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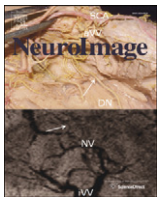

Coordinate-based meta-analysis of experimentally induced and chronic persistent neuropathic pain

Ulrike Friebel [a], Simon B. Eickhoff [b,c,d], Martin Lotze [a,*]

[a] Functional Imaging Unit, Center for Diagnostic Radiology, University of Greifswald, Germany
[b] Department of Psychiatry and Psychotherapy, RWTH Aachen University, Aachen, Germany
[c] Institute of Neuroscience and Medicine (INM-2), Research Center Jülich, Germany
[d] Jülich Aachen Research Alliance (JARA) — Translational Brain Medicine, Germany

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ABSTRACT

Differences in brain activation in experimentally induced and chronic neuropathic pain conditions are useful for understanding central mechanisms leading to chronic neuropathic pain. Many mapping studies investigating both pain conditions are now available, and the latest tools for coordinate-based meta-analysis offer the possibility of random effects statistics. We performed a meta-analysis based on a literature search of published functional magnetic resonance imaging group studies to compare patterns of activity during experimentally induced and chronic neuropathic pain, for the later including four fibromyalgia studies. Stimulus-dependent activation in experimental pain was further divided into "thermal" and "non thermal" stimuli. A conjunction of experimentally induced and chronic neuropathic pain revealed activation of the bilateral secondary somatosensory cortex, right middle cingulate cortex, right inferior parietal lobe, supplementary motor area, right caudal anterior insula, and bilateral thalamus. Primary somatosensory activation was only observed during experimental non-thermal stimulation. Chronic neuropathic pain studies showed increased activation in the left secondary somatosensory cortex, anterior cingulate cortex, and right caudal anterior insula when compared to experimentally induced pain. Activation clusters in the anterior cingulate cortex and caudal anterior insula suggest a strong emotional contribution to the processing of chronic neuropathic pain.

Introduction

Pain perception is multidimensional and includes sensory-discriminative, cognitive, and emotional aspects. Thus, cerebral processing of the experience of pain involves different networks, which are roughly divided into lateral and medial pain systems. The lateral (sensory-discriminative) pain system consists of the primary and secondary somatosensory cortices (SI and SII) and the passing through the lateral thalamic nuclei. The medial (affective–cognitive–evaluative) pain system consists of the anterior cingulate cortex (ACC) and the prefrontal cortex (PFC), mediating through medial thalamic nuclei (Brooks et al., 2002; Ingvar, 1999; Porro et al., 1998; Schnitzler and Ploner, 2000; Tracey, 2008). The insula is part of both systems, and hence in an intermediate position, with the posterior part coding intensity and lateralization of pain and the anterior part coding emotional processing of pain. Thus, the insula may play an integrative role in nociceptive processing (Brooks et al., 2002). Furthermore, the basal ganglia, cerebellum, amygdala, hippocampus, and some regions of the temporal and parietal cortices have been discussed as belonging to the "extended pain matrix" (Tracey, 2005). However, when using multimodal stimuli, some of the areas denoted as part of the "pain matrix" have been shown to be not specifically for pain processing but are instead involved in the detection of salient stimuli per se (Mouraux et al., 2011).

Several studies have described brain activation maps in response to pressure, to electrical stimuli, and to thermal pain in healthy participants; many studies have also investigated pathologic pain representation. Most studies dealing with chronic pain examine chronic neuropathic pain, which arises from a lesion or dysfunction in the peripheral or central nervous system and is either spontaneous-ongoing or stimulus-induced (Baron, 2006; Moisset and Bouhassira, 2007). However, what remains unclear is how the representation of chronic neuropathic pain (including fibromyalgia) and experimentally induced pain differs in their central representation.

Several factors may contribute to peripheral nociceptor hyperactivity. Other sensitization processes are suggested to affect the central processing of pain: secondary changes in the spinal cord dorsal horn, increased neuronal activity in response to noxious stimuli, expansion of neuronal receptive fields and spread of spinal hyperexcitability to

* Corresponding author at: Functional Imaging Unit, Center for Diagnostic Radiology and Neuroradiology, University of Greifswald, Friedrich-Löffler-Straße 23a, D-17487 Greifswald, Germany. Fax: +49 3834 866898.
E-mail address: martin.lotze@uni-greifswald.de (M. Lotze).

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other segments (Baron, 2006). These alterations have been found to be associated with different activation levels of subcortical and cortical areas in patients with neuropathic pain. For example, PET imaging has shown decreased regional cerebral blood flow (rCBF) in the thalamus, an increase in rCBF to the insular and anterior cingulate cortices, but little change in rCBF in SI and SII (Hsieh et al., 1995). Some of these results may depend on the mapping method used: decreased activity in the thalamus, a finding that has been consistently observed in PET studies in these patients, is less often seen in studies using functional magnetic resonance imaging (fMRI) (for a review see Moisset and Bouhassira, 2007).

Several studies on neuropathic pain reported increased activation in contralateral motor areas in these patients but not in areas related to experimentally induced pain processing (Apkarian et al., 2005; Peyron et al., 2004; Schweinhardt et al., 2006; Witting et al., 2006). A recent review of different imaging studies (Moisset and Bouhassira, 2007) indicated that experimentally induced physiological pain and neuropathic pain have distinct although overlapping brain activation patterns, but that there is no unique "pain matrix" or "allodynia network". However, these hypothesized distinctions have not been directly demonstrated in a quantitative summary of the accumulating neuroimaging evidence, because observer-independent mapping of convergence between previous findings is absent.

There is a controversial discussion over whether fibromyalgia is part of the neuropathologic pain family. Indeed there is still the question of what is responsible for maintaining ongoing pain when no obvious peripheral injury is found (Rowbotham, 2005). However, there are strong arguments for the classification of fibromyalgia as neuropathic pain. Fibromyalgia is characterized by widespread pain and the existence of tenderpoints plus accompanying symptoms such as fatigue, sleep abnormalities and psychological distress; however no definitive neural lesion has been defined thus far (Offenbaecher and Ackenheil, 2005). While some studies report the contribution of peripheral CNS alterations, such as altered endocrine or functional pathways (Crofford, 2005; Martínez-Lavin et al., 2003), there is evidence of abnormal activation of pain related brain regions in fibromyalgia (Staud and Domingo, 2001; Staud and Smitherman, 2002; Staud et al., 2001). Importantly, as a result of their studies, Martinez et al. claim that fibromyalgia is maintained by "relentless sympathetic hyperactivity" (Martínez-Lavin et al., 2003). Using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale they have recognized neuropathic pain characteristics in fibromyalgia patients, like stimulus-independency, chronic pain, which is associated with hyperalgesia/allodynia and pain which is dysesthetic, autonomic, evoked and paroxysmal (Martínez-Lavin et al., 2003). We included four studies investigating the pain representation in the brains of fibromyalgia patients (Giesecke et al., 2004; Gracely et al., 2002; Jensen et al., 2009; Pujol et al., 2009) in our meta-analysis (Table 1). The classification of "chronic neuropathic pain" in a more precise definition might thus be denoted as "chronic neuropathic pain, including fibromyalgia". We did also report the main effect of "chronic neuropathic pain" without those four studies in the results and in Supplementary Table 2.

