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Greater anterior insula activation during anticipation of food images in women recovered from anorexia nervosa versus controls

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Abstract

Individuals with anorexia nervosa (AN) restrict food consumption and become severely emaciated. Eating food, even thinking of eating food, is often associated with heightened anxiety. However, food cue anticipation in AN is poorly understood. Fourteen women recovered from AN and 12 matched healthy control women performed an anticipation task viewing images of food and object images during functional magnetic resonance imaging. Comparing anticipation of food versus object images between control women and recovered AN groups showed significant interaction only in the right ventral anterior insula, with greater activation in recovered AN anticipating food images. These data support the hypothesis of a disconnect between anticipating and experiencing food stimuli in recovered AN. Insula activation positively correlated with pleasantness ratings of palatable foods in control women, while no such relationship existed in recovered AN, which is further evidence of altered interoceptive function. Finally, these findings raise the possibility that enhanced anterior insula anticipatory response to food cues in recovered AN could contribute to exaggerated sensitivity and anxiety related to food and eating.

Keywords

Neuroimaging; fMRI; interoception

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1. Introduction

Anorexia nervosa (AN) is a biologically-based disorder of unknown etiology characterized by an inability to maintain a normal body weight, intense fear of gaining weight despite being underweight, and disturbed body or shape perception (American Psychiatric Association 2000). Recent studies show that genetic heritability accounts for approximately 50–80% of the risk of developing AN (Bulik *et al.* 2006) and contributes to the neurobiological factors underlying this illness (Kaye *et al.* 2009). Such factors may contribute to premorbid traits, such as anxiety (Kaye *et al.* 2004), harm avoidance (Fassino *et al.* 2002), perfectionism (Friederich and Herzog 2011), obsessionality (Anderluh *et al.* 2003; Joos *et al.* 2011a), and interoceptive deficits (Lilenfeld *et al.* 2006), that place some individuals at risk for developing an eating disorder.

The hallmark of restricting-type AN is pathological feeding behavior, namely severe and chronic reduction of food consumption. The advent of functional magnetic resonance imaging (fMRI) has allowed investigators to explore how alterations of brain function may contribute to abnormal eating behaviors in AN. Most functional MRI (fMRI) studies to date have examined the response to presentation of pictures of food in ill (underweight) AN participants compared to healthy controls. For example, an early fMRI study found elevated left insula blood oxygenation level dependent (BOLD) response when viewing images of low calorie versus high calorie drinks (Ellison *et al.* 1998). Uher et al. (Uher *et al.* 2003; Uher *et al.* 2004) found that ill AN showed greater activity in frontal and limbic regions, along with decreased activity in the inferior parietal lobule (IPL), when viewing pictures of food. Several studies (Santel *et al.* 2006; Gizewski *et al.* 2010) examined response in AN subjects to food pictures in both hungry and satiated states, which together show substantial variability in their findings but grossly implicate limbic and cognitive regions known to be involved in the visual processing of food stimuli (van der Lann *et al.* 2011).

Recent studies in obesity (Stice *et al.* 2008) have shown that it is important to investigate the anticipatory response to food. For example, animal studies show that dopaminergic neurons shift firing from the consumption of food to the anticipated consumption of food after conditioning, wherein cues associated with food consumption begin to elicit anticipatory food reward. Because AN have altered dopamine function (Frank *et al.* 2005), which is highly correlated with anxiety (Bailer *et al.* 2012), it is possible that they have an aberrant anticipatory response to cues. While a limited literature (Herpertz *et al.* 2008) suggests that AN have an aversive anticipation of palatable foods, to our knowledge, no studies have used imaging to investigate this crucial issue in AN.

High anxiety, particularly when dealing with food (Kaye *et al.* 2004; Steinglass *et al.* 2012), offers another reason to consider the influence of anticipation in AN participants. Dysregulated anticipation of future aversive events is a fundamental feature of anxiety spectrum disorders (Eysenck 1997). Anxious participants have shown enhanced activation in the right anterior insula and left dorsolateral prefrontal cortex (PFC) during the anticipation of aversive images (Simmons *et al.* 2010). Among healthy controls, anticipation of touch (Lovera *et al.* 2009) and anticipation of food pictures (Malik *et al.* 2011) have been found to activate the insula. While this activation is often greater in the stimulus condition, the group differences in affective regions are often more pronounced during the anticipatory phase (Simmons *et al.* 2006). The anterior insula has been identified as a region of interest in understanding disturbed appetite and interoceptive regulation in AN (Ellison *et al.* 1998; Kojima *et al.* 2005; Wagner et al. 2007 Nunn *et al.* 2008; Redgrave *et al.* 2008; Kaye *et al.* 2009).

The present study sought to determine whether individuals recovered from AN (RAN) have abnormal anticipatory response to viewing pictures of food. Recovered subjects were studied to avoid confounding effects of malnutrition and address possible trait characteristics of AN (see **Supplemental Materials S1**). We used the Uher pictures (Uher *et al.* 2003) to disentangle visual food stimuli anticipation and presentation in RAN compared to control women (CW). To accomplish this goal, a previously published image cueing task (Simmons *et al.* 2008) was modified to predict the presentation of food and object images. Previous studies of negative affective pictures in an anxious population (Simmons *et al.* 2006) and painful stimuli in a clinically depressed population (Strigo *et al.* 2008) have found greater insula activation during anticipation of negative stimuli, followed by a muted insula response upon presentation of the aversive stimuli. We hypothesized that RAN would display greater reactivity in anticipation of the salient food cues as evidenced by elevated anterior insula activation when compared to CW.

2. Methods

2.1. Participants

RAN participants and CW were recruited via flyers and electronic bulletin boards. Participants provided written informed consent and completed this cross-sectional study, which was approved by the University of California San Diego Human Research Protection Program. Trained doctoral level clinicians administered the Structured Clinical Interview for DSM-IV (First *et al.* 1997) and a psychiatric interview to determine eligibility and diagnosis. Fourteen RAN women (12 restricting type and 2 binging-purging type) were identified. When ill, RAN participants met criteria for DSM-IV diagnosis of AN, but never for bulimia nervosa. To be considered “recovered,” participants had to: 1) maintain a weight above 85% average body weight (Metropolitan Life Insurance Company 1959), 2) have regular menstrual cycles; and 3) have not binged, purged, or engaged in significant restrictive eating patterns for at least one year before the study. Twelve medically healthy CW, who had regular menstrual cycles since menses, were also identified. None of the CW met criteria for a current or lifetime diagnosis of an eating disorder or other Axis I disorder. Exclusion criteria for both groups included: 1) lifetime history of attention deficit hyperactivity disorder, psychotic or bipolar disorder; 2) current antidepressant or other psychiatric medication use, alcohol or substance abuse within 90 days of study participation; and 3) active medical problems or suicidal ideation.

