Summation of Second Pain in Relation to Age

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Background. Thermal stimuli delivered to skin of the arms or legs can produce a sensation of two distinct pains. These pains have been associated with activity in A-delta (first pain) and C-fiber (second pain) nociceptive fibers, respectively. Under appropriate conditions first pain decreases in intensity (adaptation) while second pain increases in intensity (slow temporal summation). Change in first and second pain to repeated stimulation of skin has not been assessed in relation to age.

Methods. Ten younger (M = 25 years) and ten older (M = 65 years) subjects participated in a study of first and second pain intensity elicited by nociceptive range heat pulses (.7 second pulses; adapting temperature 39 °C to a stimulus temperature of 51 °C) delivered to skin of arms and legs. Response times to sensations of first and second pain were assessed to provide evidence that subjects were responding to first and second pain.

Results. Age groups did not differ on pain intensity ratings of initial stimuli to previously unstimulated skin for either first or second pain. Older subjects failed to evidence slow temporal summation of second pain at the leg. Response times to first, but not second pain from the leg were delayed in the elderly. Response times to first and second pain at the arm did not differ with age. Auditory response times were slower in the older group.

Conclusions. Age did not influence pain intensity to unadapted and unsensitized skin. Slow temporal summation of second pain was not observed at the leg in the older group, suggesting that mechanisms subserving C-fiber mediated sensitization of second order nociceptive neurons may fail with age. Longer response times to first, but not second pain in older subjects may represent an age effect on myelinated (A-delta; first pain) and not unmyelinated (C-fiber; second pain) nociceptive afferents and may represent a type of small fiber peripheral neuropathy.

NOXIOUS heat delivered to skin can result in a double sensation of pain (1-5). The first is a brief, well localized, sharp or pricking-pain sensation which seldom outlasts the stimulus. In physiological studies, first or pricking pain sensation has been associated with activity in A-delta polymodal nociceptors (1,2). These A-delta nociceptors are small (1 to 5 μm), lightly myelinated fibers with a conduction velocity of 10 to 30 meters per second (6).

Under appropriate conditions, first pain is followed after a brief (.4 to 1 second) painless period by a second pain (1-5). This second pain is a diffuse, burning sensation that often outlasts the stimulus. It is associated with afferent activity in "slow nociceptive" neurons (6) or C-fibers. This class of nociceptors consists of very small (.05 to 2 μm) unmyelinated fibers which have a conduction velocity of 0.5 to 2 meters per second (6).

First and second pains differ not only in the quality of their sensations but also in their intensity as a function of repeated or continuous stimulation. The intensity of first pain to heat stimuli delivered to the same spot on forearm or lower leg decreases with repeated stimulation (3-5). This adaptation of the subjective intensity of first pain is paralleled by decreased primary afferent activity as well as decreased activity in second order nociceptive neurons in the dorsal horn of the spinal cord (3-5). The subjective intensity of second pain, in contrast, increases to repeated stimuli which have a short (<3 seconds) interstimulus interval (2-5). This increase in second pain intensity has been termed slow temporal summation (3) and is related to hyperalgesia following tissue injury (2). Slow temporal summation of second pain to brief heat pulses delivered to skin has been associated with long-latency discharges of dorsal horn neurons in response to repetitive C-fiber nociceptor activity (2-5).

Studies of age differences in pain perception involving different forms of laboratory stimuli have yielded various results, some showing decreased pain sensitivity, others increased pain sensitivity, and some indicating no age differences (7-9). In studies involving heat stimulation of skin, a majority of the studies report either no or at best very minor age effects (see 7-9 for recent reviews). None of these studies, however, has explicitly recognized that the thermal pain experience involves two distinct pain sensations: first and second pain.

The objectives of the present study were to determine if age affects: (a) intensity ratings of first or second pain; (b) adaptation of first pain; or (c) temporal summation of second pain. Response times were collected to provide evidence that subjects were responding selectively to first and second pain.
Since response times to painful stimuli may not slow with age (10,11), we also evaluated age effects on response times to first and second pain.

