Filling-in, Spatial Summation and Radiation of Pain: Evidence for a Neural Population Code in the Nociceptive System

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Abstract

The receptive field organization of nociceptive neurons suggests that noxious information may be encoded by population based mechanisms. Electrophysiological evidence of population coding mechanisms has remained limited. However, psychophysical studies examining interactions between multiple noxious stimuli can provide indirect evidence that neuron population recruitment can contribute to both spatial and intensity-related percepts of pain. In the present study, pairs of thermal stimuli (35ºC/49ºC or 49ºC/49ºC) were delivered at different distances on the leg and abdomen and subjects evaluated pain intensity and perceived spatial attributes of stimuli. Reports of radiation of pain were most frequent at 5 and 10cm distances ($\chi^2=34.107, p<0.0001$). Perceived connectivity between two noxious stimuli (filling-in) was influenced by the distance between stimuli ($\chi^2=16.756, p<0.01$), with the greatest connectivity reported at 5 and 10cm separation distances. Spatial summation of pain (SSP) occurred over probe separation distances as large as 40cm and 6 dermatomes ($p<0.05$), but was maximal at 5 and 10cm separation distances. Taken together, all three of these phenomenon suggest that interactions between recruited populations of neurons may support both spatial and intensity-related dimensions of the pain experience.
1. Introduction

At the level of the spinal cord, nociceptive information is processed by both wide dynamic range neurons (WDR) and nociceptive specific neurons (NS). Both classes of nociceptive neurons have receptive fields (RF) that are not homogenously sensitive, such that the central RF zone is more sensitive than the peripheral RF (Price et al. 1978). Accordingly, neurons within a given population, during a single noxious stimulus, have different degrees of activation depending on the position of their RF in relation to the stimulus. Given the substantial overlap of RFs of different nociceptive neurons, this graded RF organization would be predicted to allow the recruitment of neurons with progressive increases in stimulus intensity (Coghill et al. 1993; Price et al. 1978) or attentional demands (Oshiro et al. 2007; Quevedo and Coghill 2007). A large number of neurons can be recruited rostro-caudally by noxious thermal stimuli and this recruitment can extend over several segments of the spinal cord with sufficiently intense stimuli (Coghill et al. 1991). Thus, such neuron recruitment may represent one critical dimension of a population code for nociceptive information. However, the subjective availability of this information remains in question. Some authors have suggested that such population coding mechanisms may be more relevant to motor withdrawal reflexes and that population based information may be too complex to permit signal extraction at thalamo-cortical levels (Craig 2003).

Phenomena such as the spatial extent and spatial radiation of pain may represent perceptual correlates of population recruitment mechanisms. Although the total population output appears to be used to code intensity of pain, other dimensions of the
population response may be involved in the spatial perception of noxious stimuli. For example, activation of neurons that are distant from the epicenter of population activity may contribute to the perception of spatial location and/or size of stimuli.

A classic phenomenon where spatial location can be amplified and/or mislocated is radiation of pain. Radiation of pain has been attributed to the activation of peripheral zones of neighboring RF (Price et al. 1978). However, radiation of pain, by itself, does not provide conclusive evidence that population recruitment can contribute to spatial perception of pain. For example, labeled lines hypotheses of pain localization would indicate that activation of neurons with small RF’s would produce well localized pain sensations, while activation of neurons with large RFs would produce sensations of pain arising from a large area.

If radiation occurs from population recruitment during stimulation of a single site, then overlapping recruitment from two adjacent noxious stimuli would be predicted to produce a sensation of pain in the non-stimulated region between stimuli. Such a percept would be analogous to the phenomenon of filling-in that has been found in the visual, auditory, and somatosensory modalities (Cohen et al. 2003; Cohen and Legargasson 2005; Conway et al. 2005; Hsieh and Tse 2006; Komatsu et al. 2002; Liu et al. 2004; Mendola et al. 2006; Micheyl et al. 2003; Motoyoshi 1999; Valmaggia and Gottlob 2002; Welchman and Harris 2003). Finally, if radiation and filling-in are representative of spatial dimensions of population recruitment and interactions, then maximal spatial summation of pain would be predicted to occur at stimulus separation distances where radiation and filling-in are maximal. In order to test these predictions, subjects were
recruited to evaluate the perceived location and intensity of pairs of noxious thermal stimuli.

