

## Review Article

# Capacity Theory: A Neuropsychological Perspective on Shared Neural Systems Regulating Hostile Violence Prone Behavior and the Metabolic Syndrome

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## Abstract

**Introduction:** An essential characteristic of hostility is the exaggerated and prolonged response to stress this hyper-reactive stress response style has been implicated in the development of cardiovascular disease, hypertension, atherosclerosis, and even death. In addition to these cardiovascular disease processes, hostility's influence on diabetes and the metabolic syndrome is beginning to be elucidated. Diabetes is potentially devastating as this disease disrupts the fuel supply (glucose) to the body and brain adversely affecting emotional, cognitive, and behavioral functioning, particularly when glucose levels are high. Diabetics are significantly more likely to have structural changes within the brain when compared to those without diabetes. Moreover, there is some evidence to suggest that these structural changes are lateralized to the right frontal lobe.

**Conclusion:** Using the Limited Capacity Model of hostility as a guide, it is argued that hostile men show prolonged and exaggerated responses to stress as a result of a limited stress management capacity attributable to the right frontal lobe. Further, individuals with a variable and deregulated fuel supply to their brain (diabetes) exhibiting an increased and exaggerated stress response (hostility) as a result of modest regulatory capacity, should demonstrate an exacerbated stress response within negative affective and sympathetic nervous systems of the right hemisphere.

**Keywords:** Neuropsychology; Hostility; Anger; Hypoglycemia; Hyperglycemia; Aggression; Laterality; Emotion; Glucose; Diabetes; Cerebral asymmetry; Metabolic syndrome; Brain

## Introduction

An essential characteristic of hostility is the exaggerated and prolonged response to stress [1-3]. This hyper-reactive stress response style has been implicated in the development of cardiovascular disease [4-6], hypertension [7,8], atherosclerosis [9], and even death [4]. In addition to these cardiovascular disease processes, hostility's influence on diabetes and the metabolic syndrome is beginning to be elucidated [10-13]. Diabetes is potentially devastating as this disease disrupts the fuel supply (glucose) to the body and brain adversely affecting emotional, cognitive, and behavioral functioning [14,15], particularly when glucose levels are high [16]. Diabetics are significantly more likely to have structural changes within the brain when compared to those without diabetes [15,17]. Moreover, there is some evidence to suggest that these structural changes are lateralized to the right frontal lobe [17,18].

Using the Limited Capacity Model of hostility [19-23] as a guide, it is argued that hostile men show prolonged and exaggerated responses to stress as a result of a limited stress management capacity attributable to the right frontal lobe. Further, individuals with a variable and deregulated fuel supply to their brain (diabetes) exhibiting an increased and exaggerated stress response (hostility) as a result of modest regulatory capacity, should demonstrate an

exacerbated stress response within negative affective and sympathetic nervous systems [24] of the right hemisphere.

Originally derived from Type A Personality Disorder in the 1970s, research on hostility has continued to expand over time and the construct has proven to be multifaceted [25,26]. Unfortunately, the multidimensionality of this construct lends itself to controversy. The literature on hostility is robust with varying definitions and discrepancies among potentially related constructs, such as assault, indirect hostility, and resentment [27]. Despite these variances in proposed hostility models, it is argued the most crucial component of hostility is an exaggerated and prolonged stress response [1- 28]. This hyper-responsivity to stress has been shown to be related to and arguably influences the development of cardiovascular disease [4-6], hypertension [7,8], and atherosclerosis [9] and to increase the overall mortality rate in people showing a prolonged stress response [4]. In addition to the traditional cardiovascular measures of the stress response, hostility has been implicated in the decreased metabolism of lipids [29-31], cholesterol [32,33], and glucose [34-38]. Further compromising overall well being, hostile individuals also engage in unhealthy behaviors, such as smoking, drug use, and increased alcohol consumption [7,39-44].

Research has demonstrated that hostility and violence-prone

behavior are connected to diminished right frontal lobe regulatory control over negative affect perception and expression, sympathetic nervous system activation, improper social pragmatics, and improprieties [21,24,26,]. Within this framework, high hostile men have been shown to display dysregulation of right cerebral systems as evidenced through an exaggerated sympathetic stress response with cardiovascular reactivity for blood pressure, heart rate, and glucose mobilization [45]. Moreover, hostiles show diminished right frontal capacity in the regulatory control over negative affect perception and appraisal within the right cerebral hemisphere. This diminished regulatory control has been demonstrated within auditory [46,47], visual [48,49], and somatosensory modalities [50,51]. Diminished right frontal capacity has received direct support on frontal lobe measures of motor [52,53] and premotor functions [20,38,54]. High hostiles have also shown hyperreflexia, or dystonia, at the left hemibody and at the left hemiface [24,53], quantitative electroencephalographic evidence for right frontal incapacity [55], impaired frontal eye field functions [56], and neurocognitive impairments on neuropsychological measures sensitive to right frontal function [55]. These differences have been expressed theoretically in the capacity model within the neuropsychological literature [19-23]. Specifically, the capacity model asserts that, in high hostile individuals, there is a diminished capacity of the right frontal lobes ability to regulate the posterior systems of the right hemisphere.

Paralleling the neurological variances associated with hostility, there has been a recent identification of a cluster of symptoms collectively known as the Metabolic Syndrome (MS) correlated with high hostile behavior. These symptoms include increased abdominal adipose tissue, Body Mass Index (BMI), lipids, cholesterol, blood pressure, and high fasting glucose levels [57]. Further compromising their health, hostile individuals face increased significant risk for developing both cardiovascular disease [58,59] and diabetes [60,61]. Evidence also implicates high hostiles are at higher risk for overall mortality [62]. Controversy remains over the identification of a specific cause for these various health issues despite multiple pathways being suggested [63]. To add an additional element of complexity, current research suggests that the central nervous system plays a role in the development of MS [64] and maintenance of MS [65,66]. Further complicating the issue, there is emerging evidence supporting the involvement of hostility in MS [11,13,67,68].

With the considerable overlap between hostility and MS, particularly concerning cardiovascular disease and the metabolic features associated with both constructs, it is argued that the right hemispheric capacity model of hostility can be applied to MS. Specifically, it is argued that hostile violence-prone individuals may eventually develop MS due to the associated health related consequences of the exaggerated and prolonged stress response. In addition, hostility is a construct that requires further attention in those diagnosed with MS. Finally, it is argued that individuals with MS may be experiencing a similar limited capacity for regulatory control over these health related functions.

## Hostility

Hostility is plagued with controversy as it is associated with many similar constructs including anger, aggression [69], cynicism, hostile aggression, instrumental aggression [70], and non-physical

aggression [32]. In addition, there has been considerable discussion on the affective, behavioral, and cognitive components of the separate, but similar constructs of hostility, anger, and aggression [6]. The intention of this paper is not to add confusion to the literature by addressing and explaining the similarities, discrepancies, or the potential areas of overlap among these constructs [70]. Instead, hostility will be operationally defined in accordance with Smith & Seigman [1] as "...a devaluation of the worth and motives of others, an expectation that others are likely sources of wrong doing, a relational view of being in opposition toward others, and a desire to inflict harm or see others harmed" (p.26). Within Smith's analysis of hostility, there is a component of "psychophysiological reactivity" reflecting the rationale that hostile individuals have a negative attitude towards others, as well as an increased and exaggerated sympathetic physiological response to their environment [2].

As a construct, hostility appears to be stable across the lifespan, with both environmental and genetic factors implicated in its' etiology [71-75]. In terms of the environmental influence, Keltikangas-Jarvinen & Heinonen [71] found that parental influences contributed to childhood hostility levels predicting adulthood hostility levels 15 years later. Specifically, regression analysis revealed that family Socioeconomic Status (SES), parental hostility levels, and parental life dissatisfaction during childhood were predictive for adult hostility levels. Further supporting the environmental influence on hostility, Smith et al. [72] compared retrospective data from 48 sets of male twins. Correlations were conducted for past and present levels of hostility for each individual as well as for each twin set. Smith et al. concluded, "The early family environment of hostile persons seems to contain interactional patterns conducive to the development of chronic anger, resentment, and mistrust (p. 345)." In addition, these authors suggested that hostile individuals treat themselves in a manner that is consistent with the treatment they experienced in childhood.

