ETHNIC DIFFERENCES IN DIFFUSE NOXIOUS INHIBITORY CONTROLS (DNIC)

By

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Pain is a complex, multidimensional phenomenon influenced by multiple biological and psychosocial variables. Considerable evidence has demonstrated that the experience of both clinical and experimental pain differs among ethnic groups, with African Americans generally reporting greater sensitivity to chronic and experimentally induced pain; however, little research has examined the origins of these differences. It is important to understand potential ethnic differences in pain perception, because this may have important implications for diagnosing and treating pain. Differences in central pain-inhibitory mechanisms could potentially explain the differences in pain reports by African American and Non-Hispanic white individuals; however, standard laboratory pain measures do not directly assess pain inhibitory mechanisms. One method frequently used in this regard is assessment of diffuse noxious inhibitory controls (DNIC). DNIC, or counterirritation, refers to the process whereby one noxious stimulus inhibits the perception of a second painful stimulus. This phenomenon is thought to reflect

descending inhibition of pain signals. The current study evaluated responses to two commonly used experimental pain procedures in healthy young adults from two different ethnic groups: African Americans and non-Hispanic whites. Perceptual responses (e.g., pain threshold, pain ratings) as well as physiological responses (e.g., blood pressure, emg response) were assessed.

Assessment of the NFR threshold, or RIII response, is highly correlated with subjective pain thresholds, such that increases in stimulus intensity are associated with increased pain perception and is therefore frequently used in pain research. The NFR is based on the measurement of stimulus-induced spinal reflexes, and allows standardized placement and a high level of reproducibility. This measure allowed for assessment of both self-reported pain and to quantify an individual's physiological response. This was utilized along with an ischemic task for counter-irritation.

The findings of this study provide evidence of ethnic differences in the NFR and suggest group differences in the level of physiological activation of the nociceptive system. Additionally, African Americans experienced reduced endogenous pain modulation relative to whites, which suggests significant differences in descending pain inhibition. No ethnic differences were observed in reflex rates or cardiovascular response. The findings of this study may contribute to observed ethnic differences in clinical and experimental pain findings.

CHAPTER 1
INTRODUCTION

Considerable evidence has demonstrated that the experience of both clinical and experimental pain differs across ethnic groups, with the most substantial evidence demonstrating greater sensitivity to clinical and experimentally induced pain in AA compared to non-Hispanic whites. Recently, several investigators have noted ethnic differences in pain-related symptoms among a variety of chronic pain conditions (Green et al 2003). Edwards and colleagues (2001) found higher levels of pain and disability among AA relative to white patients seen in a multidisciplinary pain center. Other studies also indicate that AA with chronic pain report higher levels of pain unpleasantness, greater pain-related emotional distress, and increased pain behaviors relative to whites (Riley et al. 2002; Green et al. 2003).

Because ethnic differences in clinical pain responses can be influenced by factors such as disease severity and disparities in pain treatment, it is important to examine ethnic differences in pain perception among healthy individuals (Todd 1996;Stewart et al. 1996;Cleeland et al. 1997;McCracken et al. 2001). Laboratory studies also suggest increased experimental pain sensitivity among African Americans as compared to whites (Zatzick and Dimsdale, 1990). For instance, lower heat pain thresholds and tolerances were reported decades ago among African American subjects compared to whites by Chapman and Jones (1944), and increased sensitivity to heat pain among African Americans has been reported more recently by Edwards and Fillingim (1999) as well as Sheffield and colleagues (2000); particularly for measures of pain unpleasantness.

Similarly, cold pressor pain tolerances were lower in a combined group of African Americans and Hispanics in comparison to whites (Walsh et al. 1989). Additionally, African Americans report greater intensity and unpleasantness in response to a modified ischemic task when compared to whites, using a standardized rating scale (Campbell et al. 2004). Finally, results from our laboratory indicated significantly lower tolerance for heat pain, ischemic pain and cold pressor pain in African Americans when compared to whites. Ratings of intensity and unpleasantness of supra-threshold heat pain were also higher among African Americans than whites (Campbell et al. 2005). Thus, ethnic differences in both clinical and experimental pain responses have been widely reported; however, most previous studies have not attempted to examine the origins of these differences.

Differences in central pain-inhibitory mechanisms could potentially explain the differences in pain reports by African American and Non-Hispanic white individuals; however, standard laboratory pain measures do not directly assess pain inhibitory mechanisms. One method frequently used in this regard is assessment of diffuse noxious inhibitory controls (DNIC). DNIC, or counterirritation, refers to the process whereby one noxious stimulus inhibits the perception of a second painful stimulus. This phenomenon is thought to reflect descending inhibition of pain signals (Le Bars et al. 1979a; Price and McHaffie 1988). DNIC is presumed to operate through activation of descending supraspinal inhibitory pathways initiated by release of endogenous opioids (Le Bars et al. 1979b;Kraus et al. 1981;Roby-Brami et al. 1987;De Broucker et al. 1990).

The DNIC system has been examined extensively in non-human animals with early studies focused on the mechanisms involved in the process of DNIC; however, more

recent studies in humans have utilized the process in order to examine possible deficiencies in descending inhibitory processes in certain populations. For example, sex differences (Staud et al. 2003), and age differences (Edwards et al. 2003a) have been observed in DNIC, suggesting differing endogenous pain inhibition across certain groups. Clinical pain conditions such as fibromyalgia (Lautenbacher and Rollman 1997;Kosek and Hansson 1997;Staud et al. 2003), osteoarthritis (Kosek and Ordeberg 2000), trapezius myalgia (Leffler et al. 2002a), rheumatoid arthritis (Leffler et al. 2002b), and peripheral nerve injury (Bouhassira et al. 2003) also show evidence of impaired DNIC responses; suggesting a possible role for dysregulation of pain inhibitory systems in the acquisition or maintenance of the condition (Staud et al. 2003). Ethnic differences in DNIC may suggest that deficiencies in central inhibitory mechanisms may contribute to the more robust clinical and experimental pain responses often observed in African Americans.

Use of pain rating scales as a primary method of assessing pain perception is a frequently used and practical option; however, group differences pain reports could be related to group differences in use of the pain scales (e.g. see Campbell, et al, 2004). Thus, electrophysiological alternatives, such as the nociceptive flexion reflex (NFR), may provide important information regarding ethnic group differences in nociceptive responses, which may be less susceptible to the biases that may influence subjective rating scales (Skljarevski and Ramadan 2002). The NFR is based on the measurement of stimulus-induced spinal reflexes (Willer 1977), and can be administered in a standardization fashion, and has been shown to have adequate reproducibility. Assessment of the NFR threshold, or RIII reflex, is highly correlated with subjective pain thresholds, such that increases in stimulus intensity are associated with increased pain

perception (Willer 1977; Peters et al. 1992; Skljarevski and Ramadan 2002). This methodology permits assessment of both self-reported pain and quantification of an individual's physiological response. While numerous studies have examined changes in subjective pain threshold and NFR changes during counterirritation procedures, no studies to date have systematically examined ethnic differences in the NFR or DNIC. This study was designed to further elucidate the nature of ethnic differences in pain perception by investigating responses to DNIC using the NFR, testing the hypothesis that African Americans, relative to non-Hispanic whites, may be deficient in endogenous pain modulation.

