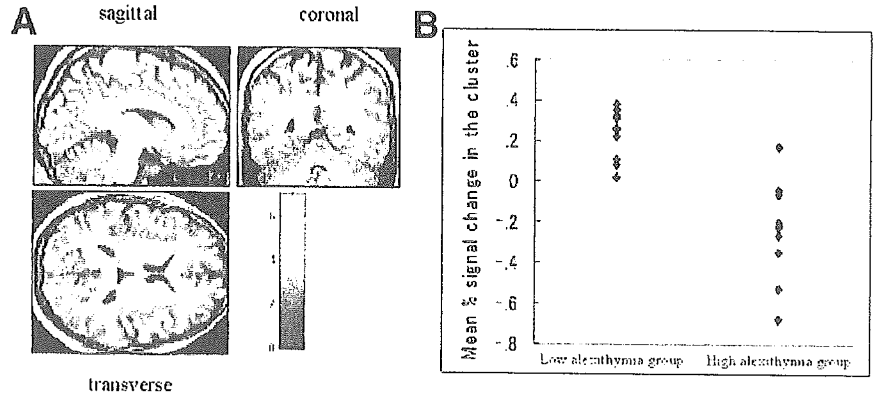

Figure 1. The region significantly less activated in the high degree of alexithymia group compared with the low degree of alexithymia group **(A)** (thresholded at $p < .001$ uncorrected at the voxel level and at $p < .05$ corrected at the cluster level for significance) and the associated adjusted responses for the between-group comparisons **(B)** (mean percentages of signal changes in the cluster) in the future happy imagery condition compared with the REST condition.

There is considerable evidence that the PCC has functions related to episodic memory (Andreasen et al 1995; Grasby et al 1993; Henson et al 1999; Maddock et al 2001). A review of functional imaging studies showed that the caudal part of the PCC was the cortical region most consistently activated by emotional stimuli compared with nominally matched, emotionally neutral stimuli (Maddock 1999). Moreover, it has been speculated that the PCC plays a role in the modulation of memory by emotionally arousing stimuli (Maddock 1999).

The PCC has strong reciprocal connections with regions engaged in memory processing, such as medial–temporal lobe memory structures and the thalamus (Bentovoglio et al 1993; Suzuki and Amaral 1994). It is also reciprocally connected to regions engaged in emotional processing, such as the ACC and the orbitofrontal cortex (Goldman-Rakic et al 1984; Musil and Olsen 1993; Van Hoesen et al 1993). These neuroanatomic findings also suggest that the PCC is involved in both memory and emotion. It is especially interesting that the ACC and PCC are connected reciprocally, whereas recent neuroimaging studies have suggested that the ACC has neural correlates of alexithymia (Berthoz et al 2002 ; Kano et al 2003). Although in our imagery task the activation of the ACC is not related to the degrees of alexithymia, the disturbance of both the ACC and PCC might comprise the various features of alexithymia having interaction.

One possible explanation for the difference between the groups in brain activation during FH imagery is that people with HDA can construct FH imagery, but in a different way than people with LDA do. It is known that the primary and secondary sensory cortices (such as the visual or auditory cortex) are activated during imagery (Cabeza and Nyberg 2000; Shergill et al 2001). But the activation of these areas did not significantly differ between subjects with HDA and subjects with LDA in any of the imagery conditions. So, we can't consider that people with HDA are less imaginal, at least on the sensory level. Together with the function of the PCC mentioned in the previous paragraph, our results indicate that subjects with LDA use memories of past emotional events to create FH imagery, but subjects with HDA rarely or never do. On the other hand, the evaluation of an emotionally salient stimulus engages a variety of cognitive processes, many of which have been considered to rely on episodic-memory retrieval (Pratto 1994). Another explanation is that the activation of the PCC is associated with the evaluation of emotional stimuli that depend on episodic memories, and subjects with HDA evaluate their FH imagery as less exciting than do subjects with LDA.

Moreover, the blood oxygen level–dependent response presented during PH and FH imagery compared with REST suggests a deactivation of the PCC in the HDA group. Recently, functional imaging studies have shown that certain brain regions, including the PCC, consistently show greater activity during resting states than during cognitive tasks. Furthermore, it has been hypothesized that these brain regions constitute a default mode network (Greicius et al 2003; Raichle et al 2001). Raichle et al (2001) speculated that in the default state, information broadly arising in the external and internal milieus is gathered and evaluated and that when focused attention is required, activity within these areas might be attenuated. The HDA group demonstrated significant activation in the fusiform gyrus and not in the PCC, whereas the LDA group demonstrated the reverse pattern of activation in the one-sample *t* test. The fusiform gyrus is related to visual attention (e.g., Mangun et al 1998). Considering the external oriented cognitive style of alexithymia (Nemiah et al 1976; Taylor et al 1997), we speculated that because the HDA subjects might have been more engaged in visual attention to displayed cue letters than in the retrieval of episodic memory, deactivation of the PCC might have been greater in subjects with HDA than in

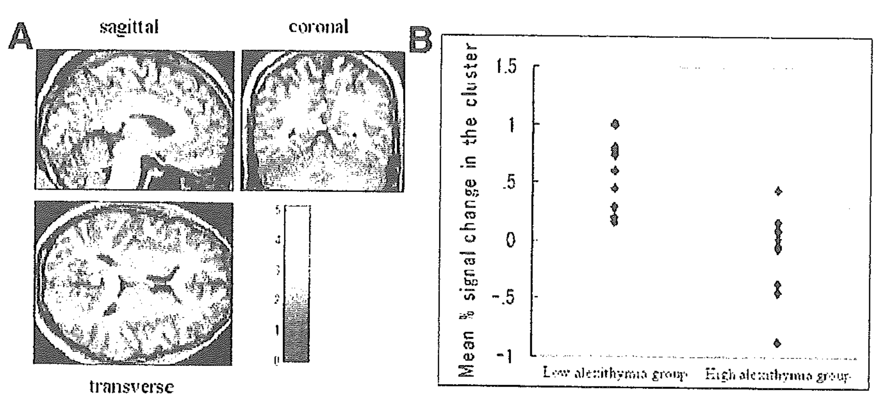

Figure 2. The region significantly less activated in the high degree of alexithymia group compared with the low degree of alexithymia group **(A)** (thresholded at $p < .001$ uncorrected at the voxel level and at $p < .05$ corrected at the cluster level for significance) and the associated adjusted responses for the between-group comparisons **(B)** (mean percentages of signal changes in the cluster) in the past happy imagery condition compared with the REST condition.

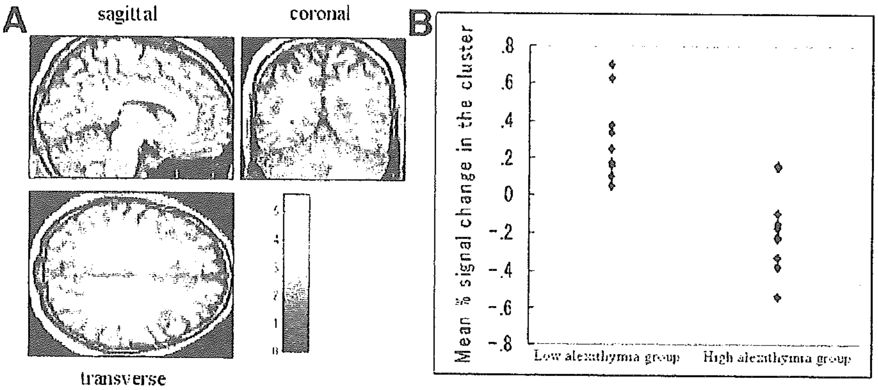

Figure 3. The region significantly less activated in the high degree of alexithymia group compared with the low degree of alexithymia group (**A**) (thresholded at $p < .001$ uncorrected at the voxel level and at $p < .05$ corrected at the cluster level for significance) and the associated adjusted responses for the between-group comparisons (**B**) (mean percentages of signal changes in the cluster) in the future happy imagery condition compared with the future neutral condition.

those with LDA, and the deactivation might likely have contributed to the between-group results.

