

Hemispheric Lateralization of Somatosensory Processing

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Coghill, Robert C., Ian Gilron, and Michael J. Iadarola. Hemispheric lateralization of somatosensory processing. *J Neurophysiol* 85: 2602–2612, 2001. Processing of both painful and nonpainful somatosensory information is generally thought to be subserved by brain regions predominantly contralateral to the stimulated body region. However, lesions to right, but not left, posterior parietal cortex have been reported to produce a unilateral tactile neglect syndrome, suggesting that components of somatosensory information are preferentially processed in the right half of the brain. To better characterize right hemispheric lateralization of somatosensory processing, $H_2^{15}O$ positron emission tomography (PET) of cerebral blood flow was used to map brain activation produced by contact thermal stimulation of both the left and right arms of right-handed subjects. To allow direct assessment of the lateralization of activation, left- and right-sided stimuli were delivered during separate PET scans. Both innocuous (35°C) and painful (49°C) stimuli were employed to determine whether lateralized processing occurred in a manner related to perceived pain intensity. Subjects were also scanned during a nonstimulated rest condition to characterize activation that was not related to perceived pain intensity. Pain intensity-dependent and -independent changes in activation were identified in separate multiple regression analyses. Regardless of the side of stimulation, pain intensity-dependent activation was localized to contralateral regions of the primary somatosensory cortex, secondary somatosensory cortex, insular cortex, and bilateral regions of the cerebellum, putamen, thalamus, anterior cingulate cortex, and frontal operculum. No hemispheric lateralization of pain intensity-dependent processing was detected. In sharp contrast, portions of the thalamus, inferior parietal cortex (BA 40), dorsolateral prefrontal cortex (BA 9/46), and dorsal frontal cortex (BA 6) exhibited right lateralized activation during both innocuous and painful stimulation, regardless of the side of stimulation. Thus components of information arising from the body surface are processed, in part, by right lateralized systems analogous to those that process auditory and visual spatial information arising from extrapersonal space. Such right lateralized processing can account for the left somatosensory neglect arising from injury to brain regions within the right cerebral hemisphere.

INTRODUCTION

Conscious awareness of tactile stimulation of the body surface has long been known to be subserved largely by brain regions opposite to the side of stimulation. Unilateral lesions to either the primary or secondary somatosensory cortex result in deficits in contralateral tactile sensibility (Greenspan and Winfield 1992; Head and Holmes 1911; Marshall 1951). In addition, direct electrical stimulation of these areas produces sen-

sations that are generally referred to a contralateral portion of the body (Penfield and Rasmussen 1955). Split-brain studies have confirmed that brain mechanisms contralateral to a tactile stimulus are sufficient for localization of light touch and temperature discrimination, regardless of the side of stimulation (Gazzaniga et al. 1963; Lepore et al. 1997). Accordingly, each cerebral cortical hemisphere has an equal capacity for fundamental aspects of somatosensory processing.

Despite the capacity of each cerebral cortical hemisphere to subservise components of somatosensory processing, substantial evidence indicates that both hemispheres can be engaged in the processing of a unilateral somatosensory stimulus via bilateral subcortical routes. For example, a psychophysical investigation of a split-brain patient indicates that both the contralateral and ipsilateral cerebral cortical hemispheres process information arising from a unilateral noxious thermal stimulus (Stein et al. 1989). Similarly, split-brain or congenitally acallosal patients retain the capacity to compare innocuous thermal information arising from the left side of the body with that arising from the right side of the body (Lepore et al. 1997). In the case of nociceptive processing, this bilateral transmission of information may involve the posterior complex and intralaminar nuclei. Neurons within these regions have predominately bilateral receptive fields (Brinkhus et al. 1979; Bushnell and Duncan 1989; Dong et al. 1978; Guilbaud et al. 1977) and receive input from neurons in the deep dorsal horn and ventral horn that also have bilateral receptive fields (Giesler et al. 1981).

In addition to contralateral and bilateral processing mechanisms, several higher-order aspects of somatosensory processing are differentially distributed between the left and right hemispheres. The right posterior parietal cortex is critical for attentional aspects of somatosensory processing, since lesions of this structure result in a unilateral neglect in which subjects have diminished awareness of tactile stimuli applied to left portions of the body (Critchley 1958; Mesulam 1981). Anecdotal evidence also suggests that right lateralized regions within the frontal cortex may play a similar role (Mesulam 1981). Additionally, functional imaging studies of chronic neuropathic pain and cluster headache indicate that the right, but not left, anterior cingulate cortex is activated in patients with pain on either side of their body (Hsieh et al. 1995, 1996). Nevertheless, current understanding of this right lateralized mechanism for somatosensory processing remains incomplete, and the degree of lateralization remains uncharacterized.

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To directly identify right lateralized brain regions engaged in somatosensory processing, we used positron emission tomography (PET) to characterize brain activation evoked during thermal stimulation of both the left and right forearms of healthy volunteers. Both painful (49°C) and innocuous (35°C) stimuli were employed to better determine which features of the stimulus were associated with hemispherically lateralized processing. Separate multiple regression analyses were utilized to first identify activation significantly related to subjects' perceptions of pain intensity (pain intensity-dependent) and then to identify activation that was common to all stimulated conditions, but which was independent from pain intensity (pain intensity-independent) (Coghill et al. 1999).

METHODS

Subjects

All subjects (5 women, 4 men) were right-handed, ranged in age from 20 to 52 (35.5 ± 3.69 yr, mean \pm SE), and were healthy with no detectable magnetic resonance imaging (MRI) abnormalities. Pre-study pregnancy tests were negative for all female subjects of child-bearing potential. All procedures were approved by the Institutional Review Board of the National Institute of Dental Research and the Radiation Safety Committee of the National Institutes of Health. All volunteers gave written, informed consent acknowledging 1) that they would receive radioactive tracers, 2) that they would experience experimental pain stimuli, 3) that all methods and procedures were clearly explained, and 4) that they were free to withdraw from the experiment at any time.

Functional imaging

Brain activation was assessed by measuring relative changes in cerebral blood flow (CBF) with $H_2^{15}O$ PET (Fox et al. 1984). Subjects were placed in the PET scanner (GE Advance scanner), fitted with a thermoplastic mask to minimize head movement, and positioned such that the most superior aspect of the cerebral cortex was within the field of view. For all subjects, the field of view extended inferiorly to encompass the ventral aspect of the cerebellum (-54.2 mm below the AC-PC plane in standard stereotaxic space). Transmission scans were performed for attenuation correction during image reconstruction. Prior to actual PET scanning, a sham scan (saline injection) was carried out to minimize anxiety associated with the PET scan procedure (Talbot et al. 1991). For all PET scans, subjects were instructed simply to lie on the bed with their eyes closed and to not move or say anything. Each PET scan was initiated on intravenous bolus injection of 10 mCi $H_2^{15}O$, with data acquisition (3D mode with septa retracted) during the 60 s following tracer arrival in the brain. Subjects received a total of 30 PET scans acquired over 2 separate sessions. These sessions were separated by an average of approximately 7 days. With positioning, a transmission scan, a sham scan, and 15 PET scans, each PET session lasted approximately 2 h. All scans were separated by 6-min intervals to minimize the duration of each scanning session. Since this interval does not permit ^{15}O in the body to decay to negligible levels, scans of residual activity were obtained prior to each PET scan for subsequent background correction (Chmielowska et al. 1998, 1999).

