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Sex differences in the cerebral BOLD signal response to painful heat stimuli

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Moulton, Eric A., Michael L. Keaser, Rao P. Gullapalli, Ranjan Maitra, and Joel D. Greenspan. Sex differences in the cerebral BOLD signal response to painful heat stimuli. Am J Physiol Regul Integr Comp Physiol 291: R257–R267, 2006.—There are limited data addressing the question of sex differences in pain-related cerebral processing. This study examined whether pain-related blood oxygenation level-dependent (BOLD) signal change measured with functional magnetic resonance imaging (fMRI) demonstrated sex differences, under conditions of equivalent pain perception. Twenty-eight healthy volunteers (17 women, 11 men) were subject to a fMRI scan while noxious heat stimuli were applied to the dorsum of the left foot. Significant BOLD signal modulation was observed in several nociceptive processing regions of interest (ROIs) in all subjects. There were no sex differences in the spatial extent of BOLD signal change for any ROI, but the signal amplitude was lower for women in most ROIs and significantly so for the primary somatosensory cortex (S1), the midanterior cingulate cortex, and the dorsolateral prefrontal cortex (DLPFC). The BOLD signal response could be positive or negative, and frequently, both polarities were observed within a single ROI. In most ROIs, women show proportionately more voxels with negative signal change than men, and this difference was statistically significant for the S1 and the DLPFC. The time course of the negative signal change was very similar to that of the positive signal change, suggesting that the latter was not “driving” the former. The location of negative and positive clusters formed distinct patterns in several of the ROIs, and these patterns suggest something other than a local “stealth” phenomenon as an explanation for the negative signal changes. Sex differences in baseline cerebral blood flow may contribute to the BOLD signal differences observed in this study.

A NUMBER OF STUDIES HAVE FOUND that women are more sensitive to experimental painful stimulation than men. Yet, this is neither a universal nor large effect, given that no differences are found in approximately one-third of the published studies, and statistically significant differences are often in the small-to-moderate range (9, 27). Nonetheless, enough of a difference is found with enough regularity to suggest that women and men may perceive painful stimuli differently. Related to this are observations from both animal and human studies that nociceptive processing may be different between men and women, thereby providing a basis for sex differences in perception and behavior (7, 19).

Only a few neuroimaging studies have reported sex differences in cerebral responses to noxious stimuli. A 15O-positron emission tomography (PET) study reported significantly greater activation in women vs. men in several regions of interest (ROIs) in response to noxious heat (24). In that report, sex differences in the PET results may have been related to sex differences in perceived pain intensity. In contrast, a subsequent PET study reported significantly greater activation in men vs. women in some of the same ROIs in response to painful laser stimuli (6), in this case, using stimuli that were matched for perceived intensity. Other PET studies have described sex differences in responses to visceral pain, although principally with chronic visceral pain patients (3, 22). The differences reported were mostly in the direction of greater activation in men, although some brain regions showed the opposite difference in the later study. An intriguing functional magnetic resonance imaging (fMRI) study reported that sex differences can be found in the pain-related activation of several cortical areas, but the observation of such differences depended on the menstrual cycle phases of the women (1).

There are clearly too few data at this point to conclude anything about sex differences in cortical responses to pain. Differences in results among the aforementioned studies can be attributable to protocol differences, but also to differences in the choice of dependent variables and analysis approaches. We sought to address this issue by looking for sex differences in several parameters of the fMRI-derived blood oxygenation level-dependent (BOLD) response to painful heat stimuli within multiple ROIs of the pain neuromatrix. Portions of these results have been reported in abstract form (11, 21).

MATERIALS AND METHODS

The data for this study were derived from a larger project comprising a dissertation thesis. The data collection methods have been described elsewhere (20) but are also provided below.

