Ethnicity and Pain: Psychosocial Stress and Stress Responses

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ABSTRACT

Mary Beth Mechlin: Ethnicity and Pain: Psychosocial Stress and Stress Responses
(Under the direction of Susan S. Girdler)

The purpose of this study was to examine biopsychosocial factors related to ethnic
differences in pain sensitivity. Forty-four African Americans (22 men, 22 women) and 44
non-Hispanic Whites (22 men, 22 women), recruited to be of equivalent SES, were tested for
pain sensitivity to ischemic pain, cold pressor pain, and the temporal summation of heat
pulses. There were no ethnic differences in perceived stress, but African Americans reported
more frequent discrimination than non-Hispanic Whites. African Americans had similar pain
thresholds, but lower pain tolerance to both the ischemic and cold pressor pain tasks.
Additionally, African Americans exhibited enhanced temporal summation relative to non-
Hispanic Whites. When examining ethnic differences in cardiovascular and neuroendocrine
variables, African Americans had lower baseline cortisol than non-Hispanic Whites.
However, there were no ethnic differences in blood pressure, norepinephrine, or cortisol
responses to stress. Regression analyses indicated that, biological variables (heart rate,
systolic blood pressure, and norepinephrine) predicted pain sensitivity in non-Hispanic
Whites, while psychosocial variables (income, education, discrimination) predicted pain
sensitivity in African Americans. The results of these studies suggest that there may be
ethnically-related differences in biopsychosocial pain regulatory mechanisms.
ACKNOWLEDGMENTS

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<tr>
<td>ACTH</td>
<td>Adrenocorticotropic Hormone</td>
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<tr>
<td>ALLO</td>
<td>Allopregnanalone</td>
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<td>ANOVA</td>
<td>Analysis of Variance</td>
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<td>BDI</td>
<td>Beck Depression Inventory</td>
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<td>BP</td>
<td>Blood Pressure</td>
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<td>CNS</td>
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<td>CRH</td>
<td>Corticotropin Releasing Hormone</td>
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<td>Diastolic Blood Pressure</td>
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<td>Experiences of Discrimination</td>
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<td>EPI</td>
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<td>GHI</td>
<td>Gross Household Income</td>
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<td>HPA</td>
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<td>HR</td>
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<td>Locus Coeruleus</td>
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<td>Nociceptive Flexion Reflexes</td>
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<td>PSR</td>
<td>Pain Sensitivity Range</td>
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<td>PSS</td>
<td>Perceived Stress Scale</td>
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<td>SBP</td>
<td>Systolic Blood Pressure</td>
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<td>SES</td>
<td>Socioeconomic Status</td>
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<td>SIA</td>
<td>Stress Induced Analgesia</td>
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<tr>
<td>SNS</td>
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CHAPTER 1
INTRODUCTION

I. Clinical and Experimental Pain Perception in Blacks.

*Blacks Report Higher Pain Severity and More Pain Interference Associated with Chronic Pain and other Medical Conditions*

Numerous studies indicate that Blacks experience more clinical pain (Edwards et al. 2001b; McCracken et al. 2001; Riley et al. 2002b) and report more pain associated with chronic medical conditions (Edward et al. 2001a) than Whites\(^1\). For example, Edwards et al. (2001b) found that among individuals with a variety of chronic pain conditions, Blacks reported greater perceived pain severity than did Whites, as measured by the Multidimensional Pain Inventory and McGill Pain Questionnaire. Blacks also reported greater pain-related disability, which was assessed by examining the amount of time it took participants to walk 100 yards and by responses on pain questionnaires that address the extent to which pain impacts daily activities. Similarly, in Blacks and Whites receiving treatment for chronic pain, McCracken et al. (2001) found that Blacks rated their pain as more severe than did Whites. Additionally, Blacks endorsed more avoidance of pain and activity, fearful thinking about pain, and pain-related anxiety. In another study involving chronic pain patients, Blacks rated their current pain higher than Whites, and indicated more

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\(^1\) Since researchers have used a variety of terms to describe an individual’s race or ethnicity, for simplicity sake, the background section refers to individuals as either Black or White. Groups that were described as African American, Negro, or Black will be referred to as Black. Groups that were described as Caucasian, non-Hispanic White, or White will be referred to as White.
suffering and disability as a result of the pain (Green et al. 2003). Ruehlman et al. (2005) examined a sample of chronic pain patients, and found that while Blacks and Whites reported similar levels of pain, Blacks reported greater pain-related interference in their daily lives than did Whites, even after controlling for age, gender, and level of education. Portenoy et al. (2004) surveyed chronic pain patients and found that Blacks reported a higher severity of pain on average over the past week and reported missing more work as a result of the pain than Whites, though there were no ethnic differences in reports of the most severe pain experienced in the last week. Tan et al. (2005) also found greater pain severity among Blacks seeking treatment for pain than among Whites seeking treatment for pain. Cano et al. (2006) found that, of individuals with chronic pain, Blacks reported higher levels of pain, pain interference, and pain-related disability relative to Whites, even after controlling for ethnic differences in education level. In a sample of patients with rheumatoid arthritis, Blacks also reported more pain than Whites, even after adjusting for ethnic differences in age, sex, education, disease duration, comorbidities, and use of disease modifying antirheumatic drugs (Bruce et al. 2007). Similarly, Golightly et al. (2005), found that among veterans with osteoarthritis, Blacks experienced greater physical pain and reduced physical functioning relative to Whites, even after controlling for a variety of factors, including gender, income, education level, and employment status. Another study reported that Black cancer patients reported more pain, higher symptom distress, and lower functional status than White cancer patients, even after controlling for education, gender, marital status, and employment status (Vallerand et al. 2005). In a sample of preschool children (ages 4-6), Black children reported more earaches, more pain in the jaw while opening or chewing, and more palpation pain in the jaw area than Whites (Widmalm et al. 1996). Husain et al. (2007)
found that in a sample of 4,000 patients undergoing treatment for depression, Blacks were significantly more likely to experience pain than their White counterparts. Blacks also have a higher prevalence of systemic lupus erythematosus, which frequently causes severe joint pain (Buckwalter et al. 2000; Jordan et al. 2002), and have a higher prevalence osteoarthritis of the knee (Jordan et al. 2002).

On the other hand, some studies have found very few or no ethnic differences in clinical pain. Riley et al. (2002b) did not find any ethnic difference in ratings of pain intensity among chronic pain patients; but, they did find that Blacks reported their chronic pain as more unpleasant than Whites did. Another study examining a chronic pain population found no differences between Blacks and Whites in ratings of pain on the McGill Pain Questionnaire or the Multidimensional Pain Inventory or Visual Analogue Scale ratings of pain intensity (Edwards et al. 2005). However, this study matched the Black and White samples for age, sex, education, work status, pain location, and pain duration, which the authors postulated was the reason for a lack of ethnic differences in chronic pain ratings. Riley et al. (2002a) found no ethnic differences in the prevalence or pain ratings of orofacial pain in a mixed gender sample of older adults, but they did find that orofacial pain had a greater behavioral impact (i.e. limiting physical activity or taking medication) on Blacks relative to Whites. Additionally, there were no differences in socioeconomic status (SES) between the Black and White samples, indicating that ethnic differences in SES may be related to ethnic differences in chronic pain. In another study, healthy undergraduate students surveyed over the phone were asked about their pain. The authors did not observe any ethnic differences in the number of times pain was experienced in the past 6 months or the intensity of pain experienced in the past 6 months (Hastie et al. 2005), but again the
Blacks and Whites in this study were of equal SES. One study even found that in a sample of healthy women, Black women were less likely to report experiencing face/jaw pain than White women, even after adjusting for SES (Plesh et al. 2002).

In summary, while there have been discrepancies in the literature, the vast majority of studies indicate that, in general, Blacks experience more clinical pain than Whites for a variety of chronic pain conditions. Additionally, Blacks frequently report greater pain interference in their daily lives, and may have a higher prevalence of certain chronic pain conditions. While the reasons for the discrepancies in ethnic differences in studies on self-reports of clinical pain intensity are unknown, it appears likely that they are the result of ethnic differences in SES of the sample participants since studies that controlled for SES of participants generally found no ethnic differences in chronic or clinical pain. Therefore, the dissertation study described in the following chapters controls for SES in order to address this gap in the literature. The ethnic differences in chronic pain may especially be a concern for treatment. A recent study indicated that when examining differences in the ratings of a patient’s pain by the patient and his/her physician, the physician underrated the experience of pain in the patient significantly more for Black patients than White patients (Staton et al. 2007). Additionally, Blacks tend to be under prescribed analgesics for their pain relative to White patients (Todd et al. 2000).

Blacks are more sensitive to Experimental Pain

In the laboratory, studies have demonstrated that experimental pain may be predictive of clinical pain since inverse relationships exist between ischemic pain tolerance and reported clinical pain severity among chronic pain populations (Edwards 2001b; Fillingim et al.
1996), and in healthy women, daily ratings of pain correlate with ratings of experimental pain (D’Antono et al. 1999). Moreover, a recent longitudinal study showed that in pain free females, sensitivity to a thermal heat stimulus was a significant predictor for the onset of chronic pain conditions (Diatachenko et al 2005). Therefore, studies comparing Blacks with other ethnic groups during experimental pain stimuli may help to clarify the nature of ethnic differences in clinical pain.

In contrast to the discrepancies that exist in clinical pain outcomes, laboratory based studies consistently indicate no ethnic differences in pain onset (i.e. pain threshold) but that Blacks have reduced pain tolerance relative to Whites. This is true for thermal heat pain (Chapman & Jones 1944; Edwards & Fillingim 1999; Campbell et al. 2005; Mechlin et al. 2005), cold pressor pain (Campbell et al. 2005; Mechlin et al. 2005), ischemic pain (Campbell et al. 2005; Mechlin et al. 2005), and pressure pain (Woodrow et al. 1972). A study by Sheffield et al. (2000) also indicated that when a thermal heat stimulus of a particular degree was applied to the forearm of participants, Blacks rated the pain from the stimulus as more intense and more unpleasant than did Whites. While many studies have indicated these ethnic differences in pain perception, it is still unclear why these differences exist. One study (Rahim-Williams et al. 2007) examined ethnic differences in pain threshold and tolerance to thermal heat pain, cold pressor pain and ischemic pain. The authors then calculated a pain sensitivity range (PSR) by subtracting an individual’s pain threshold from his/her pain tolerance. Blacks had significantly lower PSRs in response to the thermal heat pain and cold pressor pain tasks, and a marginally lower PSR to the ischemic pain task. However, when scores on a measure of ethnic identity were used as covariates in the analyses, the ethnic differences in PSRs for the thermal heat pain and ischemic pain tasks
were no longer significant, but the ethnic difference in PSR for the cold pressor pain task remained significant. This suggests that ethnic identity may be one factor contributing to ethnic differences in pain sensitivity, but is clearly not the only factor, as ethnic differences in PSRs for the cold pressor task remained significant after controlling for ethnic identity.

Nociceptive Flexion Reflexes (NFRs) are also used to study pain sensitivity and are most commonly studied by electrically stimulating the sural nerve and then measuring the withdrawal response in the ipsilateral biceps femoris muscle. NFR thresholds are generally determined by the amount of electrical stimulation necessary to produce an increase in electromyographic activity of the biceps femoris muscle of at least 1.5 standard deviations. Decreased NFR thresholds are believed to be indicative of increased pain sensitivity (Edwards et al. 2007). This method can be beneficial as it decreases the subjective aspect of pain sensitivity reports. A recent study found that Blacks had a decreased NFR threshold relative to Whites, indicating increased pain sensitivity (Campbell et al. 2008).

In summary, the results of laboratory-based studies indicate that Blacks consistently exhibit increased pain sensitivity, especially lower pain tolerance, to a variety of experimental pain procedures in laboratory settings. While the biobehavioral mechanisms contributing to increased pain sensitivity in Blacks are unknown, recent reports from our laboratory (Mechlin et al. 2005, 2007) indicate that there may be ethnic-related differences in endogenous pain regulatory mechanisms including sympathetic nervous system (SNS) and Hypothalamic-pituitary-adrenal (HPA)-axis factors (see below).
II. Increased Central Sensitization is associated with Greater Clinical and Experimental Pain

Another physiological mechanism that may contribute to increased clinical pain in African Americans is central sensitization. Central sensitization is an increase in dorsal horn neuronal membrane excitability that results in a state of hyperalgesia at the site affected (Mannion & Woolf 2000). Since the threshold of stimulation for nociceptive afferents is decreased, pain can be elicited by stimuli that were previously nonpainful (Mannion & Woolf 2000). Central sensitization can be approximated through temporal summation of heat pulses. The temporal summation procedure is an experimental model that can be used to study spinal cord neuronal mechanisms involved in central sensitization and the resulting hyperalgesia (Herrero et al. 2000). It is important to emphasize that while temporal summation and central sensitization do share some common mechanisms, such as expansion of the receptive field (Li et al. 1999), central sensitization is not synonymous with temporal summation, and in fact central sensitization can occur in the absence of temporal summation (Laird et al. 1995; Woolf 1996; De Felipe et al. 1998). The temporal summation procedure utilizes repetitive C-fiber stimulation that leads to a nonlinear increase in the response of the dorsal horn neurons resulting in hyperalgesia (Mannion & Woolf 2000). Increased sensitivity to temporal summation has been seen in a variety of clinical pain conditions, including spinal cord injury (Eide 2000), fibromyalgia (Staud et al. 2001), and temporomandibular disorders (Maixner et al. 1998). While it is not clear whether increased sensitivity to temporal summation precedes or is the result of chronic pain conditions, females (Fillingim et al. 1998) and older adults (Edwards & Fillingim 2001b), two populations who report higher levels of clinical pain (Crook et al. 1984; Unruh 1996), exhibit increased sensitivity to this procedure. This indicates a possibility that sensitivity to temporal
summation may precede chronic pain conditions, as well as provides further support for the clinical relevance of the temporal summation procedure.

While many studies have shown that Blacks exhibit increased sensitivity to peripherally induced experimental pain (Chapman & Jones 1944; Woodrow et al. 1972; Edwards & Fillingim 1999; Sheffield et al. 2000; Campbell et al. 2005; Mechlin et al. 2005) and a prior report from our lab found evidence for an ethnic difference in endogenous pain regulatory mechanisms (Mechlin et al. 2005), no studies of which we are aware have examined the possibility that increased pain sensitivity in Blacks may also involve centrally mediated spinal cord pathways.
III. Sympathetic Nervous System and Hypothalamic-Pituitary-Adrenal-Axis Responses to Stress: Endogenous Pain Regulatory Mechanisms

Research has documented that during exposure to extreme stress, animals and humans display marked reductions in pain sensitivity, a phenomenon known as Stress-Induced Analgesia (SIA). Mice that are exposed to forced swim stress or a foot shock subsequently display increased latency to tail-flick, indicative of decreased sensitivity to pain (Ford & Finn 2008). In humans, studies have found increased pain tolerance to a conditioned stimulus that was previously paired with a mental arithmetic stressor (Flor et al. 2002). SIA provides an evolutionary advantage since it is adaptive for an organism faced with a stressor to use its resources to combat the stressor, rather than attending to any pain. Therefore, stress responsive systems are believed to play a role in the experience of SIA, and hence be related to pain perception.

The SNS and HPA-axis are components of the “fight-or-flight response” and serve to stimulate, organize, and mobilize energy resources in situations that are potentially threatening (Pinel 2007). Research indicates that the amygdaloid complex, in conjunction with other parts of the limbic system, integrates and evaluates incoming information and then initiates the stress response via activation of the SNS and HPA-axis (Sah et al. 2003; Bilkei-Gorzo et al. 2008). Activation of these systems results in increases in the availability of glucose, heart rate (HR), cardiac output, systemic vasodilation, blood pressure (BP), and ventilation (Vander et al. 2001), all serving to give the body the necessary resources for managing an acute stressor.
Sympathetic Nervous System

Activation of the SNS usually begins with the stimulation of the noradrenergic cell bodies in the locus coeruleus (LC), which release norepinephrine (NE). The sympathetic nerves also stimulate the release of both epinephrine (EPI) and NE from the adrenal medulla. NE and EPI both bind to the $\beta_1$ – receptors on the heart, causing an increase in both HR and contractility, leading to an increase in cardiac output, the total amount of blood pumped out of the heart per minute (Vander et al. 2001). This increased cardiac output results in more oxygen being carried to working muscles during the defense reaction.

The SNS is also responsible for BP increases in response to stress. BP can be raised by increasing cardiac output (which occurs when HR or stroke volume increases) and/or increasing total peripheral resistance. This increase in BP in response to stress aids in increasing blood flow to muscles and organs that are needed to fight the stressor and in decreasing blood flow from muscles and organs that are not essential in meeting the physical demands of the stressor.

Hypothalamic-Pituitary-Adrenal (HPA) Axis

The HPA-axis is also activated by the central nervous system (CNS) during stress. When a stressful stimulus is perceived, the CNS signals the hypothalamus to release corticotropin releasing hormone (CRH). CRH travels to the anterior pituitary via the hypothalano-pituitary portal vessels, and stimulates the release of adrenocorticotropic hormone (ACTH) and $\beta$-endorphin into the blood stream. The ACTH in the blood stream then stimulates the release of cortisol by the adrenal cortex. Cortisol has a variety of
downstream effects including mobilizing the body’s fuel sources, enhancing vascular reactivity, and inhibiting certain immune responses. The hormones released by the HPA-axis also serve to regulate the axis via negative feedback. For example, increased concentrations of CRH, ACTH, and cortisol result in a subsequent decrease in CRH released from the hypothalamus (Vander et al. 2001). While the SNS generally reacts to acute stress almost immediately, the HPA-axis has a more delayed response to stress. For example, in healthy participants exposed to the Trier Social Stress Test (TSST), a psychosocial stress test that involves a mock interview and mental arithmetic, cortisol levels peak 25 – 30 minutes after the initiation of the stress protocol (Kirschbaum et al. 1993; 1995a, 1995b), while NE levels peak 5 – 10 minutes after the initiation of the stress protocol (Simeon et al. 2007).

While many of the functions of cortisol are documented, less is known about the role that β-endorphin, and other endogenous opioids play in the body. β-endorphin acts on both μ and δ receptors, with a greater affinity for δ receptors (Akil et al. 1984). These receptors are present in the hypothalamus, pituitary, adrenal cortex, adrenal medulla, and the nucleus tractus solitarius, which regulates autonomic function (Akil et al. 1984). Animal studies have documented increased levels of β-endorphin in response to a foot-shock stress in rats (Rossier et al. 1977) and hamsters (Huhman et al. 1990), social conflict stress, particularly in submissive animals, in rats (Dijkstra et al. 1996) and hamsters (Huhman et al. 1990), handling stress in mice (Hale et al. 2003), and a tail pinch and fox odor stress in rats (Marinelli et al. 2004). Additionally, in rats, acute administration of β-endorphin results in increased levels of ACTH (VanLoon & DeSouza 1978) and corticosterone (Haracz et al. 1981), but when β-endorphin is chronically administered, no change in ACTH is observed (VanLoon & DeSouza 1978). In humans, β-endorphin concentrations have been shown to
increase in response to a speech stressor (Sheps et al. 1995). Contrary to what has been observed in animals, one study found that i.v. administration of β-endorphin in humans resulted in decreased plasma concentrations of ACTH and cortisol, possibly indicating the role of β-endorphin in the negative feedback loops of the HPA-axis (Taylor et al. 1983). It has also been suggested that β-endorphin may be involved in promoting immune functioning (Gatti et al. 1993).