Subjects were scanned during five different conditions: 1) rest (no somatosensory stimulation), 2) 35°C stimulation of the left arm, 3) 35°C stimulation of the right arm, 4) 49°C stimulation of the left arm, and 5) 49°C stimulation of the right arm. The 1-cm-diam stimulator was applied sequentially to 6 regions (2×3 grid, 2 cm between spots, 5-s stimulus/spot; 0.5 s between spots) on the ventral surface of the forearm. Stimulation was initiated 5 s prior to tracer injection and was continued for ~ 90 s until completion of data acquisition. Subjects

rated pain intensity and unpleasantness using a mechanical visual analog scale (VAS) at the end of every PET scan and were trained in the use of this scale prior to the first PET session (Coghill et al. 1993; Price et al. 1994). Each scanning condition was repeated 6 times and was presented in a randomized order.

Image processing

Structural MRI scans (Fast gradient recalled echo, 124×1.5 mm thick sagittal images with an in-plane resolution of 0.98 mm, extended dynamic range, 256×256 matrix, 1 nexus, TE = minimum, Flip Angle = 20°) were obtained for each subject and were used for transformation of PET data into standard stereotaxic space (Collins et al. 1994; Talairach and Tournoux 1988). These MRI scans were acquired in a 1-h duration session on a different day than the PET session. PET data were movement corrected and registered with MRI data using Automated Image Registration software (Woods et al. 1992, 1993). Background data were realigned in a manner identical to that used for PET data. After spatial normalization and background correction, PET data were smoothed with a $15 \times 15 \times 10$ -mm gaussian filter to further minimize spatial variability. To minimize variability produced by global CBF changes, each PET scan was normalized to gray matter values by dividing each voxel value by the average of gray matter CBF (Chmielowska et al. 1998).

Multiple regression analyses

Multiple regression analyses were used to identify pain intensity-dependent and pain intensity-independent stimulus-induced brain activation, as described previously (Coghill et al. 1999). All regression analyses were accomplished using NIH-Functional Imaging Data Analysis Platform and were performed separately for scans of left- and right-sided stimulation. Pain intensity-dependent effects were identified by characterizing the relationship (regression coefficient) between normalized CBF changes and psychophysical ratings of pain intensity. Pain intensity-independent effects, such as simple tactile processing of the contact of the stimulator with the skin as well as more complex spatial processing of the movement of the probe over the surface of the forearm, were identified by first factoring out variability related to perceived pain intensity and then characterizing effects common to all stimulated conditions. Despite the fact that the regressor used in this second analysis consists of a step function between resting and stimulated conditions, the regression coefficient still describes changes in pain intensity-independent activation in relationship to changes in the regressor. Thus if nonstimulated scans were weighted 0 and stimulated scans were weighted 5, the predicted blood flow difference would be equal to the regression coefficient multiplied by 5. However, in order for this regressor to have a mean of zero (a requirement of this particular analysis package), stimulated scans were weighted +0.556 and nonstimulated scans were weighted -1.111 , thereby yielding a range of 1.667. In both pain intensity-dependent and -independent analyses, variability unique to individual subjects (i.e., variability that was constant across all scanning conditions for a given subject) was first factored out. Wilk's Lambda statistic was used to determine whether each regression coefficient was statistically different from zero. The Wilk's Lambda values were converted to F values and then to z -scores. To correct for multiple comparisons, the statistical reliability of voxels exceeding a z -score of 3.09 was then assessed according to the spatial extent of activation (Friston et al. 1994). The volume-wise false-positive rate was set at $<5\%$ ($P < 0.05$).

Two additional variables, psychophysical ratings of pain unpleasantness and effects due to variation in responses between scanning sessions, were also considered for inclusion in the multiple regression analysis. As in most studies of heat pain, unpleasantness ratings were highly correlated with pain intensity ratings ($r = 0.98$). Since these psychophysical variables were not orthogonal, additional analyses

with pain unpleasantness as a regressor were not performed, and pain unpleasantness findings are not discussed further. In the case of session-to-session variation, psychophysical ratings showed no statistically significant differences across scanning sessions. Furthermore, a preliminary analysis with a session nuisance variable revealed virtually no differences from a corresponding analysis when session was not considered as a nuisance variable. Thus to minimize the complexity of an already complex analysis, a variable accounting for session-to-session variation was not included in the multiple regression analysis.

Assessment of lateralized activation

Lateralization of activation foci was confirmed by regions of interest analyses (ROI). ROIs were selected in a data-driven fashion designed to provide an objective assessment of the potential lateralization of activation. Brain regions activated by either left-sided and/or right-sided stimuli were first identified by generating binary masks of statistically significant activation (i.e., statistically significant voxels identified in the spatial extent analysis described above were assigned a value of 1, while nonsignificant voxels were assigned a value of 0). These masks were then added together, such that regions with overlapping activation were identified by a value of 2. (This procedure can be visualized in the *right column* of Figs. 2 and 3, where blue and green regions represent nonoverlapping activation, and where red regions represent overlapping activation.) This volume was then converted to a binary mask describing regions of overlap (overlapping voxels = 1, nonoverlapping voxels = 0, and voxels with no activation = 0). Next, regression coefficient maps of left- and right-sided stimulation were averaged together and then multiplied by the overlap mask, such that only regions with overlapping activation had nonzero values in the averaged regression coefficient map. Then, local maxima were identified in this masked, averaged, regression coefficient map and used as targets for ROI analysis.

Two strictly conservative criteria were used to determine whether activation was hemispherically lateralized. The first criterion provided a qualitative assessment of hemispheric lateralization; a given region was required to be activated in a strictly unilateral fashion in the same hemisphere, during both left- and right-sided stimulation. This was evaluated by transposing the ROI to the corresponding stereotaxic location of the opposite hemisphere. If any statistically significant activity was present at this locus, this region was determined to exhibit at least partial bilateral activation and was excluded from further consideration. The second criterion provided a quantitative assessment of the degree of lateralization; a given ROI was required to exhibit significantly greater normalized CBF (i.e., with no variability factored out) than that of the corresponding stereotaxic location of the opposite hemisphere. This was accomplished by obtaining normalized CBF values of all PET scans for each ROI and its corresponding locus in the opposite hemisphere. A three-factor repeated measures ANOVA was then used to determine whether activation (i.e., stimulated condition–rest) was dependent on hemispheric location, stimulus temperature, and/or stimulus side. In both analyses, each ROI consisted of a single voxel ($2 \times 2 \times 2$ mm). Given that adjacent voxels are highly correlated due to the smoothness of the PET data ($15 \times 15 \times 10$ mm full-width, half-max), larger ROIs were not employed. This procedure was performed separately for pain intensity–dependent and pain intensity–independent analyses.

