Published in final edited form as:

Pain. 2010 July ; 150(1): 153–160. doi:10.1016/j.pain.2010.04.020.

Lack of Endogenous Modulation but Enhanced Decay of Prolonged Heat Pain in Older Adults

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Abstract

This study supports the hypothesis that healthy older adults exhibit decreased endogenous pain inhibition compared to younger healthy controls. Twenty-two older adults (56–77 years of age) and 27 controls ages 20–49 participated in five experimental sessions following a training session. Each experimental session consisted of five 60-second trials in which the experimental heat stimulus was presented to the thenar eminence of the left palm with or without a conditioning stimulus (cold-water immersion of the foot). The temperature for the palm (44–49°C) and foot (8–16°C) were customized for each subject. The intensity of experimental pain produced by the contact thermode was continuously measured during the 60-second trial with an electronic visual analogue scale. No significant associations were found between subjects rating of concentration and the overall inhibitory effect. Older subjects failed to demonstrate conditioned pain modulation (CPM) and showed facilitation in the trials using painful concurrent immersion of the foot. A novel aspect of the study was that we recorded “*pain offset*” (i.e., after sensations) and found that ratings for the older sample decreased at a slower rate than observed for the group of younger adults suggesting increased central sensitization among the older sample. Decrements in CPM could contribute to the greater prevalence of pain in older age. Since a number of neurotransmitter systems are involved in pain modulation, it is possible age-related differences in CPM are due to functional changes in these systems in a number of areas within the neuroaxis.

Keywords

Pain modulation; Aging; Elderly; Diffuse Noxious Inhibitory Controls (DNIC); Conditioned pain Modulation (CPM)

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Disclosure statement.

There are no actual or potential conflicts of interest for any of the authors.

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Introduction

Aging is a dynamic process in which physiological and psychological components undergo alternations and compensations in function and structure, including components involved in pain sensation. In a review of the prevalence of chronic pain, Verhaak (61) concluded that chronic pain generally increased with age, with studies usually reporting peak prevalence between the ages of 45 and 65 years, depending on the pain condition. A study in Holland found that more than 50% of persons ages 65-years and older reported current pain and of these, more than half report pain in multiple sites (44). A more telling finding was that the acute/chronic pain ratio shifts more toward chronic pain with age (20).

One explanation for increased clinical pain in older populations is that aging is associated with greater sensitivity to painful stimuli. However, several reviews have reported an increase, a decrease or stability of pain thresholds associated with aging (21,22). Measures of pain sensitivity may not optimally characterize age-related changes in pain processing; therefore experimental methods designed to test changes in pain modulatory mechanisms need to be examined. Studies of dysfunction in the human pain response have begun to use laboratory protocols that involve pain inhibition (5,31,32,34,35,38,42,53,63,66). The phenomenon of diffuse noxious inhibitory controls (DNIC) implicates the existence of an endogenous pain modulation system in humans. The basic principle of DNIC is “pain-inhibition-by-pain” where pain in a local area (experimental stimulus) is inhibited by a second pain (conditioning stimulus) that can be anywhere else in the body (65). We use the term “conditioned pain modulation” (CPM) to refer to this phenomenon.

Three studies have reported reduced pain inhibition associated with age using protocols consistent with CPM. Washington et al., (62) found that the effects of cold-water immersion of the hand on subsequently tested pain threshold were significantly less in older adults compared with young adults. Another study by Edwards et al. (16) tested the effects of concurrent cold-water immersion of the hand on temporal summation. They reported that the older sample (ages 55–67) experienced facilitation rather than inhibition during some of the trials, while younger adults demonstrated the expected CPM effects. A third study by Lariviere et al. (37) found that increased thermal pain threshold during concurrent administration of a cold-water bath was diminished for both middle-aged and older groups. To date, only Edwards’ study has reported pain facilitation with CPM in older subjects. Although each of the above studies used short probing heat pulses, the dynamic nature of Edwards’ temporal summation protocol and longer overall duration paired with a concurrent conditioning stimulus may explain the findings.

