Brain activity for spontaneous pain of postherpetic neuralgia and its modulation by lidocaine patch therapy

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Abstract

Postherpetic neuralgia (PHN) is a debilitating chronic pain condition, yet there is a lack of knowledge regarding underlying brain activity. Here we identify brain regions involved in spontaneous pain of PHN (n = 11) and determine its modulation with Lidoderm therapy (patches of 5% lidocaine applied to the PHN affected body part). Continuous ratings of fluctuations of spontaneous pain during fMRI were contrasted to ratings of fluctuations of a bar observed during scanning, at three sessions: (1) pre-treatment baseline, (2) after 6 h of Lidoderm treatment, and (3) after 2 weeks of Lidoderm use. Overall brain activity for spontaneous pain of PHN involved affective and sensory-discriminative areas: thalamus, primary and secondary somatosensory, insula and anterior cingulate cortices, as well as areas involved in emotion, hedonics, reward, and punishment: ventral striatum, amygdala, orbital frontal cortex, and ventral tegmental area. Generally, these activations decreased at sessions 2 and 3, except right anterior insular activity which increased with treatment. The sensory and affective activations only responded to the short-term treatment (6 h of Lidoderm); while the ventral striatum and amygdala (reward-related regions) decreased mainly with longer-term treatment (2 weeks of Lidoderm). Pain properties: average magnitude of spontaneous pain, and responses on Neuropathic Pain Scale (NPS), decreased with treatment. The ventral striatal and amygdala activity best reflected changes in NPS, which was modulated only with longer-term treatment. The results show a specific brain activity pattern for PHN spontaneous pain, and implicate areas involved in emotions and reward as best reflecting changes in pain with treatment.

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1. Introduction

Postherpetic neuralgia (PHN) is characterized with spontaneous pain of various qualities like sharp, stabbing and burning, and commonly accompanied with increased tactile sensitivity (allodynia) (Dworkin and Portenoy, 1996; Rowbotham and Fields, 1996; Fields et al., 1998; Dworkin, 2002; Galer et al., 2002). The condition is considered the prototypical human chronic neuropathic condition, since such patients exhibit multiple peripheral and central signs of neuropathy: decreased innervation density of the epidermis by nociceptive afferents (Oaklander, 2001); involvement of large somatic afferents in pain (Nurmikko et al., 1991); loss of cells in the involved dorsal root ganglion and of myelin and axons in the dorsal horn (Watson et al., 1988), as well as spinal cord and brainstem lesions on MRI (Haanpaa et al., 1998). Centrally, there is no clear information regarding brain elements involved in PHN pain. Evidence from animal models for neuropathic pain
shows peripheral and spinal cord re-organization see reviews (Woolf and Salter, 2000; Hunt and Mantyh, 2001; Inoue et al., 2004; Devor, 2006). Similarly to PHN patients, they exhibit behavioral signs of spontaneous pain, which can be related to increased spontaneous activity of peripheral A- and C-nociceptors (Tal et al., 1999; Wu et al., 2001) and to abnormalities in the expression and trafficking of Na⁺ channels (Devor, 2006).

Chronic pain and PHN in particular that can last from a few months to lifetime greatly diminishes the quality of life, and increases anxiety and depression (Dworkin, 2002; Sah et al., 2003). Moreover, chronic back pain is now associated with specific cognitive (Apkarian et al., 2004a), brain chemical (Grachev et al., 2004) and morphologic abnormalities (Apkarian et al., 2004b), all of which are consistent with cortical changes reflecting maladaptive reorganization that may be due to living with chronic pain.

We recently showed that intensity of chronic pain fluctuates spontaneously: PHN patients instructed to indicate their pain intensity on a continuous scale comply readily, and exhibit fluctuations of spontaneous pain with unique properties (Foss et al., 2006). Here, we utilize such ratings of fluctuations of spontaneous pain of PHN, performed during fMRI scans, to identify associated brain activity. Moreover, since lidocaine patch (Lidoderm) has been shown to be effective in decreasing PHN pain (Rowbotham et al., 1996; Guler et al., 1999, 2002; Gammanitoni et al., 2003) through the blockade of local Na-channels on peripheral afferents (Persaud and Strichartz, 2002; Chevrier et al., 2004), we use the latter as an additional parameter with which we can define brain regions involved in PHN pain by demonstrating the central effects of this therapy. Given the minimal knowledge regarding brain circuitry underlying PHN pain and for spontaneous pain of chronic pain, our starting hypothesis was that it should be distinct from that of acute pain and more similar to other chronic pain conditions, like chronic back pain.

2. Methods

2.1. Patients and screening procedures

This study was approved by the Northwestern University Institutional Review Board, and written informed consent was obtained from all participants. Participants were recruited through local media announcements and from local pain clinics. Patients were included if they fulfilled the International Association for the Study of Pain (IASP) criteria for Post Herpetic Neuralgia (PHN) (Merskey and Bogduk, 1994). All participants reported a history of shingles, including a sudden episode of rash accompanied with severe pain and sensitivity to touch in the area affected, with at least one visit to a physician where diagnosis of acute infection with varicella-zoster virus was made. All participants reported also a history of persistent pain for at least 3 months after the resolution of the acute shingles episode, with a pain intensity of at least 3 over 10 on a Visual Analog Scale (VAS) (Jung et al., 2004). Patients were tested for the presence of allodynia to brush during the interview, by gently passing a piece of foam over the painful area. The presence of allodynia was asserted if the patient reported an increase of the pain by at least 1 unit above the baseline on VAS scale. Participants were instructed that they can continue using their medications, but cannot change doses for the duration of the study (2 weeks).

