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Ethnic Differences in Diffuse Noxious Inhibitory Controls (DNIC)

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Abstract

Substantial evidence indicates that the experience of both clinical and experimental pain differs among ethnic groups. Specifically, African Americans generally report higher levels of clinical pain and greater sensitivity to experimentally induced pain; however, little research has examined the origins of these differences. Differences in central pain-inhibitory mechanisms may contribute to this disparity. Diffuse noxious inhibitory controls (DNIC), or counterirritation, is a phenomenon thought to reflect descending inhibition of pain signals. The current study assessed DNIC in 57 healthy young adults from two different ethnic groups: African Americans and non-Hispanic whites. Repeated assessments of the nociceptive flexion reflex (NFR) as well as ratings of electrical pain were obtained prior to, during and after an ischemic arm pain procedure (as well as a sham procedure). The DNIC condition (i.e. ischemic arm pain) produced substantial reductions in pain ratings as well as electrophysiologic measures of the NFR for all participants when compared with the sham condition ($p < .001$). The DNIC condition produced significantly greater reductions in verbal pain ratings among non-Hispanic whites when compared with African Americans ($p = .02$), while ethnic groups showed comparable reductions in NFR. The findings of this study suggest differences in endogenous pain inhibition between African Americans and non-Hispanic whites and that additional research to determine the mechanisms underlying these effects is warranted.

Perspective—This study adds to a growing literature examining ethnic differences in experimental pain perception. Our data suggest that these variations may be influenced by differences in descending inhibition.

Keywords

Experimental Pain; Diffuse Noxious Inhibitory Controls; DNIC; Nociceptive Flexion Reflex; NFR; Ethnic Differences

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Introduction

Understanding the relationship between race, ethnicity and pain is a topic of growing interest and importance. The term “race” distinguishes major groups of people according to a supposed biological disposition, it is focused on ancestry and a combination of physical characteristics, while “ethnicity” encompasses culture, history, experience, ancestry, and beliefs as well as biology and physical characteristics (see Edwards et al., 2001¹² for review). In recent years considerable evidence has shown that both clinical and experimental pain responses vary across ethnic groups, with African Americans (AA) generally demonstrating increased clinical pain and greater sensitivity to experimentally-induced pain when compared to non-Hispanic whites²¹. In a variety of clinical conditions, African Americans report higher levels of pain and disability^{13,39}, greater pain unpleasantness, and more pain-related emotional distress relative to non-Hispanic whites^{21,39}. Laboratory studies have shown AA to have lower heat pain thresholds and tolerances^{6,44}, and higher ratings of heat pain unpleasantness¹⁴, as well as lower cold pressor pain tolerances⁵⁰ when compared to non-Hispanic whites. Additionally, AA reported greater intensity and unpleasantness in response to a modified ischemic task relative to non-Hispanic whites, using a standardized rating scale⁵. Therefore, ethnic differences in both clinical and experimental pain have been widely reported, with the most robust differences in experimental pain found for suprathreshold measures^{3,36}.

Differences in central pain-inhibitory mechanisms could potentially contribute to 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. DNIC, or counterirritation, refers to the process whereby one noxious stimulus inhibits the perception of a second painful stimulus and is thought to reflect descending inhibition of pain signals^{26,35}. DNIC is presumed to operate through activation of descending supraspinal inhibitory pathways initiated by release of endogenous opioids^{8,24,27,41}.

DNIC 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 DNIC to examine possible deficiencies in descending inhibitory processes in certain populations. For example, sex differences⁴⁵, and age differences¹⁵ have been observed in DNIC, suggesting differing endogenous pain inhibition across certain groups. The clinical relevance of DNIC has previously been demonstrated^{17,23,55}. Clinical pain conditions such as fibromyalgia^{22,25,46}, osteoarthritis²³, trapezius myalgia²⁹, rheumatoid arthritis³⁰, and peripheral nerve injury² also show evidence of impaired DNIC responses; suggesting a possible role for dysregulation of pain inhibitory systems in the acquisition or maintenance of the condition⁴⁷. Interestingly, recent research suggests it may identify patients at risk for developing post-operative pain⁵⁵.

