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Brain Activity Associated With Painfully Hot Stimuli Applied to the Upper Limb: A Meta-Analysis

Michael J. Farrell,[1,2]* Angela R. Laird,[3] and Gary F. Egan[1,2]

[1]*Howard Florey Institute, University of Melbourne, Melbourne, Australia*
[2]*Center for Neuroscience, University of Melbourne, Melbourne, Australia*
[3]*Research Imaging Center, University of Texas Health Sciences Center San Antonio, San Antonio, Texas*

Abstract: The capacity of pain to alert against potential injury or focus attention on damaged tissue is enhanced by the intrinsically aversive nature of the experience. Finding methods to relieve pain will ultimately be facilitated by deeper understanding of the processes that contribute to the experience, and functional brain imaging has contributed substantially toward that end. An impressive body of literature has identified a distributed network of pain-related activity in the brain that is subject to considerable modulation by different stimulus parameters, contextual factors, and clinical conditions. The fundamental substrates of the pain network are yet to be distilled from the highly variable results of studies published thus far. Qualitative reviews of the pain-imaging literature have been contributory, but lack the greater surety of quantitative methods. We employ the activation likelihood estimation (ALE) meta-analytic technique to establish the most consistent activations among studies reporting brain responses subsequent to the application of noxious heat. A network of pain-related activity was replicated for stimuli to either upper limb that included two discernible regions of the mid-anterior cingulate cortex, bilateral thalami, insula, and opercula cortices, posterior parietal cortex, premotor cortex, supplementary motor area, and cerebellum. The findings of the meta-analysis resonate with other streams of information that continue to enhance our understanding of pain in the brain. The results also point toward new areas of research that may be fruitful for the exploration of central pain processing. *Hum Brain Mapp 25:129–139, 2005.*
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Key words: pain; heat; noxious stimuli; brain activity; functional neuroimaging; meta-analysis

INTRODUCTION

Pain is a universal, aversive experience. At its most benign state, low levels of pain act as a warning against potential tissue damage. When persistent, pain can be associated with profound levels of disability and psychological comorbidity. The supraspinal processes that subserve the experience of pain are of considerable biological and clinical interest. Functional brain-imaging techniques have provided an opportunity to explore critical issues about the central representation and modulation of pain. This opportunity has been embraced by the scientific community, fostering a substantial body of literature addressing fundamental and applied questions about pain and the brain. The time is now ripe for a second-order appraisal of this literature to provide another layer of interpretation to pain-imaging studies.

Conceptualization of pain as a multidimensional construct and the incapacity of isolated lesions to obviate the experi-

*Correspondence to: Michael Farrell, Howard Florey Institute, The University of Melbourne, Melbourne, VIC 3010, Australia.
E-mail: m.farrell@hfi.unimelb.edu.au

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ence of pain have argued against a spatially discrete representation of pain in the brain. In their seminal discussion of the gate control theory, Melzack and Wall [1965] dismissed the concept of a "pain center," pointing to the thalamus, limbic system, hypothalamus, brain stem reticular formation, parietal cortices, and frontal cortices as components of a network of activity associated with a sensation incorporating discriminative, affective, and cognitive dimensions. Studies over the last decade using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have provided an increasingly sophisticated understanding of the representation of pain in the brain, and have revealed a number of neuroanatomical locations of pain-related activity. A consensus about the core substrates of the pain network is emerging with several reviews contributing significantly toward that end [Derbyshire, 2000; Jones et al., 2002; Peyron et al., 2000; Porro, 2003]. Empirical meta-analytic techniques have not yet been applied to the task of collating functional imaging data across pain studies.

The pioneering work of groups from Quebec [Talbot et al., 1991] and Hammersmith [Jones, 1991] delivered the first images of pain-related activity in the human brain. The respective presence and absence of primary somatosensory cortex (S1) activity reported in the two studies contributed to an ongoing debate about the role of S1 in pain processing [Bushnell et al., 1999]. Subsequent studies have continued to produce variations on the distributed pain network, reflecting the multidimensional nature of the experience and differences in experimental parameters.

Despite the range of questions that are addressed by pain-imaging research, many experiments report details of brain activity associated with simple comparisons between noxious and innocuous stimuli. The single most common modality used to identify pain-related activity is thermal stimulation of the skin. Thermal stimulation has both logistical advantages and phenomenological attributes that explain the frequent application of heat for psychophysical and brain-imaging studies. Although outliers exist, the pain stimulus–response function for heat does not differ greatly across healthy volunteers [Gracely et al., 1988; Price et al., 1983]. This consistency of response permits the use of a fixed stimulus intensity that is likely to reliably produce a tolerable level of pain in almost all subjects, although some studies tailor stimuli according to the sensitivity of individual subjects by using psychophysical procedures. The neural substrates of pain and thermal sensations share much in common and juxtaposing brain responses to noxious and innocuous heat stimuli are more likely to identify activity that is confined to the unique elements of the pain experience.

The frequent adoption of thermal stimuli for pain-imaging studies has produced a rich vein of information with considerable potential to reveal the most regularly occurring pain-related activations, and the activation likelihood estimation (ALE) method is particularly suited to the search for the primary neuroanatomical substrates of the pain experience [Turkeltaub et al., 2002]. The objective of this meta-analysis is to review the relevant literature and use quantitative meta-analytic tools to establish the common elements of the supraspinal pain network across functional neuroimaging studies that have applied thermal stimuli to the upper limb.

