◆ Human Brain Mapping 34:109–149 (2013) ◆

Localization of Pain-Related Brain Activation: A Meta-Analysis of Neuroimaging Data

Emma G. Duerden[1,2]* and Marie-Claire Albanese[3]

[1]*Département de physiologie, Groupe de recherche sur le système nerveux central, Université de Montréal, Montréal, Québec, Canada*
[2]*Centre de recherche de l'institut universitaire de gériatrie de Montréal, Montréal, Québec, Canada*
[3]*Department of Psychology, McGill University, Montréal, Québec, Canada*

Abstract: A meta-analysis of 140 neuroimaging studies was performed using the activation-likelihood-estimate (ALE) method to explore the location and extent of activation in the brain in response to noxious stimuli in healthy volunteers. The first analysis involved the creation of a likelihood map illustrating brain activation common across studies using noxious stimuli. The left thalamus, right anterior cingulate cortex (ACC), bilateral anterior insulae, and left dorsal posterior insula had the highest likelihood of being activated. The second analysis contrasted noxious cold with noxious heat stimulation and revealed higher likelihood of activation to noxious cold in the subgenual ACC and the amygdala. The third analysis assessed the implications of using either a warm stimulus or a resting baseline as the control condition to reveal activation attributed to noxious heat. Comparing noxious heat to warm stimulation led to peak ALE values that were restricted to cortical regions with known nociceptive input. The fourth analysis tested for a hemispheric dominance in pain processing and showed the importance of the right hemisphere, with the strongest ALE peaks and clusters found in the right insula and ACC. The fifth analysis compared noxious muscle with cutaneous stimuli and the former type was more likely to evoke activation in the posterior and anterior cingulate cortices, precuneus, dorsolateral prefrontal cortex, and cerebellum. In general, results indicate that some brain regions such as the thalamus, insula and ACC have a significant likelihood of activation regardless of the type of noxious stimuli, while other brain regions show a stimulus-specific likelihood of being activated. *Hum Brain Mapp 34:109–149, 2013.*

Key words: pain; fMRI; PET; brain; human

INTRODUCTION

Advances in brain imaging techniques, including functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have permitted a detailed view of nociceptive processing in the human brain. Reviews of neuroimaging studies examining "pain-evoked" activation in the brain have reported an extensive network of cortical regions involved in nociceptive processing, including the primary (SI) and secondary (SII) somatosensory cortices, the anterior cingulate cortex (ACC), the insula, the prefrontal cortex, and the thalamus

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: The Canadian Institutes of Health Research (CIHR).

*Correspondence to: Emma G. Duerden, The Hospital for Sick Children, The Department of Diagnostic Imaging, 555 University Avenue, Toronto, ON, Canada, M5G 1Z8.
E-mail: emma.duerden@sickkids.ca

Received for publication 26 January 2011; Revised 28 May 2011; Accepted 5 July 2011
DOI: 10.1002/hbm.21416
Published online 1 December 2011 in Wiley Online Library (wileyonlinelibrary.com).

[Apkarian et al., 2005; Iadarola and Coghill, 1999; Peyron et al., 1999]. While these reviews have been important for collating information, they only report common regions of "pain-evoked" activation. For example, Apkarian et al. [2005] in their review of the pain neuroimaging literature reported that the most commonly activated region in response to noxious stimuli was the anterior insular cortex. While this information is useful in the general sense, such qualitative approaches do not permit a quantitative appreciation of the probabilistic spatial extent of "pain-related" activation nor do they allow a more detailed assessment of the relative influence of experimental variables on the likelihood of observing this activation within the broad network of regions implicated in pain processing. Recent advances in meta-analytic methods of assessing brain activation allow some of these limitations to be addressed. Meta-analysis is a statistical technique whereby data are collected, analyzed, and compared from multiple independent studies to examine a particular research question. This approach is especially relevant to the study of the cortical and subcortical responses to noxious stimuli. By its nature, pain is a multidimensional sensory experience that leads to numerous candidate areas of brain activation; meta-analysis can be a tool to help decipher the functionality of these varied regions of activation. The quantitative approach of this method yields a brain volume in which the probability of observing activation in response to noxious stimuli is computed at each voxel based on a large number of neuroimaging studies.

This review applies meta-analytic techniques to examine journal articles published between 1991 and 2011, which report peak activation coordinates in response to noxious stimuli (Study 1). Additionally, as pain can be evoked by different types of peripheral stimuli (e.g., heat, cold, impact, and capsaicin injection) and under different experimental conditions, the large number of studies included in this review facilitated the exploration of three additional fundamental questions related to the study of brain activation in response to noxious stimuli. The second analysis, presented in Study 2, addresses the specificity of activation across different stimulus modalities by comparing activation sites associated with noxious cold stimulation with those evoked by noxious heat. The third analysis (Study 3) examines the influence of one particular aspect of experimental design (the use of a resting baseline or an innocuous warm stimulus condition) on the apparent activation evoked by noxious heat stimuli. The fourth analysis (Study 4) tests for possible evidence of hemispheric dominance for activation in response to noxious stimuli. Finally, the fifth analysis (Study 5) compared activation in response to noxious muscle stimuli with noxious cutaneous stimuli.

Study 1: Brain Activation in Response to All Noxious Stimuli

To provide improved information on the localization and spatial extent of pain-related activation in the brain, the first meta-analysis explores brain activation in response to all forms of noxious stimuli applied to the skin, muscle or viscera.

Study 2: Differential Brain Activation in Response to Noxious Cold and Heat Stimuli

The second section of this review examines differences in brain regions that process experimental noxious cold stimuli in comparison to those that process noxious heat stimuli. Three previous studies have suggested that cold pain evokes a similar pattern of brain activation as that seen in response to heat pain [Casey et al., 1996; Craig et al., 1996; Tracey et al., 2000]; however, cold pain is typically induced using the cold-pressor task, which is considered a significant autonomic stressor with a high degree of unpleasantness. Kwan et al. reported large inter-individual differences in brain activation evoked by cold-pain stimulation [Kwan et al., 2000], which could be explained by the potential cultural and situational influences on pain affect. However, it is difficult to draw conclusions based on the results of these previous studies as they used relatively small numbers of subjects ($N = 6 - 13$) and did not perform any direct subtractions on the data to determine which brain areas were preferentially associated with processing noxious cold or noxious heat stimuli.

Study 3: Control Conditions for Noxious Heat

During pain-imaging experiments, noxious heat stimuli are commonly generated using contact thermodes. The probe is placed on the skin and kept at a baseline temperature (30–32°C) between stimulus presentations. During the stimulation period, the temperature is increased to reach a level that is rated as painful by the subject. The gradual rise in temperature will inherently activate fibers that transmit warmth information [Raja et al., 1999] and may trigger orienting responses towards the stimulus. Therefore, when using a resting baseline as a control condition for noxious heat stimuli, the resulting statistical maps may reflect a contamination of the "pain-related" brain activation with that associated with the warming of the skin and orienting responses that preceded the perception of pain.

Only a few imaging studies have specifically examined brain activation in response to warmth. Two of these studies reported that warm stimuli activate brain areas similar to those that process pain, with somewhat less robust activation [Becerra et al., 1999; Craig et al., 1996]; however, one group reported both similar regions and similar activation levels in the brain in response to noxious heat and innocuous warm stimuli [Moulton et al., 2005]. If innocuous warm- and noxious heat-responsive cortical neurons are distinct and coexist within spatially defined regions of the brain, then warm stimuli may be an inappropriate control for a noxious-heat condition, since a statistical comparison between the two may result in an underestimation of activation associated with noxious stimuli.

However, another potential confound may result if warm stimuli evoke activation in brain regions that do not process pain. For example, Sung et al. [2007] reported activation in several regions outside of the commonly described "pain matrix" (as well as in regions frequently associated with pain perception) evoked by warm stimuli that were perceived as pleasant and comfortable. Although Sung et al. [2007] did not present a noxious heat condition, their results underscore the potential problems that would arise in a statistical comparison for "pain-evoked" responses across regions that are more activated during a warm "control" condition (i.e., apparent inhibition by noxious heat, which may or may not be an appropriate interpretation). Furthermore, as indicated by the perceptual ratings of the warm stimuli used by Sung et al. [2007], statistical contrasts between innocuous and noxious heat stimuli may not be appropriate, as the perception of warmth is not merely a lower intensity of thermal pain or unpleasantness, but may be considered a separate sensory modality with distinctly different (positive) affective qualities. In turn, this may render the subsequent subtractions difficult to interpret.

To date, no study has compared the effects of using either a resting baseline or innocuous warm stimuli on the apparent activation in the brain in response to noxious heat stimuli. We examined the advantages and disadvantages of the two subtraction strategies by performing a meta-analysis on a similar number of studies that used one or the other contrast.

Study 4: Hemispheric Dominance for Activation in Response to Noxious Stimuli

It is generally believed that somatosensory stimuli are processed primarily or preferentially by the hemisphere that is contralateral to the point of stimulation. However, evidence from clinical studies in patients with brain lesions and from brain imaging studies of normal pain processing has called this theory into question.

Results suggesting the possibility of a bilateral pain-processing network come from psychophysical data obtained from patients. For example, hemispherectomized patients can perceive painful stimuli that are either contralateral or ipsilateral to their only functioning hemisphere, albeit with poor localization [Olausson et al., 2001]. Additionally, recent evidence from an fMRI study with callosotomized patients demonstrated that ipsilateral brain regions responsible for processing pain (SI, SII, insula, and cingulate cortex) could be activated in response to noxious heat stimuli [Duquette et al., 2008].

Neuroimaging studies examining the BOLD nociceptive signal associated with stimuli applied exclusively to one side of the body have often reported bilateral activation in a number of brain regions involved in sensory-discriminative and affective-motivational pain processing. Common regions of bilateral activation include ACC, prefrontal cortex, SII, insula, thalamus, inferior parietal lobule [for example see Bingel et al., 2004b, 2007a,b; Boly et al., 2007; Bornhovd et al., 2002; Buchel et al., 2002], and in some instances, SI [for example see Bingel et al., 2004b; Cole et al., 2008; Staud et al., 2007; Straube et al., 2008]. A previous activation-likelihood-estimate (ALE) meta-analysis examined concordant brain activation sites evoked by noxious stimuli from 22 original studies that applied stimuli to the upper arms [Farrell et al., 2005]. These authors reported that the likelihood of activation was generally bilateral, except in left prefrontal cortex and right SI. However, the finding of a significant likelihood of activation in right SI, instead of in bilateral SI (as would be predicted given that the stimuli were applied to both sides of the body) was likely due to the inclusion of a greater number of foci from studies that had presented stimuli to the left arms (Left: 249 vs. Right: 140). For this reason, it is difficult to draw conclusions about lateralization of nociceptive processing from this previous meta-analysis, as they did not perform their comparisons on a similar number of activation sites.

Additional evidence that is inconsistent with a strictly ontralateral processing of nociceptive information comes from psychophysical studies on healthy subjects suggesting a possible right-hemisphere dominance for pain processing. For example, individuals exhibit lower pain thresholds and rate pain as more intense when noxious stimuli are applied to the left side of the body (processed by the contralateral right hemisphere) [Haslam, 1970; Jensen et al., 1992; Lugo et al., 2002; Pauli et al., 1999b; Sarlani et al., 2003]. In a study of chronic pain patients, Hsieh et al. [1995] found activation lateralized to the right ACC regardless of the limb in which pain was experienced. However, other regions, such as the anterior insula, posterior parietal, lateral inferior prefrontal, and posterior cingulate cortices, were activated bilaterally.

Two imaging studies, which specifically tested for hemispheric differences in pain processing in healthy subjects, have provided additional evidence that some brain regions in the right hemisphere preferentially process pain. Coghill et al. [2001] reported right-lateralized activation in thalamus, inferior parietal lobule, dorsolateral, and dorsal prefrontal cortex in response to noxious and innocuous heat stimuli applied to either forearm. More recently, Symonds et al. [2006] described an fMRI study in which noxious electrical stimuli applied to the right and left fingertips evoked a predominant right hemispheric activation of the ACC (BA 32), the middle frontal gyrus (BA 9/46/10), the medial and superior frontal gyri (BA 6/8), ventrolateral prefrontal cortex, and the inferior parietal lobule. Both studies, however, used relatively small samples ($N = 9$), making generalizability of results rather uncertain.

To better distinguish brain regions that may participate in a lateralized dominance of pain processing, we conducted a meta-analysis on a similar number of imaging studies that applied noxious stimuli to the left or to the right side of the body.

Study 5: Neural Processing of Noxious Muscle and Cutaneous Stimuli

The majority of functional neuroimaging studies have primarily focused on exploring the cerebral mechanisms

that process cutaneous pain; however, the majority of chronic pain syndromes originate in muscles (i.e., myositides, fibromyalgia, muscle ischemia, and some forms of low back pain), joints (i.e., rheumatoid arthritis), and viscera (i.e., irritable bowel syndrome). Moreover, the sensations associated with even a minor deep tissue injury can result in prolonged allodynia near and adjacent to the site, while a minor skin injury can cause a more spatially localized sensation. Psychophysical studies have documented that painful sensations due to muscle or skin damage are perceived differently. Muscle injury is referred to as diffuse, aching, or cramping, and is often poorly localized as the sensation of muscle pain can be referred to distant sites [Arendt-Nielsen and Svensson, 2001; Graven-Nielsen and Mense, 2001; Graven-Nielsen et al., 1997; Mense, 1993]. Conversely, noxious cutaneous stimuli are described as sharp, burning and localized [Mense, 1993]. Due to the prolonged and radiating pain associated with muscle damage, it has been suggested that these types of pain are mediated by central mechanisms [Wall and Woolf, 1984]. Therefore, potentially different cerebral mechanisms are responsible for the processing of noxious muscle and cutaneous stimuli that could account for these perceptual differences. Thus, we assessed with a fifth meta-analysis whether noxious muscle stimuli evoked activation in specific or overlapping brain structures that also process noxious cutaneous stimuli.

METHODS

Article Selection

The Study 1 database (all noxious stimuli) was created from a compilation of journal articles retrieved from several sources and using noxious stimuli applied to the skin, muscle, or viscera. Articles reporting brain activation coordinates in response to noxious stimuli were retrieved initially using reference lists from the more recent reviews of "pain-evoked" activation brain imaging studies [Apkarian et al., 2005; Farrell et al., 2005]. A subsequent Medline search was initiated using the keywords: pain, noxious, PET, fMRI, experimental, and healthy. Articles were also retrieved from the references in the original research articles collected. The database variables included (1) Author names; (2) Year of publication; (3) Size of the Gaussian smoothing filter; (4) Number of subjects; (5) Stimulus modality (laser, electrical, impact, etc.); (6) System targeted by noxious stimuli (cutaneous, muscle, visceral, etc.); (7) Side of the body; (8) Body part; (9) Type of standardized space; (10) Brain activation coordinates.

We initially conducted a search of the neuroimaging literature published between 1980 and 2011 to retrieve articles that used noxious stimuli. Articles selected for inclusion in the database satisfied the following criteria: (a) data were acquired in healthy subjects; (b) the activation sites were the result of a contrast that compared a noxious stimulus condition to a resting baseline, or to a control condition, or to a noxious stimulus condition that was rated by participants as less painful, or to a no-stimulus condition conducted in a control group of participants. Likewise, articles were included in which the activation sites were determined by correlating brain activity with participants' perceptual levels of pain intensity or unpleasantness. Excluded from the analysis were studies that reported coordinates that combined painful and nonpainful stimuli.

In total 140 studies were included in the Study 1 analysis, 8 of which were based on further analysis of data from previous publications, leading to a total of 132 original articles (Table I). The majority of studies (104) used cutaneously administered stimuli (contact thermodes, laser, impact, pressure, electric shock, pinprick, topical capsaicin, or incision). However, some of these studies used more than one type of noxious stimulus within the same experimental protocol. Eleven studies used painful visceral stimuli (esophageal, rectal, stomach, and vascular distension), while four used intracutaneous stimuli (ethanol injection, capsaicin injection, electric shock, or infusion of a phosphate buffer), seven used transcutaneous stimuli (electric shock), seven used subcutaneous injections (ascorbic acid, capsaicin, and hypertonic saline), seven were intramuscular (electric shock, hypertonic saline injection, and infusion of a phosphate buffer), three were muscular, four were intracutaneous, one used intranasal gaseous CO_2, and one applied noxious stimuli to the tooth pulp. In most instances, stimuli were applied to the upper limbs (104 studies). Of the remaining studies, 22 used noxious stimuli applied to the lower limbs, 11 to the face, 3 to the trunk, and 10 were applied internally.

Study 2 consists of two meta-analyses conducted on reports selected from the database described in Study 1. The first meta-analysis was performed on 112 coordinates obtained from 9 studies that applied noxious cold stimuli to the upper limbs (Table II). The stimulus conditions included water baths, contact thermodes, and ice packs. For purposes of comparison, the second meta-analysis was conducted on 122 activation foci from 9 studies employing noxious contact heat stimuli applied to the upper limbs (Table III). Studies for the noxious heat meta-analysis were selected if they employed stimuli that were similar to those included in the noxious cold analysis in terms of stimulation site, imaging modality, and year of publication. Additionally, the stimuli included in the two meta-analyses were matched for intensity ($P = 0.57$). As the ALE method does not take into consideration the number of studies but rather the number of coordinates, the studies were also selected so that they would be matched in terms of the number of reported coordinates. A Mann-Whitney U test was performed to assess the number of coordinates reported in the studies selected for these two meta-analyses and results indicated no difference between them ($P = 0.5$).

Study 3 was created based on a search of the general meta-analysis of Study 1 for articles that used either innocuous warm stimuli or a resting baseline as a control

TABLE I. List of studies included in study I (all noxious stimuli)

					Stimuli					
Study #	Author	Year	Imaging	*N*	Type	Modality	System	Side	Body Part	Notes
1	Adler et al.	1997	PET	9	Heat	Thermal	Cutaneous	Left	Forearm	
2	Aharon et al.	2006	fMRI 1.5	6	Heat	Thermal	Cutaneous	Left	Hand	
3	Albanese et al.	2007	fMRI 1.5	8	Heat	Thermal	Cutaneous	Right	Hand	
4	Andersson et al.	1997	PET	6	Capsaicin injection	Chemical	Intracutaneous	Right	Hand and foot	
5	Apkarian et al.	2000	fMRI 1.5	7	Heat	Thermal	Cutaneous	Right	Fingers	
6	Aziz et al.	1997	PET	8	Esophageal distention	Mechanical	Visceral	Bilateral	Esophagus	
7	Becerra et al.	1999	fMRI 1.5	6	Heat	Thermal	Cutaneous	Left	Hand	
8	Becerra et al.	2001	fMRI 1.5	8	Heat	Thermal	Cutaneous	Left	Hand	
9	Bingel et al.	2002	fMRI 1.5	14	Laser	Thermal	Cutaneous	Left and Right	Hand	
10	Bingel et al.	2003	fMRI 1.5	14	Laser	Thermal	Cutaneous	Left and Right	Hand	Data are shared with Bingel et al., 2002
11	Bingel et al.	2006	fMRI 1.5	19	Laser	Thermal	Cutaneous	Left and Right	Hand	
12	Bingel et al.	2004a	fMRI 1.5	20	Laser	Thermal	Cutaneous	Left and Right	Hand and foot	
13	Bingel et al.	2004b	fMRI 1.5	18	Laser	Thermal	Cutaneous	Left	Hand and foot	
14	Bingel et al.	2007a	fMRI 3	16	Laser	Thermal	Cutaneous	Left	Hand	
15	Bingel et al.	2007b	fMRI 3	20	Heat	Thermal	Cutaneous	Left	Forearm	
16	Binkofski et al.	1998	fMRI 1.5	5	Esophageal distention	Mechanical	Visceral	Bilateral	Esophagus	
17	Boly et al.	2007	fMRI 3	24	Laser	Thermal	Cutaneous	Left	Hand	
18	Bornhovd et al.	2002	fMRI 1.5	9	Laser	Thermal	Cutaneous	Left	Hand	Data are shared with Buchel et al., 2002
19	Borsook et al.	2003	fMRI 1.5	9	Heat	Thermal	Cutaneous	Right	Face	Data are shared with Dasilva et al., 2002
20	Botvinick et al.	2005	fMRI 1.5	12	Heat	Thermal	Cutaneous	Left	Thenar Eminence	
21	Brooks et al.	2005	fMRI 3	14	Heat	Thermal	Cutaneous	Right	Face, foot, and hand	
22	Buchel et al.	2002	fMRI 1.5	9	Laser	Thermal	Cutaneous	Left	Hand	
23	Carlsson et al.	2006	fMRI 1.5	9	Electrical shock	Electrical	Cutaneous	Right	Wrist	
24	Casey et al.	1994	PET	18	Heat	Thermal	Cutaneous	Left	Arm	
25	Casey et al.	1996	PET	27	Cold	Thermal	Cutaneous	Left	Hand	
26	Casey et al.	2000	PET	11	Cold	Thermal	Cutaneous	Left	Hand	
27	Casey et al.	2001	PET	14	Heat	Thermal	Cutaneous	Left	Forearm	
28	Chen et al.	2002	fMRI 1.5	4	Heat	Thermal	Cutaneous	Left	Inner calf	

TABLE I. (Continued)

					Stimuli					
Study #	Author	Year	Imaging	*N*	Type	Modality	System	Side	Body Part	Notes
29	Christmann et al.	2007	fMRI 1.5	6	Electrical Shock	Electrical	Transcutaneous	Right	Thumb	
30	Coen et al.	2007	fMRI 1.5	7	Esophageal distention	Mechanical	Visceral	Bilateral	Esophagus	
31	Coghill et al.	1994	PET	9	Heat	Thermal	Cutaneous	Left	Forearm	
32	Coghill et al.	1999	PET	16	Heat	Thermal	Cutaneous	Right	Upper arm	
33	Coghill et al.	2001	PET	9	Heat	Thermal	Cutaneous	Left and Right	Forearm	
34	Coghill and Eisenach; Coghill et al.	2003	fMRI 1.5	17	Heat	Thermal	Cutaneous	Right	Leg	
35	Cole et al.	2008	fMRI 1.5	30	Pressure	Mechanical	Cutaneous	Right	Thumb	
36	Craig et al.	1996	PET	11	Cold	Thermal	Cutaneous	Right	Hand	
37	Craig et al.	1996			Heat	Thermal	Cutaneous	Right	Hand	
38	DaSilva et al.	2002	fMRI 1.5	9	Heat	Thermal	Cutaneous	Right	Opthalmic, Maxillary, Mandibular, thumb	
39	Davis and Pope	2002	fMRI 1.5	NR	Cold Prickle	Thermal and mechanical	Cutaneous	Right	Thenar eminence	
40	de Leeuw et al.	2006	fMRI 1.5	9	Heat	Thermal	Cutaneous	Left	Masseter muscle	
41	Derbyshire and Jones; Derbyshire et al.	1998	PET	7	Heat	Thermal	Cutaneous	Left	Hand	Data are shared with Vogt et al., 1996
42	Derbyshire et al.	1997	PET	12	Laser	Thermal	Cutaneous	Right	Hand	
43	Derbyshire and Jones; Derbyshire et al.	1998	PET	12	Heat	Thermal	Cutaneous	Right	Hand	
44	Derbyshire et al.	2002a,b	PET	21	Laser	Thermal	Cutaneous	Right	Hand	
45	Derbyshire et al.	2002a,b	PET	16	Heat	Thermal	Cutaneous	Right	Hand	
46	Derbyshire	2004	fMRI 3	8	Heat	Thermal	Cutaneous	Right	Hand	
47	Downar et al.	2003	fMRI 1.5	10	Electrical Shock	Electrical	Transcutaneous	Right	Median nerve	
48	Dunckley et al.	2005	fMRI 3	10	Heat and rectal distention	Thermal and mechanical	Cutaneous and visceral	Bilateral/ Left	Back and rectum/Foot	
49	Fairhurst et al.	2007	fMRI 3	12	Heat	Thermal	Cutaneous	Left	Hand	
50	Farrell et al.	2006	PET	10	Pressure	Mechanical	Cutaneous	Left	Thumb	
51	Ferretti et al.	2003	fMRI 1.5	8	Electrical Shock	Electrical	Cutaneous	Right	Median nerve	
52	Frankenstein et al.	2001	fMRI 1.5	12	Cold	Thermal	Cutaneous	Right	Foot	
53	Gelnar et al.	1999	fMRI 1.5	9	Heat	Thermal	Cutaneous	Right	Finger	
54	Gyulai et al.	1997	PET	5	Heat	Thermal	Cutaneous	Left	Forearm	
55	Helmchen et al.	2003	fMRI 1.5	18	Heat	Thermal	Cutaneous	Right	Hand	
56	Helmchen et al.	2006	fMRI 1.5	18	Heat	Thermal	Cutaneous	Right	Hand	Data are shared with Helmchen et al., 2003