Latest meta-analysis techniques allow adequate statistical evaluation of representation sites (Eickhoff et al., 2009; Schweinhardt et al., 2006). We used a coordinate-based technique (activation likelihood estimation; ALE) to perform a meta-analysis of studies investigating "experimentally induced pain" in healthy participants and compared the results to studies that examined patients with various "chronic neuropathic pain" disorders. Using conjunction-analysis, brain regions activated during experimentally induced and chronic neuropathic pain can be described, whereas contrast analysis of neuropathic minus experimental pain was aimed at identifying structures that provide correlates with the presence of chronic neuropathic pain alone. A related issue that we also addressed was the differentiation of the cerebral response to the two predominant experimental pain provocations in healthy participants: thermal and non-thermal stimuli, whose roles are not wholly understood. To discover differences in the representation of these two stimuli, the available neuroimaging findings on the representation of "thermal" and "non thermal" stimuli were assessed.

Material and methods

We used ALE, a meta-analysis program that was initially developed by Peter Turkeltaub (http://brainmap.org/ale/index.html; Turkeltaub et al., 2002). It is a widely used technique for coordinate-based meta-analyses of neuroimaging data. We used a revised version (Eickhoff et al., 2009), which addressed the drawbacks and limitations found with former packages. This analysis represents a shift from fixed- to random-effects inference to allow generalization of the results to the entire population of studies analyzed. In addition, the modified ALE-algorithm overcomes conceptual problems of former meta-analyses such as subjective definition of kernel sizes and anatomically non-uniform search volumes, thus increasing the specificity without losing sensitivity.

Search criteria

Papers pertaining to the coordinate-based technique were identified by searching pubmed (http://www.ncbi.nlm.nih.gov/pubmed/) using the following terms: "fMRI" and "pain" and "brain mapping"; "BOLD" and "pain"; "noxious stimuli" and "fMRI" and "brain"; "fMRI" and "neuropathic pain" and "brain mapping"; "allodynia" and "hyperalgesia" and "complex regional pain syndrome" and "CRPS" and "phantom limb pain" and "fMRI" and "brain". In addition, we also searched for authors of related articles and carefully examined the references of each retrieved paper for other potentially relevant studies. To be included in the analysis, these studies needed to have imaged and analyzed the whole head; the authors needed to have reported coordinates in standard stereotaxic space, and results had to be derived by categorical contrasts rather than correlation analyses. Furthermore, we required a t value ≥ 3 and a p value ≤ 0.001 uncorrected, or ≤ 0.05 corrected to ensure comparable specificity. Only healthy participants and pain patients that did not suffer from any neurological or psychiatric disorders were included. Studies using pharmacological challenges were likewise excluded. The filtering process yielded 36 articles for experimental pain and 17 articles for chronic neuropathic pain.

Included studies

The paradigms used in the included "experimentally induced" pain studies frequently involved other cognitive aspects besides pure (passive) pain perception. These included spatial discrimination of a noxious stimulus (Oshiro et al., 2007), temporal coding of noxious stimuli (Lui et al., 2008); temporal and intensity coding of noxious stimuli (Moulton et al., 2005; Porro et al., 1998); simultaneous coding of electrodermal reactivity (Dubé et al., 2009), influence of habituation (Becerra et al., 1999); pain perception during a cognitive task (Kong et al., 2006; Seminowicz and Davis, 2007; Seminowicz et al., 2004); and anticipation (Carlsson et al., 2006; Keltner et al., 2006; Porro et al., 2002). In addition, these studies included investigation of an analgesic effect on pain (Wiech et al., 2006); the influence of simultaneous rating (Schoedel et al., 2008) and mood (Villemure and Bushnell, 2009); pain induction under hypnosis (Derbyshire et al., 2004) and psychologically induced pain induction (Raij et al., 2005); the effect of stimulus lateralisation (Brooks et al., 2002); the effect of attention (Brooks et al., 2002), distraction (Valet et al., 2004), and predictability (Carlsson et al., 2006); and finally gender differences in pain perception (Henderson et al., 2008). Overall, there were 11 studies that measured pain sensation exclusively and 21 studies that measured another task simultaneously. Furthermore, we also used the

healthy controls of four neuropathic pain studies for the experimentally induced pain meta-analysis.

Altogether, the 36 studies on experimentally induced pain encompassed the following stimuli: thermal (n = 18); mechanical (n = 5); laser (n = 3); electrical (n = 6); ascorbic acid (n = 2); and hypertonic saline (n = 2). To reveal the differences between "thermal" and "non thermal" in the brain, we first classified the numerous stimuli. On the one hand we summarized the stimulus qualities "mechanical", "electrical", ascorbic acid", and "hypertonic saline" as "non thermal". Thermal- and laser-induced stimuli were classified as "thermal". Lateralisation of the stimuli was fairly similar, as 17 of these studies stimulated the right side of the body; 14 stimulated the left side of the body, 4 stimulated both sides; and 1 study did not report the side of the body stimulated.

21 of these studies used a contextual manipulation in addition to the noxious stimulation; these included distraction tasks, manipulating mood or evoking anticipation, and performing hypnosis.

Initially it seems impossible to dissect the activation evoked by pain from those that are context related. We therefore only included those studies that had reported pure pain induction or those studies that excluded interfering factors. This had been performed by the authors of the original investigations by subtraction of brain activation during interfering conditions from the pure pain conditions. Still, the influence of some contextual tasks cannot be totally eliminated of course, but as the revised version of the ALE program uses the random-effect approach now, the object of that meta-analysis has been to calculate above chance clustering between experiments rather than convergence across individual foci. Several different foci within the same activation derived from only one or two experiments will now not be able to reach the threshold to be reported in the probability maps (Eickhoff et al., 2009).

Importantly, only data regarding pure pain induction was used for analysis. That is, a painful condition had to be measured either against a baseline situation (10 experiments) and/or against a non-painful sensory control condition (24 experiments).

To assess the cerebral representation of chronic neuropathic pain symptoms, we included syndromes and sensitivity states that are defined by a "lesion or dysfunction of the nervous system", referring to the definition of neuropathic pain by the International Association for the Study of Pain. Studies included various signs and symptoms of neuropathic pain and neuropathic pain syndromes: allodynia (Geha, 2008; Maihöfner et al., 2006; Peyron et al., 2004; Schweinhardt et al., 2006); hyperalgesia (Maihöfner et al., 2005); postherpetic (Geha et al., 2007, 2008) and trigeminal pain (Becerra et al., 2006); complex regional pain syndrome (Gustin et al., 2010; Maihöfner et al., 2007; Maihöfner et al., 2005; Maihöfner et al., 2006); patients with burning mouth disorder (Albuquerque et al., 2006); fibromyalgia (Giesecke et al., 2004; Gracely et al., 2002; Jensen et al., 2009; Pujol et al., 2009); and syringomyelia (Ducreux et al., 2006). To reach a sufficient sample size, we also included four studies that used a stimulus that may have elicited pain in the control group (Albuquerque et al., 2006; Giesecke et al., 2004; Jensen et al., 2009; Pujol et al., 2009) but still caused a significantly stronger pain in neuropathic pain patients. Two further studies examined different forms of neuropathic pain symptoms simultaneously, and both forms were included: mechanical and cold allodynia (Becerra et al., 2006; Ducreux et al., 2006). In the study of Maihöfner et al. (2007)and the study of Gustin et al. (2010), allodynia was derived from a motor task, and the activated motor areas were not included in the meta-analysis because we considered them to be task-dependent and not pain-dependent. Nine experiments were measured against the unaffected side and eight experiments were measured against healthy controls.