CHAPTER 2
RESEARCH DESIGN AND METHODS

The final study sample consisted of fifty-seven healthy young adults (29 African American, 28 non-Hispanic white). One white individual discontinued participation following the baseline session, all other subjects completed the protocol. Demographic information is presented in Table 3-1. The University of Florida Institutional Review Board approved all study procedures. All subjects participated in two experimental sessions, lasting up to 2 hours; women were scheduled during their follicular phase (i.e. days 4-9 of the menstrual cycle) to reduce variability associated with the menstrual cycle (Riley et al. 1999). During the first session, verbal and written informed consent were obtained; after which participants completed a health history questionnaire, which indicated that all were in good health and had no prior history of pain problems, then complete a series of questionnaires assessing demographic information, mood, catastrophizing, and hypervigilance (described in detail below). Ethnicity was determined using self-report. Following completion of the questionnaires participants were instrumented (see procedure below), and rested for 10 minutes, after which their blood pressures was measured for five minutes using an automated blood pressure cuff, then their NFR threshold was determined.

During the second session, one DNIC assessment was conducted, as well as one sham DNIC ($DNIC_S$) assessment, during which an ischemic cuff was not inflated, these procedures were conducted in a counterbalanced order. Mood questionnaires were completed prior to NFR instrumentation, and participant's right arm maximum grip

strength was measured. A ten-minute rest period was then observed, followed by five minutes of continuous blood pressure readings. The level of electrical stimulation delivered during the DNIC procedure was individually determined for each subject in order to produce moderate pain, (i.e. a rating of 45 on a 0-100 scale, where 0 = no sensation and 100 = the strongest imaginable sensation of any kind). Repeated assessment of the nociceptive flexion reflex at this stimulus intensity was conducted each minute for five minutes during each of the following time periods: 1) 5-minute baseline period; 2) five minutes of ischemic arm pain (or sham ischemic procedure); 3) five-minute post ischemic (or sham) time period. Following completion of this sequence, a 10-minute rest period was observed, after which responses to another 5 minutes of electrical stimulation were assessed. After a 15-minute rest period this sequence was conducted in the same manner, under the condition (DNIC vs. sham) that was not administered during the first sequence. Following both the DNIC and $DNIC_S$ sequences participants rated their attention to the sensation in their right arm while the cuff was on, their attention to the sensation in their ankle (the site of electrical stimulation) during the time the cuff was on their right arm, as well as the degree to which the sensation in their ankle differed due to the cuff on a -100 to 100 scale (-100 = much weaker, 100 = much stronger).

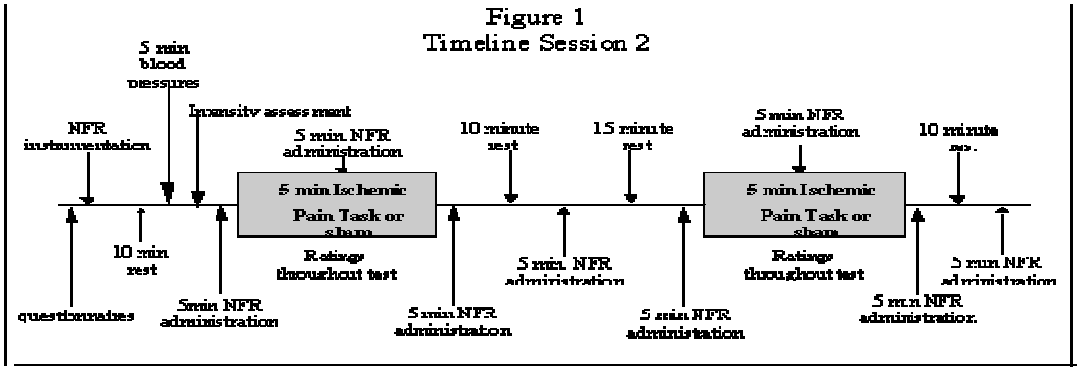


Figure 2-1. Timeline Session 2

Nociceptive Flexion Reflex Assessment

Subjects underwent electrical stimulation delivered via a bar electrode applied to the left sural nerve using Digitimer DS7A constant current stimulator (Herfordshire, UK). The nociceptive withdrawal reflex was assessed using two, 12 mm disposable Conmed (Utica, NY) electrodes, one placed over the left biceps femoris muscle, the other placed over the reference sight, which was on the left lateral epicondyle of the femur. All sights were cleaned and gently abraded to achieve an impedance of less than 10,000 Ohms prior to electrode placement. Participants were comfortably seated in a recliner in order to maintain a 60-degree angle of the knee. Electrical stimulation was applied in a series of ascending and descending steps. A 5-pulse train (1 ms pulse duration, 3 ms inter-pulse interval) was administered approximately once every 30 seconds. During reflex assessment, participants rated the perceived intensity of each pulse using a 0 to 100 rating scale (0=no sensation and 100=strongest imaginable sensation of any kind). Stimulation intensity began at 0 milli-amps (mA) and increased in 2mA steps until the nociceptive withdrawal reflex was obtained (or a maximum intensity of 40mA, or termination was requested by the participant). Stimulus intensity was then decreased in 1mA steps until the reflex was no longer observed. This procedure was repeated using 1mA steps so that the nociceptive withdrawal reflex appeared and subsided three times in total. Reflex threshold was defined as the average of the peaks during the three sequences. During the second session, stimulation was delivered at the intensity of the participant's nociceptive flexion reflex threshold, then increased until a rating of 50 was obtained, following which stimulation was reduced by .2 mA until a rating of 30 was reached. The stimulation intensity at a rating of 45 was calculated and used in all subsequent testing.

Test Stimulus

In order to elicit consistent responses, electrical stimulation during the DNIC and sham procedures was set at the intensity rated as 45 by the individual participant. This stimulation intensity was determined at the beginning of the second session as follows. Electrical stimulation was delivered at the intensity of the participant's nociceptive flexion reflex threshold (from session 1), then increased until a rating of 50 was obtained, following which stimulation was reduced by .2 mA until a rating of 30 was reached. The stimulation intensity at a rating of 45 was calculated and used in all subsequent testing.