2.2. Anticipation of food task

Participants performed a visual anticipatory task in which they viewed standardized images of food and non-food neutral valence object items (Uher *et al.* 2004) during fMRI. Participants were told that during the task a square would precede each food image and a circle would precede each object image; the task was faithful to these instructions. This allowed for measurement of brain activation during the period of anticipatory processing. Participants were asked to report the pleasantness/ unpleasantness ratings of the images immediately after the scan. A fixation cross appeared at the beginning of each trial (~8 seconds), followed by the square or circle “anticipation” stimulus (6 seconds), and the food or object image (2 seconds), for an average trial length of ~16 seconds (**Figure 1**). A total of 17 food and 17 object images were presented in a fixed pseudorandom order. During scanning, images were back-projected to the participants positioned inside the MRI scanner, at a visual angle of approximately 6°. Prior to scan, all participants received a standardized breakfast (bagel, cream cheese, banana, orange juice, skim milk: ~600 calories) with the instruction to “eat until feeling comfortably full.” Across groups, participants ate between 50-100% of the offered breakfast.

2.3. Ratings task

Food and object images were rated on a scale of 1-10 for pleasantness (1 extremely unpleasant, 10 extremely pleasant) using a computerized rating program. Ratings were collected immediately after the scan and were averaged for each individual for both food and object responses. The averaged food-versus-object difference of pleasantness ratings was entered into a two-way analysis of variance (ANOVA) with anticipatory task condition (Food Anticipation, Object Anticipation) and group (CW, RAN) as factors. In addition, the average ratings for food and object images were correlated with anticipatory brain activations in all individuals.

2.4. Scan parameters

An event-related fMRI design was used. During the task, a fMRI run sensitive to BOLD contrast (Ogawa *et al.* 1990) was collected for each participant using a Signa EXCITE (GE Healthcare, Milwaukee) 3.0 T scanner (T2* weighted echo planar imaging, TR=2000 ms, TE=30 ms, FOV=230×230mm, 64×64 matrix, 33 2.6mm axial slices with a 1.4mm gap, 290 scans, 580 seconds). FMRI acquisitions were time-locked to the onset of the task. During the same experimental session, a T1-weighted image (MPRAGE, 172 sagittal slices, TR=8.0ms, TE=4.0ms, flip angle=12q, FOV=250×250, ~1mm^3 voxels) was obtained for cross-registration of functional images.

2.5. Image analysis

Image processing and analysis was performed with the Analysis of Functional NeuroImages (AFNI) software package (Cox 1996). The preprocessed time series data for each individual were analyzed using a multiple regression model consisting of four task-related regressors of interest: 1) food anticipation trials; 2) object anticipation trials; 3) food image trials; and 4) object image trials. Five additional regressors were included in each model as nuisance regressors: three movement regressors to account for residual motion (roll, pitch, yaw), and regressors for baseline and linear trends to account for signal drifts. Percent signal change was calculated by dividing the fit for each regressor of interest by the residual baseline regressor. A Gaussian filter with a full width-half maximum of 6mm was applied to the voxel-wise percent signal change data to account for individual variation in the anatomical landmarks. Data from each participant were normalized to Talairach coordinates (Talairach and Tournoux 1988) and voxels were resampled to 4×4×4mm.

2.6. Task effects

To investigate brain activation during the food anticipation task, percent signal change for the anticipation phases (Food Anticipation, Object Anticipation, and Food Anticipation-Object Anticipation) were entered into whole brain voxel-based one-sample t-tests in both groups (RAN and CW). To investigate the brain activation during image viewing, percent signal change for the image phases was contrasted (Food Image-Object Image) in each group using a whole brain voxel-based two-sample *t*-test. Voxel thresholds were set at $P<0.005$. To control for multiple comparisons, Monte Carlo calculations were performed using the AFNI program AlphaSim (see **Supplementary Materials S2**), and it was determined that a minimum cluster volume of 1024mm^3 was required to maintain significance.

2.7. Group effects

To investigate the group differences in brain activation during the food anticipation task, three separate analyses were performed. Percent signal change for the anticipation phases (Food Anticipation, Food Image, and Food Anticipation-Object Anticipation) were entered into the whole brain voxel-based two-sample *t*-tests in between groups (RAN versus CW). A

similar group comparison was performed for the group contrast during the image phase (Food Image-Object Image). Because our primary goal was to examine group effects, we set a lower threshold for group comparisons. Voxel thresholds were set at $P<0.05$ for the single condition analysis (Food Anticipation and Object Anticipation) and image condition contrast (Food Image-Object Image) and at $P<0.01$ for the contrast analysis (Food Anticipation-Object Anticipation). AlphaSim was used to control for multiple comparisons, as described above.

2.8. Correlations with pleasantness ratings

RAN functional data during anticipation trials were correlated with trait characteristics, including perfectionism (Multi-dimensional Perfectionism Scale) (Frost *et al.* 1990), harm avoidance (Temperament and Character Inventory) (Cloninger *et al.* 1993), anxiety (State-Trait Anxiety Inventory-Version Y) (Spielberger *et al.* 1970), depression (Beck Depression Inventory-I) (Beck *et al.* 1961), and impulsivity (Barratt Impulsiveness Scale-11) (Barrett 1983). Alexithymia (Toronto Alexithymia Scale-20) (Bagby *et al.* 1994) was measured on the day of scan. Due to equipment failure, post-scan responses were not recorded in one CW and one RAN participant; thus, the pleasantness ratings analysis represents data from 11 CW and 13 RAN. Corrections were not made for multiple comparisons.

3. Results

3.1. Participant characteristics

RAN ($n=14$) and CW ($n=12$) were of similar ages and body mass index (**Table 1**). RAN scored significantly higher on overall perfectionism and harm avoidance compared to CW (**Table 1**). No group differences were observed for measures of depression, anxiety, impulsivity, or alexithymia (**Table 1**). Three RAN participants met criteria for current obsessive-compulsive disorder. Of those three participants, one presented with current and one with prior history of trichotillomania. Several RAN participants also met criteria for lifetime (but not current) anxiety and mood disorders such as social phobia (4 individuals), post-traumatic stress disorder (3 individuals), major depressive disorder (7 individuals), and generalized anxiety disorder (2 individuals). One RAN individual met criteria for past alcohol dependence.

3.2. Task performance

A between-subjects MANOVA with group and condition (food anticipation/object anticipation) was performed for both accuracy and reaction time on the continuous performance task. There were no significant group, task, or group by task effects ($P>0.05$).

