Increased Subjective Distaste and Altered Insula Activity to Umami Tastant in Patients with Bulimia Nervosa

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The aim of this study was to examine differences in brain neural activation in response to monosodium glutamate (MSG), the representative component of umami, between patients with bulimia nervosa (BN) and healthy women (HW) controls. We analyzed brain activity after ingestion of an MSG solution using functional magnetic resonance imaging (fMRI) in a group of women with BN (n = 18) and a group of HW participants (n = 18). Both groups also provided a subjective assessment of the MSG solution via a numerical rating scale. The BN group subjectively rated the MSG solution lower in pleasantness and liking than the control group, although no difference in subjective intensity was noted. The fMRI results demonstrated greater activation of the right insula in the BN group versus the control group. Compared with the HW controls, the BN patients demonstrated both altered taste perception-related brain activity and more negative hedonic scores in response to MSG stimuli. Different hedonic evaluation, expressed as the relative low pleasing taste of umami tastant and associated with altered insula function, may explain disturbed eating behaviors, including the imbalance in food choices, in BN patients.

Keywords: eating disorders, bulimia nervosa, umami, glutamate, functional magnetic resonance imaging, neuroimaging, gustation, insula

INTRODUCTION

Bulimia nervosa (BN) is a mental illness characterized by repetitive overeating and purging behaviors to prevent weight gain, and is commonly seen in young women. Patients with BN experience significant psychological, physical, and social suffering related to their ongoing eating disorder (ED), including BN-specific psychopathology. Behavioral abnormalities driven by craving for foods are a prominent feature of BN, and neuroimaging studies using food-related tasks are thus an important approach for elucidating the correlations between these behaviors and their underlying neural substrates (1, 2).

In clinical settings, BN patients describe eating behaviors including anhedonia surrounding mild flavors, pathological consumption of highly palatable foods (e.g., high sugar/fat foods), and diminished...
feelings of emotional and/or physical satiety (3). Several observational and investigative studies have clarified some skewed preferences in BN-related eating habits. For example, overeating and purging in BN patients are associated with consuming more sucrose and fat, and less protein (4, 5). Also, breads and cereals are the primary carbohydrate sources for healthy eaters, whereas fruits and vegetables are the main carbohydrate sources for BN patients (6). Several studies have indicated that food selection in BN or in postpubertal youth with bulimic symptoms is heavily biased toward increased sugar/fat caloric intake at the expense of protein calories (7, 8). Another study also found high levels of consumption of artificial sweeteners, which provide few calories but excessive sweetness, in BN patients (9). Furthermore, BN patients were unable to enjoy the taste and smell of foods, or to feel distress when they overate (10). These results suggest that BN patients might have some dysfunction in the perception and evaluation of tastes that affects a wide range of foods. 

In addition to sweetness, the five basic tastes include saltiness, sourness, bitterness, and umami (11). Umami was discovered in 1908 by isolating monosodium glutamate (MSG) from kelp (12) and is a preferred taste (13). Facial expression studies on neonatal human infant responses to stimulation with different tastes noted that umami-tasting stimuli induced eager sucking and licking movements, as well as triggering facial expressions very similar to those induced by sweet taste (14). MSG, thought to be indicative of the protein content of food (15), is widely used as a flavor-enhancing seasoning that also increases food intake (16). In fact, MSG has several physiological actions. In rats, MSG has obesity-controlling effects (17), and unlike glucose, it does not induce the expression of Fos-related protein in the nucleus accumbens (18). It also induced vagally mediated brain activity when administered intragastrically in rats (19), and promoted gastric motility when added to protein-rich meals in human (20). Behaviorally, the addition of MSG to low-calorie meals enhanced appetite and postprandial satisfaction (21), and when added to essential foods MSG improved balanced food selection in older adults and patients with diabetes (22). Thus, umami is a taste with a certain level of preferentiality, and MSG can potentially influence human physiology and nutrition.

