

Brain activity associated with pain, hyperalgesia and allodynia: an ALE meta-analysis

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Abstract The use of functional brain imaging techniques offers the possibility of uncovering the cerebral processing of the human pain experience. In recent years, many imaging studies have focused on defining a network of brain structures involved in the processing of normal pain. Additionally, it has been shown that stimulus-evoked pain, which is a frequent symptom of neuropathic pain, causes distinct patterns of brain activation. In the present study, we quantitatively analyzed the data of previous functional imaging studies. Studies were thus collected by means of a MEDLINE query. A meta-analysis using the activation-likelihood estimation method was conducted to quantify the acquired results. We then used this data to summarize and compare the cerebral activations of (i) normal and stimulus-evoked pain, (ii) thermal and mechanical pain, (iii) different types of stimulus-evoked pain (hyperalgesia, allodynia), and (iv) clinical neuropathic and experimental pain. The results suggest the existence of distinct, although overlapping, neuronal networks related to these different types of pain.

Keywords Allodynia · Cerebral activation · Functional imaging · Hyperalgesia · Neuropathic · Experimental · Nociception

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Introduction

Pain is considered a general, aversive experience. The IASP defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Merskey and Bogduk 1994). Nociceptive pain is an important factor for maintaining body integrity and preventing bodily harm. Neuropathic pain, however, is the result of a pathological condition affecting the nervous system, and the pain is lacking any obvious advantage of biological protection (Woolf and Mannion 1999; Jensen and Baron 2003). Neuropathic pain can be either spontaneous-ongoing, spontaneous paroxysmal or stimulus evoked. Stimulus-evoked pain, a typical feature of neuropathic pain (Koltzenburg et al. 1994), can be divided into allodynia or hyperalgesia (Ochoa and Yarnitsky 1993). The term hyperalgesia is used when painful stimuli are found to be more painful than normal. In contrast, allodynia describes a condition where normally innocuous stimuli evoke pain. Stimulus-evoked pain can be induced by different sensory modalities such as mechanical stimuli, cold or heat. Evoked pain can be examined under clinical conditions in peripheral or central neuropathic states in patients. Also, some symptoms of neuropathic pain can be studied in surrogate models of evoked pain in healthy controls (Treede et al. 1999; Moisset and Bouhassira 2007).

The human pain experience includes sensory-discriminative, motivational-affective, cognitive and autonomic subcomponents (Treede et al. 1999). The resulting concept of pain as a multidimensional construct argues against a spatially discrete representation of pain in the brain. Functional imaging studies over the last decade have revealed several neuroanatomical pain-related structures, including primary (S1) and secondary (S2) somatosensory

cortices, insula, prefrontal cortex (PFC) and parietal association (PA) cortices, thalamus and brain stem nuclei, thus corroborating this multidimensional concept of pain (Apkarian et al. 2005; Tracey 2008). Consequently, these brain areas are often referred as the “neuronal matrix of pain” (Melzack 1999). This pain neuromatrix is often divided into a lateral (primary and secondary sensory cortex and posterior insula) and a medial (anterior gyrus cinguli, PFC, anterior insula) system (Treede et al. 1999). The lateral system appears to encode the sensory discriminative component and the medial system the affective-motivational dimensions (Treede et al. 1999; Maihofner and Handwerker 2005). One set of studies has focused on differences in the underlying pathologic conditions or in the experimental parameters. Hereby, the larger part of the studies analyzed the network of brain structures involved in normal physiological pain, whereas differences in activation in stimulus-evoked pain in either neuropathic or experimental models were less frequently examined.

Existing reviews (Treede et al. 1999; Peyron et al. 2000; Apkarian et al. 2005; Kupers and Kehlet 2006; Moisset and Bouhassira 2007; Tracey 2008; Seifert and Maihofner 2009) summarize the results of the previous brain imaging studies in clinical pain states in general as well as in neuropathic pain. It was suggested that there is no unique network associated with neuropathic pain, and that the different symptoms of neuropathic pain syndromes like spontaneous pain and different types of evoked pain (allodynia, hyperalgesia) probably involve different cerebral mechanisms (Seifert and Maihofner 2009). Therefore, in the present study we tried to define and to compare different types of pain that could be associated with differences in cerebral processing. Firstly, we compared pain in the non-sensitized state with pain in presence of peripheral or central sensitization. This was based on the assumption that plastic changes within the nociceptive system lead to differential pain processing in the brain. For further comparisons within these categories, different subgroups were established: allodynia and hyperalgesia were compared because both phenomena are different regarding their underlying pathophysiologic mechanisms involving different fiber types (Woolf and Mannion 1999). Moreover, comparisons were drawn between thermal pain and mechanical/electrical pain in the presence and absence of sensitization, because previous studies have shown differences in patterns of brain activation during different stimulus modalities (Seifert et al. 2008). Hereby, electrical pain was allocated to mechanical pain because of the phasic character of electrical and mechanical pain stimuli in contrast to the usually tonic character of thermal stimuli. Finally, comparisons were drawn between allodynia/hyperalgesia within patients and allodynia/hyperalgesia within healthy subjects because it would be of great interest

if surrogate models for specific pain symptoms lead to different cerebral activation patterns as compared to clinical pain states.

Whereas most of the previous reviews about brain imaging in pain states are based on a qualitative evaluation, so far only one study used empirical meta-analytic techniques to collate functional imaging data across several experimental studies (Farrell et al. 2005). Hereby, quantitative meta-analytic tools were adopted to analyze the elements of the cortical pain network across studies that have applied thermal stimuli to the upper limb.

In the current meta-analysis, the activation likelihood estimation (ALE) technique was applied. The ALE technique, known as function–location meta-analysis, was developed to assist in the integration of neuroimaging results gathered from multiple studies. In this way, it is possible to verify a consistent activation pattern across experiments within a certain class of imaging studies (Fox et al. 1998). This technique offers the possibility of searching for locations of functional agreement among statistically significant effects (Turkeltaub et al. 2002) and is thus particularly suited to the search for the primary neuroanatomical substrates of the pain experience (Turkeltaub et al. 2002). So far, the ALE method has not yet been used to quantify and compare different types of experimental and clinical pain. Hence, it was the intention of this meta-analysis to apply the ALE technique as a quantitative meta-analytic tool for describing the patterns and differences of the pain networks related to either normal or stimulus-evoked pain and for detecting differences in activation depending on the stimulus modality. For this purpose, data from functional imaging studies examining patients with clinical neuropathic pain and experimental evoked pain in healthy subjects were included and analyzed.

Methods

Literature search and selection

We conducted multiple MEDLINE searches to identify imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) that investigated thermally, mechanically and electrically induced normal pain as well as mechanical and thermal allodynia or hyperalgesia in patients with neuropathic pain and in healthy subjects with experimental pain. Publications between January 1997 and end of June 2008 were included. Keywords used in the MEDLINE query included “functional imaging”, “fMRI” and “PET” in addition to “pain”, “hyperalgesia” and “allodynia”. Furthermore, we searched the reference lists of articles identified as well as

several reviews. We included studies about normal pain, allodynia and hyperalgesia in neuropathic and experimental pain. Studies about mixed pain, including studies about headache, backache and fibromyalgia, were excluded. We then screened each article for the presence of Talairach or MNI (Montreal Neurological Institute) coordinates, as only studies that included specified information about these coordinates could be included. A total of 33 studies were identified by this process. In the next step, the studies were divided into the two general groups “normal pain” and “hyperalgesia and allodynia”. The terminus “normal pain” refers to painful stimulation of different modalities in the non-sensitized state; “hyperalgesia and allodynia” refers to painful stimulation in the presence of peripheral or central sensitization to pain. For further comparisons within these categories, different subgroups were established. Comparisons were drawn between “allodynia” and “hyperalgesia”, between “thermal pain” and “mechanical and electrical pain”, between “thermal allodynia and hyperalgesia” and “mechanical allodynia and hyperalgesia” as well as between “allodynia and hyperalgesia within patients” and “allodynia and hyperalgesia within healthy subjects”. The 33 studies found contained 20 datasets on cerebral activation during normal pain (among them 10 datasets on thermal pain and 10 datasets on mechanical and electrical pain), 12 datasets on allodynia and 9 on hyperalgesia. These 21 experiments on allodynia/hyperalgesia included 8 with thermal stimulation and 12 with mechanical stimulation, as well as 13 with healthy subjects and 8 with patients, respectively. The coordinates of the subjects with left-sided evoked pain sensations were mirrored and analyzed together with data from subjects with right-sided stimulation before application of the ALE method.