Vernon et al. [75] provided evidenced for a genetic influence in hostility. In a comparison of 18 measures of aggression and hostility, the responses of 247 sets of twins were examined for heritability estimates. Multivariate analyses indicated moderate to high heritability estimates for 14 of the 18 measures, as well as for a general factor of aggression. Vernon et al. concluded that a genetic factor for hostility is present as evidenced by the consistency among the heritability estimates across measures. Additional support for the genetic influence on hostility is found with the heritability estimates for testosterone [74] and serotonin [73], both of which have been implicated in the maintenance of hostility [74,76].

Despite the controversy over the factors affecting its' development, hostile individuals appear to have an increased and extended response to stress [3]. Associated with this heightened responsivity is cardiovascular disease [4-6], hypertension [7,43], atherosclerosis [9], and an increase in metabolic factors [29,31-37].

From a neuropsychological perspective, it is argued that hostility is a negative emotion with an associated exaggerated and prolonged reaction to stress. Evidence for this position is provided by Suarez et al. [3] in an examination of large-scale physiological reactivity in high and low hostile men. 52 Caucasian men classified as either low or high hostile, were randomly assigned to non-harassment or a harassment

condition. The harassment condition involved an argumentative, challenging, and insulting experimenter as an interpersonal stressor. The high hostile men in the harassment condition demonstrated increased reactivity for systolic blood pressure, heart rate, forearm blood flow, forearm vascular resistance, norepinephrine, testosterone, and cortisol responses relative to both the non-harassed high hostile and low hostile groups. Suarez et al. argued that the hostiles evidenced sympathetic nervous system responsivity through heart rate, blood pressure, and vascular resistance measures, with hypothalamic-pituitary-axis activity evidenced through increases in norepinephrine, testosterone, and cortisol.

Of particular importance, the research by Suarez et al. [3] provided clear evidence for heightened stress levels, relative to low hostile men, in high hostile men. Moreover, this experiment confirms HPA activation during stress, which was evidenced by cortisol, testosterone, and norepinephrine increases from baseline for the high hostile-harassed condition. Suarez et al. noted that epinephrine did not increase as a result of the stress condition. The authors stated this finding is somewhat unusual, as epinephrine is thought to be a primary marker of HPA activation [77].

The exaggerated response of high hostiles to stress may explain the long standing relationship of hostility and Coronary Heart Disease (CHD) [25,39,78-84]. Miller et al. [6] confirmed this relationship via a meta-analytic review of 45 studies involving hostility and physical health. The authors concluded that hostility is an independent risk factor for mortality and CHD. According to Miller et al., hostility remains a valid predictor of CHD and death. These findings included controlling for health behavior risk factors such as smoking, diet, and physical activity. Miller et al. proposed a Transactional Model, whereby hostiles have an antagonistic and aggressive interpersonal style that results in more aggressive responses from others, and ultimately produces a reduction in social support with an increase in negative affect and stress [85]. The consequence of the increased negative affect experienced by hostiles is heightened cardiovascular reactivity, which eventually leads to CHD [86]. Despite the strong evidence for this conclusion, the precise mechanism explaining how cardiovascular reactivity develops into CHD has yet to be determined.

In a separate review, Brydon et al. [5] identified hostility as a contributing factor for CHD, providing an explanation for this relationship. Specifically, the authors concluded that individuals prone to faulty 'psychosocial factors,' namely hostility (and depression), experience stress more often, which results in a pro-inflammatory and pro-thrombotic response. The anti-inflammatory response leads to increased recruitment of leukocytes [white blood cells], lipids, smooth muscle cells, fibroblasts, and platelets to the arterial wall. When this process occurs too frequently, the unintentional byproduct of this inflammatory response is hyperplasia of the blood vessels and development of atherosclerotic plaque. This plaque, lining the inner wall of the blood vessels, can eventually result in heart attack, stroke, or death [87].

In patients already diagnosed with Coronary Artery Disease (CAD), Boyle et al. [4] stated that increased levels of hostility is potentially life threatening. These researchers gave nearly 1000 patients the Cook Medley Hostility Inventory (CMHO) subsequent to diagnosis of CAD. Hostility was found to be a predictor of CAD

severity and mortality. Here, patients with higher levels of hostility were not only at a significantly increased risk for having heightened levels of plaque in their arteries (atherosclerosis), they were more likely to die. Boyle et al. stated "the relationship between hostility and survival may be mediated by excessive, repeated, and/or prolonged activation of the sympathetic adrenal medullary system" (p.631). Moreover, they indicated the increased sympathetic activation was responsible for the development of atherosclerotic plaque and coronary events.

In an attempt to identify potential predictors of atherosclerosis, Iribarren et al. [9] argued that hostility significantly increased the likelihood of coronary artery calcification, which was thought to be a marker of subclinical atherosclerosis. As part of the Coronary Artery Risk Development in Young Adults Study (CARDIA), 374 black and white men and women were followed over 5 years. During the initial baseline, hostility levels were assessed using the CMHO. Scans were taken of the participant's aorta to assess for the level of calcification. The results indicated that baseline hostility scores correlated significantly with increased levels of coronary artery calcification. The reliable association between the hostility score and the level of calcification persisted after controlling for sex, age, race, education, alcohol consumption, smoking history, and changes in blood pressure. Additionally, during a 5-year follow up of the participants, increased scores on the CMHO were again significantly correlated with increased coronary artery calcification. Iribarren et al. stated that a number of factors including cardiovascular reactivity, blood platelet activation, reduced beta-adrenergic receptor responsiveness, and increased neuroendocrine responses were responsible for this relationship.

Beyond cardiovascular disease, hostility has been implicated in the development of hypertension. Yan et al. [7] examined hostility levels in 3308 black and white adults, 18-30 years of age, over a 15-year period as part of the Coronary Artery Risk Development in Adults (CARDIA) research. When measured using the CMHO, initial hostility levels were predictive of long-term hypertension. Interestingly, no relationship between hypertension and achievement, depression, or anxiety was found. Yan et al. concluded that, while hostility is related to hypertension, the processes concerning short-term stress and the development of long-term dysfunction remains unknown. The authors reported that hypertension occurs in conjunction with several systems including genetics, biopsychophysiological factors, daily life experiences, stress provocation, and general well being, all of which may influence blood pressure. Despite this acknowledgment, Yan et al. described how the stress response may result in hypertension as "sympathetic nervous system stimulation from acute stress, leads to cardiac output, vasoconstriction, arterial pressure elevation, impaired endothelial function, and platelet activation" (p.2146). In addition, these authors stated that both cholesterol and endocrine dysfunction are involved in hypertension, although the precise mechanisms behind these relationships were not stated.

The relationship between hypertension and hostility is evident even for initially normotensive individuals. Using the Suppression Index from the CMHO, Zhang et al. [43] stated that 'suppressed hostility' was significantly correlated with increased risk for hypertension at a 3 year follow-up for non-hypertensive, middle-aged men. Zhang et al. proposed a Suppressed Hostility Hypothesis, claiming that

highly hostile individuals avoid experiencing anger by suppressing it. The consequence of this is suppression, according to the authors, is chronic sympathetic activation, decreased parasympathetic tone, and secretion of rennin. Research by Mohrman & Heller [88] indicated that rennin secretion causes an increase in blood volume and vasoconstriction, resulting in an increase in blood pressure.

In addition to the traditional cardiovascular measures of the stress response, hostile individuals' evidence altered metabolic functioning. Specifically, hostiles have demonstrated increased levels of lipids [29,31] and cholesterol [32,33], and decreased levels of glucose [35-37]. To assess the link between cardiovascular disease and hostility, Voegelé [31] examined lipid reactivity to stress in high and low hostiles. High hostile men produced increased lipid levels, specifically triglyceride levels, when compared to low hostile men after completing a mental arithmetic and mirror star tracing stressor task. In addition, high hostile men reported increased levels of anger, frustration, anxiety, blood pressure, and heart rate. Voegelé concluded that high hostiles had increased lipid reactivity to stress because of an increase in sympathetic tone, which leads to higher circulating catecholamines that mobilize free fatty acids from fatty tissue. Voegelé termed this response pattern the hyper reactivity model. In addition to this explanation, Voegelé demonstrated that high hostiles were more likely to engage in unhealthy behaviors, including increased alcohol intake and poor diet, which could indirectly increase lipid profiles.

