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fMRI of Thermal Pain: Effects of Stimulus Laterality and Attention

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Brain activity was studied by fMRI in 18 healthy subjects during stimulation of the thenar eminence of the hand with either warm (nonpainful, 40°C) or hot (painful, 46–49°C) stimuli using a contact thermode. Experiments were performed on the right and left hand independently and with two attentional contexts: subjects either attended to pain or attended to a visual global motion discrimination task (to distract them from pain). Group analysis demonstrated that attended warm stimulation of the right hand did not produce any significantly activated clusters. Painful thermal stimulation of either hand elicited significant activity over a large network of brain regions, including insula, inferior frontal gyrus, cingulate gyrus, secondary somatosensory cortex, cerebellum, and medial frontal gyrus (corrected $P < 0.05$). Insula activity was distributed along its anterior–posterior axis and depended on the hand stimulated and attentional context. In particular, activity within the posterior insula was contralateral to the site of stimulation, tested using regions of interest (ROI) analysis: significant side × site interaction ($P = 0.001$). With attention diverted from the painful stimulus bilateral anterior insula activity moved posteriorly to midinsula and decreased in extent (ROI analysis: significant main effect of attention ($P = 0.03$)). The role of the insula in thermosensation and attention is discussed. © 2002 Elsevier Science

Key Words: **fMRI; thermode; pain; insula; attention; lateralization.**

INTRODUCTION

Current knowledge of the physiology of pain is based on several different lines of evidence ranging from identification of pain pathways using selective lesioning and immunohistochemistry to pain transmission studied by neuropharmacological manipulations and experimental neurophysiology (Albe-Fessard and Lombard, 1983; Willis and Westlund, 1997; Davis *et al.*, 1998a; Basbaum, 1999). These results have paved the way to our current understanding of how nociceptive stimuli are conveyed to and interpreted by the central nervous system. However, the way this information is processed by higher cortical structures is poorly understood. With the advent of modern neuroimaging techniques, such as positron emission tomography (PET), magnetoencephalography (MEG), electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), it is now possible to study noninvasively the neural response to pain.

The experience of pain comprises sensory, qualitative, and affective components (Melzack and Casey, 1968). These different aspects of pain are thought to be mediated by distinct brain regions (Derbyshire *et al.*, 1997), which process painful stimuli in an integrative parallel manner (Treede *et al.*, 1999). Historically, two pain pathways were described: the medial and lateral pain pathways, so called because nociceptive nerve fibers pass through the medial and lateral nuclei of the thalamus and project to higher cortical regions. The lateral pain system was considered to facilitate the sensory-discriminative component of pain, in that nociceptors from this region have been shown to project to primary (SI) and secondary (SII) sensorimotor cortex (Treede *et al.*, 1999). The medial pain system was thought to be involved in evaluation of pain quality and integration of its affective aspects, since nociceptors from the medial thalamic nuclei project to limbic regions of the brain (e.g., insula, cingulate gyrus) (Vogt *et al.*, 1987; Craig, 1998). However, the division of the pain system into lateral and medial components has been shown to be an oversimplification of multitudinous spinothalamic, thalamocortical, corticocortical, and corticospinal connections involved in the large distributed pain network (Craig, 1998; Casey, 2000). Despite the complexity of the pain system, dedicated pain-mediating projections have been identified, e.g., those from nociceptive lamina I neurons in the spinal cord, to thalamic relay points (VMpo, MDvc) which then project to anterior cingulate, insula and SII (Craig, 1998)—regions involved in both affective and sensory-discriminative pain processing (Davis *et al.*, 2000; Treede *et al.*, 2000).

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Most (Craig *et al.*, 1996; Kanda *et al.*, 2000; Tracey *et al.*, 2000), but not all (Derbyshire and Jones, 1998; Peyron *et al.*, 1999), neuroimaging studies of the pain system have demonstrated increased activity in SI in response to painful thermal stimuli, perhaps subserving stimulus localization. Several factors may have contributed to the inconsistent results, e.g., whether the stimulus was phasic (Apkarian *et al.*, 2000) or tonic (Derbyshire and Jones, 1998) or moving (Derbyshire *et al.*, 1997; Coghill *et al.*, 1999) versus stationary (Peyron *et al.*, 1999). An alternative possibility is that different affective/cognitive-evaluative aspects of these experiments may have influenced activity in SI. In particular, feedback in the large-scale cognitive network involved is likely to influence pain sensation (Mesulam, 1998). Indeed, much recent research has focused on the affective/cognitive-evaluative components of pain and their interaction with the sensory-discriminative aspect of pain (Davis *et al.*, 1998b; Porro *et al.*, 1998; Apkarian *et al.*, 1999), e.g., attention (Jones and Derbyshire, 1997), anticipation (Ploghaus *et al.*, 1999), coping strategies (Hsieh *et al.*, 1999), mood (Rainville *et al.*, 1997), pain memory (Flor *et al.*, 1997), and learning (Ploghaus *et al.*, 2000).