While the SNS and HPA-axis are generally thought of as functioning independently, they work together to prepare the body to deal with stress. Administration of CRH increases the LC firing rate, resulting in an increase in the release of NE (Chrousos & Gold 1992). Cortisol enhances vascular reactivity, therefore increasing the ability of vascular smooth muscle to constrict blood vessels in response to NE. Additionally, EPI also stimulates the secretion of ACTH, and NE helps to stimulate the release of CRH (Chrousos & Gold 1992) both resulting in an increase in release of cortisol as well (Vander et al. 2001). Redundancy in function of these two axes is likely adaptive to ensure adequate physiological response to acute stress. This idea is partially supported by the fact that both systems can be stimulated by serotonin and acetylcholine and inhibited by GABA, indicating a similar pathway of biological activation (Chrousos & Gold 1992).
IV. Allostatic Load and Chronic Stress: Impact on Physiological Stress Responses

Allostasis is the process by which the body seeks stability through change (McEwen 1998). This is particularly relevant when understanding the body’s coordinated responses to stress. For example, stress causes the release of CRH from the hypothalamus, which causes ACTH to be released from the anterior pituitary; ACTH in turn stimulates the release of cortisol from the adrenal cortex. Cortisol has many downstream effects that help the body to deal with stress, including an increase in blood glucose level, which provides feedback to the hypothalamus to decrease the release of CRH. Additionally, cortisol is involved in a negative feedback loop, so that an increase in levels of cortisol result in the decrease of ACTH secretion and consequently the decrease of further cortisol secretion, allowing the body to return to its resting state following the cessation of stress. Frequent exposure to stress, and consequently to allostatic processes, can result in a maladaptive change in stress responsive systems leading to what is referred to as allostatic load. While allostasis is considered to be an adaptive response to acute stress, allostatic load is considered to be a maladaptive response to chronic stress. In addition to stress, genes, development, and lifestyle choices can contribute to allostatic load. Three conditions are reflective of allostatic load: 1) failure to adapt to a repeated stressor, 2) a prolonged response to stress without recovery from the stressor, and 3) an inadequate response to future acute stressors (McEwen 1999). For example, after repeated elevations of BP in response to frequent stress exposure, a diminished and insufficient increase in BP in response to a subsequent stressor may develop, reflective of allostatic load. Longitudinal studies have reported that higher baseline allostatic load, as reflected in biological measures such as BP and cholesterol levels, is associated with increased risks of cardiovascular disease, decline in functioning, and
mortality (McEwen 1999). These findings indicate that chronic stress may diminish the ability of an individual to respond to new challenges (McEwen 1998).

While opposite effects have been reported (Chen & Matthews 2001; Kapuku et al. 2002), further evidence for this hypothesis has been supported by studies indicating that chronic stress is associated with a decreased cardiovascular and neuroendocrine response to acute stress (Gump & Matthews 1999; Barnes et al. 2000; Musante et al. 2000; Matthews et al. 2001; Suchday et al. 2005). A review of studies examining the relationship between chronic stress and stress reactivity by Gump and Matthews (1999), reported that in 3 out of 4 studies examining occupational stress, higher occupational stress was related to reduced BP and HR increases in response to acute stress. A recent study by Matthews et al. (2001) used a perceived stress scale, job satisfaction, and relationship satisfaction as measures of chronic stress. Their results indicated that individuals with higher levels of chronic stress exhibited blunted SBP, EPI, and NE responses to an acute speech and math task. Musante et al. (2000) found that adolescents who reported more stressful life events in the past year on the Adolescents Resources Challenge Scale exhibited decreased HR and BP responses to a car driving simulation. Additionally, lower family SES was associated with blunted BP, HR, and cardiac output reactivity to a social stressor interview. In a sample of patients with coronary artery disease, higher SES predicted greater SBP and DBP responses to a laboratory serial subtraction mental stressor (Suchday et al. 2005), indicating that the low SES individuals may have exhibited a blunted BP response to stress. Among children, Barnes et al. (2000) observed that the lower SES group exhibited blunted HR reactivity to mental stressors relative to the higher SES group. Additionally, blunted cortisol responses have been observed in chronically stressed individuals. For example, one study found that white
collar workers who reported a higher work load exhibited a blunted diurnal cortisol rhythm (Caplan et al. 1979), and Hansen et al. (2006) found that employees that reported more bullying at work exhibited a blunted cortisol response to awakening stress.

It is well established that Blacks experience more psychosocial stress than Whites, including racism and bigotry (Anderson et al. 1992), and experience more chronic stress, such as unemployment, poverty, lower social status, and substandard housing (Anderson et al. 1992; Troxel et al. 2003). We therefore postulate that Blacks generally have a greater allostatic load than Whites.
V. Ethnic Differences in Cardiovascular and Neuroendocrine Responses to Stress

Ethnic Differences in Blood Pressure and Hemodynamic Measures during Stress

Ethnic differences have been reported for BP and hemodynamic responses to stress. A variety of studies have documented greater increases in BP to laboratory stress in Blacks (Murphy et al. 1986; Light et al. 1987; Anderson et al. 1988b; Anderson et al. 1989; McAdoo et al. 1990; Treiber et al. 1990; Treiber et al. 1993; Dysart et al. 1994; Murphy et al. 1995; Duey et al. 1997; Thomas et al. 2006). On the other hand, some studies have observed decreased BP responses to stress (Fredrikson 1986; Anderson et al. 1988a; Falkner & Kushner 1989; Light et al. 1993; Mechlin et al. 2005; Wilcox et al. 2005) in Blacks relative to Whites. However, the study by Light et al. (1993) found decreased BP responses to stress in Blacks only in response to 1 of 5 stressors, and only in the male sample. There were no ethnic differences in BP reactivity in response to any of the tasks for females, and 4 of the 5 tasks for males, similar to another study (Terrell & Manuck 1996) which found no ethnic differences in BP reactivity.

While the research examining ethnic difference in BP responses to stress has yielded mixed results, more consistent are the findings that Blacks exhibit greater vascular reactivity to stress (i.e. larger increases in total peripheral resistance in response to stress; Treiber et al. 1990; Light et al. 1993; Treiber et al. 1993; Dysart et al. 1994; Terrell & Manuck 1996), while Whites have greater cardiac reactivity to stress (i.e. larger increases in cardiac output or HR; Fredrikson 1986; Anderson et al. 1988a; Light & Sherwood 1989; Falkner & Kushner 1989; Light et al. 1993; Dysart et al. 1994; Treiber et al. 1993; Terrell & Manuck 1996; Barnes et al. 2000). However, some studies have found increased HR responses to stress in Blacks relative to Whites (Murphy et al. 1986; Murphy et al. 1995), or no significant ethnic

While the reason for these discrepancies is currently unknown, multiple possibilities exist. One possibility is that ethnic differences in BP and HR responses to stress may depend on the nature of the stressors used (psychological vs. physical). For example, McAdoo et al. (1990) observed a main effect of race, indicating increased SBP and DBP reactivity in Blacks relative to Whites in response to a cold pressor test and an isometric handgrip test, but found no differences in BP reactivity for 3 psychological stressors (Stroop test, mental arithmetic, mirror trace). However, there was a race x gender interaction for 3 of the tasks, since Black females showed increased BP reactivity relative to White females to the cold pressor task, and decreased reactivity relative to White females to the arithmetic and Stroop tasks, while there were no ethnic differences in BP reactivity for the males. Further support for this is provided by the fact that the majority of the studies using physiological stressors (i.e. cold pressor, isometric handgrip, phenylephrine infusion, etc.) report increased BP reactivity in Blacks relative to Whites (Light et al. 1987; Anderson et al. 1988b; Treiber et al. 1990; Treiber et al. 1993; Dysart et al. 1994; Murphy et al. 1995; Duey et al. 1997; Thomas et al. 2006), while the majority of studies using psychological stressors (i.e. speech, arithmetic, Stroop test, etc.) report decreased BP reactivity in Blacks relative to Whites or no ethnic differences in BP reactivity (Fredrikson 1986; Anderson et al. 1988a; Falkner & Kushner 1989; Light et al. 1993; Terrell & Manuck 1996; Mechlin et al. 2005; Wilcox et al. 2005).

Similarly, for studies examining ethnic differences in HR reactivity, all except for one study (Murphy et al. 1995) in which a physiological challenge was presented found no ethnic differences in HR responses to stress (Light et al. 1987; Anderson et al. 1988b; McAdoo et
al. 1990; Treiber et al. 1990; Light et al. 1993; Treiber et al. 1993; Dysart et al. 1994; Duey et al. 1997). The study implemented by Murphy et al. (1995) was a longitudinal study, in which a psychological stressor (videogame task) was used at 5 time points, while the physiological stressor (isometric exercise) was used at 1 time point. In this study, analyses were not conducted separately by stressor type, which is the most likely explanation for finding an increased HR stress response in Blacks for a physiological stressor. The findings for ethnic differences in HR reactivity to stress are less consistent when a psychological stressor is used.

However, some contradictions to the disparate finding concerning ethnic differences in BP and HR reactivity to stress being the result of the type of task used do exist. Light et al. (1993) found no ethnic differences in BP reactivity in response to a physiological challenge (forehead cold pressor test), and 4 studies observed increased BP reactivity in Blacks in response to a psychological stressors (Murphy et al. 1986; Light et al. 1987; Dysart et al. 1994; Murphy et al. 1995). Therefore, age may also be a factor in documenting increased BP reactivity in Blacks to psychological stressors, as 3 of the 4 studies that observed increased BP reactivity among Blacks relative to Whites were conducted in children (Murphy et al. 1986; Dysart et al. 1994; Murphy et al. 1995). All of the studies conducted in individuals 18 years old or younger reported increased BP reactivity in Blacks relative to Whites (Murphy et al. 1986; Treiber et al. 1990; Treiber et al. 1993; Dysart et al. 1994; Murphy et al. 1995), and the studies conducted exclusively in older populations (ages 40 and above) reported decreased BP reactivity in Blacks relative to Whites (Fredrikson 1986; Wilcox et al. 2005). However, the results of studies conducted in individuals in between these ages have yielded mixed results. In individuals aged 18 to 30, some studies
have found increased BP reactivity in Blacks (Light et al. 1987; Anderson et al. 1988b; McDaid et al. 1990; Treiber et al. 1990; Duey et al. 1997), while others observed decreased BP reactivity in Blacks relative to Whites (Anderson et al. 1988a; Falkner & Kushner 1989), and one found no ethnic differences in BP responses to stress (Terrell & Manuck 1996).

Similarly, both studies that found increased HR responses to stress in Blacks were conducted in children (Murphy et al. 1986; Murphy et al. 1995), and decreased HR responses to stress in Blacks were observed more frequently when the sample used included individuals over the age of 40 (Fredrikson 1986; Light et al. 1993; Wilcox et al. 2005).

It is possible that during the ages of 18 and 30, the effects of increased psychosocial stress, resulting in an increased allostatic load, experienced by Blacks relative to Whites may begin to have a deleterious effect on stress-responsive physiological systems. Since increased allostatic load can take varying forms including failure to adapt to a repeated stressor, a prolonged stress response, and an inability to fully adapt to new stressors (i.e. a blunted stress response) it is possible that different studies are observing various responses to increased allostatic load. For example, studies that documented increased BP or HR responses to stress among Blacks may have been observing a failure to adapt to a repeated stressor (i.e. exposure to cold as demonstrated in the cold pressor task), while studies that documented decreased BP or HR responses to stress among Blacks may have been observing an inability to fully adapt to new stressors (i.e. the Stroop test). Further support for this is provided by the fact that studies conducted in older populations tend to document decreased HR and BP reactivity in Blacks relative to Whites (Fredrikson 1986; Light et al. 1993; Mechlin et al. 2005; Wilcox et al. 2005), indicating that the increased exposure to stressors
may have resulted in physiological changes leading to a general wearing down of stress-responsive systems and an inability to fully adapt to new stressors.

*Ethnic Differences in Resting and Stress HPA-axis Measures*

Ethnic differences in neuroendocrine responses to stress have not been as well studied as cardiovascular responses, and similar to BP and HR responses to stress, results have been mixed. Multiple studies have found no difference in 24-hour urinary cortisol levels between Black and White women (Yanovski et al. 1993, 1996, 2000) or in overnight urinary cortisol secretion in a mixed-gender sample of Blacks and Whites (Masi et al. 2004). Additionally, no differences in basal levels of cortisol were found between Blacks and Whites in a sample of veterans (Boyle et al. 2007) or in postmenopausal women (Giannopoulou et al. 2003; Wilcox et al. 2005). On the other hand, other studies have reported lower mean 24-hour urinary cortisol levels (Grewen et al. 2005) and lower levels of baseline plasma cortisol (Pratt et al. 1999; Mechlin et al. 2005) in Blacks relative to Whites.

The literature regarding ethnic differences in cortisol responses to stress is also mixed. Studies have observed no ethnic difference in cortisol levels after an exercise challenge (Yanovski et al. 2000), CRH stimulation (Yanovski et al. 1993, 1996), ACTH stimulation (Yanovski et al. 1996), or dexamethasone suppression (Yanovski et al. 1993) between Black and White women. In postmenopausal women studies have documented an increased peak cortisol response to exercise in Blacks relative to Whites (Giannopoulou et al. 2003), and that Blacks were more likely to show an increase in cortisol concentrations in response to a speech task (Wilcox et al. 2005). However, the majority of studies that find ethnic differences in the cortisol response to stress observe blunted reactivity in Blacks. For
example, a recent study observed a blunted cortisol response in Blacks to a psychological stressor relative to Whites (Chong et al. 2008), and our recent study found lower levels of cortisol at rest and in response to stress in Blacks (Mechlin et al. 2005).

In addition to typical laboratory stress tasks, researchers have examined the cortisol response to awakening, as it represents a natural, physiological stressor. One study conducted in adults (Cohen et al. 2006) and another conducted in adolescents (DeSantis et al. 2007) observed lower cortisol levels upon awakening in Blacks relative to Whites, reflecting a blunted cortisol stress response in Blacks. Additionally, in both studies, Blacks had higher cortisol levels at bedtime, which resulted in Blacks exhibiting flattened cortisol diurnal slopes relative to Whites. In adolescents these differences existed even after controlling for age, gender, depression, nicotine use, stress, emotion, SES, and amount of sleep (DeSantis et al. 2007). When examining females caring for an individual with dementia, McCallum et al. (2006) reported lower cortisol levels at awakening and flattened diurnal cortisol slopes were observed in Blacks relative to Whites. Similarly, Bennett et al. (2004) found that Blacks with lower levels of education had a blunted cortisol response to awakening stress relative to Whites, while Blacks with higher levels of education did not differ from Whites in their cortisol response to awakening stress. The flattened diurnal cortisol slope that was consistently observed in the Black samples (Cohen et al. 2006; McCallum et al. 2006; DeSantis et al. 2007) also provides support for the idea that Blacks experience increased allostatic load, as a flattened diurnal cortisol slope has also been associated with working more hours and poor relationship quality in a sample of White women (Adam & Gunnar 2001). Additionally, a study conducted in pregnant women found that, while cortisol levels
increased in White and Hispanic women from the 25th to the 31st week of pregnancy, cortisol levels decreased in Black women during this time period (Glynn et al. 2007).

While there are some inconsistencies in the literature regarding ethnic differences in the cortisol response to stress, all studies examining cortisol levels in response to awakening stress observed lower cortisol concentrations in Blacks relative to Whites (Bennett et al. 2004; Cohen et al. 2006; McCallum et al. 2006; DeSantis et al. 2007). However, when an external physiological stressor was employed, all except for one study observed no ethnic differences in the cortisol stress response (Yanovski et al. 1993, 1996, 2000). The only study that observed a greater cortisol response to a physiological stressor in Blacks (Gainnopoulou et al. 2003) was conducted in an older population (ages 50 – 61). Therefore, it is probable that the age of participants studied also influences ethnic differences in the cortisol response to stress, as when psychological stressors were employed in a younger sample (ages 18 – 47), Blacks exhibited blunted cortisol responses to stress relative to Whites (Mechlin et al. 2005; Chong et al. 2008), while when a study using a psychological stressor was conducted in an older population (ages 54- 74) Blacks exhibited an increased cortisol response to stress relative to Whites (Wilcox et al. 2005).

To our knowledge, no studies have been conducted examining ethnic differences in β-endorphin responses to stress. However, our previous study (Mechlin et al. 2007) reported no differences in baseline concentrations of β-endorphin between Blacks and Whites.

_Ethnic Differences in Resting and Stress Norepinephrine Levels_

Another stress responsive measure that has been studied in Blacks is NE. One study found that Blacks had higher 24-hour urinary NE levels than Whites (Grewen et al. 2005).
Masi et al. (2004) observed higher overnight urinary NE levels in Blacks relative Whites; however, when the authors controlled for the higher creatinine concentrations in Blacks, there were no longer ethnic differences in NE levels.

A variety of studies have reported no ethnic differences in plasma NE concentrations at baseline or in response to stress, including a cold pressor test (Stein et al. 2000; Dimsdale et al. 1990; Tischenkel et al. 1989), exercise (Tischenkel et al. 1989), a structured interview (Tischenkel et al. 1989), a math task (Dimsdale et al. 1990), and a video game task (Tischenkel et al. 1989). Similarly, two studies found no ethnic differences in diurnal changes in catecholamines (Yamasaki et al. 1998; Lichtman & Woods 1967). However, some studies have found that while no ethnic differences exist at baseline, Blacks had blunted NE responses to psychological stress (Mechlin et al. 2005) and an exercise test (Walker et al. 1992). On the other hand, Light et al. (1994) found similar baseline levels of NE in Blacks and Whites, but reported that Blacks exhibited greater increases in NE in response to a psychological stressor. While the reasons for these discrepancies are unclear, one possibility is ethnic differences of SES of the participants. Although few studies included any SES measures, the studies that reported no ethnic differences in SES of the participants also observed no ethnic differences in NE reactivity (Tischenkel et al. 1989; Dimsdale 1990), while the study that reported lower SES among Blacks also observed a blunted NE stress response among Blacks (Mechlin et al. 2005). This is consistent with prior research indicating blunted NE responses to stress among chronically stressed individuals (Matthews et al. 2001).

In summary, while results are mixed, the majority of the findings indicate that Blacks exhibit increased BP reactivity, decreased cortisol reactivity and similar NE and HR
reactivity to stress relative to Whites. However, as noted earlier, opposite results have been reported for each of these measures. While the reasons for the discrepancies in the literature concerning heightened vs. blunted cardiovascular and neuroendocrine reactivity to stress in Blacks are unclear, multiple possibilities exist, in particular age and SES of participants, and type of stress task employed, since each of these factors has been shown in other research to influence the magnitude of stress responses. Additionally, another possibility for discrepancies may involve differences in sample selection, since most of the existing research has included a Black sample that included individuals of both African descent and Caribbean descent. This is particularly relevant since one study indicated differences in cardiovascular reactivity to stress in Black Caribbean Americans as compared to Black African Americans (Arthur et al. 2004). Therefore, the dissertation project presented in the following chapters was designed to address some of these issues by: 1) including only African Americans born in the United States in order to control for differences that may be present among varying Black ethnic groups, 2) matching African Americans and non-Hispanic Whites for SES, 3) Matching the African Americans and non-Hispanic Whites for age, 4) the use of a well-validated mental stressor protocol.
VI. The Nature and Characteristics of Psychosocial Stress in Blacks

The vast majority of work on ethnic differences in acute stress responses and pain sensitivity has not examined the role chronic stress may play in these differences. The idea that ethnic differences in acute stress responses may be related to ethnic differences in chronic stress is supported by the study of Bennett et al. (2004), which found that Blacks with lower levels of education had a blunted cortisol response to awakening stress relative to Whites, while Blacks with higher levels of education did not differ from Whites in their cortisol response to awakening stress. Therefore, examining ethnic differences in chronic stress exposure is necessary to further explore ethnic differences in pain perception and cardiovascular reactivity to acute stress.

Blacks have higher mortality rates and lower life expectancies than their White counterparts (Pappas et al. 1993; Williams & Collins 1995) for a variety of medical conditions including systemic lupus erythematosus (Anderson et al. 2008), breast cancer (Lund et al. 2008), lung cancer (Birdsey et al. 2007) idiopathic pulmonary arterial hypertension (Davis et al. 2008), invasive cutaneous melanoma (Zell et al. 2008), liver transplantation (Neff et al. 2007), a percutaneous coronary intervention (Pradhan et al. 2008), sepsis (Barnato et al. 2008), and heart disease (American Heart Association 2008).