Fourteen PHN patients were entered into the study. Only 11 were analyzed: 10 females and one male, ranging in age from 46 to 85 (mean age 67.8). Of the three that were excluded, one dropped out from the study, one had faulty registration of his functional brain scans, and the third was excluded because of excessive head motion. Demographics and clinical characteristics of pain are summarized for the participants in Supplementary Table 1. Some of these parameters are derived from short-form of McGill Pain Questionnaire (Melzack, 1987). Outcomes on this questionnaire did not correlate with Lidoderm treatment effects; as a result its relationship to brain activity was not studied.

2.2. Experimental design and pain rating

Patients were asked to report the fluctuations of their spontaneous pain (in the absence of an external stimulus) using a finger-span logging device, task sp (Apkarian et al., 2001a; Foss et al., 2006). In the pre-scan session, patients learned how to use the device to continuously report changes in their spontaneous PHN pain intensity while observing their rating projected on a computer screen as a moving bar (size of the bar is a scale from 0 to 10; 0 = no pain; 10 = worst imaginable pain), or to perform a visual control task (visual control = v) where they rated the length of a bar moving at a rate approximating the variability of spontaneous PHN pain. Only patients who were able to rate properly the fluctuations of the bar during the visual task (v) with the finger-span device were entered into the study (subjects had to score a correlation r-value > +0.70 between the input and their rating, in two attempts). During fMRI brain imaging, in separate scans patients rated either their spontaneous pain, sp, or performed the visual control task, v. During brain imaging the finger device was synchronized and time locked with the fMRI image acquisition sequence. An example of pain rating taken from one of the participants is shown in Fig. 1A.

Patients were scanned at three different sessions to investigate the effect of treatment of the PHN condition with Lidoderm patches (topical 5% lidocaine) after acute and long-term use: brain scan session 1 was done at baseline before the beginning of treatment; session 2 after 6 h of use of the Lidoderm patch, and session 3 after 2 weeks of continuous use of the Lidoderm patch. The procedure consisted of asking the patients to wear the patches for 6 h after finishing session 1 scans, and then to remove the patches and perform the second scanning session. Then the participant was instructed to wear the patches continuously during the day (12 h) for two weeks and return and undergo the last, session 3, brain scan. A registered nurse instructed each patient on how to use the patch. The patients kept on using their entire physician prescribed.
2.3. Functional magnetic resonance data acquisition

Functional MRI data were acquired with a 3T Siemens Trio whole-body scanner with echo-planar imaging (EPI) capability using the standard radio-frequency head coil. Multi-slice T2*-weighted echo-planar images were obtained with the following parameters: repetition time TR = 2.5 s, echo time TE = 30 ms, flip angle = 90°, slice thickness = 3 mm, in-plane resolution = 3.475 × 3.475 mm². The 36 slices covered the whole brain, from cerebellum to the vertex. Two hundred and forty volumes were acquired per scan. At each scan session, a given patient performed first a maximum of 3 repetitions of the sp task, with one patient having one sp task scan only at session 2, and another two having no sp task scans at session 3, leaving us with a total of 47 sp task scans. After the sp task scans, each patient performed only one v task scan. We could not however obtain a v task scan at each session for all patients. This was due either to time limitation, to head motion during the scan, or to bad performance on the control task (r < 0.40, p < 0.0001). Thus, each participant had at least one scan across the three sessions, with a total of 24 task v scans. A T1-weighted anatomical MRI image was also acquired for each subject using the following parameters: TR = 2.1 s, TE = 4.38 ms, flip angle = 8°, FOV = 220 mm, slice thickness = 1 mm, in-plane resolution = 0.86 × 0.86 mm² and number of sagittal slices = 160.

2.3.1. fMRI data analysis

Patients with high levels of pain invariably move during fMRI scans, and such motion degrades brain activity. To compensate for these artifacts we performed head motion correction in two steps. The first step consisted in standard correction for head motion using MCFLIRT (FMRIB’s Software Library, www.fmrib.ox.ac.uk/fsl, Jenkinson and Smith, 2001; Jenkinson et al., 2002). In the second step, the motion corrected data were again analyzed for head motion artifacts running Independent Component Analysis (see Supplementary Methods).

The following pre-processing was applied to the motion corrected data: slice-timing correction using Fourier-space time-series phase-shifting; non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 5 mm; global (volumetric) multiplicative mean intensity renormalization; and registration to standard space using each subject’s high-resolution anatomic images as an intermediate step, using FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002).

Five of our subjects had their lesion on the right side of their body. In order to investigate whether the side of the disease affected the group brain activity, the orientation of the raw data was flipped for those five subjects in a separate analysis, so that their activity came to be as if they had the lesion on the left side. The orientation of the data, which was radiological by default, was changed using a subroutine in FSL software (FMRIB’s Software Library, www.fmrib.ox.ac.uk/fsl). The rest of the analysis was performed as with the non-flipped data.