We included a total of 17 studies for the meta-analysis of chronic neuropathic pain, with a fairly similar lateralisation. Ten of these studies applied the stimulus to both sides of the body, five studies stimulated the right side, and two stimulated the left side.

The studies used in the meta-analysis are reported in Supplementary Tables 1A and B.

Analysis

Descriptive information was extracted from each article including the authors of the paper, date published, sample size, coordinates together with the associated space (Talairach or MNI), the stimulated body area, and the stimulus quality. Meta-analysis was performed to assess regions of converging brain activation during experimentally induced pain and to compare the brain regions activated in patients with chronic neuropathic pain.

Meta-analysis algorithm

Differences in coordinate spaces (MNI- vs. Talairach-space) were first accounted for by transforming coordinates reported in Talairach-space into MNI-coordinates using linear transformation (Lancaster et al., 2007). Meta-analysis was carried out using the revised version (Eickhoff et al., 2009) of the ALE approach for coordinate-based meta-analysis of neuroimaging results (Laird et al., 2009; Turkeltaub et al., 2002). The algorithm identifies areas showing a convergence of activations across different experiments that are higher than expected under the null distribution of a random spatial association.

The key idea behind ALE is to treat the reported foci not as single points, but rather as centers for 3D Gaussian probability distributions, capturing the spatial uncertainty associated with each focus. The width of these uncertainty functions was determined based on empirical data on the between-participant and between-template variance, which represents the main components of this uncertainty. Importantly, the applied algorithm weighs the between-participant variance by the number of examined participants per study, accommodating the notion that larger sample sizes should provide more reliable approximations of the 'true' activation effect and should therefore be modeled by tighter Gaussian distributions (Eickhoff et al., 2009). The probabilities of all activation foci in a given experiment were combined for each voxel, resulting in a modeled activation map (MA-map) for this experiment. The union across these MA-maps yielded voxel-wise ALE scores describing the convergence of results at each particular location. Because neurophysiologically, activation should be predominantly localized within the gray matter, all analyses were restricted to those voxels in which a probability of at least 10% for gray matter could be assumed (based on the ICBM tissue probability maps). To distinguish 'true' convergence between studies from random convergence, i.e., noise, these ALE scores were subsequently compared to an empirical null distribution derived from a permutation procedure. This null distribution reflects a random spatial association between experiments and regards the within-experiment distribution of foci as a fixed property. Thus, a random-effects inference is invoked, focusing inference on the above-chance convergence between different experiments, not the clustering of foci within a particular experiment. Computationally, deriving this null hypothesis involved sampling a voxel at random from each of the MA-maps and taking the union of these values in the same manner as done for the (spatially contingent) voxels in the true analysis. The ALE score obtained under this assumption of spatial independence was recorded, and the permutation procedure iterated 10^{11} times to obtain a sufficient sample of the ALE null distribution. The p-value of the observed ALE is given by the proportion of equal or higher values obtained under the permutation distribution. The ALE maps reflecting the convergence of the assessed experiments were then thresholded at a cluster-level threshold of $p<0.05$ (cluster-forming threshold: $p<0.001$ at voxel-level) and converted to Z-scores for visualization. Conjunctions between meta-analyses were performed using the minimum statistic, which computationally equaled computing the intersection between the thresholded ALE results (Caspers et al., 2010).

Conjunction analysis between the two categories (experimentally induced and chronic neuropathic pain) was carried out as an intersection between the respective individual meta-analyses on observation and imitation. Results are reported for a cluster-level corrected p-value<0.05.

Differences between conditions were tested by first performing an ALE analysis separately for each condition and computing the voxel-wise difference between the ensuing ALE maps. All experiments contributing to either analysis were then pooled and randomly divided into two groups of the same size as the two original sets of experiments reflecting the contrasted ALE analyses. ALE-scores for these two randomly assembled groups were calculated and the difference between these ALE-scores was recorded for each voxel in the brain. Repeating this process 10,000 times then yielded voxel-specific estimation of differences in ALE-scores observed under the label exchange. The differences in ALE scores were then compared against this permutation distribution and only those voxels retained, which had a post-hoc probability P>0.95 for representing true differences, were retained. Moreover, effects were inclusively masked by the respective main effects, i.e., the significant effects of the ALE analysis for the particular condition.

The resulting foci were anatomically allocated by reference to probabilistic cytoarchitectonic maps of the human brain using the SPM Anatomy Toolbox (Eickhoff et al., 2005). Using a Maximum Probability Map, activations were hereby assigned to the most probable histological area at their respective location. For differentiation of the anterior insula we used the regions as proposed by Schweinhardt et al. (2006).

Meta-analysis reveals convergences of the activated regions of the included studies. Nevertheless, we use the term "activation" or "convergence of activation" to describe the resulting regions, because this terminology will be more familiar to most readers.

Results

Activation clusters during "experimentally induced pain"

The meta-analysis of "experimentally induced pain" included 36 studies of healthy participants with no reported pain disorders. Six clusters, with a total of 22 local maxima altogether were computed with the meta-analysis.

The cerebral structures representing all "experimentally induced pain" conditions included the inferior postcentral gyrus and the rolandic operculum (SII; OP 1 of the left and right hemisphere) spreading over further parts of the parietal operculum within both hemispheres (OP 3, 4) and the bilateral insula (anterior and posterior parts). There was a midline cluster (right and left middle cingulate cortex (MCC)), encroaching upon the right supplementary motor area (SMA) and the left pre-SMA. A subcortical cluster was found in the bilateral thalamus (right ventral lateral nucleus, left ventral lateral, and lateral posterior nucleus). In addition, right prefrontal activation was present in all experimentally induced pain studies. Table 1A lists the coordinates for each of the clusters (Supplementary Fig. 1).

Activation clusters during "chronic neuropathic pain"

The meta-analysis of "chronic neuropathic pain" included 17 studies investigating patients with chronic neuropathic pain disorders including fibromyalgia, applying physically innocuous stimuli or moving the painful part of their body. Nine clusters and a total of 18 local maxima showed convergence in the meta-analysis.

The representation of the "chronic neuropathic pain" condition revealed the following convergence of activation clusters: the bilateral rolandic operculum extending bilaterally over further parietal opercula (OP 3, 4) and the supramarginal gyrus (SII; OP 1), the right insula (anterior and caudal anterior part), and adjacent

