Effect of static and dynamic heat pain stimulus profiles on the temporal dynamics and interdependence of pain qualities, intensity and affect

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Abstract

Acute and chronic pains are characterized by a particular constellation of pain qualities, such as burning, aching, stinging or sharp feelings. However, the temporal pattern of specific pain qualities and their relationship with pain and affect is not well understood. In addition, little is known about how the temperature time-course of the stimulus impacts the temporal dynamics of pain qualities and the relationship between pain qualities. Therefore, we applied two types of stimuli to the feet of 16 healthy subjects, each calibrated to evoke a similar pain magnitude (50/100): static stimulus held at constant intensity and dynamic stimulus increased in intensity in small steps. Stimulus runs consisted of three 30s stimuli (either static or dynamic) with an interstimulus interval of 60s. Continuous online ratings of pain, burning, sharp, stinging, cutting and annoyance were obtained in separate runs and the evoked responses were characterized by within-stimulus adaptation (early 0-15s peak vs. late 25-40s peak) and by their temporal properties (time to onset, peak and end). The temporal profile of the burning sensation was similar to the pain and annoyance evoked by the static and dynamic stimuli. However, the sharp, stinging and cutting sensations attenuated in response to the static stimuli (p<0.01), but intensified along with pain and affect in response to the dynamic stimuli (p<0.05); whereas there was no attenuation in the evoked profiles of pain (p=0.61), annoyance (p=0.27) or burning quality (p=0.27). These data demonstrate that specific pain qualities with known differences in underlying mechanisms have distinct temporal dynamics that depend on the stimulus intensity dynamics.
INTRODUCTION

Pain is a multifaceted construct composed of intensity, affect and a myriad of pain specific qualities (Davis and Pope 2002; Kwan et al 2002; Rainville et al 1999). Hence a noxious thermal stimulus elicits sharp, burning and stinging sensations and concurrently elicits emotions like distress and annoyance (Melzack 2005; Melzack 1975). These subjective pain dimensions wax and wane in the continued presence of a noxious stimulus (Greene and Hardy 1962). This temporal variability can occur due to peripheral and central phenomenon such as nociceptor adaptation (Torebjork et al 1984) and central summation (Ochoa and Torebjörk 1989; Price and Dubner 1977; Torebjork and Ochoa 1980), descending inhibition (Bouhassira et al 2003) or due to a change in stimulus properties (Davis and Pope 2002; Grill and Coghill 2002; Yelle et al 2008). However, the temporal pattern of specific pain qualities and their relationship with pain and affect is not well understood.

Specific pain sensations such as sharp-stinging and dull-burning are associated with distinct nociceptive mechanisms and as such the temporal patterns of these sensations are likely to be distinct from each other. For instance burning sensations are associated with activation of polymodal C-fibres (Ochoa and Torebjörk 1989; Price and Dubner 1977; Torebjork and Ochoa 1980). Additionally burning sensations persist and intensify on prolonged C-fibre stimulation possibly through temporal integration of C-fibre inputs in the spinal dorsal horn. These mechanisms are also linked with encoding of prolonged pain and affect. Conversely, sharp/pricking sensations involve activation of A-delta type-2 nociceptors (Adriaensen et al 1983) and spinal dorsal horn cells such as nociceptive specific cells (Christensen and Perl 1970; Kumazawa and Perl 1978).

Prolonged A-delta type-2 nociceptor stimulation and nociceptive specific cell activation results in adaptation or ‘temporal suppression’ (Andrew and Craig 2002; Handwerker and Kobal 1993; Price and Dubner 1977; Treede et al 1995; Treede et al 1998). However, the adaptation patterns of specific pain qualities and how adaptations impact the relationship between pain intensity, quality and affect needs to be investigated.
Thus, the objectives of this study were to 1) systematically characterize the temporal profiles of the most prominent noxious heat-evoked sensations; 2) investigate the relationship and inter-dependence of specific qualities with pain intensity and affect, and 3) investigate the effect of altering the stimulus intensity profile on the temporal patterns of pain sensations and the relationship between qualities. Towards this last goal, we used two types of stimuli that were calibrated to evoke a similar magnitude of overall pain: one held at a constant temperature (static stimulus) and the other with gradual stepped increases in temperature (dynamic stimulus). We hypothesized that 1) burning sensations have a different temporal profile compared to sharp and other related qualities, 2) there is an association between the profiles of pain intensity, annoyance and burning quality, 3) the relationship between pain qualities, pain intensity and affect depends on stimulus intensity dynamics.

METHODS

Subjects

A total of 19 right-handed healthy male subjects (mean age = 27 ± 5 yrs (SD)) were recruited from staff and students within the local university and hospital communities. All subjects gave informed written consent to procedures approved by the University Health Network Research Ethics Board. Data obtained from three subjects were incomplete and discarded as they provided unreliable ratings or abnormally high pain ratings. Thus, all data are reported from a final group of 16 subjects.