MATERIALS AND METHODS

Literature Search and Selection

Successive filters were used to identify articles for inclusion in the ALE analysis. In the first instance MeSH terms (pain and brain mapping) were used with key words (heat or thermal) to identify articles published up to the end of 2003, using a standard search engine (Medline). In total, 86 articles were returned by the search. These articles were reviewed to establish that: (1) the sample included healthy volunteers; (2) heat stimuli were used; (3) in the case of contact thermodes, a contrast between innocuous warm and painfully hot stimuli were reported; (4) heat stimuli delivered with laser did not include a tactile component, or a salient nonpainful control contrast was included in the generation of activation maps; (5) stimuli were confined to either the left or right upper limb in any single contrast; (6) the field of view of the images was not confined to a restricted region of the cortex; and (7) results were reported in Talairach or Montreal Neurological Institute (MNI) coordinates. The search for articles also sought to identify any instances of multiple reports of single data sets across articles, to ensure that only one report of a study contributed to coordinates for meta-analysis. This filtering process yielded 23 articles that incorporated standardized stereotactic coordinates of activations associated with painful thermal stimulation of the left or right arm and hand of healthy volunteers.

Conditions and Experiments

Conditions included innocuous thermal stimulation, the absence of any cutaneous stimulation, and noxious thermal stimulation. Experiments included contrasts that produced activations associated with the experience of pain including noxious versus innocuous thermal stimuli applied with temperature-controlled thermodes and noxious laser stimuli versus the absence of stimulation. Articles fulfilling inclusion criteria could potentially contribute more than one contrast from a single modality if multiple sites or intensities of stimulation were employed. To reduce disproportional impact from some studies only one contrast was used from articles that parametrically manipulated pain intensity. In those instances of multiple pain contrasts, the most intense pain versus innocuous or absent stimulation was chosen. Laterality is important when considering somatosensory experiences and consequently contrasts associated with stimuli to the left and right upper limbs were tabulated separately, allowing for a single study to contribute to both, albeit discrete, data sets.

Analysis

Descriptive information was extracted from each article including imaging modality, sample size, and pain stimulus attributes. Information about stimulus modality (contact or radiant heat), location (site, side), and duration was collated. The intensity of stimuli was collated by method of derivation (fixed or response dependent). A fixed-intensity paradigm was defined as an experiment that used the same level of stimulation for all subjects. A response-dependent paradigm was defined as an experiment that used different stimuli for each subject, the intensity of stimuli used in each case being determined by a prescanning scaling procedure.

Meta-Analysis

We used the ALE analytic strategy [Turkeltaub et al., 2002] whereby results from all studies were converted to the 3D coordinate system of the Talairach atlas. The space for the analysis was divided into 2 mm × 2 mm × 2 mm voxels and a Gaussian filter of 8 mm full-width half-maximum (FWHM) was used to generate ALE maps, which were thresholded by a permutation test controlling the false discovery rate (FDR) at $P < 0.01$. A minimum cluster size was not applied. ALE maps were generated for left- and right-side pain-related contrasts. Locations of voxels with peak probabilities within clusters and cluster sizes were identified.

RESULTS

The 23 studies used in the meta-analysis are reported in Table I. They included two publications by a group from Hamburg University who split coordinates of a pain-related contrast across studies and were subsequently coded as a single report [Bingel et al., 2002, 2003]. Sample sizes ranged between 6 and 27 subjects. Most studies explored pain-related brain activity using PET (73%) and contact thermodes (68%). A single study employed hot water baths to stimulate the immersed hand. The ventral surface of the forearm (46%) and the dorsum of the hand (40%) constituted the sites of stimulation in almost equal measure with one instance each of stimulation to the upper arm, palm, and whole of hand (immersion in water bath). Laser stimuli were frequently small (e.g., 5-mm spot) and brief (e.g., 1 ms), whereas contact thermodes varied in area (0.79–9 cm^2) and were applied for longer periods that were dictated by the ramp times to achieve and recover from target temperatures. Data on pain intensity was not reported in all articles, and variation in measurement strategies across articles did not allow meaningful comparisons. In all instances, either the rationale for stimulus choice or reports of ratings of sensations associated with stimuli confirmed that the contrast of interest (pain vs. the absence of pain) had been achieved.

Clusters

The 22 studies yielded tabulated coordinates for 14 contrasts involving left-side stimulation and 10 contrasts for right-side stimulation. The ALE analysis of the left side incorporated 249 foci and the right analysis used 170 foci. The labels ascribed to the activation loci by the authors of the studies have been summarized in Table II. The number of clusters and their total volume that resulted from the respective left and right ALE analyses reflected the greater number of studies contributing to the left-side comparison (left clusters = 18, right clusters = 16, total volume left = 14,186 mm^3, and total volume right = 13,144 mm^3). Table III lists the coordinates for each of the clusters from both analyses. Anatomical labels for the clusters were derived with the Talairach Daemon [Lancaster et al., 2000].

Anterior Cingulate Cortex

All studies included in the analysis reported pain-related activity in the anterior cingulate cortex (ACC). The single largest cluster for pain on the left (PL) had a peak voxel in Brodmann area (BA) 32 (x = −2, y = 10, z = 40), but clearly extended into BA24. The left-side contrast also produced a small, discrete area of activity rostral to the primary ACC cluster that was clearly in the left hemisphere (x = −8, y = 24, z = 30). The location of two clusters for pain on the right (PR) substantially overlapped the primary ACC cluster for PL (see Fig. 1a). The more dorsal of the PR clusters had a peak voxel at the midline, (x = 0, y = 0, z = 46), whereas the slightly smaller, more rostral cluster had a peak voxel in the right hemisphere (x = 4, y = 16, z = 28). The Talairach daemon identified BA24 as the location of the two ACC clusters for PR.