The majority of studies investigating pain-related brain activity have utilized thermal stimuli, which are likely to involve thermosensory processing (Craig *et al.*, 2000). In addition to studying the effects of thermal pain, one may also examine the effect of simultaneous cognitive loading on pain-related neural activity. Two studies have investigated the effect of shifting attention away from painful stimuli (Peyron *et al.*, 1999; Petrovic *et al.*, 2000a). However, the results obtained were not in broad agreement, possibly due to differences in pain stimuli (hot versus cold pain) and the distraction task (auditory versus visual) used. To clarify the effect of attention on pain-related brain activity, we have studied 18 healthy subjects with a thermal pain protocol and recorded changes in brain activity using fMRI. Individual thermal pain thresholds were assessed prior to fMRI scanning to ensure that all subjects experienced similar pain levels. Stimuli were delivered to the right and left hand to allow disassociation of the effect of stimulus lateralization on the pain matrix. By using a visual distraction task we have examined the effect of shifting attention on pain-related activity. In studying healthy subjects we have focused on pain physiology rather than the pathophysiology present in clinical pain conditions.

SUBJECTS AND METHODS

Eighteen healthy subjects (12 male, 6 female) aged between 21 and 43 years gave fully informed written consent of their willingness to participate in this study which had local ethics committee approval. Subjects were predominantly right-handed (17/18) as assessed by the Edinburgh handedness inventory (Oldfield, 1971). Subjects were screened for the presence of neurological disease and given a general health check (heart rate, blood pressure, etc).

Prescan Assessment

Prior to fMRI, each subject was evaluated in a psychophysics laboratory to assess individual pain thresholds. Painful thermal stimuli were applied to the thenar eminence of the right and left hand separately by using a peltier thermode (Medoc, Haifa, Israel). The thermode has a square surface of area 9 cm^2 and was specially adapted for use in an MR scanner environment. Subjects were instructed to rate induced pain using a computerized visual analog scale (VAS) and potentiometer, which allowed movement of an indicator along the length of a color-coded VAS. VAS responses were on a range from 1 to 100, with 1 corresponding to "no pain" and 100 to "worst pain imaginable" (these labels appeared at either end of the VAS display). Thermode temperature was increased from baseline (35°C) to the pain stimulus level (T_{PAIN}), and subject's responses were recorded by computer. The applied temperature ranged from 35 to 49°C (highest individual value of T_{PAIN}).

The value for T_{PAIN}, to be used in the proceeding fMRI studies, was that which produced a VAS reading of between 60 and 70 and corresponded to temperatures of between 46 and 49°C. In five subjects following determination of T_{PAIN}, a "dry run" of the fMRI experiment was performed in the psychophysics laboratory to investigate possible habituation effects. The experiment utilized a block design of 15 s baseline followed by 15 s of T_{PAIN}. Each epoch was repeated 10 times, giving an experiment length of 5 min. Throughout the experiment, subjects rated the induced pain level by using the potentiometer and VAS.

Distraction Task

The distraction task stimulus consisted of a pattern of dots, all moving at the same speed of 4 degrees/s, displayed on a computer screen, and was a modified version of an experiment originally described by Newsome and Paré (1988). On a frame-by-frame basis, each dot was randomly assigned to be either "signal" or "noise." The dots assigned to be signal moved coherently either to the right or the left, while those assigned to be noise moved in random directions. On each trial the percentage of dots assigned to be "signal" varied randomly between 0% (no detectable net motion bias) and 50% (an easily detectable motion bias). For each trial, subjects were instructed to assess whether the motion bias in the pattern was either to the right or the left, and silently count the number of times the pattern moved in a predetermined direction. Each trial lasted 0.5 s with a gap of 1 s between consecutive

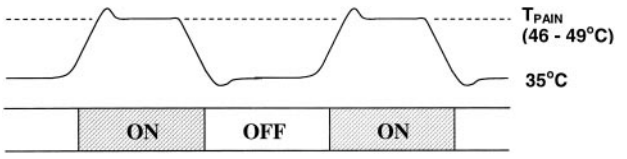

FIG. 1. Illustration of thermode heating/cooling profile. Note the nonzero rise/fall time for thermode temperature, which was compensated for by initiating temperature change approximately 2 s before the start of each epoch (shown at the base of the figure).

frames. The visual distraction task was presented to subjects by back projecting onto a screen visible through the periscope in the head coil, using an LCD projector (Epson LMP7300) connected to an Apple Macintosh G3 computer, and covered 9 × 6° of visual angle. Subjects performed the visual distraction task throughout the whole of the 5-min functional paradigms in which it was included—as such the effect of visual stimulation and silent counting were not correlated with the epochs of pain/warm and baseline and thus will not have contributed to the computed statistical maps.