The aim of this study was to test the hypothesis that older adults will fail to suppress the pain from noxious thermal stimuli administered during or following the immersion in a noxious cold-water bath whereas younger adults will demonstrate inhibition. This will also provide a test of whether older adults experience pain facilitation to concurrent and non-concurrent conditioning stimuli. In addition, we will test for age differences in “*pain offset*” (i.e., after sensations).

2. METHODS

2.1. Subjects

Forty-nine healthy subjects were recruited in a southeastern university town through newspaper and posted advertisements, or through a university affiliated Institute on Aging, subject recruitment pool. Subject and age group descriptors are presented in Table 1. The subjects were compensated at the rate of \$40 per session for their time.

Study exclusion criteria included the inability to reliably rate pain, current use of narcotics, chronic use of analgesics, current use of any tobacco products, uncontrolled hypertension, receiving treatment for hypertension with BP of greater than 140/95, serious systemic disease (e.g. diabetes, thyroid problems, etc.), neurological problems with significant changes in somatosensory and pain perception at the intended stimulation sites, cardiovascular or pulmonary disease, serious psychiatric conditions (e.g., schizophrenia, bipolar disorder), chronic pain (e.g., low back pain, postherpetic neuralgia), or any ongoing pain problem (headaches, arthritis, injury-related pain etc.). Subjects that were 72 years of age or older were administered the Mini Mental State Examination with scores of below 25 resulting in exclusion (14). Subjects refrained from use of coffee or any pain medications on the day of testing.

2.2. Study Procedures

2.2.1. Orientation and Training Session—Persons who expressed interest in participating in the study were provided a brief explanation of the general purpose and procedures of the study. If interested, they were informed about HIPAA regulations and reviewed and signed an Informed Consent Form to grant authorization for collection of health data needed to determine eligibility. Subjects then received a health assessment consisting of a health questionnaire, supplemented by clarification by interview and a blood pressure measurement. For subjects 72 years of age and older, the health assessment was supplemented by a brief neurological exam that included a 2 - point sensory test (33). Subjects were also administered the trait version of the State-Trait Anxiety Inventory (51).

Subjects then completed a training session to acquire the necessary pain rating skills and to determine the temperature of the stimuli for use in subsequent tests. The goal was to determine temperatures at which subject's experienced mild-to-moderate pain for both a 30-second heat stimulus (46–49°C) and for immersion for cold stimuli (8–16°C). The thermal training session consisted of series of 30-second trials at the volar forearm (rating practice) and the palm (determine temperature). To determine the thermode temperature for use in the experiments, the thermode temperature was set at 44°C for the first trial and increased across trials so that a stimulus response curve could be calculated. The temperatures were increased to a maximum pain rating of 40–50 (on a scale of 0–100). A similar procedure was performed at the foot using a recirculating cold-water bath set to 16°C for the first trial and decreased by 2°C per trial to a maximum pain rating of 20–30 upon a 20 second foot immersion. A rating of 20–30 was targeted to minimize any effect of distraction from the cold-water bath on pain ratings at the palm during concurrent trials. A maximum temperature of 49°C was used for heat and 8°C for cold. Subjects that fail to reach the target pain ratings were assigned 49°C for heat and 8°C for cold.

2.2.2. Testing Sessions—Subjects participated in five experimental sessions on different non-consecutive days following training. Upon arrival at the testing laboratory, subjects were seated on a comfortable chair and asked to relax for several minutes. Next, they were queried about their health, any medication use, and shown a video that described the procedure for that day. The testing began with taking two blood-pressure readings separated by 5 minutes. If there was a change of greater than 5%, subjects rested an additional 5 minutes and a third blood pressure measurement was taken. Each session consisted of five 60-second trials in which the experimental stimulus was presented to the thenar eminence of the left palm with or without the conditioning stimulus. Heat trials were separated by 3 minutes. Sessions were counterbalanced and consisted of the following protocol:

1. The focal heat stimulus to the left palm without conditioning stimulus (i.e., no water bath session; *NoB*)

2. The focal heat stimulus with concurrent neutral temperature water bath set at 23°C (*NeutralC*).
3. The focal heat stimulus with concurrent noxious cold-water immersion as a conditioning stimulus using the individualized temperature (*NoxC*).
4. The focal heat stimulus was alternated with 45-second cold-water immersions using the individualized temperature (*ALT*). The order was cold-heat, cold-heat, etc, with each heat stimulus following the paired cold-water immersion by approximately 20 seconds. As with the other sessions, heat trials were separated by 3 minutes.
5. The focal heat stimulus was preceded with five 45-second cold-water immersions separated by a 15-second withdrawal period as the conditioning stimulus (*PRIMED*).

2.2.3. Experimental stimulus (painful thermal contact)—Focal thermal stimuli (44–49°C) were administered by a Peltier-based thermode (23mm × 23mm). For each 60-second trial, the thermode was brought to a neutral temperature (33°C), and then brought into light skin contact with a solenoid. After a short period, the temperature was ramped (1.5°C/s) to the desired temperature. After 30 seconds, the thermode remained in contact with the skin but was cooled back to 33°C for the remainder of the 60 seconds. Subjects rated pain throughout the 60 seconds of thermode contact. Subsequent trials used widely spaced thermal pulses (3-minute inter-stimulus interval) to minimize sensitization.

2.2.4. Conditioning Stimulus (Water Immersion)—Cold-water immersion was used as the conditioning stimulus. The water bath was cooled by a refrigerated water circulator (Neslab, Portsmouth, NH). Water flow was maintained at a constant temperature throughout the water bath and constantly recirculated to prevent local warming or cooling around the foot. Subjects were instructed to immerse their foot to the ankle in water set at a neutral temperature (23°C) or a tailored noxious cold temperature (8–16°C). The water level was set at a height of 7 cm in order to keep the stimulated area consistent.

2.3. Pain Measures

The intensity of experimental pain produced by the contact thermode was continuously measured during the 60-second trial with an electronic visual analogue scale (eVAS). As described in Rodrigues et al. (49) and King et al. (34), the eVAS consisted of a low-friction sliding potentiometer (100mm travel) mounted to an inclined desk. Two anchors were provided for the scale: the left and right endpoints designated as ‘no pain’ and ‘most intense pain imaginable’ respectively. Subjects were instructed to move the slider in proportion to their pain intensity in real time. The position of the slider (i.e., pain intensity ratings) was automatically converted into a percentage (0–100%). A custom-built computer program collected data related to temperature (set and actual) and pain ratings. At the end of the trial, the slider automatically returned to the left endpoint (‘no pain’). Continuous ratings of heat pain provided a temporal profile of pain intensity over the trial duration.

2.4. Psychological measures

2.4.1. State Trait Anxiety Inventory—The STAI (51) has extensive normative data and is a frequent measure of anxiety in pain studies. The State-Anxiety subscale consists of 20 items that evaluate how respondents feel “right now” at this moment. The STAI has high internal consistency and can discriminate between different levels of anxiety.

2.4.2. Mini-Mental State Examination—The Mini-Mental State Examination (MMSE; 19) is a five-minute screening test that is designed to evaluate basic mental function in a person's ability to recall facts, to write and to calculate numbers. Cognitive performance as measured by the MMSE varies within the population by age and educational level. There is an inverse relationship between MMSE scores and age, ranging from a median of 29 for those 18 to 24 years of age, to 25 for individuals 80 years of age and older. A score of 25/30 or greater is considered to be within-normal limits (14).

2.4.3. Concentration—After the final trial, subjects rated their ability to concentrate on the heat applied to their palm using a scale from 0 (unable to concentrate) to 10 (total concentration).

2.5. Data analysis

The dependent variables were area under the curve (AUC) and mean peak pain ratings (PPR) collapsed across the five thermal trials for each session. The highest rating obtained during each 30-second stimulation period was categorized as the PPR for that trial. AUC for each trial was calculated by summing the recorded pain rating for each of the first 30 seconds of the trial and dividing by 30. As the thermode began cooling after 30-seconds, we defined a measure of "*pain offset*" as the pain rating from seconds 31 to 40.