Thermal stimuli

Stimuli were delivered to the ventral surface 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 16x16mm. Each subject participated in two separate experiment sessions held on different days to test static stimuli (session 1) and dynamic stimuli (session 2). The static and dynamic stimuli temperatures (i.e., targets) to be used in the main experiments were individually selected.
in a preliminary session to produce a peak pain rating of approximately 50/100 on a visual analog scale (VAS). Thus, subjects were tested with 30s static stimuli (from a baseline temperature of 35°C and a ramp rate of ~8°C/s) at various temperatures to determine the target temperature to be used in the static stimulus experiments. For the dynamic stimulus experiments, combinations of start and end dynamic stimulus temperatures were reached starting from a baseline temperature of 35°C at ~8°C/s. Each dynamic stimulus was set to be 30s in duration and to span approximately 3°C and consisted of 7 discrete steps with each step increasing 0.5°C at ~8°C/s (see Figure 1).

Experimental procedure

Each experimental session consisted of 6 stimulus runs in order to assess each of the six pain qualities of interest (see ratings description below). Each run consisted of a 15s baseline period (35°C) followed by three stimuli, each of which were separated by a 60s interval during which the probe temperature was held at the 35°C base. For each static stimulus, the thermode temperature rose at ~8°C/s until the target temperature was reached, and held at target for 30s and then returned to baseline at ~8°C/s. For each dynamic stimulus, the thermode temperature rose at ~8°C/s to the dynamic stimulus start temperature, and then approached the dynamic stimulus end temperature over 30s, consisting of 7 discrete steps with each step increasing 0.5°C at ~8°C/s. This design allowed us to investigate perceptual outcomes of clearly dissimilar stimuli (i.e., static versus dynamic) that nonetheless evoked a similar magnitude of pain for a similar duration. After every run the thermal probe was relocated to a new skin area to avoid interactions between consecutive stimulus runs.

Pain dimension ratings

A preliminary experiment was run in 4 subjects to determine the most common heat-evoked sensations evoked by a 30s static stimulus. Subjects were asked to select words from the 78 word descriptors in the McGill Pain Questionnaire (MPQ) (Melzack 1975). The sensory descriptors most commonly selected were “sharp” (4/4 subjects), “cutting” (3/4 subjects), “stinging” (4/4 subjects), and “burning” (4/4 subjects). Amongst
the affective descriptor only “annoying” was selected (4/4 subjects). Therefore, in the main study, the intensity of these 5 descriptors was assessed in addition to intensity of heat pain.

Each sensation was assessed separately allowing the subjects to focus on one sensation at a time. Therefore, subjects rated each of the six heat-evoked sensations in separate runs. The first run was used to assess heat pain intensity to establish pain at a level of 50/100 VAS across subjects and across the sessions. Subsequently, the subjects evaluated annoyance related to the pain evoked by the heat stimulus. The next four runs were delivered in a randomized order to assess sharp, cutting, stinging and burning sensations. Assessments of pain and annoyance were carried out first so that the time course of these qualities could be established before being affected by the perceived differences in time-courses of heat pain qualities.

Subjects used a 100-mm computerized VAS scale (COVAS, Medoc) to continuously rate perceived intensity of each of the six sensations. In each run 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 and for the “sharp” run, the anchors were “no sharp sensation” at the lower limit of 0 and “most intense sharp sensation 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 use the numerical values (25, 50 and 75) and in-between values to anchor the magnitude of the sensation.

All subjects underwent training to learn how to use the rating system and focus and rate one single sensation at a time prior to the experiment. 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 tingles and tiny pricks. The sensation of cutting quality, on the other hand, was conveyed as the sensation of
being cut with a knife or with paper. The remaining quality, burning, was described simply as the sensation of a burn that occurs with hot objects or with chemicals.

**Data analysis and statistics**

The magnitude of the quality time-courses were compared across an early and late stimulus period (see Figure 1). The ‘early’ peak magnitude of each quality was assessed by measuring the peak rating value within 15 seconds from stimulus onset. Each time course was also assessed for a ‘late’ peak magnitude rating during the 25-40 second period from stimulus onset. These early and late peaks were compared with each other to assess time-related adaptation or intensification in the peak magnitude of heat pain qualities. Another measure for verifying adaptation was the time to offset: the interval from the stimulus onset to the time where ratings returned to zero. Other indices of the temporal properties of evoked heat pain attributes included the time to onset and time to peak rating of each sensation from the onset of each stimulus. The effect of repeating each stimulus within a run at an interstimulus interval of 60s was assessed by comparing measures of magnitude including peaks during early stimulus period (0-15 seconds) and % change in total sensation. Total sensation was measured per stimulus as area under the response curve (AUC). In addition, the effects of stimulus repetitions on temporal properties such as time to onset and time to peak of evoked sensations across stimulus 1, 2 and 3 were also assessed.

