PAIN® 145 (2009) 350–357

PAIN®

www.elsevier.com/locate/pain

Women experience greater heat pain adaptation and habituation than men

Javeria A. Hashmi [a,b,1], Karen D. Davis [a,b,c,*]

[a] Division of Brain, Imaging and Behaviour – Systems Neuroscience, Toronto Western Research Institute, University Health Network, Toronto, Ont., Canada M5T 2S8
[b] Institute of Medical Science, University of Toronto, Canada
[c] Department of Surgery, University of Toronto, Canada

ARTICLE INFO

Article history:
Received 17 March 2009
Received in revised form 30 June 2009
Accepted 2 July 2009

Keywords:
Sex differences
Burning
Sharp
Adaptation
Habituation
Psychophysics
Heat pain

ABSTRACT

It is not clear how males and females cope with pain over time and how sensory and emotional qualities fluctuate from moment to moment, although studies of pain at discrete time points suggest that women are more pain sensitive than men. Therefore, we developed a new broader-based pain model that incorporates a temporally continuous assessment of multiple pain dimensions across sensory and affective dimensions, and normalized peak pain intensity to unmask sex differences that may otherwise be confounded by inter-individual variability in pain sensitivity. We obtained continuous ratings of pain, burning, sharp, stinging, cutting, and annoyance evoked by repeated prolonged noxious heat stimuli in 32 subjects. Strikingly, females reported more pain than males at the outset of the first exposure to pain, but then experienced less pain and annoyance than males as a painful stimulus was sustained and with repeated stimulation. Patterns of pain and annoyance attenuation in women resembled the attenuation of sharp, stinging and cutting sensations, whereas patterns of pain and annoyance in men resembled burning sensations. Taken together, these data demonstrate a prominent sex difference in the time course of pain. Notably only females demonstrate adaptation and habituation that allow them to experience less pain over time. These findings suggest a sexual dichotomy in mechanisms underlying pain intensity and annoyance that could involve specific quality-linked mechanisms. Importantly, temporal processing of pain differs between males and females when adjusted for sex differences in pain sensitivity. Our findings provide insight into sex differences in tonic and possibly chronic pains.

1. Introduction

That men and women experience evoked pain differently from each other [12] has been debated since the 1990s when it was proposed that females are generally more sensitive towards painful stimuli than males [6,13,45]. Experimental evidence showing that females had lower pain thresholds, higher pain ratings and diminished pain tolerance than men is partly due to the discrete measurements of pain intensity evoked by brief stimuli. However, sustained stimuli more closely model natural pains and the fluctuations in pain evoked throughout sustained stimuli may inform us about endogenous pain modulating processes [22,38,51,56]. Sex differences in pain modulation mechanisms are not well understood [3,6,43]. An efficient central mechanism that reduces intermittently sustained pain would be biologically more advantageous for women to cope with natural pains such as those associated with menstrual cramps and child birth. In variance to this view, it has been suggested that for brief repetitive stimuli, pain in females intensifies more with time relative to pain in males [15,18,19,35,44]. However, no sex difference was found in studies of temporal dynamics of sustained heat pain and this may be due to marked inter-individual differences in peak pain responses or due to sex differences in pain sensitivity [38,39]. Therefore, to observe sex effects specific to temporal processing of pain, sex differences in pain sensitivity may first need to be normalized.

The sensory dimension of pain comprises numerous sensory qualities but sex differences in these pain dimensions are not well understood. Many pain qualities fall into two distinguishable classes: the sharp type and the dull-burning type. The sharp type of sensations are thought to be produced during excitation of A-delta nociceptors [1,20,30,36], whereas the burning type of pain is thought to be due to activation of C-fiber nociceptors [24,27,34,40]. Recently, we discovered that sharp-type sensations adapt with sustained noxious heat stimulation but burning sensations, instead persist throughout the duration of the stimulus. This difference in adaptation patterns between sharp-type and burning

* Corresponding author. Address: Division of Brain, Imaging and Behaviour – Systems Neuroscience, Toronto Western Research Institute, University Health Network, 399 Bathurst Street, Room MP14-306 Toronto, Ont., Canada M5T 2S8. Tel.: +1 416 603 5662; fax: +1 416 603 5745.
E-mail addresses: jhashmi@uhnres.utoronto.ca (J.A. Hashmi), kdavis@uhnres.utoronto.ca (K.D. Davis).
[1] Tel.: +1 416 603 5502; fax: +1 416 603 5745.

0304-3959/$36.00
doi:10.1016/j.pain.2009.07.002

sensations thus offers a novel opportunity for investigating pain mechanisms that encode sex differences in other more global pain dimensions such as pain intensity and affect. Here, we have extended our experimental approach to characterize the temporal dynamics of heat pain in males and age-matched females. The main goal of this study was to delineate sex differences in temporal patterns of pain intensity, annoyance and the sharp- and burning-type sensations. We hypothesized that the temporal dynamics of heat pain intensity and annoyance differ between males and females and that the sex differences in heat pain dynamics are linked with temporal dynamics of specific sensory qualities of pain.

2. Methods

2.1. Subjects

A total of 38 healthy subjects (19 males and 19 females) were recruited for the study from staff and students within the local university and hospital communities. Data obtained from three male and three female subjects were incomplete and discarded as they provided unreliable ratings or abnormal ratings. Thus, all data are reported from a final group of 32 subjects. There was no significant difference between the mean age of male (27.5 ± 5 yrs (SD)) and female subjects (26.9 ± 5 yrs (SD)). All subjects gave informed written consent to procedures approved by the University Health Network Research Ethics Board.

