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Differential brain activation associated with laser-evoked burning and pricking pain: an event-related fMRI study

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Abstract

An important question remains as to how the brain differentially processes first (pricking) pain mediated by A δ -nociceptors versus second (burning) pain mediated by C-nociceptors. In the present cross-over randomized, within-subjects controlled study, brain activity patterns were examined with event-related fMRI while pricking and burning pain were selectively evoked using a diode laser. Stimuli evoking equivalent pain intensities were delivered to the dorsum of the left foot. Different laser parameters were used to elicit pricking (60 ms pulse duration) and burning (2.0 s pulse duration) pain. Whole brain group analysis showed that several brain areas were commonly activated by pricking and burning pain including bilateral thalamus, bilateral anterior insula, bilateral posterior parietal lobule, contralateral dorsolateral prefrontal cortex, ipsilateral cerebellum, and mid anterior cingulate cortex. These findings show that pricking and burning pain were associated with activity in many of the same nociceptive processing brain regions. This may be expected given that A δ and C nociceptive signals converge to a great extent at the level of the dorsal horn. Other brain regions showed differential processing. Stronger activation in the pricking pain condition was found in the ipsilateral hippocampus, bilateral parahippocampal gyrus, bilateral fusiform gyrus, contralateral cerebellum and contralateral cuneus/parieto-occipital sulcus. Stronger activation in the burning pain condition was found in the ipsilateral dorsolateral prefrontal cortex. These differential activation patterns suggest preferential importance of A δ versus C-fiber signals for these specific brain regions.

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Keywords

burning pain; event-related fMRI; diode laser; pricking pain

Introduction

Different types of nociceptive afferents evoke qualitatively different sensations. First pain is described as ‘sharp’ or ‘pricking’ and is mediated by myelinated A δ -fibers. Second pain is described as ‘dull’ or ‘burning’ and is mediated by the slower unmyelinated C-fibers. It remains largely unclear how the signals conveyed by these fibers are differentially processed in the human brain. Knowledge about the cortical representation of signals originating from C- and A δ -fiber nociceptors may provide new insights into the biological significance of these distinct pain pathways. Recently, reports emerged on differential involvement of nociceptive fibers in pain syndromes [27,44], suggesting that insights on differential nociceptor processing may be helpful in establishing better diagnoses. The ability to reliably differentiate between pain-mediating fibers may also provide unique utility in predicting the efficacy of treatments.

Few studies modeled brain responses associated with first and second pain. In a laser evoked potential (LEP) study, brain activation in response to second pain was found bilaterally in the secondary somatosensory cortex (SII) and the anterior cingulate cortex (ACC) [43], while a magnetoencephalography (MEG) study found second pain-related activation in the contralateral primary somatosensory cortex (SI) and bilateral SII [33]. However, both studies did not compare findings to the cortical processing of first pain. Studies directly comparing brain activation patterns of first and second pain consistently found largely overlapping activation patterns for both fibers, but differential processing was also found. In a MEG study, common activation was found in SII, while differential activation for first pain was found in SI and for second pain in ACC [51]. In another MEG study, common activation was found in bilateral SII, contralateral posterior parietal cortex, and in a few subjects in cingulate, insula, prefrontal, and inferior temporoparietal regions, but no differential activation was found [24]. In a recent functional magnetic resonance imaging (fMRI) study, common activation was found in bilateral thalamus, SII, posterior ACC, and ipsilateral middle insula, while significantly stronger activation for second pain was found in ACC, pre-SMA, and bilateral anterior insula [54]. Although these studies yielded valuable information, some issues arise. C-fiber stimulation can also reflect innocuous warmth processing, and pain intensity scores were frequently not reported. Further, studies did not equalize perceived pain intensity between first and second pain, which could confound perceptual quality and intensity of pain.

In the present study, event-related fMRI was used to selectively evaluate brain activity associated with pricking and burning pain induced by a diode laser. Perceived pain intensity was equalized between first and second pain. We hypothesized that the spatial representation of nociceptive signals conducted by the two fiber types would be similar to a large extent. However, differences in spatial processing were also expected, because of distinct qualitative differences in pain sensations. In addition we explored the possibility that input from the

fibers could be differentially processed in brain regions not necessarily related to the perception of pain.

