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Associations between neural correlates of visual stimulus processing and set-shifting in ill and recovered women with anorexia nervosa

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ABSTRACT

Women ill with anorexia nervosa (AN) have been shown to exhibit altered cognitive functioning, particularly poor set-shifting (SS). In this study, we investigated whether brain activation in frontal and parietal regions during visual stimulus processing correlates with SS ability. Women currently ill with AN (AN; N=14), recovered women (REC; N=14) and healthy controls (HC; N=15), viewed alternating blocks of food and non-food pictures during functional magnetic resonance imaging (fMRI). The Berg's Card Sorting Task was completed outside the scanner to measure SS. A priori regions of interest (ROIs) were defined in frontal and parietal regions. The activation during visual stimulus processing in several ROIs correlated positively with poor SS ability in REC, particularly in the left dorsal anterior cingulate cortex (dACC). The correlations with poor SS ability were opposite in AN patients, particularly in the right dACC. These findings underscore that addressing heightened levels of cognitive control associated with higher frontal activation could reduce cognitive inflexibility in recovered women. In AN, greater activation in frontal and parietal regions might be necessary to perform at normal levels during various tasks. Thus, weight restoration could be necessary for AN patients prior to addressing cognitive inflexibility.

1. Introduction

Anorexia nervosa (AN) is a severe mental disorder with a lifetime prevalence of 2% among women and a high mortality rate of 5% per decennium (Arcelus et al., 2011; Smink et al., 2013). AN is characterized by restricted eating and obsessive fears of gaining weight despite life-threatening underweight (American Psychiatric Association, 2006). Trait-related features such as rigidity and perfectionism have also been identified as being typical of people suffering from AN (Tchanturia et al., 2004). Several studies suggest that clinical features related to rigidity and perfectionism could mirror altered cognitive functioning, particularly poor set-shifting (Roberts et al., 2007).

Set-shifting (SS) refers to the ability to move back and forth between different cognitive strategies, mental sets, and behaviors (Miyake et al., 2000). Patients with AN are believed to be impaired in cognitive SS, i.e. they exhibit more rigid approaches to changing rules, and behavioral response shifting, i.e. their behaviors are stereotypical or perseverative (Zastrow et al., 2009). This cognitive inflexibility could lead to maintenance of symptoms and resistance to treatment (Steinglass et al., 2006). Multiple studies have demonstrated that patients with AN have significantly worse outcomes on SS tasks than healthy controls (HC) (Abbate-Daga et al., 2014; Roberts et al., 2007; Rose et al., 2012). Difficulties in SS have also been observed in patients recovered from AN (Holliday et al., 2005; Roberts et al., 2007), suggesting that at least some aspects of SS are trait-, rather than state-related (Tchanturia et al., 2004).

Several neuroimaging studies have demonstrated the primary role of frontostriatal pathways in SS and behavioral response alterations (Cools et al., 2004; Shafritz et al., 2005). In particular, the dorsal executive system that includes the dorsal anterior cingulate cortex (dACC), the dorsolateral prefrontal cortex (DLPFC), pars triangularis region of the inferior frontal cortex, the inferior parietal lobule, and the caudate nucleus has been indicated as the key brain system subserving response inhibition in HC (Marsh et al., 2007; Menon et al., 2001; Watanabe et al., 2002). The error

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processing system, involving medial PFC, insula, frontal operculum, and the left precuneus/posterior cingulate cortex, has been shown to be responsible for performance monitoring (Menon et al., 2001).

Patients ill with AN who demonstrate poor SS ability are overly concerned with planning and estimating consequences (Zastrow et al., 2009). Neuroimaging studies have demonstrated altered activation within the dorsal executive circuit related to impaired SS and prefrontal cortex regarding error monitoring in AN patients compared to HC. Exaggerated dorsal executive system function is associated with enhanced inhibition as well and may play a role in modulating anxiety (Kaye et al., 2013). During a target-detection task, women ill with AN showed predominant activation in frontal and parietal regions, and hypoactivation in the left and right thalamus, ACC, and ventral striatum compared to HC (Zastrow et al., 2009). In another study, AN patients did not differ from HC regarding perseverative error rate while performing the Wisconsin Card Sorting Task (WCST) (Sato et al., 2013). However, they showed decreased task-related activation in the right ventrolateral prefrontal cortex and bilateral parahippocampal cortex, but higher activation in the cingulate cortex, striatum, and insula compared to HC.