Table 1

Cluster	Foci	T value	Coordinates X	Y	Z (tal)	Probability for areas	Anatomically assigned to:
A: Main effect: experimentally induced pain (p<0.001).							
I	1)	6.08	−54	−24	25	OP 1: 50% IPC (op): 30%	Left postcentral gyrus (inferior)
	2)	5.96	−36	−2	13	Area 13	Left posterior insula
	3)	5.76	−42	−22	21	OP 1: 60% OP 3: 50% OP 4: 40%	Left rolandic operculum
	4)	3.89	−34	12	9		Left rostral-anterior insula
II	1)	5.77	6	10	41	Area 32	Right MCC
	2)	5.57	0	12	39		Left MCC
	3)	5.50	4	6	61	Area 6: 60%	Right SMA
	4)	3.81	0	30	37		Left pre SMA
III	1)	5.76	56	−22	19	OP 1: 80% OP 4: 20%	Right rolandic operculum
	2)	4.11	44	−18	21	OP 3: 30%	Right rolandic operculum
IV	1)	6.26	38	16	3		Right rostral-anterior insula
	2)	3.95	36	0	15		Right caudal-anterior insula
	3)	3.73	42	2	−5		Right posterior insula
V	1)	4.64	14	−20	9		Right thalamus
	2)	4.11	−16	−18	13		Left thalamus
VI	1)	3.65	44	50	9		Right middle frontal gyrus
	2)	3.49	48	42	5		Right inferior frontal gyrus
B: Main effect: chronic neuropathic pain (p<0.001)							
I	1)	4.86	−62	−26	23	IPC (op): 50% OP 1: 50%	Left supramarginal gyrus
	2)	4.25	−48	−24	19	OP 1: 70% OP 4: 30% OP 2: 20%	Left rolandic operculum
II	1)	4.30	−2	4	47	Area 32	Left MCC
	2)	4.22	0	24	31		Left ACC
III	1)	4.93	42	6	7	Area 13	Right caudal-anterior insula
	2)	4.09	40	14	−3		Right caudal-anterior insula
	3)	3.6	30	0	5		Right putamen
IV	1)	4.48	58	−22	19	OP 1: 80% OP 4: 20%	Right rolandic operculum
	2)	3.41	56	−36	27	IPC (cm): 60%	Right inferior parietal lobe
V	1)	4.49	14	−20	9		Right thalamus
VI	1)	3.93	−14	−20	15		Left thalamus
VII	1)	4.32	40	32	35		Right middle frontal gyrus
VIII	1)	3.64	−54	8	23	Area 44: 50% Area 45: 20%	Left inferior frontal gyrus (p. opercularis)
IX	1)	3.41	4	−4	39	Area 24	Right MCC
	2)	3.36	0	−6	37		Left MCC
C: Conjunction: experimentally induced and chronic neuropathic pain (p<0.05, corr.)							
I	1)	4.56	−60	−26	25	OP 1: 50%	Left supramarginal gyrus
	2)	4.26	−48	−24	19	OP 1: 70% OP 4: 30%	Left rolandic operculum
II	1)	4.05	2	4	47	Area 6: 20%	Right SMA
	2)	3.98	2	14	39		Left MCC
	3)	3.83	4	22	33	Area 32	Right ACC
	4)	3.34	10	−4	45		Right MCC
III	1)	4.49	58	−22	19	OP 1: 80% OP 4: 20%	Right rolandic operculum
	2)	3.16	62	−36	27	IPC (cm): 50%	Right inferior parietal lobe
IV	1)	3.87	40	16	−3	Area 13	Right rostral anterior insula
	2)	3.75	38	8	7		Right caudal-anterior insula
V	1)	4.50	14	−20	9		Right thalamus
VI	1)	3.77	−14	−20	13		Left thalamus

(continued on next page)

Table 1 (*continued*)

Cluster	Foci	T value	Coordinates X	Y	Z (tal)	Probability for areas	Anatomically assigned to:
D: Contrast: experimentally induced minus chronic neuropathic pain (p<0.05; corr.)							
I	1)	2.44	40	18	7		Right rostral-anterior insula
II	1)	2.19	−36	2	11	Area 13	Left posterior insula
III	1)	1.88	6	24	45	Area 6	Right SMA
	2)	1.86	12	10	43		Right MCC
IV	1)	2.16	38	−20	19	OP 2: 60% OP 3: 50%	Right rolandic operculum
E: Contrast: chronic neuropathic minus experimental (p<0.05; corr.)							
I	1)	2.24	−64	−26	24	OP 1: 50% IPC (op): 30%	Left supramarginal gyrus
II	1)	2.19	40	4	9	Area: 13	Right caudal-anterior insula
III	1)	1.88	−2	24	29	Area: 32	Left ACC

OP: operculum; IPC: inferior parietal cortex, IPCop: inferior parietal cortex (Opercular supramarginal area), IPCcm: inferior parietal cortex (Posterior (magnocellular) supramarginal area); MCC: mid cingulate cortex; ACC: anterior cingulate cortex; SMA: supplementary motor area.

putamen. A cluster in the midline represented the right and left MCC and the ACC in the left hemisphere. Additional convergences were observed in the thalamus bilaterally (ventral lateral nucleus) and in the prefrontal lobe (see Supplementary Fig. 1 and Table 1B).

We also compared the results of the main effect of the neuropathic pain studies with and without including the fibromyalgia studies. There were only marginal differences between both group analyses observed, such as only a unilateral inferior frontal gyrus activation cluster instead of a bilateral and no right medial frontal activation for the analysis without fibromyalgia (see Suppl. Table 2). The main results (bilateral rolandic operculum, SII, ACC, MCC, anterior insula, thalamus) were observed similarly in both group analyses. We therefore decided to include the four studies that had investigated the pain representation in the brain of fibromyalgia patients in our analysis about the representation for the "chronic neuropathic pain" group.

A conjunction analysis of the conditions of "experimentally induced pain" and "chronic neuropathic pain" confirmed the results of the main effect of both conditions, and involved the bilateral rolandic operculum (SII, OP 1), encroaching upon OP 4 and the left supramarginal gyrus. Clusters could be found in the right SMA, bilateral MCC extending to the right ACC, the right anterior insula, and bilateral thalamus (Table 1C; Fig. 1).

Structures that showed significantly stronger convergence of reported foci under one condition were assessed using contrast analyses. The contrast analysis of the conditions "experimental pain" – "chronic neuropathic pain" revealed activation clusters in the left posterior and right anterior insula, the right SMA, right MCC and right rolandic operculum (SII, OP 2, 3) (Table 1D; Fig. 1). The contrast of "neuropathic" – "experimental pain" revealed activation in the left supramarginal gyrus (OP 1, SII), the right caudal-anterior insula, and the left ACC (Table 1E; Fig. 1).

"Experimentally induced pain"; differentiation of thermal vs. non thermal

Different types of painful stimuli (i.e., thermal, mechanical, laser, electrical stimuli, ascorbic acid, and hypertonic saline) were used in the included studies assessed above. We summarized all stimulus qualities, except for thermal and laser, as "non thermal. After subdividing these stimulus qualities (thermal vs. non thermal; containing 21 and 15 studies respectively), we performed separate meta-analyses to detect the processes of pain in the brain in more detail.

Bilateral activation in the thermal condition was seen in the rolandic operculum and supramarginal gyrus (SII; OP 1), ranging over some parts of the inferior parietal cortex. Non-thermal conditions showed tighter activation: only left inferior parietal and postcentral gyrus (SII; OP 1) and right rolandic operculum (SII; OP 1) could be found. Unilateral activation of the MCC (non-thermal — right hemisphere) was accompanied by bilateral activation under thermal conditions. Bilateral activation of the insula was seen with both stimuli. Supplementary motor areas show convergent activation bilaterally under thermal and unilaterally under non-thermal conditions. The left and right thalami were activated only in thermal condition. Significant convergence of activation sites was found in frontal areas under both conditions (right hemisphere). No significant activation overlap between studies could be found in SI neither during thermal stimulation nor during non-thermal condition (see Suppl. Fig. 2 and Table 2A, B).

