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Individual differences in diffuse noxious inhibitory controls (DNIC): association with clinical variables

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Abstract

Laboratory pain research has been criticized as being irrelevant to the clinical experience of pain. Previous findings have been inconsistent with some studies suggesting that experimental pain responses may be related to the reported presence or severity of chronic pain, while others report no such associations. However, few of these studies assess a variety of laboratory pain responses, and none has assessed relationships between clinical pain and diffuse noxious inhibitory controls (DNIC) in healthy subjects. We administered questionnaire measures of pain, quality of life, and psychological variables to a sample of healthy adults participating in a laboratory study of age differences in pain responses. DNIC was not related to other laboratory pain responses, psychological variables, or physiological variables measured in the present study. Regression models predicting health-related quality of life (e.g. pain, physical functioning) revealed that age, sex, and DNIC responses explained between 10 and 25% of the variance in these dependent measures. Of the laboratory pain variables, only DNIC was the sole consistent predictor of clinical pain and physical health, with greater DNIC responses related to less pain, better physical functioning, and better self-rated health. In addition, age differences in DNIC appeared to partially mediate age differences in physical functioning. These findings highlight the potential clinical relevance of experimental pain procedures and suggest that DNIC may be the laboratory pain response most closely associated with clinical pain and health-related variables.

Keywords: Pain; Noxious; Pain modulation; Aging; Elderly; Diffuse noxious inhibitory control

1. Introduction

Administration of noxious stimuli under controlled conditions constitutes an important subdiscipline within the field of pain (see Gracely, 1999). However, while quantitative sensory testing has advanced our understanding of pain perception, disagreements frequently arise over the relation of experimental pain responses to clinical pain (Gracely, 1999). Perhaps partly due to methodological variability, research on relationships between laboratory pain responses and clinical endpoints has produced mixed results.

Relative to controls, patients with fibromyalgia (FM; Hurtig et al., 2001), whiplash (Kasch et al., 2001), headache (Bendtsen, 2000), temporomandibular disorder (TMD; Svensson et al., 2001), and irritable bowel syndrome (Whitehead et al., 2002) show enhanced pain sensitivity. Within patient groups, lower pain thresholds and tolerances predict greater pain and worse function among back pain (Clauw et al., 1999), joint pain (Pienimaki et al., 2002), TMD (Fillingim et al., 1996), chest pain (Sheps et al., 1999), and chronic pain patients (Edwards et al., 2001). Finally, pain responses relate to recent clinical pain among healthy adults (Edwards and Fillingim, 1999, 2001b; Fillingim et al., 1999). However, many studies find no relationships between clinical and experimental pain (Svensson et al., 2001), and it is unclear which laboratory pain responses are most strongly associated with the experience of pain in daily life.

Many chronic pain syndromes are characterized by reduced central nervous system (CNS) pain modulation or enhanced central sensitization. One often-studied method of engaging CNS pain inhibitory systems has been termed

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diffuse noxious inhibitory controls (DNIC; Le Bars et al., 1981; Price and McHaffie, 1988), a phenomenon whereby one noxious stimulus inhibits the pain produced by another. DNIC is assessed by measuring responses to phasic noxious stimuli before, during, and after heterotopic application of a tonic noxious stimulus. DNIC refers to the resultant decrease in phasic pain produced by supraspinally generated inhibition of wide dynamic range (Cadden, 1993; Le Bars et al., 1981) and nociceptive-specific (Hu, 1990) neurons. FM and TMD patients show diminished DNIC responses (Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997; Sigurdsson and Maixner, 1994); however, whether these effects are a cause or a consequence of having chronic pain is not known. Evidence that DNIC is related to clinical pain among healthy individuals might suggest that reduced pain-modulatory capacity is a risk factor for chronic pain. Moreover, little is known about the psychological and physiological correlates of DNIC; accordingly, we investigated DNIC's relationships with psychosocial and physiological characteristics known to have associations with pain responses (Al'Absi et al., 2002).

In addition, as pain becomes more disabling with advancing age (Helme and Gibson, 2001; Verhaak et al., 1998), and since older adults show reduced pain modulation (Edwards and Fillingim, 2001a; Edwards et al., 2003; Gibson and Helme, 2001; Washington et al., 2000), we evaluated DNIC as a mediator of age differences in health-related quality of life (HRQOL). Collectively, this investigation had three aims: (1) evaluating associations of psychological and physiological variables with DNIC, (2) investigating associations of laboratory pain responses with HRQOL, (3) assessing DNIC as a mediator of age differences in HRQOL.

2. Research design and method

2.1. Participants

The present investigation represents a follow-up analysis of an earlier laboratory study (Edwards et al., 2003). Data were initially collected on a total of 93 healthy subjects who completed a study of age differences in DNIC (see Edwards et al., 2003). Participants were recruited through posted advertisements and paid $75.00 for completing two study sessions; all study procedures were approved by the University's IRB. Of the 93 participants who provided complete laboratory data, a total of eight younger and eight older participants were unable to tolerate the cold pressor test for a sufficient length of time to study DNIC responses (see Edwards et al., 2003). Thus, the present study utilizes data from the 77 subjects (37 younger, 40 older) in whom DNIC responses could be studied. We have described this sample in detail in our previous report (Edwards et al., 2003). The younger group (59.5% female) had a mean age of 21.5 years (SD = 2.2) while the mean age for the older group (65.0% female) was 63.2 years (SD = 4.3). χ^2 Tests showed that the age groups did not differ significantly in sex or ethnic composition ($P > 0.05$).