RESULTS

Psychophysics

When assessed psychophysically, subjects clearly distinguished between painful and innocuous stimuli (Fig. 1). The 49°C stimulus produced significantly higher ratings of pain intensity than the 35°C stimulus [ANOVA $F_{(1,8)} = 14.98, P <$

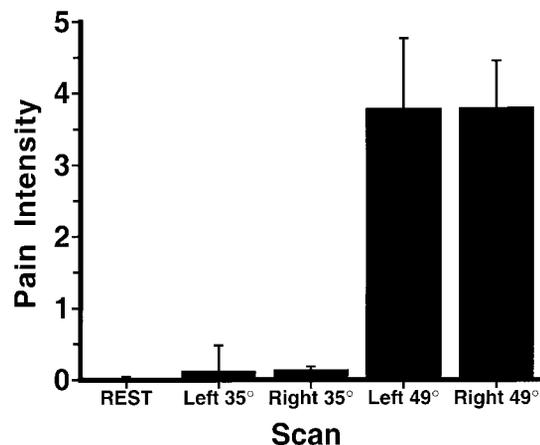


FIG. 1. Pain intensity ratings of left- and right-sided stimulation. Pain intensity ratings of right-sided stimulation were indistinguishable from those of left-sided stimulation. However, subjects readily detected differences between the neutral (35°C) and painful (49°C) stimuli.

0.0047]. Importantly, subjects' perceptions of pain intensity were unaffected by the side of stimulation [ANOVA $F_{(1,8)} = 0.01, P < 0.9112$]. Thus analyses examining the potential lateralization of pain processing are not confounded by side-to-side differences in perceived pain intensity. Additional three-factor ANOVAs confirmed that pain intensity ratings were not significantly influenced by gender or by differences between scanning sessions.

Pain intensity–dependent activation

On a qualitative level, pain intensity–dependent brain activation evoked by right-sided stimulation approximated a mirror image of that evoked by left-sided stimulation (Fig. 2). Regardless of the side of stimulation, the cerebellum, putamen, thalamus, and frontal operculum exhibited bilateral activation; the primary somatosensory cortex, the secondary somatosensory cortex, and the posterior insular cortex exhibited contralateral activation; while the anterior cingulate cortex exhibited near-midline activation that tended to be somewhat ipsilaterally located (see Table 1 for locations of activations).

Analysis of left/right overlap revealed that 31 sites, located within the cerebellum, thalamus, putamen, insula, frontal operculum, anterior cingulate cortex, and supplementary motor area were activated during both left and right-sided stimulation. The majority of these regions were activated in a bilateral fashion. Two sites, one in the left cerebellum ($x = -6.1, y = -52.5, z = -36.2$) and one in the left thalamus ($x = -10.1, y = -20.5, z = -0.2$), exhibited a qualitative lateralization (i.e., no statistically significant activation was detected in corresponding portions of the right hemisphere). However, direct statistical comparisons of these two sites revealed no significant differences in normalized CBF between hemispheres [cerebellum: $F_{(1,8)} = 1.52, P < 0.25$; thalamus: $F_{(1,8)} = 0.55, P < 0.48$], indicating that these structures tended to be activated in a bilateral fashion as well. In the case of the thalamus, a statistically significant interaction was detected between the side of stimulation and hemisphere in which the ROI was located [$F_{(1,8)} = 9.97, P < 0.0135$], although neither main effect was significant. Inspection of CBF confirmed that activation within this ROI was largely bilateral, although stimuli applied to the contralateral arm consistently evoked greater

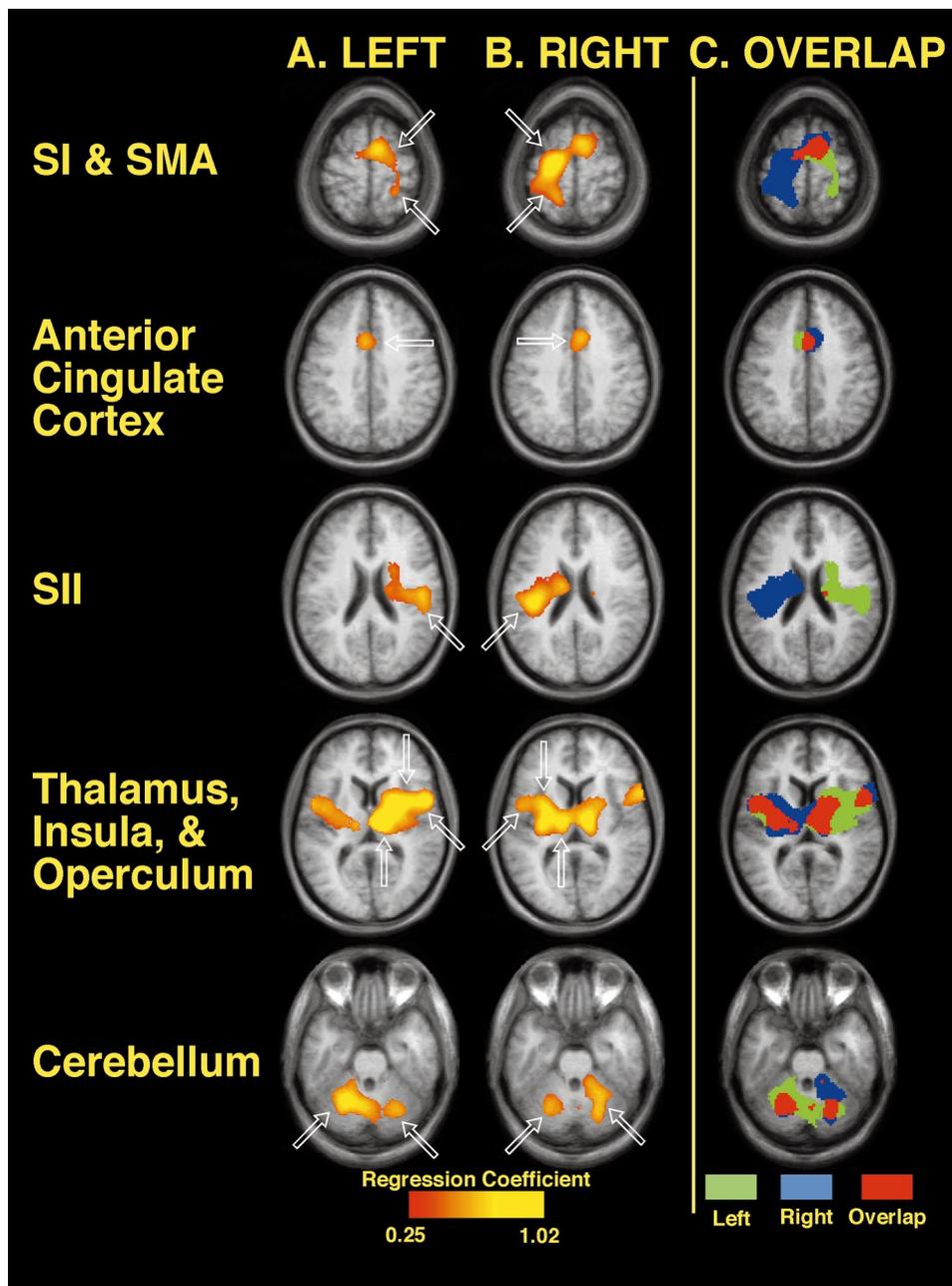


FIG. 2. Pain intensity-dependent activation. Multiple regression analyses revealed that a number of brain regions exhibited activation that was significantly related to the perceived intensity of pain. Pain intensity-related activation arising from left-sided stimulation (A) approximated a mirror image of that arising from right-sided (B) stimulation. Statistically significant regression coefficients ($P < 0.05$) are displayed in color on the gray scaled average of all 9 subjects' structural magnetic resonance imaging (MRI) data. The primary and secondary somatosensory cortices (SI and SII, respectively) exhibited predominantly contralateral activation, while other regions exhibited predominantly bilateral activation. Overlapping activation between left- and right-sided stimulation was evident in brain regions that exhibited predominantly bilateral activation (displayed in red in C). Note that image left corresponds to subject left.

