2002

# Age -related differences in endogenous pain modulation: A comparison of diffuse noxious inhibitory controls in healthy older and younger adults.

Robert Randolph Edwards
*University of Alabama at Birmingham*

# INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

**The quality of this reproduction is dependent upon the quality of the copy submitted.** Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

ProQuest Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

# AGE-RELATED DIFFERENCES IN ENDOGENOUS PAIN MODULATION: A COMPARISON OF DIFFUSE NOXIOUS INHIBITORY CONTROLS IN HEALTHY OLDER AND YOUNGER ADULTS

by

ROBERT R. EDWARDS

A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
partial fulfillment of the requirements for the degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2001

ProQuest Information and Learning Company
300 North Zeeb Road
P.O. Box 1346
Ann Arbor, MI 48106-1346

ABSTRACT OF DISSERTATION
GRADUATE SCHOOL, UNIVERSITY OF ALABAMA AT BIRMINGHAM

Degree Ph.D. Program Psychology

Name of Candidate Robert R. Edwards

Committee Chairs Roger B. Fillingim and J. Scott Richards

Title Age-Related Differences in Endogenous Pain Modulation: A Comparison of Diffuse Noxious Inhibitory Controls in Healthy Older and Younger Adults

Prior research has noted increased reports of persistent pain and diminished tolerance for certain types of laboratory-induced pain among the elderly. While explanations for these effects often propose senescent decrements in endogenous analgesic systems as an explanatory mechanism, no direct empirical evidence in humans has yet emerged. The present study was designed to evaluate the existence, nature, and clinical relevance of these putative age-related differences in endogenous pain inhibition. Groups of healthy younger (n = 45, mean age = 21.6 years, range = 18-25) and older (n = 48, mean age = 63.1 years, range = 55-67) adults participated in a 2-session laboratory assessment of diffuse noxious inhibitory controls, which was a measure of endogenous pain inhibition. Consistent with theoretical predictions, older adults demonstrated less pain modulation relative to younger adults. Endogenous pain-inhibitory capacities were unrelated to physiological responses to noxious stimulation. For both older and younger subjects, greater pain inhibition was associated with less clinical pain and improved physical functioning. These findings suggest age-associated decrements in endogenous analgesic responses and demonstrate their relevance to clinical variables.

ACKNOWLEDGMENTS

I thank the members of my dissertation committee for their guidance and support on this project. Drs. Roger Fillingim and J. S. Richards served as dissertation chairs; Drs. Marion Broome, Timothy Ness, and Alan Randich were invaluable committee members. This project would not have been possible without their assistance.

I also thank Tykeysha Powell who provided valuable assistance in subject recruitment, data collection, and data entry. I am grateful for her patience and generosity.

Finally, I thank my parents, Rob and Marilyn, and my wife Jennifer for their love and support, without which none of this would have been possible.

This work was supported by National Institutes of Health grant DE12261, by an NIH predoctoral fellowship, and by a grant from The University of Alabama at Birmingham Center for Aging.

TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

Page

LIST OF TABLES

LIST OF FIGURES

# INTRODUCTION

Noxious stimuli elicit complex physiological, affective, cognitive, and sensory responses that interact to comprise the human experience of pain. A nearly ubiquitous experience, pain is the most common presenting medical complaint and the primary motivator in health-care seeking behavior, accounting for over 80% of all physician visits (Corran & Melita, 1998; Gatchel & Turk, 1996). In one comprehensive population survey, more than 70% of the respondents reported experiencing headaches, backaches, muscle pain, or joint pain within the preceding 12 months (Sternbach, 1986), and estimates of the prevalence of chronic pain approach one third of the U.S. population (Osterweis, Kleinman, & Mechanic, 1987). Collectively, the total direct and indirect costs of pain and pain treatment exceed $100 billion, a figure that surpasses the combined costs of treating coronary artery disease, cancer, and AIDS (Fordyce, 1995).

## Aging and Clinical Pain

The experience of pain appears to be especially prevalent and disabling during the later years of life. It is generally recognized that the frequency of persistent or chronic pain is elevated among older individuals (for recent reviews see Corran & Melita, 1998; Gagliese & Melzack, 1997a, 1997b; Harkins, 1996; Harkins & Scott, 1996) and that senescence is associated with increased expectations of pain and greater interference of pain with daily activities (Crook, Rideout, & Brown, 1984; Gibson, Katz, Corran, Farrell,

& Helme, 1994). Results from a large-scale epidemiological survey indicated that older individuals reported more frequent pain, more sites of pain, and higher visual analogue scale (VAS) ratings of pain intensity than did younger respondents (Harkins, 1996). In addition, age-related increases in the prevalence of numerous painful conditions such as arthritis (Badley & Tennant, 1992) and fibromyalgia (Wolfe, Ross, Anderson, Russell, & Hebert, 1995) have been reported. One community study of older individuals found that 83% reported some current pain, with the most frequent complaints including back, joint, and muscle pains (Roy & Thomas, 1986). Additionally, several studies have compared the pain intensity ratings of elderly chronic pain patients with younger or middle-aged chronic pain patients and reported greater chronic pain intensity among the groups of elderly patients (Puder, 1988; Wilkieson, Madhok, Hunter, & Capell, 1993). Finally, neuropathic pain syndromes such as herpes zoster and trigeminal neuralgia appear to become more prevalent with advancing age (Butler, 1979; Ferrell, 1991). While conflicting epidemiological reports do exist, with several recent studies suggesting that pain complaints peak in late-middle age and taper off in elderly populations (Lipton, Pfeffer, Newman, & Solomon, 1993; Wright, Barrow, Fisher, Horsley, & Jayson 1995), the bulk of the evidence appears to suggest an enhanced experience of clinical pain, particularly chronic pain, with advancing age. Chronic pain syndromes can have severely debilitating effects in older individuals, as pain in the elderly is a major contributor to poor quality of life, reduced well-being, and physical disability (Harkins, 1996; Kahana, Kahana, Namazi, Kercher, & Stange, 1997; Scudds & Robertson, 1998).

Aging and Laboratory Pain

In contrast to the relatively consistent findings relating to senescence and its impact on clinical pain, laboratory studies of the effects of aging on pain perception have yielded somewhat contradictory and variable findings (Gagliese & Melzack, 1997b; Harkins, 1996). Although substantial evidence suggests global age-associated decrements in a number of perceptual systems such as vision and audition (Stevens, Cruz, Marks, & Lakatos, 1998), the effects of normal aging on pain perception in particular have not been fully characterized. Historically, most studies investigating age-related alterations in pain responses have examined cutaneous thermal or electrical pain thresholds or electrical pain thresholds in tooth pulp. Collectively, these studies would appear to partially confirm the conventional wisdom that pain perception diminishes with advancing age, with 10 of 19 investigators reporting increased thermal or electrical pain thresholds in the elderly (Chapman & Jones, 1944; Gibson, Gorman, & Helme, 1991; Hall & Stride, 1954; Harkins, Price, & Martinelli, 1986; Lautenbacher & Strian, 1991; Neri & Agazzani, 1984; Procacci, Bozza, & Buzelli, 1970; Schluderman & Zubek, 1962; Sherman & Robillard, 1960; Tucker, Andrew, & Ogle, 1989) and 9 of 19 reporting no age-associated differences in pain thresholds (Birren, Shapiro, & Miller, 1950; Clark & Meehl, 1971; Hardy, Wolff, & Goodell, 1943; Harkins & Chapman, 1976, 1977; Kenshalo, 1986; Mumford, 1965, 1968; Schumacher, Goodell, & Hardy, 1940).

However, laboratory pain induction procedures differ from one another along a variety of dimension such as the location of stimulated nociceptors, the time course of the pain, the pattern of afferent fibers stimulated by the procedure, and the degree to which a noxious stimulus is subject to descending inhibitory control by endogenous pain-

modulatory systems (Yu & Mense, 1990). In contrast to prior research utilizing phasic pain stimuli applied to superficial sites, several studies assessing deeper, more tonic forms of pain have noted decreased pain tolerance in elderly subjects relative to younger individuals. Specifically, pressure pain tolerance (Woodrow, Friedman, & Siegelaub, 1972) and tolerance to the cold pressor task (Walsh, Schoenfeld, & Ramamurthy, 1989) have been found to decrease steadily and significantly with advancing age. Furthermore, several studies by Harkins and Chapman (1976, 1977) have suggested that the effects of age on pain responses varied with the perceived intensity of the noxious stimuli, with elderly subjects rating more intense stimuli as more painful than younger subjects and less intense stimuli as less painful. In addition, indirect evidence for an age-related enhancement in sensitivity to tourniquet ischemia, one of the most potentially clinically relevant experimental pain stimuli (Fillingim, Maixner, Kincaid, Sigurdsson, & Harris, 1996; Fillingim, Maixner, Kincaid, & Silva, 1998), has previously been reported in patients undergoing surgery for malleolar fractures (Omerglu et al., 1997). Finally, recent results from our laboratory indicated that healthy older subjects ($\underline{n}$ = 34, mean age = 62.2 years) had significantly lower thresholds and tolerances for ischemic muscle pain than did their younger counterparts ($\underline{n}$ = 34, mean age = 22.2 years), while no age differences were observed on measures of thermal pain sensitivity (Edwards & Fillingim, in press).

Collectively, these findings suggest that the effects of age on responses to noxious stimuli may vary as a function of the pain induction task, with elderly individuals demonstrating slightly elevated pain thresholds for brief, superficial, localized stimulation but enhanced sensitivity to tonic, clinically relevant noxious stimuli applied to deep tissue structures such as muscles and joints. Globally, the findings of enhanced clinical pain re-

port and diminished tolerance for certain types of experimental noxious stimuli as a function of advancing age have led several authors to propose that both of these effects may be at least partially attributable to senescent decrements in endogenous analgesic systems (Novack et al., 1999; Yehuda & Carasso, 1997). A recent report of age-related differences in the time course of capsaicin-induced hyperalgesia (Zheng, Gibson, Khalil, Helme, & McMeeken, 2000) provided further evidence supporting this putative mechanism. Following topical application of capsaicin to younger and older groups of healthy volunteers, the resulting mechanical hyperalgesia took substantially longer to resolve among older subjects, suggesting an age-associated prolongation of the experience of pain for this sustained, C-fiber-mediated form of noxious stimulation. The authors suggested a number of possible mechanisms for the reported effects, including age-associated reductions in the capacity of the central nervous system (CNS) to reverse central sensitization at the level of the spinal cord. Accumulating evidence, therefore, appears to offer indirect support for the hypothesis that endogenous analgesic systems demonstrate progressive functional decrements in the elderly.

Aging and Endogenous Pain Modulation

While neurophysiological studies investigating the mechanisms mediating pain perception have often focused primarily on afferent pathways, substantial research suggests that pain is not transduced, transmitted, and processed in a passive manner by the CNS (Fields & Basbaum, 1999). Instead, information concerning noxious stimuli is actively modulated by endogenous neural and hormonal systems at multiple levels of the neuraxis (Basbaum & Fields, 1984; Casey, 1999; Dubner & Ren, 1999; Melzack, 1999;

Randich, 1993; Siddall & Cousins, 1995; Yaksh, 1999). Such systems may act to suppress pain transmission in the dorsal horn of the spinal cord by activating inhibitory interneurons or by direct presynaptic and postsynaptic inhibition of ascending pathways that transmit pain-related information. We (Edwards & Fillingim, in press) and others (Novack et al., 1999; Yehuda & Carasso, 1997; Zheng et al., 2000) have previously proposed that both the enhanced experience of clinical pain (e.g., increases in the frequency and severity of persistent pain complaints) and augmented sensitivity to certain types of experimental noxious stimuli (e.g., diminished tolerance for pressure, cold, and ischemic muscle pain) in senescent individuals might be accounted for by decrements in endogenous pain-inhibitory systems. That is, increases in reported pain in the elderly might be due not to enhanced afferent input related to the perception of noxious stimuli but rather to the diminishing efficacy of CNS pathways contributing to modulation and reduction of that afferent input.

Mense (1991, 1995) and colleagues (Yu & Mense, 1990) have reported that descending inhibitory pain-control systems function primarily to modulate deep pain in muscles and joints. Therefore, decrements in pain regulation may not be evident during all forms of noxious stimulation: brief, superficial, relatively localized stimuli (e.g., cutaneous thermal and electrical stimuli) may be less subject to the influences of descending antinociceptive systems. Endogenous pain-control systems have been shown to inhibit clinical pain at numerous CNS sites, including second-order spinal neurons (Basbaum & Fields, 1984; Siddall & Cousins, 1995); they may also modulate nociceptive input primarily for laboratory pain procedures which produce deep, diffuse, muscle and joint pain. Thus, if endogenous neural and hormonal pain-regulatory systems decline in efficacy

with advancing age, one would anticipate greater reports of clinical pain in muscles and joints, as well as enhanced sensitivity to certain types of experimental pain (e.g., the deep muscle pain generated by skeletal muscle ischemia) among the elderly. This is essentially the pattern of findings that has emerged from epidemiological, clinical, and laboratory-based research on aging and the experience of pain. The hypothesis that endogenous analgesic systems demonstrate functional decrements over the course of senescence appears to offer a parsimonious, though as yet unconfirmed, explanation for these findings regarding the relationships between pain and aging.

While no direct studies of the effects of age on endogenous pain modulation in humans are available, there is germane evidence from a number of animal studies. Bodnar, Romero, and Kramer (1988) reviewed research from a variety of sources suggesting that in rats multiple neural and hormonal pain-modulatory systems became progressively less efficacious with advancing age. These animal studies employed a variety of stressful conditioning stimuli designed to activate endogenous inhibitory mechanisms, with cold-water swimming being the most frequent choice of environmental stressor (Hamm & Knisely, 1985, 1986; Hamm, Knisely, & Watson, 1986; Kramer & Bodnar, 1986). In general, the results of these investigations have suggested that the magnitude of endogenous analgesic responses to noxious or stressful stimuli declines progressively as a function of increasing age. Opioid-mediated endogenous analgesic systems appear particularly susceptible to functional decline over the course of senescence (Bodnar et al., 1988; Yehuda & Carasso, 1997). Indeed, CNS levels of endogenous opioids, including beta-endorphins and enkephalins, decline with advancing age (Barden et al., 1981; Crisp et al., 1994; Gambert, Garthwaite, Pontzer, & Hagen, 1980). In addition, exogenously admin-

istered opioids produce progressively decreasing analgesic effects in aged animals (Hoskins, Burton, & Ho, 1986; Kramer & Bodnar, 1986a). Further indirect evidence for progressive age-associated decrements in endogenous analgesia derives from studies of other neurochemicals known to subserve pain inhibition. CNS cholinergic, serotonergic, and noradrenergic pathways, which participate in centrally mediated pain inhibition (Basbaum & Fields, 1984; Siddall & Cousins, 1995), all begin to demonstrate functional decrements over the course of normal aging (Bhaskaran & Radha, 1985; Ko, King, Gordon, & Crisp, 1997; D.G. Morgan, 1992; D.G. Morgan & May, 1992; D.G. Morgan, May, & Finch, 1988). For example, descending serotonergic projections are thought to partially mediate the analgesic effects of morphine and presumably of the endogenous opioids as well (Vogt, 1973; Wigdor & Wilcox, 1987). Substantial evidence derived from animal and human studies has indicated progressive decrements in absolute levels of CNS serotonin (D.G. Morgan et al., 1988), serotonergic function (Ko et al., 1997), and serotonin receptor density (D.G. Morgan, 1992; D.G. Morgan & May, 1992). Collectively, the available evidence appears to suggest substantial and potentially important effects of aging on endogenous pain modulation, with pain-modulatory capacities progressively diminishing in elderly populations. At present, however, only a single human study directly investigating age-related changes in endogenous analgesic responses has been reported. Washington, Gibson, and Helme (2000) recently examined age-related changes in endogenous analgesia produced by repeated immersion of participants' hands in painfully cold water. The results of their study suggested that older adults demonstrated less endogenous pain modulation relative to younger adults.

Diffuse Noxious Inhibitory Controls (DNIC)

One type of endogenous modulation of nociceptive input that has received extensive study has been termed Diffuse Noxious Inhibitory Controls (DNICs). Originally known as counterirritation and used widely in medicine for centuries as a method of pain relief, DNIC refers to the phenomenon of one noxious stimulus inhibiting the percept of pain produced by application of a second noxious stimulus. While animal studies may permit invasive experimental manipulations such as surgical ablation or spinal cord transection, which allow for fairly direct characterization of underlying analgesic mechanisms, investigations of endogenous analgesia in humans face a more limited range of options. DNIC-inducing procedures offer a noninvasive method for examining pain-modulatory systems in human volunteers. DNIC effects are typically demonstrated by assessing baseline responses to a phasic noxious stimulus (typically thermal or electrical stimulation applied cutaneously) and then re-assessing responses to an identical phasic stimulus following heterotopic application of a tonic noxious stimulus. Generally, responses to the phasic noxious stimulus are reduced during concurrent administration of the tonic conditioning stimulus at a distant body site, with the magnitude of the reduction serving as a proxy variable for the efficacy of endogenous analgesic systems.

A number of characteristics of DNICs have been previously described in detail (Talbot, Duncan, Bushnell, & Boyer, 1987). The primary aspects of DNIC effects include triggering by noxious stimuli applied to widespread areas of the body (Dickenson, Le Bars, & Besson, 1980; Le Bars, Dickenson, & Besson, 1979a, 1979b; Le Bars, Guilbaud, Chitour, & Besson, 1980); inhibition of spinal and medullary dorsal horn wide-dynamic-range neurons (WDR) without affecting high-threshold nociceptive-specific

mechano-sensitive neurons (Dickenson et al., 1980; Le Bars et al., 1979a, 1979b; Villanueva & Le Bars, 1986); inhibition which outlasts the duration of the noxious stimulus, although the duration of inhibition following offset of the conditioning stimulus varies from several seconds to over an hour (Price & McHaffie, 1988); and, finally, a close relationship between the strength of the diffuse noxious stimulus and the degree of inhibition produced (Le Bars, Chitour, & Clot, 1981; Villanueva & Le Bars, 1985). DNIC effects seem to be induced solely by frankly noxious stimuli; purely tactile or other innocuous stimuli are ineffective in producing DNICs as demonstrated by Le Bars and colleagues (1979a, 1979b).

The substantial, selective, widespread inhibition of WDR neurons in the dorsal horn of the spinal cord by DNIC has been characterized in animals (Cadden, 1993; Cadden, Villanueva, Chitour, & Le Bars, 1983; Le Bars et al., 1981), and many investigators have suggested that similar mechanisms (i.e., inhibitory modulation of WDR neuronal activity) are operative in the DNIC effects observed in humans (Panteleo, Duranti, & Bellini, 1988; Pertovaara, Kemppainen, Huopaniemi, & Johansson, 1987; Pertovaara, Kemppainen, Johansson, & Karonen, 1982; Price & McHaffie, 1988; Talbot, Duncan, & Bushnell, 1989; Talbot et al., 1987; Willer, De Brouker, & Le Bars, 1989; Willer, Roby, & Le Bars, 1984). Considerable evidence (Cadden et al., 1983; Le Bars et al., 1979b; Morton, Maisch, & Zimmerman, 1987) implicates supraspinal mechanisms in the activation of DNIC. For example, DNIC are not observed in patients with complete spinal cord transections (Roby-Brami, Bussel, Willer, & Le Bars, 1987) or specific medullary lesions (De Brouker, Cesaro, Willer, & Le Bars, 1990) but are present in patients with thalamic lesions (De Brouker et al., 1990). A series of lesion studies by Le Bars and colleagues

(see for reviews, Fields & Basbaum, 1999; M.M. Morgan, Heinricher, & Fields, 1994) has attempted to definitively identify the ascending and descending projections that form the neural substrates of DNIC effects in animals. While evidence for the involvement of specific pathways has been difficult to obtain, some data suggest that activation of fibers in the spinoreticular tract results in subsequent activation of descending medullary pathways involving the subnucleus reticularis dorsalis, which in turn activate inhibitory neurons in the dorsal horn of the spinal cord (Villanueva, Bouhassira, & Le Bars, 1996). Additionally, several lines of research suggest that the phenomenon of DNIC is not due to a masking of pain by a shift in attention following application of a second noxious stimulus. While attentional factors do influence pain responses (Bushnell, Duncan, Dubner, Jones, & Maixner, 1985), patients with unilateral thalamic lesions who perceived noxious electrical stimuli as nonpainful nevertheless showed substantial DNIC responses (De Brouker et al., 1990). Moreover, one study noted that application of a DNIC-producing stimulus (immersion of the hand in painfully cold water) did not affect performance on an attention-dependent visual discrimination task (Talbot et al., 1989). Finally, manipulations that alter subjects' focus of attention do not affect the magnitude of DNIC (Kakigi, 1994). Overall, application of tonic noxious stimuli has been shown to trigger diffuse pain-inhibitory effects in humans and animals. Such effects have specific neurophysiological underpinnings and are not dependent on the locus of attention.

## Clinical Relevance of DNIC

Previous research has suggested that impairments in CNS pain-regulatory systems might play a role in the onset and maintenance of several persistent pain conditions such

as fibromyalgia (Kosek & Hansson, 1997; Lautenbacher & Rollman, 1997), temporomandibular disorder (TMD; Fillingim et al., 1996; Maixner, Fillingim, Booker, & Sigurdsson, 1995; Maixner, Fillingim, Sigurdsson, Kincaid, & Silva, 1998; Sigurdsson & Maixner, 1994), and chronic myofascial pain (Graven-Nielsen, Babenko, Svensson, & Arendt-Nielsen, 1998). Empirical evidence for such propositions derives from studies indicating that DNICs are either absent or reduced relative to healthy controls in fibromyalgia patients (Kosek & Hansson, 1997; Lautenbacher & Rollman, 1997) and TMD patients (Maixner et al., 1995; Sigurdsson & Maixner, 1994). That is, administration of tonic noxious stimuli fails to affect, or effects only mild suppression of, responses to phasic noxious stimuli applied concurrently to other body sites. One recent study also suggested that DNIC effects were not present in a population of older patients with painful osteoarthritis of the hip (Kosek & Ordeberg, 2000). Interestingly, when the patients were reassessed in a pain-free state following surgical intervention (i.e., total hip replacement), DNIC functions appeared to have normalized, suggesting that DNIC effects and clinical pain states may interact in a dynamic fashion. Investigators have focused on group differences in the magnitude of DNIC between chronic pain patients and pain-free controls because DNIC offers a functional test of central pain inhibitory mechanisms in humans (Lautenbacher & Rollman, 1997). In other words, the phenomenon of DNIC, easily observable in humans, serves as a proxy for the integrity and effectiveness of multiple, interacting pain-modulatory systems. As DNICs recruit some of the functional CNS architecture known to participate in pain regulation in animals (Chitour, Dickenson, & Le Bars, 1982; Kraus, Besson, & Le Bars, 1982) as well as humans (i.e., endogenous opioidergic and serotonergic systems), findings related to DNICs may permit, to some degree,

generalization to more global pain-inhibitory systems (Kosek & Hansson, 1997; Lautenbacher & Rollman, 1997).