2.2. Thermal stimuli and ratings

Stimuli were delivered to the dorsal aspect of the right foot with a Peltier element-based contact thermal stimulator (Medoc Thermal Sensory Analyzer, TSA-2001; Ramat Yishai, Israel). The stimulation surface of the probe was 16 mm × 16 mm. We obtained continuous ratings of pain intensity evoked by a series of three heat pain stimuli (interleaved with a 60 s neutral baseline) with each stimulus held at the adjusted peak stimulus intensity for 30 s. Holding the stimulus procedure constant, we then obtained ratings of annoyance, and finally in a randomized order we obtained continuous ratings of heat-evoked sharp, stinging, cutting, and burning sensations (each quality assessed in a separate run). The evaluated attributes were selected by subjects from the McGill Pain Questionnaire (MPQ part 2) in a pilot session reported in our previous study [27]. In this pilot study, we instructed subjects to select any and all words listed on the MPQ that captured their experience evoked by a 30 s sustained heat pain stimulus held at a temperature that evoked a peak pain of 50/100 on the visual analogue scale (VAS) scale. During the pilot session, subjects chose "annoying", but not other affect-type words such as "fearful", "punishing", "wretched" or "nagging". Although "annoying" is in the MPQ "pain intensity" category, the dimensions of pain described in the MPQ represent a continuum where pain quality descriptors can belong to more than one pain dimension [11,61].

For each application of the stimulus, the thermode temperature rose at ~8 °C/s until the target temperature was reached, and held at target for 30 s and then returned to baseline at ~8 °C/s. Each of the six runs consisted of a 15 s baseline period (35 °C) followed by three stimuli (stimulus 1, stimulus 2, stimulus 3), which were separated by a 60 s interval during which the probe temperature was held at the 35 °C base. After every run the thermal probe was relocated to a new skin area to avoid interactions between consecutive stimulus runs.

Subjects used a 100-mm computerized VAS scale (COVAS, Medoc) to continuously rate perceived magnitudes of each of the six sensations (each in a separate run) evoked by the heat pain stimuli. For each subject, several 30 s tonic stimuli were used to determine the approximate temperature that evoked a peak pain intensity of 50/100. The response to each stimulus was evaluated on a separate skin area or was repeated on the same skin spot at a minimum interval of 10 min. The smallest interval between each stimulus application on separate areas was 1 min. The first stimulus was at 46 °C. This temperature was repeated at least two times so that the subject was acquainted with the rating scale. If this temperature did not produce a peak pain rating of 50/100 then the stimulus temperature was increased or decreased in iterations of 0.2–1 °C in steps until the subject reported a peak pain of 50/100.

Annoyance was evaluated after evaluating pain intensity in the second stimulus run. In the subsequent four stimuli runs, the sharp, burning, stinging and cutting qualities were evaluated in a randomized order. Verbal anchors were used to describe the 0 and 100 extremes of the scale according to the sensation being assessed in that run. For example, for the overall "pain intensity" run, the anchors were "no pain" at the lower limit of 0 and "most intense pain imaginable" at 100. Subjects were instructed to focus on one sensation at a time and rate at the lower limit (0) when they did not perceive any amount of the sensation being rated, and the upper limit (100) when the sensation was at its most intense level imaginable, and to quantify the magnitude of the sensation at any numerical value in between these numbers.

Prior to the experiment, all subjects underwent training to learn how to use the rating system and to focus and rate one sensation at a time. In addition, subjects were trained to discriminate between pain qualities evoked by the heat stimuli with the help of common concepts. For example, sharp pain was described to the subjects as the sensation of a pin prick, and stinging quality was described as sensations of tiny pricks. The sensation of cutting quality, on the other hand, was conveyed as the sensation of being cut with a knife or with a paper. The remaining quality, burning, was described simply as the sensation of a burn that occurs with hot objects or with chemicals. Since we wished to evoke a similar intensity of pain in all subjects, the training session was used to determine the stimulus temperature that evoked a peak pain intensity of approximately 50/100 on the VAS within a 30-s period of sustained heat stimulation.

2.3. Data analysis

The magnitude of total sensation was compared between an early and a late stimulus period (see Fig. 1). The early magnitude of each quality was assessed by calculating the total sensation (i.e., sum of rating in the area under the rating curve) between 0 and 20 s from stimulus onset. Each time course was also assessed during a second 'late' period during the 20–40 s intervals from stimulus onset. These early and late magnitudes were compared with each other to assess time-related adaptation or intensification in the peak magnitude of heat pain qualities. To determine the effect of repeated stimulation, data from stimuli 1, 2 and 3 within each run were calculated and compared based on the total sensation evoked by the stimulus (i.e., area under the rating curve). Sex differences in relationships between pain dimensions were assessed by first computing the absolute differences between pain intensity and each pain quality and annoyance and each pain quality. These absolute differences were assessed separately for males and females. Subsequently, these absolute difference values were compared between the sexes to directly evaluate sex differences.

Data were analyzed with SPSS (version 13.0, SPSS Inc., Chicago). The variations in peak stimulus temperature used for normalizing the effect of inter-individual differences in stimulus temperatures were regressed out, for all statistical analyses, by using peak stimulus temperature for each subject as a covariate. This was achieved with an analysis of covariance (ANCOVA) within each univariate or multivariate test which allowed a calculation of differences be-

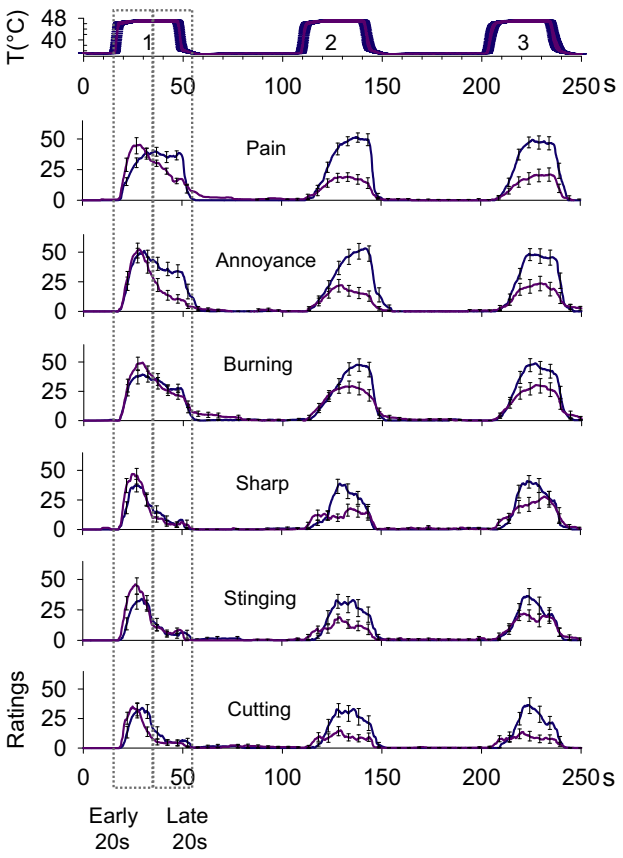

Fig. 1. Mean time courses of ratings of pain intensity, annoyance and four specific pain qualities evoked by the three heat pain stimuli (labeled 1, 2, 3 in the top panel) in males (blue lines) and females (pink lines). Error bars represent standard error of means.