The general linear model module of SPSS was used for statistical analysis. The study hypotheses about age and session differences in pain ratings were tested with a series of 2×3 mixed model analysis of variance (ANOVA). The between subject variable was group (older and younger adults) and the within subject variable was session (three). The non-water bath (*NoB*), thermode only condition served as the control trial for the alternating (*ALT*) and primed (*PRIMED*) experimental sessions and the concurrent 23.0°C immersion (*NeutralC*) served as the control for the concurrent noxious immersion session (*NoxC*). The *NoB* data was also included in the concurrent model analyses for comparison purposes. The models also included gender and thermode temperature as covariates.

To examine age differences in pain offset, we used a 2×10 mixed model ANOVA. The between subject variable was group and the within subject variable was time. The time variable consisted of pain ratings for seconds 31–40 (beginning with thermode cooling) collapsed across the 5 trials of the *NoB* session. The *NoB* session was used to eliminate any effects of the water bath. The model also included gender and thermode temperature as covariates.

3. RESULTS

3.1. Baseline Characteristics

For the contact heat, a one way-ANOVA revealed that temperatures required to produce a pain rating between 40–50 eVAS during the training session approached but did not reach statistical significance between the two groups (Table 1; $p = .079$). However, no significant difference was observed in the individualized foot immersion temperature among the groups. As expected, there was a significant negative association between individualized hand and foot temperature ($r = -.43$, $p = .002$).

There were no differences between groups on baseline anxiety as measured by the STAI-S, systolic (SBP) or diastolic (DBP) blood pressure, or skin temperature and the neck or palm. Associations between baseline DBP and the individualized hand temperature were significant ($r = .3$, $p = .04$). However, no association was found between DBP and foot temperature or between SBP and hand or foot temperature.

3.2. Inhibitory Effects and Potential Confounds

No significant associations were found between subjects rating of concentration and the overall inhibitory effect (calculated as mean AUC and PPR for each experimental session – the corresponding control session). Correlations ranged from $r = .16$ for the AUC from the *PRIMED* session to $r = -.16$ for the AUC from the *ALT* session. The association between subjects rating of concentration and AUC for pain during trials 31–40 (pain offset) after the thermode was cooling was not significant ($r = .24$).

Rating of concentration was not significantly associated with the individualized cold-water bath temperature and ranged from $r = .11$ for the *PRIMED* session to $r = -.16$ for the control bath session. However, concentration ratings were associated with the thermode temperature for the *PRIMED* session ($r = .32$, $p = .04$) and a trend was observed for the *ALT* session ($r = .30$, $p = .06$), consequently hand temperature was included as a covariate in the ANOVA models. The groups were not different on AUC [$F(1, 45) = 2.105$, $p = .154$] or PPR [$F(1, 45) = 2.074$, $p = .157$] in the NoB sessions.

3.3. Non-Concurrent Experimental Protocols

Continuous ratings during the non-concurrent trials for each session, collapsed across the five trials, are presented in Figure 1A for the younger group and Figure 1B for the older group. Across all groups and sessions, pain ratings exhibited an early phase of rapid temporal sensitization (0–15 seconds) followed by a phase of adaptation (15–25 seconds) and a second sensitization phase (25–30 seconds). The testing phase from 31–40 seconds represents a residual pain offset as the temperature of the thermode was returning to baseline of 33C.

3.3.1. Area Under Curve—Group and session main effects were not significant. The session $\times$ group interaction term was statistically significant [$F(2, 90) = 6.155$, $p = .004$] indicating that the AUC session effect differed as a function of group (see Figure 2A). Pair-wise comparisons within group indicated that the mean AUC for the *NoB* session (17.9, SD = 6.6) was significantly different than the *ALT* (11.9, SD = 7.7) and *PRIMED* (13.9, SD = 8.1) experimental sessions for the younger group. However, for the older group, there were no differences between the mean AUC for the *NoB* session (15.0, SD = 6.9), the *ALT* session (14.3, SD = 7.7) or the *PRIMED* session (14.7, SD = 8.1).

