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Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans

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Abstract

The purpose of the present study was to determine whether gender differences exist in the forebrain cerebral activation patterns of the brain during pain perception. Accordingly, positron emission tomography (PET) with intravenous injection of H₂¹⁵O was used to detect increases in regional cerebral blood flow (rCBF) in normal right-handed male and female subjects as they discriminated differences in the intensity of innocuous and noxious heat stimuli applied to the left forearm. Each subject was instructed in magnitude estimation based on a scale for which 0 indicated 'no heat sensation'; 7, 'just barely painful' and 10, 'just barely tolerable'. Thermal stimuli were 40°C or 50°C heat, applied with a thermode as repetitive 5-s contacts to the volar forearm. Both male and female subjects rated the 40°C stimuli as warm but not painful and the 50°C stimuli as painful but females rated the 50°C stimuli as significantly more intense than did the males ($P = 0.0052$). Both genders showed a bilateral activation of premotor cortex in addition to the activation of a number of contralateral structures, including the posterior insula, anterior cingulate cortex and the cerebellar vermis, during heat pain. However, females had significantly greater activation of the contralateral prefrontal cortex when compared to the males by direct image subtraction. Volume of interest comparison (t -statistic) also suggested greater activation of the contralateral insula and thalamus in the females ($P < 0.05$). These pain-related differences in brain activation may be attributed to gender, perceived pain intensity, or to both factors.

Keywords

Pain; Gender difference; Positron emission tomography; Prefrontal cortex; Insula; Thalamus

1. Introduction

There is increasing evidence that male and female subjects differ in their response to painful stimuli. The prevailing evidence suggests that while there is no reliable gender difference in pain thresholds, pain tolerance is generally higher in male when compared to female subjects (Goolkasian, 1985). The basis for this gender difference in pain perception is unknown, but it can not be accounted for by secondary factors such as criterion effects (Ellermeier and Westphal, 1995), differences in body size and skin thickness (Lautenbacher and Strian,

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1991) or social expectations (Otto and Dougher, 1985; Feine et al., 1991). This suggests there may be underlying gender differences in the neural mechanisms that mediate pain perception.

Gender differences have been reported in the size and morphology of the corpus callosum, preoptic hypothalamic area, planum temporale and in the percent of gray matter in the human brain (Swaab and Fliers, 1985; Allen et al., 1989; 1991; Witelson, 1989; Allen and Gorski, 1990, 1991; Kulynych et al., 1994). In addition, studies using the technique of positron emission tomography (PET) with $H_2^{15}O$ find gender differences in resting regional cerebral blood flow (rCBF) rate (Gur et al., 1982, 1995; Azari et al., 1992a,b) or in the cerebral metabolic rate of glucose utilization (Andreasson et al., 1994).

There have been several reports of changes in rCBF in awake humans produced by application of cutaneous heat stimulation (Jones et al., 1991; Talbot et al., 1991; Apkarian et al., 1992; Coghill et al., 1994; Casey et al., 1994, 1996; Vogt et al., 1996). These studies suggest that multiple forebrain structures, including the contralateral primary (M1/S1) and secondary somatosensory (S2) cortices, anterior cingulate cortex, insula and thalamus participate in the cerebral processing of painful cutaneous stimuli. In addition, the prefrontal cortex, premotor cortex, lenticular nucleus and cerebellar vermis show pain-related activation in some of these studies.

The gender difference in pain perception may be associated with different patterns of activation in forebrain structures. To date, however, no one has determined if gender differences exist in rCBF changes produced by cutaneous heat stimulation.

2. Subjects and methods

2.1. Subjects

Twenty right-handed volunteers (10 males and 10 females, age 18 to 39 years, matched by age and ethnic background) were paid to participate in this study. Most had no experience with magnitude estimation or other psychophysical procedures. All claimed to be in good health and specifically denied any neurological disease. None were taking analgesic or other drugs that alter central nervous system function. All had agreed to refrain from smoking or consuming alcohol or caffeine for the 24-h period immediately prior to the study. Written informed consent was obtained before each study. The consent form and protocol were approved by the Human Studies Committee of the Ann Arbor Veteran's Affairs Medical Center and by the Institutional Review Board for Human Studies at the University of Michigan Medical Center.