Conditioning Stimulus

Ischemic pain was induced using a modified submaximal effort tourniquet procedure adapted from France and Suchowiecki (1999). Following five minutes of NFR testing, participants completed 2 minutes of handgrip exercises, at which time their arm was elevated for 30-seconds, then the cuff was inflated to a pressure of 240 mm Hg (or not in the sham procedure). Five minutes of ischemic arm pain was conducted with concurrent NFR administration. At 30-second intervals, participants rated the intensity of their arm pain on 0 to 20 box scales (Coghill and Gracely, 1996). After five minutes of arm occlusion (or the sham procedure), the cuff was deflated and RIII was continued for an additional 5 minutes.

Psychological Measures

In order to determine the contribution of psychosocial factors to group differences in experimental pain responses, including DNIC, subjects completed the following psychological questionnaires.

The Pain Catastrophizing Scale (PCS) (Sullivan et al. 1995) consists of 14 items rated on a 5-point scale ranging from 0 (not at all) to 4 (all the time). Participants are

instructed to indicate the degree to which they have specified thoughts and feelings when experiencing pain. The measure assesses three dimensions of catastrophizing: rumination, magnification, and helplessness. The PCS has been validated for both clinical and nonclinical samples (Sullivan et al. 1995;Osman et al. 2000).

The Kohn Reactivity Scale (Kohn 1985) consists of 24 items that assess an individual's level of reactivity or central nervous system arousability and has been used as a measure of hypervigilance (McDermid et al. 1996). This measure has been shown to correlate negatively with pain tolerance (Dubreuil and Kohn 1986) and has been reported to have adequate internal consistency, ranging from alpha of 0.73 to 0.83 (Kohn 1985).

The Frid Scale (FRID) is a 10 item, 5-point Likert scale assessing expectancies and attitudes regarding experimental pain procedures. The measure consists of three subscales including Psychological Involvement in the experiment, Negative Expectancies regarding the experiment, and Efficacy and Control beliefs (Frid et al. 1979).

The Visual Analogue Mood Scale (VAMS) consists of 8 horizontal 100 mm VAS scales representing different aspects of mood. Participants were asked to mark their current mood by placing a vertical mark on the line. The VAMS was has been shown to have adequate validity (Killgore 1999).

CHAPTER 3
DATA REDUCTION AND ANALYSIS

Mean NFR values and verbal ratings of pain corresponding to the reflex threshold among African Americans and non-Hispanic whites were calculated, and analysis of variance (ANOVA) was conducted to characterize ethnic differences in the NFR and pain perception.

To examine differences in reflex activity during DNIC, the total number of reflexes occurring during the five minute pre-DNIC (or sham) and DNIC (or sham) assessment periods was computed. Then, a difference score (total number of pre-DNIC reflexes minus during DNIC reflexes) was calculated for each subject. A 2 (group) X 2 (condition: DNIC vs. sham) mixed model ANOVA was then conducted to determine the reliability of differences in DNIC between ethnic groups, using the change score as the dependent variable. Analysis of electrical pain ratings was conducted in a similar fashion. Specifically, the average electrical pain rating was computed for each time period (pre-DNIC or pre-sham, during DNIC or during sham), and these changes scores were used as dependent measures in mixed model ANOVAs, as described for reflex activity.

The time course of post-DNIC effects was examined using the same approach as described for DNIC analyses. Briefly, reflexes and pain ratings were averaged across the two 5-minute post-DNIC (and sham) time periods (immediately after and 10 minutes after). Then, difference scores were created by subtracting the post-DNIC (or sham) averages from the baseline (i.e. pre-DNIC or sham) average. Finally, separate 2 (ethnic

group) X 2 (DNIC vs. sham) mixed-model ANOVAs were conducted on each of the change scores (reflexes and ratings) from each time period (immediately post and 10 minutes post) in order to characterize the after effects of DNIC.

Correlational analyses were conducted to examine associations between psychological variables and baseline responses to electrical pain, including NFR intensity and ratings of electrical pain. Similar correlational analyses were conducted to examine associations between psychological variables and the magnitude of DNIC, including DNIC change scores for both reflex measures and pain ratings.

CHAPTER 4
RESULTS

No ethnic group differences in sex, age, body mass index or impedance were observed. Analysis of variance revealed significant ethnic group differences in NFR reflex ($F(1,50)=5.10$, $p = .028$; effect size = .61), with African Americans demonstrating a reflex at a lower stimulus intensity relative to non-Hispanic whites, displayed graphically in Figure 3-1. Despite the difference in intensity required to elicit a reflex between the two groups, verbal ratings of pain corresponding with the reflex did not differ. Baseline data for the pain tasks are presented in Table 3-1. However, the intensity at which participants rated a 45, used to stimulate participants during DNIC and $DNIC_S$ testing, significantly differed by ethnic group ($F(1,54)=5.77$, $p = .019$); therefore, the two groups received significantly different levels of electrical stimulation during the DNIC procedures.

The conditioning stimulus produced substantial reductions in pain ratings for all participants during the DNIC condition when compared with $DNIC_S$ condition ($p < .001$). The DNIC condition produced significantly greater reductions in verbal pain ratings among whites when compared with African Americans ($F(1,55)=4.05$, $p = .049$; effect size .65). These data are presented graphically in Figure 3-2. The number of reflexes was significantly lower during DNIC versus $DNIC_S$ stimulation ($F(1,43)=14.78$, $p < .001$), and this reduction in frequency of reflex was similar across ethnic groups. ANOVAs revealed no group differences in ratings of ischemic pain during either the DNIC or DNICs condition. Analysis of variance was conducted in order to characterize

the after effects of DNIC and the possible influence of ethnicity. No group differences were observed at the post DNIC and DNICs measurements, with both African Americans and whites returning to baseline pain ratings and baseline reflex activity during the 5-minute period following DNIC stimulation (see Figures 3-2 and 3-3).

Cardiovascular responses were evaluated in order to examine changes in blood pressure and heart rate reactivity during DNIC and potential differences in ethnicity. No significant group or condition differences emerged for any of the cardiovascular responses, see Tables 3-4 and 3-5. Ratings of attention focused on the arm, ankle and the degree to which the sensation in their ankle differed due to the cuff did not differ by group. These ratings were not correlated with magnitude of DNIC among African Americans; however, among whites, increased attention to the arm predicted greater reductions in electrical pain during DNIC, and increased attention to the arm was positively correlated with reflex frequency during DNIC, while attention to the ankle and ratings of how much the ankle sensation felt due to the ischemic procedure was negatively correlated with reflex frequency (see Table 3-3). However, ethnic group differences in DNIC remained significant even when the analysis was repeated using an ANCOVA controlling for subjects ratings of attention to the arm ($F(1,54)=5.46$, $p=.023$).

