than women without CAD, suggesting a greater evaluative component to their response to mental stress. There was no difference in brain activation patterns between men and women without CAD during mental stress.

In summary, when one is ischemic to emotional stress, brain activation occurs in areas that initiate physiologic effectors which accentuate heightened sympathetic response, decrease in parasympathetic tone with associated release of neurohormonal factors which promote augmented systemic/coronary vasculature resistance, and sympathovagal imbalance. Next we will discuss how this brain activation pattern which results in autonomic dysregulation promotes the generation of pro-inflammatory cytokines which render patients vulnerable to myocardial ischemia and/or ventricular arrhythmias.[38,39,40]

The inflammatory reflex

The inflammatory reflex is fundamental to understanding the pathophysiology of MSI, and describes a cholinergic anti-inflammatory pathway. CNS efferent activity in the vagus nerve leads to acetylcholine (ACh) release in organs of the reticuloendothelial system, including the liver, heart, spleen and gastrointestinal tract. ACh interacts with a-bungarotoxin-sensitive nicotinic receptors (ACh receptor) on tissue macrophages, which inhibit the release of TNF, IL-1, HMGB1 and other cytokines.[41,42,43] Thus the observed withdrawal of parasympathetic activity during mental stress results in the converse i.e. the release of inflammatory cytokines and attendant effects on vasomotor tone and function.

The involvement of specific brain regions, including the medial prefrontal cortex, has been reported in the vagal component of heart rate regulation during self-generated emotions.[44] We have also found these regions associated with parasympathetic withdrawal during mental stress.

Vagal efferents are distributed widely throughout the reticuloendothelial system and peripheral organs. Brain derived output through vagal efferents is therefore rapid and more precise in location than humorally mediated pathways. The heart is well enervated by vagal efferents, and low parasympathetic tone is a well-described predictor of early post-MI mortality.[45] Pyridostigmine, a reversible cholinesterase inhibitor, was recently shown to attenuate the LV systolic and diastolic dysfunction caused by mental stress in patients with CAD, thus highlighting the importance of the parasympathetic system in MSI.[46] Parasympathetic withdrawal, which has been observed during mental stress,[47] results in the generation of various inflammatory cytokines such as TNF-α. Macrophages that reside in the myocardial vasculature are a main source of TNF-α[48,49] and the release of TNF-α is a significant contributor to cardiac dysfunction and cardiomyocyte death in such diverse conditions as sepsis, chronic heart failure, ischemic reperfusion injury, and transplant rejection.[48] The rapidity with which the inflammatory reflex operates, and the wide distribution of macrophages in diseased coronary vessels, implicates this reflex as a mechanism through which mental stress acts on coronary microvascular beds. Thus, the parasympathetic withdrawal seen during mental stress causes the synthesis and release of TNF-α as well as other inflammatory cytokines by macrophages. This, in turn, results in the subsequent stimulation and release of macrophage-derived ET-1, which augments the effects of endothelial ET-1.

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As direct evidence of the role inflammation plays in MSI, our group reported a positive correlation between C reactive protein (CRP) and MSI. Each unit (1mg/ml) increase in CRP level was associated with a 20% higher risk of MSI (OR 1.2, 95%CI 1.01–1.29, p=0.04).[35] These results correlate well with the more recent findings of Kop et al[50] who reported that mental arithmetic and anger recall both cause transiently increased levels of the inflammatory markers CRP and interleukin-6 in patients with CAD. Baseline inflammatory markers were higher in CAD patients than controls as expected. Kop et al further demonstrated that patients with high catecholamine responses to mental stress also had exaggerated increases of these inflammatory markers. They hypothesized that the individuals who reacted to mental stress with higher levels of epinephrine and norepinephrine may be at increased risk of CAD progression and atherosclerotic plaque rupture due to higher circulating levels of CRP and pro-inflammatory cytokines.

We have discussed how cognitive mental stress is transduced in the brain and results in hyperactivation of sympathetic output with concomitant decrement in parasympathetic tone with the generation of inflammatory vascular factors. We next turn our attention to how this pathophysiology impacts myocardial blood flow in response to mental stress.