CBF changes than ipsilateral stimuli. Thus no hemispherically lateralized mechanism is engaged in pain intensity-dependent processing. Similar analyses of the anterior cingulate activation revealed, that although statistical (i.e., z -score) local maxima tended to be somewhat ipsilaterally located, local maxima of the regression coefficients occurred in midline locations regardless of the side of stimulation.

Pain intensity-independent activation

In sharp contrast to pain intensity-dependent activation, several brain areas exhibiting pain intensity-independent activation were lateralized to the right hemisphere (Fig. 3 and Tables 2 and 3). Analysis of left/right overlap revealed that 16 sites in the left cerebellum, right frontal operculum, right thalamus, right middle frontal gyrus, and right medial frontal

gyrus exhibited pain intensity-independent activation during both left- and right-sided stimulation. Of these 16 sites, 9 exhibited a qualitative lateralization (i.e., where no statistically significant activation was evident in corresponding portions of the opposite hemisphere, Table 3). ROI analysis of these nine sites revealed that the right thalamus, right dorsolateral prefrontal cortex (BA 9/46), right inferior parietal lobule (BA 40), and right dorsal frontal cortex (BA 6) exhibited significantly greater increases in normalized CBF than corresponding stereotaxic loci in the left hemisphere (Fig. 4, Table 3). Thus these regions exhibited strongly hemispherically lateralized activation regardless of the side or the intensity of stimulation.

Activation within three of these hemispherically lateralized regions varied in a complex manner dependent on the side of stimulation (i.e., a side \times hemisphere interaction, Table 3). These regions included both dorsolateral prefrontal loci [ven-

TABLE 1. *Pain intensity-dependent activation*

	Left-Sided Stimulation		Right-Sided Stimulation	
	Left Brain	Right Brain	Left Brain	Right Brain
	<i>Bilateral activations</i>			
Cerebellum	0.55 (−16.1 −64.5 −48.2) 0.72 (−38.1 −56.5 −48.2) 0.54 (−10.1 −52.5 −40.2) 0.63 (−46.1 −54.5 −34.2) 0.80 (−26.1 −52.5 −30.2) 0.80 (−8.1 −62.5 −22.2) 0.70 (−0.1 −68.5 −16.2) 0.70 (−0.1 −64.5 −16.2)	0.69 (37.9 −48.5 −48.2) 0.59 (33.9 −54.5 −36.2) 0.57 (39.9 −52.5 −36.2) 0.60 (27.9 −68.5 −26.2) 0.61 (21.9 −66.5 −24.2) 0.59 (17.9 −64.5 −22.2) 0.60 (17.9 −60.5 −14.2) 0.65 (3.9 −60.5 −14.2) 0.68 (1.9 −56.5 −12.2)	0.66 (−34.1 −52.5 −36.2) 0.46 (−6.1 −50.5 −34.2) 0.63 (−30.1 −58.5 −32.2) 0.61 (−20.1 −64.5 −28.2) 0.53 (−18.1 −62.5 −24.2)	0.66 (37.9 −48.5 −50.2) 0.64 (33.9 −52.5 −30.2) 0.65 (21.9 −68.5 −24.2) 0.66 (21.9 −62.5 −24.2) 0.62 (23.9 −56.5 −24.2) 0.61 (13.9 −40.5 −24.2) 0.58 (3.9 −50.5 −16.2) 0.58 (3.9 −44.5 −16.2) 0.62 (3.9 −50.5 −12.2) 0.63 (1.9 −54.5 −10.2)
Putamen	0.58 (−30.1 −10.5 1.8)	1.03 (27.9 1.5 5.8) 0.85 (25.9 3.5 13.8)	0.78 (−28.1 −4.5 11.8) 0.78 (−28.1 −10.5 13.8)	0.42 (29.9 11.5 −2.2)
Thalamus	0.53 (−16.1 −20.5 9.8) 0.62 (−12.1 −14.5 9.8) 0.56 (−18.1 −16.5 11.8) 0.54 (−16.1 −20.5 13.8)	0.89 (15.9 −8.5 11.8) 0.71 (21.9 −18.5 13.8)	0.52 (−12.1 −16.5 −0.2) 0.56 (−8.1 −14.5 −0.2) 0.61 (−4.1 −6.5 −0.2)	0.88 (9.9 −10.5 7.8) 0.72 (15.9 −4.5 9.8)
Frontal operculum	0.65 (−46.1 −0.5 7.8)	0.89 (49.9 7.5 5.8) 0.84 (53.9 5.5 9.8)	0.58 (−50.1 5.5 5.8)	0.63 (55.9 11.5 9.8)
	<i>Contralateral activations</i>			
Insula		0.97 (31.9 1.5 3.8) 0.57 (33.9 −20.5 15.8) 0.61 (37.9 −20.5 17.8)	0.86 (−30.1 −14.5 13.8)	
SII		0.61 (43.9 −18.5 15.8) 0.65 (49.9 −16.5 15.8) 0.55 (55.9 −30.5 23.8) 0.52 (43.9 −34.5 27.8) 0.57 (49.9 −34.5 27.8)	0.76 (−40.1 −28.5 21.8) 0.77 (−40.1 −24.5 21.8)	
SI/MI		0.44 (31.9 −28.5 61.8) 0.50 (21.9 −40.5 63.8) 0.44 (27.9 −30.5 63.8) 0.47 (21.9 −42.5 67.8)	0.60 (−36.1 −34.5 59.8) 0.60 (−32.1 −34.5 61.8) 0.54 (−26.1 −36.5 67.8) 0.86 (−18.1 −14.5 65.8) 0.80 (−22.1 −20.5 67.8)	
	<i>Ipsilateral and mixed activations</i>			
Anterior cingulate cortex	0.56 (−8.1 23.5 29.8) 0.54 (−6.1 15.5 31.8) 0.63 (−4.1 7.5 41.8) 0.60 (−0.1 5.5 41.8)	0.54 (1.9 9.5 39.8) 0.69 (1.9 −2.5 47.8)		0.64 (3.9 7.5 39.8) 0.66 (5.9 11.5 39.8) 0.68 (5.9 7.5 43.8) 0.68 (3.9 3.5 47.8)
Supplementary/premotor cortex	0.30 (−8.1 −8.5 71.8) 0.28 (−12.1 −6.5 71.8)	0.76 (5.9 −6.5 59.8) 0.54 (19.9 −10.5 63.8) 0.77 (5.9 −2.5 63.8)		0.76 (5.9 1.5 59.8) 0.73 (7.9 1.5 63.8) 0.73 (1.9 −0.5 53.8)
Superior parietal lobule			0.43 (−18.1 −48.5 55.8) 0.36 (−22.1 −44.5 73.8)	
Midbrain	0.63 (−0.1 −26.5 −14.2)			
Substantia Nigra	0.50 (−10.1 −20.5 −8.2)			