Thalamus

Both PR and PL were associated with bilateral activity in the thalamus. The symmetrical distribution of thalamic activity was reflected in the presence of two discrete foci for PL (x = −8, y = −16, z = 10 and x = 10, y = −20, z = 6). A single thalamic cluster with a peak voxel at (x = 10, y = −12, z = 2) was identified by the PR analysis. Although contiguous via a midline connection, the PR thalamic cluster clearly incorporated contralateral and ipsilateral components (Fig. 2, z = 0). There was considerable concordance between the PR and PL clusters, with the later extending superiorly beyond the common area, and the former having a more substantial inferior extent (Fig. 1f). The PR analysis also resulted in a small, mesial thalamic cluster at (x = −4, y = −6, z = 0).

Central Sulcus and Posterior Parietal Cortex

Activity in the region of S1 was reported in approximately half of the studies. Only one cluster, for the PR analysis, was identified as a prospective candidate for activity in S1 (BA3; x = −38, y = −26, z = 62; Fig. 1g).

Two small clusters, one from each analysis, were located in the inferior parietal lobule (IPL) (BA40) in the right hemisphere (PR, x = 54, y = −42, z = 26; PL, x = 52, y = −30, z = 26; Fig. 1e) with PR activity also in the IPL in the ipsilateral hemisphere. The cluster in question incorporates a more extensive region extending into the lateral sulcus.

TABLE I. Details of the samples and experimental procedures employed by the studies included in the meta-analysis

Publication	Imaging	n	Stimulus	Site	Side	Size (cm^2)	Duration (s)	Intensity	Primary question
Adler et al., 1997	PET	9	Contact probe	Forearm	L	NS	180	Fixed	Action of fentanyl
Becerra et al., 1999	fMRI	6; 6	Contact probe	Hand	L	9.0	29	Fixed	Habituation
Bingel, 2002, 2003	fMRI	14	Laser	Hand	L + R	0.2	0.001	Fixed	Somatotopic representation
Bornhovd et al., 2002	fMRI	9	Laser	Hand	L	0.2	0.001	Fixed	Pain-related intensity coding
Casey et al., 1996	PET	27	Contact probe	Forearm	L	2.5	5	Fixed	Cold vs. heat pain
Casey et al., 2001	PET	14	Contact probe	Forearm	L	2.5	5	Fixed	Phasic vs. tonic pain
Coghill et al., 1999	PET	16	Contact probe	Upper arm	R	0.8	5	Fixed	Pain-related intensity coding
Coghill et al., 2001	PET	9	Contact probe	Forearm	L + R	0.8	5	Fixed	Hemispheric lateralization
Derbyshire et al., 1997	PET	12	Laser	Hand	R	All hand	0.1	Subject dependent	Pain-related intensity coding
Derbyshire and Jones, 1998	PET	12	Water bath	Hand	R	2.5	150	Subject dependent	Phasic vs. tonic pain
Derbyshire et al., 2002	PET	16	Contact probe	Hand	R	12.5	15	Subject dependent	Patients vs. controls
Jones and Derbyshire, 1997	PET	6	Contact probe	Hand	R	12.5	15	Subject dependent	Patients vs. controls
Lorenz et al., 2002	PET	14	Contact probe	Forearm	L	2.5	60	Subject dependent	Hyperalgesia
Nemoto et al., 2003	PET	12	Laser	Forearm	R	0.4	120	Fixed	Action of fluvoxamine
Paulson et al., 1998	PET	12	Contact probe	Forearm	L	2.5	5	Fixed	Gender differences
Remy et al., 2003	fMRI	12	Contact probe	Hand	L	9.0	13	Subject dependent	Pain effects on cognition
Smith et al., 2002	fMRI	8	Contact probe	Hand	L	9.0	11.5	Subject dependent	Depression effects on pain
Svensson et al., 1997	PET	11	Laser	Forearm	L	9.0	0.05	Subject dependent	Skin vs. muscle pain
Svensson et al., 1998	PET	10	Contact probe	Forearm	R	0.8	4	Subject dependent	Phasic vs. tonic pain
Tolle et al., 1999	PET	12	Contact probe	Forearm	R	4×3.1	2	Fixed	Pain-related unpleasantness
Tracey et al., 2000	fMRI	6	Contact probe	Hand	L	5.8	25	Fixed	Cold vs. heat pain
Xu et al., 1997	PET	6	Laser	Hand	L	9.0	0.06	Fixed	Somatotopic representation

The stimulus duration represents the interval between onset and offset of a single application of heat, and does not necessarily indicate the total time that repeated stimuli were applied during a single PET scan or fMRI epoch. The intensity column indicates the method used to determine stimulus intensity across subjects; fixed refers to the use of a single intensity for all subjects, whereas Subject dependent indicates that the intensity was determined for each subject to achieve a uniform rating of pain.

Lateral Sulcus

Pain-related activations in the insula and opercula cortices are reported commonly and the studies included in the meta-analysis were consistent with this trend. The distribution of ALE clusters in the region of the lateral sulcus warrant careful description that goes beyond citation of coordinates for peak voxels. This caution is required because several of the clusters near the lateral sulcus have loci in either the insula, frontal operculum, or parietal operculum, but had extensive distributions that incorporated more than one neuroanatomical region. In some instances, clusters extended beyond the most lateral extent of the sulcus to include activity in the premotor area or were contiguous with regions of the posterior parietal cortex.