No ethnic group differences emerged for any of the psychological variables (see Table 3-1). Correlational analyses were conducted examining associations between responses to psychological questionnaires and NFR threshold. Psychological Involvement (a subscale of the FRID scale) and Positive Mood were positively correlated with NFR ($r= .30$, $p =.02$; $r=.35$, $p<.01$), and the rumination subscale of the PCS was negatively correlated with NFR ($r=-.29$, $p=.03$). The pattern of correlations was

consistent across both ethnic groups. In order to determine whether these psychological variables mediated ethnic group differences in the NFR threshold, analyses were repeated controlling for each of the three psychological measures that were associated with the NFR. Ethnic group differences remained significant after controlling for positive mood ($F(1,50)=5.24$, $p=.026$) and psychological involvement ($F(1,50)=4.38$, $p=.041$), and were marginally significant ($F(1,50)=3.63$, $p=.063$) after controlling for rumination. Thus, these psychological variables do not appear to mediate ethnic group differences in NFR thresholds. None of the psychological variables was significantly correlated with the magnitude of DNIC.

Table 4-1. Demographic information, means (SD) for baseline pain tasks, and psychological factors by ethnicity.

Variable	AA (n=29)	Whites (n=28)
Age (SD)	23.7 (7.1)	25.3 (8.6)
Sex (% female)	51.7	57.7
BMI (SD)	23.66 (5.19)	23.34 (3.36)
Impedance in Ω (SD)	4.05 (2.83)	4.89 (2.60)
NFR Reflex* in mA (SD)	14.99 (8.98)	20.95 (10.45)
NFR Rating (SD)	42.85 (20.68)	50.37 (25.44)
DNIC, DNICs Intensity	1.86 (.96)	2.46 (.92)
VAMS Positive Mood	178.52 (65.73)	171.96 (56.1)
VAMS Negative Mood	29.93 (33.38)	23.43 (33.38)
FRID Negative Expectancies	5.5 (1.83)	5.07 (1.44)
FRID Efficacy and Control Beliefs	11.78 (1.89)	12.55 (1.95)
FRID Psychological Involvement	11.67 (1.83)	11.91 (2.15)
PCS Rumination	1.11 (1.92)	.32 (1.15)
PCS Magnification	.11 (.35)	.07 (.19)
PCS Helplessness	.55 (2.97)	0 (0)
PCS Catastrophizing	1.78 (4.03)	.39 (1.15)
KOHN Score	68.69 (14.69)	66.04 (9.38)

* $p < .05$

Table 4-2. Means (SD) for DNIC and DNICs ratings averaged across each segment. Ischemic ratings represent summed responses during the DNIC and DNICs portions.

Variable	AA (n=29)	Whites (n=28)
DNIC Baseline 0-100	36.71 (14.21)	39.44 (16.36)
DNIC* 0-100	31.90 (13.56)	29.73 (13.02)
DNIC Post 0-100	34.55 (14.29)	36.94 (16.32)
DNIC 10min Post 0-100	36.26 (13.87)	38.60 (16.41)
DNICs Baseline 0-100	38.17 (11.76)	35.99 (14.23)
DNICs 0-100	37.02 (14.17)	35.49 (15.25)
DNICs Post 0-100	36.51 (15.21)	36.49 (17.11)
DNICs 10min Post 0-100	37.88 (14.5)	37.60 (14.71)
Ischemic Rating DNIC 0-20	109.34 (46.61)	119.75 (41.85)
Ischemic Rating DNICs 0-20	5.48 (13.45)	10.54 (22.47)

*$p < .05$

Table 4-3. Correlations between attention ratings and pain ratings and reflex frequency during DNIC.

Ethnicity	Difference Scores	Deg Attn to arm	Deg Attn to ankle	Deg different
African Americans	Pain Ratings	.02	-.09	-.04
	Reflex Freq.	.12	.001	-.09
Whites	Pain Ratings	.46*	-.27	.32
	Reflex Freq.	.41*	-.49*	-.47*

*$p < .05$

Table 4-4. Means (SD) for cardiovascular responses at baseline, DNIC and Sham for African Americans and whites.

Variable	African Americans (SD)	Whites (SD)
Baseline Systolic BP	108.27 (10.14)	108.69 (8.37)
Baseline Diastolic BP	62.11 (7.62)	61.22 (6.86)
Baseline Mean Arterial Pressure	78.64 (8.11)	77.99 (6.71)
Baseline Heart Rate	67.3 (11.3)	64.56 (9.42)
DNIC Systolic BP	112.53 (11.58)	113.99 (9.73)
DNIC Diastolic BP	67.19 (8.7)	66.86 (7.54)
DNIC Mean Arterial Pressure	84.95 (9.55)	85.09 (7.4)
DNIC Heart Rate	67.24 (11.09)	65.07 (10.07)
Sham Systolic BP	110.05 (9.09)	110.53 (8.14)
Sham Diastolic BP	64.28 (8.94)	63.88 (7.82)
Sham Mean Arterial Pressure	80.98 (8.4)	80.92 (6.98)
Sham Heart Rate	66.79 (9.67)	64.69 (8.67)

Table 4-5. Change Score means (SD) for cardiovascular responses in African Americans and whites during DNIC and Sham.

Change Scores	AA (n=29)		Whites (n=28)	
	DNIC	Sham	DNIC	Sham
Systolic BP	-4.26 (7.17)	-1.78 (5.36)	-5.29 (6.02)	-1.84 (4.72)
Diastolic BP	-5.08 (3.94)	-2.17 (4.07)	-5.64 (3.74)	-2.66 (3.78)
Mean Arterial Pressure	-6.31 (5.71)	-2.34 (5.52)	-7.11 (4.51)	-2.94 (4.21)
Heart Rate	.06 (6.32)	.51 (4.48)	-.51 (6.87)	-.13 (5.72)