2.2. Procedure

Each subject was told that the purpose of the study was to relate their brain activity, as measured by PET, to their ability to discriminate between the intensities of groups of heat stimuli delivered to the left volar forearm during the scan. They were told that the intensity of each stimulus would be constant during each of the scans and that stimulus intensity may or may not change between scans. After being positioned in the scanner, each subject was instructed in magnitude estimation based on a scale for which 0 indicated 'no heat sensation'; 7, 'just barely painful'; and 10, 'just barely tolerable pain' (Casey et al., 1993, 1994, 1996). Several practice trials were given with four to five stimulus intensities ranging from 40°C to 50°C until at least three trials at each end of the range showed that 40°C was perceived as warm but painless and that 50°C was definitely painful. Heat stimuli were delivered sequentially to six separate sites on the left volar forearm with a digitally controlled feedback contact thermode (Cygnus, Paterson, NJ) with a gold-plated copper surface contact area of 254 mm² that was heated by direct current. The temperature at the skin-thermode interface was estimated from a sensor embedded 0.83 mm below the contact plate. The temperature of the thermode was set

and held at the stimulus temperature before applying the probe to the skin. Each stimulus was 5 s in duration. Stimulation began ~10 s before the injection of H_2^{15}O for each of the six scans and continued repetitively for 60 s (~12 stimuli per scan). Subjects were asked to verbalize their rating of stimulus intensity after each scan was completed.

Ratings collected using the magnitude estimation technique were averaged for each subject at the 40°C and 50°C stimulus intensities to yield one number for that stimulus temperature. These numbers were then used to compute group means. A two-way analysis of variance (gender $\times$ stimulus) with repeated measures was used for evaluation of the psychophysical data.

2.3. PET protocol and data analysis

The scanner used in this study was a Siemens/CTI 931/08-12 with 15 tomographic slices covering an axial field of view of 10 cm. Each subject was positioned in the scanner approximately parallel to the canthomeatal line. Head position was maintained by soft restraint and laser beam positioning on facial fiducial marks. Small head motion was corrected by computer coregistration algorithm for each subject before analysis began (Minoshima et al., 1992). For each scan, the subject received a 66-mCi intravenous bolus injection of H_2^{15}O . Approximately 12 min elapsed between repeated scans. Data acquisition began 5 s after the estimated arrival of radioactivity in the brain and continued for ~60 s.

For each subject, the PET images from the three repetitions of the same experimental condition (40°C and 50°C) were averaged. These images were then coregistered with each other (head motion correction), warped to minimize differences in brain anatomy and realigned to a standard stereotactic system by an automated procedure described previously (Minoshima et al., 1992, 1993, 1994). Image pixel intensities were normalized to global cerebral activity with the use of a linear proportional model to remove baseline differences in cerebral blood flow between scans and subjects (Fox and Raichle, 1984). First-order subtraction images of heat pain were made for each subject by subtracting the images acquired during the lower intensity stimulation from those acquired during the high intensity stimulation. Statistical image analyses (Z score) and volumes of interest (VOI) analyses were performed on these image sets. The voxel-by-voxel analysis (Z score) was performed after 3-dimensional Gaussian filtering of the images (FWHM = 9 mm) to enhance signal-to-noise ratio (Friston et al., 1991). Voxels showing a significantly increased CBF compared to the average noise variance computed across all voxels (pooled variance) were identified (Worsley et al., 1992), after adjusting for multiple comparisons. The critical level of significance of activation was set at $Z = 4.0$ (Coghill et al., 1994; Casey et al., 1996).