In addition to investigations of chronic pain populations, evidence supporting the clinical relevance of DNICs has also been derived from more basic animal and human studies suggesting that the neurochemical underpinnings of DNICs are similar to those of other pain-modulatory systems. For example, overwhelming evidence links endogenous opioid systems to the modulation of nociceptive input at a variety of CNS loci (Basbaum & Fields, 1984; Dubner & Ren, 1999; Siddall & Cousins, 1995; Yaksh, 1999). Endogenous CNS and peripheral opioids have repeatedly been shown to play essential roles in a number of pain-regulatory systems in animals and humans (Bodnar et al., 1988). Similarly, substantial literature suggests that the DNIC circuitry involves multiple complex opioidergic links (Dickenson & Le Bars, 1987; Le Bars, Chitour, Kraus, Clot, Dickenson, & Besson, 1981a, 1981b; Le Bars et al., 1980; Le Bars, Willer, & De Brouker, 1992). Naloxone administration has been demonstrated to block the inhibitory effects of heterotopic nociceptive conditioning stimuli (Kraus, Le Bars, & Besson, 1981; Le Bars et al., 1980; Willer, Le Bars, & De Brouker, 1990), presumably by inhibiting opioid-dependent descending inhibitory signals. Moreover, while systemic morphine administration blocks DNICs, apparently by reducing the painfulness of the conditioning stimulus, supraspinal morphine administration may enhance DNICs by potentiating opioid-linked descending inhibition (Le Bars et al., 1981a). Furthermore, noxious stimuli have been shown to increase release of enkephalins in the spinal cord (Le Bars et al., 1992), and it has been suggested that DNIC mechanisms may be tonically activated by release of endogenous enkephalins (Noble, Fournie-Zaluski, & Roques, 1994). Thus, diffuse noxious inhibitory

controls, in reducing responses to noxious stimuli, may be subserved to a substantial degree by endogenous opioids (Le Bars et al., 1992). The suggestion that the mechanisms underlying DNIC effects are in large part opioid-dependent (Le Bars et al., 1992) raises the possibility that previously demonstrated age-associated decrements in endogenous opioid function may potentially produce impairments in DNIC-like mechanisms in the elderly.

As noted above, dysfunctions of central pain-inhibitory mechanisms in general and DNIC in particular could potentially explain the wide anatomic spread of diffuse, persistent muscle and joint pain reported more frequently by the elderly than other age groups. Lautenbacher and Rollman (1997) have suggested that naturally occurring noxious stimuli (i.e., clinical pain states) may produce DNIC-like effects which potentially serve to limit the spread of pain following a localized painful insult and that these mechanisms may be impaired in some populations of chronic pain patients. Clinical pain has previously been shown to produce DNIC effects (Cohen, Naliboff, Schandler, & Heinrich, 1983; Naliboff, Cohen, Schandler, & Heinrich, 1980; Peters & Schmidt, 1992; Peters, Schmidt, & Van Den Hout, 1989; Willer, Barranquero, Kahn, & Salliere, 1987; Willer, Bergeret, & Gaudy, 1985), and it may be the case that the chronic widespread muscle and joint pain experienced by many elderly individuals is at least in part attributable to decrements in DNICs and DNIC-related endogenous analgesic mechanisms. Though prior investigations of relationships between aging and pain have focused almost exclusively on age-related impairment of the transmission of afferent input, a more thorough understanding of age differences in responses to noxious stimuli should include characterization of efferent processes as well.

Aging and Physiological Concomitants of Pain

The relative dearth of studies investigating endogenous modulation of pain is not the only limitation in the literature relating to pain in older populations. The majority of studies investigating the relationship between aging and pain responses has focused on perceptual measures of pain (e.g., the presence or absence of pain, self-report of pain intensity, pain thresholds, ratings of suprathreshold noxious stimuli, etc.); therefore, little is known about age-associated alterations in physiological responses to noxious stimulation. Cardiovascular and neuroendocrine events, in particular, may represent adaptive responses to nociceptive input that interact with endogenous pain-modulatory systems. For example, indices of baseline cardiovascular activity (Ghione, 1996; Maixner, 1991), as well as pain-related cardiovascular reactivity (France & Stewart, 1995), are inversely associated with pain sensitivity and responses to noxious stimuli. Though the mechanisms whereby blood pressure reduces pain sensitivity have not been fully elucidated, baroreceptors, which respond to the mechanical stretch of arterial walls, appear to be involved in this hypoalgesic effect (Angrilli, Mini, Mucha, & Rau, 1997). Moreover, recent evidence has suggested that endogenous opioids may mediate the well-documented inverse relationship between blood pressure and pain sensitivity (Maixner, 1991; McCubbin & Bruehl, 1994).

Furthermore, CNS mechanisms subserving stress-induced analgesic responses are dependent on the functional integrity of the hypothalamic-pituitary-adrenal (HPA) axis (Giordano & Rogers, 1992; MacLennan et al., 1982; Watkins & Mayer, 1982). Specifically, release of cortisol in response to pain or stress has been shown to activate opioidergic endogenous pain-inhibitory systems and reduce responsiveness to noxious stimuli

(Griep et al., 1998). Moreover, chronic pain syndromes such as fibromyalgia (Griep et al., 1998), chronic low back pain (Geiss, Varadi, Steinbach, Bauer, & Anton, 1997), chronic pelvic pain (Helme, Ehlert, Hanker, & Hellhammer, 1998), and arthritis (Chikanza, Petrou, Chrousos, Kingsley, & Panayi, 1992) are characterized by hypofunction of the HPA axis, suggesting the possibility that diminished recruitment of endogenous pain modulation by cortisol contributes to the ongoing experience of pain in these conditions.

Collectively, these studies suggest the involvement of the cardiovascular system and HPA axis in shaping CNS responses to noxious stimulation. While some prior research has examined the effects of aging on absolute levels of cardiovascular reactivity (Dewhurst et al., 1991) and cortisol release (Pollard, Ungpakorn, & Harrison, 1992; Verkhratsky, Moroz, Magdich, & Kharazi, 1988), no study has yet examined the relationship between these variables and DNICs as a function of age. Moreover, only a few studies have examined cardiovascular and neuroendocrine responses to noxious stimulation as correlates or potential mediators of DNIC effects. Pertovaara and colleagues (1982, 1987) investigated modulation of electrical and thermal pain thresholds by ischemic muscle pain. Electrical and thermal thresholds were elevated in the presence of ischemic arm pain, but the magnitude of the reduction was not associated with the release of pituitary hormones. To date, no studies appear to have systematically investigated relationships between DNIC effects and activity in the cardiovascular system (i.e., neither baseline nor pain-associated cardiovascular responses have been investigated with respect to their potential association with pain modulation). Thus, the potential moderating effects of age on relationships among pain, responses of the neuroendocrine system, and cardiovascular responses to noxious stimulation have yet to be investigated.

Temporal Summation of Pain

Investigation of diffuse noxious inhibitory controls requires the selection of tonic and phasic noxious stimuli: the former is employed as the conditioning stimulus, and the latter is employed as the test stimulus. A wide variety of test stimuli have been studied, with thermal or electrical pain thresholds being the most common choices. However, no previous studies have attempted to determine what the characteristics of an ideal test stimulus would be. There is some evidence suggesting that DNIC effects are larger for C-fiber mediated noxious stimuli than for stimuli mediated primarily by A-delta fibers (Price & McHaffie, 1988). That is, concurrent administration of a tonic conditioning stimulus may reduce C-fiber mediated pain to a greater extent than A-delta fiber mediated pain. On the basis of at least one study, then, one might anticipate relatively large DNIC effects for procedures evoking primarily C-fiber activity. Administration of repetitive noxious thermal stimuli producing temporal summation of pain constitutes just such a procedure.

Temporal summation of repetitive noxious stimuli, or "wind-up," refers to the enhancement of pain caused by repeated noxious stimulation. Wind-up is a progressive, frequency-dependent facilitation that can be observed at the level of individual neurons or at the level of the organism (Herrero, Laird, & Lopez-Garcia, 2000). A well-characterized phenomenon in both animals (Li, Simone, & Larson, 1999; Mendell, 1966) and humans (Price, Hu, Dubner, & Gracely, 1977; Vierck, Cannon, Fry, Maixner, & Whitsel, 1997), the locus of action for such temporal summation appears to be multireceptive WDR spinal neurons. When peripheral afferent C fibers are activated repetitively at frequencies greater than .3 HZ, WDR neurons demonstrate progressively increasing re-

sponses to unchanging or diminishing afferent inputs. In addition, the phenomenon of wind-up is clearly affected by descending modulatory influences arising from supraspinal structures. Spinalization induces enhancement of wind-up while electrical stimulation of the dorsal columns reduces wind-up (for a review see Herrero et al., 2000). Moreover, at least one prior study has demonstrated that wind-up is subject to DNIC effects; in this particular study, application of a remote noxious stimulus significantly reduced the degree of summation in second-order neurons in the dorsal horn of the spinal cord (Schouenborg & Dickenson, 1985).

As pain induction procedures employing repetitive noxious stimulation appear to induce progressively C-fiber-mediated pain, to be generally subject to descending pain inhibition, and to be specifically modifiable by DNIC effects, repetitive thermal pulses will be used as test stimuli in the present proposal. Because the degree of inhibition observed during DNIC is greatest for C-fiber-mediated pain (Kakigi, 1994; Price et al., 1977; Watanabe et al., 1996), it is thereby hoped that the magnitude of DNICs will be maximized, rendering greater power to the present project (i.e., increasing the probability of detecting actual differences between groups). In addition, application of the phasic test stimulus to both the upper and lower limbs of the body appears important, as at least one prior study has noted greater DNIC effects on the arm (relative to the leg) following application of a noxious conditioning stimulus to a lower limb (Watanabe et al., 1996). Moreover, results of another recent investigation suggested that the effects of age on temporal summation of thermal pain differed as a function of stimulus location. Specifically, Harkins, Davis, Bush, and Kasberger (1996) observed both greater temporal summation of thermal pain on the arm and reduced temporal summation of thermal pain on

the leg in older relative to younger subjects. Thus, the methodology of the present investigation of age-associated differences in DNIC will include use of temporal summation produced by repetitive thermal stimulation at multiple body sites as the test stimulus.

Summary and Research Plan

Multiple organismic variables potentially influence pain responses; the age of the organism, in particular, is one factor that has previously been shown to affect responses to noxious stimuli (Gagliese & Melzack, 1997a, 1997b; Gibson et al., 1994; Harkins, 1996; Harkins & Scott, 1996). Prior empirical work has suggested that elderly individuals report a greater frequency and intensity of various types of clinical pain, especially chronic pain, as well as enhanced responses to certain types of noxious stimuli administered in a controlled fashion (Gagliese & Melzack, 1997b; Harkins, 1996). While a number of investigators have recently begun to propose deficits in endogenous analgesic systems as explanations for these phenomena (Novack et al., 1999; Yehuda & Carasso, 1997), empirical tests of this hypothesis in human subjects have been slow in coming. Accumulating evidence, including animal studies demonstrating senescent decrements in endogenous analgesic systems and human studies reporting functional decrements in neurochemical systems thought to mediate endogenous pain inhibition, does offer indirect support for the theory. At present, however, the existence, nature, and clinical relevance of these putative age-related differences in endogenous pain inhibition in humans remain unclear. The overarching goals of the present proposal were to investigate and characterize the nature of age-associated differences in CNS pain-modulatory systems, to examine physiological correlates of these systems, and to evaluate the relationship between

endogenous pain inhibition and the presence of clinical pain and health-related variables. As described previously, endogenous analgesic systems were studied using a methodologic paradigm incorporating diffuse noxious inhibitory controls. The specific aims of this project were as follows.

First, the study was designed to evaluate age-associated differences in endogenous pain-modulatory systems, operationalized as DNICs. Specifically, age differences in the effects of concurrent cold pain on responses to heterotopically presented repetitive thermal stimuli that produce temporal summation of C-fiber-mediated pain (i.e., wind-up) were investigated. It was hypothesized that (a) cold pain would result in greater reduction of pain intensity ratings for repetitive thermal stimuli among younger relative to older individuals, (b) cold pain would reduce temporal summation of thermal pain to a greater degree among younger relative to older subjects, and (c) the time course of observed DNIC effects on pain intensity ratings and temporal summation would be longer for younger relative to older subjects.

Second, the present project attempted to characterize age-related differences in physiological responses to noxious stimulation and to determine whether physiological responses were associated with the magnitude of the DNIC response. Specifically, sympathetic nervous system (cardiovascular) and hypothalamic-pituitary-adrenal (salivary cortisol) responses to cold pain were assessed in older and younger subjects. It was hypothesized that (a) relative to younger subjects, older adults would exhibit greater blood pressure responses and similar cortisol responses to cold pain, (b) blood pressure and cortisol responses would bear a positive linear relationship to the magnitude of the DNIC response among younger but not older subjects, and (c) physiological responses (blood-

pressure and salivary cortisol reactivity) to the experience of cold pain would at least partially mediate age-related differences in the magnitude of DNICs.

Third, the study investigated the predictive validity and clinical relevance of laboratory pain assessment of endogenous pain modulation by investigating the relationships between experimental pain responses and clinical variables. In particular, relationships between the magnitude of the DNIC response and self-reported clinical pain and general health were assessed in both younger and older subjects. It was hypothesized that (a) larger DNIC responses (i.e., greater reduction of thermal pain during concurrent cold pain induction) would be associated with less clinical pain and better physical health in both younger and older individuals, (b) older subjects would report more naturally occurring clinical pain and poorer physical health than younger subjects, and (c) these age-associated differences in health-related variables would be mediated by age-associated differences in the magnitude of DNIC.

## RESEARCH DESIGN AND METHOD

### Participants

Data were collected on a total of 102 individuals (51 younger, 51 older) recruited from within the Birmingham community. Participants were recruited through local newspaper advertisements and flyers posted throughout The University of Alabama at Birmingham campus and surrounding area. Participants were paid $75.00 for completion of both study sessions. All procedures were approved by The University of Alabama at Birmingham's Institutional Review Board for Human Use (see Appendix).

Eligible participants met the following criteria: (a) between the ages of 18 and 25 years or between the ages of 55 and 67 years; (b) no ongoing chronic pain problems; (c) not diagnosed with hypertension or taking medication for blood pressure; (d) no circulatory disorders; (e) no history of cardiac events; (f) no history of metabolic disease or neuropathy; (f) no other significant health risks; (g) not pregnant; (h) not currently using prescription analgesics, tranquilizers, antidepressants, or other centrally acting agents. Potential participants were screened by phone and invited to participate in the study if no exclusion criteria were met. Of those invited to participate, 102 of 107 (95.3%) accepted and attended the initial session. The remaining five individuals (three younger, two older) cited lack of interest or scheduling conflicts as the reason for nonparticipation.

Of the 102 study individuals electing to participate in the study, complete data were not available for all participants for a variety of reasons. In the younger participant

group, five subjects (two males, three females) completed the first session and never returned for the second session, and one young female was unable to tolerate any sequence of temporal summation trials across the range of temperatures employed in the study. In the older subject group, two females were unable to tolerate any sequence of temporal summation trials, and one female demonstrated such elevated baseline blood pressures that she was not considered an appropriate candidate to undergo the cold pressor trials. Thus, the final study sample consisted of 45 younger and 48 older participants. The younger group had a mean age of 21.6 years (SD = 2.1) and was comprised of 20 males (44.4%) and 25 females (55.6%). The older group had a mean age of 63.1 years (SD = 4.6) and was comprised of 16 males (33.3%) and 32 females (66.7%). The majority of participants in both the younger (84.5%) and older (93.8%) samples was White.

Apparatus

Contact heat stimuli were delivered via a peltier-element-based 9 $cm^2$ contact probe using a computer-controlled Medoc Thermal Sensory Analyzer (TSA-2001, Ramat Yishai, Israel). The contact probe was positioned on the skin of the forearm or ankle and affixed in place with a strap. Temperature levels were monitored by a contactor-contained thermistor and returned to a preset baseline of 32 °C by active cooling at a rate of 10 °C/s. Thermal assessment procedures utilized either an ascending method of limits or a temporal summation paradigm. For procedures using a standard ascending method of limits paradigm (i.e., assessment of warmth threshold, thermal pain threshold, and thermal pain tolerance), probe temperature increased from a constant baseline of 32 °C at a rate of 0.5 °C/s until the subject responded by pressing a hand-held button. Immedi-

ately following a button press, the probe temperature was recorded, probe temperature ceased increasing, and a rapid return to baseline ensued. For temporal summation procedures, a baseline of 40 °C and a 10 °C/s rate of rise were utilized. In order to assess temporal summation, sequences of 10 heat pulses with stimulus durations of approximately 0.5 s and interpulse intervals of approximately 2.5 s were utilized.

Assessment of cortisol levels was accomplished using measures of salivary cortisol. The assessment of cortisol in saliva represents a convenient, valid, reliable alternative to analysis of serum cortisol levels. Results from these two methods of cortisol assessment are highly correlated, and salivary cortisol levels have been shown to be sensitive to the effects of laboratory-induced stressors (Kirschbaum & Hellhammer, 1989, 1994). Additionally, salivary measures are easily repeatable, nonpainful, and nonstressful for the subject. Saliva samples were obtained using a salivette for collection as described in previous studies (Kirschbaum & Hellhammer, 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, California), in the laboratory of Dr. Douglas Weigent at The University of Alabama at Birmingham's Department of Physiology and Biophysics.

A Neslab circulating water bath (RTE-111, Portsmouth, New Hampshire) was used for all immersion trials. This device allows maintenance and rapid adjustment of circulating water temperatures. The two water temperatures utilized in the present study were 5 °C (painfully cold) and 22 °C (neutral).

Prior to and following sets of hand immersion trials, local skin temperatures on the dorsum of participants' right hands were assessed using an infrared digital thermometer.

Design and Procedures

The experiment was conducted in laboratory space provided by the Psychology Department at The University of Alabama at Birmingham. Following screening, individuals agreeing to participate in the study were scheduled for two experimental sessions, each lasting approximately 2 hr. Laboratory sessions were scheduled on nonconsecutive days and typically were separated by 1 week. Prior to participating in the first session, subjects provided verbal and written informed consent.

First session. After providing informed consent, participants completed several self-report questionnaires assessing health history, health status, general health information, and recent clinical pain symptoms. Following completion of questionnaires, subjects were instrumented for cardiovascular measures using a Dinamap 1846 SX blood pressure monitor; the cuff was placed around the right ankle, over the Popliteal artery. This placement has been shown to be reliable and valid in prior research (Mundt, Chambless, Burnham, & Heiss, 1992). A 15-min rest period ensued, during which participants relaxed quietly with their eyes closed in a semireclined position while heart rate and blood pressures were sampled every 3 min. This rest period was followed by a 5-min baseline period during which heart rate and blood pressure were sampled every minute for a total of five readings. These five readings constituted the initial baseline assessment

of cardiovascular variables. Following cardiovascular data collection, the first of three saliva samples was collected, after which thermal pain assessment was initiated.

The first thermal procedure involved assessment of warmth threshold (i.e., the temperature at which the sensation of warmth is first perceived), heat pain threshold (i.e., the temperature at which the sensation of pain is first perceived), and heat pain tolerance (i.e., the temperature at which the sensation becomes intolerable) on the left ventral forearm. As noted above, thermal assessment procedures utilized an ascending method of limits paradigm in which the probe temperature increased gradually until the subject responded by pressing a button. Standardized instructions for this and subsequent procedures were recorded on tape and played for subjects prior to beginning the procedures. Four trials of warmth threshold, 4 trials of heat pain threshold, and 4 trials of heat pain tolerance were presented. The thermode was moved between trials, and intertrial intervals of at least 30 s were maintained to avoid sensitization or habituation.

Next, following a brief rest period, temporal summation of thermal pain was evaluated. These procedures involved administration of brief, repetitive, noxious thermal stimuli to assess temporal summation of thermal pain intensity (i.e., wind-up); the present methodology is similar to procedures described and validated previously (Harkins et al., 1996; Price et al., 1977). Sequences of 10 heat pulses with stimulus durations of approximately 0.5 s and interpulse intervals of approximately 2.5 s were delivered to the left dorsal forearm and the left ankle, superior to the lateral malleolus. Each sequence of pulses was preceded by a 5-s period during which the thermode remained at a baseline temperature; participants were verbally alerted to the initiation of the sequence of pulses. Site order was counterbalanced across subjects. Subjects were instructed to verbally rate

the intensity of the pain produced by each thermal pulse using a standardized 0-100 pain intensity rating scale (Fillingim et al., 1998). Anchors on the rating scale were as follows: 0 (no sensation), 20 (just barely painful), and 100 (the most intense pain imaginable). The standardized instructions for this procedure contained information indicating to participants that each sequence of pulses would continue until (a) all 10 heat pulses had been administered; (b) the participant reported a pain intensity value of 100 on the 0-100 scale, at which point the sequence of pulses would be terminated; or (c) the subject verbally requested termination of the pulse sequence. A practice sequence with a pulse temperature of 40 °C and an intertrial adapting temperature of 32 °C was administered to participants in order to familiarize them with the procedure. Subject responses to the practice sequence were not recorded. Following the practice trial, the first actual sequence of pulses had a target temperature of 48.5 °C, with an intertrial adapting temperature of 40 °C. Further temporal summation sequences utilizing different temperatures were then applied using the following decision rules:

1. If the participant tolerated all 10 stimuli at 48.5 °C (i.e., no stimuli were rated as 100 and no request to stop the procedure was made), the target temperature was increased to 50.0 °C for the next sequence of trials and continued to increase in consecutive 1.5 °C increments on following sequences to a maximum of 53 °C. The procedure was halted if a participant rated a stimulus as 100 or requested termination of the sequence of pulses.

