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Functional Associations of Temperamental Predisposition and Brain Responses While Processing Stressful Word Stimuli Related to Interpersonal Relationships in Bulimia Nervosa Patients: an fMRI Study

Yoshie Miyake[1*], Yasumasa Okamoto[2], Keiichi Onoda[3], Yuri Okamoto[1] and Shigeto Yamawaki[2]

[1]*Health Service Center, Hiroshima University, 1-7-1, Kagamiyama, Higashi-Hiroshima, 739-8514, Japan*
[2]*Department of Psychiatry and Neurosciences, Division of Frontier Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3, Kasumi, Minami-ku, Hiroshima, 734-8551, Japan*
[3]*Department of Neurology, Shimane University, 89-1, Enya-cho, Izumo, Shimane, 693-8501, Japan*

***Correspondence to:**
Yoshie Miyake
Health Service Center,
Hiroshima University 1-7-1, Kagamiyama
Higashi-Hiroshima, 739-8514, Japan
Tel: +81-82-424-6186
Fax: +81-82-424-6178
E-mail: miyakechare@hiroshima-u.ac.jp

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Abstract

Bulimia nervosa (BN) is characterized by frequent episodes of uncontrolled overeating and difficulties in adapting to stressful situations. BN patients tend to be sensitive to frustration and impulsive. Personality traits may be associated with the abilities of BN patients to adapt to stressful situations, especially in interpersonal relationships. The aim of the present study was to investigate the functional abnormalities in various brain systems while processing stressful word stimuli related to interpersonal relationships in BN patients. Functional magnetic resonance imaging was used to examine the brain responses of 15 BN patients and 20 healthy women while processing unpleasant words related to interpersonal relationships. We also investigated the relationships between brain responses and temperament trait scale from the Temperament and Character Inventory. BN patients showed significant activations of medial prefrontal cortex and anterior cingulate cortex (ACC) while processing these words. ACC activation was significantly greater in BN patients than in healthy women. Among BN patients, the score of the harm avoidance was positively correlated with the activation of the ACC, and the score of the novelty seeking was negatively correlated with the activations in the left inferior frontal gyrus (IFC) and the insula. These results suggest that ACC activation may play crucial roles in emotional processing impairments of BN. Reduced activations of IFC and insula while processing stressful words may reflect a general failure of self-regulation. These abnormal functional responses to stressful stimuli may be involved in difficulties in adapting to stressful situations in BN patients.

Keywords

fMRI, Eating disorders, Bulimia nervosa, Interpersonal relationship stress, Temperament traits

Introduction

Eating disorders (EDs) are an important cause of physical and psychosocial morbidity in young women. EDs are classified primarily into two major categories; anorexia nervosa (AN) and bulimia nervosa (BN). Bulimia nervosa (BN) is characterized by frequent episodes of uncontrolled overeating. BN patients tend to recover from stress slowly. Peterson et al. [1] reported that stress reactivity appears to be especially important for understanding and treating BN. The psychological stressors around us include interpersonal conflicts and isolation [2]. Difficulties in adapting to stressful situations might play a role in the development of the disorders associated with BN. Cognitive theories of eating disorders (EDs) include a role for distorted beliefs about the self with content that is ostensibly unconnected to weight, shape or eating [3,4]. A recent study of BN reported that self-referent emotional information reduced neural activation in the parietal, occipital and limbic areas in BN patients compared to controls [4].