Data analysis

Descriptive information was extracted from each article including imaging modality, number of patients or healthy subjects within the sample, pain stimulus attributes and pain ratings. These data are presented in Table 1. Data on pain intensity was reported in 86% of all reviewed articles. Variation in measurement strategies among articles limited the possibility of meaningful comparisons somewhat. Pain ratings were used to determine average pain intensities within the single groups, reported as a number between 0 and 10 on the numeric rating scale. The ALE technique, a formal voxel-based meta-analytic tool using the ALE, is described in detail elsewhere (Turkeltaub et al. 2002; Laird et al. 2005). ALE is a quantitative meta-analysis method that was developed concurrently but independently by Turkeltaub (2002) and Chein (2002) and modified by Laird (2005). We used the software ALE (Research Imaging Center, University of Texas Health Science Center, San

Antonio, USA). In ALE, 3D coordinates in stereotactic space, as generally published relative to Talairach and Tournoux (1988) or MNI space (Collins et al. 1994), are pooled from a number of like studies. The procedure involves the modelling of all reported loci of maximum activation as the peaks of a 3D Gaussian probability, defined by a user-specified full-width half-maximum (FWHM). The 3D Gaussian distributions are summed to produce a statistical map that estimates the likelihood of activation for each voxel as determined by all the studies in the analysis. Only voxels that were found to be statistically significant are assigned a value. The value reported is the computed ALE value. The test was corrected to multiple comparisons using a false discovery rate (FDR) method (Laird et al. 2005). To make a valid assessment of the significance of the results, a permutation test for testing the statistic images was applied. We also employed a method for testing the differences between two ALE meta-analyses (Laird et al. 2005), the ALE subtraction meta-analysis, and for assessing the observed difference under the null hypothesis that both sets of coordinates are distributed uniformly. This analysis yields a map of clusters, performed on the threshold map, which shows regions in which the two groups of foci are significantly different. We used a Gaussian filter of 12 mm FWHM and a threshold for false discovery of $p < 0.05$ (tested with a permutation test of 5,000 permutations). The 12 mm FWHM was chosen because it closely matches the corresponding FWHM in data preprocessing of most fMRI studies and is close to the spatial variability in database coordinate locations as investigated by Eickhoff and colleagues (Eickhoff et al. 2009; Smith et al. 2009). Most other previous ALE studies used a FWHM between 10 and 15 mm (Neumann et al. 2008). However, it should be noted that the use of such a small FWHM has not been clearly justified and it might lead to a reduction in sensitivity. Salimi-Khorshidi and colleagues (Salimi-Khorshidi et al. 2009) recommended a kernel with a standard deviation σ of 15 mm corresponding to 35 mm FWHM because they found best fit with these parameters when maps were compared to ‘gold standard’ image-based meta-analysis maps. For the subtraction meta-analysis, the minimum volume to define a cluster was 100 mm³. The statistical map of ALE values yielded by the summation of the Gaussian distributions is output in the NIFTI-1-format. Furthermore, the results of a cluster-analysis performed on the threshold ALE map and based on the default minimum volume that defines a cluster, are obtained. The results contain the number of clusters, the cluster volumes and the corresponding Talairach coordinates. To visualize the results, we used MRICron (version 1 may 2008; designed by Chris Rorden; <http://www.sph.sc.edu/comd/rorden/mricron/install.html>), overlaying the statistical map of ALE values onto an anatomical template

and depicting the ALE values of the different analyses. To demonstrate the similarities and dissimilarities between different patterns of cortical activation, we overlaid maps of different groups and showed the calculated clusters of the ALE subtraction meta-analysis. As the ALE subtraction meta-analysis only shows differences between two analyses without depicting which analysis the differences are based on, we clarified the results by manually recolouring the clusters and attributing them to one of the groups compared. In the Tables (Online Resource), Talairach coordinates are presented together with the corresponding anatomical structure (gyrus, nucleus), Brodman area and functional area (e.g. S1, S2 etc.). S1 was defined as BA 1, 2 and 3. S2 was defined as the parietal operculum (extending from the lateral end of the central sulcus as the anterior border of the parietal operculum to the posterior end of the sylvian fissure as the posterior border of the parietal operculum). Based on previous studies (Disbrow et al. 2000; Jung et al. 2009), the Talairach coordinates $Y > -40$ and $Z > -30$ were defined to be the posterior border of S2. Here, we do not distinguish any further between an anterior and posterior part of the parietal operculum. The insular cortex was divided into an anterior and a posterior part: insular cortex activations with Talairach coordinates $Y > 0$ were defined as anterior insula (aIns), those with $Y < 0$ were defined as posterior insula (pIns) activations. The PFC was divided into the subareas ventral PFC (VPFC), dorsolateral PFC (DLPFC), ventrolateral PFC (VLPFC) and medial PFC (MPFC). VPFC corresponds to BA 10 (except for its medial part). DLPFC corresponds to BA 9 (except for its medial part) and to BA 46. VLPFC corresponds to BA 44, 45 and 47—except for the parts located to the frontal operculum. MPFC corresponds to those parts of BA 9 and 10 located medially in the interhemispheric fissure. BA 8 was not attributed to any of these PFC areas. M1 was defined as BA 4. The cingulate cortex was divided in ACC, PCC and residual cingulate cortex (CC) by anatomical boundaries as defined in (Talairach and Tournoux 1988).

Results

Thirty-three studies were included in the meta-analysis. fMRI and PET were used in 23 and 10 studies, respectively. The included studies and the corresponding imaging modality, number of patients or healthy subjects within the sample, pain stimulus attributes and pain ratings are presented in Table 1. The 33 studies included 41 different conditions with a sample sizes ranging between 6 and 20 subjects (Table 1). Combining these data, we formed several groups (the number of studies, the number of patients or healthy subjects, the number of included clusters and the

average pain ratings for each group is presented in Table 2). As described above, the review process revealed two potential main groupings: (a) “pain” and (b) “hyperalgesia/allodynia,” as well as eight subgroups: (c) “thermal pain”, (d) “mechanical and electrical pain”, (e) “mechanical allodynia/hyperalgesia”, (f) “thermal allodynia/hyperalgesia” (g) “allodynia”, (h) “hyperalgesia”, (i) “allodynia/hyperalgesia within healthy subjects” and (j) “allodynia/hyperalgesia within neuropathic pain patients”. In the analysis of average pain intensities, no significant differences were found between the described groups and subgroups ($p > 0.05$, U test). Details regarding the studies included, the groups and subgroups as well as the average pain intensities within the different studies are reported in Table 1. A summary of the studies included can be found in Table 2.

Comparisons were drawn between (i) “pain” and “hyperalgesia/allodynia”, (ii) “mechanical and electrical pain” and “thermal pain”, (iii) “mechanical allodynia/hyperalgesia” and “thermal allodynia/hyperalgesia”, (iv) “allodynia” and “hyperalgesia” as well as between (v) “allodynia/hyperalgesia within healthy subjects” and “allodynia/hyperalgesia within patients”. Figures 1–5 show the graphical presentation of the ALE analysis, depicting the statistical map of ALE values for the defined groups. Overlaid maps were used to demonstrate the similarities in different patterns of cerebral activation, whereas differences between conditions were shown by depicting the results of the ALE subtraction meta-analysis. A summary of the results can be found in Table 3.