tween conditions significant over and beyond the effects of the covariate.

The analyses of pain quality dynamics included univariate and multivariate statistical tests. First, within a single stimulus period, the differences between measures of heat pain attributes were compared with each other using an ANCOVA and post hoc comparisons included Bonferroni corrections. Moreover, to assess measures of pain attributes between different conditions (e.g., early stimulus period versus late stimulus period), we used a multivariate analysis of covariance (MANCOVA). In the case of a significant multivariate *F*-test, univariate tests (ANCOVA) were carried out to compare the measures of each dependent variable (i.e., pain attributes) between stimulus periods. Similarly, the effect of temperature variability between males and females was also tested with the help of post hoc univariate contrasts. For pain attribute measures evaluated at different time points (e.g., between early and late periods of stimulus 1 or between stimulus 1 and stimulus 2 or 3), MANCOVA contrasts were used. Comparisons were considered significant at a $p < 0.05$ and *t*-tests were used to evaluate difference between male and female ages and also for sex differences in selected stimulus temperatures.

3. Results

3.1. Overview of approach

For each subject, we standardized the peak magnitude of pain intensity to approximately 50/100 by adjusting the peak stimulus intensity at the beginning of each subject session. Thus, the overall pain intensity evoked by stimulus 1 did not differ significantly between males and females in either the peak pain rating ($p = 0.86$) or the total pain sensation (i.e., area under the rating curve; $p = 0.59$; see Figs. 1 and 3). The similar peak pain intensity level that was created by design between males and females requires a lower (significant at $p = 0.033$) stimulus temperature in females (45.46 ± 0.14 °C SEM) than in males (46.98 ± 0.26 °C SEM), although there was no statistically significant stimulus temperature interaction effect in any of the sex difference effects (see below for details).

Despite the similarity in peak magnitude of pain, there were marked sex differences in the temporal dynamics of pain evoked both within first application of the stimulus (stimulus 1) and also between re-applications of the stimulus (between stimuli 1, 2 and 3). These sex differences can be clearly seen in Fig. 1 depicted as the group average of males and female real time ratings of pain intensity and annoyance. The sex differences in adaptation were quantified by comparing the total sensation (area under the ratings curve) evoked within the early and late halves of the first stimulus–response period (see Section 2). Then, the sex differences in habituation were quantified by comparing total sensation evoked by stimuli 1, 2 and 3. Within each analysis, we used an analysis of covariance to confirm that the findings were due to sex differences alone and were not significantly affected by differences in stimulus intensities.

3.2. Sex differences in temporal adaptation of pain qualities evoked by stimulus 1

Females reported significantly more total pain (see Figs. 1 and 2) during the early (first 20 s) phase of stimulus 1 compared to males ($p = 0.036$). However, as the stimulus was sustained, females then reported significantly less pain and annoyance than in males ($p = 0.002$; see late phase in Figs. 1 and 2; no significant stimulus temperature interaction: $p = 0.65$). In contrast, the evoked magnitudes of the other pain attributes were not significantly different between males and females ($p > 0.05$). Interestingly though, the sharp, stinging and cutting sensations were only prominent during the early phase of the stimulus and were significantly less than the burning sensations in males ($p < 0.02$) and in females ($p < 0.01$).

The absolute change in all sensations during stimulus 1 (i.e., early versus late areas under the curve) also demonstrated significant sex differences (main sex effect $p = 0.03$; no significant stimulus temperature interaction: $p = 0.76$). These effects are depicted in Fig. 2 and clearly show that the overall pain intensity (area under the rating curve) decreased over time in females ($p = 0.013$), while it increased over time in males ($p = 0.032$). In addition, annoyance also decreased over time in females ($p = 0.001$) but not in males ($p > 0.05$). In contrast, both males and females reported significantly temporal attenuation ($p < 0.05$) in sharp, stinging and cutting pain qualities, whereas the evoked burning sensations did not change significantly with time in either sex ($p > 0.05$).

3.3. Sex differences in habituation responses to repeated painful stimulation

Females experienced a striking habituation of pain upon stimulus repetition compared to males (see Fig. 1). Quantification of this effect can be seen in Fig. 3. During the second presentation of the painful stimuli, females reported significantly less total pain intensity ($p = 0.0001$), annoyance ($p = 0.002$) and sharp ($p = 0.049$) sensations compared to males (main sex effect $p = 0.025$; no significant stimulus temperature interaction $p = 0.12$). In response to the third application of the stimulus females again reported significantly less total pain intensity ($p = 0.0001$), annoyance ($p = 0.02$) and cutting quality ($p = 0.34$; main effect $p = 0.011$; no