2. Methods

2.1 Subjects

All subjects participating in this study (6 males and 7 females) were healthy, pain and drug-free volunteers between 20 and 29 (average 24.1 years old). All subjects gave written, informed consent acknowledging that they would experience experimental painful stimuli, that all methods and procedures were clearly explained, and that they were free to withdraw from the experiment at any time without prejudice. All procedures were approved by the Institutional Review Board of Wake Forest University School of Medicine.

2.2 Stimulation Paradigms

All thermal stimuli were delivered with TSA II devices (Medoc, Ramat Yishai, Israel) using 16 x 16-mm stimulus probe(s). All stimuli were five seconds in duration and used rise and fall rates of 4°C/s. Stimuli were delivered to the leg or abdomen by a single probe or by two probes simultaneously. Paired stimuli were separated by 0, 5, 10, 20 and 40cm on the left leg. On the abdomen (Fig. 1), paired stimuli were delivered together (0cm) and separated using anatomical references (xiphoid process and anterior superior iliac spine) to standardize the dermatomes tested across subjects. Using those references, stimuli were delivered across 5 or 6 dermatomes (T6 at superior level and T11/T12 at inferior level). In within dermatomes trials, probes were placed horizontally
to stimulate the same dermatome. It is possible that during the horizontal trials the two stimuli were not confined to a single dermatome but that SSP is found when neighboring dermatomes are activated (Nielsen and Arendt-Nielsen 1997). During the whole experiment, subjects laid down on a bed and were not allowed to look at the stimuli. A hard paper screen was used around the neck to block their vision of the abdomen and leg. Two elastic bands were placed on the skin for the entire duration of the experiment to give the same tactile stimulation during all trials. Paired stimuli were electronically synchronized and monitored on a digital chart recorder (PowerLab/4sp ADInstruments). Stimulator parameters were fine-tuned to ensure that both probes delivered nearly identical stimuli simultaneously. To further reduce confounds due to slight differences in stimulus delivery between probes, the probe location (proximal/distal) was counter balanced within subjects. In order to minimize sensitization or habituation, stimuli were delivered to marked sites in a pre-determined spatial fashion and each area was only stimulated once. Moreover, both stimulus intensities and probe separation distances were randomized to avoid order effects.

Two temperatures were used in all experimental trials: 35°C as baseline and 49°C as the noxious thermal stimulus. The 49°C stimulus temperature was chosen since frankly noxious stimuli elicit a high frequency of reports of pain radiation (Price et al. 1978). Paired stimuli were delivered in multiple combinations: 1) on the legs: 49°C proximal/ 49°C distal (49°Cp/49°Cd), 49°C proximal/ 35°C distal (49°Cp/35°Cd), and 35°C proximal/ 49°C distal (35°Cp/49°Cd); 2) on the abdomen across dermatomes: 49°C superior/ 49°C inferior (49°Cs/49°Ci), 49°C superior/ 35°C inferior (49°Cs/35°Ci), and 35°C superior/ 49°C inferior (35°Cs/49°Ci); 3) on the abdomen within dermatomes: 49°C
medial (closer to the midline)/ 49°C lateral (further from the midline) (49°Cm/49°Cl),
49°C medial/ 35°C lateral (49°Cm/35°Cl), and 35°C medial/ 49°C (35°Cs/49°Ci)

Single 49°C stimuli were also applied at all stimulated sites along the leg (or
abdomen) to control for differences in sensitivity across body regions and to evaluate
possible interactions between stimuli (noxious and innocuous) such as spatial summation
of pain. An interval of 30 seconds between any two consecutive stimuli was used to
avoid long-term suppression or sensitization of nociceptive afferents (Price and Dubner
1977). Three (paired) or four (single) trials were used for each condition (distance X
combination of probes). To further minimize risks of habituation or sensitization, data
were acquired on two separate days and trials on both body sites were divided equally
across days.