Moreover, as the activation in dorsal executive circuits is related to inhibitory control and studies have demonstrated altered activation and performance pertaining to response inhibition in AN patients, it could be related to altered SS ability in AN as well. Reduced activation in the right DLPFC and hypothalamus was shown in AN-R (Anorexia nervosa: restrictive type) compared to AN-BP (Anorexia nervosa: binge-purge type, and Bulimia nervosa) in a study investigating neural correlates of response inhibition, using the Go/No Go task, even though no differences regarding task accuracy in Go and No Go trials between the groups were found (Lock et al., 2011). Furthermore, it has been shown that patients ill with AN need less inhibitory resources to maintain behavioral performance as inhibitory load increases. As the inhibitory demand during the stop signal task increases, patients ill with AN show a decreased activation in the right dACC, right MFG, and posterior cingulate cortex compared to HC (Wierenga et al., 2014). In addition, AN patients make significantly less errors than their healthy counterparts in a speeded choice-reaction task, but they also show a blunted ACC response to errors (Pieters et al., 2007).

Thus, increased capability for effortful cognitive control might be a reason why AN patients are able to override immediate rewards like food, in favor of delayed rewards, i.e. thinness, and hence maintain food restriction despite constant malnutrition (Steinglass et al., 2012). Some studies have demonstrated that in response to appetitive stimuli, women ill with AN show excessive top-down prefrontal cortical activation (Kaye et al., 2009; van Kuyck et al., 2009). In particular, medial and dorsolateral prefrontal cortex, precuneus, and ACC are among the frontal regions pertaining to cognitive control that have been found to show aberrant activation during food viewing in ill and recovered women with AN (Brooks et al., 2011; Uher et al., 2003).

This is a further analysis of data from a study on which two papers were published; one on the neuropsychology (Danner et al., 2012) and one on food-cue processing (Sanders et al., 2015). Danner et al. (2012) investigated set-shifting, central coherence, and decision making in ill women with AN, recovered women, and healthy women. AN and REC demonstrated poor SS and decision making compared to HC, indicating that a rigid thinking style might reflect stable traits in women with AN. Sanders et al. (2015) explored whether AN and REC show aberrant brain activation within top-down (TD) brain regions associated with cognitive control and bottom-up brain regions associated with reward processing during food evaluation. They found that AN and REC showed increased activation within brain regions associated with cognitive control, indicating that food-cue processing is also altered in recovered AN patients. The behavioral evidence that cognitive control is exerted in food-cue processing paradigms, however, is lacking. Nevertheless, increased frontal activation (i.e. DLPFC and ACC) in AN has previously been associated with a network that controls appetitive drives with cognitive restraint mechanisms (Brooks et al., 2012). Thus, increased activation in AN and REC in frontal regions in our previous analyses might indicate that cognitive control may indeed have been exerted.

Thus, as both AN and REC demonstrated poor SS and increased activation in brain regions involved in cognitive control in two previous studies, we reasoned that the same neural alterations may underlie poor SS ability and cognitive processing of visual stimuli in general. Therefore, the aim of the present study was to investigate whether the activation in frontal and parietal regions during visual stimulus processing (of both food and non-food images) is associated with set-shifting ability measured outside the scanner in women currently ill with AN and recovered women. We hypothesized that higher frontal and parietal activation during cognitive processing of visual stimuli may be associated with poor SS ability in women ill with AN and recovered women.

2. Methods

2.1. Participants

16 women with chronic anorexia nervosa (AN), 15 women recovered from AN (REC), and 15 healthy women (HC) were included in the study. After data quality checks (see Section 2.5), we included fourteen AN (mean age=25.6, SD=5.8y, mean duration of illness=7.7y, SD=4.2y), fourteen REC (mean age=24.8, SD=4.5y; mean duration of illness=4.3y, SD=2.7y, mean duration of recovery=4.9y, SD=2.7y), and fifteen HC without any history of psychiatric disorders (mean age=25.8, SD=5.8y) in the analyses. AN and REC participants were diagnosed by a psychiatrist according to DSM-IV criteria. The AN group consisted of in- or outpatients in an eating disorder clinic (Altrecht Eating Disorders Rintveld, Zeist, The Netherlands). The REC group consisted of former in- or outpatients screened by a resident in psychiatry. REC had been weight [body mass index (BMI) above 18.5 kg/m^2] and menstrual cycle recovered for at least 12 consecutive months. Recovery was also confirmed with their overall levels of eating pathology, given that REC did not differ from HC on the Eating Disorder Examination Questionnaire (EDEQ) (Table 1).