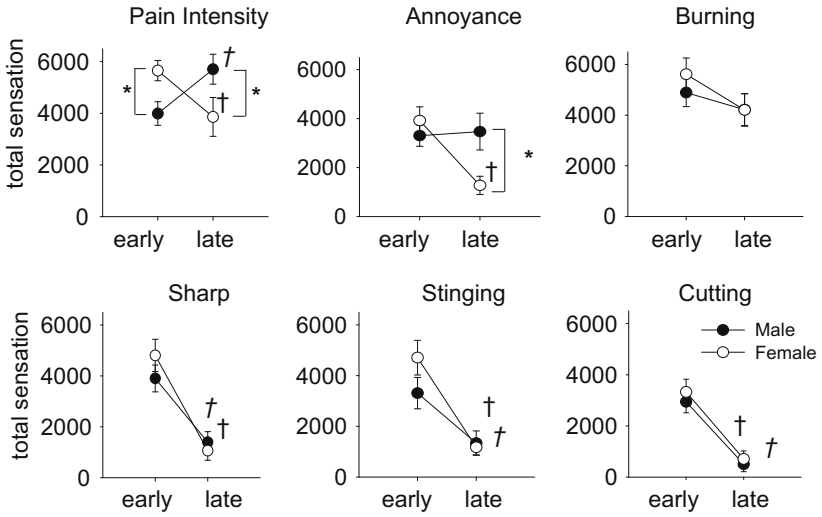

Fig. 2. Adaptation of sensations evoked during stimulus 1. Intra-stimulus attenuation or intensification was based on changes in the total sensation (i.e., area under the rating curve) evoked during the early period (0–20 s) and late period (20–40 s) of the first stimulus in the males (filled symbols) and females (empty symbols). Error bars represent standard error of means. *Significant sex difference in total sensation evoked during either the early period or the late period at $p < 0.05$. †Significant decrease or increase in total sensation evoked in the late stimulus period from the early period in males at $p < 0.05$. †Significant decrease or increase in total sensations evoked in the late period from the early period in females at $p < 0.05$.

significant stimulus temperature interaction, $p = 0.59$) sensations than males.

In females, the sensations which specifically habituated between stimuli 1 and 2 (absolute change) were pain intensity ($p = 0.0001$), annoyance ($p = 0.031$), sharp ($p = 0.0017$) and stinging qualities ($p = 0.021$; main effect $p = 0.011$; stimulus temperature effect significant $p = 0.029$). But between stimuli 1 and 3, habituations were significant only in the magnitudes of pain intensity ($p = 0.0001$), annoyance ($p = 0.046$) and burning quality ($p = 0.035$; main effect $p = 0.002$; stimulus temperature interaction significant at $p = 0.029$). In contrast, males did not report any significant change ($p = 0.46$) in pain or other sensation magnitudes with stimulus re-applications.

Since the initial magnitude of sensation may impact between-stimulus habituation effects, we also calculated habituation effects as percent changes in both sexes from the response evoked by stimulus 1. Similar to the absolute changes shown in Fig. 3, the percent changes in sensations between stimuli 1 and 2 were significantly greater in females than in males for pain intensity ($p = 0.001$), annoyance ($p = 0.006$), sharp ($p = 0.011$) and stinging ($p = 0.04$) qualities (main sex effect $p = 0.003$; stimulus temperature not significant, $p = 0.47$; Fig. 4). This effect was also observed between stimuli 1 and 3 for pain intensity ($p = 0.0001$), annoyance ($p = 0.003$), burning ($p = 0.022$), sharp ($p = 0.045$), stinging (0.025) and cutting ($p = 0.024$) quality magnitudes (main sex effect $p = 0.011$).

3.4. Sex differences in the relationships between pain qualities, pain and annoyance

Our next analysis used a unique approach to gain insight into the contribution of specific pain qualities to the general experience

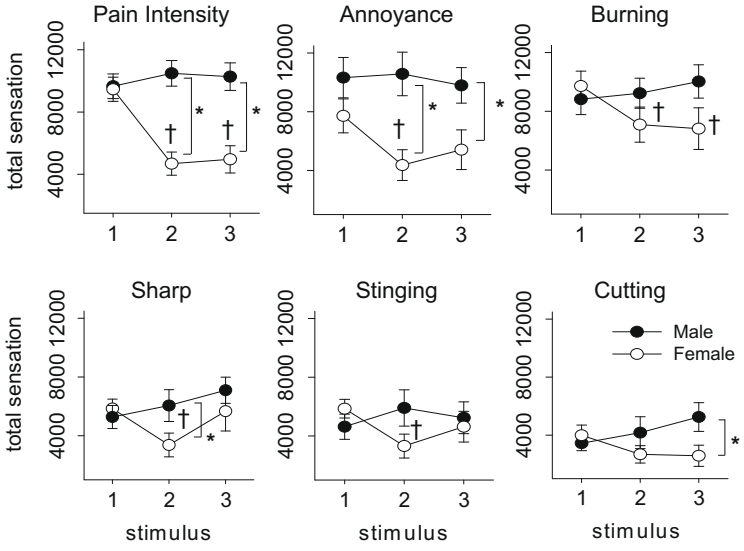

Fig. 3. Sex differences in habituation of total sensations (area under the rating curve) to repeated stimulation in males (filled symbols) and females (open symbols). Error bars represent standard error of means. *Significant sex difference ($p < 0.05$) in total sensation evoked by stimulus 1, 2 or 3. †Significant decrease or increase in total sensation evoked by stimulus 2 or 3 compared to stimulus 1 at $p < 0.05$.

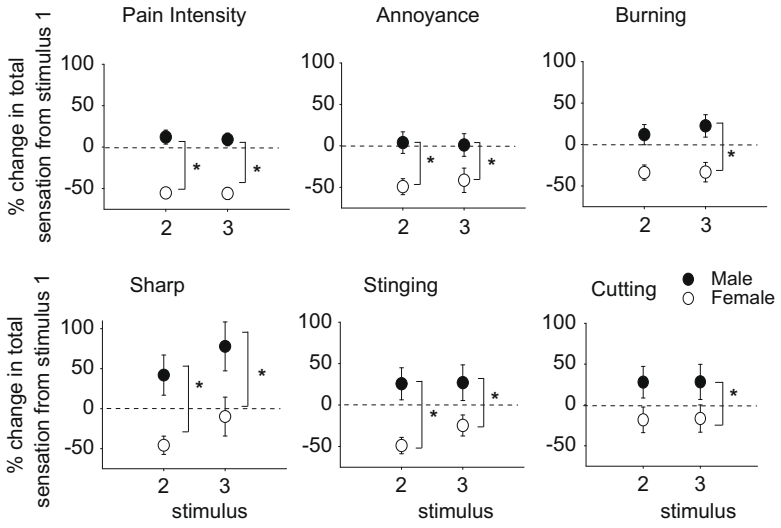

Fig. 4. Sex differences in percent change in total sensation evoked by stimuli 2 and 3 compared to stimulus 1. Error bars represent standard error of means. *Significantly greater percent reduction from stimulus 1 in females compared to males at $p < 0.05$.