2.3 Psychophysical assessment and training

Pain intensity and pain unpleasantness were rated with separate mechanical visual
analog scales (VAS) (Price et al. 1994; Price et al. 1983; Rosier et al. 2002). These 15cm
long sliding scales were anchored with the words “no pain sensation”-“the most intense
pain imaginable” and “not unpleasant at all”-“the most unpleasant imaginable”. After
subjects slid the scale to the appropriate level that corresponded to their actual pain
perception, pain ratings were quantified by a labeled numeric index (0-10 range) on the
back of the scale (out of the subjects’ view). In the first training series, a single probe
delivering different temperatures (from 35°C to 49°C) was used to give subjects
experience rating pain intensity and pain unpleasantness. In the second training series,
pairs of noxious stimuli separated by 10cm were delivered using only the two
temperatures (35°C and 49°C) used in the experiment. Subjects were asked if pain from the two stimuli was perceived as separated (two independent stimuli), connected (two stimuli interconnected to each other or they perceived pain involving the whole area between the probes), or if they felt only one stimulus (apparently only one probe was activated). This training series allowed subjects to gain experience in providing one rating (overall) for two stimuli delivered simultaneously and in performing the connectivity rating. In order to control for multi-sensory interactions, a screen blocked the subjects’ view of the stimulated area during all trials during the second training series and in the experimental trials.

2.4. Statistical analyses

Radiation of pain was assessed using the reports of connectivity during 35°C/49°C and 49°C/35°C stimulus pairs. The frequency of trials that subjects reported connection and two separate stimuli was compared with the frequency of reports that only one probe was activated (one probe condition) using the $\chi^2$ analysis. This procedure allowed radiation to be assessed in an indirect fashion and did not require subjects to actively attend to a body region in order to provide a rating. Thus, this indirect assessment is not subject to the potential confounds of expectation and attention that can occur during active ratings. Analysis of radiation was only performed for data acquired from stimulation of the leg since a significant variation of the frequency of radiation across probe separation distance would readily distinguish true radiation from effects of expectation and/or incorrect positive reports.
To analyze the relationship between frequency of radiation and inter-individual differences in pain sensitivity, a radiation index (% of trials with reports of radiation) was created from trials of pairs of noxious and neutral stimuli (49ºC and 35ºC). This index number was created by attributing a value of 1 when subjects reported that the two sites of pain were disconnected or reported that the two sites were connected during pain. A value of 0 (zero) was attributed when subjects reported that only one probe was on. The within-subjects mean of this binarized response was then calculated. Pain sensitivity was calculated by within-subjects mean of responses to single 49ºC stimuli. The relationship between these two variables was assessed by regression analysis.

To test the hypothesis that there is an optimal distance for the perception of connectivity between the two stimuli, the frequency of the trials where subjects reported connectivity between the two stimuli was compared to the frequency when subjects reported the other two conditions (separated and one probe) using the \( \chi^2 \) analysis.

To analyze the correlation between connectivity and subjects’ sensitivity, a connectivity index was created attributing to each subject a number that corresponded to the frequency of connectivity reported during trials of pairs of noxious (49ºC/49ºC) stimuli. This index was created by attributing a value of 0 when subjects reported that the two sites of pain were disconnected or only reported that one probe was on. A value of 1 was attributed when subjects reported that the two sites of pain were connected to each other (connected condition). The within subjects average of the connectivity (0 or 1) of all trials (49ºC/49ºC) was used to attribute a numerical value to the level of connectivity. The relationship between sensitivity and connectivity was assessed using a linear regression.
The two assessed aspects of pain (intensity and unpleasantness) were highly similar, so for clarity, analyses of spatial summation of pain are focused only on pain intensity. For each subject, VAS ratings were first averaged across the 3-4 presentations of each condition (stimuli X distance). Comparisons between pain ratings from pairs of 49°C/49°C and single control stimuli (49°C) were used to assess spatial summation. The average of (49°Cp/49°Cd) ratings was compared across different distances using repeated measures analyses of variance (ANOVA) to determine the optimal distance for SSP. Similar analyses were used to assess within vs. between dermatome spatial summation on the abdomen. To compare SSP across sensitive and insensitive subjects, the pain ratings during pairs of 49°C/49°C stimuli were normalized by dividing them by the ratings from single 49°C stimuli. Linear regression analysis was used to determine if percent spatial summation was related to individual differences in pain sensitivity. Also, during pairs of 49°C/49°C stimuli, a repeated measures analysis of variance was used to determine if there was a relationship between the perception of connectivity and spatial summation of pain.

