Eur Arch Psychiatry Clin Neurosci (2005) 255 : 327–333 DOI 10.1007/s00406-005-0566-x

ORIGINAL PAPER

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# Gender differences in brain activity toward unpleasant linguistic stimuli concerning interpersonal relationships: an fMRI study

Received: 9 December 2003 / Accepted: 11 October 2004 / Published online: 14 January 2005

**Abstract** Women are more vulnerable to psychosocial stressors such as interpersonal conflicts than men, and are more susceptible to some psychiatric disorders. We hypothesized that there are differences in the brain activity of men and women while perceiving unpleasant linguistic stimuli concerning interpersonal relationships, and that they underlie the different sensitivity toward these stressful stimuli.

We carried out a functional magnetic resonance imaging (fMRI) study on 13 young female adults and 13 young male adults who performed an emotional decision task including sets of unpleasant words concerning interpersonal relationships and sets of neutral words.

In the women, the unpleasant words more significantly activated the bilateral caudate nuclei and left putamen than the neutral words. However, among the men, there was no difference in the level of activation of any brain area induced by the unpleasant or neutral word stimuli. Upon performing the task, there was a significant gender difference in brain activation. Moreover, among the female subjects, the activation in the bilateral caudate nuclei and left thalamus was negatively correlated with the average rating of pleasantness of the words concerning interpersonal conflicts by the subject.

These results demonstrate gender differences in brain activity in processing unpleasant linguistic stimuli related to interpersonal conflicts. Our data suggest that the bilateral caudate nuclei and left putamen play an important role in the perception of words concerning interpersonal conflicts in women. The bilateral caudate nuclei and left thalamus may regulate a woman's sensitivity to unpleasant information about interpersonal difficulties.

**Key words** human · brain imaging techniques · stress · language

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## Introduction

There are diverse stressors around us, and they are roughly classified into two categories: physical and psychological stressors. Physical stressors include trauma, injury, physical exertion, noise, overcrowding, excessive heat or cold, and so on. Psychological stressors include stressful experiences such as time-pressured tasks, interpersonal conflict, isolation, and other types of traumatic life events [14]. As to psychiatric disorders, the available data are consistent with the view that social stress can trigger the onset of many psychiatric illnesses including major depression, anxiety disorders and eating disorders [19, 23, 31]. Interpersonal difficulties predict the propensity of depressive episodes to follow a chronic course [6].

As to susceptibility to psychiatric disorders, women are approximately three times more likely than men to experience a lifetime episode of depression [32]. The predominance of depression among women is a cross-cultural phenomenon and one of the most robust findings in psychiatric epidemiology [4]. Eating disorders are another category of psychiatric illnesses having a larger incidence among women than among men; up to 10 women for every 1 man develop an eating disorder [32]. These data indicating high susceptibility of women to psychiatric illnesses in which stress may play an im-

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portant role suggest that women are more vulnerable to psychosocial stressors such as interpersonal conflicts than men.

With regard to the neural substrates underlying the cognition of unpleasant stimuli concerning interpersonal relationships, many lesion studies and functional brain imaging studies using facial expressions, which symbolize human emotions or what people think and which are necessary as one of the ways in which people communicate with each other, of fear, anger or disgust [1, 3, 15, 16, 20, 21, 26] and vocal expressions of fear, disgust or sadness [17, 20], suggested the involvement of the amygdala and basal ganglia including the caudate and putamen. To date, however, only a few studies have examined the gender differences in brain activation while perceiving facial expressions [9, 13]. These studies analyzed the brain activation of subjects of each gender separately, but the data were not directly compared. Moreover, the neural substrates underlying the cognition of linguistic stimuli concerning interpersonal conflict remain unknown.

To investigate which areas of the brain play an important role in the perception of stressful word stimuli concerning interpersonal relationships and whether the activation of brain regions shows gender differences, we performed a functional magnetic resonance imaging (fMRI) study with a modified emotional decision task based on the task used by Tabert et al. [28].