Finney et al. [29] found similar results for lipid reactivity in both Caucasian and African American men with elevated levels of anger. Specifically, hostile men demonstrated lipid and blood pressure reactivity subsequent to a speech stressor, relative to low hostile men. Although no explanation was provided for this relationship, Finney et al. concluded that lipid reactivity is a precursor for the development of cardiovascular disease, and that men experiencing heightened levels of hostility are at increased risk for cardiovascular events.

Cholesterol, which is a substance required for cell membrane and hormone synthesis, has been found in increased levels in blood vessels associated with atherosclerosis, inflammation due to stress [89], and has been correlated with increased hostility levels. Hillbrand et al. [32] administered the Aggression Questionnaire [90] and measured blood serum cholesterol levels in a healthy, college aged population. Regression analysis revealed that anger, hostility, and verbal aggression significantly predicted cholesterol levels. Aside from the documentation of this relationship, no explanation was provided for the potential relationship between hostility and cholesterol.

Further research by Richards et al. [33] looked at a sample of healthy men and found those with elevated scores on hostility and aggression measures had increased cholesterol levels. Specifically, scores from the State Trait Anxiety Inventory demonstrated that the variable of 'angry reaction' was significantly correlated with total serum cholesterol and low-density lipoproteins. Interestingly, total serum cholesterol and low-density lipoproteins were not significantly correlated with diet. Richards et al. concluded the elevated cholesterol levels indicate that hostile men have irregularities in their mobilization of cholesterol and lipoproteins, reflective of irregularities within the stress response, although the precise mechanism for this relationship was not defined.

There is some controversy in the literature concerning hostility's

relationship to cholesterol as some researchers have documented increases in hostility only when cholesterol levels are low [91], while others report that no relationship exists between the two constructs [92]. In a sample of hospitalized men with a history of violent behavior, cholesterol levels were found to be lower than the general population [93]. However, these researchers suggested a curvilinear relationship between aggression and cholesterol, with the most frequent acts of aggression occurring with low levels of cholesterol.

Glucose, which is the primary fuel for the brain [94], is yet another correlate of hostility, and there has been a documented association between hostile behavior and poor glucose regulation [38]. Virkkunen [37] examined the role of hypoglycemia in a hostile population consisting of habitually violent offenders. Using a glucose tolerance test in which glucose irregularities are measured for several hours after the initial consumption of a glucose bolus, Virkkunen was able to demonstrate that the habitually violent offenders were significantly more likely to have hypoglycemic tendencies relative to non-violent offenders. Benton et al. [34] found similar results with a non-violent and non-diabetic population. After the participants fasted for nearly 12 hours, their hostility scores on the CMHO, Buss-Durkee Hostility Inventory, and the Rosenzweig Picture Frustration Study significantly increased, thereby providing evidence for increased hostility levels after the brain and body are deprived of an integral fuel source.

More recently, McCrimmon et al. [36] reported a positive relationship between hostility and blood glucose after participants received the hyperinsulinemic glucose clamp technique. The glucose clamp technique involves the systematic intravenous injection of insulin over an extended period of time. Once the specified level is reached, the researchers are able to "clamp" and maintain the desired level of glucose in the blood. Nondiabetic men and women evidenced increased levels of hostility after the hypoglycemic episode as indicated by elevated scores on the State-Trait Anger Expression Inventory (STAXI), as well as by the participants' self-report.

Donhoe & Benton [33] found similar results with nondiabetic women. After having participants fast overnight, the researchers administered an oral glucose tolerance test. Subjects consumed a drink containing 50g of sugar and were, subsequently, observed for several hours. They were then given the Rosenzweig Picture-Frustration Study. Results indicated that lower blood glucose levels were associated with increased scores of aggression and frustration.

In a sample of nondiabetic Caucasian and African-American men, Surwit et al. [95] demonstrated a relationship among elevated hostility scores on the CMHO, fasting insulin, and insulin sensitivity. The relationship of glucose metabolism to hostility was found to be independent of BMI. Surwit et al. explained this relationship with the stress moderation model, which proposes that hostile individuals demonstrate increased neuroendocrine reactivity to stress as the result of their interpretation of the environment as more threatening, resulting in increased likelihood to engage in conflict.

In addition to hostility's association with the metabolic factors of lipids, cholesterol, and glucose, hostile individuals are significantly more likely to engage in unhealthy behaviors [7,39-43]. Williams, Barefoot, and Schneiderman [96] noted an apparent division in the literature describing two Biobehavioral pathways that are responsible

for disease processes in hostile individuals: biological characteristics (increased cardiovascular and neuroendocrine response to stress, increased platelet activation, increased inflammatory cytokines, increased likelihood of MS) and unhealthy behaviors (smoking, alcohol intake, caloric intake, and BMI).

Evidence of hostile individuals engaging in unhealthy behaviors was provided by Scherwitz et al. [41] using data collected on 5,115 black and white men and women. Higher scores on the CMHO were strongly associated with increased tobacco and marijuana smoking, increased alcohol consumption, and greater caloric intake for all groups. These associations were particularly strong for tobacco and marijuana smoking as those individuals scoring highest on the CMHO was 1.5 times more likely to smoke relative to those individuals with the lowest scores, even after adjusting for both age and education level.

Siegler et al. [44] compared responses from 4700 men and women, taken initially during the mid 1960s and then again around 1990, on a number of health related variables. The results indicated that those individuals scoring higher on the CMHO during the time of the initial screening were significantly more likely to consume caffeine and alcohol, smoke cigarettes, and have higher BMI and lipid ratios and hypertension at the time of a 20 year follow-up.

As part of the longitudinal Normative Aging Study, Kawachi et al. [39] examined scores from the CMHO in 1300 older men that were free of cardiovascular disease at the initiation of the study. Follow-up results indicated that higher scores on the CMHO were associated with increased rates of smoking, drinking of alcohol, and BMI. Similarly, in separate analyses from the Normative Aging Study, Zhang et al. [43] reported that hostility was significantly correlated with low education level, increased caloric intake, and increased likelihood of smoking. Results from the Coronary Artery Risk Development in Young Adults Study (CARDIA) demonstrated that high hostiles (using the CMHO) were significantly more likely to have increased BMI, alcohol intake, and systolic blood pressure; and to have less education [7]. In addition, Knox et al. [40] stated that hostility is clearly linked with cigarette smoking and alcohol consumption.

Interestingly, despite the solid evidence indicating that hostiles engage in unhealthy behaviors, the literature provides little explanation for this relationship, despite the logical conclusion that these unhealthy behaviors degrade the overall health of the individual and could potentially influence the rate of cardiovascular disease, diabetes, and perhaps even the metabolic syndrome. Taken together, the consequences of hostility are visible at numerous levels. An overarching theory could potentially provide a rationale to explain the diverse findings. However, the influence of the CNS has yet to be examined and integrated with this literature.

## Hostility and the Brain

The frontal lobes have been consistently implicated in the development and expression of hostility. In a review of hostility, aggression, and the frontal lobes, Brower & Price [97] examined the literature on these topics from 1966 to 2000. A clear association between frontal lobe dysfunction and increased aggressive and antisocial behavior was found. Moreover, focal orbitofrontal injury was specifically associated with increased aggression. Supporting this

review, Tateno, Jorge, and Robinson [98] provided evidence from 89 head injured patients, concluding that those with frontal lobe injuries were significantly more likely to become aggressive during their recovery relative to non-frontal lobe injured patients. Left and right frontal lobe comparisons for aggression and hostility were not conducted. Unfortunately, the failure to indicate which frontal lobe had been damaged reflects the flawed notion of a single “frontal lobe syndrome,” and implies that the two frontal lobes are identical in both structure and function. This approach has been criticized by Damasio & Anderson [99], who write, “The notion that there is a unitary frontal lobe syndrome is not supported by anatomical or neuropsychological evidence” (p.409).