3. Results

There was no difference in pain ratings between 35°Cp/49°Cd and 49°Cp/35°Cd on the legs (p=0.5) and also in the 35°Cs/49°Ci and 49°Cs/35°Ci and 35°Cm/49°Ci and 49°Cm/35°Ci abdomen (p=0.8), for this reason both conditions were analyzed as one rating for each body site.
3.1 Radiation to the neutral probe

During pairs of 35°C/49°C and 49°C/35°C, subjects reported pain from two probes when only one was activated suggesting a radiation from the noxious stimulus to the neutral probe (Fig. 2A). This includes trials where subjects reported either two connected stimuli (connected condition) or two separate stimuli (disconnection condition) arising from the two potentially painful sites. There was a significant effect of distance between probes on the frequency of reports on pain arising from the neutral probe ($\chi^2 = 34.107, p<0.0001$). Painful sensations from the neutral probe were reported in 23% of the trials at 0cm, 46% of the trials at 5cm, 38% of the trials at 10cm, 21% of the trials at 20cm, and 9% of the trials at 40cm separation distances.

In order to determine if sensitive subjects had higher degrees of radiation, we used a regression analysis to assess the relationship between pain sensitivity (as defined by ratings of single 49°C stimuli) and % of perception of radiation (mean of 3-4 ratings/condition). No significant correlation between these two factors was found during pairs of 35°C/49°C and 49°C/35°C ($r^2=0.17; p=0.1$) pairs of stimuli (Fig. 2B).

3.2 Perceived connectivity between stimuli

The perception of connectiveness (separated, connected, and one probe,) was significantly influenced by the distance between probes ($\chi^2 = 107.129, p<0.0001$) during pairs of 49°C/49°C stimuli (Fig.3A). The frequency of each perception varied significantly over distance. Subjects felt two distinct sites of pain and no connection between them (separated condition) in 7% of trials at 0cm, 21% of trials at 5cm, 21% of
trials at 10 cm, 69% of trials at 20 cm, and 71% of trials at 40 cm separation distances ($\chi^2 = 89.457$, p<0.0001). Only one probe was reported to be activated during 66% of trials at 0 cm, 40% of trials at 5 cm, 31% of trials at 10 cm, 10% of trials at 20 cm, and 13% of trials at 40 cm separation distances ($\chi = 57.352$, p<0.0001). Subjects reported that they perceived two connected sites (connected condition) in 24% of trials at 0 cm, 35% of trials at 5 cm, 46% of trials at 10 cm, 21% of trials at 20 cm, and 14% of trials at 40 cm separation distances ($\chi^2 = 16.756$, p<0.01). There were trials that subjects reported not being able to discriminate the specific site of pain: 3% of trials at 0 cm, 4% of trials at 5 cm, 2% of trials at 10 cm, and 2% of trials at 40 cm separation distances.

Similar to reports of radiation, the frequency at which subjects reported that they felt two connected stimuli was not significantly related to their pain sensitivity (defined by responses to single 49°C stimuli) ($r^2=0.12$; p=0.2) (Fig. 3B).

3.3 Spatial summation of pain and effect of distance on the leg

There was a significant non-linear effect of distance between probes on pain intensity ratings when both probes were in the noxious range (49°C/49°C) (p<0.05) (Fig. 4A). SSP was more pronounced at 5 cm (p<0.05) and 10 cm (p<0.01) separation distances than when stimuli were delivered at other distances. The magnitude of SSP was not reliably different among stimuli delivered at 0 cm, 20 cm, and 40 cm (p=0.8), however pain intensity ratings were still significantly greater than those evoked by a single 49°C stimulus (p<0.01).
There was a trend for the degree of SSP to be inversely related to pain sensitivity. Using data from the 10cm distance where SSP was greatest, relatively insensitive subjects tended to exhibit greater SSP than highly sensitivity subjects \((r^2=0.2, p=0.09)\) (Fig.4B). During pairs of 49°C/49°C stimuli, there was no relationship between the perception of connectivity and spatial summation of pain \((p=0.1)\).