METHODS

Subjects. — Subjects consisted of a younger (n = 10, M = 25.6 years; SD = 4.2; range 21–34) and older (n = 10, M = 64.7, SD = 8.5; range 53–75 years) group of community-dwelling volunteers. Subjects did not differ in height (younger: mean height 69.6 inches; older: mean height 67.6 inches). Subjects were screened for use of medications that might influence pain, metabolic disease (e.g., diabetes), peripheral neuropathy, use of recreational drugs, alcohol abuse, and/or affective disorder.

Subjects were fully informed of their rights, signed an institution-approved informed consent form, and were assured that they could end their participation at any time without prejudice. None chose to terminate the experiment.

Stimulation and recording procedures. — Nociceptive range heat stimuli were delivered to the ventral forearm and the ankle region by a hand-held contact thermode (.81 cm surface area). The thermode design has been described previously (12). A similar device has been employed successfully to evaluate age differences in pain intensity ratings to stimuli ranging from 43 to 51 °C without attention to the differences between first and second pain (13).

Stimuli were delivered, under computer control, from an adapting temperature of 39 °C to a peak temperature of 51 °C. The rise time of the heat pulse was approximately 26.7 °C/second. Subjects were able to walk the limb at any time from the contact surface; none did.

Visual analogue scales (VASs) were employed to measure pain sensation intensity. VASs consisted of 150 mm lines with endpoints labeled NO SENSATION and THE MOST INTENSE SENSATION IMAGINABLE. Similar VASs have been validated as ratio level measures of pain and have been shown to be internally consistent measures of clinical and experimental pain (13–16).

Response times to each type of pain were assessed to provide assurance that first and second pain were indeed being evaluated. Response times were also collected to a non-noxious auditory stimulus using a simple, unsignaled auditory reaction time procedure.

The auditory reaction times served as a control procedure, since reaction times to non-noxious auditory stimuli are known to slow with age and this may not hold for painful stimuli (10,11). In previous studies showing no slowing with age to painful stimuli (10,11), no nonpainful, control stimulus was employed and it is possible that the failure to find an age effect on response times to painful stimuli might result from the subjects employed.

The auditory reaction time procedure consisted of randomly presented tones (2000 Hz; 75dB SL; .5 sec duration) over a loudspeaker placed in front of the subject. Subjects were instructed to press the response key as soon as possible after the onset of the tone. Response times were measured by computer (0.5 millisecond error). Tones were randomly presented with an interstimulus interval of 15 seconds.

Response times to the tone were based on 10 trials. In the main portion of the study, identical tones served as a warning stimulus to signal the onset of each train of heat pulses (fixed interval of .3 seconds).

Procedure. — Baseline and training sessions began by familiarizing subjects with the laboratory, purpose of the study, collection of auditory response times, and training with use of pain intensity VAS ratings. Pain tolerance was assessed, and it was determined that the target heat pulse setting of 51 °C was within tolerance for all subjects.

Subjects were informed that the heat pulses might provoke a double pain sensation. They were asked to describe in detail the sensations felt to heat pulses during the baseline procedure. Upon describing a sharp pain followed by a diffuse burning pain, they were told that the first sensation represented one type of pain and the second represented another. They were requested to focus closely on these two distinct sensations and were given practice stimuli until they reported they were confident in their ability to distinguish first and second pains. All subjects were able to distinguish first and second pain.

The intensities of first and second pain are strongly and differently influenced by stimulus history (2–5). Under appropriate procedures the intensity of first pain decreases and that of second pain increases to repeated heat pulses delivered to the same location on the hand or the foot. These changes in subjective intensity of first and second pain are dependent upon the interstimulus interval between successive pulses delivered to the same location. First pain shows a reduction in magnitude for interstimulus intervals up to 80 seconds, and second pain shows slow temporal summation when the interstimulus interval is less than 3 seconds (5).

Therefore we chose interstimulus intervals of 5 seconds for the study of adaptation of first pain and 2.5 seconds for the study of temporal summation of second pain. Stimuli in both conditions consisted of .7 second heat pulses from an adapting temperature of 39 °C to 51 °C with a rise time of approximately 27 °C/second. First pain was studied before second pain because of the long-term adaptation properties of first pain (3). Stimulation of arms and legs was counterbalanced. Previous pain VAS intensity ratings were not available to the subject.