Research from our laboratory has examined the role of both the left and the right frontal lobes in their respective roles of regulatory control over left and right posterior brain regions charged with the reception, analysis, and comprehension of information within the respective sensory modalities [28]. The approach of examining the brain as a concert of systems working together has been labeled a functional cerebral systems theory approach. This approach has evolved from research by Alexandr Luria [100,101] who theorized that the brain was organized into specific zones working together in a concerted fashion, with frontal inhibition of both the subcortical and the posterior systems. Within this framework, our laboratory has demonstrated diminished right frontal lobe regulatory control capacity in hostile men. This conclusion received support as hostile men evidence diminished regulatory control over the functions of the right cerebral hemisphere, including anger, sympathetic tone, and the perceptual biases across each sensory modality located within this division of the nervous system. In addition, hostile men have performed significantly below low hostile men on neurocognitive measures sensitive to right frontal dysfunction.

Direct evidence for diminished frontal lobe capacity in hostiles is provided in the investigation of upper motor neuron functions, where diminished capacity presents in dystonia or hyperreflexia across the contralateral (left) hemibody. Extending this line of research for the motor systems, Demaree et al. [52] examined grip strength in right handed high and low hostile men. Each group was equivalent on handedness scores with a right hemibody preference across sensory and motor domains. Hand dynamometer measurements were used to assess grip strength, which is a measure of hemispheric motor functioning. It was expected that high hostile men would demonstrate increased “antigravity” or flexor strength at the left hand, which was confirmed. Subsequently, the facial muscles were investigated with similar predictions for facial dystonia as measured in electromyographic activity over the antigravity masseter muscles at the left and the right hemifacial regions. Hostile men displayed significantly heightened facial motor tone across both the left and the right hemifacial regions in comparisons with low hostile men. Cerebral asymmetry differences were supported with reliably elevated left hemifacial motor tone in hostile men supporting the interpretation of diminished right frontal capacity. Moreover, the potential social impact of facial dystonia was discussed, where the affect conveyed within the facial expression was somewhat harsh and potentially provocative for the others in a social encounter with the hostile male [53].

The right frontal lobe has been implicated in the regulatory control over sympathetic tone with diminished capacity reflected in an exaggerated or reactive sympathetic stress response with cardiovascular measures, including systolic blood pressure and heart rate [46], and Skin Conductance Measures (SCR) [48,102]. Additionally, evidence is provided for the diminished capacity of the right frontal lobe to regulate the sensory perceptual systems of the posterior right hemisphere.

Demaree & Harrison [46] examined the auditory systems in hostile men. Using high and low hostile men, arousal levels were tested with physiological, behavioral, and laterality measures. Participants were administered an auditory dichotic listening test and then underwent a provocative pain stressor, specifically, the application of a cold pressor stimulus. The results indicate that high hostile men had increased blood pressure and heart rate, and that they correctly identified more word sounds (phonemes) at the left ear following the stressor. Relative increased levels of arousal, as well as the heightened left ear advantage, are indicative of increased right cerebral activation for the high hostile men when compared to the low hostile men. This increase in right cerebral activation in high hostile men occurred with a corresponding increase in sympathetic tone using cardiovascular measures. Diametrically opposite results were found in the low hostiles who showed heightened left cerebral activation as evidenced through a dynamic increase in right ear word sound identification and lowered heart rate and blood pressure to the stressor.

Harrison & Gorelczenko [48] assessed cerebral asymmetry in the visual perception of affect for hostile men and women. Employing a tachistoscope, participants were instructed to identify angry, happy, or neutral faces in either the left or the right visual field. Hostile participants showed faster affect perception and a negative perceptual bias restricted to the left visual field. Herridge, Harrison, Mollet, and Shenal [49] replicated and extended this research using perceptual accuracy measures within the visual modality while adding a stress component, specifically a cold pressor. Hostile men demonstrated decreased accuracy in the recognition of emotional faces within the left visual field, whereas women demonstrated symmetry across both visual fields.

Hostile men have demonstrated asymmetry for skin conductance as a primary measure of sympathetic arousal [50]. High hostiles have evidenced increased skin conductance at the left hemibody, as well as a reduced habituation rate at the left hemibody when compared to the right hemibody, subsequent to posing facial configurations consistent with anger (corrugator muscle contraction). Low hostiles evidenced prolonged habituation rates at the right hemibody suggestive of relative left cerebral activation in this group.

Williamson & Harrison [20] investigated the left and right prefrontal regions in this group evaluating cardiovascular reactivity to lateralized prefrontal stressors. The Controlled Oral Word Association Test (COWAT) and Ruff Figural Fluency Test (RFFT) were used as verbal and nonverbal frontal lobe stressors respectively. Previous research has demonstrated the COWAT to be sensitive to left frontal functioning [103], whereas the RFFT is sensitive to right frontal functioning [104,105]. High and low hostile men completed both frontal stressors. The results indicated that the verbal and nonverbal stressor tests produced diametrically opposite effects on

systolic blood pressure in high hostile men. Specifically, systolic blood pressure increased subsequent to the nonverbal stressor (RFFT), whereas systolic blood pressure decreased subsequent to the verbal stressor (COWAT). For the low hostile group, the verbal stressor (COWAT) stressor increased systolic blood pressure, whereas the nonverbal stressor (RFFT) yielded no significant changes for systolic blood pressure.

This research has implications for cardiovascular regulation in hostile men, as Williamson & Harrison [20] conclude that the frontal regions were unable to regulate blood pressure with the concurrent demand of the stressor task, citing the capacity model. This research is in accord and extends previous research on the anterior-posterior model of hostility, specifically supporting relative right posterior activation and relative right frontal deactivation for high hostile men. Diminished frontal lobe capacity was supported using electrophysiological measures with quantitative electroencephalography in related research [47,54].

Williamson et al. [106] continued this line of research. Here, the influence of hostility on cardiovascular regulation, verbal fluency, nonverbal fluency, and dichotic listening was assessed. Twenty-four high and low hostile men underwent physiological measurements of SBP, DBP, and HR before and after verbal and figural fluency tasks, which were used as stressors. It was predicted that high hostile men would produce results indicative of diminished right frontal capacity when compared with low hostile men as reflected through cardiovascular activation subsequent to the nonverbal but not the verbal stressor. As predicted, high hostile men produced a reliable increase in blood pressure when compared to baseline and to low hostile men and produced more preservative errors than did low hostile men on this task. In addition, dichotic listening performance was evaluated across undirected, directed leftward and directed rightward conditions. Differences in dichotic listening performance were expected as a function of the fluency tasks. It was predicted that high hostile men would evidence a priming effect in that a left-ear bias would be detected after the nonverbal fluency task but not the verbal fluency task. Support for this prediction was found. However, the low hostile men also displayed a priming effect at the left ear during the nonverbal fluency condition. Results are discussed within the context of the functional cerebral systems regulating emotion and cardiovascular function. Further support for the right hemispheric involvement in the regulation of cardiovascular processes has been found by Weisz et al. [107]. Baroreceptor stimulation (through a neck suction device) led to a significant rCBF increase in the anterior, inferior part of the lateral prefrontal cortex only in the right hemisphere, thereby implicating the right frontal lobe in sympathetic activity in normal men. Weisz et al. concluded that the right hemisphere plays a larger role than the left hemisphere in baroreceptor regulation. Although this research is not specific to hostility, it demonstrates the role of the right frontal lobe in sympathetic activation.

In an attempt to replicate and extend Williamson & Harrison [20], Walters, Harrison, Campbell, & Harrison [38] examined the stress response via glucose and cardiovascular regulation in high and low hostile men with concurrent left frontal lobe (Control Oral Word Association Test [verbal]) or right frontal lobe (Ruff Figural Fluency Test [nonverbal]) stress. Specifically, the glucose levels of

high hostile men were significantly higher for the nonverbal stressor when compared to the verbal stressor. For the low hostile group, glucose levels (mg/dl) remained stable, or unchanged, for both types of stress. Additionally, the high hostile men made significantly more errors on the nonverbal stressor when compared to the low hostile men. These results were interpreted within a right hemispheric model of hostility. Additionally, it was suggested that the high hostile were unable to concurrently regulate their glucose levels while completing a right frontal lobe task potentially as a result of diminished right frontal lobe capacity.