In addition to identifying regions with significant CBF increases by a voxel-by-voxel statistical subtraction analysis (Z score), volumes of interest (VOI) were identified within brain structures selected by a priori hypotheses and the results of previous PET studies (Jones et al., 1991; Talbot et al., 1991; Coghill et al., 1994; Casey et al., 1994, 1996; Svensson et al., 1997). These structures included the pre-motor, sensorimotor and anterior cingulate cortices; the insula, thalamus and the cerebellum. In this study, however, a significant peak of activation was identified by independent Z score analysis in all but two of these structures in either or both genders. The size and shape of each VOI was determined within each of the structures by employing a method similar to that described by Burton and colleagues (Burton et al., 1993). Voxels showing significant peak increases in CBF between stimulus conditions were identified within each of the brain structures of interest. The volume defined by these voxels was then progressively expanded in three dimensions to include only those contiguous voxels that showed rCBF increases that were greater than the global mean change ($P < 0.05$, uncorrected for multiple comparisons). For purposes of comparison, the responses within each VOI are expressed as the average increase in CBF within the volume of that VOI. Statistically significant within-gender rCBF increases were determined by a two-way analysis of variance

(gender $\times$ stimulus) with repeated measures for each VOI across all male or female subjects, followed by 2-sample, unpaired *t*-statistics.

In addition, statistically significant between-gender differences in rCBF were calculated after first determining the stereotactic concordance of the peak voxels within each VOI between the groups. If a peak was not present in a selected region in one gender, a VOI template derived from the other gender group was applied to the images (indicated as 'template' in Table 1). The average percentage change in CBF for each VOI was then compared between genders in the same manner as described above. Finally, select VOI were evaluated for gender differences in the average CBF response to warm (40°C) or painful (50°C) stimuli. This was done by performing two separate comparisons: male warm vs. female warm and male pain vs. female pain, looking only at those VOI that showed a significant gender difference in the previous described analysis.

3. Results

Fig. 1 shows the average psychophysical rating given by male and female subjects in response to a 40°C or 50°C stimulus using a verbal rating scale for which 0 indicated 'no heat sensation'; 7, 'just barely painful' and 10, 'just barely tolerable'. All subjects rated the 50°C stimulus as painful, and the 40°C stimulus as not painful, resulting in a significant effect of temperature (rANOVA; $P < 0.001$). However, females rated the 50°C stimulus as more noxious (i.e. more intense) than did the males (8.2 ± 0.30 and 9.3 ± 0.20 for male and female subjects, respectively; $P = 0.0052$). In contrast, no gender differences were found in the rating scores at the innocuous (40°C) temperature (2.2 ± 0.30 and 3.0 ± 0.40 for male and female subjects, respectively; $P = 0.16$).

The stereotactic coordinates and Z scores of the peak voxels within each of the ten contralateral and six ipsilateral structures that showed significant increases in rCBF in either male or female subjects or both identified as significant by Z score, or VOI analysis, are shown in Table 1. Male subjects showed significant activation only in the contralateral premotor and M1/S1 cortices and in the ipsilateral cerebellar vermis by Z score analysis. Two of these structures, the contralateral premotor cortex and the ipsilateral cerebellar vermis, were also activated in female subjects. However, female subjects showed an additional 13 significant peaks for a total of 15 peaks distributed among 12 structures in this gender group by Z score analysis: two peaks were identified in the contralateral premotor cortex, contralateral cerebellar vermis, and ipsilateral thalamus and single significant peaks were found in the contralateral anterior cingulate cortex, anterior and posterior insular cortices, and thalamus. Females also showed ipsilateral activation in the premotor and insular cortices, and in the lenticular nucleus, thalamus, and cerebellar vermis. VOI analysis (see Table 2) revealed statistically significant increases in rCBF in only one additional structure, the contralateral pre-frontal cortex (B9/46), in females and in seven additional structures in males (contralateral anterior cingulate, posterior insula, lenticular nucleus, and cerebellar vermis; ipsilateral prefrontal cortex (B46), premotor cortex, and anterior insula). The average ($\pm$ SEM) volume of the VOIs in this study was 7.95 ± 1.43 ml and 8.22 ± 1.20 ml for males and females, respectively, and this difference was not significant ($P = 0.443$).