Many have postulated that these health disparities are the result of Blacks generally being of lower SES than Whites (Ulbrich et al. 1989; Anderson et al. 1992; Williams & Collins 1995; Troxel et al. 2003), since lower SES is strongly linked to worse health outcomes (Pappas et al. 1993; Adler et al. 1994). Individuals of lower SES report more stressful events, lifetime traumatic events, and chronic stressors than do those of higher SES (Adler et al. 1994; Turner et al. 2003). A recent study examining ethnic differences in
diurnal cortisol levels in adolescents found that the parents of the Black individuals in the study were less educated and more likely to be on welfare than the parents of the White adolescents (DeSantis et al. 2007). Additionally, in that same study the Black adolescents reported more chronic stress, but not more episodic life event stress, than the Whites adolescents (DeSantis et al. 2007).

Related to SES, Blacks are more likely to live in poverty stricken neighborhoods than Whites (Drake & Pandey 1996; Wallace et al. 2003). This is of particular relevance since individuals living in poverty are more likely to experience physical abuse, sexual abuse, and child neglect (Schellenbach et al. 1991; Gelles 1992; Murata 1994; Drake & Pandey 1996). It has, therefore, been suggested that early life poverty is harmful to an individual’s health because stress regulatory mechanisms are damaged by excessive exposure to cumulative environmental risks, including traumatic stressors. Evidence for this is provided by a study by Evans & Kim (2007) which found that a longer duration of poverty exposure in childhood was associated with elevated overnight urinary cortisol and blunted SBP and DBP reactivity to stress in a sample of adolescents.

Additionally, research indicates that individuals of lower SES generally have fewer psychological and social resources to help cope with stress, and therefore have worse emotional functioning than high SES individuals in response to a stressor (Kessler 1979). However, Kessler (1979) observed that while non-Whites (a group consisting of Blacks and Puerto Ricans) reported more exposure to stress than Whites, no difference in average reports of distress were observed between Whites and non-Whites; but, non-Whites had a larger proportion of individuals reporting extreme distress. Kessler concluded that, on average,
even though non-Whites may be exposed to greater levels of stress, they may be able to more accurately cope with stress, resulting in no difference in reports of perceived stress.

In a more recent study examining exposure to stressors in children in grades 6 through 9, stressors were divided into 5 different dimensions: recent life events, total lifetime major events, chronic stressors, lifetime major discrimination, and daily discrimination. Blacks reported experiencing significantly more stressors in all five dimensions relative to Whites (Turner et al. 2003). The authors then examined ethnic differences in reports of stress based on classification of low, middle, or high SES, and still found that Blacks reported more total stress (a composite of the 5 dimensions) than non-Hispanic Whites in all 3 SES groups (Turner et al. 2003). However, ethnic differences in the individual stressor measures did differ by SES group. In the low SES group, Blacks reported more stressors in all 5 dimensions, in the high SES group Blacks reported more stressors in every dimension except recent life events, and in the middle SES group Blacks only reported a greater experience of chronic stressors and total lifetime major events. Ulbrich et al. (1989) examined 3 types of stressors in adults (average age 40): economic, health events, and undesirable events. Additionally, the individuals were classified as low, middle, or high SES. In all SES groups, Blacks reported more economic concerns, while Whites reported experiencing more health events and undesirable events. However, when examining the impact of the stressors on feelings of psychological stress, while economic concerns were associated with psychological distress in all individuals studied, health events were only associated with psychological distress in Blacks, and undesirable events were only associated with psychological distress in low-SES Blacks. Additionally, in the low-SES group, Blacks reported increased feelings of psychological stress in general relative to Whites. Therefore,
the studies of Turner et al. (2003) and Ulbrich et al. (1989) indicate that ethnic differences in exposure to stressors and the impact of stressors may differ by SES.

Discrimination is also an ethnically relevant stressor, as it is experienced more frequently among Blacks both throughout their lifetime and on a day to day basis than among Whites (Thompson 1996; Kessler et al. 1999; Schulz et al. 2000), and may be especially prevalent in lower SES neighborhoods (Turner et al. 2003; Chen & Paterson 2006). Studies have indicated that experiences of perceived discrimination strongly predict distress and major depression (Kessler et al. 1999; Schulz et al. 2000, 2006; Vines et al. 2006). Ethnic discrimination is considered by most experts to be a chronic stressor and may be one of the causes of ethnic disparities in health (James 2003; Broudy et al. 2007), including hypertension. For example, Krieger found that Black women who kept quiet and accepted unfair treatment had a greater prevalence of hypertension relative to White women (Krieger 1990). While the pathways in which chronic perceived discrimination negatively impacts health are currently unknown, research indicates that acute episodes of racism repeatedly over time may tax coping resources, changing the way individuals view and cope with their ongoing experiences (Brondolo et al. 2005; Broudy et al. 2007).

In summary, Blacks generally experience more chronic and traumatic stress as a result of their increased likelihood of living in poverty, decreased SES, and more chronic stress in the form of discrimination, regardless of SES (Schulz et al. 2000). All of these factors have been associated with worse physical and mental health, and may help to explain the increased pain sensitivity in Blacks relative to Whites.
VII. Cardiovascular, Neuroendocrine and Somatosensory Interactions: Influence on Pain Perception

*Higher Blood Pressure is Associated with Decreased Pain Sensitivity*

There is a well-established literature showing that higher BP is associated with decreased pain sensitivity (i.e. higher pain threshold or higher pain tolerance; Zamir & Shuber 1980; Maixner 1991; Bruehl et al. 1992; Sheps et al. 1992; Bragdon et al. 1997, 2002; al’Absi et al. 2000; Sheffield et al. 2000; Edwards & Fillingim 2001a; Campbell et al. 2004; Bacon et al. 2006; Lewkowski et al. 2008; Ring et al. 2008). For example, Zamir and Shuber (1980) tested normotensive and hypertensive males for sensitivity to tooth pulp stimulation. Results indicated that pain thresholds were higher in the hypertensive group than in the normotensive group. Additionally, even when the subjects were divided into groups of younger adults and older adults instead of by hypertensive status, there were significant positive correlations between pain thresholds and BP in both groups. Sheps et al. (1992) found that when thermal heat pain was applied to the forearm, pain thresholds and pain tolerance were positively related to mean arterial pressure in both normotensive and hypertensive subjects. In a study by Bruehl et al. (1992) there was a positive correlation between systolic blood pressure (SBP) and the pain rating of pressure applied to the middle finger in normotensives. Al’absi et al. (2000) examined normotensive women and classified them as either higher-BP or lower-BP via median splits. The higher-BP group reported cold pressor pain as less intense than the lower-BP group did. Bragdon et al. (2002) found that higher levels of SBP were positively correlated with higher heat pain threshold and tolerance in men but not women. Edwards & Fillingim (2001a) observed correlations between higher
SBP and higher ischemic and thermal heat pain thresholds and tolerances in a primarily Caucasian sample. A study conducted in coronary heart disease patients found that in response to an exercise stress test, patients who experienced pain during the test had lower peak levels of SBP, even after controlling for exercise duration and baseline cardiovascular variables (Bacon et al. 2006). Similarly, Ring et al. (2008) found that the decreased pain sensitivity to sural nerve stimulation following exercise was mediated by exercise-induced increases in BP.

_Individuals at Risk for Hypertension Display Decreased Pain Sensitivity_

Interestingly, decreased sensitivity to pain may even precede the development of hypertension, as individuals who are at risk for hypertension generally display less sensitivity to pain. A longitudinal study observed that lower ratings of pain intensity to a finger pressure pain in 14 year old White males were associated with higher SBP and diastolic blood pressure (DBP) at both the 5 year (Campbell et al. 2002) and 7 year follow-up visits (Campbell et al. 2003). Additionally, in that same study, Campbell et al. (2002) found that the participants with a parental history of hypertension reported the pressure pain as less severe than those without a parental history of hypertension. D’Antono et al. (1999) also observed that White women with normal-high BP and a parental history of hypertension rated cold pressor and finger pressure pain as less severe than those with low-normal BP or without a parental history of hypertension. Ditto et al (1997) observed that in a sample of White women, those with a parental history of hypertension and increased BP reactivity to a stress task rated shock-induced pain as less severe.
Nociceptive Flexion Reflexes (NFRs) have also been used to study the relationship between BP and pain sensitivity, with decreased NFR thresholds indicating increased pain sensitivity (Edwards et al. 2007). A recent study, found that normotensive individuals with a parental history of hypertension rated electrocutaneous pain as less intense than individuals without a parental history of hypertension. However, when comparing hypertensives and normotensives, no difference was observed in the NFR thresholds or reports of pain intensity to electrocutaneous stimulation (Edwards et al. 2007). Similarly, a recent study conducted in a primarily (76%) White sample (al’Absi et al. 2005), compared individuals with and without a parental history of hypertension for differences in NFR thresholds. While no differences were found in NFR thresholds, men with a parental history of hypertension reported less pain to the electrical stimulation than men without a parental history of hypertension, but this effect was not observed in women (al’Absi et al. 2005). However, France et al. (2001) found that NFR thresholds were higher in both men and women with a parental history of hypertension, indicating decreased pain sensitivity. Additionally, research indicates that individuals with a parental history of hypertension also have higher temporal summation thresholds of NFR, as measured by an NFR not being stimulated by the 1st pulse, but by one of the subsequent stimulations in a train of 5 pulses, relative to individuals without a parental history of hypertension (France et al. 2002b).

In summary, higher BP is associated with decreased pain sensitivity, even in normotensive individuals. The relationship between a family history of hypertension and decreased pain sensitivity in normotensive individuals suggests that the factors that underlie the development of hypertension may also underlie the development of increased pain sensitivity and influence pain sensitivity even before the establishment of elevated BP. This
is supported by evidence that lowering BP levels via medications or other treatments in hypertensives fail to alter their hypoalgesic responses (Ghione et al. 1988); and is consistent with the suggestion that individuals at risk for hypertension may exhibit enhanced activation of descending pain modulation pathways prior to the development of hypertension (France et al. 2002b). Taken together, the studies mentioned above demonstrate a robust finding that there is a relationship between higher BP and reduced pain sensitivity; however, these studies were conducted in primarily White participants.

While, some studies have found relationships between BP and pain sensitivity in samples that include Blacks (Bragdon et al. 1997; Sheffield et al 2000; Campbell et al. 2004), none of these studies conducted analyses separately by ethnicity to determine if this relationship also existed in Blacks. However, a recent report from our lab did conduct analyses separately by ethnicity and found that higher SBP was correlated with higher pain tolerance (decreased pain sensitivity) to thermal heat, cold pressor, and ischemic pain tasks in Whites; however, no significant relationships between SBP and pain tolerance were observed in Blacks (Mechlin et al. 2005).

Examining the relationship between BP and pain sensitivity in Blacks may help to elucidate the apparent paradox that Blacks have a higher prevalence of hypertension (American Heart Association 2008), yet increased pain sensitivity. Indeed, one study has shown that in chronic pain patients higher BP is associated with increased pain sensitivity (Bruehl et al. 1998).
The Role of Baroreceptors in the Relationship between Blood Pressure and Pain Sensitivity

The relationship between increased BP and reduced pain sensitivity is thought to be mediated by BP-induced stimulation of mechanoreceptive afferents (i.e. baroreceptors), which are involved in maintaining homeostasis. Baroreceptors are located in the carotid sinus, aortic arch, and cardiopulmonary regions of the cardiovascular system. They respond to increases in arterial pressure or blood volume, and subsequently cause an increase in parasympathetic output, which generally involves vasodilation and decreasing HR and cardiac output (Maixner 1989). Dworkin et al. (1979) studied 2 groups of rats: one with denervated baroreceptors, and a control group. The rats were taught to run on a wheel as a means of escaping aversive trigeminal nerve stimulation. On test days, rats were either infused with phenylephrine, which increases BP, or saline. The results indicated that when infused with phenylephrine control rats displayed less escape behavior to the aversive stimulation than when infused in saline. In the denervated rats, there was no difference in escape behavior based on phenylephrine or saline infusion. Similarly, other studies have found that stimulation of baroreceptor afferents in animal models has been shown to diminish somatomotor reflexes, such as tail-flick and paw licking in response to the hot plate test, indicative of analgesic-like effects (Randich & Maixner 1986; Maixner 1989, 1991).

In humans, studies have examined the relationship of pain sensitivity to natural variations in baroreceptor activation, as baroreceptors are more active during systole (the active cardiac contraction phase) than during diastole (the passive cardiac filling phase). Droste et al. (1994) observed the most severe pain ratings to an electrical pain stimulus when baroreceptors were artificially inhibited during diastole. Edwards & Fillingim (2001a) observed decreases in NFR thresholds during systole, when baroreceptors were naturally
stimulated, relative to diastole. However, a recent study (al’Absi et al. 2005) found that while no differences in pain ratings to an electrocutaneous stimulus were observed during artificial stimulation or inhibition of the baroreceptors, participants reported less pain during systole than during diastole. Similarly, another study by Edwards and colleagues (2003) did not observe any changes in NFR thresholds when baroreceptors were artificially stimulated, but did observe increased NFR thresholds during systole. Taken together, these results indicate that natural, but not always artificial, baroreceptor activation may be related to decreases in pain sensitivity (al’Absi et al. 2005).

It has been shown that Blacks have decreased baroresponses to transient BP elevation by administration of phenylephrine (an $\alpha$-adrenergic receptor agonist which causes an increase in BP) relative to Whites during wakefulness and sleep (Crisostomo et al. 1998), and that Blacks show different BP responses to postural changes relative to Asians and Whites; both findings are indicative of alterations in baroreceptor function (Goldstein & Shapiro 1995). As has been postulated for the absence of BP-pain sensitivity relationships in chronic smokers, which is thought may come about via frequent BP surges associated with smoking and a desensitization of the baroreceptor reflex pathway (Girdler et al. 2005), we hypothesize that larger stress-induced BP responses to real-life stress in Blacks, especially if occurring in the context of frequent stress exposure resulting from racism, poverty, crime, and/or lower SES (Anderson et al. 1992) may repeatedly activate baroreceptor mechanisms and, over the long-term, contribute to a desensitization of the baroreceptor reflex pathway and an uncoupling of BP-pain sensitivity relationship (Mechlin et al. 2005). Further support for this comes from studies indicating that in chronic pain patients the relationship between BP and pain sensitivity is either non-existent or in the opposite direction as expected (Bruehl et al.
1998, 2002, 2008; Bragdon et al. 2002). Consequently, these differences in baroreceptor functioning might explain the apparent paradox that Blacks have a higher prevalence of hypertension (American Heart Association 2008), yet increased sensitivity to experimental pain and more clinical pain.

*The Role of Neuroendocrine Factors in Pain Sensitivity*

In addition to activation of baroreceptors, the relationship between BP and pain sensitivity may involve endogenous opioids. McCubbin and Bruehl (1994) examined relationships between BP and perceived pain of a cold pressor task and a handgrip task following administration of either saline or naloxone, an opioid receptor antagonist. In the saline group there was a significant correlation between higher SBP and lower ratings of cold pain; however, there were no significant correlations between BP and ratings of the handgrip pain. No significant correlations were observed between BP and pain ratings for subjects in the naloxone group for either pain test. Similarly, Lewkowski et al. (2008) tested patients for pain sensitivity after administration of placebo and naltrexone. The results indicated that individuals with higher resting SBP had a higher pain tolerance and lower ratings of pain unpleasantness to a cold pressor pain task. Additionally, only in participants with higher DBP levels did naltrexone decrease pain tolerance to the cold pressor task. McCubbin et al. (2006) categorized normotensive participants as either “high-normal” or “low-normal” for BP and then tested them for sensitivity to cold pressor pain, once after administration of naltrexone and once after administration of placebo. The authors observed a negative correlation between resting SBP and the total score on the McGill Pain Questionnaire in both groups, indicating that higher SBP was associated with decreased pain sensitivity.
Additionally, only in the “high-normal” BP group did naltrexone result in an increase of pain ratings relative to placebo, further analyses indicated that this was especially true in participants with a parental history of hypertension. However, one study conducted in a mixed ethnicity sample found that higher ischemic pain thresholds and lower ratings of finger pressure pain intensity were associated with higher SBP and DBP, but naloxone administration did not alter pain thresholds or intensity, nor did it alter the relationship between BP and pain (Bruehl et al. 2002). In another primarily (77%) White sample, individuals with a parental history of hypertension rated electrocutaneous pain as less intense, and this finding was not altered by the administration of naltrexone, indicating that the relationship between BP and pain sensitivity may not be mediated by endogenous opioids (France et al. 2005). Therefore, while the possibility exists that the relationship between BP and pain is mediated by endogenous opioids, the evidence remains inconclusive.

Within the context of the defense reaction, studies have shown that higher plasma concentrations of NE, (Sagen et al. 1991; Girdler et al. 2005; Mechlin et al. 2005) cortisol (al’Absi et al. 2002; Girdler et al. 2005; Mechlin et al. 2005, 2007), and β-endorphin (Straneva et al. 2002; Mechlin et al. 2007) are associated with higher pain tolerance in primarily White samples. Injection of β-endorphin is associated with analgesia in animal models, with mice exhibiting decreased pain sensitivity to the tail-flick, hot-plate, and acetic acid writhing tests (Loh et al. 1976; Nemeroff et al. 1979) and tail-flick latency in rats (Tseng et al. 1980). Administration of naloxone (an opioid receptor antagonist) in humans blocks SIA (Willer et al. 1981), and β-endorphin knockout mice do not display swim-stress induced analgesia (Rubinstein et al. 1996). In humans, studies have shown that pain relief is associated with increased endogenous concentrations of β-endorphin immunoreactivity in the
cerebrospinal fluid (Akil et al. 1978; Hosobuchi et al. 1979). Additionally, exposure to a cold pressor stimulus resulted in increased β-endorphin concentrations in healthy adult males (Suzuki et al. 2007). When administered to humans, β-endorphin produces analgesia in clinical pain patients (Hosobuchi & Li 1978), and decreases chest pain in males, but not females (Sadigh et al. 2007). While one study found greater concentrations of β-endorphin after exercise in patients with coronary artery disease were related to decreased severity of angina pain, increased latency to onset of angina pain, and decreased duration of angina pain (Sheps et al. 1987), another found no difference in angina pain with increasing levels of β-endorphin (Jarmukli et al. 1999). However, the study by Sheps et al. (1987) utilized naturally increased concentrations of β-endorphin in response to stress, which resulted in β-endorphin concentrations increasing by approximately 35%, while Jarmukli et al. (1999) administered ketoconzole to participants, resulting in β-endorphin concentrations increasing by approximately 500%. Therefore, Jarmukli et al. (1999), may have elicited supraphysiological levels of β-endorphin, which may explain the lack of effect of increased β-endorphin levels on angina pain sensitivity. More consistent are the findings that higher levels of β-endorphin are associated with increased peripheral pain threshold and tolerance (decreased pain sensitivity; Sheps et al. 1995; Jarmukli et al. 1999; Bragdon et al. 2002; Straneva et al. 2002; Mechlin et al. 2007), though, the relationship between β-endorphin and pain sensitivity was only observed during the follicular, and not the luteal phase of the menstrual cycle (Straneva et al. 2002), and only in Whites, but not Blacks (Mechlin et al. 2007).

Our lab was also the first to study the relationship involving pain perception and allopregnanolone (ALLO) in humans. ALLO is a neuroactive metabolite of progesterone,
which has been shown to have analgesic properties in animals (Kavaliers & Wiebe 1987). ALLO is also stress-responsive, serving to negatively modulate the HPA-axis and facilitate the return to homeostasis following stress. However, a recent report from our lab indicated that while the majority of White women showed the expected stress-induced increase in ALLO, the majority of Black women exhibited a stress-induced decrease in ALLO (Girdler et al. 2006). When examining relationships between ALLO and pain sensitivity, as with other neuroendocrine measures, we found that only in Whites was there evidence for interrelationships involving ALLO, cortisol, and pain sensitivity (Mechlin et al. 2007). While ALLO is not a focus of the formal dissertation study, these results on ALLO add to evidence for ethnically-related differences in biological pain regulatory mechanisms.

