Threat-detection and attentional bias to threat in women recovered from anorexia nervosa: Neural alterations in extrastriate and medial prefrontal cortices

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RUNNING HEAD: ATTENTIONAL BIAS TO THREAT IN ANOREXIA NERVOSA

Abstract

Objective: Behavioral studies have shown that anorexia nervosa (AN) is associated with attentional bias to general threat cues. The neurobiological underpinnings of attentional bias to threat in AN is unknown. This study investigated the neural responses associated with threat-detection and attentional bias to threat in AN. **Methods:** We measured neural responses to a dot-probe task, involving pairs of angry and neutral face stimuli, in 22 adult women recovered from AN and 21 comparison women. **Results:** Recovered AN women did not exhibit a behavioral attentional bias to threat. In response to angry faces, recovered women showed significant hypoactivation in the extrastriate cortex. During attentional bias to angry faces, recovered women showed significant hyperactivation in the medial prefrontal cortex. This was due to significant deactivation in comparison women, which was absent in recovered AN women. **Conclusions:** Women recovered from AN are characterized by altered neural responses to threat cues.

Keywords: Anorexia nervosa, attentional bias, dot-probe, functional magnetic resonance imaging, medial prefrontal cortex.

INTRODUCTION

Anorexia nervosa (AN) is a potentially fatal eating disorder that predominantly affects young women (APA, 2013). The hallmark features include overvaluation of body shape and weight, relentless pursuit of thinness, and severe food-restriction accompanied by extreme weight-loss.

The central role of emotion disturbances in the development and maintenance of AN have been widely acknowledged. Individuals with AN are characterized by premorbid anxious traits (Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013) and have high levels of anxiety, even following recovery (Kaye, Bulik, Thornton, Barbarich, & Masters, 2004). They also show poor emotion regulation skills (Haynos, Roberto, Martinez, Attia, & Fruzzetti, 2014; Oldershaw, Lavender, Sallis, Stahl, & Schmidt, 2015), and it has been suggested that AN-related behaviors, such as food restriction, excessive exercising, and binge-eating/purging may function as emotion regulation strategies (Haynos & Fruzzetti, 2011).

AN and anxiety disorders (including obsessive-compulsive disorder) frequently co-occur, and the onset of clinical anxiety often predates AN (Kaye et al., 2004). Indeed, anxiety disorders increases risk of later development of AN (Meier et al., 2015). Several investigators have underscored the overlap in psychopathology between these disorders (Pallister & Waller, 2008), which raises the possibility of a shared etiology. Therefore, research and models from the field of anxiety may inform the understanding of AN.

Ample research has investigated how anxiety modulates attention to emotional stimuli. Attentional bias is observed when emotional relative to neutral stimuli interferes with behavioral performance, leading to increased response-times (RTs).

Individuals with both clinical and nonclinical anxiety are characterized by attentional bias to threat stimuli (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007). Such bias reflects an information-processing style favoring emotionally negative stimuli, and is thought to play a critical role in the development and maintenance of anxiety (Eysenck, Derakshan, Santos, & Calvo, 2007).

A wealth of studies have reported that individuals with AN show attentional bias to disorder-specific stimuli such as food and bodies (Aspen, Darcy, & Lock, 2013). It has been less clear whether or not this bias extends to general emotion cues, unrelated to AN psychopathology. Several studies report that patients with AN have an attentional bias to faces expressing anger (Harrison, Tchanturia, & Treasure, 2010), rejection (Cardi, Matteo, Corfield, & Treasure, 2013) and disgust (Cardi et al., 2015). Furthermore, these biases appear to persist following recovery (Cardi et al., 2013; Harrison et al., 2010), suggesting they reflect trait-dispositions. It has been suggested that attentional bias modification training have potential as a treatment option for AN (Renwick, Campbell, & Schmidt, 2013), which is supported by a preliminary uncontrolled study where such training was associated with improved appraisal of social stimuli and reduced anxiety in AN patients (Cardi et al., 2015).

Limbic and prefrontal brain circuits underlie the attentional mechanisms involved in threat-detection and regulation (Bishop, 2007). Limbic structures including the amygdala and insula detect and convey threat-signals, which are evaluated further in dorsomedial prefrontal cortices, and finally regulated by ventromedial and lateral prefrontal cortices (Bishop, 2007; Etkin, 2009). Attentional bias to threat may occur as a result of amplification of threat-signals in limbic circuits, and/or by attenuation of the regulatory functions of prefrontal cortices (Bishop, 2007).