Functional Imaging

During fMRI thermal stimuli were delivered to the right or left hand using the Peltier thermode, triggered by a TTL pulse from the scanner. The experimental protocol followed a block design, where the temperature of the thermode during the OFF condition was set to baseline (35°C) and to either T_{WARM} (40°C) or T_{PAIN} during the ON condition. In practice the response characteristic of the thermode was not box-like, such that the required thermode temperature was reached after a rise time of approximately 3 s. A similar, but inverted, profile was observed during thermode cooling. To account for the nonideal heating/cooling characteristics of the thermode, heating was initiated approximately 2 s before the end of the OFF period; similarly cooling began 2 s before the end of the ON period (see Fig. 1).

MR data were acquired using a 1.5 T Signa LX/NVi neurooptimized system (General Electric, Milwaukee, WI), and head motion was minimized by means of foam padding. fMRI was performed with a blood oxygenation level-dependent (BOLD) sensitive T_2-weighted multislice gradient echo EPI sequence (TE = 40 ms, TR = 3 s, flip angle = 90°, FOV = 19 cm, 64 × 64 matrix). Twenty-four contiguous 5-mm thick axial slices were prescribed parallel to the AC–PC line and covered the entire brain. For the purpose of anatomical referencing and visualization of brain activation, a high-resolution T_1-weighted 3D inversion recovery prepared gradient echo (IRp-GRASS) sequence was acquired (TE = 5.4 ms, TR = 12.3 ms, TI = 450 ms, 1.6-mm slice thickness, FOV = 20 cm, 256 × 192 matrix), with 124 coronal slices covering the whole brain.

Each fMRI paradigm consisted of 10 pairs of alternating OFF and ON epochs, with each epoch 15 s in length, giving a total scan time of 5 min. Every 3 s an entire image volume was collected, giving a total of 100 volumes per run. The experimental protocol consisted of five different paradigms:

(i) RW, attend to warm stimulus to right hand (no distraction task);
(ii) RA, attend to heat pain to right hand (no distraction task);
(iii) RV, attend to visual distraction task during heat pain to right hand;
(iv) LA, attend to heat pain to left hand (no distraction task); and
(v) LV, attend to visual distraction task during heat pain to left hand.

Experiments on the right hand always preceded those on the left; however, the ordering of individual experiments on either hand was random. When switching the thermode from the right to the left hand, care was taken to not move the subject in relation to the head coil, and subjects were instructed to remain as still as possible. Data from each experiment were transferred to a personal computer (700-MHz Pentium III, 512 Mb RAM) for analysis and visualization of significant activations. Note that of the 18 subjects only 11 were studied using the warm stimulus (RW), and due to failure of apparatus, data were not obtained for 1 subject in the LA and 2 subjects in the LV experiments. All images are displayed using neurological convention.

Data Analysis

Group analysis of functional data was performed with statistical parametric mapping (Friston *et al.*, 1995) software (SPM99, http://www.fil.ion.ucl.ac.uk/spm/). Each series of fMRI images was motion corrected using a 6-parameter rigid-body transformation to bring all EPI brain volumes (for a given experiment) into alignment, i.e., realign the last 99 acquired volumes to the first. This process produced an average realigned slice representative of the acquired EPI volumes. Subsequent normalization was performed using this mean image and the standard EPI template available in SPM99 and consisted of a 12-parameter affine transformation followed by nonlinear warping to transform each subject's data into the coordinate frame of the EPI template. This reference space is based on an "average brain" determined from 305 MRI scans of healthy subjects acquired at the Montreal Neurological Institute (Collins *et al.*, 1994). Data were smoothed using a 9-mm (FWHM) Gaussian kernel. Pixels with signal intensity correlated significantly with the hemodynamic response function were analyzed as a group, and a fixed effect model was used to compare ON and