**Chronic Stress and Pain**

The relationship of chronic stress to pain perception has not been examined in humans. However, chronic stress has been implicated in the experience of hyperalgesia in animal models via the use of the hot plate test and the formalin test (Vidal & Jacob 1982; Quintero et al. 2000; Gameiro et al. 2005). In the hot plate test, the animal is placed on a hot plate, and latency to lick paws or jump is used as a measure of pain sensitivity. In the formalin test, formalin, a mixture of formaldehyde and saline, is injected into the animal’s hind paw and the animal is observed. The animal is considered to display signs of pain if less weight is placed on the paw that was injected with formalin than on the other paws or if the animal licks or bites the affected paw. In one study, after being subjected to a chronic swim stress rats displayed behaviors consistent with increased pain sensitivity to the hot plate test and formalin test (Quintero et al. 2000). In another study, after repeated exposure to a
cold environment, latency to remove the paw or struggle in response to pressure decreased, indicative of hyperalgesia (Vidal & Jacob 1982). Hyperalgesia was also demonstrated in response to the formalin test after chronic restraint stress in rats (Gameiro et al 2005). Therefore, it is hypothesized that the increased stress experienced by Blacks, by virtue of its long-term effects on BP, NE, and cortisol, may be a mechanism contributing to increased pain sensitivity in Blacks. Our prior work was limited by the fact that psychosocial stressors were not assessed, preventing us from testing this hypothesis. The dissertation project seeks to address this gap by assessing SES, discrimination, and perceived stress in African Americans and non-Hispanic Whites, in order to examine the role that these psychosocial variables may play in ethnic differences in pain perception.

In summary, these relationships between stress-responsive biological mechanisms (i.e. BP, NE, cortisol, ALLO, β-endorphin) and pain sensitivity are thought to reflect an integrated response seen during the defense reaction (Maixner 1989). The defense reaction refers to the cardiovascular and neuroendocrine changes that occur as the result of stress. These changes are intended to prepare the body for “fight or flight.” The defense reaction is characterized by increases in SNS activity such as increases in BP, HR, and cardiac output, and the release of catecholamines (NE), and increases in HPA-axis activity such as the release of ACTH, endogenous opioids (e.g. β-endorphin), and cortisol. Elevations in arterial BP cause stimulation of baroreceptors located in the carotid sinus and the aortic arch, which then results in decreased pain sensitivity. As has been seen with animal models, chronic stress is associated with increased pain sensitivity (Vidal & Jacob 1982; Quintero et al. 2000; Gameiro et al. 2005). This may be the result of frequent exposure to stressors and/or increased reactivity to stressors over time, which may cause a desensitization of the
baroreceptors and an uncoupling of the BP-pain pathway. Therefore, ethnic differences in pain perception may be at least partially be caused by desensitized baroreceptors which are the result of more frequent exposure and greater cardiovascular reactivity to stressors among Blacks compared to Whites.
VIII. Conceptualization of Stress

It is commonly accepted that psychological stress occurs when “an individual perceives that environmental demands tax or exceed his or her adaptive capacity” (Cohen et al. 2007). In most studies psychological stress is operationally defined as either the occurrence of events that are consensually deemed as taxing an individual’s ability to cope or an individual’s responses to these events such as perceived stress or negative affect. The noxious condition which produces the stress reactions is termed the stressor (Lazarus 1966). While many studies have reported that Blacks are subjected to more stressors than Whites (Kessler 1979; Ulbrich et al. 1989; Thompson et al. 1996; Kessler et al. 1999; Schulz et al. 2000; Turner et al. 2003; DeSantis et al. 2007), the literature regarding the psychological impact of these stressors is mixed. While most studies found no ethnic differences in perceived stress (Kessler 1979; Bennett et al. 2004; Wilcox et al. 2005), one study found increased perceived stress in Blacks, but only in certain subgroups (i.e. individuals of lower SES; Ulbrich et al. 1989). Stressful events are not only damaging because of the psychological effects (perceived stress and negative affect) but also the physiological effects that they cause (Cohen et al. 2007). Stressful events activate stress-responsive systems, such as the SNS and HPA-axis, which may result in disease states when frequently or chronically activated (see above). Therefore, when researchers study stress they generally operationalize stress as the stressful event, the psychological response to the stressful event, or the physiological response to the stressful event.

The stressful event is a useful measurement because it allows researchers to examine differences between individuals in their exposure to stressors, and is the cause (both directly and indirectly) of the subsequent psychological and physiological responses. However,
individual differences in the appraisal of the stressful event may result in differences in the psychological and physiological response to the event (Cohen et al. 2007). The psychological response to the stressful event (i.e. perceived stress and negative affect) can provide a useful measurement of stress because it may give rise to psychological disorders such as anxiety and depression (Cohen et al. 2007), unhealthy behaviors such as smoking and lack of exercise (Rozanski et al. 1999), and is associated with increased cardiovascular events (Rozanski et al. 1999). However, difficulties arise when utilizing introspective reports, as social constraints and defenses may influence the validity of an individual’s verbal report (Lazarus 1966). Additionally, there may be individual differences in the interpretation of a word used to indicate an affective state (i.e. the term anxiety might have slightly different meanings across a group of individuals). Furthermore, in order for the psychological response to stress to occur, an individual must first experience a stressful event; therefore, the psychological response to stress is dependent upon the experience of a stressor.

The physiological response to the stressful event (i.e. increases in SNS and HPA-axis activity) can be a useful conceptualization of stress because acute stress responses may be predictive of the development of cardiac disease and can be studied in humans under controlled laboratory conditions (Rozanski et al. 1999). Unlike using psychological responses as an indicator of stress, physiological responses are not subject to difficulties involved with using introspective report or individual differences in interpretations of certain psychological states (Lazarus 1966). Moreover, physiological measurements may be able to detect emotional processes below the level of complete awareness (Lazarus 1966). While physiological measurements of stress also tend to be viewed as more precise and scientific
than psychological measurements of stress, physiological factors tend to vary more on a minute by minute basis relative to psychological factors, making the timing of the measurement extremely important when using physiological variables. Furthermore, when measuring blood hormone levels, there is always the possibility that circulating levels of hormones may not accurately reflect hormone levels in the brain (Lazarus 1966).

Additionally, physiological stress responses to an acute laboratory stressor may not provide the most accurate results as subjects may realize that they are not under any real threat, limiting the generalizability of the results (Lazarus 1966). Finally, similar to the psychological responses, in order for the physiological response to stress to occur, an individual must first experience a stressful event; therefore, the physiological response to stress is also dependent upon the experience of a stressor.

Given the pros and cons of the three operational definitions of stress, in order to examine the relationship between stress and ethnic differences in pain sensitivity in the present study, we chose to operationalize stress as stress exposure, since it is the exposure to stressors themselves that causes the downstream psychological and physiological responses to stress.

Most researchers agree that the increased experience of stressors among Blacks is primarily related to SES (Anderson et al. 1992; Williams & Collins 1995; Drake & Pandey 1996; Troxel et al. 2003; Wallace et al. 2003) and discrimination (Krieger 1990; Thompson 1996; Kessler 1999; Schulz et al. 2000, 2006; James 2003; Vines et al. 2006, Broudy et al. 2007). Lower SES is strongly linked to worse health outcomes (Pappas et al. 1993; Adler et al. 1994), more stressful events, lifetime traumatic events (such as physical abuse, sexual abuse, and child neglect), chronic stressors (Schellenbach et al. 1991; Gelles 1992; Adler et
al. 1994; Murata 1994; Drake & Pandey 1996; Turner et al. 2003), and discrimination (Turner et al. 2003; Chen & Paterson 2006). Additionally, research indicates that individuals of lower SES generally have fewer psychological and social resources to help cope with stress, and therefore have worse emotional functioning than high SES individuals in response to a stressor (Kessler 1979). Ethnic discrimination is also considered by most experts to be a chronic stressor and may be one of the causes of ethnic disparities in health (James 2003; Broudy et al. 2007). Studies have indicated that experiences of perceived discrimination strongly predict distress and major depression (Kessler et al. 1999; Schulz et al. 2000, 2006; Vines et al. 2006). While the pathways in which chronic perceived discrimination negatively impacts health are currently unknown, research indicates that acute episodes of racism repeatedly over time may tax coping resources, changing the way individuals view and cope with their ongoing experiences (Brondolo et al. 2005; Broudy et al. 2007). Therefore, in order to examine ethnically relevant stressors, this study examines the contribution of stressors related to SES and discrimination to ethnic differences in pain perception and stress-responsive physiological systems. Consequently, in order control for the contribution of stressors related to lower SES among Blacks, the Black and White groups were specifically recruited to have equivalent incomes. Matching the individuals for SES also allowed us to focus more strongly on the impact of discrimination stressors on ethnic differences in pain sensitivity. Additionally, to examine ethnic differences in the downstream effects of stress exposure (psychological and physiological responses to stress), perceived stress and cardiovascular and neuroendocrine responses to acute stress were also measured, though they were not our primary measures of stress.
IX. Purpose of Study

The study presented below was designed to address gaps in the literature related to biobehavioral factors that may contribute to ethnic differences in pain sensitivity, with implications for understanding ethnic disparities that exist in clinical pain. Our prior work (Mechlin et al. 2005, 2007), from a single cohort of Black and White men and women, confirmed greater sensitivity to experimental pain in Blacks. Additionally, these studies yielded the first reports of ethnic differences in endogenous (biological) pain modulation. While we hypothesized that greater psychosocial stress exposure may have contributed to both the blunted cardiovascular and neuroendocrine stress responses that we observed (Mechlin et al. 2005) and to the ‘uncoupling’ of any relationship involving cardiovascular, neuroendocrine and somatosensory interactions, that hypothesis was limited by the absence of assessment of psychosocial stress exposure. Consequently, this study was designed to address that gap by examining the associations of chronic discrimination stress as well as exposure to stressors (approximated by SES) with stress reactivity and pain sensitivity in Black and White men and women. The study was designed based on the biobehavioral model presented below.
Consistent with a diathesis-stress model, the biobehavioral model predicts that exposure to chronic and traumatic stress over the lifetime, and specific genetic variants mediating the activity of physiological pathways that underlie pain amplification (Diatchenko et al. 2005), will interact to determine vulnerability to develop clinical pain. This is consistent with two longitudinal studies showing that traumatic stress and greater perceived stress predict the development of clinical pain in initially pain free individuals (Slade et al. 2007; Young Casey et al. 2008).

The proposed model predicts that, in general, lower SES, indexed by lower income, education or occupational status, is one psychosocial factor that both directly and indirectly
influences an individual’s initial response to acute stress. Studies have indicated that low SES represents a chronic stressor, as it is associated with chronic financial problems, substandard housing, legal problems, etc. (Adler et al. 1994) and more experiences of discrimination (Chen & Patterson 2006). Therefore, since lower SES is associated with increased exposure to stressors, the model predicts that individuals of low SES will have more frequent activation of BP, SNS, and HPA-axis mechanisms. Our model also predicts that lower SES indirectly influences stress responses by its association with increased trauma exposure (Schellenbach et al. 1991; Murata 1994; Drake & Pandey 1996) and increased levels of other chronic stressors that are associated with low SES. Specifically, discrimination is experienced more frequently in low SES neighborhoods (Chen & Patterson 2006) and is also considered by most experts to be a chronic stressor and may be one of the causes of ethnic disparities in health (James 2003; Broudy et al. 2007). Therefore, the model predicts that more frequent experiences of discrimination will result in more frequent activation of stress-responsive biological mechanisms.

An overarching guiding hypothesis of the proposed model is that while exposure to psychosocial stressors early in life results in activation of SNS, HPA-axis and other stress responsive measures, chronic and/or repeated exposure to psychosocial stressors will, over time, result in a dysregulation of stress responses and an uncoupling of stress-responsive measures with pain processing. This is consistent with animal and human studies suggesting alterations in the stress response profile over time following traumatic or severe exposure to stressors (Resnick et al. 1995; Heim et al. 2000; Girdler et al. 2007), and we further predict that the uncoupling of BP levels with pain sensitivity involves a desensitization in the baroreceptor pathway due to repeated/chronic BP surges. This hypothesis that initial
heightened stress response may transition to blunted responses with repeated or chronic stress is consistent with research indicating that individuals exposed to high levels of chronic stress display blunted cardiovascular and neuroendocrine responses to acute stress (Gump & Matthews 1999; Barnes et al. 2000; Musante et al. 2000; Matthews et al. 2001; Suchday et al. 2005). Additionally, studies have indicated that individuals exposed to a traumatic stressor early in life display blunted cortisol responses to acute stress (Resnick et al. 1995; Heim et al. 2000; Girdler et al. 2007) and lower resting and stress levels of NE (Girdler et al. 2007) later in life.

The proposed model also predicts that stress-responsive physiological measures may also indirectly influence pain perception via their effect on central sensitization. While little is known about the role of stress in the development of central sensitization, it has been established that chronic pain patients exhibit increased temporal summation, a correlate of central sensitization (Fusco et al. 1997; Maixner et al. 1998; Staud et al. 2001; Price et al. 2002), and it has been speculated that exposure to frequent or major stressors may be involved in the onset of chronic pain conditions, such as fibromyalgia (Bradley 2005; Yunus 2007). Additionally, one study reported that lower cortisol levels upon awakening and a blunted diurnal cortisol slope, findings associated with high levels of chronic stress (Caplan et al. 1979; Hansen et al. 2006), predicted the development of widespread pain (McBeth et al. 2007). Therefore, the model proposes that frequent exposure to stress, as well as increased central sensitization in pain processing, will result in increased pain sensitivity.

Given that Blacks generally experience lower SES and are also exposed to more chronic stressors (Kessler 1979; Anderson et al. 1992; Williams & Collins 1995; Drake & Pandey 1996; Thompson 1996; Kessler et al. 1999; Schulz et al. 2000; Troxel et al. 2003; Turner et
al. 2003; Wallace et al. 2003), both stressors associated with low SES and also the chronic stress of ethnic discrimination, our biobehavioral model may have particular relevance for the development of clinical pain syndromes in Blacks. Indeed desensitization in baroresponses has been documented in Blacks (Goldstein & Shapiro 1995; Crisostomo et al. 1998), which our prior study speculated was the result of frequent BP surges associated with increased exposure to stressors (Mechlin et al. 2005). Additionally, the model proposes that the increased stress exposure may result in an uncoupling of BP-pain mechanisms in Blacks. This is consistent with the results from our previous study (Mechlin et al. 2005), in which Blacks were of lower SES than Whites, and stress-responsive biological measures were related to pain sensitivity in the Whites, but not Blacks.

This study was designed to examine ethnic differences in pain perception by addressing some of the gaps in the literature. Since past studies frequently grouped individuals from a variety of backgrounds into one racial group (i.e. African Americans and Caribbean Americans or Hispanics and non-Hispanic Whites), and one study found that Caribbean Americans some times display cardiovascular reactivity profiles similar to non-Hispanic Whites, while other times displaying cardiovascular reactivity profiles similar to African Americans (Arthur et al. 2004), this study only included Blacks who self-identified as African Americans and were born in the United States. Additionally, since our overarching hypothesis for the study is that ethnic differences in pain sensitivity may be related to ethnic differences in exposure to stressors, we recruited the African Americans and non-Hispanic Whites to be of equivalent SES by income, education, and occupational status, and assessed experiences of discrimination. These strategies allowed us to test six primary hypotheses presented below.
Studies have consistently reported that African Americans have similar pain thresholds but reduced pain tolerance to experimental pain relative to non-Hispanic Whites (Chapman & Jones 1944; Woodrow et al. 1972; Edwards & Fillingim 1999; Sheffield et al. 2000; Campbell et al. 2005; Mechlin et al. 2005).

1. African Americans will report similar pain thresholds for the cold pressor and ischemic pain tests, but lower pain tolerance relative to non-Hispanic Whites.

While many studies have demonstrated ethnic differences in peripheral pain, none of which we are aware have examined ethnic differences in centrally mediated pain. However, a variety of populations that are more sensitive to experimentally-induced peripheral pain are also more sensitive to temporal summation (Fillingim et al. 1998; Maixner et al. 1998; Eide 2000; Edwards & Fillingim 2001b; Staud et al. 2001).

2. African Americans will exhibit enhanced temporal summation to transient heat pulses relative to non-Hispanic Whites.

As has been frequently established in the literature, African Americans experience more discrimination than non-Hispanic Whites (Thompson 1996; Kessler et al. 1999; Schulz et al. 2000).

3. African Americans will report more experiences of discrimination than non-Hispanic Whites.

While African Americans are generally exposed to more stressors than non-Hispanic Whites, most studies find that African Americans do not report more perceived stress than non-
Hispanic Whites (Kessler 1979; Bennett et al. 2004; Wilcox et al. 2005). Additionally, since our samples are of equivalent SES, we expect that African Americans and non-Hispanic Whites will report similar levels of perceived stress.

4. African Americans and non-Hispanic Whites will report similar levels of Perceived Stress

While the literature has been mixed regarding ethnic differences in cardiovascular and neuroendocrine responses to stress, when psychological stressors are employed African Americans tend to show a stress response profile similar to chronically stressed individuals (i.e. blunted). We believe that this is due to the increased experiences of discrimination by African Americans, since this has been proposed as one cause of ethnic disparities in health (Broudy et al. 2007) as well as African Americans being of generally lower SES (Ulbrich et al. 1989; Anderson et al. 1992; Williams & Collins 1995; Troxel et al. 2003). Each individual experience of discrimination is believed to be an acute stressor; therefore, frequent experiences of discrimination may result in frequent activation of stress-responsive systems, which over time may diminish an individual’s ability to cope with a stressful situation (Broudy et al. 2007). Additionally, frequent experiences of discrimination may change an individual’s world view, causing him/her to interpret ambiguous interactions as threatening, which in turn may result in more frequent activation of stress-responsive biological systems (Broudy et al. 2007). Moreover, experiences of discrimination generally give rise to negative affect, which is associated with an increased risk for cardiovascular disease (Rozanski et al. 1999). However, prior studies that reported equivalent SES between African Americans and non-Hispanic Whites, which did not control for experiences of discrimination, reported
similar stress responses between the two ethnic groups. Therefore, we believe that using a psychological stressor (The TSST) and matching African Americans and non-Hispanic Whites for SES will result in similar cardiovascular and neuroendocrine responses to stress in both ethnic groups.

5. African Americans and non-Hispanic Whites will show similar BP, HR, NE, and cortisol responses to stress.

Our prior studies (Mechlin et al. 2005, 2007) documented significant relationships between stress-responsive biological measures and pain sensitivity in non-Hispanic Whites, but not in African Americans. We proposed that the absence of this relationship in African Americans was due to increased psychosocial stress exposure leading to an uncoupling of these biological responses and pain modulation. If that is the case, then psychosocial stress exposure may be an independent predictor of pain sensitivity in African Americans in the absence of any relationship to biological measures.

6. Higher levels of biological measures (BP, HR, NE, and cortisol) will be associated with increased pain tolerance in non-Hispanic Whites, but not in African Americans. While psychosocial measures (higher SES, lower perceived stress, less discrimination) will be associated with increased pain tolerance in African Americans.
CHAPTER 2
METHODS

Participants

A total of 88 medically healthy men (n = 44) and women (n = 44) served as participants. Half of each sex group self-identified as African American, while the other half self-identified as non-Hispanic White. Non-Hispanic Whites were the comparison group since the intent of this research was to examine mechanisms contributing to greater clinical pain in African Americans, which has been more robustly established in the literature in comparison to non-Hispanic Whites. Additionally, there is evidence that Hispanics are more sensitive to experimental pain than African Americans (Lawlis et al. 1984) and differ in their cognitive responses to somatic pain (Hastie et al. 2005). Also, since evidence exists that Asians and other minorities may differ in their cardiovascular responses to acute stress (Stoney et al. 2002) and since other minorities make up only a small percent (0.8 – 1%) of our regional distribution, sample size considerations prevented us from including these other minorities.