Smoking, left-handedness, major medical illness, and current use of dopaminergic or serotonergic medication were exclusion criteria for all three groups. In addition, a history of neurological disorder, current pregnancy, claustrophobia, and metal objects in the body that would interfere with MRI scanning were also considered to be exclusion criteria. For REC and HC groups, additional exclusion criteria included BMI (in kg/m^2) <18.5 or >25 at the time of screening, current dieting or weight-loss, and restrained eating (according to EDEQ). The study was approved by the Institutional Review Board of the University Medical Center (Utrecht). Participants provided written informed consent.

2.2. Stimuli

The fMRI paradigm, including the images, used in this study has been used before in another study with eating disorder patients at the Institute of Psychiatry in London (Uher et al., 2004, 2003). Visual stimuli consisted of food and non-food images. The food images consisted of 60 color photographs of low and high calorie, sweet and savory foods that were presented on a white

Table 1
Means and standard deviations of subject characteristics and the results of a one-way ANOVA concerning group differences.

Measure	Measures			F	p
	HC (N = 15)	AN (N = 14)	REC (N = 14)		
Age	25.80 (4.7)	25.57 (5.8)	24.79 (4.5)	0.16	0.853
BMI (kg/m^2)	21.46 (2.3)	14.63 (1.7)[a,b]	21.14 (2.0)	52.55	$p < 0.001$
Fat%	25.67 (4.6)	6.96 (6.6)[a,b]	25.0 (5.5)	49.16	$p < 0.001$
BDI total score	1.47 (3.2)	39.07 (5.9)[a,b]	7.8 (8.6)[a]	147.95	$p < 0.001$
EDEQ restrained eating	0.39 (0.7)	3.89 (0.9)[a,b]	1.21 (0.9)[a]	71.05	$p < 0.001$
EDEQ global score	0.12 (0.2)	2.72 (3.7)[a]	0.81 (0.8)	5.54	0.008
Trait anxiety (STAI score)	30.80 (5.8)	48.0 (3.3)[a]	47.9 (3.8)[a]	72.73	$p < 0.001$
State anxiety (STAI score)	31.33 (5.4)	47.5 (4.3)[a]	46.4 (4.0)[a]	57.18	$p < 0.001$
VAS mean anxiety after food images	6.0 (7.4)	55.48 (25.1)[a,b]	24.4 (26.4)	19.90	$p < 0.001$
VAS mean anxiety after non-food images	4.56 (6.1)	20.12 (23.2)[a]	9.76 (10.6)	4.03	0.026
Perseverative errors (BCST)	14.0 (3.1)	23.71 (10.7)[a]	19.86 (7.8)	5.73	0.006
Non-perseverative errors (BCST)	6.13 (2.8)	11.43 (5.7)	12.21 (10.3)	3.36	0.045
Categories completed (BCST)	8.47 (0.6)	6.36 (2.0)[a]	6.79 (2.5)	5.15	0.010

Notes: AN, women chronically ill with anorexia nervosa; BCST; Berg's Card Sorting Task; BDI, Beck's Depression Inventory; BMI, body mass index; EDEQ, Eating Disorder Examination Questionnaire; HC, healthy controls; REC, women recovered from anorexia nervosa; STAI, State-Trait Anxiety Inventory; VAS, Visual Analogue Scale.

[a] significantly different from HC $p < 0.05$.
[b] significantly different from REC $p < 0.05$.

plate on a blue background. The non-food images consisted of 60 color photographs of objects on a white circle with a blue background. All images were selected and matched according to color and visual structure. The food images were pretested for suitability for Dutch women. For this purpose, 78 food images were scored on recognizability, desire to eat, and palatability on a 5-point scale by healthy non-dieting women, yielding n = 21 ratings for each image. Based on these ratings, 60 images were selected for the fMRI task. Food images that were not recognized well or were rated as unattractive were excluded.