The percent increase in rCBF within the 10 contralateral and six ipsilateral structures that showed significant increases in CBF in either male or female subjects or both, using the results of Z score or VOI analysis are shown in Table 2. The similarities and differences in the activation patterns of male and female subjects can be visualized most easily by viewing the color-coded statistical maps of the brain activation pattern (Fig. 2). Each active region is superimposed upon a magnetic resonance image (MRI) of a normal brain that has been transformed into stereotactic coordinates (Talairach and Tournoux, 1988) for ease of

comparison. The images demonstrate, in both genders, the significant bilateral activation of the premotor cortex (+7, +15), the contralateral activation of the anterior cingulate (+41, +37), posterior insula (+7, +15), and cerebellar vermis (−12), and the ipsilateral responses in the anterior insula (+7, +15) and cerebellar vermis (−12). Three structures showed significant activation only in males: the contralateral M1/S1 cortex (+52), contralateral lenticular nucleus (+2), and the ipsilateral prefrontal cortex (+15). Only in the latter structure, however, was the rCBF response significantly greater than in females as shown when the male VOI template was applied to this structure in the female group ($P < 0.05$; asterisk, Table 2). The M1/S1 response in females was just below the level of statistical significance on Z score and VOI analysis (Fig. 2; Table 1 and Table 2). The rCBF response in the contralateral lenticular nucleus of females, although weak, was statistically comparable to that of males when analyzed with the male VOI template (Table 2). In contrast, six structures showed significant rCBF responses only in females. Of these, the responses in the contralateral cerebellar hemisphere (−25), the ipsilateral thalamus (+15) and the lenticular nucleus (+2) were not significantly greater in females than in males when compared using concordant or template VOI. The other three structures, the contralateral prefrontal cortex (+32), anterior insula (+2), and thalamus (+15) were significantly more responsive in females than in males when we used a 2-sample, unpaired *t*-statistic on the average percentage increase in CBF ($P < 0.05$; asterisks, Table 2). The significant difference in these three VOIs can not be attributed to a differential response to either the warm (40°C) or the painful (50°C) stimuli, as the statistical comparison of the mean CBF of male warm vs. female warm and male pain vs. female pain did not reveal any significant gender differences (all *P*-values > 0.20).

4. Discussion

This study has two important findings. First, our results reveal a striking degree of overlap between genders in the spatial and intensity patterns of cerebral and cerebellar activation in response to pain. Of the 16 structures shown by voxel-by-voxel (Z score) or VOI analysis to respond differentially to noxious heat, 12 were active in both genders. This comparison provides additional evidence that there is a consistent, identifiable, and possibly unique pattern of cerebral response associated with the painful stimulation in humans.

Previous reports of PET studies of pain, including those from our own facility, have offered structure-by-structure speculations about the possible functional significance of these pain-related cerebral activation patterns, based largely or in part on the results of independent behavioral, anatomical, or neurophysiological studies (Casey et al., 1994; Casey, 1996; Svensson et al., 1997). Rather than review these discussions, we wish to emphasize that our results, by revealing similarities in brain activation patterns, indicate some structures (premotor, M1/S1, anterior cingulate, posterior insula cortices, lenticular nucleus, and the cerebellum) that are unlikely to be either gender-specific or to reflect differences in perceived pain intensity.

A second important finding from this study is our report of gender differences in the perceptual and neurophysiological response to painful heat stimulation. We report that females perceive a 50°C cutaneous heat stimulus as more intense than do males. This is consistent with previous reports that male and female subjects differ in their response to painful stimuli (Feine et al., 1991; Lautenbacher and Rollman, 1993; Ellermeier and Westphal, 1995). However, this is the first study to associate these differences in pain perception with differences in nociceptive processing in the brain as revealed by positron emission tomography. We report here that the perception of the noxious heat stimulus as more intense in female subjects is associated with greater activation in the contralateral thalamus and anterior insula.