2. If the subject did not tolerate all 10 stimuli at 48.5 °C, the target temperature was decreased by 1.5 °C for each subsequent sequence of pulses (to a minimum of 44 °C)

until the subject was able to tolerate all 10 stimuli. The entire procedure was then repeated at the other body site.

This methodology permitted individual tailoring of target temperatures to the participant's thermal tolerance in order to avoid ceiling effects for temporal summation of thermal pain (e.g., rating the first stimulus as 100) or floor effects for DNICs (e.g., rating all 10 stimuli as nonpainful). In this way, the test stimulus used to assess DNIC effects, a sequence of 10 repetitive thermal stimuli, was established for each individual as the maximum temperature at which all 10 thermal stimuli were tolerated. For all temporal summation sequences, the position of the thermode was altered between sequences of pulses, and intervals of at least 2 min were maintained between sequences of pulses in order to avoid local sensitization or habituation.

Following thermal pain assessment and a subsequent 10-min rest period, baseline cardiovascular variables were reassessed. Participants again relaxed quietly with their eyes closed in a semireclined position while heart rate and blood pressures were sampled every minute for 3 min. These three readings constituted the second baseline assessment of cardiovascular variables. Next, the local skin temperature on the dorsum of the right hand was assessed using an infrared digital thermometer. Participants then provided a second saliva sample, which was collected in the same manner as the first, after which they underwent a modified repeated cold pressor task (Talbot et al., 1987, 1989; Willer et al., 1984). The task consisted of immersion of the right hand in a circulating water bath maintained at either 5 °C or 22 °C. The former temperature is generally perceived as painfully cold while the latter is approximately room temperature and is generally perceived as nonpainful. The temperature of the water bath in the first laboratory session

was randomized: water temperature in the second session was set to whichever temperature had not been experienced in the first session. Twenty seconds after hand immersion, a sequence of 10 thermal stimuli, with target temperatures set at the maximum temperature tolerated, was delivered to either the left dorsal forearm or the left ankle (again, site order for the session was counterbalanced across subjects). Participants rated the intensity of each thermal stimulus on the 0-100 scale, exactly as they had done previously. In addition, blood pressure and heart rate were sampled during immersion of the hand. The standardized instructions for the procedure directed participants to keep their hands in the water for as long as possible but explained that if the sensations became intolerable participants could remove their hands at any time. Following offset of the final thermal stimulus in the sequence of 10 pulses, participants were directed to remove their hands from the water if they had not already done so. Two minutes after finishing the first immersion, participants reimmersed their right hands in the circulating water, and temporal summation was reassessed 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 each identical to the first and second immersion trials, respectively.

In addition to participants' ratings of the thermal stimuli delivered during hand immersion, a number of other variables were also assessed. If a participant removed his or her hand from the water bath during any of the trials, the duration of immersion was noted and recorded as cold pain tolerance. During each immersion, blood pressure and heart rate were sampled approximately 30 to 40 s following placement of the right hand in the water bath. Systolic blood pressure, diastolic blood pressure, mean arterial pres-

sure, and heart rate were recorded for each immersion. During every immersion trial, participants provided two ratings of the intensity of sensations produced by water immersion. Twenty seconds after beginning immersion and just before the start of thermal stimulation, participants rated the intensity of the sensations in their right hands on the 0-100 scale described previously. In addition, at the conclusion of each immersion trial, participants provided a 0-100 rating of the maximum intensity of sensations produced by water immersion during the trial.

Following the fourth immersion, participants were given a heated towel with which to warm their hands. At 10 min postimmersion, skin temperature on the right hand was reassessed. Immediately afterward, temporal summation of thermal pain was reassessed at the two body sites, again using individually tailored maximum tolerable temperatures for each subject. A third and final saliva sample was collected at 20 min following the conclusion of the final immersion, representing the peak cortisol response to a painful stressor (Kirschbaum & Hellhammer, 1989, 1994). Finally, participants completed several questionnaires assessing their responses to the session. A graphic representation of the timeline for the experimental protocol in each session is presented in Figure 1.

The cold pressor task has been frequently utilized as a DNIC-inducing stimulus (Talbot et al., 1987, 1989; Willer et al., 1984). In the present investigation, immersion of the hand in cold water was selected as the conditioning stimulus on the basis of an earlier study comparing the efficacy of several potential conditioning stimuli in inducing DNICs (Willer et al., 1984). Results of that study demonstrated that immersion of an extremity in cold water was more effective in reducing phasic thermal pain responses than either

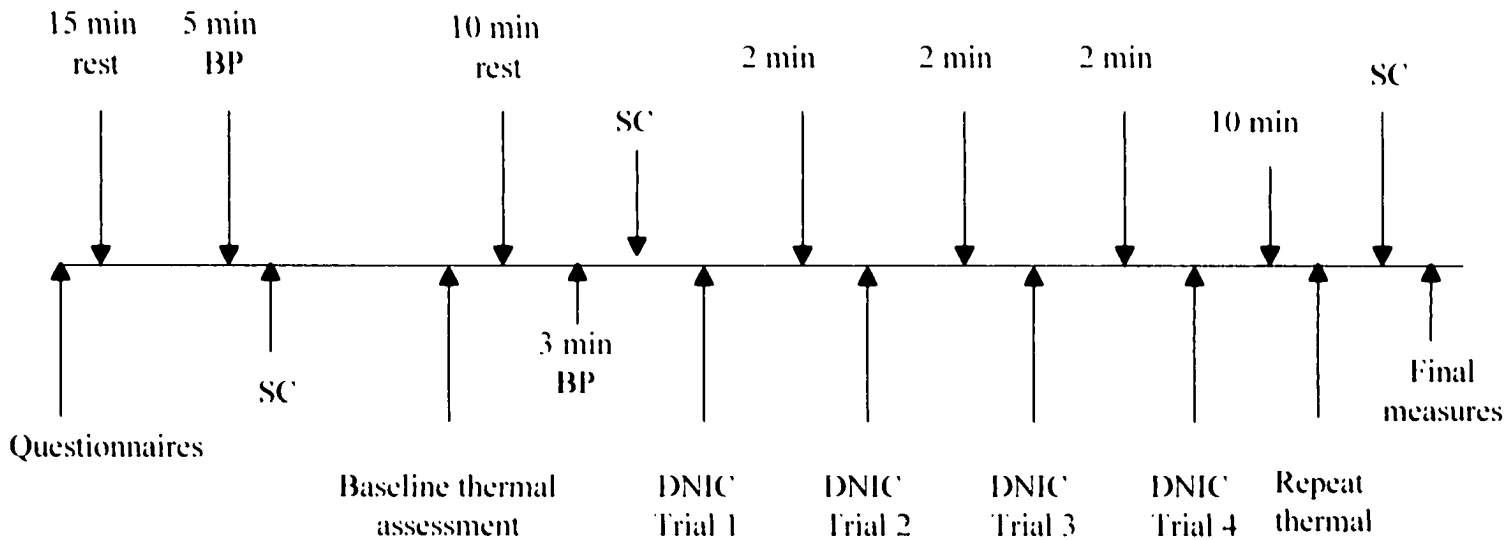


Figure 1. Timeline for experimental sessions. SC = salivary cortisol; BP = blood pressure; DNIC = diffuse noxious inhibitory controls.

ischemic or mechanical stimulation. Other previous studies have also indicated that the pain produced by immersion of an extremity in cold water results in substantial hetero-segmental decreases in responses to noxious thermal stimuli in humans (Talbot et al., 1987, 1989; Willer et al., 1984).

Second session. The second experimental session was generally scheduled from 3 to 7 days after the first session, at approximately the same time of day. Procedures for the second session were identical to those for the first session, with one exception. In the second session, the temperature of the water bath was maintained at either 5 °C or 22 °C, whichever temperature was not utilized in the first session. Otherwise, the experimental procedures and their timing did not differ from the protocol followed in the first session.

## Measures

Short-Form-36 health survey (SF-36). The SF-36 was designed to be a general indicator of health status for use in population surveys (Ware & Sherbourne, 1992). It is derived from the original Medical Outcomes Survey and contains 36 items sampling a variety of domains of health. The instrument is subdivided into the following eight sub-scales: Physical Functioning, Physical Role Limitations, Bodily Pain, Vitality, General Health Perceptions, Social Functioning, General Mental Health, and Emotional Role Limitations. Subscales were 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). In the present study, the following four subscales

were used to test study hypotheses: Physical Functioning, Physical Role Limitations, Bodily Pain, and General Health Perceptions.

Recent Health History questionnaire (RHH). This questionnaire assesses pain-related general health and clinical pain symptoms in the past 30 days; it was developed based on previous survey studies of pain in the general population (Sternbach, 1986). Subjects are asked to indicate the number and severity of the following painful events in the previous month: headache, back pain, muscle pain, joint pain, stomach pain, dental pain, or any other type of pain. This measure yields a pain-related general health score and three indices of recent pain: pain sites (the number of body regions for which pain was reported), total number of pain episodes, and average severity of pain. In the present study, all four of these variables were standardized to distributions identical to that of the SF-36 subscales (i.e., scores ranging from 0-100 where higher scores reflect less pain and fewer pain-related health problems) and were then averaged, forming a composite measure of recent pain.

Postimmersion questionnaires. Several questionnaires were constructed to assess participants' perceptions of the water immersion procedure. Four items queried participants about the extent to which immersion of the right hand in the circulating water bath had distracted attention from the thermal stimulation. The items were written as follows: (a) "I found it difficult to pay attention to the thermal stimulation"; (b) "When rating the thermal stimuli, I was distracted by the sensations in my hand"; (c) "The procedure was confusing"; (d) "I found it easy to focus on stimuli and give accurate ratings." Partici-

pants rated each item from 1 (Not at All) to 10 (Very Much). After reverse-scoring the fourth question, the four items were averaged to yield a composite measure of distraction produced by immersion. In addition, four items related to the degree of perceived effects of water immersion on the perception of thermal stimuli: (a) "The water immersion procedure decreased how painful the thermal stimuli on my left arm felt"; (b) "The water immersion procedure decreased how painful the thermal stimuli on my left leg felt"; (c) "The water immersion procedure increased how painful the thermal stimuli on my left arm felt"; (d) "The water immersion procedure increased how painful the thermal stimuli on my left leg felt." Participants also gave 0-100 ratings of the stress produced by the laboratory session involving hand immersion in the 5 °C water.

McGill Pain Questionnaire (MPQ). In addition to the other postimmersion questionnaires, participants completed the McGill Pain Questionnaire (MPQ; Melzack, 1975) following the final immersion trial. The MPQ consists of 20 groups of single-word pain descriptors with the words in each group increasing in rank order intensity. The sum of the rank values for each descriptor based on its position in the word set results in a score for the following descriptor subscales: Sensory, Affective, Evaluative, and Miscellaneous. In addition, two MPQ summary scores were calculated based on responses to each word group. The Pain Rating Index (PRI) was obtained by adding the scores for all four descriptor subscales. The number of words chosen score (NWC) was obtained by totaling the number of words selected from the list. The MPQ is among the most widely utilized measures for rating pain; it has repeatedly demonstrated good psychometric properties in a variety of samples (McDowell & Newell, 1996).

Data Reduction and Analysis

Previous findings from our laboratory (Edwards & Fillingim, in press) were used in a power analysis to estimate the necessary sample size. Results from this earlier study had suggested that the effect sizes for age differences in ischemic pain thresholds and tolerances were 1.0 and 1.4, respectively, with older subjects demonstrating lower thresholds and tolerances. In this prior study, Cohen's measure of effect size was used as a measure of the magnitude of observed effects. Briefly, Cohen's measure of effect size is calculated by dividing the difference in group means by the pooled standard deviation; it is the most commonly computed estimate of effect size for parametric data.

As no investigations of age-related differences in DNICs had yet appeared in the literature, we conservatively estimated the effect sizes of group differences in DNICs to be half of those observed for group differences in ischemic pain responses. In this case, a sample size of 80 (40 older and 40 younger participants), using the resulting range of effect sizes (.5-.7), yielded power estimates of approximately .99 for the factorial multivariate analysis of variance (MANOVA) testing group differences in DNIC effects. A still more conservative estimate of the magnitude of age-related differences in DNICs as moderate in size (i.e., d values in the range of .3) yielded an estimated power of .77 for this analysis. Thus, sample sizes of 80 or greater were considered capable of rendering adequate power to detect the specified effects.

In general, group differences in categorical variables were evaluated using chi-square tests, relationships between continuous variables were assessed by calculating Pearson product-moment correlations coefficients, and differences between older and younger participants in individual continuous variables were tested with analysis of vari-

ance (ANOVA). Specific data-analytic strategies for testing each of the study's hypotheses are presented below.

The effects of age group on DNIC were assessed using a mixed factorial MANOVA, with age group as the between subjects factor and water temperature (5 °C vs. 22 °C), stimulation site (arm vs. leg, with ratings averaged across the two sequences of stimulation at each site), and trial number (1-10) as within subjects factors. The dependent variables were change scores for each trial of the temporal summation procedure (i.e., subtraction of baseline ratings from immersion-associated ratings). Age-associated differences in the overall effect of DNICs on pain intensity ratings were assessed by examining the multivariate interaction between age group and water temperature, while age-related differences in DNIC effects on temporal summation of thermal pain were assessed by examining the three-way interaction between age group, water temperature, and trial number. ANOVA procedures were used to further characterize significant effects. In addition to the above analyses evaluating DNIC effects on average thermal ratings and temporal summation of thermal pain, a similar analysis examined DNIC effects on peak ratings during the thermal sequences (i.e., the highest of the 10 ratings of repetitive thermal stimuli). For this analysis, the dependent variable was comprised of change scores for peak ratings (peak during immersion minus peak during baseline).

Data from every participant were not necessarily included in the preceding and subsequently described analyses involving DNICs. As the phenomenon of DNIC depends on inhibition of phasic pain by a tonic noxious conditioning stimulus (Price & McHaffie, 1988; Talbot et al., 1987, 1989; Willer et al., 1984, 1989), only trials during which a participant's hand remained immersed for at least 25 s (i.e., until the time at

which the sequence of thermal stimuli began) were included in the DNIC analyses. Each participant completed a series of four DNIC trials, two with heterotopic thermal stimulation of the arm and two with stimulation of the leg. If a participant had a cold pressor pain tolerance greater than 25 s for both DNIC trials at a given site, responses at that site for both the 5 °C and 22 °C water immersions were averaged. If a participant's cold pressor tolerance was greater than 25 s for only one of the DNIC trials, only data from that immersion sequence was utilized.

In order to assess relationships between DNIC and other study variables (e.g., physiological responses to noxious stimulation, clinical pain and general health variables), the magnitude of the DNIC response was calculated for each participant. First, mean ratings of thermal stimuli were computed for baseline and immersion-associated temporal summation sequences. Next, mean baseline ratings were subtracted from mean ratings during immersion for both sessions, resulting in overall difference scores for both water temperatures. Finally, the difference scores for the session using 22 °C water were subtracted from the difference scores for the session using 5 °C water. These calculations produced, for each subject, composite DNIC scores (one for the arm and one for the leg) reflecting the average decrease in ratings during immersion in 5 °C water relative to changes during immersion in the 22 °C water. The second measure of DNIC was produced by using peak ratings (i.e., the highest rating given during a given temporal summation sequence) instead of mean ratings in the preceding calculations. This measure of DNIC reflected the decrease in peak ratings during immersion in the 5 °C water relative to changes in peak ratings during immersion in the 22 °C water. Measures of DNIC on the arm and leg were then standardized to distributions with a mean of 0 and a standard

deviation of 1. They were averaged separately at each site, as well as together, resulting in three standardized measures of DNIC: one for thermal stimulation on the arm, one for thermal stimulation on the leg, and one collective average. These measures of DNIC represented decreases in peak ratings and average ratings during immersion of the hand in 5 °C water.

Differences between age groups in blood pressure responses to noxious stimulation were evaluated using analysis of covariance (ANCOVA), with age group as the independent variable, change score (immersion-associated values minus baseline values) as the dependent variable, and the baseline value as the covariate. A similar analysis was undertaken for salivary cortisol values. As data points for salivary cortisol values were missing for a number of participants, the first two cortisol values, which were the initial and second baseline readings, were averaged to form a mean baseline value; for those participants who had valid cortisol data for only one of the baseline assessments, that value was utilized. The effects of blood pressure and cortisol reactivity on the magnitude of DNICs among older and younger participants were investigated using age-specific multiple regression. First, change scores were computed by subtracting baseline vales from immersion-associated values. Next, baseline values and change scores were inserted into a regression model predicting the magnitude of DNICs, and this analysis was performed separately for older and younger participants. In the event of a significant relationship between physiological reactivity and DNICs, cardiovascular or cortisol-related values were studied as mediators of the age differences in DNIC magnitude using ANCOVA techniques.

Age differences in clinical pain and physical health variables were assessed using univariate ANOVA. Relationships between these clinical variables and the magnitude of DNICs were evaluated by computing Pearson correlation coefficients for the entire study sample and separately for older and younger participant groups. The mediating effects of DNICs on age differences in clinical pain and general health were assessed by recalculating the above ANOVA, controlling for DNIC magnitude. If formerly significant group differences in clinical pain and physical health variables became nonsignificant with the addition of DNIC magnitude as a covariate, DNICs were considered a mediator of age differences in clinical pain and general health.

Significance and Conclusions

The findings from the present research project will provide new information regarding age-related changes in the functioning of endogenous pain-regulatory systems. Although pain in the elderly is a substantial and steadily increasing problem, both because of the resulting suffering and the enormous cost, comparatively little is known about the specific neurophysiological mechanisms that may be associated with enhanced pain in senescent populations (Gagliese & Melzack, 1997a, 1997b). At present, the presence of progressive decrements in endogenous analgesic systems appears to be one such potential mechanism acting to produce enhancements of pain and pain-related suffering in the elderly. However, despite multiple reports of age-related declines in the efficacy of pain regulation in rats and frequent speculation that such decrements may exist in humans, no empirical tests of this hypothesis have yet appeared in the literature. The present study was designed to evaluate the existence, nature, and clinical relevance of these

putative age-related differences in endogenous pain inhibition. Characterization of potential age-associated alterations in pain perception and pain modulation is an important area of research in light of the escalating direct and indirect costs of pain, the strong association between older age and increased risk of experiencing pain and pain-related disability, and the current demographic trends including rapid and substantial growth in the older strata of the population. It is hoped that research such as the present project will enhance our general knowledge of age-dependent effects on the experience of pain and may ultimately lead to improved diagnosis and treatment of painful conditions in older adults.

# RESULTS

## Participants

As noted previously, the younger group had a mean age of 21.6 years (SD = 2.1) and was comprised of 20 males (44.4%) and 25 females (55.6%). The older group had a mean age of 63.1 years (SD = 4.6) and was comprised of 16 males (33.3%) and 32 females (66.7%). The majority of participants in both the younger (84.5%) and older (93.8%) samples was White. Chi-square tests revealed that older and younger participant groups did not differ significantly in gender or racial composition ($p > .05$).

## Baseline Responses to Thermal Stimuli

Group differences in warmth thresholds, heat pain thresholds, and heat pain tolerances were examined using ANOVA. No differences between older and younger participants were observed for warmth thresholds, heat pain thresholds, and heat pain tolerances in the first session ($p > .05$). In the second session, warmth thresholds were again similar for both age groups ($p > .05$), but older subjects evidenced significantly higher heat pain thresholds and heat pain tolerances relative to younger subjects ($p < .01$). When data from both sessions were combined, heat pain thresholds ($p < .01$) and heat pain tolerances ($p < .05$) were significantly higher in older relative to younger subjects. Data for warmth thresholds, heat pain thresholds, and heat pain tolerances are presented in Table 1.

Table 1

Warmth Thresholds, Heat Pain Thresholds, and Heat Pain Tolerances

| Thermal pain variables | Younger group (n = 45) (°C) | Older group (n = 48) (°C) |
|---|---|---|
| WTH (Session 1) | 34.1 ± 1.4 | 34.3 ± 1.2 |
| WTH (Session 2) | 34.1 ± 1.2 | 34.1 ± 1.2 |
| HPTH (Session 1) | 42.7 ± 3.1 | 43.8 ± 4.1 |
| HPTH (Session 2)[a] | 41.2 ± 3.1 | 43.8 ± 3.4 |
| HPTO (Session 1) | 47.4 ± 2.3 | 47.9 ± 2.7 |
| HPTO (Session 2)[a] | 46.4 ± 2.7 | 48.0 ± 2.3 |

Note. WTH = warmth threshold; HPTH = heat pain threshold; HPTO = heat pain tolerance.
[a]age groups differ at $p < .05$.

Group differences in thermal pain ratings for the baseline temporal summation procedure at 48.5 °C were analyzed using a mixed factorial ANOVA with age group as a between-subjects factor and session, site, and trial as within-subjects factors. Figure 2 (Session 1 data) and Figure 3 (Session 2 data) present the temporal summation data for the baseline 48.5 °C stimuli. No main effect of age was observed, $F(1,90) = 2.29$, $p = .13$, and age did not interact with session, site, or trials, $p > .1$. A highly significant main effect of trials, $F(9,82) = 15.67$, $p < .001$, suggested that ratings varied across trials and that temporal summation of thermal pain occurred in both older and younger participants.

For individual participants, maximum tolerable temperatures for the temporal summation procedure were established by progressively increasing or decreasing the stimulus temperature following the baseline assessment at 48.5 °C. Group differences in maximum tolerable temperatures for the temporal summation procedure were examined using ANOVA. No significant differences emerged between older and younger subjects for either session at either body site ($p > .05$). These data are presented in Table 2.