Subjects. Twenty-eight subjects (11 male, mean age 29, range: 22–45 years old; 17 female, mean age 30, range: 23–42 years old) satisfactorily completed the study. Subjects provided written informed consent to participate in the study and were paid $25/h. Additional subjects were recruited, but excluded on the basis of psychophysical screening (n = 20; criteria described below), scheduling problems (n = 2), technical problems with fMRI scanning (n = 5), and signal

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artifacts identified during fMRI image analysis (n = 5). The University of Maryland Institutional Review Board for the Protection of Human Subjects approved the procedures and protocols for this study.

Thermal stimulation. An MR-compatible Peltier thermal probe with a 2.6 cm² contact surface (model TSA-II; Medoc) was used to apply heat stimuli. During pretesting, a 41°C search stimulus was applied to the dorsum of the subject’s foot to identify areas sensitive to innocuous heat. Six probe-sized (2.6 cm²) warmth-sensitive areas were identified and used as guides for placement of the thermal stimuli to avoid warmth-insensitive regions during the experiment (10).

The probe was preheated to a target temperature before being placed onto the subject’s foot for 16 s. A pneumatic handle attached to the thermode allowed the experimenter to continuously and consistently apply the probe with 300–400 g of pressure. Three target temperatures were selected: one innocuous (41°C) and two painfully hot. The painfully hot temperatures were determined separately for each subject based on pain tolerance. Pain tolerance was assessed during a separate test session by using an ascending series of stimuli presented in 1°C steps. Tolerance was defined as the highest temperature a subject accepted without withdrawing from the stimulus. The hottest temperature used in the fMRI sessions was identified as 1°C below pain tolerance (pain 2), and the other as 2°C below tolerance (pain 1). Subjects who described either of these temperatures as nonpainful were excluded (n = 12), as were subjects who rated the thermal intensity of the two temperatures within five points of each other on a 100-point visual analog scale (VAS) (n = 1). Subjects that had no sensation of heat with the 41°C stimulus were also excluded (n = 2). Subjects were also excluded if their pain tolerance was below 45°C (n = 3) or above our range of testing (50°C) (n = 2).

Experimental protocol. During the fMRI session, subjects were scanned while each of the 16-s target temperatures were applied three times each in random sequence. Each thermode application period was separated by 38 s. To avoid primary afferent habituation or sensitization, each thermode placement was rotated sequentially according to the warmth maps, effectively lengthening the interstimulus interval for any single stimulated area to 5 min and 8 s.

After each stimulus, subjects were presented with a computerized VAS (DAPSYS; Brian Turnquist, Johns Hopkins University, http://www.dapsys.net) via MRVision 2000 goggles (Resonance Technologies, Van Nuys, CA), at which time they rated their peak sensation of thermal intensity using an MR-compatible trackball (Fellowes, www.fellowes.com), which controlled a cursor moving along the vertical VAS. The extremes of the VAS were labeled “no warmth” and “most intense pain imaginable,” with a marker for “just painful” located at the lower quarter of the scale. Subjects were instructed to use the range from “no warmth” to “just painful” to rate nonpainful heat and to use the range from “just painful” to “most intense pain imaginable” to rate painful heat. Ratings were stored as numbers from 0–100, with 25 corresponding to “just painful.”

Voxels with Significant Change in the BOLD Signal:
Extent of Activation

Signal Amplitude Change

Fig. 1. Measurement of pain-related blood oxygenation level-dependent (BOLD) signal amplitude change across all prescribed regions of interest (ROIs). Top: extent of BOLD signal change measured as the number of significantly modulated 1-mm³ voxels, separately for two pain intensities and the two sexes. Bottom: %signal change for the same significantly modulated voxels. S1 and S2, somatosensory cortices; mid-ACC, midanterior cingulate cortex; rACC, rostral ACC; pINS, posterior insula; aINS, anterior INS; DLPFC, dorsolateral prefrontal cortex; SMA, supplementary motor area; R, right or contralateral to stimulation; L, left. Data are presented as means ± SE. **Significant sex difference at P < 0.05; ^^significant interaction of sex and pain level at P < 0.05.
The temperatures used for the pain 1 and pain 2 stimulus levels in the scanner environment were determined on an individual basis. Of the 41°C stimulus, 89% of the ratings were nonpainful warmth, whereas the prescribed pain 1 and pain 2 temperatures were both consistently painful and rated significantly different from one another [2-tailed paired Student’s t-test, t(27) = 5.57, P < 0.001]. The mean pain 1 temperature applied was 46.4°C (±1.1 SD), while the mean pain 2 temperature was 47.4°C (±1.1 SD).