Previous research has implicated both limbic and prefrontal cortices in the neuropathophysiology of AN (Kaye et al., 2013; Zhu et al., 2012). For example, studies of food-processing (visual and gustatory stimulation) typically report that AN is associated with hyperactivations in emotion-related brain circuits, including the medial prefrontal cortex and amygdala (Friederich, Wu, Simon, & Herzog, 2013; Zhu et al., 2012). Such findings indicate that AN is associated with a hyper-responsive emotion-circuitry to food stimuli (Friederich et al., 2013). Along these lines, it has been suggested that a heightened propensity towards fear-learning and greater resilience to fear-extinction underlie AN etiology (Strober, 2004). Studies have also shown that during tasks requiring cognitive control, individuals with AN exhibit aberrations in lateral and medial prefrontal cortices (Ehrlich et al., 2015; Wierenga et al., 2014; Wierenga et al., 2015), which suggest alterations within the cognitive control circuitry. Together, these studies indicate that alterations within both emotion (e.g. medial prefrontal cortex and amygdala) and cognitive control circuits (medial/lateral prefrontal cortex) underlie AN neuropathophysiology. An imbalance within or between these circuits may be related to the attentional biases observed in AN. For instance, in the presence of threat-cues, individuals with AN may be unable to adequately recruit prefrontal cortices to sufficiently modulate limbic activation, similar to what is thought to be the case with anxiety (Bishop, 2007).

As far as we know, only one study have directly measured the neural correlates of attentional bias to threat in AN. Redgrave et al. (2008) reported that attentional bias to disorder-specific threat cues was associated with hypoactivation in dorsolateral prefrontal cortices in patients with AN, suggesting decreased attentional control.

To our knowledge, no studies have investigated the neural correlates of attentional bias to disorder non-specific threat stimuli in AN. Considering the theoretical and potential therapeutic implications of attentional bias in AN, this is an important area for research. The purpose of the present study was to investigate the neural responses to threat stimuli, and attentional bias to such stimuli. To achieve this, a dot-probe task was presented to women recovered from AN during functional magnetic resonance imaging (fMRI). This task has been extensively used in other psychiatric populations, including anxiety disorders, and is efficient in eliciting attentional bias to threat in such populations (Bar-Haim et al., 2007). Similar to previous studies, we used angry faces as threat-cues. In line with what others have suggested (Harrison et al., 2010), we hypothesized that attentional bias to general (disorder non-specific) threat is a trait of individuals who develop AN. To circumvent the confounding effects of emaciation and comorbid states that could influence the processing of face stimuli (e.g. depression), we recruited women recovered from AN.

We hypothesized that women recovered from AN would show an attentional bias to threat. Similar to previous research (e.g. Cardi et al., 2013), we expected this attentional bias to be positively correlated with measures of negative affect, including emotional dysregulation and anxiety. Furthermore, we hypothesized that angry faces, and attentional bias to such faces, would be associated with increased amygdala and lateral/dorsomedial prefrontal cortex activation, reflecting heightened emotional arousal with subsequent engagement of attentional control processes. We focused on these regions as previous studies have implicated them in the brain's threat-detection and regulation circuitry (Bishop, 2007), and in the neuropathophysiology of AN (Kaye et al., 2013).

MATERIALS AND METHODS

Participants

We included 22 adult women recovered from AN and 21 comparison women (CW), all right-handed. Participants were recruited through flyers at universities, information on online internet discussion forums and on the Oslo University Hospital webpage. To reach women recovered from AN, two user-organizations for eating disorders informed their members about the project; during meetings, on their webpage, and through member magazines. Current and lifetime DSM-IV diagnoses (APA, 2000) were determined with the Structured Clinical Interview for DSM-IV Axis I Disorders version I/P (First, Spitzer, Gibbon, & Williams, 2002). During this interview, status of AN recovery was evaluated.

Women in the recovered AN group were included if they had a lifetime history of AN according to DSM-IV criteria, excluding the amenorrhoea criteria. Recovery from AN was operationalized as having maintained a body mass index (BMI) above 18 the past 12 months, and abstinence from binging and purging behavior, excessive or compulsive exercising behavior, and no severely restricted food intake for the past 12 months. Exclusion criteria for these women included: lifetime history of a psychotic disorder, lifetime history of substance abuse or dependence, any current use of narcotic substances (past 3 months), or the presence of any Axis I disorder the past 12 months. In other words, these women did not have any current Axis-I disorder.

Exclusion criteria for CW included: lifetime history of any Axis I disorder, current use of psychoactive medications or narcotic substances (past 3 months), and a first-degree relative with a history of an eating disorder. Furthermore, we excluded women who reported binging and purging behavior, excessive or compulsive

exercising, severely restricted food-intake, or had not maintained a BMI above 18 during the past 12 months.

Of the recovered AN women, three were currently using psychoactive medications. The results of this study did not change significantly when excluding these, so they were included in the final analyses. This study was approved by the regional ethics committee in Norway. All participants provided written informed consent prior to onset of the study.