In order to decrease the likelihood of irregular menstrual cycles and hormonal fluctuations associated with the perimenopause transition in females, only subjects aged 18-45 were included. All subjects were non-smokers, medically healthy, not taking any prescription medication (including oral contraceptives), and not taking any over-the-counter medication on a regular basis (e.g. nonsteroidal anti-inflammatory medications). Excluded
from participating was anyone with sickle cell disease, a chronic pain disorder (e.g. temporomandibular joint disorder, fibromyalgia, arthritis), any cardiovascular disorder (including high BP; SBP above 160mmHg or DBP above 95mmHg), or any neuroendocrine disorders (e.g. thyroid). Given the evidence that depression is associated with altered pain perception (Dickens et al. 2003), subjects scoring >12 on the Beck Depression Inventory (BDI) during the screening session were not included (but were provided with referral information). Subjects were recruited through flyers and email list serves. Each participant was paid $75 for completion of the entire study protocol.

Procedures

**Screening:** After an initial phone-screening interview, each subject was scheduled for a screening session. During this session, informed consent was first obtained. The height and weight of participants was then measured, and 3 stethoscopic BPs were taken to determine BP levels. Subjects then filled out a medical history questionnaire and the BDI. These were immediately reviewed, and only subjects that were medically healthy and scored less than 12 on the BDI were deemed eligible for the study. Once determined to be eligible, subjects filled out the psychosocial questionnaires, and underwent a practice of the temporal summation pain test to familiarize them with the procedure and reduce novelty effects. Subjects were then scheduled for one subsequent lab visit. In order to control for the influence of female menstrual cycle on pain sensitivity, women were tested during the follicular phase of their menstrual cycles (days 1-10). Additionally, during recruitment the African American and non-Hispanic White groups were matched for household income, to ensure that our samples had similar levels of SES.
Test Session: All laboratory testing sessions began between 2:00pm and 3:00pm, thus controlling for diurnal effects on neuroendocrine measures. All subjects were tested by a non-Hispanic White female experimenter. Subjects were asked to refrain from all over-the-counter medications and alcohol for 24 hours and from caffeine and exercise on the day of testing. The laboratory test session then began as described below.

The sequence of laboratory events is as follows (see Figure 1): 1) Temporal Summation Procedure (5 min); 2) Cold Pressor and Tourniquet Ischemia Tests ; counterbalancing order within ethnic and sex groups (20 min); 3) Instrumentation for BP monitoring (Suntech 4240 Exercise blood pressure monitor) and stethoscopic BP assessments to ensure reliable cuff placement and microphone position (30 min); 4) i.v. setup and recovery (20 min); 5) TSST (25 min); 6) Stress Recovery (10 min). These events are described fully below.
**Pain Testing Procedures**

*Temporal Summation Procedure:* In this task, a 1-cm diameter contact thermode is applied to the skin. The thermode is controlled by a personal computer, and the thermal probe is applied to the dominant palm. The thermode produced a train of 8 heat pulses, each at 51°C. During the train, the heat pulses were presented for 1.5 seconds, with an inter-stimulus-interval of 1.5 seconds. The temporal summation procedure is characterized by two different types of pain. The immediate sensation produced by the thermal stimulus is called “first pain” and is characterized by a sharp, pricking sensation. The sensation that occurs 1 – 1.5 seconds later is referred to as “second pain” which is characterized by a burning and
throbbing sensation. When the stimulus is repeated at small intervals, the intensity of the pain increases in a nonlinear fashion due to temporal summation. This is the result of a nonlinear increase in the response of the dorsal horn neurons (Mannion & Woolf 2000). Thus, this task allowed us to assess ethnic differences in a correlate of central sensitization (Herrero et al. 2000). Participants were asked to rate the intensity of the delayed pain sensation following each of the heat pulses. The intensity refers to the sensory component of the pain, and was rated on a visual analogue scale from 0 – 100. The train of heat pulses continued until the participant verbalized a pain intensity rating of 100 (most intense pain imaginable) or until 8 pulses had elapsed, whichever occurred first. Two dependent measures were analyzed: 1) ethnic differences in intensity ratings at each heat pulse and 2) ethnic differences in the dropout rate (i.e. report of 100 pain intensity) at each heat pulse (Maixner et al. 1998).

**The Submaximal Effort Tourniquet Procedure:** The submaximal effort tourniquet procedure produces graded increases in BP (Maixner et al. 1990) and also activates intrinsic opioid systems (Frid et al. 1979, 1981; Schull et al. 1981; Grevert et al. 1983). Additionally, the tonic nature of this stimulus produces a deep, aching pain, similar to many clinical pain syndromes (Fillingim & Maixner 1996). Thus, it is ideally suited for testing ethnic differences in pain sensitivity since African Americans experience more clinical pain.

In this procedure (Maixner et al. 1990), a tourniquet cuff was positioned on the subject’s arm and the arm placed to the side. Prior to inflating the tourniquet cuff to 200 mmHg (Hokanson E20 Rapid Cuff Inflator), the subject’s arm was raised for 30 seconds to promote venous drainage, and then the cuff is inflated, the experimenter’s stopwatch was started, and the arm returned to the side. To promote forearm ischemia, subjects engaged in
20 handgrip exercises at 30% of their maximum force with an inter-squeeze interval of 2 sec. Subjects were instructed to indicate when the sensations in their forearm or hand first became painful (pain threshold) and when they were no longer willing or able to tolerate the pain (pain tolerance). A maximum time limit of 20 min was enforced, though subjects were not informed of this limit. Also, as part of the pre-task instructions, subjects were instructed that at tolerance, but before deflating the cuff, they were to rate the sensory (intensity) component of pain and the affective (unpleasantness) component of the pain on a visual analogue scale from 0-100.

The Hand Cold Pressor Procedure: The hand cold pressor task is similar to the tourniquet procedure in that it is characterized by a deep, tonic aching sensation but, unlike the tourniquet procedure, the cold pressor elicits much larger increases in BP. Prior work from our laboratory indicated that plasma NE levels mediate the link between BP response to this task and pain tolerance (Girdler et al. 2005). Thus, this test is ideally suited for examining ethnic differences in BP and sympathetic mechanisms involved in pain perception.

In this task, a cooler containing a 4°C mixture of crushed ice and water was placed on a stool next to the subject. A water circulator was placed in the cooler to prevent the water from warming near the subject’s hand. The subject was then given instructions telling him/her to place his/her hand into the cooler so that the water level is up to a line marked on his/her wrist. Participants were asked to indicate when their hand first became painful (pain threshold) and when they were no longer willing or able to tolerate the task (pain tolerance). The subjects were also informed that there is a maximum time (unspecified) at which they would not be allowed to continue (5 minutes). As soon as the subject’s hand was submerged
up to the wrist, the timer was started. Immediately before removing the hand from the water, subjects were asked to rate the intensity and unpleasantness of the pain (as described above).

A 5-minute recovery period followed each pain procedure.

**Stress Procedures**

*Baseline:* Immediately following the i.v. setup, 20 minutes of quiet rest ensued. The first 10 minutes served as a recovery period from venipuncture. Therefore, BP was taken at minutes 11, 13, 15, 17, and 19 of the 20-minute rest period, and then averaged to constitute baseline levels. Blood was sampled at minute 20 for baseline levels of NE, β-endorphin, and cortisol.

*The Trier Social Stress Test (TSST):* A stress test which reliably induces large and consistent HPA-axis and cardiovascular responses and moderate to high subjective stress (Kirschbaum et al. 1993, 1995a, b) was used. The TSST involves the following specific components:

*Pre-Task Instructions:* Subjects were introduced to 2 people (the ‘selection committee’) after which the experimenter asked the subject to take over the role of a job applicant who was invited for a personnel interview with the company’s staff managers (the selection committee). Subjects were then instructed that after a preparation period, they should introduce themselves to the committee in a free speech of 5 minutes duration and convince the committee that they should be the perfect applicant for the position. Subjects were told that during the speech they will be tape-recorded and that the committee members are specially trained to monitor nonverbal behavior and that tape-recorded speech will be analyzed for performance.
**Preparation Period:** Following these instructions, the subject was left alone for 5 minutes to prepare his/her talk. Subjects were provided with paper and pencil for outlining their talk but were not allowed to use these notes during the talk.

**Speech:** Immediately following the 5 minute preparation period, the selection committee returned to the testing room and listened to the subject deliver his/her talk for 5 minutes. If the subject finished his/her talk before 5 minutes, the committee responded in a standardized way with prepared questions to ensure that the subject spoke for the entire 5 minutes.

**Paced Auditory Serial Addition Task (PASAT; Gronwall 1977):** Immediately following the end of the speech, the subject listened to a tape-recorded presentation of numbers from 1 to 9. Participants were told to add each number presented on the tape to the immediately preceding number and state the answer aloud. There were four series of numbers, with progressively shorter interdigit intervals. The task lasted approximately 9 minutes. The experimenter remained in the room to monitor performance.

**Task Assessments:** Two questionnaires (one for the speech and one for the PASAT) were administered after the cessation of the PASAT task. Using a likert scale, the questionnaire asks the participant to draw a vertical line on a continuum indicating 1) how difficult s/he found the task; 2) how tense s/he was during the task; 3) how well s/he was able to concentrate during the task; and 4) how much effort s/he put into the task.

**Stress Recovery:** The subject sat alone and quiet for 10 minutes.

**Cardiovascular and Neuroendocrine Sampling during TSST:** Blood pressure measures were taken at minutes 1, 3, and 5 of the Preparation Period, minutes 1, 3, and 5 of Speech, and minutes 2, 4, 6, and 8 of the PASAT and averaged to constitute task levels.
was sampled at the end of minute 2 of speech delivery and at the end of minute 2 of the PASAT since catecholamines peak within the first minutes of stress and have a very short half-life (3 min). These time points are also associated with peak cardiovascular responses. Blood was sampled for cortisol immediately following the Stress Recovery since peak cortisol concentrations are reliably found 10 - 30 minutes after stress cessation in the TSST protocol (Kirschbaum et al. 1995a, b; Kudielka & Kirschbaum 2005).

**Measurements**

**Blood Pressure/Automated Arm Cuff System:** The Suntech Exercise Blood Pressure Monitor, Model 4240 (SunTech Medical Instruments, Inc., Raleigh, NC) provided automated measurement of BP during the test session. The Suntech Exercise BP Monitor uses the auscultatory technique, with R-wave Gating. This BP monitor is accurate within +/- 2 mmHg between 0 mmHg and 300 mmHg. Prior to initiating the baseline rest period, at least three standard stethoscopic BPs were taken simultaneously with the automated pressures in order to ensure correct microphone placement and cuff positioning.

**Ischemic and Cold Pain Sensitivity:** Behavioral measures of pain sensitivity were assessed during the ischemic and cold pain tests. Two categories of behavioral measures were made: 1) Subjects’ voluntary reports of pain onset (i.e. threshold) and pain tolerance; and 2) subjects’ reports of the sensory (i.e. intensity) and affective (i.e. unpleasantness) components for each pain task.

**Central Sensitization:** Behavioral measures reflecting enhanced temporal summation of heat stimuli (e.g. central sensitization) were assessed via the subjects’ report of the intensity of this pain test at each heat pulse (via 0 –100 visual analogue scales). A secondary
measure involved comparing ethnic groups for differences in drop-out rate (i.e. rate at which an intensity of 100 is reported and the pulses are discontinued) at each heat pulse.

**Neuroendocrine Measures:**

**Plasma cortisol:** Concentrations were determined using radioimmunoassay (RIA) techniques commercially available from ICN Biomedical, Inc. The intra- and inter-assay coefficients of variation from the assay are 4.7% and 7.6%, respectively. The sensitivity of the assay is excellent at 0.07 µg/dL, and the specificity high, showing 0.05 – 2.2% cross-reactivity with similar compounds, except prednisolone, where 94% cross-reactivity is obtained.

**Plasma Norepinephrine:** Concentrations were determined using the high performance liquid chromatography (HPLC) technique. ALL HPLC procedures were conducted at the Core Laboratory jointly funded by the UNC Hospitals General Clinical Research Center. The lower limit of quantification with this system is 25 pg/mL, and the intra- and inter-day coefficients of variation are less than 10%.

**Plasma β-endorphin:** Levels of β-endorphin in EDTA plasma were determined following extraction by ELISA using a kit from MD Biosciences (St. Paul, Minnesota). The intra- and inter-assay coefficients of variation from the assay are approximately 5% and 14%, respectively, and the assay sensitivity is .01 ng/mL.

**Questionnaire Data:**

**Personal and Family Health History:** This questionnaire was administered at the initial screening session, and assessed each subject’s personal and family health history, including information on cardiovascular and other diseases, illnesses, medication use, etc. This questionnaire also includes the measures of SES described below.
**Socioeconomic Status:** We used three different indices of SES for each individual based on education, gross household income (GHI), and occupation. For education, subjects were assigned a score (1 – 4) based on degree: 1) less than a high school education; 2) high school degree or GED; 3) college degree; or 4) post-graduate degree. GHI was based on total household income (e.g. from earnings, unemployment, workers compensation, social security, alimony, child support, etc.) during the preceding calendar year. Based on the 2007 US Census Bureau measurement of Poverty Thresholds (Department of Health and Human Services 2007), which do not vary within the 48 contiguous states, are updated annually, and determine poverty status according to size of family and age of members; a score of 1-4 was assigned based on the relationship of GHI adjusted for number of persons in family unit to the national poverty threshold level: 1) GHI at or below poverty threshold; 2) GHI greater than one but less than two times the poverty threshold; 3) GHI between two and three times poverty threshold; and 4) GHI greater than three times poverty threshold. For occupational status, we relied on the Hollingshead Codes where job categories are ranked from 0 – 9. The Hollingshead scale shows a high degree of correspondence with other validated occupational scales (Deonandan et al. 2000).

**Beck Depression Inventory** (Beck & Beamesderfer 1974) was used to measure depressive symptoms. This 21-item scale comprehensively assesses dysphoric symptoms, including affective, cognitive, somatic, overt behavior and interpersonal symptoms of depression. The BDI possesses a high degree of internal consistency with a mean alpha coefficient of .81 for nonpsychiatric populations (Beck et al. 1988), and a reasonable amount of validity with mean correlations of the BDI with clinical ratings and other questionnaires being 0.60 and 0.74 respectively in nonpsychiatric populations (Beck et al. 1988). The BDI
was used to determine that none of the subjects included in the study were currently depressed, and to ensure that the African American and non-Hispanic White samples were matched for depressive symptoms, since depression can influence pain sensitivity (Dickens et al. 2003).

**Self-Evaluation Questionnaire STAI form Y-2** (Spielberger 1983) is a questionnaire that was used to measure how anxious an individual generally feels. The questionnaire has 20 statements, and the participant chose if s/he felt that way almost never, sometimes, often, or almost always. The STAI has very high internal consistency (mean $\alpha = 0.89$), a high degree of reliability (mean test-retest reliability $r = 0.88$; Gros et al. 2007), and good validity since individuals with current anxiety scored significantly higher than individuals without anxiety (Kabacoff et al. 1997). The STAI was used to ensure that African Americans and non-Hispanic Whites were matched for anxiety levels, since studies have shown that anxiety may relate to pain sensitivity (Keogh et al. 2006).

**Cohen’s Perceived Stress Scale** (PSS; Cohen et al. 1983) was used as a measure of perceived stress. The PSS is a 14-item scale that gives an indication of how much stress an individual has felt in the past month. The subject reports his/her perceived stress on a 5-point scale. The PSS has a high degree of reliability (mean $\alpha = 0.84$) and good validity (mean correlations of PSS with symptomological measures = .52 to .76; Cohen et al. 1983).

**Experiences of Discrimination** (EOD; Krieger 1990, Krieger & Sidney 1996; Krieger et al. 2005; See Appendix) was used as a measure of perceived racism. The EOD asks individuals to report not only if they have felt discriminated against because of their race in a variety of locations, but also how often they have felt this way (range of 0 – 5 for each setting, range of 0 – 45 for entire scale). Additionally, this scale assesses how individuals
respond to unfair treatment (actively or passively). The EOD has good reliability with alpha coefficients ranging from 0.67 to 0.86 and a test-retest correlation of 0.70 and good validity, as it correlated highly with other measures of latent discrimination ($r = 0.79$) and is significantly related to psychological stress ($rs = 0.71$ to 0.93; Krieger et al. 2005).

**Data Reduction and Analyses**

Since the focus of this study is ethnic differences in pain sensitivity and cardiovascular reactivity to stress, our study was not powered to examine ethnic by sex interactions, hence all of our analyses were collapsed across sex. Further justification for collapsing our analyses across sex comes from our prior work, which indicated no sex by ethnic interactions in pain sensitivity, or sex differences in correlations of pain tolerance to biological measures. Additionally, there is little evidence to suggest that ethnic differences that we predict in psychosocial measures will vary by sex (personal communication with Dr. Christopher Edwards). Finally, our preliminary analyses did not indicate robust sex by ethnic interactions for our primary pain sensitivity measures (i.e. threshold, tolerance, and temporal summation wind-up index; Table 1).
Table 1: Mean (± SEM) Pain Sensitivity as a Function of Ethnicity and Gender

<table>
<thead>
<tr>
<th></th>
<th>African American Females (n = 22)</th>
<th>Non-Hispanic White Females (n = 22)</th>
<th>African American Males (n = 22)</th>
<th>Non-Hispanic White Males (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold Pressor Threshold</td>
<td>21 (3.0)</td>
<td>19 (2.8)</td>
<td>23 (3.9)</td>
<td>22 (2.8)</td>
</tr>
<tr>
<td>Cold Pressor Tolerance A</td>
<td>63 (17.9)</td>
<td>109 (21.7)</td>
<td>87 (22.2)</td>
<td>142 (23.4)</td>
</tr>
<tr>
<td>Cold Pressor Intensity B</td>
<td>69 (2.5)</td>
<td>73 (4.1)</td>
<td>73 (3.6)</td>
<td>60 (4.9)</td>
</tr>
<tr>
<td>Cold Pressor Unpleasantness B</td>
<td>56 (5.7)</td>
<td>63 (5.0)</td>
<td>68 (4.3)</td>
<td>53 (5.8)</td>
</tr>
<tr>
<td>Ischemic Pain Threshold C</td>
<td>215 (50)</td>
<td>183 (38)</td>
<td>344 (66)</td>
<td>211 (39)</td>
</tr>
<tr>
<td>Ischemic Pain Tolerance A,C</td>
<td>362 (64)</td>
<td>531 (90)</td>
<td>564 (85)</td>
<td>694 (79)</td>
</tr>
<tr>
<td>Ischemic Pain Intensity B</td>
<td>51 (4.8)</td>
<td>56 (4.2)</td>
<td>62 (5.2)</td>
<td>43 (5.6)</td>
</tr>
<tr>
<td>Ischemic Pain Unpleasantness D</td>
<td>45 (6.0)</td>
<td>62 (5.8)</td>
<td>62 (5.6)</td>
<td>55 (4.9)</td>
</tr>
<tr>
<td>Wind-Up Index E</td>
<td>40 (6.2)</td>
<td>24 (4.2)</td>
<td>32 (4.6)</td>
<td>24 (3.4)</td>
</tr>
</tbody>
</table>

A: non-Hispanic Whites > African Americans, p < .05  
D: non-Hispanic White Females > African American Females, p < .05  
B: African American Males > non-Hispanic White Males, p < .05  
E: African Americans > non-Hispanic Whites, p < .05  
C: Males > Females, p < .05

For all demographic and baseline characteristics a one-way Analysis of Variance (ANOVA) was conducted with ethnicity as the grouping variable. To examine ethnic differences in sensitivity to cold pressor and ischemic pain 2 (Ethnicity) x 2 (Time: Threshold vs. Tolerance) repeated measures ANOVAs with time (Threshold vs. Tolerance) as the repeated measure, were used. A similar strategy was employed for temporal summation, with a 2(Ethnicity) x 8 (Pulse Number) repeated measures ANOVA used to examine ethnic differences in the intensity ratings of the temporal summation-induced pain. Additionally, a delta score (Highest heat pulse intensity rating – Intensity rating for first heat pulse) was calculated for each subject, providing a wind-up index (Bhalang et al. 2005), and a one-way ANOVA with ethnicity as the grouping variable was conducted. Chi-square
analyses were employed to examine ethnic differences in the drop out rate for the temporal summation procedure.

