Neural Correlates of Alexithymia in Response to Emotional Stimuli: A Study of Anorexia Nervosa Patients

Yoshie MIYAKE\textsuperscript{1)}, Yasumasa OKAMOTO\textsuperscript{1}), Keiichi ONODA\textsuperscript{1)}, Naoko SHIRAO\textsuperscript{2)}, Tomoyuki MANTAN\textsuperscript{1)} and Shigeto YAMAWAKI*\textsuperscript{1,*)

1) Department of Psychiatry and Neurosciences, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan
2) Hiroshima Prefectural Mental Health Welfare Center, Hiroshima, Japan

ABSTRACT

Individuals with alexithymia are typically unable to identify, understand, or describe their own emotions. Patients with anorexia nervosa (AN) have been shown to have high levels of alexithymia, and the latter trait may play an important role over the course of AN. However, relatively little is known about the underlying neurobiological relationships between alexithymia and AN. The aim of this study was to investigate the relationship between alexithymia level and brain activation in patients with AN. Thirty female patients participated in this study. Alexithymia was measured using the 20-item Toronto Alexithymia Scale. Functional magnetic resonance imaging was used to identify the brain regions that display abnormal hemodynamic activity while patients with AN were engaged in an emotional decision-making task. There was significant activation in the amygdala during the task, but not in the posterior and anterior cingulate cortices (PCC, ACC). However, PCC and ACC activation did vary as a function of alexithymia level. These results suggest that alexithymia in AN patients is associated with a deficit in the cognitive evaluation of negative emotions concerning body image. Alexithymia might play a crucial role in the emotional processing impairments that are often observed in AN patients, and this trait might ultimately help to better account for the psychopathological mechanism that underlies AN.

Key words: Alexithymia, Anorexia nervosa, Functional MRI

Anorexia nervosa (AN) is characterized not only by aberrant patterns of weight regulation and eating behavior, including such symptoms as extreme restriction of food intake or binge eating, but also by a disturbance in attitudes toward weight and body conformation, as well as the perception of body shape\textsuperscript{51}. AN is an important cause of physical and psychosocial morbidity in young women\textsuperscript{16}.

Several studies have reported high levels of alexithymia in patients with AN\textsuperscript{6,7,10,11,13,44,50}. Alexithymia is a multifaceted personality construct, which collectively represents a deficit in the cognitive processing of affect. Alexithymia appears to be one factor that predisposes patients to several physical and psychiatric illnesses\textsuperscript{49}. The salient features of this construct are as follows: 1) difficulty identifying and describing subjective feelings; 2) difficulty distinguishing between feelings and the bodily sensations that are associated with emotional arousal; 3) constricted imaginal capacities; and 4) an externally oriented cognitive style\textsuperscript{36}. Taylor et al stated in their review\textsuperscript{48} that alexithymia is a general deficit in emotional regulation that actually reflects three more specific kinds of deficit: 1) deficits in the cognitive–experiential component of the emotional response system; 2) deficits in the interpersonal regulation of emotions; and 3) constricted imaginal capacities. There are several reasons to believe that this construct could play a major role in the psychiatric course of AN patients, who appear to suffer from significant deficits in emotion regulation. Lack of insight and the externally oriented thinking style of many alexithymic individuals may interfere with their capacity to benefit from psychotherapeutic interventions. Bruch has suggested that

*Corresponding author: 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.
Phone: +81-82-257-5205, Fax: +81-82-257-5209 E-mail: yamawaki@hiroshima-u.ac.jp
the difficulties in distinguishing and describing feelings are main features of AN, and are related to a sense of general inadequacy and/or feelings of a lack of control over one's life [6–9].

