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The Association of Cognitive Function with Autonomic-Cardiovascular Reactivity to and Recovery From Stress

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ABSTRACT

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The contribution of stress in the development of chronic and terminal disease has garnered significant interest in contemporary research. The current study aims to look at how performance in domains of cognitive function may affect autonomic-cardiovascular reactivity and recovery to psychologically stressful tasks as such reactions, over time, may contribute to the development of cardiovascular disease.

The current study analyzed data from 209 healthy middle-age adults. This included four neuropsychological tests utilized here to represent abilities in four different cognitive domains: response inhibition, mental flexibility, verbal memory, and non-verbal memory. The participants were also introduced to three psychologically stressful tasks while blood pressure, heart rate, and spectral components of heart rate variability measurements were taken during the tasks and the post-task recovery period.

Results showed no significant relationship between blood pressure reactivity or recovery and cognitive function. No significant relationship was found between heart rate variability reactivity and cognitive function. Results showed no significant relationship between blood pressure reactivity or recovery and cognitive function. No significant relationship was found between heart rate variability reactivity and cognitive function. However, superior performance in response inhibition was significantly positively

associated with both LF-HRV ($p = .04$) and HF-HRV ($p = .02$) in the immediate recovery phase and HF-HRV ($p = .02$) in the delayed recovery phase. Such findings suggest that greater response inhibition abilities may contribute to greater vagally induced recovery from stressful tasks. Such a response can be considered healthy and likely acts as a protective factor against the development of cardiovascular disease.

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NOMENCLATURE

BP	Blood Pressure, mmHg
HR	Heart Rate, beats per minute
HRV	Heart Rate Variability
LF-HRV	Low Frequency HRV
HF-HRV	High Frequency HRV
LF: HF-HRV	High Frequency / Low Frequency Ratio HRV

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CHAPTER I

INTRODUCTION

Long term psychological stressors have become increasingly prevalent part of modern life for many individuals. While such stress is often associated to the development of various medical conditions such as ulcers or back pain, there is relatively little research on the long term physiological impact such reactions to psychological stress may create. In a recent study by Banks, Marmot, Oldfield and Smith (2006), it is found out that middle-aged American adults are less healthy than their equivalent British counterparts. These findings were significant in the research causes of diabetes, hypertension, heart disease, myocardial infarction, stroke, lung disease, and cancer despite controlling for traditional risk factors. The differences in health between two similar populations certainly raise the question of the significance of the impact of non-traditional risk factors can have in the development of chronic and terminal disease, even after taking into account the traditional risk factors.

Cardiovascular disease, in particular, has been the leading cause of death in the U.S. for the past 80 years (Greenlund, Giles & Keenan, 2006). Despite recent declines over the past several decades, cardiovascular disease continues to be the leading cause of death in adults in the United States, accounting for almost 950,000 deaths annually – more than 40% of all deaths (American Heart Association, 2001). Additionally, cardiovascular disease is the cause of substantial healthcare expenditures. For example, cardiovascular disease treatment has projected to be an estimated $448.5 billion in direct and indirect costs in 2008 (Rosamond et al., 2008). Most commonly, cardiovascular disease is the result of a progressive narrowing of the blood vessels that supply

oxygenated blood to the heart over an extended period of time, some progression even take decades to develop. This vessel narrowing can ultimately lead to heart failure, myocardial infarction, arrhythmia, and angina due to cardiac ischemia. A major contributor to coronary heart disease development is atherosclerosis, a degenerative and inflammatory syndrome promoting the accumulation of cholesterol and cellular waste products in the vascular system that remodel peripheral blood vessels and impair the optimal functioning and blood flow of vessels surrounding the heart (Libby, 2002, 2005; Rosamond et al., 2008). Additionally, an individual's vulnerability to acute events such as atheroma and thrombosis affect the development of cardiovascular disease (Buja & Willerson, 1981; Davies & Thomas, 1985; Falk, 1983; Fuster, 1994; Lefkowitz & Willerson, 2001; Libby, 2001).

It is now recognized that the likelihood that such acute conditions can trigger a more serious cardiovascular event is increased by cardiovascular changes related to environmental, emotional, and behavioral stressors that are of personal relevance to the individual (Bhattacharyya & Steptoe, 2007; Steptoe & Brydon, 2009; Strike & Steptoe, 2005). Only about 50% of the variance of cases of cardiovascular disease can be predicted by traditional risk factors, including family history, obesity, smoking, diabetes mellitus, and hypercholesteremia (Roig et al., 1987). The variance unaccounted for by this has led researchers to investigate non-traditional risk factors such as chronic stress. For years, psychological stress has been associated in the development of coronary heart disease and other cardiovascular problems (Brotman et al., 2007; Holmes et al., 2006; Krantz et al., 1988; Manuck et al., 1988). The current study aims to see whether markers of increased risk for future cardiovascular disease may be related to various trait levels of

performance in certain domains of cognitive function and how such cognitive function likely impacts how an individual may react to stress.

CHAPTER II

BACKGROUND

Allostasis and Arousal

To explain the relationship between chronic stress and compromised health, Sterling and Eyer (1988) proposed the concept of allostasis. Allostasis refers to the body's ability to adapt and adjust to environmental demands by matching the demands of the environment with physiological responses. For example, human heart rate fluctuates throughout the day in response to environmental demands (e.g., increasing during activity and decreasing during sleep). To coordinate an efficient response to environmental demands, central nervous system control is essential to allow an organism to prepare and maintain the physiological level of arousal needed to respond to demands and then to adjust these levels downward when the stress diminishes. McEwen and Stellar (1993) defined this physiologically compromised state as allostatic load. They described allostatic load as the strain which the body produce with repeated ups and downs of the physiological response, the elevated activity of physiologic systems under stress and changes in metabolism, and the impact of wear and tear on a number of organs and tissues, that can predispose the organism to disease. McEwen and Stellar went on to suggest that increased arousal or allostatic load should be activated in response to cognitive interpretations of specific external stressors in the environment. Thus, allostatic load should, in turn, act as an explanatory variable linking such external stressors to internal physiologic events (Evans & Lepore, 1992). If, for example, an organism were to become vulnerable to physical attack, the body would increase energy levels and physiological arousal in order for the organism to either escape or confront the threat.

The physiological responses involved with this is the "fight or flight" response as well as recovery once the threat is no longer present, represents the allostatic load. According to McEwen and Stellar (1993), if the stress is chronic and intense (as is common in modern day situations), there is more strain on the internal system than if the stress is episodic. Given the costs of physiological arousal, organisms undergoing chronic stress and chronic arousal may experience depleted physiological resources which lead to decreased levels of physiologic response to future stimuli. To summarize, allostasis allows an organism to adapt to stress by supporting a state of physiological arousal, but prolonged strain on the system due to chronic stress can result in physiological and psychological damage. Thus, the construct of allostasis helps to explain how prolonged stress influences physical health outcomes, such as cardiovascular disease (Kamark & Jennings, 1991), immunosuppression (Schneiderman & Baum, 1992), diabetes (Bradley, 1988), and psychological outcomes, such as depression (Avison & Turner, 1988) and anxiety (Eckenrode, 1984). In this regard, the previously cited researches have demonstrated that chronic stress is associated with negative health outcomes. However, the mechanisms that may contribute to individual differences in allostatic load are not yet very clear. The current study may shed greater light on the role that trait levels of cognitive functioning play in individual differences in allostatic load.

Cardiovascular Reactivity

The current study utilizes cardiovascular reactivity as a physiologic marker to measure bodily reactions to stress. Cardiovascular reactivity is generally defined as a change in an individual's hemodynamic responses from a resting state to a subsequent behavioral state related to internal or external stressors (Obrist, 198; Treiber et al., 2003).

This encompasses any change in cardiac (heart rate, heart rate variability) or vascular (blood pressure, pulse rate) responses by the body. In a general sense, stress-related cardiovascular reactivity is assumed to be a marker of autonomic function (Dunlap & Pfeiffer, 1989). Numerous control mechanisms regulate and integrate the functions of the cardiovascular system in order to supply blood to specific body areas according to the organism's needs (Dampney et al., 2002). When homeostasis is challenged, a reproducible cardiovascular reactivity pattern is elicited (i.e. a change in blood pressure, heart rate or other hemodynamic parameters) (Rosenman, 1991). These blood pressure and heart rate responses to psychological challenge can be used as an index of cardiovascular autonomic activity (Wieling & Karemaker, 1999). Over time, an individual's response to stress may ultimately affect at least one of several pathophysiological pathways that can lead to permanent changes. Permanent changes can include decreased heart rate variability, elevated blood pressure, or elevated heart rate.

The "reactivity hypothesis", a model linking stress to cardiovascular disease (Krantz & Manuck, 1984; Manuck, 1994) postulates that cardiovascular reactivity may play a role as a marker or mechanism in the pathogenesis of cardiovascular disease through the complex interaction of multiple physiological systems guided by the actions of the central nervous system. Thus, an individual or situation characterized by high levels of cardiovascular reactivity may be related to higher risk for development and exacerbation of cardiovascular disease. Despite inconsistencies in the literature, there is a current and growing body of evidence suggesting that a link between cardiovascular reactivity and measures of subclinical and clinical cardiovascular disease exists. Studies have shown that cardiovascular reactivity is related both cross-sectional and

longitudinally to heart disease and hypertension. In one of the earliest studies the literature, Keys, Taylor, Blackburn, Brozek, Anderson and Simonson (1971), examined blood pressure responses to the cold pressor task in 279 healthy middle-aged men as a predictor of the development of coronary heart disease over a 20-year follow-up. The investigators defined exaggerated task-related reactivity as anything greater than a 20 mm Hg change in diastolic blood pressure. Those who met this criterion were 2.4 times more likely to experience a myocardial infarction or die of coronary heart disease-related causes than those who were less physiologically reactive to the task. More recently, Light, Dolan, Davis and Sherwood (1992) discovered that heart rate reactivity on a reaction time test predicted the blood pressure levels of a group of middle aged adults. The test includes predicting the reaction time of the same group 10 to 15 years later, even after taking into account traditional risk factors such as resting blood pressure levels and parental history of hypertension. Similarly, Matthews, Woodall and Allen (1993) found this to be true in a population of adolescents. More recently, Tuomisto, Majahalme, Kähönen, Fredrikson, and Turjanmaa (2005) also discovered that increased blood pressure reactivity to certain psychological stimuli may differentially predict the development of BP elevation or hypertension 9 to 12 years later when looking at a population of middle aged men. Longitudinal studies have also linked cardiovascular reactivity in individuals with pre-existing essential hypertension (Alderman et al., 1990) and coronary heart disease (Krantz, Sheps, Carney & Natelson, 2000). However, a recent review of the literature by Treiber et al., (2003) suggests that a number of studies have not found such correlations between cardiovascular reactivity and future disease development. For example, Carroll, Davey-Smith, Willemsen, Sheffield, Sweetnam,

Gallacher and Elwood (1998) reported negative findings in a large (N = 1493) sample of men (average age is 56.8 years). Their data showed that blood pressure responses to the cold pressor task were unrelated to 9-year incidence of cardiovascular disease or mortality. Treiber et al., (2003) suggest that the reason for a lack of consistency in the literature is due to a need for increased emphasis on statistical power requirements, measurement standardization, and investigation of mechanisms and moderating factors that may influence these associations.

In addition to reactivity, the inability of cardiovascular recovery from stress may also be an important risk factor for cardiovascular disease. Cardiovascular recovery generally refers to either the time required for cardiovascular parameters to return to baseline levels after termination of stress or the extent of elevation in cardiovascular parameters that remains during a post-task period (Linden, Earle, Gerin, & Christenfeld, 1997). It has been hypothesized that the duration of stress-related cardiovascular responses may be as important as the response magnitude in the development of cardiovascular diseases (Christenfeld, Glynn, & Gerin, 2000; Schwartz et al., 2003). Accumulating evidence suggests that recovery from stress may be related to future health status. Results from three studies indicate that elevated post-exercise blood pressure is associated with an increased risk of developing hypertension up to 10 years later (Davidoff et al., 1982; Singh et al., 1999; Tanji et al., 1989). In addition, Treiber and colleagues (2001) reported that average blood pressure and heart rate recovery across physical and psychological tasks predicted resting rate of these physiological indicators over a 4-year period. When coupled with heightened cardiovascular reactivity, poor recovery could accelerate vascular changes, potentially leading to an earlier onset of

chronic illness (e.g. hypertension, cardiovascular disease). It is also possible that poor recovery could bring about these pathophysiological changes in the absence of heightened reactivity. Evidence of recovery from cardiovascular stress as a reliable independent indicator of disease is also a possibility to consider. As mentioned above, results from previous studies indicate that measures of recovery (Davidoff et al., 1982; Singh et al., 1999; Tanji et al., 1989, Treiber et al., 2001) are able to be used to predict long term rates of cardiovascular functioning and likelihood of disease development. In at least one study, however, (Treiber et al., 2001) reactivity measures were more consistent predictors than recovery measures of resting blood pressure (BP) at four annual follow-up evaluations. Although the existing findings are somewhat mixed, they do suggest that poor cardiovascular recovery from stress may also be an independent indicator for later chronic disease states.

Among measures of cardiovascular reactivity, heart rate variability is of particular interest in the current study. Heart rate variability is a measure of the continuous interplay between sympathetic and parasympathetic influences on heart rate that yields information about autonomic flexibility and represents the physiological basis for emotion regulation. The sympathetic and parasympathetic branches of the autonomic nervous system influence the length of time between consecutive heartbeats in an antagonistic manner (Applehans & Lueken, 2006). Parasympathetic influence is mediated by acetylcholine on vagal modulation. Under resting conditions, heart rate is primarily under the control of vagal tone (Levy, 1971) and vagal modulation. Increased heart rate can be due to increased sympathetic influence and/or decreased parasympathetic activity. This corresponds to a shorter beat interval while slower heart rates have a longer beat interval.

The sympathetic influence on heart rate is largely mediated through the release of epinephrine and norepinephrine. These neurotransmitters activate adrenergic receptors that result in AMP mediated phosphorilation of membrane proteins and lead to increases in calcium (Trautwein & Kameyama, 1986) and current (Brown, DiFrancesco & Noble, 1979; Difrancesco, Ferroni, Mazzanti, Tromba, 1986) causing increased diastolic depolarization in the sino-atrial node. These variations in heart rate may be seen on an ECG and the time between what is often referred to as normal-to-normal intervals (intervals between adjacent QRS complexes resulting from sinus node depolarizations) or the instantaneous heart rate may be determined (Malik, 1996). These changes may be analyzed to determine heart rate variability.