A conjunction analysis of the conditions of "non thermal" and "thermal pain" confirmed the results of the main effect of both conditions and showed activation in bilateral rolandic operculum and supramarginal gyrus (SII, OP 1) and right sided SMA. Furthermore, MCC was activated in the right hemisphere. Bilateral activation could be found in the insula (left: middle/posterior parts, right: anterior parts) (Table 2C and Fig. 2).

The contrast analysis of the conditions "non thermal" – "thermal" showed activation in bilateral SII (Area OP 1) and right mid orbital frontal gyrus. This is the only calculation showing right SI (Areas 1, 2) being activated (see Fig. 2, Table 2D). The opposite contrast "thermal" – "non thermal" revealed activation in the right supramarginal gyrus (IPC; SII), left MCC extending to the ACC, left caudal-anterior and posterior insula, bilateral thalamus and right inferior frontal gyrus (Table 2E and Fig. 2).

Discussion

The application of a nociceptive stimulus (temperature, chemicals, laser, electric stimuli, etc.) evoked activation in SI, SII, the cingulate cortex, the insula, and the thalamus. Because this network is also active in patients with chronic neuropathic pain, one question is which mechanism activates this "pain matrix" when no noxious stimulus is applied. Our meta-analysis did not provide evidence for consistent SI activation for all "experimentally induced" and "chronic neuropathic pain" conditions, but revealed SI activation if the analysis was restricted to paradigms applying non-thermal stimuli. In contrast, SII was activated in all conditions, and the MCC was consistently activated during experimental and chronic neuropathic pain. Conversely, the ACC was predominantly active in the meta-analysis of patients with chronic neuropathic pain and in the subgroup of "thermal" pain in the experimental pain studies. The insula was bilaterally activated in experimentally induced pain and unilaterally (right) activated with chronic neuropathic pain. Subdivisions of the insula were activated differently depending on whether pain was experimentally induced or chronic: for chronic neuropathic pain conditions, only the anterior part was also activated, whereas for experimental pain the posterior insula was activated. The thalamus was activated bilaterally during both conditions. The inferior frontal gyrus showed right-sided activation for experimentally induced pain and left-sided activation during chronic neuropathic pain.

The cingulate cortex

The contrast analysis of thermal minus non-thermal reveals activation of the left ACC, especially in Brodmann's Area (BA) 24. The ACC can be subdivided into three parts: an anterior portion (aACC, BA 32), a posterior portion (BA 23) and an intermediate part (BA 24), which fulfills functions of both the anterior and posterior portions (Kwan et al., 2000). More anterior portions of the ACC might encode an increased attentional involvement in response to a stimulus, while posterior areas

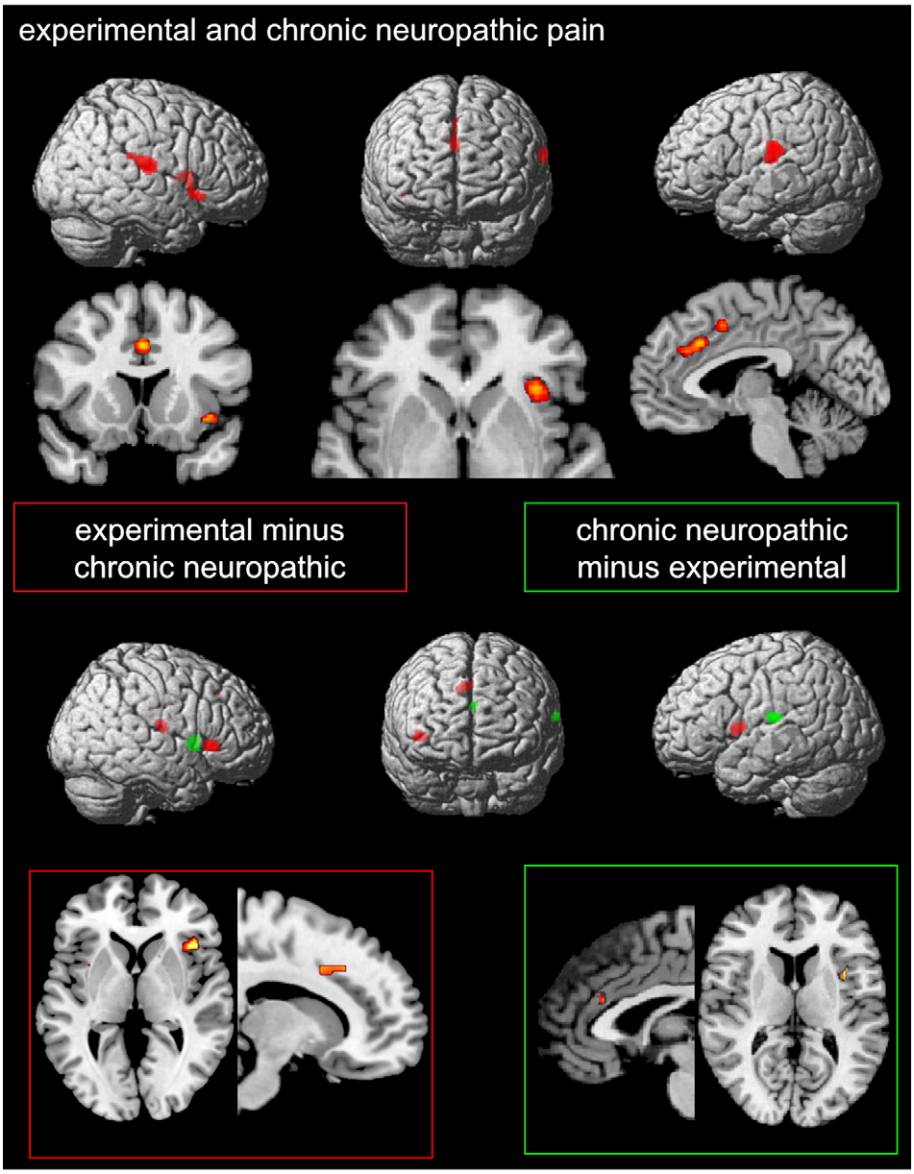

Fig. 1. Top two image lines: Conjunction analysis of experimental and neuropathic pain. Bottom two image lines: Contrast between conditions. The conjunction as well as the contrast analyses of the conditions "experimentally induced" and "chronic neuropathic pain" projected on the SPM-render brain hemispheres (left and right side view) and slices of the single subject template from SPM. The *conjunction analysis* "experimental and chronic neuropathic pain" showed activation in bilateral SII, right SMA, bilateral MCC and right ACC, right insula and bilateral thalamus; coronal ($y = 14$), axial ($z = -3$), sagittal ($x = 4$). The *contrast analysis* of the conditions "experimental pain" – "chronic neuropathic pain" (red frame) showed activation of the right anterior insula (including right opercular gyrus) and left posterior insula, the right SMA and right MCC; axial ($z = 7$), sagittal ($x = 12$). The *contrast analysis* of the conditions "chronic neuropathic pain" – "experimental pain" (green frame) showed significant results in left SII, right mid-insula and left ACC; sagittal ($x = -2$), axial ($z = 9$).

of the ACC might code for a sensori-integrative aspect of pain processing (Kwan et al., 2000; Tracey et al., 2000). Thermal stimuli might therefore be especially associated with increased attention to the stimulus. Furthermore concomitant activation of the anterior cingulate is reported for thermal distress (Craig et al., 1996; Craig, 2000).