3.3.2. Peak Pain Rating—Group and session main effects were not significant. The session $\times$ group interaction term was statistically significant [$F(2, 90) = 8.971$, $p < .001$] indicating that the PPR session effect differed as a function of group (see Figure 2B). Pair-wise comparisons within group indicated that the adjusted mean PPR for the *NoB* session (32.4, SD = 10.7) was significantly different than the *ALT* (21.8, SD = 11.0) and *PRIMED* (25.0, SD = 11.4) experimental sessions for the younger group. However, for the older group, there were no differences between the adjusted mean PPR for the *NoB* session (27.8, SD = 10.4), the *ALT* session (26.8, SD = 10.8) or the *PRIMED* session (26.3, SD = 11.2).

3.4. Concurrent Experimental Protocols

Two of the younger subjects did not complete one of the concurrent protocols; consequently data from 25 younger and 22 older adults are reported. Continuous ratings during the concurrent trials for each session, collapsed across the five trials, are presented in Figure 3A for the younger group and Figure 3B for the older group. The profiles for the concurrent trials were similar to those from the non-concurrent trials.

3.4.1. Area Under Curve—Group and session main effects were not significant. The session $\times$ group interaction term was statistically significant [$F(2, 90) = 6.727$, $p = .003$]

indicating that the AUC session effect differed as a function of group (see Figure 4A). Pair-wise comparisons within group indicated that the mean AUC differed across all three sessions (*NoB*, 17.9, SD = 6.8; *NeutralC*, 15.0, SD = 8.2; and *NoxC*, 11.9, SD = 7.2.) for the younger group. However, for the older group, there were no differences between the mean AUC for the *NoB* session (15.0, SD = 6.5), the *NeutralC* session (13.5, SD = 7.8), and *NoxC* session (15.7, SD = 6.9).

3.4.2. Peak Pain Rating—Group and session main effects were not significant. The session x group interaction term was statistically significant [$F(2, 90) = 8.513, p = .001$] indicating that the PPR session effect differed as a function of group (see Figure 4B). Pair-wise comparisons within group indicated that the adjusted mean PPR for the *NoB* session (32.0, SD = 10.7) was different from the *NeutralC* session (25.2, SD = 11.7) and *NoxC* session (22.6, SD = 11.2) for the younger group. However, the PPR for the *NeutralC* and *NoxC* sessions were not different ($p > .05$). For the older group, there were no differences between the mean AUC for the *NoB* session (27.6, SD = 10.4), the *NeutralC* session (25.2, SD = 11.3), and *NoxC* session (28.6, SD = 10.8).

3.4.3. Post-hoc Analysis—Based on our planned analyses, we concluded that there were no age differences in pain inhibition as measured by PPR during the *NoxC* session compared to the *NeutralC* session (the concurrent control session), as they were not different for either group. However, we tested this explicitly by calculating a PPR inhibition score (*NeutralC* – *NoxC*) and testing for group differences using ANOVA, continuing to make adjustments for sex and thermode temperature. Group differences were statistically significant [$F(1,45) = 6.882, p = .012$], with the younger group experiencing pain inhibition (adjusted mean = 3.1, SD = 8.0) and the older group experiencing enhancement of pain (adjusted mean = -3.3, SD = 7.9).

3.5. Pain Off-set Effects

Pain ratings for the *NoB* session for time 31–40, as the thermode was cooled back to 33°C, for both groups is presented in Figure 5. As expected the time main effect was statistically significant [$F(9,405) = 63.054, p < .001$]. In addition, the group x time interaction term was statistically significant [$F(9,405) = 3.711, p = .011$]. Pair-wise comparisons between groups indicated that the mean pain rating was higher for the younger group for time 31–33; however the mean pain rating was higher for the older group for time 37–40. Entering the mean peak as a covariate, the differences at time 31–33 are no longer different, but the effects for time 37–40 remain significant indicating that older adults have greater pain after-sensation following stimulus offset than younger adults. A similar conclusion was reached when a carry-over percentage was calculated as the percentage decline from 31-second rating to 39-second rating (e.g. 31-sec = 40 eVAS and 39-sec = 10 eVAS) represents a 75% decrease. The younger group experienced a reduction of 94% (SD = 14) whereas the older group experienced a reduction of 78% (SD = 30).