2.3. Neuropsychological measures

A computerized version of the Berg's Card Sorting Task (BCST; Berg, 1948) was used to measure set-shifting. This task consists of 128 cards that vary in color (red, green, yellow, and blue), number (one to four), and symbol (triangles, stars, crosses, and circles). Four cards are presented on the screen. One additional card is presented that has to be matched to one of the four cards according to an unknown rule. A rule of the task corresponds to either the color, number, or symbol. After each response, the participant receives feedback on whether the response was right or wrong. After 10 consecutive right responses, a rule changes without notice. The test ends when the participant either completes all nine categories (each rule corresponds to a category) or sorts out all 128 cards. Perseverative errors, non-perseverative errors, and categories completed were scored. A response is categorized as a perseverative error when the card is matched according to a previous rule. Thus, perseverative errors correspond to difficulties in switching from one set to another. Non-perseverative errors constitute all errors, except the responses that would have been right under the previous rule (i.e. perseverative errors). Categories completed corresponds to the number of times the participant manages to sort the card right in 10 consecutive trials.

2.4. Study design

Participants were scanned on a 3T Philips Achieva using a 3D-PRESTO SENSE sequence (TR/TE = 22.5/33 ms, flip = 10°, voxel size = 4 × 4 × 4 mm, dynamic scan duration = 608 ms). During a 12-minute functional scan, subjects were presented with food and non-food images in six alternating 30-s blocks. Each block consisted of 10 food (F) or non-food (NF) images. In addition, 3 blocks of rest (36 s) were included. Each stimulus was presented for 3 s. Each block was preceded by an instruction on screen, e.g. 'Imagine eating/using the food/object presented' in order to cognitively engage participants in a task rather than merely present them appetitive stimuli for passive viewing. This approach has been used previously in imaging studies about visual image processing in AN (Brooks et al., 2012, 2011; Kim et al., 2012). After every block, participants were instructed to rate their anxiety and desire to eat on a visual analogue scale.

2.5. fMRI data preprocessing

fMRI data were preprocessed and analyzed with the SPM8 software package (Wellcome Department of Imaging Neuroscience, London, United Kingdom, (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) in conjunction with the MarsBar toolbox (http://marsbar.sourceforge.net/) run with MATLAB R2014A (The Mathworks Inc., Natick, MA). The functional volumes of every subject were realigned to the first volume of the first run, globally normalized to Montreal Neurological Institute space (MNI space) retaining 4 × 4 × 4 mm voxels, and spatially smoothed with a Gaussian kernel of 8 mm full width at half maximum. Plots of each subject's realignment parameters were visually checked for excessive motion (> 4 mm translation, > 2.3 degrees rotation). Also, the mean functional image was inspected for artifacts for every subject. Based on this, data from one REC and two AN subjects were excluded from the analyses, leaving a sample of n = 15 for HC, and n = 14 for AN and REC.

A statistical parametric map was generated for every subject by fitting a box car function to each time series, convolved with the canonical hemodynamic response function. Data were high-pass filtered with a cut-off of 128 s.

2.6. Behavioral data analyses

Statistical Package for the Social Sciences (SPSS) version 20 was used for behavioral data analyses. For each participant, task-induced anxiety scores were calculated by subtracting anxiety scores after viewing blocks of non-food from those after viewing foods, and vice versa. A one-way ANOVA with Bonferroni correction for pairwise comparisons was used to establish group differences regarding clinical, personality, and neuropsychological

Table 2
Brain regions with significant correlations between food/non-food processing and perseverative errors in women ill with AN (N = 14), recovered women (N = 14), and healthy women (N = 15).

Region	Side	k	Peak MNI-coordinates			Z	r	F/NF	Group
			x	y	z				
dACC/anterior cingulate cortex	R	11	18	44	18	3.61	−0.82	F	AN
			18	36	18	3.47	−0.82	F	AN
Paracentral lobule	R	13	14	−40	54	3.75	−0.80	F	AN
Precuneus	L	7	−10	−68	46	3.56	−0.76	F	AN
DLPFC/superior frontal gyrus	R	4	18	48	22	3.44	−0.83	NF	AN
dACC/superior frontal gyrus	L	6	−14	12	46	3.60	0.80	F	REC
VLPFC/inferior frontal gyrus, pars triangularis	L	4	−34	40	10	3.85	0.85	F	REC
Anterior insula	L	15	−38	24	6	3.98	0.70	NF	REC
		3	−30	16	−10	3.42	0.78	NF	REC
dACC/middle cingulate cortex	L	4	−6	32	38	3.56	0.81	NF	REC
		3	−2	−20	46	3.29	0.79	NF	REC
Medial PFC/superior frontal gyrus, medial	L	6	−6	56	22	3.55	0.84	NF	REC

Notes: L, left hemisphere; R, right hemisphere; k, number of voxels; x, y, z, Montreal Neurological Institute (MNI) coordinates in mm indicate the location of the peak voxel; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; PFC, prefrontal cortex; VLPFC, ventrolateral prefrontal cortex, F, food images; NF, non-food images, AN, women ill with AN, REC, women recovered from AN; HC, healthy women. Results are thresholded at $p < 0.001$ uncorrected with a cluster extent of k = 3 and z-score > 3.

characteristics (Table 1).