TABLE I. (Continued)

					Stimuli					
Study #	Author	Year	Imaging	*N*	Type	Modality	System	Side	Body Part	Notes
57	Henderson et al.	2007	fMRI 3	23	Hypertonic Saline Injection	Mechanical	Intramuscular and subcutaneous	Right	Leg and forearm	
58	Hofbauer et al.	2001	PET	10	Heat	Thermal	Cutaneous	Left	Hand	
59	Hofbauer et al.	2004	PET	15	Heat	Thermal	Cutaneous	Left	Forearm	
60	Hsieh et al.	1996	PET	4	Ethanol Injection	Chemical	Intracutaneous	Right	Upper arm	
61	Iadarola et al.	1998	PET	13	Capsaicin injection	Chemical	Subcutaneous	Left	Forearm	
62	Iannilli	2008	fMRI 1.5	18	Electric shock, Gaseous CO^2	Electrical and chemical	Cutaneous and intranasal	Right	Forehead and trigeminal branch	
63	Ibinson et al.	2004	fMRI 1.5	6	Electrical shock	Electrical	Cutaneous	Right	Median nerve	
64	Jantsch et al.	2005	fMRI 1.5	8	Electrical Shock	Electrical	Cutaneous	Left	Upper incisor	
65	Keltner et al.	2006	fMRI 4.0	16	Heat	Thermal	Cutaneous	Left	Hand	
66	Kong et al.	2006	fMRI 3	16	Heat	Thermal	Cutaneous	Right	Forearm	
67	Korotkov et al.	2002	PET	16	Hypertonic Saline Injection	Mechanical	Intramuscular	Left	Tricep	
68	Koyama et al.	2003	fMRI 1.5	9	Heat	Thermal	Cutaneous	Right	Leg	
69	Koyama et al.	2005	fMRI 1.5	10	Heat	Thermal	Cutaneous	Right	Leg	
70	Kupers et al.	2004	PET	10	Hypertonic Saline Injection	Mechanical	Intramuscular	Right	Masseter muscle	
71	Kurata et al.	2002	fMRI 3	5	Heat	Thermal	Cutaneous	Left and Right	Forearm	
72	Kurata et al.	2005	fMRI 3	6	Heat	Thermal	Cutaneous	Right	Forearm	
73	Ladabaum et al.	2001	PET	15	Gastric Distention	Mechanical	Visceral	Bilateral	Stomach	
74	Ladabaum et al.	2001	fMRI 1.5	10	Gastric Distention	Mechanical	Visceral	Bilateral	Stomach	
75	Lorenz et al.	2002	PET	14	Heat	Thermal	Cutaneous	Left	Forearm	
76	Lorenz et al.	2008	fMRI 1.5	11	Pressure	Mechanical	Cutaneous	Right	Tibia	
77	Lu et al.	2004	fMRI 3	10	Gastric Distention	Mecahnical	Visceral	Bilateral	Gastric fundus	
78	Lui et al.	2008	fMRI 1.5	14	Pin Prick	Mechanical	Cutaneous	Right	Hand	
79	Maihofner et al.	2004	fMRI 1.5	11	Heat and topical capsaicin	Thermal and chemical	Cutaneous	Left	Forearm	
80	Maihofner and Handwerker	2005	fMRI 1.5	12	Pin prick and topical capsaicin	Mechanical and thermal	Cutaneous	Left	Forearm	
81	Maihofner et al.	2006	fMRI 1.5	14	Heat and impact	Thermal and mechanical	Cutaneous	Right	Forearm	
82	Maihofner et al.	2011	fMRI 1.5	12	Impact	Mechanical	Cutaneous	Left	Hand	
83	Mainero	2007	fMRI 3	11	Heat/Capsaicin	Thermal/ Chemical	Cutaneous	Right	Ophthalmic	
84	May et al.	1998	PET	7	Capsaicin injection	Thermal	Subcutaneous	Right	Forehead	
85	Mochizuki et al.	2007	fMRI 3	14	Cold	Thermal	Cutaneous	Left and	Wrist and hand	

TABLE I. (Continued)

					Stimuli					
Study #	Author	Year	Imaging	*N*	Type	Modality	System	Side	Body Part	Notes
86	Mohr et al.	2008	fMRI 1.5	17	Heat	Thermal	Cutaneous	Right	Thigh	
87	Mobascher et al.	2010	fMRI 3	12	Laser	Heat	Cutaneous	Left	Hand	
88	Moulton et al.	2011	fMRI 3	11	Heat	Thermal	Cutaneous	Left	Hand	
89	Nash et al.	2010	fMRI 3	28	Hypertonic saline injection	Mechanical	Muscular and subcutaneous	Right	Masseter muscle and Jaw	
90	Nemoto et al.	2003	PET	12	Laser	Thermal	Cutaneous	Right	Forearm	
91	Niddam et al.	2002	fMRI 3	10	Electrical Shock	Electrical	Intramuscular	Left	Hand	
92	Ochsner et al.	2006	fMRI 3	13	Heat	Thermal	Cutaneous	Right	Forearm	
93	Oshiro et al.	2007	fMRI 1.5	12	Heat	Thermal	Cutaneous	Left	Leg	
94	Owen et al.	2008	fMRI 3	14	Heat	Thermal	Cutaneous	Left	Hand	
95	Owen et al.	2010	fMRI 3	13	Hypertonic saline injection	Mechanical	Muscular	Left	Forearm	
96	Paulson et al.	1998	PET	20	Heat	Thermal	Cutaneous	Left	Forearm	
97	Petrovic et al.	2002	PET	7	Cold	Thermal	Cutaneous	Left	Hand	
98	Petrovic et al.	2004a	PET	7	Cold	Thermal	Cutaneous	Left	Hand	Data are shared with Petrovic et al., 2002
99	Petrovic et al.	2004b	PET	10	Cold	Thermal	Cutaneous	Left	Hand	
100	Peyron et al.	1999	PET	7	Heat	Thermal	Cutaneous	Left and Right	Hand	
101	Pogatzki-Zahn et al.	2010	fMRI 3	30	Incision	Tissue damage	Cutaneous	Right	Forearm	
102	Porro et al.	1998	fMRI 1.5	24	Ascorbic acid injection	Chemical	Subcutaneous	Left and Right	Foot	
103	Porro et al.	2002	fMRI 1.5	26	Ascorbic Acid Injection	Chemical	Subcutaneous	Left and Right	Foot	
104	Qiu et al.	2006	fMRI 3	13	Laser	Thermal	Cutaneous	Right	Hand	
105	Raij et al.	2005	fMRI 3	14	Laser	Thermal	Cutaneous	Left	Hand	
106	Rainville et al.	1997	PET	8	Heat	Thermal	Cutaneous	Left	Hand	
107	Remy et al.	2003	fMRI 3	12	Heat	Thermal	Cutaneous	Left	Hand	
108	Rolls et al.	2003	fMRI 3	8	Pressure	Mechanical	Cutaneous	Left	Hand	
109	Ruehle et al.	2006	fMRI 1.5	11	Electrical Shock	Electrical	Transcutaneous and Intracutaneous	Right	Foot	
110	Sawamoto et al.	2000	fMRI 1.5	10	Laser	Thermal	Cutaneous	Right	Hand	
111	Schneider et al.	2001	fMRI 1.5	6	Vascular Distention	Mechanical	Vascular	Left	Foot	
112	Schoedel et al.	2008	fMRI 1.5	11	Impact	Mechanical	Cutaneous	Left	Middle finger	
113	Schreckenberger et al.	2005	PET	10	Infusion of phosphate buffer	Mechanical	Intracutaneous and intramuscular	Left	Hand	

TABLE I. (Continued)

					Stimuli					
Study #	Author	Year	Imaging	*N*	Type	Modality	System	Side	Body Part	Notes
114	Seifert and Maihofner	2007	fMRI 1.5	12	Cold	Thermal	Cutaneous	Right	Forearm	
115	Seifert et al.	2010	fMRI 3	10	Pin Prick	Mechanical	Cutaneous	Right	Forearm	
116	Seminowicz et al.	2004	fMRI 1.5	16	Electrical Shock	Electrical	Transcutaneous	Left	Median nerve	
117	Seminowicz and Davis	2006	fMRI 1.5	22	Electrical Shock	Electrical	Transcutaneous	Left	Median nerve	
118	Seminowicz and Davis	2007	fMRI 1.5	23	Electrical Shock	Electrical	Transcutaneous	Left	Median nerve	
119	Song et al.	2006	fMRI 3	12	Cold and distention	Thermal and Mechanical	Cutaneous and visceral	Left/ bilateral	Foot/rectum	
120	Sprenger et al.	2006	PET	8	Heat	Thermal	Cutaneous	Right	Forearm	
121	Stammler et al.	2008	fMRI 1.5	12	Pin prick	Mechanical hyperalgesia	Cutaneous	Right	Forearm	
122	Staud et al.	2007	fMRI 3	11	Heat	Thermal	Cutaneous	Right	Foot	
123	Straube et al.	2008	fMRI 1.5	24	Electrical Shock	Electrical	Cutaneous	Left	Finger	
124	Strigo et al.	2003	fMRI 1.5	7	Esophageal Distention and Heat	Mechanical and thermal	Visceral and Cutaneous	Bilateral	Esophagus and Chest	
125	Strigo et al.	2005	fMRI 1.5	7	Esophageal Distention and Heat	Mechanical and thermal	Visceral and Cutaneous	Bilateral	Esophagus	
126	Svensson et al.	1997	PET	10	Electrical Shock and laser	Electrical and thermal	Intramuscular and Cutaneous	Left	Forearm and Elbow	
127	Svensson et al.	1998	PET	10	Heat	Thermal	Cutaneous	Right	Forearm	
128	Symonds et al.	2006	fMRI 3	9	Electrical shock	Electrical	Transcutaneous	Left and Right	Index finger	
129	Talbot et al.	1991	PET	8	Heat	Thermal	Cutaneous	Right	Forearm	
130	Terekhin and Forster	2006	fMRI 1.5	14	Impact	Mechanical	Cutaneous	Right	Index Finger	
131	Thunberg et al.	2005	PET	19	Hypertonic Saline Injection	Mechanical	Intramuscular	Right	Erector Spinae muscle	
132	Tolle	1999	PET	12	Heat	Thermal	Cutaneous	Right	Forearm	
133	Tracey et al.	2000	fMRI 1.5	6	Cold and heat	Thermal	Cutaneous	Left	Hand	
134	Uematsu et al.	2011	fMRI 1.5	17	Pressure	Mechanical	Muscular	right	Calf	
135	Vandenbergh et al.	2005	PET	11	Gastric Distention	Mechanical	Visceral	Bilateral	Stomach	
136	Vogt et al.	1996	PET	7	Heat	Thermal	Cutaneous	Left	Hand	
137	Wagner et al.	2007	PET	7	Heat	Thermal	Cutaneous	Right	Forearm	
138	Weigelt et al.	2010	fMRI 1.5	13	Electric shock	Electrical	Cutaneous	Bilateral	Upper and lower canines	
139	Xu et al.	1997	PET	6	Laser	Thermal	Cutaneous	Left	Foot and hand	
140	Yilmaz et al.	2010	fMRI 1.5	21	Pressure	Mechanical	Cunateous	Left	Index finger	

Study 1 (all noxious stimuli): List of studies reporting brain activation coordinates evoked by externally and internally applied noxious stimuli. Abbreviations: fMRI, functional magnetic resonance imaging; PET, positron emission tomography; *n*, sample size; NR, not reported.

TABLE II. List of studies included in study 2 (noxious cold)

				Stimuli				
Author	Year	Imaging	Subject (*N*)	Modality	System	Side	Body Part	NRS
Casey et al.	2000	PET	11	Thermal	Cutaneous	Left	Hand	NR
Casey et al.	1996	PET	27	Thermal	Cutaneous	Left	Hand	7.89
Craig	1996	PET	11	Thermal	Cutaneous	Right	Hand	NR
Davis and Pope	2002	fMRI 1.5	NR	Thermal/mechanical	Cutaneous	Right	Palm	NR
Mochizuki et al.	2007	fMRI 3	14	Thermal	Cutaneous	Left	Wrist	7
Petrovic et al.	2002	PET	7	Thermal	Cutaneous	Left	Hand	5.3
Petrovic et al.	2004b	PET	10	Thermal	Cutaneous	Left	Hand	5.9
Seifert and Maihofner	2007	fMRI 1.5	12	Thermal	Cutaneous	Right	Forearm	4.08
Tracey et al.	2000	fMRI 1.5	6	Thermal	Cutaneous	Left	Hand	7.9

Study 2 (noxious cold): List of studies reporting brain activation coordinates evoked by noxious cold stimuli. Abbreviations: fMRI, functional magnetic resonance imaging; PET, positron emission tomography; NR, not reported; NRS, Numerical rating scale.

condition for evaluating brain activation associated with noxious heat stimuli (applied to any part of the body). Nine studies that reported 131 activation foci described in the Study 1 database matched the inclusion criterion for examining noxious heat in comparison to a warm control condition (Table IV). Nine studies that reported a total of 149 coordinates from Study 1 met our inclusion criterion of comparing noxious heat stimuli with a resting baseline (Table V). These nine studies were matched to those included in the first analysis according to the following criteria: imaging modality, number and extent of activation sites, year of publication, and site of stimulation (Table IX). The pain intensity ratings reported in the two sets of studies were not significantly different from one another ($P = 0.9$). A Mann-Whitney U test applied to the data indicated no significant differences between the numbers of activation foci included in the two meta-analyses ($P = 0.5$).

Study 4 examined a possible hemispheric dominance for processing noxious stimuli. The database for Study 1 was searched to select different sets of studies that applied noxious stimuli either exclusively to the left side or to the right side of the body. For both meta-analyses, studies were selected if they applied stimuli to the arms, legs, or sides of the face. However, to simplify the comparison, the meta-analysis included studies that used stimuli generated using contact thermodes or laser stimuli, since other modalities of noxious stimulation may evoke activation that is unequally weighted in terms of the intensity or emotional valence, which might lead to a nonuniform comparison among studies and brain activation coordinates. The data from the studies included in both meta-analyses were from contrasts that resulted from a noxious stimulus (heat or cold) compared to either a resting baseline or a control condition (innocuous warm or cool). Coordinates that were reported based on correlations of pain ratings with percent blood-oxygen-level-dependent (BOLD) signal change were also included in the analyses. Studies were excluded if they applied stimuli to the midline (back or chest), simultaneously to both sides of the body, or if they reported data combined from scans in which stimuli were applied to either side of the body.

TABLE III. List of studies included study 2 (noxious heat)

					Stimuli				
Author	Year	Imaging	Subject (*N*)	Type	Modality	System	Side	Body Part	NRS
Botvinick et al.	2005	fMRI 1.5	12	Heat	Thermal	Cutaneous	Left	Forearm	7
Brooks et al.	2005	fMRI 3	14	Heat	Thermal	Cutaneous	Right	Hand	5.5
Casey et al.	2001	PET	14	Heat	Thermal	Cutaneous	Left	Forearm	8.93
Coghill et al.	1994	PET	9	Heat	Thermal	Cutaneous	Left	Forearm	8
Lorenz et al.	2002	PET	14	Heat	Thermal	Cutaneous	Left	Forearm	6
Maihofner et al.	2006	fMRI 1.5	14	Heat	Thermal	Cutaneous	Right	Forearm	4
Nemoto et al.	2003	PET	12	Laser	Thermal	Cutaneous	Right	Forearm	7.6
Tracey et al.	2000	fMRI 1.5	6	Heat	Thermal	Cutaneous	Left	Hand	7.7
Xu et al.	1997	PET	6	Laser	Thermal	Cutaneous	Left	Hand	NR

Study 2 (noxious heat): List of studies reporting brain activation coordinates evoked by noxious heat stimuli. Abbreviations: fMRI, functional magnetic resonance imaging; PET, positron emission tomography; NR, not reported; NRS, Numerical rating scale.

TABLE IV. List of studies included in study 3 (noxious heat vs. warm)

					Stimuli				
Author	Year	Imaging	Subject (*N*)	Type	Modality	System	Side	Body Part	NRS
Adler et al.	1997	PET	9	Heat	Thermal	Cutaneous	Left	Forearm	6.7
Botvinick et al.	2005	fMRI 1.5	12	Heat	Thermal	Cutaneous	Left	Hand	7
Casey et al.	2001	PET	14	Heat	Thermal	Cutaneous	Left	Forearm	8.93
Vogt et al.	1996	PET	7	Heat	Thermal	Cutaneous	Left	Hand	6.2
Derbyshire et al.	1997	PET	12	Laser	Thermal	Cutaneous	Right	Hand	7
Derbyshire and Jones; Derbyshire et al.	1998	PET	12	Heat	Thermal	Cutaneous	Right	Hand	5.85
Ochsner et al.	2006	fMRI 3	13	Heat	Thermal	Cutaneous	Right	Forearm	7
Svensson et al.	1998	PET	10	Heat	Thermal	Cutaneous	Right	Forearm	8
Wagner et al.	2007	PET	7	Heat	Thermal	Cutaneous	Right	Forearm	6.8

Study 3 (noxious heat vs. warm): List of studies reporting brain activation coordinates evoked by noxious heat stimuli in comparison to a warm control condition. Abbreviations: fMRI, functional magnetic resonance imaging; PET, positron emission tomography; NR, not reported; NRS, Numerical rating scale.

The left-sided meta-analysis included 43 studies and a total of 694 coordinates (Table VI). Studies chosen for the right-sided meta-analysis were matched to those included in the left-sided meta-analysis based on the year of publication, the imaging modality, and the site of stimulation. Additionally, to have an equal number of coordinates to compare across the two sets of studies, we selected 40 studies for the right-sided meta-analysis (Table VII). The studies were matched for stimulus intensity as determined by comparing subjects' ratings using an unpaired t-test ($P = 0.08$). A Mann-Whitney U test was performed to assess the mean and the distribution of coordinates reported in the studies included in the two comparison groups, which indicated that no single study unduly influenced the calculations of the meta-analyses ($P = 0.190$).

Study 5 examined potential regional specificity for processing noxious muscle stimuli in comparison to noxious cutaneous stimuli. The Study 1 database was searched for articles that had reported activation in response to noxious stimuli applied to muscles and resulted in a total of 10 studies (Table VIII). An equal number of studies that applied noxious stimuli to the skin were selected for purposes of comparison and were matched to the noxious muscle stimuli studies based on the year of publication, the imaging modality, and the site of stimulation (Table IX). An unpaired t-test revealed no significant differences in pain intensity ratings obtained for the sets of studies included in either meta-analysis ($P = 0.9$). The noxious muscle stimuli studies reported a total of 172 coordinates and the noxious cutaneous studies reported 133 activation foci. A Mann-Whitney U test showed no significant differences between the two sets of coordinates reported for the two meta-analyses ($P = 0.5$).

TABLE V. List of studies included in study 3 (noxious heat vs. resting baseline)

					Stimuli				
Author	Year	Imaging	Subject (*N*)	Type	Modality	System	Side	Body Part	NRS
Albanese et al.	2007	fMRI 1.5	8	Heat	Thermal	Cutaneous	Right	Hand	7
Coghill et al.	1994	PET	9	Heat	Thermal	Cutaneous	Left	Forearm	8
Coghill et al.	2001	PET	9	Heat	Thermal	Cutaneous	Left	Forearm	7.6
Kurata et al.	2005	fMRI 3	6	Heat	Thermal	Cutaneous	Right	Hand	6.8
Kurata et al.	2002	fMRI 3	5	Heat	Thermal	Cutaneous	Right	Forearm	7
Maihofner et al.	2006	fMRI 1.5	14	Heat	Thermal	Cutaneous	Right	Forearm	4.3
Nemoto et al.	2003	PET	12	Laser	Thermal	Cutaneous	Right	Forearm	7.4
Tracey et al.	2000	fMRI 1.5	6	Heat	Thermal	Cutaneous	Left	Hand	7.7
Xu et al.	1997	PET	6	Laser	Thermal	Cutaneous	Left	Hand	NR

Study 3 noxious heat vs. resting baseline: List of studies reporting brain activation coordinates evoked by noxious heat stimuli in comparison to a resting baseline. Abbreviations: fMRI, functional magnetic resonance imaging; PET, positron emission tomography; NR, not reported; NRS, Numerical rating scale.