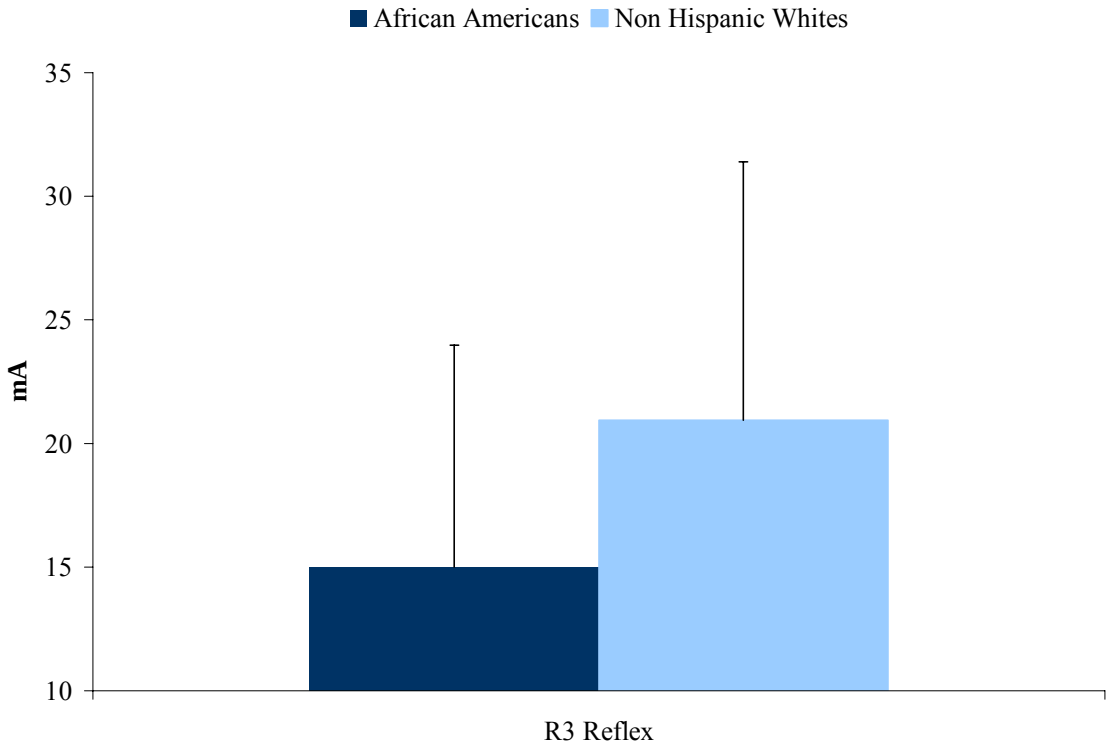
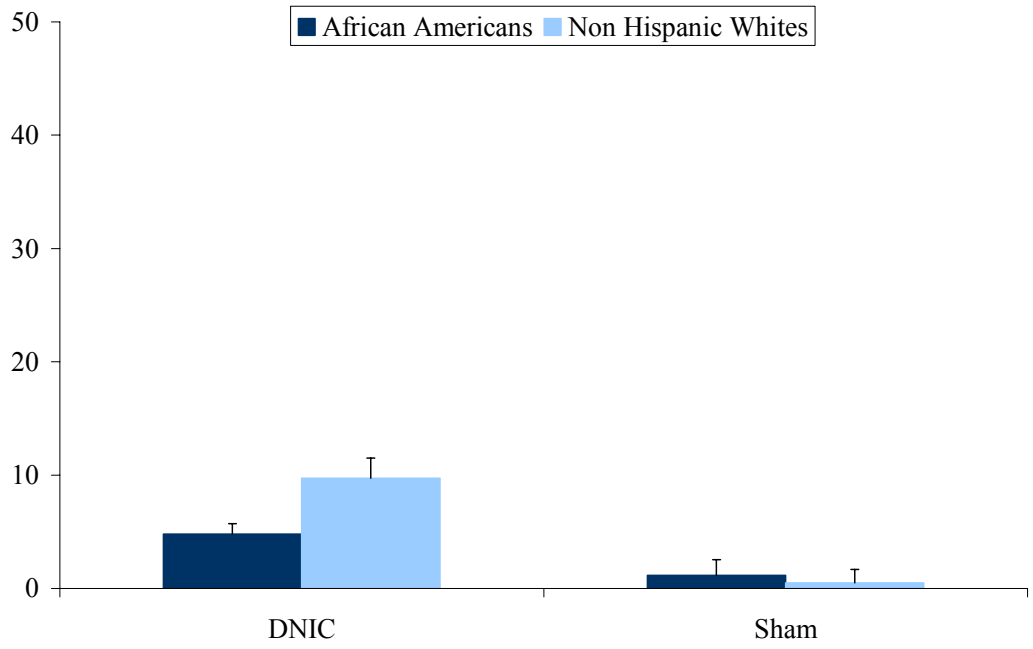
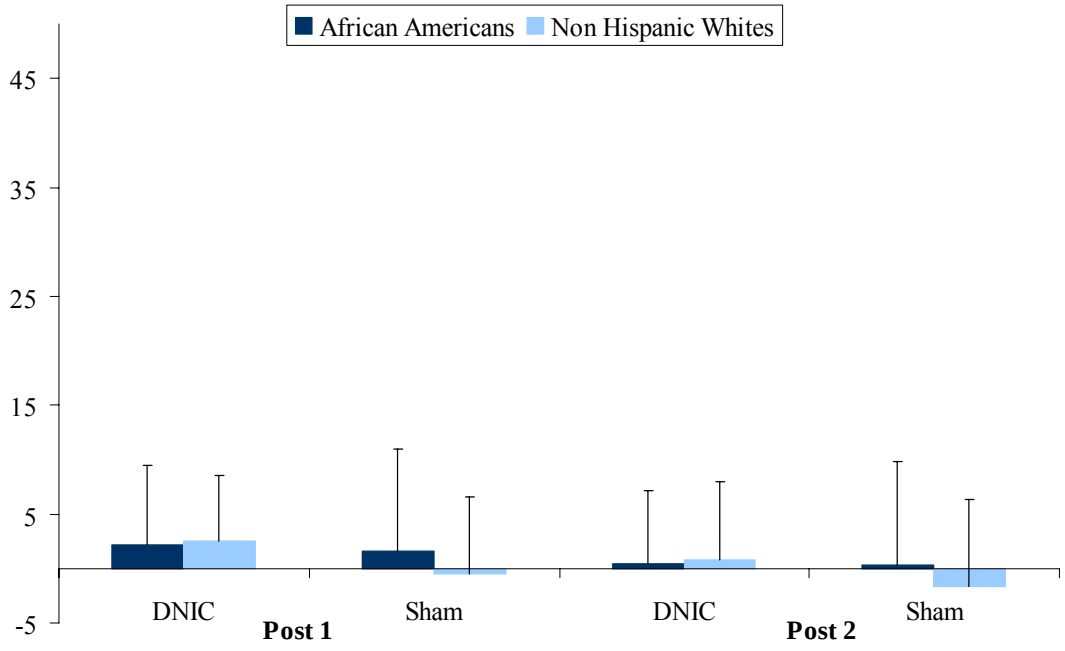