Spontaneous pain (sp) and visual (v) ratings were convolved with a canonical hemodynamic response function and used in a general linear model as the primary vectors of interest.
(FEAT Version 5.4). Two of our patients (patient 7 and 14 in Supplementary Table 1) had minimal or no pain at session 3 and therefore, they did not report any pain fluctuations, making impossible the identification of BOLD events with their pain rating time series. Therefore, those scans were dropped from session 3. Given the fact that sp time series spanned a wide spectrum of frequency ranges (Foss et al., 2006), different high-pass temporal filters were used for each scan, so as to eliminate 15% of the low frequency range of the power spectrum. Hence, our high-pass temporal filters ranged from 50 to 300 s (see Supplementary Methods).

2.3.1.1. fMRI statistical analysis. BOLD time series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich et al., 2004). Z-statistic images were thresholded at \( z > 2.3 \) and a (repeated-measures corrected) cluster significance threshold of \( p = 0.01 \) (Worsley et al., 1992). We also tested a higher threshold (cluster threshold \( p = 0.005 \)) but this did not reveal any important changes in activity patterns. The following second level contrasts were computed: \( sp_1, sp_2, sp_3 \) (average activity for sp for each session and across all treatment sessions) and \( v_1, v_2, v_3 \) and \( v_{all} \). Only positive activity was determined for these contrasts, after masking each with the map generated for \( sp_{all} \) at a threshold of \( z > 0 \). This mask avoids false positive activations due to decreased activity in \( v \), by limiting the outputs to only brain regions where spontaneous pain resulted in positive activity. Treatment effect was studied by a one-way ANOVA (using the model: \( 1, 0, -1 \), for sessions 1, 2 and 3 scans, respectively) to determine brain activity for specific regions of interest using linear correlation, for which parameter estimates (P.E., betas from general linear model) were extracted for a 1 cc (3 x 3 x 3 voxels) volume at specific coordinates of interest. Brain activity change across sessions was correlated to pain parameter changes with sessions. We will report the effects of these parameters in a separate analysis, for which parameter estimates (P.E., betas from general linear model) were extracted for a 1 cc (3 x 3 x 3 voxels) volume at specific coordinates of interest. Brain activity change across sessions was correlated to pain parameter changes with sessions.

2.3.1.2. Temporal BOLD signal plots. The BOLD signal was extracted, using our own Matlab script, based on the pain rating \( sp \) time series. Epochs where pain was higher than the average of a given time series were identified using patients’ own pain ratings. At the transition from mean to higher pain ratings a fixed-size window, \( 17.5 \) s wide and spanning the upstroke (two TRs backwards and 5 TRs forwards; \( TR = 2.5 \) s; \( 17.5 \) s in total), was used to average across all such epochs. The width of this window was determined by the observation that the mode of the amount of time when the PHN pain is higher than average is one TR across all the sp runs, and by the need to show the slow return to baseline. The corresponding brain activity BOLD signal was averaged within each session for each subject, and averaged across subjects. Resultant BOLD signal is in arbitrary MR units. The same approach was also used on the pain ratings to delineate the time profile of the ratings in the same window as for determining BOLD responses.

3. Results

3.1. Influence of lidocaine treatment on pain

Treatment with Lidocontrol patch led to a significant decrease in pain intensity (mean rating of fluctuations of spontaneous pain), and in the NPS score in 9 out of 11 patients, both after 6 h (session 2) and after 2 weeks of treatment (session 3), a response rate similar to published clinical trials (Gammaitoni et al., 2003). Fig. 1B (left panel) shows the group-average time course of pain-rating signal in absolute scale, mean pain ratings (mid panel) and NPS score (right panel) are also shown as a function of session. Average pain intensity for all patients at session 1 was \( 4.9 \pm 0.5 \) (mean \( \pm \) SEM), \( 3.7 \pm 0.7 \) at session 2, and \( 2.9 \pm 0.6 \) at session 3 \((F_{(2,8)} = 109; p < 0.01); \) session 2 and session 3 mean pain is significantly less than in session 1, \( p < 0.01 \) for both; on a 0–10 scale). Moreover, 7 out of 10 pain descriptors in NPS (Galer and Jensen, 1997) showed a significant improvement with treatment, except for dull, cold, and deep (Supplementary Table 2). Total NPS score, summed over descriptors that showed treatment effect, across all patients decreased primarily with 2-weeks of treatment: \( 41.7 \pm 5.1 \) at session 1; \( 40.5 \pm 5.7 \) at session 2; and \( 27.1 \pm 6.2 \) at session 3 \((F_{(2,20)} = 11, p < 0.01)\). The majority of our patients had their lesion on the trunk. The distribution of the affected areas is shown in Fig. 1C.

3.2. Brain activity for sp and v tasks

Spontaneous PHN pain shows characteristic fluctuations over the 10-min span of the scanning run (Foss et al., 2006). One such example of rating taken from one patient is shown in Fig. 1A. The brain activity identified for such ratings constitutes the main outcome for spontaneous PHN pain, sp; similarly rating the size of the bar presented visually, \( v \), is the motor/cognitive/visual control for sp.
We show the activation pattern for both the rating of the spontaneous PHN pain (spall) (Fig. 2A) and the visual rating (vall) (Fig. 2B), after averaging across all sessions. Brain regions activated in the spall (see Supplementary Table 3) can be grouped in three main clusters, and are reminiscent of the acute pain map in normal subjects (Apkarian et al., 2005), mainly, left thalamus, bilateral striatum, left secondary somatosensory cortex (SII), bilateral insula, left anterior cingulate cortex (ACC), right orbitofrontal cortex (OFC) (BA11), and cerebellum.