The thermosensory aspect of thermal pain is encoded by the insula (Craig, 2000), which will be described in detail later. Keeping in mind, that the anterior insula is functionally connected to the ACC, these areas represent a processing of emotional response to painful stimuli (Craig, 2002; Dubé et al., 2009). The activation of the ACC during pain may reflect the role of this structure in the regulation of behavioral and emotional response to pain, in the regulation of cognitive processes to cope with pain, and in the regulation of modulatory pain mechanisms (Rainville, 2002).

In our meta-analyses, the ACC showed activation under chronic neuropathic pain conditions but not under experimentally induced pain. However, most (22/36) studies on experimentally induced pain had reported ACC activation, but the meta-analyses did not. In contrast, MCC activation was observed in all investigated conditions.

Consistent with our results, the meta-analysis of Farrell et al. (2005) predominantly reported mid ACC-activation, which is consistent with the findings of the MCC by Palomero-Gallagher et al. (2009). Likewise, Peyron et al. reported the MCC as the most commonly activated structure in imaging studies after nociceptive stimulation (Peyron et al., 2000). These meta-analyses associated this region with cognitive processes, especially response selection and motor inhibition.

The ACC is responsible for expressing emotions, mood, and generating autonomic responses, and therefore coding the

Table 2

Cluster	Foci	T value	Coordinates x	y	z (tal)	Probability for areas	Anatomically assigned to:
A: Main effect: experimental thermal pain condition (p<0.001).							
I	1)	6.52	−2	12	39	Area 32	Left MCC
	2)	4.42	4	6	61	Area 6: 60%	Right SMA
	3)	4.19	2	0	53	Area 6: 50%	Left SMA
	4)	3.79	6	−2	47	Area 24	Right MCC
II	1)	5.96	−42	−22	21	OP 1: 60% OP 3: 50% OP 4: 40%	Left rolandic operculum
	2)	4.35	−56	−26	27	IPC (op): 60% OP 1: 60%	Left supramarginal gyrus
	3)	3.81	−60	−36	25	IPC (op): 40% OP 1: 30%	Left inferior parietal lobe
III	1)	6.05	40	18	3		Right anterior insula
	2)	4.33	46	18	−5		Right inferior frontal gyrus
	3)	3.68	42	4	−5	Area 13	Right posterior insula
IV	1)	5.08	−16	−18	13		Left thalamus
	2)	4.66	10	−18	11		Right thalamus
	3)	3.84	−6	−20	3		Left thalamus
V	1)	5.62	62	−24	27	OP 1: 40% IPC (op): 30%	Right supramarginal gyrus
	2)	4.91	56	−22	19	OP 1: 80%	Right rolandic operculum
	3)	4.09	44	−16	21	OP 3: 40%	Right rolandic operculum
VI	1)	4.86	−36	0	11		Left posterior insula
	2)	4.58	−34	12	7		Left anterior insula
VII	1)	3.99	38	0	15		Right caudal-ant. insula
VIII	1)	4.04	48	42	7		Right middle frontal gyrus
B: Main effect: experimental non thermal condition (p<0.001)							
I	1)	6.42	−54	−24	23	OP 1: 70%	Left postcentral gyrus
	2)	4.42	−48	−38	27	IPC (cm): 60% OP 1: 30%	Left inferior parietal lobe
II	1)	4.66	8	20	41	Area 32	Right MCC
	2)	4.23	6	6	61	Area 6: 50%	Right SMA
III	1)	5.27	50	−24	23	OP 1: 80%	Right rolandic operculum
	2)	3.63	62	−20	17	OP 1: 60%	Right rolandic operculum
IV	1)	5.08	−36	−4	15		Left anterior insula
V	1)	4.08	38	14	7	Area 13	Right anterior insula
VI	1)	4.14	−42	2	−1	Area 13	Left posterior insula
VII	1)	3.87	56	12	11	Area 44: 60% Area 45: 30%	Right inferior frontal gyrus
VIII	1)	4.45	8	58	−5		Right mid orbital gyrus
C: Conjunction: non thermal and thermal (p<0.05; corr.)							
I	1)	4.27	6	8	45		Right MCC
	2)	4.02	6	6	61	Area 6: 50%	Right SMA
II	1)	4.35	−56	−26	27	IPC (PFop): 60% OP 1: 60%	Left supramarginal gyrus
	2)	4.06	−48	−22	21	OP 1: 50% OP 3: 40%	Left rolandic operculum
	3)	3.53	−50	−24	17	OP 1: 70% TE 1.0: 40%	Left superior temporal gyrus
III	1)	4.37	54	−22	19	OP 1: 60%	Right rolandic operculum
	2)	3.55	54	−28	27	OP 1: 70% IPC (PFop): 50% IPC (PFcm): 30%	Right rolandic operculum
IV	1)	4.31	−36	−2	13		Left posterior insula
C: Conjunction: non thermal and thermal (p<0.05; corr.)							
V	1)	4.08	38	14	7		Right anterior insula
VI	1)	3.64	−42	2	1		Left middle insula
D: Contrast: non thermal minus thermal (p<0.05; corr.)							
I	1)	2.67	44	−30	25	OP 1: 80%	Right rolandic operculum
II	1)	2.95	−54	−20	23	OP 1: 60%	Left postcentral gyrus
III	1)	2.23	−46	−42	29	IPC(cm): 50%	Left supramarginal gyrus
IV	1)	2.10	60	−24	53	Area 1: 70% Area 2: 30%	Right postcentral gyrus
VI	1)	2.08	6	58	−3		Right mid orbital frontal gyrus
E: Contrast: thermal minus non thermal (p<0.05; corr.)							
I	1)	4.86	−16	−20	13		Left thalamus
	2)	3.84	−6	−20	3		Left thalamus
	3)	3.67	10	−14	13		Right thalamus
II	1)	4.00	−6	18	31	Area 24	Left ACC
	2)	3.78	−2	12	37		Left MCC
III	1)	3.35	44	18	−7	Area 47	Right inferior frontal gyrus
IV	1)	3.38	−38	−24	11	Area 13	Left posterior insula
V	1)	2.84	−40	10	7		Left caudal-ant. insula
VI	1)	2.58	68	−26	29	IPC (op): 50%	Right supramarginal gyrus

OP: operculum; IPC: inferior parietal cortex, IPCop: inferior parietal cortex (opercular supramarginal area), IPCcm: inferior parietal cortex (posterior (magnocellular) supramarginal area); MCC: mid cingulate cortex; ACC: anterior cingulate cortex; SMA: supplementary motor area.

unpleasantness and subjective component of pain (Palomero-Gallagher et al., 2008; Vogt et al., 2003). It follows that there is consistentactivation of the ACC in chronic neuropathic pain, given the clinical picture of many chronic pain patients.

The supplementary motor area

Our analysis of experimentally induced pain studies also found activation of the pre-SMA and SMA, similar to the meta-analysis of Farrell et al. (2005). Each subdivision of the MCC is concerned with different tasks in motor processing via the SMA and pre-SMA to execute avoidance reactions and escape reflexes (Vogt et al., 2003). Thus, a potential role for the MCC is contribution to motor responses via the pre-SMA and SMA during the pain experience, to achieve fast avoidance reactions. In contrast, this meta analysis of chronic neuropathic pain studies did not show activation in motor areas (SMA or pre-SMA), which may be related to the persistent stimulation that cannot be avoided by a flight reaction.

The insula

Both, experimentally induced and chronic neuropathic pain showed right anterior insula activations. Experimental pain furthermore induced bilateral posterior insula activation. The left posterior insula activation seems to be highly specific to experimentally induced pain.