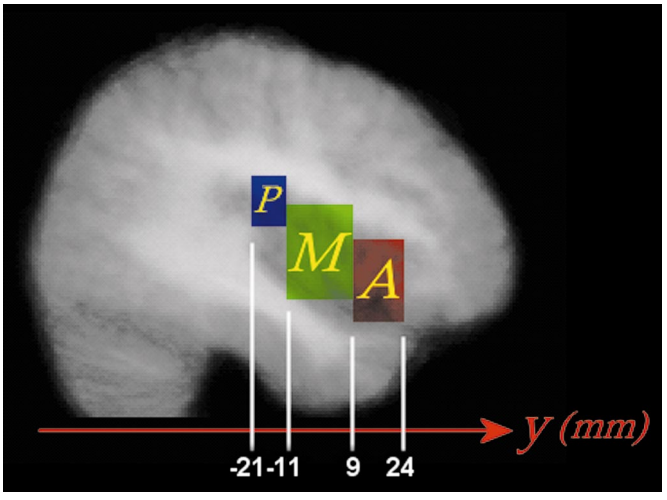

FIG. 2. Placement of region of interests (ROI), shown overlain on sagittal section through the right insula of the average anatomical brain. Three ROIs were placed in both right and left insula, to cover anterior (A), middle (M), and posterior (P) regions. Anatomically these ROIs include tissue from the anterior gyrus brevis (A), middle and posterior gyrus brevis (M), and anterior gyrus longus (P) (Varnavas and Grand, 1999). Note that the posterior region included the dorsal margin of the middle/posterior insula (as described in Craig *et al.*, 2000). For comparison to activation maps (Fig. 3) the Talairach *y*-coordinates of each region are shown.

OFF epochs. Motion correction parameters were not used as covariates in these analyses. Statistically significant clusters of activity were recorded for each condition. Only those clusters with a corrected *P* value of 0.05 or less and 10 voxels or greater in volume are reported.

For subsequent visualization of activated brain regions, an average brain was determined by normalizing each subject's anatomical scan (3D FIR-p-GRASS) to a T1-weighted template available in SPM99. The resultant normalized volumes were averaged to produce an anatomical scan representative of all 18 subjects. The location of significantly activated regions was assessed by superimposing the results from group analysis on the average brain using in-house software (mri3dX, http://www.mariarc.liv.ac.uk/software.html). By using this software the coordinates reported by SPM (which were in "MNI space") were transformed to the stereotaxic coordinate frame developed by Talairach and Tournoux (1988) and thus enabled comparison to a reference atlas for appropriate neuroanatomical localization.

Regions of Interest (ROI) Analyses

To assess the significance of differences in regional activity reported by SPM we performed ROI analyses (Singh *et al.*, 2000). In particular, ROIs were defined in the insula to test the hypothesis that activity within this region depended on the experimental condition, i.e., the hand being stimulated or the attentional context of the experiment. Based on the mean anatomical brain (see above), ROIs were defined to include anterior (2.25 cm^3), middle (4 cm^3), and posterior (1.95 cm^3) insula in the right and left hemispheres, giving a total of six regions (see Fig. 2). ROIs were also defined in right and left cingulate gyrus (Brodmann areas 23 and 24). Using mri3dX, signal intensity within each ROI was extracted from images representing the amplitude of the BOLD response for each individual for each of the four conditions (RA, RV, LA, and LV). These values were compared using a general linear model (GLM, repeated measures ANOVA), for assessment of main effects and interactions, with SPSS (SPSS Inc., Chicago, IL). By using this analysis, main effects of attentional focus, stimulation site, and side of activity and their interactions were investigated. In addition to performing ROI analyses, we also employed small volume corrections (SVC (Worsley *et al.*, 1996)) to analyze data from SI and thalamus. Based on results from a separate experiment performed in our laboratory (data not shown) a 2-cm-radius sphere was positioned over the region of SI corresponding to the thenar, with MNI coordinates (−42, −27, 66) and (42, −27, 66). The coordinates of the 2-cm-radius spherical SVC used in the thalamus were (0, −18, 6).

RESULTS

The results from the offline psychophysics recordings in 5 subjects demonstrated no effect of habituation over the 5-min experimental duration, with the predetermined painful stimulus temperature (T_{PAIN}). No statistically significant clusters larger than 10 pixels were obtained following group analysis of fMRI data collected with the warm stimulus for 11 subjects (compared to baseline 35°C). Following painful stimulation a common pattern of brain activation was observed for each of the pain paradigms (see Table 1). The main brain structures activated were the insula, cingulate gyrus (CG), SII, cerebellum, medial frontal gyrus (MFG), and inferior frontal gyrus (IFG), with most regions represented bilaterally. Within this basic pain matrix were regions (predominantly insula) whose activity was related to stimulus laterality or was modulated by the distraction task during painful stimulation (i.e., attending to pain/distracted from pain). These findings are presented in Figs. 3 and 4. When considering the effect of stimulus laterality, no activation was observed for SI (see Table 1). The absence of SI activity from the observed pain matrix was investigated using a SVC (see Subjects and Methods); with this approach a small activated region (corrected $P < 0.05$) was found in contralateral SI during RV (Talairach coordinates −36, −30, 59). Similarly, a SVC was used to investigate absence of thalamus activity (see Table 1): small activated clusters (corrected $P < 0.05$) were found for the following conditions RA (12,