of pain intensity and affect (herein represented by the ratings of annoyance). Our aim was to determine whether there were sex differences in the relationships between specific pain qualities and either pain intensity or annoyance. Towards this goal, we calculated the differences in between total sensation of pain intensity (or annoyance) and the total sensation of each pain quality evoked by each application of the stimulus (Fig. 5, stimuli 2 and 3). There were no sex differences in the difference between pain intensity (or annoyance, right panel) and the other specific pain qualities over the entire stimulus 1 ($p < 0.05$). However, this approach

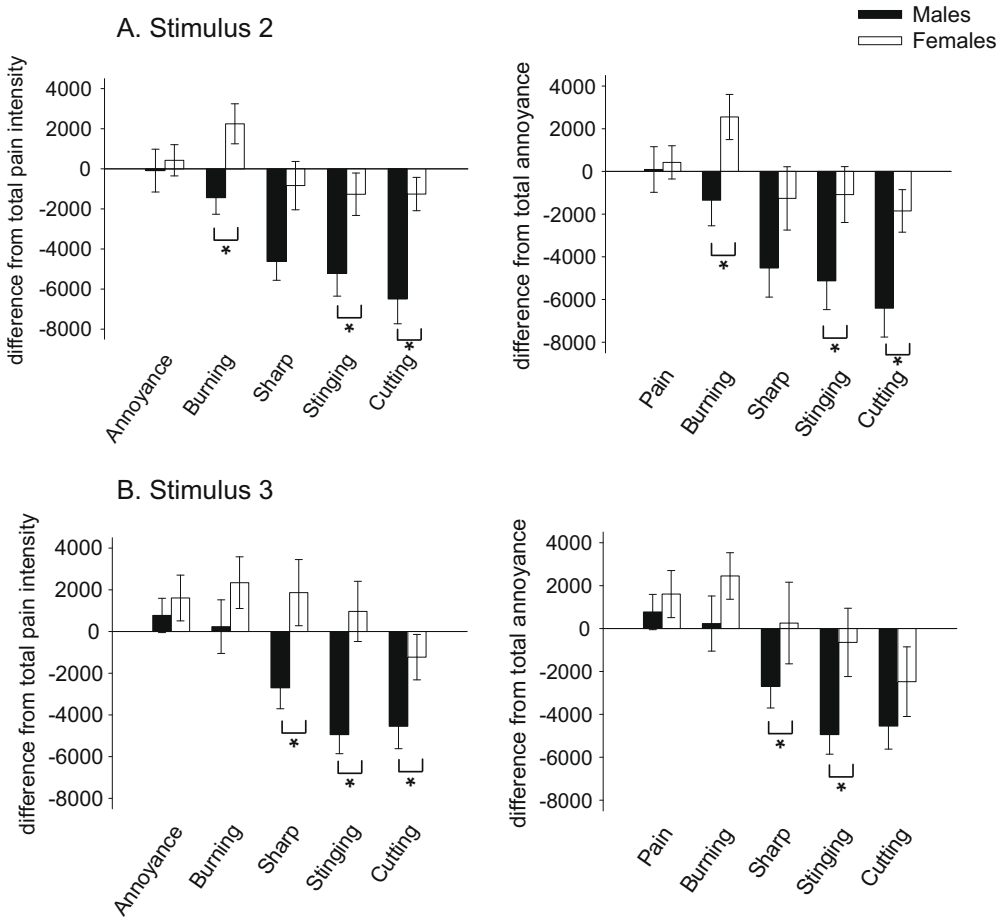

Fig. 5. Difference between the total evoked specific pain qualities and pain intensity (left panels) or annoyance (right panels) during the second and third stimulus. Total sensations were calculated from the area under the rating curve for each sensation evoked during stimulus 2 (A) and during stimulus 3 (B). Error bars represent standard error of means. * Significant sex differences ($p < 0.05$) in comparisons between each pain quality and either pain intensity or annoyance).

revealed several sex differences in response to stimulus 2 ($p < 0.05$; main sex effect $p = 0.048$; no stimulus temperature interaction, $p = 0.22$) and 3 ($p < 0.05$; main sex effect $p = 0.040$; no stimulus temperature interaction, $p = 0.64$). Notably, males reported of a significantly greater difference between pain intensity and sharp, stinging and cutting quality magnitudes than females in response to stimulus 2, and stimulus 3 (see 5). This sex effect was also observed when pain qualities were contrasted with annoyance in response to stimulus 2 (main sex effect $p = 0.022$, no stimulus temperature interaction, $p = 0.39$) for all pain qualities ($p < 0.05$) except for the sharp sensations evoked by stimulus 2 ($p = 0.122$); moreover, the sex effect did not meet significance in response to stimulus 3 (main sex effect $p = 0.10$).

4. Discussion

Here we show that when the intensity of noxious heat stimuli is fixed to evoke a common initial peak pain, pain in females prominently adapts and habituates while pain in males is evoked consistently over time. Our data also point to a neurobiological mechanism underlying sex differences in pain attenuation based on the finding that in females, pain and annoyance adapt in concert with the adaptation of sensations associated with A-delta nociceptors (sharp, stinging, cutting) but males experience sustained pain and annoyance that are more similar to the burning sensations associated with C-fiber nociceptors. Based on these findings, we suggest a putative sexual variance in the temporal mechanisms that encode pain intensity and affect.