Normal pain compared to allodynia and hyperalgesia

Normal pain stimuli led to brain activations in areas of the pain neuromatrix (see Fig. 1a, the locations of activation clusters and corresponding maximal ALE values are reported in Table 1, Online Resource). In detail, activations were found in the bilateral secondary somatosensory cortex (S2), the bilateral anterior and contralateral posterior insula, the contralateral anterior cingulate gyrus (ACC), the contralateral cingulate cortex (CC), the bilateral PFC, the ipsilateral inferior parietal lobe (IPL), the contralateral primary motor cortex (M1) and the bilateral thalamus. Furthermore, contralateral activation was found in parts of the basal ganglia (putamen, caudate) (coded red in Fig. 1a).

Allodynia/hyperalgesia activated bilateral S2, bilateral anterior and posterior insula, bilateral CC, bilateral PFC, bilateral IPL and the bilateral thalamus. Furthermore, activation was found in parts of bilateral basal ganglia and contralateral cerebellum (coded blue in Fig. 1a).

Compared to normal pain, allodynia/hyperalgesia induced a significantly stronger activation of bilateral S2,

Table 1 Included studies

References	Imaging technique	Group	Stimulus	Setting	<i>n</i>	Site	Pain rating
1. (Baron et al. 1999)	fMRI	mechanical hyperalgesia	von Frey monofilaments	Healthy subjects, sensitisation with capsaicin	9	Arm, r	51/100
2. (Bingel et al. 2003)	fMRI	Mechanical pain	LASER, pinprick sensation	Healthy subjects	14	Hand, b	/
3. (Bingel et al. 2006)	fMRI	Mechanical pain	LASER, pinprick sensation	Healthy subjects	19	Hand, b	/
4. (Bingel et al. 2007)	fMRI	Thermal pain	Heat	Healthy subjects	20	Hand, l	59–80/100
5. (Ducreux et al. 2006)	fMRI	Mechanical allodynia	Brush	Patients with cervical syringomyelia	6	Hand, b	61/100
	fMRI	Thermal allodynia	Cold (22°C)	Patients with cervical syringomyelia	6	Hand, b	59/100
	fMRI	Thermal pain	Cold (4°C)	Healthy subjects	6	Hand, b	56/100
6. (Geha et al. 2008)	fMRI	Mechanical allodynia	Brush	Patients with postherpetic neuropathy	11	Body and limb, b	/
7. (Hoffman et al. 2004)	fMRI	Thermal pain	Heat (47.6°C)	Healthy subjects	14	Leg, r	8/10
8. (Iadarola et al. 1998)	PET	mechanical allodynia	Brush	Healthy subjects, sensitisation with capsaicin	13	Arm, l	/
9. (Lorenz et al. 2002)	PET	Thermal allodynia	Thermal (31.7°C)	Healthy subjects, sensitisation with capsaicin	14	Arm, l	6/10
	PET	Thermal pain	Heat (41.1°C)	Healthy subjects	14	Arm, l	3,1/10
10. (Lui et al. 2008)	fMRI	Mechanical pain	Pneumatic device	Healthy subjects	11	Hand, r	25/100
11. (Maihofner et al. 2004)	fMRI	Mechanical allodynia	Brush	Healthy subjects, sensitisation with capsaicin/heat	11	Arm, l	/
12. (Maihofner and Handwerker 2005)	fMRI	Pinprick hyperalgesia	Pinprick	Healthy subjects, sensitisation with capsaicin	12	Arm, l	47/100
	fMRI	Thermal hyperalgesia	Heat	Healthy subjects, sensitisation with capsaicin	12	Arm, l	47/100
13. (Maihofner et al. 2005)	fMRI	Mechanical hyperalgesia	Von Frey monofilaments	Patients with CRPS	12	Arm and leg, b	10/100
14. (Maihofner et al. 2006)	fMRI	Mechanical pain	Ballistic apparatus	Healthy subjects	14	Arm, r	40/100
	fMRI	Mechanical pain	Heat	Healthy subjects	14	Arm, r	/
15. (Maihofner et al. 2007)	fMRI	Mechanical pain	Ballistic apparatus	Healthy subjects	14	Hand, b	50/100
	fMRI	Mechanical hyperalgesia	Ballistic apparatus	Healthy subjects, sensitisation with UVB	14	Hand, b	50/100
16. (Mohr et al. 2008)	fMRI	Thermal hyperalgesia	Heat	Healthy subjects, sensitisation with capsaicin	17	Leg, r	4–6/10
17. (Qiu et al. 2006)	fMRI	Mechanical pain	LASER, pinprick sensation	Healthy subjects	13	Hand, r	70/100
18. (Petrovic et al. 1999)	PET	mechanical allodynia	Brush	Patients with mononeuropathy	5	Leg, b	5,2/10
19. (Peyron et al. 1998)	PET	Thermal allodynia	Cold	Patients with Wallenberg-syndrome	9	Leg and arm, b	6,2/10
	PET	Electrical pain	Electrical	Patients with Wallenberg-syndrome	9	Leg and arm, b	4,5/10
20. (Rogers et al. 2004)	fMRI	Thermal pain	Heat (56.2°C)	Healthy subjects	8	Arm, l	5,8/10
21. (Seifert et al. 2007)	fMRI	Thermal hyperalgesia	Thermal (35 to 53.5°C)	Healthy subjects, sensitisation with UVB	14	Arm, r	40/100
	fMRI	Mechanical hyperalgesia	Pinprick	Healthy subjects, sensitisation with UVB	14	Arm, r	8/10
22. (Seifert et al. 2008)	fMRI	Thermal allodynia	Cold (25°C)	Healthy subjects, sensitisation with menthol	12	Arm, r	4,1/10
	fMRI	Thermal pain	Cold (15°C)	Healthy subjects	12	Arm, r	40/100

Table 1 continued

References	Imaging technique	Group	Stimulus	Setting	<i>n</i>	Site	Pain rating
23. (Seminowicz et al. 2004)	fMRI	Electrical pain	Electrical (10–40 mA)	Healthy subjects	16	Arm, l	20–50/100
24. (Seminowicz and Davis 2007)	fMRI	Electrical pain	Electrical (different currents)	Healthy subjects	23	Arm, l	40–60/100
25. (Schoedel et al. 2008)	fMRI	Mechanical pain	Pneumatic device	Healthy subjects	11	Hand, r	25/100
26. (Schweinhardt et al. 2006)	fMRI	Mechanical allodynia	Brush	Patients with neuropathy	8	Leg and arm, b	40/100
27. (Sprenger et al. 2006)	fMRI	Thermal pain	Heat	Healthy subjects	12	Arm, r	44,5/100
28. (Symonds et al. 2006)	fMRI	Electrical pain	Electrical (110–240 mA)	Healthy subjects	9	Arm, b	68/100
29. (Wagner et al. 2007)	PET	Thermal pain	Heat (46°C)	Healthy subjects	7	Arm, r	8/10
30. (Wiech et al. 2005)	fMRI	Thermal hyperalgesia	Heat	Healthy subjects, sensitisation with capsaicin	15	Arm, l	74/100
31. (Witting et al. 2001)	PET	Mechanical allodynia	Brush	Healthy subjects, sensitisation with capsaicin	8	Arm, l	61/100
32. (Witting et al. 2006)	PET	Mechanical allodynia	Brush	Patients with neuropathy	9	Leg and arm, b	/
33. (Xu et al. 1997)	PET	Mechanical pain	LASER, pinprick sensation	Healthy subjects	6	Leg and arm, l	3,8/10