The limited capacity model is an extension of Kinsbourne's functional cerebral space. [108-110]. The premise behind this theory is "When the human operator, while fully engaged in an attention-demanding task, is required simultaneously to perform a second such task, he typically loses efficiency on the main task" [109] Williamson & Harrison [20], Walters, Harrison, Campbell, & Harrison [38], and Williamson et al. [106] applied this concept to a population with an emotional dysregulation, specifically hostility, and concluded that, due to a limited capacity of the frontal regions, hostile participants are unable to endure frontal lobe stress and maintain their baseline sympathetic arousal rates. This inhibition of frontal lobe regulation results in increased sympathetic arousal.

The literature on hostility also supports a right hemispheric model of hostility for healthy individuals as evidenced using Positron Emission Tomography (PET) to assess brain activation to anger inductions [105,111]. Kimbrell et al. [111] used PET to measure regional cerebral blood flow changes as a function of the emotional response. Subsequent to the anger induction, the participants displayed significant increases at the right thalamic and the right temporal regions, whereas there was significant deactivation at the right frontal regions. Kimbrell et al. concluded that transient levels of anger provide unique regional brain activation, which includes a relative deactivation of the right frontal lobe.

On a neurochemical level of analysis, Rubia et al. [112] administered an amino acid cocktail to deplete tryptophan (precursor to serotonin) before subjects underwent an fMRI. The rationale for the depletion of serotonin was that it was intended to provide evidence for the lateralization of serotonin regulation, and to further the examination of serotonin's role in aggression and hostility. In a double-blind sham controlled design, subjects consumed either the tryptophan depletion cocktail, or a sham amino acid cocktail, and then completed a 'go/no go' task while undergoing fMRI. Subjects consuming the tryptophan depletion cocktail demonstrated right orbital and right inferior prefrontal deactivation, whereas right middle temporal and left temporal regions were activated during the frontal lobe task. Although not stated explicitly by the authors, the deactivation of the right prefrontal region subsequent to the serotonin depletion implicates this region for the involvement of hostility.

Using EEG, Hewing et al. [113] examined both anger scores as well as left and right frontal lobe activation during baseline. The results indicated that subjects with elevated 'anger-out' and lowered 'anger-control' scores displayed increased left frontal activation relative to right frontal lobe deactivation during baseline conditions. Although the authors proposed a left frontal lobe activation model of anger, their data also supports the right hemispheric model of hostility, as

the heightened anger scores were associated with decreased right frontal lobe activity.

Given this evidence, a right hemispheric model of hostility is proposed in which the right frontal lobe is unable to regulate the exaggerated and prolonged stress response in high hostiles. Moreover, the over activation of this stress response reflects a limited capacity within the right frontal lobe to regulate sympathetic tone. In addition to the limited capacity, it is argued that high hostiles are more likely to have a hyperreflexia sympathetic response as the result of interpreting ambiguous situations as negative and having an interpersonal style that elicits aggression from others [6]. This is more clearly demonstrated in facial dystonia and especially at the left hemiface, which conveys a harsh or less dynamically responsive facial affect [53]. Unfortunately, this activation pattern has health related consequences, and these consequences have considerable overlap with a newly defined syndrome: Metabolic Syndrome.

## The Metabolic Syndrome

The literature on MS begins with Reaven's lecture given to the American Diabetes Association in 1988. During this lecture, Reaven described and articulated a relationship between insulin resistance and hypertension. Over time, additional metabolic factors were incorporated to include increased levels of cholesterol, lipids, and body mass and the clustering of symptoms was eventually labeled MS [114].

Since the time of its initial description, there has been controversy over the exact definition and specified criteria concerning MS [60]. To further this point, the authors of the Joint Statement of the American Diabetes Association and the European Association for the Study of Diabetes challenged the use of the term "syndrome," as the literature on MS is robust with discrepancies, and controversy remains for the predictive value of the subcomponents [115]. To further their critique of the literature, Kahn et al. write that due to the inconsistencies within the literature a "...more serious examination of whether medical science is doing any good by drawing attention to and labeling millions of people with a presumed disease that does not stand on firm ground" (p. 2299).

According to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), the criteria for the diagnosis of MS includes three or more of the following five symptoms: abdominal obesity; waist circumference (> 102 cm in men, >88 in women); hypertriglyceridemia (> 159 mg/dL); low high-density lipoprotein cholesterol (<40 mg/dl in men, <50 mg/dl in women); high blood pressure (>130/85 mmHg); and high fasting glucose (> 110mg/dL) [57]. It should be noted the Adult Treatment Panel does not make mention of, or list, any emotional components (including hostility), as a criteria in the diagnosis of MS.

Aside from the health risks associated with each of the specific subcomponents, there is also a significant risk for individuals with MS to develop cardiovascular disease and Type II Diabetes [60,61]. Younger patients (less than 50 years of age) with MS are up to 5.8 times more likely to experience a cardiovascular event, such as heart attack or stroke, relative to patients without MS [59]. Patients over the age of 70 with MS are at very high risk for a cardiovascular event

[58]. In addition to the relationship with cardiovascular disease, MS is significantly associated with mortality [62].

MS is becoming increasingly present in the normal population. Basing their sampling data on the 2000 census, Ford et al. [57] reported that 22% or 46 million Americans meet criteria for MS. The rates of MS are similar for men and women. However, the data for MS were evaluated according to the number of metabolic abnormalities (0-5), rather than identifying which metabolic abnormalities were present. It could be that the subcomponents are unique for men and women, although there are no data to suggest, or disconfirm, this claim. In terms of race and ethnicity, Mexican-Americans had the highest percentage rates when compared to Caucasians and African Americans. When stratified by age, Alexander, Landsman, Teutsch and Haffner [116] stated that 44% of the U.S. population over 50 years of age meets criteria for MS, thereby suggesting that the rate of MS doubles after age 50, and that nearly one half of the US population suffers from this condition.

With respect to cause, the current research has not yet detected a common pathophysiologic mechanism [63]. However, the driving force behind MS appears to be central adipose tissue and insulin resistance [57,114-117]. Despite the consensus that obesity and insulin dysfunction seem to be the two primary factors for the development of MS, controversy remains as to which factor, visceral fat [117] or insulin resistance [118], is ultimately responsible for the development of MS. In a review of the literature, Despres [117] argued that obesity, specifically visceral adipose tissue, is the defining characteristic that allows for the development of MS. Despres stated that obesity is the precipitating factor for the development of lipidemia, insulin resistance, glucose intolerance, a pro-inflammatory and pro-thrombotic profile, as well as hypertension. Further, Despres noted that when individuals with MS lose weight, their entire metabolic profile improves. Contrary to the pathway described by Despres [117], Ferrannini's [118] review of the literature supports the influence of insulin resistance for the development of MS. Ferrannini contended that insulin's inability to metabolize glucose results in dyslipidemia, hypertension, and vascular dysfunction, which ultimately leads to MS. However, Ferrannini noted the complexity of the syndrome and that each of the factors related to insulin resistance is part of a larger, integrated system where "these homeostatic systems are under multifactorial, redundant control" (p.49).

Aside from the precipitating factors of MS, there is also a genetic/environmental dispute. Shmulewitz et al. [119] examined pedigrees developed from family history and genetic data on the island of Kosrae in Micronesia to assess the genetic influence for the development of MS. Results indicated that significant heritability factors exist for the metabolic syndrome factors including obesity, diabetes, hypertension, and dyslipidemia. Shmulewitz et al. implicated specific chromosomes, as well as potential general environmental factors for the development of MS, although the specific environmental influences were not specified.

To assess the environmental impact for the development of MS, Lehman, Taylor, Kiefe, and Seeman [120] assessed early family environment as part of the 15 year CARDIA study. Structural equation modeling revealed that childhood Socio Economic Status (SES) and risky early family environment were significantly associated with MS.