Posterior insula activation in experimental pain is suggested to reflect basic sensory aspects of nociceptive input rather than the (subjective) experience of pain (e.g. Apkarian et al., 2005). In particular, it has been described that – in contrast to the activation in the caudal-anterior insula – the activation in the posterior insula is

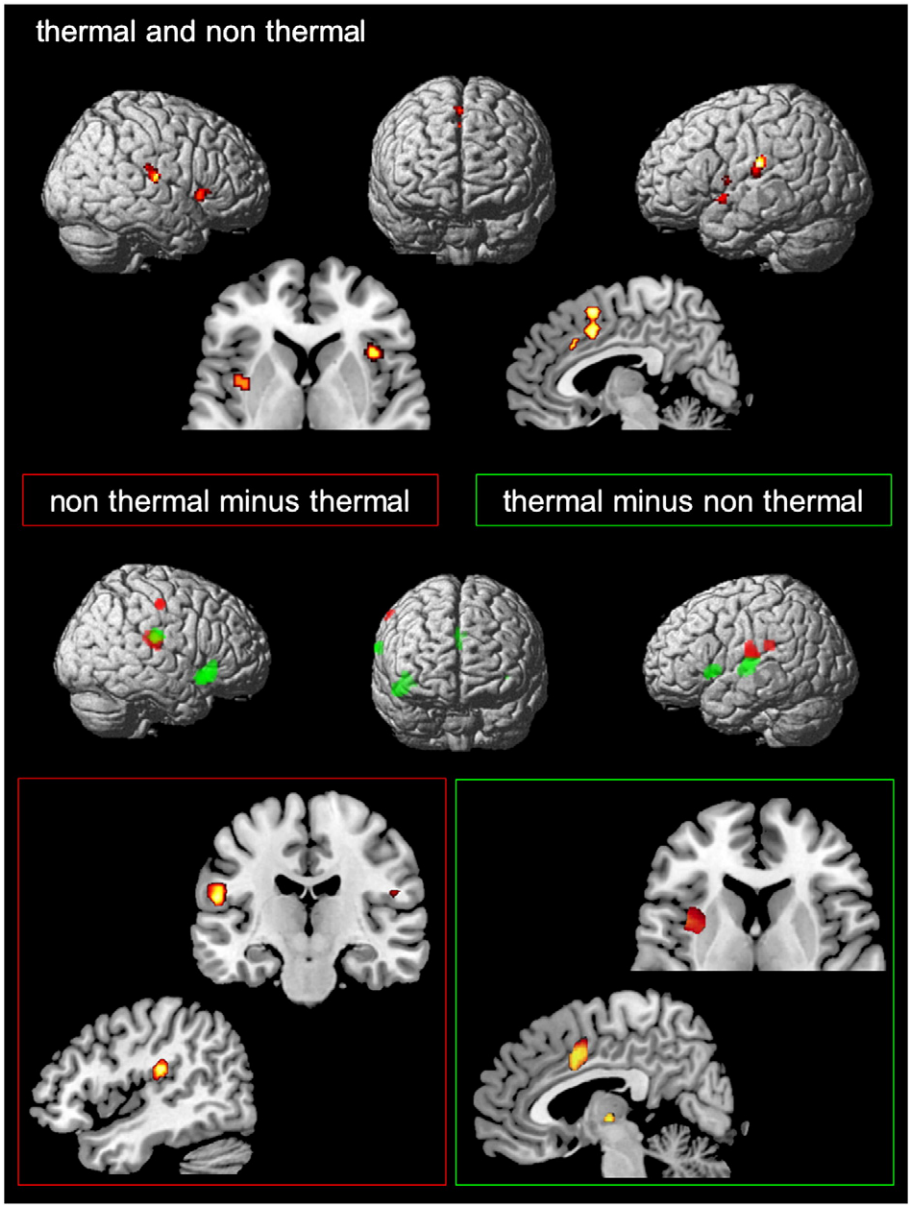

Fig. 2. The conjunction as well as the contrast analyses of the conditions "thermal" and "non thermal" projected on the SPM-render brain hemispheres (left and right side view) and slices of the single subject template from SPM. The *conjunction analysis*, "thermal and non-thermal pain" showed significant results in bilateral SII, unilaterally activated SMA and MCC (both in the right hemisphere) and bilateral activation of the insula; axial ($z = 1$), sagittal ($x = 6$). The *contrast analysis* of the conditions "non thermal" – "thermal" (red frame) showed activation in right SI, bilateral SII, and right mid orbital gyrus; sagittal ($x = 44$), coronal ($y = -20$). The opposite *contrast* "thermal" – "non thermal" (green frame) revealed activity in right SII, left middle/posterior insula, left ACC and MCC, right inferior frontal gyrus and bilateral thalamus; sagittal ($x = -6$), axial ($z = 7$).

associated with the intensity of the applied painful stimulus and not with the subjective appraisal of pain intensity (Craig et al., 2000).

Additionally, anterior as well as posterior parts of the insula was activated under the individual meta-analyses of the "thermal" as well as "non thermal" condition. However, only the thermal minus non-thermal contrast revealed an activation of the left posterior insula.

In keeping with the work of Craig et al. the human thermosensory cortex was located in the insular cortex, specifically in the middle/posterior insula (Craig, 2000). Likewise Brooks and colleagues reported activation of the posterior insula by thermal and nociceptive stimuli (Brooks et al., 2005). The posterior insula codes the intensity of pain, its laterality, and provides a rough localization of the noxious stimulus via its own somatotopic reference system (Bjornsdotter et al., 2009; Brooks et al., 2005; Kong et al., 2006). Conclusively, this reference of one's physical state within the insula, in turn motivating appropriate behavior and autonomic reactions, indicating its role in thermoregulation and integration in homeostasis (Craig, 2000). Interestingly, this posterior insula activation is predominantly observed in the left hemisphere. This might be caused by the fact that most of the studies (13 of 15) using thermal stimulation stimulated the right hand. This contralateral activation of the posterior insula supports reports of Brooks et al. (2002, 2005).

In contrast, the anterior insula has been found to be significantly activated during nociceptive stimulation (Schweinhardt et al., 2006). If activation maxima of experimentally induced pain studies are plotted, most of these fall in the caudal-anterior part of the insula (Schweinhardt et al., 2006). The same activation area is predominantly activated when the intensity of perceived allodynia is correlated with activation

magnitude during the application of brush-stimuli in neuropathic pain patients (Schweinhardt et al., 2006). The anterior insula has extensive connections with the orbitofrontal regions, anterior cingulate cortex and autonomic structures and is therefore involved in autonomic reactions, affective-motivational functions, and the association of emotions with former painful experiences (Dubé et al., 2009; Ingvar, 1999; Ostrowsky et al., 2002).

Chronic neuropathic pain is associated with activation of the right caudal-anterior insula. This area integrates both, the perceived intensity of the pain and its affective components (Ingvar, 1999; Schweinhardt et al., 2006). The emotional emphasis of perception and the up-regulated autonomic function during this state suggest a characteristic picture of patients with chronic neuropathic pain.