3.3. Image ratings

A between-subjects MANOVA, using Wilks' criterion (Λ) as the omnibus test statistic, was run to assess group differences on the post-scan images ratings. Using a Bonferroni correction for follow-up comparisons, CW and RAN groups (**Table 1**) were not significantly different in the post-scan pleasantness ratings for images of food, $F(1,22)=1.070$, $P=0.312$, images of objects, $F(1,22)=0.112$, $P=0.741$, or the difference between food and object pleasantness ratings, $F(1,22)=0.86$, $P=0.772$. Both the CW ($t(10)=3.748$, $P=0.004$) and RAN ($t(12)=2.427$, $P=0.032$) groups reported significantly higher pleasantness ratings for images of food versus objects.

3.4. Functional neuroimaging

3.4.1. Task effects—In a one-sample *t*-test, the RAN group activated the inferior frontal gyrus, occipital lobes, anterior and superior cinguate gyrus, and bilateral amygdalae, during

object anticipation; they activated the right middle frontal gyrus, occipital lobes, and posterior cingulate gyrus during food anticipation. In contrast, the CW group activated the occipital lobes and left middle frontal gyrus during object anticipation, and during food anticipation, the occipital lobes and the left inferior frontal gyrus (**Table 2**). Lower pregenual ACC activation was observed in RAN versus CW when viewing images of objects versus food (Object Images>Food Images) (Volume: 2048mm^3, XYZ=0,21,32). For CW, greater activation was found for RAN versus CW in the precuneus (Brodmann's area [BA] 7) in response to viewing food versus object images (Food Images>Object Images) (Volume: 1024mm^3, XYZ=1,−71,40). For the comparison of viewing food and object images across groups, no significant clusters survived thresholding.

3.4.2. Group by task effects—During anticipation of food, RAN had greater activation than CW in the putamen, superior gyrus, and medial frontal (BA 10), while RAN had less activation than CW in the IPL (**Figure 2, Table 3**). When viewing images of food, RAN had greater activation than CW in the IPL, insula, and lateral orbitofrontal cortex and less activation in the medial temporal gyrus (**Figure 3, Table 3**). The between-group contrast for the activation difference between food anticipation and object anticipation (P<0.01) revealed one region of significant interaction in BA 13 of the right ventral anterior insula, F(1,25)=29.30, P<0.001 (Volume: 1344μL, XYZ=38,11,−8). This interaction was driven by greater insula activation in RAN versus CW while anticipating images of food, F(1,25)=16.33, P<0.001, and by deactivation of the insula in RAN while anticipating images of objects, F(1,25)=6.93, P=0.015 (**Figure 4A,B**). Two-tailed paired t-tests revealed that right anterior insula response to Food Anticipation versus Object Anticipation was significantly lower in CW, t(14)=−3.73, P=0.003, but greater in RAN, t(14)=3.91, P=0.002 (**Figure 4B**). No significant group-by-condition interactions were observed when comparing Food Images and Object Images. When the significance threshold was lowered to P<0.05, an additional region of interest was observed in the right medial dorsal nucleus of the thalamus (Volume: 2304μL, XYZ=−4,−16,11; data not shown).

3.5. Behavioral-functional correlation

No significant correlations were observed with pleasantness ratings for either food or object images (XYZ=38,11,−8; **Figure 4C**). Greater insula activation in CW was significantly related (r^2=0.59, P=0.03) to more positive pleasantness ratings, when calculated as the averaged difference between pleasantness of food and pleasantness of objects images. In contrast, there was no such relationship in RAN (r^2=0.004). There were no significant correlations between insula activation and behavioral measures.

4. Discussion

This is the first neuroimaging study to investigate brain activation during the anticipation and viewing of food images versus object images in a group of individuals recovered from AN. This paper presents two major findings. First, compared to CW, RAN individuals showed greater activation of the right ventral anterior insula (**Figure 4A**) when anticipating food images versus object images (**Figure 4B**). Second, insula activation was significantly correlated with food pleasantness ratings in the CW group but not in the RAN group. In conjunction, these findings highlight the complex relationship, from both clinical and neurobiological perspectives, between food and food anticipation in anorexia nervosa.

4.1. Anticipatory activation in the anterior insula

During object anticipation, CW activation patterns were similar to those seen in other studies of anticipation in healthy populations, showing activation in the anterior insula (Adolphs *et al.* 2000; Samanez-Larkin *et al.* 2007). Importantly, in contrast to CW, RAN

showed elevated anterior insula activation when anticipating food images but not object images (**Figure 4**). The ventral anterior insula is cytoarchitectonically closest to the limbic cortex and is extensively connected to other subcortical regions (Dupont *et al.* 2003), providing a link to socio-emotional function (Kurth *et al.* 2010). Importantly, the human gustatory cortex maps to the right anterior insula and bilateral central insula (Kurth *et al.* 2010) and serves as the primary taste cortex (Sanchez-Juan and Combarrors 2001; Small 2010). Other studies from our group found that insula activation during anticipation depends on stimulus intensity rather than valence (Simmons *et al.* 2008; Lovera *et al.* 2009). Pre-existing conditions are thought to create increased sensitivity to an impending arousing stimulus (Strigo *et al.* 2008). While speculative, it is possible that an enhanced anticipatory response to images of food in RAN could explain the exaggerated sensitivity of the anterior insula and the anxiety experienced with regard to their relationship to food. This interpretation matches the observed affective reactivity seen in AN to food-related stimuli (Brockmeyer *et al.* 2011; Steinglass *et al.* 2012). It should be emphasized that these data support a correlational relationship between insula dysfunction and the dissociation of anticipation versus experience of food in AN individuals, although a causal mechanism remains uncertain. It is important to note that greater activation in the insula during anticipation cues versus the viewing of food images does not necessarily imply that subjects are more responsive to the food image cue than the food image, rather, that the response to food images may be related to a dampened or multi-faceted response.

The anterior insula has been implicated in conditions of risk and uncertainty (Mohr *et al.* 2010) and is a primary region of interest in the pathophysiology of anxiety (Paulus and Stein 2006). Studies in anxiety and pain have found that the insula plays a key role in the anticipation of aversive stimuli (Ploghaus *et al.* 1999; Porro *et al.* 2002; Simmons *et al.* 2004; Simmons *et al.* 2006). It is well known that individuals with AN tend to be anxious (Kaye *et al.* 2004), and there is accumulating evidence that they have altered insula function (Ellison *et al.* 1998; Kojima *et al.* 2005; Wagner et al. 2007; Redgrave *et al.* 2008; Kaye *et al.* 2009).

We did not, however, find any relationship between baseline measures of trait or state anxiety and right insula activation. Moreover, there was no relationship to measures of depression or OCD. Thus, greater activity in the right ventral anterior insula among RAN individuals appears to be related to anticipation of the emotionally salient food stimuli and not to their baseline level of anxiety. This lack of a relationship between anxiety and insula activation in AN corresponds to a lack of correlation between insula activation and food image ratings in the current study.