2.2. Protocol and procedures

Participants completed two 2-h experimental sessions on non-consecutive days; many of these procedures are described in a previous publication dealing with this sample (Edwards et al., 2003) and are summarized here. Prior to the initial laboratory session, subjects completed several health-related and psychological questionnaires (see Section 2.3).

2.2.1. Blood pressure

In each laboratory session, after a 10-min rest period, a Dinamap 1846 SX blood pressure monitor was used to assess baseline cardiovascular activity each minute for 5 consecutive minutes. These five readings were averaged to obtain baseline values for resting mean arterial pressure (MAP) and heart rate (HR). Because both arms were involved in assessing DNIC, the cuff was placed on the right ankle, over the Popliteal artery (see Mundt et al., 1992).

2.2.2. Salivary cortisol

Saliva samples were obtained using a salivette for collection as described in previous studies (Kirschbaum and Hellhammer, 1994). Salivary cortisol levels obtained in this manner are highly correlated with serum cortisol levels (Kirschbaum and Hellhammer, 1989, 1994). A piece of cotton containing a small amount of citric acid to stimulate saliva production was placed in the mouth for approximately 60 s. Following collection, samples were labeled and frozen immediately. Cortisol levels were determined by radioimmunoassay (RIA) using commercially available kits (Coat-A-Count Cortisol, Diagnostic Products Corporation, Los Angeles, CA). Baseline salivary cortisol was assessed at two time points per session: once following the baseline cardiovascular assessment (see above) and once immediately prior to beginning the cold pressor trials (see below).

2.2.3. Thermal pain procedures

We assessed heat pain threshold (HPTH), and heat pain tolerance (HPTO) on the left volar forearm as in previous studies (Edwards and Fillingim, 2001a). Heat stimuli were delivered using an ascending method of limits paradigm with a Medoc Thermal Sensory Analyzer (TSA-2001, Ramat Yishai, Israel).

2.2.4. Temporal summation procedures

Next, following a 10-min rest period, we administered sequences of brief, repetitive, noxious thermal stimuli to assess temporal summation of thermal pain intensity (Edwards and Fillingim, 2001b; Edwards et al., 2003). Sequences of 10 consecutive 0.5-s heat pulses with interpulse intervals of approximately 2.5 s were delivered to the left dorsal forearm and the left ankle. Subjects

verbally rated the intensity of each thermal pulse on a 0–100 rating scale (Fillingim et al., 1998). During their first session, all subjects were familiarized with the procedures using a practice trial that consisted of a series of 10 thermal stimuli at 40 °C, with an adapting temperature of 32 °C, delivered to the left dorsal forearm. Data from the practice trial were not recorded as it was used entirely for training purposes. Following the practice trial, the position of the thermode was altered and two sequences of pulses with a target temperature of 48.5 °C, and an inter-trial adapting temperature of 40 °C were delivered. One sequence of pulses at this temperature was delivered to the left forearm and one to the left ankle, in randomized order. Subjects were able to terminate any sequence of thermal stimuli at any time. In a prior study, we found that a sequence of 10 brief thermal stimuli at approximately this temperature was well-tolerated by most healthy adults (Edwards and Fillingim, 2001b). A measure of the amount of temporal summation was obtained by subtracting the first rating from the highest rating in the 10-pulse sequence. Next, participants underwent a procedure whereby the intensity of thermal stimuli in a temporal summation sequence was titrated to the maximum tolerable temperature (i.e. the highest temperature at which a participant was able to tolerate all 10 stimuli). This procedure was performed in order to avoid a floor effect during the DNIC procedure and because data from a previous investigation had suggested that DNIC effects were greatest on measures of second pain (Price and McHaffie, 1988), which presumably would be most evident at suprathreshold test stimulus intensities. Ratings of temporal summation stimuli at this maximum tolerated temperature were obtained at baseline and during water immersion in order to assess DNIC, as described in our earlier report (Edwards et al., 2003).

2.2.5. DNIC trials

Following thermal pain assessment, participants underwent a series of cold pressor tasks consisting of immersion of the right hand for 1 min in a circulating water bath (Neslab, RTE-111, Portsmouth, NH) maintained at either 5 or 22 °C, depending on the session. The order of water temperatures was randomized across sessions. Twenty seconds after commencing hand immersion, a temporal summation sequence (i.e. 10 thermal pulses) with target temperatures set at the maximum temperature tolerated was delivered to either the left dorsal forearm or the left ankle (again, site order was randomized), and participants rated the pain intensity of each thermal stimulus. Two minutes after finishing the first immersion, participants re-immersed their hands in the water, and temporal summation was re-assessed on either the left dorsal forearm or the left ankle, whichever site was not stimulated in the first trial. A third and fourth trial of hand immersion followed, each separated by 2 min and identical to the first and second trials, respectively. Each session therefore included four DNIC trials in which the right hand was immersed in water (the conditioning stimulus) and thermal pain responses were assessed on either the left arm (two trials) or left leg (two trials). In one session, the temperature of the water bath was set at 5 °C, while in the other session (i.e. the control session) the temperature was set at 22 °C.