Recently, brain imaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been used to identify the specific brain areas that might underlie abnormal functioning, in both AN patients and individuals with high levels of alexithymia. In AN patients, the amygdala is activated when the patients view pictures of high-calorie drinks or morphed images of their own bodies [15,45]. A previous PET study reported that AN patients showed hypometabolism in the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC) and dorsolateral prefrontal cortex compared with controls [34]. However, AN is a very complex diagnostic entity, and despite considerable scientific research, the functional brain system abnormalities that might underlie the emotional impairment observed in AN remain elusive and poorly understood. Numerous studies have found that alexithymia may be associated with a higher level cognitive deficit in the estimation of emotional inputs—in which the ACC plays a crucial role—rather than a lack of neuronal response in structures that underlie lower level processing of emotional stimuli [16,20]. These studies suggest that the limbic structure of alexithymic and non-alexithymic individuals do not differ, and that impaired ACC functioning might instead be uniquely associated with alexithymia. Moreover, the medial prefrontal cortex (MPFC), adjacent to the ACC, has also been activated in numerous neuroimaging studies of emotion [41], and it has been reported that this structure is also impaired in alexithymic subjects [5]. Finally, alexithymia also appears to be associated with PCC dysfunction, at least during the performance of various mental imagery tasks [1,31]. Lane et al stressed that the core feature of alexithymia is a deficit in the conscious awareness of emotions (e.g., differentiating between emotions, symbolizing emotions, and adequately appreciating the complex nature of emotional experiences) [28]. Thus, alexithymia refers to impairments in both affective and cognitive processing. However, relatively little is known about the brain mechanisms by which this trait may predispose individuals to AN.

The purpose of the present study was to explore whether AN patients with alexithymia have deficits in the cognitive evaluation of negative emotions concerning body image, and if so, at what level emotional processing is impaired. We therefore examined the relationship between alexithymia levels and brain activation while AN patients performed an emotional decision-making task. We first used fMRI to examine brain activation during the processing of both unpleasant words concerning body image and neutral words. A regression analysis was then performed to clarify the relationships between brain activation and scores on the 20-item Toronto Alexithymia Scale (TAS-20). We hypothesized that the degree of ACC and PCC activation during emotional processing would vary with the level of alexithymia.

**MATERIALS AND METHODS**

**Participants**

Thirty patients with AN were recruited from a pool of outpatients. Exclusion criteria for the study were presence of metallic implants, claustrophobia, and presence of an Axis I or II psychiatric diagnosis other than AN. The Structured Clinical Interviews for DSM-IV Axis I and II Disorders [17,18] were conducted with all participants. All patients fulfilled DSM-IV diagnostic criteria for AN. At least two senior psychiatrists interviewed the patients to ensure that diagnoses were accurate. All participants were right-handed Japanese women. Handedness was determined using the Edinburgh Handedness Inventory [38]. The study was conducted according to a protocol approved by the ethics committee of the Hiroshima University School of Medicine. All participants gave informed written consent prior to their participation.

**Psychological assessment**

A psychological assessment of all participants was conducted before scanning. The Japanese version of the TAS-20 was used to measure alexithymia levels. The TAS-20 is the most commonly-used psychometrically valid measure of alexithymia [5,40], and the Japanese version also enjoys high reliability and construct validity [20]. The TAS-20 has a three-factor structure, and the factors include: 1) difficulty identifying feelings; 2) difficulty describing feelings; and 3) externally-oriented thinking. We also used the Japanese version of the Eating Disorders Inventory-2 (EDI-2) [21] to evaluate psychological and behavioral features related to eating disorders.

**Stimuli and task**

We used the emotional decision-making task developed by Shirao et al [47]. For our study, 30 unpleasant words concerning body image were chosen from Japanese-language dictionaries/thesauri. Thirty neutral words were selected from the database of Toglia and Battig [52], and were translated into Japanese (Fig. 1A). The selected words were used to generate three-word sets of unpleasant body image words (for example, "obesity", "heavy" and "overweight"), and sets of neutral words (for example, "center", "question" and "moment"). Each word set comprised a unique combination of three words. The word sets were
presented in six alternating blocks across two conditions (task condition and control condition) in three cycles (Fig. 1B). Unpleasant word sets were presented during the body image condition (task condition), and neutral word sets were presented during the neutral condition (control condition). Each block began with a 3 s cue identifying the condition (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. Blood oxygen level-dependent (BOLD) response was recorded during the six blocks of each word task. During each interstimulus interval, a fixation cross appeared on the center of the screen. Participants were instructed either to select the most unpleasant word from each relevant word set based on their personal knowledge and experience, or to select the word they thought to be the most neutral from each relevant word set. Participants indicated their choices by pressing 1 of 3 buttons on a response pad in the MRI scanner.