TABLE VI. List of studies included in study 4 (noxious stimuli applied to the left side of the body)

Author	Year	Imaging	FWHM	Subject (*N*)	Stimuli			Side	Body Part	NRS	Notes
					Type	Modality	System				
Adler et al.	1997	PET	6	9	Heat	Thermal	Cutaneous	Left	Forearm	6.7	
Aharon et al.	2006	fMRI 1.5	5	6	Heat	Thermal	Cutaneous	Left	Hand	8.2	
Becerra et al.	1999	fMRI 1.5	NR	6	Heat	Thermal	Cutaneous	Left	Hand	7.24	
Becerra et al.	2001	fMRI 1.5	6	8	Heat	Thermal	Cutaneous	Left	Hand (dorsum)	7.8	
Bingel et al.	2003	fMRI 1.5	6	14	Laser	Thermal	Cutaneous	Left	Hand	NR	
Bingel et al.	2004a	fMRI 1.5	6	20	Laser	Thermal	Cutaneous	Left	Hand and foot	NR	
Bingel et al.	2004b	fMRI 1.5	6	18	Laser	Thermal	Cutaneous	Left	Hand	NR	
Bingel et al.	2007a	fMRI 3	8	16	Laser	Thermal	Cutaneous	Left	Hand	4	
Bingel et al.	2007b	fMRI 3	8	20	Heat	Thermal	Cutaneous	Left	Forearm	6.7	
Boly et al.	2007	fMRI 3	6	24	Laser	Thermal	Cutaneous	Left	Hand	8	
Bornhovd et al.	2002	fMRI 1.5	6	9	Laser	Thermal	Cutaneous	Left	Hand	8	Data are shared with Buchel et al. [2002]
Botvinick et al.	2005	fMRI 1.5	12	12	Heat	Thermal	Cutaneous	Left	Thenar Eminence	7	
Buchel et al.	2002	fMRI 1.5	6	9	Laser	Thermal	Cutaneous	Left	Hand	8	
Casey et al.	1994	PET	NR	18	Heat	Thermal	Cutaneous	Left	Arm	8.9	
Casey et al.	1996	PET	9	27	Cold	Thermal	Cutaneous	Left	Hand	8.9	
Casey et al.	2000	PET	9	11	Cold	Thermal	Cutaneous	Left	Hand	NR	
Casey et al.	2001	PET	9	14	Heat	Thermal	Cutaneous	Left	Forearm	8.93	
Chen et al.	2002	fMRI 1.5	6	4	Heat	Thermal	Cutaneous	Left	Inner calf	8.2	
Coghill et al.	1994	PET	20	9	Heat	Thermal	Cutaneous	Left	Forearm	7.8	
Coghill et al.	2001	PET	13.3	9	Heat	Thermal	Cutaneous	Left	Forearm	7.8	
de Leeuw et al.	2006	fMRI 1.5	3	9	Heat	Thermal	Cutaneous	Left	Face	4.4	
Derbyshire and Jones; Derbyshire et al.	1998	PET	20	7	Heat	Thermal	Cutaneous	Left	Hand	6.7	Data are shared with Vogt et al. [1996]
Dunckley et al.	2005	fMRI 3	5	10	Heat	Thermal	Cutaneous	Left	Foot	6.5	
Fairhurst et al.	2007	fMRI 3	5	12	Heat	Thermal	Cutaneous	Left	Hand	5.7	
Gyulai et al.	1997	PET	20	5	Heat	Thermal	Cutaneous	Left	Forearm	6.7	
Hofbauer et al.	2001	PET	14	10	Heat	Thermal	Cutaneous	Left	Hand	6	
Hofbauer et al.	2004	PET	14	15	Heat	Thermal	Cutaneous	Left	Forearm	6	
Keltner et al.	2006	fMRI 4	8	16	Heat	Thermal	Cutaneous	Left	Hand	8.2	
Kurata et al.	2002	fMRI 3	0.5	5	Heat	Thermal	Cutaneous	Left	Forearm	7.6	
Lorenz et al.	2002	PET	9	14	Heat	Thermal	Cutaneous	Left	Forearm	4.6	
Oshiro et al.	2007	fMRI 1.5	5	12	Heat	Thermal	Cutaneous	Left	Leg	6.4	
Owen et al.	2008	fMRI 3	8	14	Heat	Thermal	Cutaneous	Left	Hand	8	
Paulson et al.	1998	PET	9	20	Heat	Thermal	Cutaneous	Left	Forearm	8.75	
Petrovic et al.	2002	PET	16	7	Cold	Thermal	Cutaneous	Left	Hand	5.3	
Petrovic et al.	2004a	PET	16	7	Cold	Thermal	Cutaneous	Left	Hand	5.3	Data are shared with Petrovic et al., [2002]
Petrovic et al.	2004b	PET	10	10	Cold	Thermal	Cutaneous	Left	Hand	5.9	
Raij et al.	2005	fMRI 3	8	14	Laser	Thermal	Cutaneous	Left	Hand	6.5	
Rainville	1997	PET	NR	8	Heat	Thermal	Cutaneous	Left	Hand	7.5	
Remy et al.	2003	fMRI 3	8	12	Heat	Thermal	Cutaneous	Left	Hand	6.3	
Svensson et al.	1997	PET	15	11	Laser	Thermal	Cutaneous	Left	Elbow	7.9	
Tracey et al.	2000	fMRI 1.5	1.5	6	Heat and cold	Thermal	Cutaneous	Left	Hand	7.8	
Vogt et al.	1996	PET	20	7	Heat	Thermal	Cutaneous	Left	Hand	NR	
Xu et al.	1997	PET	NR	6	Laser	Thermal	Cutaneous	Left	Hand and foot	NR	

Study 4 (noxious stimuli applied to the left side of the body): List of studies reporting brain activation coordinates evoked by noxious stimuli applied to the left side of the body. Abbreviations: fMRI, functional magnetic resonance imaging; PET, positron emission tomography; NR, not reported; NRS, Numerical rating scale.

TABLE VII. List of studies included in study 4 (noxious stimuli applied to the right side of the body)

					Stimuli						
Author	Year	Imaging	FWHM	Subject (*N*)	Type	Modality	System	Side	Body Part	NRS	Notes
Albanese et al.	2007	fMRI 1.5	6	8	Heat	Thermal	Cutaneous	Right	Hand	7	
Apkarian	2000	fMRI 1.5	5	7	Heat	Thermal	Cutaneous	Right	Fingers	5.95	
Bingel et al.	2003	fMRI 1.5	6	14	Laser	Thermal	Cutaneous	Right	Hand	NR	
Bingel et al.	2004a	fMRI 1.5	6	20	Laser	Thermal	Cutaneous	Right	Hand and foot	NR	
Borsook et al.	2003	fMRI 1.5	6	9	Heat	Thermal	Cutaneous	Right	Face	6.1	Data are shared with DaSilva et al., [2002]
Brooks et al.	2005	fMRI 3.0	2	14	Heat	Thermal	Cutaneous	Right	Face, hand, and foot	5.5	
Coghill et al.	1999	PET	13.3	16	Heat	Thermal	Cutaneous	Right	Upper Arm	5.1	
Coghill et al.	2001	PET	13.3	9	Heat	Thermal	Cutaneous	Right	Ventral Forearm	7.8	
Coghill and Eisenach; Coghill et al.	2003	fMRI 1.5	7.5	17	Heat	Thermal	Cutaneous	Right	Leg	7.43	
Craig	1996	PET	18	11	Cold and heat	Thermal	Cutaneous	Right	Hand	NR	
DaSilva et al.	2002	fMRI 1.5	6	9	Heat	Thermal	Cutaneous	Right	Face and thumb	6.1	
Davis and Pope	2002	fMRI 1.5	6	0	Cold	Thermal/mechanical	Cutaneous	Right	Thernar eminence	NR	
Derbyshire et al.	1997	PET	10	12	Laser	Thermal	Cutaneous	Right	Hand	7	
Derbyshire and Jones; Derbyshire et al.	1998	PET	8	12	Heat	Thermal	Cutaneous	Right	Hand	5.85	
Derbyshire et al.	2002a,b	PET	12	21	Laser	Thermal	Cutaneous	Right	Hand	6.6	
Derbyshire et al.	2002a,b	PET	10	16	Heat	Thermal	Cutaneous	Right	Hand	6	
Derbyshire	2004	fMRI 3.0	10	8	Heat	Thermal	Cutaneous	Right	Hand	5.6	
Frankenstein et al.	2001	fMRI 1.5	8	12	Cold	Thermal	Cutaneous	Right	Foot	5.8	
Gelnar et al.	1999	fMRI 1.5	5	9	Heat	Thermal	Cutaneous	Right	Finger	3.4	
Helmchen et al.	2003	fMRI 1.5	5	18	Heat	Thermal	Cutaneous	Right	Hand	6.3	
Helmchen et al.	2006	fMRI 1.5	5	18	Heat	Thermal	Cutaneous	Right	Hand	6.3	Data are shared with Helmchen et al., 2003
Kong et al.	2006	fMRI 3.0	8	16	Heat	Thermal	Cutaneous	Right	Forearm	7.4	
Koyama et al.	2003	fMRI 1.5	5	9	Heat	Thermal	Cutaneous	Right	Leg	6.8	
Koyama et al.	2005	fMRI 1.5	5	10	Heat	Thermal	Cutaneous	Right	Leg	3.8	
Kurata et al.	2002	fMRI 3.0	0.5	5	Heat	Thermal	Cutaneous	Left	Forearm	7	
Kurata et al.	2005	fMRI 3.0	4	6	Heat	Thermal	Cutaneous	Right	Forearm	6.8	
Maihofner et al.	2006	fMRI 1.5	4	14	Heat	Thermal	Cutaneous	Right	Forearm	4.3	
Mohr et al.	2005	fMRI 1.5	5	16	Heat	Thermal	Cutaneous	Right	Hand	6.3	Data are shared with Helmchen et al., 2003
Mohr et al.	2008	fMRI 1.5	8	17	Heat	Thermal	Cutaneous	Right	Thigh	5.1	
Nemoto et al.	2003	PET	16	12	Laser	Thermal	Cutaneous	Right	Forearm	7.6	
Ochsner et al.	2006	fMRI 3.0	6	13	Heat	Thermal	Cutaneous	Right	Forearm	7	
Qiu et al.	2006	fMRI 3.0	8	13	Laser	Thermal	Cutaneous	Right	Hand	NR	
Sawamoto et al.	2000	fMRI 1.5	5.16	10	Laser	Thermal	Cutaneous	Right	Hand	9.2	

TABLE VII. (Continued)

Author	Year	Imaging	FWHM	Subject (*N*)	Stimuli						
					Type	Modality	System	Side	Body Part	NRS	Notes
Seifert and Maihofner	2007	fMRI 1.5	4	12	Cold	Thermal	Cutaneous	Right	Forearm	4.08	
Sprenger et al.	2006	PET	6	8	Heat	Thermal	Cutaneous	Right	Forearm	7.4	
Staud et al.	2007	fMRI 3.0	4	11	Heat	Thermal	Cutaneous	Right	Foot	4.5	
Svensson et al.	1998	PET	12	10	Heat	Thermal	Cutaneous	Right	Forearm	8	
Talbot et al.	1991	PET	7	8	Heat	Thermal	Cutaneous	Right	Forearm	8	
Tolle	1999	PET	8	12	Heat	Thermal	Cutaneous	Right	Forearm	5.7	
Wagner et al.	2007	PET	12	7	Heat	Thermal	Cutaneous	Right	Forearm	6.8	

Study 4 (noxious stimuli applied to the right side of the body): List of studies reporting brain activation coordinates evoked by noxious stimuli applied to the right side of the body. Abbreviations: fMRI, functional magnetic resonance imaging; PET, positron emission tomography; NR, not reported; NRS, Numerical rating scale.

Quantitative Analyses

Probabilistic maps of activation evoked by all noxious stimuli (Study 1), noxious cold and heat stimuli (Study 2), noxious stimuli in comparison to a resting baseline or innocuous warm stimuli (Study 3), noxious stimuli applied to the left and right sides of the body (Study 4), and noxious stimuli applied to muscle and skin (Study 5), were generated using the ALE analytic strategy as described by Laird et al. [2005]. Briefly, the ALE statistic is calculated for each voxel in the template MRI signifying the probability of evoking activation in response to noxious stimuli. Reported coordinates were recorded in their original space and then transformed into Talairach space [Talairach and Tournoux, 1988] using a conversion provided in the GingerALE (v.1.0) software [Lancaster et al., 2007]. The ALE maps were created by smoothing the activation foci using a full-width half maximum (FWHM) of 8 mm, which was the average size of the Gaussian smoothing filter among the studies included in the Study 1 database. This latter step ensures that the data are a realistic reflection of the peak activation sites as all data included in the analysis were smoothed by an average Gaussian smoothing filter of this size. The statistical significance of the ALE maps was determined by performing a permutation test ($N = 5{,}000$) and the data were thresholded using a false discovery rate (FDR) correction of $q = 0.05$ [Genovese et al., 2002]. The ALE method calculates the likelihood that one peak (out of the total number of peaks) actually occurred within a given voxel in the template MRI and tests this against the null hypothesis that the points are randomly distributed across the brain. The resulting ALE values indicate that the likelihood that any single peak of the total peaks actually occurred in a single voxel located in the template MRI. These ALE values range from ~ 0.003 to a theoretical maximum of 1.0.

Subtraction Analyses

To test for brain regions preferentially associated with the processing of noxious cold or heat stimuli (Study 2), noxious heat compared to innocuous warm or a resting baseline (Study 3), right or left sided noxious stimuli (Study 4), and muscle or cutaneous pain (Study 5), we performed a voxel-by-voxel subtraction of the two ALE maps included in each of the four meta-analyses.

The analysis involved the subtraction of the ALE values in condition 2 from the ALE values in condition 1 at each voxel (Step 1). Two sets of random peak coordinates are then generated using the same number of peaks observed in conditions 2 and 1 and the random ALE maps undergo a pair-wise subtraction (Step 2). Subsequently, this method of random peak generation and subtraction is repeated 5,000 times (Step 3). This process results in a single statistical map representing a null distribution of activation peaks (Step 4). At each voxel, the observed ALE statistic in the original subtraction map (Step 1) is compared to the

TABLE VIII. List of studies included in study 5 (noxious muscle stimuli)

Author	Year	Imaging	Subject (*N*)	Stimuli			Side	Body Part	NRS	Notes
				Type	Modality	System				
Henderson et al.	2007	fMRI 3	23	Hypertonic Saline Injection	Mechanical	Intramuscular	Right	Leg	6.5	
Henderson et al.	2007	fMRI 3	23	Hypertonic Saline Injection	Mechanical	Intramuscular	Right	Forearm	7	Data are shared with Henderson et al., 2007
Korotkov et al.	2002	PET	16	Hypertonic Saline Injection	Mechanical	Intramuscular	Left	Tricep	3.2	
Kupers et al.	2004	PET	10	Hypertonic Saline Injection	Mechanical	Intramuscular	Right	Masseter muscle	7.5	
Nash et al.	2010	fMRI 3	28	Hypertonic saline injection	Mechanical	Muscular	Right	Masseter muscle	4.73	
Niddam et al.	2002	fMRI 3	10	Electrical Shock	Electrical	Intramuscular	Left	Hand	2.22	
Owen et al.	2010	fMRI 3	13	Hypertonic saline injection	Mechanical	Muscular	Left	Forearm	6	
Schreckenberger et al.	2005	PET	10	Infusion of phosphate buffer	Mechanical	Intramuscular	Left	Hand	4	
Svensson et al.	1997	PET	10	Electrical Shock	Electrical	Intramuscular	Left	Forearm	7.5	
Thunberg et al.	2005	PET	19	Hypertonic Saline Injection	Mechanical	Intramuscular	Right	Erector spinae muscle	4.6	
Uematsu et al.	2011	fMRI 1.5	17	Pressure	Mechanical	Muscular	Right	Calf	4.7	

Study 5 (Noxious muscle stimuli): List of studies reporting brain activation coordinates in response to noxious stimuli applied to muscles. Abbreviations: fMRI, functional magnetic resonance imaging; PET, positron emission tomography; NRS, Numerical rating scale.

random ALE statistic subtraction map (Step 4) and a P value is generated to denote the statistical significance of the test. The ALE map is then thresholded at $P < 0.05$ using the FDR method.

RESULTS

Study 1: All Noxious Stimuli

An ALE analysis was performed on 2,873 coordinate points associated with activation in response to all noxious stimuli. The greatest likelihood of evoking activation in the cortex in response to all types of noxious stimuli was in the right anterior insula (ALE = 0.238) and ACC (BA 24, ALE = 0.245; Fig. 1). The resulting ALE values reflect the likelihood of activation in a single voxel, which is a very small region of gray matter within the insula and ACC. The likelihood of activation occurring in the full brain regions is of course much larger. Note that these ALE values are large compared with the likelihood (0.003) of the highest value in the background noise being interpreted as an activated voxel during the permutation testing.

Additional cortical regions with significant likelihoods of activation were observed in left insula (ALE = 0.219), bilateral SII (right: ALE = 0.186; left: ALE = 0.182), the prefrontal cortex (right BA 44, ALE = 0.144; left BA 10, ALE = 0.099), and SI/PPC (right: ALE = 0.064; left: ALE = 0.07). A complete list of brain regions with significant likelihoods of being activated is detailed in Table X.

Study 2: Noxious Cold Versus Noxious Heat

An ALE analysis was performed on 112 coordinate sites compiled from the nine studies that used noxious cold stimuli applied to the upper limbs. For the noxious cold stimuli meta-analysis, the likelihood of activation was significant in several brain regions involved in affective pain processing such as bilateral insula/claustrum (right: ALE = 0.03; left: ALE = 0.028), right subgenual ACC (ALE = 0.023) and the amygdala (ALE = 0.012; Table XI).

For the comparative noxious heat meta-analysis, the ALE analysis was conducted on 122 coordinates that were published in the nine selected studies. Areas with the most significant likelihood of activation associated with noxious heat stimulation were observed in bilateral insula/claustrum (right: ALE = 0.033; left: ALE = 0.025), the left ACC (ALE = 0.024), the right thalamus [ALE = 0.029, and SII (ALE = 0.021; Table XII)].

TABLE IX. List of studies included in study 5 (Noxious cutaneous stimuli)

				Stimuli					
Author	Year	Imaging	Subject (*N*)	Type	Modality	System	Side	Body Part	NRS
Koyama et al.	2005	fMRI 1.5	10	Heat	Thermal	Cutaneous	Right	Leg	3.7
Raij et al.	2005	fMRI 3	14	Laser	Thermal	Cutaneous	Left	Hand	6.2
DaSilva et al.	2002	fMRI 1.5	9	Heat	Thermal	Cutaneous	Right	Mandibular (V3)	6
Brooks et al.	2005	fMRI 3	14	Heat	Thermal	Cutaneous	Right	Face	5.5
Symonds et al.	2006	fMRI 3	9	Electrical shock	Electrical	Transcutaneous	Left	Index finger	4.5
Maihofner et al.	2004	fMRI 1.5	11	Heat	Thermal	Cutaneous	Left	Forearm	3.9
Fairhurst et al.	2007	fMRI 3	12	Heat	Thermal	Cutaneous	Left	Hand	5.71
Seminowicz et al.	2004	fMRI 1.5	16	Electrical shock	Electrical	Transcutaneous	Left	Median nerve	5.5
Dunckley et al.	2005	fMRI 3	10	Heat	Thermal	Cutaneous	Bilateral	Back	5.8
Lorenz et al.	2008	fMRI 1.5	11	Pressure	Mechanical	Cutaneous	Right	Tibia	4.6

Study 5 (Noxious cutaneous stimuli): List of studies reporting brain activation coordinates in response to noxious stimuli applied to the skin for purposes of comparison with noxious stimuli applied to muscles. Abbreviations: fMRI, functional magnetic resonance imaging; PET, positron emission tomography; NRS, Numerical rating scale.

Both types of stimuli were found to significantly activate the ACC [Brodmann Area (BA) 24], and insula (Supporting Information Fig. 1). Statistical subtractions of the noxious cold and noxious heat maps revealed that the likelihood of noxious cold-related activation was significantly greater in the amygdala and the subgenual ACC (BA 25/47; Table XIII) while the likelihood of noxious heat-related activation was significantly greater in bilateral SII (Table XIV).

Study 3: Noxious Heat Minus Warm Versus Noxious Heat Minus Resting Baseline

An initial ALE analysis was conducted on 131 coordinate sites compiled from the nine studies that used a warm-stimulus control in comparison to noxious heat stimulation. Results of this ALE analysis yielded 31 regions with a significant likelihood (ranging from 0.013 to 0.048) of showing "pain-related" brain activation. The greatest likelihood that activation will be evoked in the cortex in response to noxious heat stimuli in comparison to warm was in the anterior and posterior cingulate gyrus (BA 24, ALE = 0.048 and BA 23, ALE = 0.029), the insula (ALE = 0.028), followed by SI and SII (both ALEs = 0.014; Table XV). Additionally, the likelihood of evoking activation in response to noxious heat stimuli was significant within the cerebellum, thalamus, and basal ganglia.

The nine studies that used a resting baseline in comparison to noxious heat stimulation had a total of 149 coordinate sites that were then subjected to an ALE analysis. As expected, the noxious heat versus baseline condition yielded a substantially greater number of activation loci than had been observed in the more restrictive comparison of noxious heat to warm stimulation (40 vs. 31 regions). Brain regions of interest that had a significant likelihood of exhibiting stimulus-related activation in comparison to a resting baseline were observed throughout the cortex and included the ACC (BA32, 0.042), the inferior frontal gyrus (BA 44, 0.026), the insula (0.024), SI (0.019), and SII (left and right: 0.014), and the superior frontal gyrus BA 6, 0.021); see Table XVI for a complete list.

The two sets of peak ALE values (noxious heat vs. warm and noxious heat vs. resting baseline) were examined for common brain regions demonstrating a significant likelihood of being activated using either type of contrast. It was evident that for both types of contrasts, the likelihood of activation was significant within the ACC (BA 24), supplementary motor area (SMA), insula, SII, and thalamus (Supporting Information Fig. 2).

We performed a direct subtraction of the two maps to assess significant differences in the patterns of activation that resulted from the two analysis strategies. Studies using a no-stimulation baseline control as a comparison for noxious heat stimuli were more likely to reveal stimulus-related activation in the anterior portion of the ACC (BA 32; ALE = 0.039; Table XVII), and SI/PPC (ALE = 0.019); while those using a warm-control condition as a comparison were significantly more likely to observe noxious-heat-related activation in the middle regions of the ACC (BA 24; ALE = 0.048), and the posterior cingulate cortex (ALE = 0.029; Table XVIII).

Study 4: Left- Versus Right-Sided Stimuli

ALE maps of noxious stimuli applied to the left side of the body were created using the 694 coordinates extracted from the publications included in the left-sided meta-analysis. According to predictions, analysis of studies using left-sided stimulation showed a substantially larger number of sites with significant activation-likelihood values in the contralateral right hemisphere, compared to those observed in the left hemisphere (31 vs. 18). The most statistically significant ALE sites were located in the right insula (ALE = 0.11) and right ACC (ALE = 0.095). Significant ALE values were

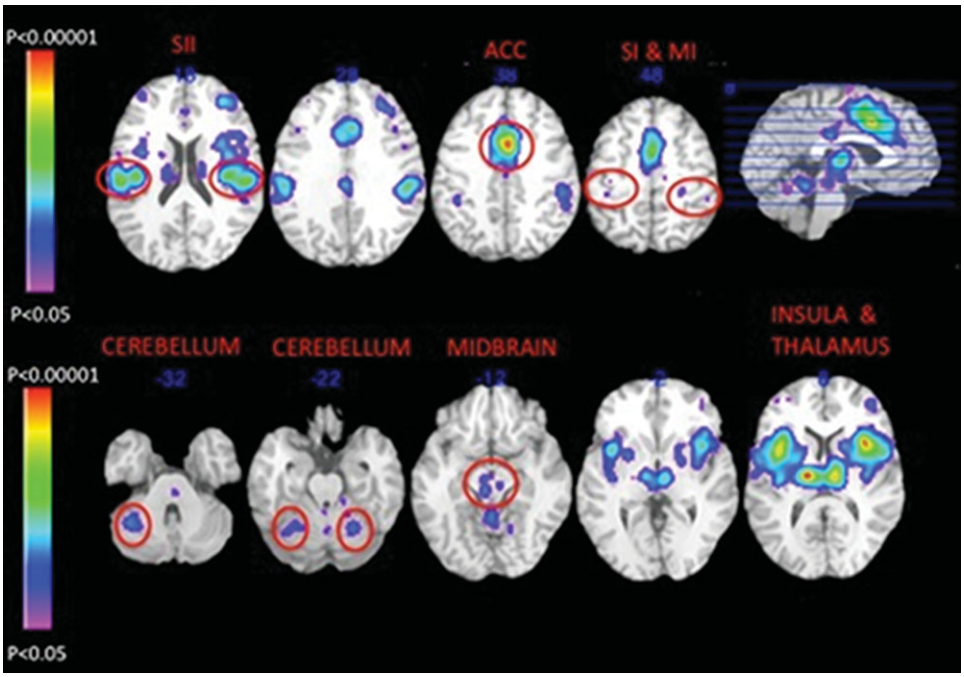

Figure 1.

Study 1: ALE map describing the likelihood of evoking activation in the brain in response to noxious stimuli applied to the skin, muscle, or viscera. Brain regions having a significant likelihood of being activated by noxious stimuli included the secondary somatosensory cortex (SII), the anterior cingulate cortex (ACC), the primary somatosensory and motor (SI/MI) cortices, the cerebellum, the midbrain, and the insula (anterior, middle, and dorsal posterior regions), and the thalamus. The z-values for the horizontal images are in Talairach space [Talairach and Tournoux 1988].

also found in bilateral thalamus (right: ALE = 0.089; left: ALE = 0.082). Other brain regions that also had a significant likelihood of being activated are listed in Table XIX.