Frequency-based analyses of heart rate variability are based on the fact that the variations in heart rate produced by sympathetic and parasympathetic nervous system activity occurs at different speeds. Power spectral density (PSD) analysis allows one to estimate how power is distributed as a function of frequency (Malik, 1996). Several methods of spectral analysis (fast fourier transform, point process, and autoregressive procedures) are used to calculate and mathematically quantify components of heart rate variability. These methods may be broken down into parametric and non-parametric methods. Non-parametric methods allow for a simpler algorithm (fast fourier transform) and higher processing speed. Parametric methods allow for smoother spectral components that can be distinguished without having to identify pre-selected frequency bands, easier processing of power components and their individual central frequency components, and an accurate estimation of PSD in smaller samples. While three main frequency bands are expressed, two main frequency regions or bands (Hz) are used to

determine heart rate variability reliably: high frequency (HF) and low frequency (LF) power. The third frequency band, very low frequency power (VLF), is a much less defined component of heart rate variability and lacks a coherent non-harmonic component that is stable and allows for removal of baseline or trend distribution. Therefore, this component is generally not considered to be an accurate measure for short-term (less than five minutes) electrocardiogram recording and interpretation (Malik, 1996). The measurement of these power components is usually made in absolute values of power (milliseconds squared). HF power primarily reflects respiratory-modulated parasympathetic outflow, whereas LF power is subject to both substantial sympathetic influence and varying amounts of parasympathetic contribution. The LF/HF ratio has been proposed, by some investigators, as an index of relative balance of sympathovagal influences on the heart, with higher LF/HF ratios reflecting increased sympathetic activity and/or decreased parasympathetic tone. The sympathetic nervous system is slow acting and mediated by norepinephrine while parasympathetic action is fast acting and mediated by acetylcholine. While the heart may be dually innervated, literature suggests that the heart is generally under the tonic inhibitory control of parasympathetic influences via the vagus nerve (Jose & Collison, 1970). Thus, low heart rate variability reflects reduced parasympathetic nervous system influence or increased sympathetic nervous system stimulation. This autonomic imbalance leads to lack of flexibility of the individual when dealing with stressors the individual might encounter in the future. A loss of the ability to normally modulate heart rate may increase the likelihood of developing coronary artery disease or related illnesses (Huikuri et al., 1999; Brook & Julius, 2000; Thayer & Friedman, 2004).

Additional factors associated with low heart rate variability include hostility, anxiety, and depression. Several studies suggest that these psychological factors may combine with stress exposure to result in lower heart rate variability. Sloan et al., (2001) found that participants who scored high on a trait measure of hostility showed greater reductions in heart rate variability in response to mental, but not physical, stressors. There is also evidence that persons high in depressive symptoms show decreases in heart rate variability at a greater rate in response to mental stress than similar non-depressed persons (Hughes & Stoney, 2000). In related findings, heart rate variability has been shown to be significantly lower in depressed coronary artery disease patients when compared to non-depressed patients (Carney et al., 1995) and decreased rate in individuals with high levels of anxiety (Kawachi, Sparrow, Vokonas & Weiss, 1995).

With regards to blood pressure reactivity and related risk for hypertension, three large epidemiological studies that enrolled a large cohort of normotensive subjects and followed them for 20 or more years have provided reasonable evidence that the extent of blood pressure response to a stressor task may foretell an increased risk for the development of essential hypertension (Wood, Sheps, Elveback & Schirger, 1984; Menkes et al., 1989, Kasagi, 1995). The studies by Borghi, Costa, Boschi, Mussi and Ambrosioni (1986) and Falkner, Kushner, Onesti and Angelakos (1981) suggest that reactivity in young borderline hypertensive subjects can be used to predict stable essential hypertension several years later. Findings from a number of larger studies that have documented relationships between reactivity to behavioral tasks and subsequent resting blood pressure levels have shown generally positive results. Additionally, the results from a number of other studies indicate that the relationship between cardiovascular

reactivity and subsequent resting blood pressure level can be documented based on responses to challenge in children (Treiber et al., 2001; Murphy, Alpert & Walker, 1992), adolescents (Matthews, Woodall & Allen, 1993), young adults (Markovitz, Raczynski, Wallace, Chettur & Chesney, 1998), and middle-aged individuals (Matthews, Woodall & Allen, 1993). All reports showed associations between stressor-related blood pressure reactivity and blood pressure elevations within 1 to 6 year range and some showed an impressive degree of internal replication across tasks and time. There is also evidence that blood pressure may be elevated when no concrete external stressor is present but an individual continues to be under cognitive load (Schwartz et al., 2003). Fauvel, Quelin, Ducher, Rakotomalala and Laville (2001) suggest that blood pressure may be elevated during the perceived experience of a stressor, but that may be unrelated to the general pattern of greater cardiovascular reactivity. However, the mechanisms by which environmental stressors might lead to elevated blood pressure (i.e. hypertension), remain poorly specified. The control of blood pressure results from actions of the kidneys, central and autonomic nervous systems, hypothalamic-pituitary-adrenal axis, vascular endothelium, and other pathways (Black, Bakris & Elliott, 2001). In the development of hypertension, a distinction must be made between short-term factors that initiate blood pressure elevation, and long-term self-perpetuating mechanisms that sustain the hypertensive state. The set of factors that initially raise blood pressure may be quite distinct from the factors that perpetuate hypertension. By the time blood pressure is elevated, the initiating factors may no longer be acute blood pressure elevations in response to stress and are usually attributed to chronically increased sympathetic nervous system activity. Long-term regulatory changes that may perpetuate hypertension include

vascular remodeling and endothelial dysfunction (Gibbons, 1998). Vascular remodeling involves alterations in vessel architecture, including decreased lumen diameter and rarefaction (in which the number of micro vessels is reduced), both of which lead to a chronic increase in vascular resistance. This process is the result of hemodynamic changes in blood flow and blood pressure and also changes in the level of vasoconstrictive and vasodilatory substances. Vascular remodeling may facilitate the transition from an initial high cardiac output stage of hypertension to a high total peripheral resistance state (Gibbons, 1998).

However, it should be noted that a number of cognitive and affective processes are necessary in order for an individual to initiate the autonomic changes present in cardiovascular reactivity and recovery. The attentional processes are necessary to properly grasp the external stimuli that are eliciting the stress response (Gaillard & Kramer, 2001) and the ability to inhibit certain prepotent responses also play an important role in guiding goal-directed behavior. Cognitive functions such as working memory, sustained attention, behavioral inhibition, and mental flexibility are all important components that are related to pre-frontal cortical activity (Arnsten & Goldman-Rakic, 1998). Working memory processes are necessary to associate external stimuli with memories of similar events and affective processes are needed to give these stimuli emotional valence and intensity, causing associated internal stress (Gianaros, May, Siegle, & Jennings, 2005). Mental flexibility is necessary in the development of possible coping strategies that allow one to adapt to stressful circumstances (Glynn, Christenfield & Gerin, 2002). Finally, pre-frontal inhibition plays an important role in overriding sub-cortical influences and guiding recovery associated with physiologic

reactions to stressful events (Waldstein & Katzel, 2005). Deficits in cognitive abilities such as mental flexibility, attention, and memory have also been found to be present during negative affective states, including depression and anxiety (Hammar, Lund & Hugdahl, 2003; Airaksinen, Larsson, Lundberg & Forsell, 2004; Castaneda et al., 2008). An example of the way in which these processes interact is associated with the "fight or flight" instinct which is previously mentioned. Attentional processes must focus on a specific external stimulus. Working memory must compare this to the memory of previous threats in order to decide if the stimulus is a stressor. From there, the amygdala mediates the "fight or flight" that urges an individual to confront or avoid a threat. However, the pre-frontal cortex is able to mediate this instinct, when deemed an inappropriate response, primarily through the use of the neurotransmitter GABA. It is possible that autonomic disregulation can be related to a decline in attention and cognitive performance and that such a decline in cognitive ability can exacerbate other factors related to autonomic dysfunction. Studies examining delayed responding, working memory, and executive function in relation to heart rate variability (Johnsen, Eid, Laberg, & Thayer, 2002; Hansen, Johnsen, Sollers, Stenvik & Thayer, 2003) states that performance did not differ on simple or choice reaction times, but that tasks associated with pre-frontal cortical activity and executive function resulted in poorer performance in both speed and accuracy from individuals with low heart rate variability as opposed to their high variability counterparts.

Affective Regulation and Autonomic-Cardiovascular Reactivity

A number of investigations have looked at the link between cognition, emotion regulation and associated autonomic activation. For example, a study examining the

effects of inhibitory response and heart rate variability to emotional stimuli, Johnsen et al., (2003) found that a group of dental phobic subjects had longer reaction times in reacting to color-incongruent and dental related words than color-congruent and neutral words on an altered Stroop task. This delay suggests difficulty in inhibiting pre-potent responses. Additionally, the study found that greater heart rate variability was associated with faster reaction times, which is consistent with the idea that there is a link between vagally mediated heart rate variability, inhibitory ability, and emotion. Lesion studies, such as those performed by Tranel and Damasio (1994), have suggested that the inferior parietal area, ventro-medial prefrontal area, and the anterior cingulate gyrus are important for linking emotional stimuli to physiological responses. This reaction was present regardless of whether pleasant or unpleasant stimuli were introduced. More recent neuroimaging studies (Damasio et al., 2000; Lane, Chua & Dolan, 1999; Lane et al., 1997) have demonstrated that cortical structures, subcortical structures, including the amygdala, thalamus, and hypothalamus, and midbrain structures to activate concurrently and lead to an increase in heart rate and skin conductance during either pleasant or unpleasant stimuli. Recent literature (Gianaros & Sheu, 2009; Thayer & Ruiz-Padial, 2006) have included a number of structures including the anterior cingulate, insular cortex, orbitofrontal, and ventromedial prefrontal cortices, amygdala, the paraventricular and related nuclei of the hypothalamus, the periaqueductal gray matter, the parabrachial nucleus, the nucleus of the solitary tract, the nucleus ambiguus, the ventrolateral medulla, the ventromedial medulla, and the medullary tegmental field.

The cingulate cortex has shown significant evidence of being involved in cardiovascular reactivity evoked by stressors. The cingulate cortex is a medial cortical

brain system that supports cognitive, emotional, nociceptive, skeletal-motor, and visceromotor processes. Three distinct functional subdivisions of the cingulate cortex are generally identified: a rostral affective division, a dorsal cognitive-motor division and a caudal evaluative-monitoring division (Bush et al., 2000; Devinsky et al., 1995; Paus, 2001; Vogt, 2005; Vogt et al., 1992; Vogt et al., 1995). In addition to supporting cognitive functions and those related to emotion, evidence suggests that the cingulate subdivisions play a role in mediating stressor-evoked cardiovascular reactivity. The perigenual anterior cingulate cortex is viewed to support several stress-related functions, including the appraisal of salient environmental events, the subjective experience of aversive behavioral states, and the regulation of behavioral and autonomic responses to aversive stimuli (Bush et al., 2000; Critchley, 2005; Paus, 2001; Phillips et al., 2003; Vogt, 2005; Wager et al., 2009a; Wager et al., 2009b). Imaging evidence demonstrates that the perigenual anterior cingulate cortex is engaged during negative mood initiation, anticipatory anxiety, and scenarios involving possible negative social evaluation (George et al., 1995; Mayberg et al., 1999; Straube et al., 2009; Wager et al., 2009a, 2009b). It is also engaged when distracting emotional information is presented during a demanding cognitive task performance (Mohanty et al., 2007) and when one is committing self-relevant and negatively evaluated errors during cognitive tasks (Kiehl et al., 2000). Both animal and human studies have ascertained the perigenual anterior cingulate cortex to have reciprocal circuitry with the orbital and medial prefrontal cortex, insula, amygdala, portions of the thalamus, hypothalamus, periaqueductal grey, pons, medulla, and the pre-sympathetic intermediolateral cell column of the spinal cord (Barbas, 2000; Barbas et al., 2003; Buchanan and Powell, 1993; Chiba et al., 2001; Critchley, 2005; Freedman et al.,

2000; Öngür et al., 1998; Öngür and Price, 2000; Vogt, 2005). Through this circuit, it may have an important role in supporting stressor-evoked autonomic and cardiovascular reactivity.

Portions of the dorsal anterior cingulate cortex are generally seen as supporting processes related to attention, effortful executive control, and conflict and error monitoring. These processes are represented by connections of reciprocal circuitry with the lateral prefrontal cortex, motor and supplementary motor cortex, and posterior parietal cortex (Vogt & Pandya, 1987). Specifically, the dorsal anterior cingulate cortex areas monitor conflicts between competing streams of incompatible information. After a conflict is detected, dorsal anterior cingulate cortex areas engage prefrontal, motor, and parietal cortices to resolve conflicts and minimize behavioral error by modulating attention, working memory, and motor control processes (Botvinick et al., 2001; Hester et al., 2004; Holroyd & Coles, 2002; Ridderinkhof et al., 2004a, 2004b, Koski & Paus, 2000; Paus, 2001; Paus et al., 1998). Growing evidence also implicates areas of the dorsal anterior cingulate cortex in stress-related behavioral processes associated with physiological reactivity. These areas are engaged by states of pain-related anxiety (Ochsner & Gross, 2005; Vogt et al., 2003), intentional regulation of autonomic activity (Critchley et al., 2001, 2002), awareness of subjective emotional experiences (Lane et al., 1998), and even social rejection associated with activation of the hypothalamic-pituitary-adrenal stress response axis (Eisenberger et al., 2007). This suggests that the area may be important for generating autonomic and cardiovascular responses via projections to network of cortical and subcortical areas to support volitional, cognitive, and emotional behaviors.