The distribution of pain-related activity near the lateral sulcus could be summarized as bilateral through the anterior and middle portions and confined to the contralateral side in the most posterior part of the insula and parietal operculum. Generally, PL clusters near the lateral sulcus were of greater spatial extent and more likely to demonstrate symmetry across the midline in the anterior and middle portions of the sulcus. Although less robust, the PR

TABLE II. Neuroanatomical labels used to describe locations of activation associated with thermal pain

Publication	ACC	Insula	Thalamus	Lent. N.	S2	Cerebellum	S1/M1	Premotor	Midbrain	IPL	SMA
Adler et al., 1997	C	—	I	—	—	—	—	—	—	—	C
Becerra et al., 1999	M	I	C	—	C	I	C	I	—	—	I
Bingel, 2002, 2003	B	B	B	B	B	I	B	—	B	—	—
Bornhovd et al., 2002	I	B	—	—	B	—	B	—	—	—	—
Casey et al., 1996	C	C	B	C	C	I	C	B	M	—	—
Casey et al., 2001	B	B	B	C	B	B	C	B	—	—	—
Coghill et al., 1999	M	B	B	B	B	I	C	B	—	—	C
Coghill et al., 2001	I	C	B	B	C	B	C	B	I	—	I
Derbyshire et al., 1997	I	C	B	B	—	—	C	B	—	B	—
Derbyshire and Jones, 1998	B	B	I	I	C	I	—	—	—	—	—
Derbyshire et al., 2002	I	C	B	B	—	I	—	—	I	B	—
Jones and Derbyshire, 1997	C	—	—	C	—	—	—	—	M	I	—
Lorenz et al., 2002	C	B	I	C	C	—	—	—	—	C	—
Nemoto et al., 2003	B	B	B	B	C	B	—	—	M	C	—
Paulson et al., 1998	C	B	B	B	—	B	C	B	—	—	—
Remy et al., 2003	I	I	C	—	—	—	—	B	—	—	—
Smith et al., 2002	C	C	—	—	B	B	—	—	—	—	—
Svensson et al., 1997	C	C	C	C	C	I	C	I	—	—	—
Svensson et al., 1998	C	C	C	C	C	B	C	C	—	—	—
Tolle et al., 1999	B	—	C	C	—	—	—	—	M	—	—
Tracey et al., 2000	I	B	C	C	B	—	C	C	—	B	M
Xu et al., 1997	C	B	C	C	B	B	—	B	—	—	—
Ipsilateral	27	9	14	5	0	32	0	9	9	5	9
Contralateral	41	32	32	41	36	0	45	9	0	9	9
Bilateral	23	45	41	32	32	32	9	36	5	14	0
Not reported	0	14	14	23	32	36	41	45	68	73	77

The percentages of unilateral, bilateral, and absent activations are summarized.
ACC, anterior cingulate cortex; Lent. N., lentiform nuclei; S2, secondary somatosensory cortex; S1/M1, primary somatosensory and motor cortices; IPL, inferior parietal lobule; SMA, supplementary motor area; B, bilateral; C, contralateral; I, ipsilateral; M, midline.

clusters frequently occupied common voxels with PL clusters or the margins of clusters from the respective analyses were in close proximity.

The peak voxels for each of the clusters in the region of the sulcus (Fig. 2) are reported collectively in Table III under the heading of insula and opercula cortices. Of bilateral PR clusters evident in the anterior/mid-insula cortices (Fig. 2, z = 0), only the contralateral of the two extends laterally into the operculum (Fig. 2, slices z = 0 to z = 8). This contralateral PR cluster overlaps to a degree with a smaller ipsilateral PL cluster near the juncture of insula and opercula cortices (Fig. 2, z = 4). Although not contiguous, PL clusters in the left hemisphere occupy a similar territory to the contralateral PR cluster. The contralateral PL cluster in the right lateral sulcus is of similar spatial extent and orientation to its PR counterpart, extending into the operculum beyond the fundus of the insula. Although bilateral, pain-related activity in the anterior/middle portion of the lateral sulcus thus has a contralateral predominance.

The pain-related ALE clusters in the posterior portion of the insula were contralateral for both PR and PL. The peak voxels for each of the clusters (PL, x = 38, y = −20, z = 16; PR, x = −50, y = −24, z = 20) are both in the parietal operculum and have substantial lateral extents; however, the most medial portions of both clusters incorporate the fundi of the insulae (Fig. 1f, 2, z = 16).

Prefrontal Cortex

The PR analysis was notable for an absence of any clusters in the prefrontal cortex. Two small clusters, both in the right hemisphere, were identified by the PL analysis. These clusters were located in the inferior (BA10; x = 38, y = 46, z = 2) and superior frontal gyri (BA9; x = 28, y = 40, z = 30).