2.7. Subject level analyses

Two conditions were modelled, i.e. the average activation of food viewing, and the average activation of non-food viewing. Two so-called contrast images were calculated for each participant by subtracting the mean activation at baseline from the mean activation of food viewing (F > Rest), and the mean activation at baseline from the mean activation of non-food viewing (NF > Rest). In addition, the mean anxiety levels for each participant after viewing blocks of foods and non-foods were calculated. The average activations across the three groups during food and non-food processing are reported in the Supplement (Table 1 in Supplement) as background information and as material for meta-analysis.

2.8. Group level analyses

Based on literature pertaining to SS ability and cognitive control, a priori regions of interest (ROIs) were defined in several frontal and parietal regions. Anatomical mask for the superior, inferior, and middle frontal gyri, anterior, middle, and posterior cingulate cortex, insula, precuneus, paracentral lobule, inferior parietal gyrus, and caudate was constructed using the AAL atlas with the use of the Wake Forest University Pickatlas toolbox (Maldjian et al., 2003; Tzourio-Mazoyer et al., 2002). For all structures, the anatomical mask was dilated by 1 mm to account for anatomical variation and smoothing effects.

To test how set-shifting correlates with visual stimulus processing in the ROIs, the contrast images for evaluating foods and non-foods were entered into a one-sample *t*-test with perseverative errors, non-perseverative errors, and categories completed as covariates for each group. Small Volume Correction (SVC) was applied to each ROI with a threshold for peaks at $p < 0.001$ uncorrected with an extent threshold of k > 3 voxels and an additional criterion of z-score > 3. The mean beta values in significant clusters in each ROI were extracted with the use of the MarsBar toolbox [marsbar.sourceforge.net]. For the significant clusters, corresponding indicative Pearson's correlation coefficients were calculated in SPSS. Additionally, mean beta values from significant clusters were correlated with the mean task-induced anxiety during evaluating foods/non-foods, and trait-anxiety (STAI-T; Spielberger and Gorsuch, 1983). To facilitate future meta-analyses, we also provide the whole-brain results thresholded at $p < 0.001$ uncorrected with a cluster extent of k > 3 voxels and z-score > 3 (Table 2–4 in Supplement).

3. Results

3.1. Descriptive variables

The results of the one-way ANOVA and post-hoc pairwise comparisons regarding subject characteristics can be found in Table 1. The three groups did not differ in age. Women ill with AN had significantly lower BMI and fat percentage compared to healthy and recovered women. In comparison to HC, AN and REC had significantly higher scores on BDI and EDEQ subscale restrained eating, whereas AN had significantly higher EDEQ global score in comparison to HC. There were statistically significant differences in depressive symptoms and restrained eating between REC and AN as well. Both AN and REC scored significantly higher on trait and state anxiety than HC, whereas there were no statistical differences between AN and REC. The average task-induced anxiety after evaluating food images was significantly higher for AN compared to HC and REC. After evaluating non-foods, AN also exhibited greater average task-induced anxiety than HC. The three groups did not differ in their non-perseverative errors. Compared to HC, AN made significantly more perseverative errors and completed less categories. There were no statistically significant differences between HC and REC, although there was a trend for REC making more perseverative errors ($p = .149$) and completing less categories than HC ($p = .062$).

3.2. Correlations between food evaluation and set-shifting measures

3.2.1. Perseverative errors

During food and non-food processing, activations in several ROIs correlated with perseverative errors in AN and REC (Table 2, Fig. 1). Activations in the right dACC, left precuneus, and right paracentral lobule correlated negatively with perseverative errors in AN during food processing. There was also a negative correlation between perseverative errors and right DLPFC activation in AN during non-food processing. In REC, left dACC activation correlated positively with perseverative errors during food and non-food processing. Activations in the left anterior insula, and left medial PFC correlated positively with perseverative errors during