The posterior cingulate cortex supports evaluative processes that include the ability to maintain a general representation of the environment, appraising the emotional salience of environmental events, and monitoring for threatening or otherwise stressful environmental stimuli (Gusnard et al., 2001; Maddock, 1999; Vogt & Laureys, 2005; Vogt et al., 2006). These processes are supported by reciprocal circuitry between the posterior cingulate cortex, perigenual anterior cingulate cortex, and parahippocampal cortices (Vogt & Laureys, 2005; Vogt et al., 2006). A recent meta-analysis (Maddock, 1999) also implicates the posterior cingulate cortex in the automatic appraisal of unpleasant stimuli. Neuroimaging evidence also indicates that the posterior cingulate cortex is a major component of a distributed network of functionally and anatomically connected brain systems (including dorsal and ventral medial prefrontal cortex, medial and lateral parietal cortex, and areas of the medial and lateral temporal cortex) that all show coherent and relatively high levels of metabolic activity during resting states (Buckner et al., 2008; Fox and Raichle, 2007; Fox et al., 2007; Greicius et al., 2003; Gusnard et al., 2001). Activities in components of this network are thought to attend to interoceptive information, such as changes in autonomic functioning (Nagai et al., 2004). There is also substantial evidence that when cognitive effort and attentional resources are redirected to the external environment to support goal-directed behaviors, activity in the posterior cingulate cortex and other components of this network are markedly curtailed. This is likely due to the need to focus neural activity on demands related to environmental challenges and execute outwardly directed action rather than focusing on internal functioning (Buckner et al., 2008; Gusnard et al., 2001). While the posterior cingulate cortex lacks the many direct connections with other important areas related to

autonomic and cardiovascular regulation, such as the perigenual anterior cingulate cortex, dorsal anterior cingulate cortex, insula, and amygdala, neuroimaging studies demonstrate that stressor-evoked autonomic and cardiovascular reactions are in conjunction with changes in posterior cingulate cortex activity (Gianaros et al., 2005b, 2007, 2008; Wong et al., 2007). Gianaros et al., (2005b, 2007, 2008) found individuals classified as stable high blood pressure reactors have been shown to express enhanced posterior cingulate cortex activation to a Stroop color-word interference stressor when compared to less reactive counterparts who consistently showed expected patterns of deactivation in the posterior cingulate cortex during effortful task performance. Wong et al. (2007) demonstrated that an effortful isometric handgrip exercise evoked transient increases in heart rate and blood pressure and decreases in posterior cingulate cortex and ventromedial prefrontal cortex activity among healthy young men and women. Further analyses of a time series revealed that activity changes in the ventromedial prefrontal cortex, but not the posterior cingulate cortex, were directly associated with time related and exercise-induced changes in heart rate. Wong et al. (2007) theorized that posterior cingulate cortex activity may be suspended during effortful behavioral tasks and that this change is not instrumental for associated task-related changes in autonomic or cardiovascular function. Thus, posterior cingulate cortex activity is likely to correspond to the evaluative appraisal of self-referential information, and possibly environmental contexts and stressors, which may indirectly relate to autonomic and cardiovascular functioning because of concurrent changes in the activity of ventromedial and other visceromotor cortices (O'Connor et al., 2007).

In addition the cingulate cortex, the insular cortex has also been significantly implicated in cardiovascular reactivity responses. The insular cortex is a brain region that has efferent and afferent connections, similar to those of the anterior cingulate, the orbital, and the medial prefrontal cortex. This includes connections with the amygdala, hypothalamus, thalamus, periaqueductal grey area, pons, and nucleus of the solitary tract innervating peripheral target organs (e.g., the heart) (Augustine, 1996; Cechetto, 1994; Öngür & Price, 2000; Verberne & Owens, 1998). Multi-synaptic afferent relays from all peripheral target organs project to the insular cortex. These projections are routed via the nucleus of the solitary tract, parabrachial pontine nuclei, ventral posterior and mediodorsal thalamic nuclei, and the lateral hypothalamic area in a viscerotopic fashion (Craig, 2003, 2005). These connections have been thought to allow for integration between interoceptive physiologic information, appraisals of emotion-related stimuli, and adaptive behavioral and autonomic responses (Craig, 2005; Critchley, 2005; Paulus & Stein, 2006). The insula is activated when an individual is confronted by behavioral challenges that elicit aversive responses and negative emotional stimuli (Feldman-Barrett & Wager, 2006; Phan et al., 2002; Taylor et al., 2003; Klein et al., 2007). Numerous studies involving brain lesions, neural stimulation, neuroanatomical tracing, and neuroimaging implicate the insular cortex in autonomic and cardiovascular regulation (Allen & Cechetto, 1992, 1993; Allen et al., 1991; Cechetto, 1994; Cechetto & Chen, 1990; Oppenheimer, 1993; Ruggiero et al., 1987; Verberne and Owens, 1998; Yasui et al., 1991). Clinical evidence has also revealed that ischemic strokes selectively involving the insula elevate risk for cardiac arrhythmia (Cheung & Hachinski, 2000; Colivicchi et al., 2004, 2005). There is mixed evidence to suggest that the insular regulation of

autonomic and cardiovascular function may be lateralized. Several studies suggest that the left insula is more likely to be involved in regulating parasympathetic cardiovascular control and in mediating responses related to decreases in blood pressure and heart rate, while the right insula is implicated in sympathetic cardiovascular control and in mediating responses that relate to increased blood pressure and heart rate (Craig, 2005; Kimmerly et al., 2005; Oppenheimer et al., 1992; Oppenheimer et al., 1996). However, some neuroimaging evidence found bilateral and left insular activation to be associated with blood pressure reactivity evoked by mental stressor tasks (Gianaros et al., 2005a; 2007, 2008). Other evidence suggested heightened levels of resting neural activity in the right insular cortex predict subsequently greater stressor-evoked blood pressure reactions across individuals (Gianaros et al., 2009). Neuroimaging literature regarding stressor induced changes in cardiovascular reactivity showed direct correlations with concurrent changes in functional neural activity (Critchley et al., 2000; Gianaros et al., 2005). Critchley et al., (2000) tested whether changes in mean arterial pressure correlated with concurrent changes in functional neural activation when evoked by two different stressors. Results showed that increased mean arterial pressure evoked by the stressors correlated on a within-individual basis with increased cerebral blood flow to the perigenual and mid-anterior areas of the cingulate cortex, the orbitofrontal cortex, postcentral gyrus, insula, and cerebellum. These findings were replicated and extended in a subsequent functional magnetic resonance imaging (fMRI) study of twenty older adults (Gianaros et al., 2005) where participants completed a version of the Stroop color-word interference task. Results showed that increased mean arterial pressure induced via stressor correlated on a within individual basis with greater activation in the perigenual

and mid-anterior cingulate cortex, insula, medial and lateral prefrontal cortex, supplementary motor area, and regions of the temporal, inferior parietal, and occipital cortex. Subcortical regions in which greater activation correlated with increased mean arterial pressure included the basal ganglia, lentiform area bordering the extended amygdala and caudate, thalamus, cerebellum, and periaqueductal grey area (Gianaros et al., 2005). In an fMRI study of individual differences in stressor-evoked autonomic reactivity using a version of the Stroop color-word interference task, Gianaros et al. (2007) found that a larger task-induced rise in autonomic reactivity co-varied with heightened activation of the perigenual anterior cingulate cortex, the medial prefrontal cortex, insula, posterior cingulate cortex, the lateral prefrontal cortex, and cerebellum. No associations with activation in other corticolimbic regions thought to be involved in cardiovascular regulation, particularly the amygdala, midbrain and brainstem areas. However, in a follow-up study Gianaros et al., (2008) found that individuals who exhibited greater stressor-evoked blood pressure reactivity showed greater stressor evoked perigenual anterior cingulate cortex, posterior cingulate cortex , insula, and amygdala activation and a stronger positive functional connectivity between the amygdala and perigenual anterior cingulate cortex and between the amygdala and pons. The authors did suggest that the pons may represent a relay area that specifically links individual differences in stressor-evoked amygdala activity with the peripheral expression of autonomic reactions. They point to neuroanatomical evidence that the amygdala expresses reciprocal connections with pontine cell groups critical for cardiovascular control (Dampney, 1994; Hopkins & Holstege, 1978; Miller et al., 1991) and that the pons is known to relay afferent cardiovascular information to higher levels of

the neurological areas, including the amygdala (Dampney, 1994). Gianaros & Sheu suggest that one possibility is individual differences in autonomic reactivity maybe due to differential signaling between the amygdala and the pons or other pre-autonomic areas. For example, the authors believe that stronger efferent signaling from the amygdala to pre-autonomic areas could reflect stronger descending commands for rises in blood pressure during acute stressful experiences and stronger afferent signaling could reflect stronger ascending negative feedback to the amygdala that inhibits excessive blood pressure increases.

The amygdala, particularly the central nucleus, has been implicated in playing a significant role in emotional processing related to cardiovascular reactivity. A key function of the amygdala in processing environmental stressors is the assignment of behavioral salience and valence to environmental stimuli (Davis & Whalen, 2001; LeDoux, 2003; Sah et al., 2003b; Zald, 2003). Previous research has shown (Bechara et al., 1995) that selective bilateral lesions of the amygdala prevent the possibility of conditioning and physiological response to aversive stimuli. The amygdala accomplishes such tasks by integrating sensory inputs from distributed cortical, thalamic, and brainstem afferent relays. Sensory inputs are relayed through thalamic and cortical-thalamic pathways to the lateral nucleus, basolateral nucleus, and the accessory basal nucleus (Doux, 2003; Sah, Faber, Lopez, De Armentia & Power, 2003a, b). From the basolateral nucleus, those stimuli that are judged to be behaviorally relevant are relayed to the central nucleus. The central nucleus is the major site of output commands and relays adaptive changes in behavior and/or physiology via the stria terminalis to lateral and paraventricular hypothalamic nuclei and to periaqueductal, medullary, and pre-autonomic

nuclei. The central nucleus is also networked with the perigenual and dorsal regions of the anterior cortex and the insula (Amaral & Price, 1984; McDonald, 1998; Morecraft et al., 2007; Price, 2003). Evidence suggests that the amygdala plays a pivotal role in interrelating cortical processes related to the coordination of stressor-evoked changes in behavior and cardiovascular reactivity (Berntson et al., 1998; Dampney, 1994; Saper, 2002; Smith & DeVito, 1984; Smith et al., 1984; Westerhaus & Loewy, 2001). Studies involving lesions to the central nucleus of the amygdala in rats show that this can impede exaggerated stress induced blood pressure reactions in those genetically prone to hypertension (Galeno et al., 1984; Sanders et al., 1994) and prevent the development of hypertension induced by chronic stress (Fukumori et al., 2004). The amygdala can regulate heart rate and blood pressure reactivity via influence of the baroreceptor reflex, a negative-feedback control mechanism that constrains arterial pressure around a regulatory set point by modulating efferent autonomic outflow (Berntson et al., 1998; Dampney, 1994; Saha, 2005, Eckberg, 1992). The baroreceptor reflex controls beat-by-beat changes by adjusting parasympathetic and sympathetic control over heart rate, cardiac output, and vascular resistance to maintain autonomic functioning within the homeostatic range to match ongoing metabolic demands (Guyenet, 2006). Changes in these functions are reflected in low-frequency heart rate variability reactions to evoked stressors. As a negative-feedback loop, the baroreceptor reflex relies on afferent projections from stretch-sensitive cardiopulmonary mechanoreceptors and chemoreceptors that signal changes to the nucleus of the solitary tract. Activation of the nucleus of the solitary tract activates vagal nuclei in the medulla and inhibits pre-sympathetic nuclei in the rostroventrolateral medulla and spinal column. The amygdala

can also suppress the sensitivity of the baroreceptor reflex through inhibition of the nucleus of the solitary tract and activation of the rostroventrolateral medulla (Berntson et al., 1998; Dampney, 1994; Saha, 2005; Saper, 2002). By coupling sympathetic inhibition and parasympathetic activation, the baroreceptor reflex can maximize blood pressure reduction. Sympathetic inhibition leads to a drop in peripheral resistance, while parasympathetic activation leads to a depressed heart rate and contractility. The combined effects will dramatically decrease blood pressure. Similar projections as those from the amygdala are found in the cingulate and medial prefrontal cortex and insula, allowing control of the baroreceptor reflex and associated regulatory mechanisms (Berntson et al., 1998; Dampney, 1994; Saper, 2002). Given these similarities and evidence that sensitivity of the baroreceptor reflex is suppressed by psychological stressors in humans (Reyes del Paso et al, 2004; Steptoe and Sawada, 1989), and suppressed baroreceptor reflex sensitivity has been associated with the severity of preclinical and clinical cardiovascular disease (Gianaros et al., 2002; De Ferrari et al., 2007; La Rovere et al., 1998; La Rovere et al., 2008; Schwartz et al., 1992), it has been suggested that the amygdala and corticolimbic areas and associated baroreceptor reflex could account for some of the individual differences in cardiovascular reactivity and risk of cardiovascular disease (Berntson et al., 1998).

It is important to consider the role of ascending influences of baroreflex and related interoceptive information in modulating the neural circuitry. In particular, evidence shows that visceral afferent activity can influence a range of centrally-mediated cognitive, emotional, and behavioral processes via feedback mechanisms (Adam, 1998; Berntson et al., 2003; Cameron, 2002; Craig, 2003; Critchley, 2005; Dworkin, 1993).