At a lower level of significance, the PCC was less active in the HDA group than in the LDA group during the PH imagery condition compared with REST. These results, together with the result of the group comparison in FH > REST and FH > FN contrasts, suggest that it is difficult for individuals with HDA to imagine happy events. Our results support the speculation of previous researchers that the restricted imaginal capacities of people with alexithymia limit the extent to which individuals with HDA can modulate negative emotions by imaginative activities that have positive connotations, such as fantasy, dreams, interest, and play (Krystal 1988; Mightes and Cohen 1992). According to Bagby et al (1994b), within the correlation between the TAS-20 and the subscales of extraversion, alexithymia was associated significantly and negatively with the tendency to experience positive emotions. Our data support their idea that alexithymia is associated with a low proneness to experience positive emotions; however, in the PH > PN contrast, there was no significant difference between the groups. Our subjects usually chose daily acts as PN events, and these events were often more recent and more familiar than PH events. Meanwhile, the recency (Piefke et al 2003) and familiarity (Kosaka et al 2003) of autobiographical memory seem to increase PCC activity. The recency and familiarity of PN events might have confounded and diminished the difference between PH and PN conditions in the activation of PCC. To reach a conclusion about the difference in happy imagery between these two groups, further studies controlling these factors are needed.

There is another possible explanation for the groups having differed significantly only in the FH imagery condition. That is, our results might support the speculation of previous researchers that individuals with HDA find it hard to imagine something that they have never experienced. Clinical observations suggest that individuals with HDA seem to be swayed too much by minutiae of superficial "external" things and cannot imagine invisible, intangible things, such as mental content or the future (Marty and de M'Uzan 1963; Taylor et al 1997). They can recall intact their past experience, but they cannot process their experience or imagine events they have never experienced. Our results, however, suggested that the groups did not differ from each other in the FS and FN imagery conditions compared with REST. For FN events, our subjects usually chose daily acts that they had already experienced. We consider that this might explain why the groups did not differ in the FN condition. Moreover, although we did not discuss this in the Results section, the PCC was less active in the HDA group than in the LDA group during FS compared with REST and in FS compared with FN (number of voxels in cluster: 96 and 97, respectively) when the threshold was set at an uncorrected $p < .001$ at the voxel level in an a priori hypothesized region (Elliott et al 2000). On the other hand, there was no difference between the groups in PCC activation during PS compared with REST or during PS compared with PN, even at this lower threshold.

Meanwhile, discrepancies were observed between brain activation and subjective rating results. In general, the different responses to sad and happy imagery conditions were as follows. There were no significant differences in brain activation between the HDA and LDA groups in sad imagery conditions, but there were such differences in subjective ratings between the groups. For happy imagery conditions, on the other hand, the opposite was found: there were no significant differences between the groups in subjective ratings, but such differences were found in brain activation. These results seem to be paradoxical. We speculate that there were no significant differences between the groups in brain activation during sad imagery in the scan, but there might have been differences between the groups in brain activation when the subjects reported the subjective ratings after the scan. Several investigators suggested that alexithymia might involve a "decoupling" of the subjective and physiologic components of the emotional response to stressful stimuli—that is, a higher degree of alexithymia was associated with fewer subjective responses and greater physiologic reactivity (Martin and Pihl 1986; Papciak et al 1985). The results of these previous studies might suggest that subjects with alexithymia have deficiencies in conscious awareness of emotion. In previous neuroimaging studies of alexithymia, the ACC and MPFC have been reported as the neural correlates of conscious awareness of emotion. Studies of decoupling theory have focused exclusively on negative emotion. Berthoz et al (2002) reported that the activation of the ACC/MPFC was lower during negative stimuli and higher during positive stimuli in people with alexithymia than in people without it. Kano et al (2003) found that although the activation of ACC was lower in subjects with alexithymia than in those without it in response to an angry face, there was no difference between groups in the ACC activation in response to a happy face. These results also suggest that "decoupling" occurs in relation to negative emotion but not to positive emotion. If so, when brain activations differ between HDA and LDA subjects during happy imagery, subjective ratings should also differ between HDA and LDA subjects. In this study, however, no significant differences were found in subjective ratings of intensity of emotion during the happy imagery conditions. This might have been influenced by the difference in effect size between brain activation and subjective rating. Neuroimaging is a much more powerful tool than traditional behavior methods for detecting subtle relationships between two variables (Canli and Amin 2002). In fact, in spite of the small sample size, subjective ratings of the intensity of emotion tended to be higher in the LDA group than in the HDA group for PH and FH, although not significantly.

On the other hand, to our surprise, there was no significant difference in the activation of the ACC/MPFC region between the groups for which we had an a priori hypothesis. The small sample size might explain the absence of such a difference. In fact, a qualitative comparison of brain activation by the one-sample *t* test suggested that the LDA group had significantly greater activity than the HDA group in the ACC/MPFC region during PS imagery. And if the subjects with HDA had poorer imaginal capacity than those with LDA, the activation of this area during the control condition, that is, REST condition (during which free recall could occur) and the neutral imagery condition, could be greater in the LDA group. In fact, ACC activation in the LDA group was significantly greater in PN than in REST in this study, whereas no ACC activation was found in the HDA group during PN. Furthermore, the brain activity detected by the one-sample *t* test was poorer than it was in George et al (1995), which showed bilateral limbic and paralimbic activation, including that of the ACC/MPFC. We considered that factors such as the shorter time interval among tasks, which might have resulted in mutual influence, or the shorter duration of imagery generation in this study than in the PET study of George et al (1995) might have influenced these differences in results between the two studies. Next, no difference between the groups was observed in the limbic structure (i.e., the amygdala, the hippocampal formation, and the hypothalamus), which plays a central role in emotional responses to simple perceptual aspects of stimuli. This finding is consistent with previous studies that found that the limbic area is not associated with alexithymia (Berthoz et al 2002; Kano et al 2003). Furthermore, no difference between the groups was observed in the insular cortex or in the orbitofrontal cortex; these cortices have been discussed in numerous neuroimaging studies about emotional recall/imagery (Phan et al 2002) and general emotional processing (Bechara et al 2000). This absence of activity might be attributable to the imaging method used. Whereas activation of these regions has been reported mainly in PET studies, it is known to be difficult to detect the activation of these areas by fMRI for susceptibility artifact (Ojemann et al 1997). Thus, our study cannot conclude that there is no relationship between emotional imagery disturbance related to alexithymia and these important brain regions, except for the PCC. Further studies considering these points are needed.

There are some limitations to this study. First, because of the small sample size, we might have failed to identify activation differences between HDA and LDA in other imagery conditions. Second, the sensory modalities of imagery (e.g., auditory, olfactory) involved in each event, in addition to visual sensation, differed not only between subjects but within each subject. This might have been a confounding factor, although it is difficult to control these factors because autobiographical memory is usually multimodal and because imagery, in which sensory modality is restricted, is different from daily experiences, especially emotional ones. Third, the subjects' retrospective ratings of their imagery and intensity of emotion might have been inaccurate, especially if the subjects with HDA had trouble with episodic memory. Finally, some subjects might have been unable to refrain from imagery and emotion or other cognitive activity during the rest periods. The level of each subject's cognitive activity during these rest periods might also be a confounding factor. Further studies considering these points are needed.

In conclusion, the present study revealed that the reduced activation of PCC in subjects with HDA was associated with the disturbance of FH imagery. The disturbance of FH imagery can reduce motivation and hope, and it might be an important factor in the construction of deficits in the emotional regulation of alexithymia. We suggest that PCC might play a crucial role in alexithymia-related imagery disturbance. Although this study has several limitations, the present results are meaningful as the first report to demonstrate neural correlates of imagery disturbance in alexithymia.