In the visual control task, v, the patients attempt to mimic their own pain rating, with the difference that in v they estimate the magnitude for a visual stimulus instead of their own pain. Hence, the areas activated are mainly visuospatial attention areas such as the right visual cortex, bilateral posterior superior parietal cortices, right primary motor area (MI) and left primary motor (MI) and somatosensory area (SI), in addition to the cerebellum, the right mid frontal gyrus (BA9/46), and the right inferior temporal gyrus (TG) (See Supplementary Table 4).

Average brain activity for the visual control task at each session increased from v1 to v2 to v3 (see Supplementary Figure 1). A similar but smaller increase was also seen in the pain-rating task (Supplementary Figure 2). For this reason we performed a correlation analysis for both tasks with mean spontaneous pain. We determined the modulation of brain activity for sp and v tasks with pain intensity by using mean pain intensity as a covariate. Fig. 3 shows the influence of pain intensity on across-sessions averaged brain activity for tasks, sp and v. The resultant map is generally similar for both tasks: activity in medial and lateral prefrontal regions was positively correlated, while posterior parietal attentional areas were negatively correlated with mean pain intensity. This result shows that brain activity for both tasks is influenced by the level of spontaneous pain, implying that the level of pain influences task performance in general. This idea is further corroborated by the observation that in the visual task there is a trend in improvement in rating ability with sessions (mean correlation between the visual input and the actual rat-

![Fig. 2. Brain activity maps for rating spontaneous pain of PHN, and the control visual task. (A) Average brain activity across the three sessions (spall) shows significant increased brain activity in multiple brain areas. Arrow 1 indicates L SII/insula, arrow 2 points to ACC activity. (B) Average brain activity across all three sessions for the visual control task (vall). Arrow 3 indicates L PPC activity, and arrow 4 indicates activity in L SI/MI. Supplementary Tables 3 and 4 provide the complete list of regions activated in A and B, respectively. (For abbreviations see Table 1).](image)

![Fig. 3. Pain intensity has a large effect on brain activity for rating spontaneous pain of PHN, and for rating the visual control task. Brain activity for rating spontaneous pain (sp) or rating visual control (v) task was correlated with the average pain rating at the time of the scan. Generally, in both tasks similar regions were modulated with average spontaneous PHN pain: medial and lateral prefrontal areas were positively modulated (arrow 1), while posterior parietal attentional areas (arrow 2) were negatively modulated.](image)
ing shows a borderline session dependence; mean r-value = 0.66, SD = 0.19; one-way ANOVA comparing r-values across the three sessions, $F_{2,22} = 3.3, p < 0.06$.

This in turn reinforces the need for correcting brain activity by a control condition performed at the same pain level, that is the necessity of subtracting $v$ from $sp$ at each treatment session. Our finding indicates that the intensity of spontaneous pain impacts brain activity for any task that the subject attempts to perform. Therefore, the decreased brain activity reported for pain tasks in many clinical pain conditions (Derbyshire, 1999; Peyron et al., 2000; Apkarian et al., 2005) is most likely a reflection of the presence of the spontaneous pain, and is not specific to the task being investigated.

### 3.3. Brain activity for spontaneous pain of PHN

To isolate brain activity specifically for spontaneous pain of PHN we examine the contrast between $sp$ and $v$ $(sp - v)$, for each session and for the average across all sessions. Resultant activations are shown in Fig. 4, and corresponding coordinates are in Table 1. Overall, spontaneous PHN pain maps to areas involved in sensory-discriminative and, affective processing as well as hedonic experience, while treatment decreases this activity. In session 1, $(sp - v)_1$ (Fig. 4A), activity is seen in left thalamus and bilateral SII/insula (sensory areas); ACC (BA 24/32) (affective); and bilateral ventral striatum, amygdala, and OFC (BA 11) (hedonic); as well as in hypothalamus, left inferior temporal gyrus (BA 22), and left visual /precuneus cortices (BA17/7) within the occipitoparietal sulcus. Brain activity decreases markedly in session 2, $(sp - v)_2$ (Fig. 4B), where bilateral insula, right SII and right amygdala are still activated. In session 3, $(sp - v)_3$ (Fig. 4C), only left SII, right amygdala and the cerebellum are active after 2 weeks of Lidoderm use. Across-sessions average brain activity for the spontaneous PHN pain, $(sp - v)_{all}$ (Supplementary figure 3A), resulted in the same significantly active areas seen in session 1, except for the thalamus which was not activated for across-sessions average. Flipping the brain orientation in the 5 patients who had a right sided lesion does not change the map for the $(sp - v)_{all}$, and still do not show activity in the thalamus (Supplementary Figure 3B). Statistical subtraction of the flipped average from the non-flipped one (map in Supplementary Figure 3B – map in Supplementary Figure 3A) does not yield any significant clusters.