Materials and Methods

Subjects

Ten healthy volunteers (5 females and 5 males; 1 left-handed) completed this study. Of these ten participants, one subject reported a significantly higher pain intensity rating (VAS rating of 76 on a 0–100 scale) during the burning pain condition in the fMRI session than the other subjects. Statistical analysis identified the pain rating of this subject as a significant outlier; therefore this subject was excluded from further analysis. Four additional subjects were screened for this study but were excluded from full participation based on the following criteria: dual sensation of pricking and burning pain upon stimulation ($n=1$), inconsistent pain ratings ($n=1$), or insensitivity to laser stimuli within the safety margins ($n=2$). Mean age of the remaining nine subjects who completed the study was 29.7 ± 8.7 SD (standard deviation), ranging from 22 to 49 years. Participants who completed the study had at least 4 years of college education, none of them suffered from a serious medical or psychiatric illness, they were good sleepers (mean 7.1 ± 1.1 SD hours a night), all except one subject didn't smoke, they used small amounts of caffeinated drinks (mean 1.3 ± 0.8 SD per day), used alcohol moderately (mean 2.1 ± 2.3 SD glasses a week), and exercised light to moderately. One female was in her early follicular phase of her menstrual cycle, two females were in their mid-luteal phases, and two women were in their premenstrual phases when tested. The University of Maryland Institutional Review Board for the Protection of Human Subjects approved the procedures and protocol for this study and the participants' informed consent was obtained in accordance with the Declaration of Helsinki.

Stimulation paradigms

A diode laser (LASS-10M, Lasmed LLC, CA, USA; patented in 2004) with power of 20 W, wavelength of 980 nm, and an adjustable spot diameter between 1 and 5 mm diameters was used to apply the painful stimuli to the skin of the dorsum of the left foot. Selective activation of A δ -fibers was accomplished by using a diode laser with high rate heating, high energy, brief pulses, and small spot sizes. Selective activation of C-fibers was accomplished by low rate heating with long pulses, low energy and larger spot sizes [62,64,66,68]. The diode laser has been previously used to selectively activate transient receptor potential vanilloid (TRPV1 and TRPV2) positive cells [32], to selectively activate C- and A- δ fibers in rats [62], to elicit a heat-activated inward current I_{heat} in dorsal root ganglion neurons of rats in vitro, and to elicit laser-evoked potentials (LEPs) associated with activation of A δ - and C-nociceptors in humans [28,67]. The diode laser distributes energy principally at the level of cutaneous nociceptive endings (20–570 μm) [59], due to less absorption ($\sim 0.5 \text{ cm}^{-1}$ for 970 nm) thereby avoiding superficial skin lesions [36,45]. Accordingly, it allows for simultaneous and homogeneous heating at skin depth 20–570 μm [40,67]. Other commonly used lasers such as the CO₂ or Thulium-YAG laser show higher absorption ($\sim 63 \text{ cm}^{-1}$ for 2010 nm for Thulium and $\sim 300 \text{ cm}^{-1}$ for 10.2 μm for CO₂ lasers) and more superficial distribution of energy [57]. As they require conduction through tissue to reach nociceptive endings, risk of burns is higher than with the diode laser. Further, the delay time between