BN patients tend to be impulsive and show disinhibited personality characteristics [5, 6]. Several studies have reported that ED patients differ from healthy controls in reward and punishment sensitivity as measured with the Temperament and Character Inventory (TCI) [7, 8]. The TCI has been used previously to deepen our understanding of the personality traits of ED patients and to allow for correlational inferences based on neurophysiologic, therapeutic and prognostic perspectives [9]. Some studies have shown that ED is commonly related to specific personality traits and particularly elevated harm avoidance (HA) [10, 11]. Temperamental data have revealed that high novelty seeking (NS) represents a specific genetic predisposition to binge-purging behaviors when other predisposing factors to ED coexist [11-13]. Temperamental traits are potentially associated with specific genetic and biological substrates that are relatively consistent and stable over time [14, 15]. They are said to be heritable, stable across time and dependent on genetic and neurobiological factors [16]. Amianto et al. [17] reported that anger mediation between cooperativeness, and binge eating and impulsive behaviors confirm the relevance of relational dynamics in the expression of these core eating symptoms in BN patients. Personality traits may influence or be associated with the abilities of BN patients to adapt to stressful situations and manage their disease. Recent relevant biological studies have reported significant associations between various dimensions of temperament and brain activity based on Cloninger's model. Gardini et al. [16] suggested that individual differences in the temperament dimensions might reflect structural variance in specific brain areas. Youn et al. [18] reported that NS is primarily correlated with the activities of the substantia nigra and several temporal regions and that HA and reward dependence (RD) were primarily correlated with the activities of the temporal lobe and orbitofrontal gyrus in a positron emission tomography (PET) study. One functional magnetic resonance imaging (fMRI) study demonstrated that blood oxygen level dependent (BOLD) signals are correlated with scores on various personality scales, and these signals suggest that variations in personality traits might partially account for variations in the neural responses of particular brain regions [19]. Neurobiological vulnerabilities have been implicated in the pathogenesis of ED [8]. Marsh et al. [20] reported that general self-regulatory functions demonstrated impulsive response on a behavioral level and front striatal dysfunction in BN. Understanding how the abnormalities in brain function that are related to personality traits might cause or maintain BN may lead to more successful interventions for BN. However, there is little data regarding the brain functions associated with the temperamental predisposition in BN patients.

The purpose of the present study was to investigate the relationships between functional abnormalities and temperament trait scale scores from the TCI in BN patients during the processing of stressful words related to interpersonal relationships in an fMRI experiment. Our previous research found that the left medial prefrontal cortex (mPFC) of BN patients were significantly activated in response to negative body-image words and suggested that the mPFC is associated with the functional abnormalities of brain systems in BN patients [21]. Joos et al. [22] substantiates a key role of lateral prefrontal dysfunction, which is a brain region involved in impulsive control, in BN patients. The binge eating/purging group showed significantly greater activations of the bilateral precentral gyrus, anterior cingulated cortex (ACC), and middle and superior temporal gyrus than healthy groups during a response inhibition task [23]. In the present study, we hypothesized that the BN patients would show prefrontal cortex (PFC) and ACC activations that are associated with the aspects of temperament that are specific to BN.

Materials and Methods

Participants

Fifteen BN patients were recruited from a pool of outpatients. For the comparison with BN patients, twenty healthy women were recruited via a community announcement. The exclusion criteria for the study were the presence of metallic implants, claustrophobia, and the presence of any Axis I or II psychiatric diagnosis other than BN. The Structured Clinical Interviews for DSM-IV Axis I and II Disorders [24,25] were conducted with all of the participants. The healthy women participated in our previous study [26]. All patients fulfilled the DSM-IV diagnostic criteria for BN. Additionally, at least two senior psychiatrists interviewed the patients to ensure that the diagnoses were accurate. Three of the patients were taking antidepressant medication. All participants were right-handed Japanese women. Handedness was determined using the Edinburgh Handedness Inventory [27]. The clinical characteristics of the participants were averaged, and the group comparison was made by using a *t* test. The study was conducted according to a protocol approved by the ethics committee of the Hiroshima University School of Medicine. All participants provided written informed consent prior to their participation.

Psychological assessment

The psychological assessments of all of the participants were conducted prior to scanning. The four temperament scales of the Japanese-version of the TCI [28] were used to assess temperament. We also used the Japanese version of the Eating Disorders Inventory-2 (EDI-2) [29] to further examine our participants' eating problems.

Stimuli and task

We used the emotional decision-making task developed by Shirao et al. [30]. For our study, 30 unpleasant words related to interpersonal relationships were chosen from Japanese-language dictionaries/thesauri. Thirty neutral words were selected from the database of Toglia and Battig [31] and translated into Japanese (Figure 1a). The unpleasant words and neutral words did not significantly differ with regard to word length nor familiarity [32]. The selected words were used to generate three-word sets of unpleasant words related to interpersonal relationships (for example, 'contempt', 'betrayal' and 'disappointment') and sets of neutral words (for example, 'center', 'region' 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 and control conditions) in three cycles (Figure 1b). The unpleasant word sets were presented during the task condition, and the neutral word sets were presented during the control condition. Each block began with a 3 s cue that identified the condition (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 (Figure 1c). The BOLD responses were recorded during the six blocks of each word task. A fixation cross appeared at the center of the screen during each interstimulus interval. In the task condition, the participants were instructed to select the most unpleasant word from each word set based on their personal knowledge and experience; in the control condition, they were instructed to select the most neutral word from each word set. The participants indicated their choices by pressing one of three buttons on a response pad in the MRI scanner.