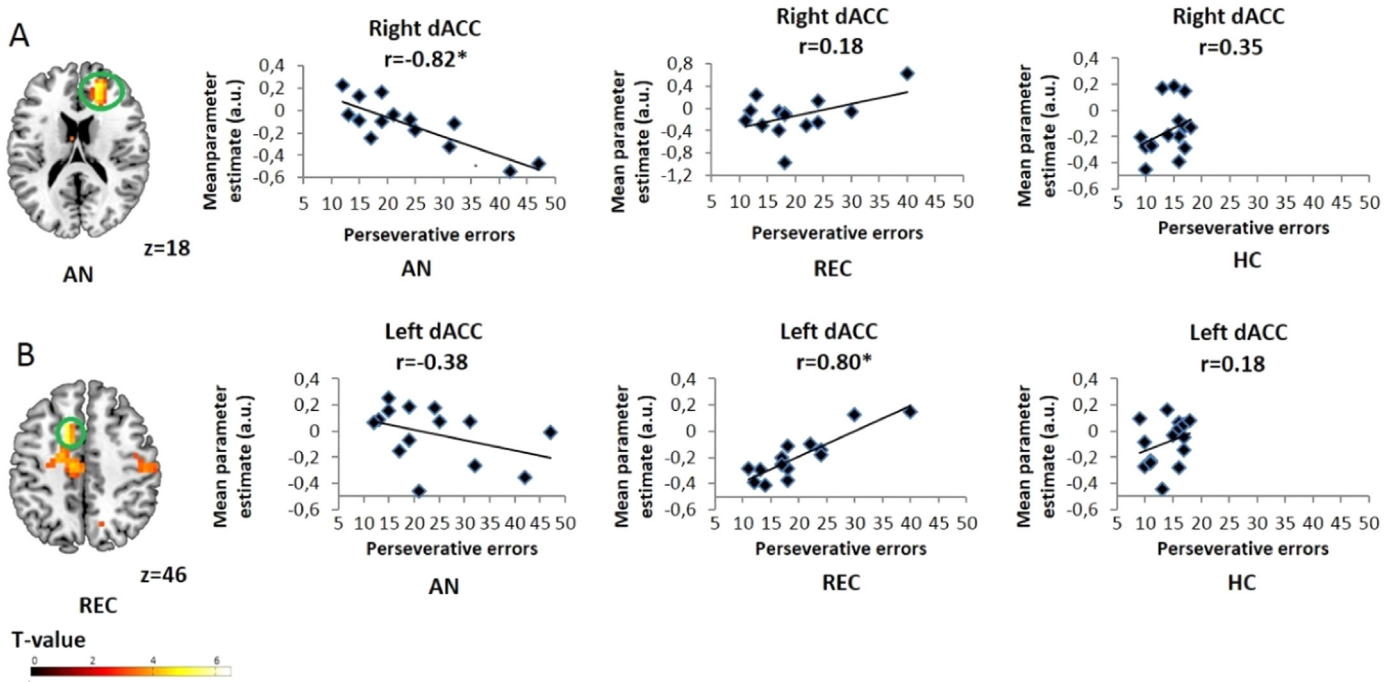

Fig. 1. Brain regions in which food viewing activation correlates with perseverative errors. A) correlations between perseverative errors and the right dorsal anterior cingulate cortex (dACC)/anterior cingulate cortex activation (MNI: 18, 44, 18) in AN, REC, and HC; B) correlations between perseverative errors and the left dACC/superior frontal gyrus activation (MNI: −6, 56, 22) in AN, REC, and HC. *- a significant correlation between perseverative errors and food viewing. For visualization purposes, the T-maps are thresholded at T > 2.7.

non-food processing in REC. Left VLPFC activation correlated positively with perseverative errors in REC during food processing. In HC, there were no correlations with perseverative errors in any of the ROIs, but note the relatively low standard deviation in this group (Table 1).

3.2.2. Non-perseverative errors

During food processing, the activation in the right dACC correlated negatively with non-perseverative errors in AN (Table 3). In HC, the right dACC and right DLPFC activations correlated positively with non-perseverative errors during non-food processing. There were no correlations in the ROIs with non-perseverative errors in REC during food and non-food processing.

3.2.3. Categories completed

The activation in the right paracentral lobule correlated positively with categories completed in AN during food viewing (MNI: 14, −40, 50, z=3.43, r=0.80). No significant correlations in REC and HC with categories completed were found.