Animal research has shown that baroreceptor activation can decrease cortical arousal (Adam, 1998; Dworkin, 1993) and inhibit the processing of nociceptive stimuli (Dworkin et al., 1979). Similar research in humans has found baroreceptor activation may similarly influence nociceptive processing (Edwards et al., 2002), particularly via corticolimbic and brainstem pathways (Gray et al., 2009). Functionally, these cardiovascular and visceral feedback mechanisms have been implicated not only in adaptive stressor responding, but also in increased risk for hypertension and cardiovascular disease (McCubbin, 1993; Rau & Brody, 1994; Zamir & Maixner, 1986). Ascending cardiovascular and visceral afferent information arising from both the sympathetic and parasympathetic branches of the autonomic nervous system may impact other central processes supporting stressor-related cognitive functions and behavioral responses, including amygdala-mediated attention, memory and arousal processes (Cahill & McGaugh, 1998; Kapp et al., 1992; McGaugh et al., 1996) and cortically-mediated decision-making processes important for guiding adaptive behaviors (Bechara et al., 1999). The primary node in the brainstem that is instrumental for relaying ascending visceral afferent information to higher-level corticolimbic systems involved in blood pressure control is the nucleus of the solitary tract (Berntson et al., 2003; Dampney, 1994; Guyenet, 2006). Specifically, afferent signals due to autonomic changes that are detected by peripheral arterial baroreceptors in the carotid sinus and aortic arch are transmitted via the glossopharyngeal and vagal nerves, which terminate within the nucleus of the solitary tract. From the nucleus of the solitary tract, multi-synaptic projections are issued to medullar and pre-autonomic brainstem, midbrain, and hypothalamic regions, and higher-level corticolimbic systems, such as the amygdala,

insular cortex, and areas of the cingulate, medial and orbital pre-frontal cortices (Allen and Cechetto, 1992, 1993; Allen et al., 1991; Berntson et al., 2003; Buchanan and Powell, 1993; Dampney, 1994; Dampney et al., 2002, 2003; Verbene and Owens, 1998). Viewed as components of an integrated system relying on pathways for the processing and feedback, these higher-level corticolimbic systems may represent afferent visceral information regarding dynamic (e.g., stressor evoked) autonomic changes in the service of adaptive and dynamic cardiovascular regulation (Dampney, 1994; Dampney et al., 2002). For example, an individual exposed to an environmental stressor would experience a rise in blood pressure that triggers an afferent signal which would be relayed to the nucleus of the solitary tract for representation by higher level corticolimbic areas. In turn, this afferent information is likely to modulate ongoing activity in corticolimbic areas in either a positive or negative feedback manner, which could further modulate descending corticolimbic signaling with midbrain and brainstem circuits. This signaling would serve to adjust ongoing autonomic, neuroendocrine, and cardiovascular functioning. This interplay of afferent and efferent systems would then impact the magnitude and even duration of stressor-evoked blood pressure changes. Thus, higher-level corticolimbic areas should not only be viewed only for their top-down influences over stressor-evoked blood pressure reactivity, but also as cyclic processes with a bottom-up feedback component from autonomic systems may serve to affect the magnitude and duration of a stressor induced autonomic-cardiovascular reactions through positive and negative feedback mechanisms. These cyclic negative feedback processes are likely what govern an individual's recovery time back to baseline levels of autonomic activity. Given this, it is possible that individuals with a tendency to show exaggerated

cardiovascular and autonomic reactions may also exhibit disregulated patterns of feedback and top-down processing between higher-level corticolimbic systems and lower-level midbrain and brainstem circuits, which may reflect impairments in efferent and visceral afferent regulatory mechanisms (Gianaros et al., 2008). Such disregulated connectivity also likely corresponds to impairments as Thayer and Lane (2000) describe in their theory of neurovisceral integration. Figure 1 illustrates a possible model that was derived from the work of Gianaros & Sheu (2009), Berntson et al., (1998), Dampney (1994), Saha (2005), Saper (2002), Thayer & Lane (2000), and Westerhaus & Loewy (2001). There remains some question as to whether there is a hemispheric specialization related to the autonomic arousal that occurs due to an emotional response. The aforementioned research (Damasio et al. 2000; Lane, Chua & Dolan, 1999; Lane et al, 1997) has generally suggested left hemisphere subcortical activation during emotional arousal. However, electrophysiological data presents evidence of right cortical activation during unpleasant stimuli. Hagemann, Waldstein & Thayer, (2003) suggest that such findings are best explained by the joint function of two inhibitory mechanisms; one that is ipsilateral and inhibits efferent subcortical structures and another, which is contralateral.

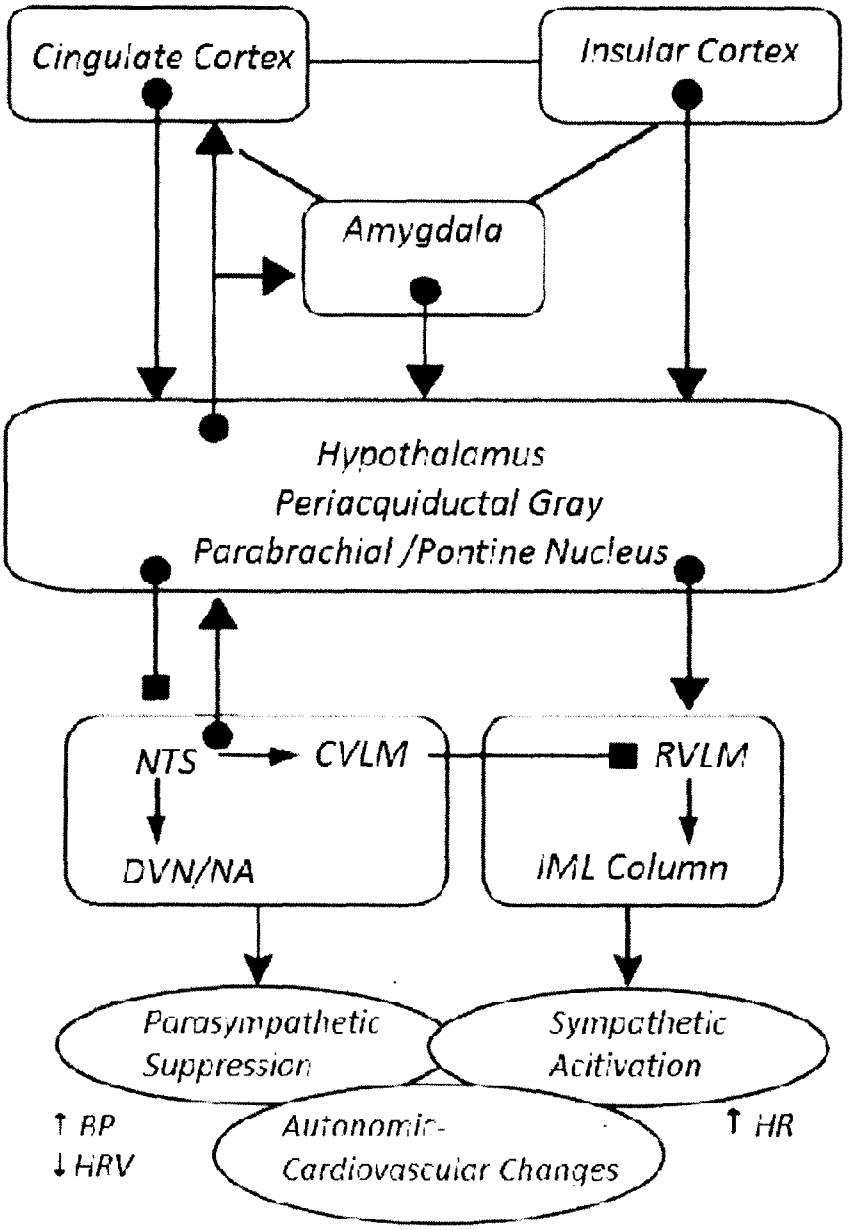

Figure 1. Conceptual diagram of selected brain systems processing of stressor-related information. PVN; paraventricular nucleus; LHA, lateral hypothalamic area; NTS,nucleus of the solitary tract; DVN, dorsal vagal nucleus; NA, nucleus ambiguous; CVLM, caudalventrolateral medulla; RVL, rostral ventrolateral medullary; IML, intermediolateral cell column; HR, heart rate; HRV, heart rate variability; BP, blood pressure. Blocked endpoints denote inhibitory influences and arrowed endpoints denote excitatory influences.

The Relation of Executive Function, Attention Regulation and Autonomic Function

While several models have been proposed to explain the association between the emotion-related central nervous system function and autonomic response patterns, it is those that have tied cortical and subcortical systems together that have shown the most promise. One conceptual model of cardiovascular reactivity proposed by Lovallo and colleagues (Lovallo, 2005; Lovallo & Gerin, 2003) integrates concepts of stressor appraisal theory (Holroyd & Lazarus, 1982; Lazarus & Folkman, 1984) with neurobiological concepts derived from animal research models regarding neural control of cardiovascular systems (Bard, 1928; Cannon, 1928, 1932). According to cognitive stressor appraisal theory, stress is a transactional process in response to a real or perceived demand that is evaluated as threatening or benign, depending on the individual and their respective adaptive coping resources (Cohen et al., 2007; Monroe, 2008). Additionally, coping responses that ensue from such processes are believed to influence risk for and resilience against ill health, including cardiovascular disease (McEwen, 2007).

Lovallo's conceptual model suggests that these processes related to the stressor appraisal theory and the resulting neural commands resulting in physiological and behavioral stress reactions are instantiated in rostral or corticolimbic brain systems that are located above the level of the hypothalamus in the neuroaxis. Hence, according to this model, the individual differences found in stressor-evoked cardiovascular reactivity would likely originate from altered stressor-related activity along three reciprocally interacting levels neural activity that lead from the corticolimbic systems to midbrain and brainstem relay pathways and neuromodulatory systems and, finally, to the peripheral

target organs (i.e., the heart and vasculature) that are physiologically affected by the neural inputs. In this instance, the corticolimbic systems allow for the evaluative cognitive appraisal of self-relevant psychological and environmental stressors. After appraising such demands, corticolimbic systems are theorized to reciprocally signal to generate adaptive coping behaviors that include metabolically supportive changes in the reactivity of the target organ (e.g., peripheral changes in cardiac output and blood pressure) via midbrain and brainstem relay pathways and neuromodulatory systems. An individual's tendency to express increased neural activation in response to an evoked stressor in corticolimbic systems could, therefore, mediate the peripheral expression of exaggerated cardiovascular reactivity. The corticolimbic systems implicated in Lovallo's model to regulate stressor evoked cardiovascular reactions include networked divisions of the cingulate and medial prefrontal cortices, amygdala, and septal nuclei. Specific relay pathways and neuromodulatory systems used by corticolimbic systems to regulate the acute expression of cardiovascular reactions include the hypothalamus, ventral tegmentum, pontine raphe nucleus, and locus ceruleus.

Critchley (Critchley et al., 2000, 2003; Critchley, 2005) developed a neurobiological model of emotional and cognitive integration utilizing neuroimaging and lesion evidence. This model suggests that functional subdivisions of several corticolimbic brain systems suggested by the above model from Lovallo, including the cingulate and medial prefrontal cortices, insula, and amygdala, are posited to play an instrumental role in calibrating autonomic and cardiovascular reactions to stressor evoked adaptive behavior. Several neuroimaging studies have shown that behaviorally-evoked changes in cardiovascular and cardiac-autonomic activity are correlated directly with neural activity

within areas of the cingulate and medial prefrontal cortices, often in interaction with activity in the insula, amygdala, and relay regions of the thalamus, hypothalamus, midbrain and brainstem (e.g., Critchley, 2005; Critchley et al., 2000; Critchley et al., 2003; Gianaros et al., 2004; 2005a; 2007; 2008; Gray et al., 2009b; Lane et al., 2001; Matthews et al., 2004; Mujica-Parodi et al., 2009; O'Connor et al., 2007; Wager et al., 2009a; Wager et al., 2009b). Additionally, lesion studies of patients with damage to the cingulate cortex done in parallel with these neuroimaging studies further implicate this particular corticolimbic system as being critical for coordinating autonomic and cardiovascular adjustments with emotional and cognitive behaviors (Critchley, 2005; Critchley et al., 2003).

The model of neurovisceral integration originally developed by Thayer and Lane (2000) attempts to account for the complex interplay of cognitive, affective, behavioral and physiologic activity that occurs as a result of affective states. The model suggests that these interconnections are broken down into functional units that respond to specific types of stimuli. One such functional unit is the central autonomic network (Benarroch, 1993; 1997). Thayer and Lane suggest that the central autonomic network is a common central functional network. They have acknowledged that many competing models comprise similar brain structures including the anterior executive network (Devinsky, Morrell & Vogt, 1995), and the emotion circuit (Damasio, 1998). These structures are also very similar to those identified in the models by Critchley and Lovallo. The central autonomic network is associated with the processes of response organization and selection, and serves to control psychophysiological resources in attention and emotion (Thayer & Lane, 2000; Friedman & Thayer, 1998; 1997). This network functions as an

integrated component of an internal regulation system through which the brain is able to control an array of visceromotor, neuroendocrine, and behavioral responses, which are necessary for the completion of the goal-directed behavior and adaptability. Structurally, this network is comprised of the anterior cingulate, insular cortex, and ventro-medial pre-frontal cortices, the central nucleus of the amygdala, the paraventricular nucleus of the hypothalamus and related regions, the periaquaductal gray matter, the parabrachial nucleus, the nucleus of the solitary tract, the nucleus ambiguous, the ventrolateral medulla, ventromedial medulla, and the medullary tegmental field. The output of the central autonomic network is mediated through the pre-ganglionic sympathetic and parasympathetic neurons. These neurons innervate the heart through the stellate ganglia and the vagus nerve. The actions of these two inputs to the sino-atrial node of the heart are the source of heart rate variability over a given period of time (Saul, 1990). Sensory information from organs, such as the heart, also feedback to the central autonomic network and affect further changes in the system. Thus, the actions of the central autonomic network can be directly linked to heart rate variability and this variability can also be viewed as an index of neural feedback between the central and peripheral nervous system and central-autonomic integration.

The central autonomic network is under tonic inhibitory control through the use of gamma-aminobutyric acid (GABA) interneurons that are in the nucleus of the solitary tract. Disruption of this pathway has been shown to lead to hypertension and sinus tachycardia (Benarroch, 1993, 1997; Masterman & Cummings, 1997). This inhibitory control by the prefrontal cortex via GABAnergic extensions extends to sympathoexcitatory subcortical threat circuits are activated, such as those involving the

amygdala and related projections to autonomic, endocrine, and other physiological systems (Amat et al., 2005; Thayer & Ruiz-Padial, 2006; Thayer, 2007; Davidson, 2000).

CHAPTER III

CURRENT STUDY

Given that a significant body of previous work has suggested a relation between cognitive function and autonomic-cardiac reactivity (as measured by heart rate variability, blood pressure, and heart rate), there still remains the question of exactly which areas of cognitive domain account for the individual differences in autonomic-cardiac reactivity response and associated recovery. Previous research by Waldstein and Katzel (2005) has established that higher stress-induced systolic and diastolic blood pressure reactivity is associated with poorer performance on tests of immediate and delayed verbal memory and executive function (i.e., response inhibition). The authors suggest that these differences account for between 3% and 8% of the variance in measures. Waldstein and Katzel (2005) was one of the few studies focused on the relations of cognitive functioning to autonomic reactivity in participants. Previous studies relating blood pressure response to neuropsychological testing did not relate to variability in cognitive performance (Pierce & Elias, 1993). Responses elicited in that study were modest compared to those seen in the Waldstein and Katzel study. Though, other recent findings also indicate that increased autonomic variability was associated with poorer performance on cognitive tests, including executive function, or with cognitive impairment in both hypertensive and normotensive older adults (Bellelli, Pezzini, Bianchetti & Trabucchi, 2002; Kanemaru, Kanemaru & Kuwajima, 2001). Additionally, the authors had previously theorized that repeated episodes of stress-induced reactivity during daily life may enhance cerebrovascular damage by inducing periods of cerebral hypoperfusion or vasospasm, perhaps due to compromised autoregulatory capacity in

older adults (Waldstein, Siegel, Lefkowitz, Maier, Pelletier, et al., 2004). Given that cerebral hypoperfusion is thought to be particularly important to the ultimate development of dementia (Meyer, Rauch, Rauch & Haque, 2000), the authors also investigated significant associations between enhanced blood pressure reactivity and indexes of silent cerebrovascular disease assessed by MRI in a small subset of the participants (i.e., increased white matter disease and silent brain infarction) (Waldstein, Siegel & Lefkowitz, 2004) and suggested a relation between blood pressure reactivity and poorer cognitive function may be mediated, in part, by silent cerebrovascular disease. However, they did not rule out the possibility that a third neurobiological variable may simultaneously lead to both enhanced BP reactivity and poorer cognitive function.