This study was designed to further elucidate the nature of ethnic differences in pain perception by investigating responses to DNIC using the nociceptive flexion reflex (NFR); an electrophysiological procedure based on the measurement of stimulus-induced spinal reflexes⁵¹. This methodology permits assessment of both self-reported pain and quantification of an individual's electrophysiological response.

Materials and Methods

A total of 57 healthy young adults (29 African American 51.7% female, 28 non-Hispanic white, 57.7% female) were recruited through flyers dispersed throughout a large Southeastern university community. Stringent inclusion criteria assured that all individuals were in good health, had no prior history of pain problems or psychiatric disorders. Participants completed two experimental sessions, each lasting up to 2 hours. Upon arrival for the first session, verbal

and written informed consent was obtained. Participants were then instrumented (see procedure below), and rested for 10 minutes, after which their blood pressure was measured for five minutes using an automated blood pressure cuff. Next, their baseline NFR threshold was determined as described below. During the second session, an additional evaluation and tailoring of electrical stimulation was performed as well as one DNIC assessment and one sham DNIC (S-DNIC) assessment, conducted in randomized order (see Figure 1 for timeline). All study procedures were approved by the University of Florida Institutional Review Board.

TESTING PROCEDURES

Nociceptive Flexion Reflex Assessment—All stimulating and recording sites were cleaned and gently abraded to achieve an impedance of less than 10,000 Ohms prior to electrode placement. Electrical stimulation was delivered via a Nicolet bar electrode applied to the left sural nerve, using a Digitimer, DS7A constant-current stimulator (Hertfordshire, UK). The nociceptive withdrawal reflex was assessed using two electrodes, one placed over the left biceps femoris muscle, the other placed over the reference site, the left lateral epicondyle of the femur with a DelSys, Bagnoli-2 differential amplifier. EMG was recorded and processed using a CED Micro1401 analog-to-digital converter and Spike2 software. Participants were seated in a reclining chair in order to maintain a 60-degree angle of the left knee. The nociceptive flexion reflex was operationally defined according to Rhudy and France³⁷ as a mean rectified EMG response in the 90–150 ms post-stimulus interval that exceeded mean rectified EMG activity during a 60 ms pre-stimulus baseline interval (–65 to –5 ms) by at least 1.5 *SD*. This criterion was used both throughout NFR threshold assessment (conducted during the first session only and reported elsewhere⁴) and in use of the NFR as a test stimulus for DNIC 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). This intensity scale, which uses general sensory anchors rather than pain-specific anchors, was selected for two primary reasons. First, it allows ratings of both painful and nonpainful electrical stimuli. Second, it has been argued that between subject and between group comparisons may be more valid when using general labeled scales such as this one^{1,10}. We have previously found that a rating of approximately 30 on this scale corresponds to the pain threshold (unpublished data).

Test Stimulus—At the start of the second session, an electrical stimulation analysis was conducted in order to identify the intensity at which participants rated electrically induced pain as a “45” on a 0–100 scale, chosen in order to yield a customized, moderately intense, tailored stimulus level. Electrical stimulation began 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. In order to identify an electrical stimulus that produced moderate pain, the stimulation intensity at a rating of 45 was calculated for each participant and used in all subsequent testing; consisting of several five minute blocks of electrical stimulation described in Figure 1. Participants rated each stimulus (one per minute) on the 0 – 100 scale; these ratings were averaged over each five minute block of stimulation. This yielded four separate ratings of the electrical stimulus for each condition: a baseline rating, a rating during the conditioning (or sham) stimulus, a rating 5 minutes after the conditioning (or sham) stimulus (post 1 rating), and a rating 15 minutes after the conditioning (or sham) stimulus (post 2 rating).