2.3. Questionnaires

2.3.1. Perceived DNIC

Two items queried participants about the extent to which immersion of the right hand in the circulating water bath had reduced the pain from the thermal stimulation. The items were written as follows: (a) 'the cold water procedure (on my right hand) decreased how painful the thermal stimuli on my left arm felt'; (b) 'the cold water procedure (on my right hand) decreased how painful the thermal stimuli on my left leg felt.' Participants rated both items from 1 (not at all) to 10 (very much). These two items were averaged to yield a composite measure of perceived DNIC effects.

2.3.2. Sense of mastery (SOM)

The seven-item SOM scale (Pearlin et al., 1981) was used to assess respondents' general sense of life control and mastery. Total scores on the SOM range from 7 to 28, with higher scores indicating increasing perceptions of mastery. The SOM has been found to be psychometrically sound, demonstrating good reliability and convergent validity in diverse populations (Marshall and Lang, 1990).

2.3.3. Profile of mood states—bi-polar (POMS)

The POMS (Lorr and McNair, 1988) consists of 72 mood-related words; subjects indicate the extent to which each item describes their current mood. The POMS assesses both positive and negative effective dimensions. It has been validated against other measures of mood and is sensitive to subtle differences in effective state. In the present analyses, the global indices of positive and negative effects were utilized.

2.3.4. Multidimensional health locus of control (MHLC)

The MHLC (Wallston et al., 1978) is an 18-item instrument assessing three dimensions of health-specific locus of control. In the present study, only the six-item internal health locus of control (IHLC) subscale, which measures the extent of perceived personal control over physical health, was utilized. The IHLC subscale has demonstrated acceptable reliability and validity (Wallston and Wallston, 1983).

2.3.5. Kohn reactivity scale (KRS)

The KRS (Kohn, 1985) is a 24-item measure of reactivity, a construct which is related to hypervigilance. KRS scores are inversely related to pain tolerance, and positively correlated with ratings of pain intensity produced by noxious stimuli (Dubreuil and Kohn, 1986).

2.3.6. Perceived stress scale (PSS)

The PSS (Cohen et al., 1983) is a 14-item measure of the perceived amount of stress an individual has experienced over the past month. The reliability and validity of the PSS are well-established (Cohen et al., 1983), and it is a commonly used measure of non-specific life stress.

2.3.7. Short-form-36 health survey (SF-36)

The SF-36 is a widely used general measure of health status (Ware and Sherbourne, 1992); it consists of 36 items sampling a variety of domains of physical and mental health. Subscales of the SF-36 are linearly transformed to standardized 0–100 scales where higher scores reflect better health, improved functioning, and fewer limitations. The reliability and validity of the SF-36 and its subscales have been repeatedly demonstrated in a variety of populations (Ware, 1996), including samples of patients with chronic pain. As in previous work with chronic low back pain patients (Clauw et al., 1999), we utilized the following subset of SF-36 subscales as an index of clinical pain and physical health: physical functioning (PF), physical role (PR), bodily pain (BP), and general health (GH). Each subscale consists of 2–10 items; in general, SF-36 items inquire about health states either currently or over the past 4 weeks. For example, the BP subscale (two items) queries respondents about the degree of pain (from 'none' to 'very severe') and interference of pain with daily activities (from 'not at all' to 'extremely') over the past month. The PF subscale (10 items) consists of questions about current physical limitations (from 'not limited at all' to 'limited a lot') in performing a variety of physical tasks from walking one block to vigorous running.

2.4. Data reduction and analysis

Variables that were assessed multiple times were averaged within sessions, across sessions, and across sites, when relevant. For example, temporal summation of thermal pain at 48.5 °C was assessed at two body sites (i.e. the left arm and left leg) during both sessions. Thus, the temporal summation variable used in the regression analyses consists of the average degree of temporal summation across these four trials.

A composite measure of DNIC was computed using data from the DNIC trials in each session. Change scores were calculated for each trial of the temporal summation procedure (i.e. subtraction of baseline ratings from immersion-associated ratings), and these values were then averaged. This gives a measure of the mean difference in thermal pain ratings from baseline to immersion. In addition, we calculated the difference in peak pain ratings (i.e. the highest of the 10 ratings of repetitive thermal stimuli) from baseline to immersion and averaged these across DNIC trials. Next, the average change in mean pain ratings and peak pain ratings during the 22 °C water immersion session was subtracted from the values from the 5 °C water immersion session. This gives a controlled (i.e. the effects from the neutral water temperature session are subtracted) measure of the degree to which thermal pain ratings change as a function of heterotopic cold pain. At this point, two summary variables exist: a measure of the decrease in average thermal pain ratings during painful cold relative to the non-painful control immersion, and a measure of the decrease in peak pain ratings during painful cold relative to the control condition. In order to combine these two variables into a single composite score, and for ease of presentation, both of these variables were standardized across subjects to distributions with a mean of 0 and a standard deviation of 1. These two standardized scores were then averaged The resultant value (labeled 'mean standardized DNIC score' in Table 1) is a composite measure of the number of standard deviations of change in thermal pain ratings as a function of hand immersion in the painfully cold water. See Appendix A for sample calculations.