4. DISCUSSION

The results of this study support the hypothesis that healthy older adults exhibit decreased endogenous pain inhibition compared to young healthy controls. We found that older subjects failed to demonstrate pain reduction with a painful conditioning stimulus and showed facilitation in the trials using a painful concurrent immersion of the foot in a cold-water bath. A number of studies have reported a reduction or absence of endogenous pain inhibition among older subjects using experimental pain paradigms which activate CPM using brief stimuli (16,37,62). These assessments of DNIC-like responses in humans have been tested either during concurrent or alternating administration of both stimuli. However,

this report is the first to compare the influences of both concurrent and non-concurrent conditioning stimulus. An additional novel aspect of the study was that we recorded *pain offset* and found that ratings for the older sample decreased at a slower rate than observed for the group of younger adults suggesting decreased inhibition and/or increased sensitization among the older sample.

4.1. Age Differences in Conditioned Pain Modulation

Reduction of CPM associated with age has been proposed to be due to changes in several descending inhibitory systems, that could contribute to the greater prevalence of pain in older age (22). Since a number of neurotransmitter systems are involved in pain modulation, it is possible age-related differences in CPM are due to functional changes at different levels of the neuroaxis. Evidence supporting this hypothesis is mainly observed in animal studies, where aging is associated with reductions in neuronally- and hormonally-mediated opioid and non-opioid pain modulation systems, (4,25,26,27). A functional consequence of the impairment is characterized by the observation of age-related decrease in β -endorphin (7). β -endorphin is a key biological mediator released during times of stress and pain (30,64). Consequently, reduced efficacy of pain modulation with age could be associated with decrements of β -endorphin at rest or response to painful stimulation.

One possibility is that the cold immersion procedure traditionally has been used to evaluate physiological responses to stress (29,40,43). The “pressor” response is often characterized by changes in cardiovascular systems (1,56), the activation of the autonomic nervous system (40,41,57), and hypothalamic-pituitary-adrenal (HPA) axis (36,60). Since cold immersion may engage systems related to stress-induced analgesia, it is possible that decreased pain inhibition with advancing age is due to reduced SIA. Using a CPM paradigm, younger participants often report higher levels of stress and distraction associated with cold-water immersion compared to the older group (16). We did not assess the level of stress produced by the water bath.

It is interesting that we found apparent inhibition during the *NeutralC* trials in comparison to the *NoB* condition for the younger cohort but not for the older cohort. Latuenbacher and colleagues have also reported that a strong but not subjectively painful conditioning stimulus can produce pain inhibition in healthy controls, but not for fibromyalgia patients. (38,39). If this effect involves a similar mechanism as CPM, this further supports loss of endogenous modulation in older adults.

4.2. Pain Offset

The observation that the older cohort reported lingering pain during a reduction of thermode temperature is new. Whether or not this observation is related to after-sensations requires further investigation. There are a number of studies that have documented the phenomenon of after-sensations following temporal summation in chronic pain patients (23,48,50,52,54) and following application of capsaicin (68,69). In these studies, the authors have speculated that after-sensations following dynamic experimental pain manipulations reflect central sensitization (CS). The observation of CS in psychophysical experiments is associated with neuroplastic changes in neuronal cell activity particularly in second order neurons of the spinal and trigeminal dorsal horn (12,45). Prolonged after-discharges in second order neurons may also be involved in after-sensation (15). One question to be asked is if the observation of a longer pain off-set in older adults is related to the maintenance of temporal summation due to CS. It is possible that the aging nervous system undergoes changes resulting in enhancement of neuronal hyperexcitability, which could increase the central processing of noxious input and reduce the resolution of CS. Another possibility is that this effect is related to decreased inhibition associated with CPM in the older adults.