Supplementary Motor Cortex and Premotor Cortex

The PL and PR analyses both resulted in clusters with peak voxels in the right supplementary motor area (Fig. 1g). Other clusters with peak voxels in the premotor area were associated primarily with the PL analysis, although there were small areas of overlap between clusters from the two analyses at the margin of the premotor cortex and the lateral sulcus in each hemisphere (Fig. 1a,b). The axial views of this region clearly demonstrate more robust activity associated with PL (Fig. 2, z = 8). The PL cluster in the right hemisphere is contiguous with voxels in the opercula and insula cortices. The PL analysis also produced clusters in BA6 at (x = 10, y = 6, z = 50) and (x = 26, y = 16, z = 52). The former

TABLE III. Results of ALE for contrasts between pain and innocuous heat applied to the left or right upper limb

		Stimulation									
		Left					Right				
Region	Side	x	y	z	ALE	Volume	x	y	z	ALE	Volume
Anterior cingulate	—	−2	10	40	0.049	3,112	4	16	28	0.035	1,104
	—	−8	24	30	0.022	104	0	0	46	0.030	1,424
Insula + opercula											
Claustrum	I	−36	2	8	0.025	224	30	10	14	0.022	192
Claustrum	C	—	—	—	—	—	−50	−4	6	0.027	2,016
BA13	I	−38	16	6	0.026	288	42	16	−2	0.022	256
BA13	C	38	−20	16	0.046	1,344	−50	−24	20	0.030	1,352
BA13	C	32	4	6	0.036	2,560	—	—	—	—	—
Thalamus	I	−8	−16	10	0.049	2,456	10	−12	2	0.032	3,576
	C	10	−20	6	0.049	1,904	−4	−6	0	0.023	128
Parietal cortex											
BA3	C	—	—	—	—	—	−38	−26	62	0.022	424
BA40	C	52	−30	26	0.026	392	—	—	—	—	—
BA40	I	—	—	—	—	—	54	−42	26	0.021	128
Frontal cortex											
BA10	C	38	46	2	0.021	104	—	—	—	—	—
BA9	C	28	40	30	0.024	104	—	—	—	—	—
Premotor cortex											
BA6	I	−48	0	12	0.032	704	—	—	—	—	—
BA6	C	26	−16	52	0.044	960	—	—	—	—	—
BA6	C	10	6	50	0.022	128	—	—	—	—	—
SMA	C	6	−6	62	0.035	480	6	2	62	0.020	152
Lentiform nuclei	I	—	—	—	—	—	24	−2	2	0.022	384
Cerebellum											
Vermis	—	4	−58	−12	0.030	712	4	−48	−14	0.034	904
	I	−26	−56	−16	0.023	200	24	−58	−22	0.033	688
	C	38	−52	−36	0.023	120	−20	−64	−26	0.020	176
Superior temporal gyrus	I	—	—	—	—	—	56	8	0	0.018	240

Coordinates are given in Talairach space; cluster volumes are given in mm^3 and activation location is denoted relative to the side of stimulation (I, ipsilateral; C, contralateral) except for loci near the midline.
BA, Brodmann area.

of these clusters was in close proximity to the most dorsal extent of a PR cluster with a peak voxel in BA24, whereas the latter seemed unique to the result of the PL analysis.

Lentiform Nuclei

There was only one cluster from the PR analysis that had a peak voxel in the lentiform nucleus (x = 24, y = −2, z = 2); however, common voxels from the two analyses that are located at the margin of the right putamen were from clusters that extended into the nucleus (Fig. 2, z = 4). A cluster from the PR comparison in the left hemisphere also extended beyond the insula into the putamen (Fig. 2, z = 4).

Cerebellum

Vermal clusters from the PR (x = 4, y = −48, z = −14) and PL (x = 4, y = −58, z = −12) analyses had a common area of overlap, but extended in anterior and posterior directions respectively. These two clusters seemed lateralized to the right hemisphere (Fig. 1d). Bilateral clusters in the cerebellar hemispheres were in evidence for both the PR (contralateral, x = −20, y = −64, z = −26; ipsilateral, x = 24, y = −58, z = −22) and PL (contralateral, x = 38, y = −52, z = −36; ipsilateral, x = −26, y = −56, z = −16) analyses.

DISCUSSION

Pain arising from brief, noxious, thermal stimulation is associated with a reproducible network of brain activity. The consistency of activation patterns between left- and right-side stimulation, and by implication across different laboratories and samples, lends weight to the conclusion that the results of the ALE analysis represent an archetypal brain response to brief noxious cutaneous stimulation.

The nature of the pain paradigm explored in this meta-analysis warrants elaboration. The experience of pain is subject to considerable modulation that is dependent upon contextual factors. The early experience of pain reduces the

risk of injury by facilitating escape reflexes and more complex behaviors. Ongoing pain after injury can enhance repair by protecting vulnerable tissues in the early course of recovery. Upregulation of pain responses from stimuli to and near injured tissues (hyperalgesia) further facilitates protective postures and behaviors during the tissue-healing phase. Under usual circumstances, ongoing pain and hyperalgesia abate as tissue healing occurs. The biological implications of pain that persists beyond the healing phase are less apparent, and it is little surprise that physical and psychological comorbidity are frequent components of suffering associated with chronic pain.

The meta-analysis reported herein draws on a paradigm that is best described as the early warning function of pain. Individual stimuli and blocks of stimulation were short lived and although frankly painful, were of insufficient intensity to cause tissue damage. Exteroceptive elements of pain arising from application of a heat source include attentional and orientating mechanisms that are informed by sensory/discriminative functions such as stimulus intensity coding and localization. The affective domain of pain, a defining quality of the experience [Merskey and Bogduk, 1994], has been conceptualized as incorporating primary and secondary components [Price, 2000]. The aversive nature of pain, its primary unpleasantness, is an inherent aspect of the sensation that would characterize all the paradigms employed by the studies in the meta-analysis. More elaborate, secondary emotional responses to pain can not be inferred reliably from the experimental strategies used by the studies, but would presumably be muted. The appraisal of familiar sensations in the contrived, highly controlled context of a functional imaging experiment would be less likely to arouse overtly negative emotional responses. Constraints on movement consistent with appropriate imaging techniques could produce a relatively unique response set that diverges from transient pain in a natural environment. Withdraw reflexes and conscious escape behaviors that are triggered and motivated by nociceptive and pain processes, respectively, must be suppressed by subjects in imaging experiments. This situation could impact on central processes involved in pain-related motor response selection and execution in a fashion that is idiosyncratic to imaging paradigms. Possible exceptions to this postulate are movements associated with facial expressions that may occur at a rela-