Of the many functional magnetic resonance imaging (fMRI) studies of BN patients, those using taste stimuli are considered particularly useful because they directly examine dysfunction in the perception and evaluation of food as a reward (23). To date, fMRI studies of BN patients using taste or flavor stimuli have found abnormal responses to sweet and high-fat cream in specific regions of the brain including the insula, anterior cingulate cortex, orbitofrontal cortex, and ventral striatum (24–28). Although differences across the presented tasks limit comparisons of these studies, Kaye et al. have proposed that patients with EDs have a disorder in the ventral neural pathway formed by the insula, orbitofrontal cortex, amygdala, anterior cingulate cortex, and related regions of the brain, leading to abnormalities in food-related reward evaluation (29). However, those studies were limited by using only highly pleasant tastes, sweetness, or fats.

On another front, it is assumed that the neurophysiology of disgusting stimuli processing may also be important for elucidating the pathogenesis of aberrant eating behaviors in EDs (30, 31). In fact, feelings of disgust influence the modulation of food intake in human (32). Furthermore, BN patients or women with abnormal eating attitudes showed altered disgust sensitivity to food-related stimuli (33–35). More recently, Monteleone et al. investigated the brain response to bitter taste of quinine concomitantly with sweet taste in BN patients (36). Their study focused on the processing of universally aversive taste stimulus, which showed decreased brain response in the amygdala and insula to the bitter taste in BN patients.

Monosodium glutamate has higher hedonic impact than water, but lower impact than sucrose (37). So, it is reasonable to consider that umami does not present high pleasantness on equal terms to sweetness, but it does offer a certain level of pleasantness, contrary to the bitterness that is widely considered as disgusting. In the present study, for the first time, we aimed to investigate the representations of umami in brain of BN patients compared with healthy women (HW). We hypothesized that BN patients show alterations of brain responses to taste based not only on sweetness and fat (obviously pleasant tastes) or bitterness (obviously aversive taste), but also umami (moderately pleasant taste). We thus investigated the brain responses to MSG stimuli in BN patients to determine whether these patients have lost the ability to properly perceive and evaluate umami tastant or its rewarding/satisfying feelings.

**MATERIALS AND METHODS**

**Participants**

We recruited 41 women in total, 21 patients with BN and 20 HW participants. Three patients and 2 HW were excluded due to major head motion, greater than 1.0 mm translation or 2.0° rotation, after preprocessing of fMRI, and thus we finally examined a total of 36 women, 18 with BN and 18 healthy participants. BN patients were recruited by clinical referrals from Chiba University Hospital, as well as other local psychiatric hospitals and clinics. Patients were assessed by senior psychiatrists at Chiba University Hospital using the Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient Edition (SCID-I/P) (38). Most of the patients were to undergo cognitive-behavioral therapy at the Department of Psychiatry of Chiba University Hospital after this study. All patients met the current DSM-IV criteria for BN. Four patients reported comorbid depression, while two patients had used selective serotonin reuptake inhibitors (sertraline and fluvoxamine, respectively). No patients had met criteria for drug or alcohol abuse or dependence, mental retardation, current high risk of suicide, or psychotic symptoms. HW participants matched for age and gender were recruited through local advertisements. All HW participants were without a history of EDs or any psychiatric, serious medical or neurological illness, and they were not on medication. All participants were female native Japanese speakers, between age 18 and 36 (mean = 26.10, SD = 5.68 years). The Research Ethics Committee of Chiba University Hospital approved all procedures, and written informed consent was obtained from all participants prior to scanning. All experiments were performed in accordance with the Helsinki Declaration.
The magnetic resonance imaging study was done at 16:00 o'clock, 4 h after ingestion of a meal. The trial was registered as UMIN ID: 00000100220. For this study, an aqueous solution of 0.05 M MSG plus 0.102 M (0.6%) sodium chloride was used as stimulus. Salt supplementation was used because the taste intensity experienced with MSG is related to the NaCl concentration (39). Moreover, NaCl is often present in foods containing MSG, so supplemented MSG actually represents a more natural taste stimulus (39). In a preliminary study, we noted that the addition of 0.102 M sodium chloride to MSG solution adequately increased the subjective intensity of taste (3). The concentration of MSG was determined by reference to our and others’ preliminary studies (3, 22, 40).