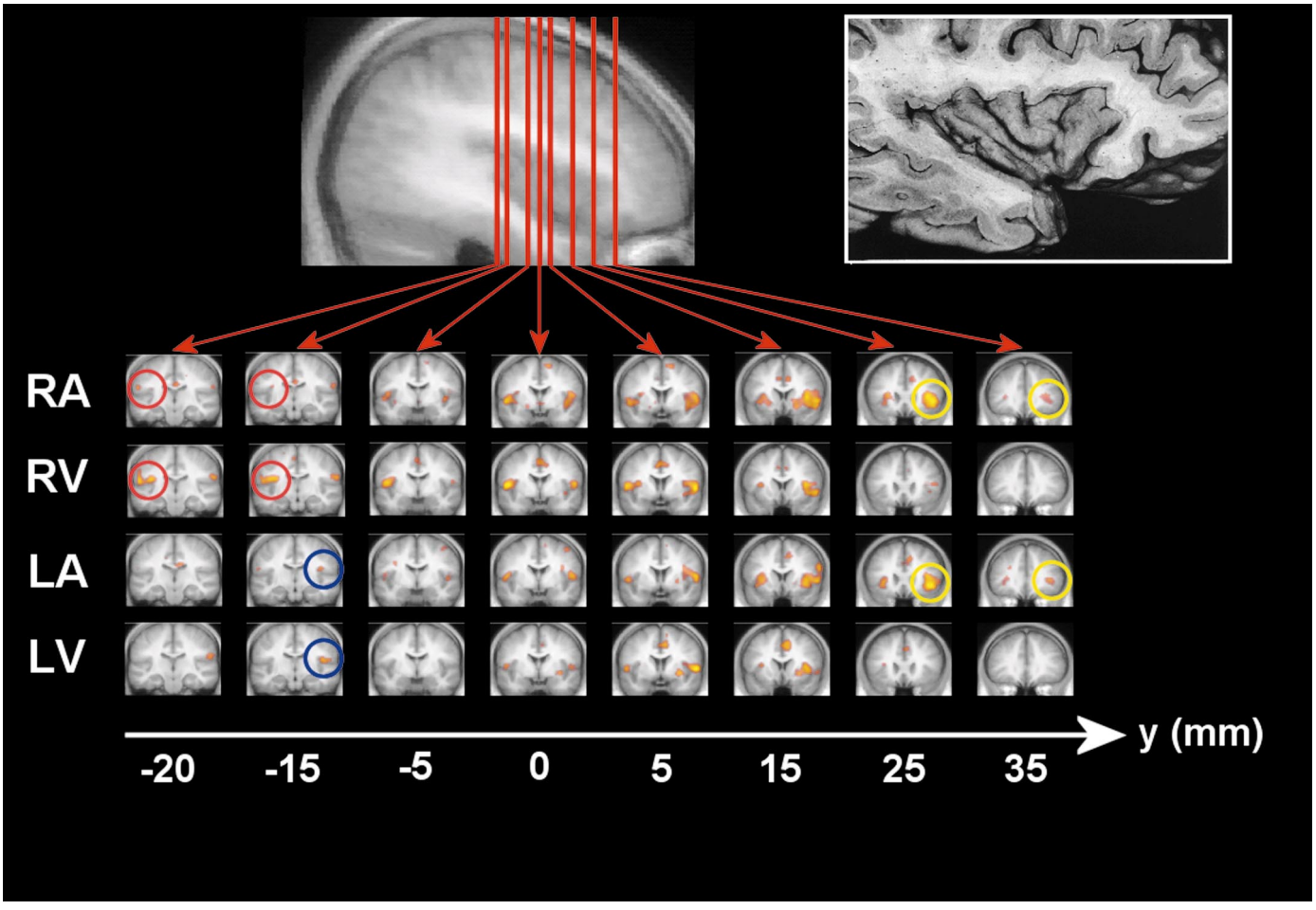

FIG. 3. The effect of stimulus lateralization and attention on statistical maps for each experimental condition: RA, RV, LA, and LV. The distribution of activation sites is shown on coronal sections taken through the insula and Talairach *y*-coordinates shown below each image (activated voxels are significant at p (corrected) < 0.05). Anatomical images represent the average of all 18 subjects' structural images and are displayed using neurological convention, i.e., right is right, left is left. For reference a sagittal section through the right insula is shown with the location of each coronal slice indicated; also shown is an anatomical slide of the insula (with permission (Duvernoy, 1999)) to show the relevant anatomical features. Attended painful stimulation activated more anterior regions of the insula than distracted stimulation (see yellow circles on anterior coronal sections). Also demonstrated is the effect of stimulus laterality on activation of posterior insula cortex (foci of activity are highlighted with colored circles, right hand stimulation, red; left hand stimulation, blue). Posterior insula activity switched sides when the stimulus was transferred from hand to hand and did not depend on the attentional context during stimulation.

−5, 11 and −3, −3, −3), LA (3, −3, 6 and 15, −9, −2) and LV (15, −17, 12).