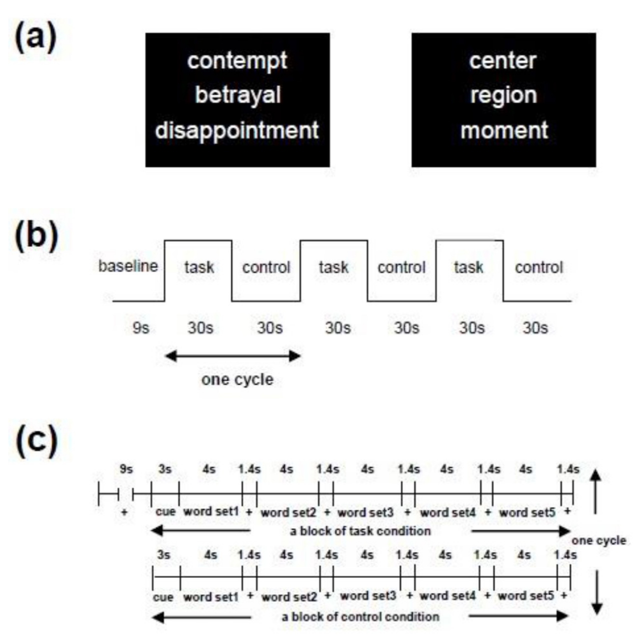

Figure 1: Design of the study task.

Evaluation of the unpleasantness and familiarity of the word stimuli

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

Image acquisition

The fMRI scans were performed using a Magnetom Symphony Maestro Class MRI scanner (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 encompassed the entire brain and consisted of 28 axial slices, and the slice thickness was 4.0 mm with no gap. 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 × 64, which produced a voxel dimension of 4.0 × 4.0 × 4.0 mm. After functional scanning, structural scans were acquired using a T1-weighted gradient echo pulse sequence (TR = 12 ms; TE = 4.5 ms; Flip angle = 20°; FOV = 256 mm; voxel dimensions of 1.0 × 1.0 × 1.0 mm) to facilitate localization.

fMRI analysis

The image processing and statistical analyses were performed using the 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 each fMRI run were discarded to allow for stabilization of the magnetization. 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 [33]. We first identified brain regions that showed significant responses during the task condition compared with the control condition in each group. Next, we performed a two-sample *t*-test to identify group differences. The data were considered significant at a threshold of $p < 0.001$ that was uncorrected at the voxel level if the voxels belonged to a cluster of activation with an extent of at least 10 voxels. For the BN patients, the images were entered into a regression analysis to identify the brain regions in which the magnitudes of brain activation were significantly correlated with the scores on the temperament dimensions of the TCI and the subjective ratings of the words. To test for region-specific covariate effects, the estimates were compared using two linear contrasts (positive or negative correlations). The data were considered significant at a threshold of $p < 0.001$ that was uncorrected at the voxel level.

Results

Participant characteristics

As shown in Table 1, the average TCI scores of the BN patient for NS, HA, RD, and PT were 50.8 (range: 43-63), 63.2 (range: 47-78), 40.8 (range: 28-50), and 11.4 (range: 7-14), respectively. The average TCI scores of the control subjects for NS, HA, RD, and PT were 47.4 (range: 34-59), 53.4 (range: 32-67), 45.0 (range: 35-54), and 13.2 (range: 11-17). Our BN patients exhibited significantly higher HA and lower RD and PT scores than the control subjects. The BN patients scored significantly higher on all of the subscales of the EDI-2 than the control subjects. No temperament scores or EDI-2 scores were significantly correlated with the participants' ages or body mass index (BMI).

The ratings of familiarity for the two categories of words did not differ significantly between the BN patients (mean familiarity score for interpersonal relationship words = 4.3 and neutral words = 4.2) and the control subjects (mean familiarity score for interpersonal relationship words = 4.5 and neutral words = 4.6). However, all of the participants rated the interpersonal relationship words to be significantly more unpleasant than the neutral words (mean unpleasantness scores for the interpersonal relationship words = 1.9 and neutral words = 3.9, $p < 0.001$ in the BN patients; mean unpleasantness scores for the interpersonal relationship words = 2.1 and neutral words = 4.0, $p < 0.001$ in the control subjects). Neither the ratings of unpleasantness nor the ratings of familiarity within each word category differed significantly between the BN patients and the control subjects.

Table 1: Clinical characteristics of the participants.