Multiple brain regions exhibited activation that was significantly related to the perceived intensity of painful stimulation. All regions had $z > 3.09$ and $P < 0.05$. Regression coefficients are displayed for each statistically significant local maximum, with the location of the local maxima in parentheses. All coordinates (x, y, z) are according to standard, stereotaxic space (Talairach and Tournoux 1988).

tral: $F_{(1,8)} = 6.05$, $P < 0.0393$; dorsal: $F_{(1,8)} = 6.23$, $P < 0.0372$] and the dorsal frontal locus [$F_{(1,8)} = 15.04$, $P < 0.0047$]. In all three of these regions, the magnitude of normalized CBF change was larger when the arm ipsilateral to the ROI was stimulated, regardless of the hemisphere being exam-

ined. In other words, stimulation of the right arm evoked greater CBF changes in the right hemisphere ROI than did stimulation of the left arm, while stimulation of the left arm evoked greater CBF changes in the left hemisphere ROI than did stimulation of the right arm (Fig. 4).

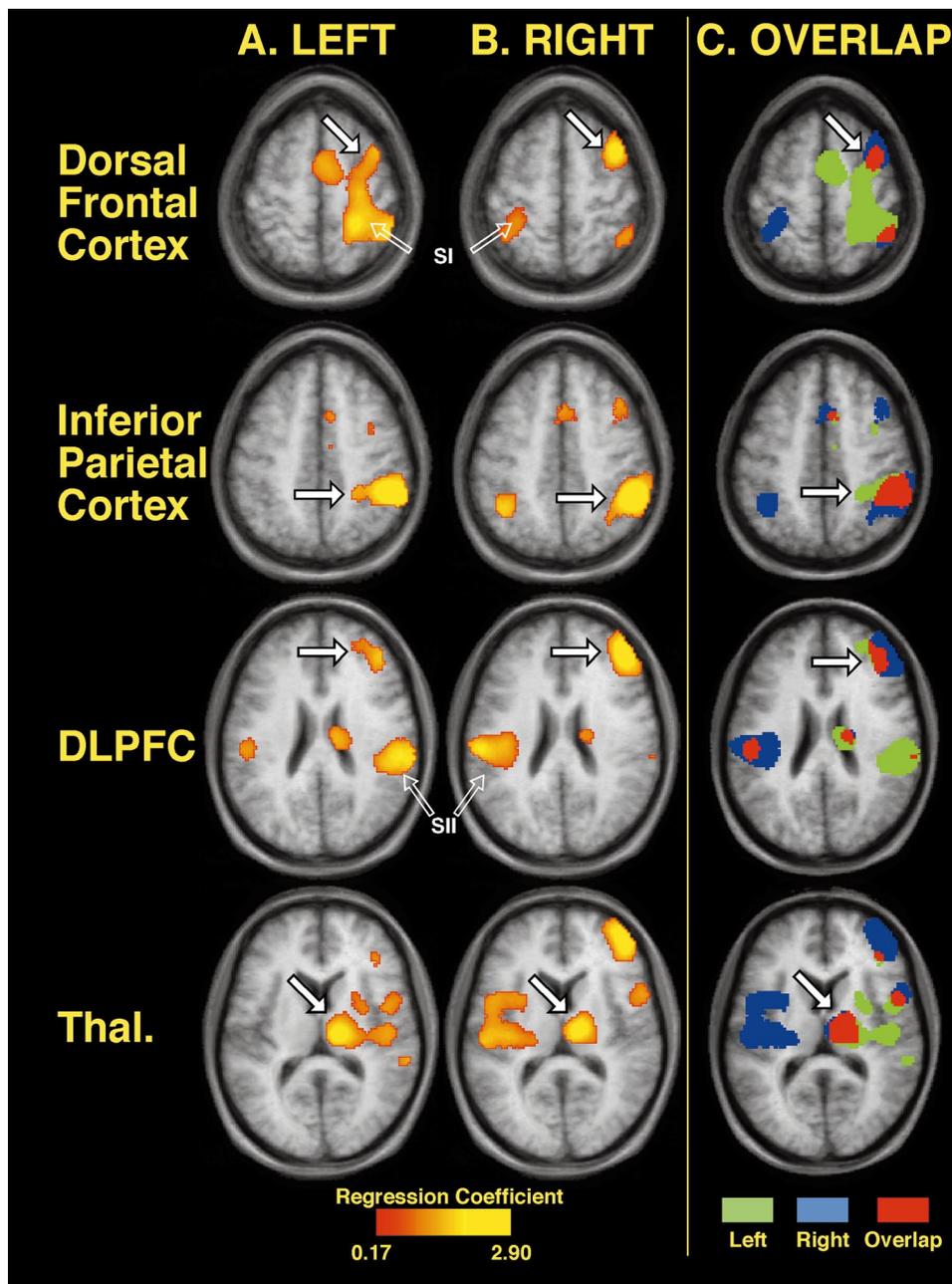


FIG. 3. Topography of brain regions exhibiting activation lateralized to the right hemisphere. Multiple regression analyses revealed that left-sided (A) and right-sided (B) thermal stimulation produced statistically reliable pain intensity–independent activation of right lateralized regions (denoted by solid arrows) of the dorsal frontal cortex, inferior parietal cortex, dorsolateral prefrontal cortex (DLPFC), and thalamus (Thal.). Statistically significant regression coefficients ($P < 0.05$) are displayed in color on the gray scaled average of all 9 subjects' structural MRI data. These right lateralized activations overlapped to a large extent (displayed in red in C), indicating that common portions of these areas are activated by stimuli applied to either side of the body. In addition to the right lateralized activation, contralateral activation of the primary (SI) and secondary (SII) somatosensory cortices is also evident (A and B). Note that image left corresponds to subject left and that slice locations correspond to those in Table 3.

Additionally, a number of brain regions exhibited either contralateral or bilateral pain intensity–independent activation. Regardless of the side of stimulation, the primary and secondary somatosensory cortices exhibited clearly contralateral activation, while structures such as the frontal operculum, ventral portions of the inferior parietal lobule, supplementary motor area, and cerebellum exhibited either contralateral or bilateral activation (Table 2).