Details of the samples and experimental procedures employed in the studies included in the meta-analysis. *n* number of examined subjects, *r* stimulation on the right side, *l* stimulation on the left side, *b* stimulation on both sides, *ACC* anterior cingulate cortex, *CC* cingulate cortex, *aIns* anterior insula, *pIns* posterior Insula, *DLPFC* dorsolateral prefrontal cortex, *MPFC* medial prefrontal cortex, *VLPFC* ventrolateral prefrontal cortex, *VPFC* ventral prefrontal cortex, *S1* primary somatosensory cortex, *S2* secondary somatosensory cortex, *M1* primary motor cortex, *PM* premotor cortex, *SMA* supplementary motor area, *IPL* inferior parietal lobule, *SPL* posterior parietal lobule

Table 2 Summary of the included studies

	Groups	Subgroups	Studies (<i>n</i>)	Subjects (<i>n</i>)	Clusters (<i>n</i>)	NRS
Number (<i>n</i>) of studies, number of patients or healthy subjects, number of included clusters, average pain ratings (NRS)	Pain	Total	20	246	404	5.4 ± 0.41
		Thermal	10	107	296	5.8 ± 0.65
		Mechanical/electrical	10	139	108	4.5 ± 0.49
	Allodynia/hyperalgesia	Total	21	231	392	5.2 ± 0.37
		Healthy subjects	13	165	270	4.7 ± 0.30
		Patients	8	66	122	4.8 ± 0.69
		Thermal	8	99	188	5.6 ± 0.42
		Mechanical/electrical	13	132	204	4.8 ± 0.65
		Allodynia	12	112	198	4.8 ± 0.65
		Hyperalgesia	9	119	194	5.6 ± 0.42

ipsilateral CC, bilateral PFC, contralateral basal ganglia and contralateral cerebellum (coded blue in Fig. 1b). Inversely, during normal pain stimuli, significantly stronger activation was found in the ipsilateral aIns, ipsilateral pIns, contralateral ACC and CC, contralateral PFC, bilateral thalamus and bilateral basal ganglia (coded red in Fig. 1b). Significant differences in activation were also detected in subregions of the contralateral anterior insular cortex, with increases during both conditions in each subregion, respectively.

Thermal pain versus mechanical pain

Thermal stimuli in the non-sensitized condition activated bilateral S2, bilateral anterior and posterior insula, contralateral ACC and CC, bilateral PFC, bilateral IPL, contralateral superior parietal lobule (SPL), bilateral thalamus, contralateral M1 and contralateral basal ganglia (coded red in Fig. 2a, the locations of activation clusters and corresponding maximal ALE values are reported in Table 2, Online Resource).

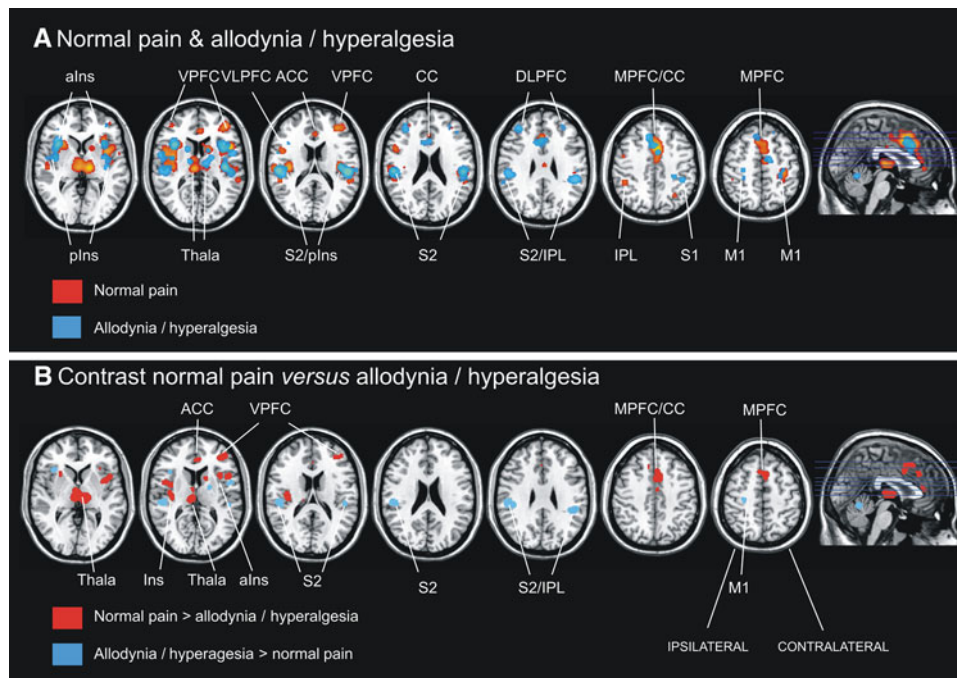


Fig. 1 Normal pain as compared to allodynia/hyperalgesia. Graphical representation of the ALE values. **a** Normal pain and allodynia/hyperalgesia. **b** Contrast normal pain versus allodynia/hyperalgesia. Graphical representation of the ALE values of each of the mentioned groups and results of ALE for contrasts of the ALE subtraction meta-analysis. Neuroanatomical labels describe locations of activation associated with the different kinds of painful stimulation. ACC

anterior cingulate cortex, CC cingulate cortex, *Ins* insula, *alns* anterior insula, *pIns* posterior Insula, *DLPFC* dorsolateral prefrontal cortex, *MPFC* medial prefrontal cortex, *VLPFC* ventrolateral prefrontal cortex, *VPFC* ventral prefrontal cortex, *Thala* thalamus, *S1* primary somatosensory cortex, *S2* secondary somatosensory cortex, *M1* primary motor cortex, *IPL* inferior parietal lobule, *SPL* posterior parietal lobule, *SMG* supramarginal gyrus

Mechanical stimuli in the non-sensitized condition activated bilateral S1, bilateral S2, ipsilateral aIns, bilateral CC, bilateral PFC, bilateral IPL and ipsilateral basal ganglia (coded blue in Fig. 2a).

When compared statistically, thermal pain induced a stronger activation of the bilateral S2, bilateral anterior and posterior insula, contralateral ACC, bilateral CC, bilateral PFC, bilateral IPL, contralateral SPL, bilateral thalamus and bilateral basal ganglia (coded red in Fig. 2b). Mechanical pain induced stronger activation of the contralateral supplementary motor area (SMA) and the supramarginal gyrus.

Mechanical versus thermal allodynia/hyperalgesia

Mechanical allodynia/hyperalgesia activated bilateral S1, bilateral S2, bilateral anterior and posterior insula, bilateral ACC, contralateral CC, bilateral PFC, bilateral IPL, ipsilateral SPL, contralateral thalamus, bilateral basal ganglia, bilateral cerebellum and the brainstem (coded red in Fig. 3a, the locations of activation clusters and corresponding maximal ALE values are reported in Table 3, Online Resource).

Thermal allodynia/hyperalgesia activated contralateral S1, bilateral S2, bilateral aIns, contralateral pIns, bilateral CC, bilateral PFC, ipsilateral IPL, bilateral thalamus and contralateral cerebellum (coded blue in Fig. 3a).

Comparing mechanical and thermal stimuli during hyperalgesia, mechanical stimulation led to a stronger activation of ipsilateral S1, bilateral S2, contralateral aIns, ipsilateral pIns, bilateral PFC, ipsilateral IPL and SPL, ipsilateral cerebellum and the brainstem (coded red in Fig. 3b); thermal stimulation showed increased activation of the bilateral aIns, the contralateral pIns, the bilateral CC, the contralateral basal ganglia and the contralateral cerebellum (coded blue in Fig. 3b).

Allodynia versus hyperalgesia

Allodynia induced activation of contralateral S1, bilateral S2, bilateral aIns, bilateral pIns, contralateral CC, bilateral PFC, bilateral IPL, bilateral thalamus, contralateral basal ganglia, bilateral cerebellum and the brainstem (coded red in Fig. 4a, the locations of activation clusters and corresponding maximal ALE values are reported in Table 4, Online Resource).