Data were analyzed with SPSS (version 13.0). To study the dynamics of heat pain qualities evoked by two different types of stimuli (i.e., static, dynamic), we pre-set stimulus temperatures for each subject to evoke a peak pain of approximately 50/100 on the VAS scale. This heat pain level was achieved at an average temperature 47°C ± 1°C (SD) with the static stimulus. For the dynamic stimuli, this heat pain level was achieved with a start temperature of 45 °C ± 1°C (SD) and end temperature of 48 °C ± 1°C (SD) (see Figure 1). Despite the small variations in peak stimulus temperature, for all statistical analyses, the effect of different stimulus temperatures was regressed out by using peak stimulus temperature for each subject as a covariate. This was achieved with analysis of covariance within each univariate or multivariate test which allowed a
calculation of differences between conditions significant over and beyond the affects of the covariate.

Analyses of pain and pain attribute dynamics mainly consisted of univariate or multivariate tests. First, within a single condition, the differences between measures of heat pain attributes were compared with each other using a univariate analysis of covariance (ANCOVA) and post hoc comparisons used Bonferroni corrections for multiple comparisons. Moreover, to assess measures of pain attributes between different conditions (examples of conditions include static versus dynamic stimuli, or early versus late stimulus period), we used a multivariate analysis of covariance (MANCOVA). In the case of a significant multivariate F-test, univariate tests were carried out to compare measures of each dependent variable (i.e. pain attributes) between conditions. Similarly, the effect of temperature variability between conditions was tested with post hoc univariate contrasts. For pain attribute measures evaluated at different time points (e.g. between early and late or between stimulus 1, 2 and 3), MANCOVA with repeated measures contrasts were used. Comparisons were considered significant at a p<0.05.

RESULTS

Responses to the First Static and Dynamic Stimulus

GENERAL TEMPORAL PROPERTIES. The group average ratings for each sensation evoked by the first stimulus of each static and dynamic run are shown in Figure 1. Overall, the static stimuli and dynamic stimuli evoked a similar magnitude of heat pain. Specifically, there was no significant differences in peak ratings of heat pain (p=0.28) between the first static and first dynamic stimulus. Similarly, the total amount of heat pain (i.e., area under the curve) (p=0.43) evoked by the first static stimulus and dynamic stimulus was not significantly different from each other (Fig 1, 2). However, there were prominent differences between static and dynamic stimulus-evoked temporal patterns of the other specific heat pain attributes.
First, the time to onset of all heat pain qualities evoked by the static stimuli showed no significant differences amongst the heat pain qualities (p=0.186). Onset times evoked by the dynamic stimuli seemed to vary more between subjects (see Figure 2, left panel), but there were no significant differences in onset times between heat pain qualities evoked by the dynamic stimulus (p=0.17). Furthermore, the onset times of sensations evoked by the static stimuli were not significantly different from those evoked by the dynamic stimuli (p=0.13). In addition, the differences in temperature between peak temperatures of static stimuli and early target temperatures of dynamic stimuli did not significantly influence the onsets of pain attributes evoked by the static and dynamic stimuli (p=0.15).

The time to peak rating (see Figure 2, right panel) varied significantly between heat pain attributes in response to the static stimuli (main effect: p=0.001). These different times to peak were not due to differences in stimulus temperatures used across subjects (p=0.86). Post-hoc tests revealed that peak ratings of sharp (p=0.001), stinging (p=0.026) and cutting (p=0.001) qualities evoked by the static stimuli occurred significantly earlier than peak rating of heat pain (see Figure 2) but no other post-hoc inter-comparisons were significant (p> 0.05). Conversely, the time to peak rating for the qualities evoked by the dynamic stimuli did not vary significantly between pain attributes (p=0.87). Thus, a comparison between static and dynamic stimuli evoked times to peak of all evaluated pain attributes showed a significant overall effect (p=0.0001), but temperature variability between subjects was not a significant factor (p=0.55). Post hoc comparisons showed that for all heat pain qualities, the time to peak ratings was significantly longer in response to the dynamic stimuli compared to the static stimuli responses (p>0.05).