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Naoko Shirao · Yasumasa Okamoto · Go Okada · Kazutaka Ueda · Shigeto Yamawaki

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

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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

N. Shirao, M. D., Ph. D. · Y. Okamoto, M. D., Ph. D. ·
G. Okada, M. D., Ph. D. · K. Ueda, Ph. D. · S. Yamawaki, M. D., Ph. D.
Core Research for Evolutional Science and Technology (CREST)
Japan Science and Technology Corporation (JST)
Seika, Japan

N. Shirao, M. D., Ph. D. · Y. Okamoto, M. D., Ph. D. ·
G. Okada, M. D., Ph. D. · K. Ueda, Ph. D. ·
S. Yamawaki, M. D., Ph. D. (✉)
Dept. of Psychiatry and Neurosciences
Division of Frontier Medical Science
Programs for Biomedical Research
Graduate School of Biomedical Sciences
Hiroshima University
1-2-3 Kasumi, Minami-ku
Hiroshima, 734-8551, Japan
Tel.: +81-82/257-5207
Fax: +81-82/257-5209
E-Mail: yamawaki@hiroshima-u.ac.jp

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.

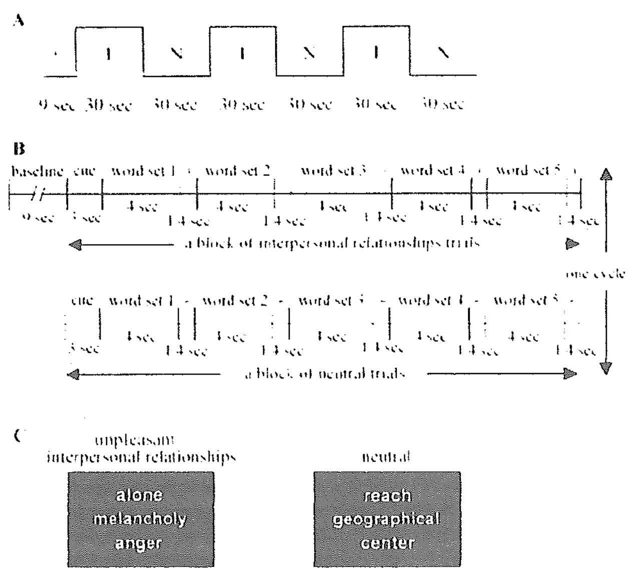

Fig. 1 The design of the task used in this study. **A** Overview of block-designed stimulus presentation paradigm for the tasks. Six alternating blocks of word sets of unpleasant words concerning interpersonal relationships (I) and neutral words (N) were successively presented. The total scan time of 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

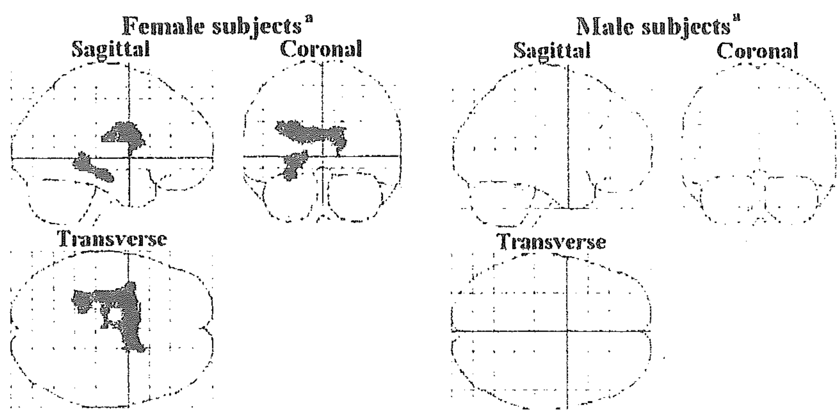

Fig. 2 Significant brain activation associated with unpleasant words concerning interpersonal relationships than to the neutral words among the female subjects. Three-dimensional "look-through" projections of statistical parametric maps of the brain regions are shown ([a] One-sample Student's t-test; 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-

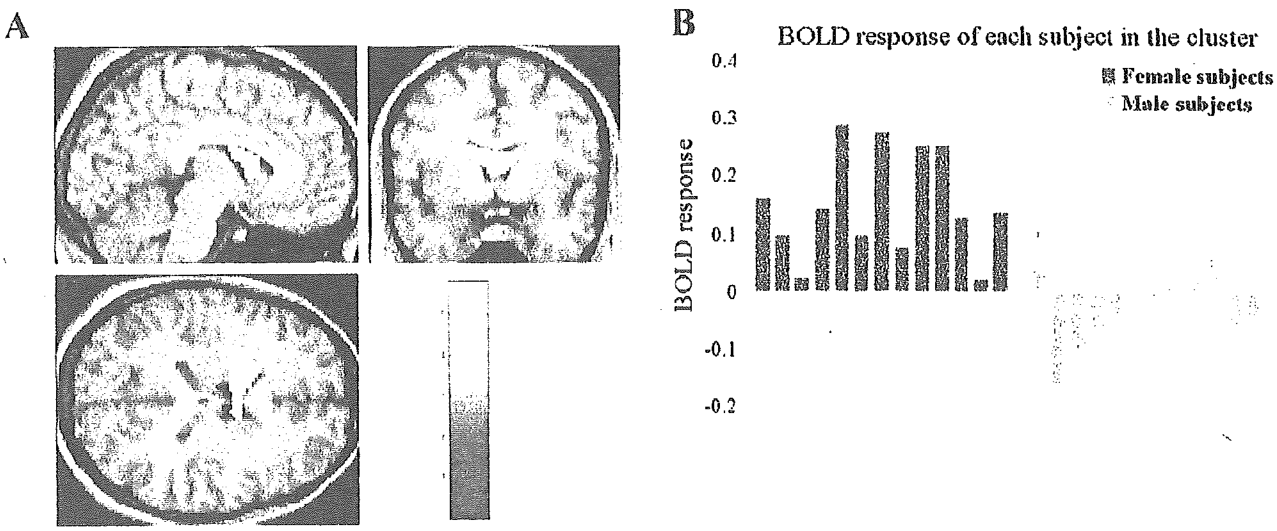

Fig. 3 Brain regions showing significantly greater activation in the female subjects than in the male subjects while performing the emotional decision task on unpleasant words concerning interpersonal relationships compared to neutral words. **A** Clusters of activation are overlaid onto a T1-weighted 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

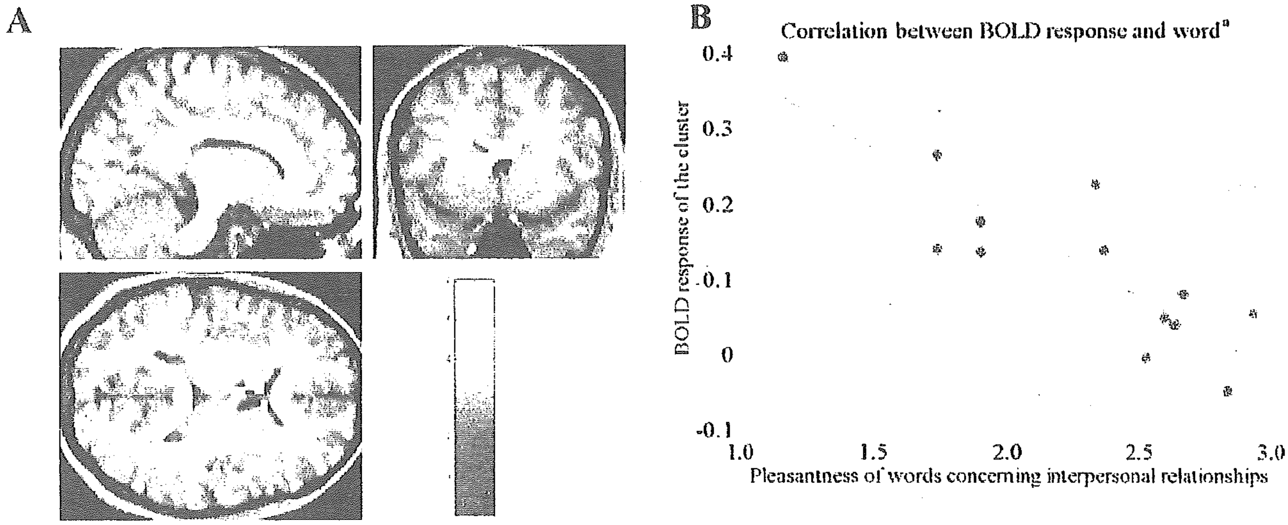

Fig. 4 Relationship between the degree of activation of brain areas and the average rating of pleasantness of words concerning interpersonal relationships among the 13 female subjects. **A** Clusters of activation are overlaid onto a T1-weighted anatomical MR image. The T-levels of activation are color-coded 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.