### 3.4. Effect of Lidoderm treatment on brain activity

The above results demonstrate that brain activity for spontaneous PHN pain is decreasing with treatment. However, the analysis does not indicate which areas are statistically significantly modulated with treatment. We tested the latter by modeling treatment effect as a monotonic decrease with sessions. The hypothesis is based on the decrease in intensity of spontaneous pain in sessions 2 and 3, the decrease in NPS in session 3, and on the assumption that continued Lidoderm use will result in further decrease in brain activity in regions involved in pain. This model was tested only for brain regions identified to be positively active for spontaneous PHN pain across sessions (that is areas where $(sp - v)_{all}$ $z$-values $> 0$), using a one-way ANOVA statistical analysis. Fig. 5 and Table 2 summarize this result. Regions decreasing in activity with treatment included: left thalamus, hypothalamus, left SI/MI (BA3/4), left SII/insula, bilateral ventral striatum, and precuneus (BA7), and right OFC (BA11). The right inferior frontal
Brain regions activated for spontaneous pain of PHN, \( sp - v \) contrast, within and across sessions

<table>
<thead>
<tr>
<th>Region</th>
<th>Coordinates contrast(^a)</th>
<th>Z-value (SP – v)(_{all})</th>
<th>Region Index (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( sp - v )(_{all})</td>
<td>( X ) -12 ( Y ) 3.13 ( Z ) 12</td>
<td>NS</td>
<td>(SP – v)(_{all})</td>
</tr>
<tr>
<td>L OFC (11)</td>
<td>(-24 -26 -12)</td>
<td>NS</td>
<td>+Mid FG(10)</td>
</tr>
<tr>
<td>L Vis/Preccun (17/7)</td>
<td>(-16 -72 28)</td>
<td>NS</td>
<td>+Mid FG (10)</td>
</tr>
<tr>
<td>R Mid Frontal G (10)</td>
<td>(44 8) 3.37</td>
<td>NS</td>
<td>Same</td>
</tr>
<tr>
<td>Mid ACC (32)</td>
<td>(-2 8 40) 2.66</td>
<td>NS</td>
<td>Same</td>
</tr>
<tr>
<td>Rostral ACC (9/32)</td>
<td>(-4 24 20 ) 3.90</td>
<td>NS</td>
<td>Same</td>
</tr>
<tr>
<td>L Inf Temporal G (37)</td>
<td>(-54 -44 -18) 4.25</td>
<td>NS</td>
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</tr>
<tr>
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</tr>
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</tr>
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<td>Same</td>
</tr>
<tr>
<td>R Amygdala</td>
<td>(22 2 -18) 3.95</td>
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</tr>
<tr>
<td>L V Striatum</td>
<td>(-12 20 6) 2.72</td>
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<td>Same</td>
</tr>
<tr>
<td>R V Striatum</td>
<td>(16 14 ) -12 4.13</td>
<td>NS</td>
<td>Same</td>
</tr>
<tr>
<td>L SII</td>
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</tr>
<tr>
<td>R SII</td>
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<td>NS</td>
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</tr>
<tr>
<td>R OFC (11)</td>
<td>(28 48 -12) 3.15</td>
<td>NS</td>
<td>Same</td>
</tr>
</tbody>
</table>

Activated region names and coordinates are shown for \( sp - v \)\(_{all}\). Only peak z-values in each brain region are shown for each treatment session. For the flipped data, \( sp - v \)\(_{all}\) flipped, z-values and brain regions are shown; regions with no activity are left blank. The \( sp - v \)\(_{all}\) contrast contained 13 clusters: cluster 1, 102 voxels, \( p < 0.01 \); cluster 2, 110 voxels, \( p < 0.01 \); cluster 3, 151 voxels, \( p < 10^{-3} \); cluster 4, 281 voxels, \( p < 10^{-6} \); cluster 5, 282 voxels, \( p < 10^{-6} \); cluster 6, 673 voxels, \( p < 10^{-12} \); cluster 7, 5588 voxels, \( p < 10^{-12} \). *Abbreviations used:* L, left; R, right; Inf, inferior; G, gyrus; V, ventral; Mid, middle; m, medial; ACC, anterior cingulate cortex; BS, brainstem; Cun, cuneus; DLPFC, dorsolateral prefrontal cortex; MI, primary motor cortex; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PPC, posterior parietal cortex; Preccun, precuneus; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; and SMA, supplementary motor cortex. Numbers in parentheses, Brodmann areas.

\(^a\) Coordinates taken from peak voxels of \( sp - v \)\(_{all}\).

\(^b\) Cluster index for \( sp - v \)\(_{all}\).

gyrus/anterior insula (BA 47) was the only region showing increased activity with treatment.

We investigated the treatment effect further by examining activity patterns for specific brain regions of interest derived from across-session average activity map (Fig. 4A) and from the treatment map (Fig. 5). Extracted activities were related to treatment sessions, and to pain intensity and NPS descriptors (Fig. 6, Table 3). Table 3 lists correlations between regional brain activities on the one hand, and mean ratings of spontaneous PHN pain (pain intensity) or the 7 NPS descriptors modulated with treatment on the other hand. The correlations were calculated for across session changes in these parameters. All regions investigated are listed. All three anterior cingulate regions examined show a negative correlation; insular regions show both positive and negative correlations; while left amygdala, and especially left and right ventral striatum are positively correlated with change in pain parameters (Table 3).