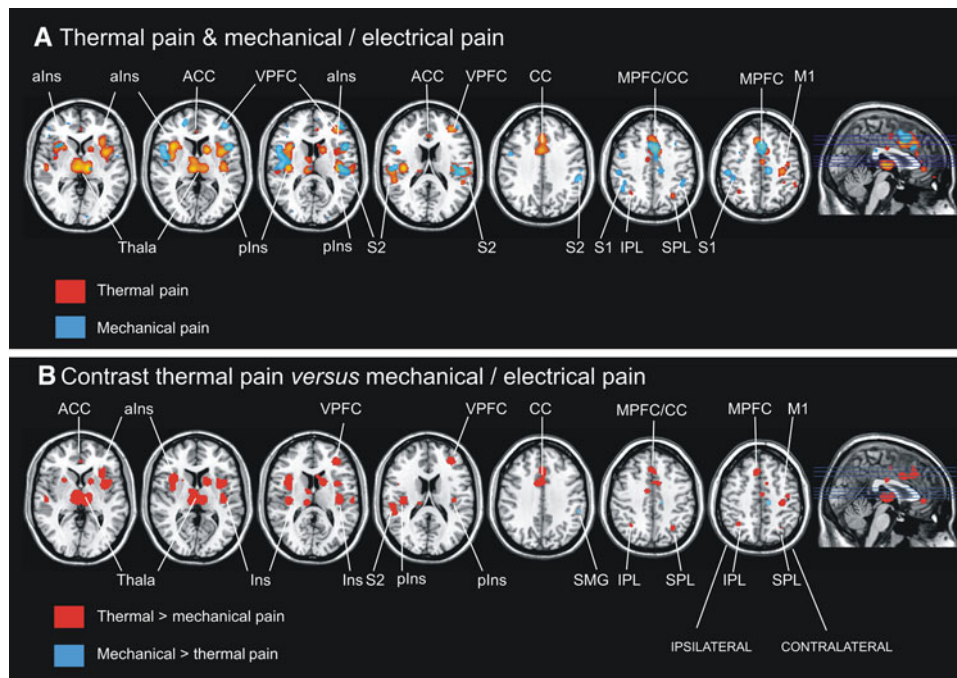


Fig. 2 Normal Pain: thermal compared to mechanical stimuli. Graphical representation of the ALE values. **a** Thermal pain and mechanical pain. **b** Contrast thermal versus mechanical pain. Graphical representation of the ALE values of each of the mentioned groups and results of ALE for contrasts of the ALE subtraction meta-analysis. Neuroanatomical labels describe locations of activation associated with the different kinds of painful stimulation. ACC

anterior cingulate cortex, CC cingulate cortex, *Ins* insula, *alns* anterior insula, *plns* posterior Insula, *DLPFC* dorsolateral prefrontal cortex, *MPFC* medial prefrontal cortex, *VLPFC* ventrolateral prefrontal cortex, *VPFC* ventral prefrontal cortex, *Thala* thalamus, *S1* primary somatosensory cortex, *S2* secondary somatosensory cortex, *M1* primary motor cortex, *IPL* inferior parietal lobule, *SPL* posterior parietal lobule, *SMG* supramarginal gyrus

Hyperalgesia activated bilateral S1, contralateral S2, bilateral *alns*, contralateral *plns*, contralateral ACC, ipsilateral CC, bilateral PFC, bilateral IPL, ipsilateral SPL, ipsilateral thalamus and contralateral cerebellum (coded blue in Fig. 4a).

While allodynia produced a significantly stronger activation of contralateral S1, bilateral S2, bilateral *plns*, bilateral PFC, ipsilateral IPL, ipsilateral thalamus, contralateral basal ganglia, ipsilateral cerebellum and the brainstem (coded red in Fig. 4b), hyperalgesia led to a more intense activation of bilateral S1, contralateral S2, contralateral *alns*, ipsilateral CC, bilateral PFC, contralateral IPL, ipsilateral SPL and contralateral cerebellum (coded blue in Fig. 4b).

Allodynia/hyperalgesia in healthy subjects versus patients

Evoked pain in healthy subjects activated ipsilateral S1, bilateral S2, bilateral *alns*, contralateral ACC, bilateral CC, bilateral PFC, bilateral IPL, ipsilateral thalamus, bilateral basal ganglia and contralateral cerebellum (coded red in Fig. 5a, the locations of activation clusters and corresponding maximal ALE values are reported in Table 5, Online Resource).

Evoked pain in patients with neuropathic pain activated bilateral S2, the ipsilateral *alns* and *plns*, the bilateral PFC, the contralateral IPL, the contralateral thalamus, the contralateral basal ganglia, the bilateral cerebellum and the brainstem (coded blue in Fig. 5a).

Compared to the patients, the activation in healthy subjects was stronger in ipsilateral S1, bilateral anterior and posterior insula, contralateral ACC, bilateral CC, bilateral PFC, bilateral IPL, ipsilateral thalamus and bilateral cerebellum (coded red in Fig. 5b). In patients, contralateral S2, contralateral SMA and ipsilateral cerebellum were significantly more activated as compared to healthy subjects (coded blue in Fig. 5b).

Discussion

The aim of this study was to quantitatively analyse the results of a large number of neuroimaging studies investigating normal and stimulus-evoked pain. Thereby, the terminus “normal pain” refers to painful stimulation of different modalities in the non-sensitized state; “hyperalgesia and allodynia” refers to painful stimulation in the presence of peripheral or central sensitization to pain.

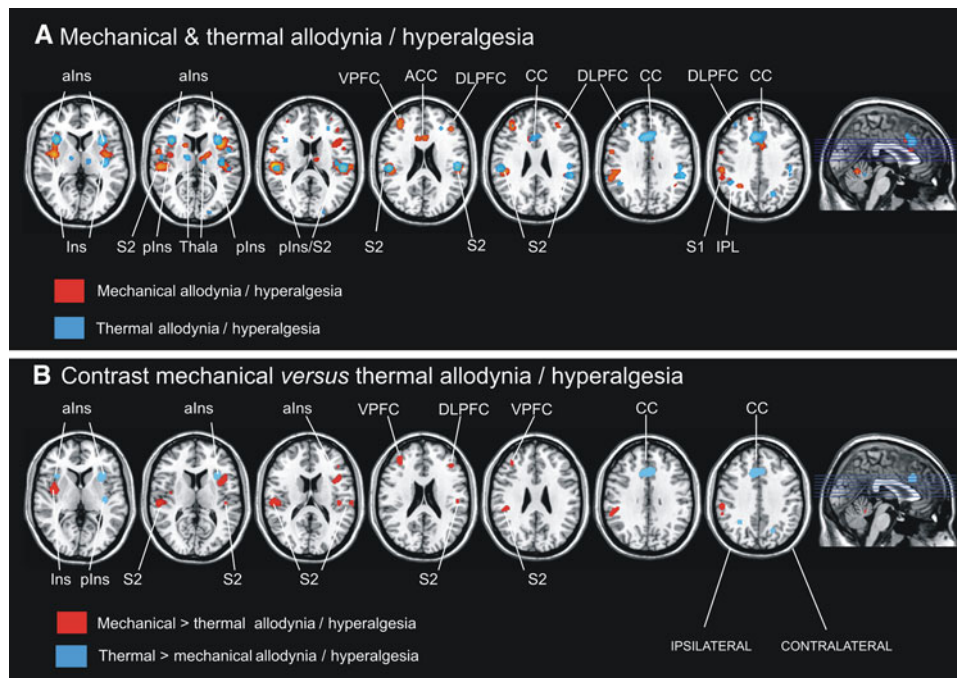


Fig. 3 Allodynia/hyperalgesia: thermal compared to mechanical stimuli. Graphical presentation of the ALE values. **a** Thermal and mechanical allodynia/hyperalgesia. **b** Contrast thermal versus mechanical allodynia/hyperalgesia. Graphical representation of the ALE values of each of the mentioned groups and results of ALE for contrasts of the ALE subtraction meta-analysis. Neuroanatomical labels describe locations of activation associated with the different kinds of painful stimulation. ACC anterior cingulate cortex, CC

cingulate cortex, *Ins* insula, *alns* anterior insula, *plns* posterior Insula, *DLPFC* dorsolateral prefrontal cortex, *MPFC* medial prefrontal cortex, *VLPFC* ventrolateral prefrontal cortex, *VPFC* ventral prefrontal cortex, *Thala* thalamus, *S1* primary somatosensory cortex, *S2* secondary somatosensory cortex, *M1* primary motor cortex, *IPL* inferior parietal lobule, *SPL* posterior parietal lobule, *SMG* supra-marginal gyrus

A further intention of the study was the comparison of cerebral activation during (i) normal and evoked pain, (ii) during different stimulus modalities, (iii) the difference between allodynia and hyperalgesia and (iv) during experimentally and clinically evoked pain. In the analysis of the average pain intensities, no significant differences were found between the described groups and subgroups. Therefore, group comparisons can be made under the assumption of equal pain intensities.