**ADAPTATION: INTRA-STIMULUS ATTENUATION AND INTENSIFICATION.** Several heat pain qualities showed remarkable attenuation during the static stimuli, sometimes dissipating before the stimulus ended (see Figure 1). We used 2 measures to quantify this attenuation: peak ratings that occurred during the early and the late periods of the
For the first index of attenuation, we compared the peak ratings evoked during the early phase (0-15s of stimulus) and the late phase (25-40s) of the static stimulus. Overall across all heat pain dimensions, the early and late peak ratings were significantly different (p=0.0001), and this finding was not affected by variability in stimulus temperatures (p=0.83). As shown in Figure 3A (left panel), post-hoc tests showed that significant attenuation of peak ratings occurred for the sharp (p=0.0001), stinging (p=0.004) and cutting (p=0.0001) qualities, but not for the pain (p=0.61), annoyance (p=0.27) or burning (p=0.27). Thus, there were no significant differences between late peak ratings of burning quality, pain and annoyance. On the other hand, the adapted late peak ratings of sharp, stinging and cutting qualities were significantly less in magnitude compared with pain, annoyance and burning quality (p>0.05; see Figure 3). In addition, there was no significant difference between late peaks of sharp, stinging and cutting heat pain qualities.

For a second index of attenuated responses to static stimuli, and to validate the findings based on the peak ratings, we compared the time to offset of all pain attributes with each other (see Figure 3B). There was a significant main effect of pain attribute on the time to offset in response to static stimuli (p=0.0001); this variability was not significantly influenced by stimuli temperatures (p=0.10). The second level post-hoc tests revealed that the offset times of the sharp, stinging and cutting qualities were significantly shorter (i.e., an earlier attenuation) than the offset times of pain (p<0.0001), annoyance (p<0.001) or burning (p<0.001). The offset times of pain, annoyance and burning quality were not significantly different from each other (p=0.99). Similarly the offset times of sharp, stinging and cutting qualities were not significantly different from each other (p>0.05).

In contrast to the adaptation evoked by the static stimuli, none of the pain sensations attenuated during the late phase of dynamic stimuli (see Figure 3A, right
Instead, nearly all pain attributes showed significantly more intense peak magnitude (overall $p=0.018$) during the late period compared with the peaks evoked during the early period of the dynamic stimulus. In addition, the difference between early and late dynamic stimulus temperature did not significantly effect the differences between early and late peak magnitude ($p=0.26$). As shown in Figure 3A, post-hoc tests indicated that peak ratings increased with time for all pain qualities ($p<0.05$) except the cutting quality ($p=0.38$). Moreover, there were no significant differences in offset times evoked by the dynamic stimuli amongst the six evoked sensations ($p=0.57$); and none of the evaluated sensations ended before dynamic stimulus offset (see Figure 3B). Thus, when static and dynamic stimulus evoked offset times were compared with each other, the offset values of pain ($p=0.062$) and annoyance ($p=0.85$) were not significantly different (overall $p=0.0001$). In contrast, the offset times of sharp ($p=0.045$), stinging ($p=0.0001$) and cutting ($p=0.0001$) qualities occurred significantly earlier in response to the static stimulus when compared with offset of these heat pain attributes evoked by the dynamic stimulus. However, burning quality did not attenuate earlier in response to the static stimulus, but rather persisted longer for the static stimulus ($p=0.011$) compared to the dynamic stimulus. The difference in heat pain quality offset values between static and dynamic stimuli was not affected by variability between peak stimulus temperatures ($p=0.57$).

**Effects Of Repeated Stimulation On Temporal Relationships Between Pain Attributes**

The temporal properties of sensations evoked by the static and dynamic stimuli were clearly affected by repeated stimulation (see Figure 4) despite the long (60s) inter-stimulus interval.

First, as shown in Figure 5A, the time to onset of heat pain attributes were significantly longer (main effect $p=0.0001$) for the second and third stimuli compared to the first stimulus. Thus, in comparison with responses to the first stimulus, the onsets of all pain qualities occurred significantly later ($p<0.05$) in response to the second static stimulus ($p=0.001$) and the third static stimulus ($p=0.0001$).
Second, the times to peak of all heat pain attributes were also significantly delayed in response to the second (p=0.0001) and third static stimuli (p=0.0001; overall p=0.0001) when compared with responses to the first static stimuli. Moreover, in order to investigate the effect of stimulus repetition on changing temporal relationships between pain attributes, the peak times of pain attributes were compared with each other. As already noted, in response to the first static stimuli, evoked responses of sharp, stinging and cutting sensations peaked significantly earlier than the evoked response of heat pain. On the other hand, in response to stimulus 2 and stimulus 3, all pain attributes peaked at durations similar to the time to peak of heat pain. Moreover, in response to stimulus 2, there was no significant difference between times to peak of heat pain and any of the heat pain attributes (p>0.05). Nevertheless, annoyance peaked significantly later than stinging (p=0.044) and cutting (p=0.002) sensations. Moreover, the burning quality peaked significantly later than cutting quality (p=0.015). But, none of the other comparisons were significant (p>0.05). The F-test between times to peak in response to stimulus 2 was significant at p=0.0001. In contrast, there was no significant difference in times to peak between any of the pain attributes in response to stimulus 3 (p=0.14).