Regional activity in left ventral striatum, left amygdala, and the left thalamus again shows a significant decrease with treatment; where the striatal response...
occurs only during long-term treatment, thalamic response only during short-term treatment, while amygdala response during both short- and long-term treatments (Fig. 6A and B first panels, and Fig. 6D). No treatment effect is seen in the left mid insula (Fig. 6C, first panel), and a significant decrease is only seen for acute treatment in the ACC (Fig. 6E). Similarly to ACC and left thalamus, left SI and left SII regional activity decreased only with acute treatment (data not shown). On the other hand, the right inferior frontal gyrus/anterior insula shows a significant increase in activity with treatment, but only with acute treatment (Fig. 6F, first panel). The change in regional activity in relation to the change in NPS descriptors as a function of treatment sessions is also shown in Fig. 6. The correlation coefficients change significantly between acute and long-term treatment for left ventral striatum (for surface descriptor), left amygdala (for intense descriptor), and right inferior frontal gyrus/anterior insula (for intense descriptor) (Fig. 6A, B, and F, last panels). There is an important difference in these changes between the first two brain regions in comparison to right inferior frontal gyrus/anterior insula. In striatum and amygdala regions, pain descriptor to activity relationship switches from a negative correlation to a positive one, while in the right inferior frontal gyrus/anterior insula the opposite pattern is seen, with 6 h in contrast to 2 week Lidocaine treatment, indicating that these areas are differentially modulated by acute and long-term treatment. Left thalamus, SI, SII, OFC, and ACC regions examined did not correlate or only negatively correlated with pain parameters.

We did examine the temporal properties of BOLD in a number of regions. Only the temporal pattern of left ventral striatum BOLD decreased with treatment (Fig. 7, right). In comparison, the magnitude of change in spontaneous pain fluctuations (Fig. 7, left) shows a systematic, but non-significant, decrease with treatment. Therefore, the BOLD signal decrease is more likely a reflection of the change in absolute value magnitude in spontaneous pain rather than in the temporal pattern of the change in spontaneous pain.

4. Discussion

The results show that by relating fluctuations of spontaneous pain to fMRI, and using a proper control task, we can identify brain regions involved in spontaneous PHN pain, which maps to sensory (thalamus, SI, SII, and insula), affective (anterior cingulate, insula), as well as hedonic regions (ventral striatum, amygdala, ventral tegmentum, and orbital frontal cortex). We use responses to Lidoderm therapy and correlations with changes in neuropathic pain scale to functionally subdivide the identified brain areas. It should be noted that the lack of a placebo group obviates making specific statements as to the mechanisms by which Lidoderm is modulating pain perception and related brain activity. Only a subset of the areas involved in PHN pain respond to Lidoderm therapy, which in turn can be subdivided to regions that respond to short-term therapy, and others that respond to longer-term therapy. The acute responses to therapy are observed mainly in sensory and affective regions, while longer-term responses are observed in brain areas implicated more in hedonic and emotional processing. Bilateral ventral striatum seems the region that most tightly reflects the spontaneous pain of PHN, since it is highly activated in the baseline session, decreases in activity with treatment,
and the change in activity across sessions is correlated to almost all NPS descriptors that decreased with treatment.

This is the first study documenting brain activity for spontaneous pain in PHN patients. There are very few studies regarding brain activity for human neuropathic
pain conditions, the majority of these examine responses to external stimuli (Hsieh et al., 1995; Hsieh et al., 1999; Apkarian et al., 2001b; Gracely et al., 2002; Giesecke et al., 2004; Peyron et al., 2004; Maihofner et al., 2006), and in many of these cases perception or stimulus conditions are not matched between contrasts, which complicates interpretation of obtained results. Therefore, our study is comparable only to few others (Hsieh et al., 1995; Hsieh et al., 1999) where brain activity for ongoing pain was contrasted before and after a therapeutic manipulation. However, the lack of an internal control in these studies confounds the results, the necessity of which is illustrated in Fig. 3.

The methodology used here involved online ratings of perception. A similar approach has been used to identify brain activity abnormalities in bowel disorder patients with chronic pain (Kwan et al., 2005). We have used this approach for assessing stimulus-evoked pain and spontaneous pain in various chronic pain groups and in healthy subjects (Baliki et al., 2005, 2006). In healthy subjects and using thermal painful stimuli (Baliki et al., 2006), we observe that ratings of perceived pain activate brain regions commonly seen during acute pain (Apkarian et al., 2005). Therefore, we can state that the activations observed in the current study for PHN spontaneous pain are not a reflection of the method.

Many of the brain regions observed involved in spontaneous pain of PHN are areas commonly seen for acute pain in normal subjects, especially thalamus, S1, SII, parts of insula, and anterior cingulate regions (Apkarian et al., 2005). Thalamus, S1, SII, and parts of insula, code sensory-discriminative components of acute pain both in intensity and in somatotopy (for example, see (Derbyshire et al., 1997; Davis et al., 1998; Coghill et al., 1999; Casey et al., 2001; Buchel et al., 2002), and (Bingel et al., 2003, 2004; Brooks et al., 2005; Henderson et al., 2006)). Of these areas, left thalamus, S1 and SII decreased in activity with 6-h Lidoderm treatment but not with longer-term treatment, and were not related to NPS pain descriptors. The lack of relationship between NPS descriptors and these activations is consistent with the observation that NPS measures were not affected with short-term therapy. The anterior cingulate activity had a similar response pattern. Mid-anterior cingulate activity, at a site closely approximating the brain region specifically shown to be modulated by pain unpleasantness rather than pain intensity for acute pain (Rainville et al., 1997; Hofbauer et al., 2001), was in fact negatively correlated with changes in mean spontaneous PHN pain intensity, and was not correlated with changes in NPS descriptors as a result of treatment. Thus, although these regions are active during spontaneous PHN pain and decrease with short-term treatment, given the lack of a positive relationship with reported pain, we cannot assert that they are directly involved in the reported PHN pain. In contrast, some insular regions

### Table 3

Correlation matrix for change in regional BOLD and change in pain intensity and 7 NPS descriptors across sessions.