	BN patients (n = 15)	Control (n = 20)	t	p
Age (years)	26.1 ± 7.2	25.6 ± 4.6	0.24	0.805
Body mass index (kg/m^2)	22.1 ± 4.4	19.3 ± 1.9	2.31	<0.05
Education (years)	13.8 ± 1.4	15.6 ± 1.5	3.92	<0.001
Duration of BN (years)	5.6 ± 4.2			
Temperament and Character Inventory				
Novelty seeking	50.8 ± 5.9	47.4 ± 7.1	1.47	0.15
Harm avoidance	63.2 ± 8.2	53.4 ± 9.5	3.14	<0.01
Reward dependence	40.8 ± 5.8	45.0 ± 5.3	2.14	<0.05
Persistence	11.4 ± 2.1	13.2 ± 1.9	2.40	<0.05
Self-directedness	50.1 ± 8.3	69.2 ± 10.5	5.73	<0.001
Cooperativeness	70.8 ± 7.0	76.4 ± 5.0	2.70	<0.05
Self-transcendence	27.1 ± 5.9	29.5 ± 8.0	0.95	0.34
Eating Disorder Inventory-2				
Total score	126.2 ± 44.8	33.2 ± 14.9	7.72	<0.001
Drive for thinness	14.7 ± 4.0	2.9 ± 4.1	8.37	<0.001
Bulimia	12.3 ± 5.7	1.0 ± 1.4	7.40	<0.001
Body dissatisfaction	18.5 ± 6.8	8.5 ± 5.4	4.80	<0.001
Ineffectiveness	16.1 ± 6.6	4.6 ± 3.4	6.17	<0.001
Perfectionism	6.4 ± 3.6	1.6 ± 1.5	4.77	<0.001
Interpersonal distrust	8.3 ± 4.2	3.3 ± 2.9	4.04	<0.001
Interoceptive awareness	12.7 ± 7.6	0.7 ± 1.2	5.90	<0.001
Maturity fears	9.4 ± 6.4	3.3 ± 2.7	3.40	<0.01
Ascetism	8.0 ± 4.6	1.9 ± 1.1	4.93	<0.001
Impulse regulation	8.9 ± 6.0	0.4 ± 0.8	5.43	<0.001
Social insecurity	10.9 ± 4.0	4.8 ± 3.4	4.68	<0.001

Results are shown as the mean ± the standard deviation.

BN = bulimia nervosa; t = test value; p = p-value.

fMRI results

Brain activation during the task

Compared to the control task, the interpersonal-relationship word task condition resulted in significant activations of the mPFC and the left ACC (Brodmann area: BA 10) in the BN patients (Figure 2a and Table 2). No significant activations were found in the control subjects. The activations in the right mPFC (BA 9, 10), the ACC (BA 9, 32) and the left parietal lobule (BA 7) were significantly greater in the BN patients than in the control subjects during the task (Figure 2b and Table 2). No temperament scores or the subjective ratings of the words were significantly correlated with the activations of these areas. No brain area exhibited significantly greater activation in the control subjects than in the BN patients.

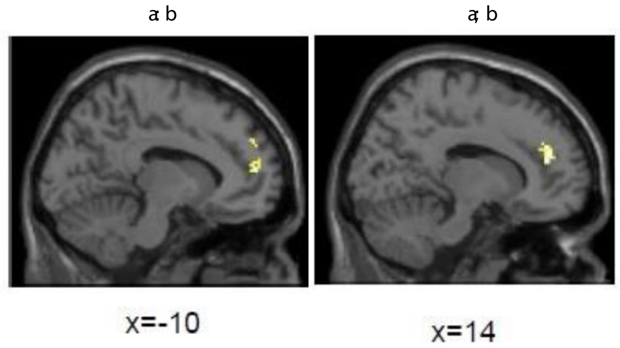

Figure 2: Brain activations during the task in the BN patients. **(a)** Brain activation during the task. **(b)** Group comparison.

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

	MNI coordinates x	y	z	BA	Size Voxel	Z
BN patients						
L medial frontal gyrus	-10	54	12	10	141	3.77
L anterior cingulate gyrus	-2	50	14	10		3.08
R medial frontal gyrus	14	48	20	10	14	3.22
Control subjects						
No significant results						
BN patients > Control subjects						
R medial frontal gyrus	14	42	18	9/10	86	3.80
R anterior cingulate gyrus	10	44	28	9		3.47
L anterior cingulate gyrus	-12	22	18	32	23	3.48
L parietal lobe	-14	60	42	7	10	3.53
Control subjects > BN patients						
No significant results						

All areas exceeding the threshold of $p < 0.001$ uncorrected at the voxel level and belonging to a cluster of activation with an extent of at least 10 voxels are displayed.

x, y, z: location in MNI coordinates.