Group differences in categorical variables were evaluated using χ^2 tests and group differences in continuous variables were tested with *t*-tests and analysis of variance (ANOVA). Zero-order relationships among continuous variables were assessed with Pearson correlation coefficients. Hierarchical multiple regression was used to test

Table 1
Descriptive data for older and younger adults

	Younger ($n = 37$)	Older ($n = 40$)
Thermal pain variables (*mean* ± *SD*)		
Heat pain threshold (°C)	42.1 ± 2.6*	43.8 ± 3.4
Heat pain tolerance (°C)	47.1 ± 2.1*	48.3 ± 2.0
Mean pain rating (0–100) of 48.5 °C stimuli	49.4 ± 23.5	41.1 ± 19.1
Mean temporal summation at 48.5 °C	15.4 ± 11.7	17.2 ± 12.0
Mean standardized DNIC score[a]	−0.34 ± 0.64***	0.31 ± 0.90
Perceived DNIC (0–10)	4.2 ± 2.6	3.3 ± 2.8
	Younger ($n = 36$)	Older ($n = 38$)
Physiological measures (*mean* ± *SD*)		
Mean arterial pressure (mmHg)	91.6 ± 10.9***	101.2 ± 10.5
Heart rate (bpm)	72.4 ± 10.8	69.6 ± 10.3
Salivary cortisol[b] (μg/dec)	0.49 ± 0.41	0.45 ± 0.62
	Younger ($n = 37$)	Older ($n = 37$)
Self-report (psychological) measures (*mean* ± *SD*)		
Sense of mastery scale (0–28)	23.6 ± 3.1	22.4 ± 3.3
Internal health locus of control (0–36)	25.2 ± 4.5	24.6 ± 4.5
Perceived stress scale (0–56)	20.2 ± 6.5**	15.5 ± 6.2
Positive mood (POMS) (0–90)	56.9 ± 11.5*	64.4 ± 13.8
Negative mood (POMS) (0–90)	28.9 ± 14.7**	16.8 ± 14.7
Kohn reactivity scale (24–120)	70.8 ± 4.6*	73.7 ± 5.1

Age groups differ at $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. DNIC, diffuse noxious inhibitory controls; POMS, profile of mood states.

[a] Data are standardized to distributions with means of zero and standard deviations of one. Negative scores denote suppression of pain ratings during 5 °C water immersion.

[b] Mean levels of salivary cortisol are statistically adjusted for time of day.

the influence of laboratory pain variables on HRQOL. The potential mediating effects of DNIC were also evaluated using hierarchical regression; we examined the association between age and HRQOL before and after inserting DNIC scores as predictor variables.

3. Results

3.1. Laboratory pain responses in older and younger adults

As suggested in our previous report (Edwards et al., 2003), HPTH and tolerance, averaged across sessions, were higher in older than in younger adults ($P < 0.05$). No age differences were noted for mean ratings of repetitive thermal stimuli or for the amount of temporal summation occurring in response to these repetitive stimuli. Finally, group differences did emerge on a standardized measure of DNIC; on average, thermal pain ratings decreased by approximately 1/3 of a standard deviation in younger adults while increasing nearly 1/3 in older adults during concurrent stimulation with noxious cold (see Table 1). For figures depicting temporal changes in thermal pain responses at baseline and during immersion, please refer to Figs. 3–6 in our earlier report (Edwards et al., 2003). Interestingly, perceived DNIC ratings did not vary significantly as a function of age, with both groups indicating that noxious cold decreased the thermal pain slightly less than 'somewhat' (see Table 1).

3.2. Baseline physiological characteristics of older and younger adults

Consistent with prior findings (Edwards and Fillingim, 2001a), significantly higher MAPs were observed among the older participants. HR, however, did not differ by age. Similarly, no age effects were evident for baseline levels of salivary cortisol (see Table 1).

3.3. Baseline psychological characteristics of older and younger adults

No group differences were apparent on the SOM and IHLC scales, suggesting that older and younger adults did not differ in their sense of general or health-specific self-efficacy. Older adults did report less perceived stress and less negative mood than their younger counterparts ($P < 0.01$). In addition, higher levels of reactivity on the KRS and positive mood on the POMS ($P < 0.05$) were reported by the older group (see Table 1).

3.4. Inter-correlations among thermal pain responses

As expected, HPTH and tolerance were highly positively correlated. In addition, each was significantly negatively correlated with thermal pain ratings and with the magnitude of temporal summation, which were positively related to one another. Interestingly, the magnitude of DNIC was not significantly associated with any of these other thermal pain variables, perhaps suggesting that endogenous pain-modulatory systems are subserved by different mechanisms than those that govern less complex pain responses (see Table 2).

Table 2
Relationships among pain responses: partial correlations controlling for age

Variables	HPTH	HPTO	TS	0–100 rating	DNIC
HPTH	1				
HPTO	0.65*	1			
TS	−0.42*	−0.49*	1		
0–100 rating	−0.37*	−0.55*	0.61*	1	
DNIC	0.14	0.09	−0.06	−0.07	1

*$P < 0.005$. HPTH, heat pain threshold; HPTO, heat pain tolerance; TS, temporal summation of heat pain; 0–100 rating, mean ratings of repetitive 48.5 °C stimuli on the arm and leg; DNIC, diffuse noxious inhibitory control.

3.5. Prediction of DNIC

A stepwise multiple regression predicting standardized DNIC scores was performed on the entire sample. As we have previously noted that DNIC varies across age groups, age was forced into the model first, and subsequent variables entered the regression equation only if they added significantly ($P < 0.15$) to the explained variance. Additional predictor variables were demographic (sex), psychological (SOM, PSS, POMS, IHLC, and KRS scores), physiological (baseline MAP, HR, and salivary cortisol), and perceived DNIC scores. Results of this analysis are presented in Table 3. After entry of age on the first step explained 11% of the variance in DNIC, only perceived DNIC scores entered the regression model, explaining an additional 8% of the variance.