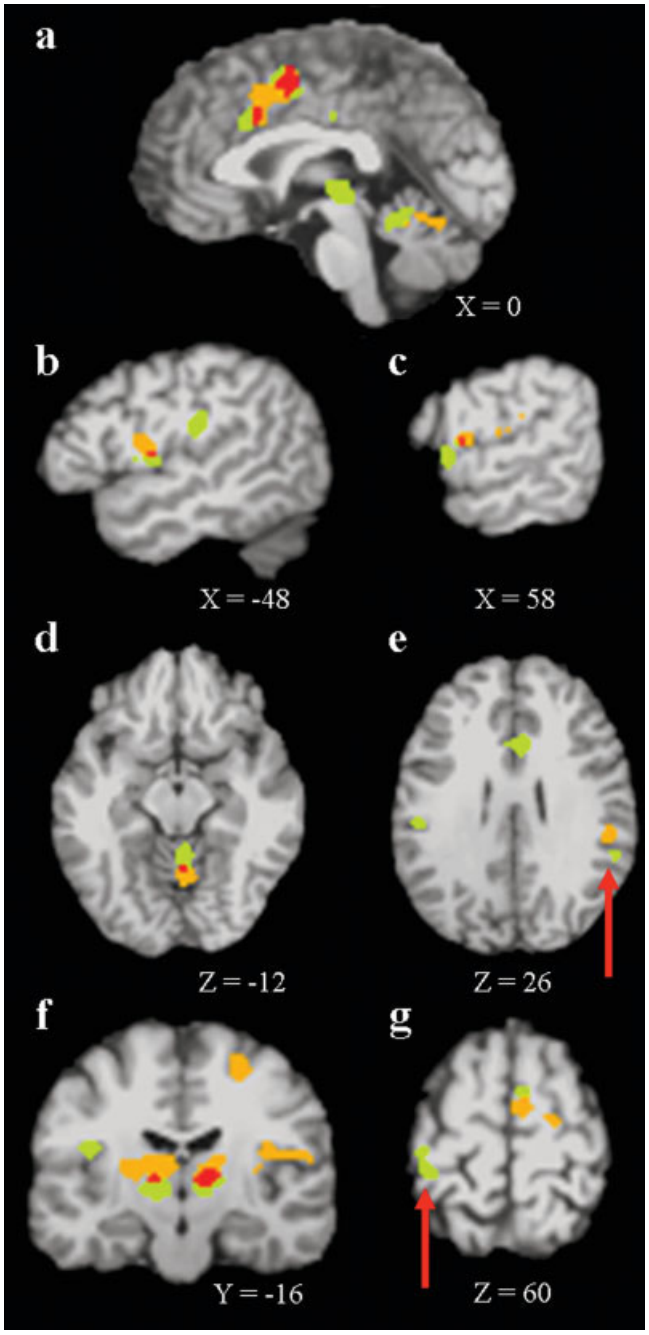

Figure 1.

Meta-analytic activation map based on all primary studies of painful stimuli applied to either the left (orange voxels) or right upper limb (green) or either limb (red, representing areas of activation common to either side of stimulation, not stimulation of both limbs). **a:** Midline sagittal section (x = 0) showing a common region of activity in the cingulate motor area (red) and discrete regions for lateralized stimulation more rostrally. **b, c:** Concordant bilateral activation for either stimulation side in premotor cortex. **d:** Right-side concordant activation in the vermis of the cerebellum for stimulation on either side. **e:** Discrete regions of activation in the right inferior parietal lobule for left and right stimulation (indicated with red arrow). **f:** Significant regions of bilateral thalamic activation for both stimulation sides, and contralateral insula/opercula activation. **g:** Discrete activation in primary sensorimotor cortex for right-side stimulation (indicated with red arrow). Axial slices are orientated with the right hemisphere on the right side. Coordinates are according to the convention of negative x-values to the left of the midline, negative y-values posterior of the anterior commissure, and negative z-values inferior to the anterior commissure.

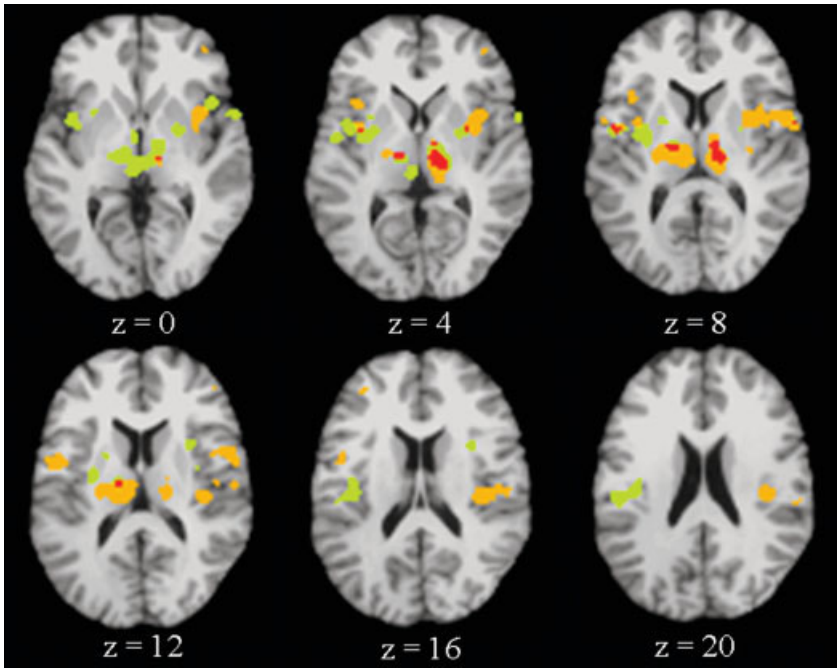

Figure 2.