In order to examine ethnic differences in cardiovascular and neuroendocrine responses to stress 2(Ethnic) x 2 or 3(Condition: Baseline, Stress; 3 time points for BP, HR, and NE, 2 time points for cortisol) repeated measures ANOVAS with condition (Baseline, Speech Stress, PASAT Stress) as the repeated measure were employed. To examine ethnic differences in perception of stress, one-way ANOVAS were conducted with ethnicity as the grouping variable for each of the different factors.

To examine the relationship of BP to pain sensitivity, consistent with other published reports (al’Absi et al. 2000) a median split was conducted within each ethnic group, and then a 2(Group: Higher or Lower BP) x 2(Time: Threshold vs. Tolerance) repeated measures ANOVA was conducted separately for each ethnic group. The same strategy was used for NE, cortisol, and β-endorphin. In order to reduce the number of separate analyses, only baseline values were examined for their relationship to pain sensitivity.

Multiple stepwise regressions were performed in order to examine predictors of pain sensitivity. Again, in order to reduce the number of separate analyses, we selected only baseline endogenous pain modulators, SES variables, and EOD items since our results confirmed robust differences between ethnic groups in EOD (Table 4), and since indicators of SES are so robustly related to measures of health status (Pappas et al. 1993; Adler et al. 1994). Thus, the following predictors were entered into the regression model: baseline measures of SBP, DBP, HR, NE, cortisol, and β-endorphin, education, income, Hollingshead score, and EOD items. Based on African Americans experiencing more discrimination in some situations rather than others, in order to reduce Type I error rates, we limited our
regression analyses to only those EOD items that differed by ethnic group (discrimination experienced at school, getting hired for a job, at work, getting service in a store or restaurant, on the street or in a public setting, and the total EOD score). When examining possible predictors of temporal summation, individuals who did not report any temporal summation (i.e. a wind-up index of 0) were excluded from analyses (n = 3).

In stepwise regression each independent variable specified is entered into the regression one at a time until all variables have been added with the provision that each meets a specified criterion. The criterion employed by SAS, the statistical software used for these analyses, was one of significance level \( p < .15 \). Furthermore, the stepwise approach involves an additional procedure in which all variables are reexamined after the addition of other variables to verify that each remains a significant and independent predictor. Thus, this approach helps to circumvent the problem of multicolinearity of independent variables.
CHAPTER 3

RESULTS

Demographic and Baseline Characteristics

As summarized in Table 2, ethnic groups did not differ in age or baseline measures of DBP, HR, NE, or β-endorphin. African Americans had higher BMIs \( F(1, 87) = 8.81, p < .01 \) and a trend toward higher resting SBP \( F(1, 87) = 3.03, p < .10 \). Non-Hispanic Whites had higher baseline cortisol \( F(1, 71) = 4.54, p < .05 \) than African Americans. As summarized in Table 3, and consistent with our recruitment strategy to ensure equivalency between groups in income, African Americans and non-Hispanic Whites did not differ in any of our SES measures (education, income, or occupational status), nor did they differ on BDI, Spielberger Trait Anxiety, or PSS measures. As expected, African Americans reported more total EOD than non-Hispanic Whites \( F(1, 87) = 54.71, p < .0001 \). The individual items that African Americans reported more discrimination for included discrimination at school, at work, in getting hired for a job, in getting service at a restaurant or store, and on the street or in a public setting (Table 4).
Table 2: Mean (±SEM) Demographic and Baseline Characteristics as a Function of Gender and Ethnicity

<table>
<thead>
<tr>
<th></th>
<th>African Americans (n = 44)</th>
<th>Non-Hispanic Whites (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.2 (1.11)</td>
<td>23.7 (0.79)</td>
</tr>
<tr>
<td>BMI ^A</td>
<td>27.8 (0.97)</td>
<td>24.3 (0.68)</td>
</tr>
<tr>
<td>Systolic Blood ^B Pressure (mmHg)</td>
<td>117 (1.70)</td>
<td>112 (1.74)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>67.7 (1.20)</td>
<td>66.1 (1.09)</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>66.5 (1.38)</td>
<td>63.5 (1.23)</td>
</tr>
<tr>
<td>Norepinephrine (pg/mL)</td>
<td>249 (13.8)</td>
<td>235 (12.6)</td>
</tr>
<tr>
<td>Cortisol (pg/mL) ^A</td>
<td>5.76 (0.42)</td>
<td>7.64 (0.55)</td>
</tr>
<tr>
<td>β-endorphin (ng/mL)</td>
<td>0.12 (0.01)</td>
<td>0.10 (0.01)</td>
</tr>
</tbody>
</table>

A: African Americans > non-Hispanic Whites, p < .05
B: African Americans > non-Hispanic Whites p < .10
Table 3: Mean (±SEM) Demographic and Baseline Characteristics as a Function of Ethnicity

<table>
<thead>
<tr>
<th></th>
<th>African Americans (n = 44)</th>
<th>Non-Hispanic Whites (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>2.61 (0.12)</td>
<td>2.77 (0.14)</td>
</tr>
<tr>
<td>Income (based on poverty status)</td>
<td>2.88 (0.17)</td>
<td>3.18 (0.17)</td>
</tr>
<tr>
<td>Hollingshead Occupational Status</td>
<td>5.14 (0.24)</td>
<td>4.73 (0.26)</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>3.55 (0.50)</td>
<td>2.68 (0.48)</td>
</tr>
<tr>
<td>Spielberger Trait Anxiety</td>
<td>34.1 (1.14)</td>
<td>34.3 (1.34)</td>
</tr>
<tr>
<td>Perceived Stress Scale</td>
<td>19.6 (1.0)</td>
<td>17.3 (0.97)</td>
</tr>
<tr>
<td>Experiences of Discrimination (Total Scale Score) (^A)</td>
<td>9.26 (0.99)</td>
<td>1.28 (0.42)</td>
</tr>
</tbody>
</table>

For Education and Income each individual was assigned a score of 1-4 based on the following criteria:

Education: 1 = Less than High School; 2 = Graduated High School; 3 = College Degree; 4 = Post-graduate Degree

Income: 1 = Gross Household Income (GHI) at or below poverty level; 2 = GHI 1 – 2 times poverty level; 3 = GHI 2 – 3 times poverty level; 4 = GHI > 3 times above poverty level

For Occupational Status each individual was assigned a score 0 – 9 based on the Hollingshead Scale, with higher scores reflecting higher occupational status

\(^A\): African Americans > non-Hispanic Whites, \(p < .05\)
Table 4: Mean (±SEM) Frequency of Discrimination Occurrences as a Function of Ethnicity

<table>
<thead>
<tr>
<th></th>
<th>African Americans (n = 44)</th>
<th>Non-Hispanic Whites (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Getting Medical Care</td>
<td>0.16 (0.08)</td>
<td>0.02 (0.02)</td>
</tr>
<tr>
<td>Getting service in a store or</td>
<td>2.53 (0.30)</td>
<td>0.27 (0.14)</td>
</tr>
<tr>
<td>restaurant A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Getting credit, banking loans,</td>
<td>0.19 (0.13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>or a mortgage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On street or in a public setting A</td>
<td>2.19 (0.31)</td>
<td>0.60 (0.21)</td>
</tr>
<tr>
<td>From Police of in the Courts</td>
<td>0.89 (0.22)</td>
<td>0.02 (0.02)</td>
</tr>
</tbody>
</table>

A: African Americans > non-Hispanic Whites p < .01

Effects of Ethnicity on Pain Sensitivity

Cold Pressor Pain

As summarized in Table 5, analyses revealed a main effect of ethnicity for cold pressor pain sensitivity (F(1, 86) = 4.45, p < .05). However, there was also a significant Time Point x Ethnic interaction (F(1, 86) = 6.90, p < .05). In order to explore this interaction, simple effects analyses were conducted separately for pain threshold and pain tolerance. These analyses indicated that while there were no ethnic differences in pain threshold (F(1, 86) = 0.41, p > .50), African Americans had lower pain tolerance to the cold pressor pain task (F(1,
87) = 5.61, p < .05) relative to non-Hispanic Whites. There were no ethnic differences in intensity or unpleasantness ratings.

**Ischemic Pain**

*Threshold and Tolerance*

Similar to the cold pain task, a Time Point x Ethnic interaction emerged for the ischemic pain task (F(1, 85) = 12.71, p < .001). While there were no ethnic differences in ischemic pain threshold (F(1, 85) = 2.65, p > .10), African Americans had marginally lower ischemic pain tolerance relative to non-Hispanic Whites (F(1, 85) = 3.50, p = .06). There were no ethnic differences in intensity or unpleasantness ratings.

| Table 5: Mean (± SEM) Pain Threshold, Tolerance, Intensity, and Unpleasantness |
|---------------------------------|-----------------|-----------------|
|                                 | African Americans | Non-Hispanic Whites |
|                                 | (n = 44)          | (n = 44)         |
| Cold Pressor Threshold (sec)    | 22 (2.4)          | 20 (1.9)         |
| Cold Pressor Tolerance (sec) A  | 75 (14.2)         | 125 (16.0)       |
| Cold Pressor Pain Intensity     | 71 (2.2)          | 67 (3.3)         |
| (0 – 100)                       |                  |                  |
| Cold Pressor Pain Unpleasantness| 62 (3.6)          | 58 (3.8)         |
| (0 – 100)                       |                  |                  |
| Ischemic Threshold (sec)        | 278 (42)          | 197 (27)         |
| Ischemic Tolerance (sec) B      | 460 (54)          | 613 (60)         |
| Ischemic Pain Intensity (0 – 100)| 56 (3.6)          | 49 (3.6)         |
| Ischemic Pain Unpleasantness    | 53 (4.3)          | 58 (3.8)         |
| (0 – 100)                       |                  |                  |

A: non-Hispanic Whites > African Americans, p < .05
B: non-Hispanic Whites > African Americans, p = .06
**Temporal Summation**

For the repeated measures ANOVA, there was a main effect of heat pulse ($F(7, 602) = 107.49, p < .0001$), indicating that all subjects experienced temporal summation (an increase in pain intensity rating for the first heat pulse to the last heat pulse). There was also a significant Ethnic x Pulse interaction ($F(7, 602) = 3.68, p < .001$), this was the result of African Americans demonstrating a greater degree of temporal summation as reflected in the difference between the highest intensity rating and the first intensity rating, indexing wind-up (mean wind-up index = 36 vs. 24; $F(1, 86) = 5.78, p < .05$; Figures 2 & 3). There was no difference in the number of non-Hispanic Whites vs. African Americans who rated the intensity of the pain as 100 and stopped the procedure ($ns = 4$ and 8, respectively).

**Figure 2: Average Intensity Rating for Each Heat Pulse as a Function of Ethnicity**

![Intensity Rating Graph](image)

Pulse x Ethnic Interaction ($F(7, 602) = 3.68, p < .001$)
Figure 3: Wind-up Index as a Function of Ethnicity

Figure 3: African Americans exhibit a higher wind-up index (increase in pain ratings from 1st heat pulse to highest pain rating) than non-Hispanic Whites
Cardiovascular and Neuroendocrine Reactivity to Stress (Table 6)

**Blood Pressure and Heart Rate:** Both stressors significantly increased SBP ($F(2, 170) = 269.64, p<.0001$), DBP ($F(2, 170) = 263.18 p < .0001$), and HR ($F(2, 172) = 142.31, p < .0001$) in all subjects. There were no effects of ethnicity for SBP, DBP, or HR, nor were there any significant stress x ethnic interactions for any of the cardiovascular measures.

**Norepinephrine and Cortisol:** Both stressors significantly increased plasma NE in all subjects ($F(2, 142) = 19.67, p < .0001$). There were no main effects of ethnicity or Stress x Ethnic interactions for NE. Contrary to expectations, stress was not associated with an overall increase in plasma cortisol levels in either ethnic group.

<table>
<thead>
<tr>
<th>Table 6: Mean (± SEM) Biological Measures During Rest and Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Baseline SBP (mmHg)</td>
</tr>
<tr>
<td>Speech Stress SBP (mmHg)</td>
</tr>
<tr>
<td>Math Stress SBP (mmHg)</td>
</tr>
<tr>
<td>Baseline DBP (mmHg)</td>
</tr>
<tr>
<td>Speech Stress DBP (mmHg)</td>
</tr>
<tr>
<td>Math Stress DBP (mmHg)</td>
</tr>
<tr>
<td>Baseline HR (bpm)</td>
</tr>
<tr>
<td>Speech Stress HR (bpm)</td>
</tr>
<tr>
<td>Math Stress HR (bpm)</td>
</tr>
<tr>
<td>Baseline Norepinephrine</td>
</tr>
<tr>
<td>Speech Stress Norepinephrine (pg/mL)</td>
</tr>
<tr>
<td>Math Stress Norepinephrine (pg/mL)</td>
</tr>
<tr>
<td>Baseline Cortisol</td>
</tr>
<tr>
<td>Post-Stress Cortisol (pg/mL)</td>
</tr>
</tbody>
</table>

A: non-Hispanic Whites > African Americans, $p < .05$
Perceptions of the Stress Tasks:

Following the stress tasks, participants were asked to rate both the speech and math tasks on four dimensions: 1) how difficult the task was; 2) how tense they felt during the task; 3) their ability to concentrate during the task; and 4) how much effort they put into the task. Analyses indicated that there were no ethnic differences in the ratings of dimensions listed above for the speech task (Fs(1, 87) = 0.17 – 2.45, ps > .10). However, African Americans reported more difficulty concentrating during the math task (6.5 vs. 5.1; F(1, 87) = 5.76, p < .05) than the non-Hispanic Whites. There were no ethnic differences in perceptions of task difficulty, tension, or effort for the math task (Fs(1, 87) = 0.14 – 1.79, ps > .10).

Relationship of Physiological Variables to Pain Sensitivity

Blood Pressure and Heat Rate: For non-Hispanic Whites, there were no SBP-status group differences (higher resting SBP vs. lower resting SBP) in cold pain threshold or tolerance. However, for the ischemic pain task a SBP-status Group x Time interaction emerged (F( 1, 42) = 4.84), p < .05). Subsequent analyses indicated that in non-Hispanic Whites the higher SBP group had a higher tolerance to the ischemic pain task than the lower SBP group (740 sec vs. 496 sec; F(1, 43) = 4.37, p < .05; Figure 4). SBP status was not associated with either cold pressor pain or ischemic pain sensitivity in African Americans (see Figure 4 for ischemic pain). Neither DBP nor HR status were associated with differences in pain sensitivity for either ethnic group.
Figure 4: Ischemic Pain Sensitivity as function of Baseline SBP in non-Hispanic Whites

Non-Hispanic Whites
Time x SBP Group p < .05
*Difference at Tolerance p < .05

African Americans
No Significant Effects

Figure 4: Mean (±SEM) ischemic pain threshold and tolerance levels as a function of higher vs. lower baseline SBP group in non-Hispanic Whites (top panel) and African Americans (bottom panel)
**Norepinephrine, Cortisol, and β-endorphin:** In non-Hispanic Whites there was a significant effect of baseline NE group for the cold pressor task (F(1, 42) = 6.34, p < .05), since the higher-NE group had higher threshold (25 sec vs. 15 sec) and tolerance (160 sec vs. 90 sec) to the cold pressor task relative to the lower-NE group. For African Americans there were no NE-group differences for the cold pressor task (Figure 5).

**Figure 5: Mean (±SEM) cold pressor pain threshold and tolerance levels as a function of higher vs. lower baseline NE group in non-Hispanic Whites (top panel) and African Americans (bottom panel).**
For the ischemic pain task there was a trend of NE group for the non-Hispanic Whites (F(1, 42) = 2.93, p < .10), since the higher-NE group had a marginally higher ischemic pain threshold (239 vs. 156 sec) and tolerance (700 sec vs. 525 sec; Figure 6). In contrast to the pattern seen for non-Hispanic Whites, African Americans in the higher-NE group had lower pain threshold (151 vs. 378 sec) and lower pain tolerance (267 vs. 614 sec) to the ischemic pain task ((F(1, 41) = 13.17, p < .001; Figure 6).

Figure 6: Mean (±SEM) ischemic pain threshold and tolerance levels as a function of higher vs. lower baseline NE group in non-Hispanic Whites (top panel) and African Americans (bottom panel)
There were no associations between either baseline cortisol or baseline β-endorphin status (higher or lower) and cold pressor pain or ischemic pain sensitivity in either non-Hispanic Whites or African Americans.

There were also no significant differences involving BP, HR, NE, or cortisol status groups and the temporal summation wind-up indices for either ethnic group.

**Predictors of Pain Sensitivity**

Separate regression analyses were conducted in each ethnic group to determine which baseline biological, SES, and discrimination measures predicted pain sensitivity in non-Hispanic Whites and African Americans. Since the ethnic groups differed on questions assessing perceived discrimination, and because SES is so strongly related to all forms of poor health (Pappas et al. 1993; Adler et al. 1994), we selected these variables for analyses involving potential ethnic differences in the relationship of psychosocial stress and pain sensitivity. Thus, the following predictor variables were entered into the model: baseline measures of SBP, DBP, HR, NE, cortisol, and β-endorphin; education; income; Hollingshead occupational status score; and the frequency scores for the discrimination items reported more frequently in African Americans: discrimination experienced at school, getting hired for a job, at work, getting service in a store or restaurant, on the street or in a public setting, and the total EOD score.
For the non-Hispanic Whites (Table 7) there was a trend for cold pressor pain threshold levels to be positively predicted by baseline NE (F(1, 41) = 2.88, p < .10), accounting for 6.7% of the variance in pain threshold. Thus, higher baseline NE tended to predict greater cold pressor pain threshold.

For cold pressor pain tolerance baseline HR was a negative predictor and baseline NE was a positive predictor, together accounting for 17% of the variance in pain tolerance in the non-Hispanic Whites (F(2, 41) = 3.98, p < .05). Therefore, lower levels of baseline HR and higher levels of baseline NE predicted greater cold pressor tolerance.

Baseline NE and Hollingshead occupational status scores accounted for 19.8% of the variance in ischemic pain threshold (F(2, 39) = 4.83, p < .05) in non-Hispanic Whites, indicating that higher baseline NE and higher occupational status were associated with greater ischemic pain threshold levels.

There was also a trend for baseline SBP to positively predict ischemic pain tolerance (F(1, 41) = 3.6, p < .07), accounting for 8.3% of the total variance in non-Hispanic Whites. Thus, higher baseline SBP was associated with higher ischemic pain tolerance.

None of the variables entered into the model significantly predicted temporal summation wind-up index scores in non-Hispanic Whites.
Table 7: Stepwise Regression Analyses in non-Hispanic Whites  
(n = 44)

<table>
<thead>
<tr>
<th>Criterion/Predictor Variable</th>
<th>F</th>
<th>β</th>
<th>Partial R²</th>
<th>Full Model R²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cold Pressor Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Norepinephrine</td>
<td>2.88*</td>
<td>0.259</td>
<td>0.067</td>
<td>0.067*</td>
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<tr>
<td><strong>Cold Pressor Tolerance</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Heart Rate</td>
<td>6.18**</td>
<td>-0.374</td>
<td>0.093</td>
<td></td>
</tr>
<tr>
<td>Baseline Norepinephrine</td>
<td>3.60*</td>
<td>0.285</td>
<td>.077</td>
<td>0.170**</td>
</tr>
<tr>
<td><strong>Ischemic Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Norepinephrine</td>
<td>6.10**</td>
<td>0.354</td>
<td>0.124</td>
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</tr>
<tr>
<td>Hollingshead Score</td>
<td>3.60*</td>
<td>0.271</td>
<td>0.074</td>
<td>0.198**</td>
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<tr>
<td><strong>Ischemic Tolerance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Systolic Blood</td>
<td>3.60*</td>
<td>0.287</td>
<td>0.083</td>
<td>0.083*</td>
</tr>
<tr>
<td>Pressure</td>
<td></td>
<td></td>
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<tr>
<td><strong>Temporal Summation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No Significant Predictors</td>
<td></td>
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</tbody>
</table>

#p < .15, *p < .10, **p < .05  
F = F value for testing null hypothesis that the regression coefficient equals 0  
β = Standardized regression coefficient
In the African Americans (Table 8) cold pressor pain threshold was positively predicted by income and negatively predicted by discrimination encountered when being hired for jobs, with these factors together accounting for 19.5% of the variance in cold pain threshold (\(F(2, 32) = 3.88, \ p < .05\)). Therefore, higher income and fewer experiences of discrimination when being hired for a job were associated with greater cold pressor pain threshold levels.