**fmRI data acquisition and processing**

The fmRI scan was performed using a Magnetom Symphony Maestro Class (Siemens, Tokyo, Japan; 1.5 Tesla). A time-course series of 63 volumes was acquired during the task with T2*-weighted, gradient echo, echo planar imaging (EPI). Each volume consisted of 28 axial slices, and slice thickness 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 (FOV) was 256 mm and the matrix size was 64 x 64, giving voxel dimensions of 4.0 x 4.0 x 4.0 mm. After functional scanning, structural scans were acquired using a T2-weighted gradient echo pulse sequence (TR=12 ms; TE=4.5 ms; Flip angle=20°; FOV=256 mm; voxel dimensions of 1.0 x 1.0 x 1.0 mm) to facilitate localization.

**fmRI analysis**

Image processing and statistical analyses were performed using Statistical Parametric Mapping 5 (SPM5) software (Wellcome Department of Cognitive Neurology, London, UK), implemented in Matlab (Mathworks, Inc., Natick, MA). The first two volumes of the fmRI run were discarded because magnetization was unsteady. Each set of functional volumes was realigned to the first volumes, spatially normalized to a standard template based upon the Montreal Neurological Institute (MNI) reference brain, and finally smoothed using a 12-mm full-width, half-maximum Gaussian filter. We conducted group analyses according to a random effect model that permitted inferences to the general population. We identified brain regions that showed significant responses during the task condition as compared to the control condition. The data were given the threshold of p < 0.001 uncorrected at the voxel level and belonged to a cluster of activation with an extent of at least 250 voxels.

The images were entered into a regression analysis to locate brain regions in which the magnitude of brain activation was significantly correlated with scores on the psychological measures. The data were thresholded at p < 0.001 uncorrected at the voxel level for regions about which there was no clear hypothesis. For regions about which we had an a priori hypothesis, the height and extent of thresholds were set to p < 0.01 uncorrected at the voxel level. The x, y and z coordinates were provided in Montreal Neurological Institute (MNI) brain space. The labeling of areas given by the software was then confirmed via comparison with activation maps overlaid on MNI-normalized structural MR images.

**Evaluation of unpleasantness and familiarity of the word stimuli**

Each participant was asked to rate the unpleasantness and familiarity of all words presented during the experiment on a scale from 1 (very unpleasant; very unfamiliar) to 7 (very pleasant; very familiar). These ratings were obtained immediately after scanning. The words were presented in a randomized order in a table format. Subjective ratings were averaged for each category of words.

**RESULTS**

**Participant characteristics**

As shown in Table 1, the average total TAS-20
scores for the participants was 63.6. The average score on factor 1 was 24.1, the average score on factor 2 was 20.0, and the average score on factor 3 was 19.6. The average total EDI-2 score was 105.4. The average score on the “body dissatisfaction” items of the EDI-2 was 13.0 (s.d. = 6.17), and the average score on “drive for thinness” items was 10.4 (s.d. = 6.43).

**Evaluation of the word stimuli**

All participants rated the negative words as significantly more unpleasant than the neutral words (see Table 1), suggesting that the task manipulation of emotionality was successful. No correlation was found between the unpleasantness ratings of the word stimuli and the total TAS-20 score.

**Table 1.** Clinical characteristics of the participants

<table>
<thead>
<tr>
<th></th>
<th>AN patients (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.2 ± 6.5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>15.4 ± 1.7</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.7 ± 1.7</td>
</tr>
<tr>
<td>Duration of eating disorder (years)</td>
<td>6.17 ± 4.0</td>
</tr>
<tr>
<td>Eating Disorder Inventory-2 score</td>
<td>105.4 ± 35.8</td>
</tr>
<tr>
<td>Toronto Alexithymia Scale-20 score</td>
<td>63.6 ± 9.6</td>
</tr>
<tr>
<td>factor 1 (difficulty identifying feeling)</td>
<td>24.1 ± 5.6</td>
</tr>
<tr>
<td>factor 2 (difficulty describing feeling)</td>
<td>20.0 ± 3.9</td>
</tr>
<tr>
<td>factor 3 (externally oriented thinking)</td>
<td>19.6 ± 3.3</td>
</tr>
</tbody>
</table>

Evaluation of the word stimuli

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Body-image words</td>
<td></td>
</tr>
<tr>
<td>unpleasantness</td>
<td>1.9 ± 0.6</td>
</tr>
<tr>
<td>familiarity</td>
<td>4.4 ± 1.5</td>
</tr>
<tr>
<td>Neutral words</td>
<td></td>
</tr>
<tr>
<td>unpleasantness</td>
<td>3.7 ± 0.4</td>
</tr>
<tr>
<td>familiarity</td>
<td>4.2 ± 0.7</td>
</tr>
</tbody>
</table>

Results are shown as mean ± s.d.
*from 1 (very unpleasant; very unfamiliar) to 7 (very pleasant; very familiar).