superficial skin heating and heating at 450 μm skin depth could be up to several seconds [60]. Different parameters of laser stimulation were used to elicit pricking and burning pain sensations. For pricking pain, short pulses of 60 ms with a spot size of 1 mm in diameter were applied and the laser beam was positioned 5 cm from the skin surface. The mean intensity used to evoke pricking pain was 715 mJ/mm^2 , ranging from 390 to 868 mJ/mm^2 . For burning pain, long pulses of 2 seconds duration with a spot size of 5 mm in diameter were applied with the laser beam positioned 15 cm from the skin surface. The mean intensity used to evoke burning pain was 468 mJ/mm^2 , ranging from 428 to 499 mJ/mm^2 . An aiming beam of 670 nm wavelength was used to identify the stimulated area. The differential activation of the burning and pricking pain was confirmed by the subjects' verbal reports. For this purpose, subjects were asked to consider several mechanical- and temperature-related descriptors, partly adapted from the McGill pain questionnaire, and to identify which descriptors applied to their sensation. Reports of "pricking" and "sharp" were interpreted as associated with A δ -fiber stimulation while reports of "warm/hot" and "burning" were considered to be associated with C-fiber stimulation. Intensities for pricking and burning pain were chosen based on subjects' perceived pain threshold and pain perception. Before MRI scanning, in a separate screening session, sequences of laser stimuli was given which started with low, often undetectable levels, and intensities were increased stepwise until pain of around 20 on a visual analogue scale (VAS) ranging between 0 (no pain) and 100 (maximum tolerable pain) was reported. This relatively low pain intensity was chosen to avoid burns that could potentially occur with more intense stimulation, particularly for less pain sensitive individuals. Then, this stimulus level was repeated and adjusted if necessary until a response near 20 was given reliably for 10 consecutive stimuli of similar intensity. Mean pain intensity ratings for the pricking pain stimuli was 22.4 ($\pm\text{SD}=6.7$) and mean pain intensity for the burning pain stimuli was 25.4 ($\pm\text{SD}=6.6$) in the screening session. To avoid sensitization or fatigue of the nociceptors, the stimulation site on the dorsum of the foot was slightly different for the pricking and burning pain stimulation. Also, the temperature of the skin surface can affect the sensitivity to the laser pulse; with lower skin temperatures, higher energy levels need to be used to reach the same level of pain perception. Therefore the temperature of the foot surface was monitored carefully at the start and end of each functional run. The foot was kept warm by means of a reheatable bean sock between sessions.

Experimental design

Subjects participated in two sessions; a screening session and a MRI scanning session one or two days later. In the screening session, subjects were tested for their sensitivity to the experimental procedure. During the MRI scans, laser stimuli were presented in separate blocks of burning or pricking pain stimuli, with 30 stimuli in each block. The order of presentation of pricking and burning pain stimuli in this MRI session was counter-balanced across subjects. An event-related design was used and the inter-stimulus-interval varied between 14 and 18 seconds in a random sequence trial by trial to reduce anticipatory effects and artifacts occurring at fixed frequencies. A stimulus-free baseline period of 30 seconds was given before and after the presentation of each block of stimuli. After this last baseline period, subjects were asked to rate the average pain intensity across all stimuli in the block on a computerized VAS (DAPSYS; Brian Turnquist, Johns Hopkins University, <http://>

www.dapsys.net) using an MR-compatible trackball (Fellowes, www.fellowes.com), which controls a cursor moving along a vertical VAS. The extremes of the VAS were labeled “no sensation” and “most intense pain imaginable,” with a marker for “just painful” located at the lower quarter of the scale. Subjects were instructed to use the range from “no sensation” to “just painful” to rate non-painful sensations and to use the range from “just painful” to “most intense pain imaginable” to rate painful sensations. Ratings were stored as numbers from 0 to 100 with 25 corresponding to “just painful.” This scale was chosen to give the subject the opportunity to rate intensities below pain thresholds in case the average stimulus intensity was not painful. Subjects practiced with this computerized VAS scale on the screening session. Scores on this 25–100 pain intensity scale were converted to a 0–100 pain intensity scale to allow comparison with rating data collected during the screening session. Subjects were also asked to rate average pain unpleasantness using the same trackball on a 0 (not unpleasant at all) to 100 (most unpleasant imaginable) scale. Lastly, they were asked to choose descriptors representing their laser-evoked sensations from a list, partly adapted from the McGill pain questionnaire.

For stimulus presentation, the laser beam was mounted in a MRI compatible micromanipulator stand which could be adjusted in vertical and horizontal directions. The stand was fixed to a movable table to allow easy repositioning after application of each stimulus. One investigator stayed in the scanner room during the MRI sessions to change the position of the laser beam after each stimulus. Before each stimulus was applied, the distance of the laser collimator to the skin was confirmed by measurements with a ruler without touching the skin.