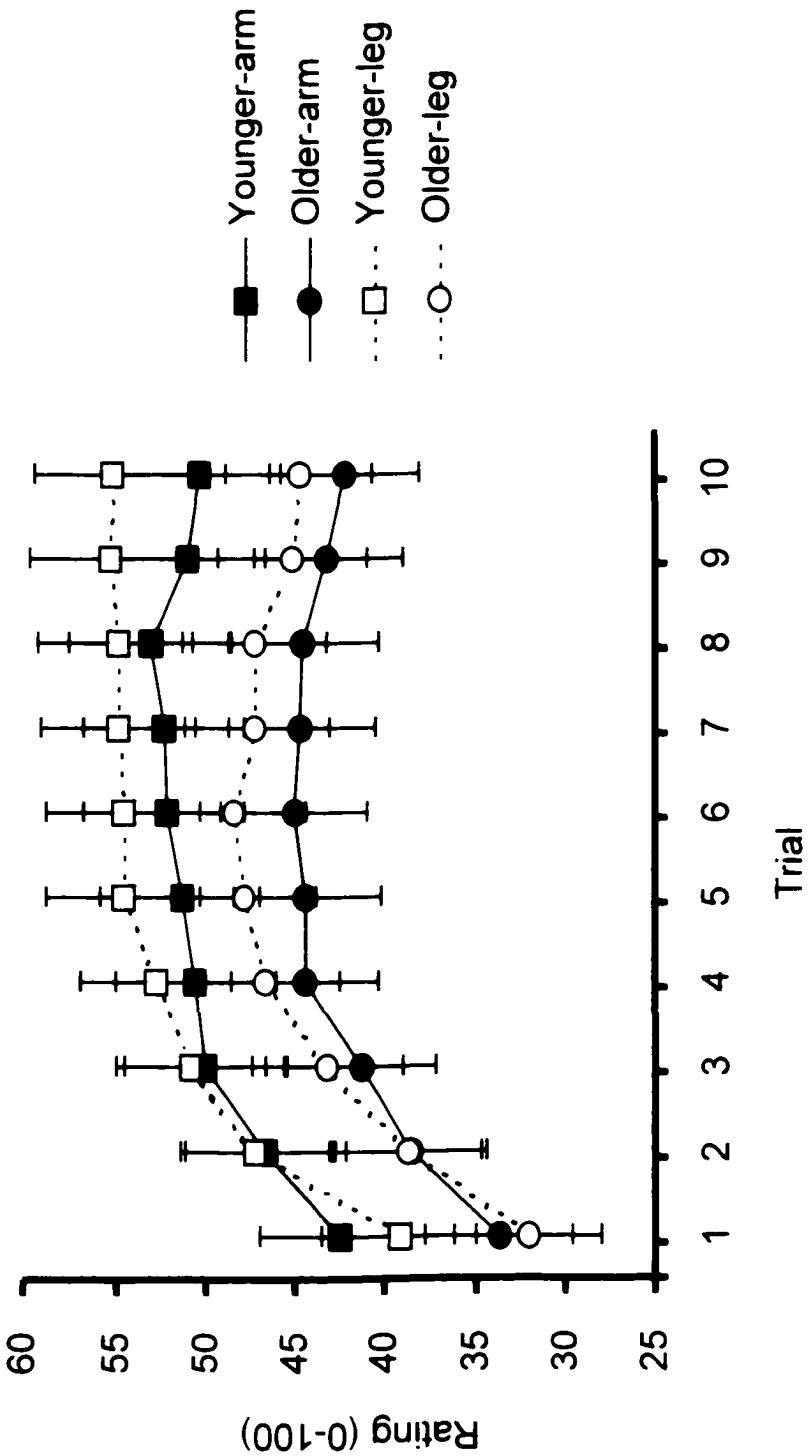


Figure 2. Session 1 ratings of thermal stimuli at 48.5 °C.

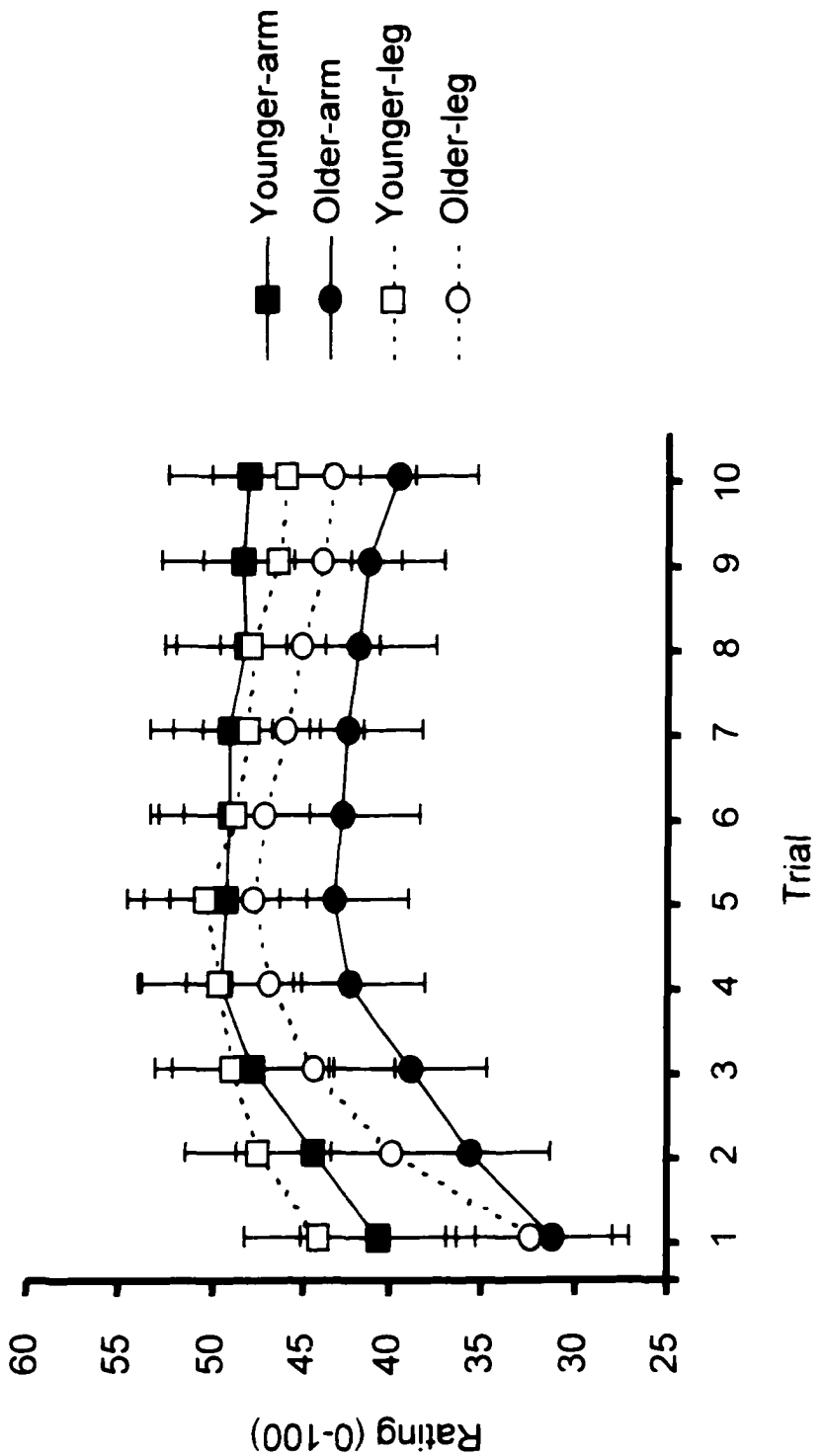


Figure 3. Session 2 ratings of thermal stimuli at 48.5 °C.

Table 2

Maximum Tolerable Temperatures for Temporal Summation of Thermal Pain

| Maximum tolerated temperature | Younger group (n = 45) (°C) | Older group (n = 48) (°C) |
|---|---|---|
| Arm (Session 1) | 51.3 ± 2.3 | 51.8 ± 1.9 |
| Arm (Session 2) | 51.5 ± 2.0 | 51.8 ± 1.8 |
| Arm (both sessions) | 51.4 ± 2.0 | 51.8 ± 1.8 |
| Leg (Session 1) | 50.9 ± 2.2 | 51.2 ± 2.2 |
| Leg (Session 2) | 51.1 ± 2.2 | 51.2 ± 2.3 |
| Leg (both sessions) | 51.0 ± 2.0 | 51.2 ± 2.1 |

Note. Groups do not differ at $p < .05$ for any comparison.

Responses to Repeated Water Immersions

All participants underwent a total of eight hand immersions in the circulating water bath. One session included four consecutive immersions in water maintained at 22 °C, while the other session included four consecutive immersions in water maintained at 5 °C. Each immersion could last for a maximum of 70 s, a duration that represented the total amount of time required to complete the concurrent temporal summation procedure. Prior to commencing the water immersion procedures, participants were instructed that they could remove their hands from the water at any time if the sensations became intolerable. Ratings (0-100) of the intensity of sensations produced by the immersion were obtained after 20 s of immersion (i.e., at initiation of the temporal summation sequence) and again at the conclusion of the immersion.

For immersions at 22 °C, no participant in either age group removed his or her hand from the water prior to the termination. In addition, mean ratings of the intensity of sensations produced by the 22 °C water after 20 s of immersion did not differ between

younger ($M$ = 9.0, $SD$ = 8.3) and older ($M$ = 10.9, $SD$ = 9.9) participants ($p > .05$). Similarly, mean ratings of the intensity of sensations produced by the 22 °C water at the conclusion of the immersion period did not differ between younger ($M$ = 10.1, $SD$ = 9.9) and older ($M$ = 11.6, $SD$ = 10.3) participants ($p > .05$).

For immersions at 5 °C, chi-square tests were employed to assess differences between older and younger subjects in the proportion of individuals who were unable to tolerate the immersion for 70 s. These data are presented in Table 3. For the first and second immersions, no age differences were observed ($p > .05$); for the third and fourth immersions, significantly higher percentages of younger individuals were able to tolerate the cold water for the entire 70-s period ($p < .05$). Similar findings emerged when the dependent variable was the tolerance time (in seconds) for each immersion (see Table 3). ANOVA revealed no significant differences between age groups for the first three immersions, but, on the fourth immersion, younger subjects tolerated the 5 °C water for significantly longer than did the older subjects, $F(1,91) = 3.7$, $p < .05$. No age differences were noted for ratings of the intensity of sensations produced by the 5 °C water during any of the immersions (see Table 3).

Skin Temperature Effects

In each session, skin temperature on the dorsum of the right hand was assessed prior to immersion and 10 min following immersion. A mixed factorial ANOVA revealed a significant effect for time of assessment, $F(1,68) = 100.6$, $p < .001$, as well as an overall effect of age group, $F(1,68) = 6.1$, $p < .05$. These data are presented in Table 4. Skin temperatures following hand immersion were substantially lower than preimmersion

Table 3

Responses to Repeated Immersions at 5 °C

| Variables | Younger group (n = 45) | Older group (n = 48) |
|---|---|---|
| Trial 1: Proportion < 70 s | 48.9% | 60.4% |
| Trial 2: Proportion < 70 s | 42.2% | 52.1% |
| Trial 3: Proportion < 70 s[a] | 31.1% | 52.1% |
| Trial 4: Proportion < 70 s[a] | 26.6% | 50.0% |
| Trial 1: Immersion time (s) | 50.4 ± 22.7 | 47.4 ± 22.7 |
| Trial 2: Immersion time (s) | 51.6 ± 25.1 | 48.4 ± 24.8 |
| Trial 3: Immersion time (s) | 55.4 ± 23.9 | 47.0 ± 24.6 |
| Trial 4: Immersion time (s)[a] | 57.1 ± 23.4 | 47.2 ± 25.0 |
| Trial 1: Rating at 20 s | 71.0 ± 23.8 | 74.5 ± 24.1 |
| Trial 2: Rating at 20 s | 72.0 ± 22.2 | 77.2 ± 21.0 |
| Trial 3: Rating at 20 s | 70.9 ± 23.1 | 77.8 ± 21.3 |
| Trial 4: Rating at 20 s | 70.3 ± 23.1 | 78.1 ± 21.9 |
| Trial 1: Final rating | 86.1 ± 15.9 | 87.0 ± 17.2 |
| Trial 2: Final rating | 85.0 ± 16.5 | 86.9 ± 15.5 |
| Trial 3: Final rating | 83.5 ± 17.6 | 87.2 ± 16.3 |
| Trial 4: Final rating | 82.6 ± 17.4 | 88.2 ± 15.1 |

[a]Older and younger subject groups differ at $p < .05$.

Table 4

Preimmersion and Postimmersion Skin Temperatures

| Time of Assessment | Younger (n = 34) (°F) | Older (n = 36) (°F) |
|---|---|---|
| Before 5 °C immersion | 86.7 ± 5.8 | 83.5 ± 14.4 |
| After 5 °C immersion[a] | 79.7 ±7.2 | 75.0 ± 7.7 |
| Before 22 °C immersion | 87.6 ± 5.4 | 85.2 ± 5.7 |
| After 22 °C immersion | 78.5 ± 5.5 | 77.3 ± 5.2 |

[a]Older and younger subject groups differ at $p < .05$.

skin temperatures, regardless of the water temperature. A follow-up univariate ANOVA indicated that skin temperature was lower for older relative to younger subjects following immersion in the 5 °C water, $F(1,68) = 6.9$, $p < .05$; no other age differences in skin temperature were observed.

DNIC Effects in Older and Younger Subjects

A total of 37 younger and 40 older participants had at least one analyzable DNIC trial. No age group differences were noted in the proportion of participants who did not tolerate any of the four cold pressor trials for at least 25 s ($p > .05$).

Ratings of repetitive thermal stimuli during each session were converted to difference scores by subtracting baseline thermal ratings from immersion-associated ratings for each trial of the temporal summation procedure. A significant main effect of trial emerged, $F(9,648) = 27.8$, $p < .0001$, indicating that mean difference scores varied across trials. Additionally, an interaction of trial and temperature, $F(9,648) = 4.8$, $p < .01$, revealed that changes in difference scores across trials were dependent on the temperature of the water in which participants' hands were immersed. Finally, a significant Age Group X Temperature interaction was observed, $F(9,648) = 8.6$, $p < .005$, suggesting that the effect of hand immersion varied as a function of the water temperature and age group. These data were also analyzed using peak ratings (the highest rating assigned to any of the 10 thermal stimuli in a sequence) instead of individual ratings of all 10 stimuli. This analysis again revealed a significant interaction between age group and temperature, $F(1,72) = 8.0$, $p < .01$, suggesting that peak ratings for the temporal summation procedure were jointly affected by age and water temperature. Because older and younger subject

groups differed slightly on measures of tolerance for the cold pressor task, the above data were re-analyzed, this time controlling for mean 5 °C tolerance times. Controlling for pain tolerance did not alter the significance of any of the previously reported effects ($p < .01$).

In order to elucidate the above findings, the data for older and younger subjects were analyzed separately. Results for younger subjects, with thermal stimulation on the arm, are presented in Figure 4. A repeated measures ANOVA revealed a significant Temperature X Trial interaction, $F(9,324) = 6.3$, $p < .001$), and follow-up univariate ANOVAs indicated that hand immersion in the 5 °C water significantly suppressed thermal pain ratings below baseline for Trials 8-10 of the temporal summation procedure ($p < .05$). Hand immersion in 22 °C water had no significant effects on thermal pain ratings ($p > .05$).

Results for older subjects, with thermal stimulation on the arm, are presented in Figure 5. A repeated measures ANOVA revealed a significant main effect of temperature, $F(1,38) = 5.8$, $p < .05$. Follow-up univariate ANOVAs indicated that, relative to baseline, hand immersion in the 5 °C water significantly increased thermal pain ratings for Trials 1-3 of the temporal summation procedure ($p < .05$). In addition, thermal pain ratings for stimuli on the arm were significantly reduced from baseline levels on Trials 5-10 during immersion in the 22 °C water ($p < .05$).

Data for younger subjects, with thermal stimulation on the leg, are presented in Figure 6. A repeated measures ANOVA again produced a significant interaction of temperature and trial, $F(9,306) = 2.0$, $p < .05$. Follow-up ANOVAs indicated that, similar to the findings for stimulation on the arm, hand immersion in the 5 °C water significantly

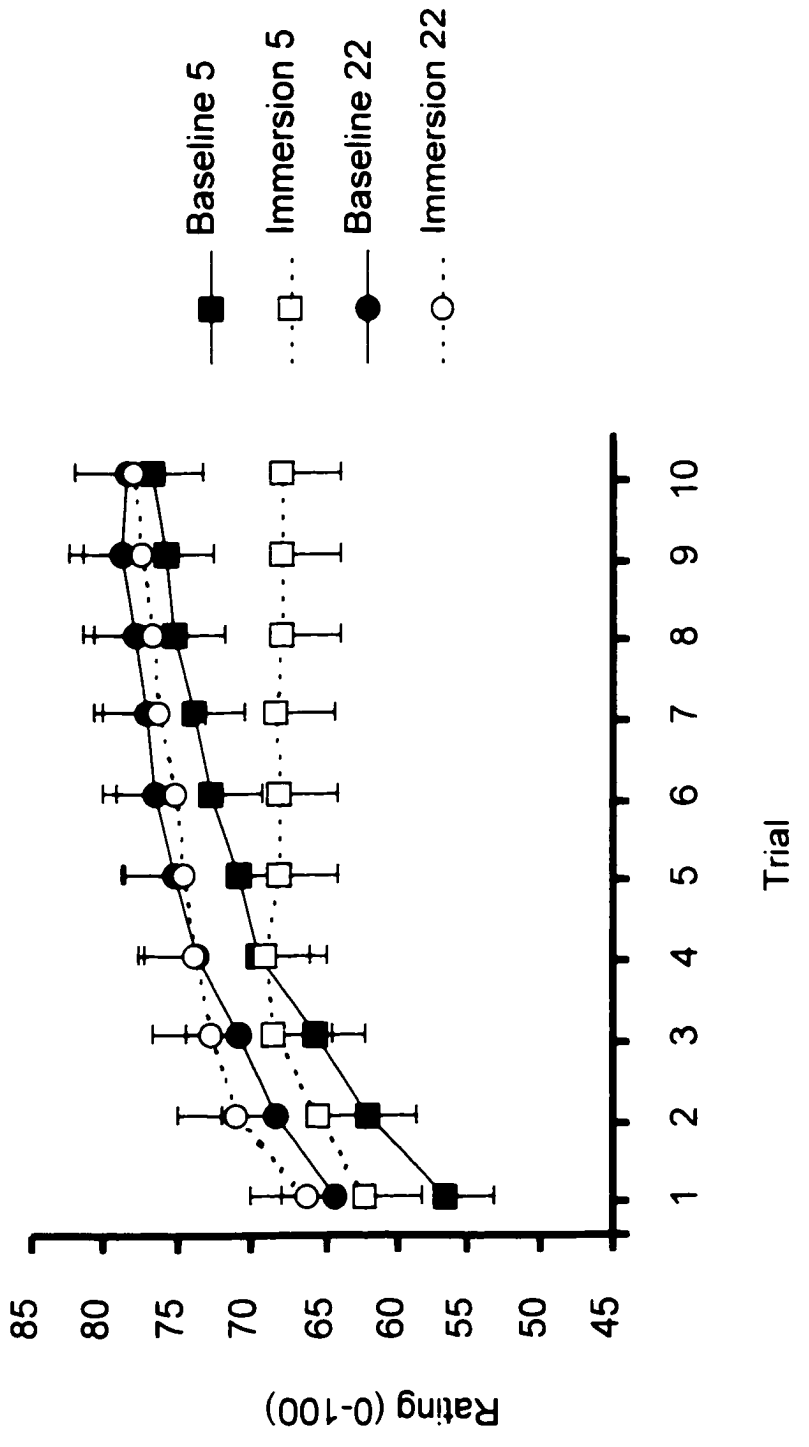


Figure 4. Ratings of thermal stimuli on the arm for younger participants.

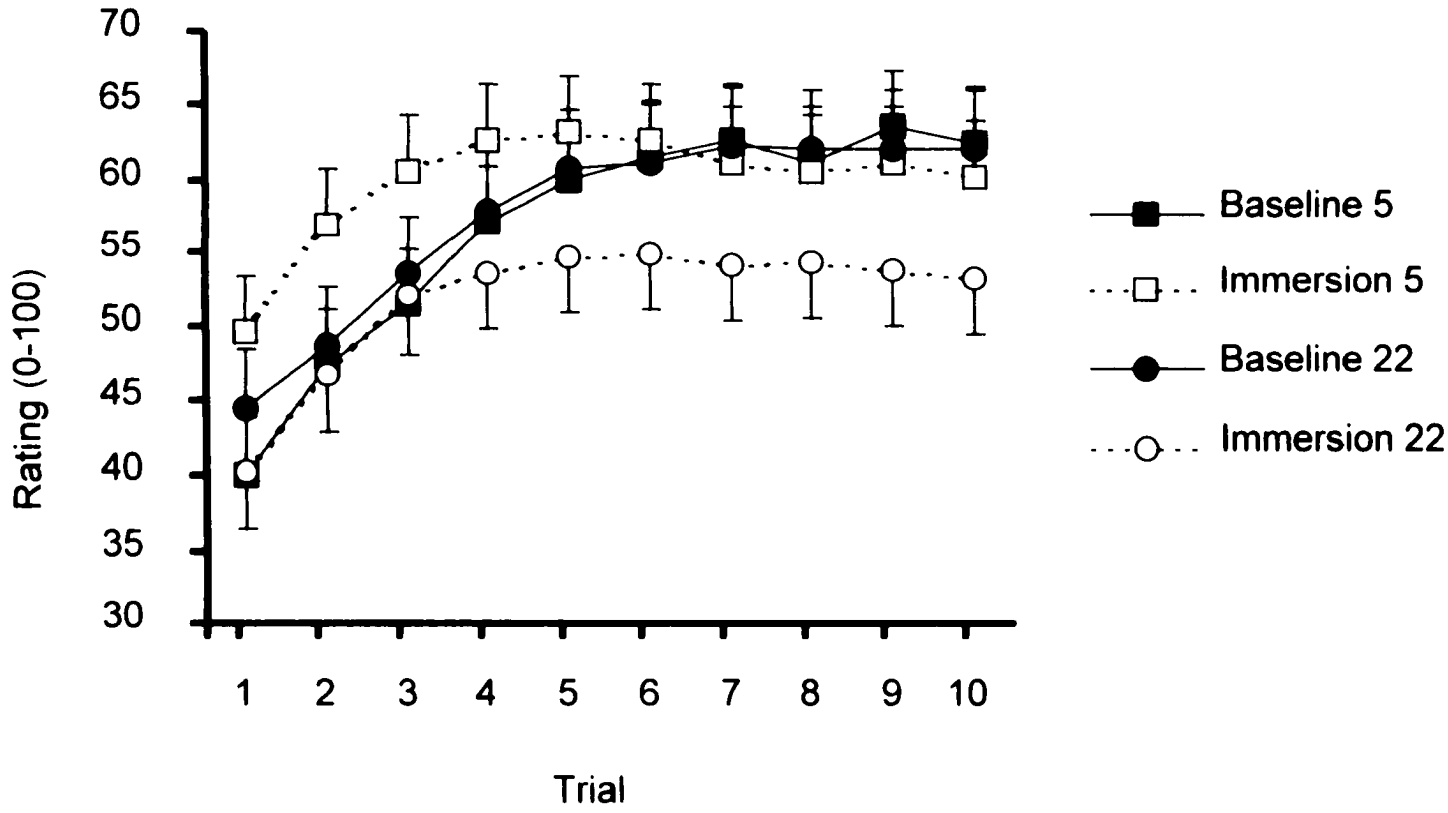


Figure 5. Ratings of thermal stimuli on the arm for older participants.