Further, these authors argue that SES and risky family environment influenced the development of MS by increased associations with hostility, depression, and poor quality of social contacts.

Aside from the genetic and environmental influence on MS, increased levels of chronic stress may increase the likelihood of MS. Vitaliano et al. [121] reported that chronic stress predicted MS diagnoses in men over age 60 relative to women over 60 years of age. Moreover, older men experiencing chronic levels of stress were 3 to 12 times more likely to develop MS at the time of the 30-month follow-up. Unfortunately, MS diagnosis for this group also predicted coronary heart disease. Vitaliano et al. also noted an increase in poor health behaviors moderating the relationship between chronic stress and MS. No additional pathway was provided.

It is apparent that there are multiple roads to MS, including the genetic, environmental, and chronic stress routes, all of which focus exclusively on peripheral functioning. To add a further layer of complexity, there is "an emerging model in which a rich bidirectional neuronal communication between the CNS and peripheral organs plays a key role in the control of peripheral metabolism" [66]. These authors posited that MS is primarily composed of the increased levels of central adipose tissue and insulin levels and the brain communicates with the periphery through hormonal signaling (leptin, insulin) and macronutrient sensing (glucose). Using neuronal tracing data, Perez-Tilve et al. demonstrated that the Paraventricular Nucleus (PVN) and the Supra Chiasmatic Nucleus (SCN) of the hypothalamus are primarily responsible for energy balance and metabolism and are directly in contact with endocrine and neuroendocrine outputs.

Furthering the notion that the CNS is directly involved in the development of MS, Krier et al. [65] argued faulty neuronal feedback is responsible. Using a neuronal tracer, Kreier et al. established that the liver, pancreas, and intraabdominal fat share the same vagal motor neurons, thereby providing evidence for the direct communication between the organs themselves and the CNS. Moreover, the tracer injected into the adipose tissue was visible within the spinal cord, PVN, Medial Preoptic Area (MPO), SCN, and the amygdala. Kreier et al. claim that the neuronal tracer provides substantial and clear evidence that the CNS and the PNS communicate directly. It should be noted, the "visibility" of the tracer diminishes as it travels away from its origin in the adipose tissue. This may be an important factor as it is possible the tracer may not have been "seen" in the frontal lobes due to diffraction of the signal as it was transmitted through the CNS.

Kreier et al. [65] proposed a feedback loop between the hypothalamus and brain stem exists with the adipose tissue of the liver, pancreas, and intra-abdominal fat. It was argued the hypothalamus attempts to regulate these systems and faulty regulation of the signal from the adipose tissue eventually results in diabetes. Specifically, Kreier et al. theorized that a miscommunication occurs in the system when the brain is signaling to produce more glucose (reduce insulin production) while the organs are already absorbing glucose, thereby resulting in elevated glucose levels. Kreier et al. reported this occurs during the dawn-phenomenon and may eventually lead to diabetes. Further, these authors implicated increases in adipose tissue, lipids, and related health problems that are the result of overeating as well as a lack of physical exercise, which "might induce confusing feedback to

the brain” (p.1145), thereby resulting in further difficulties regulating the peripheral organs.

Early life experiences have been demonstrated to result in changes within the CNS that could influence the development of MS. In a review of MS, Singh et al. [64] provide evidence that environmental stress experienced during the first two years of life results in the release of anti-inflammatory substances [tumor necrosis factor alpha (TNF-alpha), C-Reactive Protein (CRP), cytokines, and interleukins], which “may serve as signals for programming or adaptations” (p.558). According to Singh et al. these anti-inflammatory substances disrupt the production of fatty acids, thereby reducing the protection provided by the fatty acids to the neurons. In addition, the anti-inflammatory response products damage the SCN, pineal and pituitary glands, olfactory bulb, and the hypothalamus if the exposure occurs during the early stages of development. Damage to these regions disrupts insulin resistance and hypothalamic function, ultimately allowing for the development of MS. Despite this compelling evidence, Singh et al. does not mention additional brain regions that may be involved in the development of MS. Specifically, the authors did not discuss the inhibitory or regulatory role of the frontal lobes over these named brain regions.

Given the relationship between the brain and MS, there is additional support specifically linking hostility to MS. This association is evident even in childhood and adolescence. In a sample of 134 African American and European American children ages 8-10 and 15-17, Raikkonen et al. [13] assessed hostility (CMHO) and MS during an initial screening, and then again during a 3 year follow up. ANOVA results indicated that baseline hostility scores predicted MS diagnoses for children and adolescences that did not have MS diagnoses at baseline. The authors suggested obesity and insulin resistance were primarily responsible for the association between hostility and MS. However, no further explanation was provided explaining this relationship.

Further evidence supporting the relationship between hostility and MS in adulthood is presented. As part of the Normative Aging Study, Niaura et al. [11] reviewed data from 1081 men that were initially evaluated between 1987 and 1991 for the assessment of psychosocial and biomedical correlates of aging. After the initial assessment of health and hostility, the subjects completed a follow-up evaluation that occurred 1-4 years later. The results showed that hostility was positively correlated with caloric intake, BMI, Waist-to-Hip Ratio (WHR), cholesterol, triglycerides, and insulin level, whereas hostility was negatively correlated with education level. These initial correlations were followed up with structural equation modeling, and Niaura et al. demonstrated that hostility was indirectly related to MS as this relationship was mediated by both BMI and WHR. It was concluded that the high hostile men were obese and insulin resistant, which in turn resulted in elevated blood pressure and serum lipids. This sequence of vascular changes provides evidence for hostility as a predicting factor of MS.

Nelson et al. [122] examined data from the Swedish Adoption/Twin Study of Aging (SATSA) to assess the relationship between MS, cynicism, and cardiovascular disease. Nelson et al. reported they were specifically interested in cynical hostility, rather than the traditional use of hostility, and used the 9 item Cynical scale taken

from the CMHO. Beginning in 1984, Swedish twins that were reared together and apart were followed until 1994. During this time, cynical hostility was assessed, as were the cardiovascular risk factors of blood pressure, cholesterol, insulin, glucose, and WHR. Cardiovascular disease was assessed by history of angina pectoris, heart attack, and/or stroke. Initial analyses revealed none of the cardiovascular risk factors by themselves mediated the relationship between hostility and cardiovascular disease. However, when the risk factors were combined into a “metabolic syndrome” factor, multivariate regression analysis revealed cynical hostility significantly predicted MS, with MS then predicting cardiovascular disease. Nelson et al. concluded the latent construct of MS mediated the relationship between hostility and cardiovascular disease.

When individuals are diagnosed as having both heightened levels of hostility and MS, the effects can be deadly. As part of the Normative Aging Study, Todaro et al. [68] examined the combined effect of these two constructs on heart disease. Here, hostility was assessed using the CMHO. Myocardial infarction was determined with Electrocardiogram (ECG). MS was assessed using the criteria specified by the Adult Treatment Panel III. Using multivariate regression analysis, the results indicated that both hostility and MS significantly predicted myocardial infarction. Additionally, high hostile men with MS were 4 times more likely to develop myocardial infarction regardless of sociodemographic and health related behaviors such as smoking, diet, and alcohol consumption. Todora et al. concluded, “Hostility may provide additional prognostic information to the assessment of CHD in patients with the metabolic syndrome” (p.224). To explain these findings, Todora et al. reported that hostility’s relationship to MS, and to MS and CHD combined, is the result of dysregulation of sympathetic and neuroendocrine arousal.

Treatment of MS primarily attempts to improve general physical well being. Fonesca [123] reports the best overall treatment for MS is weight loss and exercise, and additional pharmacological treatments are available for the individual subcomponents. Ford et al. [57] report that the keys to ameliorating the potentially deadly effects of MS are education, reducing weight, increasing physical activity, and managing the individual components of this disorder.

As noted earlier, there is strong support that connects hostility with the individual sub-components of MS. Specifically, hostility has been implicated in the role of heightened blood pressure [7,8], increased lipids [11,29,31,124], increased and decreased cholesterol levels [33,125], and decreased glucose levels [34-37,95,126]. Although each of these sub-factors does not provide a direct relationship with MS, it is suggestive of one. Additionally, it is possible that due to the recent identification of MS [127], the research on this construct may still be in its infancy.