## Methods

### Subjects

Thirteen men (mean age, 25.3 y; S.D., 2.8 y; range, 21–30 y) and 13 women (mean age, 24.9 y; S.D., 3.3 y; range, 21–30 y) participated in this study. All of the subjects were right-handed and native Japanese speakers. Handedness was determined using the Edinburgh Handedness Inventory [18]. The subjects had no history of psychiatric, neurological, nor other major medical illness, and had never been treated with a psychotropic medication. To eliminate age-related effects, the subjects of the two genders were age-matched. This study was conducted using a protocol that was approved by the Ethics Committee of Hiroshima University School of Medicine. All subjects provided written informed consent for participation in the study.

### Emotional decision task

We used the emotional decision task [28], with some modifications. The words used in the task were selected from the database of Toglia and Battig [30], which includes 2854 words that have been rated on several items such as familiarity and pleasantness, from one (very unfamiliar; very unpleasant) to seven (very familiar; very pleasant) with four as the midpoint. For the current study, 30 highly unpleasant words concerning interpersonal relationships and 30 neutral words were selected from the database and translated into Japanese. The highly unpleasant words and neutral words did not significantly differ with regard to word length (mean word length: Interpersonal relationships vs. Neutral = 2.8 vs. 3.1 in Japanese letters; $P = 0.293$ by two-tailed two-sample Student's t-test) nor familiarity (mean, 4.2 vs. 4.3; $P = 0.808$ by two-tailed Wilcoxon single-rank test) [25]. The words in each of the two groups consisted of nouns, verbs, adjectives and adverbs.

The selected words were used to generate word sets of unpleasant words concerning interpersonal relationships and word sets of neutral words. Each word set was comprised of a unique combination of three words. The word sets were presented in six alternating blocks of word sets composed of unpleasant words concerning interpersonal relationships and neutral word sets (three cycles; Fig. 1A). Each block began with a 3-s cue indicating whether the block consisted of word sets of unpleasant words concerning interpersonal relationships or neutral word sets. Five word sets were presented in each block. Each word set was shown for 4 s with a 1.4-s inter-stimulus interval (ISI) (Fig. 1B and C). The blood oxygen level-dependent (BOLD) response was recorded during three blocks of unpleasant words concerning interpersonal relationships and to three blocks of neutral words. During each ISI, a fixation-cross placed centrally on the screen replaced the word set. Baseline functional magnetic resonance (fMR) images were obtained during a 9-s interval prior to the first block of trials, during which the subject viewed a centrally placed fixation-cross. During each trial, the word set was projected to the center of the subject's field of view via an SVGA computer-controlled projection system. The timing of presentation of word sets was controlled by Presentation Software Version 0.51 (Neurobehavioral Systems, Inc., San Francisco, CA) and the word sets were presented in a randomized order.

Immediately before fMRI scanning was begun, the subject was given 10 practice trials (5 unpleasant word sets and 5 neutral word sets). The words presented in the practice trials did not overlap with the experimental words.

The subject was given the instructions before fMRI scanning was started. The subject was instructed to select the most unpleasant word from each word set of unpleasant words based on his/her personal knowledge and experience. For each word set of neutral words, the subject was instructed to select the word that he/she thought was the most neutral. The subject was asked to respond by pressing one of three buttons on a response pad in the MRI scanner.