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Gender differences in brain activity generated by unpleasant word stimuli concerning body image: an fMRI study

NAOKO SHIRAO, YASUMASA OKAMOTO, TOMOYUKI MANTANI, YURI OKAMOTO and SHIGETO YAMAWAKI

Background We have previously reported that the temporomesial area, including the amygdala, is activated in women when processing unpleasant words concerning body image.

Aims To detect gender differences in brain activation during processing of these words.

Method Functional magnetic resonance imaging was used to investigate 13 men and 13 women during an emotional decision task consisting of unpleasant words concerning body image and neutral words.

Results The left medial prefrontal cortex and hippocampus were activated only among men, and the left amygdala was activated only among women during the task; activation in the apical prefrontal region was significantly greater in men than in women.

Conclusions Our data suggest that the prefrontal region is responsible for the gender differences in the processing of words concerning body image, and may also be responsible for gender differences in susceptibility to eating disorders.

Declaration of interest None. Funding detailed in Acknowledgement.

Eating disorders, which have been associated with concerns about body shape and size (American Psychiatric Association, 1994), are about 10 times more common in women than in men (Weissman & Olfson, 1995). A possible reason for this difference in susceptibility might be a gender difference in the neural processing of unpleasant information about body image. We previously reported that women showed amygdalar activation while processing unpleasant words concerning body image and perceived these words to be emotionally negative (Shirao *et al*, 2003*a*). The medial prefrontal cortex has connections to the amygdala, constituting an interaction zone between emotional and cognitive processing (Drevets & Raichle, 1998). In this study we compared the brain activation between men and women while processing these words. We predicted that the amygdala would be less activated and the medial prefrontal cortex more activated in men than in women during the emotional decision task.

METHOD

Study sample

An age-matched sample of 13 men (mean age 25.3 years, s.d.=2.8, range 21–30) and 13 women (mean age 25.2 years, s.d.=3.2, range 21–30) participated in this study (P=0.949 by two-tailed, two-sample Student's t test). Participants were recruited by community announcement and paid incentives equivalent to their transportation expenses. All of them were right-handed and were native Japanese speakers. Handedness was determined using the Edinburgh Handedness Inventory (Oldfield, 1971). According to self-report, participants had no history of psychiatric, neurological or other major medical illness, and had never been treated with a psychotropic medication. There was no significant difference in the average years of education between men and women: men 15.2 (s.d.=1.6) *v.* women 14.9 (s.d.=2.5); P=0.645 by two-tailed, two-sample Student's t-test. The average body mass index of the men was 22.4 kg/m^2 (s.d.=3.2, range 18.0–31.3) and that of the women was 21.5 kg/m^2 (s.d.=3.7, range 18.8–28.4); P=0.543 by two-tailed two-sample Student's t-test. The average of the total Eating Disorder Inventory – 2 (EDI–2; Garner, 1991) scores of men was 45.5 (s.d.=28.4, range 9–103) and that of women was 37.9 (s.d.=23.5, range 7–85); P=0.330 by two-tailed Wilcoxon single-rank test. The average score for the item 'body dissatisfaction' for the men was 7.43 (s.d.=5.45, range 2–19) and for the women was 11.31 (s.d.=7.00, range 0–22); P=0.330 by two-tailed Wilcoxon single-rank test. The study was conducted using a protocol approved by the ethics committee of Hiroshima University School of Medicine. All individuals provided written informed consent for participation in the study.

Emotional decision task

We used the emotional decision task developed by Tabert *et al* (2001), with some modifications. The words used in the task were selected from the database of Toglia & Battig (1978), which includes 2854 words that have been rated on several items such as familiarity and pleasantness, on a scale of 1 (very unfamiliar; very unpleasant) to 7 (very familiar; very pleasant), with 4 as the mid-point. For our study, 30 neutral words were selected from the database and translated into Japanese. We also selected 30 highly unpleasant words concerning body image, chosen from Japanese-language dictionaries and thesauri. The two groups of words did not significantly differ with regard to word length (mean length in Japanese letters: body image words 3.2, neutral words 3.1; P=0.575 by two-tailed, two-sample Student's t-test). Our previous validation study comparing women who had eating disorders with a control group of healthy women showed that there was no significant difference in familiarity between the two categories of words (eating disorder group mean familiarity score: body image words 4.2; neutral words 4.1, P=0.727; control group mean familiarity score: body image words 3.9, neutral words 4.1, P=0.218, by two-tailed Wilcoxon single-rank test) and there was no significant difference in the familiarity ratings of words concerning body image between women with eating disorders and the control group (P=0.365 by two-tailed Wilcoxon single-rank test), whereas there were significant differences in pleasantness between the two categories of words (mean pleasantness score in the eating disorder group: body image words 2.4, neutral words 3.9, P=0.0002; mean pleasantness score in the control group: body image words 3.0, neutral words 4.0, P=0.0001, by two-tailed Wilcoxon single-rank test) and there were significant differences in the ratings of pleasantness between the eating disorders group and the control group (P=0.030 by two-tailed Wilcoxon single-rank test) (Shirao *et al*, 2003*b*). Both lists of words contained nouns, verbs, adjectives and adverbs.

The selected words were used to generate sets of unpleasant words concerning body image and sets of neutral words. Each word set comprised a unique combination of three words. The word sets were presented in six alternating blocks of two conditions (the task condition and the control condition) in three cycles (Fig. 1). During the task condition unpleasant word sets were presented, and during the control condition neutral word sets were presented. Each block began with a 3 s cue identifying the condition by displaying the word 'task' or 'control'. Five word sets were presented in each block. Each word set was shown for 4 s with a 1.4 s interstimulus interval (Fig. 1). The blood oxygen level-dependent (BOLD) response was recorded during three blocks of unpleasant words and three blocks of neutral words. During each interstimulus interval, a fixation cross placed centrally on the screen replaced the word set. Baseline functional magnetic resonance images were obtained during a 9 s period prior to the first block of trials, during which the individual viewed a centrally placed fixation cross. During each trial, the word set was projected to the centre of the person's field of view by a Super Video Graphics adapter 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, USA) and the word sets were presented in a randomised order. Immediately before functional magnetic resonance imaging (fMRI) scanning was begun, each participant was given ten practice trials (five unpleasant word sets and five neutral word sets). The words presented in the practice trials did not overlap with the experimental words.

Participants were instructed to select the most unpleasant word from each set of unpleasant words based on their personal knowledge and experience, and for each set of neutral words, participants were instructed to select the word that they thought was the most neutral; they indicated their choice by pressing one of three buttons on a response pad in the MRI scanner.

Image acquisition and processing

The MRI scanner used was a Magnex Eclipse 1.5 T Power Drive 250 (Shimadzu Medical Systems, Kyoto, Japan). A time-course series of 63 volumes was acquired with T_2*-weighted, gradient echo, echo planar imaging (EPI) sequences. Each volume consisted of 28 slices, each 4.0 mm thick with no gap, encompassing the entire brain. The interval between two successive acquisitions of the same image (time to repetition, TR) was 3000 ms, the time to echo (TE) was 55 ms and the flip angle was 90°. The field of view was 256 mm and the matrix size 64 × 64, giving voxel dimensions of 4.0 mm × 4.0 mm × 4.0 mm. After fMRI scanning, structural scans were acquired using a T_1-weighted gradient echo pulse sequence (TR 12 ms, TE 4.5 ms, flip angle 20°, field of view 256 mm, voxel dimensions 1.0 mm × 1.0 mm × 1.0 mm), to facilitate localisation and co-registration of the functional data.

Image processing and statistical analysis were performed using Statistical Parametric Mapping (SPM) 99 software (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Inc., Natick, MA, USA). The first two volumes of the fMRI run (pre-task period) were discarded because the magnetisation 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 T_1 anatomical images were co-registered to the first functional images in each individual and aligned to a standard stereotaxic space, using the Montreal Neurological Institute (MNI) T_1 template in SPM99. The calculated non-linear transformation was applied to all functional images for spatial normalisation. Finally, the fMRI images were smoothed with a 12 mm full-width, half-maximum Gaussian filter.