3.3. Correlations with anxiety

There were many significant correlations between the mean task-induced anxiety and trait anxiety and food and non-food processing activation in three groups in the ROIs (Tables 5–6 in Supplement). In AN, the left precuneus activation correlated negatively with self-reported acute anxiety during non-food processing (MNI: −10, −56, 10, z=3.28, r=−0.64). Activation in the left DLPFC correlated positively with trait anxiety in HC during food (MNI: −18, 52, 6, z=3.49, r=0.89) and non-food (MNI: −18, 56, 6, z=3.34, r=0.64) processing, whereas activation in the left dACC during food processing correlated positively with trait anxiety in HC (MNI: −14, 40, 10, z=3.47, r=0.89).

4. Discussion

To our knowledge, this is the first study to investigate how visual stimulus processing relates to set-shifting ability in recovered and chronically ill women with AN. We measured neural activation during visual stimulus processing with an fMRI task in which participants evaluated food and non-food images. Since

Table 3
Brain regions with significant correlations between food/non-food processing and non-perseverative errors in women ill with AN (N=14), recovered women (N=14), and healthy women (N=15).

Region	Side	k	Peak MNI-coordinates			Z	r	F/NF	Group
			x	y	z				
dACC/middle cingulate cortex	R	3	10	−36	46	3.30	−0.81	F	AN
dACC/anterior cingulate cortex	R	16	6	44	30	4.37	0.58	NF	HC
			10	36	26	3.20	0.58	NF	HC
DLPFC/superior frontal gyrus, medial	R	4	6	56	18	3.33	0.77	NF	HC

Notes: L, left hemisphere; R, right hemisphere; k, number of voxels; x, y, z, Montreal Neurological Institute (MNI) coordinates in mm indicate the location of the peak voxel; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; F, food images; NF, non-food images, AN, women ill with AN, REC, women recovered from AN; HC, healthy women. Results are thresholded at p < 0.001 uncorrected with a cluster extent of k=3 and z-score > 3.

several studies have indicated that women ill with AN and recovered women exhibit altered activation in brain regions regarding cognitive control during processing disease-salient visual stimuli (Uher et al., 2003; Brooks et al., 2011), it has been proposed that altered frontal functioning may enhance food restriction in those ill with AN and therefore help maintain symptoms (Kidd and Steinglass, 2012). To measure SS ability, a BCST task was completed outside the scanner. A deficit in cognitive functioning indicated by poor SS ability could also be a mechanism that facilitates maintenance of AN symptoms and resistance to treatment.

In our study, we could confirm that poor SS ability is associated with higher frontal activation during food and non-food viewing in REC. The activation in left dACC, left DLPFC, and left medial PFC correlated positively with perseverative errors in REC. dACC and DLPFC are part of the cognitive control network (Cole and Schneider, 2007). dACC plays a role in conflict monitoring (Bush et al., 2002; Carter and van Veen, 2007) and self-referential processing, and DLPFC plays a role in implementing cognitive control and increasing the level of control when needed (MacDonald et al., 2000). Moreover, in ill and recovered AN patients, dACC activation has been consistently found to differ (Pieters et al., 2007; Uher et al., 2003), and to be linked to an excessive effort to restrict food intake (Kim et al., 2012). Thus, positive correlations between perseverative errors and dACC and DLPFC activation in REC during visual stimulus processing could be related to altered activation in brain regions governing self-referential mental activity and cognitive control over food intake.

There was also a positive correlation between left anterior insula activation and perseverative errors in REC. Insula activation is believed to underlie anxiety-related neural responses (Kent and Rauch, 2003), as the activation of anterior insula has consistently been shown to be elevated in anxious participants during the anticipation of aversive images (Oberndorfer et al., 2011), and in ill and recovered AN patients in response to food images (Kim et al., 2012; Oberndorfer et al., 2013). In an another study, the improvement in SS skills in patients with AN was predicted by lower left VLPFC/insula activation during a SS task after treatment with cognitive-behavioral therapy (Garrett et al., 2014). The authors speculated that greater activation in the insula was modulated by heightened anxiety. However, in our study, the left anterior insula activation was not correlated with the anxiety measures in REC. Thus, our results contribute to the growing body of evidence that suggests that the activation of insula is altered in AN. Furthermore, greater insula activation that is associated with cognitive inflexibility in REC in our study is not modulated by anxiety. Taken together, our results suggest that higher activation in frontal regions involved in self-referential processing and cognitive control, but not anxiety, is associated with poor SS ability in REC.