4.2. Insula correlation with pleasantness

For most people, food is inherently pleasant. In fact, for CW, food-versus-object pleasantness ratings significantly correlated with anticipatory insula activation (XYZ=38,11,−8; **Figure 4C**). Similarly, other studies have found that healthy control subjects show a significant positive relationship between pleasure for tastes of food and insula activation (Spetter *et al.* 2010). While both control and RAN groups activate the anterior insula in response to pleasant tastes (Cowdrey *et al.* 2011), a relationship between activation and perceived pleasantness was notably absent in the RAN group (see **Supplemental Materials S3**). As seen previously (Cowdrey *et al.* 2011), the CW and RAN groups did not differ in subjective pleasantness ratings, suggesting that these findings were not related to diminished ratings in the RAN group. A previous study from our group (Wagner *et al.* 2007) found that for CW, pleasantness ratings for sweet taste were positively correlated with insula signal, whereas the RAN participants displayed no such relationship.

RAN activation in the anterior insula is dissociated from self-report of the pleasantness of food and food stimuli.

4.3. Dissociation between anticipation and sensation in RAN

The response of RAN individuals to strong or salient interoceptive stimuli appears to be complex. Currently, only a few published studies are available to elucidate this mechanism. A separate study from our group (Strigo *et al.* 2013) assessing neural substrates of pain anticipation in RAN supports the unique role of the right anterior insula and anticipation of salient information within this population. Interestingly, when anticipating pain, RAN subjects also showed greater activation versus controls in the right anterior insula, as well as in the dorsolateral PFC (dlPFC) and cingulate. In contrast, when sensing pain, the RAN subjects showed greater activation versus controls within the dlPFC and decreased activation within the posterior insula. Similarly, prior studies from our group (Wagner et al. 2007; Oberndorfer *et al.* 2013) found that compared to controls RAN had diminished anterior insula response to tastes of sucrose.

Considered together, these studies of physiologically salient stimuli (food and pain) suggest that RAN demonstrate a mismatch between anticipatory and objective responses. Such a mismatch suggests altered integration that possibly leads to a disconnect between reported and actual interoceptive states. This proposed mechanism of anticipatory dissociation in the insula has been considered with regard to other psychiatric disorders. Specifically, the insula is thought to code interoceptive prediction error, signaling mismatch between actual and anticipated bodily arousal, which in turn elicits subjective anxiety and avoidance behavior (Paulus and Stein 2006). Along with interoceptive difficulties, this may also be tied to the preponderance of alexithymia in AN (Sexton *et al.* 1998), which also is related to increased insula activation and is thought to be tied to deficits in emotional processing (Heinzel *et al.* 2010). Future studies are needed to explore the role of insula dysregulation in AN symptomatology, specifically the discordance of anticipating versus experiencing salient stimuli, within the context of frontal and limbic circuitry.

4.4. Anticipation and emotion in AN

AN individuals tend to be obsessed with food and anticipating food, spending many hours per day counting calories, reading recipes, and cooking for others. Still, food is highly emotional (Brockmeyer *et al.* 2011) and associated with anxiety (Steinglass *et al.* 2012), and just the thought of food appears to generate substantial discomfort. Interestingly, Joos and colleagues (Joos *et al.* 2011b) showed that this emotional salience is reflected functionally by increased right amygdala activity in ill restricting-type AN viewing similar images of foods (Uher *et al.* 2003; Uher *et al.* 2004) The authors posited that pathologic thoughts and behaviors in AN individuals may be mediated by dysregulation of neural networks responsible for processing food stimuli of various modalities, which underlies exaggerated amygdala response. Our study did not observe similar amygdala response to food images. However, our cohort consisted of women recovered from AN who may not experience as profound an emotional response to food images as acutely ill AN subjects. It is also possible that the anticipation of viewing non-salient food images may have further diminished their emotional impact.

Given that food is an inherently emotional stimulus in AN, a mismatch between limbic hyperarousal and cognitive control may be tied to both interoceptive and emotional processing deficits in this recovered population. We observed right anterior insula hyperactivity in response to anticipating food images. It is worth noting that, similar to Joos *et al.*, we did not observe differences of insula response in RAN individuals viewing food images. The present study adds to a growing literature that collectively suggests that

dysregulation of insula function may contribute to disconnection between the approach and avoidance of food in AN.

4.5. Anticipation and reward error detection in RAN

Anticipation of an event may engage different neurocircuitry than detecting error of prediction (Knutson and Wimmer 2007), which may also be disturbed in AN individuals. Using a temporal difference model to test dopamine-related brain reward response to sweet tastes, Frank *et al*. (Frank *et al.* 2012) found that ill restricting-type AN individuals had increased right insula, striatal, and dlPFC response compared to controls during error detection. The insula findings described by Frank and colleagues are localized to BA 13 and lateralized to the right, similar to the present findings. As described above, this region of the insula is the primary taste cortex and is also involved in interoceptive processing. It is possible that exaggerated right anterior insula response during error detection may in fact be due to the sweet taste stimulus that informed subjects of a predictive error during this task. However, exaggerated insula response may also reflect aberrant error detection in AN individuals, suggesting the possibility of a shared role of the insula in processing anticipation and error detection. Taken together, AN individuals demonstrate exaggerated insula response to both anticipated and unexpected stimuli when compared to healthy control women.

4.6. Inferior parietal and medial prefrontal findings

In contrast to prior studies (Uher *et al.* 2003; Uher *et al.* 2004), we found significantly *lower* IPL activation during anticipation of food images, but *greater* IPL activation when RAN viewed images of food, compared with CW. Additionally, we found that food anticipation engaged the medial prefrontal inhibitory network significantly more in RAN compared to CW (**Table 3**), consistent with past studies in both RAN (Uher *et al.* 2003) and ill AN (Uher *et al.* 2003; Uher *et al.* 2004; Gizewski *et al.* 2010). These findings are discussed in greater detail in **Supplementary Materials S4**.

4.7. Comparison to prior studies with image presentation

The current study used the pictures of food developed by Uher (Uher *et al.* 2003). The Uher study, which compared nine RAN and nine CW (and 8 ill AN), differed in study design. Uher presented four sets of pictures: 1) food images, 2) color and shape matched object images, 3) emotionally aversive images, and 4) object images. Our study only used the first two sets of stimuli but also employed anticipatory cues directly preceding the food and object images. As discussed above, in prior research, arousing (specifically aversive) stimuli resulted in a greater activation prior to the stimulus, which led to subsequent decreased activation during the stimuli in affective (Strigo *et al.* 2008) or attentional (Simmons *et al.* 2006) regions. This reciprocal reaction during the stimulus that results from separating the cognitive preparation from the physical representation of the stimulus can obscure direct comparison of the stimulus phase. Thus, in light of the known dissociation of the affective impact from resultant behavior, and in the context of the proposed mechanism, the current study is in direct agreement with prior work.