**Table 2.** Areas with significant activation during the task condition compared with the control condition

<table>
<thead>
<tr>
<th></th>
<th>MNI coordinates</th>
<th>RA Size</th>
<th>(Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td>AN patients (n=30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L amygdala</td>
<td>-22</td>
<td>-8</td>
<td>-14</td>
</tr>
<tr>
<td>L superior temporal gyrus</td>
<td>-58</td>
<td>-40</td>
<td>14</td>
</tr>
<tr>
<td>R amygdala</td>
<td>28</td>
<td>0</td>
<td>-12</td>
</tr>
<tr>
<td>R brainstem</td>
<td>6</td>
<td>-40</td>
<td>-24</td>
</tr>
</tbody>
</table>

All areas exceeding the extent threshold of p<0.001 uncorrected at the voxel level and belonging to a cluster of activation with an extent of at least 250 voxels are displayed.

L: left; R: right; RA: Brodmann area. (Z): Z-score.

**fMRI results (Brain activation during the task)**

Compared with the control condition, the task condition resulted in significant activation of the amygdala, left superior temporal gyrus, and brainstem, as depicted in Fig. 2 (see also Table 2).

**fMRI results (Regression analysis)**

Regression analysis revealed a significant negative correlation between total TAS-20 score and the BOLD response of the PCC ([x = -22, y = -62, z = 10]; r = -0.476, p = 0.007), in the task condition relative to the control condition (see Fig. 3). The BOLD response of the PCC was negatively correlated with scores on factor 1 of the TAS-20 (difficulty identifying feeling; [x = -22, y = -62, z = 10]; r = -0.362, p = 0.04), factor 2 of the TAS-20 (difficulty describing feelings; [x = -22, y = -64, z = 10]; r = -0.442, p = 0.01), and factor 3 of the TAS-20 (externally oriented thinking; [x = 18, y = -52, z = 6]; r = -0.510, p = 0.003). Similarly, the BOLD response of the ACC in the task condition relative to the control condition was negatively correlated with scores on factor 3 of the TAS-20 ([x = 8, y = 34, z = 2]; r = -0.560, p = 0.001), as well as scores on factor 2 ([x = -6, y = 16, z = 26]; r = -0.362, p = 0.04), albeit at a lower statistical threshold. Neither body mass index (BMI) nor participant age was correlated with the BOLD response observed in any brain region.

**Fig. 2.** Brain activation during the task condition compared with the control condition.

Brain areas showing significantly greater activation during the task condition compared with the control condition. Clusters of activation are overlaid onto a T1-weighted anatomical MR image (uncorrected p < 0.001 at the voxel level).
**DISCUSSION**

We used an emotional decision-making task to identify the brain areas that are activated in AN patients during the perception of unpleasant body image related words. There was significant activation in the amygdala, but not in the ACC and PCC, while AN patients engaged in the emotional decision-making task. Moreover, significant correlation was found between alexithymia level and activation of the ACC and PCC, but not the amygdala.

We found that the amygdala was activated in the task condition compared with the control condition. Previous studies have suggested that the amygdala is strongly associated with the rapid detection of stimuli that signal threat. Especially, the amygdala responds to emotional stimuli when processed outside of conscious awareness \(^{24,35}\). The amygdala can trigger unconscious or rudimentary aversive responses \(^{28,37}\). In AN patients, the amygdala is activated when these patients view pictures of high-calorie drinks \(^{15}\), suggesting that visual images of high-calorie foods constitute fearful stimuli for these patients. The excessive amygdala activation that we observed here suggests that AN patients may process unpleasant body image words as fearful information in unconsciousness. In addition, activation of the limbic structures (i.e. the amygdala, the hippocampal formation and the hypothalamus) did not vary with level of alexithymia in this study. This finding is supported by previous fMRI studies which indicate that activity in the limbic area is not associated with alexithymia \(^{6,20}\).