In contrast with effects of static stimulus repetition, dynamic stimulus repetition did not significantly alter time to peak of pain attributes. Hence, there were no significant differences in time to peak between stimulus 2 and 1 (p=0.32) or between stimulus 3 and 1 (p=0.5). Nevertheless, like static stimuli repetitions, dynamic stimulus repetition (stimulus 2 and 3) also caused a delay in onset of evoked heat pain attributes (p=0.0001; see Figure 5A and 5B) compared with responses to stimulus 1. Therefore, in response to stimulus 2, the onset of all pain attributes (p<0.05) occurred significantly later compared with responses to stimulus 1 (p=0.0001). Similarly, in response to stimulus 3, the pain sensation onsets were significantly delayed compared with responses to stimulus 1 (p=0.01) and onsets of most pain attributes were significantly affected (p<0.05), with the exceptions of the onset responses of burning and stinging qualities that did not change significantly between stimulus 3 and stimulus 1.
Stimulus repetition also resulted in a significant suppression of the early (0-15s) peak ratings in pain attributes evoked by static stimuli ($p=0.0001$) and the dynamic stimuli ($p=0.0001$) (see Figure 6). Hence, in response to the second and third static stimuli, the early peaks of all heat pain attributes ($p<0.05$) were significantly less when compared with early peaks evoked by the first static stimulus. Similarly, the early peak responses to the second and third dynamic stimuli were significantly lower compared with responses to the first dynamic stimuli effecting pain, annoyance, stinging and cutting qualities ($p<0.01$; over all $p=0.016$). However, stimulus repetition had no effect on early peak ratings of sharp quality either in response to the second dynamic stimulus or the third dynamic stimulus ($p>0.05$). Moreover, the early peaks of burning sensations evoked by the second dynamic stimulus were also significantly decreased when compared with responses to the first dynamic stimulus ($p=0.026$), but as shown in Figure 6B, this effect was not sustained for the third dynamic stimulus ($p=0.83$).

Stimulus repetition also attenuated the total magnitude of sensations (i.e., area under the response curve) for the dynamic stimuli ($p=0.0001$; see Figure 6B), but not for the static stimuli ($p=0.19$). Post-hoc comparisons showed that total magnitude of pain ($p=0.0001$), annoyance ($p=0.0001$), and stinging ($p<0.001$) qualities in response to dynamic stimulus 2 and 3 were significantly reduced compared with stimulus 1. Burning sensations were also significantly reduced ($p=0.006$) in response to stimulus 2, but not in response to stimulus 3 ($p=0.37$). The other pain attributes did not show a significant attenuation during dynamic stimulus repetitions ($p>0.05$). In addition, the effect of variability in stimulus temperature on effects of stimulus repetitions was not significant in any comparison ($p>0.05$) reported above.

**DISCUSSION**

These findings provide strong evidence that temporal fluctuations in specific heat pain qualities occurs in distinct relationship with pain and annoyance. Moreover, heat pain qualities follow specific temporal patterns that are closely affected by static or
dynamic stimulus intensity profiles. These findings build on our previous studies of sensations evoked by painfully cold stimuli (Davis 1998; Davis and Pope 2002; Harrison and Davis 1999) and provide further insight into mechanisms encoding different pain qualities. Notably, this study suggests an important role for temporal fluctuations in heat pain qualities and in mechanisms that encode stimulus and/or heat pain perception properties. The key observations are:

1) Specific qualities such as sharp and burning demonstrate distinct temporal patterns conceivably due to differences in underlying mechanisms. Hence, the temporal pattern of an evoked sharp quality was remarkably similar to temporal patterns of stinging and cutting qualities, but was distinct from the temporal pattern of a burning quality.

2) The static and dynamic stimulus intensity profiles had a marked effect on temporal patterns of heat pain qualities and their relationship with pain and annoyance. The sharp, stinging and cutting qualities evoked at stimulus onset eventually dissipated when the stimulus intensity was held static, but intensified when stimulus intensity was varied. The temporal profile of the burning quality was similar to the temporal profiles of pain and annoyance in response to static and dynamic stimuli. In contrast, the temporal patterns of sharp, stinging and cutting sensations showed a relationship with pain and annoyance only when evoked by the dynamic stimuli and during the early period of the static stimuli.

3) Stimulus repetition altered the temporal patterns of pain qualities, but did not alter the stimulus profile specific relationships between pain qualities, affect and pain.