In AN, higher activation in frontal and parietal regions was associated with better SS ability, which is in contrast to our hypothesis. In AN, the correlations with perseverative errors were reversed, mainly localized in the right hemisphere, and specific to processing of food images. Localization in the right hemisphere instead of the left as in HC and REC is consistent with cases that have reported AN symptoms in patients with right prefrontal lesions (Javaras et al., 2008; Trummer et al., 2002). Left precuneus, right DLPFC, and right paracentral lobule activations were negatively correlated with perseverative errors, and the right dACC activation was negatively correlated with perseverative and non-perseverative errors during food processing. Hence, lower activation in those frontal and parietal regions in AN patients is associated with elevated perseverative errors.

This is surprising, given that in REC, higher frontal activation correlated positively with poor SS ability. Nevertheless, it could be hypothesized that in ill AN patients, greater recruitment of frontal and parietal regions as well as greater activation in these regions is necessary to perform at normal levels during various working memory tasks. In a study using an n-back test, the activation in several frontal regions, i.e. superior frontal gyri, right MFG, and left inferior frontal gyrus, was negatively correlated with BMI in AN patients, even though the patient group did not differ from healthy controls regarding their performance (Castro-Fornieles et al., 2010). Likewise, successful inhibition in a Go/No Go task in restrictive-type AN patients has been shown to be associated with greater recruitment of brain regions underlying visual attention and visual working memory, i.e. precuneus and parietal cortex (Lock et al., 2011). The necessity for greater recruitment of frontal and parietal regions during various working memory tasks could also generalize to other tasks, such as visual stimulus processing. This could explain why we found negative correlations between brain activation and SS ability in AN, but not in REC or HC. This hypothesis, however, should be further tested in another study, since no firm conclusions can be drawn based on our data.

Taken together, our results suggest that higher activation in frontal and parietal regions in AN during processing disease-related stimuli, i.e. food, is associated with cognitive flexibility. Perhaps higher activation in frontal and parietal regions during processing disease-salient stimuli observed in some studies (Brooks et al., 2011; Uher et al., 2004) does not reflect enhanced capacity to restrict food intake. Rather, it could merely reflect altered activation that is due to nutritional status. In fact, separate neural correlates underlying state and trait characteristics of AN have been identified, with recovered women showing greater activation within the dACC and lateral PFC to visual food stimuli compared to AN (Uher et al., 2003). Additionally, dACC activation during food viewing has been shown to be positively correlated with bodyweight in REC (Uher et al., 2003), and activation within PFC has shown to be negatively correlated with BMI in AN during an n-back test (Castro-Fornieles et al., 2010).

There are some limitations to the study. First, the sample sizes were small. Second, by design we contrasted chronic AN patients with patients recovered from AN for at least a year. Thus, results might be different if more similar patients groups were compared. Additionally, the variability in the perseverative error rate in HC was low which could explain why we did not find any correlations between visual stimulus processing and perseverative errors in frontal and parietal regions in that group. Furthermore, even though participants were instructed to cognitively engage rather than passively view the images, we do not know to what extent all the participants complied with the instructions. Food images, however, elicited greater anxiety during food processing in REC and AN, indicating some compliance with the task. Finally, it must be noted that we did not assess brain activation related to set-shifting, but rather the association between SS ability and visual stimulus processing. Future studies employing set-shifting fMRI tasks could help confirm our results.

In conclusion, we found that higher activation in frontal regions during visual stimulus processing is associated with poor SS ability in women recovered from AN. This may be attributed to alterations in brain regions related to cognitive control. AN patients, however, showed an opposite pattern of correlations with SS difficulties in comparison to REC. It is plausible that women ill with AN might need compensatory as well as greater recruitment of frontal and parietal regions in order to perform at normal levels during various tasks. If that were the case, weight restoration might be necessary in women ill with AN prior to addressing cognitive inflexibility. Considering that compared to HC, AN and REC demonstrated worse SS ability that correlated with brain activation during visual stimulus processing, Cognitive Remediation Therapy (CRT) could be of help to both patient groups. CRT has been developed to improve neuropsychological weakness in AN patients, i.e. set-shifting and central coherence (Tchanturia, 2014;

Tchanturia et al., 2013). CRT, targeting rigid thinking styles and excessive focus on detail, is a promising treatment that has demonstrated its ability to elicit improvements in cognitive functioning in AN patients that also persist post-intervention (Brockmeyer et al., 2014; Dingemans et al., 2014; Lock et al., 2013). Therefore, CRT could be of potential help to AN and REC in terms of changing rigid and perfectionistic clinical features that are evident in both groups due to elevated perseverative errors observed in our study.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pscychresns.2016.07.004.

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