Image acquisition. Functional MRI scans were carried out using the rectilinear echo planar imaging (EPI) method with a 1.5T Philips Eclipse scanner (formerly Marconi Medical Systems, Cleveland, OH). A gradient echo single shot EPI sequence was used to provide 3.2 × 3.2-mm acquired resolution over a 24-cm field of view (FOV). These images were zero padded to 128 × 128 pixels to provide a resolution of 1.875 × 1.875 mm. T2* weighting from this sequence was accomplished with a gradient echo time (TE) of 35 ms. The repetition time (TR) was 2000 ms, which allowed the cerebrum to be covered using 23 slices, with a slice thickness of 6 mm and no gaps between slices. High-resolution anatomical volumetric scans (4.5 ms TE, 29 ms TR, 92 slices, with a slice thickness of 1.5 mm and a 0.938 × 0.938 mm in-plane resolution over a 24-cm FOV) were acquired for anatomical reference of the functional slices.

Image processing and analysis. Image processing and statistical analysis were performed using AFNI (http://afni.nimh.nih.gov). The first four volumes were removed from the functional scan series to allow for signal equilibration. For motion correction, functional time series images were spatially registered to the first of the remaining volumes using the AFNI script 3dvolreg. Spiking artifacts in any time series that exceeded 2.5 SDs of the overall signal were reduced using the AFNI routine 3dDespike. Time series were temporally smoothed using a moving three-point weighted (0.15–0.70–0.15) average. To increase the signal-to-noise ratio and to accommodate interindividual differences in brain morphology, spatial blurring was applied to the images for all time points using a 5-mm full-width, half-maximum Gaussian blur. Linear, second-order, and third-order trends within the time series were removed, and voxelwise normalization was achieved by dividing the signal intensity at each time point by the voxel’s mean intensity. If required, the high-resolution anatomical images were manually registered to the functional images to achieve maximum alignment using the AFNI software routine Nudger.

A general linear model (GLM) was used to identify regions in the brain of individual subjects whose signal variation was significantly related to the experimental protocol. Through voxelwise regression of fMRI signal time courses, the GLM was used to model temporally discrete responses, or regressors, to each of four conditions: the three levels of thermal stimulation, and the rating task. The timing of the experimental paradigm dictated which intervals of the signal corresponded to each condition. The responses were modeled using a boxcar with a 4-s lag. Previous analysis with multiple lags indicated that 4 s was at least as appropriate as other likely alternatives (20).

To create statistical parametric maps, Monte Carlo simulations were run to estimate the likelihood of detecting false positives over multiple comparisons (3dAlphaSim in AFNI). It was determined that an individual voxel threshold of P < 0.01 and a cluster threshold of four voxels (in original coordinate space) provided a corrected overall alpha of P < 0.05. Given this threshold criteria, a BOLD signal change map was first created on the basis of the full F value of the GLM model for each voxel. Subsequently, partial F BOLD signal change maps for both the pain 2 and pain 1 regressors were created as subsets of the full F-map under this same threshold criteria. The pain 2 and pain 1 partial F-maps and the anatomical scans were then spatially normalized to fit the human brain atlas of Talairach-Tournoux (33), and the voxels were resampled to 1 × 1 × 1 mm.