Using group analysis according to a random effect model that allowed inference to the general population (Friston *et al*, 1999), we first identified brain regions that showed a significantly greater response to unpleasant word sets in comparison with the response to neutral word sets among

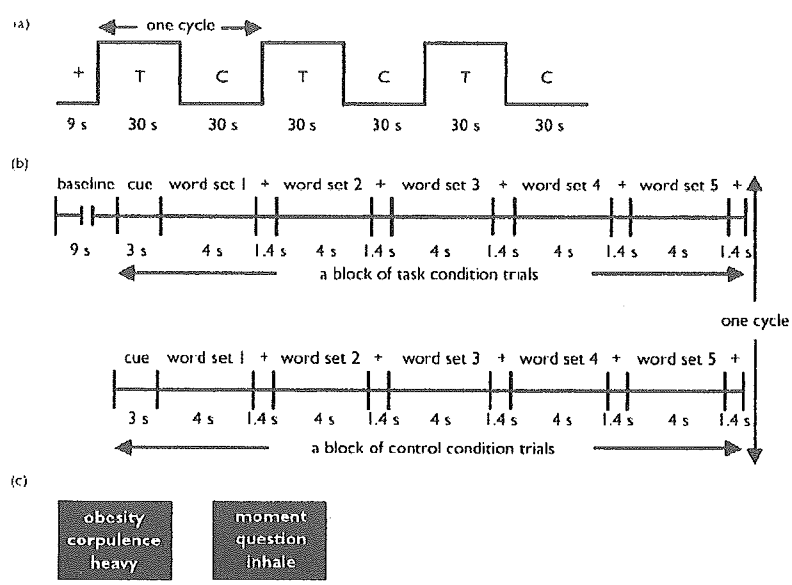

Fig. 1 Design of the study task. (a) Six alternating blocks of task condition (T) trials and control condition (C) trials were presented successively; the total scan time was 189 s (3 min and 9 s), yielding 63 images of 28 axial slices (1764 images). (b) Blocks of task condition and control condition trials were preceded by a baseline imaging period. Each block began with a cue ('task' or 'control'). The participant selected the word judged to be the most unpleasant or most neutral in each word set, by pressing one of three buttons. (C) Translations of typical word sets presented in this study (left-hand block, task condition; right-hand block, control condition).

male and among female participants, as brain areas related to the cognition of unpleasant word stimuli concerning body image in men and women, respectively. We then took the data of 13 of the 15 women who had participated in our previous study (Shirao *et al*, 2003*a*) and directly compared the activation of the entire brain in the male and female sub-samples using the two-sample Student's *t*-test. The resulting set of voxel values for each contrast constituted an SPM{t} map. The SPM{t} maps were then interpreted by referring to the probabilistic behaviour of Gaussian random fields. The data were given an initial threshold at an uncorrected $P<0.001$ at the voxel level, and regions about which we had an *a priori* hypothesis were reported at this threshold (Elliott *et al*, 2000). For regions about which there was no clear hypothesis, a more stringent threshold of $P<0.05$ corrected at the cluster level of multiple comparison was used. The *x*, *y* and *z* coordinates provided by SPM, which were in MNI brain space, were converted to the *x*, *y* and *z* coordinates in Talairach & Tournoux's (TT) brain space (Talairach & Tournoux, 1988) using the following formulae:

(a) $x_{TT}=x_{MNI}\times 0.88-0.8$;

(b) $y_{TT}=y_{MNI}\times 0.97-3.32$;

(c) $z_{TT}=y_{MNI}\times 0.05+z_{MNI}\times 0.88-0.44$.

Labels for brain activation foci were obtained in Talairach coordinates using the Talairach Daemon software (Research Imaging Center, University of Texas, TX, USA), which provides accuracy similar to that of neuroanatomical experts (Lancaster *et al*, 2000). The labelling of areas given by this software was then confirmed by comparison with activation maps overlaid on MNI-normalised structural images.

Evaluation of pleasantness and familiarity of the word stimuli

Each participant was asked to rate the pleasantness and familiarity of all the words presented in the tasks on a scale from 1 (very unfamiliar; very unpleasant) to 7 (very familiar; very pleasant), immediately after scanning. For this rating procedure the list of words was presented in randomised order in a table format.

RESULTS

Rating of words

The ratings of familiarity with the two categories of words did not significantly differ among men (mean familiarity score: unpleasant words 3.8, neutral words 4.4, $P=0.054$ by two-tailed Wilcoxon single-rank test) or women (mean familiarity score: unpleasant words 4.3, neutral words 4.3, $P=0.456$). However, all participants rated the unpleasant words concerning body image as significantly more unpleasant than the neutral words (mean pleasantness score: unpleasant words 3.1, neutral words 4.1, $P=0.007$ in men; unpleasant words 2.7, neutral words 4.1, $P=0.002$ in women). Neither the ratings of pleasantness nor the ratings of familiarity in each word category significantly differed between the male and female groups.

Brain activation

In men there was significantly greater activation of the left hippocampus, left superior temporal gyrus, left fusiform gyrus and left medial frontal gyrus when the emotional decision task involved unpleasant words compared with neutral words, whereas the women showed significantly greater activity of the left parahippocampal gyrus including amygdala, left thalamus and right caudate body in the same comparison (Table 1, Fig. 2).

The two-sample Student's *t*-test revealed that there was a significantly higher BOLD response in the left apical prefrontal region in men than in women during the unpleasant word task compared with neutral word task (Table 1, Fig. 3). No brain area showed significantly higher activation in women than in men during any of the tasks.

Correlation between psychological data and brain activation

Among the 13 women participants, activation in the left apical prefrontal area, which was significantly lower than that in men during the unpleasant words task, was negatively correlated with the total EDI–2 score (Spearman's rank-order correlation analysis: correlational coefficient -0.699, $P=0.008$). There was no correlation between any brain area showing significant BOLD response and the EDI–2 scores or the pleasantness rating of the unpleasant words.

DISCUSSION

We used the emotional decision task to examine the brain areas engaged in the perception of unpleasant words concerning body image and to compare the patterns of brain activation in men and women. Our results showed that the left medial part of the frontal gyrus, the left limbic area excluding the amygdala, the left superior temporal gyrus and the left fusiform gyrus play an important part in processing

Table 1 Relative increases in brain activity associated with unpleasant words concerning body image (task) and neutral words (control)

	Cluster	BA	*t* score	Coordinates[1]		
				x	*y*	*z*
Men (*n*=13)						
Left hippocampus	696*		9.59	−32	−13	−13
Left superior temporal gyrus		21	6.54	−50	−7	−8
Left fusiform gyrus		20	6.35	−43	−25	−17
Left medial frontal gyrus	359*	9	5.71	−4	53	9
Left superior frontal gyrus		10	5.34	−15	51	18
Women (*n*=13)						
Left parahippocampal gyrus	404*	37	7.08	−17	−13	−15
Left thalamus	485*		6.08	−3	−11	11
Right caudate body			4.65	10	1	5
Men > women						
Left apical prefrontal region	144	9	4.36	−15	49	20

BA, Brodmann area.
1. Stereotaxic coordinates were derived from Talairach & Tournoux (1988) 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 comissural line (positive=superior).
*Areas exceeding the extent threshold of $P<0.05$ corrected at the cluster level, all other areas exceeding the height threshold of $P<0.001$ uncorrected at the cluster level and belonging to a cluster of activation with an extent of at least 140 voxels are displayed.