The anterior insula and thalamus are structures with direct anatomical interconnections. For example, the anterior insula receives input from the posterior portion of the ventromedial thalamus (Friedman and Murray, 1986; Cechetto and Saper, 1987; Barbaresi et al., 1992), an area that has been shown to receive a strong projection from lamina I of the spinal cord (Craig et al., 1985; Craig, 1991) and to contain a high concentration of nociceptive neurons (Craig et al., 1994). These nociceptive neurons in the thalamus are topographically organized and have small receptive fields that have been demonstrated to code for stimulus intensity (Hutchison et al., 1994; Craig et al., 1994). It is possible, therefore, that the increased activation of these two forebrain structures in the females in our study reflects their higher ratings of heat pain intensity. In this study, it is not possible to uniquely associate the gender or psychophysical differences with the different cerebral activation patterns. Any or all of the activation pattern differences could be due to either or both of these variables. However, future studies may want to consider equalizing perceived intensities across groups. The prediction based on this study would be that the group differences in activation in the thalamus and anterior insula would then disappear.

One other forebrain structure, the prefrontal cortex (B46), showed a significant gender difference. Both males and female subjects showed unilateral activation in prefrontal cortex, but within opposing hemispheres. The significance of this finding is unknown, but it may reflect gender differences in dominance in hemispheric processing of painful stimuli, similar to gender differences in hemispheric dominance reported in language processing (Shaywitz et al., 1995; Trenerry et al., 1995). That activation of the prefrontal cortex may underlie the affective component of this painful stimulus is suggested by the work of Derbyshire and colleagues (Derbyshire et al., 1994). This finding adds to a growing body of evidence for gender differences in neural processing (Reite et al., 1993; Kimura, 1987, 1992, 1996; Kulynych et al., 1994; Esposito et al., 1996).

In conclusion, this study identified forebrain structures that may be ubiquitous in the processing of painful stimuli, perhaps not only in humans, but in other species as well. Secondly, we suggest that the prefrontal cortex may play an important role in mediating gender differences in the perceptual and neurophysiological response to painful heat stimulation.

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Fig. 1.

The mean ($\pm$ SEM) psychophysical pain rating from 10 male and 10 female subjects following application of the contact heat thermode. The pain rating was based on 0 = 'no heat sensation'; 7 = 'just barely painful'; and 10 = 'just barely tolerable pain'. Each point is the average of three trials in each subject during the scan session. The asterisk indicates a significant difference in pain tolerance between male and female subjects ($P = 0.0052$).

Fig. 2.

Color-coded statistical maps of the sites of increases in regional cerebral blood flow (rCBF) during discrimination between the intensities of innocuous (40°C) and noxious (50°C) heat contact stimuli in male and female subjects. All stimuli were applied to the subjects left forearm. The right hemisphere of the brain magnetic resonance image (MRI) template is on the left of the figure. This template is the brain of a single normal subject transformed onto the stereotactic coordinates of the human brain atlas used in this study (Talairach and Tournoux, 1988). Images are presented in alternating sets of male (M) and female (F) maps for ease of direct visual comparison. Below each set of columns of images is the stereotactic location with respect to the commissural line (+, superior; -, inferior) (Talairach and Tournoux, 1988). The numbers by the color bar show the Z scores corresponding to the standard deviation of each region from the mean CBF increase. The colored regions in this figure include all structures showing CBF increases above the mean at a $P = 0.05$ level of significance, uncorrected for multiple comparisons.

Table 1

Stereotactic coordinates (ML, AP, SI) and Z scores of the peak voxels of each brain region activated during noxious (50°C) contact heat stimulus