Other studies examined ill AN individuals viewing food images in fasted and satiated states (Santel *et al.* 2006; Gizewski *et al.* 2010). When hungry, AN exhibited diminished activation in the right visual occipital cortex (Santel *et al.* 2006) and elevated activation in the PFC, postcentral cortex, and left anterior insula, relative to controls (Gizewski *et al.* 2010). When satiated, AN displayed greater activation in the left IPL (Santel *et al.* 2006) and the left insula (Gizewski *et al.* 2010) versus controls. Overall, these studies are consistent with the present findings of increased right anterior insula activation during anticipation of food images.

4.8. Limitations

In this study, we investigated a group of women recovered from AN. While metabolic problems complicate imaging in currently ill AN participants, the present RAN group findings are similar to findings in studies that examined currently ill AN patients (Uher *et al.* 2003; Uher *et al.* 2004), suggesting that a generalization is plausible. Also, anticipation of food stimuli has been compared to actual oral consumption of food in healthy (O'Doherty *et al.* 2002; Small *et al.* 2008) and obese (Stice and Spoor 2008) populations, but anticipation of visual food stimuli has not been assessed. It should be noted that the experience of a picture of food differs from the consumption of food, and comparisons using actual food stimuli should be addressed in future studies.

The current study also had several limitations of study design and analysis. The RAN group had a number of comorbid disorders. We lacked power to determine how these may have contributed to the current findings. Additionally, two of our 14 RAN participants were binge-purge subtype, which could potentially confound the results. These participants were kept in the sample to maintain power. While subjective pleasantness ratings were recorded, no data were collected regarding the potentially anxiety-provoking nature of the stimuli. As correction for multiple comparisons was not made in the exploratory correlation analysis, it is possible that the positive correlation observed between image pleasantness ratings and right anterior insula activity in CW may be due to chance.

Finally, with this anticipatory task, we expected to observe group and condition activation differences beyond the right anterior insula in regions that process anticipation and uncertainty. Group comparisons in fact yielded differences in the frontal cortex, right dorsal striatum, and thalamus (**Table 3**), though these group differences failed to reach significance in the group-by-task comparison. Larger group sizes will help elucidate activation differences in neurocircuitry related to anticipation.

4.9. Conclusion

We found that: (1) RAN women compared to CW showed greater activation of the anterior insula during anticipation of food versus object images, and (2) while anticipating the visual food cue, insula activation positively correlated with image pleasantness ratings in CW but not RAN. Anticipation of the food image was thus decoupled from the subjective experience of viewing food images in RAN individuals. These are novel findings in the anticipatory behavior and corresponding neural response of RAN individuals that together support the possibility of a dysregulation of interoceptive processing in AN.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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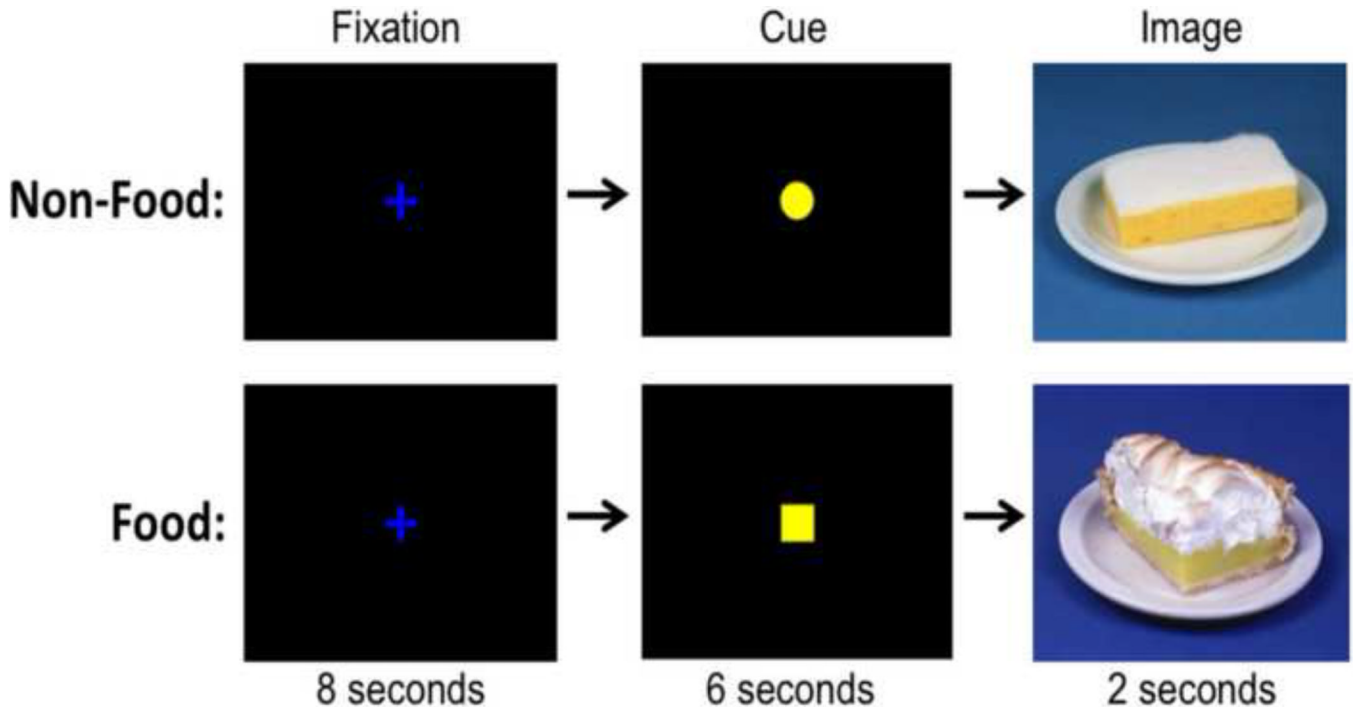

FIGURE 1. Task design

Anticipation paradigm based on a previously published cueing task (Peper *et al.* 2009) using images of food and object images obtained by Uher et al. (Uher *et al.* 2003).