<table>
<thead>
<tr>
<th></th>
<th>ACC1</th>
<th>ACC2</th>
<th>ACC3</th>
<th>L Ins1</th>
<th>L Ins2</th>
<th>L Ins3</th>
<th>R Ins</th>
<th>R OFC</th>
<th>L VS</th>
<th>R VS</th>
<th>L Amyg</th>
<th>R Amyg</th>
<th>L Tha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain intensity</td>
<td>-0.43*</td>
<td>-0.56*</td>
<td>-0.45*</td>
<td>0.52*</td>
<td>0.03</td>
<td>0.39</td>
<td>-0.06</td>
<td>0.07</td>
<td>0.28</td>
<td>0.40*</td>
<td>-0.08</td>
<td>0.09</td>
<td>0.08</td>
</tr>
<tr>
<td>Intense</td>
<td>-0.12</td>
<td>-0.16</td>
<td>-0.31</td>
<td>0.22</td>
<td>-0.31</td>
<td>0.41*</td>
<td>0.23</td>
<td>0.03</td>
<td>0.55*</td>
<td>0.62*</td>
<td>0.56*</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>Sharp</td>
<td>-0.13</td>
<td>-0.29</td>
<td>-0.32</td>
<td>0.07</td>
<td>-0.31</td>
<td>0.28</td>
<td>0.12</td>
<td>-0.01</td>
<td>0.48*</td>
<td>0.53*</td>
<td>0.41*</td>
<td>-0.01</td>
<td>0.16</td>
</tr>
<tr>
<td>Hot</td>
<td>0.14</td>
<td>0.01</td>
<td>-0.21</td>
<td>-0.10</td>
<td>-0.47*</td>
<td>0.20</td>
<td>0.18</td>
<td>-0.02</td>
<td>0.15</td>
<td>0.46*</td>
<td>0.54*</td>
<td>-0.28</td>
<td>-0.07</td>
</tr>
<tr>
<td>Sensitive</td>
<td>-0.40*</td>
<td>-0.34</td>
<td>-0.33</td>
<td>0.39</td>
<td>-0.03</td>
<td>0.32</td>
<td>-0.37</td>
<td>0.03</td>
<td>0.41*</td>
<td>0.42*</td>
<td>0.16</td>
<td>0.12</td>
<td>0.02</td>
</tr>
<tr>
<td>Itch</td>
<td>0.21</td>
<td>0.02</td>
<td>0.24</td>
<td>0.07</td>
<td>0.07</td>
<td>-0.16</td>
<td>0.31</td>
<td>-0.11</td>
<td>-0.38</td>
<td>0.22</td>
<td>-0.20</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Unpleasant</td>
<td>-0.22</td>
<td>-0.30</td>
<td>-0.49*</td>
<td>0.12</td>
<td>-0.35</td>
<td>0.54*</td>
<td>0.34</td>
<td>-0.06</td>
<td>0.62*</td>
<td>0.70*</td>
<td>0.36</td>
<td>0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Surface</td>
<td>-0.45*</td>
<td>-0.31</td>
<td>-0.51*</td>
<td>0.38</td>
<td>-0.26</td>
<td>0.51</td>
<td>0.59*</td>
<td>-0.03</td>
<td>0.42*</td>
<td>0.65*</td>
<td>0.16</td>
<td>0.21</td>
<td>-0.13</td>
</tr>
</tbody>
</table>

Correlations are calculated for change across sessions 1 and 2, sessions 1 and 3, and sessions 2 and 3 in BOLD and in each parameter (n = 9). Pain intensity is mean rating of spontaneous PHN pain. Subscripts for each brain area are the specific regions investigated, with coordinates: ACC1 (6, 32); ACC2 (2, 22, 20); ACC3 (2, 26, 18); L Ins1 (−38, −2, 0); L Ins2 (−46, −16, 12); L Ins3 (−42, 4, 0); R Ins = R insula/inferior Frontal gyrus (38, 20, −18); R OFC (14, 22, −18); L VS (−12, 16, 6); R VS (20, 10, 6); L Amyg (−24, 2, −18); R Amyg (22, 2, −18); L Tha (−16, −26; 12); Amyg, amygdala; ACC, anterior cingulated cortex; insula; OFC, orbitofrontal cortex; significant correlations = *; r-values > 0.6 significant, observed only in VS. Repeat-measure correction is not necessary since most regions examined already show whole-brain repeat-measure corrected treatment effects.