3.6. Prediction of SF-36 subscale scores

Scores for older and younger adults on the SF-36 subscales are presented in Table 4. Three older participants failed to complete the SF-36; data are presented for the 37

Table 3
Results of hierarchical stepwise regression analysis predicting DNIC

Step	Variable	R^2 change	F-value	Standardized β	P-value
1	Age	0.11	7.35	0.28	0.008
2	Perceived DNIC	0.08	5.83	−0.28	0.02

Final model: $F(2, 71) = 6.87$, $P < 0.002$, $R^2 = 0.19$. Variables entered but not remaining ($P > 0.15$) in stepwise regression: sex, SOM, PSS, POMS, IHLC, KRS, MAP, HR, salivary cortisol. SOM, sense of mastery; PSS, perceived stress scale; IHLC, internal health locus of control; KRS, Kohn reactivity scale; MAP, mean arterial pressure; HR, heart rate.

Table 4
Scores on SF-36 subscales (mean ± SD)

SF-36 subscales	Younger ($n = 37$)	Older ($n = 37$)
General health (0–100)	79.1 ± 13.8	77.6 ± 18.2
Physical functioning (0–100)	93.2 ± 19.2*	84.6 ± 15.4
Physical role (0–100)	95.3 ± 15.4*	81.1 ± 31.7
Bodily pain (0–100)	76.2 ± 16.5	73.7 ± 16.1

Age groups differ at *$P < 0.05$. Higher SF-36 subscale score represents better functioning (e.g. less pain, better health).

younger and 37 older subjects who provided responses. While no group differences emerged for perceived GH and BP, older adults did demonstrate lower scores on the PF and PR subscales ($P < 0.05$).

Initially, we dichotomized participants according to whether or not they demonstrated a DNIC response. Those whose composite DNIC scores were negative (suggesting a suppression of thermal pain ratings during concurrent cold pain) were compared with those whose DNIC scores were zero or positive (suggesting no change or an increase in thermal pain ratings during cold pain). A χ^2 test revealed that a greater proportion ($P < 0.05$) of younger participants showed DNIC responses (64.9%) relative to older participants (29.7%). A series of factorial ANOVAs was performed, with age group (younger vs. older) and DNIC category (DNIC response vs. no DNIC response) as the independent variables, and the SF-36 subscales as the dependent variables (see Fig. 1). Significant effects of DNIC category were observed only for the BP [$F(3, 70) = 3.89$, $P < 0.05$] and PF [$F(3, 70) = 5.83$, $P < 0.02$] subscales, and no interactions between DNIC category and age group were noted (all P-values for interaction terms >0.1).

In order to examine the unique associations of DNIC with HRQOL, a series of hierarchical regression analyses were performed with the four SF-36 subscale scores as dependent variables and with age, sex, and experimental pain responses as predictor variables. In each analysis, age and sex were forced into the model in the first step, followed by each of the thermal pain variables, with DNIC responses entering the equation last.

Table 5 shows the results of the regression analysis predicting scores on the BP subscale. The overall model captured 24% of the variance in BP scores, though neither age, sex, nor any of the thermal pain variables emerged as significant predictors. Surprisingly, there was a trend ($P = 0.08$) for higher HPTO to be associated with lower BP values (i.e. more pain). Only DNIC responses were significantly associated with BP, accounting for 17% of the variance; greater DNIC magnitude (i.e. a more negative value for the DNIC variable, reflecting greater suppression of thermal pain ratings during cold water immersion) was related to less reported pain (i.e. higher scores on the SF-36 subscales reflect better HRQOL: less pain, in this case).

In the regression model predicting PF scores, the predictor variables explained 20% of the variance (see Table 6). Age was significantly ($P < 0.05$) related to PF in an inverse fashion, indicating that older adults reported poorer PF. The regression coefficient for DNIC was also significant ($P < 0.05$); the negative sign indicated that greater DNIC responses (i.e. more negative scores on the DNIC composite variables) were associated with improved self-reported PF.

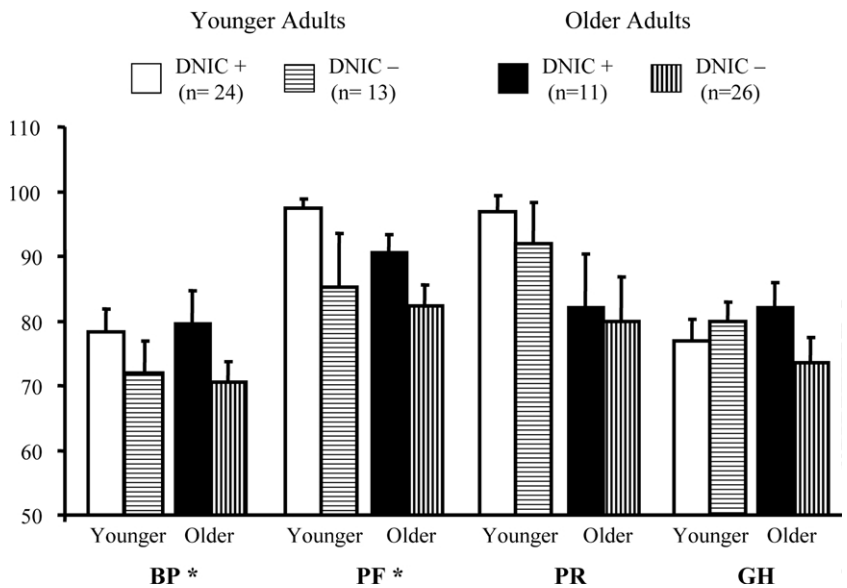

Fig. 1. Mean SF-36 subscale scores as a function of DNIC responses in younger and older adults. Error bars reflect standard errors. DNIC + refers to a suppression of thermal pain during cold pain. DNIC − refers to either no change or an increase in thermal pain during cold pain. *Overall effect ($P < 0.05$) of DNIC category.