4.3. Facilitation for Older Adult in the Concurrent Condition

While most CPM studies report a reduction in pain sensitivity in the presence of a conditioning stimulus, two other studies have reported an enhancement of pain responses, both using concurrent administration of the testing and conditioning stimuli (16,34). It is possible that facilitation might be dependent on the temporal presentation of the stimuli (i.e., favoring concurrent) and more dynamic testing stimuli (i.e., changes in pain sensitivity). For example, Lariviere et al. (37) assessed thermal pain thresholds, which might not engage mechanisms underlying facilitation. An additional explanation could be that older subjects are less able to process multiple noxious stimuli simultaneously. Thus, with a concurrent paradigm, older subjects cannot subjectively separate the stimuli, possibly due to cognitive overload. Since each study utilizes a different methodology, further research is needed to evaluate the relevance and repeatability of this observation before any real conclusions can be generated; however, our data suggest that this facilitatory response emerges only with concurrent stimulation.

4.4. Methodological Issues

Since attention has been shown to influence the perception of experimental pain (2,48,58,59) and CPM (39,53), we assessed the possibility that the level of attention could be related to the magnitude of pain suppression. Based on ratings of concentration following the experimental procedure, no age-related differences were observed in subject's ability to accurately rate the intensity of heat pain at their palm during sessions with or without a water bath.

A potential limitation is that older subjects had lower overall pain ratings. The older group may have exhibited less CMP because of lower pain; however, the differences in inhibition were not proportional to differences in pain ratings. In addition, it would not explain the increased pain for the *NoxC* condition. As they received the same training session as younger subjects, we can only speculate why this occurred. The older subjects may have sensitized more than younger subjects during the longer training session, appearing to need a lower temperature to reach a peak of 40–50. Thus, once experimental sessions were started, the chosen temperature and subsequent pain ratings were lower. Another possibility is inhibition over multiple testing sessions and desensitization across testing days has been reported (3,47), but post-hoc analysis did not support this. Older subjects may have been more sensitive throughout the training session due to anxiety, but there were no group differences in anxiety scores or autonomic measures.

We administered thermal stimuli to the palm because of the increased presence of C-fibers and enhanced sensitivity at the thenar eminence (24,55). There is evidence that age may have a differential effect on A-delta and C-fiber response. As a result, older subjects may employ C-fiber mediated sensations to a greater extent than those transmitted by A-delta fibers (8,28). In addition, activity of C-nociceptors are implicated in transmission of late pain sensations (14), the sensation of burning (6,11,67), prevalence of chronic pain (46,54), and interact with certain inflammatory signals (9,10).

4.5. Clinical Implications

Increasing evidence indicates that laboratory pain responses are associated with clinical pain (17), and some evidence suggests that deficiencies in pain inhibition may be particularly predictive of clinical pain. For example, using a concurrent CPM paradigm, Edwards et al (16) found that better pain inhibition was associated with less pain, better physical functioning, and better self-rated health in a sample of healthy younger and older adults. Data from clinical samples further supports the clinical relevance of laboratory measures of CPM. Patients with painful osteoarthritis showed significantly poorer pain inhibition

compared to healthy controls upon initial testing; however, after their arthritis pain had been successfully treated surgically, their inhibitory responses were normalized (35). Recently, Yartnitsky and colleagues (66) reported that laboratory CPM measures, but not other measures of experimental pain, predicted risk for developing chronic pain following thoracotomy. Patients exhibiting strong inhibition of stimulus induced pain pre-operatively, were at significantly lower risk of experiencing chronic pain after surgery. Given these previous findings, it seems plausible that the reduced pain inhibition in older adults may be associated with age-related increases in the frequency and intensity of clinical pain. Additional research is needed to directly address this possibility.