Distilled water was used to control for activation related to receiving and swallowing a liquid. The rinsing effect also prevented smearing of the stimulus and enhanced its perception. The MSG solution and water were delivered into the participant’s mouth via separate polyethylene tubes at room temperature (24°C). The tubes were connected to a mouthpiece held between the lips, and the tips of the tubes were placed in the oral cavity to enable delivering solutions to the anterior domain of the tongue. Solutions were delivered with syringe pumps manually at the time indicated by computer and a trained technician who prepared the start according to a signal 1 s before delivery. The tubes were filled with the respective solutions by syringe prior to the scanning sessions.

Before scanning, the participants were instructed as follows: “(i) In this examination, you will be administered a taste solution via a mouthpiece repeatedly. (ii) In line with the administration of the solution, roll the solution around on the tongue and continue tasting. (iii) According to the instructions on the screen, swallow the solution.” Each trial was defined by the following sequence: application of taste stimulus fluid (1 s), tasting (10 s), swallowing (2 s), resting (8 s), rinsing (4 s), swallowing (2 s), and resting (13 s, Figure 1A). The taste stimulus consisted of 0.7 ml volume of the MSG solution given as a bolus. Participants were instructed to swallow the fluid before the first “resting” period. The instructions were provided via a screen hung on the top of the bore that the participants viewed using an angled mirror mounted above the head coil. After “tasting,” “swallowing,” and the first “resting,” the participant was delivered 0.7 ml of distilled water. Participants were instructed to swallow the water before the second “resting” period in the same way. Trials were repeated regularly eight times after looking at a fixation cross for 20 s. Total scan time was 340 s.

At Chiba University, all participants underwent MR imaging using a scanner equipped with a 32-channel phased-array head coil (Discovery MR750 3.0 T, General Electric Healthcare, Waukesha, WI, USA). Images were collected by gradient-recalled echo-planar imaging sequence (echo time, 30 ms; repetition time, 2,000 ms; number of slices, 36; flip angle, 76°; acquisition matrix, 64 × 64; slice thickness, 3.7 mm; field of view, 24.0 cm; bandwidth, 111.11 kHz). fMRI images were analyzed using SPM8 software (Wellcome Institute of Neurology, University College London, London, UK, http://www.fil.ion.ucl.ac.uk/spm) running under MATLAB®2013a (The MathWorks, Inc., Natick, MA, USA). Data from the first five volumes were discarded to avoid transient magnetization. Other volumes were realigned to the first one of each scanning session to correct for subject motion, and were spatially normalized into the standard space defined by the Montreal Neurological Institute template. Then, the images were smoothed with an 8-mm isotropic Gaussian kernel.

First level contrast images for each participant were generated on a voxel-by-voxel basis using a general linear model with the “tasting” period (10 s in each trial) as task conditions and the remaining period (“water rinsing” period and waiting phase before and after water rinsing that comprise the total 30 s) as baseline conditions. The design matrix employed a box-car function convolved with the canonical hemodynamic response function, with time and dispersion derivatives. Realignment parameters were included as a nuisance covariate to control for head motion. Next, in order to confirm task-related activation in the whole brain, one-sample t-tests were performed for all participants’ data [P < 0.001 with familywise error (FWE) correction at peak level and q < 0.05 with false discovery rate (FDR) correction at cluster level]. Such tests were also conducted for each group’s data (P < 0.05, with FWE correction at peak level and q < 0.05 with FDR correction at cluster level). Thirdly, in order to detect a group difference in the response to MSG stimuli between the BN and control groups, we performed two-sample t-tests on the effects of tasting the MSG solution (small volume corrections, P < 0.05, FWE corrected at the voxel level) after a priori whole-brain analysis thresholded at P < 0.001, uncorrected for multiple comparisons and more than 54, which was computed as the number of expected voxels per cluster. It is known that populations affected by depressive or anxiety symptoms are characterized by a higher disgust sensitivity threshold (41), which might affect food intake (42). In addition, there is evidence that anxiety itself can affect food intake (42). So, we additionally investigated group differences with depression and anxiety scores as nuisance covariates, respectively. Regions-of-interest in taste processing, which are the left and right insula and anterior cingulate cortex, were defined using the automated anatomical labeling atlas in the PickAtlas (43) for small volume correction.