The meta-analytic approach used in the present study is ALE. ALE is a coordinate-based meta-analysis (CBMA) approach. Other available CBMA methods are kernel density analysis (KDA) (Wager et al. 2004a) and multi-level kernel density analysis (MKDA) (Wager et al. 2007, 2009). ALE involves the modelling of all reported loci of maximum activation as the peaks of a 3D Gaussian probability defined by a specified FWHM. The 3D Gaussian distributions are summed to produce a statistical map that estimates the likelihood of activation for each voxel as determined by all the studies in the analysis. In contrast, KDA uses a spherical kernel and produces maps showing the number of given foci within a given radius (Salimi-Khorshidi et al. 2009) and MKDA creates a binary map for

each study, showing locations with one or more foci within a given radius, the binary maps are then averaged giving the proportion of studies having any foci within a given radius from a voxel (Salimi-Khorshidi et al. 2009; Wager et al. 2009) which should prevent that results are driven by single studies reporting multiple neighbored foci in one area. There are several limitations to CBMA approaches that should be noted here. CBMA are based on activation foci reported in journal articles or submitted to databases. Thus, there is a significant loss of information because only the coordinates of maxima are used. Furthermore, the activation foci in the single studies can vary depending on differences in data analysis and thresholding procedures applied to the datasets (Salimi-Khorshidi et al. 2009). Therefore, image-based meta-analysis (IBMA) approaches using full statistical images have relevant advantages over CBMA. IBMA methods combine whole brain statistic maps rather than a summary of them (Salimi-Khorshidi et al. 2009). However, in common practice, neuroimaging studies rarely provide the full statistical image data (Salimi-Khorshidi et al. 2009; Wager et al. 2009). Salimi-Khorshidi and colleagues (Salimi-Khorshidi et al. 2009) compared coordinate- (ALE, KDA, MKDA) and image-

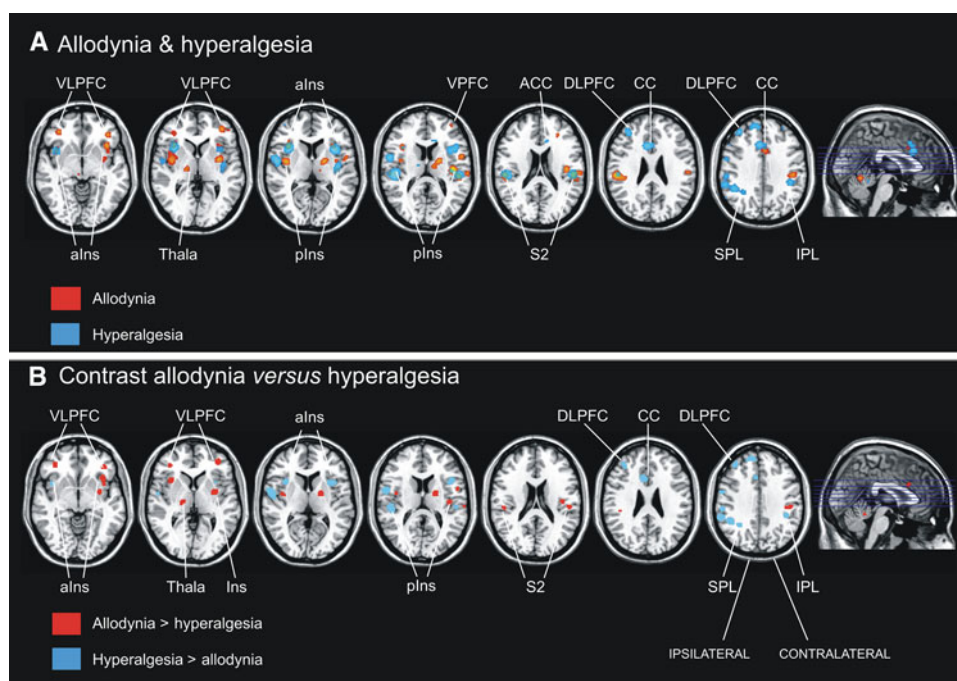


Fig. 4 Allodynia as compared to hyperalgesia. Graphical representation of the ALE values. **a** Allodynia and hyperalgesia. **b** Contrast allodynia versus hyperalgesia. Graphical representation of the ALE values of each of the mentioned groups and results of ALE for contrasts of the ALE subtraction meta-analysis. Neuroanatomical labels describe locations of activation associated with the different kinds of painful stimulation. ACC anterior cingulate cortex, CC

cingulate cortex, *Ins* insula, *alns* anterior insula, *pIns* posterior Insula, *DLPFC* dorsolateral prefrontal cortex, *MPFC* medial prefrontal cortex, *VL PFC* ventrolateral prefrontal cortex, *VPFC* ventral prefrontal cortex, *Thala* thalamus, *S1* primary somatosensory cortex, *S2* secondary somatosensory cortex, *M1* primary motor cortex, *IPL* inferior parietal lobule, *SPL* posterior parietal lobule, *SMG* supra-marginal gyrus

based meta-analytic approaches for a dataset from 15 fMRI studies from a single centre and found the greatest similarity between IBMA and ALE.

Most of the studies employed in this meta-analysis incorporate an innocuous control of similar modality, used to identify pain-specific activity. Although this is a common approach, there is a certain degree of ambiguity regarding the extent to which activations reflect functions that are common across both innocuous and noxious sensory processing. Therefore, in spite of the evaluation of contrasts between noxious and innocuous stimuli, the possibility that a signal increase from a brain region during painful stimulation might reflect both pain and other sensory experiences cannot be excluded (Coghill et al. 1999). Consequently, the ALE results do not per se represent cerebral activity exclusively related to pain (Laird et al. 2005). Furthermore, limitations of the study emerge from the fact that in spite of the high subcategorization, the necessity of including studies with diverse initial conditions in the same group or subgroup was unavoidable. Diverse study conditions that were at least partially summarized into one category include (i) different sides and locations of stimulation (e.g. arm or leg; left or right),

(ii) different stimuli (stimulation with ballistic apparatus, brush, von Frey monofilaments, pinprick stimuli, laser stimuli, contact thermodes), (iii) different causes for the existence of evoked pain (neuropathic pain states in patients; surrogate models of stimulus-evoked pain with use of capsaicin, heat or UV-B radiation in healthy subjects), (iv) the use of different measuring techniques (fMRI or PET) and (v) inconstant activation thresholds applied to the functional data in the included studies. Taking these preconditions into account, this analysis can generally be regarded as a confirmation of the numerous results demonstrated in previous experimental studies, allowing for the drawing of direct comparisons between different cerebral patterns of activation, evoked by different painful stimuli.

Here, we focussed on four main points of interest: (i) brain processing of normal pain compared to stimulus evoked pain, (ii) the effect of stimulus modality, (iii) the difference between allodynia and hyperalgesia and (iv) the difference between experimental and clinical pain. The results suggest the existence of distinct, although overlapping, neuronal networks related to these different types of pain which will be discussed in the following in detail.