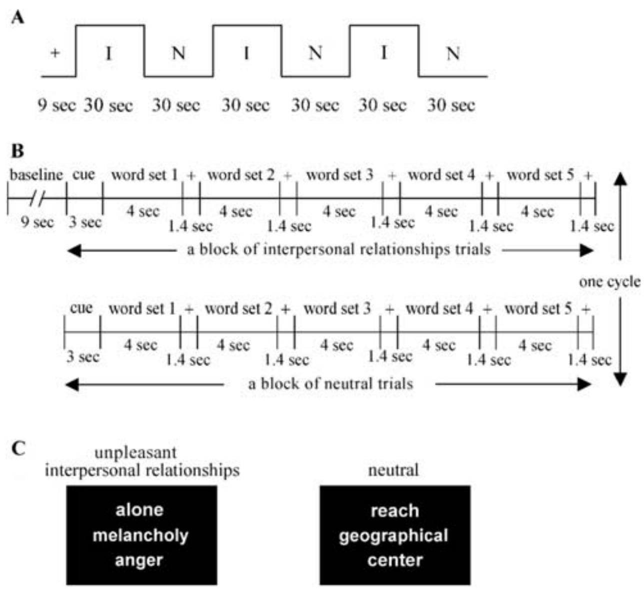


**Fig. 1** The design of the task used in this study. **A** Overview of block-designed stimulus presentation paradigm for the tasks. Six alternating blocks of word sets of unpleasant words concerning interpersonal relationships (I) and neutral words (N) were successively presented. The total scan time of each task was 189 s (3 min and 9 s), while yielding 63 images of 28 axial slices (1764 images). **B** Blocks of word sets of unpleasant words concerning interpersonal relationships and neutral word sets preceded by baseline fMRI measurement. Each block began with a cue indicating "unpleasant words concerning interpersonal relationships" or "neutral words". The subject was instructed to select the word that he/she judged to be the most unpleasant or neutral, respectively, in each word set, by pressing one of the three buttons. **C** Typical examples of word sets presented in this study that are translated into English. The actual word sets consisted of Japanese words

### Image acquisition and processing

Functional MRI was performed with a MAGNEX ECLIPSE 1.5T Power Drive 250 (Shimadzu Medical Systems, Kyoto, Japan). A time-course series of 63 volumes was acquired with T2*-weighted, gradient echo, echo planar imaging (EPI) sequences. Each volume consisted of 28 slices, and the thickness of each slice was 4.0 mm with no gap, encompassing the entire brain. The interval between two successive acquisitions of the same image (TR) was 3000 ms, the echo time (TE) was 55 ms, and the flip angle was 90°. The field of view was 256 mm and the matrix size was 64*64, giving voxel dimensions of 4.0*4.0*4.0 mm. After functional MRI scanning, structural scans were acquired using a Tl-weighted gradient echo pulse sequence (TR = 12 ms; TE = 4.5 msec; Flip angle = 20°; FOV = 256 mm; voxel dimensions of 1.0*1.0*1.0 mm), and they facilitated localization and coregistration of the functional data.

Image processing and statistical analysis were performed using Statistical Parametric Mapping 99 (SPM99) software (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Inc., Natick, MA). The first two volumes of the fMRI run (pre-task period) were discarded because the magnetization was unsteady, and the remaining 61 volumes were used for the statistical analysis. Images were corrected for motion and realigned with the first scan of the session, which served as the reference. The T1 anatomical images were coregistered to the first functional images in each subject and aligned to a standard stereotaxic space, using the Montreal Neurological Institute (MNI) T1 template in SPM99. The calculated nonlinear transformation was applied to all functional images for spatial normalization. Finally, the functional MR images were smoothed with a 12-mm full-width, half-maximum (FWHM) Gaussian filter.

Using group analysis according to a random effect model that allowed inference to the general population [8], we first identified brain regions that showed a significant response to word sets of unpleasant words concerning interpersonal relationships in comparison with the response to neutral word sets among the male subjects and among the female subjects, as brain areas related to the cognition of stimuli of unpleasant words concerning interpersonal relationships in males and females, respectively. Next, we directly compared the activation of the entire brain of the subjects of each gender, using the two-sample Student's t-test. The resulting set of voxel values for each contrast constituted an SPM map. The SPM maps were then interpreted by referring to the probabilistic behavior of Gaussian random fields. The data were initially thresholded at $P < 0.001$ uncorrected at the voxel level and at $P < 0.05$ corrected at the cluster level.