As previously, the regression analysis of pain intensity–independent effects accurately predicts the normalized CBF differences between all stimulated conditions and rest (Coghill et al. 1999). For example, during right-sided stimulation, the right posterior parietal cortex had a regression coefficient of 2.81, which when multiplied by the range of the regressor (1.667), would predict an activation of 4.68. Observed values in the PET data

(right-sided 35°C stimulation: 4.37; right-sided 49°C stimulation: 4.61) closely approximate the predicted value.

Overlap between pain intensity–dependent and pain intensity–independent activation

Many brain regions exhibited both pain intensity–dependent and pain intensity–independent activation, consistent with previous findings using subtraction techniques (Coghill et al. 1994; Iadarola et al. 1998). For example, both the primary and secondary somatosensory cortices, supplementary motor cortex, thalamus, frontal operculum, and left cerebellar hemisphere exhibited both pain intensity–dependent and pain intensity–independent responses (Tables 1 and 2). In contrast, the cerebellar vermis and anterior cingulate cortex exhibited activation that was predominantly pain intensity dependent,

TABLE 2. *Pain intensity-independent activations*

	Left-Sided Stimulation		Right-Sided Stimulation	
	Left Brain	Right Brain	Left Brain	Right Brain
	<i>Contralateral activations</i>			
SI		2.18 (25.9 – 38.5 61.8)	1.24 (–32.1 – 38.5 57.8) 1.21 (–32.1 – 38.5 61.8)	
SII		1.62 (49.9 – 20.5 15.8) 1.78 (53.9 – 24.5 19.8) 1.87 (49.9 – 32.5 21.8) 1.99 (57.9 – 28.5 23.8)	1.75 (–52.1 – 20.5 19.8) 1.66 (–42.1 – 24.5 21.8)	
	<i>Right-lateralized activations</i>			
Thalamus		1.92 (19.9 – 18.5 13.8) 1.81 (15.9 – 16.5 17.8)		2.20 (13.9 – 10.5 11.8)
Inferior parietal lobule (dorsal)		1.38 (31.9 – 42.5 39.8) 2.59 (49.9 – 38.5 43.8)	1.77 (–40.1 – 52.5 49.8)	2.81 (49.9 – 44.5 47.8)
Dorsolateral prefrontal cortex		1.55 (39.9 37.5 21.8) 1.46 (37.9 41.5 21.8) 1.21 (33.9 49.5 21.8) 1.15 (27.9 47.5 25.8) 1.67 (39.9 33.5 31.8) 1.57 (41.9 29.5 33.8)		2.83 (43.9 45.5 17.8)
Dorsal frontal cortex		1.33 (35.9 – 0.5 55.8) 1.36 (33.9 – 2.5 59.8)		2.17 (39.9 7.5 55.8)
	<i>Mixed activations</i>			
Cerebellum	2.32 (–28.1 – 60.5 – 46.2) 1.76 (–28.1 – 48.5 – 44.2) 2.04 (–38.1 – 58.5 – 34.2) 1.58 (–36.1 – 54.5 – 30.2) 1.29 (–16.1 – 68.5 – 26.2) 1.22 (–20.1 – 60.5 – 26.2) 1.59 (–26.1 – 46.5 – 26.2)		2.24 (–32.1 – 64.5 – 42.2) 1.75 (–34.1 – 48.5 – 38.2) 1.91 (–34.1 – 58.5 – 36.2) 1.74 (–34.1 – 52.5 – 36.2)	1.54 (23.9 – 54.5 – 46.2) 1.46 (23.9 – 54.5 – 42.2) 1.35 (25.9 – 54.5 – 38.2) 1.33 (33.9 – 54.5 – 34.2) 1.55 (29.9 – 66.5 – 26.2)
Frontal operculum		1.83 (49.9 1.5 3.8)	1.58 (–46.1 1.5 7.8) 1.60 (–50.1 3.5 7.8) 1.38 (–38.1 7.5 9.8)	1.92 (43.9 19.5 1.8) 1.47 (55.9 5.5 7.8) 1.47 (55.9 9.5 7.8)
Inferior parietal lobule (ventral)	1.49 (–52.1 – 24.5 27.8) 1.64 (–52.1 – 30.5 29.8)	1.77 (47.9 – 36.5 25.8)	1.84 (–52.1 – 26.5 25.8) 1.81 (–50.1 – 32.5 29.8) 1.75 (–48.1 – 28.5 29.8) 1.47 (–48.1 – 40.5 33.8)	
Medial frontal gyrus		1.55 (7.9 – 8.5 53.8) 1.69 (3.9 – 0.5 53.8) 1.60 (1.9 3.5 55.8)	1.36 (–2.1 5.5 51.8)	1.28 (1.9 7.5 49.8)
Prefrontal cortex (frontal pole)				1.91 (31.9 41.5 – 14.2) 2.04 (37.9 45.5 – 12.2) 2.07 (43.9 49.5 – 10.2)
Premotor cortex		1.84 (23.9 – 16.5 69.8) 1.82 (21.9 – 12.5 69.8)		
Superior parietal lobule			1.51 (–38.1 – 48.5 51.8) 1.22 (–36.1 – 44.5 55.8)	
Putamen/caudatum		1.08 (29.9 1.5 11.8)		
Insula			1.48 (–34.1 – 20.5 11.8) 1.10 (–32.1 3.5 13.8)	

Multiple brain regions exhibited activation that was independent of perceived intensity. All regions had $z > 3.09$ and $P < 0.05$. Regression coefficients are displayed for each statistically significant local maximum, with the location of the local maxima in parentheses. All coordinates (x, y, z) are according to standard, stereotaxic space (Talairach and Tournoux 1988).

TABLE 3. *Hemispherically lateralized pain intensity-independent brain activation*

Region	Coordinates (x, y, z)	Difference Between Hemispheres
<i>Quantitatively lateralized regions</i>		
Right thalamus	13.9 -14.5 11.8	$F = 7.21$ $P < 0.0277$ T
Right inferior parietal lobule (BA 40)	51.9 -44.5 45.8	$F = 15.70$ $P < 0.0042$
Right DLPFC (BA 9/46)	43.9 41.5 23.8	$F = 7.15$ $P < 0.0282$ A
(BA 9)	43.9 35.5 31.8	$F = 9.85$ $P < 0.0138$ A
Right dorsal frontal cortex (BA 6)	39.9 9.5 57.8	$F = 10.80$ $P < 0.0111$ A
<i>Qualitatively lateralized regions</i>		
Left cerebellum	-32.1 -64.5 -42.2	$F = 2.50$ $P < 0.1522$ T
	-30.1 -42.5 -42.2	$F = 2.07$ $P < 0.1879$ T
Right inferior parietal lobule (BA 40)	63.9 -30.5 23.8	$F = 2.30$ $P < 0.1679$
Right medial frontal gyrus (BA 6)	5.9 13.5 45.8	$F = 2.07$ $P < 0.1879$

Several brain regions in the right hemisphere exhibited activation during both left- and right-sided stimulation. This activation was significantly greater in the right hemisphere than in corresponding locations in the left hemisphere. All coordinates (x, y, z) are according to standard, stereotaxic space (Talairach and Tournoux 1988) and are derived from the local maxima of overlapping activation. T, significant main effect of temperature; DLPFC, dorsolateral prefrontal cortex; A, significant hemisphere*arm interaction.

whereas the dorsal frontal, dorsolateral prefrontal, and inferior parietal foci exhibited activation that was primarily independent from perceived pain intensity.