The ALE analysis for right-sided stimuli was calculated on 699 coordinates taken from the studies. Surprisingly, the number of statistically significant activation sites was equivalent in both hemispheres (24 vs. 24), rather than being concentrated in the left hemisphere, as suggested by the traditional view of preferential cutaneous processing through the contralateral sensory pathways. The highest likelihood of evoking activation in response to noxious stimuli applied to the right side of the body was found in right anterior insula (ALE = 0.11). Other regions showing high likelihood values were the left insula (ALE = 0.1), bilateral SII (right = 0.084; left = 0.091), left thalamus (ALE = 0.082), and the right ACC (BA 24, ALE = 0.081). These results provide strong support for a right hemispheric dominance for pain processing. A complete list of the ALE values for right-sided noxious stimulation is in Table XX.

When directly comparing noxious stimuli applied to the right or left side of the body, the greatest likelihood of evoking activation in the cortex in response to noxious stimuli presented to either side of the body was in the right anterior insula. Additionally, in both meta-analyses large clusters of likelihood estimate values were significant within the right ACC (Supporting Information Fig. 3).

Upon performing the subtractions, (left-sided stimuli minus right-sided stimuli) the results showed preferential likelihood values that were significant within contralateral (right) SI, MI, PPC, and the superior frontal gyrus, and the ipsilateral (left) midbrain (Table XXI). The likelihood of activation evoked by right-sided stimuli was significant (exclusively) within contralateral (left) SI, ACC (BA32), MI, inferior parietal lobule, and the medial frontal gyrus. However, some regions in the right hemisphere were also found to have distinctive activation likelihood values in response to right-sided stimuli such as ACC (BA 32), the inferior parietal lobule, and the middle frontal gyrus (Table XXII).

Study 5: Noxious Muscle Versus Cutaneous Stimuli

An ALE analysis was applied to the 172 activation foci reported for the 10 studies that applied noxious stimuli to muscles. Some brain regions demonstrating significant ALE

TABLE X. Spatial location and extent of ALE values for study 1 (all noxious stimuli)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Left	Thalamus		−14	−16	8	0.272	<0.000001	1	96168
Right	Anterior insula		36	12	8	0.238	<0.000001		
Right	Thalamus		10	−18	6	0.227	<0.000001		
Left	Anterior insula		−36	4	6	0.219	<0.000001		
Left	Posterior insula		−40	−20	16	0.191	<0.000001		
Right	SII	40	52	−26	22	0.186	<0.000001		
Left	SII	40	−52	−24	20	0.182	<0.000001		
Right	Anterior insula		36	−20	16	0.175	<0.000001		
Right	Inferior frontal gyrus	44	50	2	10	0.144	<0.000001		
Left	Putamen		−24	−2	6	0.097	<0.000001		
Right	Putamen		20	8	4	0.085	<0.000001		
Left	Inferior frontal gyrus	6	−54	−2	8	0.081	<0.000001		
Left	Inferior frontal gyrus	43	−54	−6	12	0.079	<0.000001		
Left	Posterior insula		−38	−18	−4	0.072	<0.000001		
Right	IPL	40	46	−38	42	0.072	<0.000001		
Left	Lentiform nucleus		−24	0	−2	0.068	<0.000001		
Left	IPL	40	−58	−38	28	0.064	<0.000001		
Right	Lentiform nucleus		20	−4	0	0.064	<0.000001		
Right	IPL	40	52	−44	38	0.059	<0.000001		
Right	IPL	40	46	−54	44	0.046	0.0008		
Right	Cingulate gyrus	32/24	2	8	38	0.245	<0.000001	2	2420
Right	Cingulate gyrus	32	6	22	28	0.127	<0.000001		
Left	Anterior cingulate gyrus	32	−2	32	22	0.057	<0.000001		
Right	Medial frontal gyrus	6	2	−10	64	0.047	0.0004		
Right	Middle frontal gyrus	10	34	42	20	0.099	<0.000001	3	5872
Right	Superior frontal gyrus	9	28	40	30	0.079	<0.000001		
Right	Middle frontal gyrus	10	42	46	12	0.078	<0.000001		
Right	Middle frontal gyrus	47	38	38	−6	0.046	0.0006		
Left	Cerebellum		−34	−56	−32	0.071	<0.000001	4	3224
Left	Cerebellum		−30	−58	−30	0.071	<0.000001		
Left	Cerebellum		−22	−60	−24	0.056	<0.000001		
Right	Cerebellum		0	−48	−16	0.085	<0.000001	5	2384
Right	Cerebellum		4	−62	−16	0.063	<0.000001		
Right	Cerebellum		24	−60	−22	0.067	<0.000001	6	2024
Right	Cerebellum		18	−62	−14	0.054	<0.000001		
Right	Cerebellum		18	−48	−22	0.047	<0.000001		
Left	Cingulate gyrus	23	0	−28	28	0.082	<0.000001	7	1440
Left	Cingulate gyrus	24	0	−20	36	0.051	<0.000001		
Left	SI	2	−32	−36	60	0.065	<0.000001	8	1432
Left	MI	4	−32	−24	52	0.060	<0.000001		
Left	MI	4	−38	−26	62	0.057	<0.000001		
Right	MI	4	32	−28	56	0.073	<0.000001	9	1176
Left	IPL	40	−40	−40	40	0.066	<0.000001	10	816
Right	SI/PPC	5	20	−44	64	0.064	<0.000001	11	560
Left	Superior frontal gyrus	10	−34	48	18	0.052	0.0002	12	496
Left	Middle frontal gyrus	9	−32	38	26	0.043	0.0001		
Right	MI	6	26	−16	52	0.055	0.0002	14	264
Right	Inferior frontal gyrus	9	48	6	26	0.045	0.0001	15	104

ALE values for Study 1. ALE values refer to the likelihood of obtaining activation evoked by noxious stimuli in a given voxel of the standard template MRI. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster : The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; IPL, inferior parietal lobule; SI, primary somatosensory cortex; PPC, posterior parietal cortex; SII, secondary somatosensory cortex; MI, primary motor cortex.

values included the anterior insula (ALE = 0.037), thalamus ($P = 0.04$), and the anterior (BA 24:ALE = 0.025 and 32:ALE = 0.023) and posterior cingulate (ALE = 0.021; Table XXIII).

A comparable number of studies were included in a comparative meta-analysis that used 133 activation foci obtained from studies that had applied noxious stimuli to

TABLE XI. Spatial location and extent of ALE values for study 2 (noxious cold)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Right	Anterior insula/Claustrum		28	6	12	0.030	<0.00001	1	1656
Right	Anterior insula		40	8	0	0.013	0.0006		
Left	Anterior insula		−38	6	4	0.028	0.0002	2	1520
Left	Claustrum		−36	−8	4	0.013	0.001		
Left	Anterior insula		−38	4	14	0.013	0.0006		
Left	Cingulate gyrus	32	−10	6	40	0.021	<0.00001	3	1496
Right	Cingulate gyrus	24	2	2	36	0.019	<0.00001		
Left	Cingulate gyrus	32	0	10	38	0.017	0.0002		
Left	Thalamus		0	−20	6	0.023	<0.00001	4	1232
Right	Thalamus		6	−22	14	0.014	<0.00001		
Right	Thalamus		16	−22	12	0.014	0.001		
Right	Thalamus		4	−12	12	0.013	0.001		
Left	Claustrum		−30	10	14	0.015	0.0002	5	712
Left	Claustrum		−30	12	10	0.014	0.0006		
Left	Putamen		−26	6	12	0.014	0.0002		
Left	Putamen		−18	4	8	0.014	0.0002		
Left	Caudate		−12	8	10	0.013	0.001		
Right	Cingulate gyrus	24	12	14	30	0.023	<0.00001	6	656
Right	Thalamus		12	−4	8	0.021	<0.00001	7	552
Right	Middle frontal gyrus	10	42	46	12	0.020	<0.00001	8	544
Left	SI/PPC	43	−54	−6	14	0.019	<0.00001	9	520
Right	Subgenual ACC	47/25	18	18	−10	0.023	<0.00001	10	496
Right	Medial frontal gyrus	25	10	16	−14	0.013	0.0004		
Right	Claustrum		38	−14	8	0.020	<0.00001	11	400
Left	Putamen		−22	12	−8	0.024	<0.00001	12	384
Right	Claustrum		36	−4	0	0.020	<0.00001	13	352
Right	MI	4	32	−26	56	0.017	<0.00001	14	328
Right	SII		46	−24	16	0.016	<0.00001	15	256
Left	SII		−40	−46	46	0.016	0.0006	16	248
Right	Midbrain		8	−20	−2	0.014	0.005	17	240
Left	Medial frontal gyrus	6	−4	−10	56	0.014	0.001	18	240
Right	Inferior frontal gyrus	9	50	4	24	0.014	<0.00001	19	232
Right	Inferior frontal gyrus	9	52	10	26	0.014	<0.00001		
Left	Superior frontal gyrus	10	−26	44	18	0.013	0.0006	20	184
Left	Middle frontal gyrus	10	−30	38	14	0.013	0.001		
Right	Posterior insula		50	−40	18	0.014	0.001	21	152
Right	Posterior insula		44	−36	20	0.013	0.0006		
Right	Cerebellum		2	−58	−20	0.013	0.001	22	72
Right	Middle frontal gyrus	9	38	28	32	0.012	<0.00001	23	72
Right	Middle frontal gyrus	9	38	28	34	0.012	<0.00001		
Right	Lingual gyrus	19	30	−68	−2	0.011	0.002	24	64
Right	Superior frontal gyrus	10	28	54	4	0.012	0.001	25	64
Right	Premotor	6	50	−2	10	0.011	0.004	26	64
Right	Posterior insula		36	−16	20	0.012	0.001	27	64
Right	Paracentral lobule	31	6	−10	46	0.013	0.001	28	64
Left	Cingulate gyrus	24	0	0	46	0.013	0.0006	29	64
Right	MI	4	24	−22	50	0.013	0.0008	30	64
Right	Cerebellum		26	−64	−22	0.013	0.0008	31	56
Right	Thalamus		12	−30	6	0.013	0.0004	32	56
Right	Anterior insula		38	18	8	0.013	0.0004	33	56
Left	Thalamus		−10	−16	8	0.012	0.003	34	56
Right	Posterior insula		46	−12	12	0.013	0.001	35	56
Left	Cingulate gyrus	32	−10	18	26	0.013	0.0004	36	56
Right	Cingulate gyrus	24	6	−10	32	0.013	0.0002	37	56
Right	SI	3	44	−24	52	0.013	0.0004	38	56
Left	Fusiform gyrus	19	−22	−66	−6	0.013	0.001	39	48
Right	Superior frontal gyrus	6	12	−6	64	0.013	0.0002	40	48

TABLE XI. (Continued)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Left	Midbrain		−4	−18	−10	0.013	0.0008	41	40
Left	Putamen		−20	16	2	0.012	0.002	42	40
Left	Cerebellum		−36	−56	−32	0.012	0.002	43	32
Right	Parahippocampal gyrus	35	22	−8	−22	0.012	0.002	44	32
Right	Amygdala		24	−8	−22	0.012	0.002		
Right	Amygdala		22	−8	−20	0.012	0.002		
Right	Amygdala		24	−8	−20	0.012	0.002		

ALE values for Study 2 (noxious cold). ALE values refer to the likelihood of obtaining activation evoked by noxious cold stimuli in a given voxel of the standard template. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; IPL, inferior parietal lobule; SI, primary somatosensory cortex; PPC, posterior parietal cortex; SII, secondary somatosensory cortex; MI, primary motor cortex.

the skin. Significant ALE values were found in SII (ALE = 0.035), thalamus (ALE = 0.027), mid-insula (ALE = 0.032), and the ACC (BA 42:ALE = 0.027; Table XXIV).

Upon examination of the ALE values for each meta-analysis, both types of stimuli were found to significantly activate SII, ACC, dorsal posterior insula, and the thalamus (Supporting Information Fig. 4).

Subsequent subtraction analyses (noxious muscle stimuli minus noxious cutaneous stimuli) revealed a significant likelihood of spatially specific activation in response to noxious muscle stimuli in the precuneus (ALE = 0.021; Table XXV), the posterior cingulate (BA 32; ALE = 0.021), the dorsolateral prefrontal cortex (DLPFC BA 9; ALE = 0.017), and the cerebellum (ALE = 0.019). The reverse subtraction (noxious cutaneous stimuli—noxious muscle stimuli) showed a preferential likelihood of activation in SI (ALE = 0.022) and the ventrolateral prefrontal cortex (VLPFC BA 47; ALE = 0.016; Table XXVI).

DISCUSSION

Study 1: Meta-Analysis of Activation Evoked by All Types of Noxious Stimuli

We explored common brain regions activated by noxious stimuli by performing a meta-analysis on the activation sites reported by 140 fMRI and PET studies published between 1991–2011. In contrast to previous reviews, our approach provides a quantitative assessment of activation in the brain in response to noxious stimuli through the creation of likelihood estimate maps, which permit precise localization of cortical regions involved in processing pain. The maps can be particularly useful for targeting subregions of a brain area such as SII, which has no anatomically distinct boundaries to delineate the extent and location of where to predict activation evoked by noxious stimuli.

Our results are consistent with previous qualitative reviews of the literature that have described a "pain network" comprised of SI, SII, ACC, insula, prefrontal cortex, and the thalamus [Apkarian et al., 2005; Iadarola and Coghill, 1999; Peyron et al., 1999]. The results are somewhat consistent with one of these previous reviews [Apkarian et al., 2005] that found the insula to be the most commonly reported activation site evoked by noxious stimuli. However, our quantitative results expand upon these previous reviews by providing the precise spatial location and extent of the likelihood of activation in response to noxious stimuli, thus providing more detailed and accurate information that is based on previous data. Using this data driven method, the left thalamus, the right ACC, bilateral anterior insulae, and left dorsal posterior insula had the highest likelihood of activation in response to noxious stimuli, providing a new quantitative 3D matrix in which to predict pain-evoked activation. In addition, although largely confirming findings from qualitative reviews, the results of this study point to the inclusion of the posterior cingulate cortex and the basal ganglia as key brain regions involved in processing nociception.

An important finding was that in the cortex, the right ACC (BA 32/24) had the highest likelihood of being activated in response to noxious stimuli. The ACC has been implicated in processing the emotional salience or unpleasantness of painful stimuli as suggested by research in animals and humans. This region receives nociceptive input from dorsal horn neurons via the medial-dorsal (MD) and intralaminar thalamic nuclei [Giguere and Goldman-Rakic 1988; Goldman-Rakic and Porrino 1985; Krettek and Price 1977; Wang and Shyu 2004]. Cingulotomy for alleviation of chronic pain reduces affective responses with no concomitant disruption of the ability to appreciate somatosensory aspects of painful stimuli [Ballantine et al. 1967; Foltz and White 1962]. Additionally, a number of functional neuroimaging studies have also implicated the ACC in processing affective aspects of pain [Kulkarni et al., 2005; Rainville et al., 1997]. For example, hypnotic modulation of pain unpleasantness was correlated with ACC activation, with no concurrent changes in regions involved in sensory-discriminative processing [Rainville et al., 1997].

TABLE XII. Spatial location and extent of ALE values for study 2 (noxious heat)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Left	Anterior insula		−40	18	6	0.025	<0.00001	1	4432
Left	Posterior insula		−44	−24	16	0.024	<0.00001		
Left	Lentiform Nucleus		−22	0	−2	0.024	<0.00001		
Left	Lentiform Nucleus		−22	−10	8	0.018	0.0004		
Left	Mid-insula/claustrum		−34	4	6	0.017	0.0002		
Left	Anterior insula/claustrum		−34	10	6	0.017	0.0002		
Left	Anterior insula		−30	18	8	0.017	0.0004		
Left	Lentiform Nucleus		−24	−4	6	0.016	<0.00001		
Left	Posterior insula/claustrum		−34	−16	10	0.014	0.0006		
Right	Mid-insula/claustrum		34	4	10	0.033	<0.00001	2	2432
Right	Anterior insula/claustrum		34	12	6	0.030	<0.00001		
Right	Thalamus		12	−20	4	0.029	<0.00001	3	1544
Right	Thalamus		10	−10	6	0.013	0.001		
Left	Cingulate Gyrus	32	−4	10	40	0.024	0.0002	4	1288
Left	Cingulate Gyrus	24	−4	12	32	0.016	0.0002		
Right	SII	40	52	−30	22	0.021	0.0002	5	1160
Right	Posterior insula	40	52	−22	14	0.014	0.0006		
Right	Lentiform Nucleus		30	−14	8	0.018	<0.00001	6	688
Right	Posterior insula		32	−10	18	0.018	0.0002		
Right	Cingulate Gyrus	24	2	−4	44	0.020	<0.00001	7	576
Left	Thalamus		−12	−24	12	0.022	<0.00001	8	552
Right	Inferior Frontal Gyrus		38	46	2	0.021	<0.00001	9	464
Right	Caudate		16	8	12	0.021	<0.00001	10	368
Left	MI	4	−32	−22	50	0.020	<0.00001	11	304
Right	Cingulate Gyrus	32	4	22	26	0.018	<0.00001	12	256
Left	Anterior insula		−46	6	16	0.013	0.0006	13	168
Left	Inferior Frontal Gyrus	44	−48	0	12	0.013	0.0008		
Right	Middle Frontal Gyrus	46	42	36	24	0.014	<0.00001	14	152
Right	Superior Frontal Gyrus	9	40	34	28	0.013	0.0004		
Right	Anterior insula		46	6	16	0.014	0.0002	15	144
Right	Inferior Frontal Gyrus	44	52	6	12	0.014	0.0006		
Left	Posterior insula		−40	−4	10	0.013	0.0006	16	80
Left	Superior Temporal Gyrus	42	−54	−30	14	0.013	0.001	17	80
Right	Thalamus		6	−18	14	0.013	0.0008	18	72
Left	Posterior insula		−52	−34	20	0.013	0.0006	19	64
Left	Cingulate Gyrus	24	−10	4	30	0.013	0.001	20	64
Right	Lentiform Nucleus		24	4	16	0.014	0.0006	21	56
Right	IPL	39	48	−62	38	0.013	0.0008	22	56
Left	Medial Frontal Gyrus	6	0	−10	52	0.013	0.0008	23	56
Right	Lentiform Nucleus		22	−4	12	0.012	0.001	24	48
Right	Posterior insula		36	−18	20	0.012	0.001	25	48
Left	Superior Frontal Gyrus	6	−4	8	60	0.013	0.0008	26	48
Right	Medial Frontal Gyrus	6	2	−12	62	0.011	0.003	27	48
Right	Cerebellum		30	−76	−28	0.013	0.001	28	40
Right	Cerebellum		8	−60	−12	0.012	0.001	29	40
Right	Precentral Gyrus	6	50	−4	38	0.012	0.001	30	40
Right	SI		20	−36	52	0.013	0.001	31	40
Right	Middle Frontal Gyrus	6	18	−10	58	0.013	0.001	32	40
Left	Cerebellum		−28	−40	−42	0.012	0.001	33	32
Right	Cerebellum		18	−72	−30	0.012	0.001	34	32
Left	Cerebellum		−20	−60	−20	0.013	0.001	35	32
Right	Cerebellum		0	−52	−16	0.012	0.001	36	32
Right	Inferior Frontal Gyrus	47	42	20	−4	0.013	0.001	37	32
Right	Posterior insula/claustrum		36	−6	0	0.013	0.001	38	32
Right	Lentiform Nucleus		20	10	0	0.012	0.001	39	32
Right	SII	42	56	−12	12	0.013	0.001	40	32
Left	Posterior insula		−48	−20	24	0.012	0.001	41	32

TABLE XII. (Continued)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Left	IPL	40	−62	−40	28	0.012	0.001	42	32
Right	Cingulate Gyrus	23	4	−22	28	0.012	0.001	43	32
Right	Medial Frontal Gyrus	8	14	30	38	0.012	0.001	44	32
Left	Paracentral Lobule	5	−10	−34	46	0.012	0.001	45	32

ALE values for Study 2 (noxious heat). ALE values refer to the likelihood of obtaining activation evoked by noxious heat stimuli in a given voxel of the standard template. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann's Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; SI, primary somatosensory cortex; IPL, inferior parietal lobule; SII, secondary somatosensory cortex; MI, primary motor cortex.

However, the ACC may also subserve some sensory-discriminative aspects of pain processing. Electrophysiological studies, in both humans and animals, have reported neuronal firing frequencies in the ACC that were correlated with stimulus intensity [Hutchison et al., 1999; Yamamura et al. 1996]. Additionally, a crude somatotopic organization of nociceptive stimuli has been reported in this region, thus implicating the ACC in stimulus localization [Arienzo et al., 2006]. An important note is that these findings have been questioned as several electrophysiological studies have reported that the ACC contains large, bilateral receptive fields [Hutchison et al., 1999; Kuo and Yen, 2005; Sikes and Vogt 1992]. Based on these previous findings, the significant likelihood of evoking activation in the ACC in response to noxious stimuli may reflect both the processing of the affective component of pain and potentially the localization of stimuli applied to the body.

Bilateral anterior insulae and the left dorsal posterior insula were other cortical regions that had a significant likelihood of being activated by noxious stimuli. The insula is a complex, multisensory integration area that is involved in processing many aspects involved with the conscious experience of pain such as affect [Berthier et al., 1988; Schon et al., 2008], autonomic activity [Cameron and

TABLE XIII. Spatial location and extent of ALE values for study 2 (noxious cold minus noxious heat)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Right	Cingulate Gyrus	24	12	14	30	0.023	<0.00001	1	408
Left	Anterior insula		−40	6	2	0.023	<0.00001	2	384
Right	Lentiform Nucleus		26	6	12	0.022	<0.00001	3	360
Right	Middle Frontal Gyrus	10	42	46	12	0.020	0.0002	4	360
Right	Subgenual ACC	25/47	18	18	−10	0.023	<0.00001	5	344
Left	SII	43	−54	−6	14	0.018	0.0002	6	296
Right	Thalamus		12	−4	8	0.019	0.0002	7	280
Left	Lentiform Nucleus		−22	12	−8	0.022	<0.00001	8	264
Left	Thalamus		0	−20	6	0.021	<0.00001	9	248
Left	IPL	40	−40	−46	46	0.016	<0.00001	10	232
Left	Cingulate Gyrus	32	−10	6	40	0.019	<0.00001	11	224
Right	MI	4	32	−26	56	0.017	0.0002	12	208
Right	Posterior insula/claustrum		38	−14	8	0.016	0.0004	13	88
Right	Inferior Frontal Gyrus	9	52	10	26	0.014	0.002	14	88
Left	Cingulate Gyrus	24	0	2	36	0.015	0.002	15	64
Right	Lingual Gyrus	19	32	−68	−2	0.011	0.002	16	48
Right	Mid-insula/claustrum		36	−2	−2	0.013	0.002	17	48
Right	Posterior insula		46	−24	16	0.013	0.001	18	40
Left	Superior Frontal Gyrus	10	−26	44	18	0.013	0.0008	19	40
Left	Caudate		−12	8	10	0.013	0.002	20	32
Left	Cerebellum		−36	−54	−32	0.012	0.003	21	24
Right	Parahippocampal Gyrus	35	22	−8	−22	0.012	0.003	22	24
Right	Amygdala		24	−8	−22	0.012	0.003		
Right	Amygdala		24	−8	−20	0.012	0.004		

ALE values for Study 2. ALE maps of noxious heat were subtracted from noxious cold. ALE values refer to the likelihood of obtaining activation in response to noxious cold stimuli in a given voxel of the standard template. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; IPL, inferior parietal lobule; SII, secondary somatosensory cortex; MI, primary motor cortex.