Self-report measures

Immediately prior to the MRI session, all participants completed the following self-report measures: Spielberger State-Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970), Difficulties in Emotion Regulation Scale (Gratz & Roemer, 2004), Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and Eating Disorder Examination-Questionnaire (Fairburn & Beglin, 2008). These measures were included to characterize levels of emotion-related psychopathology in participants, and to elucidate behavioral and neural findings through correlational analyses. Following the MRI session, participants were weighed in order to calculate their BMI.

Dot-probe task description and analysis

The dot-probe task was used to elicit neural responses associated with threat-detection and attentional bias to threat (MacLeod, Mathews, & Tata, 1986). Trials began with a 500 millisecond (ms) fixation point, followed by a pair of faces (cues) on the left and right side of the screen for 500 ms. An asterisk (probe) replaced one of

the faces, and were visible for 1100 ms or until a response had been made. Participants were instructed to determine the location of the probe (left or right) as quickly and accurately as possible.

The face-pairs consisted of 40 actors (half were female) from the Karolinska Directed Emotional Faces picture-set (Lundqvist, Flykt, & Öhman, 1998), where each pair displayed either an angry-neutral combination, or a neutral-neutral combination of the same actor. There were three conditions: 1) trials in which the probe replaced the angry face in an angry-neutral face pair (for the purpose of this study, referred to as “congruent” trials), 2) trials in which the probe replaced the neutral face in an angry-neutral face pair (referred to as “incongruent” trials), and 3) control trials in which a neutral-neutral face pair was replaced by a probe in either the left or right side of the screen. Congruent and incongruent trials differed only in the location of the probe. For jittering purposes, null trials consisting of a fixation point of varying duration was included.

Scheduling the order of conditions (including null trials) were determined with the OPTSEQ2 tool (Dale, 1999). Each participant was presented with 75 trials for each of the three conditions (total 225 trials, not including null trials). For each trial, the face-pair image was randomly selected, and location of the angry faces was counterbalanced. Outlier trials were defined by an RT below 200 and above 1000 ms, and were excluded from analyses together with incorrect trials (total 95 trials, 0.01% of all trials, equally distributed across conditions and groups). RTs and accuracy were analyzed with group x condition (2 x 3) ANOVA models. The attentional bias index was calculated by subtracting the mean RT of congruent from incongruent trials. One sample t-tests were used to determine if mean attentional

bias index differed significantly from zero in recovered AN women. To explore correlates of attentional bias, the attentional bias index was correlated with BMI and all self-report measures, within each group separately. Effect sizes for independent and dependent t-tests are reported using Cohen's *d*.

MRI data acquisition

Images were recorded with a 3 Tesla Achieva MRI scanner (Philips, Eindhoven) equipped with an 8-channel Philips SENSE head coil. Functional images were acquired using a T2*-weighted single-shot echo-planar sequence (TR/TE = 2100/30 ms, flip angle = 80º; FOV = 240 x 240 mm, matrix = 80 x 80). For each participant, 36 axial slices covering the whole brain were acquired in an interleaved order, aligned with the AC-PC line (voxel size = 3 x 3 x 3 mm, slice gap = 0.5 mm). The five first volumes of each run were discarded to avoid saturation effects.

MRI Data analysis

MRI images were preprocessed using the SPM8 toolbox (http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (MATLAB and Statistics Toolbox Release 2012b, The Mathworks, Inc., Natick, MA, US). Functional images were slice-time corrected, realigned to the mean scan, and co-registered to each individual's structural image. They were then normalized and smoothed with a 10 mm full-width half maximum kernel using the DARTEL toolbox in SPM8 (Ashburner, 2007). We have previously reported that groups have similar global brain tissue volumes and regional gray matter volumes (Bang, Rø, & Endestad, 2016b).

A fixed-effects model was created for each participant. Regressors for the onsets of congruent, incongruent, and control trials were created, and convolved with the canonical hemodynamic response function. Outlier and incorrect trials were modelled as a regressor of no interest. Additional regressors corresponding to the six movement parameters were included. A 128-seconds temporal high-pass filter was applied to the data, and serial correlations were accounted for by using an autoregressive model. The following T-contrasts were specified: congruent + incongruent > control (threat-detection), and incongruent > congruent (attentional bias). The former contrast captures the average activation of congruent and incongruent trials over control trials, and therefore the effect of angry faces. The latter contrast captures the attentional bias to threat, where reallocation of attention is required if a bias is present. These contrasts were submitted to random-effects models using t-tests.