DISCUSSION

These results demonstrate that a right lateralized fronto-parietal-thalamic mechanism is engaged during somatosensory processing. The presence of this lateralized activation during both painful and innocuous stimulation indicates that these brain regions are engaged in the processing of stimulus features common to both levels of thermal stimulation. In contrast, activation that was significantly related to perceived pain intensity was either bilaterally or contralaterally localized, underscoring the relative independence of these two processes.

Distribution of pain intensity-dependent and -independent activation

Regardless of the side of stimulation, pain intensity-dependent activation was detected within a diverse array of brain regions previously demonstrated to be engaged in the processing of acute heat pain (Casey et al. 1996; Coghill et al. 1994, 1999; Derbyshire and Jones 1998; Paulson et al. 1998; Talbot et al. 1991; Vogt et al. 1996; see Coghill 1999 for review). In general, the distribution of pain intensity-related activation corresponded closely with regions known to exhibit graded responses to noxious thermal stimulation (Coghill et al. 1999). Pain intensity-dependent activation was localized to contralat-

eral regions of the primary somatosensory cortex, secondary somatosensory cortex, insular cortex, and bilateral regions of the cerebellum, putamen, thalamus, anterior cingulate cortex, and frontal operculum. In contrast to these results, pain intensity-dependent activation of the secondary somatosensory cortex and adjacent caudal insular regions was predominantly bilateral in a previous investigation (Coghill et al. 1999). Two potential factors may account for this different interhemispheric distribution of activity. First, the previous investigation employed a somewhat higher stimulus intensity (50°C) than used presently (49°C). Given that the ipsilateral hemisphere is engaged only by relatively high levels of noxious stimulus intensity, bilateral activation would be predicted by the use of a more robust noxious stimulus (Stein et al. 1989). Second, the ventral forearm was stimulated in the present investigation, while the lateral aspect of the upper arm (approximately 5 cm distal to the shoulder) was stimulated previously. Neurons within the secondary somatosensory cortex that respond to stimulation of distal portions of limbs have predominantly contralateral receptive fields, while those responding to stimulation of more proximal structures, such as the trunk, have predominantly bilateral receptive fields (Burton and Carlson 1986; Robinson and Burton 1980). Thus differences in stimulus location could also account for the contralateral distribution of activity within the secondary somatosensory region observed in the present investigation.

As shown previously, the multiple regression approach can accurately distinguish pain intensity-independent activation from pain intensity-dependent activation (Coghill et al. 1999). In the present investigation, activation of dorsal frontal (BA 6), dorsolateral prefrontal (BA 9/46), and inferior parietal loci (BA 40) during thermal stimulation was primarily pain intensity-independent, while portions of the primary somatosensory cortex, secondary somatosensory cortex, supplemental motor area, thalamus, and the frontal operculum exhibited both pain intensity-dependent and -independent activation (Fig. 4 and Tables 1 and 2). In contrast, only frontal polar and dorsolateral prefrontal loci exhibited pain intensity-independent activation in a previous study of contact heat pain (Coghill et al. 1999). The detection of additional regions exhibiting pain intensity-independent activation may be attributed to the use of a more sensitive stimulus site (ventral forearm vs. lateral upper arm) as well as greater statistical power in the present study (6 scans/condition vs. 1–2 scans/condition).

Determination of hemispherically lateralized activity

Highly conservative criteria were used to determine whether activation was hemispherically lateralized. A given brain region was required to be activated in a strictly unilateral fashion in the same hemisphere during both left- and right-sided stimulation. This region was then required to exhibit significantly greater activity than that of the corresponding stereotaxic location within the opposite hemisphere. These criteria were chosen 1) to eliminate bilaterally active regions from consideration, 2) to protect against the possibility of sub-threshold activations in the "inactive" hemisphere, 3) to provide a reproducible standard for assessing lateralization, and 4) to provide the closest parallels with clinical data from patients with unilateral lesions of regions with functional lateralization. Brain regions with consistently asymmetric, but bilateral (or trends

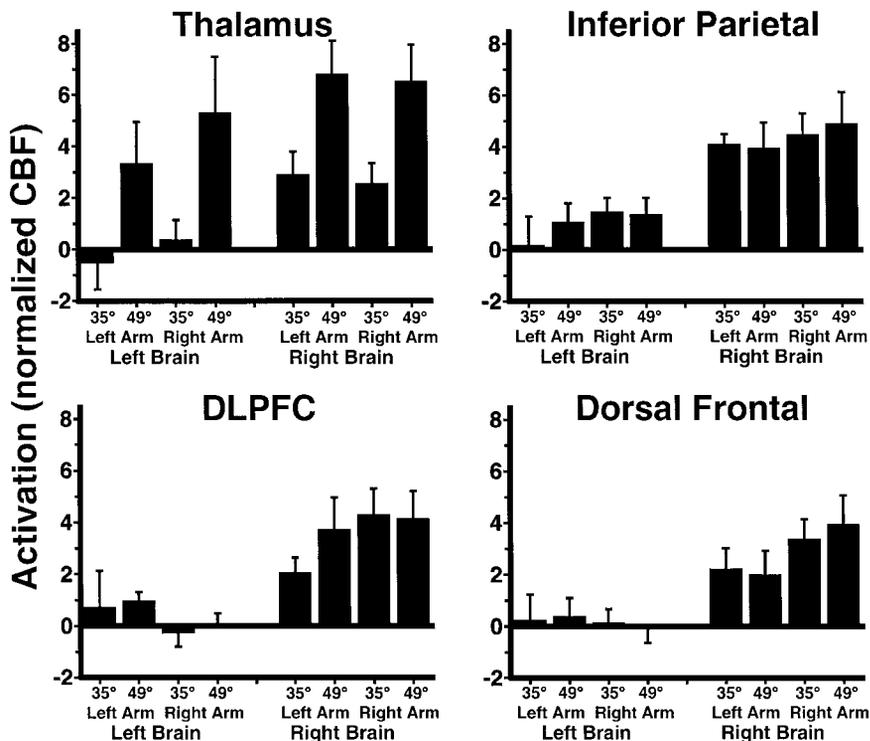


FIG. 4. Magnitude of hemispherically lateralized activation. Regardless of the side of stimulation, activation of the thalamus, inferior parietal cortex, dorsolateral prefrontal cortex (DLPFC), and dorsal frontal cortex was significantly greater in the right hemisphere than in the left (see Table 1 for locations and statistical results). Importantly, none of these lateralized regions exhibited activation that was dependent on the side of stimulation. However, the thalamus, but no other lateralized region, exhibited statistically significant effects due to stimulus temperature ($F = 11.18$, $P < 0.01$).

toward bilateral) activity were not considered to be hemispherically lateralized. Unilateral lesions to bilaterally active brain regions clearly have a less detrimental effect on function than similar lesions to a lateralized region. Thus clearly lateralized activity is of greater clinical relevance than such asymmetric, but bilateral activation.