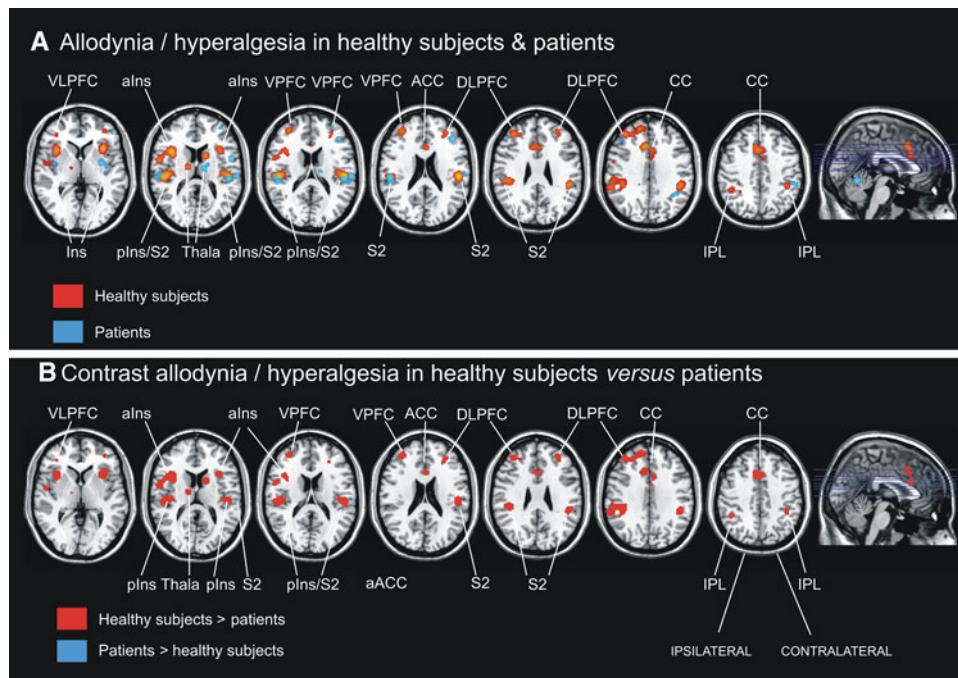


Fig. 5 Allodynia/hyperalgesia in healthy subjects as compared to patients with neuropathic pain. Graphical representation of the ALE values. **a** Allodynia/hyperalgesia in healthy subjects and patients. **b** Contrast allodynia/hyperalgesia in healthy subjects versus patients. Graphical representation of the ALE values of each of the mentioned groups and results of ALE for contrasts of the ALE subtraction meta-analysis. Neuroanatomical labels describe locations of activation associated with the different kinds of painful stimulation. ACC

anterior cingulate cortex, CC cingulate cortex, Ins insula, aIns anterior insula, pIns posterior Insula, DLPFC dorsolateral prefrontal cortex, MPFC medial prefrontal cortex, VLPFC ventrolateral prefrontal cortex, VPFC ventral prefrontal cortex, Thala thalamus, S1 primary somatosensory cortex, S2 secondary somatosensory cortex, MI primary motor cortex, IPL inferior parietal lobule, SPL posterior parietal lobule, SMG supramarginal gyrus

Normal pain compared to allodynia and hyperalgesia

Normal pain stimuli led to widespread brain activations in areas of the pain neuromatrix (Fig. 1a). Interestingly, in our meta-analysis no significant activation was detected in S1 for either condition. The role of S1 in pain processing per se is under extensive debate, as there are several imaging studies that did not show S1 activation in response to painful stimulation. In an early meta-analysis (Peyron et al. 2000), an absence of pain-induced S1 activation in imaging studies was reported in roughly 50% of the studies. S1 activation was linked to larger amounts of stimulated body surface, thus, spatial summation (Peyron et al. 2000). Another, non-quantitative meta-analysis of fMRI and PET studies reported pain-induced S1 activation in only 36 of 65 studies which investigated normal subjects (Apkarian et al. 2005). It can be speculated that some of these S1 activations in fMRI and PET studies are a result of tactile afferents simultaneously activated by the applied noxious stimulus (Forss et al. 2005). On the other hand, nociceptive projections from the thalamus to S1 (Apkarian and Shi 1994) and to specific nociceptive neurons in S1 (Kenshalo and Isensee 1983) have been demonstrated in animals.

Compared to normal pain, allodynia/hyperalgesia induced a significantly stronger activation of bilateral S2, ipsilateral CC, bilateral PFC, contralateral basal ganglia and contralateral cerebellum. Inversely, activation of the ipsilateral aIns, ipsilateral pIns, contralateral ACC and CC, contralateral PFC, bilateral thalamus and bilateral basal ganglia was significantly stronger after normal pain stimuli. The aIns activation during allodynia/hyperalgesia was located more rostral ipsilateral, but more caudal contralateral to painful stimulation. A possible reason for the increased activity in various brain areas (PFC, ACC, thalamus, insula) during normal pain as compared to allodynia/hyperalgesia could be (i) the presence of nociceptive input during baseline due to additional ongoing pain induced by the experimental pain model or the clinical condition or (ii) an adaptive mechanism, which may involve the endogenous pain modulatory system (Bingel et al. 2007; Lebel et al. 2008).

The effect of stimulus modality

The effect of stimulus modality was tested by comparing studies with thermal stimuli to those with mechanical or

Table 3 Patterns of activation

	S1	S2	Insula		CC		PFC				PPC		Thal	
			aINS	pINS	ACC	CC	DLPFC	VPFC	VLPFC	Other	IPL	SPL		
Activations														
Normal pain	/	B	B	C	C	C	I	B	B	/	I	/	B	
Allodynia/hyperalgesia	/	B	B	B	/	B	B	/	B	B	B	/	B	
Normal thermal pain	/	B	B	B	C	C	/	C	/	I	B	C	B	
Normal mechanical pain	B	B	I	/	/	B	/	B	B	/	B	/	/	
Mechanical allodynia/hyperalgesia	B	B	B	B	B	C	C	I	I	B	I	I	C	
Thermal allodynia/hyperalgesia	C	B	B	C	/	B	I	C	/	/	B	/	B	
Allodynia	C	B	B	B	/	C	/	C	B	I	B	/	B	
Hyperalgesia	B	C	B	C	C	I	I	/	/	B	B	I	I	
Healthy subjects allodynia/hyperalgesia	I	B	B	/	C	B	B	I	I	I	B	/	I	
Patients allodynia/hyperalgesia	/	B	I	I	/	/	B	C	/	I	C	/	C	
Contrasts														
Normal pain > allodynia/hyperalgesia	/	/	B	I	C	C	/	C	C	C	/	/	B	
Allodynia/hyperalgesia > normal pain	/	B	C	/	/	I	/	/	/	B	/	/	/	
Thermal pain > mechanical pain	/	B	B	B	C	B	/	C	/	I	B	C	B	
Mechanical pain > thermal pain	/	/	/	/	/	/	/	/	/	/	/	/	/	
Mechanical a./h. > thermal a./h.	I	B	C	I	/	/	C	I	I	C	I	I	/	
Thermal a./h. > mechanical a./h.	/	/	B	C	/	B	/	/	/	/	/	/	/	
Allodynia > hyperalgesia	C	B	/	B	/	/	/	/	B	I	I	/	I	
Hyperalgesia > allodynia	B	C	C	/	/	I	I	/	/	B	C	I	/	
Healthy subjects a./h. > patients a./h.	I	/	B	B	C	B	B	I	B	I	B	/	I	
Patients a./h. > healthy subjects a./h.	/	C	/	/	/	/	/	/	/	/	/	/	/	