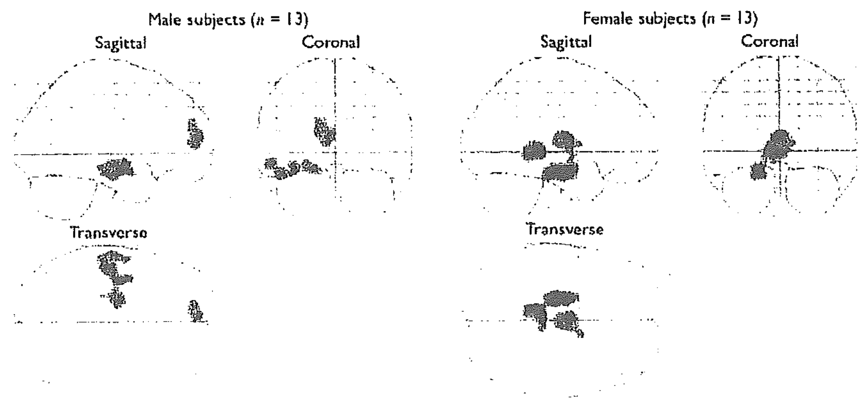

Fig. 2 Brain areas showing significantly greater activation during the task condition compared with the control condition. Three-dimensional 'look-through' projections of statistical parametric maps of the brain regions are shown (one-sample Student's *t*-test; corrected $P < 0.05$ at the cluster level; n=13; d.f.=12).

unpleasant words concerning body image in men.

Lack of amygdalar activation in men

Consistent with our hypothesis, the amygdala did not show significant activation among men; however, the gender difference of the BOLD response in the amygdala was not significant by two-sample Student's *t*-test.

The amygdala has been suggested by many studies to be strongly associated with stimuli signalling threat. Human lesion and imaging studies consistently indicate that the amygdala is concerned in fear conditioning (Morris *et al*, 1998), in the recognition of fearful facial expressions (Adolphs, 1999) and in the evocation of fearful emotional responses from direct stimulation (Halgren *et al*, 1978). The amygdala is also considered to be important in the detection of environmental threat (Scott *et al*, 1997), including verbal stimuli (Isenberg *et al*, 1999). Therefore, the lack of significant activation in the amygdala among men suggests that men may not process unpleasant words concerning body image as fearful information, whereas women seem to do so.

Medial prefrontal cortex and emotional processing

The significant activation in the medial part of the frontal gyrus – Brodmann areas (BAs) 9 and 10; medial prefrontal cortex – was only detected in men, and there was a significantly higher BOLD response in men than in women in the left apical prefrontal region (BA 9) when performing the unpleasant word task compared with the neutral word task by two-sample Student's *t*-test. These results were consistent with our hypothesis. Many previous studies have suggested that the medial prefrontal cortex might have a role generally in emotional processing. It is reported that visual stimuli that evoke emotions, such as films or pictures, activated the medial prefrontal cortex, and that recall of various emotions such as happiness, sadness and disgust, and a mixture of these emotions, all separately engaged this brain region (Lane *et al*, 1997; Reiman *et al*, 1997). Several more recent studies suggest that when people turn their attention inwards to assess self-relevant attributes or emotional awareness, activity increases in the medial prefrontal cortex (Johnson *et al*, 2002; Zysset *et al*, 2002). The medial prefrontal cortex has connections to limbic structures, including the amygdala, constituting an interaction zone between emotional processing and cognitive processing (Drevets & Raichle, 1998), and this region may have a role in modulating the emotional response in the amygdala and other limbic structures. Limbic structures, including the amygdala, are likely to respond to emotional stimuli at a sensory or perceptual level (Reiman *et al*, 1997), whereas the medial prefrontal cortex may be involved in the cognitive aspects of emotional processing, such as attention to emotion, appraisal or identification of emotion (Drevets & Raichle, 1998). From this viewpoint, the gender differences detected in our study may demonstrate differences of cognitive pattern in men and women. Our results suggest the possibility that men processed the emotional decision task including words concerning body image more cognitively rather than emotionally, and activation in the medial prefrontal cortex was prominent; on the other hand, women processed this task more emotionally rather than cognitively, and the medial prefrontal cortex did not exhibit any significant activation. Both men and women perceived the unpleasantness of the words concerning body image to the same degree, according to their subjective ratings, but the fMRI data suggest that their processes are different: women are likely to use more intuitive processing whereas men use more rational processing. This discrepancy between the genders in cognitive style related to body image may contribute to the large gender difference in susceptibility to eating disorders.

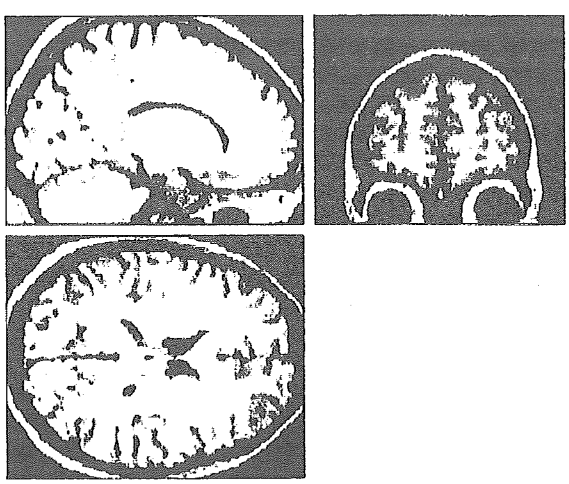

Fig. 3 Brain regions showing significantly greater activation in men than in women during the task condition of the emotional decision task compared with the control condition. Clusters of activation are overlaid onto a T_1-weighted anatomical magnetic resonance image. The white spots show areas of high activation. Two-sample Student's t-test; uncorrected $P < 0.001$ in height; n=26 (13 men, 13 women); d.f.=24.

Another possible explanation of the different patterns of activation in the medial prefrontal cortex between men and women may be the difference in men's familiarity with the unpleasant word set compared with the neutral words. Although the ratings of familiarity were not different between men and women (P=0.133 by Mann–Whitney U test), there was a trend for male participants to be less familiar with the unpleasant words concerning body image than with the neutral words (P=0.054 by two-tailed Wilcoxon single-rank test). When processing unfamiliar words concerning body image, men might turn more attention inwards, and subsequently the BOLD response in the medial prefrontal cortex was higher than while processing neutral words.

Among women, correlational analysis revealed that the BOLD response in the left apical prefrontal region (BA 9), which was significantly lower in women than in men, was negatively correlated with total EDI–2 scores; in other words women with higher EDI–2 scores exhibited lower activity in this brain area. These results suggest the possibility that the apical prefrontal region might be involved in the pathophysiology of eating disorders.

Comparison with other neuroimaging studies

To our knowledge, two fMRI studies concerning body image distortion have investigated the effects of pictorial body image stimuli in women with anorexia nervosa and healthy controls (Seeger *et al*, 2002; Wagner *et al*, 2003). One study reported that patients with anorexia nervosa showed activation in the right amygdala, right fusiform gyrus and brain-stem associated with stimulation with their own body image whereas healthy controls showed activation only in the fusiform gyrus (Seeger *et al*, 2002), and the other reported that patients with anorexia nervosa showed greater activation in the prefrontal cortex and the inferior parietal lobule than did controls (Wagner *et al*, 2003). The latter authors explain the discrepancy between these results as a consequence of the design of the task. Many differences in the experimental conditions between these studies and ours make it difficult to compare the brain activation data, but a possible explanation of the discrepancy between the study by Wagner *et al* (2003) and our study is the age of the participants: those in the former study were adolescents (approximately 15 years old), whereas we recruited young adults (approximately 25 years old). An fMRI study which investigated the brain activation of adult and adolescent men and women while processing emotional facial expressions reported that the adult men and adolescents (both boys and girls) showed significant activation in the bilateral orbitofrontal cortex and anterior cingulate cortex in response to an angry face, whereas the adult women showed significant activation in the left amygdala in addition to these brain areas (McClure *et al*, 2004). These results suggest that the patterns of neural responses to emotional stimuli may be different in adults and adolescents.

A positron emission tomography study of gender differences in brain activation patterns during recognition of emotional facial expressions revealed that greater amygdalar activation was observed in women and greater medial frontal activation was observed in men (Hall *et al*, 2004); these authors suggest that men might take a more analytic approach and might regulate their emotional reaction to the stimuli more than women. Although the categories of stimuli are different, these results support our findings.

Study limitations

Our study has some limitations. First, we did not administer a structured interview when selecting the participants; however, they had no psychiatric or neurological illness at the time of their participation, although we cannot rule out its occurrence in the future. Second, participants were asked to rate only the unpleasantness and familiarity of the words used. If we had also asked about the fearfulness induced by the stimuli, we might have found gender differences in subjective rating and the results with brain image data would have been more clear-cut. Last, although our data

CLINICAL IMPLICATIONS

- Gender differences in brain activation suggest differences between men and women in the style of cognition toward unpleasant stimuli concerning body image.
- This discrepancy in cognitive style may have relevance to the large gender difference in susceptibility to eating disorders.
- The medial prefrontal cortex may be the brain area linked to the pathophysiology of eating disorder.