We first ran a one-sample t-test on each of the contrasts specified above, across both groups. This was done to describe the hemodynamic responses to the events of interest, but is not the primary focus of this study. Between-group t-tests were then performed on each of the contrasts, comparing the hemodynamic responses between women recovered from AN and CW. For these analyses, we first investigated between-group differences within a priori regions of interest (ROIs), followed by exploratory whole-brain analyses.

Four ROIs were specified; the amygdala, superior frontal gyrus (which include the dorsomedial prefrontal cortex), middle frontal gyrus, and inferior frontal gyrus. A maximum probability atlas (www.brain-development.org) was used to specify the ROIs (Gousias et al., 2008; Hammers et al., 2003). These regions were chosen

because they have previously been implicated in the neuropathophysiology of AN, and because they are known to be involved in threat-detection and attentional bias to threat (Bishop, 2007).

To correct our alpha level for multiple comparisons, alpha levels were determined with Monte Carlo simulations using the AlphaSim implementation in the REST toolbox (Song et al., 2011, www.restfmri.net). Minimum cluster sizes (k_e) required to achieve a corrected alpha level of $p < .05$ with a primary voxel-wise alpha level of $p < .001$ for our ROIs (combined) was determined. We also used Monte Carlo simulations to determine the minimum cluster sizes required to achieve a whole-brain corrected alpha level of $p < .05$, with a primary voxel-wise alpha level of $p < .001$. Such cluster-extent based thresholds provide good sensitivity, at the expense of spatial specificity (Woo, Krishnan, & Wager, 2014). In line with recommendations, we used a conservative primary alpha-level threshold of $p < .001$ (Woo et al., 2014). We report our results from both the ROI and whole-brain analyses using these corrected thresholds. All results are reported using Montreal Neurological Institute coordinates (MNI).

To further characterize significant between-group effects, we performed follow-up analyses of raw β-weights (averaged across significant clusters), which were extracted using the Marsbar toolbox (Brett, Anton, Valabregue, & Poline, 2002).

RESULTS

Participant characteristics

Recovered AN and CW were of similar age, but BMI was significantly higher for CW (see Table 1). The recovered AN women scored significantly higher (i.e. more symptomatic) on all self-report measures. All participants scored below the suggested (Norwegian) cut-off value of 2.50 on the Eating Disorder Examination-Questionnaire (Rø, Reas, & Stedal, 2015), indicating non-pathology. Half of the recovered AN women (*n* = 11) had a history of AN binging-purging subtype, while the remaining half (*n* = 11) had a history of AN restricting subtype. Clinical characteristics of the recovered AN women are reported in Table 1.

Please insert Table 1 about here

Behavioral results

Overall mean accuracy was 99.31% (SD = 0.97%) for the recovered AN group and 98.94% (SD = 1.17%) for the CW group. All participants achieved an accuracy of 96% or higher. There were no significant main effect of group (p = .285) or condition (p = .344), and no group x condition interaction effect (p = .971) on accuracy.

Overall mean RT was 442.47 ms (SD = 56.84) for the RAN group and 444.10 ms (SD = 56.98) for the CW group. There was a significant main effect of condition on RTs (F[1.75, 84] = 3.843, p = .03). Post-hoc t-tests showed that incongruent trials (mean = 446.14, SD = 57.99) were associated with significantly higher RTs compared to control trials (mean = 441.55, SD = 56.64; t[42] = 2.673, p = .011, d = 0.41), but no other differences between conditions were significant. There was no

main effect of group (p = .926) or group x condition interaction effect (p = .386) on RT.

Recovered AN women did not exhibit an attentional bias to threat, evidenced by non-significant one-sample t-test of the attentional bias index (mean = 2.35, SD = 13.73, t[21] = 0.804, p = .430). Furthermore, the attentional bias index did not differ between recovered AN women and CW (t[41] = -0.802, p = .427).

There was a significant correlation between attentional bias to angry faces and the Difficulties in Emotion Regulation Scale for recovered AN women (r_s = .448, p = .036). A similar trend-level significant association was observed within the CW group (r_s = .415, p = .062). For both groups considered separately, attentional bias to angry faces was not associated with BMI or any of the other self-report measures (all p > .11).

MRI results

Whole-brain one-sample t-tests (corrected for multiple comparisons) across both groups showed that presence of an angry face (threat-detection) was associated with significantly increased activation in the bilateral dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, and left middle temporal gyrus. Incongruent trials relative to congruent trials (attentional bias) were associated with significantly increased activation in bilateral cerebellum and ventral visual cortices, and significantly less activation in the supramarginal gyrus.