Image acquisition

Functional MRI scans were acquired using echo planar imaging (EPI) on a 3.0 T Tim Trio scanner (Siemens Medical Solutions, Malvern, PA) with an 8-channel head coil with parallel imaging capability. A gradient echo single shot EPI sequence was used to provide 3.594×3.594 -mm acquired resolution over a 23-cm field of view (FOV). T2* weighting from this sequence was accomplished with a gradient echo time (TE) of 30 ms and flip angle 90° . The repetition time (TR) was 2,000 ms, which allowed the whole brain to be covered using 24 slices, with a slice thickness of 6 mm and no gaps between slices. An interleaved slice sequence was used. A 3D T1 MP-RAGE volumetric scan was acquired for anatomical reference of the functional scans with parameters: 3.44 ms TE, 2250 ms TR, 900 ms TI, flip angle 9° , 96 slices, slice thickness of 1.5 mm and a 0.9×0.9 mm in-plane resolution over a 23 cm FOV.

Image processing and analysis

Analysis of Functional NeuroImages (AFNI; <http://afni.nimh.nih.gov>) was used for image processing and analysis. The first four volumes were removed from the functional scan series to allow for signal equilibration. Remaining volumes were corrected for slice timing differences, and spatially aligned to the first volume for motion correction. Spiking artifacts were reduced (Despike routine in AFNI) and the time series were temporally smoothed using a moving three-point weighted average. After co-registration to the T1-weighted structural volume, the functional volumes were normalized in stereotactic space (Talairach

template) and spatially smoothed using a 5-mm full-width, half-maximum Gaussian blur. Linear, second-order, and third-order trends within the time series were removed, and voxelwise normalization was achieved by dividing the signal intensity at each time point by the voxels mean intensity.

A general linear model (GLM) was used to model temporally discrete responses to pricking or burning pain stimuli. Responses were modeled with a voxelwise regression of fMRI signal time courses assuming a standard gamma-response function. Based on the timing of the stimulus delivery it was predicted that the peak of burning pain condition would be delayed compared to the pricking pain condition. This was indeed confirmed when GLM regressions were performed at multiple lag times of event-related average waveforms from significant clusters. The peak amplitude for the burning pain condition occurred approximately 2 seconds later than the peak for the pricking pain condition. Further, the waveform for the pricking pain condition was best matched with a 2 second delay on the gamma function. Based on this observation, a lag of 2 seconds was used for data derived from the pricking pain condition and a lag of 4 seconds was used for data derived from the burning pain condition.

Individual activation maps were created to determine individual differences in activation, based on a region of interest (ROI) approach. ROIs included the thalamus, the foot representation of the SI, SII, the posterior insula, the anterior insula, rostral ACC, mid-ACC, the supplementary motor area (SMA), and the dorsolateral prefrontal cortex (DLPFC). Anatomic criteria for these a priori ROIs have been given elsewhere [38]. Significant voxel clusters were identified on group activation maps for pricking and burning pain separately.

Additionally, group analyses were performed on whole brain activation. A group overlap map was created of voxel clusters that were commonly activated in both conditions. Further, group contrast maps were calculated of activation that differed significantly between the pricking and burning pain conditions. Functionally activated regions were identified based on anatomical locations with the underlying structural images. The data were corrected for multiple comparisons by using minimum cluster size thresholds as determined by the AFNI routine AlphaSim. The minimum cluster size threshold for the ROI activation analyses was 4 voxels in original space which corresponds to $\sim 310 \text{ mm}^3$ with $p < 0.01$. The minimum cluster size threshold in the group overlap analysis was 4 voxels in original space which corresponds to $\sim 310 \text{ mm}^3$ at an overall $p < 0.01$, with a minimum individual voxel threshold of $p < 0.01$ in each region. In the group contrast analysis, the minimum cluster size was 6 voxels in original space which corresponds to $\sim 465 \text{ mm}^3$ at an overall $p < 0.05$, with a minimum individual voxel threshold of $p < 0.05$ in each region.

Results

Behavioral data

Stimulus intensities for the pricking and burning pain conditions were determined on an individual basis in a screening session preceding the MRI session. Subjects were also asked to rate their overall pain intensity and pain unpleasantness after each functional scan in the MRI session. No significant differences in pain intensity or unpleasantness ratings were

found between the screening and the MRI sessions, or between the burning and pricking pain conditions within each session (Figure 1). Therefore, the stimuli felt equally painful in both sessions, and, importantly, pain intensities were perceptually equalized among subjects for the different pain conditions, despite some variations in foot skin temperatures. The foot dorsum was found to be significantly cooler in the pricking than the burning pain condition (mean=31.3°C, $\pm$ SD=0.90 for pricking pain and mean=32.3°C, $\pm$ SD=0.52 for burning pain; $p<0.036$), even though these conditions were presented in a counterbalanced order across subjects. No significant effect of order of stimulation was found, i.e., the foot was not warmer when the pricking pain condition followed the burning pain condition. Further, as can be expected, the temperature of the foot cooled down significantly over the time course of each functional scan ($p<0.045$), but no significant interaction was found for temperature change between the start and end of each functional run and pain conditions.