4.6. Summary and Conclusion

In summary, the present findings extend previous research investigating CPM among older adults using continuously-rated, sustained thermal pain stimuli as well as both concurrent and alternating application of cold water as the conditioning stimulus. Specifically, we report that older adults show deficiencies in endogenous pain inhibition assessed with both concurrent and non-concurrent testing protocols. Moreover, we showed that older adults exhibit pain facilitation with a concurrent noxious stimulus, but not with an alternating stimulus. In addition, under baseline conditions, older adults showed slower thermal pain offset, which may be similar to prolonged after-sensations (50,53). The mechanisms underlying these results, as well as their clinical relevance merit additional investigation.

Acknowledgments

This research was supported by a University of Florida College of Dentistry Seed Grant, NIH-NIDCR grant T32 DE007200, NIH/NIA grant AG033906, and the UF Comprehensive Center for Pain Research.

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Figure 1.

Temporal profile of continuous ratings during the non-concurrent sessions with trials without the water bath (*NoB*, asterisk) or with a 45-second cold-water immersion of the foot, which was either presented prior to (*PRIMED*, open circle) or alternated with (*ALT*, closed circle) the focal heat stimulus. Intensity of heat pain at the palm was averaged across the five thermal trials for (a) younger and (b) older subjects.

Figure 2.

Comparison of non-concurrent conditioning stimuli on focal heat pain in younger and older adults. Subjects rated heat pain without a water bath (*NoB*, open bar) or after immersion of their foot into a painfully cold-water bath. For the CPM sessions, subjects either repeatedly immersed their foot for five times followed by heat pain (*PRIMED*, gray bar) or alternated foot immersion with the heat stimulus (*ALT*, darkened bar). AUC (A) and peak pain ratings (B) of heat pain were recorded during a 30-second testing trial.

Figure 3.

Temporal profile of continuous ratings during the concurrent sessions with trials without the water bath (*NoB*, asterisk) or with a concurrent 45-second water immersion of the foot at 23°C (*NeutralC*, open circle) or painfully cold (*NoxC*, closed circle) water. Intensity of heat pain at the palm was averaged across the five thermal trials for (a) younger and (b) older subjects.

Figure 4.

Comparison of concurrent conditioning stimuli on focal heat pain in younger and older adults. Subjects rated heat pain without a water bath (*NoB*, open bar) or during immersion of their foot into 23°C (*NeutralC*, darkened bar) or painfully cold (*NoxC*, gray bar) water. AUC (A) and peak pain ratings (B) of heat pain were recorded during a 30-second testing trial.

Figure 5.

For the *NoB* session, temporal profile of continuous ratings following cooling of the thermode to the resting baseline temperature of 33.0°C for younger (open circle) and older adults (closed circle). Ratings were obtained 10 seconds following the 30-second heat trial. Older adults reported pain longer than younger adults during this period, which might serve as a measure of “pain offset.”

Table 1

Subject and age group descriptors.

	Younger group N = 27	Older group N = 22	P-value
Age (mean, SD)	25.3 (8.8)	65.2 (6.9)	
Age (range)	20–49	56–77	
Gender (% female, n)	63% (n=17)	59% (n=18)	>.05
STAI (mean, SD)	22.9 (1.7)	23.6 (1.9)	>.05
Heat Stimulus temperature	47.8(1.2)	47.2 (1.0)	>.05
Cold Water temperature	11.4 (2.2)	11.2(3.1)	>.05
Baseline systolic blood pressure ^a	112.7(13.9)	118.0 (11.2)	>.05
Baseline diastolic blood pressure ^a	75.6 (6.9)	74.4 (8.4)	>.05
Concentration rating – no bath ^b	8.7 (1.5)	9.2(1.1)	>.05
Concentration rating – neutral bath ^b	9.0(1.1)	8.9 (1.4)	>.05
Concentration rating – concurrent noxious bath ^b	8.8(1.1)	9.0(1.1)	>.05
Concentration rating – alternating bath ^b	9.1(1.4)	9.0 (1.8)	>.05
Concentration rating – primed bath ^b	9.3 (0.8)	9.1(1.3)	>.05

^aBlood pressure was the final stabilized pre-testing reading averaged across all sessions.

^bConcentration rating and skin temperature data was not available on 5 younger and 1 older subjects