Threat-detection was not associated with any significant between-group differences in hemodynamic responses within our a priori ROIs. Subsequent whole-brain analyses however, showed that threat-detection produced significantly less

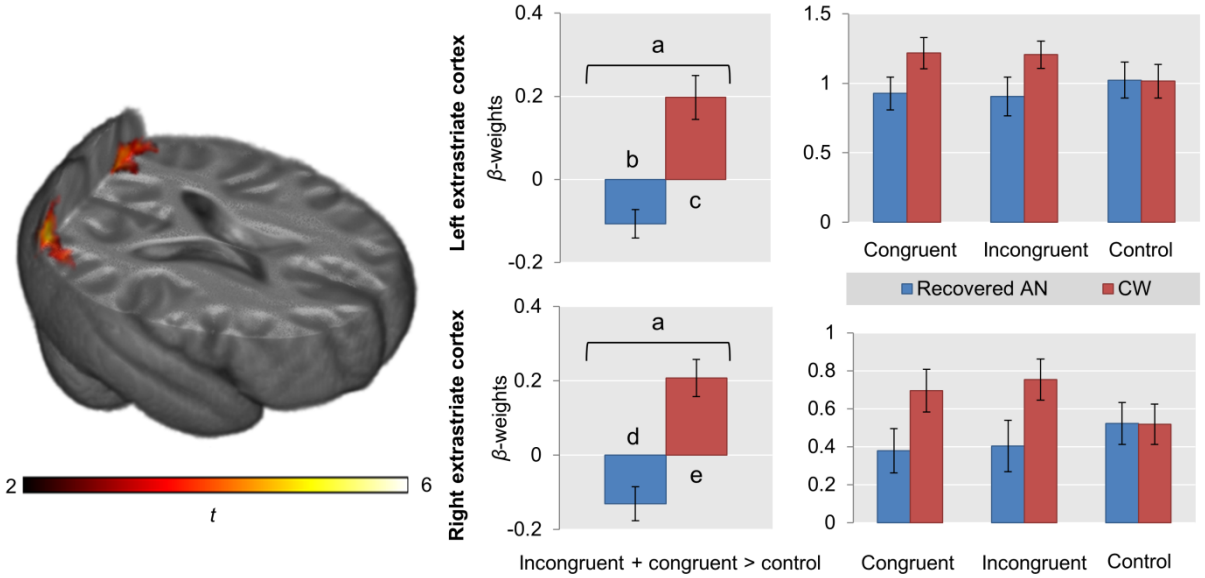
activation in the left (x = -36, -87, z = 15, t[41] = -4.948, z = 4.356, k_e = 177) and right (x = 36, y = -84, z = 24, t[41] = -5.755, z = 4.899, k_e = 132) extrastriate cortex in recovered AN women compared to CW (Brodmann areas 18/19, see Figure 1). Follow-up one-sample t-tests of the extracted β-weights showed that CW exhibited increased activation in left (t[20] = 3.753, p = 0.001) and right (t[20] = 4.169, p < 0.001) extrastriate cortex during trials containing an angry face, relative to trials containing only neutral faces. Recovered AN women showed the opposite pattern, with decreased activation in the left (t[21] = -3.140, p = 0.005) and right (t[21] = -2.834, p = 0.010) extrastriate cortex during trials containing an angry face relative to trials containing only neutral faces. Thus, angry faces enhanced activation in the extrastriate cortex for CW but not for recovered AN women.

The attentional bias comparison produced greater activation in the left medial prefrontal cortex (mPFC), located within our a priori ROI in the superior frontal gyrus (Brodmann area 10, x = -6, y = 57, z = 18, t[41] = 4.606, z = 4.111, k_e = 43) in recovered AN women compared to CW (see Figure 2). Follow-up one-sample t-tests of the β-weights revealed that while CW showed decreased activation during incongruent compared to congruent trials (t[20] = -5.372, p < 0.001), recovered AN women showed no differentiated response to the two conditions (t[21] = 1.569. p = .132). There were no additional between-group differences in the in the remaining ROIs, and whole-brain analyses revealed no additional significant effects.