![Fig. 7. Temporal profile for pain ratings and for BOLD signal in ventral striatum. Left panel shows the average change in pain ratings from baseline (same data as in Fig. 1A, left panel, after removing baselines, expressed in TR timescale rather than in seconds), across patients and in session 1 (filled circles), session 2 (empty circles) and session 3 (inverted triangles). Overall, the pain ratings show a small, statistically non-significant, decrease in magnitude and duration. Right panel shows the percentage change in BOLD signal in the left ventral striatum (from Fig. 6A), extracted for the same time windows as in left panel. This is the only brain region where we can identify a decrease in BOLD temporal pattern with treatment; before treatment (filled circles) to after treatment (inverted triangles, sessions 2 and 3, bars are SEM). Time is in TR = 2.5 s.](image-url)
are positively correlated with mean pain, while other areas are positively correlated to various NPS descriptors and also decrease in activity during long-term treatment. Thus, these insular regions satisfy all the conditions to be involved in spontaneous PHN pain. Generally the lack of involvement of thalamus, SI, and SII in the long-term treatment is consistent with earlier observations of decreased cortical activity in clinical pain conditions in contrast to acute pain, as has been pointed in systematic reviews of the literature (Derbyshire, 1999; Peyron et al., 2000; Apkarian et al., 2005).

Multiple insular areas are activated for acute pain in contrast to non-painful touch (Price, 2000; Apkarian et al., 2005), in anticipation of pain (Ploghaus et al., 1999), pain empathy (Singer et al., 2004; Saarela et al., 2006), unpleasantness of pain (Schreckenberger et al., 2005), insular lesions can lead to pain neglect-like behavior (Berthier et al., 1988), and stimulation within insula evokes painful experiences (Ostrowsky et al., 2002). Thus, insula is regarded as critically involved in encoding sensory as well as affective components of acute pain. The role of the insula in spontaneous PHN pain seems complex and heterogeneous with distinct portions showing opposite responses to treatment. This is not peculiar to chronic pain, since a similar observation has been made in acute pain in normal subjects as the pain intensity was hypnotically manipulated (Hofbauer et al., 2001). The increased activity in right anterior insula suggests that gustatory processing in PHN patients should be changing with Lidoderm treatment, paralleling enhanced gustatory processing observed in chronic back pain (Small and Apkarian, 2006). It has been suggested that insula responds to ‘interoceptive’ states (Craig, 2002; Critchley et al., 2004). However, other recent studies suggest that anterior insula may be involved in more general cognitive processing (Kong et al., 2005; Dosenbach et al., 2006). Similarly to the insula, mid and rostral anterior cingulate has also been implicated in other function besides pain: activated for motivational drive, reward, gain or loss, conflict-monitoring or error prediction, and attentional changes or anticipation (Barch et al., 2001; Ridderinkhof et al., 2004), as well as in pain empathy (Singer et al., 2004; Saarela et al., 2006). Thus, relative changes along these dimensions between short- and long-term therapy may commonly explain the distinct responses of both anterior cingulate and parts of insula.

Orbital frontal cortex, amygdala, ventral tegmentum, and ventral striatum were active during baseline spontaneous pain of PHN, and decreased with treatment; most importantly, bilateral ventral striatum reflected changes in almost all NPS descriptors that decreased with treatment. These regions together are part of the reward, addiction, hedonic and emotional circuitry of the brain (Schultz et al., 2000; Volkow and Fowler, 2000; Kringelbach, 2005). They are only rarely observed activated in acute pain and only in the early phase for painful thermal stimuli in normal subjects (Becerra et al., 2001). The role of this circuitry in pleasure and rewarding conditions has been extensively documented, yet little is known regarding its role in aversive conditions (Jensen et al., 2003; Seymour et al., 2005), and the present study and our study in chronic back pain (Baliki et al., 2006) are the first to directly implicate this ‘reward’ circuitry in chronic clinical pain states. Sustained high pain for spontaneous chronic back pain involves a unique activation of this reward circuitry, with the exception that prefrontal activity seems more prominent and localized more superiorly within the medial prefrontal cortex (Baliki et al., 2006). The similarity of involvement of reward circuitry between the two chronic pain conditions is striking, while the differences need further studies. The ventral striatum has access to representations of reward and thereby processes information regarding motivational control of goal-directed behavior (Schultz et al., 2000), and in a conditioned electrical shock paradigm it exhibits an anticipatory response to the aversive stimulus (Jensen et al., 2003). More relevant to the present study are observations of the responses of components of reward circuitry in a Pavlovian learned pain relief from a tonic painful condition, where various components exhibit either reward or aversion prediction activity, and both signals appear co-expressed in ventral striatum (Seymour et al., 2005). In spontaneous pain of PHN, we presume that the involvement of reward circuitry implies that the condition is more emotional than acute pain and induces decreased motivated behavior, as commonly observed in chronic pain patients.

A recent anatomical study shows that the ventral striatum and amygdala receive direct nociceptive projections from non-peptidergic IB4 neurons terminating in spinal cord lamina II (Braz et al., 2005). In contrast, the spinothalamic pathways, composed mainly of SP/CGRP peptidergic afferents, is the pathway thought to be mediating nociceptive inputs to lateral thalamus, SI, SII, and parts of insula. The results of the present study suggest that Lidoderm therapy affects the latter pathway with short-term treatment and the IB4-pathway with longer-term treatment, and only by affecting the IB4-pathway related responses does it give rise to perceptually detectable decrease in spontaneous PHN pain. Therefore, at least for spontaneous pain and in PHN and chronic back pain there seems to be a shift in the brain pain-related circuitry, away from sensory-representational cortical areas, favoring instead hedonic/reward sub-cortical areas, making the condition perhaps more sub-conscious and impacting on motivational drives.
Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2006.09.014.

References