No significant predictors emerged for cold pressor pain tolerance.

Ischemic pain threshold was positively predicted by income and negatively predicted by education, with these two variables together accounting for 19% of the variance in pain threshold (\(F(2, 33) = 3.65, \ p < .05\)). Thus, higher income but lower education were associated with greater ischemic pain threshold levels. In order to explore, in a post-hoc fashion, the unexpected relationship between higher levels of education and lower ischemic pain thresholds, those reporting a high school diploma or GED as the highest level of educational attainment (\(n = 21\)) were compared with those reporting a college or post-graduate degree (\(n = 14\)) for endogenous pain modulators. The African Americans with higher education had higher plasma NE at rest and in response to both stressors relative to the less educated group (\(F(1, 32) = 3.88, \ p = 0.5\)). This suggests greater sympathetic activation in the African Americans with higher education levels, and is also consistent with the lower baseline NE group having a higher ischemic pain threshold and tolerance than the higher baseline NE group in African Americans but not in non-Hispanic Whites (Figure 5).

The experience of discrimination in a public setting and baseline SBP positively predicted ischemic pain tolerance and baseline NE negatively predicted ischemic pain tolerance in African Americans, accounting for a total of 30% of the variance in ischemic pain tolerance (\(F(3, 33) = 4.31, \ p < .05\)). Thus, more experiences of discrimination in a public setting,
higher baseline SBP, and lower baseline NE predicted greater ischemic pain tolerance. In order to explore, in a post hoc fashion, the unexpected relationship between more experiences of discrimination in a public setting and greater ischemic pain tolerance, African Americans reporting discrimination in public (n = 21) were compared with African Americans who did not report discrimination in public (n = 15) for biological pain modulators. Those who experienced public setting discrimination had significantly higher levels of β-endorphin (0.14 vs. 0.09 ng/mL; F(1, 35 = 12.74, p < .01) and a greater cortisol response to stress (mean cortisol change = +0.71 vs. – 1.0 pg/mL; F(1, 34) = 5.58, p < .05), suggesting greater HPA-axis activation in those reporting more frequent discrimination.

None of the variables entered into the model significantly predicted temporal summation wind-up index scores in African Americans.

Table 8: Stepwise Regression Analyses in African Americans (n = 44)

<table>
<thead>
<tr>
<th>Criterion/Predictor Variable</th>
<th>F</th>
<th>β</th>
<th>Partial R²</th>
<th>Full Model R²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cold Pressor Threshold</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td>6.25**</td>
<td>0.401</td>
<td>0.13</td>
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<tr>
<td>Hired for a Job Discrimination</td>
<td>2.59#</td>
<td>-0.259</td>
<td>0.065</td>
<td>0.195**</td>
</tr>
<tr>
<td><strong>Cold Pressor Tolerance</strong></td>
<td></td>
<td></td>
<td></td>
<td>No Significant Predictors</td>
</tr>
<tr>
<td><strong>Ischemic Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td>6.36**</td>
<td>0.447</td>
<td>0.096</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>3.62*</td>
<td>-0.336</td>
<td>0.095</td>
<td>0.190**</td>
</tr>
<tr>
<td><strong>Ischemic Tolerance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public Setting Discrimination</td>
<td>7.23**</td>
<td>0.423</td>
<td>0.112</td>
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</tr>
<tr>
<td>Baseline Norepinephrine</td>
<td>4.85**</td>
<td>-0.339</td>
<td>0.088</td>
<td></td>
</tr>
<tr>
<td>Baseline Systolic Blood Pressure</td>
<td>4.34**</td>
<td>0.330</td>
<td>0.101</td>
<td>0.301**</td>
</tr>
<tr>
<td><strong>Temporal Summation</strong></td>
<td></td>
<td></td>
<td></td>
<td>No Significant Predictors</td>
</tr>
</tbody>
</table>

*p < .15, *p < .10, ** p < .05  
F = F value for testing null hypothesis that the regression coefficient equals 0  
β = Standardized regression coefficient
African Americans experience more clinical pain (Edwards & Fillingim 2001b; McCracken et al. 2001; Riley et al. 2002b) and report more pain associated with chronic medical conditions (Edwards & Fillingim 2001a) than Caucasians. Increased sensitivity to experimental pain has also been documented, with a clear pattern of African Americans having similar pain threshold but reduced pain tolerance relative to Caucasians (Chapman & Jones 1944; Woodrow et al. 1972; Edwards & Fillingim 1999; Sheffield et al. 2000; Campbell et al. 2005; Mechlin et al. 2005). However, the reasons for these ethnic differences in pain sensitivity are not yet known, and the study presented here was conducted in order to explore mechanisms by which African Americans may be more sensitive to pain. The results of our study, that African Americans had similar pain thresholds but reduced pain tolerance to the cold pressor and ischemic pain tasks relative to non-Hispanic Whites, are consistent with previous findings reviewed above and confirm that our sample is representative of samples used in our prior study.

Our results also indicated that African Americans exhibit enhanced temporal summation relative to non-Hispanic Whites. This is the first study of which we are aware to examine ethnic differences in centrally mediated pain, in this case, indexed by temporal summation of heat pain intensity. We do believe that the magnitude of the ethnic differences in temporal summation wind-up index scores are significant enough to have a clinical impact, as they are similar to differences that have been observed between fibromyalgia patients and pain-free
controls (Staud et al. 2001). The observed enhanced temporal summation may be indicative of central sensitization of pain processing in African Americans. If African Americans do experience enhanced central sensitization, which leads to hyperalgesia (Price et al. 2002), this may explain the increased pain sensitivity that has been observed in African Americans in a variety of studies (Chapman & Jones 1944; Woodrow et al. 1972; Edwards & Fillingim 1999; Sheffield et al. 2000; Campbell et al. 2005; Mechlin et al. 2005). Central mechanisms are believed to be involved in the development and/or maintenance of chronic pain (Mannion & Woolf 2000), and enhanced temporal summation to experimental pain relative to pain free individuals has been observed in various chronic pain conditions (Fusco et al. 1997; Maixner et al. 1998; Price et al. 2002). This may be of particular relevance to African Americans, since African Americans generally experience more chronic pain than non-Hispanic Whites (Edwards et al. 2001b; McCracken et al. 2001; Riley et al. 2002b). As has been postulated for chronic pain patients, enhanced temporal summation in African Americans may indicate that there are ethnic differences in central pain systems that control the temporal integration of CNS responses to noxious stimuli (Maixner et al. 1998), and provides further support for ethnic differences in endogenous pain regulatory mechanisms (Mechlin et al. 2005, 2007). Additionally, the enhanced central sensitization experienced by African Americans may be indicative of their having an increased risk for developing chronic pain.

The results regarding ethnic differences in baseline cardiovascular and neuroendocrine measures were consistent with our expectations. African Americans had marginally higher SBP compared to non-Hispanic Whites, which is consistent with their increased prevalence of hypertension (American Heart Association 2008). While the literature regarding ethnic differences in resting HR is mixed, studies conducted in
individuals aged 18 – 45 (our sample’s age range) also found no ethnic differences in resting HR (Persky et al. 1979; Hinderliter et al. 2004). The equivalent levels of baseline NE were also expected, as the majority of studies have not observed ethnic differences in resting levels of NE (Lichtman & Woods 1967; Tischenkel et al. 1989; Dimsdale et al. 1990; Walker et al. 1992; Light et al. 1994; Yamasaki et al. 1998; Stein et al. 2000; Masi et al. 2004; Mechlin et al. 2005). Additionally, the lack of ethnic differences in baseline β-endorphin concentrations is consistent with our prior study (Mechlin et al. 2007). The lower levels of baseline cortisol we observed in African Americans compared to non-Hispanic White is consistent with our prior study (Mechlin et al. 2005), as well as the work of others (Pratt et al. 1999; Grewen et al. 2005). Although the majority of studies have observed similar levels of baseline cortisol between African Americans and non-Hispanic Whites, all of those were conducted in samples with average ages ranging from 35 to 64 (Yanovski et al. 1993, 1996, 2000; Giannopoulou et al. 2003; Masi et al. 2004; Wilcox et al. 2005; Boyle et al. 2007), while the average ages of participants in this study and two others which found lower baseline cortisol among African Americans ranged from 15 to 27 (Pratt et al. 1999; Mechlin et al. 2005).

With the exception of the cortisol response to stress (discussed below), our stress manipulation was adequate to elicit a significant stress response in all biological measures for both ethnic groups. The fact that we did not observe any robust ethnic differences in cardiovascular or neuroendocrine reactivity to stress was consistent with our hypothesis that only including Blacks of African heritage that were born in the United States, controlling for age of participants, using a well-validated psychological stress procedure, and matching African Americans and non-Hispanic Whites for SES (an index of chronic stress), would result in the two groups exhibiting similar biological responses to stress. This provides
support for the idea that lower SES among African Americans is related to ethnic differences in stress responses. Indeed, lower childhood SES has been associated with increased cardiovascular reactivity to stress in a sample of adults (mean age = 35 years) including both African Americans and Caucasians, although there was no relationship between current SES and cardiovascular reactivity to stress (Williams et al. 2008). Similarly, studies conducted in exclusively African American samples found that lower neighborhood SES was associated with increased cardiovascular reactivity to stress in a sample of young men (mean age = 18; Kapuku et al. 2002), and that lower parental education (an index of SES for children) was associated with increased cardiovascular reactivity in African American girls and boys (mean age = 14 years; Wilson et al. 2000). On the other hand, when examining older adults, lower current SES is associated with decreased cardiovascular reactivity to stress among coronary artery disease patients (mean age = 62 years; Suchday et al. 2005) and among male public servants (mean age = 43 years; Carroll et al. 1997). Similarly, lower SES has been associated with decreased cortisol reactivity to stress in older adults but not younger adults (Neupert et al. 2006). In regard to NE, studies that reported no ethnic differences in SES observed no ethnic differences in NE reactivity (Tischenkel et al. 1989; Dimsdale 1990), while our prior work reported lower SES among African Americans and observed a blunted NE stress response among African Americans (Mechlin et al. 2005), consistent with research indicating blunted NE responses to stress among chronically stressed individuals (Matthews et al. 2001). Therefore, we believe that by controlling for SES in our study, the African Americans and non-Hispanic Whites were better matched in their exposure to stressors, resulting in African Americans not having as much of an increased allostatic load relative to non-Hispanic Whites.
Past research has demonstrated that allostatic load, measured by stress-responsive physiological variables, provides a useful tool for examining the relationship between lower SES and worse health outcomes (Kubzansky et al. 1999). A study conducted in a sample of older men (mean age = 60), reported that lower levels of education predicted higher allostatic load; though, this relationship was mediated by hostility levels of the participants (Kubzansky et al. 1999). However, this study was limited by the fact that it only included males and the sample was primarily Caucasian, thereby limiting the generalizability of the results to females and individuals of other ethnic groups (i.e. African Americans). A longitudinal study found that men and women from lower income families in high school and/or lower incomes at the age of 50 were more likely to have a higher allostatic load than individuals that had a higher family income in high school or at the age of 50 (Singer & Ryff 1999). However, a positive parent-child relationship proved to be somewhat protective of the negative impact of low SES on allostatic load, as individuals who reported a positive relationship with their parents had a lower allostatic load than individuals who reported a negative relationship with their parents regardless of childhood or adult income. Unfortunately, this study did not mention ethnicity of the participants, and was severely limited by inadequate statistical techniques. Another longitudinal study (MacArthur Study of Successful Aging) found that among older men and women (ages 70 – 79), lower levels of education were associated with higher allostatic load, and that this higher allostatic load mediated the relationship between lower SES and a greater incidence of mortality (Seeman et al. 2004). However, 82% of the individuals in the study were Caucasian, again limiting the generalizability to other ethnic groups. A similar study conducted in elderly Taiwanese men and women (mean age = 72) living in Taiwan found that lower levels of education, income,
and occupational status were all individually associated with higher allostatic load. While this study was not conducted in Americans, the authors compared the levels of biological measures used to determine allostatic load in the Taiwanese sample with levels obtained in the MacArthur Study of Successful Aging and found no robust differences. Therefore, this study adds to the literature by observing a relationship between lower SES and greater allostatic load in an ethnic group other than Caucasians (Weinstein et al. 2003). Taken together these studies indicate that there is a strong link between SES and allostatic load in multiple ethnic groups, although other variables may influence this relationship.

Contrary to expectations, we did not observe an increase in cortisol concentrations in response to stress. While we are not sure of the reasoning behind this, one possibility is the time of day that the TSST was administered. Studies have indicated that cortisol levels rise for approximately the first hour an individual is awake, and then decline steadily throughout the rest of the day (Clow et al. 2004; Cohen et al. 2006). Research has shown that cortisol levels show only small spontaneous fluctuations in the late afternoon as compared to the morning (Weitzman et al. 1971). Therefore, many studies that aim to observe a cortisol response to stress have been conducted in the late afternoon to early evening (Kirschbaum et al. 1995a, b, 1999). However, the majority of studies examining ethnic differences in cortisol responses to stress have been conducted in the morning, shortly after waking, which may explain the discrepancies in the literature regarding heightened vs. blunted cortisol responses to stress in African Americans. While our baseline cortisol samples were never collected before 3:00pm, it is likely that our samples needed to be taken even later in the day in order to minimize spontaneous fluctuations in cortisol levels.
While we did not capture a significant cortisol response to stress, our stress levels of cortisol may still contain useful information regarding ethnic differences in cortisol concentrations. The cortisol response to awakening has been used to study ethnic differences in the cortisol stress response as it represents a natural physiological stressor. As previously stated, cortisol levels rise for approximately the first hour an individual is awake, and then decline steadily throughout the rest of the day (Clow et al. 2004; Cohen et al. 2006). All studies examining ethnic differences in response to awakening stress observed a blunted cortisol response in African Americans (Bennett et al. 2004; Cohen et al. 2006; McCallum et al. 2006; DeSantis et al. 2007). The diurnal slope of cortisol (decrease throughout the day) is also used to study stress, as a flattened diurnal cortisol slope (smaller decrease throughout the day) is thought to be indicative of increased exposure to stressors (Cohen et al. 2006). Indeed, multiple studies have found a flattened diurnal slope in African Americans relative to non-Hispanic Whites (Cohen et al. 2006; McCallum et al. 2006; DeSantis et al. 2007). Therefore it is possible that the decreases in cortisol concentrations in response to stress in non-Hispanic Whites (though not statistically significant) may indicate that we were capturing the natural diurnal decrease in cortisol throughout the day. However, in the African American sample a slight (though non-significant) increase in cortisol concentrations in response to stress was observed, which may be related to a flattened diurnal cortisol slope.

The lack of ethnic differences in cardiovascular and neuroendocrine responses to stress may be due to the strict inclusion/exclusion criteria, in addition to controlling for SES, used to select our sample. For example, Anderson et al. (1992) suggested that one reason for increased BP reactivity to stress in African Americans may be due to the fact that African Americans are more likely to have hypertension; however, our study excluded individuals
with hypertension. Additionally, ethnic differences that generally exist in SES (and therefore in exposure to stress, including traumatic stress) may well contribute to the reported ethnic differences in stress reactivity. Though few, if any, of these prior studies on ethnic differences in stress reactivity assessed or controlled for SES, including our prior work (Mechlin et al. 2005). Thus, our recruitment strategy in the present study based on equivalent income levels is a likely factor in our failure to observe any ethnic differences in cardiovascular or neuroendocrine reactivity to stress. However, it is important to note that, as seen in prior studies (Pratt et al. 1999; Grewen et al. 2005; Mechlin et al. 2005), African Americans displayed lower levels of baseline cortisol, which is not inconsistent with exposure to high levels of chronic stress (Caplan et al. 1979; McEwen 1998; Hansen et al. 2006). Additionally, although African Americans and non-Hispanic Whites were matched for SES they were not matched for discrimination stressors. Therefore, while African Americans and non-Hispanic Whites may have had equivalent exposure to stressors related to SES, African Americans were exposed to more stressors related to discrimination, even though there were no differences in perceived stress. Hence, the lower baseline levels of cortisol observed may be reflecting the increased exposure to discrimination stressors in African Americans. Additionally, the lower baseline levels of cortisol may be reflective of a dysregulation of the HPA-axis, which has been associated with various illnesses (McEwen 1998).

A variety of ethnic differences in HPA-axis activity have been observed, and researchers have postulated that ethnic differences in prevalence of certain diseases may be the result of differences in HPA-axis activity (Chong et al 2008). As previously stated, when a stressful stimulus is perceived, the HPA-axis causes the hypothalamus to release CRH.
CRH travels to the anterior pituitary and stimulates the release of ACTH and β-endorphin into the bloodstream. The ACTH in the bloodstream then stimulates the release of cortisol by the adrenal cortex. Studies by Yanovski et al. found that while African Americans have similar levels of resting ACTH, administration of exogenous CRH results in much higher concentrations of ACTH in African Americans relative to non-Hispanic Whites, but no differences in cortisol concentrations (Yanovski et al. 1993, 1995, 1996). Similarly, exercise, which stimulates the HPA-axis, also results in increased concentrations of ACTH but not cortisol in African Americans relative to non-Hispanic Whites (Yanovski et al. 2000).

However, another study found that in response to a mental stressor (TSST), African Americans had lower ACTH and cortisol levels than non-Hispanic Whites, even after controlling for SES (Chong et al. 2008). Additionally, some studies have shown that during pregnancy African American women have lower levels of CRH than their non-Hispanic Whites counterparts (Holzman et al. 2001; Glynn et al. 2007). Although, one study found that while CRH levels were lower in African American pregnant women, there were no ethnic differences in ACTH, but African Americans had lower cortisol levels than non-Hispanic White women at the end of their pregnancies (Glynn et al. 2007). No studies of which we are aware have reported ethnic differences in β-endorphin concentrations (Mechlin et al. 2005, 2007).

Since CRH causes the co-release of ACTH and β-endorphin from the anterior pituitary, and ethnic differences have been observed in ACTH and cortisol concentrations, but not β-endorphin concentrations, it is likely that ethnic differences in HPA-axis activity occur in the CRH-ACTH-cortisol pathway, but not the CRH-β-endorphin pathway. This is also supported by the fact that studies that reported increased ACTH in response to CRH...
challenge and exercise also reported no ethnic differences in cortisol concentrations (Yanovski et al. 1993, 1995, 1996, 2000). Upon further examination, the researchers found that African Americans had a much greater concentration of ACTH-immunoreactivity (used to measure ACTH) compared to non-Hispanic Whites, which was actually the result of a greater concentration of nonintact ACTH. This nonintact ACTH is believed to be bioinactive; therefore, while African Americans had higher concentrations of ACTH, the concentrations of bioactive ACTH were similar between African Americans and non-Hispanic Whites, resulting in no differences in the amount of cortisol being released (Yanovski et al. 1996). If there is a dysregulation in the CRH-ACTH-cortisol pathway but not the CRH-β-endorphin pathway, this would explain why we found ethnic differences in cortisol but not β-endorphin concentrations. Additionally, it might explain the indirect relationship we observed in African Americans between β-endorphin and pain sensitivity (African Americans who reported greater discrimination in a public setting had higher ischemic pain tolerance, which we believe was the result of their also having higher β-endorphin concentrations), which was not observed between cortisol and pain sensitivity.