Table 5
Results of hierarchical regression analysis predicting the SF-36 bodily pain subscale

Step	Variable	R^2 change	F-value for variable	Standardized β	P-value
1	Age	0.01	0.50	−0.10	0.49
	Sex		0.28	−0.06	0.60
2	HPTH	0.01	0.45	0.08	0.52
3	HPTO	0.04	3.13	−0.32	0.08
4	0–100 rating	0.00	0.23	−0.06	0.65
5	TS	0.01	0.49	−0.10	0.49
6	DNIC	0.17	14.21	−0.45	0.001

Final model: $F(7, 66) = 2.89$, $P < 0.02$, $R^2 = 0.24$. HPTH, heat pain threshold; HPTO, heat pain tolerance; TS, temporal summation of heat pain; 0–100 rating, mean ratings of repetitive 48.5 °C stimuli on the arm and leg; DNIC, diffuse noxious inhibitory control.

Table 6
Results of hierarchical regression analysis predicting the SF-36 physical functioning subscale

Step	Variable	R^2 change	F-value for variable	Standardized β	P-value
1	Age	0.09	4.04	−0.23	0.04
	Sex		2.43	−0.18	0.12
2	HPTH	0.01	0.35	0.08	0.56
3	HPTO	0.03	2.53	0.27	0.10
4	0–100 rating	0.00	0.18	0.04	0.75
5	TS	0.00	0.14	0.02	0.90
6	DNIC	0.07	5.48	−0.29	0.02

Final model: $F(7, 66) = 2.30$, $P < 0.04$, $R^2 = 0.20$. HPTH, heat pain threshold; HPTO, heat pain tolerance; TS, temporal summation of heat pain; 0–100 rating, mean ratings of repetitive 48.5 °C stimuli on the arm and leg; DNIC, diffuse noxious inhibitory control.

Several variables emerged as predictors of the PR subscale of the SF-36 (see Table 7). Again, age demonstrated a significant association, with older adults reporting lower PR scores. HPTH was marginally positively related to PR ($P = 0.07$), while, unexpectedly, thermal pain ratings were positively related to PR scores (i.e. higher pain ratings predict better PR scores). DNIC responses again emerged as a significant predictor, explaining an additional 6% of the variance, with greater DNIC magnitude predicting better PR scores. Overall, the regression model was highly significant ($P < 0.004$), accounting for 25% of the variance in PR responses.

Finally, a similar regression analysis with GH subscale scores as the dependent variable failed to produce a significant overall prediction model, explaining only 10% of the variance in GH ratings (see Table 8). Only DNIC responses emerged as a significant predictor of GH ($P = 0.05$), accounting for 6% of the variance in GH scores, with more DNIC associated with improved GH ratings.

3.7. Mediating role of DNIC in age differences in physical function

In order to determine whether age group differences in DNIC mediated age differences in HRQOL, the effects of age group on the PF and PR subscales of the SF-36 were re-analyzed while statistically controlling for DNIC

Table 7
Results of hierarchical regression analysis predicting the SF-36 physical role subscale

Step	Variable	R^2 change	F-value for variable	Standardized β	P-value
1	Age	0.08	5.76	−0.28	0.01
	Sex		0.01	0.00	0.98
2	HPTH	0.04	3.24	0.21	0.07
3	HPTO	0.01	0.29	0.09	0.58
4	0–100 rating	0.05	4.84	0.28	0.03
5	TS	0.01	0.36	−0.09	0.55
6	DNIC	0.06	5.48	−0.28	0.02

Final model: $F(7, 66) = 3.10$, $P < 0.008$, $R^2 = 0.25$. HPTH, heat pain threshold; HPTO, heat pain tolerance; TS, temporal summation of heat pain; 0–100 rating, mean ratings of repetitive 48.5 °C stimuli on the arm and leg; DNIC, diffuse noxious inhibitory control.

Table 8
Results of hierarchical regression analysis predicting the SF-36 general health subscale

Step	Variable	R^2 change	F-value for variable	Standardized β	P-value
1	Age	0.00	0.18	−0.05	0.67
	Sex		0.02	0.00	0.96
2	HPTH	0.01	0.68	0.10	0.39
3	HPTO	0.01	1.00	0.17	0.32
4	0–100 rating	0.02	1.47	0.19	0.22
5	TS	0.00	0.03	0.02	0.89
6	DNIC	0.06	4.11	−0.26	0.05

Final model: $F(7, 66) = 1.37$, $P = 0.26$, $R^2 = 0.10$. HPTH, heat pain threshold; HPTO, heat pain tolerance; TS, temporal summation of heat pain; 0–100 rating, mean ratings of repetitive 48.5 °C stimuli on the arm and leg; DNIC, diffuse noxious inhibitory control.

magnitude by including DNIC in a regression equations predicting HRQOL on the basis of age. Results of these analyses indicated that age was significantly associated with SF-36 PF scores before ($\beta = -0.25$, $P = 0.03$), but not after ($\beta = -0.14$, $P = 0.22$), adjusting for group differences in DNIC, suggesting a potential mediating effect of DNIC scores. Similarly, when analyzing SF-36 PR scores, age was associated with PR scores ($\beta = -0.28$, $P = 0.01$), but inserting DNIC scores into the regression equation eliminated the significance of the effect of age on PR ($\beta = -0.17$, $P = 0.13$).