Subjects further choose among a set of descriptors to characterize the sensory qualities they felt after each functional run in the MRI session. In general, subjects used the same descriptors in the fMRI session as the training session. For the pricking pain condition all subjects used the descriptors ‘sharp’ and ‘stinging’, while for the burning pain condition all subjects used the descriptors ‘burning’ and/or ‘hot’. However, three subjects also used the descriptors ‘burning’ and/or ‘hot’ in the pricking pain conditions while three (partly different) subjects also used ‘stinging’ and ‘sharp’ in the burning pain condition. Upon query, these sensations were described as distinctly different from those evoked by the other stimulus condition. The ‘burning’ and/or ‘hot’ sensation in the pricking pain condition was described as a ‘sharp hot prick’, not associated with a dull burning pain as described in the burning pain condition. The ‘stinging’ or ‘sharp’ sensation in the burning pain condition was described as a sensation which was clearly associated with the concomitant burning sensation, and different from the pinprick sensation evoked in the other stimulus condition. In the training session it was also verified that subjects did not experience “double sensations” with these stimuli, indicating that perceptions were not based on volleys of A- and C-fiber inputs driven together with the same stimulus.

Imaging results

Single subject analysis—Pricking and burning painful stimuli commonly activated brain regions frequently identified in pain neuroimaging studies, including the thalamus, SI, SII, anterior and posterior insula, DLPFC, cerebellum, rostral and mid ACC, and SMA. The time course of the BOLD signal change in selected classical pain ROIs associated with the presentation of pricking and burning painful stimuli is presented in Figure 2. As evident in this figure, the activation associated with the burning pain stimuli peaked about 2 seconds later than the activation associated with the pricking pain stimuli. This pattern was consistent for all the brain regions responding to both types of stimuli. Several mechanisms could account for this finding. First, this temporal difference could be explained by the fact that the stimulus duration for the burning pain condition was nearly 2 seconds longer than the pricking pain condition, and that afferent activation in the burning pain condition would be maximal near the end of that stimulation period. Activation time of the nociceptors was different due to the stimulation parameters necessary to selectively activate the fibers. Second, the difference in conduction velocities between A δ - and C-fibers are also likely to

contribute to the temporal difference between pricking pain and burning pain related activation. Third, differences in central processing of information conducted by the afferents, such as spinothalamic versus a more propriospinal pathway could potentially result in differences in arrival time at the cortical level. Different lags for the pricking and burning pain conditions were used for further analysis, such that an additional 2 second delay was used for the burning pain compared to the pricking pain condition.

Table 1 represents the individual variation in activation of several regions previously associated with pain processing and selected for the ROI analysis. Many areas show consistent activation within and between subjects, however some areas, such as SI and the thalamus in the burning pain condition, only show activation in a limited number of subjects. The thalamus only showed activation in about half of the subjects for the burning pain condition, yet in almost all subjects for the pricking pain condition.

Group analysis—Following individual subject analysis, the activation common to the burning and pricking pain conditions was identified by a group overlap map (Figure 3; overall $p < 0.01$, corrected for cluster size). Significant overlap in activation was found for pricking and burning pain in several brain areas, including the bilateral thalamus, bilateral anterior insula, bilateral posterior parietal lobule, mid-ACC, contralateral dorsolateral prefrontal cortex, and ipsilateral cerebellum (Table 2 and Figure 3).

Pricking and burning pain also evoked differential responses in selective brain regions. Group contrast maps were used to identify differential activation between pricking and burning pain conditions. Several areas showed stronger activation following pricking pain compared to burning pain (overall $p < 0.05$, corrected for cluster size), including the ipsilateral hippocampus, bilateral parahippocampal gyrus, bilateral fusiform gyrus, contralateral cerebellum, and contralateral cuneus/parieto-occipital sulcus. Only one area showed stronger activation with burning compared to pricking pain: a region in the ipsilateral middle frontal gyrus, comprising part of the DLPFC (Table 3, Figure 4).