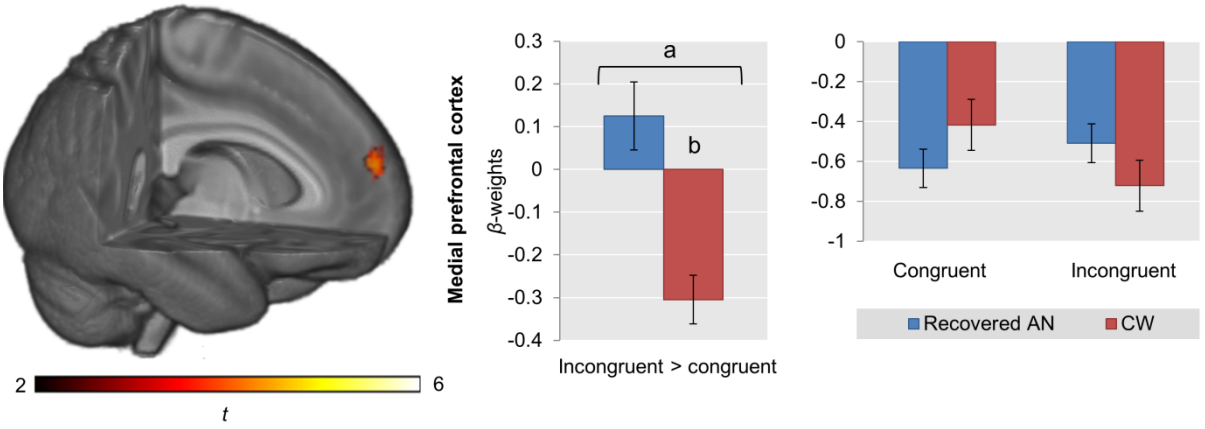
To further elucidate the group differences in mPFC and extrastriate cortex activation, contrast activations in these clusters were correlated with BMI, self-report measures, and clinical characteristics within each group separately. The mPFC contrast activation showed a significant negative association with lowest weight ever

(r_s = -.546, p = .009) in the recovered AN group, showing that lower lifetime weight is associated with higher activation in the mPFC during attentional bias. No other significant associations emerged from these analyses (all p > .23).

Please insert Figure 1 about here



Please insert Figure 2 about here



DISCUSSION

In this study, we investigated the neural responses associated with threat-detection and attentional bias to threat among women recovered from AN. Relative to CW, threat-detection was associated with reduced activation in the extrastriate cortex in women recovered from AN. Moreover, attentional bias was associated with increased activation in the mPFC among women recovered from AN compared to CW, indicating differential attentional processes between groups.

Contrary to our hypothesis, women recovered from AN did not exhibit a behavioral attentional bias to threat, and did not differ from CW in behavioral performance. These findings are inconsistent with some previous studies. Attentional bias to threat has been demonstrated in both ill and recovered patients, using a variety of disorder non-specific emotional stimuli (i.e. words and faces) and task paradigms (Cardi et al., 2015; Cardi et al., 2013; Harrison et al., 2010). However, some studies have failed to find similar biases to general threat stimuli in AN, supporting the behavioral findings in our study. Using a pictorial dot-probe task similar to ours, Schneier and colleagues (2016) found no evidence of an attentional bias to angry faces in patients with AN. Another study (Schober et al., 2014) investigated attentional bias to negatively valenced words (including social threat words) using a dot-probe task, and did not find an attentional bias to such stimuli in patients with AN. The reasons for the discrepant behavioral findings in AN are unclear.

However, the attentional system may be biased towards the processing of negative emotional cues even in the absence of impaired behavioral performance, due to compensatory processes that are not observable at the behavioral level (see

Eysenck et al., 2007). Such compensatory processes may be at play in AN. If this is the case, a behavioral attentional bias would only be evident in AN individuals who do not successfully engage such compensatory processes. This could account for the partly discrepant findings from behavioral studies of attentional bias to threat in AN. In line with our hypothesis, self-reported emotion regulation correlated positively with attentional bias to threat for both groups, raising the possibility that behavioral attentional bias is only observed in subgroups of AN individuals who are characterized by high emotion dysregulation. However, unlike some previous studies (Cardi et al., 2013; Telzer et al., 2008), and in contrast to our hypothesis, we did not detect a significant correlation between anxiety and attentional bias to threat. Similar null-correlations between measures of anxiety and attentional bias to threat have previously been reported in AN (Schneier et al., 2016; Schober et al., 2014), underscoring the cross-study variability of findings.

In line with our hypothesis, we did find evidence of differential neural responses to threat cues between groups, which could reflect compensatory attentional processes. Compared to CW, women recovered from AN showed increased activation of the mPFC in response to incongruent relative to congruent probes. Closer inspection of the hemodynamic responses showed that this effect was due to CW showing more relative deactivation during incongruent compared to congruent trials. In contrast, recovered AN women failed to exhibit this deactivation.

Deactivations of medial prefrontal cortices from an implicitly modelled baseline are in line with other studies of emotion processes (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010). The observed relative deactivation during incongruent vs. congruent trials among CW could reflect evaluative or regulatory attentional

mechanisms involved in negative emotion processing, as this part of the mPFC (Brodmann area 10) supports both functions (Etkin, Egner, & Kalisch, 2011). It is possible that this deactivation in CW occurred because angry faces elicit evaluative processes, which are discontinued or suppressed during incongruent trials to allow for fast reallocation of attention to the probe, which is not necessary for congruent trials where the probe replaces the angry face. The observed failure among women recovered from AN to deactivate this region suggests that this suppression is inefficient. Also, lowest lifetime weight was negatively correlated with mPFC activation during the incongruent vs. congruent contrast, suggesting it has some relevance to illness severity.