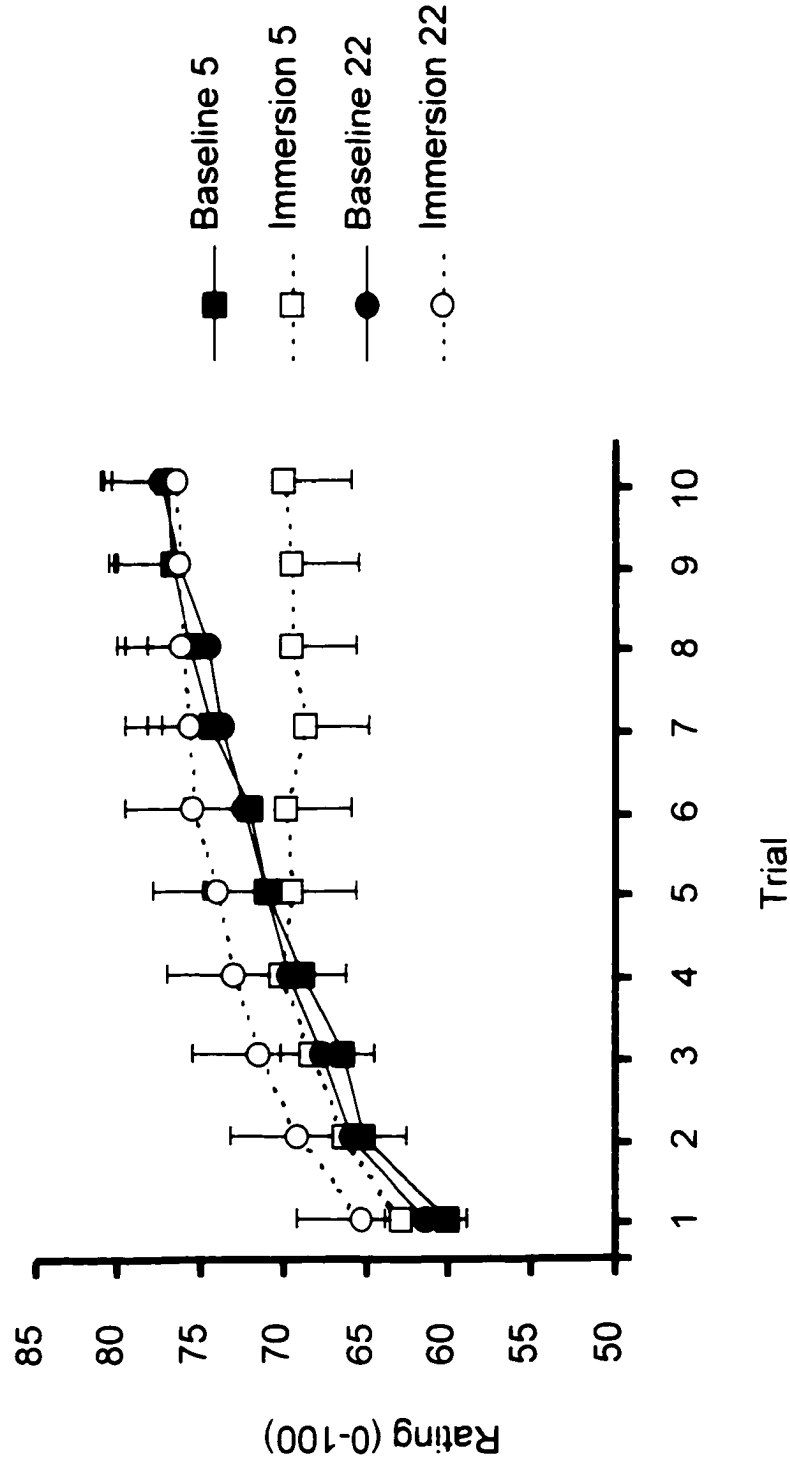


Figure 6. Ratings of thermal stimuli on the leg for younger participants.

suppressed thermal pain ratings below baseline for Trials 7-10 of the temporal summation procedure ($p < .05$). Hand immersion in 22 °C water again had no significant effects on thermal pain ratings ($p > .05$).

Finally, data for older subjects, with thermal stimulation on the leg, are shown in Figure 7. A repeated measures ANOVA revealed a significant main effect of temperature, $F(1,39) = 5.9$, $p < .05$. Follow-up univariate ANOVAs indicated that hand immersion in the 5 °C water significantly increased thermal pain ratings above baseline levels for Trials 1-5 of the temporal summation procedure ($p < .05$). Hand immersion in 22 °C water had no significant effects on ratings of thermal stimuli delivered to the leg ($p > .05$).

In each session, temporal summation of thermal pain was reassessed 10 min after completion of the final immersion trial. For both older and younger subjects, ratings of repetitive thermal stimuli following immersion in the 5 °C water were compared to baseline thermal ratings in order to evaluate the persistence of DNIC effects. A repeated measures ANOVA was performed for each age group. Postimmersion ratings did not differ from baseline ratings for either younger, $F(1,34) = 1.02$, $p > .05$, or older, $F(1,37) = .03$, $p > .05$, participants, suggesting that by 10 min following the final cold water immersion the effects of the tonic conditioning stimulus (i.e., cold water immersion) on the perception of heterotopic noxious thermal stimuli had ceased.

In order to assess relationships between the magnitude of DNICs and other study variables (i.e., physiological responses to noxious stimulation, clinical pain and general health variables) standardized measures of DNIC magnitude were computed. Composite DNIC scores that reflected the average decrease in pain ratings and the decrease in peak

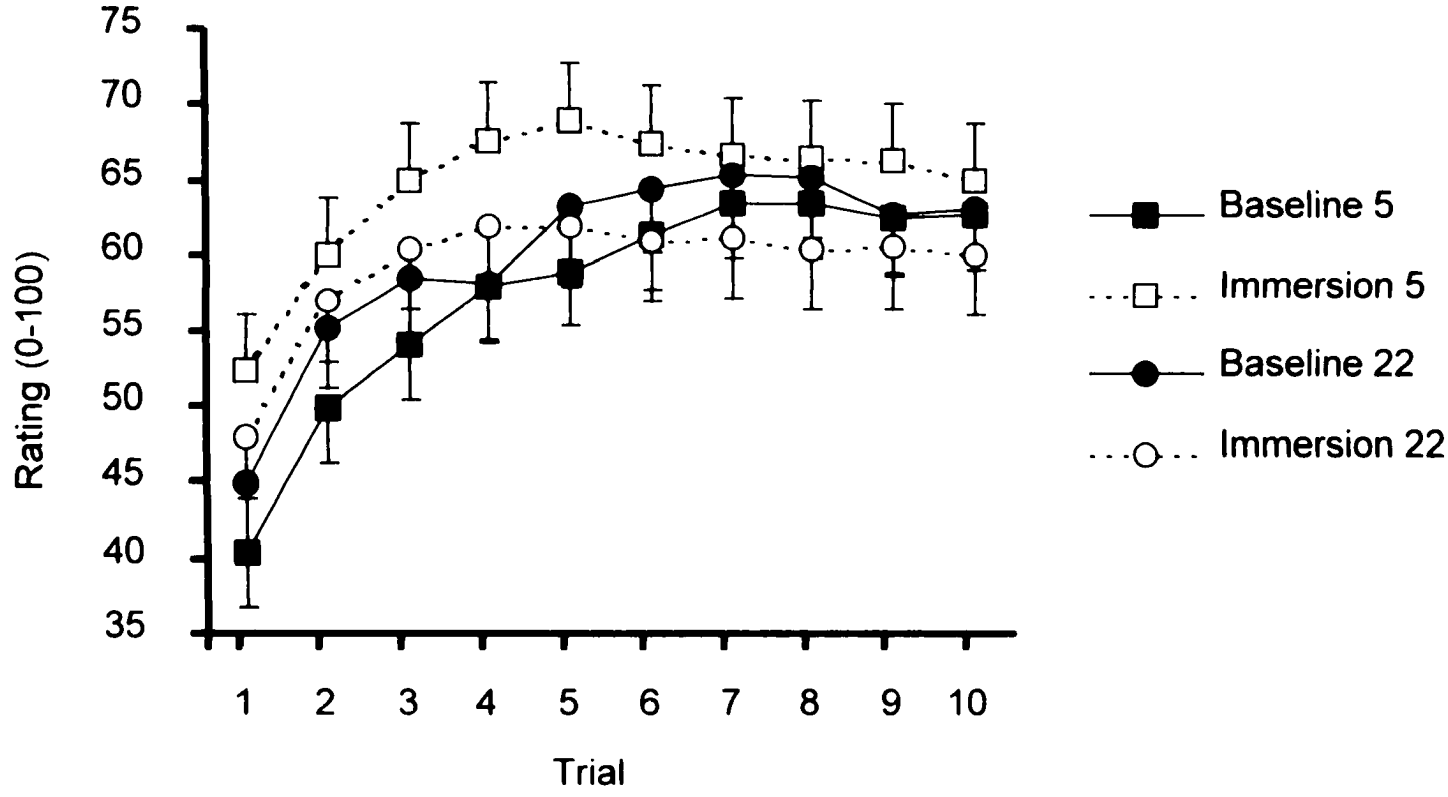


Figure 7. Ratings of thermal stimuli on the leg for older participants.

ratings during immersion in 5 °C water relative to changes during immersion in the 22 °C water were computed for thermal stimulation on the arm, on the leg, and at both sites combined. Younger participants demonstrated greater DNIC responses relative to older participants for thermal stimuli administered to the arm, $F(1,74) = 5.1$, $p < .05$; to the leg, $F(1,73) = 8.8$, $p < .005$; and at both sites combined, $F(1,75) = 11.0$, $p < .005$. Standardized DNIC variables appear in Table 5.

Table 5

Standardized DNIC Magnitudes

| DNIC site | Younger | Older |
|---|---|---|
| Arm | -.26 ± .84 | .25 ± 1.10 |
| Leg | -.34 ± .88 | .31 ± 1.00 |
| Both sites | -.33 ± .70 | .28 ± 0.90 |

Note. Data are standardized to distributions with means of 0 and standard deviations of 1. Negative scores indicate suppression of thermal ratings during 5 °C water immersion relative to 22 °C water immersion. Older and younger groups differ at $p < .05$. DNIC = diffuse noxious inhibitory controls.

Posttask Questionnaires

On average, older subjects ($M = 39.7$, $SD = 26.5$) found the session less stressful, $F(1,73) = 4.4$, $p < .05$, than did younger subjects ($M = 52.1$, $SD = 24.3$). Slight age differences in the distraction produced by water immersion were evident for both sessions. Following both sessions (i.e., immersion at 5 °C and immersion at 22 °C), younger subjects reported significantly more distraction during water immersion relative to older subjects ($p < .05$). These data are presented in Table 6. The amount of distraction was unrelated ($p > .05$) to the magnitude of DNICs in the entire sample or within age groups ($p > .05$), and controlling for distraction scores (i.e., entering distraction scores as a co-

variate in the factorial ANOVAs assessing age differences in the magnitude of DNIC) did not reduce the significance of the DNIC effects reported previously ($p < .01$). Finally, as demonstrated in Table 6, no age differences were noted in participants' reports of the extent to which hand immersion diminished the painfulness of the thermal stimuli ($p < .05$). Several significant associations between subjective perceptions of DNICs and actual DNIC magnitude were noted. Younger participants' estimates of the degree to which hand immersion in the 5 °C water diminished the painfulness of the thermal stimuli applied to the leg were significantly associated with the magnitude of DNICs on the leg ($r = -.45$, $p < .01$), while a similar relationship between perceptions of DNICs on the arm and the actual magnitude of DNICs on the arm emerged within the older participant group ($r = -.35$, $p < .05$).

Table 6

Responses to Postimmersion Questionnaires Assessing Distraction Produced by Water Immersion and Subjective Perceptions of DNIC

| Postimmersion ratings (0-10) | Younger ($n = 35$) | Older ($n = 36$) |
|---|---|---|
| Distraction (5 °C)[a] | 4.2 ± 1.8 | 3.4 ± 1.6 |
| Distraction (22 °C)[a] | 2.7 ± 1.2 | 2.0 ± 1.2 |
| Decrease arm (5 °C) | 4.0 ± 2.8 | 3.3 ± 2.8 |
| Decrease leg (5 °C) | 3.9 ± 2.8 | 3.3 ± 2.8 |
| Decrease arm (22 °C) | 2.9 ± 2.3 | 1.8 ± 1.3 |
| Decrease leg (22 °C) | 2.8 ± 2.1 | 2.3 ± 2.4 |

Note. DNIC = diffuse noxious inhibitory controls.
[a]Age groups differ at $p < .05$.

Postimmersion MPQ scores were compared in younger and older participants using univariate ANOVAs. Significant age differences emerged on the PRI, $F(1,73) = 13.1$, $p < .001$, and NWC, $F(1,73) = 43.1$, $p < .001$, with older adults demonstrating lower PRI

and NWC scores. Analysis of specific subscales revealed that younger participants had higher scores on the sensory ($p < .01$) and miscellaneous ($p < .05$) subscales of the MPQ. MPQ data are presented in Table 7. Relationships between MPQ responses and DNIC magnitude were assessed separately for older and younger subject groups. Among younger participants, a larger magnitude of DNICs on the leg was associated with higher PRI ($r = -.40$, $p < .05$) and NWC ($r = -.41$, $p < .05$) scores. Among older participants, relationships in the opposite direction were observed. A larger magnitude of DNIC on the leg was associated with lower scores on the PRI ($r = .50$, $p < .005$) and on the NWC ($r = .39$, $p < .05$).

Table 7

Scores on the McGill Pain Questionnaire

| MPQ variable | Younger ($n = 35$) | Older ($n = 39$) |
|---|---|---|
| NWC[a] | 17.2 ± 6.6 | 9.4 ± 4.7 |
| PRI[a] | 31.8 ± 12.8 | 22.2 ± 12.7 |
| Sensory[a] | 16.9 ± 8.0 | 10.1 ± 8.2 |
| Affective | 1.7 ± 2.7 | 1.1 ± 2.0 |
| Evaluative | 3.6 ± 1.6 | 3.3 ± 1.7 |
| Miscellaneous[a] | 9.6 ± 3.6 | 7.6 ± 3.9 |

Note. MPQ = McGill Pain Questionnaire; NWC = number of words chosen; PRI = Pain Rating Index.
[a]Older and younger groups differ at $p < .05$.

Relationships between the magnitude of DNICs and responses to the tonic conditioning stimulus (i.e., immersion of the hand in 5 °C water) were computed for older and younger participant groups. Among younger subjects, greater DNIC responses on the leg were associated with greater cold-related pain intensity rated at the initiation ($r = -.38$, $p < .05$) and completion ($r = -.35$, $p < .05$) of the temporal summation sequence but were not

related to mean cold pressor tolerance times ($p > .05$). Among older subjects, the magnitude of DNICs was not associated with ratings of cold pain intensity or with cold pressor tolerance times ($p > .05$).

Comparison of Physiological Responses in Older and Younger Subjects

Age differences in cardiovascular reactivity associated with the repeated cold pressor task were assessed using ANCOVA. For systolic blood pressure, diastolic blood pressure, and mean arterial pressure, change scores were computed by subtracting baseline values from mean immersion-associated values. Then, change scores were compared in older and younger participant groups using baseline values as covariates.

For systolic blood pressure, diastolic blood pressure, and mean arterial pressure change scores, significant age differences were observed after controlling for baseline values ($p < .05$), suggesting that cardiovascular reactivity to the repeated cold pressor task was greater among older participants relative to younger participants. Values for systolic blood pressure, diastolic blood pressure, and mean arterial pressure at baseline and during cold water immersion are presented in Figure 8.

Next, relationships between cardiovascular measures and responses to noxious stimuli were evaluated for older and younger subjects. Table 8 presents correlations among the following variables: baseline measures of systolic blood pressure and mean arterial pressure (averaged across the two sessions), responses to noxious thermal stimuli, and responses to cold water immersion. Among younger subjects, higher baseline systolic blood pressure and mean arterial pressure were consistently associated with diminished sensitivity to thermal and cold pain. Among older subjects, systolic blood pressure

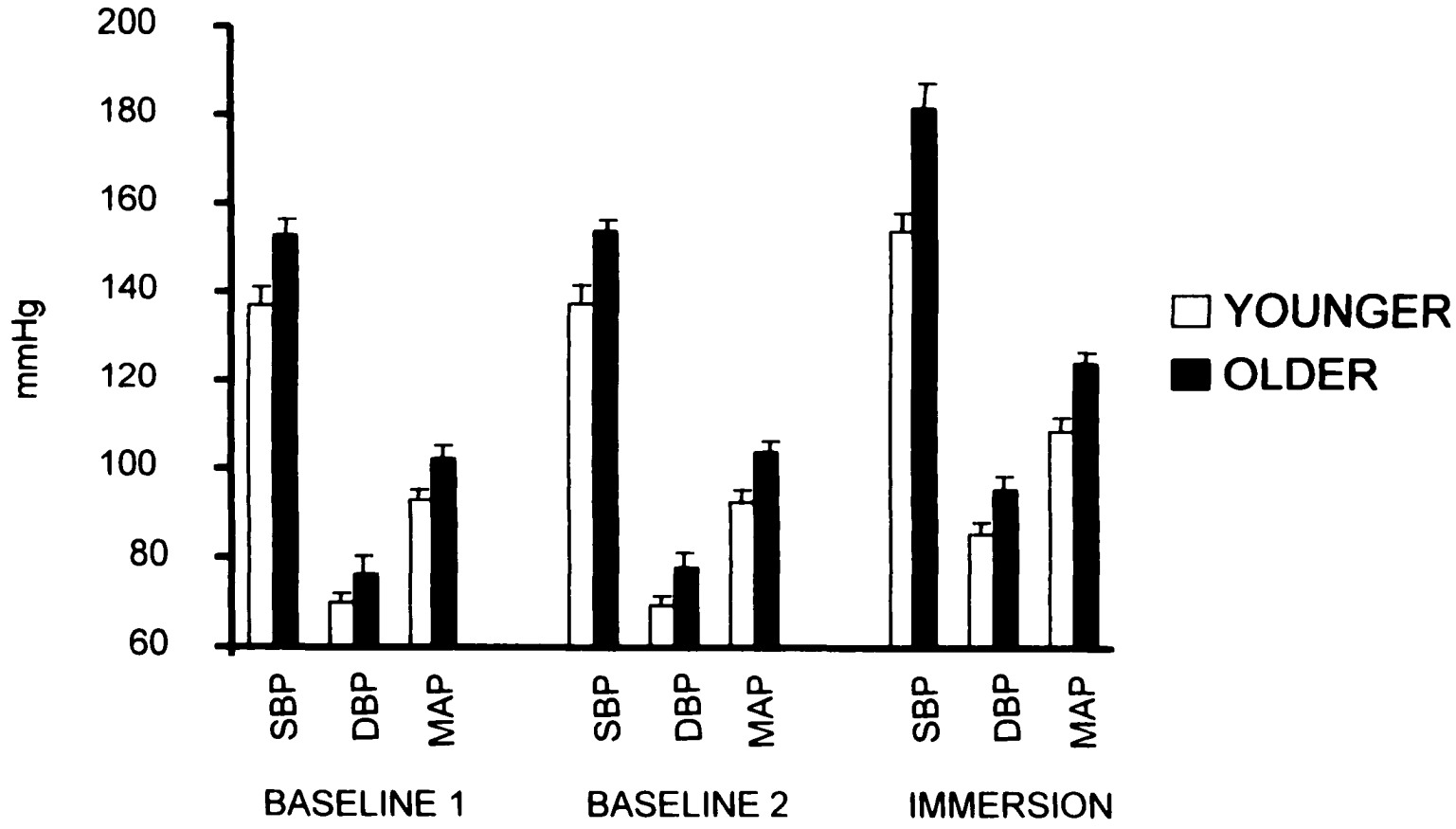


Figure 8. Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Mean Arterial Pressure (MAP).

and mean arterial pressure were positively associated with mean tolerance times on the cold pressor task but were not significantly correlated with other thermal and cold pain responses. None of these correlation coefficients differed significantly as a function of age group ($p > .05$). However, a chi-square analysis revealed that a significantly ($p < .05$) larger proportion of correlations between cardiovascular variables and pain responses were statistically significant within the group of younger participants (10/14 or 71.4%) relative to the proportion of significant correlations within the group of older participants (2/14 or 14.8%).

Table 8

Correlations Between Baseline Cardiovascular Activity and Responses to Noxious Stimuli

| | Younger ($n = 45$) | | Older ($n = 48$) | |
|---|---|---|---|---|
| Pain variable | Baseline SBP | Baseline MAP | Baseline SBP | Baseline MAP |
| HPTH | .35[a] | .29[a] | .13 | .18 |
| HPTO | .37[a] | .28 | .25 | .25 |
| Thermal max-arm | .33[a] | .23 | .19 | .21 |
| Thermal max-leg | .41[a] | .32[a] | .10 | .06 |
| 5 °C rating-initial | -.41[a] | -.39[a] | -.09 | -.04 |
| 5 °C rating-final | -.45[a] | -.41[a] | -.12 | -.03 |
| 5 °C tolerance | .16 | .13 | .28[a] | .30[a] |

Note. HPTH = heat pain threshold; HPTO = heat pain tolerance; max-arm = maximum temperature tolerated on the arm; max-leg = maximum temperature tolerated on the leg; SBP = systolic blood pressure; MAP = mean arterial pressure.
[a] $p < .05$

A series of regression analyses was performed in order to evaluate relationships between measures of DNICs and cardiovascular reactivity, while controlling for baseline cardiovascular measures. Reactivity scores were computed by subtracting baseline systolic blood pressure and mean arterial pressure from immersion-associated systolic blood

pressure and mean arterial pressure during the 5 °C water immersion session. Next, separate regression equations, with measures of DNICs as the dependent variables, were computed for older and younger subjects. The independent variables in these equations were baseline cardiovascular activity and reactivity scores. Baseline systolic blood pressure, baseline mean arterial pressure, systolic blood pressure reactivity, and mean arterial pressure reactivity did not predict composite DNIC scores at either body site for either age group ($p > .05$).