A lateralized response was found for all pain conditions in a small region of the posterior insula (see Table 1 and Fig. 3, $y = -20$ and -15 mm), which was contralateral to the hand stimulated and did not depend on the attentional context of the experiment. ROI analyses support this finding (see Fig. 4). The posterior insula ROI contralateral to the site of stimulation was significantly more active than the equivalent ROI ipsilateral to stimulation, which was confirmed using a GLM to investigate the interaction between the site of stimulation and side of posterior insula activity ($P = 0.001$), while the main effect of attention was not significant ($P = 0.638$). Posterior insula activity was located close to the lateral sulcus, but could be clearly distinguished from activity in SII. Activity in SII was present bilaterally during RA and RV, though for stimulation of the left hand was present in right SII only during LV.

During attended painful stimulation of the right (RA) or left hand (LA), a large primarily right-sided region of activity was observed over the anterior insula and IFG and extended from $y = 0$ to 35 mm (see Fig. 3). During distracted stimulation of the right (RV) or left hand (LV), the clusters of functional activity in right and left insula moved posteriorly, appearing on slices from $y = 0$ to 15 mm and were absent from more anterior slices. Attended painful stimulation of the right (RA) or left (LA) hand was associated with larger volumes of right anterior insula activity (32.1 and 18.9 cm^3, respectively) than the equivalent experiments

TABLE 1

Summary of Obtained Activation Sites from SPM Group Analysis for the Four Experimental Pain Conditions

	Condition			
Region	RA (N = 18)	RV (N = 18)	LA (N = 17)	LV (N = 16)
Ant. insula				
R	36,18,5	—	42,20,−6	—
L	−30,24,7	—	−36,23,−4	—
Mid. insula				
R	—	39,9,8		36,12,5
L	—	−54,−3,8	−36,12,2	−36,9,8
Post. insula				
R	—	—	42,−17,20	45,−14,15
L	−39,−20,20	−42,−20,20	—	—
SII				
R	66,−16,23 (43)	63,−31,24 (43)	—	60,−22,20 (43)
L	−63,−22,23 (43)	−63,−25,18 (43)	—	—
IFG				
R	57,8,−1 (47)	54,9,−3 (47)	57,9,2 (47)	57,6,−1 (47)
L	−57,−3,0 (47)	—	—	−57,3,0 (47)
ACG				
R	6,16,32 (24)	6,19,32 (32)	9,19,38 (32)	3,22,35 (32)
L	−9,11,35 (32)	—	−3,19,35 (32)	—
MCG				
R	—	—	—	6,8,38 (24/32)
L	—	−6,5,38 (24/32)	—	−3,5,38 (24/32)
PCG				
R	0,−19,29 (23)	—	—	—
L	—	—	—	—
Cerebellum				
R	24,−60,−27	21,−56,−15	—	—
L	−36,−60,−33	—	−18,−69,−20	—
FG				
R	—	—	—	—
L	—	—	−54,−6,9 (6)	—
MFG				
R	—	—	39,42,26 (46/9)	−30,48,31 (9)
L	—	—	−27,36,20 (46)	—

Note. The Talairach coordinates (R-L, A-P, S-I) and Brodmann areas (where appropriate, in parentheses) are shown. Ant. insula, anterior insula; Mid. insula, middle insula; Post. insula, posterior insula; SII, secondary somatosensory cortex; IFG, inferior frontal gyrus; ACG, anterior cingulate gyrus; MCG, middle cingulate gyrus; PCG, posterior cingulate gyrus; FG, frontal gyrus; MFG, medial frontal gyrus. Reported activation sites are based on a corrected p of 0.05 (whole brain correction).

(RV, LV) with attention diverted to the visual task (18.9 and 10.7 cm^3, respectively). The significance of these observations was tested using a GLM to assess main effects of site of stimulation and side of activation and attentional context, as well as any possible interactions. These analyses supported the observation of reduced anterior insula activity during distracted painful stimulation (RV, LV) when compared to attended stimulation (RA LA): there was a main effect of attention (P = 0.03). There was also a significant main effect of side (P = 0.005), confirming the observation that the effect of attention/distraction primarily affects right anterior insula (see Fig. 4).

Activity in cingulate gyrus was also distributed along the A-P direction, with the majority of activity within ACG (BA24). Activity within this region was predominantly right sided, irrespective of hand stimulated or attentional focus, as revealed by ROI analysis (main effect of side, P = 0.005). An effect of stimulation site was found in posterior cingulate (BA23); activity in right or left ROI was significantly greater for stimulation of the left hand than for the right, irrespective of attentional focus (main effect of site, P = 0.01).