Hyperactivation of the mPFC have been reported in numerous studies of patients during the acute phase of AN (see Zhu et al., 2012 for a review). The majority of studies reporting such hyperactivations used disorder-specific stimuli such as food and bodies. Similar to our results, Redgrave and colleagues (2008) reported medial prefrontal hyperactivations during attentional bias to emotional cues in ill patients with AN. The stimuli in their study were disorder-specific, and together with our results suggest that medial prefrontal alterations in AN may reflect general emotion-related attentional processes. Unfortunately, Redgrave et al. did not investigate the parameter estimates (e.g. β-weights) associated with individual conditions, so it is not clear if these hyperactivations reflected relative activation or deactivation compared to the other conditions.

Hyperactivations of prefrontal cortices during the dot-probe task have been reported in other psychiatric populations as well. Monk and colleagues (2006) reported that patients with generalized anxiety disorder show ventrolateral prefrontal

cortex hyperactivation in response to trials containing angry faces. Activation in the ventrolateral prefrontal cortex was also positively correlated with anxiety, suggesting the hyperactivations reflect compensatory processes. Similarly, another study (Fani et al., 2012) showed that in response to angry faces, adult patients with post-traumatic stress disorder exhibited hyperactivations in the dorsolateral and dorsomedial prefrontal cortex, partly coinciding with the area in which the recovered AN women in our study showed hyperactivations (Brodmann area 10). These hyperactivations were observed despite the fact that no behavioral attentional bias to threat was present in the clinical group, similar to our own findings. Together, these studies are in line with our results, and suggest that in psychiatric populations characterized by emotional distress, angry faces in the context of the dot-probe task are associated with alterations in prefrontal cortices, most likely reflecting increased attentional control and emotional arousal.

Compared to CW, women recovered from AN also showed decreased activation of the extrastriate cortex in response to angry faces relative to neutral ones. During detection of threat cues, both limbic and prefrontal regions project signals to visual areas, biasing the visual processing of the stimuli (Bishop, 2007). The extrastriate cortex is also involved in the core processing of faces (Haxby, Hoffman, & Gobbini, 2002). Interestingly, patients with post-traumatic stress disorder also show hypoactivation in occipital areas in response to angry faces (Fani et al., 2012), suggesting this alteration may not be specific to AN.

Less activation in the extrastriate cortex among recovered AN women could reflect altered reward or saliency processing of faces. In this context, it is worth noting that women recovered from AN are impaired on tasks requiring the

identification of emotions in faces (Oldershaw et al., 2011), and there is evidence to suggest that AN is associated with attentional bias to faces per se, regardless of valence (Harrison et al., 2010). Reduced resting functional connectivity within occipital visual areas have been reported in both ill and recovered AN patients (Favaro et al., 2012).

Also, an electroencephalography study showed that early neural responses to emotional faces are reduced in both ill and recovered patients (Hatch et al., 2010), supporting the notion that early and automatic processing of emotional stimuli are altered in AN. Similar decreased early neural responses to emotional faces have also been noted in patients with social anxiety disorder (Mueller et al., 2009). One study (Moody et al., 2015) showed that patients with AN have increased functional connectivity between the fusiform face area and precuneus/posterior cingulate gyrus during processing of low-frequency neutral facial images. This pattern was also observed for patients with body dysmorphic disorder. These studies indicate that alterations in face processing may not be unique to AN, but shared across different psychiatric groups. In contrast, one study found no altered neural responses to emotional faces in women recovered from AN (Cowdrey, Harmer, Park, & McCabe, 2012), underscoring the need for more research on the neural responses to emotional cues in AN. Unfortunately, we did not investigate how participants experienced the faces, so we don't know if the recovered AN women in this study subjectively experienced the faces differently than CW.

In contrast to our hypothesis, we did not detect any amygdala alterations in the recovered AN women. Several studies have reported amygdala hyperactivations in AN when disorder-specific stimuli are used (Joos et al., 2011; Miyake et al., 2010).

Amygdala hyperactivations in response to disorder-specific stimuli have also been reported in several other psychiatric disorders, including post-traumatic stress disorder, social anxiety disorder, and specific phobia (Etkin, 2007). It is possible that amygdala alterations in AN are only evident in response to disorder-specific material, which are highly salient for these individuals. However, in a previous study, we showed that emotional conflict processing is associated with differential amygdala activation in women recovered from AN (Bang, Rø, & Endestad, 2016a), although this was due to relative less activation in the recovered AN group. This suggests that AN is associated with amygdala alterations, but that these are not evident in response to angry faces or attentional bias to angry faces. Our study is the first to report on neural correlates of disorder non-specific attentional bias to threat in AN, and future studies are needed to shed further light on these neurophysiological processes in AN. As we included women recovered from AN, we do not know to what extent emaciation modulates the neural alterations reported in this study, and if similar alterations are present in currently ill patients with AN.