Axial views are at 4-mm intervals from z = 0. The color scheme and orientation of images is identical to that described in the legend to Figure 1. Bilateral pain-related activity is apparent at the anterior/mid-insula for both sides of stimulation. The clusters at the posterior end of the insula are confined to the contralateral side relative to stimulation. Although not incorporated invariably within a single cluster, the general pattern is of activity spreading beyond the insula into the adjacent operculum. At the anterior end of the lateral sulcus, the lateral extent of activity encompasses the premotor cortex on the surface of the brain. At the posterior end of the sulcus activity extends into the posterior parietal cortex.

tively unconscious level during the experience of pain [Craig et al., 2001]. It is clear from this discussion of the multiple facets of pain that the central representation of the experience is likely to occur in a distributed network, as was indeed the case.

Most contrasts employed in this meta-analysis incorporate an innocuous control of like modality. The rationale for this approach is to identify activity that is unique to the experience of pain as opposed to tactile sensation generally. In many respects, this approach is well founded although some reservations persist about the degree to which activations reflect functions that are common across both innocuous and noxious sensory processing. A significant increase in signal from a brain region during painful stimulation does not preclude the possibility that the region is involved in processes common to both pain and other sensory experiences, albeit in an intensity-dependent manner [Coghill et al., 1999]. Consequently, when considering the results of the ALE analysis, it is important to acknowledge that pain-related activity in this context does not translate to a network that is dedicated exclusively to pain perception per se.

The peripheral elements of nociception, including small-diameter primary afferent myelinated Aδ and unmyelinated C fibres, enter the spinal cord through the dorsal root and terminate in laminae I and V [Almeida et al., 2004]. Projections from cells with nociceptive input in the dorsal horn ascend in the contralateral spinothalamic tract. In addition to terminations in the major homeostatic regions of the brainstem, spinothalamic neurons project to nuclei in medial and ventral posterior lateral regions of the thalamus. An anatomical and functional distinction is made frequently between lateral and medial pain pathways that are constituted by the targets of projections from the respective groups of thalamic nuclei [Treede et al., 1999]. The classic termination of the spinothalamic pathway, the primary somatosensory cortex is synonymous with the lateral pain pathway and has been ascribed with sensory/discriminative functions. Mesial structures, most notably the ACC, have mutual connections with the medial dorsal nucleus and are likely to be involved in the affective/motivational component of the pain experience.

The ALE results clearly demonstrate consistent bilateral activations of the thalami for painful stimuli to both the left and right upper limbs. The spatial resolutions of the techniques providing the data for the meta-analysis disallow any inferences about the respective medial/lateral positions of thalamic activations; however, the clusters extend to both the medial and posterior/lateral regions of the thalamus. Anatomical studies and cord lesions or direct stimulation of the thalamus in humans suggest that the spinothalamic pathway is predominantly contralateral to the peripheral elements of nociceptive and thermoafferent modalities

[Nathan et al., 2001; Ohara and Lenz, 2003; Zhang et al., 2000], although there is some anatomical evidence of ipsilateral spinothalamic projections [Grottel et al., 1999]. Robust ipsilateral thalamic activity associated with pain may reflect the contribution of corticothalamic input or projections to the thalamus from brainstem regions in receipt of ascending nociceptive input [Millan, 1999]. Resolving the question of differential localization and functional implications of contra- and ipsilateral thalamic pain-related activations may benefit from the concurrent application of tractography and fMRI. Event-related paradigms in combination with images with brief repetition times and circumscribed field of view at higher resolutions could provide significant insights into the behavior and mutual connections of thalamic nuclei during the experience of pain.

Activity in the contralateral primary somatosensory cortex was in evidence only for stimulation of the right upper limb. Among the studies examined in this meta-analysis, S1 activity was reported by approximately half the authors. A role for S1 in discriminative pain processing is not inconsistent with the variance in activity across studies. Stimulus attributes likely to influence the magnitude and region of S1 activity, such as intensity, size, site, and duration varied considerably from study to study. It has been noted in a previous review and subsequently supported by empirical testing that decreasing stimulus size is associated with diminishing probability of identifying pain-related S1 activity [Apkarian et al., 2000; Peyron et al., 2000]. The exception to this trend seems to be the reasonably consistent reports of S1 activations subsequent to spot-like laser stimuli. Duration of stimuli also seems to have a significant effect on the likelihood of pain-related S1 activity. Of the S1-positive studies in the meta-analysis, 83% involved isolated, or repeated brief stimuli (5 s or less). Paradigms incorporating stimuli more than 5 s were much less likely to evoke S1 activity (20%; $\chi^2(1) = 8.8$, $P < 0.003$). The reason for this temporal effect is not readily apparent, especially in light of a recent report of persistent S1 activity associated with prolonged, tonic stimulation [Downar et al., 2003]. The reason for the respective presence and absence of right and left contralateral S1 ALE clusters is not immediately apparent. The relative frequency of stimulus parameters including duration, localization, and size are similar across the two sides of stimulation. It seems likely that a combination of factors rather than any single effect has militated against the appearance of a contralateral S1 cluster with left-side stimulation. It is salient that although present, the left S1 cluster for the right-side stimulation was of modest spatial extent. Despite the lack of consistency across the two ALE analyses, it would be imprudent to underplay the contribution of S1 to pain processing given the sensitivity of activations in this region to the vagaries of stimulus attributes.