First pain procedure. — Heat pulses were delivered in trains of 1 to 5 pulses (interstimulus interval 5 sec) to a spot on the distal portion of the forearm and leg. The probe was moved between trains of pulses and the same spot was not restimulated. Because of possible differential effects of task demands on older compared to younger subjects, subjects were instructed to rate pain intensity for only the final stimulus in each stimulus train. Response times were collected for each heat pulse. Each train of stimuli (1 to 5 heat pulses) was delivered four times to both arm and leg in counterbalanced order.

Second pain procedure. — The procedure for study of second pain was identical to that employed for first pain, with the exception that the interpulse interval between stimuli in each train was shortened to 2.5 seconds and subjects were...
instructed to press the response key upon the perception of second pain. VAS ratings were made, as for first pain intensity ratings, for the intensity of the last heat pulse in each series. Response times were recorded for each stimulus.

Subjects had no difficulty performing the response time and the VAS pain intensity rating procedures.

**Data analyses.** — Due to a programming problem, the computer failed to collect responses for the final stimulus in the 5-stimulus trains, and these data are therefore omitted. Group differences in intensity and response times were assessed by a multivariate, repeated measures design with Groups as the between-subjects factor and Trials (1–4 stimuli), Location (arm and leg), and Pain Type (first and second pain) as within-subjects effects. Post hoc univariate F-tests and paired t-tests were employed as appropriate.

**RESULTS**

**Main Effects of Age**

Age groups did not differ on overall pain intensity ratings \[F(1,18) = \text{n.s.}\]. Table 1 presents VAS means, standard deviations and summary F-tests for each type of pain at each location. With trials collapsed, groups were similar in their ratings of both first and second pain. The main effect of pain type was also not significant \[F(1,18) = \text{n.s.}\].

**Pain Type**

The interaction of Pain Type and Trials was significant \[F(3,48) = 13.53; p < .001\] and was consistent with previous findings of decreased first and increased second pain under appropriate conditions (1–5). The Pain Type by Trials interaction is shown in Figure 1 for each group of subjects.

**First pain.** — Suppression of first pain was observed \[F(3,54) = 2.89; p = .04\]. First pain decreased for both age groups for leg (Figure 1, top right panel) but not for the older group for stimuli delivered to the arm (top left panel). The young group had a 40% first pain reduction across stimuli delivered to the arm (see Figure 1, top left panel). The interaction of Trials by Group for stimuli delivered to the arm, however, was not significant \[F(3,54) = 1.07; p = .37\]. Similarly, the interactions of Trials by Group by Location \[F(3,54) = 1.70; p = .18\] and Trials by Group \[F(3,54) = .42; p = .74\] and the location main effect \[F(1,18) = .45\] were not significant.

**Second pain.** — The expected effect of increased second pain across all stimuli was not obtained \[F(3,54) = 2.00; p = .125\], but several important interactions were statistically significant. The interactions of Location by Trials by Group \[F(3,54) = 3.23; p = .03\] and Location by Trials \[F(3,54) = 3.71; p = .02\] were significant (Figure 1, lower panels).

**Table 1. Pain Intensity Ratings for First and Second Pain in Younger and Older Adults**

<table>
<thead>
<tr>
<th></th>
<th>Arm</th>
<th>Leg</th>
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<tbody>
<tr>
<td></td>
<td>First Pain</td>
<td>Second Pain</td>
</tr>
<tr>
<td>Younger Group</td>
<td>Mean</td>
<td>18.91</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>13.05</td>
</tr>
<tr>
<td>Older Group</td>
<td>Mean</td>
<td>19.72</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>12.24</td>
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\[F(1,18) = \text{n.s.}, \text{n.s.}, \text{n.s.}, \text{n.s.}\]

*Intensity ratings were to visual analogue scales (VASs) for 51 °C heat pulses delivered to arm and leg. Values of average ratings across trains of heat pulses.