The finding that higher SBP was related to higher pain tolerance to the ischemic pain task in non-Hispanic Whites is in accordance with previous studies (Zamir & Shuber 1980; Maixner 1991; Bruehl et al. 1992; Sheps et al. 1992; Bragdon et al. 1997, 2002; al’Absi et al. 2000; Sheffield et al. 2000; Edwards & Fillingim 2001; Campbell et al. 2004; Bacon et al. 2006; Lewkowski et al. 2008; Ring et al. 2008). The relationship between increased BP and reduced pain sensitivity is thought to be mediated by BP-induced stimulation of mechanoreceptive afferents (i.e. baroreceptors) since stimulation of these visceral afferents in animal models has been shown to diminish somatomotor reflexes indicative of analgesic-like
effects (Dworkin et al. 1979; Randich & Maixner 1986; Maixner 1989, 1991). In humans, natural increases in baroreceptor activity are also associated with decreased pain sensitivity (Droste et al. 1994; Edwards et al. 2001c; Edwards et al. 2003; al’Absi et al. 2005). While no studies have examined baroreceptor mediation of pain sensitivity as a function of ethnicity, it has been shown that African Americans have decreased baroresponses to transient BP elevation relative to Caucasians during sleep (Crisostomo et al. 1998), and that they show abnormal BP responses to postural changes, indicative of alterations in baroreceptor function (Goldstein & Shaprio 1995). Thus, diminished baroreceptor function in African Americans may contribute to the absence of a relationship between BP and pain sensitivity.

As has been postulated for the absence of BP-pain sensitivity relationships in chronic smokers and chronic pain patients (Bruehl et al. 1998, 2002, 2008; Bragdon et al. 2002; Girdler et al. 2005), we previously speculated (Mechlin et al. 2005) that larger stress-induced BP responses to real-life stress in African Americans, especially if occurring in the context of frequent stress exposure resulting from chronic stress, including chronic ethnic discrimination (Thompson 1996; Kessler et al. 1999; Schulz et al. 2000; Troxel et al. 2003), may repeatedly activate baroreceptor mechanisms and, over the long-term, contribute to a desensitization of the baroreceptor reflex pathway and an uncoupling of BP-baroreceptor mechanisms. In the present cohort of African Americans, however, while there was no relationship between SBP and pain sensitivity when analyses were based on a median split of baseline SBP levels, when SBP was entered as a continuous variable in the regression model it did positively predict greater ischemic pain tolerance in African Americans. Since median splits dichotomize the predictor variable (i.e. SBP), the variability of the predictor variable is
reduced, resulting in decreased statistical power. Consequently, many statisticians consider analyses conducted with a continuous predictor variable to be stronger than median splits (MacCallum et al. 2002). Therefore, we believe that the finding of no relationship between SBP and ischemic pain tolerance in African Americans is most likely a Type II error, and that higher SBP was, in fact, associated with higher ischemic pain tolerance in our cohort of African Americans. While this finding is in contrast to our previous report, which found no relationship between BP and pain sensitivity in African Americans (Mechlin et al. 2005), differences in sample characteristics may explain this discrepancy. In the current report African Americans and non-Hispanic Whites were of similar levels of SES; however, in the prior study African Americans were less educated (lower SES) than non-Hispanic Whites (Mechlin et al. 2005). Therefore, the current sample of African Americans may have had fewer chronic stressors related to SES, resulting in fewer BP surges, and thus protecting them from an uncoupling of blood-pressure pain sensitivity pathways.

Expected relationships between higher levels of NE and increased pain tolerance were found in non-Hispanic Whites for both the ischemic and cold pressor pain tasks (Sagen et al. 1991; Girdler et al. 2005; Mechlin et al. 2005). However, in African Americans, while there was no relationship between NE and cold pressor pain, the higher NE group had lower pain threshold and tolerance to the ischemic pain task. Our previous research documented the same relationship in African Americans, with higher baseline NE related to lower ischemic pain tolerance (Mechlin et al. 2005); however, since these were the only significant correlations observed in African Americans for that study, and since the relationships were in the opposite direction expected, we had assumed that the correlations were spurious. While the finding that higher NE is associated with lower pain threshold and tolerance is contrary to
prior findings in animals (Sagen et al. 1991) and primarily Caucasian samples of healthy humans (Girdler et al. 2005; Mechlin et al. 2005), some research has indicated that chronic pain patients may show a (reverse) hypersensitivity to NE, such that administration of NE in certain types of chronic pain results in increased pain, while it has no effect on healthy controls (Davis et al. 1991; Torebjork et al. 1995; Ali et al. 2000). Similar results have been obtained in some animal models of chronic pain (Xanthos et al. 2008). Thus, the finding that higher NE is associated with lower pain thresholds and tolerance in African Americans may provide further support for ethnic differences in endogenous pain regulatory mechanisms, and may be a marker or risk factor for the development of chronic pain in the future.

While the lack of a relationship between cortisol or β-endorphin and pain sensitivity in African Americans was in accordance with our previous results (Mechlin et al. 2005), the fact that we did not find any relationships between higher cortisol or β-endorphin and reduced pain sensitivity in the non-Hispanic Whites was unexpected, as this has been documented previously in the literature (al’Absi et al. 2002; Girdler et al. 2005; Mechlin et al. 2005, 2007). While the absence of such relationships in the present study remains unexplained, the significant circadian influence on cortisol combined with our sampling strategy may provide some insight. Specifically, the fact that we did not observe a cortisol stress response, suggests that we may have conducted our study at the wrong time of day, when the circadian influence is associated with the descending diurnal cortisol slope (Kirschbaum et al. 1995a). Thus, if we sampled cortisol at a different time during the day when levels were at a more steady state, perhaps we would have seen a relationship between cortisol and pain sensitivity. Our failure to observe relationships between β-endorphin and pain sensitivity may have resulted from not collecting stress samples of β-endorphin, relying
instead exclusively on baseline samples, though that decision was based on lack of
established time course for capturing a β-endorphin response to mental stress. In previous
studies showing relationships between β-endorphin and pain sensitivity in humans, β-
endorphin has been administered to participants (Hosobuchi & Li 1978; Sadigh et al. 2007);
or changes in β-endorphin concentrations were measured in response to a pain procedure
(Akil et al. 1978; Hosobuchi et al. 1979; Suzuki et al. 2007), exercise test (Sheps et al. 1987),
a speech stressor (Sheps et al. 1995; Bragdon et al. 2002), or pharmacological manipulation
(Jarmukli et al. 1999). Additionally, Jarmukli et al. (1999) did not find any effect of
circulating, basal β-endorphin levels on angina pain. And in fact, Sheps et al. (1995) found a
relationship between pain sensitivity and β-endorphin for stress levels of β-endorphin, but not
baseline levels of β-endorphin. In fact, only 2 studies of which we are aware (Straneva et al.
2002; Mechlin et al. 2007) found a relationship between baseline levels of β-endorphin and
pain sensitivity. An additional possibility for an absence of relationships involving HPA-axis
factors and pain sensitivity is that our sample size may not have been large enough to detect
such relationships; however, this is unlikely since our sample sizes were similar to or larger
than previous studies documenting relationships between HPA-axis measures and pain
sensitivity (al’Absi et al. 2002; Girdler et al. 2005; Mechlin et al. 2005, 2007). Additionally,
when cortisol and β-endorphin were entered into the regression model as potential predictors
of pain sensitivity, neither of them emerged as possible predictors at a significance level of p
< .15, the criterion employed by the statistical software. This indicates that the lack of
relationship between HPA-axis measures and pain sensitivity was probably not due to a lack
of power as the result of a small sample size, since the relationships did not approach
statistical significance.
In non-Hispanic Whites, regression analyses indicated that increased pain threshold and pain tolerance were predicted primarily by biological measures (higher levels of NE and SBP and lower HRs), which is consistent with previous research (Maixner et al. 1991; Sagen et al. 1991; Sheffield et al. 2000; al’Absi et al. 2002; Girdler et al. 2005; Mechlin et al. 2005). The only SES measure to predict pain sensitivity in non-Hispanic Whites was occupational status, with higher occupational status predicting higher ischemic pain threshold. In contrast, for the African Americans, higher pain threshold and tolerance were predicted by higher levels of income, SBP, discrimination in a public setting and lower levels of education, NE, and discrimination in being hired for a job. While the finding that higher levels of education were associated with lower ischemic pain threshold in African Americans is in contrast to general models of SES and health outcomes, these models often fail to take into account the importance of contextual factors in assessing the SES-health link. The possibility exists that African Americans with higher levels of education may, under certain conditions, actually be exposed to more chronic stressors. This is supported in part by our own post-hoc analyses showing higher plasma NE in African Americans with more education, potentially indicative of greater stress-induced sympathetic activation. This idea is also supported by research of others which reported that African Americans of both lower SES and higher SES reported more stressors than African Americans of middle SES (Turner et al. 2003). Additionally, this is also supported by a study (Light et al. 1995) which found that African Americans with high status jobs who were also high active copers had higher BP at work and higher DBP at rest and during mental stressors relative to other African Americans and non-Hispanic Whites. In a similar vein, the possibility exists that African Americans with higher levels of education experience more workplace discrimination, consistent with the evidence that
higher SES does not protect against perceived discrimination (Vines et al. 2006), which could account for the relationship we observed between greater discrimination in the job setting and greater pain sensitivity.

In contrast, another indicator of SES (i.e. income) positively predicted both cold pressor and ischemic pain threshold in African Americans, such that higher income was associated with less sensitivity to noxious stimuli. This differential influence of education and income on pain sensitivity is consistent with more recent conceptualizations regarding SES and health, whereby different indicators of SES can have different effects on health outcome. For example, a study conducted in adolescents found that while no relationships were observed between cortisol and family education and occupational status, lower family income and savings were both correlated with lower resting cortisol, consistent with the idea that increased stress (i.e. lower SES) may be associated with blunted cortisol levels. Additionally, lower family savings was associated with higher SBP and HR, but family income, education, and occupational status were not associated with SBP and HR (Chen & Paterson 2006). It has been postulated that family education may be related to knowledge about healthy behaviors, while family income is likely related to access to resources and healthcare. Therefore, income may have stronger relationships with some health measures since knowledge about healthy behaviors may be irrelevant if individuals do not have access to the necessary resources to engage in a healthy lifestyle (Chen & Paterson 2006).

Our regression analyses indicated that in general, the biological stress measures were more robust predictors of pain sensitivity in non-Hispanic Whites, while discrimination stress and indices of SES were more robust predictors in African Americans; findings that are not inconsistent with our previous results (Mechlin et al. 2005, 2007). However, our post-hoc
analyses suggest that the relationship between psychosocial stressors and pain sensitivity in African Americans may involve stress-related alterations in endogenous pain moderators, as evidenced by the fact that African Americans with higher levels of education (and greater pain sensitivity) had greater concentrations of NE, and African Americans who reported experiencing discrimination in a public setting (and lesser pain sensitivity) had greater concentrations of β-endorphin. These findings for heightened SNS and HPA-axis activity being associated with higher education levels and experiences of discrimination, respectively, are consistent with the idea that African Americans may be exposed to unique psychosocial chronic stressors. The fact that biological measures may indirectly predict pain sensitivity in African Americans (i.e. through their relationship with SES) indicates that in order to understand the increased risk for chronic pain conditions in African Americans, further research should focus on these complex biopsychosocial relationships in African Americans.

It was surprising that none of the biological or psychosocial stress measures were associated with temporal summation wind-up index scores. However, no studies of which we are aware have specifically examined the relationship between verbal ratings of temporal summation pain and biological measures. While the reason for our not finding a relationship between biological or psychosocial measures and temporal summation is currently unknown multiple possibilities exist. One possibility is that there are anatomical differences in the location of pain processing between central sensitization and the peripheral pain tests that were utilized in this study. Since central sensitization occurs as the result of increased neuronal excitability at the level of the dorsal horn in the spinal cord, it is possible that this pain pathway is more isolated, and less interactive with other physiological systems. Therefore, the relationships observed between ischemic and cold pressor pain and biological
measures may not be present for central sensitization, since central sensitization is the result of changes that occur before the message is sent to the brain. Another possibility is that, similar to the redundancy observed with stress-responsive biological systems, there may be multiple pain processing pathways. Redundancy in pain processing pathways would serve as an evolutionary advantage so that when one system is damaged, an organism could still perceive pain in order to increase awareness of any possible injuries; though this is not an explanation for why one pathway appears to be stress-responsive and the other pathway (temporal summation) does not. It is also possible that genetics may determine sensitivity to central sensitization rather than stress-responsive biological systems, as different genetic variants are associated with increased sensitivity to experimental pain (Diatchenko et al. 2005). However, examining the relationship between biological measures and central sensitization is particularly important since chronic pain patients exhibit increased temporal summation (Fusco et al. 1997; Maixner et al. 1998; Staud et al. 2001; Price et al. 2002), and it has been speculated that exposure to frequent or major stressors may be involved in the onset of chronic pain conditions, such as fibromyalgia (Bradley 2005; Yunus 2007).

Additionally, one study reported that lower cortisol levels upon awakening and a blunted diurnal cortisol slopes, findings associated with high levels of chronic stress (Caplan et al. 1979; Hansen et al. 2006), predicted the development of widespread pain (McBeth et al. 2007). Therefore future studies need to be conducted to examine whether enhanced temporal summation and frequent exposure to stressors (and resultant physiological responses to stressors) act independently or synergistically in the development of chronic pain.

As a result of the findings in the current study, our biobehavioral model has been slightly modified.
In this biobehavioral model, as before, lower SES both directly and indirectly influences an individual’s initial response to acute stress. However, it is important to note that, as with the previous model, each of the indices of SES separately influences physiological responses to stress, and hence pain sensitivity as well. This is particularly important as our results indicated that higher income predicted less sensitivity to pain in African Americans, whereas higher levels of education were associated with greater sensitivity to pain. We postulated that the relationship between higher levels of education and greater sensitivity to pain in African Americans was the result of individuals with more education having higher levels of NE, which was associated with greater sensitivity to ischemic pain in the African American sample. Thus, each of the indices of SES separately influence stress responses and thereby pain sensitivity as well. As before, the model also
predicts that lower SES indirectly influences stress responses by its association with increased trauma exposure (Schellenbach et al. 1991; Murata 1994; Drake & Pandey 1996) and increased levels of other chronic stressors, including discrimination, that are associated with low SES.

As with the previous model, an overarching hypothesis is that while exposure to psychosocial stressors early in life results in normal activation of SNS, HPA-axis and other stress responsive measures, chronic and/or repeated exposure to psychosocial stressors will, over time, result in a dysregulation of stress responses and an uncoupling of stress-responsive measures with pain processing. This idea is supported by our results because little evidence of ethnic differences in the physiological measures were observed when African Americans and non-Hispanic Whites were matched for SES. By matching the samples for SES, we believe that African Americans and non-Hispanic Whites were exposed to similar levels of chronic stressors, and therefore had a similar frequency of physiological responses to stress. Since the frequency of physiological responses to stress was similar between the two groups, we did not observe robust dysregulations in stress-responsive biological systems in African Americans relative to non-Hispanic Whites. Similarly, we observed a relationship between higher BP and greater pain tolerance in both African Americans and non-Hispanic Whites. Therefore, this model predicts that similar levels of SES will result in similar relationships between stress-responsive biological measures and pain sensitivity. However, SES is not the only factor influencing stress-responsive physiological systems and pain sensitivity, as we did observe a blunted level of baseline cortisol in African Americans. The fact that some ethnic differences remained despite controlling for SES is likely due to the experience of more chronic stressors that may not be solely the result of SES, such as discrimination.
Indeed, our results indicated that discrimination was associated with pain tolerance in African Americans but not non-Hispanic Whites. Therefore, as before, our model includes that other chronic stressors, which may or may not be related to SES (i.e. discrimination), also influence stress responses and hence pain perception.

Since we did not observe any relationships between temporal summation and biological measures, the model no longer shows stress-responsive biological measures predicting central sensitization. Instead, we have added genetics as a possible cause of increased central sensitization as well as general pain sensitivity, since different genetic variants are associated with increased sensitivity to experimental pain (Diatchenko et al. 2005). Additionally, as before, the model predicts that increased central sensitization in pain processing will result in increased pain sensitivity. Genetics is also shown as being a cause of SES and other chronic stressors, since ethnicity (a genetic factor) is strongly associated with SES and chronic stressors.

There are limitations to our study that should be noted. First, in the regression analyses, we used single items from the discrimination questionnaire as predictors of pain sensitivity. However, this approach is partially supported by prior work indicating that different forms of discrimination may differentially predict health outcomes (Brondolo et al. 2008). Further research should include discrimination measures that are validated using factor analysis to identify subscales composed of numerous items identifying discrimination that occurs in different settings. The fact that our samples were relatively young and homogenous may limit the generalizability of our findings. Additionally, the generalizability of our findings to African Americans is limited because our ethnic groups were matched for SES, while African Americans are generally of lower SES than non-Hispanic Whites.
However, this was advantageous since it allowed us to partial out the effects of ethnic differences in SES on pain sensitivity. Another limitation related to SES may be that we only assessed current SES and did not assess childhood SES. This may be particularly relevant since one study showed that a longer duration of poverty in childhood was associated with elevated urinary cortisol and blunted SBP and DBP reactivity to stress (Evans & Kim 2007). Therefore, studies recruiting individuals reflecting the entire spectrum of SES from both ethnic groups and measuring childhood SES are warranted to look at the influence both current and early life stress may have on pain perception. Additionally, examining if the negative effects of low childhood SES can be undone by high adult SES and if the protective effects of high childhood SES can be abolished by low adult SES will provide further insight into the complex biopsychosocial relationship between SES and pain sensitivity. While controlling for ethnic differences in SES but not ethnic differences in exposure to discrimination stressors allowed us to more accurately measure the contribution of discrimination stressors to biological stress responses and pain sensitivity, future studies that recruit African Americans and non-Hispanic Whites who report equal levels of discrimination will also be helpful in further elucidating the role of psychosocial stressors in ethnic differences in stress responses and pain sensitivity. Although recruiting African Americans that report few experiences of discrimination would be extremely difficult, with intensive recruitment strategies this could be achieved, as there were African Americans in the current study who did not report any experiences of discrimination.

In conclusion, we replicated previous reports that African Americans have similar pain thresholds but lower pain tolerances than non-Hispanic Whites, and extended this body of work by showing that African Americans also exhibit increased temporal summation
relative to non-Hispanic Whites. We did not find any ethnic differences in cardiovascular or neuroendocrine reactivity to stress, which we postulate may be the result of our samples being matched for SES. We also found that while pain sensitivity was primarily predicted by biological measures in non-Hispanic Whites, it was primarily predicted by psychosocial measures (discrimination stress and SES) in African Americans. These findings suggest ethnic differences in biobehavioral mechanisms contributing to pain perception and indicate the need for future studies examining more comprehensive assessments of ethnically relevant psychosocial factors.
APPENDIX

EOD Scale

This questionnaire is going to ask about how you and others like you are treated, and how you typically respond.

1. If you feel you have been treated unfairly do you usually: (please select the best response)
   a. Accept it as a fact of life
   b. Try to do something about it

2. If you have been treated unfairly, do you usually: (please select the best response)
   a. Talk to other people about it
   b. Keep it to yourself

3. Have you ever experienced discrimination, been prevented from doing something, or been hassled or made to feel inferior in any of the following situations because of your race, ethnicity, or color? If the answer to any of the following questions is yes, please indicate about how many times this occurred in each setting.
   o At school: Yes No
     ▪ How many times did this happen?
       □ Once
       □ Two or Three Times
       □ Four or More times
   o Getting hired or getting a job: Yes No
     ▪ How many times did this happen?
       □ Once
       □ Two or Three Times
       □ Four or More times
   o At work: Yes No
     ▪ How many times did this happen?
       □ Once
       □ Two or Three Times
       □ Four or More times
   o Getting housing: Yes No
     ▪ How many times did this happen?
       □ Once
       □ Two or Three Times
       □ Four or More times
   o Getting medical care: Yes No
     ▪ How many times did this happen?
       □ Once
       □ Two or Three Times
- Four or More times
- Getting service in a store or restaurant: Yes No
  - How many times did this happen?
    - Once
    - Two or Three Times
    - Four or More times
- Getting credit, banking loans, or a mortgage: Yes No
  - How many times did this happen?
    - Once
    - Two or Three Times
    - Four or More times
- On the street or in a public setting: Yes No
  - How many times did this happen?
    - Once
    - Two or Three Times
    - Four or More times
- From the police or in the courts: Yes No
  - How many times did this happen?
    - Once
    - Two or Three Times
    - Four or More times
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