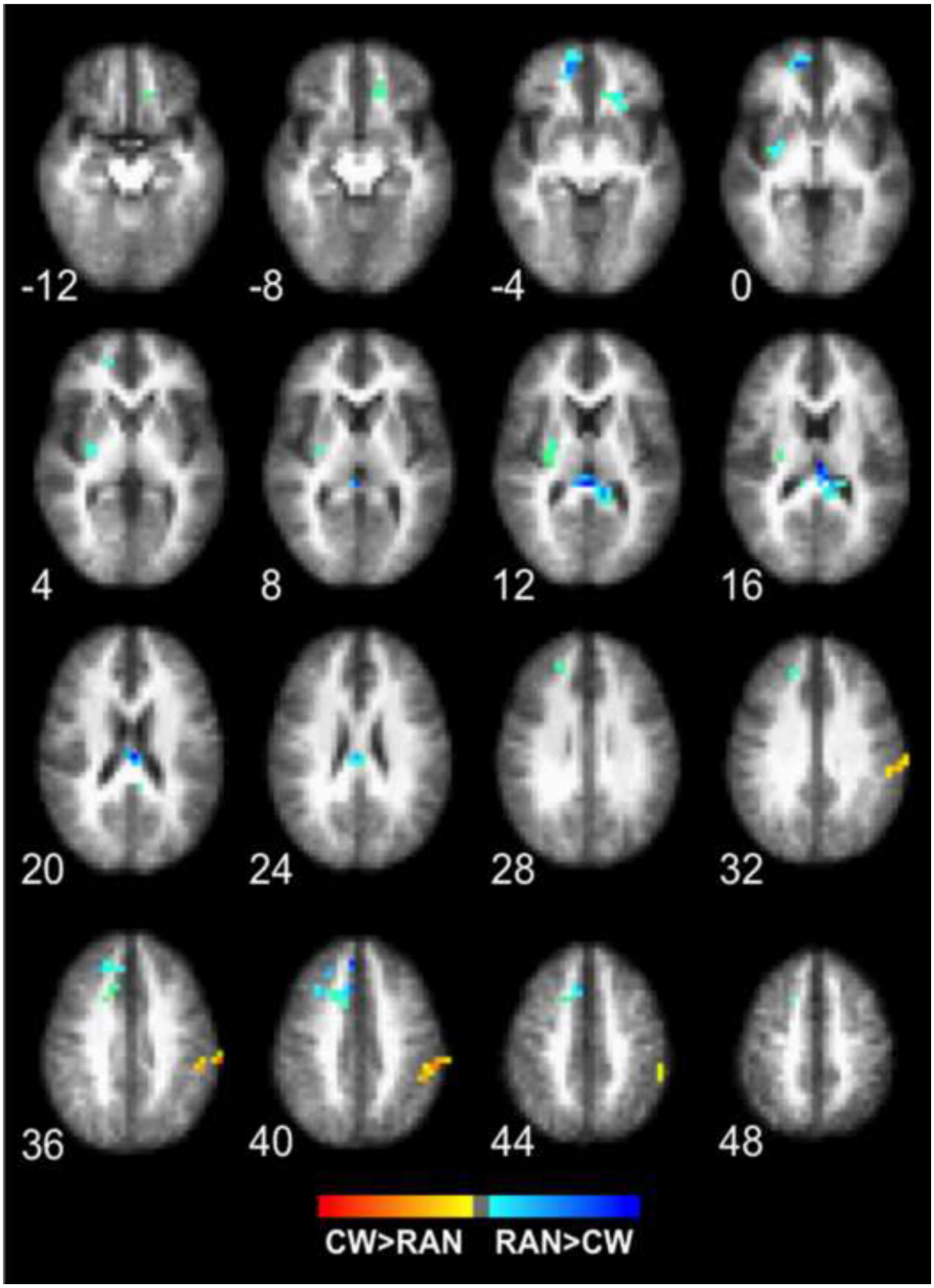

FIGURE 2. Group Effects during Food Anticipation (*P*<0.05, minimum cluster volume 1024mm^3)

Axial images are displayed in Talairach Z coordinates (Talairach and Tournoux 1988). Control women (CW). Women recovered from anorexia nervosa (RAN).