Figure 4-1. NFR (SD) in mA for African Americans and whites

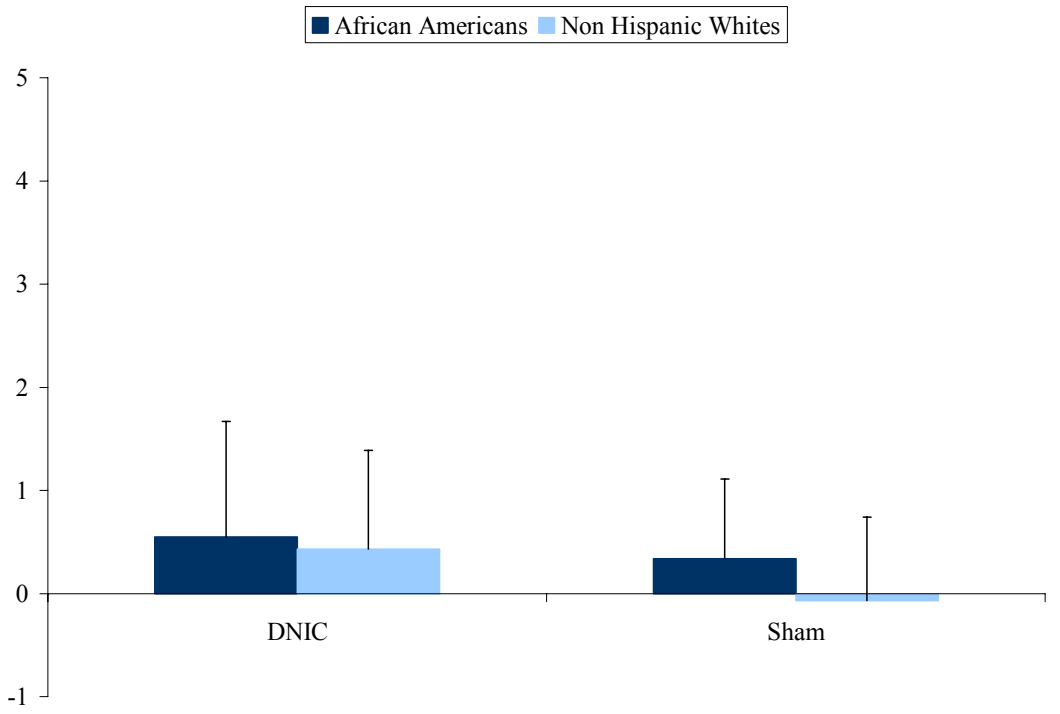


A

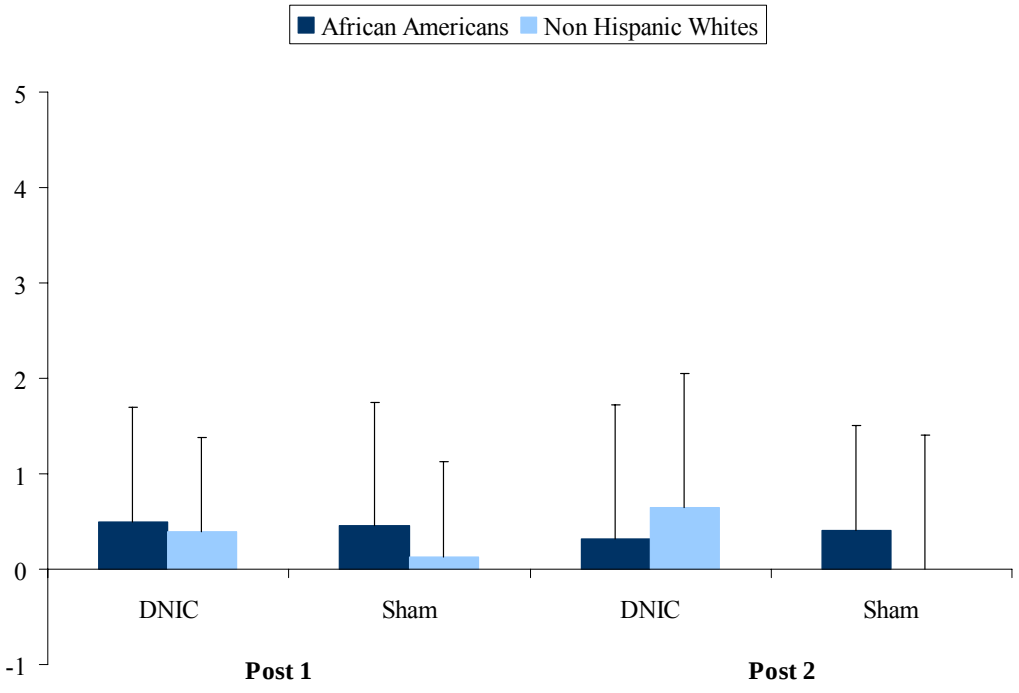


B

Figure 4-2. Difference scores (SD) for verbal responses during DNIC and SHAM assessments. A) Difference scores of pain ratings during DNIC and Sham. B) Difference scores of pain ratings during DNIC and Sham for Post1 and Post2.



A



B

Figure 4-3. Difference scores for reflex frequency during DNIC and SHAM assessments, as well as post and post 2 assessments for African Americans and whites. A) Difference scores of reflexes during DNIC and Sham. B) Difference scores of reflexes during DNIC and Sham for Post1 and Post2.

CHAPTER 5
DISCUSSION

The findings of this study provide evidence of ethnic differences in the NFR, such that African Americans required less electrical stimulation to produce a spinally-mediated nociceptive muscle reflex. Because the NFR is thought to be a more objective physiological nociceptive measure, the current findings add additional substance to the existing evidence that African American individuals may demonstrate greater sensitivity to noxious stimuli compared to whites. The NFR is based on measurement of stimulus-induced spinal reflexes and is therefore thought to be independent of the reporting biases sometimes associated with subjective pain ratings. Our findings suggest the factors contributing to ethnic differences in pain sensitivity may do so in part by altering nociceptive responses at the spinal level. The mechanisms underlying ethnic group differences in this spinally-mediated nociceptive reflex cannot be determined from this study; however, based on the current available evident, the most likely explanation may be that descending pain inhibition may be more robust among whites, which could reduce the nociceptive reflex. In this regard, Mechlin and colleagues (2005) recently demonstrated that stress-induced pain regulatory mechanisms involving blood pressure, norepinephrine, and cortisol functioned more effectively among whites than African Americans. It is worth noting that ethnic group differences in descending pain modulation could be mediated by fundamental biological differences, via psychosocial factors (e.g. expectations, pain beliefs) and/or the combination of these factors. Indeed, our findings demonstrate associations between the NFR and psychological variables.

Specifically, greater psychological involvement and higher positive mood correlated positively with NFR, while higher scores on the rumination subscale of the Pain Catastrophizing Scale predicted lower NFR. While these psychological variables did not mediate the group differences we observed in the NFR, it is plausible that other psychological processes not assessed in this study may have contributed to the group difference.