The present study will attempt to replicate and extend the findings in Waldstein and Katzel (2005) by examining whether differences in pre-frontal cortical abilities (verbal and non-verbal memory, mental flexibility, and response inhibition) account for any variance in individual differences related to autonomic-cardiac reactivity. Specifically, the study will test whether these cortical abilities determine any significant differences either reactivity or recovery of blood pressure, heart rate, and heart rate variability. This study will test current models of neurobiology reviewed above that suggest pre-frontal cortical activity may inhibit sub-cortical structures in the course of goal-directed behavior. In turn, the degree to which inhibition of affective processes occurrence will influence respective changes in autonomic regulation during periods of stress. The differing levels of sympathetic activation to stressors in the environment will dictate variations in the level of physiologic responsiveness and stress hormones released into the body. This, in particular, is important when looking for indicators of long-term

cognitive dysfunction. Given what the previous research has suggested, we would theorize that individuals with high trait levels of attention, memory, mental flexibility, or executive function are better protected against the threat of stressful stimuli than those with lower trait levels. Thus, those with higher levels of these protective traits would likely elicit significantly lower levels of reactivity to an evoked stressor than those with lower levels. Additionally, there is the question of whether these higher trait levels of cognitive functioning will aid in recovery from stressors. It is possible that differences in recovery are responsible for the differences seen in the development of long term cardiovascular disease. Alternatively, and perhaps more likely, it is possible that individuals that possess traits beneficial in stress-induced reactivity also have an advantage in recovery from a stressor induced event. In either case, it is hypothesized that greater trait levels of cognitive function allow one to recover more quickly from stressful external stimuli. Specifically, it is hypothesized that:

I. Higher trait levels of response inhibition, mental flexibility, and verbal and non-verbal memory will be associated with a significantly lower than expected level of stress-induced responding in cardiovascular reactivity as compared to those with lower trait levels.

II. Higher trait levels of response inhibition, mental flexibility, and verbal and non-verbal memory will be associated with significantly earlier and more substantive recovery from stress-induced cardiovascular reactivity as compared to those with lower trait levels.

CHAPTER IV

METHOD

Participants

The participants consisted of 360 adult individuals, 180 men and 180 women, between 30 and 55 years of age, from the greater southwestern Pennsylvania (Allegheny County) area and recruited from a larger study. Subjects were not excluded from participation based on HIV status or ethnicity and were recruited in proportion to their ethnic representation in the local population. All subjects recruited to take part in the study were generally in good health and without reported clinical history of atherosclerotic disease (e.g., myocardial infarction, congestive heart failure), cardiovascular problems (rheumatic heart fever, abnormal heart rhythm, heart valve problem) or related treatment (angioplasty, bypass, and pacemaker), angina or peripheral arterial disease claudication. Individuals suffering from other severe and chronic diseases affecting general health [within the past year] (e.g., cancer, chronic kidney or liver disease, diabetes, thyroid problems, asthma, lung problems, chronic pain) and Central Nervous System (CNS) disorders or neurological deficits (multiple sclerosis, Parkinson's disease, muscular dystrophy, stroke, transient ischemic attack, embolism, epilepsy or convulsive disorders, head injury, loss of consciousness) were also excluded. They were also required to not be taking any medications that would interfere with cardiovascular function. This included cardiovascular, psychotropic, serotonergic, glucocorticoid, lipid lowering, diabetic, or weight-loss drugs, and those drugs prescribed for irritable bowel syndrome.

Additionally, participants were excluded if they had severe hypertension (a BP of 180/110 mm Hg or greater), secondary hypertension due to chronic renal insufficiency (as indicated by a creatinine level greater than 1.8 mg/dl), suspected hyperaldosteronism, a potassium level of less than 3.5 mg/dl, or heavy alcohol consumption (considered to be more than 21 drinks per week), diabetes, being significantly overweight or obese (indicated by a body mass index of 40 or greater), the presence of an eating disorder such as bulimia nervosa or anorexia nervosa, or bariatric (gastric bypass) surgery. These exclusionary characteristics were identified during participation in the previous study. Finally, because some of the cardiovascular measures associated with the study may be affected by pregnancy or lactation-related hormone changes, pregnant or lactating women were not eligible for participation in the study (Monk et al., 2001; Altemus et al., 2001).

Procedure

Participants completed 4 hours of neuropsychological testing and 3 hours of cardiovascular reactivity testing at the Behavioral Physiology Laboratory at the University of Pittsburgh on two separate days. Participants were asked to forgo consumption of alcohol 24 hours prior to neuropsychological assessment as well as medications and dietary supplements for 12 hours prior to session (e.g., cold medications, weight loss aids, sleeping pills, muscle relaxants, sleeping pills, and pain medication). Prior to cardiovascular reactivity session, participants were asked to forgo caffeine 4 hours prior session, nicotine 1 hour prior, medications and dietary supplements for 12 hours prior to session (e.g., cold medications, weight loss aids, sleeping pills, muscle relaxants, sleeping pills, pain medication) and vigorous exercise 4 hours prior to sessions.

Attention and memory were assessed using the Wechsler Memory Scale – 3rd Ed. (WMS-III). Verbal memory was evaluated by means of the Logical Memory subtests Part I (Immediate Recall) and Part II (Delayed Recall) of the WMS-III. Part I of this subtest consists of two stories, story A is read once to the examinee, which then orally provides any information recalled. Story B is read twice to the examinee, with any recalled information provided after each reading (Lezak, 2004). The examiner records the number of free recall units and thematic units, which represent more general information, that are provided by the examinee. The examinee is instructed to try to remember the stories because he or she will be asked to tell them again later. Following 30 minutes of other testing, Part II is administered and the examinee is asked to provide any information recalled from Story A and then Story B. A standard cue is provided if the examinee has no memory of a story. The recall and thematic unit scores are again recorded. Fifteen yes/no recognition memory questions are then asked about each story and the recognition memory scores are recorded (Wechsler, 1997). Nonverbal memory was evaluated by the Visual Reproduction subtests Part I (Immediate Recall) and Part II (30 minutes Delayed Recall) of the WMS-III. This subtest consists of five drawings that an examinee is required to view. The examinee is then asked to reproduce the design from memory immediately after the drawing is removed from view. After approximately 30 minutes has passed, the examinee is again asked to reproduce all the designs from memory (Lezak, 2004).

The WMS-III was designed using a large normative sample (N = 1250) with good representation of a wide age range of individuals. The test is currently in its third revision and has been designed to assess memory, learning, and working memory (Lezak, 2004).

Reliability coefficients for immediate memory are .93 for auditory memory and .82 for visual memory. Reliability for associated delayed recognition tasks is .87 auditory and .83 visual delayed. Logical Memory and Visual Reproduction subtests both have reliability coefficients above .70 as well for both immediate and delayed tasks. Haaland, Price and Larue (2003) have shown that the instrument is sensitive to differences in memory encoding, storage, and retrieval even between normally aging subjects.

The Stroop Color-Word Test measures working memory, response inhibition and cognitive interference, which are dimensions of executive function. The test is based on the finding that interference in stimuli changes reaction times (Stroop, 1935). The standard format of the task is composed of three parts. The subject is initially required to read words representing names of some basic colors in black ink. In the second part, he/she must name the color of non-interference objects (e.g. XXX). The third part is the subtest of interference. The subtest of interference is based on the assumption that looking at the name of a color that differs from the actual color of the word (e.g. the word red is written in green) (Lezak, 2004). However, the subject tends to read the name instead of saying the color in which the word is written (which is what the instruction requires). When reading quickly, the person gets into a conflict-filled stressful situation because the answer is influenced by the learned reaction (in this case by the tendency to read words, not to name the colors) and the subject must inhibit said reaction in order to complete the task.

MacLeod (1991) completed a review of literature related to the Stroop test. The review showed that although there was some inconsistency in the findings, studies by Smith and Nyman (1974) and Schubo and Hentschel (1977, 1978) suggested that

reliability for this test is good. Santos and Montgomery (1962) directly examined reliability, finding it to be good and uninfluenced by events interpolated between test and retest. Uechi (1972) also reported high reliability. In the most comprehensive study, Jensen (1965) concluded that, with multiple administrations, the Stroop test was probably more reliable than any other comparative psychometric test of the time. Additionally, there is a body of literature that has suggested selective inhibition is the mechanism with defines with Stroop effect. Specifically, Neill and Westberry (1987) studied speed-accuracy differences and inter-trial intervals and found evidence that after broad activation, selective inhibition is used to restrict processing to just the relevant information. More recently, Kane and Engle (2003) have shown that individual differences in working memory can also predict Stroop performance.

Trail Making Test parts A and B will assess perceptual-motor speed and executive function (e.g., mental flexibility). The Trail Making Test was originally designed as part of the Army Individual Test Battery (1944) and has since included in a number of general and specific-purpose neuropsychological test batteries (e.g., Halstead-Reitan Battery, Reitan, & Wolfson, 1993). The test is given in two parts: Trail Making, Part A (TMT-A) involves drawing a line connecting consecutive numbers from 1 to 25. Part B (TMT-B) involves drawing a similar line, connecting alternating numbers and letters in sequence (i.e., 1-A-2-B and so on). The time to complete each 'trail' is recorded. In the standardized administration procedure, examiners point out errors as they occur, and error-correction influences the time to complete a trail (Lezak, 2004; Reitan & Wolfson, 1993). Initially, interpretation of the test rested on the assumption that the difference in completion time between TMT-B and TMT-A reflected the additional cognitive control

required to switch between sequential numbers and letters, a process generally referred to as executive control. TMT-A was assumed to provide a baseline for motor and visual control and speed that could then be compared to the time cost of executive control for each individual. In addition to the completion times of TMT-A and TMT-B, two derived scores are often used for interpretive purposes: the B-A difference, and the B/A ratio. These derived scores are calculated to assess relative performance for TMTB and TMT-A, providing information somewhat independent of motor speed and visual scanning speed (Corrigan & Hinkeldey, 1987; Heaton, Nelson, Thompson, Burke, & Franklin, 1985; Lamberty, Putnam, Chatel, Bieliauskas, & Adams, 1994). Slowed performance on TMT-B relative to TMT-A indicates cognitive impairment, specified by some as impaired ability to execute and modify a plan of action (Golden,1981) or general frontal lobe dysfunction (Ameiva, Lafont, Auriacombe, Rainville, Orgogozo, Dartigues, & Fabrigoule, 1998; Pontius & Yudowitz, 1980). The current study utilized the B/A ratio score.

Participants in this study also completed a psychophysiological assessment. Generally, a psychophysiological assessment related to research in cardiovascular reactivity involves eliciting a stress response via physical or psychological stressors. In laboratory studies, these stressors often require individuals to complete demanding tasks that (a) entail consequences, either negative or positive, of motivational or personal relevance, and (b) prompt a coping response that enables successful task performance and engagement (Kamarck and Lovallo, 2003). The most common psychological stressors used to evoke cardiovascular reactivity are those that require engaging in difficult or frustrating cognitive tasks that tax executive control processes (e.g., solving mental

arithmetic problems, preparing and delivering speeches on interpersonally distressing topics, working memory tasks, inverted or mirror-image tracing, and Stroop color-word interference tasks). Common are physical stressors that involve immersing a limb in painfully cold water (cold pressor task) or squeezing a handgrip dynamometer to maintain a constant amount of muscular tension over a prolonged period of time (isometric exercise). In most individuals, such stressors will evoke measurable cardiovascular changes from a baseline state. However, it is recognized that individuals differ markedly in the magnitude, pattern, and duration of cardiovascular changes and that some individuals appear to have a trait-like (dispositional) tendency to reliably express relatively large-magnitude (exaggerated) and sometimes prolonged stressor-evoked increases in cardiovascular activity, which are implicated in coronary heart disease risk.

Subjects were presented with three cognitive and psychomotor tests designed to mimic tasks encountered in daily life. A Stroop interference task, a memory task, and a tracking task were utilized for this study. Measures of blood pressure (BP) and continuous measures of heart rate (HR) [by EKG leads attached on the surface of the skin] were taken during these tasks. Subjects engaged in three, 6-minute experimental tasks chosen to evoke negative emotions. Each task was preceded by a 10-minute baseline rest period. The initial rest period served to calculate a baseline for HR, BP, and heart rate variability (HRV). Each of the following baseline periods were used to calculate recovery as compared to the initial baseline. HRV is calculated using the QRS complexes recorded on an electro cardiogram (ECG). Three components of HRV are commonly used and will be utilized in the current study: low-frequency heart rate

variability (LF-HRV), high-frequency heart rate variability (HF-HRV), and a ratio score of high and low frequency hear rate variability (LF: HF-HRV). HF-HRV is generally considered to be associated with vagal tone via respiratory sinus arrhythmia. LF-HRV is considered to be associated with sympathetic outflow, but has been shown to be associated with vagal tone as well. LF: HF-HRV is considered to be a better indicator of any changes in HRV due to sympathetic outflow.