### 3.4 Spatial summation of pain across dermatomes

Spatial summation of pain was similar within and across dermatomes on the abdomen (Fig. 5). Pairs of 49°C/49°C stimuli were rated greater than single 49°C stimuli both across dermatomes (5-6 dermatomes vertical separation) and within dermatomes (horizontal separation equal to vertical separation) \((p<0.05)\). There was no difference in spatial summation of pain between both conditions, despite the fact that probes in the across dermatome condition were 5-6 dermatomes apart \((p=0.5)\) (Fig. 1). However, ratings for 49°C/49°C vertical and 49°C/49°C horizontal conditions were greater than 49°C/49°C together condition \((p<0.01\) and \(p<0.05\) respectively). When stimuli were applied side-by-side there was a non-significant trend for ratings to be greater than those evoked by single 49°C stimuli \((p=0.08)\).

The frequency of perception of connectivity varied significantly over conditions \(\chi^2=16.486, p<0.001\). Subjects felt two distinct sites of pain and no connection between them (separated condition) in 48% of trials in the across dermatomes condition (vertical) and 67% of trials within dermatomes condition (horizontal) \((\chi = 5.257, p<0.05)\). Only one probe was reported to be activated during 29% in the trials at across dermatomes condition (vertical) and 4% of trials within dermatomes condition (horizontal) \((\chi^2 =\)
16.404, p<0.0001). Subjects reported that they perceived two connected sites (connected condition) in 23% of trials at across dermatomes condition (vertical) and 28% of trials within dermatomes condition (horizontal) ($\chi^2 = 0.6, p<0.4$). During pairs of 49°C/49°C stimuli, there was no relationship between the perception of connectivity and spatial summation of pain ($p=0.1$).

3.5 Spatial summation of pain was not evoked by expectation

There was no difference in pain ratings between single 49°C stimuli and pairs of 49°C/35°C stimuli on the leg ($p=0.5$) (Fig.6A) or on abdomen (Fig.6B ($p=0.2$). Also, subjects reported that they were unaware if there were one or two probes on the skin because two elastic bands (used to hold the probes) were placed on the skin during the whole duration of the experiment. Eight out thirteen subjects reported at least one time that there was connection between two perceived stimuli when only one probe was placed on the skin. This indicates that the number of probes on the skin was not clear to subjects. This caused similar tactile stimulation during all trials and therefore did not provide tactile cues that could have altered pain expectations during pairs of stimuli.

Discussion

Population-based mechanisms of nociceptive processing remain poorly understood due to lack of information about how large numbers of nociceptive neurons respond to incoming afferent information. The present psychophysical data provide strong, yet indirect evidence that neuron recruitment contributes importantly to spatial dimensions of
pain. This recruitment of neurons can support interactions between multiple stimuli and can produce different perceptions such as radiation, spatial summation and filling-in.

4.1 Radiation

During clinical evaluation, the reported area of pain does not always reflect the origin of nociceptive information (de Leeuw et al. 1995a; b; Kreiner and Okeson 1999; Naranjo Hernandez et al. 1992). This mismatch between the site and source of pain can provoke equivocation on diagnosis and, in consequence, treatment failure (Farella et al. 2002; Harris et al. 1993; Okeson and Falace 1997). Experimentally, mislocation of somatosensory information has been reported for noxious (Price et al. 1978) and innocuous thermal (Green 1977; Green 1978; Taus et al. 1975), electrical (Hardy et al. 1967; Higashiyama and Hayashi 1993), chemical (Green and Flammer 1989), and tactile (Culver 1970; Green and Flammer 1989) stimuli.

Radiation of pain has been typically studied by asking subjects to rate the perceived intensity of a neutral stimulus (Green 1977; Green 1978; Higashiyama and Hayashi 1993). This procedure allows direct assessment of spatial radiation but also involves cognitive factors such as attention to the potential stimulated sites. In the present study, radiation of pain was assessed using a new approach where subjects were not asked to rate pain intensity from the neutral probe. Instead, the perception of connectivity was used to indirectly determine if pain was perceived at both stimulus locations. When pairs of 35°C + 49°C stimuli were delivered and subjects reported feeling two noxious stimuli that were either connected or disconnected, it indicates that noxious stimuli were perceived at the neutral temperature probe (Fig. 2). Since this
procedure does not require direction of attention to the neutral probe (35°C) and allowed surreptitious assessment of radiation of pain, the perception of radiation is minimally amplified by active cognitive factors such as attention and expectation. Lack of visual input further reduced effects of attention and expectation. Tactile cues produced by the probe and/or elastic bands could also have contributed to amplification of radiation by expectation (Carlsson et al. 2000; Green 1978; Johnson et al. 1998; Koyama et al. 2005; McCaul and Malott 1984; Miron et al. 1989; Mullen and Suls 1982; Sawamoto et al. 2000; Suls and Fletcher 1985; Tracey et al. 2002). However, the observed radiation could not be explained only by expectation because it varies across distances.