TABLE XIV. Spatial location and extent of ALE values for study 2 (noxious heat minus noxious cold)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Left	Putaman		−22	0	−2	0.024	0.005	1	1072
Right	Anterior insula/claustrum		34	12	6	0.023	<0.00001	2	960
Right	Mid-insula/claustrum		34	2	10	0.023	<0.00001		
Right	Anterior insula		34	22	8	0.014	0.002		
Left	Anterior insula		−40	18	6	0.025	<0.00001	3	616
Left	Anterior insula		−30	20	8	0.014	0.001		
Right	SII/IPL		52	−32	22	0.020	0.0002	4	584
Left	Posterior insula		−44	−24	16	0.024	<0.00001	5	576
Right	Thalamus		14	−20	4	0.021	<0.00001	6	504
Right	Posterior insula		32	−8	18	0.017	<0.00001	7	360
Right	Lentiform Nucleus		30	−14	8	0.016	0.0004		
Left	Thalamus		−12	−24	12	0.022	<0.00001	8	360
Right	Inferior Frontal Gyrus		38	46	2	0.020	<0.00001	9	352
Left	MI	4	−32	−22	50	0.020	<0.00001	10	296
Right	Cingulate Gyrus	32	4	22	26	0.018	<0.00001	11	200
Right	Caudate		14	8	12	0.020	0.0002	12	168
Left	Cingulate Gyrus	24	−6	12	32	0.014	0.001	13	112
Left	Cingulate Gyrus	24	0	−6	42	0.015	0.001	14	72
Left	Superior Temporal Gyrus	42	−54	−30	14	0.013	0.003	15	64
Right	Anterior insula		46	6	16	0.013	0.0004	16	64
Right	Inferior frontal gyrus	44	52	6	12	0.013	0.002		
Right	Middle Frontal Gyrus	46	42	36	24	0.014	0.0008	17	40
Right	Cingulate Gyrus	23	2	−22	28	0.012	0.003	18	32
Right	SII/IPL	39	48	−62	38	0.013	0.0008	19	32
Left	SI/PPC	5	−10	−34	46	0.012	0.003	20	32
Left	SI/PPC	5	−10	−32	46	0.012	0.003		
Right	SI/PPC	5	30	−42	58	0.012	0.004	21	32
Left	Posterior insula		−52	−34	20	0.012	0.002	21	24
Left	Posterior insula		−48	−20	24	0.012	0.003	21	24

ALE values for Study 2. ALE maps of noxious cold were subtracted from noxious heat pain. ALE values refer to the likelihood of obtaining activation in response to noxious heat vs. noxious cold in a given voxel of the standard template. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x,* medial-lateral; *y,* anterior posterior; *z,* superior-inferior; IPL, inferior parietal lobule; SI/PPC, primary somatosensory cortex/posterior parietal cortex; MI, primary motor cortex.

Minoshima, 2002; Cechetto and Saper, 1987; Critchley et al., 2000; Gianaros et al., 2007; Yasui et al., 1991; Zhang et al., 1999], interoception [Critchley et al., 2004], and temperature [Craig et al., 2000]. The anterior insula receives input from peripheral autonomic receptors, and therefore it may become activated during affective tasks or during the perception of pain due to increases in heart rate, changes in blood pressure, etc. [Cechetto and Saper, 1987; Yasui et al., 1991; Zhang et al., 1999]. A number of neuroimaging studies have reported activation in the insula during tasks that involve heightened autonomic activity [Cameron and Minoshima, 2002; Critchley et al., 2000; Gianaros et al., 2007]. Furthermore, the right anterior insula also has a key role in interoception, or monitoring the internal state of the body [Critchley et al., 2004]. The dorsal posterior insula has been shown to receive nociceptive input from the posterior portion of the ventromedial nucleus in the thalamus [Blomqvist et al., 2000; Craig and Dostrovsky 2001; Craig et al., 1994]. Brain activation in this region, as revealed by fMRI, is directly related to changes in temperature [Craig et al., 2000], indicating that it is a primary locus for processing thermosensory information. In turn, a significant likelihood of obtaining activation in response to noxious stimuli in the insula may reflect an increased awareness of physiological functions during exposure to noxious stimuli.

While the anterior insula is a major site for emotional processing, it also processes sensory-discriminative aspects of pain perception. For example, direct electrophysiological stimulation of the anterior insula produces painful and nonpainful somesthetic responses [Ostrowsky et al., 2002; Penfield and Faulk, 1955]. Furthermore, an imprecise somatotopic organization was reported in the insula based on electrophysiological stimulation and functional neuroimaging of this region [Henderson et al., 2007; Ostrowsky et al., 2000].

Surprisingly, the likelihood of activation in SI was significant even though the values reported in this region are from the global analysis and included studies that stimulated different parts of the body. As this region has a

TABLE XV. Spatial location and extent of ALE values for study 3 (noxious heat minus warm)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Left	SII		−50	−4	6	0.027	<0.00001	1	3432
Left	Anterior insula		−48	6	4	0.015	0.0002		
Left	Anterior insula		−44	6	2	0.015	0.0008		
Left	Inferior frontal gyrus	44	−46	8	12	0.014	0.0004		
Right	Anterior insula		38	8	−4	0.028	<0.00001	2	1448
Right	Mid-insula		38	0	12	0.020	<0.00001		
Right	Cingulate gyrus	24	4	2	38	0.027	<0.00001	3	1440
Left	Cingulate gyrus	24	−6	−4	40	0.022	<0.00001		
Right	Medial frontal gyrus		2	0	52	0.014	0.001		
Right	Cingulate gyrus	24	6	20	24	0.048	<0.00001	4	1096
Right	Thalamus		6	−20	0	0.026	<0.00001	5	824
Right	Thalamus		12	−22	8	0.016	0.0004		
Left	Cingulate gyrus	23	−2	−22	32	0.029	<0.00001	6	800
Right	Cerebellum		16	−58	−12	0.027	<0.00001	7	752
Right	Putamen		30	−14	8	0.018	0.0002	8	712
Right	Posterior insula		36	−12	16	0.015	0.0004		
Right	Posterior insula		34	−22	14	0.014	0.0002		
Right	Posterior insula		36	−18	20	0.014	0.0006		
Left	Posterior insula		−40	−20	16	0.029	<0.00001	9	648
Left	Thalamus		−8	−16	8	0.017	<0.00001	10	480
Right	Thalamus		30	44	20	0.026	<0.00001	11	360
Left	Thalamus		−22	−16	10	0.014	0.0002	12	208
Left	Putamen		−26	−20	12	0.014	0.0004		
Right	SII		48	−38	30	0.014	0.0008	13	184
Right	SII		52	−34	24	0.013	0.0008		
Right	Cerebellum		22	−58	−28	0.014	0.0008	14	168
Right	Cerebellum		22	−60	−32	0.014	0.001		
Left	SII		−50	−26	28	0.014	0.0004	15	152
Left	SI	2	−48	−20	26	0.014	0.002		
Right	Cingulate gyrus	32	4	42	12	0.013	0.0006	16	120
Left	Cingulate gyrus	24	0	38	6	0.013	0.002		

ALE values for Study 3. ALE values refer to the likelihood of obtaining activation in response to noxious heat stimuli contrasted with innocuous warm stimuli in a given voxel of the standard template. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; SI, primary somatosensory cortex; PPC, posterior parietal cortex; SII, secondary somatosensory cortex.

detailed somatotopic organization, the activation peaks were in different locations of the postcentral gyrus. Another important factor is that large individual differences in the location of the central sulcus may reduce the ability to detect spatially restricted activation in SI based on multiple-subject averaging [Geyer et al., 2000]. Therefore, the probabilistic values in SI produced by this meta-analysis may not accurately reflect the likelihood of activation in this region in individual studies.

The role of SI in the perception of pain has been disputed since some of the first published experiments in the early 20th century and continues to this day. This began with an early report by Head and Holmes [1911] that pain perception remained intact after damage to SI. Subsequent electrophysiological studies demonstrated contradictory findings, whereby neuronal responses to noxious stimuli were recorded in SI [Chudler et al. 1990; Kenshalo et al., 2000; Kenshalo and Isensee 1983]. Later brain imaging studies reported mixed findings with some studies reporting activation in SI [e.g., Talbot et al., 1991] and others finding an absence of SI activation [e.g., Jones et al., 1991]. These results could be due to many factors; however, these meta-analyses of all existing brain imaging studies of nociception have provided evidence that SI is involved in the processing of some aspects of nociception, although with a relatively small likelihood of being activated in response to noxious stimuli.

The meta-analysis has also identified cortical regions that are not typically associated with nociceptive processing, such as the posterior cingulate gyrus. Activation in the posterior cingulate cortex is often reported in pain neuroimaging studies as a finding being unrelated to processing noxious stimuli, as its role in pain processing has not been thoroughly explored. However, studies in animals have indicated that this region receives a direct projection from the main pain and temperature

TABLE XVI. Spatial location and extent of ALE values for study 3 (noxious heat vs. baseline)

Side	Region	BA	*X*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Left	Cingulate gyrus	32	−2	10	40	0.042	<0.00001	1	3768
Left	Cingulate gyrus	24	−4	12	30	0.029	<0.00001		
Left	Cingulate gyrus	24	0	−2	44	0.024	<0.00001		
Left	Cingulate gyrus	32	−8	24	30	0.014	0.0002		
Left	Supplementary motor area	6	0	−10	52	0.013	0.004		
Right	SII	43	50	−18	16	0.020	<0.00001	2	2408
Right	Posterior insula		36	−20	16	0.020	<0.00001		
Right	IPL	40	48	−34	28	0.018	0.0004		
Right	IPL	40	56	−30	24	0.016	0.0002		
Right	IPL	40	60	−30	26	0.016	0.0002		
Right	SII	40	50	−32	34	0.014	0.0008		
Right	SII		56	−12	12	0.014	0.0006		
Right	Putaman		30	2	8	0.032	<0.00001	3	1952
Right	Mid-insula/claustrum		30	4	12	0.031	<0.00001		
Left	Mid-insula		−40	2	8	0.024	0.0002	4	1360
Left	Anterior insula		−46	6	16	0.013	0.003		
Left	Posterior insula		−42	−10	12	0.013	0.002		
Left	Mid−insula/claustrum		−30	4	8	0.013	0.001		
Left	Thalamus		−16	−20	12	0.037	<0.00001	5	1032
Right	Inferior frontal gyrus	44	52	6	10	0.026	<0.00001	6	824
Right	Cerebellum		0	−66	−16	0.023	<0.00001	7	784
Right	Cerebellum		2	−62	−14	0.021	0.0002		
Right	Thalamus		12	−20	4	0.027	<0.00001	8	760
Right	Cerebellum		20	−66	−24	0.020	<0.00001	9	656
Right	Cerebellum		30	−76	−28	0.014	0.0004		
Left	Posterior insula		−44	−24	16	0.024	<0.00001	10	576
Right	Medial frontal gyrus	6	6	−6	62	0.019	0.0002	11	408
Left	Putaman		−22	0	−2	0.022	<0.00001	12	312
Right	PPC	5	22	−42	66	0.021	<0.00001	13	280
Left	MI	4	−32	−22	50	0.020	0.0002	14	264
Right	SI	3	30	−30	62	0.019	<0.00001	15	264
Left	Putaman		−28	−14	10	0.014	0.0004	16	256
Left	Putaman		−22	−10	8	0.014	0.001		
Left	Putaman		−30	−12	2	0.013	0.002		
Right	Posterior insula		32	−10	18	0.017	0.0002	17	248
Left	Cerebellum		−22	−54	−28	0.016	0.0006	18	240
Right	Premotor cortex	6	46	0	30	0.018	<0.00001	19	232
Right	Cerebellum		38	−54	−36	0.017	0.0004	20	216
Right	Anterior insula		36	18	8	0.015	0.0004	21	160
Left	Superior frontal gyrus		−10	−8	72	0.021	<0.00001	22	152

ALE values for Study 3. ALE values refer to the likelihood of obtaining activation evoked by noxious heat stimuli in comparison to resting baseline. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; IPL, inferior parietal lobule; SI, primary somatosensory cortex; PPC, posterior parietal cortex; SII, secondary somatosensory cortex; MI, primary motor cortex.

transmitting pathway in the spinal cord, the spinothalamic tract, [Apkarian and Shi, 1998] and contains nociceptive neurons [Sikes et al., 2008] thus suggesting it processes sensory-discriminative aspects of pain. Additionally, the meta-analysis identified motor regions that invariably become activated during a pain imaging experiment. As of late, pain neuroimaging studies often discount activation in motor regions because of preparatory motor responses. However, Melzack and Wall [1965] noted in their seminal work on peripheral and central processing of pain that motor responses are an integral part of the exposure to a noxious stimulus. They note that many actions can occur after a noxious stimulus is applied to the body such as a startle response and orienting of the head and eyes. Therefore, the significant likelihood of activation in motor areas found in the current experiment reinforces this long held view of pain processing. Additionally, several motor areas, such as the nuclei in the basal ganglia, are directly responsive to noxious stimuli [Chudler and

TABLE XVII. Spatial location and extent of ALE values for study 3 (noxious heat vs. baseline minus noxious heat vs. warm)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Left	Cingulate gyrus	32	−2	10	40	0.039	<0.00001	1	2168
Left	Cingulate gyrus	24	−6	14	30	0.029	<0.00001		
Left	Cingulate gyrus	32	−8	24	30	0.013	0.002		
Right	SII	43	50	−18	16	0.020	<0.00001	2	1040
Right	SII	40	60	−30	26	0.015	0.0004		
Right	SII	42	56	−12	12	0.014	0.0008		
Right	Putamen		30	2	6	0.027	<0.00001	3	944
Left	Thalamus		−16	−20	12	0.035	<0.00001	4	688
Right	Inferior frontal gyrus	44	54	6	10	0.026	<0.00001	5	624
Right	Cerebellum		0	−66	−16	0.023	<0.00001	6	536
Right	Cerebellum		20	−66	−24	0.020	0.0004	7	488
Right	Cerebellum		30	−76	−28	0.014	0.0008		
Left	Mid-insula		−40	0	8	0.019	<0.00001	8	448
Left	Anterior insula		−38	12	12	0.014	0.002		
Right	Medial frontal gyrus	6	6	−6	62	0.019	0.0006	9	320
Right	SI/PPC		22	−42	66	0.021	0.0002	10	240
Left	MI	4	−32	−22	50	0.020	0.0002	11	224
Right	SI	3	30	−30	62	0.019	0.0004	12	216
Left	Putamen		−22	0	−4	0.021	0.0002	13	192
Left	Posterior insula		−44	−26	16	0.018	<0.00001	14	168
Right	Thalamus		14	−20	4	0.018	0.0002	15	160
Right	Inferior frontal gyrus	6	46	0	30	0.017	0.0004	16	152
Right	Cerebellum		38	−54	−36	0.016	0.0002	17	144
Left	Superior frontal gyrus	6	−10	−8	72	0.021	0.0002	18	120
Right	Posterior insula/claustrum		30	−8	18	0.016	0.0002	19	112

Study 3: ALE values refer to the likelihood of obtaining activation evoked by noxious heat stimuli in comparison to resting baseline minus ALE values obtained for noxious heat in comparison to innocuous warm stimuli. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; SI, primary somatosensory cortex; PPC, posterior parietal cortex; SII, secondary somatosensory cortex; MI, primary motor cortex.

TABLE XVIII. Spatial location and extent of ALE values for study 3 (noxious heat vs. warm minus noxious heat vs. baseline)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* values	Cluster #	Volume (mm^3)
Right	Cingulate Gyrus	24	6	20	24	0.048	<0.00001	1	976
Left	Cingulate Gyrus	23	−2	−22	32	0.029	<0.00001	2	600
Right	Anterior insula	13	38	8	−4	0.028	<0.00001	3	464
Right	Cerebellum		16	−58	−12	0.021	<0.00001	4	256
Right	Lentiform Nucleus		30	−14	8	0.018	0.0002	5	192
Left	Superior Temporal Gyrus	22	−50	−4	6	0.021	<0.00001	6	184
Right	Cingulate Gyrus	24	6	0	38	0.019	<0.00001	7	184
Left	Posterior insula	13	−38	−20	14	0.018	0.0004	8	152
Right	Mid-insula	13	38	−2	12	0.016	0.001	9	136
Left	Cingulate Gyrus	24	−6	−6	40	0.018	0.0004	10	112
Right	Thalamus		4	−20	0	0.017	<0.00001	11	104
Left	Thalamus		−4	−14	8	0.015	0.001	12	104

Study 3: ALE values refer to the likelihood of obtaining activation evoked by noxious heat stimuli in comparison to innocuous warm stimuli subtracting ALE values obtained for noxious heat minus baseline. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior.

TABLE XIX. Spatial location and extent of ALE values for Study 4 (noxious stimuli applied to the left side of the body)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Right	Thalamus		10	−20	6	0.089	<0.00001	1	18,008
Left	Thalamus		−12	−16	10	0.082	<0.00001		
Left	Mid-insula/claustrum		−34	2	8	0.069	<0.00001		
Right	Thalamus		16	−18	14	0.055	<0.00001		
Left	Anterior insula		−32	12	10	0.044	<0.00001		
Right	Thalamus		10	−6	6	0.042	0.0002		
Left	Midbrain		−2	−16	−8	0.036	<0.00001		
Right	Lentiform Nucleus		18	−6	0	0.032	<0.00001		
Right	Putamen		2	−28	−6	0.029	<0.00001		
Left	Lentiform Nucleus		−28	−10	4	0.028	<0.00001		
Left	Anterior insula		−40	6	−4	0.027	0.0004		
Right	Posterior insula		36	−20	18	0.108	<0.00001	2	17,912
Right	Mid-insula/claustrum		32	4	12	0.098	<0.00001		
Right	IPL	40	52	−30	26	0.073	<0.00001		
Right	Superior Temporal Gyrus	22	52	4	8	0.050	<0.00001		
Right	IPL	40	46	−34	40	0.031	0.0001		
Right	Anterior insula		46	10	0	0.027	0.0002		
Right	Posterior insula/claustrum		36	−12	−4	0.022	0.002		
Right	Cingulate Gyrus	24	2	4	38	0.095	<0.00001	3	12,552
Right	Medial Frontal Gyrus	6	2	2	52	0.079	<0.00001		
Right	Medial Frontal Gyrus	6	10	8	50	0.049	<0.00001		
Left	Cingulate Gyrus	24	−8	16	28	0.048	<0.00001		
Left	Medial Frontal Gyrus	6	−2	−10	52	0.037	<0.00001		
Right	Cingulate Gyrus	24	8	−12	40	0.037	<0.00001		
Right	Medial Frontal Gyrus	6	8	−10	52	0.027	<0.00001		
Right	Superior Frontal Gyrus	6	14	−6	62	0.026	0.0004		
Left	IPL	40	−52	−32	28	0.032	<0.00001	4	1384
Left	IPL		−50	−36	22	0.032	<0.00001		
Left	SII		−56	−22	20	0.030	0.0002		
Left	Cerebellum		−34	−56	−30	0.033	<0.00001	5	1352
Left	Cerebellum		−28	−54	−30	0.031	<0.00001		
Left	Cerebellum		−24	−56	−18	0.031	<0.00001		
Right	SI/PPC	5	22	−42	64	0.040	<0.00001	6	1048
Right	SI	3	30	−30	62	0.033	<0.00001		
Right	Cerebellum		4	−58	−14	0.032	<0.00001	7	864
Right	Cerebellum		0	−50	−16	0.026	0.001		
Right	Precentral Gyrus	6	26	−16	54	0.042	<0.00001	8	784
Right	MI	4	34	−18	58	0.026	0.001		
Right	Middle Frontal Gyrus	10	32	40	22	0.029	<0.00001	9	720
Right	Middle Frontal Gyrus	10	40	38	22	0.029	0.0004		
Right	Superior Frontal Gyrus	9	28	40	30	0.026	0.0004		
Left	SII		−40	−24	14	0.029	<0.00001	11	456
Right	Inferior Frontal Gyrus		38	22	6	0.027	0.0006	12	184
Right	Cerebellum		24	−66	−24	0.025	0.001	13	160
Right	Paracentral Lobule	5	8	−40	60	0.030	0.0004	14	152
Left	Posterior insula/claustrum		−34	−18	4	0.025	0.0004	15	128
Right	Cingulate Gyrus	32	4	22	26	0.027	0.001	16	128
Left	Cingulate Gyrus	32	−6	32	−4	0.028	0.0006	17	104

ALE values for Study 4. ALE values refer to the likelihood of obtaining activation evoked by noxious stimuli applied to the left side of the body. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; IPL, inferior parietal lobule; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; MI, primary motor cortex.

Dong, 1995] with some regions showing a nociceptive somatotopic organization [Bingel et al., 2004a] consistent with an involvement in stimulus localization.

To conclude, this meta-analysis represents a comprehensive quantitative review identifying the specific location and spatial extent of activation evoked by noxious

TABLE XX. Spatial location and extent of ALE values for (noxious heat applied to the right side of the body)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Right	Anterior insula		34	12	8	0.105	<0.000001	1	41,464
Left	Mid-insula		−38	4	4	0.100	<0.000001		
Left	SII		−54	−26	22	0.091	<0.000001		
Right	SII		56	−22	20	0.084	<0.000001		
Left	Posterior insula		−38	−20	14	0.082	<0.000001		
Left	Thalamus		−16	−16	10	0.082	<0.000001		
Right	Thalamus		4	−18	4	0.069	<0.000001		
Right	Thalamus		12	−12	8	0.054	<0.000001		
Right	Lentiform Nucleus		24	−2	8	0.049	<0.000001		
Left	Precentral Gyrus	43	−54	−8	12	0.043	<0.000001		
Right	Precentral Gyrus	44	50	6	12	0.040	<0.000001		
Right	Mid-insula		36	−2	14	0.040	<0.000001		
Right	Inferior Frontal Gyrus	47	42	18	−2	0.039	<0.000001		
Left	Lentiform Nucleus		−20	4	10	0.038	<0.000001		
Left	Precentral Gyrus	6	−52	−4	6	0.035	<0.000001		
Left	Thalamus		−4	−26	0	0.035	<0.000001		
Right	Posterior insula		38	−14	16	0.034	<0.000001		
Right	Posterior insula		44	−14	16	0.033	<0.000001		
Right	Inferior Frontal Gyrus		42	26	4	0.026	<0.000001		
Left	Lentiform Nucleus		−20	12	0	0.025	0.0008		
Left	Supramarginal Gyrus	40	−54	−38	32	0.022	0.002		
Right	Cingulate Gyrus	24	4	8	36	0.081	<0.000001	2	14,016
Right	Cingulate Gyrus	32	6	22	26	0.067	<0.000001		
Left	Cingulate Gyrus	24	−4	−4	42	0.062	<0.000001		
Left	Cingulate Gyrus	32	−2	24	38	0.046	<0.000001		
Left	Anterior Cingulate	24	−4	20	24	0.045	<0.000001		
Left	Medial Frontal Gyrus	8	−10	26	42	0.025	0.001		
Left	SII	3	−32	−34	60	0.049	<0.000001	3	1664
Left	MI	4	−38	−24	62	0.034	<0.000001		
Right	Middle Frontal Gyrus	10	30	44	20	0.036	<0.000001	4	1424
Right	Middle Frontal Gyrus	10	42	46	14	0.030	0.0002		
Right	Superior Frontal Gyrus	9	38	36	26	0.028	<0.000001		
Right	Middle Frontal Gyrus	9	38	30	30	0.024	0.001		
Left	Cerebellum		−34	−54	−36	0.034	<0.000001	5	968
Left	Cerebellum		−20	−62	−24	0.033	<0.000001		
Left	Cerebellum		−30	−58	−30	0.029	<0.000001		
Right	Cerebellum		22	−58	−24	0.040	<0.000001	6	720
Right	Cerebellum		2	−46	−16	0.034	<0.000001	7	616
Right	IPL	40	50	−32	34	0.038	<0.000001	8	480
Left	Supramarginal Gyrus	40	−40	−40	36	0.042	<0.000001	9	480
Left	Cerebellum		−4	−56	−28	0.028	0.0002	10	328
Right	Cerebellum		4	−62	−16	0.034	<0.000001	11	288
Right	IPL	40	50	−46	38	0.031	<0.000001	12	280
Left	Middle Frontal Gyrus	10	−30	46	4	0.033	<0.000001	13	216
Left	Angular Gyrus	39	−40	−58	34	0.030	0.0002	14	160
Left	Medial Frontal Gyrus	6	−4	−20	66	0.027	<0.000001	15	128
Right	Uncus	36	20	−4	−34	0.025	0.001	16	104
Right	Medial Frontal Gyrus	6	6	2	62	0.025	0.0008	17	104

Study 4: ALE values refer to the likelihood of obtaining activation evoked by noxious heat stimuli applied to the right side of the body. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; IPL, inferior parietal lobule; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; MI, primary motor cortex.

stimuli in the brain. Given the all-inclusive nature of the types of stimuli included in the analysis, the specific role of these structures in processing noxious stimuli cannot be addressed within the limits of the current study. More detailed information can be obtained by contrasting activation likelihood estimates associated with distinct noxious stimuli as discussed in the following sections.