LIMITATIONS

- We did not use a structured interview when selecting participants.
- We asked the participants to rate only pleasantness and familiarity of the word stimuli and we could find no clear relationship between brain activation and the subjective rating of the words concerning body image.
- It is unclear whether the patterns of activation in the prefrontal area were specific to the stimuli concerning body image.

NAOKO SHIRAO, MD, PhD, YASUMASA OKAMOTO, MD, PhD, TOMOYUKI MANTANI, MD, Department of Psychiatry and Neurosciences, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, and Core Research for Evolutional Science and Technology (CREST), Japan Science and Technology Corporation, Seika; YURI OKAMOTO, MD, PhD, Hiroshima University Health Service Center, Hiroshima; SHIGETO YAMAWAKI, MD, PhD, Department of Psychiatry and Neurosciences, Graduate School of Biomedical Sciences, Hiroshima University, and CREST, Seika, Japan

Correspondence: Dr Shigeto Yamawaki, Department of Psychiatry and Neurosciences, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. Tel: +81 82 257 5207; fax: +81 82 257 5209; e-mail: yamawaki@hiroshima-u.ac.jp

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suggest that there is differential activation of the brains of men and women when processing unpleasant words concerning body image, we cannot conclude whether these results are specific to unpleasant stimuli concerning body image or would apply to a wide range of unpleasant stimuli. Among women, a lower BOLD response in the prefrontal region compared with men while processing unpleasant words concerning body image exhibited a negative correlation with the total EDI–2 score, but it is unclear whether this brain region is the focal area responsible for susceptibility to eating disorders.

In conclusion, our study revealed that the paralimbic area including the amygdala was activated only in women and that the left medial prefrontal cortex was activated only in men while performing the emotional decision task with unpleasant words concerning body image. These results suggest that gender differences in brain activation might explain the differences in the style of cognition towards unpleasant stimuli concerning body image. Further studies comparing people who have eating disorders with healthy controls and which include general unpleasant word stimuli to contrast with words specific to body image are needed to elucidate the neural substrate responsible for the onset of eating disorders.

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Distorted Images of One's Own Body Activates the Prefrontal Cortex and Limbic/Paralimbic System in Young Women: A Functional Magnetic Resonance Imaging Study

Mitsuhaya Kurosaki, Naoko Shirao, Hidehisa Yamashita, Yasumasa Okamoto, and Shigeto Yamawaki

Background: *Our aim was to study the gender differences in brain activation upon viewing visual stimuli of distorted images of one's own body.*

Methods: *We performed functional magnetic resonance imaging on 11 healthy young men and 11 healthy young women using the "body image tasks" which consisted of fat, real, and thin shapes of the subject's own body.*

Results: *Comparison of the brain activation upon performing the fat-image task versus real-image task showed significant activation of the bilateral prefrontal cortex and left parahippocampal area including the amygdala in the women, and significant activation of the right occipital lobe including the primary and secondary visual cortices in the men. Comparison of brain activation upon performing the thin-image task versus real-image task showed significant activation of the left prefrontal cortex, left limbic area including the cingulate gyrus and paralimbic area including the insula in women, and significant activation of the occipital lobe including the left primary and secondary visual cortices in men.*

Conclusions: *These results suggest that women tend to perceive distorted images of their own bodies by complex cognitive processing of emotion, whereas men tend to perceive distorted images of their own bodies by object visual processing and spatial visual processing.*

Key Words: Body image, functional MRI, prefrontal cortex, amygdala, gender differences, eating disorders

Young women not only are more concerned about body shape and size, but also more harshly judge their own body shape and size than men. Eating disorders (EDs) are one category of psychiatric illness having a larger incidence among women than among men; women are approximately 10 times more likely to experience a lifetime episode of ED than men (Weissman et al 1995). One possible cause of this gender difference in susceptibility to ED may be that the cognitive processing of visual information about body image differs between men and women, and women are more sensitive to information about body image than men.

Several functional magnetic resonance imaging (fMRI) studies on EDs have investigated brain activation upon presentation of images of foods or body shape. In fMRI studies, women with an ED showed an activation of the limbic/paralimbic system and medial prefrontal cortex (PFC) upon viewing images of high calorie foods (Ellison et al 1998; Uher et al 2003, 2004). Functional MRI studies in which female subjects were shown their own distorted images indicated that women with ED showed activation of the limbic system, PFC and the parietal lobe (Seeger et al 2002; Wagner et al 2003). A few neuroimaging studies specifically investigated gender differences in brain activation. Shirao et al (2005) reported that in an emotional decision task involving unpleasant word stimuli about body image, men showed increased PFC activation whereas women showed only amygdala activation.

However, there has been no study on gender differences in the pattern of brain activation upon viewing distorted images of one's own body. We hypothesized that the differences in brain activation while processing body image stimuli between the two genders involve a discrepancy in activation of the limbic area including the amygdala, paralimbic area and prefrontal cortex. We used fMRI to investigate the brain activity of young men and young women while they were engaged in a "body image task" using distorted images and real images of the subject's own body.

Methods and Materials

Subjects

Eleven women and 11 men participated in this study. All of the subjects were right-handed as determined by the Edinburgh Handedness Inventory (Oldfield 1971). Subjects were asked to fill out a written questionnaire regarding his/her own medical history. According to the self-reported responses, the subjects had no history of psychiatric, neurological, or other medical illness, and had never been treated with a psychotropic medication. We limited the female subjects in this study to women between the ages of 20 and 30 years, since young women even in the nonclinical population are often sensitive to body image and since ED commonly occurs in young women. To eliminate age-related effects, the subjects of the two genders were age-matched. To minimize the effect of the body shape proportion of the subjects in the two groups, we matched the body mass index (BMI) of the male and female subjects. Also, to minimize the effects of eating behavior, body image distortion and psychological features of the subjects in the two groups, we matched the score of the total Eating Disorder Inventory-2 (EDI-2) of the male and female subjects. The Clinical characteristics of the subjects

From the Department of Psychiatry and Neurosciences (MK, HY, YO, SY), Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University; Department of Child Psychiatry (NS), Hiroshima City Funairi Hospital, Hiroshima; Core Research for Evolutional Science and Technology (MK, NS, HY, YO, SY), Japan Science and Technology Corporation, Seika, Japan.

Address reprint requests to Shigeto Yamawaki, M.D., Ph.D., Department of Psychiatry and Neurosciences, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan; E-mail: yamawaki@hiroshima-u.ac.jp.

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Table 1. Characteristics of the Subjects

	Women (n = 11)	Men (n = 11)	t-value	p-value
Age (y)	24.5 ± 3.4	24.8 ± 3.1	−.194	.8478
Range	21–30	20–30		
BMI (kg/m^2)	19.9 ± 1.3	20.8 ± 1.4	−1.533	.1409
Range	18.1–22.8	18.5–23.8		
EDI-2	45.5 ± 21.4	35.8 ± 14.5	1.247	.2268
Range	21–89	8–60		

p-values were obtained with the unpaired t-test. EDI-2, Eating Disorder Inventory-2; BMI, body mass index.

are summarized in Table 1. The scores on the subscales of EDI-2 are summarized in Table 2. The protocol of this study was approved by the Ethics Committee of Hiroshima University School of Medicine. After a complete description of the study was provided to the subjects, written informed consent was obtained.

Paradigm

The aim of this study was to investigate the neuronal processing of visual stimulation of fat or thin body image. We developed and created the paradigm, which consisted of a pair of distorted body image and real image, so that the subjects would recognize their own body image on comparison of two images. We thought that it was possible to elucidate the cognitive and emotional processing of visual stimulation of fat or thin body image by analyzing fMRI data on performing our paradigm.