4. Discussion

The present results add to the characterization of DNIC in healthy subjects and provide evidence for the clinical relevance of pain assessment in the laboratory. It is now widely recognized that information concerning noxious stimuli is actively modulated by multiple endogenous neural and hormonal systems (see Fields and Basbaum, 1999), and that such modulation may be either antinociceptive or pronociceptive in nature (Fields and Basbaum, 1999). The balance between inhibition and facilitation may vary substantially across individuals and may also vary systematically as a function of age. The present study illustrates both these inter-individual and systematic variabilities. Since the experience of clinical pain and responses to experimental noxious stimuli administered are both modulated by the CNS (Dubner and Ren, 1999; Fields and Basbaum, 1999), laboratory-based assessment of DNIC may offer a representation of this balance of facilitation and inhibition, with the potential implication that DNIC responses may be predictive of the clinical experience of pain. The present report attempts to further characterize DNIC, and to evaluate its correlates and clinical relevance.

Our sample demonstrated age differences on a number of variables. Consistent with prior research (Dewhurst et al., 1991; Edwards et al., 2001), blood pressure was greater among older relative to the younger participants. In contrast, no age effects were evident for baseline levels of salivary cortisol; this is consistent with evidence from human and animal studies suggesting that in the absence of disease, aging has minimal effects on circulating cortisol (Urban, 1992). On the psychological measures, no age differences emerged for measures of self-efficacy. However, older adults did report less perceived stress, less negative mood, more positive mood, and greater reactivity than their younger counterparts. Some researchers have suggested that negative mood is reduced in samples of healthy elderly individuals (Gagliese and Melzack, 1997; Parmelee, 1997), which is generally consonant with the present findings. Interestingly, none of these physiological or psychological variables was significantly associated with DNIC responses. Furthermore, the magnitude of DNIC was also not related to any of the other pain responses measured in this sample (i.e. threshold, tolerance, suprathreshold ratings, temporal summation). These findings suggest that the specific pain-modulatory system associated with DNIC is not dependent on the functioning of the cardiovascular or HPA systems, is not mediated by psychosocial factors such as mood, self-efficacy, or reactivity, and may be subserved by mechanisms different from those that govern other pain responses. In the present investigation, only age and an individual's perception of DNIC were associated with DNIC magnitude, and these variables explained less than 20% of the variance in DNIC responses. Thus, the mechanisms underpinning the phenomenon of DNIC in humans remain largely unknown; however, further findings provide evidence that assessment of DNIC may provide information relevant to an individual's HRQOL.

In spite of the fact that the present sample was highly selected and that only healthy individuals were enrolled, several age differences in HRQOL did emerge from the data. Consistent with prior research, older participants reported poorer PF and greater limitations in fulfilling PRs relative to younger subjects (for reviews see Gagliese and Melzack, 1997; Gibson et al., 1994). More interestingly, the magnitude of DNIC was associated with each of the SF-36 subscales in a consistent direction. Greater DNIC responses were related to less pain, better physical function, and improved self-rated GH. Other laboratory pain responses showed less consistent relationships with HRQOL and none

of these other variables was associated with the pain-related SF-36 subscale (BP). A final set of analyses suggested a potential mediating effect of DNIC scores on age differences in HRQOL. Clearly, a wide array of factors influences the experience of pain and perceptions of physical health among older adults (Gagliese and Melzack, 1997). The present findings appear to suggest that declines in DNIC-like mechanisms may be one of the multiplicity of pathways by which age-related decrements in perceived PF are produced.

While several previous studies have reported relationships between laboratory pain variables and clinical pain (Fillingim et al., 1996, 1999; Gil et al., 1995; Lautenbacher et al., 1994), to our knowledge, no prior investigators have directly evaluated the clinical relevance of DNIC in healthy individuals. The finding that larger degrees of analgesic responses to heterotopic noxious stimuli are related to reports of less clinical pain and better PF in daily life suggests that common mechanisms may shape responses to noxious stimulation both inside and outside of the laboratory. Moreover, the present results suggest that DNIC may be one of the more clinically relevant laboratory pain responses, perhaps because DNIC assesses the efficacy of CNS pain-modulatory systems more directly than other experimental pain variables. In this study, individuals differed widely in their DNIC responses, with effects ranging from substantial inhibition to equally substantial facilitation. Though the present findings await independent replication, these data provide preliminary evidence for: (a) the contribution of age-associated declines in endogenous analgesia to enhanced clinical pain and diminished physical function in elderly populations, and (b) the importance of individual differences in pain modulation to shaping HRQOL across the lifespan.