Foremost, as suggested by other studies [16,45,49], females did show more sensitivity to pain than males in two measures: first, they required lower stimulus temperatures to evoke a similar intensity of pain to males. Second, their pain ratings were greater than those of males during the initial period of the stimulus. This suggests that female sensitivity is prominent in the immediate period after stimulus onset. A correlate of this latter phenomenon has been shown with other tonic pain models, where females, but not males report of a dynamic rise in pain intensity, but later this sex effect dissipates [16,28,35,56]. Another prominent sex difference previously reported is that females detect pain at lower stimulus intensities than males [44,52]. One factor that may contribute to greater female pain sensitivity during the stimulus onset phase could be a sex difference in skin thickness. Male hairy skin is thicker than female hairy skin [31,58]. Thinner skin in women then, could allow for faster and more effective heat transduction [53] and would thus evoke more intense pain during transduction related with skin heat equilibration [22,25,56]. The sex difference in skin thickness may explain why female pain is more pronounced than male pain during the early phase. This factor may also explain why an adjustment in temperature of approximately 1 °C was required to normalize peak pain intensity between males and females. However, female sensitivity during the onset phase can also be due to a sex difference affecting central mechanisms. For instance, it has been suggested that females demonstrate a greater peak pain at stimulus onset and this phenomenon possibly reflects the activity pattern of A-delta nociceptors that show robust activity at stimulus onset and later adapt on sustained stimulation [27,57]. It is interesting that females are also more sensitive than males in detecting onset of sensory modalities such as tactile [21,59,62], olfactory [5,8,29] gustatory [4,17,60] and visual modalities [48]. Therefore it may also be that females are sensitive to onset of a variety of sensory inputs in general and therefore female sensitivity during pain onset may be linked to a central multimodal mechanism.

The attenuation of heat pain and annoyance in females hitherto unknown. Supporting evidence comes from a previous report from our laboratory that has shown greater attenuations of heat pain in females compared to males [9]. These findings contradict previous studies that used tonic or brief repetitive stimuli [14,47,50,56]. Thus, studies that used sustained stimuli did not observe a sex difference during the late stimulus period while that used brief repetitive stimuli showed that pain intensified with time to a greater extent in females. The reasons for these discrepancies are not entirely clear but may point to differences in stimulus parameters such as its duration, rise rate and intensity. One study has demonstrated marked inter-individual variation in prolonged pain patterns when tested with a single stimulus intensity and thus no significant sex differences were observed [38]. Thus it is plausible that sex differences that may otherwise be confounded by inter-individual variability in pain sensitivity [38] are unmasked when stimulus intensities are adjusted to evoke a similar peak pain magnitude in all subjects. Our results also vary from those studies that adjusted stimulus intensity to normalize peak pain across subjects. It is clear that the methods for normalizing peak pain differ between studies and unlike previous pertinent studies we normalized peak pain using stimulus parameters (rate of rise, duration) that were identical to the test stimuli. Alternatively, because low stimulus temperatures can cause adaptation in pain, female pain adaptation may be due to a lower stimulus temperature relative to males [26,32]. Therefore, as a precaution, we used an analysis of covariance to calculate differences specific to variability in male and female responses. Another potential explanation for the sex differences is that women simply provided less reliable ratings than men. However, this is unlikely since the rating variances were similar for men and women. Furthermore, the within-stimulus and between-stimulus changes in ratings were consistently that of attenuation for most sensations. Our findings clearly demonstrate that noxious stimuli within a certain range of stimulus intensities evoke different temporal patterns of pain in males and females. Taken together with other studies [9,56], our findings suggest that sex differences in pain sensitivity may be time-dependent. Thus, some of the principles gleaned from observing sex differences in simple measurements of pain intensity may not necessarily accurately reflect the full pain experience over time, particularly when sex differences in pain intensity have been normalized.

In our study, we sought to better understand sex differences in pain modulation and so systematically interrogated sex differences in temporal patterns of multiple dimensions of pain.

It is not clear why pain and annoyance adapted in the females but not in the males, however, viewed in the light of other pain dimensions; our data suggest that adaptation of the sharp pain quality may have played a role in the overall pain attenuations. We also observed a prominent relationship between pain/annoyance ratings and burning sensations in the ratings of both males and females and this relationship has also been suggested by some other reports [42,46]. Surprisingly though, only in females were the pain and annoyance ratings similar to sharp, stinging and cutting sensations. To our knowledge, this sex difference in the relationships between pain dimensions and the role of sharp sensations has not been reported before. Although intriguing, it is not clear why in males there was no adaptation in pain despite adaptations in sharp, stinging and cutting sensations. The role of sharp versus burning sensations in pain intensity and annoyance ratings needs further study. Although, we do not know the precise mechanism responsible for these sex differences, we do know that sharp/stinging sensations on one hand and the burning sensations on the other hand are evoked by two distinct mechanisms in the periphery (i.e., A-delta and C-fibers, respectively) [1,46,54]. Moreover, difference between the adaptation patterns of sharp and burning sensations can be accounted for by classically known response patterns of neuronal correlates of these two sensations at the peripheral and central levels [2,27,33,37,41,55,57]. Thus, the present findings may suggest that neurobiological mechanism

linked to sharp-type sensations such as the myelinated nociceptor and its central corollaries may be involved in pain and annoyance encoding mechanisms in females to a greater extent than in males.

A consequence of these considerations is that sex differences in pain sensitivity involve neurobiological mechanisms. These findings negate an emerging view in which sex differences in pain can be mainly accounted for by stereotypical gender roles, anxiety and other psychological factors [10,52]. However, a role of neurobiology in determining pain-related sex differences should not be ignored because numerous animal studies [7,23] and some human studies have underscored sexual variance in the pain system.

A few issues suggest some caution when interpreting our results. The evidence presented here was obtained with a single pain modality, a range of stimulus intensities and with one particular type of stimulus duration. It is known that experimental variables strongly affect the outcomes of pain studies [6,23] and hence, generalizing sex differences in pain control based on only one set of experimental conditions would be unwarranted. Despite this limitation, the time-related sex differences in pain sensitivity were prominent and clearly suggest that hypotheses about sex differences in pain should be constrained by the temporal uncertainty of pain responses.