## Application of the Right Hemispheric Model of Hostility to MS

Hostility, as a construct, has evolved since it was first introduced into the literature. Cook and Medley [128] first operationally defined hostility using the MMPI, and hostility was included as a part of Type A Personality Disorder during the 1970s [129]. Since that time, hostility has been identified as a unitary construct, with an exaggerated and prolonged stress response [3]. In addition, high

hostile individuals are at significant risk for developing cardiovascular disease [5,6], coronary artery calcification [9], hypertension [7,43], and for dying [4,6]. While these correlates reflect traditional elements within the cardiovascular system, additional metabolic characteristics have been examined including heightened levels of lipids [29,31] and cholesterol [32,33], and altered levels of glucose [35-38,95]. Adding to these health related problems, individuals with increased levels of hostility are significantly more likely to smoke cigarettes and marijuana, drink alcohol, consume excess calories, and be overweight [7,39-43].

Given this evidence, it is argued that hostile individuals are more prone to an exaggerated and prolonged stress response. The hyper-activation of the stress response is thought to be reflective of dysfunction within the right hemisphere. Specifically, a right hemispheric model of hostility is provided in which the frontal regions have a limited capacity for regulating the stress response [19,20,38,47,106].

As the hostility construct continues to evolve, there is an increasing overlap with MS. This newly described syndrome applies to overweight men and women that have elevated levels of blood pressure, glucose, lipids, and cholesterol [Adult Treatment Panel III; 57]. Moreover, these individuals are at significant risk for developing both cardiovascular disease [58,59] and diabetes [60,61], and are at higher risk for mortality [62]. Controversy remains over of the cause of this syndrome, and multiple pathways have been identified including genetic [119], environmental [120], and chronic stress [64,121,130]. In addition, both the brain [64-66,130] and hostility [11,13,67,68] have been implicated for the development of this syndrome.

With the considerable overlap between hostility and MS, it is argued that there is a relationship between these two constructs, and there is moderate support suggesting hostile individuals are at risk for developing MS. However, the specifics concerning causality warrants further investigation. In addition, it is argued that the right hemispheric model of hostility can be applied to MS, and may provide an explanation as to how these two constructs are related. Moreover, the advantages and disadvantages of applying this model also require further exploration. Finally, it is argued that individuals with MS may be potentially experiencing a similar limited capacity within the right frontal lobe. In conclusion, a theoretical test of this model will be provided.

## Integration of the Right Hemispheric Model of Hostility with MS

In terms of causality or time course, the relationship between hostility and MS requires further exploration. The literature supports the relationship between hostility and MS [11,13,67,68]; however, the exact mechanism for this relationship remains unclear. Niaura et al. [11] stated that hostility was indirectly related to MS through elevated BMI and WHR. Raikonen et al. [13] reported elevated hostility scores at baseline were predictive of later MS diagnosis for children and adolescents due to an increase in obesity and insulin resistance. Nelson et al. [67] documented the relationship between hostility and MS, although no explanation was provided. Todaro et al. [68] stated hostility results in the development of MS through a dysregulation of increased sympathetic and neuroendocrine arousal.

Specifically concerning a time course, only the data provided by Raikonen et al. [13] and Niaura et al. [11] implicate hostility as a precipitating factor in the development of MS. However, it should be noted that hostility has preceded cardiovascular reactivity [20,46,48-50, 106], cardiovascular disease [4,5,6,9], hypertension [7,8], and death [4], as well as the metabolic factors of lipids [29,31], cholesterol [32,33], and glucose [35-37]. By themselves, these factors do not demonstrate that hostility precedes the development of MS, although the pattern is suggestive of causality.

It is argued hostility leads to MS by an over exaggerated and prolonged stress response due to dysfunction within the right hemisphere. Although the right hemispheric model of hostility provides an explanation and rationale for this relationship, the explicit mechanisms behind this relationship are not stated. Unfortunately, the specifics concerning the harmful effects of the stress response are continuing to be elucidated in the literature.

Suarez et al. [3] reported that an over active stress response, as has been noted with hostility, develops into cardiovascular disease over time. This disease process occurs after continued secretion of stress related products into the blood stream, eventually damaging the inner lining of the blood vessels. "Physiologic hyperresponsivity is thought to promote endothelial damage via hemodynamic (e.g. sheer stress, turbulence) and catecholamine-induced metabolic changes (e.g. platelet aggregation, lipolysis, down-regulation of low density lipoprotein receptors)" (p. 78). Here, cardiovascular disease is the long-term effect of the increased metabolic factors as they travel in the blood. These factors include platelets, lipids, and proteins that are released when the body is responding to stress, ultimately disrupting normal blood flow.

Bryden et al. [5] stated hostile individuals experience stress more often, which results in a pro-inflammatory and pro-thrombotic response. Here, increased recruitment of leukocytes, lipids, smooth muscle cells, fibroblasts, and platelets interact with the arterial wall. Atherosclerotic plaque develops when this process occurs too frequently, due to the disruption of the normal functioning of the inner lining of the blood vessels.

Charmandari, Tsigos, and Chrousos [131] elucidated how stress can lead to MS. These authors state that gluconeogenesis (the creation of new glucose), which they reported is the hallmark feature of the stress response, induces insulin resistance through the release of glucocorticoids. This process interferes with normal glucose control and "Overtime, progressive glucocorticoid-induced visceral adiposity causes further insulin resistance and deterioration of glycemic control" (p.271). When this process is carried out over extended periods of time, it eventually leads to hyperglycemia (diabetes) and hyperlipidemia (increased lipids and cholesterol) both of which have been implicated with MS, cardiovascular disease, and hostility.

Singh, Kartik, Otsuka, Pella, and Pella [130] described stress in terms of sympathetic and parasympathetic responding on a molecular level. These authors reviewed data that associates sympathetic activation with increased levels of cortisol, catecholamines, serotonin, rennin, aldosterone, angiotensin, and free radicals, whereas parasympathetic activation is associated with acetylcholine, dopamine, nitric oxide, endorphins, coenzyme Q10, antioxidants,

and other protective factors. Despite not being described here, the literature has implicated a number of these factors in cardiovascular disease.

Although not a direct result of the stress response, or of right frontal lobe functioning, engaging in unhealthy behaviors (such as alcohol consumption, poor dietary choices, and smoking) could also explain how hostility allows for the development of MS. Perhaps it is the increased BMI and caloric intake as a result of poor diet that explains the relationship between the two constructs [7,39,41,42]. As noted in the MS literature, BMI and obesity seem to play a crucial role in the development of MS [57,114-117].

There is an additional implication for the integration of the right hemispheric model concerning the continued and prolonged levels of stress. As noted earlier, it is argued high hostiles have a limited capacity to regulate their sympathetic tone, anger [132], and glucose mobilization [38]. In terms of MS, there is substantial peripheral dysfunction as evidenced by the increased prevalence for obesity, hypertension, triglyceridemia, cholesterolemia, and hyperglycemia, all of which disrupt normal functioning within the body. Potentially, this peripheral dysfunction provides additional challenges to the right frontal lobe, which is attempting to regulate the sympathetic response and negative effect. Although there is little data to support this notion, evidence can be found with Woo, Ma, Robinson, and Yu [133], specifically concerning the stress response of diabetics. For example, Woo et al. report that when diabetics experience a hyperglycemic episode, they continue to mobilize glucose in response to stress, thereby further increasing their glucose levels. It is logical that peripheral dysfunction could disrupt CNS activity, particularly with insulin dysfunction. Glucose is the primary fuel for the brain and is involved in nearly all of the brain's activities to include all cognitive abilities and nearly all cellular processes. Moreover, when the brain is deprived of glucose, the far frontal regions are affected prior to the posterior regions [94]. This could potentially result in a disruption of the right frontal region's ability to inhibit a reflex glucose release, ultimately leading to a continued, and unrestricted, mobilization of glucose instability in the associated affective systems, sympathetic system, and for cognitive processing.