The x-, y- and z-coordinates provided by SPM, which were in Montreal Neurological Institute brain space, were converted to the x-, y-, and z-coordinates in Talairach and Tournoux's (TT) brain space [29] using the following formula: $\{TT\_x = MNI\_x \cdot 0.88 - 0.8; TT\_y = MNI\_y \cdot 0.97 - 3.32; TT\_z = MNI\_y \cdot 0.05 + MNI\_z \cdot 0.88 - 0.44\}$. Labels for brain activation foci were obtained in Talairach coordinates using the Talairach Daemon software (Research Imaging Center, University of Texas, TX), which provides accuracy similar to that of neuroanatomical experts [10]. The labeling of areas given by this software was then confirmed by comparison with activation maps overlaid on MNI-normalized structural MR images.

### Evaluation of pleasantness and familiarity with the word stimuli

Each subject was asked to rate the pleasantness and his/her familiarity with all of the words presented in the tasks on a 7-point scale from one (very unfamiliar; very unpleasant) to seven (very familiar; very pleasant), immediately after scanning. All of the words used in the tasks were printed in a table in randomized order.

## Results

### Rating of words

The rating of familiarity with the two categories of words did not significantly differ among all of the subjects (mean, Interpersonal relationships vs. Neutral = 4.2 vs. 4.3; $P = 0.798$ by two-tailed Wilcoxon single-rank test), among women (4.1 vs. 4.3; $P = 0.695$), and among men (4.3 vs. 4.4; $P = 0.700$). However, the subjects rated the unpleasant words concerning interpersonal relationships as significantly more unpleasant than the neutral words (all subjects, Interpersonal relationships vs. Neutral = 2.3 vs. 4.1, $P = 0.000083$; women, 2.3 vs. 4.1, $P = 0.0015$; men, 2.4 vs. 4.1, $P = 0.0015$).

Neither the rating of pleasantness nor the rating of familiarity in each word category significantly differed between the male and female subjects.

### Functional MRI scan: brain activation in the subjects of each gender

Among the female subjects, there was significantly greater activation of the bilateral caudate body, left putamen and left parahippocampal gyrus when performing the emotional decision task on unpleasant words concerning interpersonal relationships than when performing the task on neutral words. However, among the male subjects, there was no significant difference in the level of activation of any brain region when performing the task on unpleasant words concerning interpersonal relationships or when performing the task on neutral words (Table 1, Fig. 2).

In the female subjects, the two-sample Student's t-test revealed that there was a significantly higher BOLD response than the male subjects in the bilateral caudate body and left putamen when performing the task on unpleasant words concerning interpersonal relationships than when performing the task on neutral words (Table 1, Fig. 3). No brain area was more significantly activated in the male subjects than in the female subjects during any of the tasks.

We could not attribute these activations to a particular structure with the resolution of our data since we performed the smoothing procedure to facilitate intersubject averaging.

### Correlation between psychological data and brain activation

Among the female subjects, simple regression analysis considering the entire brain revealed that the average rating of pleasantness of the unpleasant words concerning interpersonal relationships by a subject was negatively correlated with the BOLD response in some brain areas including the bilateral caudate nuclei and left thal-

**Table 1** Relative increases in brain activity associated with unpleasant words concerning interpersonal relationships (task) and neutral words (control)