Anatomical reference maps. The locations of active voxel clusters within both partial F-masks were categorized into different ROIs based on structural landmarks (20). A priori ROIs included the foot representation in primary somatosensory cortex (S1), secondary somatosensory cortex (S2), the posterior insula (pINS), the anterior insula (aINS), rostral ACC (rACC), midanterior cingulate cortex (mid-ACC), the supplementary motor area (SMA), and the dorsolateral prefrontal cortex (DLPFC). The foot area of S1 was defined as the paracentral lobule and the portion of the postcentral gyrus extending from the midline of the brain laterally to the beginning of the curve of the incus. S2 was marked as part of the parietal operculum located on the upper bank of the Sylvian fissure and behind the postcentral gyrus. The pINS was identified as the insula located within the depths of the Sylvian fissure at the same rostral-caudal level as S2. The aINS consisted of the rest of the insula rostral to the pINS. The ACC as a whole was identified as the area between the corpus callosum and cingulate sulcus, extending caudally from the anterior boundary of the splenium of the corpus callosum, to the rostral termination of the cingulate sulcus. The ACC was divided into rACC and mid-ACC by a division in the coronal plane through the subcallosal striatum, which approximately splits Brodmann area 24 (BA 24) and BA 24’. SMA was marked as the area immediately above the ACC, superior to the cingulate sulcus, and stretched anterior-posteriorly from the caudal limit of the ACC to the beginning of the superior frontal gyrus. The DLPFC was marked as the triangular and opercular parts of the inferior frontal gyrus that includes BA 44, 45, and 46.

For the voxel clusters identified within each ROI, two measures were derived: spatial extent and signal amplitude. With regard to significantly activated voxel counts for each ROI, a 2 × 2 mixed ANOVA was performed, consisting of a within-subjects factor of stimulus intensity (pain 1 and pain 2) and a between-subjects factor of sex (men and women). Voxel count data were subject to a logarithmic transformation before statistical analysis to more closely approximate a normal distribution.

![Percentage of significantly modulated voxels with negative BOLD signal changes](http://afni.nimh.nih.gov)

** Fig. 2. Percentage of significantly modulated voxels with a negative signal change. Data are presented as means ± SE. **Significant sex difference at P < 0.05; ^^significant interaction of sex and pain level at P < 0.05.
For signal amplitude analysis of the ROI single trial averages, the average of the first four time points (0–8 s into the cycle or the “baseline” of the signal response) was subtracted from the average of time points 7–14 (14- to 28-s cycle or the estimated “peak” of the signal response) for each subject. To characterize the signal amplitude responses of each ROI, a 2 × 2 mixed ANOVA was performed on this signal intensity change data, as described above for the spatial extent data. On the basis of analysis of the data distribution, no logarithmic transformation of these data was deemed necessary.

Analysis of direction of voxel signal change. Subsequently, positive and negative BOLD signal changes were separately analyzed. Any significantly activated voxel was deemed a negative BOLD signal change if it had a negative value for its regressor coefficient in the original GLM model, whereas any significantly activated voxel was deemed a positive BOLD signal change if it had a positive value for its regressor coefficient. One analysis consisted of testing whether the percentage of negative signal change voxels (percentage of significantly modulated voxels, not percentage of all voxels in the anatomically defined ROI) differed significantly between men and women, separately for each ROI and for the two painful levels of stimulation. Subsequently, two 2 × 2 mixed ANOVAs were conducted for voxel counts and signal amplitude change, separately for voxels only showing positive BOLD signal change and voxels only showing negative BOLD signal change.

Locations of positive and negative voxel clusters. Within a given ROI for each subject and for each painful temperature, the largest voxel cluster containing only significantly activated positive voxels and the largest voxel cluster containing only significantly activated negative voxels were separately mapped. Using the AFNI routine 3dclust, the center of mass coordinate in Talairach coordinate space was derived for each positive and negative voxel cluster. A 2 × 2, repeated-measures ANOVA (signal change direction and temperature) was used to test for significant differences in location of the x-, y-, and z-axes, separately for each ROI.