The secondary somatosensory cortex

Meta-analyses of Peyron et al. (2000) and Farrell et al. (2005) showed consistent activation of the operculoinsular cortex and reported distinct foci near the Sylvian fissure. Although some of these activation loci may be assigned to the anterior insula, the others are clearly part of the operculoinsular cortex, a region corresponding to the retroinsular/SII interface. The ALE approach used here clearly separated activation of the posterior insula and the opercular region, including the SII. Consistent with other meta-analyses and other studies (Ogino, 2005; Peyron et al., 2000; Youell et al., 2004), SII was activated during all pain conditions investigated. Different parts of the parietal operculum were simultaneously involved: OP 1 and OP 3, and with a lower intensity, OP 4, which suggests a distinct representation of nociceptive information within SII. This observation was reported in animal and human studies showing that painful stimuli are represented in three different locations within the contralateral SII region/parietal operculum: the SII area (OP 1), the parietal ventral area (OP 4), and the ventral somatosensory region (OP 3), all within a rough somatotopic order (Disbrow et al., 2000; Disbrow, 2003; Eickhoff et al., 2006a,2006b, 2007). The distinct representation, and rough somatotopy within SII confirm its role in spatial discrimination. Parts of the parietal operculum contribute differently to pain perception (Eickhoff et al., 2006b). Because there was no activation of a preferential opercular part for the different stimulus conditions in our analysis, a general contribution of the SII region is likely. Likewise, the exact somatotopic assignment of the noxious stimulus seems to play a secondary role.

The primary somatosensory cortex

In contrast to SII, SI was not consistently activated in all pain studies in our meta-analyses, but showed consistent activation only in the contrast of the non-thermal minus thermal pain condition. This finding is consistent with observations by Farrell et al. (2005) and Peyron et al. (2000), who both reported inconsistent SI activation in their respective qualitative meta-analyses. This indicates that neuroimaging studies can reveal elicited activation, deactivation, and no visible activation of SI (Bushnell et al., 1999). SI activation after mechanical stimulation, and stimulation with hypertonic saline, ascorbic acid and electrical stimulation are similar; the representation site suggests a function of SI in coding the intensity of a stimulus and localizing it, for both nociceptive and innocuous input. However, the SI is known to be less sensitive in detection of nociceptive than for tactile processing (Ploner et al., 1999; Treede et al., 2000). By using laser stimulation, however, Bingel et al. demonstrated that SI is capable of discriminating the side of stimulation, even in the absence of concomitant tactile stimulation (Bingel et al., 2003). Their data thus indicated an involvement of SI in the spatial coding of pain. How may this be reconciled with the absence of SI in the present meta-analyses? Potentially, the lack of significant convergence within SI may relate to the somatotopic organization within this region. In the current study experiments assessing pain delivered to multiple body parts have been pooled. Variability of the evoked activation along the somatotopic map, in combination with a potentially less robust involvement of SI compared to other regions, may have resulted in non-significant convergence of SI activation sites. The approach of subtraction analysis (stimulus condition – control condition) may have led to an apparent absence of a net effect of the SI, in particular, when somatosensory input was controlled. In summary, the SI seems not to have a role in pain perception per se but only in the coding of associated somatosensory information (Petrovic et al., 2002).

Inferior frontal and prefrontal areas

Frontal activation in our meta-analyses was not consistent and differed with respect to the hemispheric representation between experimental (right IFG) and chronic neuropathic pain (left IFG). Contrasting experimental minus chronic neuropathic pain confirmed the stronger convergence in the right inferior frontal gyrus for the former condition. However, prefrontal activation sites, which have been described as important in the processing of chronic neuropathic pain, were not observed in our meta-analysis. Others (Farrell et al., 2005) have described dorsolateral prefrontal activation during pain perception, showing lateralization to the right hemisphere (Ingvar, 1999) as well. Likewise, a meta-analysis not based on coordinate statistical mapping indicated that activation in the prefrontal cortex was most frequently reported in patients with neuropathic pain (Apkarian et al., 2005). Although, the PFC has an important modulatory effect on the perception of pain (Casey, 1999), a coordinate-based meta-analysis may miss pain-associated activation because representation locations between participants and studies may vary dramatically in tertiary areas.

The contrast thermal minus non-thermal contrast revealed activation of the orbital part of the inferior frontal gyrus. In accordance with Craig et al. (2002) the orbitofrontal cortex was most strongly activated with subjective thermal perception. Through secondary processing of information in those regions thermal stimuli and other bodily feelings are differentiated and evaluated according to the body's homeostatic needs.

The descending and ascending pain system is differently involved

Chronic neuropathic pain is associated with alterations in the descending modulatory system (Ren and Dubner, 2002; Urban and Gebhart, 1999). Our meta-analysis of chronic neuropathic pain revealed differences in the experimental pain paradigms, mainly in structures that influence the descending modulatory system. In particular, the perigenual part of the ACC is associated with the descending modulatory system (May, 2008; Zambreanu et al., 2005). We observed activation of the ACC in patients with chronic neuropathic pain. The reason for this observation is not clear, but our findings may be explained by long lasting pain states. Several studies have reported enhanced connectivity between rACC and periaqueductal gray (PAG) during placebo analgesia (Bingel et al., 2007; Petrovic et al., 2002; Wager et al., 2007). The PAG also controls the spinal cord via the rostroventral medulla (RVM, (Bingel et al., 2007; Ren and Dubner, 2002). However, it is not clear whether ACC directly influences pain perception (cortico-cortical), or whether it has a supervisory role on the PAG/RVM to promote or suppress incoming nociceptive signals, or both.

In man, top-down modulatory mechanisms of pain control have been studied with placebo experiments. These studies demonstrated that ACC-activation is not specific for neuropathic pain, rather its modulation is highly associated with the perceived pain intensity. Placebo increases coupling between the rostral ACC and the PAG. The stronger the coupling, the less activation is observed in subcortical and cortical pain-sensitive regions (Eippert et al., 2009). Interestingly,

the dorsal ACC is particularly associated with processes which have a role in the appraisal of pain intensity depending on opioidergic neurotransmission (Eippert et al., 2008). The hyperactivation of ACC might therefore also perpetuate the dysesthesia of chronic neuropathic pain.

The contrast analysis of neuropathic minus experimental pain revealed a significant activation of the anterior insula, ACC, and supramarginal gyrus. The increased ACC and anterior insular activation observed in studies investigating neuropathic pain point to an increased affective dimension in chronic pain patients.

Limitations of the study

This meta-analysis applied statistics over different groups of studies. In order to provide a critical statistical power (ALE meta-analyses need about 10–15 experiments for statistical power and construct validity; Laird et al., 2009) we had to subdivide imaging studies on different pathological conditions into the condition of chronic neuropathic pain. The same had to be performed for different applications of experimental pain in healthy subjects. Some of these groups might not be perfectly gathered but we argue that by using the statistical ALE-approach false positive results are quite improbable and activation sites which are not typical for the majority of the group will not show significant results.

Conclusion

Overall, our meta-analysis revealed consistent activation of the pain matrix. In particular, the SII and MCC showed converging activation during all pain conditions. Although the activation of SII represents the somatosensory component of pain, the MCC represents secondary processes, especially the motor response. Among other connections, those in the supplementary motor area allow individuals to escape the source of pain. The contrast analysis of neuropathic minus experimental pain revealed activation in the ACC and anterior insula underlining the important role for emotions and autonomic reactions, contributing to the suffering of patients with chronic neuropathic pain.

Supplementary materials related to this article can be found online at doi:10.1016/j.neuroimage.2011.07.022.

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