Pain-related activity in the cingulate cortex was the most consistent report among studies selected for the meta-analysis. The spatial extent of the cingulate clusters identified by the ALE technique is consistent with a heterogeneous functional role for this region in pain processing. There was a clear distinction between two loci for the analysis of right-side stimulation that occupied areas in common with the contiguous cluster associated with left-side stimulation. Both loci were within the mid-ACC, located at and rostral to the vertical projection of the anterior commissure. The more posterior of the loci is in a region of BA24 that is notable for cytological features, including a dense layer V incorporating small and large pyramids, that suggest a role in pain-related motor output [Vogt et al., 2003]. The more anterior of the cingulate loci has been implicated by functional imaging in fear/anxiety states and covaries with manipulation of pain unpleasantness subsequent to hypnotic suggestion [Rainville et al., 1997; Vogt et al., 2003]. It seems very likely that activity in this region of the cingulate is related closely to the affective domain of the pain experience. Although robust, the cingulate clusters were in a relatively discrete region that was consistent across the two sides of stimulation. More extensive areas of cingulate cortex have been reported for pain-related contrasts but are clearly not of sufficient consistency across studies to survive empirical scrutiny. A notable example is perigenual cingulate activity, which is reported more frequently for contrasts that include upregulated or downregulated pain states [Bantick et al., 2002; Lorenz et al., 2002]. The discrete locale of the ALE cingulate clusters may have important implications for cingulotomy as a treatment for intractable pain. The efficacy and side effects of neurosurgery could be enhanced and ameliorated respectively by more targeted approaches.

The ALE clusters in the insula and opercula cortices showed considerable uniformity across the two analyses. There are clearly two broad regions of activity that can be encapsulated as bilateral anterior insula/operculum and contralateral posterior insula/operculum. The most intense interest in the literature of pain seems to have focused on the more posterior of the two regions [Craig, 2002; Treede et al., 2000]. At present, there is not a consensus on the exact role of pain-related activity in the posterior insula and parietal operculum. Both anatomical components of this region are projection sites for ventral posterior thalamic nuclei, including the posterior portion of the ventral medial nucleus, which is the primary source of nociceptive input for the insula [Craig et al., 1994; Stevens et al., 1993]. Cells with nociceptive responses in the traditional S2 region have rarely been described [Treede et al., 2000]. A similar lack of electrophysiological data is also the case for the adjacent dorsal insula. Direct stimulation of the insula in humans has elicited painful responses [Ostrowsky et al., 2002], and lesions incorporating S2 and adjacent insula have fundamental effects on the quality of pain sensations evoked by contralateral peripheral stimulation [Greenspan et al., 1999]. The results of the meta-analysis provide further impetus for investigations that will refine our understanding of the role of this region in pain processing.

The implicit call to action that accompanies the sudden onset of pain is an integral component of the broader pain experience. The instinct to withdraw from a painful stimulus must be suppressed by subjects during functional brain-

imaging experiments of pain. Both the desire to escape and the inhibition of withdraw may be related to the consistent pain-related activity in elements of the motor network for left and right painful stimulation. The possibility also exists that some of these regions may have a more direct role in sensory processes, a hypothesis that has been entertained for the role of the cerebellum in nociception [Saab and Willis, 2003]. The lack of tangible motor outputs associated with the experience of pain in the scanning environment leaves much in doubt. There would be considerable merit in the design of paradigms that incorporate independent and interacting conditions of pain and movement execution. Evidence from other sources, notably experiments employing transcranial magnetic stimulation [Summers et al., 2004; Svensson et al., 2003], would suggest that there is mutual inhibition of the primary motor and somatosensory cortices during pain and movement, respectively. It seems very likely that this type of interaction would also find expression in other components of the motor and pain networks.

The results of the ALE analysis would suggest that pain-related activity in the inferior parietal lobule (BA40) is confined to the right hemisphere. The posterior parietal cortex has extensive connections with the primary and secondary somatosensory cortices and projects via the insula cortex to a number of limbic structures [Cipolloni and Pandya, 1999]. Behavioral responses in monkeys with ablation of the analogous region (7b) support a role for this cortical area in the perception of intrusion or threat from a noxious stimulus [Dong et al., 1996]. This perceptual process seems dependent on the extensive convergence of afferent input in the region of the posterior parietal cortex. Exteroceptive senses, notably vision, have been strongly implicated in the contribution of the posterior parietal cortex to pain processing.

CONCLUSIONS

This meta-analysis of activations associated with noxious thermal stimuli has identified a widely distributed pain matrix. Many elements of the supraspinal pain network have a contralateral or bilateral distribution that is consistent for stimuli either side of the midline. Some findings have dovetailed neatly with other threads of information, such as the convergence of the pattern of mid-ACC activity and more recent characterizations of the cytoarchitecture of this region. Other findings, such as the robust nature of ipsilateral thalamic activity and widespread activity in the motor network, provide considerable impetus for future explorations of these pain-related phenomena.

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