Kreier et al. [65] provide further evidence for peripheral dysfunction within the body creating additional challenges for the brain to regulate insulin secretion. As noted earlier, Kreier et al. stated an increase in adipose tissue, lipids, as well as overeating, and a lack of physical exercise, eventually disrupts the feedback loop between the brain, liver, and pancreas. Here, the increased fatty food intake makes it more difficult for the hypothalamus to properly regulate insulin secretion.

There are distinct benefits and shortcomings of applying the right hemispheric model of hostility to MS. The primary advantage of the application is that it implicates the brain in the development of this syndrome. As noted earlier, research is beginning to demonstrate the role of the brain in the development [64] and progression [65,66] of MS. For example, Singh et al. report that exposure to the anti-inflammatory response products during the first two years of life, damages several crucial brain regions that play a role in the development of MS.

Another advantage to examining the role of the brain in this syndrome is the allowance for an additional level of analysis that could potentially provide a theoretical foundation to guide and clarify the research on MS. Instead of focusing on signs and symptoms of MS, which seem to vary [60], this approach provides a central theory to help explain this syndrome. An additional benefit includes keeping the focus on the interactions between the brain and the body, which could potentially explain some of the variance surrounding the signs, symptoms, and causes [115]. Moreover, continued understanding of the brain's response to stress may have beneficial implications for reducing sympathetic arousal. For example, it may be beneficial to decrease the amount of stress placed on the right frontal lobe as a way to control for unbridled sympathetic reactivity. Kinsbourne's Functional Cerebral Space model states that performance decreases as a function of completing two behaviors concurrently that are close in functional cerebral space. It is logical that additional tasks involving the right frontal lobe could interfere with these metabolic functions. We provided evidence for this claim by using verbal and nonverbal fluency tasks as left and right frontal lobe stressors in a hostile population. The high hostiles performed poorly on nonverbal fluency, which was thought to be a function of right frontal lobe dysfunction. In addition, when the high hostiles were exposed to this right frontal stressor, there was a resultant increased in heart rate, blood pressure [20,106] and glucose [38] as it was thought the high hostiles were unable to complete the right frontal lobe stressor and regulate their sympathetic arousal concurrently.

Future research could test these findings on a population with MS. Continuing with the limited capacity model, additional frontal lobe tasks should interfere with metabolic functioning. For example, frontal eye field [134] tasks, require substantial frontal lobe resources, and should potentially result in altered metabolic functioning when individuals with a limited right frontal capacity complete them. Oxygen saturation levels, when depleted, may further activate sympathetic drive essential for vital functions [135].

Applying the right hemispheric model of hostility to MS also allows for the transference of treatment options that have been successful with high hostiles. For example, as described by Miller et al. [6] and Smith et al. [2], hostile individuals have an interpersonal style that elicits hostile and aggressive interactions from others, resulting in heightened levels of stress. To reduce the hostile interactions and the associated sympathetic arousal, cognitive behavioral therapy has proven to be efficacious in the treatment of anger [136]. The techniques learned include the identification of anger provoking stimuli, deep breathing techniques, relaxation training, and increasing problem solving skill abilities. These techniques could potentially be applied to individuals with MS to reduce the interpersonal interactions that are associated with specific stressors. As noted by Vitaliano et al. [121], the reduction of chronic levels of stress could have prevented measures on the development of MS in older men.

Despite these benefits, the application of the right hemispheric model has several limitations, primarily concerning the failure of the model to address additional brain regions that may become activated during the stress response. For instance, Davidson, Ekman, Saron, Senulis, & Friesen [137] and Harmon-Jones [138] claim that the left frontal lobe is responsible for anger expression [132]. The rationale

for not incorporating the left frontal activation model is that it does not explain the exaggerated stress response experienced by hostile individuals. Instead, anger is discussed in terms of approach behavior, which is not relevant here.

Finally, this model does not explain how the increased activation is eventually reduced. Perhaps a better comprehension of the brain regions responsible for regulatory control will promote an improved understanding of the relationship between hostility and MS. For example, Masi, Hawkley, Rickett, & Cacioppo [139] suggest that a dysfunctional vagus cranial nerve, which normally seeks to regulate heart rate, can result in chronic disease. In an optimal state, the vagus alters the Sinoatrial (SA) node, which is commonly referred to as the pacemaker of the heart, and heart rate is either appropriately increased or decreased [140]. Masi et al. [139] suggest an aging, or dysfunctional, vagus is implicated in the development of diabetes, obesity, hypertension, and congestive heart failure. These authors report that the vagus may be responsible for regulating the response to constantly changing glucose levels. The regulation of glucose mobilization and absorption is thought to be reflective of sympathetic and parasympathetic activation, respectively, and dysfunctional regulation results in either hypoglycemia or hyperglycemia. For example, when glucose levels are high, the vagus activates pancreatic  $\beta$ -cells to release insulin (parasympathetic activation) in an attempt to reduce glucose levels. When glucose levels are low, pancreatic  $\alpha$ -cells activate to release glycogen (sympathetic activation). Masi et al. conclude that impaired regulation of the glucose system can result in either hyperglycemia (diabetes) or hypoglycemia.

Interestingly, the intentions of Masi et al. are in parallel to the current paper as evidenced by the notion of a bi-directional relationship between the body and brain, as well as the influence of the brain on disease processes. However, Masi et al. approach this objective from a subcortical level, rather than from a theory based on higher level cerebral systems. Unfortunately, Masi et al. do not mention executive brain regions that may be influencing, or regulating, the vagus.

Vagal dysfunction has also been specifically implicated in anger and hostility. There is evidence that hostile individuals experience prolonged levels of stress because their parasympathetic tone is diminished due to an inability to return to a non-excitatory state [141]. Here, it is argued that vagal dysfunction impairs the ability to reduce heart rate and anger, resulting in prolonged sympathetic arousal.

In a continuation of this research, Thayer and Friedman [142], and more recently, Thayer & Brosschot [143], cite additional brain regions that could be influencing the vagus' ability to regulate heart rate. Specifically, these authors provide a dynamical systems approach that describes an organism as a "complex set of reverberating circuits or sub-systems working together in a coordinated fashion" [142]. Within this framework, these authors provide evidence for a reciprocal inhibitory cortico-subcortical system that is both structural and functional. Using heart rate variability, it is proposed that a network "permits the prefrontal cortex to inhibit subcortical structures" [143], which would include heart rate variability.

Both the dynamical systems and the limited capacity model

organize the brain according to systems working together in an integrated fashion. However, the right hemispheric model of hostility describes the consequences of limited resources within the right frontal lobe, resulting in an exaggerated and prolonged stress response for hostile individuals. This model was specifically developed from the hostility literature and has been used to explain and guide research on this construct, specifically concerning lateralized cerebral resources. It is now being applied to MS given the substantial overlap between the constructs.

In order to assess the applicability of the right hemispheric model of hostility to MS additional research is required. To strengthen the relationship between hostility and MS, continued correlational evidence to assess the predictive value of hostility for MS is warranted. To address the brain function of individuals with MS, the left and right frontal lobes should be analyzed for diminished capacity in regulatory control. In accord with Walters, Harrison, Campbell, & Harrison [38], Williamson & Harrison [20], and Williamson, Walters, & Harrison [106], the left and the right frontal lobes could be assessed using both verbal and nonverbal fluency measures. Here, it would be predicted that individuals with MS would demonstrate diminished right frontal lobe regulatory control as evidenced by poor performance on neuropsychological measures sensitive to right frontal function. In addition, exposure to right frontal stressors should result in altered metabolic functioning as a result of limited capacity [19-23,28]. Finally, it may be beneficial to assess hostility levels after individuals are diagnosed with MS.

## Conclusion

Using the Limited Capacity Model of hostility as a guide, it is argued that hostile men show prolonged and exaggerated responses to stress as a result of a limited stress management capacity attributable to the right frontal lobe. Further, individuals with a variable and deregulated fuel supply to their brain (diabetes) exhibiting an increased and exaggerated stress response (hostility) as a result of modest regulatory capacity, should demonstrate an exacerbated stress response within negative affective and sympathetic nervous systems of the right hemisphere.

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