Strengths of the current study include the thorough diagnostic evaluation, extensive inclusion criteria, and the use of a well-established attentional bias task. Limitations of the study include its cross-sectional design, which does not enable us to differentiate brain scarring effects resulting from prolonged AN and malnutrition from trait dispositions. Moreover, to increase power and sensitivity of our analyses, we only included angry and neutral faces. Therefore, the effects of other emotional valences were not investigated. Also, we did not measure participants' subjective experience of the faces, so it is not known if groups differed in their emotional response to angry faces. Lastly, our study had a modest sample size, and a number

of possible confounders; including BMI, self-reported psychopathology, and emotion regulation difficulties. However, we investigated associations between these possible confounders and the neural responses that differed between groups, but no significant correlations were found.

To conclude, our results support the notion that women who develop AN are characterized by altered neural responses to threat cues, and display differential attentional processes to such stimuli, which may reflect compensatory processes. This could explain some of the discrepant findings of behavioral attentional bias to threat in AN, which may only be evident under certain contexts such as high cognitive load, or with particularly salient stimuli (i.e. food and bodies) for which compensatory mechanisms fail to maintain performance. Further studies are needed to characterize the behavioral and neurophysiological aspects of threat-detection and bias in AN.

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Table 1. Participant characteristics.

	Recovered AN (*n* = 22)	CW (*n* = 21)	Two sample t-test		
Characteristic	Mean ± SD	Mean ± SD	*t (df)*	*p*	*d*
Age	27.32 ± 5.14	26.00 ± 4.71	0.96 (41)	.386	0.27
Body Mass Index (kg/m^2)[a]	20.39 ± 1.66	21.85 ± 1.76	-2.70 (38)	.010	-0.85
STAI trait	38.77 ± 11.48	28.67 ± 6.42	3.54 (41)	.001	1.09
STAI state	32.14 ± 8.16	26.10 ± 5.22	2.88 (41)	.006	0.88
DERS total	77.36 ± 24.47	62.24 ± 14.61	2.45 (41)	.019	0.75
BDI	6.36 ± 7.94	1.86 ± 2.73	2.47 (41)	.018	0.76
EDE-Q global	0.84 ± 0.74	0.20 ± 0.17	3.90 (41)	<.001	1.19
Lowest lifetime weight[b]	71.84 ± 9.18 (range: 46 – 85)				
Age of AN onset	17.36 ± 4.17 (range: 11 – 32)				
Duration of illness (months)[c]	32.86 ± 27.47 (range: 6 – 120)				
Duration of recovery (months)[c]	51.62 ± 42.70 (range: 12 – 192)				

Abbreviations - AN, anorexia nervosa; CW, comparison women; STAI, Spielberger state-trait inventory; DERS, Difficulties with emotional regulation; BDI, Beck depression inventory; EDE-Q, Eating disorder examination-questionnaire; *d*, Cohen's *d* effect size.

[a] Data not available for three recovered anorexia nervosa women.

[b] Expressed as percentage of ideal weight, according to height, age, and gender.

[c] Data not available for one recovered anorexia nervosa woman.

FIGURE CAPTIONS:

Figure 1. Significant group differences in extrastriate cortex in response to angry faces (threat-detection). Brain activation clusters show the significant between-group differences in the left and right extrastriate cortex during threat-detection (incongruent + congruent > control). Bar-plots show *β*-weights (with standard error of mean) extracted from the cluster. *β*-weights from both the contrasts and the individual conditions (inset) are displayed. Activation maps are overlaid on a group average anatomical template, rendered in 3D. AN: anorexia nervosa, CW: comparison women.

a = two-sample t-test, $p < .001$.

b = one-sample t-test, $p = .005$.

c = one-sample t-test, $p = .001$.

d = one-sample t-test, $p = .010$.

e = one-sample t-test, $p < .001$.

Figure 2. Significant group differences in medial prefrontal cortex during attentional bias to threat. Brain activation clusters show the significant between-group differences in the left medial prefrontal cortex during attentional bias to threat (incongruent > congruent). Bar-plots show *β*-weights (with standard error of mean) extracted from the cluster. *β*-weights from both the contrast and the individual conditions (inset) are displayed. Activation maps are overlaid on a group average anatomical template, rendered in 3D. AN: anorexia nervosa, CW: comparison women.

a = two-sample t-test, $p < .001$.

b = one-sample t-test, $p < .001$.