| | Cluster | BA[a] | t-score | x | y | z |
|---|---|---|---|---|---|---|
| Female subjects (n = 13) | | | | | | |
| Left putamen | 1503 | | 7.82 | –22 | –1 | 17 |
| Left caudate body | | | 7.47 | –6 | 1 | 19 |
| Right caudate body | | | 6.17 | 6 | –1 | 19 |
| Left parahippocampal gyrus | 437 | 36 | 5.89 | –22 | –42 | –8 |
| | | 35 | 5.82 | –24 | –23 | –16 |
| Right fusiform gyrus | 161 | 37 | 5.41 | 29 | –46 | –11 |
| | | 37 | 4.77 | 26 | –52 | –19 |
| | | | 4.12 | 20 | –56 | –26 |
| Female subjects (n = 13) > Male subjects (n = 13) | | | | | | |
| Left caudate body | 1146 | | 5.78[b] | –6 | 1 | 17 |
| Left putamen | | | 5.58[b] | –20 | –1 | 17 |
| Right caudate | | | 4.53 | 6 | 3 | 10 |
| Female subjects (n = 13) – inversely correlated with pleasantness of word stimuli | | | | | | |
| Left caudate body | 412 | | 6.07 | –11 | 6 | 11 |
| Right caudate body | | | 6.01 | 6 | 4 | 18 |
| Left thalamus | | | 5.71 | –1 | –5 | 8 |

Stereotaxic coordinates were derived from the human atlas of Talairach and Tournoux [23] and refer to the medial-lateral position (x) relative to the midline (positive = right), anterior-posterior position (y) relative to the anterior commissure (positive = anterior), and superior-inferior position (z) relative to the commissural line (positive = superior). [a] *BA* Brodmann area; [b] corrected $P < 0.05$ at the voxel level and all other areas; [c] corrected $P < 0.05$ at the cluster level

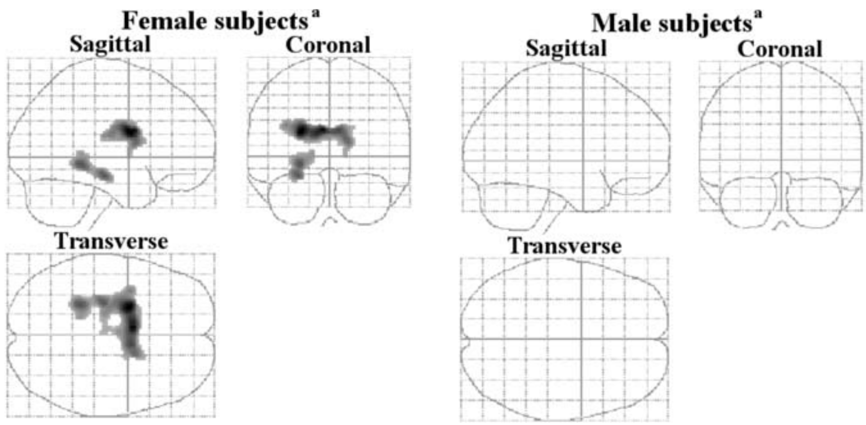


**Fig. 2** Significant brain activation associated with unpleasant words concerning interpersonal relationships than to the neutral words among the female subjects. Three-dimensional "look-through" projections of statistical parametric maps of the brain regions are shown ([a] One-sample Student's t-test; corrected $P < 0.05$ at the cluster level; n = 13; df = 12)

amus ($P < 0.05$ corrected in extent) (Table 1, Fig. 4). Among the male subjects, the average rating of pleasantness of the unpleasant words concerning interpersonal relationships by a subject was not significantly correlated with the BOLD response in any brain area.

## Discussion

In the present study, we used the emotional decision task with unpleasant words concerning interpersonal relationships and neutral words to examine the brain areas engaged in the perception of unpleasant words concerning interpersonal relationships and to compare the pattern of brain activation between the female and male subjects. Our results showed that the bilateral caudate nuclei and left putamen are important in processing unpleasant words concerning interpersonal relationships, specifically in women. In our study, the male subjects did not have significantly greater activation in any area of the brain toward stimuli of unpleasant words concerning interpersonal relationships than toward the stimuli of neutral words. One possible reason for the difference is gender differences in specific cognitive functions. Men show superior spatial memory and women demonstrate superior verbal memory, and women rely on emotional content to a greater degree in the processing of information [5]. Men and women may take different strategies and may show different patterns of the brain activation during the same task. From this viewpoint, the women were considered to have processed word stimuli in this task with more emotional context than men. To further clarify these points, additional studies that directly compare the brain acti-