Previous research exploring psychological correlates of NFR have provided mixed results. For example, neither catastrophizing nor anxiety were found to be associated with NFR, while both variables predicted subjective pain ratings in response to electrical stimulation (France et al., 2002; French et al., 2005). It may be important to note that France and colleagues used the catastrophizing subscale of the Coping Strategies Questionnaire (CSQ), while we assessed catastrophizing with the PCS, which yields separate subscales, one of which (i.e. the Helplessness subscale) is equivalent to the CSQ catastrophizing scale. Indeed, our results showed an association only between the Rumination subscale of the PCS, and the Helplessness subscale was not associated with the NFR. Thus, it may be that only specific components of catastrophizing predict NFR thresholds.

Other investigators have reported significant psychological modulation of NFR thresholds. For example, induction of positive and negative mood increased and decreased the NFR, respectively (Rhudy, et al, 2005). Moreover, a brief session of pain coping skills training significantly increased NFR thresholds among patients with osteoarthritis of the knee (Emery, et al, 2006), and hypnotic analgesia also increased NFR thresholds (Kiernan et al., 1995; Wade, et al, 1997). Thus, previous research provides

additional evidence that psychological manipulations can influence NFR thresholds, and the present study extends these findings, providing further support for psychological contributions to NFR thresholds. The role of psychosocial processes in mediating ethnic group differences in the NFR merits additional investigation.

The results of the current study further indicate that African Americans experienced reduced DNIC relative to whites, which suggests significant differences in endogenous pain inhibition between African Americans and whites. This may be one factor contributing to observed ethnic differences in clinical and experimental pain findings. The process under which DNIC operates is thought to reflect influences of complex descending inhibitory systems, potentially mediated by endogenous opioids. However, studies examining DNIC under conditions of administration of an opioid antagonist, such as naloxone, have provided mixed results. Naloxone administration has been shown to block descending pain inhibition, resulting in no DNIC-induced analgesic effect in some studies (Willer et al., 1990); however, others have demonstrated no effects of opioid blockade on DNIC (Edwards et al., 2004, Le Bars et al., 1992). Thus, the exact mechanisms whereby DNIC produces its effects are unknown. Indeed, it seems likely that the hypoalgesic effects of a conditioning stimulus could result from multiple biological and psychosocial processes, whose relative importance may vary across studies.

Another possible contributor to DNIC could be cardiovascular responses. While cardiovascular reactivity has been associated with hypoalgesia (Bruehl et al. 1997; McCubbin and Bruehl, 1994), the link between DNIC and cardiovascular reactivity has received minimal attention. A recent study (Mechlin et al, 2005) examined regulatory

mechanisms involving stress-induced increases in blood pressure, norepinephrine, and cortisol functioning on pain response in African Americans and whites, and found these physiological changes to be more strongly associated with reduction of pain responses among white participants. While our results are generally consistent with those of Mechlin in that we also observed more effective endogenous pain inhibition among whites, cardiovascular reactivity was not associated with the magnitude of DNIC in either ethnic group in the current study. This may be due to the low level of cardiovascular reactivity observed during the tourniquet procedure in our study.

The effects of DNIC are thought to be long-lasting when a conditioning stimulus is applied to heterotopic areas of the body (Le Bars et al. 1979a; Dickenson and Le Bars 1983;Villanueva and Le Bars 1995). In humans, heterotopic noxious stimuli inhibit the spinal nociceptive flexion (RIII) reflex, which is controlled by spinal transmission of nociceptive signals (Willer et al. 1984;Willer et al. 1989). In our sample, while the conditioning stimulus reduced the frequency of NFR reflexes for the group as a whole, no ethnic differences in reduction of reflexes were evident. Moreover, the effects of DNIC in this study were relatively brief, as pain ratings and NFR frequency returned to baseline immediately after the cessation of the conditioning stimulus.

One potential explanation of the DNIC response might be distraction from the test stimulus by the conditioning stimulus. Some previous research would argue that DNIC is not simply a form of distraction. For example, many studies have reported that the analgesic effects of DNIC outlast the conditioning stimulus with which it was elicited by several minutes and up to several days (LeBars et al., 1992; Willer et al., 1990). DNIC has been used in dental pain studies, where ischemic arm pain and ice applied to the hand

not only increased the tolerance of dental pain, but also reduced sensitivity and swelling around teeth (Willer et al., 1990). DNIC has also been shown to reduce the NFR reflex (in humans and nonhuman animals), which is thought to be less influenced by distraction (Le Bars et al., 1992). DNIC effects have been observed in paraplegic and tetrapalegic patients (Roby Brami et al., 1987), whose actual RIII reflexes did not differ from normal controls (spinal reflexes intact), suggesting that DNIC activates descending inhibitory pathways modulating the spinal transmission of nociceptive information. Nonetheless, distraction could be a potential mechanism adding to DNIC's effectiveness. Several investigators have examined this connection. Willer and colleagues (1990) had participants perform mental calculation during several different pain tasks, attempting to induce DNIC, which did not occur. Edwards and others (2003; 2004) asked participants about distraction effects, and had them read vignettes, without DNIC effects. Finally, Staud and colleagues (2003) examined differences between fibromyalgia patients and healthy women, as well as comparing a sample of healthy men and women. A traditional DNIC and a DNIC plus distraction task was employed using temporal summation of heat pain and a hot water bath. Participants were verbally reminded to attend to one stimulus over the other. Significant sex differences emerged and both DNIC and DNIC plus distraction produced significant effects. The DNIC plus distraction was somewhat more effective in men and in fibromyalgia patients. This study suggests that DNIC effects may be enhanced when paired with distraction.

While we did not observe long-lasting differences in reflex rates or emg activity, attentional ratings were obtained. Ratings of distraction by the conditioning stimulus predicted greater DNIC-induced reductions in electrical pain ratings (but not reductions

in NFR frequency), but only among whites. However, the ethnic group differences in DNIC remained significant after controlling for distraction ratings. Thus, distraction may have contributed to the DNIC effect on electrical pain ratings, but does not appear to account for the ethnic group difference in DNIC.

Several limitations should be considered when interpreting the results of the present study. First, all of the tasks were acute, controlled painful laboratory experiences over which the participants had control; therefore, these results may be less generalizable to a clinical pain population. However, the clinical relevance of DNIC has previously been demonstrated by multiple investigators (Edwards et al. 2003b; Kosek & Ordeberg, 2000). Another possible limitation may come from stimulating participants at different intensities depending on their verbal ratings pain. Most studies examining DNIC using the NFR use 120% of an individual's NFR threshold; however, in our sample this would have caused great differences in individual's pain ratings of the stimuli. This may have contributed to our inability to observe ethnic group differences in reflex rates. Another limitation may be the possibility of habituation with frequent use of the NFR stimuli, one per minute; however, previous results show habituation to be highly dependent on the interstimulus interval, and observed habituation with stimulation every 5 seconds, but no habituation with stimulation 25 seconds apart (Sandrini, et al, 2005).