TABLE XXI. Spatial location and extent of ALE values for study 4 (left-sided stimuli minus right-sided stimuli)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Right	Posterior insula		36	−20	18	0.093	<0.000001	1	3024
Right	Posterior insula/claustrum		38	−14	8	0.040	<0.000001		
Right	Cingulate Gyrus	24	4	2	38	0.047	<0.000001	2	2576
Right	Medial Frontal Gyrus	6	2	2	54	0.046	<0.000001		
Right	Medial Frontal Gyrus	6	12	8	50	0.043	<0.000001		
Right	Cingulate Gyrus	24	8	−12	42	0.029	<0.000001		
Right	Medial Frontal Gyrus	6	8	−10	52	0.024	0.0008		
Right	Mid-insula/claustrum		32	4	12	0.055	<0.000001	3	1976
Right	Thalamus		16	−18	14	0.049	<0.000001	4	1488
Right	Thalamus		10	−20	4	0.041	<0.000001		
Right	SII		52	−30	26	0.058	<0.000001	5	1272
Right	SI/PPC	5	22	−42	64	0.039	<0.000001	6	880
Right	SI	3	30	−30	62	0.031	0.0002		
Right	Precentral Gyrus	6	26	−16	54	0.041	<0.000001	7	712
Right	MI	4	34	−18	58	0.025	0.0008		
Left	Thalamus		−10	−16	10	0.035	<0.000001	8	416
Left	Thalamus		−6	−20	16	0.027	0.0002		
Left	Midbrain		−2	−16	−10	0.031	<0.000001	9	304
Left	Cingulate Gyrus	24	−10	16	28	0.035	<0.000001	10	264
Right	Inferior frontal gyrus	44	52	2	4	0.031	<0.000001	11	240
Left	Cerebellum		−24	−56	−18	0.029	0.0002	12	232
Right	SI/PPC	5	8	−40	60	0.030	<0.000001	13	168
Right	Superior Frontal Gyrus	6	14	−6	62	0.025	0.001	14	160
Left	Medial Frontal Gyrus	6	−4	−12	56	0.026	0.0004	15	152
Right	Lentiform Nucleus		18	−6	0	0.025	0.0004	16	144
Right	Thalamus		10	−4	2	0.022	0.002		
Left	Mid-insula		−46	2	14	0.027	0.0006	17	136
Left	Cingulate gyrus	32	−6	32	−4	0.028	<0.000001	18	128
Left	Posterior insula		−50	−36	22	0.027	0.0002	19	128

ALE values for Study 4. ALE values for applying noxious stimuli to the left side of the body subtracting the ALE maps for applying stimuli to the right side of the body. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; SI, primary somatosensory cortex; PPC, posterior parietal cortex; SII, secondary somatosensory cortex; MI, primary motor cortex.

Study 2: Noxious Cold Compared with Noxious Heat

This is the first meta-analysis of brain imaging data to directly compare noxious cold with noxious heat. The most important finding from the noxious cold meta-analysis was that these stimuli were associated with the activation of a number of sensory and affective pain processing cortical regions, including bilateral insular cortices, the right ACC, subcallosal gyrus, SII, and the right amygdala. In comparison, the highest likelihood of obtaining activation in response to noxious heat was localized in bilateral insulae and thalamus. Based on the subtraction analysis (noxious heat minus noxious cold), noxious-heat related activation was more likely to occur in somatosensory cortices, which perhaps reflects the substantially lesser autonomic reaction and unpleasantness associated with these stimuli [Rainville et al., 1992].

To date, very few imaging studies have explored the neural representations of noxious cold and noxious heat pain within the same experimental protocol [Casey et al., 1996; Craig et al., 1996; Tracey et al., 2000]. In one study, Tracey et al. [2000] reported that cold and heat pain activated similar brain areas. However, these authors applied cold stimuli using relatively short (30 s) stimuli delivered via a computer-controlled thermode that were potentially not as aversive as the stimuli used in the other cold-pain studies included in the meta-analysis.

Some studies in the meta-analysis administered noxious cold stimuli using the cold pressor task, which involves the immersion of a limb into freezing water for several minutes. In general, subjects report cold-pain sensations to be "aching" and "deep," in comparison to heat pain, which has been described as "stinging" and "superficial" [Davis et al., 1998]. Additionally, subjects rate cold pain as more unpleasant than heat pain [Greenspan et al., 2003; Rainville et al., 1992]. In turn, the findings from the noxious cold meta-analysis are in line with results showing high probabilistic values in regions associated with emotional processing and negative affect such as the

TABLE XXII. Spatial location and extent of ALE values for study 4 (right-sided stimuli minus left-sided stimuli)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Left	SI		−54	−26	22	0.067	<0.000001	1	8128
Left	Anterior insula		−38	6	4	0.066	<0.000001		
Left	Posterior insula		−38	−18	12	0.061	<0.000001		
Left	SII		−56	−10	12	0.039	<0.000001		
Left	Precentral Gyrus	6	−52	−4	6	0.030	0.0004		
Left	Cingulate Gyrus	32	−2	24	40	0.042	<0.000001	2	2256
Right	Cingulate Gyrus	32	6	20	26	0.042	<0.000001		
Right	Cingulate Gyrus	32	2	24	32	0.040	<0.000001		
Left	Cingulate Gyrus	24	−2	20	24	0.033	<0.000001		
Left	Medial Frontal Gyrus	8	−10	26	42	0.025	0.0008		
Right	Anterior insula		34	14	8	0.079	<0.000001	3	1648
Left	Cingulate Gyrus	32	−8	8	38	0.041	<0.000001	4	1568
Left	Superior Frontal Gyrus	6	0	12	48	0.034	<0.000001		
Right	Cingulate Gyrus	32	8	12	40	0.033	<0.000001		
Right	Cingulate Gyrus	32	12	14	38	0.033	<0.000001		
Left	SI	3	−32	−34	60	0.049	<0.000001	5	1528
Left	MI	4	−38	−24	62	0.033	<0.000001		
Right	SII	40	56	−22	20	0.051	<0.000001	6	656
Left	Cingulate Gyrus	24	−6	−4	42	0.049	<0.000001	7	528
Right	Lentiform Nucleus		24	−4	8	0.040	<0.000001	8	480
Left	Supramarginal Gyrus	40	−40	−40	36	0.042	<0.000001	9	432
Right	Cerebellum		22	−56	−26	0.032	<0.000001	10	296
Left	Cerebellum		−4	−54	−28	0.027	0.0006	11	240
Right	IPL	40	50	−46	38	0.031	0.0002	12	232
Left	Middle Frontal Gyrus	10	−30	46	4	0.033	<0.000001	13	224
Left	Lentiform Nucleus		−20	4	10	0.032	<0.000001	14	224
Right	Inferior Frontal Gyrus	47	42	20	−4	0.032	<0.000001	15	208
Left	Anterior insula		−32	20	4	0.029	0.0006	16	176
Right	Thalamus		2	−16	4	0.032	<0.000001	17	168
Left	Angular Gyrus	39	−40	−58	34	0.030	0.0002	18	160
Right	Middle Frontal Gyrus	46	42	46	16	0.024	0.001	19	144
Left	Thalamus		−4	−26	0	0.029	<0.000001	20	120
Left	Cerebellum		−34	−52	−38	0.027	<0.000001	21	104

ALE values for Study 4. ALE values refer to the likelihood of obtaining activation evoked by noxious stimuli applied to the right side of the body subtracting the ALE maps for applying noxious stimuli to the left side of the body. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; MI, primary motor cortex.

amygdala, insula, and the ACC [Mayberg et al., 1999; Neugebauer et al., 2004; Wiech and Tracey, 2009]. The subgeniculate area of the ACC projects to the amygdala, hypothalamus, and the periaqueductal gray, brain regions known to process emotional motivational stimuli, and also autonomic processing, indicating that the increased likelihood of activation in these regions during noxious cold stimuli may reflect both affect-related physiological and behavioral reactions that occur during unpleasant stimuli. In line with these findings is that activation has been reported in the ACC and the amygdala for noxious muscle stimuli, but not for noxious cutaneous stimuli when presented within the same experimental design [Takahashi et al., 2011]. These findings were also related to the enhanced emotional response elicited by muscle stimuli.

Study 3: Localizing Activation in Response to Noxious Heat Stimuli

In this systematic study, we examined the effects of using either innocuous warm stimuli or a resting baseline as the control condition on the apparent brain activation evoked by noxious heat stimuli. As expected, our findings indicate that contrasts with a resting baseline suggest a more widespread network of brain regions activated by the noxious stimuli. This was demonstrated by the greater number of ALE peaks, the larger clusters of significant ALE values, and the detection of activation peaks outside of the classical spino-thalamo-cortical system (e.g., in the superior frontal gyrus). Of particular interest, the contrast with a resting baseline has the advantage of increasing the

TABLE XXIII. Spatial location and extent of ALE values for study 5 (noxious muscle stimuli)

Side	Region	BA	*x*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Right	Anterior insula		36	14	10	0.037	<0.000001	1	6168
Left	Thalamus		−12	−16	8	0.04	<0.000001	2	4984
Left	Cingulate gyrus	24	0	16	24	0.025	<0.000001	3	1904
Left	Mid-insula		−34	2	20	0.026	<0.000001	4	1888
Left	Posterior insula		−36	−22	12	0.034	<0.000001	5	1616
Right	PPC	40	64	−22	22	0.026	<0.000001	6	896
Right	Middle frontal gyrus	10	32	42	16	0.034	<0.000001	7	848
Left	Precentral	6	−56	−2	8	0.027	<0.000001	8	704
Left	IPL		−58	−38	28	0.023	<0.000001	9	672
Left	SII	41	−58	−18	14	0.023	<0.000001	10	488
Left	Posterior cingulate gyrus	23	−4	−26	28	0.021	0.0002	11	440
Left	Cingulate gyrus	32	−8	30	24	0.023	<0.000001	12	352
Left	Posterior insula		−38	−18	−6	0.024	<0.000001	13	344
Right	Cingulate gyrus	32	8	10	38	0.019	0.0002	14	344
Left	Superior temporal gyrus	22	−50	6	−6	0.024	<0.000001	15	328
Left	Precuneus	7	−8	−70	36	0.021	0.0001	16	320
Left	Cerebellum		−2	−26	−14	0.022	<0.000001	17	312
Right	Cerebellum		24	−62	−18	0.022	<0.000001	18	280
Left	Cerebellum		−38	−54	−36	0.021	<0.000001	19	272
Left	Middle frontal gyrus	9	−30	40	28	0.02	<0.000001	20	272
Left	Anterior insula		−28	16	2	0.015	0.001	21	152

ALE values for Study 5. ALE values refer to the likelihood of obtaining activation evoked by noxious stimuli applied to the skin. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; SII, secondary somatosensory cortex; MI, primary motor cortex; PPC, posterior parietal cortex.

likelihood of detecting stimulus-evoked activation in SI, an area that is often missed because of a variety of factors difficult to control in brain imaging studies, as discussed above.

A major finding from the meta-analysis in which innocuous warm stimuli was used as a control condition for noxious heat was the localized peak ALE values in BA 24 of the ACC. This important result suggests that the pain

TABLE XXIV. Study 5 (noxious cutaneous stimuli)

Side	Region	BA	*X*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Right	Thalamus		14	−18	4	0.027	<0.00001	1	4328
Left	Mid-insula		−38	−2	4	0.032	<0.00001	2	4064
Right	Dorsal posterior insula		42	−18	14	0.035	<0.00001	3	1696
Left	Cingulate gyrus	24	−2	−4	44	0.027	<0.00001	4	1424
Right	Anterior insula		36	10	0	0.02	<0.00001	5	960
Right	IPL	40	48	−28	26	0.017	0.0002	6	648
Left	SII		−58	−20	22	0.021	<0.00001	7	472
Right	Mid-insula/Mid-Clastrum		36	−4	6	0.017	<0.00001	8	408
Left	Cingulate gyrus	24	0	16	26	0.017	<0.00001	10	384
Left	SII		−50	−30	16	0.024	<0.00001	11	368
Right	IPL	40	26	−36	54	0.022	<0.00001	12	368
Right	Precentral gyrus	44	48	2	8	0.017	0.004	13	320
Right	Posterior insula		44	−10	−4	0.02	<0.00001	14	304
Right	SI/PPC	7	28	−44	46	0.017	<0.00001	15	296
Right	IPL		52	−44	28	0.016	<0.00001	16	280
Right	Inferior frontal gyrus	47	40	28	2	0.016	0.0002	17	272
Left	Middle frontal gyrus	9	−24	32	30	0.013	0.0004	18	200

ALE values for Study 5. ALE values refer to the likelihood of obtaining activation evoked by noxious stimuli applied to muscles. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; IPL, inferior parietal lobule; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; MI, primary motor cortex; PPC, posterior parietal cortex.

TABLE XXV. Spatial location and extent of ALE values for study 5 (noxious muscle stimuli minus noxious cutaneous stimuli)

Side	Region	BA	*X*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Right	Anterior insula		36	16	10	0.029	<0.000001	1	3288
Left	Anterior insula		−34	2	20	0.026	<0.000001	2	784
Left	Thalamus		−12	−16	10	0.027	<0.000001	3	720
Right	Middle frontal gyrus	10	32	42	14	0.034	<0.000001	4	704
Left	Thalamus		−16	−26	14	0.022	<0.000001	5	664
Left	Cingulate gyrus	32	−4	20	38	0.023	<0.000001	6	664
Left	Precentral gyrus	6	−56	−2	8	0.027	<0.000001	7	656
Right	SII		64	−24	22	0.023	<0.000001	8	584
Left	Posterior insula		−36	−24	10	0.03	<0.000001	9	560
Left	Posterior insula		−40	−18	20	0.028	<0.000001	10	416
Left	Superior temporal gyrus		−50	6	−6	0.024	<0.000001	11	296
Right	Cerebellum		24	−62	−18	0.022	<0.000001	12	288
Left	Cingulate gyrus	32	−8	30	24	0.023	<0.000001	13	288
Left	Precuneus	7	−8	−70	36	0.021	<0.000001	14	272
Left	Posterior cingulate gyrus	23	−4	−26	28	0.021	<0.000001	15	256
Right	Thalamus		6	−22	8	0.022	<0.000001	16	248
Left	IPL	40	−60	−38	26	0.021	<0.000001	17	232
Left	Transverse temporal gyrus		−58	−16	12	0.019	<0.000001	18	208
Right	Thalamus		14	−10	8	0.016	0.0004	19	184
Left	Cerebellum		−40	−54	−36	0.019	<0.000001	20	176
Left	IPL	40	−56	−28	32	0.016	0.0008	21	168
Left	Midbrain		−2	−26	−14	0.021	<0.000001	22	160
Left	Middle frontal gyrus	9	−30	40	28	0.017	0.0002	23	152

ALE values for Study 5. ALE values refer to the likelihood of obtaining activation evoked by noxious muscle stimuli in comparison to noxious cutaneous stimuli. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; IPL, inferior parietal lobule; SII, secondary somatosensory cortex; MI, primary motor cortex; PPC, posterior parietal cortex.

versus warm contrast may not simply reveal a subset of activation peaks detected in pain versus baseline. Electrophysiological studies have recorded neurons in the ACC responding to noxious stimuli, with or without attentional modulation, or solely during attentive tasks [Davis et al., 2000; Hutchison et al., 1999]. An fMRI study examined

TABLE XXVI. Spatial location and extent of ALE values for study 5 (noxious cutaneous stimuli minus noxious muscle stimuli)

Side	Region	BA	*X*	*y*	*z*	ALE value	*P* value	Cluster #	Volume (mm^3)
Left	Mid-insula		−38	−4	6	0.022	<0.000001	1	1048
Right	Posterior insula		42	−20	14	0.031	<0.000001	2	968
Left	Cingulate gyrus	24	−2	−4	44	0.024	<0.000001	3	592
Right	Midbrain		4	−16	−8	0.019	0.0002	4	384
Left	Thalamus		−6	−10	12	0.018	0.0004	5	344
Right	SII		48	−28	26	0.017	0.0006	6	344
Left	SII		−50	−30	16	0.024	<0.000001	7	312
Right	Anterior insula		36	10	0	0.018	0.0006	8	256
Right	SI		26	−36	54	0.022	<0.000001	9	240
Left	SI		−58	−20	22	0.020	0.0002	10	192
Left	Putamen		−26	6	−6	0.016	0.0002	11	144
Right	Inferior frontal gyrus	47	40	28	2	0.016	0.0002	12	144
Right	Precuneus	7	28	−44	46	0.017	0.0008	13	144
Right	SII		52	−44	28	0.016	0.0004	14	128

ALE values for Study 5. ALE values refer to the likelihood of obtaining activation evoked by noxious cutaneous stimuli in comparison to noxious to the skin stimuli. Coordinates are in Talairach space [Talairach and Tournoux 1988]. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm^3). Abbreviations: BA, Brodmann Area; *x*, medial-lateral; *y*, anterior posterior; *z*, superior-inferior; SII, secondary somatosensory cortex; PPC, posterior parietal cortex.

BOLD activity either during the presentation of a painful stimulus or an attention-demanding task [Davis et al., 1997]. Activation evoked by pain was reported in BA 24, while the attention-demanding task activated BA 32. In these results, the significant probabilistic value in BA 32 for the pain vs. baseline condition might reflect attentional resources directed towards the stimuli. Notably, this cluster largely overlapped with another cluster that had a significant likelihood of being activated in the pain versus warm contrast, consistent with increased attention-related responses to pain. However, the more ventral peaks found in the pain versus warm contrast are consistent with a spino-thalamo-cortical input to BA 24 [Sikes and Vogt, 1992], which might be more closely related to the processing of noxious signals and to the experience of pain. Potentially, the likelihood of activation in BA 24 area could also be a result of weaker signal change in this region in response to innocuous warm stimuli or even "deactivation," or negative signal change. Certainly, activation only in response to innocuous warm stimuli has been found to produce activation in this region [e.g., Becerra et al., 1999]. Therefore, the findings suggest that BA 24 does process innocuous warm stimuli, but not more so than noxious stimuli. Deactivation or negative signal in response to warm stimuli may also have produced a better contrast to localize pain-specific activation in the brain. The neurophysiological mechanisms underlying negative BOLD-signal change in functional neuroimaging data are unclear, and have been a focus of interest in the brain imaging literature [Kastrup et al., 2008; Menon et al., 1995; Shmuel et al., 2002, 2006]. It has been theorized that negative BOLD-signal change in the somatosensory system may be a result of inhibitory surround receptive fields [Apkarian et al., 2000]. Whether similar mechanisms may underlie the processing of innocuous warm stimuli in the ACC remains uncertain; however, this may explain the stronger signal change in response to noxious stimuli when using an innocuous warm control. In any case, whether the signal change in BA 24 in response to innocuous warm stimuli is absent, weak, or negative, an important incentive for using warmth as a control for pain is that it may help to discriminate activation associated with nociceptive processes and pain experiences from cognitive processes involved in the encoding and attention to both noxious and innocuous stimuli.

Study 4: Hemispheric Lateralization of Nociceptive Processing

This fourth meta-analysis examined the hemispheric lateralization of nociceptive processing by comparing two groups of independent studies that reported brain activation coordinates evoked by noxious stimuli applied either to the left or the right sides of the body. Regardless of whether the left or the right sides of the body received noxious stimulation, the meta-analysis revealed that the most significant probabilistic values were in the right insular cortex. Additionally, the other region to show large clusters and significant ALE values for both analyses was the right ACC (BA 24).

The likelihood of activation in the contralateral hemisphere was significant within right SI, MI, PPC, and the superior frontal gyrus, for the left-sided stimuli. For the right-sided meta-analysis, the likelihood of contralateral activation was significant within left SI, ACC (BA32), MI, inferior parietal lobule, and the medial frontal gyrus.

In the ipsilateral hemisphere, the likelihood of activation was significant within the midbrain for the left-sided stimuli. The likelihood of activation in the ipsilateral hemisphere for right-sided stimuli was significant within the ACC (BA 32), inferior parietal lobule, and the middle frontal gyrus.

Findings from this meta-analysis provide credence to the previously proposed right hemispheric dominance for pain processing [Craig, 2005]. This is likely due to the role of the right hemisphere in mediating affective processing, which has been seen across a number of sensory modalities [Borod et al., 1998; Coen et al., 2009; Killgore and Yurgelun-Todd, 2007]. Pain in itself is recognized as an emotional state, and in turn is highly modifiable by emotions and mood [Meagher et al., 2001; Villemure and Bushnell, 2002], an effect recently shown to involve the right anterior insula [Craig, 2005; Roy et al., 2009]. An additional consideration is that unlike sensory aspects of pain, emotional responses to pain do not depend on localization, and therefore may not rely on precise spatial topographically organized maps. This is consistent with our findings of significant activation likelihood within contralateral SI.

It should be noted that the majority of studies included in the meta-analysis tested only right-handed individuals, and therefore the results may not be applicable to the population as a whole. In turn, the results may reflect differential pain processing by right-handed people. For example, pain is more tolerable when presented to the dominant (right) side of the body [Pauli et al., 1999a]. In contrast, pain sensitivity measures in left-handed people are essentially equivalent for stimuli presented to either side of the body [Pauli et al., 1999b]. Therefore, left-handed individuals may process pain either in additional brain regions or in a more distributed fashion in comparison to right-handed people.

Study 5: Differential Processing Associated with Noxious Muscle and Cutaneous Stimuli

The fifth meta-analysis examined preferential neural processing associated with noxious muscle or cutaneous stimuli. Common areas that had a similar likelihood of being activated by both types of stimuli included the thalamus, anterior cingulate cortices, the anterior, mid- and posterior insula cortices, SII, and the posterior parietal cortices. These findings are consistent with evidence

suggesting that convergence of afferent inputs in the periphery terminate on projection neurons in the spino-thalamic tract [Mense, 1993]. Additionally, electrophysiological studies have recorded responses in neurons in the dorsal horn [Amano et al., 1986; Asato and Yokota, 1989] and the thalamus [Kawakita et al., 1993] to noxious cutaneous, muscle, and visceral stimuli.

The likelihood of activation specifically associated with noxious muscle stimuli was significant in the precuneus, the mid/posterior cingulate gyrus, the DLPFC and the cerebellum. The likelihood of activation in some of these regions may be more associated with cognitive aspects of processing muscle pain as this type of pain is generally unavoidable and often evokes uncontrollability [Graven-Nielsen and Mense 2001], and freezing behavior [Fanselow 1986; Rhudy and Meagher 2000]. Therefore, the likelihood of activation in the posterior cingulate cortex may be associated with the aversive nature of the stimuli as activation in this region has been associated with the fear of a noxious stimulus [Ochsner et al., 2006].

Noxious cutaneous stimuli were associated with a significant likelihood of activation in SI and the VLPFC. Cutaneous receptive fields are located in SI with a discrete somatotopic organization [Geyer et al., 1999; Kenshalo et al., 2000]. The significant likelihood of activation in this region likely reflects the fact that cutaneous stimuli are often well localized on the body.