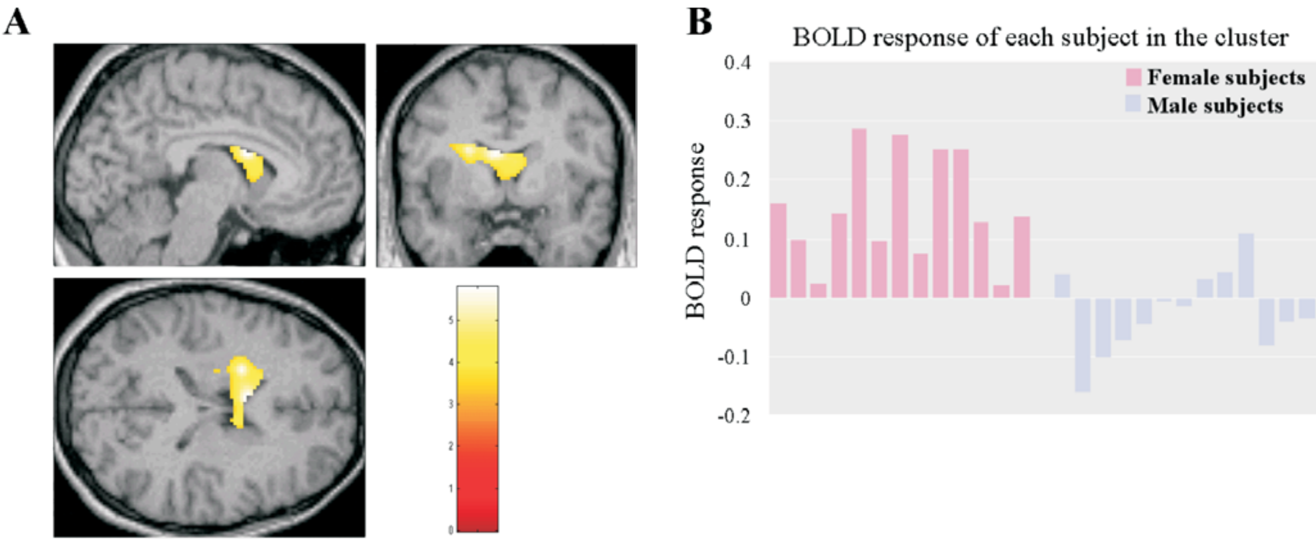


**Fig. 3** Brain regions showing significantly greater activation in the female subjects than in the male subjects while performing the emotional decision task on unpleasant words concerning interpersonal relationships compared to neutral words. **A** Clusters of activation are overlaid onto a T1-weighted anatomical MR image. The T-levels of activation are color-coded from red to yellow. Two-sample Student's t-test; corrected $P < 0.05$ in extent; $n = 26$ (13 male and 13 female subjects); $df = 24$. **B** Each bar in the graph indicates the raw data of each subject in the cluster. Pink bars represent activation in the female subjects, and pale blue bars represent activation in the male subjects