BA = Brodmann area; (Z) = Z –score; L = left; R = right.

Regression analysis

The brain regions in which the scores on the temperament dimension were significantly correlated with the BOLD responses of BN patients are shown in Table 3. The NS score was negatively correlated with the activations in the left inferior frontal gyrus (IFC) (BA47) (Figure 3a), the right superior frontal gyrus (SFC) (BA8) and the insula (BA 13). The HA

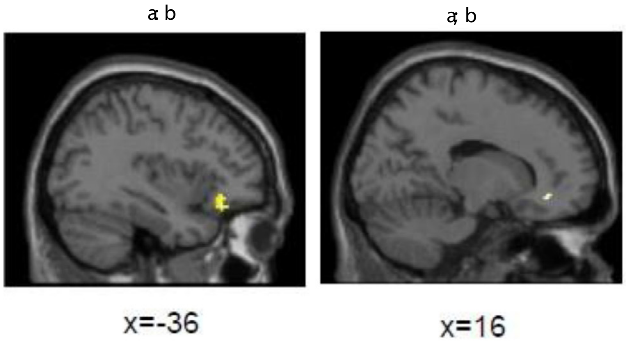

Figure 3: Brain activations during the task in the BN patients. **(a)** Negative correlation with the NS score. **(b)** Positive correlation with the HA score.

Table 3: Areas with activations that significantly correlated with TCI scores in BN patients.

	MNI coordinates			BA	Size	Z	r	p
	x	y	z		Voxel			
TCI score								
Positive correlation with NS								
No significant results								
Negative correlation with NS								
L inferior frontal gyrus	-36	32	-14	47	36	3.88	-0.77	<0.001
R superior frontal gyrus	10	42	54	8	11	3.75	-0.72	0.002
R insula	40	-10	14	13	15	3.52	-0.66	0.006
L insula	-42	-40	16	13	8	3.31	-0.69	0.004
Positive correlation with HA								
L inferior parietal lobule	-64	-42	28	40	29	3.65	0.75	<0.001
L superior temporal gyrus	-58	-62	20	39	8	3.56	0.62	0.01
R anterior cingulate gyrus	16	38	-10	10	1	3.03	0.61	0.01
L anterior cingulate gyrus	-2	-18	30	23	1	2.99	0.58	0.02
Negative correlation with HA								
No significant results								
Positive correlation with RD								
No significant results								
Negative correlation with RD								
L superior parietal lobule	-18	-60	52	7	23	3.46	-0.68	0.004
L superior frontal gyrus	-22	30	48	8	6	3.31	-0.68	0.004
Positive correlation with PT								
R middle frontal gyrus	32	44	30	9/10	8	3.49	0.79	<0.001
Negative correlation with PT								
No significant results								

x, y, z: location in MNI coordinates.

TCI = Temperament and Character Inventory; BA= Brodmann area; (Z) = Z –score; L = left; R = right. NS = novelty seeking; HA = harm avoidance; RD = reward dependence; PT = persistence.

score was positively correlated with the activations in the ACC (BA 24, 32) (Figure 3b), the left inferior parietal lobule (IPL) (BA 40) and the left superior temporal gyrus (BA 39). The RD score was negatively correlated with the activations in the left superior parietal lobule (BA7) and the left SFC (BA8). The PT score was positively correlated with the activations in the right middle frontal gyrus (BA 9/10). Neither participant age nor BMI was correlated with the BOLD responses observed in any brain region. There was no significant correlation between the brain activation and the subjective ratings of the words.

Discussion

We investigated the relationships between temperamental predispositions and brain responses in BN patients during the processing of stressful word stimuli related to interpersonal relationships. The activations of the mPFC and the left ACC were significantly increased in the task condition compared to the control condition. All participants rated the interpersonal relationship words as significantly more unpleasant than the neutral words; this suggests that the task manipulation of emotionality was successful. The activation of the ACC was positively correlated with the HA score. The activations in the left IFC and the insula were negatively correlated with NS score. To our knowledge, this is the first study to investigate the relationships between temperament traits and brain responses to interpersonal relationship stimuli in BN patients.