RESULTS

Pain ratings. The pain ratings were significantly different for the two stimulus intensities, but not significantly different between men and women (pain 1 mean ratings: men = 55, women = 51; pain 2 mean ratings: men = 70, women = 72; sex factor P = not significant). Additionally, although women received slightly weaker stimuli on average, there was no significant group difference in the temperatures used for men vs. women (pain 1 average temperature: men = 46.5°C, women = 46.3°C; pain 2 average temperature: men = 47.5°C, women = 47.3°C; sex factor P = not significant).

Imaging responses. The spatial extent of significantly activated voxels was not significantly different between men and women for any of the ROIs, despite a large variation across ROIs (Fig. 1, top). In contrast, the amplitude of BOLD signal change (%signal change) was significantly greater for men in

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**Fig. 3.** Measurement of pain-related BOLD signal amplitude change considering only those voxels with a significant positive signal change. Data are presented as means ± SE. **Significant sex difference at P < 0.05; ^^significant interaction of sex and pain level at P < 0.05.**

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S1 cortex (bilaterally) and mid-ACC, whereas the DLPFC showed a significant interaction between sex and stimulus intensity (Fig. 1, bottom). Other regions showed a nonsignificant sex difference in the same direction, including the aINS and the rACC.

Because significant BOLD signal change was based on the $F$ statistic of the regression, significant BOLD signal change could reflect either positive or negative BOLD signal change. When the positive and negative signal changes (based on the sign of the coefficient produced by the regression) were examined separately, we observed that whereas most of the activated clusters were positive, there was a fraction of clusters that had negative signal change in most subjects in almost every ROI. The percentage of negative BOLD voxels varied greatly across ROIs, but almost all ROIs showed the same trend of a larger percentage of negative BOLD signals for women, at least for the pain 2 stimuli (Fig. 2).

When considering only significant positive voxels, there was no significant sex difference in spatial extent of activation for any ROI (Fig. 3, top). However, when significant negative voxels were considered, there was often a trend for greater extent in women than in men, which was found to be statistically significant for contralateral S1 and DLPFC, and for the pain 2 level of stimulation for the ipsilateral aINS (Fig. 4, top).

Despite this sex difference in the spatial extent of negative BOLD signal change, there was no apparent or statistical sex difference in the signal amplitude (Fig. 4, bottom).

To examine the time course of these responses, single trial averages were generated for each ROI, separately for the two levels of painful stimulation and averaged across subjects. This was done for all significantly activated clusters and then separately for positive and negative signal change clusters (Fig. 5). In general, the negative BOLD signal resembled a mirror image of the positive BOLD signal with no apparent lag in the response. Furthermore, there is no apparent sex difference in the response waveform when reviewing positive or negative responses separately but only when averaging across both positive and negative significantly activated voxels.

The locations of the positive vs. negative clusters were found to be nonrandomly organized in some ROIs. Those ROIs along the midline (rACC, mid-ACC, and SMA) showed a very distinct pattern of positive signal clusters lying near the midline, with negative clusters flanking laterally. This pattern can be seen to some extent in individual subject’s results (Fig. 6), but is more evident in group maps (Fig. 7). Other ROIs had a less obvious segregated organization. On the basis of statistical analyses, several ROIs demonstrated significant nonrandom cluster organizations (Table 1). In the mediolateral (x) axis, the right DLPFC showed positive clusters significantly more lat-

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![Voxels with Significant Negative Change in the BOLD Signal](image1)

![Signal Amplitude Change](image2)

**Fig. 4.** Measurement of pain-related BOLD signal change considering only those voxels with a significant negative signal change. Data are presented as means ± SE. **Significant sex difference at $P < 0.05$; ^^significant interaction of sex and pain level at $P < 0.05$.**

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eral than negative clusters. In the anterior-posterior (y) axis, the SMA showed positive clusters significantly more anterior than were negative clusters. In the dorsoventral (z) axis, the mid-ACC, the rACC, and right S2 showed positive clusters significantly more superior than negative clusters. One should note that when these statistics are subject to Bonferroni correction; only the y-coordinate for SMA still retains significance at $P < 0.05$.