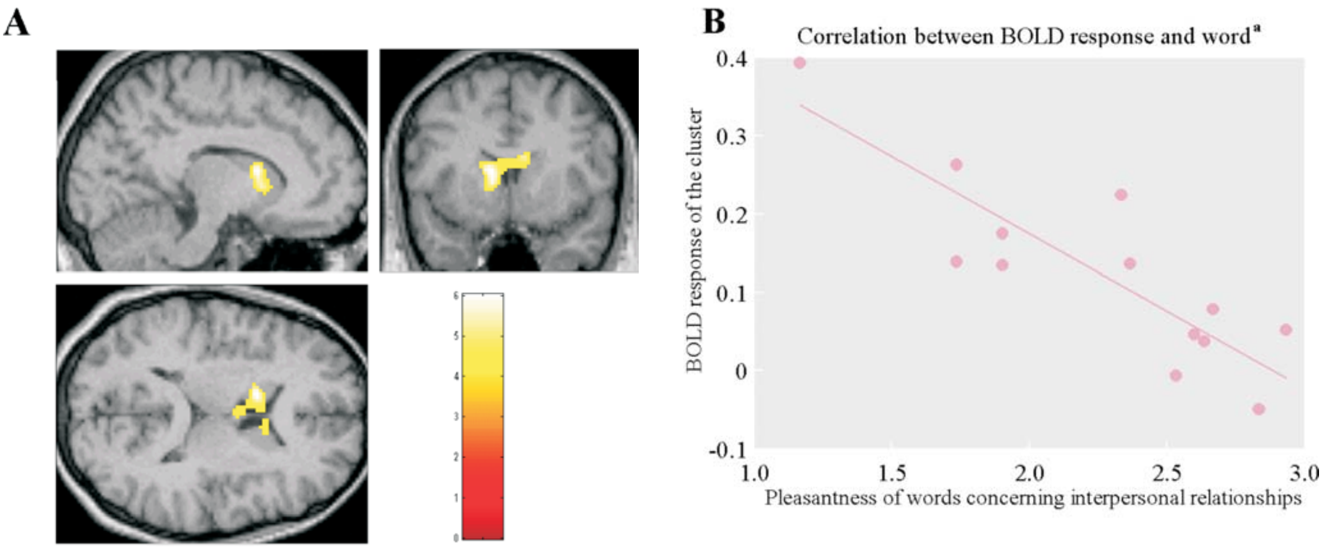


**Fig. 4** Relationship between the degree of activation of brain areas and the average rating of pleasantness of words concerning interpersonal relationships among the 13 female subjects. **A** Clusters of activation are overlaid onto a T1-weighted anatomical MR image. The T-levels of activation are color-coded from red to yellow. Correlation analysis was performed on the entire brain and several brain areas showed a significant correlation. Simple regression analysis; corrected $P < 0.05$ in extent; $n = 13$; $df = 11$. **B** The scatter diagram demonstrates the correlation between the BOLD response of this cluster and the average rating of pleasantness of the words concerning interpersonal relationships among the 13 female subjects ([a] Spearman's rank-order correlation analysis; correlation coefficient = – 0.851; $P = 0.00068$; $n = 13$)

vation of female and male subjects while processing visual stimuli such as unpleasant facial expressions as nonverbal stimuli concerning negative interpersonal relationships are needed. Another possible reason for the gender differences in brain activation is the involvement of some behavioral differences between men and women. In this study, we only have two behavioral data, rating of familiarity and pleasantness of the words used in this study, and these parameters did not explain the gender differences of the brain activity. Further studies are needed to make clear what kinds of behavioral differences exist between men and women which affect the brain activations.

Several studies have indicated the involvement of the caudate nucleus and putamen in processing negative facial expressions of disgust. For instance, a neuropsychological study reported that patients with Huntington's disease, which is characterized by specific lesions in the caudate nuclei, showed impaired responses to facial expressions of disgust [27], and thereafter it was reported in an fMRI study that facial expressions of disgust activated the putamen in healthy subjects [26]. Also, in another functional MRI study using four different stimuli, i. e., facial and vocal expressions of each of fear and disgust, only the facial expressions of disgust activated the caudate-putamen [20]. These studies indicate that the caudate nuclei and putamen play an important role in the perception of facial expressions of disgust. We used unpleasant linguistic stimuli concerning interpersonal relationships in the present study and detected significant activation in the area of the caudate nuclei and putamen in the female subjects. This result may suggest that the caudate nuclei and putamen play an important role in the processing of disgust with regard to interpersonal conflict regardless of the sort of stimulus, whether it is verbal or nonverbal.