Current symptoms were assessed by the Eating Disorders Examination Questionnaire (EDE-Q) (44), Bulimic Investigatory Test, Edinburgh (BITE) (45), Patient Health Questionnaire (PHQ-9) (46), and Generalized Anxiety Disorder scale (GAD-7) (47). EDE-Q is a well-known self-report questionnaire that assesses an ED-related symptom profile. EDE-Q includes four subscale scores—restricting (EDE-Qr), eating concern (EDE-Qe), shape concern (EDE-Qs), and weight concern (EDE-Qw). Each subscale score is the mean score of the items forming that subscale, while the global score (EDE-Qg) is the mean of the four subscale scores. The BITE is a 33-item self-report questionnaire designed...
FIGURE 1 | Task design and brain regions activated during tasting monosodium glutamate (MSG) solution. Functional magnetic resonance imaging task design, timeline of events, a representative timecourse of observed blood-oxygen-level dependent (BOLD) responses (A). Brain regions activated during tasting the MSG solution for all participants (B, left) and patients with BN and HW (C). BOLD signal responses to MSG stimuli [(B), right]. Statistical maps were thresholded at \( P < 0.001 \) with familywise error (FWE) correction at peak level (B) or \( P < 0.05 \) with FWE correction at peak level (C). Then, both were thresholded at \( q < 0.05 \) with false discovery rate correction at cluster level. During tasting solution, BOLD signal response was shown in the right anterior insula for all participants. The bar graph [(B), right] represents relative activations in the right insula \((x, y, z = 34, 18, 8)\) in response to MSG stimuli between the two groups. The error bar represents 90% of CI. A, anterior; BN, patients with bulimia nervosa; CI, confidence interval; HW, healthy women participants; L, left.
to assess symptoms of bulimia or binge eating. BITE is composed of two subscales: the symptom assessment scale (BITE-sas) and the severity scale (BITE-ss). The former measures the degree of symptoms present, and the latter provides an index of the severity of binging and purging behaviors as defined by their frequency. PHQ-9 is an easy-to-use screening tool for assessing current depressive symptoms, with a total score >10 (on a 0–27 scale) indicating clinically significant depression. GAD-7 is a simple assessment tool to measure a participant's current anxiety, based on a total score range of 0–21 (higher scores represent greater anxiety). Immediately after scanning, participants were asked to complete a questionnaire including the existence of the feeling of umami, saltiness, and any other taste such as sweetness, sourness, and bitterness in the solution as well as subjective ratings for pleasantness, preference, and intensity of taste for the solution received in the scanner, with numerical ratings on a scale from 5 (extremely unpleasant to −5 (extremely unpleasant), including zero (neutral), and 10 (extremely intense) to 0 (tasteless), respectively.

Statistical Analyses
The non-parametric correlations among the subjective ratings of taste, each of the scales for the clinical measures (EDE-Qg, EDE-Qr, EDE-Qe, EDE-Qw, BITE-sas, BITE-ss, PHQ-9, and GAD-7), and the eigenvariate of the peak voxel defined in the primary gustatory regions (48, 49) activated with the MSG solution in all participants were calculated using SPSS version 21 (IBM Corp., Armonk, NY, USA).