The observed radiation of pain is consistent with the concept that intensely noxious stimuli recruit activity over a widely distributed population of neurons (Coghill et al. 1991). Sufficiently intense activation of neurons outside of the epicenter of the activated population may give rise to the perceptual experience that pain is spreading from the stimulated area (Fig. 7).

4.2 Filling-in

Filling-in is a phenomenon that allows the nervous system to interpolate missing information in order to construct representations of continuous surfaces and demonstrates that physical stimuli presented do not necessary correspond to the final perception (Komatsu et al. 2002). This phenomenon has been reported across visual, auditory and somatosensory modalities (Cohen et al. 2003; Cohen and Legargasson 2005; Conway et al. 2005; Hsieh and Tse 2006; Komatsu et al. 2002; Liu et al. 2004; Mendola et al. 2006;
In the present study, this perceptual construction of continuous sensation was assessed by asking the subjects how they spatially perceived the overall stimulation during pairs of noxious stimuli. Subjects could report that they perceived only one activated site, two disconnected activated sites, two activated sites that were connected, or they could not make a spatial evaluation. The classification of the sensation as arising from two connected sites is consistent with the filling-in phenomenon (Komatsu et al. 2002). This perception of pain where no stimulus was delivered represents another spatial mismatch between the actual and perceived stimulated areas that would be consistent with population recruitment (Fig. 3).

As with radiation of pain, the observed perception of filling-in is consistent with the concept that noxious stimuli recruit activity over a widely distributed population of neurons (Fig. 7). Thus, if two neuronal populations are activated by the two painful stimuli such that there is an overlap of both populations, neurons in the overlapping region would be ideally positioned to contribute to the production of a final perception that there is connectivity between the two stimuli.

4.3 Spatial summation of pain

SSP is a classical example of integration between multiple noxious stimuli. The present investigation found SSP over 40cm distances between stimuli on the leg (Fig. 4A) and up to 5-6 dermatomes on the abdomen (Fig. 5). The present data indicate that SSP is modulated by the spatial distribution of the stimuli. It was expected that the highest SSP
would be seen when probes were closest together (i.e. 0cm apart) (Defrin and Urca 1996) and that SSP would decrease with increasing probe separation. However on the leg, pain intensity increased as probe separation increased from 0cm, 5cm to 10cm and then decreased as probes separation was increased to 20 and 40cm (Fig. 4A). SSP on the abdomen was also greater when stimuli were separated either vertically (across dermatomes) or horizontally (within dermatomes) than when they were placed side-by-side. In fact, SSP was not significant when stimuli were delivered side-by-side. Although initially counter-intuitive, this finding of non-monotonic changes in spatial summation of pain across stimulus separations distances provides further evidence for population recruitment. Given the relatively large receptive field sizes of nociceptive neurons, delivery of two noxious stimuli in relatively close proximity would be predicted to activate a neuronal population that would be generally similar to that activated by one stimulus alone. This scenario is consistent with the relatively weak SSP seen at 0cm separation distances. However, when stimuli are at an “optimal distance” from each other, each stimulus may activate somewhat different neuronal populations that overlap to some extent (Fig. 7). The overlap of these populations may enable neurons which normally are not activated by either stimulus to reach the threshold and contribute to the final output, and/or may produce facilitated responses in neurons which were weakly activated by one stimulus alone. Consistent with this notion, spatial summation of pain was optimal at 5-10cm separation distances. These distances were also characterized by the most frequent reports of radiation and filling-in.