A second important finding of the present study was that the BOLD response observed in the PCC was negatively correlated with level of alexithymia in our sample of AN patients. A review of functional imaging studies found that the caudal portion of the PCC is the cortical region most consistently activated by emotional stimuli, relative to nominally matched emotionally neutral stimuli \(^{30}\). Moreover, it has been speculated that the PCC plays a key role in the modulation of memory functioning by emotionally arousing stimuli \(^{30}\). The PCC has reciprocal connections with other regions that are often engaged in higher emotional subjective processing, including the ACC \(^{22,53}\). In a previous SPECT study, decreased regional cerebral blood flow (rCBF) was observed in the PCC in AN patients as compared to controls \(^{55}\). Another study reported that increases in rCBF were observed in the PCC following treatment of AN patients \(^{33}\). These researchers suggested that this decreased perfusion in the PCC might be partially related to the pathophysiology of AN. Our results, therefore, suggest that a relative deactivation of the PCC in AN patients could be related to the impairments in the higher subjective emotional processing that are hallmarks of alexithymia.

In addition, ACC BOLD response was also negatively correlated with alexithymia level in AN patients. The ACC is a pivotal component of the brain networks that direct various emotional and cognitive functions \(^{14,64}\). As part of the rostral limbic system, the ACC serves to modulate various internal emotional responses \(^{14,62}\). The ACC is also considered to be an integral component of awareness and insight \(^{2,14,64}\). According to the hypothesis of Lane et al. \(^{25}\), environmental events can trigger an emotional response, but in alexithymic indi-

---

**Fig. 3.** Activation in brain regions negatively correlated with Toronto Alexithymia Scale-20 scores. (A) Left posterior cingulate cortex (x=-22, y=-62, z=10). The threshold for illustration was set at uncorrected \(p < 0.01\). (B) Correlation between BOLD response and Toronto Alexithymia Scale-20 score.
viduals, this emotional response is often characterized by a relatively impoverished conscious experience of the emotion itself. This theory of alexithymia suggests that people with this condition exhibit less ACC activation, the ACC being an area known to play a role in determining an individual’s capacity to experience emotion in a differentiated and complex way. Consistent with this assumption, recent neuroimaging studies have suggested that impairment in ACC functioning is a neural correlate of alexithymia. The disturbances in the ACC might be reflected in rather serious damage to the conscious awareness of emotion and the emotion regulation system in AN patients with alexithymia.

Several investigators have suggested that alexithymia might involve a “decoupling” of the subjective and physiological components of the emotional response to stressful stimuli—that is, a higher degree of alexithymia is associated with reduced subjective responding but greater physiological reactivity. These results might suggest that alexithymic subjects have deficiencies in the conscious awareness of emotions. Therefore, our results also suggest that a hyperactivation in the amygdala is related to the greater physiological reactivity and a deactivation of the ACC and PCC to impairment in the subjective processing of emotions in AN. Difficulties with identifying feelings may reduce the capacity of AN patients to adapt to stressful situations. Such situations generate an emotional overflow that alexithymic subjects may apprehend less by their emotional and cognitive features than by their associated somatic indexes. If this is so, alexithymia could conceivably affect the clinical course of AN.

Our study has some limitations. First, the nature of our sample limits the generalizability of our findings. Most of the patients included here had a chronic course, having been ill for many years. It is likely that the role of body image disturbance varies over the course of the illness. Second, our AN patients all showed low BMI. However, BMI did not significantly affect the brain activation observed in this study, and some studies have reported that alexithymia is unrelated to BMI. Finally, our results might have not been peculiar to AN. Recently, high prevalences of alexithymia have been reported in various psychiatric disorders, such as somatoform disorders and anxiety disorders. Further studies considering these points are needed.

In conclusion, our neuroimaging results suggest that AN patients may process unpleasant body image-related words as fear-inducing information. Moreover, PCC and ACC activation both varied with alexithymia level during the processing of unpleasant information concerning body image. We suggest that alexithymia might play a crucial role in the emotional processing impairments that are often observed in AN patients, and this construct might ultimately help to better account for the psychopathological mechanism underlying AN.

ACKNOWLEDGMENTS

This study was partially supported by Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and the Research on Psychiatric and Neurological Diseases and Mental Health, Ministry of Health, Labour and Welfare, Japan.

(Received October 20, 2008)
(Received November 26, 2008)

REFERENCES

A lexithymia and Anorexia Nervosa


43. Rastam, M., Gillberg, C., Gillberg, I.C. and Johansson, M. 1997. Alexithymia in anorexia ner-