Discussion

Event-related fMRI was used to evaluate brain activation patterns associated with pricking and burning pain induced by a diode laser. Only few studies directly compared these pain conditions and the present study is innovative regarding perceptually equalizing pain perception between conditions and assuring that the stimulation of C-fibers was painful. Several brain regions were found to be commonly activated, but differential activation was observed for select brain regions.

Individual variation in brain activation

Pain-evoked activation in the brain was found bilaterally in all predefined ROIs. SI activation upon painful laser-evoked stimulation has been reported previously [4,5], although it was least consistently activated among the subjects in the present study. SI activity is often absent in pain imaging studies [14]. It is hypothesized that in the present study, it was hard to identify significant clusters of activation in SI because the foot representation is relatively small. Both the ipsilateral and contralateral thalamus were only activated in about half of the

subjects in the burning pain condition, but in most or all subjects in the pricking pain condition. Along with tissue volume considerations described above, differences in activation in the thalamus could result from time-dispersed arrival of input from the fibers evoked by the laser. In the burning pain condition, the stimulus was of longer duration and signals are likely to arrive at the thalamus more dispersed than in the pricking pain condition.

Shared neural representation

Conjunction analysis indicated overlap in activation of pricking and burning pain in several brain areas including thalamus, insula, mid-ACC, cerebellum, contralateral DLPFC, and the posterior parietal lobe. Activation in these brain areas are typically found in pain imaging studies [2,29,46,53,55,61]. The findings of the present study demonstrate that these brain areas are associated with pain processing of both types of nociceptive input. Common activation to pricking and burning pain is expected since A δ and C nociceptive signals converge to a great extent at the level of the dorsal horn (e.g., [31,52]). Overlap in the cortical representation of these pain conditions may possibly reflect a role of these regions in representing pain salience [23]. Nevertheless, A δ - and C-fiber mediated nociceptive signals are neurobiologically distinct which implies some level of differential CNS processing.

Differences in brain activation

Group contrast analyses identified brain areas that were differentially activated in the burning versus pricking pain condition, including the hippocampal formation, cerebellum, fusiform gyrus, cuneus/parieto-occipital sulcus, and DLPFC.

While not typically considered a nociceptive processing region, activation in the hippocampal formation has been previously reported in response to painful heat [21,50] and laser stimulation [3]. The hippocampal formation has been traditionally associated with recent memory consolidation [1], spatial memory [16,30], and fear-initiated avoidance behavior [35]. Studies using specific conditioning paradigms demonstrated that the hippocampus is also involved in learning associations between pain and predictive cues [49,50]. It is perhaps in its role in learned associations that the differential activation between pain pathways in the hippocampus has relevance. Given the need for precise timing of information for appropriately learned associations, it would be reasonable to propose that nociceptive signals from the A δ -fibers provide the most useful input. A separate cluster of activation was identified in the fusiform gyrus adjacent to the activated region of the parahippocampal gyrus. Given that there is no prior evidence of nociceptive input to the fusiform gyrus, the most conservative interpretation would be that it represents an extension of parahippocampal gyrus activation.

Activity in the cerebellum is frequently found in pain neuroimaging studies. Cerebellar activation is generally considered to be primarily associated with motor responses [12]. Some studies point to a more direct role of the cerebellum in pain processing by showing release of endogenous opioids upon electrical stimulation of the cerebellum in animals [22]. The need for temporally precise information may also be relevant for brain areas involved in

initiating, propagating, and executing defensive motor responses to first pain [12,25,47,56,58].

Differential activation was also found for a multi-sensory integration region: the parieto-occipital sulcus. This area is recognized as a site of integration of innocuous somatosensory signals and visual information [15]. A network of motor, pain, and sensory areas including the posterior parietal cortex was previously found to be activated in response to a prickle sensation evoked by noxious cold stimuli [19]. Because the parieto-occipital sulcus is not routinely found activated in pain neuroimaging studies, it remains to be determined whether preferential A δ nociceptive activation is a consistent property of this region.