Myocardial blood flow and endothelial function

Mental stress induces heterogeneity of myocardial perfusion in patients with CAD. In the earliest demonstration of this effect, Deanfield et al[51] used PET to demonstrate that 12 of 16 patients with CAD and positive exercise stress tests developed regional myocardial perfusion abnormalities during mental stress. Although the rate-pressure product was lower with MSI compared to exercise stress, the degree of the perfusion defects was comparable. Others have demonstrated similar effects using different imaging modalities.[52]

In a PET study of patients with CAD, our group compared the coronary flow reserve (CFR) response during mental stress to the CFR during persantine infusion.[53] Using this technique, we measured absolute blood flow. We noted that mental stress often resulted in impaired myocardial blood flow in coronary distributions served by epicardial vessels with subcritical epicardial blockages. Furthermore, the regions with lower myocardial blood flow reserve during mental stress showed increased coronary microvascular resistance compared to vascular beds with normal CFR. These findings have been shown by others using different techniques,[54] which suggests that impairment of the vasomotor response in the coronary microvascular bed is an essential feature of MSI. Coronary angiography studies have similarly shown that mental stress promotes epicardial coronary vasoconstriction in vascular beds with subcritical disease.[55,56] In addition, this mental stress-induced vasoconstriction occurs in the same coronary segments that demonstrate a paradoxical constrictor response to intracoronary ACh infusion.[55] In total, these findings implicate the coronary endothelium and, in particular, endothelial dysfunction in the pathophysiology of MSI.

Role of the peripheral adrenergic system and ET-1

In patients with CAD, mental stress produces an increase in sympathetic tone evidenced by elevations of epinephrine and norepinephrine.[57] Norepinephrine has an important role in vasomotor tone during mental stress, causing vasoconstriction via its effects on vascular smooth muscle.

There is increasing evidence that local endothelial factors, like endothelin-1 (ET-1), play an important role in mediating this vasoconstriction response to norepinephrine. For example, at concentrations that exert only a minimal direct pressor effect, ET-1 was found to nearly double the degree of vasoconstriction that was observed during an infusion of norepinephrine in diseased coronary artery segments.[58] During a laboratory mental stress,

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the blockade of ET-1 by the specific endothelin-A receptor blocker BQ-123 significantly attenuated the degree of vasoconstriction observed during norepinephrine infusion.[59] These findings suggest that sympathetic activation may act through ET-1 to produce arterial vasoconstriction, particularly in the microvascular bed. Furthermore, we have observed in preliminary data a rise of ET-1 in CAD subjects during a mental stress provocation.

Mental stress, autonomic tone and inflammation

The vasoconstrictive effects of ET-1 may last for hours. In contrast, MSI is a transient condition that resolves in most cases when the stress is terminated. Therefore, additional factors are required to explain the vascular findings in MSI studies. Autonomic dysregulation in response to mental stress promotes the aforementioned Inflammatory processes which promotes further factors as well as accentuate the biologic effect of such factors upon the coronary vasculature. For example as previously mentioned, the "inflammatory reflex", states that the reduction in parasympathetic tone and ACh, serves to generate macrophage release of TNF-α. In turn, TNF-α, a potent pro-inflammatory cytokine, can provoke the release of ET-1 from macrophages[60,61] and has been observed in combination with ET-1 to promote vasoconstriction of the microvascular bed.[62] TNF-α significantly impairs endothelial function, and is thought to be involved in atherosclerotic plaque rupture, coronary artery vasospasm, and ischemic injury.[63]

The hyperactivation of the sympathetic nervous system during mental stress also plays an important pro-inflammatory role, working through α-2 receptors to increase production of TNF-α and comparable agents and substantially augment the vascular effects of ET-1.

Thus the mental stress response is initiated in the CNS which results in the divergence of the autonomic nervous system with an increase in sympathetic and decrease in parasympathetic tone (Figure 3). This divergence serves to promote the generation of inflammatory vascular factors, and synergistically promotes vascular endothelial dysfunction and vasoconstriction which results in myocardial ischemia.

Mental stress and genetics

There may be individual, inheritable differences in the degree of adrenergic stimulation triggered by MSI. Hassan et al[64] recently reported that individual responses to mental stress may arise in part from genetic polymorphisms of the beta-1 adrenergic receptor (ADRB1). They demonstrated that patients homozygous for the Ser49 allele of the ADRB1 gene (codon 49) were 3 times more likely to have MSI on myocardial perfusion imaging than carriers of an alternative allele. Much work remains to be done to identify other genetic determinants underlying the individual variation in the neurohormonal activation of MSI.

Prognostic implications and clinical application

In patients with known CAD, MSI has consistently been shown to be associated with an increased risk of adverse cardiovascular outcomes and mortality.[15,16,65] The PIMI investigators have reported on the largest population studied in the laboratory regarding the prognostic significance of MSI in their multi-center study. In this study of 196 patients who had undergone mental stress testing in the laboratory, patients were followed for an average of 5.2 years. During the follow-up period there were 17 deaths. New wall motion abnormalities during laboratory mental stress were seen in 40% of those who subsequently died, but only 17% of those who survived (rate ratio=3.0; $p<0.04$). Other indicators of ischemia during MS testing, including LV ejection fraction and/or ECG changes did not predict death, a finding with important implications for future research. This is the only controlled study to show an effect of mental stress on death.