DISCUSSION

Thermal pain applied to the thenar of the right and left hands in 18 subjects produced bilateral increases in BOLD signal in the insula, inferior frontal gyrus, SII, and cingulate gyrus. This basic pain matrix could, in part, be modified by switching the side of painful stimulation (laterality effects) or by distracting subjects from pain using a visual stimulus (cognitive effects). The only brain region conforming to a sensory-

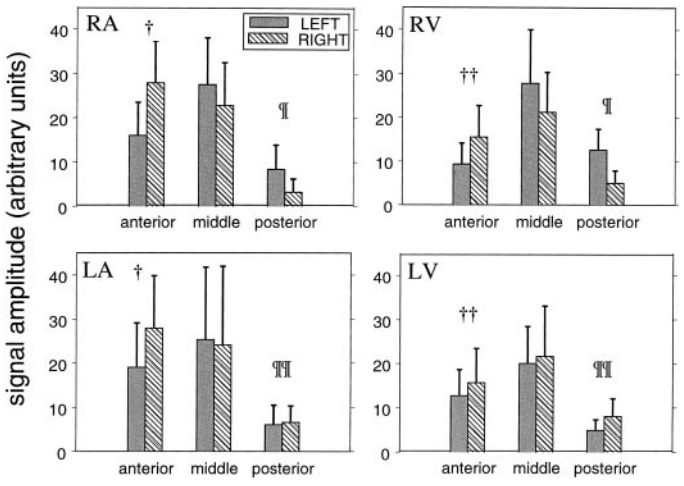

FIG. 4. Summary of ROI analysis. Activity (based on amplitude of BOLD response) for each subject was extracted from the ROIs defined in anterior, middle, and posterior insula, and the mean is plotted with error bars representing 2 SE. The results demonstrate left > right posterior insula activity for right hand stimulation (¶), a situation that is reversed for left hand stimulation (¶¶). The interaction between site of stimulation and side of posterior insula activity was tested using a general linear model (repeated measures ANOVA, see Results) and confirmed the observation that posterior insula activity was contralateral to the hand stimulated ($P = 0.001$). Note also that activity in the anterior insula ROIs appears to be greater during attended stimulation of either hand (RA, LA, †), than when subjects were distracted from pain (RV, LV, ††). The significance of this observation was tested using a GLM, which demonstrated a significant main effect of side (right > left, $P = 0.005$) and attention (RA/LA > RV/LV, $P = 0.03$).

discriminative role was a relatively small area in posterior insula, which showed a contralateral response and was not affected by the distraction task (site × side interaction, $P = 0.001$; main effect of attention, $P = 0.638$). The effect of distraction was most pronounced in the insula, where the main pain-related region of activity shifted from anterior to central insula during distracted stimulation of the right or left hand (main effect of attention, $P = 0.03$). The volume of activation was greatest in the anterior insula during attended painful stimulation of the right or left hand and was reduced when subjects were distracted.

In common with other studies of pain, we have shown a large distributed network of brain regions involved with pain sensation and processing. However, unlike the majority of published pain studies, our initial data analysis did not demonstrate any significantly activated clusters in the hand region of SI or the thalamus (see Table 1). Undoubtedly there are nociceptive neurons within SI (Treede *et al.*, 1999; Kanda *et al.*, 2000), and the thalamus has a role in pain processing (Bushnell and Duncan, 1989; Davis *et al.*, 2000). The absence of activity in these regions was investigated using a small volume correction for the thenar region of contralateral SI and medial thalamus (see Subjects and Methods). By using this approach a small cluster of activity was found in SI, though for only one of the four experimental conditions (RV), while regions of activity were found for three of the four experiments in the thalamus (RA, LA, and LV). In a recent fMRI study (Becerra *et al.*, 1999) contralateral activity was found in the thalamic relay point (VMpo) in response to thermal pain. This particular study used a nonparametric analysis technique, which is better able to discriminate activations which do not follow the pattern predicted by convolution of the hemodynamic response function with the boxcar function, as used for statistical inference in the present study. The lack of robust thalamic activation in this study may also be due to rapid habituation of thalamic activity during the 5-min experiments (Petrovic *et al.*, 2000b).

Electrophysiology experiments (Dong *et al.*, 1989) have demonstrated the presence of nociceptive sites within SII, but their distribution and the precise role for SII remains unclear (Treede *et al.*, 2000). SII nociceptors are probably involved in the assessment of stimulus quality in addition to pain sensation (Treede *et al.*, 2000). Bilateral SII activity has been reported in a PET study of cold pain by Petrovic *et al.* (2000a) and agrees with physiological studies (Dong *et al.*, 1989) in primates. Our data partially support this finding; however, activity was found almost exclusively during stimulation of the right hand. Further experimentation is required to assess the significance of this finding, in particular, whether this result relates to the handedness of subjects. We were reliably able to distinguish between activation sites in SII and those in posterior insula (see Fig. 3). Due to limitations of the resolution in PET studies, and visualization of activation sites using axial slices, these regions have previously been grouped as somatosensory association areas (Petrovic *et al.*, 2000a) and thus may have led to confusion about the exact site of activity.