Although the contralateral (right) DLPFC was commonly activated in both the pricking and burning pain condition, the ipsilateral (left) DLPFC was found to be significantly more activated in the burning pain condition. Transcranial magnetic stimulation studies demonstrate that prefrontal regions can modulate pain perception. Stimulation of the DLPFC increased pain tolerance upon hand immersion in cold water, however only when stimulated on the right hemisphere [26]. Significant effects of left prefrontal stimulation were found on decreased patient-controlled analgesia use [6]. It has been postulated that pain modulation in these regions occurs by means of attentional control of pain. Lesion studies, neuronal recordings, and neuroimaging findings demonstrate that a network of frontal and parietal structures is involved in attentional control [13,17,34]. In a previous study, the perceptual illusion of ‘paradoxical heat’, isolated from the perception of pain, was associated with activity in the right anterior-mid insula [20]. The current study specifically focuses on the perception of pain and the findings suggest that the C-fiber mediated nociceptive signals engage the left DLPFC to a greater extent than the A δ mediated signals.

It should be noted that differential information processing may occur in principle nociceptive processing regions of the cerebrum in a manner that is not easily resolved with fMRI. For instance, the relatively low temporal resolution of fMRI limits its ability to detect differences in the timing of neural processing associated with different nociceptive inputs. Additionally, fMRI is not likely to be able to discern the situation in which small discrete neural modules are differentially active within a given ROI, which may very well be the case for the early nociceptive processing regions [18].

Selective activation of nociceptive fibers

Laser stimulation selectively activates nociceptors while avoiding concomitant activation of mechanoreceptors [48]. Imaging studies show that laser stimulation commonly activates cortical areas including SI, SII, insula, amygdala, ACC, and multiple prefrontal regions (e.g., [5,7]). However, previous studies frequently activated nociceptors simultaneously rather than selectively. Selective activation of A δ - or C-nociceptors can be achieved by making use of differences in resistance to ischemic pressure between fibers [9–11], differences in heat thresholds between fibers [37], differences in distribution density of the fibers [8,41,42], and differential responses of fibers to the heating rate of the skin and to pharmacological treatment [40,62–66,68]. The present study was designed to separate C- and A δ -fiber activation by exploiting differences in thermal thresholds, rate of thermal activation sensitivity, and spatial properties of the nociceptor types. Previous studies using contact heat

stimulation found that low heating rates (in the range of 1-2°C per second) evoked nociceptive responses that were primarily mediated by C-fibers while high heating rates (in the range of higher than 2°C per second) produced nociceptive responses primarily mediated by Aδ-fibers [63,64,66,68]. With laser stimulation, these same principles apply although heating rates are faster [39].

Conclusion

The principle finding from the present study is that many brain areas are commonly engaged in processing of pricking and burning pain, mediated by Aδ- and C-fiber nociceptors, respectively. Yet, there are some regions that show preferential activation related to Aδ- versus C-fiber input. Stronger activation in the pricking pain condition was found in the hippocampal formation, cerebellum, fusiform gyrus, and cuneus/parieto-occipital sulcus. Stronger activation in the burning pain condition was found in the dorsolateral prefrontal cortex. It remains to be determined whether such differences are related to perception, motor reactions, or other aspects of nociceptive processing.

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Figure 1.
Pain intensity and pain unpleasantness ratings.

The boxplots presented on the left side of the figure represent pain intensity ratings for each session and pain stimulation separately. Additionally, individual scores for each subject are presented as open dots in the box plots. A, mean pain intensity rating over 10 trials as determined in the screening session for the burning and pricking conditions separately. B, average pain intensity rating over a block of 30 trials in the MRI session for the burning and pricking conditions separately. No significant differences in pain intensity ratings were found between conditions of burning and pricking pain in the screening session or the MRI session. The boxplots presented on the right side of the figure represent pain unpleasantness ratings for each session and pain stimulation separately. A, average pain unpleasantness rating over 10 trials in the screening session. B, average unpleasantness rating over a block of 30 trials in the MRI session. Also, no significant differences in pain unpleasantness ratings were found between conditions of burning and pricking pain in the screening session or the MRI session.

Pricking pain

Burning pain

Figure 2.

Time course of brain activation following pricking and burning pain.