Taken together, females experienced less evoked pain with time, after an initial phase of greater sensitivity than males. Moreover, female pain sensitivity was more similar to the temporal pattern of sharp pain sensations; these sensations were robustly evoked by stimulus onset, but dissipated during the latter half of the stimulus. In contrast, pain responses of males were similar to the pattern of burning sensations which were evoked throughout the stimulus duration. A consequence of these considerations is that the generalization of females as more pain sensitive than males depends strongly on the time of pain measurement.

Conflicts of interest

The authors have no conflicts of interest with this study.

Acknowledgements

This study was funded by the Canadian Institutes of Health Research (CIHR MOP 53304). Karen D. Davis is a Canada Research Chair in Brain and Behaviour. J.A.H. was funded by a University of Toronto Clinician Scientist Trainee Fellowship, Purdue Pharma OGSST scholarships and CIHR Strategic Training Program: Pain Molecules to Community Fellowship.

References

[1] Adriaensen H, Gybels J, Handwerker HO, Van Hees J. Response properties of thin myelinated (A-delta) fibers in human skin nerves. J Neurophysiol 1983;49:111–22.
[2] Adriaensen H, Gybels J, Handwerker HO, Van HJ. Nociceptor discharges and sensations due to prolonged noxious mechanical stimulation – a paradox. Hum Neurobiol 1984;3:53–8.
[3] Baad-Hansen L, Poulsen HF, Jensen HM, Svensson P. Lack of sex differences in modulation of experimental intraoral pain by diffuse noxious inhibitory controls (DNIC). Pain 2005;116:359–65.
[4] Bartoshuk LM, Duffy VB, Miller IJ. PTC/PROP tasting: anatomy, psychophysics, and sex effects. Physiol Behav 1994;56:1165–71.
[5] Bengtsson S, Berglund H, Gulyas B, Cohen E, Savic I. Brain activation during odor perception in males and females. Neuroreport 2001;12:2027–33.
[6] Berkley KJ. Sex differences in pain. Behav Brain Sci 1997;20:371–80.
[7] Berkley KJ, Zalcman SS, Simon VR. Sex and gender differences in pain and inflammation: a rapidly maturing field. Am J Physiol Regul Integr Comp Physiol 2006;291:R241–4.
[8] Dalton P, Doolittle N, Breslin PAS. Gender-specific induction of enhanced sensitivity to odors. Nat Neurosci 2002;5:199–200.
[9] Defrin R, Pope G, Davis KD. Interactions between spatial summation, 2-point discrimination and habituation of heat pain. Eur J Pain 2008;12:900–9.
[10] Edwards RR, Haythornthwaite JA, Sullivan MJ, Fillingim RB. Catastrophizing as a mediator of sex differences in pain: differential effects for daily pain versus laboratory-induced pain. Pain 2004;111:335–41.
[11] Fernandez E, Boyle GJ. Affective and evaluative descriptors of pain in the McGill pain questionnaire: reduction and reorganization. J Pain 2002;3:70–7.
[12] Fillingim RB. Sex, gender, and pain: women and men really are different. Curr Rev Pain 2000;4:24–30.
[13] Fillingim RB, Maixner W. Gender differences in the responses to noxious stimuli. Pain Forum 1995;4:209–21.
[14] Fillingim RB, Maixner W, Kincaid S, Silva S. Sex differences in temporal summation but not sensory-discriminative processing of thermal pain. Pain 1998;75:121–7.
[15] France CR, Suchowiecki S. A comparison of diffuse noxious inhibitory controls in men and women. Pain 1999;81:77–84.
[16] Frot M, Feine JS, Bushnell MC. Sex differences in pain perception and anxiety. A psychophysical study with topical capsaicin. Pain 2004;108:230–6.
[17] Gandelman R. Gonadal hormones and sensory function. Neurosci Biobehav Rev 1983;7:1–17.
[18] Gazerani P, Andersen OK, Arendt-Nielsen L. A human experimental capsaicin model for trigeminal sensitization. Gender-specific differences. Pain 2005;118:155–63.
[19] Ge HY, Madeleine P, Arendt-Nielsen L. Gender differences in pain modulation evoked by repeated injections of glutamate into the human trapezius muscle. Pain 2005;113:134–40.
[20] Georgopoulos AP. Functional properties of primary afferent units probably related to pain mechanisms in primate glabrous skin. J Neurophysiol 1976;39:71–83.
[21] Goldreich D, Kanics IM. Tactile acuity is enhanced in blindness. J Neurosci 2003;23:3439–45.
[22] Granot M, Sprecher E, Yarnitsky D. Psychophysics of phasic and tonic heat pain stimuli by quantitative sensory testing in healthy subjects. Eur J Pain 2003;7:139–43.
[23] Greenspan JD, Craft RM, LeResche L, Arendt-Nielsen L, Berkley KJ, Fillingim RB, Gold MS, Holdcroft A, Lautenbacher S, Mayer EA, Mogil JS, Murphy AZ, Traub RJ. Studying sex and gender differences in pain and analgesia: a consensus report. Pain 2007;132:S26–45.
[24] Hallin RG, Torebjork HE. Electrically induced A and C fibre responses in intact human skin nerves. Exp Brain Res 1973;16:309–20.
[25] Hardy JD, Stolwijk JAJ, Hammel HT, Murgatroyd D. Skin temperature and cutaneous pain during warm water immersion. J Appl Physiol 1965;20:1014–21.
[26] Hardy JD, Stolwijk JAA, Hoffman D. Pain following step increase in skin temperature. In: Kenshalo DR, editor. The Skin Senses. Springfield: Thomas; 1968. p. 444–57.
[27] Hashmi JA, Davis KD. Effect of static and dynamic heat pain stimulus profiles on the temporal dynamics and interdependence of pain qualities, intensity, and affect. J Neurophysiol 2008;100:1706–15.
[28] Jensen MT, Petersen KL. Gender differences in pain and secondary hyperalgesia after heat/capsaicin sensitization in healthy volunteers. J Pain 2006;7:211–7.
[29] Koelega HS, Koster EP. Some experiments on sex differences in odor perception. Ann NY Acad Sci 1974;237:234–46.
[30] Konietzny F, Perl ER, Trevino D, Light A, Hensel H. Sensory experiences in man evoked by intraneural electrical stimulation of intact cutaneous afferent fibers. Exp Brain Res 1981;42:219–22.
[31] Krackowizer P, Brenner E. Thickness of the human skin: 24 points of measurement. Phlebologie 2008;37:83–92.
[32] LaMotte RH. Intensive and temporal determinants of pain. In: Kenshalo DR, editor. Sensory functions of the skin of humans. New York: Plenum; 1979. p. 327–58.
[33] LaMotte RH, Campbell JN. Comparison of responses of warm and nociceptive C-fiber afferents in monkey with human judgments of thermal pain. J Neurophysiol 1978;41:509–28.
[34] LaMotte RH, Torebjork HE, Robinson CJ, Thalhammer JG. Time-intensity profiles of cutaneous pain in normal and hyperalgesic skin: a comparison with C-fiber nociceptor activities in monkey and human. J Neurophysiol 1984;51:1434–50.
[35] Lariviere WR, McBurney DH, Frot M, Balaban CD. Tonic, phasic, and integrator components of psychophysical responses to topical capsaicin account for differences of location and sex. J Pain 2005;6:777–81.
[36] Mackenzie RA, Burke D, Skuse NF, Lethlean AK. Fibre function and perception during cutaneous nerve block. J Neurol Neurosurg Psychiatry 1975;38:865–73.
[37] Mendell LM, Wall PD. Responses of single dorsal cord cells to peripheral cutaneous unmyelinated fibres. Nature 1965;206:97–9.
[38] Naert AL, Kehlet H, Kupers R. Characterization of a novel model of tonic heat pain stimulation in healthy volunteers. Pain 2008;138:163–71.
[39] Nielsen CS, Staud R, Price DD. Individual differences in pain sensitivity: measurement, causation, and consequences. J Pain 2009;10:231–7.
[40] Ochoa J, Torebjork E. Sensations evoked by intraneural microstimulation of C nociceptor fibres in human skin nerves. J Physiol 1989;415:583–99.
[41] Price DD, Dubner R. Mechanisms of first and second pain in the peripheral and central nervous systems. J Invest Dermatol 1977;69:167–71.
[42] Price DD. Psychological and neural mechanisms of the affective dimension of pain. Science 2000;288:1769–72.
[43] Pud D, Sprecher E, Yarnitsky D. Homotopic and heterotopic effects of endogenous analgesia in healthy volunteers. Neurosci Lett 2005;380:209–13.
[44] Quiton RL, Greenspan JD. Sex differences in endogenous pain modulation by distracting and painful conditioning stimulation. Pain 2007;132:S134–49.