Figure 1. Top panels: visual analogue scale (VAS) ratings of pain intensity to repeated stimuli under conditions known to suppress first pain at arm (top left) and leg (top right). Bottom panels: VAS pain intensity ratings to repeated stimuli under conditions known to produce slow temporal summation of second pain at arm (bottom left) and leg (bottom right). Stimuli were 0.7 sec heat pulses (39 °C adapting temperature to a stimulus intensity of 51 °C). Suppression of first pain studied with an interstimulus interval of 5 sec and slow temporal summation of second with an interstimulus interval of 2.7 sec. Older subjects evidenced an unexpected decrease in second pain intensity from the leg under conditions usually associated with temporal summation of second pain. Pain intensity ratings were to the last stimulus in each series in order to avoid temporal pressure on subjects. The only statistically significant effect was for second pain intensity at the leg, where significant age interactions were obtained and a significant difference was observed for the intensity rating of the 4th stimulus in the series (see text).
These significant interactions were due to a failure of the older group to experience an increase in second pain to repeated stimuli delivered to the leg.

Both groups had a significant increase in second pain across trials for stimuli delivered to the arm (Figure 1, bottom left). Second pain intensity at the arm increased approximately 21% for young and 83% for elderly subjects (see Figure 1). For the leg, second pain intensity increased approximately 22% for the young group but decreased 26.1% across repeated stimuli in the older group. By the 4th stimulus to the leg, the elderly subjects rated the intensity of their second pain as significantly less than the young subjects $[F(1,18) = 7.65; p = .013]$. This was the only intensity rating that differed between the groups, and it suggests that older subjects did not experience slow temporal summation of second pain at the leg.

Response Times — Pain Type and Location

Response times should be influenced by location (arm faster than leg) and pain type (first pain faster than second pain). Since both intensity and response times changed across stimuli within trials, only response times to the first stimulus in each series were employed in this analysis. Table 2 summarizes response time differences by pain type.

As expected, responses to second pain were significantly slower than to first pain at both arm (mean difference .310 sec) and leg (mean difference .428 sec). Location effects are also summarized in Table 2. As expected, responses to first pain at the leg were longer (.266 sec) compared to the arm. The same held true for the location effect for second pain response times which were .384 seconds longer from leg than from arm (see Table 2). These results indicate that subjects were selectively rating intensity of first and second pains under the different experimental conditions.

Age Effects on Response Times

Auditory. — Auditory response times were longer $[F(1,17) = 5.81; p = .03]$ in older ($M = .471$ sec; $SD = .198$) compared to younger ($M = .315$ sec; $SD = .050$) subjects.

First pain response times. — Ignoring location, the older group was slower $[F(1,18) = 6.54; p = .02]$ in responding to first pain compared to the young subjects. Post hoc tests showed this was due to a significant age effect at leg $[F(1,18) = 7.51; p < .01]$ but not arm $[F(1,18) = 2.81; p = .11]$. These findings are shown in Table 3 and Figure 2. As shown in Figure 2, all first pain response times to stimuli delivered to the leg were significantly slower in older compared to younger subjects (all $p < .05$ or lower; see Figure 2, top right).

Second pain response times. — The groups did not differ on response times to second pain $[F(1,18) = n.s.]$. As shown in Figure 2 and Table 3, second pain response times were remarkably similar in the two groups.

Summary. — First pain response times to stimuli delivered to the leg were unexpectedly delayed in the elderly. Within-group differences (paired $t$-test) for pain type as a function of location are given in Table 3. These results parallel those presented in Table 2 but illustrate the overall location and pain type findings for each group. In the younger group, response times to first pain were .318 seconds longer for the leg compared to the arm. The comparable figure for the older subjects was almost twice as large (.607 sec, see Table 3). The parallel location differences for second pain response times were remarkably similar in the two age groups (bottom of Table 3). As indicated in Table 3, groups differed significantly for first pain response times to stimuli delivered to the legs but not the arms.

DISCUSSION

The lack of consistent age difference in pain intensity...
Figure 1. RTs were for each stimulus presented. Older subjects had longer first pain RTs compared to younger subjects, and this was statistically significant. For responses to stimuli delivered to the leg. Stimulation conditions were as in Figure 2. RTs were for each stimulus presented.

ratings agrees with other studies employing similar stimuli. With one exception the results indicate greater similarities than differences in perceived intensities of supra-threshold thermal pain in young and older healthy volunteers. One exception to this was noted. A significant age difference in pain intensity ratings was observed in that the elderly failed to show slow temporal summation of second pain from the leg (Figure 1).