**DISCUSSION**

By using heat stimuli that evoked the same pain intensity in men and women, we found significant differences in BOLD signal amplitude in some ROIs, such that significantly greater BOLD signal increases were found for men in S1 cortex, mid-ACC, and DLPFC. This same trend was observed in most other ROIs, as well. More detailed examination indicated that
this difference is largely attributable to a greater proportion of voxels demonstrating significant negative BOLD signal changes in women vs. men.

It should be pointed out that the basis for identifying significance of BOLD signal change was the $F$ statistic of the GLM regression (a combination of full and partial $F$ values). Relying on the $F$ statistic ignores the distinction between positive and negative signal changes. If instead, a $t$ statistic was used (noting only the positive $t$ values, as is typically done) those results would look very much like the data presented here for positive signal change only, which portrayed a very different picture with respect to sex differences. Thus it is clearly quite important to note which test statistic is used to define significant signal change when evaluating fMRI data.

**Negative BOLD signal change.** Although the negative BOLD signal is often ignored in fMRI studies, another pain imaging study specifically evaluated negative BOLD responses to painful stimuli (25). This study described both positive and negative BOLD signal changes in response to painful stimulation in many of the same ROIs found in the present study, including S1, cingulate cortex, and SMA. Also in agreement with the present study, the Porro et al. study (25) described 1) a very similar time course for the positive and negative signals, and 2) a wide variation in the proportion of negative signals across ROIs.

The meaning of negative BOLD signal change is a topic of considerable discussion in the neuroimaging field. In principle, a negative BOLD response should reflect decreased blood flow prompted by a decrease in brain activity in that region. One explanation for this type of phenomenon is that with stimulation (or onset of any particular event), some brain regions will become silenced in order for other brain regions to function properly. The concept of the default network has been offered, in which certain brain regions are often found to decrease the BOLD signal in concert with attention-demanding event onset of various types (12). This network appears to operate at a large scale and includes brain regions, such as inferior parietal, posterior cingulate, medial temporal, and medial prefrontal cortices. For the most part, these brain regions do not overlap with the pain-related ROIs evaluated in this study. The one exception is the proximity of the inferior parietal region identified as a part of the default network with the parietal region associated with S2. Yet, in the present study, the BOLD signals derived from S2 did not behave remarkably differently from those derived from many other ROIs and did not show a greater negative signal change than other ROIs. Thus, at least as it is currently envisioned, this concept of the default network is not apparently applicable to the results described here.

Another possibility is that the negative signal change reflects a steal phenomenon, in which the brain regions experiencing an increase in blood flow (thus positive BOLD signal change) do so at the expense of surrounding brain regions. This idea cannot be discounted altogether, but several aspects of the signal responses make this explanation less likely. First, although the positive and negative clusters are relatively close to one another, they are usually not adjacent, nor do the negative clusters surround the positive clusters. Second, in many instances, the positive clusters are found without any negative clusters, and in a few cases negative clusters appear without any positive clusters. Third, the waveform of the negative signal changes simultaneously with the positive signal change rather than lagging behind. Some of these properties of the
negative signal change are similar to those reported in recent visual system studies. Smith et al. (32) documented negative BOLD signal changes in the V1, V2, and V3 cortices, both nearby and remote from positive BOLD signal changes in response to localized grating stimuli. Similar results were reported by Shmuel et al. (30), who also demonstrated a very similar time course of the positive and negative signal changes. Both studies argued that the spatial separation and the temporal coincidence of the two signals make it unlikely that a local blood steal phenomenon could be responsible for the negative signal.