Conditioning Stimulus—Ischemic pain was induced using a modified submaximal effort tourniquet procedure^{31,32,33}, as this has been shown to increase participant safety, has a brief exposure time and reduces participant attrition¹⁸. Following five minutes of baseline NFR testing, the 10 cm wide straight segmental blood pressure cuff (model SC-10) was applied to the participant’s right arm. They completed 2 minutes of handgrip exercises, after which time

their arm was elevated for 30-seconds. The arm was then occluded by inflating the blood pressure cuff to a pressure of 240 mm Hg (or not in the sham procedure) using a Hokanson cuff inflator and air source (Bellevue, WA). 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 a 0 to 20 validated box scale, which includes verbal descriptors between neutral and extremely intense⁷. After five minutes of arm occlusion (or the sham procedure), the cuff was deflated and NFR assessment continued for an additional 5 minutes (post 1). After a ten minute break, an additional five minutes of NFR was repeated (post 2).

An identical sequence occurred during the sham assessment. Specifically, five minutes of baseline NFR testing was observed, then 2 minutes of handgrip exercises were completed (the blood pressure cuff was applied to the arm, the machine was on and the participant's arm raised for 30 seconds; however, the cuff was not inflated). Five minutes of NFR testing occurred while the ischemic cuff was loosely wrapped around the participant's arm. The post 1 and post 2 assessments for sham were conducted as described above. These conditions were randomized and a 15 minute break was observed between each condition.

Cardiovascular Assessment—After participants were instrumented, seated and positioned, a ten minute rest period was observed, after which five minutes of baseline blood pressure readings (systolic, diastolic, mean arterial pressure and heart rate) were measured with a Dinamap (Critikon, Tampa, FL) blood pressure cuff applied to the left arm. Cardiovascular measures were also assessed once per minute for five minutes during the DNIC and S-DNIC segments.

Attention Questions—Participants were asked to rate their level of attention focused on the arm and also asked to rate their attention toward their ankle on a 0 – 100 scale (where 0 = no attention and 100 = complete attention), as well as the degree to which the sensation in their ankle differed due to the cuff on a –100 – 0 – 100 scale (where –100 = complete reduction in ankle pain, 0 = no difference and 100 = complete increase in ankle pain) immediately after the DNIC and S-DNIC portions of testing, prior to the post 1 NFR assessments.

Data Reduction and Analysis

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. 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 change scores were used as dependent measures in mixed model ANOVAs, as described for reflex activity.

The time course of post-DNIC effects was examined by averaging reflexes and ratings separately for the two post-DNIC periods (i.e. 5-minutes post-DNIC and 15-minutes post-DNIC). Mixed model ANOVAs were conducted in order to characterize the after effects of DNIC as described above for the DNIC analyses. Mixed model ANOVAs were used to examine cardiovascular responses across experimental conditions and ethnic groups. Correlational analyses were conducted to examine associations between attentional variables and the magnitude of DNIC, including DNIC change scores for both reflex measures and pain ratings.

Results

Demographic data for each ethnic group are presented in Table 1; there were no significant differences in age, sex, BMI, or baseline cardiovascular measures. As previously reported in this cohort⁴, African Americans ($M = 14.99$ mA, $SD = 8.98$) demonstrated an NFR reflex threshold at a lower stimulus intensity relative to non-Hispanic whites ($M = 20.95$ mA, $SD=10.45$).

DNIC Findings

For the electrical stimulus, the intensity at which participants reported moderate pain, identified by a rating of 45, differed significantly by ethnic group ($F(1,54)=5.77$, $p < .05$); therefore, African Americans ($M = 18.6$ mA, $SD = .96$) received significantly lower levels of electrical stimulation during the DNIC procedures compared to non-Hispanic whites ($M = 24.6$ mA, $SD = .92$). A main effect of DNIC condition (i.e. DNIC vs. S-DNIC) on ratings of electrical pain emerged, indicating that the conditioning stimulus produced significant reductions in pain ratings for both ethnic groups during the DNIC condition when compared with the S-DNIC condition ($F(1,54)=8.56$, $p < .005$). However, there was also a significant ethnic group X DNIC condition interaction, such that the DNIC condition produced significantly greater reductions in pain ratings among non-Hispanic whites when compared with African Americans ($F(1,54)=4.03$, $p = .02$), while no group differences were found for DNIC-S. These data are presented graphically in Figure 2. The ethnic difference in DNIC remains significant even after controlling for sex and the difference in stimulus intensity ($p < .012$). While the pre-DNIC ratings did not significantly differ by group, they were slightly higher in the non-Hispanic white group and were somewhat lower during the DNIC period. ANCOVA revealed that during DNIC pain ratings differed significantly by groups ($p = 0.018$) after controlling for pre-DNIC pain ratings.