These limitations notwithstanding, our findings provide evidence of ethnic differences in the NFR as well as ethnic group differences in the effects of ischemic arm pain on ratings of electrical pain, but not on NFR reflex frequency. We also observed associations between psychological factors and the NFR, though these variables did not account for the observed ethnic differences. The current findings provide further

evidence for the existence of ethnic differences in experimental pain perception, and suggest potential ethnic group differences in inhibitory processes, though the mechanisms underlying this effect are not known. Though this type of endogenous pain modulation has received extensive attention in recent years and considerable evidence has amassed for its experimental utility, the current finding of ethnic differences in DNIC does not necessarily explain clinical or experimental differences observed in pain perception. Future studies should focus on the clinical relevance and implications for care, such as studying ethnic differences in DNIC in clinical pain models. Future studies may also pursue a better understanding of the mechanisms involved in ethnic differences in DNIC by examining the role of distraction and other psychological factors as well as the possible contribution of endogenous opioids. .

APPENDIX A
DNIC CHANGES SCORES

Change Score means (SD) for ratings and reflexes in African Americans and whites.

Change Scores	AA (n=29)		Whites (n=28)	
	DNIC	Sham	DNIC	Sham
Ratings During	4.81 (5.1)	1.14 (7.4)	9.7 (9.4)	.49 (6.3)
Ratings Post	2.16 (7.26)	1.66 (9.29)	2.51 (6.1)	-.5 (7.09)
Ratings Post 2	.45 (6.71)	.28 (9.53)	.84 (7.1)	-1.61 (7.99)
Reflexes During	.55 (1.12)	.34 (.77)	.43 (.96)	-.07 (.81)
Reflexes Post	.5 (1.18)	.45 (1.3)	.39 (.99)	.13 (1.01)
Reflexes Post 2	.32 (1.36)	.41 (1.1)	.65 (1.37)	0 (1.45)

APPENDIX B
QUESTIONNAIRES

PCS

Directions: Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures, or surgery. We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are 14 statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 not at all	1 to a slight degree	2 to a moderate degree	3 to a great degree	4 all the time

1._____ I worry all the time about whether it will end.

2._____ I feel I can't go on.

3._____ It's terrible and I think it's never going to get any better.

4._____ It's awful and I feel that it overwhelms me.

5._____ I feel I can't stand it anymore.

6._____ I become afraid that the pain will get worse.

7._____ I keep thinking of other painful events.

8._____ I anxiously want the pain to go away.

9._____ I can't seem to get it out of my mind.

10._____I keep thinking about how much it hurts.

11._____I keep thinking about how badly I want the pain to stop.

12._____There's nothing I can do to reduce the intensity of the pain.

13._____I wonder whether something serious may happen.

14._____I feel my life isn't worth living.

Kohn

The items which follow all concern your feelings and experience in common, everyday situations. There are no right or wrong answers. Please just answer each item as honestly as you can; however, please work quickly, as your first impression is quite likely to be the most accurate. For each item, place the number that best represents your reaction to the item-statement in the space to the right:

1, if you Disagree Strongly with the statement.
2, if you Disagree with the statement.
3, if you Neither Disagree Nor Agree with the statement.
4, if you Agree with the statement.
5, if you Agree Strongly with the statement.

1. If I went on an ocean voyage I'd be sure to get seasick. _____
2. Jumping right into ice-cold water doesn't bother me. _____
3. I can't stand driving fast at night. _____
4. I can often work well when I'm feeling quite sick. _____
5. I need strict quiet to study or think well. _____
6. Being out on really cold days doesn't bother me as much as most people. _____
7. I can't stand staying in a sauna or steam bath for very long. _____
8. There are very few midway rides that make me uncomfortable. _____
9. I've often had motion sickness. _____
10. I can concentrate on what I'm doing even when I'm in pain. _____
11. I could never bathe or shower in ice-cold water. _____
12. I can work reasonably well even when I feel emotionally upset. _____
13. I can always feel when it's time to come in form the cold. _____
14. Driving fast at night doesn't bother me. _____
15. I could never study when I'm feeling sick. _____
16. I've hardly ever had motion sickness. _____
17. I avoid the cold outdoors as much as I can during the worst of the winter. _____
18. There are times when I enjoy an ice-cold shower or bath. _____
19. I can't stand a lot of midway rides. _____
20. Pain doesn't bother me as much as it does most people. _____
21. I can't stand much hard physical labor. _____
22. I'd be very surprised if I got seasick on an ocean voyage. _____

23. It would take a lot to make me jump into ice-cold lake water. _____

24. I like staying in saunas or steam-baths longer than most people can stand to stay _____

FRID SCALE

Please indicate in the alternatives given below how <u>you think right now</u>.

1.	I want to avoid the situation	1 not at all	2	3	4	5 very much so
2.	I believe I can tolerate the pain	1 not at all	2	3	4	5 very much so
3.	I see the experience as a challenge	1 not at all	2	3	4	5 very much so
4.	I think the procedure will be painful	1 not at all	2	3	4	5 very much so
5.	I know that nothing concerning this experiment “can really hurt me”	1 not at all	2	3	4	5 very much so
6.	I care that other people may notice my weaknesses	1 not at all	2	3	4	5 very much so
7.	I think this experiment will be interesting	1 not at all	2	3	4	5 very much so
8.	I expect to suffer unpleasant after- effects	1 not at all	2	3	4	5 very much so
9.	I believe that my participation is important	1 not at all	2	3	4	5 very much so
10.	I expect to be in control of the situation	1 not at all	2	3	4	5 very much so

VAMS

Please indicate how you are feeling right now by placing one mark on each line. The mark should be placed along the line at the point that best reflects how you feel right now.

Neutral ——————————————————— Tense

Neutral ——————————————————— Sad

Neutral ——————————————————— Happy

Neutral ——————————————————— Tired

Neutral ——————————————————— Angry

Neutral ——————————————————— Energetic

Neutral ——————————————————— Relaxed

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BIOGRAPHICAL SKETCH

Claudia M. Campbell received her Bachelor of Science degree in psychology with a minor in women's studies from the University of Florida in 2001. As a result of her interdisciplinary background, she developed an interest in the psychological aspects of diversity, specifically in the field of pain research. Upon completion of her bachelor's degree, Ms. Campbell accepted a research assistant position in the sensory testing laboratory of Dr. Roger Fillingim. Thus, she has been able to pursue her research endeavors investigating sex and ethnic differences in pain perception. She received her Master of Science degree in clinical psychology from the University of Florida in 2004 and continues her work through the pursuit of a doctoral degree in clinical and health psychology at the University of Florida.

Ms. Campbell has also been the recipient of several awards from the American Pain Society, which include a Citation Award, acceptance into their "Residence Program" and four Young Investigator Awards, the latter two of which facilitated travel to the national meetings. Current memberships include the American Pain Society and the Disparities Special Interest Group of the American Pain Society.