As previously noted, the clinical relevance of DNIC has been demonstrated in several samples of chronic pain patients. Individuals with FM and TMD show diminished DNIC responses (Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997; Sigurdsson and Maixner, 1994). However, none of these studies was longitudinal and it is not clear whether the diminished efficacy of DNIC in chronic pain patients is a contributor to chronic pain, a consequence of having a chronic pain, some combination of both, or neither. The findings of the present study, that positive relationships are present in healthy subjects between pain modulation and HRQOL, appear to suggest that impaired DNIC responses are unlikely to be entirely a consequence of having chronic pain. It certainly seems possible that pain-modulatory capacity represents a stable individual difference variable that contributes to one's experience of clinical pain and physical health. However, our cross-sectional design precludes definite conclusions.

A number of limitations should temper interpretation of these findings. First, we studied a healthy sample within fairly limited age ranges, which did not permit examination of DNIC responses across the full lifespan or across a range of health states. The health of our sample may, in part, explain the low to modest magnitude of the association between DNIC and clinical measures. However, a benefit of our approach is the ability to investigate the association of DNIC and clinically relevant variables uncontaminated by the presence of disease states or significant physical impairment. Second, we were unable to identify mechanisms mediating DNIC effects; however, previous evidence suggests that DNIC is at least in part opioid-mediated (Willer et al., 1990). Third, and relatedly, we only assessed a limited number of the vast range of potential physiological and psychological parameters that might be important in shaping DNIC responses. Fourth, as mentioned earlier, the cross-sectional design does not permit conclusions regarding the direction of the association between DNIC and HRQOL. Although we have speculatively interpreted these data as suggesting that CNS pain-inhibitory systems influence the experience of clinical pain, it may also be the case that this association works in the opposite direction. For example, one recent study of osteoarthritis patients reported no DNIC effects in the patients when they were experiencing pain; however, when the patients were reassessed in a pain-free state (i.e. following surgery), their DNIC responses did not differ from those of the controls, suggesting that DNIC effects and clinical pain states may interact in a dynamic fashion (Kosek and Ordeberg, 2000). Though we studied generally healthy individuals, they did, on average, experience some pain (i.e. if all of them were completely pain-free, there could have been no association between pain and DNIC responses) and it is possible that the relatively mild pain experienced by our subjects had an adverse impact on the pain-modulatory systems subserving DNIC.

Despite its limitations, the present study may prove valuable in extending our previous work on age differences in pain modulation (Edwards et al., 2003), in characterizing the complex phenomenon of DNIC, and in demonstrating the clinical relevance of laboratory pain procedures. To the extent that reduced DNIC responses constitute a risk factor for pain, enhancing pain-modulatory capacity may become an important focal point for pain management. Summing up, our results suggest that DNIC responses are unrelated to blood pressure, cortisol levels, psychological variables, or other laboratory pain responses. The magnitude of DNIC, however, is related to self-reported HRQOL, and age differences in DNIC partially explain age differences in physical function. Further studies will be required to determine DNIC's correlates, malleability, and role in predicting the onset or course of chronic pain.

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Appendix A

Sample computation of standardized composite DNIC scores.

Steps		Sample younger subject	Sample older subject
(1)	Compute mean heat pain ratings (i.e. average the 0–100 ratings of the 10 stimuli at the maximum tolerated intensity on the arm and the leg) at baseline for each session	5 °C (baseline), 64.8 22 °C (baseline), 66.3	5 °C (baseline), 55.5 22 °C (baseline), 54.7
(2)	Compute the mean heat pain ratings during immersion	5 °C (immersion), 55.1 22 °C (immersion), 66.5	5 °C (immersion), 58.0 22 °C (immersion), 52.7
(3)	Calculate change scores for mean heat pain ratings during each session (i.e. subtract the value at baseline from the value during immersion)	5 °C session, −9.7 22 °C session, +0.2	5 °C session, +2.5 22 °C session, −2.0
(4)	Compute the mean peak heat pain rating (i.e. the average of the highest rating of a stimulus on the arm and a stimulus on the leg) at baseline for each session	5 °C (baseline), 74.5 22 °C (baseline), 76.0	5 °C (baseline), 64.0 22 °C (baseline), 64.0
(5)	Compute the mean peak heat pain rating during immersion	5 °C (immersion), 62.2 22 °C (immersion), 75.8	5 °C (immersion), 69.1 22 °C (immersion), 62.1
(6)	Calculate change scores for peak pain ratings during each session	5 °C session, −12.3 22 °C session, −0.2	5 °C session, +5.1 22 °C session, −1.9
(7)	Calculate the difference in average rating change scores across the sessions (i.e. subtract the two values in each cell of row #3)	Difference, −9.9	Difference, +4.5
(8)	Calculate the difference in peak rating change scores across the sessions (i.e. subtract the two values in each cell of row #6)	Difference, −12.1	Difference, +7.0
(9)	Standardize the difference score in row #7	Standardized difference score, −0.41	Standardized difference score, +0.29
(10)	Standardize the difference score in row #8	Standardized difference score, −0.52	Standardized difference score, +0.37
(11)	Average these standardized difference score to create a composite DNIC score	Mean standardized DNIC score, −0.46	Mean standardized DNIC score, +0.33
(12)	Interpretation	For this subject, thermal pain ratings decreased, on average, by nearly 1/2 of a standard deviation during painful cold relative to the neutral control condition	For this subject, thermal pain ratings increased, on average, by approximately 1/3 of a standard deviation during painful cold relative to the neutral control condition

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