Absence of hemispherically lateralized pain intensity-dependent activation

Direct comparison between left- and right-sided stimulation did not reveal any hemispherically lateralized pain intensity-dependent activation. This finding contrasts with two reports of right-lateralized pain-related anterior cingulate activation, the first involving eight patients with neuropathic pain (4 left leg/4 right leg), and the second involving four patients with cluster headache (2 right lateralized/2 left lateralized) (Hsieh et al. 1995, 1996). Affective and other cognitive responses to inescapable, clinical pain are significantly different from those elicited by escapable, experimental pain (Price 1999). Accordingly, differences between the present findings and those obtained during clinical pain states may be attributed differences in brain activation supporting intensity-related processing and brain activation supporting the various higher order affective and cognitive sequelae of clinical/chronic pain. Given that affective responses were not assessed in the two clinical pain studies showing lateralized anterior cingulate activation, further investigations explicitly examining the lateralization of pain-related affective processing will be needed to confirm this possibility.

Right lateralized pain intensity-independent activation

In sharp contrast with pain intensity-dependent activation, several brain regions exhibiting pain intensity-independent

activation demonstrated a clear right hemispheric lateralization (Table 3). These regions included the right thalamus, right posterior parietal cortex (BA 40), right dorsolateral prefrontal cortex (BA 9/46), and right dorsal frontal cortex (BA 6). Of these right lateralized regions, the thalamus exhibited a relatively complex response in that there was a lateralized pain intensity-independent effect, and a more bilateral pain intensity-dependent effect (Figs. 2–4). As can be seen in Fig. 4, the right thalamus was always activated to a greater extent than the left thalamus, regardless of the side or intensity of stimulation. However, 49°C stimulation consistently produced a larger activation than 35°C stimulation in both left and right portions of the thalamus. If these pain intensity-dependent effects had been removed in the ROI analysis, the distribution of activity would likely resemble the patterns of activity in other right-lateralized regions. The left cerebellum also exhibited lateralized pain intensity-independent activation, but was not considered to be completely lateralized due to extensive bilateral activity during painful stimulation.

Brain regions displaying right-lateralized pain intensity-independent activation may be involved in several processes. The thermal stimuli employed in the present investigation are relatively complex with several attributes that are common to both the innocuous (35°C) and painful (49°C) temperatures (i.e., pain intensity-independent components). For example, the thermal stimulator was repeatedly placed against the subjects' forearms and subsequently repositioned after 5 s of stimulation of any given locus. Thus neural mechanisms supporting the detection of changes in the sensory environment may potentially contribute to the lateralized pain intensity-independent activation. Changes in somatosensory stimuli have been determined to activate the secondary somatosensory cortex, right (ipsilateral) regions of the insula, portions of the frontal operculum, and the supplementary motor area/cingulate

motor area, among other regions (Downar et al. 2000). Such activation was clearly detected in the present investigation (Table 2). However, none of these regions overlap with the hemispherically lateralized, pain intensity-independent activation of the thalamus, inferior parietal cortex (BA 40), dorsolateral prefrontal cortex (BA 9/46), and dorsal frontal cortex (BA 6). Thus other processes may contribute more substantially to this lateralized activation. Processing of dynamic spatial aspects of the thermal stimuli may also contribute to pain intensity-independent activation. During the course of the 90 s of stimulation, the thermal stimulator was sequentially moved among six spatially distinct skin regions on the ventral forearm. Thus both neutral and painful stimuli are likely to evoke equal activation associated with spatial cognition. We propose therefore that the observed right lateralized activation reflects processing of spatial attentional/awareness components of somatosensory information.

Spatial/attentional processing in the right inferior parietal and dorsolateral prefrontal cortices

Studies of both lesion subjects and split-brain patients have long noted a right hemisphere dominance for spatial attentional processing in extrapersonal space (Gazzaniga 1995; Mesulam 1981). The right lateralized network of brain regions engaged during somatosensory processing is similar to the fronto-parieto-cingulate network engaged in extrapersonal spatial processing. For example, portions of the right posterior parietal cortex have been demonstrated to be activated during the processing of visuo-spatial information and sound movement (Coull and Nobre 1998; Griffiths et al. 1998; Nobre et al. 1997). In the present investigation, the left inferior parietal cortex was activated only during right-sided stimulation, whereas the right inferior parietal cortex was activated during both left and right-sided stimulation (Fig. 3). This is consistent with the observation that the left posterior parietal cortex processes information from contralateral space while the right posterior parietal cortex processes information from both spatial hemifields (Mesulam 1981; Nobre et al. 1997). The right dorsolateral prefrontal cortex has been demonstrated to be important for sustained attention, while more dorsal portions of the frontal cortex adjacent to the superior frontal sulcus have been demonstrated to be engaged in the processing of spatial working memory (Coull et al. 1998; Courtney et al. 1998). Anatomic studies in monkeys suggest that these frontal and parietal regions are reciprocally connected with each other and with the thalamus, providing one explanation for the right lateralized activation of the thalamus (Morecraft et al. 1993; Selemon and Goldman-Rakic 1988). Consistent with this connectivity, lesions involving the right thalamus, particularly the posterolateral portion, are associated with tactile extinction and/or neglect (Kumral et al. 1995; Watson et al. 1981).

Right lateralized activation of the posterior parietal and dorsolateral prefrontal cortex has previously been detected during a somatosensory attention task in which subjects were required to detect pauses in a volley of von Frey hair stimuli applied to the left or right great toe (Pardo et al. 1991). Similarly, right posterior parietal activation has been reported during direction of attention to thermal stimulation of the hand (Peyron et al. 1999). Also, both right posterior parietal and right prefrontal regions have been shown to be activated during

evaluation of relatively small differences in innocuous cool stimuli (applied only to the right hand), a task likely to place significant demands on directed attentional processing (Craig et al. 2000). The thermal stimulation paradigm in the present investigation placed minimal demands on directed attentional processes. Only three levels of stimuli (none, neutral, and painful) were employed, and these were readily distinguishable. Furthermore, stimulus temperatures remained constant during each PET scan. However, the contact of the 1-cm-diam stimulator on the ventral forearm is a readily detectable, robust stimulus that is clearly capable of capturing attention, regardless of stimulus temperature. Thus the right lateralized activation may also reflect automatic (i.e., stimulus-driven), rather than directed, attentional processes that contribute to awareness of the body and objects contacting the body surface. Such a role is clearly suggested by the loss of passive awareness of the left side of the body during neglect syndromes resulting from right hemisphere lesions (Critchley 1958).

In summary, these findings provide direct evidence that right lateralized brain mechanisms analogous to those that process information in extrapersonal (i.e., visual and auditory) space process information arising from intrapersonal (i.e., somatosensory) space. Importantly, this lateralized pattern of activation is distinct from the predominantly contralateral/bilateral pain intensity-related activation. Thus common mechanisms process components of information arising from both innocuous and noxious thermal stimuli.

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