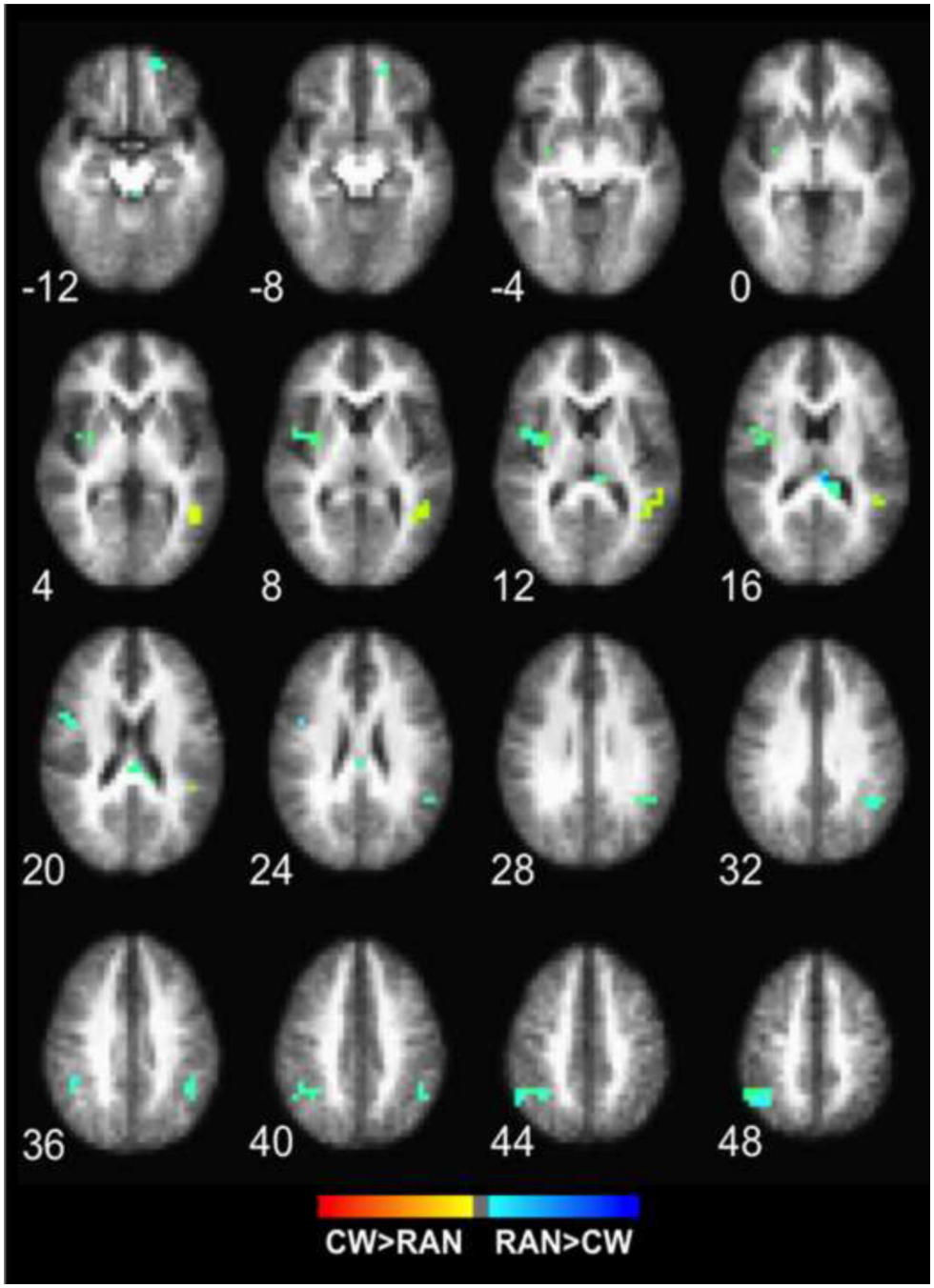

FIGURE 3. Group Effects during Food Images (*P*<0.05, minimum cluster volume 1024mm^3)
Axial images are displayed in Talairach Z coordinates (Talairach and Tournoux 1988). Control women (CW). Women recovered from anorexia nervosa (RAN).

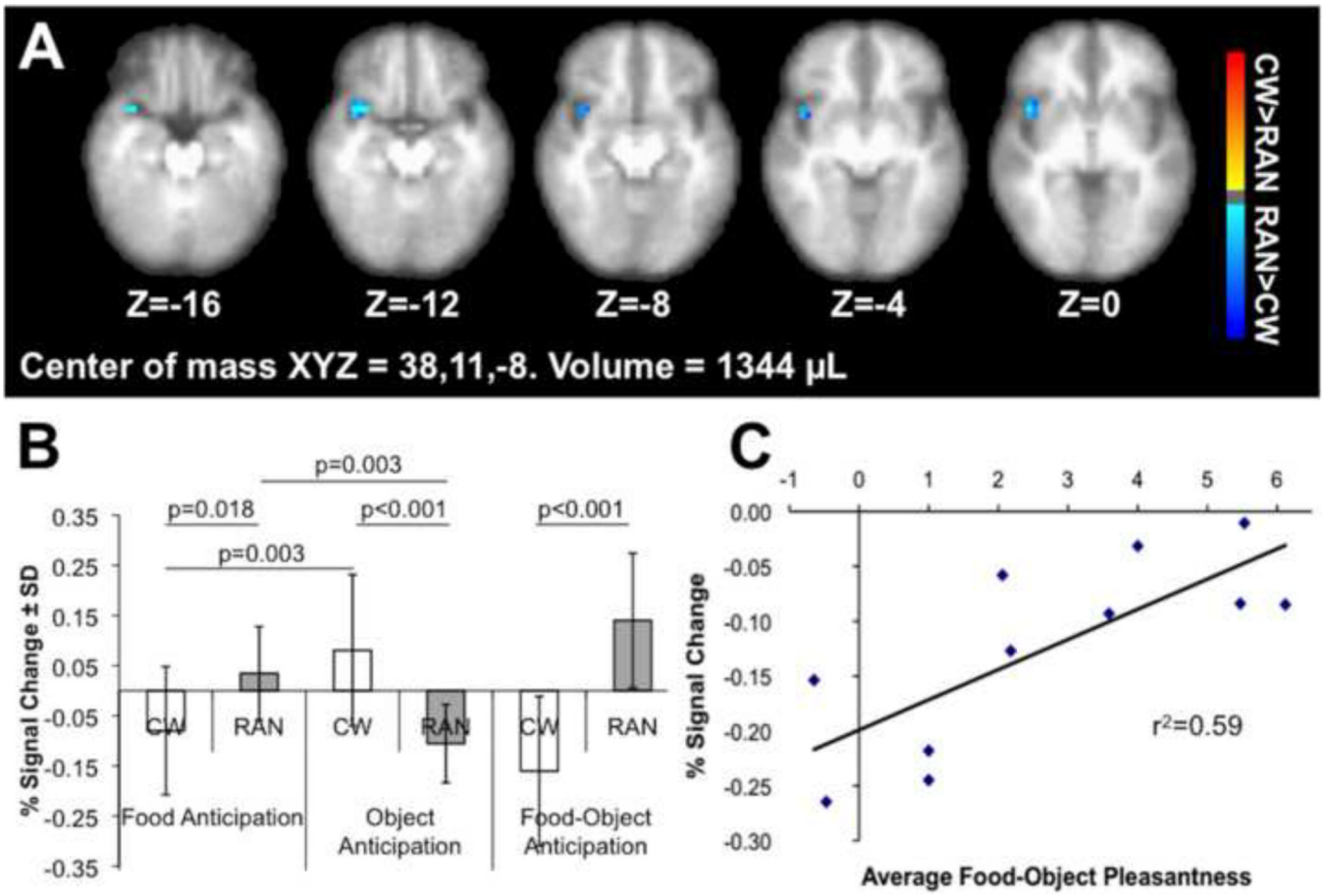

FIGURE 4. Group (CW,RAN) by Condition (Food Anticipation, Object Anticipation) whole brain comparison

Regions of interest were thresholded at $P<0.01$ with a minimum cluster volume of 1024mm^3. **(A)** One significant region of interest was identified in the right anterior inferior insula (1344mm^3) characterized by **(B)** significantly increased response to anticipation of food, $P=0.018$, and significantly decreased response to anticipation of object images, $P<0.001$, in women recovered from anorexia nervosa (RAN) versus control women (CW). Post-hoc 2-tailed paired *t*-tests yielded significant within group and within condition differences. **(C)** The average difference of food and object pleasantness ratings showed a significant positive correlation with Food Anticipation – Object Anticipation percent signal change in this right anterior insula region in CW ($r^2=0.59$) but not RAN (data not shown).

TABLE 1

Subject Demographics. Control women (CW) and women recovered from anorexia nervosa (RAN) groups were similar in age and current body mass index. **Self-Assessments.** RAN scored significantly higher for overall perfectionism and harm avoidance compared to CW. No group differences were observed for depression, anxiety, impulsivity, or total alexithymia. Beck Depression Inventory-I (BDI) (Beck *et al.* 1961). State-Trait Anxiety Inventory-Version Y (STAI-Y) (Spielberger *et al.* 1970). Barratt Impulsiveness Scale-11 (BIS-11) (Barrett 1983). Multi-dimensional Perfectionism Scale (MPS) (Frost *et al.* 1990). Temperament and Character Inventory (TCI) (Cloninger *et al.* 1993). Toronto Alexithymia Scale-20 (TAS-20) (Bagby *et al.* 1994). **Pleasantness Ratings.** Subjective pleasantness ratings of food ($F(1,22)=1.070$, $P=0.312$) and object ($F(1,22)=0.112$, $P=0.741$) images were similar between control women (CW, N=11) and women recovered from anorexia nervosa (RAN, N=13). Subjective pleasantness ratings of food images were significantly greater than object images for both CW ($t(10)=3.748$, $P=0.004$) and RAN ($t(12)=2.427$, $P=0.032$) groups.