Cardiovascular reactivity is considered to be a reliable psychophysiological construct describes the patterns, magnitude, and/or mechanisms of cardiovascular responses to psychological stress (Girdler et al., 1995). Recent research has suggested that cardiovascular reactivity is stable between periods of days and months, but findings related longer periods (i.e. years) are inconsistent and sparse (Kamarck & Lovallo, 2003). Additionally, cardiovascular reactivity was found not to overlap with other tests of autonomic function, suggesting good construct validity and was at least moderately stable across stressors varying in the type of underlying response system elicited (e.g., cardiac vs. vascular; active vs. passive). Finally, Kamarck & Lovallo (2003) found that while there is evidence of good construct validity, there are inconsistencies when translating findings to the real world. There are considerable individual differences in cardiovascular reactivity, differences that are related neither to how engaging the task is nor to how well research participants perform the task (Krantz, Manuck & Win, 1986; Turner, 1994).

With regard to computational procedures, there is cumulative evidence from cardiovascular reactivity research that change scores computed by subtraction procedures (e.g., subtracting baseline from task levels of a cardiovascular parameter) and regression procedures (e.g., regressing task on baseline levels and retaining the residual values)

show adequate statistical (test-retest) reliability when such scores are averaged across multiple stressors sharing similar task dimensions (Kamarck et al., 1992; Kamarck and Lovallo, 2003; Llabre, Spitzer, Saab, Ironson, & Schneiderman, 1991; Manuck et al., 1995). Having utilized numerous psychometric principles in this study, such averaging and normalizing of these parameters should minimize nuisance or error variance attributable to the idiosyncratic features of particular stressors and also maximizes the likelihood of capturing the dispositional properties of a given cardiovascular reactivity measure, which are thought to be of most importance for predicting cardiovascular disease risk across individuals (Kamarck & Lovallo, 2003). While far less research has been done on the reliability of measurement of cardiovascular recovery in laboratory studies (largely due to the fact that interest this marker is more recent and fewer studies regarding its efficacy have been published), similar procedures were taken to ensure that the reliability of recovery measures in this study.

With regards to the limitations of this method research, previous researchers have noted that cardiovascular reactivity patterns vary not only as a function of dispositional tendencies of the individual subject, but also as a function of the stressor used in the experimental paradigm (Kamarck & Lovallo, 2003; Gianaros & Sheu, 2009). For example, a specific experimental stressor may require either an active or passive coping behavior. Additionally, the stressor or necessary response may be physical or psychological in nature (Obrist, 1981). The neurobiological consequences of such differences could suggest the involvement of different brain circuits and pathways resulting in divergent or even comparable patterns of observable cardiovascular reactivity. For example, a subject attempting to passively cope with the physical pain

imposed by a cold pressor task may evoke a rise in BP and HR because of an increase in vascular resistance due to a temperature-induced stimulation of alpha-adrenergic receptors located on peripheral blood vessels. In contrast, attempting to actively cope with psychological stress, imposed by the Stroop color-word interference task, may evoke an equivalent rise in BP and HR because of a mixed increase in cardiac output and vascular resistance resulting from a centrally-orchestrated stimulation of beta- and alpha-adrenergic receptors located on the myocardium and blood vessels, respectively (Gianaros & Sheu, 2009). Thus, a particular stressor and associated cardiovascular changes evoked should be grounded by the caveat that different stressors may elicit different (and sometimes similar) patterns of cardiovascular reactivity (e.g., equivalent rises in BP, HR, etc.) via diverse neurobiological and peripheral response mechanisms. Additionally, such mechanisms may differ in their predictive relevance for cardiovascular disease risk (Kamarck & Lovallo, 2003; Obrist, 1981, Gianaros & Sheu, 2009).

An additional issue that has been noted in the literature is that the ability to quantify cardiovascular reactivity in an accurate manner is complicated by physiological factors and statistical issues related to the reliable measurement of change (Gianaros & Sheu, 2009). Specifically, the magnitude and direction of change from baseline of a given cardiovascular parameter often depends on the initial (baseline) level of that parameter. This phenomenon, referred to as the principle of initial values, suggests that higher overall levels of a given physiological parameter will tend to predict subsequently smaller levels of observed change and likely directionally negative change in said parameter (Berntson et al., 1994; Stern et al., 2001; Wainer, 1991; Wilder, 1967). Alternatively, lower baseline levels of a given physiological parameter will tend to predict larger levels

of observed change and likely directionally positive change in said parameter. To limit these tendencies in the present study, residual change scores were utilized in other for an individual's own baseline scores to serve as a reference point for change. However, even using these measures an individual's response level will likely vary according to the principal of initial values.

Participants were also asked to complete two questionnaires regarding their affective (Positive Affect-Negative Affect Schedule) and cognitive (i.e., Stress Appraisal Measure) reactions to the tasks. These measures were used to measure their state emotional reactions to the task. The Positive Affect Negative Affect Schedule (PANAS) is a 20-item self-report measure of mood in the present moment. Each item is rated on a five-point scale and the items produce two sub-scales: a positive affect scale and a negative affect scale. Internal consistency reliabilities in the literature fall in the .8 range, and the positive affect subscale correlates negatively with measures of depression, while the negative affect scale correlates highly with measures of depressed mood and anxiety (Watson & Tellegen, 1988). More recent studies have shown Cronbach's alpha as .82 for positive affect and .76 for negative affect (Suhr & Tsanadis, 2007).

Stress appraisal measure (SAM) by Peacock and Wong (1990) was used to assess the perceived level of stress among the sample. The measure consists of 28 statements rated on a scale from 1 to 5 (not at all, slightly, moderately, considerably and extremely). These statements include questions about the their feelings towards the task and whether they feel that it is likely to be resolved (e.g. Do you feel anxious, Do you have the ability to do well, Do you feel that the problem is unresolvable, Are you eager to tackle the problem, etc) There are seven subscales of the measure and each subscale consists of four

statements, which assess both primary and secondary cognitive appraisal as well as overall stressfulness. The three primary appraisal scales included Threat, Challenge, and Centrality. The three secondary appraisal scales included Controllable-by-Self, Controllable-by-Others, and Uncontrollable-by-Anyone. The seventh scale of the SAM is a more general scale to index overall perceived stressfulness. Peacock and Wong (1990) summarized three studies which found the six specific factors to have good internal consistency (scores ranged from 0.73 to 0.86) and convergent validity. Threat and challenge subscales each accounted for unique variance on the stressfulness subscale, suggesting that they were tapping distinct dimensions of the overall experience. However, there is some question as to whether other factors may be present (Roesch & Rowley, 2005). Currently, the SAM is the only measure of cognitive appraisal in the literature that has theoretical and psychometric support for its validity.

CHAPTER V

RESULTS

Data Reduction

Four cognitive factors represented the independent variables or predictors in this study: mental flexibility, response inhibition, verbal memory and non-verbal memory. Scores from four neuropsychological tests were chosen to represent measurements of each of the four cognitive factors. A ratio score (B/A) derived from the two components of the Trail Making Test was used as a representation of mental flexibility. A ratio score was chosen to factor out the perceptual-motor component of the Trail Making Test and focus more on mental flexibility. Response inhibition was represented by the scaled scores on the interference task of the Stroop Color-Word Test. Verbal memory was represented by a summation of scaled scores for both items and thematic events recalled on the Logical Memory I and II subtests of the WMS-III. Similarly, non-verbal memory was represented by scaled score totals of both item and thematic scores on the Visual Reproduction I and II subtests of the WMS-III. Each of these four scores was converted into a standardized z-score for analysis.

Regarding the physiological measures (systolic BP, diastolic BP, HR, LF-HRV, HF-HRV, and LF: HF-HRV) were utilized as measurements of physiological response to a cognitive stressor. Resting or baseline scores for each participant were represented by the initial baseline measured prior to the administration of the first stressor task. This score was chosen over an average of baseline scores in order to acquire physiological measures that were closest to the participants' true baseline measures. Task scores for each participant were calculated using an average of the psychological changes elicited

through each of the three stressor tasks in order to maximize reliability and variance that occurs due to trait characteristics as indicated by previous research (Kamark & Lovallo, 2003). Recovery scores for BP tasks were similarly averaged together to create a recovery score representing seven minutes post-task recovery. For HR and HRV measures, ten minutes of post-task recovery data was available. Therefore, recovery scores were broken into two five-minute intervals in order to more accurately discern patterns in psychological change among participants. For purposes of data analysis, the mean cardiovascular values obtained within each period (resting, task, recovery) were compared to residual change scores obtained by performing a regression of the cardiovascular levels obtained during the rest periods preceding the laboratory challenges. Residual change scores were used rather than raw averages to compensate for baseline differences among individuals, thus resulting in a more "pure" measure of reactivity and recovery.

Preliminary Analysis

The data from the 360 original participants was again screened to remove the data of any individuals who were missing data in any of the dependent or independent variable categories. Additionally, any participant with scores greater than 3.29 standard deviations in either direction for the relevant categories was also removed from the sample. After removing these participants, the final sample size was 209 participants. The vast majority of the participants were removed due to missing data in at least one of the categories utilized for this study. The reason for removing these participants from the study was two-fold. Any individual without a complete set of baseline physiological measures would not be able to produce a residual change score as these scores are estimates of

change based on individual baseline performance. Additionally, given the large number of subjects available in the database, using only those with a full set of results did not affect the power of the study while being able to ensure the results were from a more consistent dataset. A small number of subjects were excluded due to outlier scores. Given the fact that these outlier scores were often more than 10 standard deviations away from the mean, it is likely that these scores were due to experimental error.

A preliminary power analysis was completed to ensure that the 209 individuals were an adequate sample size. Power analyses showed the sample size has appropriate power to obtain a statistically significant result even when adjusting for the three other independent variables ($r = .93$). This is in line with previous research related to the topic have shown statistically significant differences between groups with sample sizes of 12 to 20 individuals per group (Davig, Larkin, & Goodie, 2000; Krantz et al., 1988). These studies have shown power values of .70 or more and have been classified as medium to large power by Cohen (1988).

Pearson product moment and point biserial correlations were computed for relations among sex, age, education, race, handedness, subscale scores for the PANAS (positive and negative affect scales) and SAM (all seven subscales) to examine potential covariates. All cognitive factors were found to have significant covariation with education and SAM threat scale. As these cognitive factors will be included in all analysis, both education and the SAM threat scale will be included in the first step of all regressions. Utilizing these covariates in all regressions will help account for educational differences and differing levels of anxiety. The covariates found to significantly correlate with systolic BP included sex, the PANAS Negative Affect scale, the PANAS Positive

Affect scale, the SAM Challenge scale, and the SAM Control Self scale and will also be added to the first step of all regressions involving systolic BP. The covariates found to significantly correlate with diastolic BP were sex, the PANAS Positive Affect scale, the SAM Challenge scale, and the SAM Centrality scale, which were added to the first step of those regressions. The covariates found to significantly correlate with HR were sex, race, and the SAM Control Self scale. Similarly, these covariates were added to first step of regressions involving HR. The covariates found to significantly correlate with LF-HRV were sex and the SAM Control Other scale. None of the covariates tested showed a significant correlation to HF-HRV, so only education and SAM threat scale were controlled for in the first step of those regressions. However, sex and age showed a significant correlation to the LF: HF-HRV score. As previously mentioned, all regressions will include covariates for the cognitive predictors and then each covariate found to significantly correlate with a physiologic variable was added to the first step of the hierarchical regression related to the respective dependent variable. (See Tables 1-6 for details regarding correlations.)

Table 1

Correlations between Mean Baseline Physiological Measures and Covariates

COVARIATES	PHYSIOLOGICAL MEASURES					
	BP – Systolic (mean baseline) *(r, p)*	BP – Diastolic (mean baseline) *(r, p)*	Heart Rate (mean baseline) *(r, p)*	LF-HRV (mean baseline) *(r, p)*	HF - HRV (mean baseline) *(r, p)*	LF: HF-HRV (mean baseline) *(r, p)*
Sex (Males = 1, Females = 2)	-.51**, .00	-.37**, .00	.29**, .00	-.14*, .04	-.10, .15	-.26**, .00
Age (Years)	-.03, .70	.06, .37	-.05, .48	-.11, .10	-.10, .12	.16*, .02
Race (White = 1, Black = 2)	.01, .90	. 10, .17	-.14*, .03	-.02, .71	-.02, .78	-.11, .11
Education (Years: post-secondary, 0-8)	-.10, .17	-.06, .38	-.05, .43	.04, .52	.05, .43	.02, .75
Total Handedness Scale (Right handed= 13, Left handed= 39)	-.07, .34	-.04, .56	.07, .32	.02, .74	.01, .84	.01, .93

N = 209

* = $p < .05$

** = $p < .01$

Table 2

Correlations between Mean Baseline Physiological Measures and PANAS Subscales

PANAS SUBSCALES	PHYSIOLOGICAL MEASURES					
	BP – Systolic (mean baseline) *(r, p)*	BP – Diastolic (mean baseline) *(r, p)*	Heart Rate (mean baseline) *(r, p)*	LF-HRV (mean baseline) *(r, p)*	HF-HRV (mean baseline) *(r, p)*	LF: HF- HRV (mean baseline) *(r, p)*
PANAS - Positive Affect Scale (0 = not at all, 50 = extremely)	.01, .96	.03, .72	-.09, .18	.07, .26	.07, .28	-.01, .87
PANAS – Negative Affect Scale (0 = not at all, 50 = extremely)	.01, .99	-.03, .73	.02, .83	-.06, .34	-.07, .32	-.04, .54

N = 209

* = $p < .05$

** = $p < .01$

Table 3

Correlations between Mean Baseline Physiological Measures and SAM Subscales

SAM SUBSCALES	PHYSIOLOGICAL MEASURES					
	BP – Systolic (mean baseline) *(r, p)*	BP – Diastolic (mean baseline) *(r, p)*	Heart Rate (mean baseline) *(r, p)*	LF-HRV (mean baseline) *(r, p)*	HF- HRV (mean baseline) *(r, p)*	LF:HF-HRV (mean baseline) *(r, p)*
SAM Threat Scale (1 = not at all, 5 = extremely)	.22**, .01	.18**, .01	.03, .60	-.04, .56	-.04, .55	-.01, .85
SAM Challenge Scale (1 = not at all, 5 = extremely)	-.09, .17	.03, .68	.11, .09	-.09, .18	-.08, .21	.06, .33
SAM Centrality Scale (1 = not at all, 5 = extremely)	.16*, .02	.11, .12	.03, .65	-.03, .69	-.03, .64	-.01, .94
SAM Self Control Scale (1 = not at all, 5 = extremely)	.00, .99	.10, .15	.16*, .02	-.08, .22	-.07, .26	.03, .61
SAM Other Control Scale (1 = not at all, 5 = extremely)	.16, .03	.16, .02	.12, .06	-.13*, .04	-.11, .08	.05, .46
SAM Uncontrolled Scale (1 = not at all, 5 = extremely)	.14*, .05	.22**, .00	-.12, .07	-.04, .58	-.05, .46	.05, .42
SAM Stress Scale (1 = not at all, 5 = extremely)	.09, .17	.06, .42	-.02, .71	-.04, .59	-.04, .57	-.04, .57