Temporal patterns of sharp type and burning qualities are determined by mechanisms that are classically implicated in evoking these sensations

The similarity in temporal patterns of sharp, stinging and cutting sensations suggests that these percepts are evoked by common mechanisms. Classical studies unequivocally link sharp and stinging pain sensations with activity in A-delta nociceptors (Adriaensen et al 1983; Campbell and LaMotte 1983; Davis 1998; Georgopoulos 1976; Konietzny et al 1981; Mackenzie et al 1975; Schady et al 1983; Torebjork and Hallin 1973), whereas burning sensations have been associated with activity in C-fibers.
Studies on nociceptive primary afferents indicate that the marked attenuation in
the sharp type sensations during prolonged static stimulation may have been caused by
adaptation of activity in A-delta type 2 nociceptors. For instance, such adaptation has
been observed in A-delta type nociceptor activity in response to a 30s laser stimulus
(Treede et al 1995; Treede et al 1998), and similar adaptations have been reported with
prolonged contact heat stimuli (Adriaensen et al 1983). In addition to primary afferent
activity, prolonged noxious stimulation with stimulus modalities that evoke sharp heat
and mechanical pains has also been shown to suppress the activity within specific spinal
pathways. Thus, responses of mechano-sensitive or mechanoheat-sensitive lamina 1
dorsal horn cells have shown such adaptations when stimuli were held at a static intensity
(Andrew and Craig 2002; Christensen and Perl 1970; Kenshalo, Jr. et al 1979;
Kumazawa and Perl 1978). Moreover, these neurobiological systems adapted when brief
stimuli were repeated and when the stimuli were prolonged.. Therefore, nociceptor
adaptations in these previous studies (Adriaensen et al 1983; Slugg et al 2000; Treede et
al 1995; Treede et al 1998) have been ascribed to fatigue in signal transduction
mechanisms caused by prolonged stimulation (Cesare and McNaughton 1996).
Nevertheless, the role of cellular fatigue in thus observed adaptations in pain perception
has not been entirely clear (Treede 1995). This study suggests that adaptation to static
activity is not due to fatigue in signal transduction mechanisms induced by prolonged
stimulation. This presumption is based on our finding that despite a similar duration of
static and dynamic stimuli, the evoked sharp sensations were suppressed only in response
to static intensity stimuli. Hence, perhaps spinal mechanisms and/or supra spinal feed
back loops that are known to modulate presynaptic firing properties (Hu and Sessle 1988;
Koltzenburg and Handwerker 1994) (Sessle et al 1981) may be involved in this
adaptation..
In addition, the evoked patterns of sharp type sensations indicate that sharp type heat pain sensations are evoked particularly in response to a rise in stimulus intensity. Similarly, pain-signaling nociceptors that are linked with evoking sharp pain sensations, such as A-delta nociceptors, are known to increase their responses in relation to stimulus intensity. For example, both A-delta type 2 nociceptors and mechano-sensitive lamina 1 cells can encode stepped increases in brief stimulus intensity (Andrew et al 2003; Christensen and Perl 1970; Treede et al 1995; Treede et al 1998). In addition, graded increases in stimulus intensity evokes more intense sharp and stinging pain qualities (Acosta et al 2001b; Acosta et al 2001a). Therefore, we postulate that increase in stimulus intensity evokes sharp pain sensations mediated by a unique set of mechanisms.

*Static and dynamic stimuli evoke temporal summation of pain through different mechanisms*

In contrast to the sharp type sensations, the burning heat pain sensations did not adapt with time, but (along with pain and annoyance) rather persisted to the end of the static heat pain stimulus. This temporal relationship between pain and burning quality has also been classically demonstrated with repetitive heat pain stimuli. Thus, brief repetitive heat pain stimuli held at static intensity evoke a burning sensation and pain that intensify with time: a phenomenon referred to as ‘temporal summation’ of heat pain. (Price and Dubner 1977; Staud et al 2006; Vierck, Jr. et al 1997). Interestingly, pronounced temporal summation is thought to be a hallmark of several types of chronic pains (Meeus and Nijs 2007; Sarlani et al 2007), and so stimuli that evoke temporal summation are now used as a clinical tool to evaluate sensory abnormalities in chronic pain populations (Rolke et al 2006; Treede 2003). Moreover, mechanisms of temporal summation are putatively known and involve temporal integration of C-fiber inputs or ‘wind-up’ in spinal dorsal horn cells (Mendell and Wall 1965). Both wind-up and temporal summation are linked with central sensitization of pain systems (Herrero et al 2000; Russo et al 1998).
In addition to brief repetitive stimuli, prolonged heat pain (or tonic) stimuli have also been used to evoke temporal summation of pain, but the profiles of specific sensations have not been investigated (Granot et al 2006). Moreover, the mechanisms whereby prolonged stimuli evoke temporal summation are not clearly known. However, it is believed that repetitive heat pain stimuli and static prolonged stimuli evoke pain and burning sensations through spinal wind-up of C-fiber inputs. This is because pain and burning sensations are evoked persistently throughout the duration of a prolonged heat pain stimulus, whereas, activity in polymodal C-fibers nociceptors adapts after an early dynamic phase of activity. This mismatch between evoked sensation and nociceptor activity has been ascribed to spinal mechanisms similar to wind-up induced with repetitive heat pain stimuli (Adriaensen et al 1984a; Andrew and Greenspan 1999; LaMotte et al 1984). In addition to spinal mechanisms, repetitive and prolonged stimuli evoke similar responses possibly due to similar temperature dynamics within the skin (Granot et al 2006; Mauderli et al 2003) and thus, may engage similar heat transduction mechanisms (Lumpkin and Caterina 2007). Another indication of a similarity between tonic and repetitive stimulation induced temporal summation was presented by the contrast between profiles of sharp type and burning sensations. Thus unlike the persistent burning sensations, sharp sensations were suppressed on prolonged static stimulation which corresponds to temporal suppression of sharp sensations in response to brief repetitive stimuli. This repetitive stimulus related suppression in sharp sensations was ascribed to adaptation in A-delta nociceptor activity (Herrero et al 2000; Price and Dubner 1977).