Time course of BOLD signal change in selected ROIs following laser stimulation in the (A) pricking pain and (B) burning pain conditions. Stimulation onset was at 0 seconds. The right side of the brain is contralateral to stimulation. Error bars represent standard errors.

Figure 3.

Activation and overlap maps.

Activation maps for the pricking (column 1) and burning (column 2) pain conditions separately, and the overlap map of activation between these conditions (column 3; superimposition of the two activation maps). The left side of each image corresponds to the right side of the brain, which is contralateral to stimulation. Functional activation maps are overlaid on a normalized anatomical MRI in Talairach space. The coordinates of slice cuts through the axial and sagittal planes are presented in the images. The color bar represents the extent of activation in z-scores of the pricking and burning pain activation maps. The minimum cluster size threshold in the group overlap analysis was 4 voxels in original space at an overall $p < 0.01$.

Figure 4.

Contrast maps.

Brain regions differentially activated by the burning and pricking pain stimulation. The left side of each image corresponds to the right side of the brain, which is contralateral to stimulation. Functional run activation is overlaid on a normalized anatomical MRI in Talairach space. The coordinates of slice cuts through the axial and coronal planes are presented in the images. Orange regions represent stronger activation in the pricking versus burning condition, while blue areas represent stronger activation in the burning versus pricking condition. In the group contrast analysis, the minimum cluster size was 6 voxels in original space at an overall $p < 0.05$.

Table 1:

Individual subject activation in pain-related regions for each condition.

Region	Side	Pricking pain (n = 9)	Burning pain (n = 9)
Thalamus	Ipsilateral	7	5
	Contralateral	9	4
SI	Ipsilateral	3	3
	Contralateral	7	3
SII	Ipsilateral	9	8
	Contralateral	8	6
Anterior-INS	Ipsilateral	8	7
	Contralateral	8	7
Posterior-INS	Ipsilateral	7	6
	Contralateral	8	6
DLPFC	Ipsilateral	7	7
	Contralateral	8	8
Rostral-ACC	Midline	7	6
Mid-ACC	Midline	7	6
SMA	Midline	9	8

Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; INS, insula; SMA, supplementary motor cortex

Table 2:

Region	Side	Pricking pain				Burning pain			
		TAL coordinates		Z-score		TAL coordinates		Z-score	
		x	y	z		x	y	z	
Thalamus	Ipsilateral	-8	-1	9	4.05	-5	-17	10	3.95
	Contralateral	6	-2	7	3.62	11	-3	13	3.80
Anterior Insula	Ipsilateral	-37	14	8	4.35	-39	11	3	3.43
	Ipsilateral	-37	-8	16	3.34	-30	-5	19	3.15
Anterior Cingulate Cortex	Contralateral	39	5	19	4.15	43	17	20	3.88
	Midline	-2	17	30	3.35	-1	19	37	3.38
Dorsolateral Prefrontal Cortex	Contralateral	36	3	24	4.47	42	12	31	5.11
	Ipsilateral	-57	-33	25	4.22	-56	-39	26	4.07
Posterior Parietal Lobe	Contralateral	50	-30	15	3.51	47	-37	20	3.14
	Ipsilateral	-36	-50	-29	3.43	-38	-53	-37	3.46
Cerebellum									

Abbreviations: TAL, Talairach coordinates (x,y,z). Note that activation maps for each condition separately show activation in more regions than shown here. Data presented in this table represents overlap in activation between conditions.

Table 3:

Brain regions showing a significant contrast for pricking versus burning pain.

Region	Side	TAL coordinates			Volume (mm ³)	Z-score
		x	y	z		
<u>Pricking > burning</u>						
Hippocampus	Ipsilateral	−29	−16	−10	805	3.43
Parahippocampal gyrus	Ipsilateral	−11	−34	−4	465	2.52
	Contralateral	20	−34	−1	476	3.14
Fusiform gyrus	Ipsilateral	−36	−43	−9	901	3.62
	Contralateral	30	−40	−12	585	3.56
Cerebellum	Contralateral	8	−66	−25	1133	3.23
Cuneus/parieto-occipital sulcus	Contralateral	7	−80	17	1047	2.72
<u>Burning > pricking</u>						
Dorsolateral Prefrontal Cortex	Ipsilateral	−34	27	34	511	−2.61