N = 209

* = $p < .05$

** = $p < .01$

Table 4

Correlations between Cognitive Predictors and Covariates

COVARIATES	COGNITIVE PREDICTORS			
	Trails Ratio Score (Secs) *(r, p)*	Stroop Score (T-score) *(r, p)*	Verbal Memory (0-70) *(r, p)*	Nonverbal Memory (0-50) *(r, p)*
Sex (Males = 1, Females = 2)	-.09, .21	.05, .47	.22, .06	-.13, .07
Age (Years)	.15, .06	-.04, .61	-.01, .95	-.07, .31
Race (White =1, Black =2)	.17, .07	-.18, .06	-.18, .12	-.08, .23
Education (Years: Post-secondary, 0-8)	-.25**, .00	.18**, .01	.21**, .01	.31**, .00
Total Handedness Scale (Right handed= 13, Left handed= 39)	-.07, .28	.12, .09	.04, .55	.01, .86

N = 209

* = $p < .05$

** = $p < .01$

Table 5

Correlations between Cognitive Predictors and PANAS Subscales

PANAS SUBSCALES	COGNITIVE PREDICTORS			
	Trails Ratio Score (Secs) *(r, p)*	Stroop Score (T-score) *(r, p)*	Verbal Memory (0-70) *(r, p)*	Nonverbal Memory (0-50) *(r, p)*
PANAS - Positive Affect Scale (0 = not at all, 50 = extremely)	-.13, .07	.03, .70	.02, .73	.07, .31
PANAS – Negative Affect Scale (0 = not at all, 50 = extremely)	.09, .20	-.01, .99	-.14, .06	-.01, .93

N = 209

* = $p < .05$

** = $p < .01$

Table 6

Correlations between Cognitive Predictors and SAM Subscales

SAM SUBSCALES	COGNITIVE PREDICTORS			
	Trails Ratio Score (Secs) *(r, p)*	Stroop Score (T-score) *(r, p)*	Verbal Memory (0-70) *(r, p)*	Nonverbal Memory (0-50) *(r, p)*
SAM Threat Scale (1 = not at all, 5 = extremely)	.21**, .01	-.16*, .02	-.21**, .01	-.26**, .00
SAM Challenge Scale (1 = not at all, 5 = extremely)	.11, .13	-.11, .11	-.04, .61	-.16, .20
SAM Centrality Scale (1=not at all, 5 = extremely)	.19, .06	-.09, .19	-.07, .33	-.17, .13
SAM Self Control Scale (1 = not at all, 5 = extremely)	-.19, .06	.06, .37	.08, .28	.03, .61
SAM Other Control Scale (1 = not at all, 5 = extremely)	-.06, .39	.03, .69	.12, .10	.07, .33
SAM Uncontrolled Scale (1 = not at all, 5 = extremely)	.09, .06	-.11, .11	-.05, .30	-.12, .08
SAM Stress Scale (1 = not at all, 5 = extremely)	.10, .16	-.02, .74	-.17, .07	-.09, .17

N = 209

* = $p < .05$

** = $p < .01$

Main Study Analysis

To maximize the unique information provided by each neuropsychological test and to best determine the contributing role of other variables, multiple hierarchical regressions were utilized to examine each cognitive predictor variable (i.e. mental flexibility, response inhibition, verbal memory and non-verbal memory). Comparisons were completed for cardiovascular reactivity levels, post-task cardiovascular recovery levels immediately following the task (five minutes), and recovery levels after a delayed rest period (five minutes). BP recovery was measured using a single recovery period (seven minutes). Regression coefficients for all regressions included systolic and diastolic BP, HR, and spectral components of HRV including: HF-HRV, LF-HRV, and LF: HF-HRV. For each hierarchical regression, any covariates found to be significantly related to the cardiovascular or cognitive measures were entered in as the first level of predictors. The second level of predictors was each of the four individual cognitive factors being investigated.

The regression results for the Task period showed no significant correlation between systolic BP and mental flexibility ($p = .66$; covariates: Sex, Education, PANAS Negative Affect scale, PANAS Positive Affect scale, SAM Threat Scale, SAM Centrality Scale & SAM Uncontrollable Scale), response inhibition ($p = .95$; covariates: Sex, Education, PANAS Negative Affect scale, PANAS Positive Affect scale, SAM Threat Scale, SAM Centrality Scale & SAM Uncontrollable Scale), non-verbal memory ($p = .66$; covariates: Sex, Education, PANAS Negative Affect scale, PANAS Positive Affect scale, SAM Threat Scale, SAM Centrality Scale & SAM Uncontrollable Scale) or verbal memory ($p=.64$; covariates: Sex, Education, PANAS Negative Affect scale, PANAS

Positive Affect scale, SAM Threat Scale, SAM Centrality Scale & SAM Uncontrollable Scale). Similarly, the task period showed no significant correlation between diastolic BP and mental flexibility ($p = .17$; covariates: Sex, Education, PANAS Positive Affect scale, SAM Threat Scale & SAM Uncontrollable Scale), response inhibition ($p = .17$; covariates: Sex, Education, PANAS Positive Affect scale, SAM Threat Scale & SAM Uncontrollable Scale), non-verbal memory ($p = .19$; covariates: Sex, Education, PANAS Positive Affect scale, SAM Threat Scale & SAM Uncontrollable Scale) or verbal memory ($p=.44$; covariates: Sex, Education, PANAS Positive Affect scale, SAM Threat Scale & SAM Uncontrollable Scale). The task period results for HR showed no significant correlation between HR and mental flexibility ($p = .26$; covariates: Sex, Education, SAM Threat Scale & SAM Self Control Scale), response inhibition ($p = .42$; covariates: Sex, Education, SAM Threat Scale & SAM Self Control Scale) or non-verbal memory ($p = .47$; covariates: Sex, Education, SAM Threat Scale, & SAM Self Control Scale). Scores on the verbal memory were also non-significant, but were marginally significant ($p = .07$; covariates: Sex, Education, SAM Threat Scale & SAM Self Control Scale). No significant relationship was seen between LF-HRV and mental flexibility ($p = .68$; covariates: Sex, Education, SAM Threat Scale & SAM Other Control Scale), non-verbal memory ($p = .23$; covariates: Sex, Education, SAM Threat Scale & SAM Other Control Scale), or verbal memory ($p = .88$; covariates: Sex, Education, SAM Threat Scale & SAM Other Control Scale). A significant positive correlation between LF-HRV and scores in response inhibition ($p = .04$; covariates: Sex, Education, SAM Threat Scale & SAM Other Control Scale) was found. Results for HF-HRV were similar to HR as mental flexibility ($p = .31$; covariates: Education & SAM Threat Scale),

response inhibition ($p = .09$; covariates: Education & SAM Threat Scale) and non-verbal memory ($p = .42$; covariates: Education & SAM Threat Scale) were non-significant, while scores on the verbal memory did come close to significance ($p = .07$; covariates: Education & SAM Threat Scale). The results of LF: HF-HRV showed no significant or close to significant results to mental flexibility ($p = .34$; covariates: Sex, Age, Education & SAM Threat Scale), response inhibition ($p = .74$; covariates: Sex, Age, Education & SAM Threat Scale), non-verbal memory ($p = .17$; covariates: Sex, Age, Education & SAM Threat Scale), or verbal memory ($p = .16$; covariates: Sex, Age, Education & SAM Threat Scale). (See Table 7 for further details regarding task period regression.)

Table 7

Regression Scores for Blood Pressure and Heart Rate Variability during the Task Period

PHYSIOLOGICAL MEASURES	COGNITIVE FACTORS			
	Trails Ratio Score (Secs) *(B, p)*	Stroop Score (T-score) *(B, p)*	Verbal Memory (0-70) *(B, p)*	Non-verbal Memory (0-50) *(B, p)*
BP –Systolic (Mean Task)	.04, .66	-.01, .95	.04, .64	.04, .66
BP –Diastolic (Mean Task)	.12, .17	-.11, .17	-.06, .44	.11, .19
Heart Rate (Mean Task)	-.08, .26	-.06, .43	.13, .07	-.05, .47
LF-HRV (Mean Task)	.03, .68	.15*, .04	-.08, .23	-.01, .88
HF-HRV (Mean Task)	.08, .31	.13, .09	-.13, .07	.06, .42
LF: HF-HRV (Mean Task)	-.07, .34	.03, .74	.10, .17	-.10, .16

N = 209

* = $p < .05$

** = $p < .01$

The regression results for the BP recovery period (seven minutes) showed no significant correlations. Systolic BP did not show any significant relation to mental flexibility ($p = .95$; covariates: Sex, Education, PANAS Negative Affect scale, PANAS Positive Affect scale, SAM Threat Scale, SAM Centrality Scale & SAM Uncontrollable Scale), response inhibition ($p = .25$; covariates: Sex, Education, PANAS Negative Affect scale, PANAS Positive Affect scale, SAM Threat Scale, SAM Centrality Scale & SAM Uncontrollable Scale), non-verbal memory ($p = .32$; covariates: Sex, Education, PANAS Negative Affect scale, PANAS Positive Affect scale, SAM Threat Scale, SAM Centrality Scale & SAM Uncontrollable Scale), or verbal memory ($p = .41$; covariates: Sex, Education, SAM Threat Scale, PANAS Negative Affect scale, PANAS Positive Affect scale, SAM Centrality Scale & SAM Uncontrollable Scale). Similarly, no significant correlations were found between diastolic BP and mental flexibility, but it was marginally significant ($p = .06$; covariates: Sex, Education, PANAS Positive Affect scale, SAM Threat Scale & SAM Uncontrollable Scale). Scores for response inhibition ($p = .81$; covariates: Sex, Education, PANAS Positive Affect scale, SAM Threat Scale & SAM Uncontrollable Scale), non-verbal memory ($p = .22$; covariates: Sex, Education, SAM Threat Scale & SAM Uncontrollable Scale), and verbal memory were also non-significant ($p = .87$; covariates: Sex, Education, SAM Threat Scale & SAM Uncontrollable Scale). (See Table 8 for further details regarding regression for BP recovery.)

The regression results for the immediate task recovery period (first five minutes) showed a significant negative relationship between HR and both mental flexibility ($p = .04$; covariates: Sex, Education, SAM Threat Scale & SAM Self Control Scale) and

response inhibition ($p = .01$; covariates: Sex, Education, SAM Threat Scale & SAM Self Control Scale). However, non-verbal memory ($p = .97$; covariates: Sex, Education, SAM Threat Scale & SAM Self Control Scale) and verbal memory tests were non-significant ($p = .11$; covariates: Sex, Education, SAM Threat Scale & SAM Self Control Scale). A significant positive correlation was also found between LF-HRV and scores in the response inhibition ($p = .04$; covariates: Sex, Education, SAM Threat Scale & SAM Other Control Scale). However, no significant correlation was found between LF-HRV and mental flexibility ($p = .68$; covariates: Sex, Education, SAM Threat Scale & SAM Other Control Scale), non-verbal memory ($p = .23$; covariates: Sex, Education, SAM Threat Scale & SAM Other Control Scale), or verbal memory ($p = .88$; covariates: Sex, Education, SAM Threat Scale & SAM Other Control Scale). Results for HF-HRV similarly showed a significant positive relationship with response inhibition ($p < .01$; covariates: Education & SAM Threat Scale) and no significant relationship with mental flexibility ($p = .09$; covariates: Education & SAM Threat Scale), non-verbal memory ($p = .32$; covariates: Education & SAM Threat Scale), and verbal memory ($p = .28$; covariates: Education & SAM Threat Scale). Results for the LF: HF-HRV showed a significant negative relation to mental flexibility ($p = .05$; covariates: Sex, Age, Education & SAM Threat Scale), but showed no significant relationship to response inhibition ($p = .94$; covariates: Sex, Age, Education & SAM Threat Scale), non-verbal memory ($p = .55$; covariates: Sex, Age, Education & SAM Threat Scale), or verbal memory ($p = .16$; covariates: Sex, Age, Education & SAM Threat Scale). Of note, the covariate of sex showed a significant relationship to the LF: HF-HRV score ($p = .05$). (See Table 9 for further details regarding regression for immediate recovery of HRV.)

The regression results for the delayed recovery period (second five minutes) showed a significant negative correlation between HR and mental flexibility ($p = .05$; covariates: Sex, Education, SAM Threat Scale & SAM Self Control Scale) and response inhibition ($p = .02$; covariates: Sex, Education, SAM Threat Scale & SAM Self Control Scale). However, non-verbal memory ($p = .53$; covariates: Sex, Education, SAM Threat Scale & SAM Self Control Scale) and verbal memory tests were non-significant ($p = .99$; covariates: Sex, Education, SAM Threat Scale & SAM Self Control Scale). No significant correlation was found LF-HRV and scores response inhibition ($p = .07$; covariates: Sex, Education, SAM Threat Scale & SAM Other Control Scale), mental flexibility ($p = .60$; covariates: Sex, Education, SAM Threat Scale & SAM Other Control Scale), non-verbal memory ($p = .41$; covariates: Sex, Education, SAM Threat Scale & SAM Other Control Scale), or the verbal memory ($p = .11$; covariates: Sex, Education, SAM Threat Scale & SAM Other Control Scale). Results for HF-HRV showed a significant positive relationship with response inhibition ($p = .01$; covariates: Education & SAM Threat Scale). However, mental flexibility ($p = .41$; covariates: Education & SAM Threat Scale), non-verbal memory ($p = .46$; covariates: Education & SAM Threat Scale), and verbal memory ($p = .18$; covariates: Education & SAM Threat Scale) were non-significant. The results of LF: HF-HRV showed no significant relation to mental flexibility ($p = .10$; covariates: Sex, Age, Education & SAM Threat Scale), response inhibition ($p = .28$; covariates: Sex, Age, Education & SAM Threat Scale), non-verbal memory ($p = .65$; covariates: Sex, Age, Education & SAM Threat Scale), or verbal memory ($p = .51$; covariates: Sex, Age, Education & SAM Threat Scale). Of note, the

covariate of sex again showed a significant difference in LF: HF-HRV ($p = .02$). (See Table 10 for further details regarding regression for delayed recovery of HRV.)