A main effect of DNIC condition also emerged for the number of reflexes observed over the 5 minute conditioning period, with a significantly lower number of reflexes during DNIC versus S-DNIC stimulation ($F(1,42) = 8.35$, $p < .01$). No main effect of ethnic group or interaction was found for the number of EMG reflexes ($ps > .10$). ANOVAs revealed no group differences in ratings of ischemic pain during the DNIC condition. Analysis of variance was conducted in order to characterize the after effects of DNIC and the possible influence of ethnicity. No significant differences were observed at the post DNIC and S-DNIC measurements, with both African Americans and non-Hispanic whites returning to baseline pain ratings and baseline reflex activity during the 5-minute period following DNIC stimulation.

Cardiovascular responses were evaluated to examine changes in blood pressure and heart rate reactivity during DNIC and S-DNIC. No significant group or condition effects emerged for any of the cardiovascular responses. These data are presented in Table 1. Change scores were computed for each cardiovascular measure by subtracting the baseline value from the response during DNIC. These change scores were then correlated with the DNIC differences scores for pain ratings and reflex activity. None of these correlations were significant (all $ps > .05$).

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 non-Hispanic whites, increased attention to the arm predicted greater reductions in electrical pain during DNIC ($r=0.46$, $p < .05$). In order to determine whether attention to the arm accounted for the ethnic group difference in DNIC-induced reduction in electrical pain, these data were re-analyzed with an ANCOVA using attention ratings as the covariate. Ethnic group differences in DNIC

remained significant even when controlling for subjects ratings of attention to the arm along with the electrical stimulation intensity ($p < .05$).

Discussion

The findings of this study indicate that concurrent ischemic pain produced significant reductions in the number of EMG reflexes in both groups, and the magnitude of this effect was similar across groups. However, ischemic pain produced greater reductions in electrical pain ratings among non-Hispanic whites compared to African Americans. This suggests that for self reported pain, African Americans experienced reduced DNIC relative to non-Hispanic whites, which implies differences in endogenous pain inhibition between African Americans and non-Hispanic whites. This may be one factor contributing to observed ethnic differences in clinical and experimental pain responses. DNIC is thought to reflect influences of complex descending inhibitory systems, potentially mediated by endogenous opioids. However, opioid antagonism reverses DNIC in some⁵³ but not all^{16,28} human studies, suggesting that nonopioid mechanisms may underlie some forms of DNIC.

Other physiological processes that may contribute to ethnic group differences in endogenous pain modulation have received scant attention. A recent study³⁴ examined regulatory mechanisms involving stress-induced increases in blood pressure, norepinephrine, and cortisol functioning on pain response in African Americans and a primarily non-Hispanic white group (Caucasian/Other), and found these physiological changes to be more strongly associated with reduction of pain responses among Caucasian/Other participants. While our results are generally consistent with Mechlin in observations of more effective endogenous pain inhibition among non-Hispanic 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 in our study. This low level of reactivity is likely due to the fact that we assessed cardiovascular responses to DNIC and DNIC-S after the handgrip exercise had been completed, and the most robust cardiovascular response to the ischemic procedure occurs during the handgrip exercise³¹.