RESULTS
Characteristics of Participants
Demographic and clinical characteristics of female BN patients and HW participants are summarized in Table 1. The two groups did not differ in terms of age, period of education, body mass index, and handedness. On the other hand, BN patients exhibited higher symptoms and severities of ED, depression, and anxiety [EDE-Qg, BN (mean): 4.29, HW (mean): 1.31, P < 0.001; BITE-ss, BN (mean): 13.17, HW (mean): 1.44, P < 0.001; BITE-sas, BN (mean): 24.44, HW (mean): 6.56, P < 0.001; PHQ-9, BN (mean): 12.83, HW (mean): 4.56, P < 0.001; GAD-7, BN (mean): 8.39, HW (mean): 4.78, P = 0.022]. Mann–Whitney U tests revealed that the BN group differed significantly from the control group in all of the dimensional assessments. BN patients reported not only symptoms of BN, but also higher depressive and anxiety symptoms, compared with HW participants.

Subjective Evaluations of the Taste Solution
All participants replied that they felt umami and saltiness to the taste stimulus (0.05 M MSG in 0.102 M NaCl). No participants discerned any tastes other than umami and saltiness. Subjective ratings for the taste solution are summarized in Table 2. Significant differences in the pleasantness [−5 to 5 scale, BN (mean): −1.44, HW (mean): 0.61, P = 0.006] and preference [−5 to 5 scale, BN (mean): −0.67, HW (mean): 1.11, P = 0.047] ratings were observed between BN and HW. BN patients experienced

| TABLE 1 | Demographic and clinical data of patients with bulimia nervosa (BN) and healthy women (HW) participants. |
|----------|-----------------|-----------------|-----------------|
|          | BN              | HW              | P-value         |
|          | Mean  | SD       | Range           | Mean  | SD       | Range           |         |
| Number of participants (n) | 18    |          |                  | 18    |          |                  |         |
| Age (years) | 25    | 5.63     | (18.6–36.3)     | 27.09 | 5.69     | (20.7–36.4)     | 0.285<sup>a</sup> |
| Education (years) | 13.89 | 1.94     | (11–18)         | 14.56 | 1.04     | (12–16)         | 0.211<sup>a</sup> |
| Duration of illness (years) | 3.25  | 3.41     | (0.6–6.5)       | –     | –        | –               | –        |
| BMI (kg/m<sup>2</sup>) | 20.21 | 1.62     | (18.2–23.7)     | 20.51 | 1.44     | (18.8–22.8)     | 0.55<sup>a</sup> |
| Handedness (L/R; n) | 1/17  |          |                  | 1/17  |          |                  |         |
| EDE-Qg | 4.29  | 1.11     |                  | 1.31  | 0.71     |                  | <0.001<sup>b</sup> |
| EDE-Or | 4.12  | 1.56     |                  | 0.6   | 0.62     |                  | <0.001<sup>b</sup> |
| EDE-Qe | 3.94  | 1.23     |                  | 0.67  | 0.57     |                  | <0.001<sup>b</sup> |
| EDE-Qw | 4.5   | 1.13     |                  | 1.74  | 1.16     |                  | <0.001<sup>b</sup> |
| EDE-Qs | 4.58  | 1.23     |                  | 2.17  | 1.21     |                  | <0.001<sup>b</sup> |
| BITE-sas | 13.17 | 4.94     |                  | 1.44  | 0.98     |                  | <0.001<sup>b</sup> |
| BITE-sas | 24.44 | 3.05     |                  | 6.56  | 4.2      |                  | <0.001<sup>b</sup> |
| PHQ-9 | 12.83 | 5.37     |                  | 4.56  | 3.2      |                  | <0.001<sup>b</sup> |
| GAD-7 | 8.39  | 5.07     |                  | 4.78  | 3.26     |                  | 0.022<sup>a</sup> |
| Comorbidities (n) | 4     |          |                  | –     |          |                  | –        |
| Medication (n) | 2     |          |                  | –     |          |                  | –        |

BMI, body mass index; BITE, Bulimic Investigatory Test, Edinburgh; BITE-sas, the symptom assessment scale of BITE; BITE-ss, the severity scale of BITE; EDE-Q, Eating Disorders Examination Questionnaire; EDE-Qe, eating concern; EDE-Qw, global score, the average of the four subscale scores; EDE-Qr, restricting; EDE-Qs, shape concern; EDE-Qw, weight concern; GAD-7, Generalized Anxiety Disorder scale; PHQ-9, Patient Health Questionnaire; SSRIs, selective serotonin reuptake inhibitors.