	CW			RAN			
	Mean	**Std. Dev.**	**Range**	**Mean**	**Std. Dev.**	**Range**	***P***
Age	26.0	6.8	18-39	28.9	6.6	21-44	0.280
Body Mass Index	21.9	1.0	20-24	22.0	1.6	19-25	0.947
Age of Onset	-	-	-	13.3	2.4	10-19	-
Disease Duration (Years)	-	-	-	7.4	7.4	2-25	-
Years Recovered	-	-	-	8.1	4.8	1-16	-
BDI: Depression	2.7	3.4	0-10	3.7	3.9	0-13	0.490
STAI-Y: State Anxiety	26.5	7.5	20-47	28.5	7.7	20-50	0.510
STAI-Y: Trait Anxiety	29.5	6.8	21-46	34.0	9.8	20-56	0.198
BIS-11: Motor Impulsivity	21.3	2.9	17-26	20.6	4.6	14-32	0.650
BIS-11: Attentional Impulsivity	13.3	3.0	11-20	13.8	4.9	9-25	0.794
BIS-11: Non-Planning Impulsivity	19.3	4.0	12-25	21.0	5.4	14-31	0.368
MPS: Overall Perfectionism	66.4	14.1	42-84	93.8	21.6	61-128	0.001
TCI: Harm Avoidance	7.7	2.9	2-13	14.5	7.6	3-27	0.008
TAS-20: Total Alexithymia	36.4	7.0	28-55	36.5	8.9	26-62	0.989
Food Pleasantness	5.1	1.7	2.3-7.4	4.4	1.5	2.0-6.8	0.312
Object Pleasantness	2.4	2.1	1.5-4.9	2.7	2.0	1.5-4.7	0.714

TABLE 2

Task Effects ($P<0.005$, minimum cluster volume 1024mm^3)

Main effect regions of activation during anticipation of food and non-food visual stimuli are presented.

Group	Condition	mm^3	#	X	Y	Z	Region of Interest	BA
CW	Food Anticipation	2752	43	35	−62	−8	R Fusiform Gyrus	37
		1984	31	−41	−56	−7	L Occipital Lobe, Sub-Gyral WM	
		1664	26	−27	−80	−2	L Occipital Lobe, Sub-Gyral WM	
		1408	22	−43	35	10	L Inferior Frontal Gyrus	46
	Object Anticipation	5120	80	34	−76	−5	R Inferior Occipital Gyrus	19
		4544	71	−41	−54	−12	L Fusiform Gyrus	37
		2752	43	−29	−82	−4	L Inferior Occipital Gyrus	19
		1984	31	−44	21	23	L Middle Frontal Gyrus	46
RAN	Food Anticipation	10176	159	−1	−48	39	Posterior Cingulate Gyrus	31
		9536	149	−36	−69	−5	L Occipital Lobe, Sub-Gyral WM	19
		3840	60	1	50	4	Medial Frontal Gyrus	10
		3520	55	32	−81	0	R Middle Occipital Gyrus	18
		1472	23	44	−52	−8	R Temporal Lobe, Sub-Gyral WM	
		1024	16	−25	−70	35	L Precuneus	7
		1024	16	−25	−38	49	L Parietal Lobe, Sub-Gyral WM	
	Object Anticipation	8896	139	−39	−56	−10	L Fusiform Gyrus	37
		3904	61	28	−43	−14	R Fusiform Gyrus	37
		3712	58	43	−55	−8	R Occipital Lobe, Sub-Gyral WM	
		3264	51	31	−84	−2	R Occipital Lobe, Sub-Gyral WM	
		3072	48	43	31	11	R Inferior Frontal Gyrus	46
		3008	47	47	8	26	R Inferior Frontal Gyrus	9
		2880	45	25	−7	−13	R Amygdala	
		2368	37	−28	−88	−2	R Occipital Lobe, Sub-Gyral WM	
		2368	37	1	−30	28	Cingulate Gyrus	
		2304	36	−24	−5	−14	L Amygdala	
		1920	30	−1	−51	29	Anterior Cingulate Gyrus	32
		1152	18	39	−13	47	R Precentral Gyrus	6
		1088	17	−16	−21	64	L Precentral Gyrus	6

CW: Control women. RAN: Women recovered from anorexia nervosa. Main effect regions of interest obtained in conditions viewing food or non-food images are not presented. Brodmann's area (BA). Talairach coordinates (X,Y,Z) (Talairach and Tournoux 1988). Volume (mm^3). Number of voxels (#).

TABLE 3

Group Effects ($P<0.05$, minimum cluster volume 1024mm^3)

Activation differences between women recovered from anorexia (RAN) versus control women (CW) are presented for anticipation of food and viewing food images. Ordered by Talairach coordinates (X,Y,Z) (Talairach and Tournoux 1988), refer to Figure 3 and Figure 4 for images. Brodmann's area (BA). Volume (mm^3). Number of voxels (#).

Condition	mm^3	#	X	Y	Z	Region of Interest	BA	Direction
Food Anticipation	1280	20	−16	31	−8	L Medial Frontal Gyrus	10	RAN>CW
	1280	20	13	51	−2	R Superior Frontal Gyrus	10	RAN>CW
	1344	21	28	−10	7	R Dorsal striatum, Putamen		RAN>CW
	2944	46	−3	−31	16	L Thalamus, Pulvinar		RAN>CW
	1664	26	−53	−32	37	L Inferior Parietal Lobule	40	CW>RAN
	1536	24	14	15	41	R Medial Frontal Gyrus	32	RAN>CW
	1088	17	15	33	36	R Medial Frontal Gyrus	8	RAN>CW
Food Images	1216	19	27	−67	−35	R Inferior Cerebellum		CW>RAN
	1088	17	−33	−73	−34	L Posterior Cerebellum		RAN>CW
	1344	21	2	−34	−21	Anterior Cerebellum		RAN>CW
	1344	21	−22	50	−16	L Superior Frontal Gyrus	11	RAN>CW
	1600	25	−44	−49	9	L Superior Temporal Gyrus	39	CW>RAN
	1408	22	−41	−49	9	L Superior Temporal Gyrus	39	RAN>CW
	2304	64	39	−1	13	R Insula	13	RAN>CW
	1216	19	−7	−31	18	L Posterior Cingulate Gyrus	23	RAN>CW
	2432	38	41	−51	44	R Inferior Parietal Lobule	40	RAN>CW