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The identification of specific psychologic factors that contribute to the risk of MSI may help determine when mental stress testing is likely to provide important prognostic information. For example, patients with easily provokable anger and hostility have twice the incidence of CAD with a 5-fold increased risk of recurrent MI.[66] Hostility has also been associated with the accelerated progression of atherosclerosis[67] and a higher rate of post-angioplasty restenosis.[68] Data from our group demonstrates that patients identified by interview as having a hostile, angry, emotionally arousable psychological profile have an increased risk of MSI,[9] suggesting that this type of clinical assessment may be useful in identifying patients for whom mental stress testing may provide prognostic cardiovascular information. Stress can be modified through numerous approaches including stress management, meditation, and cognitive behavioral therapy, and treatment strategies specifically tailored to decrease mental stress have been shown to decrease the incidence of cardiovascular events.[69,70]

Conclusions

Much work has been done to illuminate the pathophysiology of mental stress ischemia, but much more work remains to be completed before mental stress testing enters clinical practice as a viable diagnostic strategy to benefit patients at risk. The further identification of risk factors to help stratify patients into low, intermediate, and high risk probabilities for mental stress ischemia, similar to the Framingham Risk score, would be a major advance in this direction. Published reports using noninvasive techniques, which outline a “mental stress test”, are emerging.[71] A national consensus statement defining guidelines for mental stress testing, similar to those existing for exercise stress testing, would promote the standardization of future research in the field. The increasing demands of a competitive modern global society require that we broaden our understanding of the impact of these cognitive adjustments on our biology.

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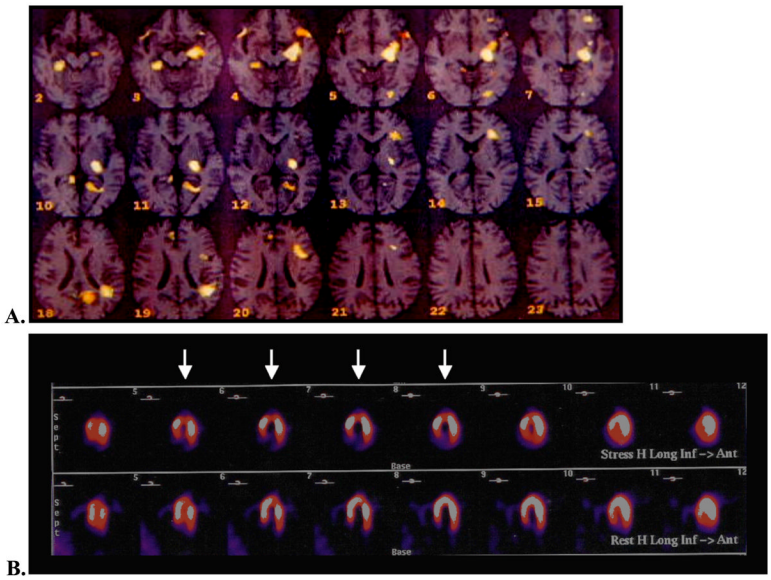

Figure 1.
Top Panel: Brain activation of the Frontal Medial Gyrus and Limbic Hippocampal structures and associated Anterior Cingulate Gyrus.
Bottom Panel: Myocardial Blood flow Image during Mental Stress with reversible ischemia of the apex (arrows).