Slow temporal summation of second pain and hyperalgesia is mediated by C-fiber nociceptors and results from sensitization of secondary nociceptive cells in the dorsal horn. Failure for sensitization to occur might result in decreased protective behaviors following tissue damage or inflammation. Such a loss of sensation for second pain likely accounts for damage to the feet associated with obtunded pain sensitivity in diabetic peripheral neuropathy. It may also be related to clinical observations of atypical pain presentation in older individuals but appears contradictory to the fact that neuropathic conditions (i.e., post herpetic neuralgia) increase with age. The present study employed subjects without a history of neuropathic pain, allodynia, or hyperalgesia and without history of metabolic condition associated with large fiber peripheral neuropathy. To our knowledge, a decrease in second pain, under the conditions of stimulation employed here, has not been previously reported. If replicated, the present finding of a failure of slow temporal summation of second pain would indicate an age-related decrease in central nervous system nociceptive processing associated with hyperalgesia.

Recently, Chakour, Gibson, Bradbeer, and Helm (20), employing a selective compression blockade of A-delta, but not C-fibers, reported that older subjects employ C-fiber mediated second pain more that A-delta mediated first pain sensations in making pain intensity judgments at stimulation levels that are near pain threshold. Chakour et al. (20) interpreted the elevated thresholds and lower pain intensity ratings as evidence of impaired A-delta fiber mediated thermal nociceptive function in older adults. The present pain intensity results, based on stimuli that are well above pain threshold, indicate no difference in first pain intensity ratings but impaired function of A-delta transmission properties.

The finding that elders employ C-fiber more than A-delta nociception in making judgments about near-threshold thermal pain (20) is not at variance with our results of supra-threshold equivalence with age of first and second pain ratings of previously unstimulated skin or the finding of an age-dependent failure in slow temporal summation in the older adult. The combination of these results suggests that aging may play a more dynamic role in both peripheral and central processes subserving nociception than previously thought (7-10,13). Further research contrasting the very punctate thermal pain associated with brief laser stimulation (usually less than 100 msec) and longer duration contact thermal stimuli as employed here will determine if the differences in findings between these studies are due to an interaction of age and stimulus intensity (13) or other properties of these quite different thermal stimuli.

Response times to the auditory stimuli were longer in the old compared to the younger group. The few studies that have evaluated response times to noxious stimuli in relation to age have focused on pain from the facial region and have reported no age differences (10,11). It is very interesting that responses to first pain were significantly longer in the older group to stimuli delivered to the leg, but not to the arm, and that no age effects were observed for response times to second pain.

A-delta fibers, which are thought to mediate the sensation of first pain, have been shown to slow approximately 10 to 15% with age in rats, while unmyelinated C-fibers, which mediate the sensation of second pain and slow temporal summation of second pain, evidenced no change in conduction velocities (21). Based on light and electron microscopy study of normal sural nerve, Ochoa and Mair (22) reported an increase in the number of degenerating A-delta class, small myelinated fibers with age. Regeneration was associated with shortening of the internodal length in the A-delta class fibers, which presumably would result in increased conduction time and which could account for the age differences in response times to first pain observed here. The distal to proximal age
effect for response times to first pain (Figure 2) is consistent with a selective small fiber peripheral neuropathy.

Summary

The results of the present study support previous findings which show small or no changes in pain intensity with age for contact thermal stimuli delivered to previously unstimulated (non-adapted or sensitized) areas of the arm and leg (13,17,19). The results, however, do raise questions as to whether the dynamic properties of first and second pain are equally invariant with aging. Evidence is presented for a selective age effect on response times to first, but not second pain. The slowing with age in response times to first pain is greater for more distal sites of stimulation. It is likely that this slowing in response time to first pain is a function of changes in the conduction properties of A-delta class fibers and represents, to our knowledge, the first demonstration of a possible, selective small-fiber peripheral neuropathy in apparently asymptomatic older individuals. This merits further study employing electrophysiological procedures.

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REFERENCES


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