We revealed that the activation of the ACC was significantly positively correlated with the HA score. The activation of the ACC was significantly greater in the BN patients than in the control subjects. HA reflects the intensity of responses to signals of aversive stimuli and is thus related to learning to inhibit behavior to avoid punishment and frustration. Some neuroimaging studies have suggested that the ACC is a pivotal component of the brain networks that direct various emotional and cognitive functions [34, 35]. The ACC serves to modulate various internal emotional responses [36]. The ACC is also considered to be an integral component of awareness and insight [34, 35, 37]. Eisenberger et al. [38] suggested that the ACC is involved in social pain. An fMRI experiment revealed that a significant increase in ACC activity occurs when participants are socially isolated during a virtual game of catch [38]. Social pain involves unpleasant affects that are experienced upon social injury, specifically when social relationships are threatened, damaged, or lost [39]. The BN patients may have tended to feel more socially isolated and stressed during the perception of stressful word stimuli in this study. We suggest that greater activation of the ACC in response to stressful stimuli might also play a crucial role in the emotional processing impairments that are often observed in BN patients when interpersonal relationships are damaged.

Moreover, the activations of the left IFC, the insula and the SFC were negatively correlated with the NS scores of the BN patients. Individuals with high NS scores are characterized as impulsive or excitable. High NS represents a specific genetic predisposition to binge-purging behaviors when other predisposing factors to ED coexist [11-13]. The left IFC has been implicated in self-regulatory control and particularly inhibitory control [40]. The insula has been implicated in affective processing, including emotional and interoceptive awareness and self-regulation [41]. Insular dysfunction is associated with increased threat perception [42]. The activity of the SFC was negatively correlated with the NS score and the RD score. The SFC is also involved in self-awareness [43]. BN patients are thought to belong to the impulsive pole of the spectrum, but no significant differences in the NS scores between the BN patients and the control subjects were observed in this study. Understanding the impulsive aspect of BN may help guide treatments or allow for improved outcome prediction [44]. The uncontrolled overeating exhibited by BN patients seems to suggest the presence of pathological impulsiveness and a lack of inhibitory control. Therefore, one possible interpretation of the reduced activations of the IFC, insula and SFC in response to stressful stimuli observed in BN patients is that the presentation of the stressful words elicited the impulsive aspect of BN in these patients.

We found a significant activation in the mPFC and left ACC in the BN patients during the task, but these areas did not show significant activation among the control subjects. The mPFC is related to general emotional processing and evaluative judgment [45, 46]. Somerville et al. [47] reported that healthy people with low self-esteem showed modulation of responses in their ventral ACC and mPFC in response to social feedback but that people with high self-esteem showed no changes in this region in response to feedback. Onoda et al. [48] reported that people with lower self-esteem show increased social pain and dorsal ACC activity than do people with higher self-esteem, and the observed dorsal ACC activity was associated with mPFC activity. McAdams and Krawczyk [49] suggested that neural responses to social feedback in the ACC and mPFC might provide a biological mechanism that connects social cognitive responses and self-esteem with eating pathology. Low self-esteem has been related to the onset of bulimic symptoms [50]. Therefore, one possible interpretation of the mPFC and ACC activations during the task may be associated with the subjects' low self-esteem, and this process may be associated with the onset of binge eating in BN patients.

It is important to note that our study has some limitations. First, the nature of our sample limits the generalizability of our findings. Although the majority of the included patients had a chronic disease course and had been ill for many years, the duration of BN did not significantly affect any of the brain activations observed in this study. Second, Although BN patients fulfilled the DSM-IV diagnostic criteria for BN, the current version is DSM-V. Also, we used SPM5 for the image processing and statistical analyses in this study. There are more recent versions of SPM. Further studies that consider these points are needed. Third, we did not consider the multiple other language related issues before settling on a test set. Further studies are also needed to consider this. Fourth, although BN patients are thought to belong to the impulsive pole of the spectrum, there was no significant difference in the NS scores between our BN patients and the control subjects in this study. Further confirmation of our results and further studies of personality traits in BN that use instruments other than the TCI are required to make our results more useful for understanding BN. Finally, because our sample size is small, our results may not be specific to BN. This study did not consider other subgroups of ED or the regression analysis in the control subjects. Further studies that consider this point are needed.

Conclusion

Our study indicated the relationship between functional responses to interpersonal relationship stress and temperamental predisposition in BN patients. We suggest that these functional abnormalities may also play a crucial role in the emotional processing impairments and difficulties in adapting to stressful situations in BN patients.

Acknowledgments

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