Regarding the relationship between the degree of brain activation and the ratings of pleasantness and familiarity with the word stimuli by the subjects, simple regression analysis among the 13 female subjects showed that the average rating of pleasantness of the unpleasant words concerning interpersonal relationships by a subject was inversely correlated with the BOLD response in the bilateral caudate nuclei and left thalamus. As described above, the caudate nuclei are involved in the processing of stimuli related to disgust. Furthermore, the intensity of the BOLD response of this area was correlated with the subjective sensitivity of the individual towards the unpleasant words concerning interpersonal relationships, and this suggests that the caudate nucleus may play a key role in the regulation of sensitivity to external stimuli of disgust. As to the thalamus, an fMRI study revealed that the BOLD signal in the left thalamus was significantly increased during processing of high-valence facial expressions including happy and angry expressions [7], and several functional neuroimaging studies reported that the thalamus was activated when viewing films, viewing sets of pictures, or recalling personal experiences that evoked happiness, sadness or disgust [11, 12, 22]. These results suggest that the thalamus is activated rather unspecifically during the processing of both pleasant and unpleasant stimuli that span a variety of different emotions including anger, sadness and disgust. Although the thalamus may be activated regardless of the emotional valence, it is interesting that the more unpleasant the female subject felt the word stimuli were, the greater the magnitude of activity in the bilateral caudate nuclei and left thalamus.

Previous studies on patients with localized brain lesion have provided evidence that the human amygdala plays a role in evaluation of information containing negative emotion [2, 3, 24, 33]. However, these results suggest that activation of the amygdala may be particularly associated with fear, anger and threat rather than with all negative emotions.

There are some limitations in the present study. First, the resolution of our data was relatively low because we performed the smoothing procedure in order to facilitate intersubject averaging. This made it difficult to attribute the activation to a particular brain structure. Second, we did not perform a structured interview in selecting the subjects for participation in this study. Nevertheless, they had no psychiatric nor neurological illness at the time of their participation, although we can not predict their occurrence in the future. Third, this study was targeted to only young adults to improve the statistical power; therefore, it is unclear whether these results apply to all age groups. Finally, although our data suggest that there is differential activation of the brain of men and women when perceiving unpleasant stimuli related to interpersonal conflicts and that women are more sensitive to stimuli concerning interpersonal conflicts, these data are not sufficient to conclude that bilateral caudate nuclei, left putamen and left thalamus are the neural substrates that underlie the high susceptibility of women to psychiatric illnesses in which stress may play an important role. Further studies are needed to confirm that these brain areas are involved in the susceptibility of women to psychiatric illnesses.

Further studies are also needed to reveal the differences in brain activation in response to stressful word stimuli concerning interpersonal relationships between psychiatric patients or psychiatric patients in remission and healthy subjects in each gender.

In conclusion, fMRI revealed that the bilateral caudate nuclei and left putamen were activated in 13 young female adults while performing the emotional decision task with unpleasant words concerning interpersonal relationships, and that these brain areas were more strongly activated in women than in men. In addition, the magnitude of activation of the bilateral caudate nuclei and left thalamus was negatively correlated with the subject's average rating of pleasantness of the unpleasant words concerning interpersonal relationships, only among the female subjects. These results suggest the involvement of qualitative factors in the activation of the bilateral caudate nuclei and left putamen in response to stimuli evoking disgust and the possibility of the role of the bilateral caudate nuclei and left thalamus in the regulation of sensitivity to external information of disgust related to interpersonal relationships.

Further studies that compare psychiatric subjects and healthy subjects are needed to elucidate the vulnerability to psychiatric illnesses in which stress may play a major role.

**Acknowledgments** This study was supported by the Research on Psychiatric and Neurological Diseases and Mental Health, Ministry of Health, Labor and Welfare, Japan.

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