[45] Riley III JL, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. Pain 1998;74:181–7.
[46] Robinson CJ, Torebjork HE, LaMotte RH. Psychophysical detection and pain ratings of incremental thermal stimuli: a comparison with nociceptor responses in humans. Brain Res 1983;274:87–106.
[47] Robinson ME, Wise EA, Gagnon C, Fillingim RB, Price DD. Influences of gender role and anxiety on sex differences in temporal summation of pain. J Pain 2004;5:77–82.
[48] Rodriguez-Carmona M, Sharpe LT, Harlow JA, Barbur JL. Sex-related differences in chromatic sensitivity. Vis Neurosci 2008;25:433–40.
[49] Sarlani E, Farooq N, Greenspan JD. Gender and laterality differences in thermosensation throughout the perceptible range. Pain 2003;106:9–18.
[50] Sarlani E, Grace EG, Reynolds MA, Greenspan JD. Sex differences in temporal summation of pain and after sensations following repetitive noxious mechanical stimulation. Pain 2004;109:115–23.
[51] Strulov L, Zimmer EZ, Granot M, Tamir A, Jakobi P, Lowenstein L. Pain catastrophizing, response to experimental heat stimuli, and post-cesarean section pain. J Pain 2007;8:273–9.
[52] Thompson T, Keogh E, French CC, Davis R. Anxiety sensitivity and pain: generalisability across noxious stimuli. Pain 2008;134:187–96.
[53] Tillman DB, Treede RD, Meyer RA, Campbell JN. Response of C fibre nociceptors in the anaesthetized monkey to heat stimuli: correlation with pain threshold in humans. J Physiol 1995;485:767–74.
[54] Torebjork HE, Hallin RG. Perceptual changes accompanying controlled preferential blocking of A and C fibre responses in intact human skin nerves. Exp Brain Res 1973;16:321–32.
[55] Torebjork HE, LaMotte RH, Robinson CJ. Peripheral neural correlates of magnitude of cutaneous pain and hyperalgesia: simultaneous recordings in humans of sensory judgments of pain and evoked responses in nociceptors with C-fibers. J Neurophysiol 1984;51:325–39.
[56] Tousignant-Laflamme Y, Pagθ S, Goffaux P, Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. Brain Res 2008;1230:73–9.
[57] Treede RD, Meyer RA, Raja SN, Campbell JN. Evidence for two different heat transduction mechanisms in nociceptive primary afferents innervating monkey skin. J Physiol (Lond) 1995;483:747–58.
[58] Tur E. Physiology of the skin – differences between women and men. Clin Dermatol 1997;15:5–16.
[59] Van Boven RW, Hamilton RH, Kauffman T, Keenan JP, Pascual-Leone A. Tactile spatial resolution in blind Braille readers. Neurology 2000;54:2230–6.
[60] Velle W. Sex differences in sensory functions. Perspect Biol Med 1987;30:490–522.
[61] Verkes RJ, Van der Kloot WA, Van der MJ. The perceived structure of 176 pain descriptive words. Pain 1989;38:219–29.
[62] Woodward KL. The relationship between skin compliance, age, gender, and tactile discriminative thresholds in humans. Somatosens Mot Res 1993;10:63–7.