Table 8

Regression Scores for Blood Pressure Variability During the Recovery Period

PHYSIOLOGICAL MEASURES	COGNITIVE FACTORS			
	Trails Ratio Score (Secs) *(B, p)*	Stroop Score (T-score) *(B, p)*	Verbal Memory (0-70) *(B, p)*	Non-verbal Memory (0-50) *(B, p)*
BP - Systolic (Mean Recovery)	.01, .95	.09, .25	.06, .41	.08, .32
BP – Diastolic (Mean Recovery)	.15, .06	.02, .81	.01, .87	.10, .22

N = 209

* = $p < .05$

** = $p < .01$

Table 9

Regression Scores for Heart Rate Variability during the Immediate Recovery Period

PHYSIOLOGICAL MEASURES	COGNITIVE FACTORS			
	Trails Ratio Score (Secs) *(B, p)*	Stroop Score (T-score) *(B, p)*	Verbal Memory (0-70) *(B, p)*	Non-verbal Memory (0-50) *(B, p)*
Heart Rate (Mean Immediate Recovery)	-.16*, .04	-.19**, .01	.01, .99	-.12, .11
LF-HRV (Mean Immediate Recovery)	.01, .98	.18**, .01	-.09, .21	.02, .82
HF-HRV (Mean Immediate Recovery)	.13, .09	.21**, .00	-.07, .32	.08, .28
LF: HF-HRV (Mean Immediate Recovery)	-.15*, .05	-.01, .94	.04, .55	-.10, .16

N = 209

* = $p < .05$

** = $p < .01$

Table 10

Regression Scores for Heart Rate Variability During the Delayed Recovery Period

PHYSIOLOGICAL MEASURES	COGNITIVE FACTORS			
	Trails Ratio Score (Secs) *(B, p)*	Stroop Score (T-score) *(B, p)*	Verbal Memory (0-70) *(B, p)*	Non-verbal Memory (0-50) *(B, p)*
Heart Rate (Mean Delayed Recovery)	-.15*, .05	-.17*, .02	.01, .99	-.05, .53
LF-HRV (Mean Delayed Recovery)	-.04, .59	.14, .07	-.11, .11	.06, .41
HF- HRV (Mean Delayed Recovery)	.06, .41	.21**, .01	-.09, .18	.05, .46
LF: HF-HRV (Mean Delayed Recovery)	-.13, .10	-.08, .28	.05, .51	-.03, .65

N = 209

* = $p < .05$

** = $p < .01$

A Bonferroni correction was instituted to ensure that statistical significance does not falsely occur due to multiple comparisons. In this case, the Bonferroni corrected value used was based on the number of independent variables (four) and covariates (between two and seven) used for each regression. The results of the Bonferroni correction for the task period showed a non-significant correlation between LF-HRV and response inhibition ($p = .16$). The corrected results for the immediate post-task recovery period showed a non-significant correlation for HR ($p = .06$) and response inhibition. However, LF-HRV ($p = .04$), and HF-HRV ($p = .02$) had a significant positive relationship with response inhibition. Additionally, there was no significant correlation between HR ($p = .26$) or LF: HF-HRV score ($p = .19$) and mental flexibility. The corrected results for the delayed post-task recovery period did not show a significant correlation between HR and response inhibition ($p = .14$) or mental flexibility ($p = .34$). However, HF-HRV ($p = .02$) and response inhibition continued to show a significant positive correlation.

CHAPTER VI

DISCUSSION

It was hypothesized that those individuals with higher levels of cognitive function would exhibit significantly lower levels of stress reactivity and significantly higher levels of post-task recovery. However, there was only one significant result in the task found after the regression analysis, a significant positive relationship between LF-HRV and Stroop Interference scores. However, that result was shown to be non-significant after a Bonferroni correction analysis was applied. Given the depth of literature regarding BP and HRV reactions to stress, it was expected that more significant relationships would have been seen in the task period. These findings need further investigation to determine why the reactions in this study did elicit similar reactions to previous studies including those using similar data from the same larger study. The two most likely possibilities for explaining such a difference from the literature are related to the method of calculation used in this study. Many of the studies that reported significant findings used singular task measures compared to an individual baseline. The current study utilized averaged scores for both the cognitive variables and the physiological measures used. The reason for averaging these measures was to better represent trait abilities of participants with regards to cognitive performance and physiological reactivity rather than using a representation of a single instance, making them more generalized to a variety of circumstances. The other difference seen between the current study and others cited earlier is the use of residual change scores. Residual change scores are computed by comparing task reactivity and recovery scores recorded during physiological testing to estimates of ideal individual reactivity and recovery scores mathematically predicted

using an individual's own baseline scores. Thus, while previous studies generally compared simple change scores (those scores obtained comparing individuals to an overall average from participants), the current study compares an individual's reactivity and recovery scores to ideals based on his or her own baseline scores to take into account individual differences in reactivity. These differences were less prevalent in the recovery period than the task period, but may have played the same role in seeing fewer results than expected. It is possible that in averaging scores for physiological reactivity, some amount of difference between subjects was removed due to the tasks being in sequence and a lack of time between tasks to allow all participants to recover back to baseline norms and, therefore, recovery differences may influence subsequent task differences.

In the immediate recovery period, the corrected results show that response inhibition performance appears to be a significant predictor of changes in both HF-HRV and LF-HRV changes during recovery from an evoked stressor. Furthermore, response inhibition showed a positive correlation with both HF-HRV and LF-HRV; that is to say that individuals who performed better on the Stroop Interference task had a tendency to show significantly higher levels of HRV change than predicted when presented with psychologically taxing stressor tasks. This may suggest that those individuals who possess greater response inhibition trait abilities (as represented by Stroop Interference Task scores) are able to recover more quickly following a stressful task than those with poor response inhibition abilities, who do not fully recover and have decreased HRV. Given that both HF-HRV (parasympathetic) and LF-HRV (sympathetic and parasympathetic) showed significant differences in relation to Stroop Interference scores, it may suggest that both parasympathetic and sympathetic processes differ in those with

greater response inhibition as opposed to those with relatively weaker response inhibition abilities. However, given that LF: HF-HRV showed no significant relationship to response inhibition, it is more likely that vagal influence may play a greater role in these differences and sympathetic responses play lesser role.

In the delayed recovery period, those with higher scores in response inhibition continued to show evidence of a significant relationship with HF-HRV changes while LF-HRV was no longer significant. However, the direction of these changes remained consistent in the delayed period. Thus, those with those with better scores on a test of response inhibition evidenced greater changes in HF-HRV. As previously mentioned, HF-HRV primarily reflects respiratory-modulated parasympathetic outflow, whereas LF-HRV is subject to both substantial sympathetic influence and varying amounts of parasympathetic contribution. Given that HF-HRV continued to show a significant relationship to response inhibition while LF-HRV did not, this would provide further support that individuals with better response inhibition abilities are likely to show significantly better cardiovascular recovery stemming from vagally controlled parasympathetic influences. Alternatively, given the differences seen LF-HRV during the task and immediate recovery period, it is possible that superior response inhibition abilities may also have some effect on sympathetic influences affecting autonomic arousal. Thus, the LF-HRV differences seen may relate to sympathetic and parasympathetic influences while HF-HRV differences seen extending into the delayed recovery period are more likely due to the ongoing vagally controlled parasympathetic influences after the differences in sympathetic influence have reduced between these groups due to the removal of the external stressor. However, whether response inhibition

affects sympathetic reaction to a stressor or not, the results do suggest that response inhibition abilities may play a significant role in influencing parasympathetic activity during recovery from a cardiovascular stressor.

It should also be noted that prior to the Bonferroni correction a number of other significant findings were present and should be discussed. The most consistent of these findings is related to HR and cognitive factors. Specifically, HR was found to be significantly negatively related to both response inhibition and mental flexibility both in the immediate and delayed recovery period. Said another way, greater ability in either response inhibition or mental flexibility were associated with less change than expected in HR throughout the recovery period. While these findings seem counterintuitive given the HRV findings, it may simply be that HR is not a very clear indicator of cardiovascular response to stress as several covariates were found to have an effect on heart rate. Another possibility is that such findings may simply suggest that those with better cognitive function are less likely to have less of a response during the task period and, thus, produce less change in the recovery period. Given that a similar pattern of negative correlation was found with LF: HF-HRV during the immediate task recovery period, this may also suggest that those with lower scores on cognitive measures evidence greater sympathetic change during recovery. Several regressions also showed some large but non-significant differences in HR an LF: HF-HRV related to mental flexibility scores. It may be that mental flexibility is related to change in sympathetic activity. An additional issue that does need to be noted is that inhibition does play a role in the mental flexibility (Trails B) task (as inhibition is needed to efficiently accomplish switching between numbers and letters) as well. Thus, at least some of the differences seen may be

related to a common response inhibition and mental flexibility component, such as a greater ability to handle multiple or complex tasks. As this ability was less prominent in the memory tasks, it may explain why those tasks showed no significant relationship to physiological measurements. One future avenue of further study may be to delineate whether a specific ability like response inhibition or some more complex group of abilities, such as a multi-tasking ability (one that may include the ability to divide attention between multiple tasks, plan or prioritize between them, and inhibit all but the most important tasks), may more accurately reflect differences found in HRV. Finally, while a number of covariates were found to have a significant relationship with both cognitive and physiological variables utilized here, participant sex had a particularly strong relationship to LF: HF-HRV. Several previous studies have suggested that a relationship between sex and HRV may be affected by female hormone levels. Greater HRV and vagal activity has been found in the follicular phase (Sato et al., 1995; Saeki et al., 1997) and greater sympathetic activity during the luteal phase (Guasti et al., 1999; Yildirir et al., 2002) compared with other phases of the menstrual cycle have been reported. Previous research has also suggested greater sympathetic activity during peak progesterone levels of the luteal phase (Sato et al., 1995; Guasti et al., 1999; Yildirir et al., 2002) and increased HR and lower HRV in post-menopausal women following combined oestrogen/progesterone hormone replacement therapy (HRT) (Christ et al. 2002) as possible evidence that progesterone may cause vagal inhibition. Such differences are most likely to be highlighted by in LF: HF-HRV scores which look more clearly at sympathetic influences in HRV.

Regarding the previous findings by Waldstein and Katzel (2005) discussed earlier, the current study failed to replicate their findings with regard to systolic and diastolic BP reactivity. Additionally, the findings in the previous study regarding logical memory were not found to be significantly related to any autonomic measure utilized in the current study. The marginally significant findings related to the Trail Making Test in the current study were not found to be significant by Waldstein and Katzel. There are several reasons that this may have occurred. The most likely of these reasons is that Waldstein and Katzel used individual test scores rather than collapsed trait scores to compare individuals. The delayed recall measures in the Waldstein and Katzel study were less significant than the immediate recall measures for both systolic and diastolic BP, only achieving marginal significance with diastolic BP. It is possible that in combining all Logical Memory measurements into a single score may have led to a much more conservative measurement in this case. The current study also utilized residual change scores, or deviation from predicted individual change, rather than raw change differences. Waldstein and Katzel also did not utilize any correction procedures which could have further lead to the differences seen here. It should also be noted that in the current study as well as in the Waldstein and Katzel (2005) study, BP measures covaried with a number of affective measures and other relevant factors, thus making smaller significant findings difficult to attain. That said, it should be noted that response inhibition (as measured by Stroop Interference scores) was found to be a significant factor related to both systolic and diastolic BP by Waldstein and Katzel (2005) was also shown to be a significant factor related to both LF-HRV and HF-HRV recovery in the current study. Given that this cognitive test was most similar to the one utilized in the Walstein and Katzel, it is

certainly worth considering that this factor may play a significant underlying role in autonomic reactivity. To a lesser degree, HR was also implicated in being affected by response inhibition giving further credence to this consideration. Taking into account the previous findings and those in the current study, there is certainly strong evidence that inhibition plays a significant role in response and recovery to environmentally evoked stressors. Given the importance of pre-frontal inhibition in other behavioral contexts, it would certainly make intuitive sense that these same pre-frontal regions play a critical role is regulating stressor evoked reactions. There is significantly less evidence that other cognitive factors play a critical role in autonomic reactivity and recovery. It may be that these factors simply play a much less direct role in the process than inhibition and the current paradigm may be limited in not seeing those contributions. Certainly, the neuropsychological tasks utilized to tap these domains may not portray the most accurate representation of these abilities when pertaining to stressor evoked responses. As mentioned earlier, it is possible that a more complex group of cognitive abilities are responsible for such autonomic differences with response inhibition only being part of a larger picture. One additional avenue of research utilized in the current study is discussed by Treiber et al., (2001), who have suggested the possibility that such reactivity patterns may not be most accurately seen using static methods such as averaging scores, but rather through a time series curve that estimates changes. While HRV may be considered a time series measurement, BP and HR were not analyzed using a time series approach in the current study. However, this is a promising area of interest that may lead to further discovery regarding the effect that cognitive factors have on autonomic abilities, particularly given the significant findings related to HRV found in the current study.

CHAPTER VII

CONCLUSION

The current study does provide evidence that superior performance in response inhibition was significantly positively associated with both LF-HRV ($p = .04$) and HF-HRV ($p = .02$) in the immediate recovery phase and HF-HRV ($p = .02$) in the delayed recovery phase. These findings would suggest that response inhibition likely plays a significant role is vagally controlled HRV recovery from stress, but a less significant, if any, role affecting sympathetic influences. However, a number of questions remain with regard to the role cognitive abilities may play in BP reactivity and recovery as Waldstein and Katzel (2005) found significant relationships to cognitive abilities, but the current study failed to replicate those findings. Additionally, no significant relationship was seen between any cognitive domains and HRV during the task reactivity period. While, there has not been much literature tying cognitive abilities to task reactivity, there are a significant number of previous work that suggests significant differences in task reactivity. While it is certainly possible that cognitive performance does not affect task reactivity and only has a significant impact in the recovery period, the question remains whether the methods of data reduction and calculation in the current study were too conservative. Alternatively, the use of standard static measures for BP and HR may have contributed to the lack of findings and time series measure of change for such physiological measures may uncover significant differences. Studies using data reduction and calculation methods found more commonly in the literature as well as those utilizing a more complex time series measure would clarify whether the significant and non-significant findings in the current study are due to differences in calculation between

studies or if complex physiological differences are at play in HRV recovery that may not be seen in other physiological measures.

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