On the other hand, heat pain and burning sensations also intensified with time in response to the dynamic stimulus. However, unlike centrally mediated summation of static intensity inputs, the dynamic stimulus evoked intensification of pain and burning quality likely involves a corresponding increase in activity of nociceptive afferents. Thus, it has been observed that heat pain stimuli with stepped rise in intensity, similar to stimulus used in the present study evoked a corresponding increase in polymodal C-fiber activity with each temperature elevation (Gallar et al 1993). Moreover, A-delta nociceptive afferents are known to encode stimulus intensity, and thus the intensification
Heat pain qualities

in dynamic stimulus-evoked sharp sensations could be due to an increasing activity in the related nociceptors (Treede et al 1995; Treede et al 1998) that are then transmitted to central nociceptive pathways (Christensen and Perl 1970). Thus, the dynamic stimulus-evoked temporal pattern of pain putatively involves a relatively linear translation of increasing sensory inputs from A-delta and C-fibers generated in response to each stepped increase in stimulus intensity. In contrast, the static stimulus evoked pattern of pain may be mediated centrally and may result from of a non-linear temporal integration of nociceptive inputs.

**Stimulus repetition alters temporal dynamics of heat pain sensations without affecting relationships between pain dimensions**

Exposure to the first stimulus induced fatigue/habituation type effects that prominently altered the time-course of evoked sensations on subsequent exposures to heat pain stimuli. These inter-stimulus interactions occurred despite a 60s long inter stimulus interval. Fatigue or habituation have been often reported to occur in responses of nociceptors (Adriaensen et al 1984b; Tillman et al 1995) (LaMotte and Campbell 1978; Treede et al 1995; Treede et al 1998) on repetitive stimulation. Such fatigue or delay in onset of nociceptor activity could be responsible for the delayed onset of pain qualities and reduction in early peak magnitudes observed in response to static and dynamic stimulus repetitions. On the other hand, the dynamic stimulus-evoked times to peak and late peaks (see Figure 4) did not show fatigue. Similarly, nociceptors are also known to respond to increase in intensity of heat pain stimuli delivered to the same receptive fields without reduction in peak activity or fatigue (Treede et al 1995).

The static stimulus repetitions, on the other hand accompanied prominent changes in the times to peak of pain qualities. Thus, the fatigue related delays in onset, and changes in time to peak observed with stimulus repetition shifted the peaks of pain, annoyance and burning sensation towards the late period of the static stimulus. However, the most prominent effect of these changes was that the times to peak of sharp, stinging and cutting pain qualities became synchronized with pain in response to the second static
stimulus and with all other evaluated pain attributes in response to the third static stimulus. In addition, static stimulus repetition at 60 second intervals did not increase or decrease the total magnitude, hence ruling out sensitization or habituation; instead the effects of repetition particularly affected temporal properties. These temporal re-adjustments could be due to residual heat remaining in the skin after the first exposure to the stimulus. But, the gradual re-adjustments that lead to an alignment between times to peak of all pain attributes in response to the third static stimulus is plausibly due to central mechanisms that modulate pain. On the other hand, the time to peak did not show changes when dynamic stimuli were repeated, hence indicating that responses to the dynamic stimuli were closely linked with nociceptor responses to changes in temperature.

Prolonged stimuli evoke sharp and burning pain at a similar delay.

Burning heat pain sensations evoked by brief thermal stimuli classically arise 1000-1500 ms later than sharp sensations. This occurs presumably due to the faster conduction velocity of A-delta primary afferents that evokes an early sensation of sharp pain (also called first pain). In comparison, the slower conduction velocity of unmyelinated C-fibers is implicated in the delayed onset of burning sensation (or second pain) (Campbell and LaMotte 1983; Handwerker and Kobal 1993; Price and Dubner 1977). Hence, we were surprised that in the current study there was no temporal difference between the onset times to sharp and burning sensations. Furthermore, our onset times of about 4-5 seconds cannot be fully accounted for by typical A-delta and C-fiber conduction (about 1-2s) and a motor reaction (about 1s). We confirmed that the absence of temporal difference in the onset of sharp and burning sensations was not due to variability in stimulus temperatures between subjects.