CONCLUSIONS AND FUTURE WORK

Substantial information from functional brain imaging research can be gained through our ability to combine results across multiple studies that used a large variety of experimental conditions. Meta-analytic techniques permit the extraction of common patterns of brain responses thought to reflect the processes that are common across studies. This meta-analysis provides a detailed assessment of brain responses to different types of noxious stimuli. This technique allowed for an objective, quantitative determination of findings across imaging studies, and produced a spatial likelihood map of activation evoked by noxious stimuli. Meta-analyses can be used to expand upon the findings of single studies in that they permit the collation of data across studies to examine robustness and heterogeneity of findings. An important consideration is that single studies are often limited by time and financial ability to test large numbers of subjects. The average number of subjects that were tested in the Study 1 database was 12.5. Therefore, meta-analyses can be used to identify brain regions that are consistently activated in response to noxious stimuli across studies, despite the limitations pertaining to single studies. In addition to providing very strong confirmatory evidence for the activation of brain areas typically associated with pain, and supporting a right-hemisphere dominance in the processing of noxious stimuli, the detailed analyses further demonstrated significant differences associated with the type of noxious stimulus employed, as well as the control condition used to reveal noxious-related responses.

While this work provides confirmatory evidence for the involvement of SI, SII, ACC, insula, prefrontal cortex, thalamus, and basal ganglia in processing nociceptive stimuli, it is not possible to determine based on the results of this study if any of these brain regions have pain-specific responses or work in a network to produce the perception of pain. Several recent studies have called into question the specificity of brain responses to pain [Baliki et al., 2009; Iannetti et al., 2008; Mouraux and Iannetti, 2009; Mouraux et al., 2011]. Some brain regions such as the ACC, insula and SII have been shown to respond to multimodal stimuli with no evidence of a nociceptive specific response [Mouraux et al., 2011]. In that study, neural responses were correlated with the magnitude of the stimulus indicating that the pattern of brain activation seen in response to pain may only be a reflection of estimating pain intensity. In these analyses, data were obtained from several studies that required participants to rate the intensity of the stimuli. A future meta-analysis could compare and contrast data from studies that required rating the stimuli during the experiment with those that simply presented noxious stimuli to subjects in the absence of qualitative estimation of the stimuli.

Future research lies in comparing data from this work with brain activation associated with spontaneously induced pain in chronic pain patients. Few studies have directly compared brain activation evoked by chronic and acute pain; however, a review article indicated that chronic pain patients were more likely to have activation in the prefrontal cortex [Apkarian et al., 2005]. A whole brain meta-analysis would offer a more expansive comparison with patient data to explore additional areas of the brain demonstrating differential activation in response to chronic versus acute pain.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Gary Duncan (University of Montreal) for aiding in the development of the experimental methodology and providing comments on an earlier version of the manuscript. Additionally, the authors are indebted to Joyce Fu and Jen-I Chen for aiding in data entry.

REFERENCES

Adler LJ, Gyulai FE, Diehl DJ, Mintun MA, Winter PM, Firestone LL (1997): Regional brain activity changes associated with fentanyl analgesia elucidated by positron emission tomography. Anesth Analg 84:120–126.

Aharon I, Becerra L, Chabris CF, Borsook D (2006): Noxious heat induces fMRI activation in two anatomically distinct clusters within the nucleus accumbens. Neurosci Lett 392:159–164.

Albanese MC, Duerden EG, Rainville P, Duncan GH (2007): Memory traces of pain in human cortex. J Neurosci 27:4612–4620.

Amano N, Hu JW, Sessle BJ (1986): Responses of neurons in feline trigeminal subnucleus caudalis (medullary dorsal horn): To cutaneous, intraoral, and muscle afferent stimuli. J Neurophysiol 55:227–243.

Andersson JL, Lilja A, Hartvig P, Langstrom B, Gordh T, Handwerker H, Torebjork E (1997): Somatotopic organization along the central sulcus, for pain localization in humans, as revealed by positron emission tomography. Exp Brain Res 117:192–199.

Apkarian AV, Shi T (1998): Thalamocortical connections of the cingulate and insula in relation to nociceptive inputs to the cortex. In: Ayrapeytyan SN, Apkarian AV, editors. Pain mechanisms and management. Amsterdam, Berlin, Oxford, Tokyo, Washington DC: TOS Press. pp 212–220.

Apkarian AV, Gelnar PA, Krauss BR, Szeverenyi NM (2000): Cortical responses to thermal pain depend on stimulus size: A functional MRI study. J Neurophysiol 83:3113–3122.

Apkarian AV, Bushnell MC, Treede RD, Zubieta JK (2005): Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 9:463–484.

Arendt-Nielsen L, Svensson P (2001): Referred muscle pain: Basic and clinical findings. Clin J Pain 17:11–19.

Arienzo D, Babiloni C, Ferretti A, Caulo M, Del Gratta C, Tartaro A, Rossini PM, Romani GL (2006): Somatotopy of anterior cingulate cortex (ACC) and supplementary motor area (SMA) for electric stimulation of the median and tibial nerves: An fMRI study. Neuroimage 33:700–705.

Asato F, Yokota T (1989): Responses of neurons in nucleus ventralis posterolateralis of the cat thalamus' to hypogastric inputs. Brain Res 488:135–142.

Aziz Q, Andersson JL, Valind S, Sundin A, Hamdy S, Jones AK, Foster ER, Langstrom B, Thompson DG (1997): Identification of human brain loci processing esophageal sensation using positron emission tomography. Gastroenterology 113:50–59.

Baliki MN, Geha PY, Apkarian AV (2009): Parsing pain perception between nociceptive representation and magnitude estimation. J Neurophysiol 101:875–887.

Ballantine HT Jr., Cassidy WL, Flanagan NB, Marino R Jr. (1967): Stereotaxic anterior cingulotomy for neuropsychiatric illness and intractable pain. J Neurosurg 26:488–495.

Becerra L, Breiter HC, Wise R, Gonzalez RG, Borsook D (2001): Reward circuitry activation by noxious thermal stimuli. Neuron 32:927–946.

Becerra LR, Breiter HC, Stojanovic M, Fishman S, Edwards A, Comite AR, Gonzalez RG, Borsook D (1999): Human brain activation under controlled thermal stimulation and habituation to noxious heat: An fMRI study. Magn Reson Med 41:1044–1057.

Berthier M, Starkstein S, Leiguarda R (1988): Asymbolia for pain: A sensory-limbic disconnection syndrome. Ann Neurol 24:41–49.

Bingel U, Quante M, Knab R, Bromm B, Weiller C, Buchel C (2002): Subcortical structures involved in pain processing: Evidence from single-trial fMRI. Pain 99:313–321.

Bingel U, Quante M, Knab R, Bromm B, Weiller C, Buchel C (2003): Single trial fMRI reveals significant contralateral bias in responses to laser pain within thalamus and somatosensory cortices. Neuroimage 18:740–748.

Bingel U, Glascher J, Weiller C, Buchel C (2004a): Somatotopic representation of nociceptive information in the putamen: An event-related fMRI study. Cereb Cortex 14:1340–1345.

Bingel U, Lorenz J, Glauche V, Knab R, Glascher J, Weiller C, Buchel C (2004b): Somatotopic organization of human somatosensory cortices for pain: A single trial fMRI study. Neuroimage 23:224–232.

Bingel U, Lorenz J, Schoell E, Weiller C, Buchel C (2006): Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain 120:8–15.

Bingel U, Rose M, Glascher J, Buchel C (2007a): fMRI reveals how pain modulates visual object processing in the ventral visual stream. Neuron 55:157–167.

Bingel U, Schoell E, Herken W, Buchel C, May A (2007b): Habituation to painful stimulation involves the antinociceptive system. Pain 131:21–30.

Binkofski F, Schnitzler A, Enck P, Frieling T, Posse S, Seitz RJ, Freund HJ (1998): Somatic and limbic cortex activation in esophageal distention: A functional magnetic resonance imaging study. Ann Neurol 44:811–815.

Blomqvist A, Zhang E-T, Craig AD (2000): Cytoarchitectonic and immunohistochemical characterization of a specific pain and temperature relay, the posterior portion of the ventral medial nucleus, in the human thalamus. Brain 123:601–619.

Boly M, Balteau E, Schnakers C, Degueldre C, Moonen G, Luxen A, Phillips C, Peigneux P, Maquet P, Laureys S (2007): Baseline brain activity fluctuations predict somatosensory perception in humans. Proc Natl Acad Sci U S A 104:12187–12192.

Bornhovd K, Quante M, Glauche V, Bromm B, Weiller C, Buchel C (2002): Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: A single-trial fMRI study. Brain 125:1326–1336.

Borod JC, Cicero BA, Obler LK, Welkowitz J, Erhan HM, Santschi C, Grunwald IS, Agosti RM, Whalen JR (1998): Right hemisphere emotional perception: Evidence across multiple channels. Neuropsychology 12:446–458.

Borsook D, DaSilva AF, Ploghaus A, Becerra L (2003): Specific and somatotopic functional magnetic resonance imaging activation in the trigeminal ganglion by brush and noxious heat. J Neurosci 23:7897–7903.

Botvinick M, Jha AP, Bylsma LM, Fabian SA, Solomon PE, Prkachin KM (2005): Viewing facial expressions of pain engages cortical areas involved in the direct experience of pain. Neuroimage 25:312–319.

Brooks JC, Zambreanu L, Godinez A, Craig AD, Tracey I (2005): Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. Neuroimage 27:201–209.

Buchel C, Bornhovd K, Quante M, Glauche V, Bromm B, Weiller C (2002): Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: A parametric single-trial laser functional magnetic resonance imaging study. J Neurosci 22:970–976.

Bushnell MC, Duncan GH, Hofbauer RK, Ha B, Chen JI, Carrier B (1999): Pain perception: Is there a role for primary somatosensory cortex?Proc Natl Acad Sci U S A 96:7705–7709.

Cameron OG, Minoshima S (2002): Regional brain activation due to pharmacologically induced adrenergic interoceptive stimulation in humans. Psychosom Med 64:851–861.

Carlsson K, Andersson J, Petrovic P, Petersson KM, Ohman A, Ingvar M (2006): Predictability modulates the affective and sensory-discriminative neural processing of pain. Neuroimage 32:1804–1814.

Casey KL, Minoshima S, Morrow TJ, Koeppe RA (1996): Comparison of human cerebral activation pattern during cutaneous warmth, heat pain, and deep cold pain. J Neurophysiol 76:571–581.

Casey KL, Svensson P, Morrow TJ, Raz J, Jone C, Minoshima S (2000): Selective opiate modulation of nociceptive processing in the human brain. J Neurophysiol 84:525–533.

Casey KL, Morrow TJ, Lorenz J, Minoshima S (2001): Temporal and spatial dynamics of human forebrain activity during heat pain: Analysis by positron emission tomography. J Neurophysiol 85:951–959.

Cechetto DF, Saper CB (1987): Evidence for a viscerotopic sensory representation in the cortex and thalamus in the rat. J Comp Neurol 262:27–45.

Chen JI, Ha B, Bushnell MC, Pike B, Duncan GH (2002): Differentiating noxious- and innocuous-related activation of human somatosensory cortices using temporal analysis of fMRI. J Neurophysiol 88:464–474.

Christmann C, Koeppe C, Braus DF, Ruf M, Flor H (2007): A simultaneous EEG-fMRI study of painful electric stimulation. Neuroimage 34:1428–1437.

Chudler EH, Dong WK (1995): The role of the basal ganglia in nociception and pain. Pain 60:3–38.

Chudler EH, Anton F, Dubner R, Kenshalo DR Jr. (1990): Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: Effect of interstimulus interval. J Neurophysiol 63:559–569.

Coen SJ, Gregory LJ, Yaguez L, Amaro E Jr., Brammer M, Williams SC, Aziz Q (2007): Reproducibility of human brain activity evoked by esophageal stimulation using functional magnetic resonance imaging. Am J Physiol Gastrointest Liver Physiol 293:G188–G197.

Coen SJ, Yaguez L, Aziz Q, Mitterschiffthaler MT, Brammer M, Williams SC, Gregory LJ (2009): Negative mood affects brain processing of visceral sensation. Gastroenterology 137:253–261, e251–252.

Coghill RC, Eisenach J (2003): Individual differences in pain sensitivity: Implications for treatment decisions. Anesthesiology 98:1312–1314.

Coghill RC, Talbot JD, Evans AC, Meyer E, Gjedde A, Bushnell MC, Duncan GH (1994): Distributed processing of pain and vibration by the human brain. J Neurosci 14:4095–4108.

Coghill RC, Sang CN, Maisog JM, Iadarola MJ (1999): Pain intensity processing within the human brain: A bilateral, distributed mechanism. J Neurophysiol 82:1934–1943.

Coghill RC, Gilron I, Iadarola MJ (2001): Hemispheric lateralization of somatosensory processing. J Neurophysiol 85:2602–2612.

Coghill RC, McHaffie JG, Yen YF (2003): Neural correlates of interindividual differences in the subjective experience of pain. Proc Natl Acad Sci U S A 100:8538–8542.

Cole LJ, Farrell MJ, Gibson SJ, Egan GF (2010): Age-related differences in pain sensitivity and regional brain activity evoked by noxious pressure. Neurobiol Aging 31:494–503.

Craig AD (2005): Forebrain emotional asymmetry: A neuroanatomical basis?Trends Cogn Sci 9:566–571.

Craig AD, Dostrovsky JO (2001): Differential Projections of thermoreceptive and nociceptive lamina i trigeminothalamic and spinothalamic neurons in the cat. J Neurophys 86:856–870.

Craig AD, Bushnell MC, Zhang ET, Blomqvist A (1994): A thalamic nucleus specific for pain and temperature sensation. Nature 372:770–773.

Craig AD, Reiman EM, Evans A, Bushnell MC (1996): Functional imaging of an illusion of pain. Nature 384:258–260.

Craig AD, Chen K, Bandy D, Reiman EM (2000): Thermosensory activation of insular cortex. Nat Neurosci 3:184–190.

Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ (2000): Cerebral correlates of autonomic cardiovascular arousal: A functional neuroimaging investigation in humans. J Physiol 523(Pt 1):259–270.

Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ (2004): Neural systems supporting interoceptive awareness. Nat Neurosci 7:189–195.

DaSilva AF, Becerra L, Makris N, Strassman AM, Gonzalez RG, Geatrakis N, Borsook D (2002): Somatotopic activation in the human trigeminal pain pathway. J Neurosci 22:8183–8192.

Davis KD, Pope GE (2002): Noxious cold evokes multiple sensations with distinct time courses. Pain 98:179–185.

Davis KD, Taylor SJ, Crawley AP, Wood ML, Mikulis DJ (1997): Functional MRI of pain- and attention-related activations in the human cingulate cortex. J Neurophysiol 77:3370–3380.

Davis KD, Kwan CL, Crawley AP, Mikulis DJ (1998): Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. J Neurophysiol 80:1533–1546.

Davis KD, Hutchison WD, Lozano AM, Tasker RR, Dostrovsky JO (2000): Human anterior cingulate cortex neurons modulated by attention-demanding tasks. J Neurophysiol 83:3575–3577.

de Leeuw R, Davis CE, Albuquerque R, Carlson CR, Andersen AH (2006): Brain activity during stimulation of the trigeminal nerve with noxious heat. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 102:750–757.

Derbyshire SW, Jones AK (1998): Cerebral responses to a continual tonic pain stimulus measured using positron emission tomography. Pain 76:127–135.

Derbyshire SW, Jones AK, Gyulai F, Clark S, Townsend D, Firestone LL (1997): Pain processing during three levels of noxious stimulation produces differential patterns of central activity. Pain 73:431–445.

Derbyshire SW, Vogt BA, Jones AK (1998): Pain and Stroop interference tasks activate separate processing modules in anterior cingulate cortex. Exp Brain Res 118:52–60.

Derbyshire SW, Nichols TE, Firestone L, Townsend DW, Jones AK (2002a): Gender differences in patterns of cerebral activation during equal experience of painful laser stimulation. J Pain 3:401–411.

Derbyshire SW, Jones AK, Creed F, Starz T, Meltzer CC, Townsend DW, Peterson AM, Firestone L (2002b): Cerebral responses to noxious thermal stimulation in chronic low back pain patients and normal controls. Neuroimage 16:158–168.

Derbyshire SW, Whalley MG, Stenger VA, Oakley DA (2004): Cerebral activation during hypnotically induced and imagined pain. Neuroimage 23:392–401

Downar J, Mikulis DJ, Davis KD (2003): Neural correlates of the prolonged salience of painful stimulation. Neuroimage 20:1540–1551.

Dunckley P, Wise RG, Fairhurst M, Hobden P, Aziz Q, Chang L, Tracey I (2005): A comparison of visceral and somatic pain processing in the human brainstem using functional magnetic resonance imaging. J Neurosci 25:7333–7341.

Duquette M, Rainville P, Alary F, Lassonde M, Lepore F (2008): Ipsilateral cortical representation of tactile and painful information in acallosal and callosotomized subjects. Neuropsychologia 46:2274–2279.

Fairhurst M, Wiech K, Dunckley P, Tracey I (2007): Anticipatory brainstem activity predicts neural processing of pain in humans. Pain 128:101–110.

Farrell MJ, Laird AR, Egan GF (2005): Brain activity associated with painfully hot stimuli applied to the upper limb: A meta-analysis. Hum Brain Mapp 25:129–139.

Farrell MJ, Egan GF, Zamarripa F, Shade R, Blair-West J, Fox P, Denton DA (2006): Unique, common, and interacting cortical

correlates of thirst and pain. Proc Natl Acad Sci U S A 103:2416–2421.
Ferretti A, Babiloni C, Gratta CD, Caulo M, Tartaro A, Bonomo L, Rossini PM, Romani GL (2003): Functional topography of the secondary somatosensory cortex for nonpainful and painful stimuli: An fMRI study. Neuroimage 20:1625–1638.
Foltz EL, White LE (1968): The role of rostral cingulumotomy in "pain" relief. Int J Neurol 6:353–373.
Frankenstein UN, Richter W, McIntyre MC, Remy F (2001): Distraction modulates anterior cingulate gyrus activations during the cold pressor test. Neuroimage 14:827–836.
Gelnar PA, Krauss BR, Sheehe PR, Szeverenyi NM, Apkarian AV (1999): A comparative fMRI study of cortical representations for thermal painful, vibrotactile, and motor performance tasks. Neuroimage 10:460–482.
Genovese CR, Lazar NA, Nichols T (2002): Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 15:870–878.
Geyer S, Schleicher A, Zilles K (1999): Areas 3a, 3b, and 1 of human primary somatosensory cortex. Neuroimage 10:63–83.
Geyer S, Schormann T, Mohlberg H, Zilles K (2000): Areas 3a, 3b, and 1 of human primary somatosensory cortex. Part 2. Spatial normalization to standard anatomical space Neuroimage 11:684–696.
Gianaros PJ, Jennings JR, Sheu LK, Derbyshire SWG, Matthews KA (2007): Heightened functional neural activation to psychological stress covaries with exaggerated blood pressure reactivity. Hypertension 49:134–140.
Giguere M, Goldman-Rakic PS (1988): Mediodorsal nucleus: Areal, laminar, and tangential distribution of afferents and efferents in the frontal lobe of rhesus monkeys. J Comp Neurol 277:195–213.
Goldman-Rakic PS, Porrino LJ (1985): The primate mediodorsal (MD): Nucleus and its projection to the frontal lobe. J Comp Neurol 242:535–560.
Graven-Nielsen T, Mense S (2001): The peripheral apparatus of muscle pain: Evidence from animal and human studies. Clin J Pain 17:2–10.
Graven-Nielsen T, Arendt-Nielsen L, Svensson P, Jensen TS (1997): Quantification of local and referred muscle pain in humans after sequential i.m. injections of hypertonic saline. Pain 69:11–17.
Greenspan JD, Roy EA, Caldwell PA, Farooq NS (2003): Thermosensory intensity and affect throughout the perceptible range. Somatosens Mot Res 20:19–26.
Gyulai FE, Firestone LL, Mintun MA, Winter PM (1997): In vivo imaging of nitrous oxide-induced changes in cerebral activation during noxious heat stimuli. Anesthesiology 86:538–548.
Haslam DR (1970): Lateral dominance in the perception of size and of pain. Q J Exp Psychol 22:503–507.
Head H, Holmes G (1911): Sensory disturbances from cerebral lesions. Brain 34:102–254.
Helmchen C, Mohr C, Erdmann C, Petersen D, Nitschke MF (2003): Differential cerebellar activation related to perceived pain intensity during noxious thermal stimulation in humans: A functional magnetic resonance imaging study. Neurosci Lett 335:202–206.
Helmchen C, Mohr C, Erdmann C, Binkofski F, Buchel C (2006): Neural activity related to self- versus externally generated painful stimuli reveals distinct differences in the lateral pain system in a parametric fMRI study. Hum Brain Mapp 27:755–765.
Henderson LA, Gandevia SC, Macefield VG (2007): Somatotopic organization of the processing of muscle and cutaneous pain in the left and right insula cortex: A single-trial fMRI study. Pain 128:20–30.
Hofbauer RK, Rainville P, Duncan GH, Bushnell MC (2001): Cortical representation of the sensory dimension of pain. J Neurophysiol 86:402–411.
Hofbauer RK, Fiset P, Plourde G, Backman SB, Bushnell MC (2004): Dose-dependent effects of propofol on the central processing of thermal pain. Anesthesiology 100:386–394.
Hsieh JC, Belfrage M, Stone-Elander S, Hansson P, Ingvar M (1995): Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. Pain 63:225–236.
Hsieh JC, Hannerz J, Ingvar M (1996): Right-lateralised central processing for pain of nitroglycerin-induced cluster headache. Pain 67:59–68.
Hutchison WD, Davis KD, Lozano AM, Tasker RR, Dostrovsky JO (1999): Pain-related neurons in the human cingulate cortex. Nat Neurosci 2:403–405.
Iadarola MJ, Coghill RC (1999): Imaging of pain: Recent developments. Curr Opin Anaesthesiol 12:583–589.
Iadarola MJ, Berman KF, Zeffiro TA, Byas-Smith MG, Gracely RH, Max MB, Bennett GJ (1998): Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET. Brain 121(Pt 5):931–947.
Iannetti GD, Hughes NP, Lee MC, Mouraux A (2008): Determinants of laser-evoked EEG responses: Pain perception or stimulus saliency?J Neurophysiol 100:815–828.
Iannilli E, Gerber J, Frasnelli J, Hummel T (2007): Intranasal trigeminal function in subjects with and without an intact sense of smell. Brain Res 1139:235–244.
Ibinson JW, Small RH, Algaze A, Roberts CJ, Clark DL, Schmalbrock P (2004): Functional magnetic resonance imaging studies of pain: An investigation of signal decay during and across sessions. Anesthesiology 101:960–969.
Iwamura Y, Tanaka M, Iriki A, Taoka M, Toda T (2002): Processing of tactile and kinesthetic signals from bilateral sides of the body in the postcentral gyrus of awake monkeys. Behav Brain Res 135:185–190.
Jantsch HH, Kemppainen P, Ringler R, Handwerker HO, Forster C (2005): Cortical representation of experimental tooth pain in humans. Pain 118:390–399.
Jensen R, Rasmussen BK, Pedersen B, Lous I, Olesen J (1992): Cephalic muscle tenderness and pressure pain threshold in a general population. Pain 48:197–203.
Kastrup A, Baudewig J, Schnaudigel S, Huonker R, Becker L, Sohns JM, Dechent P, Klingner C, Witte OW (2008): Behavioral correlates of negative BOLD signal changes in the primary somatosensory cortex. Neuroimage 41:1364–1371.
Kawakita K, Dostrovsky JO, Tang JS, Chiang CY (1993): Responses of neurons in the rat thalamic nucleus submedius to cutaneous, muscle and visceral nociceptive stimuli. Pain 55:327–338.
Keltner JR, Furst A, Fan C, Redfern R, Inglis B, Fields HL (2006): Isolating the modulatory effect of expectation on pain transmission: A functional magnetic resonance imaging study. J Neurosci 26:4437–4443.
Kenshalo DR Jr., Isensee O (1983): Responses of primate SI cortical neurons to noxious stimuli. J Neurophysiol 50:1479–1496.
Kenshalo DR, Iwata K, Sholas M, Thomas DA (2000): Response properties and organization of nociceptive neurons in area 1 of monkey primary somatosensory cortex. J Neurophysiol 84:719–729.