Integration across dermatomes has been found using different approaches. For example, SSP was found across neighboring dermatomes (Douglass et al. 1992; Staud et
al. 2004) or even bilaterally using the same dermatome (Nielsen and Arendt-Nielsen 1997). In agreement with previous studies, SSP was found within and across dermatomes in the leg and abdomen. Noxious stimuli can be integrated at different levels of the neuraxis (Bouhassira et al. 1992; Gall et al. 1998; Morton et al. 1988; Morton et al. 1987; Wall 1978; 1980; Willer et al. 1989) and this integration includes central sites (Andersen et al. 1994; Price 1972; Price et al. 1977), as well as peripheral sites (Davis et al. 1993; Defrin et al. 2003; Graven-Nielsen and Mense 2001; Martin et al. 1987) or both central and peripheral sites (Price et al. 1977; Price et al. 1989). In the present study, stimulation of abdomen using the same distance between noxious thermal stimuli within and across (5 or 6 dermatomes away) dermatomes, there was no difference in spatial summation of pain (p=0.5) (Fig. 5). This provides strong evidence that the integration between stimuli can take place not only at the peripheral level but also can occur centrally.

4.5 Individual differences in spatial tuning of nociceptive processing

Radiation of pain is influenced by the intensity of stimuli (Price et al. 1978) and the recruitment of neurons at the spinal cord level is greater at higher noxious temperatures (Coghill et al. 1991). Thus, highly sensitive subjects were predicted to experience greater radiation, filling-in, and SSP. However, the present findings indicate that individual differences in pain intensity sensitivity have minimal relationship with individual differences of these spatial aspects of pain. Therefore, different dimensions of neural population responses appear to be used for spatial vs. intensity-related processes (Fig. 8). For example, spatial percepts may be derived from the extent of neuronal activity above a certain threshold while intensity may be derived from the total
population output. This distinction is further supported by the different patterns of brain activity evoked during discrimination of pain location vs. pain intensity (Oshiro et al. 2007). Thus, although studies of individual differences in pain have focused on intensity, individual differences in spatial tuning may represent an important and distinct dimension of the pain experience.

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References


Figure Legends

Figure 1
Stimulated areas in the abdomen. a: Using anatomical references, pairs of stimuli were delivered across dermatomes. The superior probe was positioned 5cm below the xiphoid process in an area approximating the T6 dermatome, while the inferior probe was positioned 5cm above the iliac spine in the vicinity of the T11/T12 dermatome. b: The distance “X” was used to place the probes in a horizontal orientation where spatial summation was evaluated within dermatomes. c: Pairs of stimuli also were delivered side-by-side to evaluate the influence of separation of stimuli during spatial summation of pain (b vs. c).

Figure 2
The perception of radiation of pain and pain sensitivity. a: During 35°C/49°C stimulus pairs, subjects reported pain from the neutral probe (35°C) at all distances. The most frequent reports of pain radiation occurred at separation distances of 5 and 10cm. b: Individual differences in the perceptions of radiation of pain were not influenced by individual differences in pain sensitivity.

Figure 3
The relationship between spatial perceptions of pairs of noxious stimuli (49°C/49°C) and stimulus separation distance. a: Frequency of reports of only one probe activated. b: Frequency of reports that the perceived pain was not restricted to the area under the activated probes but extended to connect the two stimuli. The highest reports of
connectivity were found at 10cm ($\chi = 17.149$, $p<0.01$). These reports are consistent to the filling-in phenomenon found in other systems. **c:** Frequency of reports of two separate painful stimuli. **d:** Pain sensitivity and the perception of connectivity between two painful stimuli. There was no correlation between individual differences in pain sensitivity and the perception of connectivity during pairs of noxious stimuli.

Figure 4

Spatial summation of pain at different distances. **a:** On the leg, SSP was found up to 40cm distance between stimuli ($p<0.05$) and was maximal at 10cm ($p<0.01$). There was no difference in SSP at 0cm, 20cm, and 40cm separation distances ($p=0.8$). **b:** Pain sensitivity and spatial summation of pain. There was no correlation between individual differences in pain sensitivity and spatial summation of pain during pairs of noxious stimuli.

Figure 5

Spatial summation of pain on the abdomen. SSP was present when stimuli were delivered up to 6 dermatomes apart from each other. There was no difference between and across dermatomes ($p=0.5$). However, SSP was greater when stimuli were separated vertically and horizontally than when they were side-by-side ($p<0.01$ and $p<0.05$ respectively).
Pain intensity was not modulated by the presence of a neutral probe. There was no difference between single 49°C stimuli and combined 49°C and 35°C stimuli. Thus, the presence of a thermal neutral probe did not increase pain intensity.