The only area observed in our study which demonstrated sensory-discriminative characteristics was the posterior margin of the insula, which exhibited the expected contralateral response to shifting a painful stimulus from the right to the left hand and was not affected by the visual distraction task. In an earlier study (Derbyshire and Jones, 1998) of painful thermal stimulation of the right hand, increased rCBF was found in contralateral posterior insula. The posterior insula has recently been described as thermosensory cortex (Craig *et al.*, 2000) and is the target for projections from the dorsomedial nucleus (VMpo) of the thalamus. The Talairach coordinates for the left posterior insula in this study, Craig's, and Derbyshire and Jones' are all in good agreement: (−39, −20, 20), (−36, −22, 24), and (−40, −20, 16), respectively.

Two PET studies have investigated the role of attention on the neurophysiological response to pain (Peyron *et al.*, 1999; Petrovic *et al.*, 2000a). Peyron *et al.* used an auditory distraction task to investigate modification of

brain activity during hot painful stimulation (~47°C) of the right or left hand. They demonstrated a pain "intensity encoding matrix," which included bilateral insula/SII and contralateral thalamus and an "attentional network" comprising right prefrontal and posterior parietal cortices and ACG. Contrary to their study, we observe ACG activity irrespective of attentional context and no additional activity during distracted stimulation (RV, LV) in right prefrontal or posterior parietal cortices. The absence of ACG activity during attended pain, as recorded by Peyron *et al.*, may relate to coping strategies developed during training of subjects (Hsieh *et al.*, 1999), while the other regions observed may be specific to the auditory stimulus used for distraction. Our finding of reduced anterior insula activity during distracted stimulation of either hand may relate explicitly to attentional processes or reflect reduced subjective pain intensity. At present we cannot distinguish between these two possible explanations for the observed effect, as no behavioral data were acquired during scanning of subjects. Future experiments will address this problem.

Petrovic *et al.* used a cold pressor test to record brain activity in response to painfully cold (~0°C) and cold (~20°C) stimuli, with and without a visual distraction task (perceptual maze (Ghatan *et al.*, 1995)). Pain (no distraction) elicited activation in contralateral SI and bilaterally in SII, mid-/anterior insula, and ACG. The effect of the distraction task during pain was to decrease activity in BA43, defined as somatosensory association area (including SII) and periaqueductal gray/midbrain, and increase activity in lateral orbitofrontal regions, whereas the remainder of the pain matrix remained unaltered by the distraction task. In general, these results are not in agreement with the present study, where we have found modification in the size and location of activity in the insula in response to a visual distraction task during pain and neither decreased activity in SII (where present) or increased activity in orbitofrontal regions. However, the raw data presented by Petrovic *et al.* for right and left insula activity appear to be significantly reduced during cold/pain with the maze task when compared to cold/pain alone. Petrovic *et al.* also acknowledge that areas close to posterior insula/SII were not resolved in their study, which may explain some discrepancies between our (fMRI) data and their PET study.

To further refine our understanding of the pain system, event-related fMRI studies will be required with online psychophysics recordings. Measurement of the behavioral response may increase sensitivity for detection of pain-related brain activity (Porro *et al.*, 1998; Apkarian *et al.*, 1999; Davis *et al.*, 2000) and may reveal brain regions related to pain affect (Rainville *et al.*, 1997) or those regions whose time course is best modeled with such data (Davis *et al.*, 1998b). However, it is difficult to obtain behavioral data during fMRI experiments utilizing a block design with relatively short interstimulus intervals, since inevitably brain activity related to the response selection and execution process confounds the activation maps obtained. Event-related fMRI experiments would avoid these problems and allow further investigation of effects of anticipation (Ploghaus *et al.*, 1999) and learning (Ploghaus *et al.*, 2000), in relation to diverted attention pain experiments. Additionally, techniques could be used to determine the functional connectivity between different brain regions (Biswal *et al.*, 1995) during the experience of pain.

By using painful thermal stimuli applied to the thenar of the right and left hand, we have investigated the pain matrix at the supraspinal level. Of prime interest were the nature of cortical responses to lateralized painful stimuli and the interaction of a distraction task with the observable pain matrix. In response to pain, a consistent pattern of activation was found across the cerebrum, but superimposed on the expected pain matrix were laterality-specific and attention-specific effects, which were located in the insula. In particular, the dorsal margin of the posterior insula was found to demonstrate a contralateral response to painful thermal stimuli: a finding that extends the work of Craig *et al.*, in that thermosensory cortex appears to be present in both left and right insula. While the posterior insula appears to subserve a thermosensory/discriminative function, anterior insula activity was dependent on the attentional context of painful stimulation and was significantly attenuated when subjects were distracted from pain. This study builds upon earlier reports of pain-related brain activity, in that the insula has been shown to consist of discrete functional/anatomic units whose activity depends on stimulus laterality and attention.

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