Activation of selected brain regions during the different analyzed conditions

/ no significant activation, *I* ipsilateral activation, *C* contralateral activation, *B* bilateral activation

electrical stimuli in both normal and evoked pain. Thermal pain in the non-sensitized condition led to a stronger activation of bilateral S2, bilateral anterior and posterior insula, contralateral ACC, bilateral CC, bilateral PFC, bilateral IPL, contralateral SPL, bilateral thalamus and bilateral basal ganglia. The observed activation pattern is consistent with the ALE meta-analysis of Farrell et al. (Farrell et al. 2005) on brain activity associated with painfully hot stimuli applied to the upper limb. Mechanical pain induced stronger activation in the contralateral SMA and the supramarginal gyrus. Thus, thermal stimuli in the non-sensitized condition showed more robust activation in the pain neuromatrix in general. Comparing mechanical and thermal stimuli during pain sensitization, mechanical stimulation induced a stronger activation of ipsilateral S1, bilateral S2, contralateral aIns, ipsilateral pIns, bilateral PFC, ipsilateral IPL and SPL, ipsilateral cerebellum and the brainstem. Thermal stimulation induced stronger activation in bilateral aIns, contralateral pIns, bilateral CC, contralateral basal ganglia and contralateral cerebellum. Interestingly, in the sensitized state bilateral PFC (VPFC, DLPFC) was significantly more strongly activated by mechanical allodynic or hyperalgesic stimulation. The PFC

is involved in high-level pain modulatory systems and modulates other areas, including the brainstem which is involved in pain modulation (Lorenz et al. 2003). It also plays a key role in placebo cognition (Wager et al. 2004b). The results here suggest that it responds differentially depending on the stimulus modality and the presence of sensitization to pain.

Allodynia compared to hyperalgesia

We found significant differences between allodynia and hyperalgesia. Allodynia produced a significantly stronger activation in parts of contralateral S1, bilateral S2, bilateral pIns, bilateral PFC (VLPFC), ipsilateral IPL, ipsilateral thalamus, contralateral basal ganglia, ipsilateral cerebellum and the brainstem. Hyperalgesia induced stronger activation of parts of bilateral S1, of contralateral S2, contralateral aIns, ipsilateral CC, bilateral PFC (DLPFC), contralateral IPL, ipsilateral SPL and contralateral cerebellum. The pathophysiologic mechanisms underlying hyperalgesia and allodynia are different. Hyperalgesia can be divided into primary hyperalgesia (in damaged tissue) and secondary hyperalgesia (in the surrounding tissue).

Primary hyperalgesia exists for different submodalities (e.g. heat, cold and mechanical stimuli) and is induced by the sensitization of nociceptors. Secondary hyperalgesia, however, results from sensitization at the spinal or supraspinal level following a barrage from nociceptors. Sensitization of dorsal horn neurons is predominantly generated by C-fibre input, particularly from the group of the so called silent nociceptors (Schmidt et al. 1995; Ziegler et al. 1999; Schmeltz et al. 2000). Alternatively, hyperalgesia (mainly towards cold stimuli) can be generated by lesion-induced disinhibition and disintegration phenomena at all levels of the neuraxis (Ochoa and Yarnitsky 1994; Woolf and Mannion 1999). The phenomenon of dynamic mechanical allodynia is the result of a completely different mechanism. In allodynia, A-beta fibre input normally projecting to the tactile system may gain a pathological connection to the nociceptive system (Woolf and Mannion 1999). Thus, different underlying pathophysiologic mechanisms may explain the differences observed in the present meta-analysis of cerebral activity during both conditions.

Experimental pain compared to clinical neuropathic pain

Finally, we tested for a difference between experimental and clinical neuropathic pain. Compared to the results in patients, the activation was stronger in healthy subjects in ipsilateral S1, bilateral anterior and posterior insula, contralateral ACC, bilateral CC, bilateral PFC, bilateral IPL, ipsilateral thalamus and bilateral cerebellum. In patients, contralateral S2, contralateral SMA and ipsilateral cerebellum were significantly more activated as compared to in healthy subjects. There are possible mechanisms that could explain the stronger activations observed in healthy subjects as compared to patients in most areas of the pain neuromatrix: (i) An elevated baseline activity in patients could lead to a decrease in the measurable differences in activity or to a pronunciation of the results in healthy subjects. This elevated baseline level may result from continuous noxious input to the brain in patients with clinical pain syndromes which suffer often from spontaneous ongoing pain. The elevation of basal activity may lead to altered responsiveness of some (e.g. those contralateral to the painful stimuli) or all areas of the pain neuromatrix. We also cannot exclude that such changes in basal activity in patients contributes to an increased level of variance of pain-stimuli-induced brain activations. (ii) As thermal stimuli were used in 46% of the studies in healthy subjects but only in 25% of the studies in patients and since thermal stimulation generally induced stronger patterns of activation, the different proportions of the chosen stimuli could have influenced this result. (iii) Adaptation to noxious stimuli and endogenous pain inhibition may also have

led to reduced activations in the patient group. (iv) The higher number of included studies, examined subjects and clusters in healthy subjects can confound the results. (v) There may exist somatosensory deafferentation of cortical targets in neuropathic pain patients. And finally, (vi) abnormal resting state activity in several areas in patients but not controls may alter the measured pain-related activity increases. It should be noted that there is previous work showing a more rostral activity in the aIns during clinical pain in patients compared to experimental pain in healthy subjects (Schweinhardt et al. 2006). However, in the present meta-analysis, we did not observe a rostral shift of activation in the aIns in patients as compared to healthy subjects. This may be the result of an increased baseline activity (due to ongoing spontaneous pain) in the rostral aIns in the clinical pain group.

Limitations of the study are: (i) the coordinates of the subjects with left-sided evoked pain sensations were mirrored and analyzed together with data from subjects with right-sided stimulation before application of the ALE method. This implicates the hypothesis that there is no relevant hemispheric difference in pain processing. However, there is evidence that there is lateralization of nociceptive processing in the human brain, especially the operculoinsular cortex (Schlereth et al. 2003; Youell et al. 2004). In both studies, the hemispheric lateralization was of minor strength. (ii) The spatial discrimination power of the ALE approach influences the results. However, the 12 mm FWHM used here is a moderate parameter. (iii) Coordinates of peak activation are included in the present study. Subsidiary peaks within the same structure are not always reported specifically in the included studies. (iv) The statistical ALE approach used here is able to test for above-chance clustering of individual foci (fixed effects analysis) and not for results from different experiments (random-effects analysis) (Eickhoff et al. 2009). However, only random effects analysis would allow generalization of the results beyond the analyzed studies (Eickhoff et al. 2009). Therefore, Eickhoff and colleagues (Eickhoff et al. 2009) very recently proposed a revised algorithm for ALE analysis which includes a method that calculates the above-chance clustering between experiments (random-effects analysis). The fixed effects analysis is a limitation of our present study because results cannot be generalized to the entire population.

Conclusion

This meta-analysis using the activation likelihood estimation (ALE) method compared cerebral activations due to different types of pain stimuli under normal and pathological conditions. We summarized and compared the

cerebral activations of (i) normal and stimulus-evoked pain, (ii) thermal and mechanical pain, (iii) different types of stimulus evoked pain (hyperalgesia, allodynia), and (iv) clinical and experimental pain. We found increased activity during stimulus-evoked pain in S2 and increased activity during normal non-sensitized pain in ACC, PFC and the thalamus. We hypothesize that the latter may be the result of an increased baseline activity during the presence of central sensitization. When different stimulus modalities were compared, we found increased activity during thermal stimuli as compared to mechanical and electrical stimuli in insula, ACC, PFC and the thalamus. When pain induced brain activity in the presence of sensitization was compared between patients with clinical pain and healthy subjects with experimental pain, increased activity was detected in insula, ACC, PFC, S2 and thalamus in healthy subjects. Again, this may be the result of an increased baseline activity in patients with clinical pain. In general, the results suggest the existence of distinct, although overlapping, neuronal networks related to these different types of pain.

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