<sup>a</sup>Two-sample t-tests.

<sup>b</sup>Mann–Whitney U tests.
relatively low pleasantness and liking with the MSG solution. On the other hand, there was no significant difference in the intensity of taste ratings between the BN and control groups [0–10 scale, BN (mean): 6.16, HW (mean): 5.33, P = 0.152].

### Table 3

| Region | Hemisphere | MNI coordinates | Z-score | Voxels | P\textsubscript{FWE}-value |
|--------|------------|-----------------|---------|--------|--------------------------|
|        |            | x    | y    | z    |              |                  |
| All participants |          |      |      |      |              |                  |
| Precentral/postcentral gyrus | L       | −60  | −12  | 30   | 7.61         | 998              | <0.001 |
|                    | L       | −44  | −18  | 38   | 6.54         | <0.001           |
|                    | L       | −62  | 6    | 22   | 5.57         | <0.001           |
| Precentral/postcentral gyrus | R       | 56   | −6   | 38   | 7.00         | 1,891            | <0.001 |
|                    | R       | 54   | −6   | 30   | 7.00         | <0.001           |
|                    | R       | 64   | 4    | 22   | 6.86         | <0.001           |
| Superior frontal gyrus | L       | −8   | −6   | 60   | 6.53         | 487              | <0.001 |
|                    | R       | 8    | 0    | 60   | 6.45         | <0.001           |
| Insula | R            | 34   | 18   | 8    | 6.25         | 155              | <0.001 |
|                    | R            | 38   | 10   | 2    | 5.66         | <0.001           |
| Cerebellum | L       | −36  | −62  | −34  | 5.94         | 126              | <0.001 |
|                    | L       | −12  | −66  | −28  | 5.70         | <0.001           |
|                    | L       | −20  | −68  | −32  | 5.54         | <0.001           |
| Middle frontal gyrus | R       | 32   | 42   | 24   | 5.93         | 55               | <0.001 |
| BN | Precentral/postcentral gyrus | L       | −58  | −14  | 30   | 6.94         | 1,085            | <0.001 |
|                    | L       | −44  | −18  | 40   | 6.13         | <0.001           |
|                    | L       | −64  | −8   | 18   | 5.56         | <0.001           |
| Precentral/postcentral gyrus/inferior frontal gyrus/insula | R       | 50   | −8   | 30   | 6.22         | 3,454            | <0.001 |
|                    | R       | 32   | 42   | 26   | 6.12         | <0.001           |
|                    | R       | 56   | −6   | 18   | 5.96         | <0.001           |
| Supplementary motor area/middle frontal gyrus | R       | 10   | 0    | 62   | 5.83         | 956              | <0.001 |
|                    | L       | −4   | 10   | 50   | 5.52         | <0.001           |
|                    | L       | −2   | −2   | 60   | 5.36         | 0.001            |
| Superior frontal gyrus/middle frontal gyrus | L       | −30  | 46   | 20   | 5.48         | 333              | 0.001 |
|                    | L       | −26  | 48   | 6    | 4.74         | 0.018            |
| Cerebellum | L       | −36  | −62  | −34  | 5.15         | 252              | 0.003 |
|                    | L       | −12  | −64  | −28  | 4.86         | 0.011            |
| HW | Precentral/postcentral gyrus | L       | −60  | −12  | 30   | 5.94         | 319              | <0.001 |
|                    | R       | 58   | −4   | 38   | 5.51         | 908              | 0.001 |
|                    | R       | 62   | 4    | 20   | 5.44         | <0.001           |
|                    | R       | 30   | −4   | 22   | 5.40         | <0.001           |

Activated brain regions are defined by thresholding at P < 0.001 (for all participants) or P < 0.05 (for each group) with FWE correction at peak level, and q < 0.05 with false discovery rate correction at cluster level.

BN, patients with bulimia nervosa; FWE, familywise error; HW, healthy women participants; MNI, Montreal Neurological Institute.