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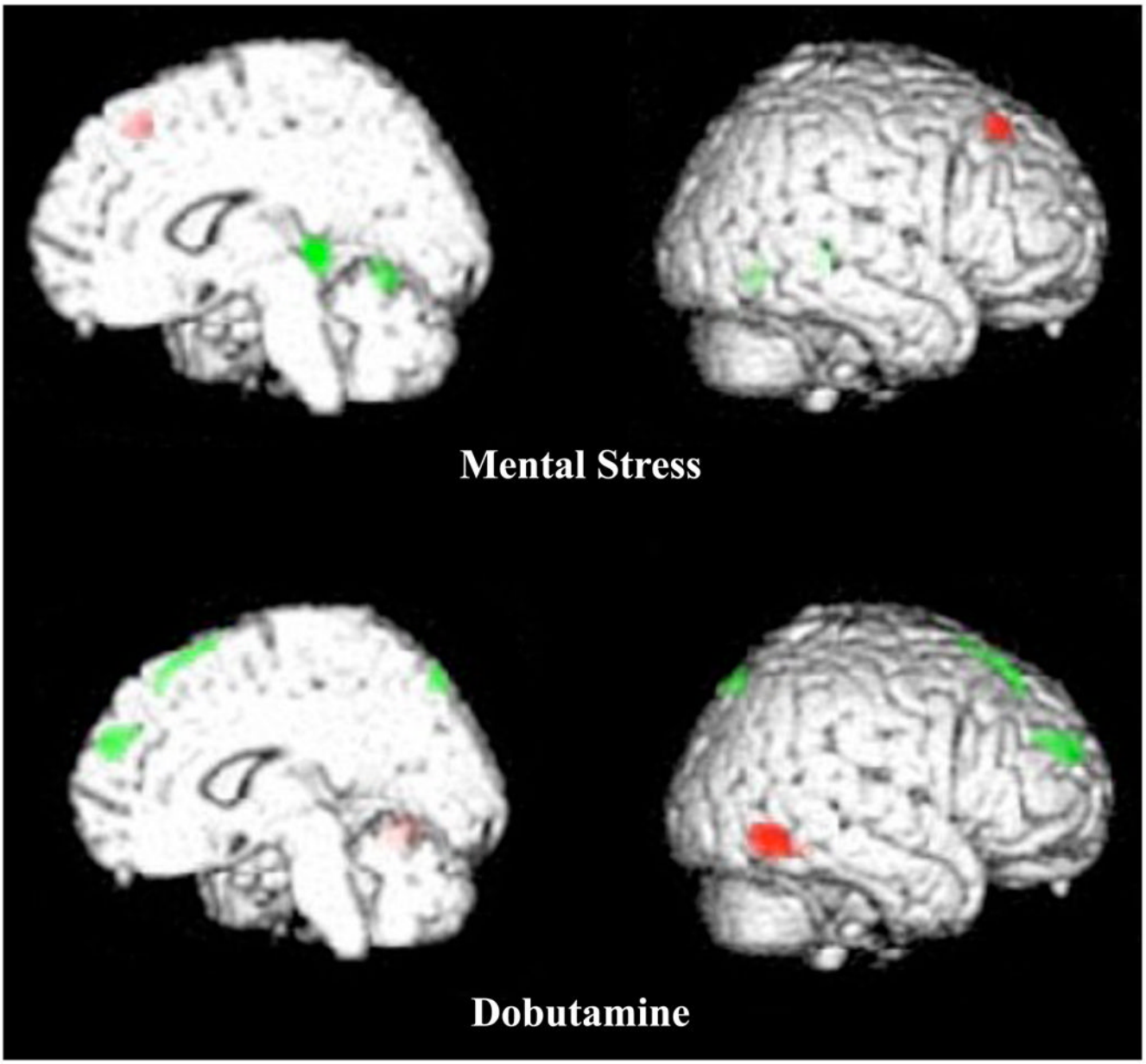

Figure 2.

Top panel is the brain activation during mental stress and associated myocardial ischemia. Bottom panel is the brain map of the same subject ischemic to a demand surrogate for exercise with dobutamine infusion. Grey (Green for online version) is activation and black (Red for online version) is deactivation.

Brain activations during mental stress occurs in subcortical areas associated with emotion, memory and Neurohormonal sympathetic regulation. Deactivation occurs in the frontal evaluative areas, such as the dorsal lateral prefrontal cortex association with parasympathetic tone. During dobutaine the activations are associated with somatosensory areas in the periphery of the cortex

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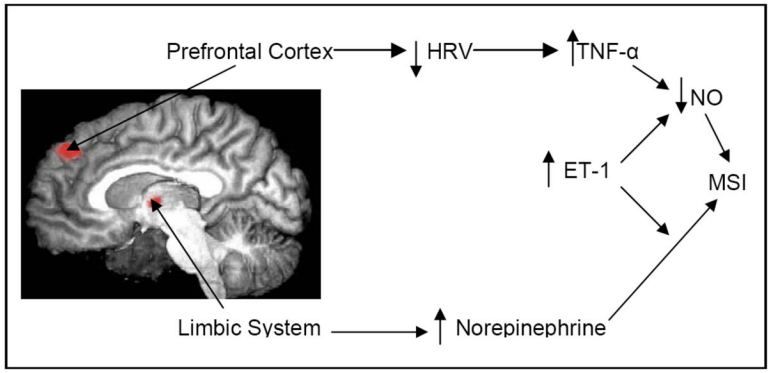

Figure 3.

Mental Stress Provocation results in activation of visceral effectors from the CNS that promote parasympathetic withdrawal (HRV) and accentuation of sympathetic tone (Norepinephrine). This imbalance promotes inflammatory vascular factors which serve to promote vascular dysfunction and results in Mental Stress Ischemia (MSI)

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Table 1

Physiologic Responses to Mental Stress & Exercise

	Mental Stress	Exercise
Heart Rate	+	+++
Systolic BP	++	+++
Diastolic BP	+	↔/−
SVR	+/++	↔/−
Angina	+/−	++