The effects of DNIC are thought to be intensity-dependent and long-lasting when a conditioning stimulus is applied to heterotopic areas of the body^{9,26,49}. In humans, heterotopic noxious stimuli inhibit the spinal nociceptive flexion reflex (NFR), which is controlled by spinal transmission of nociceptive signals^{52,54}. 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. It remains unclear why the conditioning stimulus reduced ratings to a greater extent in non-Hispanic whites, while EMG activity did not differ between groups. While the NFR threshold differed in electrical intensity level between the two groups, it is possible that the ratings of supra-threshold electrical pulses used as the test stimulus may reflect the more affective-motivational aspect of pain perception as has previously been suggested^{14,39,44}. Moreover, that ethnic group differences in pain inhibition were reflected in reduced pain ratings but not in reflex responses may indicate that ethnic group differences in pain modulation are not related to descending inhibition of spinal nociceptive transmission. Rather, perhaps ethnic group differences can be attributed to higher cortical mechanisms of pain inhibition³⁸. Additionally, 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 is that the conditioning stimulus serves as a distraction from the test stimulus. One of the most common counterarguments is that the analgesic effects of DNIC outlast the conditioning stimulus by several minutes and up to several days^{28,53}. However, this was not the case in our study, as electrical pain responses returned

to baseline immediately after the conditioning stimulus. Thus, distraction may have contributed to DNIC in our study. Consistent with this, 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 non-Hispanic whites. However, the ethnic group difference 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 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^{17,23,55}. Another possible limitation may result from our decision to tailor the test stimulus based on participants' verbal pain ratings. 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. Due to the wide variability in NFR threshold between African Americans and non-Hispanic whites, a stimulus tailored based on ratings of perceived intensity was used. Adapting stimulus intensity to perceptual levels has been used in other DNIC studies^{20,48} and has the distinct advantage of reducing floor and ceiling effects¹⁹, thus making it quite appropriate for use in examination of pain responses when wide individual differences may be observed. Additionally, the tailored stimulus intensity was between approximately 117 – 124% of NFR thresholds, suggesting that the two groups did not receive drastically different levels of stimulation relative to their NFR thresholds. Further, when intensity level was used as a covariate, our findings remained significant. Nevertheless, our choice to tailor the test stimulus based on perceived intensity may have contributed to our observation of ethnic differences in DNIC being reflected in reduced pain ratings but not in reflex responses. Additionally, a potential limitation may include the scale used to assess pain perception of the test stimulus. This scale excludes conventional anchors (i.e. no pain, worst pain imaginable) which may vary as a result of individual differences in their use^{5,40}. However, cross-modality matching techniques have shown that pain assessments using scales anchored by "most intense sensation of any kind" as opposed to "most intense pain" specifically, are thought to reduce variability between groups¹¹. While the scale does not mention pain per se, several studies have shown that a close relationship exists between the NFR reflex threshold and pain threshold⁴². As we used a stimulation intensity greater than the NFR reflex threshold level we believe these ratings correspond to an individual's pain level. Moreover, our only data directly relating this scale to the pain threshold are as yet unpublished, which is a limitation. 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 apart⁴³.

These limitations notwithstanding, our findings provide evidence of ethnic group differences in endogenous pain modulation as measured by DNIC. The current findings provide further evidence for the existence of ethnic differences in pain processing. 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 findings 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 using opioid blockade, in order to characterize the extent to which endogenous opioids are mediating ethnic differences.

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Figure 1.
Timeline for Session 2

*** $p < .02$**

Figure 2.
DNIC and S-DNIC electrical pain stimuli ratings averaged across each testing segment.

Table 1

Demographic information, means (SD) for pre-testing and cardiovascular measures 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)
BL Systolic Blood Pressure	108.3 (10.1)	108.7 (8.4)
BL Diastolic Blood Pressure	62.1 (7.6)	61.2 (6.9)
BL Heart Rate	67.3 (11.3)	64.6 (9.4)
DNIC Systolic Blood Pressure	112.5 (11.6)	114.0 (9.7)
DNIC Diastolic Blood Pressure	67.2 (8.7)	66.9 (7.5)
DNIC Heart Rate	67.2 (11.1)	65.1 (10.1)
S-DNIC Systolic Blood Pressure	110.0 (9.1)	110.5 (8.1)
S-DNIC Diastolic Blood Pressure	64.3 (8.9)	63.9 (7.8)
S-DNIC Heart Rate	66.8 (9.7)	64.7 (8.7)