Conceptual mechanism of filling-in and spatial summation of pain. \textbf{a:} Pairs of stimuli delivered side-by-side activate a very similar population of neurons. There are increases in the discharge of single neurons that are stimulated in the central areas of their RF (black bars) and their activation (approximately 2.3) is beyond the threshold (1.0) to contribute to the spatial location of stimuli (dashed line). Neurons that receive stimulation at intermediary RF zones (blue bars) (approximately 1.3) are also able to reach the localization threshold. Other neurons that are stimulated in more peripheral RF zones (green bars) are not able to contribute to spatial location of the stimulated area (approximately 0.8). At distant areas, neurons are not activated (red bars). The total output (7.2) from all of this activation gives an afferent signal that is used to process intensity-related information downstream in the system. \textbf{b:} Filling-in during population recruitment. When stimuli are separated at an optimal distance, two overlapping neuronal populations are recruited. Some neurons (orange bar) that before were not able to reach the localization threshold level, are now recruited because they receive low level input from both stimuli and accordingly, contribute to filling-in. The neurons that are stimulated in the center of their RFs (black bars) only receive afferent input from one probe and their activation is somewhat diminished (1.7) when compared to panel (a)
where those neurons the neurons are activated by both stimuli. However, in consequence of the greater number of neurons recruited, the total population output is greater (9.4) than when two stimuli are placed side-by-side (a) or placed at further distances (c). Thus, SSP is more pronounced. c: When stimuli are located at further separation distances, each stimulus activates independent populations of neurons that interact minimally with each other. In consequence there is no perception of spatial connection between stimuli (filling-in) and SSP is less pronounced than when more neurons are recruited (b). In fact, there is no difference in the population output between panel (a) and panel (c) (approximately 7.2). However the mechanisms that produce spatial summation in both situations are different. In panel (a) spatial summation is driven mainly by increased activation of single neurons and in panel (b) spatial summation is produced by the increase of number of neurons recruited. This is in agreement with the present psychophysical data where spatial summation of pain was not different in 0, 20, and 40cm separation distances but was more pronounced at 5 and 10cm separation distance.

Figure 8

Individual differences in sensitivity and the perception of filling-in. It was expected that subjects with higher sensitivity also could have more radiation and perception of filling-in. However, there was no correlation between pain sensitivity and the perception of connectivity between the two stimuli. Here a hypothetical representation of population activity during pairs of stimuli at an “optimal separation distance” is shown in four different situations where subjects have perception of connectivity independently of their pain sensitivity. The perception of connectivity is due
to the overlapping of the population activity between the two sites. **a:** Neuronal population distribution of activity for a highly sensitive subject with high connectivity. During pairs of simultaneously noxious stimuli, this subject would perceive a continuous area of pain (gray horizontal bar under the graphic). **b:** Neuronal population distribution of activity for a low sensitivity subject with high connectivity. During pairs of simultaneously noxious stimuli, similarly to panel (a), this subject would perceive a continuous area of pain (gray horizontal bar under the graphic). **c:** Neuronal population distribution of activity for a highly sensitive subject with low connectivity. During pairs of simultaneously noxious stimuli, this subject would perceive two separated areas of pain (two gray horizontal bars under the graphic). **d:** Neuronal population distribution of activity for a low sensitive subject with low connectivity. During pairs of simultaneously noxious stimuli, this subject would perceive two separated areas of pain (two gray horizontal bars under the graphic).
Fig. 2

A

- Perception of connectivity
- Perception of disconnection

B

Percentage of radiation to neutral probe

Distance between stimuli (cm)

Pain sensitivity (VAS)
Fig. 3

A. One Probe

B. Connected

C. Disconnected

D. Connectivity within/across dermatomess
Fig. 4

A

B

\[ r = 0.2; p = 0.09 \]
Fig. 5

Condition

VAS
Fig. 6

A

VAS

Condition

B

VAS

Condition
Fig. 7  

A  

Neuronal activity  

$S_1$ $S_2$  

B  

Neuronal activity  

$S_1$ $S_2$  

C  

Neuronal activity  

$S_1$ $S_2$