Salivary Cortisol

Salivary cortisol values from the first two samples collected in each session were averaged to obtain a baseline value. As indicated previously, in cases in which salivary cortisol data were available for only one of the first two time points, the single available value was used as the baseline value. Because prior research has demonstrated that cortisol values are highly related to the time of day at which the sample was taken (Kirschbaum & Hellhammer, 1989), baseline and postimmersion salivary cortisol values were statistically adjusted for time of day using regression analysis.

Cortisol data were analyzed using a factorial ANOVA with two within subjects factors, temperature (5 °C vs. 22 °C) and time (baseline vs. postimmersion), and one between subjects factor, age group. No significant main effects or interactions were observed ($p > .05$), suggesting that older and younger subjects did not differ in levels of salivary cortisol, that cortisol levels were unchanged from baseline to postimmersion assessment, and that cortisol responses to hand immersion in 5 °C water did not differ from

cortisol responses to immersion in 22 °C water. Cortisol values for older and younger subjects at all time points are presented in Table 9.

Table 9

Mean Levels of Salivary Cortisol, Statistically Adjusted for Time of Day

| Assessment time | Younger (n = 32) (μg/dec) | Older (n = 34) (μg/dec) |
|---|---|---|
| Baseline (5 °C session) | .49 ± .50 | .43 ± .52 |
| Postimmersion (5 °C session) | .43 ± .38 | .41 ± .54 |
| Baseline (22 °C session) | .49 ± .37 | .48 ± .77 |
| Postimmersion (22 °C session) | .44 ± .36 | .46 ± .90 |

Note. Groups do not differ at $p < .05$ for any variables.

As with baseline indices of cardiovascular activity, baseline levels of salivary cortisol (averaged across the two experimental sessions) were evaluated for associations with responses to noxious thermal and cold stimuli. Correlational analyses revealed no significant relationships between baseline salivary cortisol and either thermal pain variables (i.e., heat pain threshold, heat pain tolerance, and maximum tolerable temperatures for temporal summation) or cold pain variables (i.e., initial pain ratings, final pain ratings, and cold pain tolerance) among either older or younger participant groups ($p > .05$).

A regression analyses was performed in order to evaluate relationships between measures of DNICs and salivary cortisol reactivity, while controlling for baseline cortisol levels. A reactivity score was computed by subtracting baseline cortisol values from immersion-associated cortisol values during the 5 °C water immersion session. Next, separate regression equations, with the composite measures of DNICs as the dependent variable, were computed for older and younger subjects. The independent variables in these

equations were baseline cortisol and cortisol reactivity. Neither baseline cortisol nor cortisol reactivity was significantly associated with the DNIC score on either the arm or the leg for either age group ($p > .05$).

Measures of Clinical Pain and General Health

Data derived from the SF-36 comprised four subscales: General Health, Physical Functioning, Role Physical, and Body Pain. In addition, standardized scores from the RHH were included in the analyses. No age differences were found for the general health and body pain subscales of the SF-36 or for RHH standardized scores ($p > .05$). Differences did emerge on the physical functioning and role physical subscales, with older subjects reporting lower levels of physical functioning, $F(1,73) = 4.6$, $p < .05$, and diminished abilities to fulfill physical roles, $F(1,73) = 5.6$, $p < .05$, relative to younger subjects. SF-36 data for younger and older subjects are presented in Table 10.

Table 10

Scores on SF-36 Subscales and the Recent Health History Survey

| Clinical variables | Younger ($n = 37$) | Older ($n = 38$) |
|---|---|---|
| General health | 79.1 ± 13.8 | 77.7 ± 18.0 |
| Physical functioning[a] | 93.2 ± 19.2 | 84.6 ± 15.4 |
| Role physical[a] | 95.3 ± 15.4 | 81.6 ± 31.7 |
| Body pain | 76.2 ± 16.5 | 73.7 ± 16.1 |
| RHH | 79.5 ± 13.4 | 85.2 ± 12.7 |

Note. RHH = recent health history questionnaire.
[a]Age groups differ at $p < .05$.

Relationships between SF-36 subscales and DNIC magnitude were assessed using Pearson correlations, and results of these analyses are presented in Table 11. For the

Table 11

Pearson Correlations Between DNIC and Clinical Variables

| | Total Sample (n = 75) | | | Younger (n = 37) | | | Older (n = 38) | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Arm | Leg | Total | Arm | Leg | Total | Arm | Leg | Total |
| GH | -.16 | -.21 | -.23[a] | .05 | -.02 | -.04 | -.27 | -.33[a] | -.34[a] |
| PF | -.24[a] | -.22[a] | -.28[a] | -.11 | -.09 | -.13 | -.29 | -.25 | -.31[a] |
| RP | -.29[a] | -.17 | -.28[a] | -.34[a] | -.12 | -.31[a] | -.22 | -.10 | -.19 |
| BP | -.29[a] | -.28[a] | -.35[a] | -.32[a] | -.31[a] | -.44[a] | -.26 | -.24 | -.34[a] |
| RHH | -.07 | -.03 | -.07 | -.16 | -.11 | -.19 | -.14 | -.11 | -.14 |

Note. Higher scores on GH, PF, RP, BP, and RHH represent better health status (i.e., better general health, better physical functioning, better ability to fulfill physical roles, less pain); Arm = standardized magnitude of DNIC when the thermal test stimulus is applied to the arm; Leg = standardized magnitude of DNIC when the thermal test stimulus is applied to the leg; Total = overall standardized magnitude of DNIC; GH = general health; PF = physical functioning; RP = role physical; BP = body pain; RHH = recent health history questionnaire.

[a] $p < .05$

overall sample, greater DNIC magnitude was associated with better general health and physical functioning, better ability to fulfill physical roles, and less body pain. Among younger subjects, similar relationships were observed for the role physical and body pain subscales; however, within the group of older subjects, the magnitude of DNIC was significantly associated with scores on the general health, physical functioning, and body pain subscales. RHH scores were not significantly associated with DNIC magnitude within either age group, although the relationships were in the expected direction (i.e., larger DNIC effects associated with lower levels of recent pain). In order to determine whether group differences in DNIC mediated group differences in health, the effects of age group on the physical functioning and role physical subscales of the SF-36 were re-analyzed while statistically controlling for DNIC magnitude. Results of these analyses indicated that after adjusting for group differences in DNIC no significant age differences

remained for scores on the physical functioning, $F(1,72) = 1.9$, $p = .16$, or role physical, $F(1,72) = 2.6$, $p = .11$, subscales.

## DISCUSSION

The results of the present study provide evidence for stimulus-specific age-associated alterations in responses to noxious stimuli, for age-related differences in the magnitude of DNICs, and for the clinical relevance of laboratory pain procedures assessing endogenous pain-inhibitory systems. Collectively, the present findings suggest that the effects of concurrent cold pain on responses to heterotopic noxious thermal stimuli may vary as a function of age. Simultaneous cold pain diminished responsiveness to brief, repetitive thermal stimuli only among younger participants, and effects within the older group included either no reduction in thermal pain perception or an apparent enhancement of sensitivity to thermal stimulation. Further analyses indicated that these DNIC effects were not associated with measures of blood pressure or salivary cortisol reactivity. Finally, the magnitude of DNIC responses was related to several general health and clinical pain-related variables within both participant age groups. The study findings also suggested that differences in DNIC as a function of age might mediate age differences in physical health and physical functioning.

Collectively, the results of the present study tend to parallel reports from prior investigations. In a finding consistent with most previous work in the area (for reviews see Gagliese & Melzack, 1997b; Harkins, 1996), older and younger adults differed little on baseline measures of thermal pain responses, with the few significant differences suggesting diminished sensitivity on the part of older participants. Younger participants

demonstrated lower thermal pain thresholds and tolerances relative to the older group, but only in the second session. For measures of warmth threshold during both sessions, heat pain threshold and heat pain tolerance in the first session, mean ratings of thermal pain intensity at two different body sites over two sessions, temporal summation of thermal pain at two body sites over two sessions, and maximum tolerable repetitive thermal stimulation temperatures at both body sites for both sessions, no significant age differences emerged. Globally, it appears that similarities in responses to noxious thermal stimuli outweigh differences across age groups. While the few significant age differences in thermal pain responses were in the direction of diminished thermal pain sensitivity among older adults, the magnitude of the effects was relatively small.

Similarly, age differences in responses to repeated cold water immersion were fairly modest, though the effects of age that did emerge suggested diminished tolerance for the cold water immersion procedure among the older study participants (as opposed to possible increases in threshold and tolerance for thermal stimulation). Relative to the younger group, lower proportions of older adults tolerated the 5 °C water for the full DNIC procedure on the third and fourth trials of the immersion procedure. This finding is consistent with the one previously published study of age-related differences in responses to the cold pressor pain (Walsh et al., 1989) in which older adults demonstrated diminished tolerance for cold pain relative to younger adults. In the present study, age differences appeared only after repeated stimulation: while cold pain tolerance increased steadily across trials for younger subjects, no such change was observed within the older subject group. This effect appears similar to the results observed in the recent study of age differences in capsaicin-induced hyperalgesia (Zheng et al., 2000). These investiga-

tors found that, while elderly participants were less sensitive to the initial effects of capsaicin (i.e., pain onset was significantly delayed), the time course of hyperalgesia was substantially lengthened. One of the proposed explanations for these results centered on diminished pain-modulatory capacity in the elderly, resulting in a slower reversal of the hyperalgesic state. Similar effects may have been operative in the present study, in which cold pressor tolerance did not increase across trials among the elderly, potentially as a consequence of inadequate endogenous analgesic mechanisms.

In light of the present findings regarding age-related differences in DNIC magnitude, the possibility that ongoing tonic noxious stimulation (i.e., repeated cold pressor trials) produced progressive enhancements of endogenous analgesia in younger but not older participants seems plausible. Whatever the mechanism, the present findings suggest that age-associated differences in responses to noxious cold emerge only after repeated stimulation; the nature of the observed differences suggests a lack of adaptation to the tonic noxious stimulation among older adults. As with measures of thermal pain, the age-related differences in responses to noxious cold were of relatively small magnitude. It is interesting to note, however, that age effects on experimental pain responses varied across modalities of pain induction, as we have previously reported (Edwards & Fillingim, in press).

The results of the present study are roughly consistent with one recently published study of age differences in pain modulation. Following data collection for the present project, a study of age-associated differences in endogenous analgesic responses in humans appeared in the journal Pain (Washington et al., 2000). The authors of this study examined the effects of repeated immersion of the hand in cold water on thermal and

electrical pain thresholds in samples of young and elderly volunteers. In contrast to typical DNIC stimulation paradigms, the phasic test stimuli (thermal and electrical stimuli) were applied to the same body site as the tonic conditioning stimuli (cold water immersion). In this investigation, thresholds were assessed preimmersion and postimmersion on the same hand that was placed in the painfully cold water. The results of the study indicated that thresholds for thermal and electrical pain increased immediately following a series of repeated cold pressor trials. However, the increase in thresholds in the postimmersion period was significantly greater among younger relative to older subjects, suggesting potential decrements in a DNIC-like endogenous analgesic system in the elderly participants. The authors suggested that diminished efficacy of pain inhibition in the elderly might reduce the capacity of older adults to cope with persistent pain and could contribute to age-associated variation in the report of clinical pain. While the methodology of the present investigation differs in several important aspects from that of the Washington et al. (2000) study (i.e., differences in the phasic test stimuli, differences in the timing of the tonic conditioning task, and heterotopic presentation of the conditioning and test stimuli), their findings offer independent support for the validity of the present study's hypotheses.

Collectively, the present findings suggest that the magnitude of DNICs produced by immersion of the hand in cold water differs as a function of age. Among younger participants, 5 °C water immersion was associated with diminished responses to repetitive noxious thermal stimuli relative to the 22 °C water immersion condition. Mean ratings and peak ratings of the thermal stimuli were reduced from baseline levels during concurrent 5 °C water immersion, with the effects occurring primarily for the last few

stimuli in the sequence of 10 pulses. The effects for older subjects are somewhat more difficult to interpret. Immersion of the hand in 5 °C water actually resulted in significantly increased thermal pain ratings for the first three to five thermal stimuli in the temporal summation sequence. In addition, hand immersion in the 22 °C water was associated with reduced ratings of the intensity of thermal stimuli applied to the arm. Some investigators have reported that the percepts of pain arising from different sources of noxious stimulation may summate, producing additive effects when multiple noxious stimuli are perceived concurrently (Algom, Raphaeli, & Cohen-Raz, 1987a, 1987b). However, the vast majority of studies in which multiple noxious stimuli are applied simultaneously to heterotopic body sites report DNIC effects in which the perception of pain in one area of the body inhibits the perception of pain in other areas (Panteleo et al., 1988; Pertovaara et al., 1982, 1987; Price & McHaffie, 1988; Talbot et al., 1987, 1989; Willer et al., 1984, 1989).

Several methodological differences between the present study and prior investigations may be relevant here. First, the test stimuli employed in the present study (i.e., sequences of repetitive noxious thermal stimuli) were substantially more intense and more temporally sustained than those used in previous work. We administered a series of 10 rapid thermal pulses at the maximum tolerable temperature for each participant. Perhaps as a consequence of this choice of test stimuli, the suppressing effects of tonic cold pain on thermal pain responses were slight, even among younger participants. Indeed, Washington et al.'s (2000) recent investigation of age differences in endogenous analgesia, which utilized a conditioning stimulus quite similar to the cold pressor procedure that we employed, noted increases in thermal and electrical pain thresholds of up to 100%.

Their results indicated that even elderly participants demonstrated significant increases in thermal and electrical pain thresholds following tonic cold pain induction, though DNIC effects were substantially larger among the younger subjects. In the present study, mean DNIC effects did not approach those effect sizes, and younger participants showed slight, though significant, reductions in ratings of thermal pain intensity primarily during the later stages of the temporal summation procedure. Thus, given a situation in which endogenous analgesic systems that are presumably fully effective (i.e., those within the younger participant group) can effect only slight suppression of heterotopic noxious stimuli, it may be the case that, in populations with relatively impaired or deficient endogenous analgesic systems (i.e., older adults), facilitation rather than inhibition arises during situations in which multiple noxious stimuli are experienced.

Interestingly, relationships between the perceived intensity of the noxious cold and the degree of DNICs appeared to vary across age groups. Among younger individuals, higher ratings of cold pressor pain were associated with a larger magnitude of DNIC response when the thermal test stimuli were applied to the leg. This finding is consistent with several previous studies of DNICs which evaluated relationships between the perceived painfulness of the tonic conditioning stimulus and the perceived painfulness of the test stimulus (Willer et al., 1984, 1989; Witting, Svensson, Arendt-Nielsen, & Jensen, 1998). These studies have reported significant inverse correlations between pain ratings for the conditioning stimulus and the test stimulus. That is, more painful conditioning stimuli are associated with lower ratings of pain for the test stimuli. Several other investigators have failed to find such relationships, however (Lautenacher & Rollman, 1997; Pertovaara et al., 1987), and no published studies have reported correlations between the

perceived painfulness of a conditioning stimulus and the magnitude of the DNIC response (i.e., reductions in ratings of the test stimulus from baseline during concurrent application of the conditioning stimulus). In the present study, relationships in a direction opposite to that expected were found among older participants, and higher MPQ ratings of the painfulness of the repeated cold pressor procedure were associated with lesser degrees of DNIC when the thermal test stimuli were applied to the leg. This novel and unexpected finding is rather difficult to explain, although an analysis of the neurophysiological systems thought to underpin the phenomenon of DNIC suggests at least one possibility.

Fields and Basbaum (1999) described a complex interplay of descending facilitatory and inhibitory controls in the CNS. Noxious stimuli activate multiple CNS processing networks, some of which exert antinociceptive effects while others may be pronociceptive. In anesthetized rats, the diffuse inhibitory effects resulting from application of noxious somatic stimuli override the facilitatory effects of those same noxious stimuli on WDR neurons (Bouhassira, Bing, & Le Bars, 1993; M. M. Morgan et al., 1994), resulting in a net inhibitory effect. However, in the absence of fully effective descending modulatory systems, the facilitatory effects of a noxious stimulus on WDR neurons could potentially result in a net increase in the percept of pain produced by multiple concurrently administered noxious stimuli. This hypothesis might explain both the increase in ratings of thermal stimuli during stimulation with noxious cold and the finding of an inverse correlation between DNIC magnitude and the perceived painfulness of the conditioning stimulus among older participants. In the absence of effective endogenous inhibitory systems, simultaneous administration of multiple highly intense noxious stimuli may

evoke facilitation rather than inhibition, with more intensely painful stimulation generating greater degrees of facilitation. At least one previous study (Graven-Nielsen et al., 1998) has noted that several noxious stimuli applied to somatotopic areas may produce additive effects, suggesting that, under certain conditions, central integration of multiple pain-related inputs may produce summation rather than suppression.

For both older and younger participants, responses to noxious thermal stimuli had returned to baseline levels by the 10-min postimmersion reassessment period, suggesting that the inhibitory or facilitatory effects of 5 °C water immersion were relatively transient. These data are consistent with most previous studies of DNIC in humans (Price & McHaffie, 1988; Talbot et al., 1987), which suggest relatively time-limited inhibitory effects of the conditioning stimulus. In addition, the recent investigation of age differences in endogenous analgesia (Washington et al., 2000) reported that thermal and electrical pain thresholds had returned to baseline by the 1-hr posttask assessment period.

The observed age differences in the effects of repeated cold pain on endogenous analgesic responses were not attributable to differences in local skin temperature or to attentional variables. The finding that skin temperature among older adults returned to baseline more slowly than among younger subjects is consistent with previous reports of age-associated decreases in microcirculation (Balin, 1992; Balin & Lin, 1989), a phenomenon which could certainly account for this effect. However, postimmersion local skin temperatures were not significantly correlated with the magnitude of DNIC, indicating that age differences in skin temperature recovery did not relate directly to age differences in the effects of cold-water immersion on thermal pain responses. In addition, while younger subjects reported greater distraction as a consequence of cold-water im-

mersion, statistically adjusting for these differences did not alter the outcome of age group comparisons in the magnitude of DNIC effects. Although attention clearly influences pain responses (Bushnell et al., 1985), DNIC effects may be relatively insensitive to manipulations of attentional variables (De Brouker et al., 1990; Kakigi, 1994; Talbot et al., 1989). Consistent with the previous conclusion that attentional focus is relatively unrelated to the phenomenon of DNIC, in the present study, distraction scores were unrelated to the magnitude of DNIC for both older and younger participants.

The physiological measures collected as indices of sympathetic nervous system and HPA axis activity (blood pressure and salivary cortisol, respectively) were generally unrelated to the magnitude of DNICs among both older and younger participant groups. Consistent with our predictions, as well as previous research on pain-related cardiovascular reactivity (Dewhurst et al., 1991; Edwards & Fillingim, in press), older adults did demonstrate substantial elevations in baseline systolic blood pressure, diastolic blood pressure, and mean arterial pressure relative to younger adults, as well as enhanced systolic blood pressure, diastolic blood pressure, and mean arterial pressure reactivity during hand immersion in the 5 °C water. However, neither baseline cardiovascular activity nor cardiovascular reactivity to cold water immersion was related to the magnitude of DNIC responses. Interestingly, baseline indices of cardiovascular activity tended to be inversely associated with sensitivity to thermal and cold pain, but these relationships were present to a significantly greater degree among younger participants. This finding is consistent with a previous study in which we observed age-specific relationships between cardiovascular variables and ischemic pain responses (Edwards & Fillingim, in press). The results of our earlier study, buttressed by the present findings, suggest that the pain-

inhibitory system associated with increased arterial blood pressure may be less effective in modulating pain in older adults. Increased arterial blood pressure is associated with hypoalgesia (Angrilli et al., 1997; France & Stewart, 1995; Ghione, 1996; Maixner, 1991), and endogenous opioids may mediate this inverse relationship between blood pressure and pain sensitivity (Maixner, 1991; McCubbin & Bruehl, 1994). The finding that relationships between blood pressure and responses to noxious stimuli are reduced or absent among older adults suggests potential decrements in this well-documented endogenous analgesic system. While the specific mechanisms supporting these findings have yet to be identified and described, decreased baroreceptor sensitivity (Borst, 1996) as well as generally compromised opioid function in older adults (Morley, Flood, & Silver, 1990) may play influential roles. That is, older adults may have a reduced capacity to recruit endogenous pain-inhibitory systems as a consequence of failure to adequately stimulate baroreceptors or to mount an effective opiate response to such stimulation.

Unlike cardiovascular responses, measures of salivary cortisol did not vary as a function of age group. Older and younger adults demonstrated similar cortisol levels at baseline and following hand immersion in both 5 °C and 22 °C water. The cortisol concentrations observed in saliva in the present study are quite similar to previously published studies employing similar methods of salivary cortisol analysis (Jones, Rollman, & Brooke, 1997), suggesting that our method of assessment was likely to be valid. Contrary to study hypotheses, cortisol levels did not rise following repeated hand immersion in cold water. The cold pressor task is a substantial systemic challenge, and it was anticipated that a measurable stress response would be produced. Prior laboratory-based studies using experimental stress paradigms (Jones et al., 1997), exercise stimulation (Droste,

Greenlee, Schreck, & Roskamm, 1991), and a cold pressor task (Bullinger et al., 1984) have all demonstrated increases in cortisol levels following stress, exercise, or pain. However, the previously mentioned study of cortisol responses to a cold pressor task (Bullinger et al., 1984) assessed plasma cortisol, which may be a more sensitive indicator of task-associated changes in cortisol levels. It is also possible that the intermittent nature of the cold pressor task utilized in the present study failed to produce cortisol responses as robust as those produced by more sustained stress-inducing tasks. Cortisol responses to laboratory stressors appear to be rather variable. One recent study reported no changes in plasma cortisol during the performance of two stressful, cognitively demanding tasks (Kang & Fox, 2000). In addition, the investigators noted a steady decline in cortisol levels beginning shortly after the conclusion of the tasks. Finally, anticipatory stress related to apprehension regarding the laboratory procedures might have contributed to elevations in baseline cortisol values, masking any effects of the repeated cold pressor procedure on participants' cortisol levels.