### Table 2

| Region | Numerical rating scale for pleasantness, preference, and intensity with taste solution. |
|--------|---------------------------------------|
|        | Bulimia nervosa | Healthy women | P-value |
|        | Mean   | SD   | Mean   | SD   |
| Pleasantness (between −5 and 5) | −1.44  | 2.25  | 0.61   | 1.79  | 0.006\textsuperscript{*} |
| Preference (between −5 and 5)   | −0.67  | 2.74  | 1.11   | 2.17  | 0.047\textsuperscript{a} |
| Intensity (between 0 and 10)     | 6.16   | 1.82  | 5.33   | 1.41  | 0.152\textsuperscript{a} |

\textsuperscript{*}Mann–Whitney U tests.
null
FIGURE 2 | Group differences of blood-oxygen-level dependent signal responses to monosodium glutamate (MSG) stimuli between patients with BN and HW. The BN group showed higher activation in the right middle insula, bilateral superior frontal gyrus, anterior cingulate cortex, and right middle frontal gyrus compared with the control group at the initial whole-brain exploration threshold at \( P < 0.001 \) uncorrected for multiple comparisons and more than 54 voxels, which was computed as the number of expected voxels per cluster. No brain regions showed smaller activation in the BN group compared with the control group. Statistical maps are shown in sections of regions-of-interest of right insula (A, left) and anterior cingulate (B, left). The bar graphs represent contrast estimates in the right middle insula \([x, y, z = 36, -4, 8, (A), \text{right} ]\) and the anterior cingulate cortex \([x, y, z = 0, 34, 12, (B), \text{right} ]\) in response to MSG stimuli in the two groups. The error bar represents 90% of CI. A, anterior; ACC, anterior cingulate cortex; BN, patients with bulimia nervosa; CI, confidence interval; HW, healthy women participants; L, left; MFG, middle frontal gyrus; SFG, superior frontal gyrus.

Although the brain activity in the right insula in the HW group increased with decreasing subjective pleasantness for the MSG stimuli, that in the BN group was not affected. Interestingly, several studies reported that brain activation to tastes in the right insula decreased as unpleasantness of taste decreased in healthy subjects (65, 66). Our result is consistent with those findings. On the other hand, BN patients showed deregulated insula activation regardless of the scores of pleasantness of the MSG solution.
These results also reinforce our hypothesis of an inability in BN patients to evaluate umami taste properly.

In our results, BN patients showed higher activation in the dorsal anterior cingulate cortex, whereas the orbitofrontal cortex and pregenual anterior cingulate cortex, regions most often reported in co-activation with the orbitofrontal cortex in taste-related studies (67), were not significantly activated in the two groups. The dorsal anterior cingulate cortex is known to reflect the unpleasantness of taste stimuli (68, 69). Higher activation in the dorsal anterior cingulate cortex to MSG stimuli in BN patients compared with HW participants might reflect the perceived relatively low pleasantness or liking of the taste in BN patients.

As previously mentioned, some fMRI studies have investigated the brain responses to taste stimuli in BN with regard to food-reward processing errors in BN. Patients with current BN showed reduced anticipatory responses in the insula to a (sweet) chocolate milkshake (24), and in the insula and striatum to the sweet taste of sucrose (26). Individuals who had recovered from BN showed increased responses in the insula to sucrose (27), and in the striatum to high-fat flavor (whipping cream) (28). These studies showed reduced anticipatory and exaggerated consummatory responses to taste stimuli with hedonic impact, suggesting that this pattern of responding to food-reward might account for deficits in reward evaluating before eating, and excessive reward evaluating in food consumption, which might support the disturbed eating behavior in BN. The enhanced insula activity in the consummatory phase found in our study is consistent with the results of these previous studies, although there are conflicting results among them. Frank et al. reported that participants with recovered BN showed decreased activity in the right anterior cingulate cortex and left cuneus when tasting glucose (25). Bohon and Stice also reported reduced activity in the right insula of patients with current BN related to consummatory, and not just anticipatory, responses to chocolate milkshake (24). To establish a consistent theory on the taste response pattern of BN patients with regard to food-reward processing errors, more data must be accumulated for the future studies.