Before the fMRI examination, we took digital photographs of each subject's whole body against a monotonous, light-colored background. The subject wore a white T-shirt and blue jeans, and was in the standing position. We changed the width of the image of the individual from −25 to +25% of the width in the original image by using Paint Shop Pro Version 8.02 (Jasc Software, Inc., Eden Prairie, Minnesota), to obtain ten distorted images with different degrees of thinness or fatness. For each subject, we used the following images of the subject: undistorted original image, fat-body images (width at +5, +10, +15, +20, or +25% of the width of the individual in the original image), undistorted original image with a red cross on the body, and thin-body images (width at −5, −10, −15, −20, or −25% of the width of the individual in the original image).

Using these distorted images and original images, we created image sets which consisted of three types of pairs of images: 1) pairs of a fat-body-image (gaining weight image) and real-image (undistorted original image); 2) pairs of the real-image and the real-image with a red cross; and 3) pairs of a thin-body-image (losing weight image) and real-image (Figure 1A). We used the block-designed fMRI paradigm which consisted of three different blocks of tasks: fat-image task, real-image task, thin-image task (Figure 1B). Each block began with a 3-sec cue indicating whether the block consisted of the fat-image task, real-image task, or thin-image task. Five image sets were presented in each block. Each image set was shown for 5 sec with a 1-sec inter-stimulus-interval (ISI). Three different blocks were presented in one cycle. Our paradigm consisted of three cycles (Figure 1C). The blood oxygen level-dependent (BOLD) response was recorded during the three blocks of fat-image task, real-image task, or thin-image task. During each ISI, a fixation-cross placed centrally on the screen replaced the image set. Baseline functional magnetic resonance images were obtained during a 9-sec interval prior to the first block of trials, during which the subject viewed a centrally placed fixation-cross. During each trial, the image set was projected to the center of the subject's field of view via a super video graphics array (SVGA) computer-controlled projection system. The timing of presentation of image sets was controlled by Presentation Software Version .76 (Neurobehavioral Systems, Inc., San Francisco, California) and the image sets were presented in random order.

Immediately before fMRI scanning was begun, the subject was given 2 practice trials (1 fat-image task and 1 real-image task). In the practice trials, sample image sets of a girl were presented instead of pictures of the subject (Figure 1A). The subject was given instructions before the practice trials. In the fat-image tasks and thin-image tasks, the subject was instructed to select the more unpleasant image from each image set. In the real-image tasks, the subject was instructed to select the image with the red cross on the body. The subject was asked to respond by pressing one of two buttons on a response pad in the MRI scanner.

MRI Acquisition and Processing

Functional MRI of the brain was performed with a MAGNEX ECLIPSE 1.5T Power Drive 250 (Shimadzu Medical Systems, Kyoto, Japan). A time-course series of 102 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 msec, the echo time (TE) was 55 msec, and the flip angle was 90°. The field of view was 256 mm

Table 2. Scores of the Subscales of EDI-2

	Total	Drive for Thinness	Body Dissatisfaction	Bulimia	Ineffectiveness	Perfectionism
Women	45.5	4.09	9.18	1.82	5.09	.45
Men	35.8	1.27	4.91	.73	4.73	3.73

	Interpersonal Distrust	Interoceptive Awareness	Maturity Fears	Asceticism	Impulse Regulation	Social Insecurity
Women	4.18	3.91	2.45	3.18	2.73	3.55
Men	4.82	1.45	4.00	4.64	.82	5.82

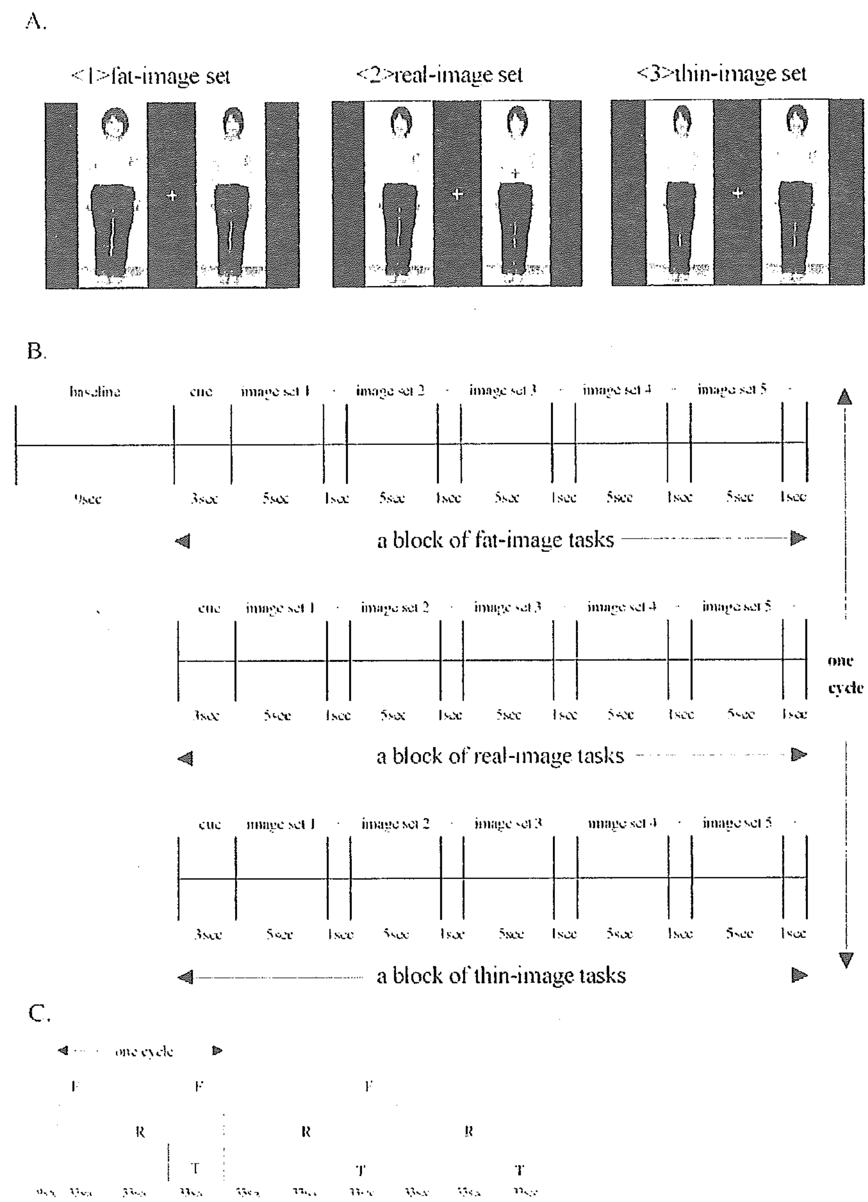

Figure 1. The design of the paradigm used in this study. **(A)** Sample image sets of the subject's own body that were presented to the subject. **(B)** Blocks of fat-image, real-image and thin-image tasks were preceded by baseline. Each block began with a cue indicating "fat," "real" or "thin." The subject was instructed to select the more unpleasant image from each image set for the fat-image task or thin-image task, and to select the image with a red cross on the body for the real-image task, by pressing one of two buttons. **(C)** Overview of block-designed stimulus presentation paradigm for the tasks. Nine alternating blocks of fat-body image (F), real-body image (R), and thin-body image (T) tasks were presented successively. The total scan time was 306 sec (5 min and 6 sec), while yielding 102 images of 28 axial slices (2856 images).

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 msec; TE = 4.5 msec; Flip angle = 20°; field of view (FOV) = 256 mm; voxel dimensions of 1.0 × 1.0 × 1.0 mm), and they facilitated localization and coregistration of the functional data.

Data Analysis

Image processing and statistical analysis were performed using Statistical Parametric Mapping 99 (SPM99) software (Wellcome Department of Cognitive Neurology, London, United Kingdom) implemented in Matlab (Mathworks, Inc., Natick, Massachusetts). The first two volumes of the fMRI run (pre-task period) were discarded because the magnetization was unsteady, and the remaining 100 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 image 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 (Friston et al 1999), we first identified brain regions that showed a significant response to image sets containing a distorted body image in comparison with the response to image sets containing two real body images among the female subjects and among the male subjects, as brain areas related to the cognition of body image stimuli in women and men, 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 {T} map. The