In addition to the lack of association with age, cortisol levels were unrelated to participants' responses to noxious stimuli in general and to the magnitude of DNIC in particular. A number of prior investigations in rats have suggested that cortisol might be involved in stress-induced analgesia, perhaps by activating serotonergic or opioidergic analgesic mechanisms (Bodnar, Glusman, Brutus, Spiaggia, & Kelly, 1979; Lewis, 1986; Sutton, Fleshner, Mazzeo, Maier, & Watkins, 1994). Thus, it was hypothesized that the magnitude of DNICs would be partially dependent on cortisol activity or reactivity. However, no such relationships between DNIC magnitude and cortisol values emerged.

suggesting that the neurophysiological systems interacting to produce endogenous analgesia in the present study are not dependent on HPA axis activation.

Clinical pain and general health variables were measured using two well-validated questionnaires and evaluated for relationships with DNIC magnitude. In spite of the fact that the present sample was highly selected and that only quite healthy individuals were enrolled, several age differences in clinical variables did emerge from the data. Consistent with prior research, older participants reported poorer physical functioning and greater limitations in fulfilling physical roles relative to younger subjects (for reviews see Gagliese & Melzack, 1997b; Gibson et al., 1994). No effects of age on clinical pain report were observed for either the SF-36 body pain subscale or for the RIHI survey of recent pain symptoms and pain-related general health, possibly as a result of the rather strict exclusion criteria for the study (e.g., those individuals with chronic pain conditions or use of prescription pain medications were excluded from the study). Interestingly, the magnitude of DNIC, as assessed by suppression of thermal pain responses during tonic cold pain, was associated with some measures of general health and clinical pain variables in the entire sample, within the group of younger participants, and within the group of older participants. Larger magnitudes of DNIC were associated with improved physical functioning, better ability to fulfill physical roles, and less clinical pain, at least as assessed by the SF-36. While several previous studies have reported relationships between laboratory pain variables and clinical pain (Fillingim, Edwards, & Powell, 1999; Fillingim et al., 1996; Gil et al., 1995; Lautenbacher, Rollman, & McCain, 1994), to our knowledge, no prior investigators have directly evaluated the clinical relevance of DNIC. The significant relationships of DNIC variables with clinical pain and general health

variables, in the expected directions, are encouraging and begin to demonstrate the clinical relevance of these procedures. Theory and prior empirical work indicate that the experience of clinical pain and responses to experimental noxious stimuli administered in a controlled setting are modulated by descending inhibitory mechanisms at multiple levels of the CNS (Dubner & Ren, 1999; Fields & Basbaum, 1999). The finding that larger degrees of endogenous analgesic responses are related to reports of less clinical pain and better physical functioning in daily life suggests that common mechanisms may shape responses to noxious stimulation both inside and outside of the laboratory. Moreover, after controlling for the magnitude of DNICs, age differences in physical functioning and the ability to fulfill physical roles were rendered nonsignificant, suggesting that decrements in DNICs may mediate age-associated reductions in physical health. Though the present findings await independent replication, these data provide preliminary evidence for the role of age-associated declines in endogenous analgesic systems in the previously observed enhancement of clinical pain and decrements in physical functioning in elderly populations.

Despite clear evidence for age-associated increases in the prevalence and adverse impact of persistently painful conditions, substantial evidence suggests that the elderly are at elevated risk for undertreatment of pain. Adults aged 65 years or older represent over 12% of the population, and that proportion is rapidly expanding. However, individuals in this age range typically comprise well under 5% of the clientele of multidisciplinary pain management clinics (Gibson, Farrell, Katz, & Helme, 1996). One recent study concluded that older adults are less frequently referred to such pain management programs and are more likely to be denied treatment on the basis of age-related admission

criteria (Kee, Middaugh, Redpath, & Hargadon, 1998). The elderly are generally less likely to be offered behavioral and nonpharmacological therapies for pain, although the available evidence suggests that older pain patients accept these therapies when offered and derive as much benefit from multidisciplinary pain treatment as younger pain patients (for a review see Gibson et al., 1996). The findings of the present study suggest that the experience of clinical pain in the elderly may differ from the experience in younger populations. The present results, together with the findings of another recent study (Washington et al., 2000), suggest that endogenous analgesic systems may decline in efficacy with advancing age, providing an additional contributory mechanism to the experience of clinical pain in elderly populations. Given that elderly adults are more likely to experience chronic pain and to be disabled by the experience of pain than younger populations (Scudds & Robertson, 1998), the elderly may require enhanced, not restricted, options for management of their pain. Further investigation into the nature and neurophysiological substrates of age-associated decrements in pain-modulatory systems may produce a more thorough characterization of the experience of pain in the elderly, potentially improving treatment options for the substantial population of older adults suffering from chronically painful conditions.

The present study includes a number of limitations that should temper interpretation of these findings. First, it is unclear whether the results of the present study are applicable outside of the relatively healthy population studied here. In the current investigation, subjects who reported a history of chronic pain or current use of psychopharmacological agents were excluded. Thus, the many older adults who suffer from chronically painful disorders or are receiving treatment for painful conditions were not represented in

this study of healthy individuals. Second, the older participant group in the present study had a relatively limited age range (55-67 years old), which did not permit examination of age-associated changes in pain responses and endogenous pain modulation across the full lifespan. Third, the study did not include direct investigation of the mechanisms underlying the observed effects. The present data suggest that cardiovascular and HPA responses to noxious stimulation did not mediate pain inhibition but do not provide evidence for an alternative explanatory mechanism. Thus, the specific nature of the age-associated difference in the magnitude of DNICs remains unknown, though an ongoing line of research is investigating endogenous opioid involvement in the observed effects. Fourth, the magnitude of the DNIC effects among younger subjects was relatively slight. The recent study by Washinton and colleagues (2000) noted substantially greater reductions in pain following repeated stimulation with noxious cold than the reductions observed in the present study. Moreover, for some of the test stimuli we observed facilitation rather than inhibition of pain responses during concurrent noxious stimulation among older adults. This seems to be an unusual effect and is inconsistent with most of the previously published literature relating to DNICs. Fifth, while a number of relationships between the magnitude of DNICs and the clinical variables did achieve statistical significance, these associations were modest in magnitude (i.e., correlations on the order of .3 to .4), leaving the majority of variance in self-reported clinical pain and general health variables unaccounted for.

Despite its limitations, however, the present study contributes to the ongoing characterization of the complex relationships between normal aging and the experience of pain. In sum, though a complete explanation of the mechanisms underlying age-related

differences in pain perception and pain report is as yet unavailable, the results of the present study suggest a diminished capacity for endogenous analgesia among older adults. While many similar findings have emerged from animal studies, only one other investigation has reported such decrements among humans. In the present study, age differences were observed in the effect of a tonic noxious conditioning stimulus on the perception of a phasic test stimulus. While younger adults demonstrated decreases in average and peak ratings for repetitive thermal stimuli, older adults evidenced either increases or no changes in thermal pain ratings during concurrent perception of noxious cold. Further indirect support for the hypothesis that pain modulation becomes less effective with advancing age was derived from the observation of age-specific relationships between cardiovascular function and pain responses. Specifically, blood pressure appeared to be more highly related to pain sensitivity (in an inverse fashion) among younger participants, suggesting potential decrements in the efficacy of this well-characterized system of descending inhibitory pain control. Finally, the present study provided evidence for the clinical relevance of laboratory pain procedures. The magnitude of endogenous pain inhibition was related to several variables assessing general health, physical functioning, and clinical pain, and age differences in DNIC appeared to mediate the observed age differences in physical function. Future studies investigating putative mechanisms underpinning this effect, such as age-associated decrements in endogenous opiate function, may eventually lead to a more comprehensive characterization of pain in the elderly and potentially to improvements in geriatric pain management.

## REFERENCES


Algom, D., Raphaeli, N., & Cohen-Raz, L. (1987a). Integration of noxious stimuli across separate somatosensory communications systems: A functional theory of pain. Journal of Experimental Psychology: Human Perception and Performance, 12, 92-102.

Algom, D., Raphaeli, N., & Cohen-Raz, L. (1987b). Pain combines additively across different sensory systems: A further support for the functional theory of pain. Perceptual and Motor Skills, 65, 619-625.

Angrilli, A., Mini, A., Mucha, R., & Rau, H. (1997). The influence of low blood pressure and baroreceptor activity on pain responses. Physiology and Behavior, 62, 391-397.

Badley, E. M., & Tennant, A. (1992). Changing profile of joint disorders with age: Findings from a postal survey of the population of Calderdale, West Yorkshire, U.K. Annals of Rheumatic Disorders, 51, 366-371.

Balin, A. K. (1992). Skin diseases. In J. G. Evan & T. F. Williams (Eds), Oxford textbook of geriatric medicine (pp. 445-458). New York: Oxford University Press.

Balin, A. K., & Lin, A. N. (1989). Skin changes as a biological marker for measuring the rate of human aging. In A. K. Balin & A. N. Lin (Eds), Aging and the Skin (pp. 43-75). New York: Raven Press.

Barden, N., Dupont, A., Labrie, F., Merand, Y., Rouleau, D., Vaudry, H., & Boissier, J. (1981). Age-dependent changes in the beta-endorphin content of discrete rat brain nuclei. Brain Research, 208, 209-212.

Basbaum, A., & Fields, H. L. (1984). Endogenous pain control systems: Brain-stem spinal pathways and endorphin circuitry. Annual Review of Neuroscience, 7, 309-338.

Bhaskaran, O., & Radha, E. (1985). Monoamine levels and monoamine oxidase activity in different regions of rat brain as a function of age. Mechanisms of Aging and Development, 23, 151-160.

Birren, J. E., Shapiro, H. B., & Miller, J. H. (1950). The effect of salicylate upon pain sensitivity. Journal of Pharmacology and Experimental Therapeutics, 100, 67-71.

Bodnar, R. J., Glusman, M., Brutus, M., Spiaggia, A., & Kelly, D. D. (1979). Analgesia induced by cold-water stress: Attenuation following hypophysectomy. Physiology and Behavior, 23, 53-62.

Bodnar, R. J., Romero, M. T., & Kramer, E. (1988). Organismic variables and pain inhibition: Roles of gender and aging. Brain Research Bulletin, 21, 947-953.

Borst, S. (1996). Autonomic nervous system. In J. E. Birren (Ed.), Encyclopedia of gerontology: age, aging, and the aged (pp. 141-147). San Diego, CA: Academic Press.

Bouhassira, D., Bing, Z., & Le Bars, D. (1993). Studies of brain structures involved in diffuse noxious inhibitory controls in the rat: The rostral ventromedial medulla. Journal of Physiology, 463, 667-687.

Bullinger, M., Naber, D., Pickar, D., Cohen, R. M., Kalin, N. H., Pert, A., & Bunney, W. E. (1984). Endocrine effects of the cold pressor test: Relationships to subjective pain appraisal and coping. Psychiatry Research, 12, 227-233.

Bushnell, M. C., Duncan, G. H., Dubner, R., Jones, R. L., & Maixner, W. (1985). Attentional influences on noxious and innocuous cutaneous heat detection in monkeys and humans. Journal of Neuroscience, 5, 1103-1110.

Butler, R. N. (1979). Pain in the elderly: Patterns change with age. Journal of the American Medical Association, 241, 2491-2492.

Cadden, S. W. (1993). The ability of inhibitory controls to "switch-off" activity in dorsal horn convergent neurones in the rat. Brain Research, 628, 65-71.

Cadden, S. W., Villanueva, L., Chitour, D., & Le Bars, D. (1983). Depression of activities of dorsal horn convergent neurons by propriospinal mechanisms triggered by noxious inputs: Comparison with diffuse noxious inhibitory controls (DNIC). Brain Research, 275, 1-11.

Casey, K. L. (1999). Forebrain mechanisms of nociception and pain: Analysis through imaging. Proceedings of the National Academy of Sciences USA, 96, 7668-7674.

Chapman, W. P., & Jones, C. M. (1944). Variations in cutaneous and visceral pain sensitivity in normal subjects. Journal of Clinical Investigation, 23, 81-91.

Chikanza, I. C., Petrou, P., Chrousos, G. P., Kingsley, G., & Panayi, G. P. (1992). Defective hypothalamic response to immune and inflammatory stimuli in patients with rheumatoid arthritis. Arthritis and Rheumatism, 35, 1281-1288.

Chitour, D., Dickenson, A. H., & Le Bars, D. (1982). Pharmacological evidence for the involvement of serotonergic mechanisms in diffuse noxious inhibitory controls (DNIC). Brain Research, 236, 329-337.

Clark W. C., & Meehl, L. (1971). Thermal pain: A sensory decision theory analysis of the effect of age and sex on d, various response criteria, and 50% pain threshold. Journal of Abnormal Psychology, 78, 202-212.

Cohen, M. J., Naliboff, B. D., Schandler, S. L., & Heinrich, R. (1983). Signal detection and threshold measurement to loud tones and radiant heat in chronic low back pain patients and cohort controls. Pain, 6, 245-252.

Corran, T. M., & Melita, B. (1998). Pain in later life. In B. Carter (Ed.), Perspectives on pain: Mapping the territory (pp. 243-63). New York: Oxford University Press.

Crisp, T., Stafinsky, J. L., Hoskins, D. L., Dayal, B., Chinrock, K. M., & Uram, M. (1994). Effects of aging on spinal opioid-induced antinociception. Neurobiology of Aging, 15, 169-174.

Crook, J., Rideout, E., & Brown, G. (1984). The prevalence of pain complaints in a general population. Pain, 18, 299-314.

De Brouker, T., Cesaro, P., Willer, J. C., & Le Bars, D. (1990). Diffuse noxious inhibitory controls in man. Involvement of the spinoreticular tract. Brain, 113, 1223-1234.

Dewhurst, G., Wood, D. A., Walker, F., Lampe, F. C., Jeffreys, M., Cooper, M., & Williams, J. D. (1991). A population survey of cardiovascular disease in elderly people: Design, methods, and prevalence results. Age & Ageing, 20, 353-360.

Dickenson, A. H., & Le Bars, D. (1987). Supraspinal morphine and descending inhibitions acting on the dorsal horn of the rat. Journal of Physiology, 384, 81-107.

Dickenson, A. H., Le Bars, D., & Besson, J. M. (1980). Diffuse noxious inhibitory controls (DNIC). Effects on trigeminal nucleus caudalis neurones in the rat. Brain Research, 200, 293-305.

Droste, C., Greenlee, M. W., Schreck, M., & Roskamm, H. (1991). Experimental pain thresholds and plasma beta-endorphin levels during exercise. Medicine and Science in Sports and Exercise, 23, 334-342.

Dubner, R., & Ren, K. (1999). Endogenous mechanisms of sensory modulation. Pain, 84(Suppl. 6), S45-S53.

Edwards, R. R., & Fillingim, R. B. (in press). Age-associated differences in responses to noxious stimuli. The Journal of Gerontology, Series A: Biological and Medical Sciences.

Ferrell, B. A. (1991). Pain management in elderly people. Journal of the American Geriatric Society, 39, 64-73.

Fields, H. L., & Basbaum, A. I. (1999). Central nervous system mechanisms of pain modulation. In P. D. Wall & R. Melzack (Eds), Textbook of pain (pp. 309-329). New York: Churchill Livingstone.

Fillingim, R. B., Edwards, R. R., & Powell, T. (1999). The relationship of sex and clinical pain to experimental pain responses. Pain, 83, 419-425.

Fillingim, R. B., Maixner, W., Kincaid, S., Sigurdsson, A., & Harris, M. B. (1996). Pain sensitivity in patients with temporomandibular disorders: Relationship to clinical and psychosocial factors. The Clinical Journal of Pain, 12, 260-269.

Fillingim, R. B., Maixner, W., Kincaid, S., & Silva, S. (1998). Sex differences in temporal summation but not sensory-discriminative processing of thermal pain. Pain, 75, 121-127.

Fordyce, W. E. (1995). Back pain in the workplace: Management of disability in nonspecific conditions. Task Force on Pain in the Workplace. Seattle, WA: IASP Press.

France, C. R., & Stewart, K. M. (1995). Parental history of hypertension and enhanced cardiovascular reactivity are associated with decreased pain ratings. Psychophysiology, 32, 571-578.

Gagliese, L., & Melzack, R. (1997a). The assessment of pain in the elderly. In D. Mostofsky & J. Lomranz (Eds.), Handbook of pain and aging (pp. 69-96). New York: Plenum Press.

Gagliese, L., & Melzack, R. (1997b). Chronic pain in elderly people. Pain, 70, 3-14.

Gambert, S. R., Garthwaite, T. L., Pontzer, C. H., & Hagen, T. C. (1980). Age-related changes in central nervous system beta-endorphin and ACTH. Neuroendocrinology, 31, 252-255.

Gatchel, R. J., & Turk, D. C. (1996). Psychological approaches to pain management: A practitioner's handbook. New York: The Guilford Press.

Geiss, A., Varadi, E., Steinbach, K., Bauer, H., & Anton, F. (1997). Psychoneuroimmunological correlates of persisting sciatic pain in patients who underwent discectomy. Neuroscience Letters, 237, 65-68.

Ghione, S. (1996). Hypertension-associated hypalgesia: Evidence in experimental animals and humans, pathophysiological mechanisms, and potential clinical consequences. Hypertension, 28, 494-504.

Gibson, S. J., Farrell, M. J., Katz, B., & Helme, R. D. (1996). Multidisciplinary management of chronic nonmalignant pain in older adults. In B. A. Ferrell & B. R. Ferrell (Eds), Pain in the elderly (pp. 91-99). Seattle, WA: IASP Press.

Gibson, S. J., Gorman, M. M., & Helme, R. D. (1991). Assessment of pain in the elderly using event-related potentials. In M. R. Bond, J. E. Charleton, & C. J. Woolf (Eds), Proceedings of the VIth World Congress on Pain (pp. 527-533). New York: Elsevier.

Gibson, S. J., Katz, B., Corran, T. M., Farrell, M. J., & Helme, R. D. (1994). Pain in older persons. Disability and Rehabilitation, 10, 127-139.

Gil, K. M., Phillips, G., Webster, D. A., Williams, D. A., Thompson, R. J., & Kinney, T. (1995). Experimental pain sensitivity and reports of negative thoughts in adults with sickle cell disease. Behavior Therapy, 26, 273-291.

Giordano, J., & Rogers, L. (1992). Putative mechanisms of buspirone-induced antinociception in the rat. Pain, 50, 365-372.

Graven-Nielsen, T., Babenko, V., Svensson, P., & Arendt-Nielsen, L. (1998). Experimentally-induced muscle pain induces hypoalgesia in heterotopic deep tissues, but not in homotopic deep tissues. Brain Research, 787, 203-210.

Griep, E.N., Boersma, J. W., Lentjus, E. G., Prins, A. P. A., Van Der Korst, J. K., & De Kloet, E. R. (1998). Function of the hypothalamic-pituitary-adrenal axis in patients with fibromyalgia and back pain. The Journal of Rheumatology, 25, 1374-1381.

Hall, K. R. L., & Stride, E. (1954). The varying response to pain in psychiatric disorders: A study in abnormal psychology. British Journal of Medical Psychology, 27, 48-60.

Hamm, R. J., & Knisely, J. S. (1985). Environmentally-induced analgesia: An age-related decline in an endogenous opioid system. Journal of Gerontology, 40, 268-274.

Hamm, R. J., & Knisely, J. S. (1986). Environmentally-induced analgesia: An age-related decline in a neurally mediated, non-opioid system. Psychology and Aging, 1, 195-201.

Hamm, R. J., Knisely, J. S., & Watson, A. (1986). Environmentally-induced analgesia: An age-related decline in a hormonally mediated nonopioid system. Journal of Gerontology, 41, 336-341.

Hardy, J. D., Wolff, H. G., & Goodell, H. (1943). The pain threshold in man. American Journal of Psychiatry, 99, 744-751.

Harkins, S. W. (1996). Geriatric pain: Pain perceptions in the old. Pain Management, 12, 435-459.

Harkins, S. W., & Chapman, C. R. (1976). Detection and decision factors in pain perception in young and elderly men. Pain, 2, 253-264.

Harkins, S. W., & Chapman, C. R. (1977). The perception of induced dental pain in young and elderly women. Journal of Gerontology, 32, 428-435.

Harkins, S. W., Davis, M. D., Bush, F. M., & Kasberger, J. (1996). Suppression of first pain and slow temporal summation of second pain in relation to age. Journal of Gerontology, 51A, M260-265.

Harkins, S. W., Price, D. D., & Martinelli, M. (1986). Effects of age on pain perception: Thermonociception. Journal of Gerontology, 41, 58-63.

Harkins, S. W., & Scott, R. B. (1996). Pain and presbyalgos. In J. E. Birrin (Ed.), Encyclopedia of gerontology: Age, aging, and the aged (pp. 247-60). San Diego, CA: Academic Press.

Helme, C., Ehlert, U., Hanker, J., & Hellhammer, D. (1998). Abuse-related posttraumatic stress disorder and alterations of the hypothalamic-pituitary-adrenal axis in women with chronic pelvic pain. Psychosomatic Medicine, 60, 309-318.

Herrero, J., Laird, J. M. A., & Lopez-Garcia, J. A. (2000). Wind-up of spinal cord neurons and pain sensation: Much ado about something? Progress in Neurobiology, 61, 169-203.

Hoskins, B., Burton, C. K., & Ho, I. K. (1986). Differences in morphine-induced antinociception and locomotor activity in mature adult and aged mice. Pharmacology, Biochemistry, and Behavior, 25, 599-605.

Jones, D. A., Rollman, G. B., & Brooke, R. I. (1997). The cortisol response to psychological stress in temporomandibular dysfunction. Pain, 72, 171-182.