Nonetheless, previous studies have also noted such a discrepancy in onset latency of pain sensation which is significantly longer than the calculated latency based on speed and distance of axonal conduction healthy subjects (LaMotte et al 1984). This prolonged latency in all pain sensations alike suggests a delay induced by stimulus appraisal mechanisms required to discriminate and cognitively evaluate a particular sensation.
amongst the milieu of others. Even if a specific sensation is evoked at a certain delay, the concomitant presence of other sensations could mask its onset. Thus, with brief contact and with laser stimuli, sharp sensations are known to adapt rapidly, allowing quick identification of the delayed onset of dull-burning sensations. Another impediment in distinguishing temporal differences in onset could be the relatively slower (8°C/s) rise time of the device used in our study in comparison with other studies. Nevertheless, the delayed onset of sensations warrants further investigation into brain mechanisms that evaluate onset of sensations.

CONCLUSIONS

This study provides evidence for two distinct mechanisms in pain perception: the first mechanism evokes sharp-type pain qualities that dissipate during a static noxious stimulus and a second mechanism that evokes persistent sensations of burning quality, pain and affect in response to noxious stimuli. Thus, the temporal dynamics of specific pain qualities play a consequential role in both stimulus perception and in pain perception.

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FIGURE LEGENDS

Figure 1
Raw averaged time courses of pain attributes evoked by the first static and dynamic stimuli. Blue lines and pink lines represent time-courses of stimulus and pain attributes specific to either static stimuli or dynamic stimuli respectively. Error bars represent standard error of means displayed at 1 error bar every 3-4s for the ratings.

Figure 2
Temporal properties of the response to the first static and dynamic stimuli. The time to onset of the 6 sensations are shown on the left and the time to peak for each sensation are shown on the right for the static (filled bars) and dynamic stimuli (empty bars). i, represents qualities with a significantly different time to peak compared to pain intensity.
Error bars represent standard error of means.

Figure 3
Adaptation (intra-stimulus attenuation or intensification) of the responses to the first static and the dynamic stimuli. A. The peak ratings for the early and late phases are shown for the static (filled bars) and dynamic stimuli (empty bars).
*, indicates significant differences between early and late peak ratings evoked by the same stimulus.
B. The time to offset measured as the interval from the stimulus onset to the time where ratings returned to zero.
*, β, i, α represent a significantly different offset time (p<0.05) for a particular sensation compared to the offset time for burning, pain intensity or annoyance (evoked by the same stimulus).

Error bars represent standard error of means

Figure 4

Raw averaged time courses of pain attributes evoked by static and dynamic stimuli 1, 2 and 3. Blue lines and pink lines represent time-courses of stimulus and pain attributes specific to either static stimulus or dynamic stimuli respectively. Error bars represent standard error of means displayed at 1 error bar every 3-4s for the ratings.

Figure 5:

Habituation effects on temporal properties of sensations evoked by static and dynamic stimuli. Habituation effects were assessed based on changes in time to onset of each sensation (A) and time to peak of each sensation (B)

* indicates significant differences compared to stimuli 1 at p<0.05

Error bars represent standard error of means.

Figure 6:

Habituation effects on the response magnitudes of sensations evoked by static and dynamic stimuli. Habituation effects were assessed based on the peak rating for each sensation during the early (first 15s) phase (A), and for the % change in the total magnitude of sensation (i.e., area under the curve) (B),

* indicates significant differences in absolute values compared to stimulus 1 (A) or a significant % change from stimuli 1(B) at p<0.05

Error bars represent standard error of means.
Fig 2

Time to Onset

Time to Peak

* Static

* Dynamic
Fig 3

A

B

Static

Dynamic

Peak Rating

Time to offset (s)

Early

Late

Early

Late

Pain

Annoyance

Burning

Sharp

Stinging

Cutting

Peak Rating

Time to offset (s)

Pain

Annoyance

Burning

Sharp

Stinging

Cutting

* * * * * * * * * * * *
Fig 5

A  Static Stimulus

- Time to onset (s)
  - Stimulus 1
  - Stimulus 2
  - Stimulus 3

B  Dynamic Stimulus

- Time to onset (s)
  - Stimulus 1
  - Stimulus 2
  - Stimulus 3

- Time to Peak (s)
  - Stimulus 1
  - Stimulus 2
  - Stimulus 3

* Static Stimulus
* Dynamic Stimulus
Fig 6

A  Static Stimulus

Peak ratings during early 15s

B  Dynamic Stimulus

% change in total sensation from stimulus 1

Fig 6

A  Static Stimulus

Peak ratings during early 15s

B  Dynamic Stimulus

% change in total sensation from stimulus 1