	Heat pain: male (ML, AP, SI; Z score)	Heat pain: female (ML, AP, SI; Z score)
<i>Contralateral</i>		
Prefrontal cortex (B9/46)	Template; Z < 3.00	-28, 41, 29; Z = 3.61
Premotor cortex (B6)	-60 -1, 9; Z = <u>5.38</u>	-53, 1, 7; Z = <u>5.03</u>
		-44, -4, 7; Z = <u>4.97</u>
M1/S1 cortex	-26, -17, 54; Z = 4.16	-24, -13, 52; Z = 3.94
Anterior cingulate	-6, 1, 36; Z = 3.98	-10, -13, 43; Z = 4.04
Anterior insula	Template; Z < 3.00	-33, 1, 0; Z = <u>5.36</u>
Posterior insula	-39, -24, 9; Z = 3.99	-39, -22, 16; Z = 4.07
Lenticular nucleus	-21, -15, 0; Z = 3.91	Template; Z < 3.00
Thalamus	Template; Z < 3.00	-15, -17, 14; Z = 4.69
Cerebellar hemisphere	Template; Z < 3.00	-37, -49, -36; Z = 4.02
Cerebellar vermis	-8, -71, -11; Z = 3.84	-6, -55, -14; Z = <u>5.21</u>
		-8, -42, -20; Z = 4.00
<i>Ipsilateral</i>		
Prefrontal cortex (B46)	33, 44, 16; Z = 3.23	Template; Z < 3.00
Premotor cortex (B6)	53, -4, 14; Z = 3.82	57, 5, 9; Z = 4.34
Insula	35, 3, 7; Z = 3.65	30, -6, 14; Z = <u>5.35</u>
Lenticular nucleus	24, -19, 9; Z = 3.57	19, -13, 2; Z = 4.54
Thalamus	3, -22, 7; Z = 3.21	6, 19, 16; Z = 4.58
		12, -13, 11; Z = 4.58
Cerebellar vermis	10, -55, -9; Z = 4.90	26, -55, -18; Z = 4.07

ML, mm medial-lateral from midline, left positive; AP, mm anterior-posterior from anterior commissure, anterior positive; SI, mm superior-inferior relative to the commissural line, superior positive. Coordinates based on the atlas of Talairach and Tournoux (1988). If a peak was not present in a selected region in one gender, a VOI template derived from the other gender group was applied to the images. This is indicated by 'template' in the column under either male or female. Numbers in bold font indicate CBF increases found to be significant using Z scores analysis (≥ 4.0); underlined numbers indicate CBF increases found to be significant using VOI analysis.

Table 2

Percent change in rCBF

	Heat pain: male	Heat pain: female
<i>Contralateral</i>		
Prefrontal cortex (B9/46)	0.68 ± 0.70	<u>2.94 ± 0.75</u> *
Premotor cortex (B6)	3.08 ± 1.02	2.96 ± 0.51
M1/S1 cortex	3.10 ± 0.47	3.11 ± 0.70
Anterior cingulate	<u>2.94 ± 0.48</u>	2.78 ± 0.90
Anterior insula	1.04 ± 0.63	<u>2.96 ± 0.40</u> *
Posterior insula	<u>3.03 ± 0.81</u>	2.78 ± 0.47
Lenticular nucleus	<u>3.24 ± 0.81</u>	2.09 ± 0.66
Thalamus	1.33 ± 0.48	2.83 ± 0.56 *
Cerebellar hemisphere	2.68 ± 1.51	3.42 ± 0.89
Cerebellar vermis	<u>3.61 ± 0.90</u>	2.99 ± 0.49
		2.89 ± 0.63
<i>Ipsilateral</i>		
Prefrontal cortex (B46)	<u>3.24 ± 0.73</u> *	0.26 ± 1.17
Premotor cortex (B6)	<u>2.95 ± 0.62</u>	2.88 ± 0.53
Anterior insula	<u>3.12 ± 0.87</u>	3.29 ± 0.70
Lenticular nucleus	2.95 ± 1.18	2.84 ± 0.53
Thalamus	2.97 ± 0.32	3.02 ± 0.65
		3.31 ± 1.27
Cerebellar vermis	3.21 ± 0.84	2.66 ± 0.81

The average percent increases in rCBF for each of the 16 regions reaching statistical significance in the voxel-by-voxel (Z score) or VOI (*t*-value) analysis for male and female subjects. Numbers in bold font indicate CBF increases found to be significant using Z scores analysis (≥ 4.0); underlined numbers indicate CBF increases found to be significant using VOI analysis. Significance of increases in rCBF in each VOI within genders was determined by paired *t*-statistics with Bonferroni correction for multiple comparisons, in this case $P < 0.0033$.

* Significant difference between the genders in the percent increase in rCBF in a structure using an unpaired *t*-test.