Kahana, B., Kahana, E., Namazi, K., Kercher, K., & Stange, K. (1997). The role of pain in the cascade from chronic illness to social disability and psychological distress in later life. In D. Mostofsky & J. Lomranz (Eds), Handbook of pain and aging (pp. 185-206). New York: Plenum Press.

Kakigi, R. (1994). Diffuse noxious inhibitory control. Reappraisal by pain-related somatosensory evoked potentials following CO2 laser stimulation. Journal of the Neurological Sciences, 125, 198-205.

Kang, D. H., & Fox, C. (2000). Neuroendocrine and leukocyte responses and pulmonary function to acute stressors. Annals of Behavioral Medicine, 22, 276-285.

Kee, W. G., Middaugh, S. J., Redpath, S., & Hargadon, R. (1998). Age as a factor in admission to chronic pain rehabilitation. The Clinical Journal of Pain, 14, 121-128.

Kenshalo, D. R. (1986). Somesthetic sensitivity in young and elderly humans. Journal of Gerontology, 41, 732-742.

Kirschbaum, C., & Hellhammer, D. H. (1989). Salivary cortisol in psychobiological research: An overview. Neuropsychobiology, 22, 150-169.

Kirschbaum, C., & Hellhammer, D.H. (1994). Salivary cortisol in psychoneuroendocrine research: Recent developments and applications. Psychoneuroendocrinology, 19, 313-333.

Ko, M. L., King, M. A., Gordon, T. L., & Crisp, T. (1997). The effects of aging on spinal neurochemistry in the rat. Brain Research Bulletin, 42, 95-98.

Kosek, E., & Hansson, P. (1997). Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. Pain, 70, 41-51.

Kosek, E., & Ordeberg, G. (2000). Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. Pain, 88, 69-78.

Kramer, E., & Bodnar, R. J. (1986a). Age-related decrements in morphine analgesia: aparametric analysis. Neurobiology of Aging, 7, 185-191.

Kramer, E., & Bodnar, R. J. (1986b). Age-related decrements in the analgesic response to cold water swims. Physiology and Behavior, 36, 875-880.

Kraus, E., Besson, J., & Le Bars, D. (1982). Behavioral model for diffuse noxious inhibitory controls (DNIC): Potentiation by 5-hydroxytryptophan. Brain Research, 231, 461-465.

Kraus, E., Le Bars, D., & Besson, J. (1981). Behavioral confirmation of "diffuse noxious inhibitory controls" (DNIC) and evidence for a role of endogenous opiates. Brain Research, 206, 495-499.

Lautenbacher, S., & Rollman, G. B. (1997). Possible deficiencies of pain modulation in fibromyalgia. The Clinical Journal of Pain, 13, 189-195.

Lautenbacher, S., Rollman, G. B., & McCain, G. A. (1994). Multi-method assessment of experimental and clinical pain in patients with fibromyalgia. Pain, 59, 45-53.

Lautenbacher, S., & Strian, F. (1991). Similarities in age differences in heat pain perception and thermal sensitivity. Functional Neurology, 6, 129-135.

Le Bars, D., Chitour, D., & Clot, A. M. (1981). The encoding of thermal stimuli by diffuse noxious inhibitory controls (DNIC). Brain Research, 230, 394-399.

Le Bars, D., Chitour, D., Kraus, E., Clot, A. M., Dickenson, A. H., & Besson, J. M. (1981a). Effect of naloxone upon diffuse noxious inhibitory controls (DNIC) in the rat. Brain Research, 204, 387-402.

Le Bars, D., Chitour, D., Kraus, E., Clot, A. M., Dickenson, A. H., & Besson, J. M. (1981b). The effects of systemic morphine upon diffuse noxious inhibitory controls (DNIC) in the rat: Evidence for a lifting of certain descending inhibitory controls of dorsal horn convergent neurons. Brain Research, 215, 257-274.

Le Bars, D., Dickenson, A. H., & Besson, J. M. (1979a). Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. Pain, 6, 283-304.

Le Bars, D., Dickenson, A. H., & Besson, J. M. (1979b). Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-convergent neurones, supraspinal involvement, and theoretical implication. Pain, 6, 305-327.

Le Bars, D., Guilbaud, G., Chitour, D., & Besson, J. M. (1980). Does systemic morphine increase descending inhibitory controls of dorsal horn neurons involved in nociception. Brain Research, 202, 233-244.

Le Bars, D., Willer, J. C., & De Brouker, T. (1992). Morphine blocks descending pain inhibitory controls in humans. Pain, 48, 13-20.

Lewis, J. L. (1986). Multiple neurochemical and hormonal mechanisms of stress-induced analgesia. Annals of the New York Academy of Sciences, 467, 194-204.

Li, J., Simone, D. A., & Larson, A. A. (1999). Wind-up leads to characteristics of central sensitization. Pain, 79, 75-82.

Lipton, R., Pfeffer, D., Newman, L., & Solomon, S. (1993). Headaches in the elderly. Journal of Pain Symptom Management, 8, 87-97.

MacLennan, A. J., Drugan, R. C., Hyson, R. L., Maier, S. F., Madden, J., & Barchas, J. D. (1982). Corticosterone: A critical factor in an opioid form of stress-induced analgesia. Science, 215, 1530-1532.

Maixner, W. (1991). Interactions between cardiovascular and pain modulatory systems: Physiological and pathophysiological implications. Journal of Cardiovascular Electrophysiology, 2, S2-12.

Maixner, W., Fillingim, R., Booker, D., & Sigurdsson, A. (1995). Sensitivity of patients with painful temporomandibular disorders to experimentally-evoked pain. Pain, 63, 341-351.

Maixner, W., Fillingim, R., Sigurdsson, A., Kincaid, S., & Silva, S. (1998). Sensitivity of patients with painful temporomandibular disorders to experimentally-evoked pain: Evidence for altered temporal summation of pain. Pain, 76, 71-81.

McCubbin, J., & Bruehl, S. (1994). Do endogenous opioids mediate the relationship between blood pressure and pain sensitivity in normotensives? Pain, 57, 63-67.

McDowell, I., & Newell, C. (1996). Measuring health: A guide to rating scales and questionnaires. New York: Oxford University Press.

Melzack, R. (1975). The McGill Pain Questionnaire: Major properties and scoring methods. Pain, 1, 277-299.

Melzack, R. (1999). From the gate to the neuromatrix. Pain, 84(Suppl. 6), S121-S126.

Mendell, L. M. (1966). Physiological properties of unmyelinated fiber projection to the spinal cord. Experimental Neurology, 16, 316-332.

Mense, S. (1991). Nociception from skeletal muscle in relation to clinical muscle pain. Pain, 54, 241-289.

Mense, S. (1995). Mechanisms of pain in hindlimb muscles: Experimental findings and open questions. In B. J. Sessle, P. S. Bryant, & R. A. Dionne (Eds), Temporomandibular disorders and related pain conditions (pp. 63-69). Seattle, WA: IASP Press.

Morgan, D. G. (1992). Neurochemical changes with aging: Predisposition toward age-related mental disorders. In J. E. Birren, R. B. Sloane, & G. D. Cohen (Eds), Handbook of mental health and aging (pp. 183-91). New York: Academic Press.

Morgan, D. G., & May, P. C. (1992). Age-related changes in synaptic neurochemistry. In E. L. Schneider, & J. W. Rowe (Eds), Handbook of the biology of aging (pp. 219-254). New York: Academic Press.

Morgan, D. G., May, P. C., & Finch, C. E. (1988). Neurotransmitter receptors in human aging and Alzheimer's disease. In A. K. Sen, & T. Lee (Eds), Receptors and ligands in neurological disorders (pp. 120-147). Cambridge, England: Cambridge University Press.

Morgan, M. M., Heinricher, M. M., & Fields, H. L. (1994). Inhibition and facilitation of different nocifensor reflexes by spatially remote noxious stimuli. Journal of Neurophysiology, 72, 1152-1160.

Morley, J. E., Flood, J. F., & Silver, A. J. (1990). Opioid peptides and aging. Annals of the New York Academy of Sciences, 579, 123-132.

Morton, C. R., Maisch, B., & Zimmerman, M. (1987). Diffuse noxious inhibitory controls of lumbar spinal neurons involve a supraspinal loop in the cat. Brain Research, 410, 347-352.

Mumford, J. M. (1965). Pain perception threshold and the adaptation of normal human teeth. Archives of Oral Biology, 10, 957-968.

Mumford, J. M. (1968). Pain perception in man on electrically stimulating the teeth. In A. Soulairac, J. Cahn, & J. Charpentier (Eds), Pain (pp. 224-229). London: Academic Press.

Mundt, K. A., Chambless, L. E., Burnham, C. B., & Heiss, G. (1992). Measuring ankle systolic blood pressure: Validation of the Dinamap 1846 SX. Angiology, 43, 555-566.

Naliboff, B. D., Cohen, M. J., Schandler, S. L., & Heinrich, R. (1980). Signal detection and threshold measurement for chronic back pain patients, chronic illness patients, and cohort controls. Radiant heat stimuli. Journal of Abnormal Psychology, 90, 56-60.

Neri, M., & Agazzani, E. (1984). Aging and right-left asymmetry in experimental pain measurement. Pain, 19, 43-48.

Noble, F., Fournie-Zaluski, M. C., & Roques, B. P. (1994). Paradoxical analgesia induced by low doses of naloxone is not potentiated by complete inhibition of enkephalin degradation. Neuropharmacology, 33, 135-140.

Novack, J. C., Lovell, J. A., Steusse, S. L., Cruce, W. L. R., McBurney, D. L., & Crisp, T. (1999). Aging and neuropathic pain. Brain Research, 833, 308-310.

Omerglu, H., Gunel, U., Bicimoglu, A., Tabak, A., Ucaner, A., & Guney, O. (1997). The relationship between the use of tourniquet and the intensity of postoperative pain in surgically treated malleolar fractures. Foot and Ankle International, 18, 798-802.

Osterweis, M., Kleinman, A., & Mechanic, D. (1987). Pain and disability: Clinical, behavioral, and public policy perspective. Washington, DC: National Academy Press.

Panteleo, T., Duranti, R., & Bellini, F. (1988). Effects of heterotopic ischemic pain on muscular pain threshold and blink reflex in humans. Neuroscience Letters, 85, 56-60.

Pertovaara, A., Kemppainen, P., Huopaniemi, T., & Johansson, G. (1987). Pain and stress: Correlation of stress hormone release to pain modulation in man. Annals of Clinical Research, 19, 83-86.

Pertovaara, A., Kemppainen, P., Johansson, G., & Karonen, S. (1982). Ischemic pain nonsegmentally produces a predominant reduction of pain and thermal sensitivity in man: A selective role for endogenous opioids. Brain Research, 251, 83-92.

Peters, M. L., & Schmidt, A. J. M. (1992). Differences in pain perception and sensory discrimination between chronic low back pain patients and healthy controls. Journal of Psychosomatic Research, 36, 47-53.

Peters, M. L., Schmidt, A. J. M., & Van Den Hout, M. A. (1989). Chronic low back pain and the reaction to repeated acute stimuli. Pain, 39, 69-76.

Pollard, T., Ungpakorn, G., & Harrison, G. A. (1992). Some determinants of population variation in cortisol levels in a British urban community. Journal of Biological Sciences, 24, 477-485.

Price, D. D., Hu, J. W., Dubner, R., & Gracely, R. H. (1977). Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. Pain, 3, 57-68.

Price, D. D., & McHaffie, J. G. (1988). Effects of heterotopic conditioning stimuli on first and second pain: A psychophysical evaluation in humans. Pain, 34, 245-252.

Procacci, P., Bozza, G., & Buzelli, G. (1970). The cutaneous pricking pain threshold in old age. Gerontologic Clinics, 12, 213-218.

Puder, R. S. (1988). Age analysis of cognitive-behavioral group therapy for chronic pain outpatients. Psychology and Aging, 3, 204-207.

Randich, A. (1993). Neural substrates of pain and analgesia. Arthritis Care and Research, 6, 171-177.

Rinne, J. O. (1987). Muscarinic and dopaminergic receptors in the aging human brain. Brain Research, 404, 162-168.

Roby-Brami, A., Bussel, B., Willer, J. C., & Le Bars, D. (1987). An electrophysiological investigation into the pain-relieving effects of heterotopic nociceptive stimuli. Brain, 110, 1497-1508.

Roy, R., & Thomas, M. (1986). A survey of chronic pain patients in an elderly population. Canadian Journal of Family Practice, 32, 513-516.

Schluderman, E., & Zubek, J. P. (1962). Effect of age on pain sensitivity. Perception and Motor Skills, 14, 295-301.

Schouenborg, J., & Dickenson, A. H. (1985). The effects of a distant noxious stimulation on A and C fiber evoked flexion reflexes and neuronal activity in the dorsal horn of the rat. Brain Research, 360, 23-32.

Schumacher, G. A., Goodell, H., & Hardy, J. D. (1940). Uniformity of the pain threshold in man. Science, 92, 110-112.

Scudds, R., & Robertson, J. (1998). Empirical evidence of the association between presence of musculoskeletal pain and physical disability in community-dwelling senior citizens. Pain, 75, 229-235.

Sherman, E. D., & Robillard, E. (1960). Sensitivity to pain in the aged. Canadian Medical Association Journal, 83, 944-947.

Siddall, P., & Cousins, M. (1995). Pain mechanisms and management: An update. Clinical and Experimental Pharmacology and Physiology, 22, 679-688.

Sigurdsson, A., & Maixner, W. (1994). Effects of experimental and clinical noxious counterirritants on pain perception. Pain, 57, 265-275.

Sternbach, R. A. (1986). Survey of pain in the United States: The Nuprin pain report. Clinical Journal of Pain, 2, 49-53.

Stevens, J., Cruz, A., Marks, L., & Lakatos, S. (1998). A multimodal assessment of sensory thresholds in aging. Journal of Gerontology, 53B, P263-272.

Sutton, L. C., Fleshner, M., Mazzeo, R., Maier, S. F., & Watkins, L. R. (1994). A permissive role of corticosterone in an opioid form of stress-induced analgesia: Blockade of opiate analgesia is not due to stress-induced hormone release. Brain Research, 663, 19-29.

Talbot, J. D., Duncan, G. H., & Bushnell, M. C. (1989). Effects of diffuse noxious inhibitory controls (DNICs) on the sensory-discriminative dimension of pain perception. Pain, 36, 231-238.

Talbot, J. D., Duncan, G. H., Bushnell, M. C., & Boyer, M. (1987). Diffuse noxious inhibitory controls (DNICs): Psychophysical evidence in man for intersegmental suppression of noxious heat perception by cold pressor pain. Pain, 30, 221-232.

Tucker, M. A., Andrew, M. F., & Ogle, S. J. (1989). Age-associated change in pain threshold measured by transcutaneous neuronal electrical stimulation. Age and Ageing, 18, 241-246.

Verkhratsky, N. S., Moroz, E. V., Magdich, S. O., & Kharazi, L. I. (1988). Steroid-hormone-secretion-regulating system in old age. Gerontology, 34, 41-47.

Vierck, C. J., Cannon, R. L., Fry, G., Maixner, W., & Whitsel, B. L. (1997). Characteristics of temporal summation of second pain sensations elicited by brief contact of glabrous skin by a preheated thermode. Journal of Neurophysiology, 78, 992-1002.

Villanueva, L., Bouhassira, D., & Le Bars, D. (1996). The medullary subnucleus reticularis dorsalis (SRD) as a key link in both the transmission and modulation of pain signals. Pain, 67, 231-240.

Villanueva, L., & Le Bars, D. (1985). The encoding of thermal stimuli applied to the tail of the rat by lowering the excitability of trigeminal convergent neurons. Brain Research, 330, 245-251.

Villanueva, L., & Le Bars, D. (1986). Indirect effects of intrathecal morphine upon diffuse noxious inhibitory controls (DNICs) in the rat. Pain, 26, 233-243.

Vogt, M. (1973). The effect of lowering the 5-hydroxytryptamine content of the rat spinal cord on analgesia produced by morphine. Journal of Physiology, 236, 483-498.

Walsh, N. E., Schoenfeld, L., & Ramamurthy, S. (1989). Normative model for cold pressor test. American Journal of Physical Medicine and Rehabilitation, 68, 6-11.

Ware, J. E. (1996). The SF-36 Health Survey. In I. McDowell, & C. Newell (Eds), Measuring health (pp. 446-456). New York: Oxford University Press.

Ware, J. E., & Sherbourne, C. D. (1992). The MOS 36-item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. Medical Care, 30, 473-483.

Washington, L. L., Gibson, S. J., & Helme, R. D. (2000). Age-related differences in the endogenous analgesic response to repeated cold water immersion in human volunteers. Pain, 89, 89-96.

Watanabe, S., Kakigi, R., Hoshiyama, M., Kitamura, Y., Koyama, S., & Shimojo, M. (1996). Effects of noxious cooling of the skin on pain perception in man. Journal of the Neurological Sciences, 135, 68-73.

Watkins, L., & Mayer, D. (1982). Organization of endogenous opiate and non-opiate pain control systems. Science, 216, 1185-1192.

Wigdor, S., & Wilcox, G. L. (1987). Central and systemic morphine-induced antinociception in mice: Contribution of descending serotonergic and noradrenergic pathways. Journal of Pharmacological and Experimental Therapeutics, 242, 90-95.

Wilkieson, C. A., Madhok, R., Hunter, J. A., & Capell, H. A. (1993). Toleration, side effects and efficacy of sulphasalazine in rheumatoid arthritis patients of different ages. Quarterly Journal of Medicine, 86, 501-505.

Willer, J. C., Barranquero, A., Kahn, M. F., & Salliere, D. (1987). Pain in sciatica depresses lower limb nociceptive reflexes to sural nerve stimulation. Journal of Neurology, Neurosurgery, and Psychiatry, 50, 1-5.

Willer, J. C., Bergeret, S., & Gaudy, J. H. (1985). Epidural morphine strongly depresses nociceptive flexion reflexes in patients with postoperative pain. Anesthesiology, 63, 675-680.

Willer, J. C., De Brouker, T., & Le Bars, D. (1989). Encoding of nociceptive thermal stimuli by diffuse noxious inhibitory controls in humans. Journal of Neurophysiology, 62, 1028-1038.

Willer, J. C., Le Bars, D., & De Brouker, T. (1990). Diffuse noxious inhibitory controls in man: Involvement of an opioidergic link. European Journal of Pharmacology, 182, 347-355.

Willer, J. C., Roby, A., & Le Bars, D. (1984). Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. Brian, 107, 1095-1112.

Witting, N., Svensson, P., Arendt-Nielsen, L., & Jensen, T. S. (1998). Differential effect of painful heterotopic stimulation on capsaicin-induced pain and allodynia. Brain Research, 801, 206-210.

Wolfe, F., Ross, K., Anderson, J., Russell, I. J., & Hebert, L. (1995). The prevalence and characteristics of fibromyalgia in the general population. Arthritis and Rheumatism, 38, 19-28.

Woodrow, K. M., Friedman, G. D., & Siegelaub, A. B. (1972). Pain tolerance: Differences according to age, sex, and race. Psychosomatic Medicine, 34, 548-556.

Wright, D., Barrow, S., Fisher, A. D., Horsley, S. D., & Jayson, M. I. V. (1995). Influence of physical, psychological, and behavioral factors on consultations for back pain. British Journal of Rheumatology, 34, 156-161.

Yaksh, T. L. (1999). Regulation of spinal nociceptive processing: Where we went when we wandered onto the path marked by the gate. Pain, 84(Suppl. 6), S149-S152.

Yehuda, S., & Carasso, R. (1997). A brief history of pain perception and pain tolerance in aging. In D. Mostofsky, & J. Lomranz (Eds), Handbook of pain and aging (pp. 19-34). New York: Plenum Press.

Yu, X. M., & Mense, S. (1990). Response properties and descending control of rat dorsal horn neurons with deep receptive fields. Neuroscience, 39, 823-831.

Zheng, Z., Gibson, S. J., Khalil, Z., Helme, R. D., & McMeeken, J. M. (2000). Age-related differences in the time course of capsaicin-induced hyperalgesia. Pain, 85, 51-58.

# APPENDIX

## APPROVAL FROM THE INSTITUTIONAL REVIEW BOARD

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Office of the Institutional Review Board for Human Use

Form 4 IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

The Institutional Review Board for Human Use (IRB) has an approved Multiple Project Assurance with the Department of Health and Human Services and is in compliance with 21 CFR Parts 50 and 56 and ICH GCP Guidelines. The Assurance became effective on January 1, 1999 and the approval period is for five years The Assurance number is M-1149, identification number 01.

| | |
|---|---|
| Principal Investigator: | FILLINGIM, ROGER B |
| Protocol Number: | **F990318004** |
| Protocol Title: | *Endogenous Opioid Modulation of Sensory Responses in Healthy Older and Younger Adults (Age-Associated Differences in Endogenous Pain Modulation)* |

The IRB reviewed and approved the above named project on 4 14 99 The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services This Project will be subject to Annual continuing review as provided in that Assurance

This project recieved FULL COMMITTEE review

IRB Approval Date: 4/14/99

Date IRB Approval Issued 04-29-99

Ferdinand Urthaler, MD
Ferdinand Urthaler, M D
Chairman of the Institutional Review Board
for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB

The University of Alabama at Birmingham
1120 Administration Building • 701 South 20th Street
Birmingham, Alabama 35294-0111 • (205) 934-3789 • FAX (205) 934-1301

**GRADUATE SCHOOL**
**UNIVERSITY OF ALABAMA AT BIRMINGHAM**
**DISSERTATION APPROVAL FORM**
**DOCTOR OF PHILOSOPHY**

**Name of Candidate** Robert R. Edwards

**Graduate Program** Psychology

**Title of Dissertation** Age-Associated Differences in Endogenous Pain Modulation: A Study of Diffuse Noxious Inhibitory Controls in Healthy Older and Younger Adults

**I certify that I have read this document and examined the student regarding its content. In my opinion, this dissertation conforms to acceptable standards of scholarly presentation and is adequate in scope and quality, and the attainments of this student are such that he may be recommended for the degree of Doctor of Philosophy.**

**Dissertation Committee:**

| Name | | Signature |
|---|---|---|
| J. Scott Richards | **Co-Chair** | |
| Roger B. Fillingim | **Co-Chair** | |
| Marion E. Broome | | |
| Timothy J. Ness | | |
| Alan Randich | | |

**Director of Graduate Program**

**Dean, UAB Graduate School**

**Date** 8/24/02