Another idea proposed to explain the negative signal change is that a high baseline blood flow may not require a compensatory increase following neural activation. In that instance, only the oxygenation changes associated with increased metabolism, not the compensatory increase in blood flow and oxygenated blood volume, would occur, resulting in a signal decrease (31). This concept may be relevant here, as noted below.

**Sex differences in BOLD signal.** The few neuroimaging studies that have examined sex differences in pain-evoked responses are conflicting but methodologically disparate enough to preclude precise comparisons. Paulson et al. (24) reported greater regional cerebral blood flow (rCBF) in many cortical ROIs of women vs. men in response to painful contact heat but used comparable stimuli levels that were significantly more painful for the women. Thus it is possible that this rCBF difference is not reflecting sex differences in neural processing, but rather is due to the perceived pain intensity difference. Similar PET studies have shown significant correlations between rCBF measures and perceived pain intensity in many ROIs (5). Derbyshire et al. (6) used heat pain (laser) stimuli evoking comparable pain intensity for all subjects and described significantly less rCBF for women vs. men in several ROIs (including S1, S2, thalamus, insula, and midcingulate cortices), and the opposite difference in only the perigenual cingulate cortex. Neuroimaging studies of visceral pain, while often targeting patients with IBS, have also described significant sex differences in response (3, 22). (See also, in this issue of AJP Regulatory, Integrative and Comparative Physiology, Berman et al., Ref. 3a).

Sex differences in neuroimaging responses have been described for other neural systems but very few of other sensory systems. Levin et al. (18) and Kaufmann et al. (17) described greater extent and amplitude of BOLD responses in men vs. women in striate cortex using flickering visual stimuli. Addi-
tionally, Kaufmann et al. (17) reported nonsignificant sex differences in the same direction in extrastriate cortex. However, Kastrup et al. (16) and Hedera et al. (15) reported lower BOLD signal contrasts in men, using similar stimuli. Thus it is still too early to draw any firm conclusions regarding the generalization of sex differences in sensory-evoked BOLD responses.

If, as noted above, baseline cerebral blood flow is an important factor in producing negative signal change, then it is relevant that women often exhibit a higher baseline global CBF than men (13, 14, 28). Part of this difference may be explained by animal studies showing that estrogen increases cerebral glucose metabolism in multiple brain regions (4, 23). In addition, human PET studies have demonstrated significant effects of estrogen manipulations upon imaging results. Berman et al. (2) manipulated the hormone levels of premenopausal women and found that rCBF responses in cognitive tasks were reduced in hypoestrogenic conditions despite comparable performance. A comparison of postmenopausal women either taking or refraining from estrogen replacement therapy (ERT) revealed

Fig. 7—Continued

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Sex differences in experimental pain perception—sometimes. Despite the considerable literature demonstrating sex differences in experimental pain sensitivity, in the present study, we did not find significant differences. The design of this study was to use stimulus levels that evoked the same perceived intensity for all subjects, and we did achieve very similar ratings for men and women for each of the two pain levels. However, on the basis of an expected sex difference, one would predict that a significantly lower temperature would be used for women vs. men to evoke the same pain intensity. Although there was a difference in that direction, it was small and statistically insignificant. In attempting to understand this result, one should consider the following. Although sex differences are often found in experimental pain studies, they are not always found. A meta-analysis pointed out that studies using phasic heat stimuli showed the least consistent results in terms of sex differences in pain (27). In the present study, stimulus values were derived from the subjects’ pain tolerance levels, which is not a common approach. One might even expect that sex differences would be more pronounced at pain tolerance than at threshold (29). However, one study that specifically looked for sex differences in tolerance to contact heat stimuli failed to find a significant difference (8). Regardless of this variability described in the literature, the present study allows for the evaluation of sex differences in pain-related fMRI responses under conditions of nearly equivalent stimulus levels and nearly equivalent perceived intensity.

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