Killgore WD, Yurgelun-Todd DA (2007): The right-hemisphere and valence hypotheses: Could they both be right (and sometimes left)?Soc Cogn Affect Neurosci 2:240–250.

Kong J, White NS, Kwong KK, Vangel MG, Rosman IS, Gracely RH, Gollub RL (2006): Using fMRI to dissociate sensory encoding from cognitive evaluation of heat pain intensity. Hum Brain Mapp 27:715–721.

Korotkov A, Ljubisavljevic M, Thunberg J, Kataeva G, Roudas M, Pakhomov S, Radovanovic S, Lyskov E, Medvedev S, Johansson H (2002): Changes in human regional cerebral blood flow following hypertonic saline induced experimental muscle pain: A positron emission tomography study. Neurosci Lett 335:119–123.

Koyama T, McHaffie JG, Laurienti PJ, Coghill RC (2003): The single-epoch fMRI design: Validation of a simplified paradigm for the collection of subjective ratings. Neuroimage 19:976–987.

Koyama T, McHaffie JG, Laurienti PJ, Coghill RC (2005): The subjective experience of pain: Where expectations become reality. Proc Natl Acad Sci U S A 102:12950–12955.

Krettek JE, Price JL (1977): The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat. J Comp Neurol 171:157–191.

Kuo CC, Yen CT (2005): Comparison of anterior cingulate and primary somatosensory neuronal responses to noxious laser-heat stimuli in conscious, behaving rats. J Neurophysiol 94:1825–1836.

Kupers RC, Svensson P, Jensen TS (2004): Central representation of muscle pain and mechanical hyperesthesia in the orofacial region: A positron emission tomography study. Pain 108:284–293.

Kurata J, Thulborn KR, Gyulai FE, Firestone LL (2002): Early decay of pain-related cerebral activation in functional magnetic resonance imaging: Comparison with visual and motor tasks. Anesthesiology 96:35–44.

Kurata J, Thulborn KR, Firestone LL (2005): The cross-modal interaction between pain-related and saccade-related cerebral activation: A preliminary study by event-related functional magnetic resonance imaging. Anesth Analg 101:449–456, table of contents.

Kwan CL, Crawley AP, Mikulis DJ, Davis KD (2000): An fMRI study of the anterior cingulate cortex and surrounding medial wall activations evoked by noxious cutaneous heat and cold stimuli. Pain 85:359–374.

Ladabaum U, Minoshima S, Hasler WL, Cross D, Chey WD, Owyang C (2001): Gastric distention correlates with activation of multiple cortical and subcortical regions. Gastroenterology 120:369–376.

Laird AR, Fox PM, Price CJ, Glahn DC, Uecker AM, Lancaster JL, Turkeltaub PE, Kochunov P, Fox PT (2005): ALE meta-analysis: Controlling the false discovery rate and performing statistical contrasts. Hum Brain Mapp 25:155–164.

Lancaster JL, Tordesillas-Gutierrez D, Martinez M, Salinas F, Evans A, Zilles K, Mazziotta JC, Fox PT (2007): Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. Hum Brain Mapp 28:1194–1205.

Lorenz IH, Egger K, Schubert H, Schnurer C, Tiefenthaler W, Hohlrieder M, Schocke MF, Kremser C, Esterhammer R, Ischebeck A, Moser PL, Kolbitsch C (2008): Lornoxicam characteristically modulates cerebral pain-processing in human volunteers: A functional magnetic resonance imaging study. Br J Anaesth 100:827–833.

Lorenz J, Cross DJ, Minoshima S, Morrow TJ, Paulson PE, Casey KL (2002): A unique representation of heat allodynia in the human brain. Neuron 35:383–393.

Lu CL, Wu YT, Yeh TC, Chen LF, Chang FY, Lee SD, Ho LT, Hsieh JC (2004): Neuronal correlates of gastric pain induced by fundus distension: A 3T-fMRI study. Neurogastroenterol Motil 16:575–587.

Lugo M, Isturiz G, Lara C, Garcia N, Eblen-Zaijur A (2002): Sensory lateralization in pain subjective perception for noxious heat stimulus. Somatosens Mot Res 19:207–212.

Lui F, Duzzi D, Corradini M, Serafini M, Baraldi P, Porro CA (2008): Touch or pain? Spatio-temporal patterns of cortical fMRI activity following brief mechanical stimuli. Pain 138:362–374.

Maihofner C, Handwerker HO (2005): Differential coding of hyperalgesia in the human brain: A functional MRI study. Neuroimage 28:996–1006.

Maihofner C, Schmelz M, Forster C, Neundorfer B, Handwerker HO (2004): Neural activation during experimental allodynia: A functional magnetic resonance imaging study. Eur J Neurosci 19:3211–3218.

Maihofner C, Herzner B, Otto Handwerker H (2006): Secondary somatosensory cortex is important for the sensory-discriminative dimension of pain: A functional MRI study. Eur J Neurosci 23:1377–1383.

Maihofner C, Seifert F, Decol R (2011): Activation of central sympathetic networks during innocuous and noxious somatosensory stimulation. Neuroimage 55:216–224.

Mainero C, Zhang WT, Kumar A, Rosen BR, Sorensen AG (2007): Mapping the spinal and supraspinal pathways of dynamic mechanical allodynia in the human trigeminal system using cardiac-gated fMRI. Neuroimage 35:1201–1210.

May A, Kaube H, Buchel C, Eichten C, Rijntjes M, Juptner M, Weiller C, Diener HC (1998): Experimental cranial pain elicited by capsaicin: A PET study. Pain 74:61–66.

Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, Silva JA, Tekell JL, Martin CC, Lancaster JL, Fox PT (1999): Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. Am J Psychiatry 156:675–682.

Meagher MW, Arnau RC, Rhudy JL (2001): Pain and emotion: Effects of affective picture modulation. Psychosom Med 63:79–90.

Melzack R, Wall PD (1965): Pain mechanisms: A new theory. Science 150:971–979.

Menon RS, Ogawa S, Hu X, Strupp JP, Anderson P, Ugurbil K (1995): BOLD based functional MRI at 4 Tesla includes a capillary bed contribution: Echo-planar imaging correlates with previous optical imaging using intrinsic signals. Magn Reson Med 33:453–459.

Mense, S (1993): Nociception from skeletal muscle in relation to clinical muscle pain. Pain 54:241–289.

Mobascher A, Brinkmeyer J, Warbrick T, Musso F, Schlemper V, Wittsack HJ, Saleh A, Schnitzler A, Winterer G (2010): Brain activation patterns underlying fast habituation to painful laser stimuli. Int J Psychophysiol 75:16–24.

Mochizuki H, Sadato N, Saito DN, Toyoda H, Tashiro M, Okamura N, Yanai K (2007): Neural correlates of perceptual difference between itching and pain: A human fMRI study. Neuroimage 36:706–717.

Mohr C, Binkofski F, Erdmann C, Buchel C, Helmchen C (2005): The anterior cingulate cortex contains distinct areas dissociating external from self-administered painful stimulation: A parametric fMRI study. Pain 114:347–357.

Mohr C, Leyendecker S, Helmchen C (2008): Dissociable neural activity to self- vs. externally administered thermal hyperalgesia: A parametric fMRI study. Eur J Neurosci 27:739–749.

Moulton EA, Keaser ML, Gullapalli RP, Greenspan JD (2005): Regional intensive and temporal patterns of functional MRI activation distinguishing noxious and innocuous contact heat. J Neurophysiol 93:2183–2193.

Moulton EA, Elman I, Pendse G, Schmahmann J, Becerra L, Borsook D (2011): Aversion-related circuitry in the cerebellum: Responses to noxious heat and unpleasant images. J Neurosci 31:3795–804.

Mouraux A, Iannetti GD (2009): Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. J Neurophysiol 101:3258–3269.

Mouraux A, Diukova A, Lee MC, Wise RG, Iannetti GD (2011): A multisensory investigation of the functional significance of the "pain matrix". Neuroimage 54:2237–2249.

Nash PG, Macefield VG, Klineberg IJ, Gustin SM, Murray GM, Henderson LA (2010): Bilateral activation of the trigeminothalamic tract by acute orofacial cutaneous and muscle pain in humans. Pain 151:384–393.

Nemoto H, Toda H, Nakajima T, Hosokawa S, Okada Y, Yamamoto K, Horiuchi R, Endo K, Ida I, Mikuni M, Goto F (2003): Fluvoxamine modulates pain sensation and affective processing of pain in human brain. Neuroreport 14:791–797.

Neugebauer V, Li W, Bird GC, Han JS (2004): The amygdala and persistent pain. Neuroscientist 10:221–234.

Niddam DM, Yeh TC, Wu YT, Lee PL, Ho LT, Arendt-Nielsen L, Chen AC, Hsieh JC (2002): Event-related functional MRI study on central representation of acute muscle pain induced by electrical stimulation. Neuroimage 17:1437–1450.

Ochsner KN, Ludlow DH, Knierim K, Hanelin J, Ramachandran T, Glover GC, Mackey SC (2006): Neural correlates of individual differences in pain-related fear and anxiety. Pain 120:69–77.

Olausson H, Ha B, Duncan GH, Morin C, Ptito A, Ptito M, Marchand S, Bushnell MC (2001): Cortical activation by tactile and painful stimuli in hemispherectomized patients. Brain 124:916–927.

Oshiro Y, Quevedo AS, McHaffie JG, Kraft RA, Coghill RC (2007): Brain mechanisms supporting spatial discrimination of pain. J Neurosci 27:3388–3394.

Ostrowsky K, Isnard J, Ryvlin P, Guenot M, Fischer C, Mauguiere F (2000): Functional mapping of the insular cortex: Clinical implication in temporal lobe epilepsy. Epilepsia 41:681–686.

Ostrowsky K, Magnin M, Ryvlin P, Isnard J, Guenot M, Mauguiere F (2002): Representation of pain and somatic sensation in the human insula: A study of responses to direct electrical cortical stimulation. Cereb Cortex 12:376–385.

Owen DG, Bureau Y, Thomas AW, Prato FS, St Lawrence KS (2008): Quantification of pain-induced changes in cerebral blood flow by perfusion MRI. Pain 136:85–96.

Owen DG, Clarke CF, Ganapathy S, Prato FS, St Lawrence KS (2010): Using perfusion MRI to measure the dynamic changes in neural activation associated with tonic muscular pain. Pain 148:375–386.

Pauli P, Wiedemann G, Nickola M (1999a): Pain sensitivity, cerebral laterality, and negative affect. Pain 80:359–364.

Pauli P, Wiedemann G, Nickola M (1999b): Pressure pain thresholds asymmetry in left- and right-handers: Associations with behavioural measures of cerebral laterality. Eur J Pain 3:151–156.

Paulson PE, Minoshima S, Morrow TJ, Casey KL (1998): Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. Pain 76:223–229.

Penfield W, Faulk MEJ (1955): The insula: Further observations on its function. Brain 78:445–470.

Petrovic P, Petersson KM, Hansson P, Ingvar M (2002): A regression analysis study of the primary somatosensory cortex during pain. Neuroimage 16:1142–1150.

Petrovic P, Petersson KM, Hansson P, Ingvar M (2004a): Brainstem involvement in the initial response to pain. Neuroimage 22:995–1005.

Petrovic P, Carlsson K, Petersson KM, Hansson P, Ingvar M (2004b): Context-dependent deactivation of the amygdala during pain. J Cogn Neurosci 16:1289–1301.

Peyron R, Garcia-Larrea L, Gregoire MC, Costes N, Convers P, Lavenne F, Mauguiere F, Michel D, Laurent B (1999): Haemodynamic brain responses to acute pain in humans: Sensory and attentional networks. Brain 122(Pt 9):1765–1780.

Pogatzki-Zahn EM, Wagner C, Meinhardt-Renner A, Burgmer M, Beste C, Zahn PK, Pfleiderer B (2010): Coding of incisional pain in the brain: A functional magnetic resonance imaging study in human volunteers. Anesthesiology 112:406–417.

Porro CA, Cettolo V, Francescato MP, Baraldi P (1998): Temporal and intensity coding of pain in human cortex. J Neurophysiol 80:3312–3320.

Porro CA, Baraldi P, Pagnoni G, Serafini M, Facchin P, Maieron M, Nichelli P (2002): Does anticipation of pain affect cortical nociceptive systems?J Neurosci 22:3206–3214.

Qiu Y, Noguchi Y, Honda M, Nakata H, Tamura Y, Tanaka S, Sadato N, Wang X, Inui K, Kakigi R (2006): Brain processing of the signals ascending through unmyelinated C fibers in humans: An event-related functional magnetic resonance imaging study. Cereb Cortex 16:1289–1295.

Raij TT, Numminen J, Narvanen S, Hiltunen J, Hari R (2005): Brain correlates of subjective reality of physically and psychologically induced pain. Proc Natl Acad Sci U S A 102:2147–2151.

Rainville P, Feine JS, Bushnell MC, Duncan GH (1992): A psychophysical comparison of sensory and affective responses to four modalities of experimental pain. Somatosens Mot Res 9:265–277.

Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC (1997): Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277:968–971.

Raja S, Meyer R, Ringkamp M, Campbell J (1999): Peripheral neural mechanisms of nociception. In: Wall PD, Melzack R, editors. Textbook of Pain. New York: Churchill Livingston. pp11-57.

Remy F, Frankenstein UN, Mincic A, Tomanek B, Stroman PW (2003): Pain modulates cerebral activity during cognitive performance. Neuroimage 19:655–664.

Rolls ET, O'Doherty J, Kringelbach ML, Francis S, Bowtell R, McGlone F (2003): Representations of pleasant and painful touch in the human orbitofrontal and cingulate cortices. Cereb Cortex 13:308–317.

Roy M, Piche M, Chen JI, Peretz I, Rainville P (2009): Cerebral and spinal modulation of pain by emotions. Proc Natl Acad Sci USA 106:20090–5.

Ruehle BS, Handwerker HO, Lennerz JK, Ringler R, Forster C (2006): Brain activation during input from mechanoinsensitive versus polymodal C-nociceptors. J Neurosci 26:5492–5499.

Sarlani E, Farooq N, Greenspan JD (2003): Gender and laterality differences in thermosensation throughout the perceptible range. Pain 106:9–18.

Sawamoto N, Honda M, Okada T, Hanakawa T, Kanda M, Fukuyama H, Konishi J, Shibasaki H (2000): Expectation of pain enhances responses to nonpainful somatosensory

stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: An event-related functional magnetic resonance imaging study. J Neurosci 20:7438–7445.

Schneider F, Habel U, Holthusen H, Kessler C, Posse S, Muller-Gartner HW, Arndt JO (2001): Subjective ratings of pain correlate with subcortical-limbic blood flow: An fMRI study. Neuropsychobiology 43:175–185.

Schoedel AL, Zimmermann K, Handwerker HO, Forster C (2008): The influence of simultaneous ratings on cortical BOLD effects during painful and non-painful stimulation. Pain 135:131–141.

Schon D, Rosenkranz M, Regelsberger J, Dahme B, Buchel C, von Leupoldt A (2008): Reduced perception of dyspnea and pain after right insular cortex lesions. Am J Respir Crit Care Med 178:1173–1179.

Schreckenberger M, Siessmeier T, Viertmann A, Landvogt C, Buchholz HG, Rolke R, Treede RD, Bartenstein P, Birklein F (2005): The unpleasantness of tonic pain is encoded by the insular cortex. Neurology 64:1175–1183.

Seifert F, Maihofner C (2007): Representation of cold allodynia in the human brain–a functional MRI study. Neuroimage 35:1168–1180.

Seifert F, Fuchs O, Nickel FT, Garcia M, Dörfler A, Schaller G, Kornhuber J, Sperling W, Maihofner C (2010): A functional magnetic resonance imaging navigated repetitive transcranial magnetic stimulation study of the posterior parietal cortex in normal pain and hyperalgesia. Neuroscience 170:670–677.

Seminowicz DA, Davis KD (2006): Cortical responses to pain in healthy individuals depends on pain catastrophizing. Pain 120:297–306.

Seminowicz DA, Davis KD (2007): Interactions of pain intensity and cognitive load: The brain stays on task. Cereb Cortex 17:1412–1422.

Seminowicz DA, Mikulis DJ, Davis KD (2004): Cognitive modulation of pain-related brain responses depends on behavioral strategy. Pain 112:48–58.

Shmuel A, Yacoub E, Pfeuffer J, Van de Moortele PF, Adriany G, Hu X, Ugurbil K (2002): Sustained negative BOLD, blood flow and oxygen consumption response and its coupling to the positive response in the human brain. Neuron 36:1195–1210.

Shmuel A, Augath M, Oeltermann A, Logothetis NK (2006): Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. Nat Neurosci 9:569–577.

Sikes RW, Vogt BA (1992): Nociceptive neurons in area 24 of rabbit cingulate cortex. J Neurophysiol 68:1720–1732.

Sikes RW, Vogt LJ, Vogt BA (2008): Distribution and properties of visceral nociceptive neurons in rabbit cingulate cortex. Pain 135:160–174.

Song GH, Venkatraman V, Ho KY, Chee MW, Yeoh KG, Wilder-Smith CH (2006): Cortical effects of anticipation and endogenous modulation of visceral pain assessed by functional brain MRI in irritable bowel syndrome patients and healthy controls. Pain 126:79–90.

Sprenger T, Valet M, Boecker H, Henriksen G, Spilker ME, Willoch F, Wagner KJ, Wester HJ, Tolle TR (2006): Opioidergic activation in the medial pain system after heat pain. Pain 122:63–67.

Stammler T, De Col R, Seifert F, Maihofner C (2008): Functional imaging of sensory decline and gain induced by differential noxious stimulation. Neuroimage 42:1151–1163.

Staud R, Craggs JG, Robinson ME, Perlstein WM, Price DD (2007): Brain activity related to temporal summation of C-fiber evoked pain. Pain 129:130–142.

Straube T, Schmidt S, Weiss T, Mentzel HJ, Miltner WH (2008): Sex differences in brain activation to anticipated and experienced pain in the medial prefrontal cortex. Hum Brain Mapp 30:689–98.

Strigo IA, Duncan GH, Boivin M, Bushnell MC (2003): Differentiation of visceral and cutaneous pain in the human brain. J Neurophysiol 89:3294–3303.

Strigo IA, Duncan GH, Bushnell MC, Boivin M, Wainer I, Rodriguez Rosas ME, Persson J (2005): The effects of racemic ketamine on painful stimulation of skin and viscera in human subjects. Pain 113:255–264.

Sung EJ, Yoo SS, Yoon HW, Oh SS, Han Y, Park HW. (2007) Brain activation related to affective dimension during thermal stimulation in humans: a functional magnetic resonance imaging study. Int J Neurosci 117:1011–1027.

Svensson P, Minoshima S, Beydoun A, Morrow TJ, Casey KL (1997): Cerebral processing of acute skin and muscle pain in humans. J Neurophysiol 78:450–460.

Svensson P, Johannsen P, Jensen TS, Arendt-Nielsen L, Nielsen J, Stodkilde-Jorgensen H, Gee AD, Baarsgaard Hansen S, Gjedde A (1998): Cerebral blood-flow changes evoked by two levels of painful heat stimulation: A positron emission tomography study in humans. Eur J Pain 2:95–107.

Symonds LL, Gordon NS, Bixby JC, Mande MM (2006): Right-lateralized pain processing in the human cortex: An FMRI study. J Neurophysiol 95:3823–3830.

Takahashi K, Taguchi T, Tanaka S, Sadato N, Qiu Y, Kakigi R, Mizumura K. Painful muscle stimulation preferentially activates emotion-related brain regions compared to painful skin stimulation. Neurosci Res (in press).

Talairach J, Tournoux P (1988): Co-planar stereotaxic atlas of the human brain. New York: Thieme.

Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH (1991): Multiple representations of pain in human cerebral cortex. Science 251:1355–1358.

Terekhin P, Forster C (2006): Hypocapnia related changes in pain-induced brain activation as measured by functional MRI. Neurosci Lett 400:110–114.

Thunberg J, Lyskov E, Korotkov A, Ljubisavljevic M, Pakhomov S, Katayeva G, Radovanovic S, Medvedev S, Johansson H (2005): Brain processing of tonic muscle pain induced by infusion of hypertonic saline. Eur J Pain 9:185–194.

Tölle TR, Kaufmann T, Siessmeier T, Lautenbacher S, Berthele A, Munz F, Zieglgänsberger W, Willoch F, Schwaiger M, Conrad B, Bartenstein P (1999): Region-specific encoding of sensory and affective components of pain in the human brain: a positron emission tomography correlation analysis. Ann Neurol 45:40-7.

Tracey I, Becerra L, Chang I, Breiter H, Jenkins L, Borsook D, Gonzalez RG (2000): Noxious hot and cold stimulation produce common patterns of brain activation in humans: A functional magnetic resonance imaging study. Neurosci Lett 288:159–162.

Uematsu H, Shibata M, Miyauchi S, Mashimo T (2011): Brain imaging of mechanically induced muscle versus cutaneous pain. Neurosci Res 70:78–84.

Vandenbergh J, Dupont P, Fischler B, Bormans G, Persoons P, Janssens J, Tack J (2005): Regional brain activation during proximal stomach distention in humans: A positron emission tomography study. Gastroenterology 128:564–573.

Villemure C, Bushnell MC (2002): Cognitive modulation of pain: How do attention and emotion influence pain processing?Pain 95:195–199.

Vogt BA, Derbyshire S, Jones AK (1996): Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging. Eur J Neurosci 8:1461–1473.

Wagner KJ, Sprenger T, Kochs EF, Tolle TR, Valet M, Willoch F (2007): Imaging human cerebral pain modulation by dose-dependent opioid analgesia: A positron emission tomography activation study using remifentanil. Anesthesiology 106:548–556.

Wall PD, Woolf CJ (1984): Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. J Physiol 356:443–458.

Wang CC, Shyu BC (2004): Differential projections from the mediodorsal and centrolateral thalamic nuclei to the frontal cortex in rats. Brain Res 995:226–235.

Wiech K, Tracey I (2009): The influence of negative emotions on pain: Behavioral effects and neural mechanisms. Neuroimage 47:987–994.

Weigelt A, Terekhin P, Kemppainen P, Dörfler A, Forster C (2010): The representation of experimental tooth pain from upper and lower jaws in the human trigeminal pathway. Pain 149:529–538.

Xu X, Fukuyama H, Yazawa S, Mima T, Hanakawa T, Magata Y, Kanda M, Fujiwara N, Shindo K, Nagamine T, Shibasaki H (1997): Functional localization of pain perception in the human brain studied by PET. Neuroreport 8:555–559.

Yasui Y, Breder CD, Saper CB, Cechetto DF (1991): Autonomic responses and efferent pathways from the insular cortex in the rat. J Comp Neurol 303:355–374.

Yilmaz P, Diers M, Diener S, Rance M, Wessa M, Flor H (2010): Brain correlates of stress-induced analgesia. Pain 151:522–529.

Zhang ZH, Dougherty PM, Oppenheimer SM (1999): Monkey insular cortex neurons respond to baroreceptive and somatosensory convergent inputs. Neuroscience 94:351–360.