From a different perspective, it is notable that the insula might work as the key neural structure responsible for disgust processing (70, 71). Vicario et al. suggests that the insula might be the hub structure linking each domain of disgust, not just food-related disgust, in consort with other interconnected brain regions such as the orbitofrontal cortex, striatum, and anterior cingulate cortex (41). Although little is known concerning BN, the involvement of insula dysfunction to altered disgust processing is well-known in AN, and in people with hyperphagia such as obesity (41). Furthermore, as previously mentioned, a recent fMRI study revealed altered insula response to the highly aversive stimulation that is bitterness with quinine in BN patients (36). Since the possibility exists that BN patients might perceive the MSG solution as an aversive stimulus, our results which showed higher activation in the right insula and more negative hedonic scores in response to MSG stimuli might indicate altered processing of disgust not only to highly aversive taste stimuli but also to a wide range of taste stimuli in the current BN patients.

Sweetness, a widely preferred taste, has intense hedonic impact (72), and it may lead to binging or overconsumption (73). On the other hand, MSG also has a greater hedonic impact than water, but a lower impact than sucrose (37). The present study indicates that BN patients might have impaired function in evaluating not only highly pleasant tastes but also tastes with mild pleasantness such as umami, with the possibility that they tend to perceive a wide range of tastes as disgust. Thus, our study suggests the importance of not only controlling excessive palatable foods, but also supporting restoration of appreciation for moderate taste in BN patients.

Several limitations of the present study should be noted. First, because of a lack of accurate and objective examination methods, we were unable to investigate the actual eating habits and preferences of the participants in this study. Also standardized meals prior to the scanning and assessment of subjective ratings on the distilled water and satiety level during scanning would allow for a more accurate analysis of the brain responses to umami tastant. Second, this fMRI study focused only on umami tastant; sweetness and other taste stimuli were not tested. If sweetness and the other tastes were compared simultaneously in the same participants, the significance and specificity of brain responses to umami tastant would be clearer. Furthermore, we did not measure
disgust sensitivity and disgust propensity in our participants. Considering the involvement of their factors in umami activation to aversive stimuli (74), assessment of disgust sensitivity and disgust propensity might help us to attain more reasoned interpretation of our results. In addition, the participants in the study were all Japanese women, who are obviously familiar with Japanese diet and dietary culture, which is deeply involved in applying umami flavoring to various dishes. There are clear inter-individual differences in sensitivity to MSG, and in familiarity to the umami taste, in European cultures (75). Our design limited the generalizability of our conclusions, especially in people of other cultures. Further, we did not exclude participants with depression and those taking medication, although they comprised a small number. Although significant neural response difference in the right insula between the BN group and HW groups survived after control for depression and anxiety (Tables S1 and S2 in Supplementary Material, respectively), our results could have been influenced by these factors. Another limitation relates to our task not excluding the effects of anticipation for taste stimuli on neural responses. Future studies that investigate independently both consummatory and anticipatory phases will help understand neural substrates in patients with BN more clearly.

In conclusion, this is the first study that investigated brain responses to umami tastant in BN patients. The results demonstrated altered perception and hedonic evaluation to umami tastant in BN patients, which might contribute to imbalance in food choices and disordered feelings of satisfaction and pleasure when eating a well-balanced diet.

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ETHICS STATEMENT

The Research Ethics Committee of Chiba University Hospital approved all procedures, and written informed consent was obtained from all participants prior to scanning. All experiments were performed in accordance with the Helsinki Declaration.

AUTHOR CONTRIBUTIONS

RS, YH, and MN designed the project and RS, MT, and TT prepared and provided the MSG solution. RS, YH, NN, KM, and YM, performed the experiment and collected the data. YH and RS analyzed the data. RS and YH drafted the manuscript. MN, DM, MI, and ES supervised this study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fpsyt.2017.00172/full#supplementary-material.

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