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Blunted neural response to implicit negative facial affect in anorexia nervosa

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ABSTRACT

Background: People with anorexia nervosa (AN) have difficulties in a wide range of social-emotional processes. Previous work suggests atypical involvement of the prefrontal cortex (PFC), amygdala, insula, and fusiform gyri during social-emotional processing in AN.
Methods: Twenty women with AN and twenty healthy comparison (HC) women were presented with happy, fearful, and neutral faces during a functional magnetic resonance imaging study. Group differences were investigated in the following regions of interest: lateral PFC, amygdala, insula, and fusiform gyri.
Results: The HC participants showed significantly increased recruitment of the ventrolateral PFC and amygdala in the fearful > neutral contrast relative to the AN participants. The AN participants showed a significantly increased recruitment of a small cluster in the right posterior insula in the happy > neutral contrast.
Conclusions: These findings are in line with the hypothesis that people with AN have a blunted response to negative and atypical exaggerated response to positive emotionally provoking stimuli.

1. Introduction

Difficulties in social-emotional processing are believed to play an important role both in the onset and maintenance of anorexia nervosa (AN) (Treasure, Corfield, & Cardi, 2012; Treasure & Schmidt, 2013). A wide range of anomalies in social-emotional processing and reactivity to emotional stimuli have been documented in people with acute AN (Bora & Köse, 2016; Caglar-Nazali et al., 2014; Davies et al., 2016). Furthermore, longitudinal cohort studies have reported that difficulties in social cognition and social communication at admission are important predictors of poor treatment outcome at 3- to 18-year follow-up (Nielsen et al., 2015; Speranza, Loas, Wallier, & Corcos, 2007). Thus, these difficulties may contribute to the maintenance of the illness and further understanding of these processes is of importance.

Behavioural studies have documented difficulties in a range of different aspects of social-emotional processing in acute AN (Bora & Köse, 2016; Caglar-Nazali et al., 2014; Davies et al., 2016). Some experimental studies have suggested difficulties in explicit processing of social-emotional cues, such as recognition of facial expressions, in AN (Caglar-Nazali et al., 2014; Oldershaw et al., 2011). However, more recent studies have suggested that these difficulties may be driven by anomalies in interpretation and reactivity to social-emotional cues in

AN (Ambwani et al., 2015; Dapelo, Surguladze, Morris, & Tchanturia, 2016). Indeed, people with AN perceive emotionally provoking stimuli to be more negative and colder than healthy comparison (HC) participants (Ambwani et al., 2015; Cardi et al., 2014). Additionally, relative to HCs, people with AN display reduced facial affect in response to emotionally provoking stimuli (Davies et al., 2016). Taken together, these findings suggest that there may be specific anomalies in implicit processing and reactivity to social-emotional cues in AN and further exploration of the neural mechanisms that underlie these processes may be of interest.

Few studies have examined the neural processes that underlie difficulties in social-emotional processing and reactivity to emotional stimuli in people with AN. A recent review reported reduced response in prefrontal regions, including the lateral and medial prefrontal cortex (PFC), while viewing social behaviour in acute AN (McAdams & Smith, 2015). Further, one of the included studies found that reduced response in the lateral and medial PFC to social behaviour at admission to treatment was associated with poorer outcome at discharge (Schulte-Rüther, Mainz, Fink, Herpertz-Dahlmann, & Konrad, 2012). A recent study investigating implicit processing of happy faces of increasing intensity found greater linear increase in activation of the fusiform gyrus in people with acute AN relative to HCs (Fonville, Giampietro,

Surguladze, Williams, & Tchanturia, 2014). Another study, using a more explicit task, found reduced amygdala response in people recovered from AN relative to HCs in response to negative facial expressions when the faces were coupled with the congruent emotion label (Bang, Ro, & Endestad, 2016). Despite the relative paucity of research in this field, these findings suggest possible anomalies in the recruitment of frontal, amygdala, and visual attentional regions in social-emotional processing in AN.

More work has been conducted in anxiety and mood disorders, which are common comorbid disorders in AN and share similar difficulties in social-emotional processing and reactivity to emotional stimuli (Davies et al., 2016; Hambrook, Brown, & Tchanturia, 2012; Treasure, Stein, & Maguire, 2015). A recent meta-analysis found that relative to HCs, people with depression showed hyperactivation of regions associated with appraisal including amygdala, insula, and fusiform gyrus, during implicit processing of negative facial affect (Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2013). Additionally, increased activation of these regions was associated with reduced recruitment of regions associated with emotion down-regulation, including the lateral PFC (Groenewold et al., 2013). Similarly, people with generalised and social anxiety disorders show reduced activation of lateral PFC and associated hyperactivation of the amygdala when processing negative emotional stimuli including negative facial expressions (Mochcovitch, da Rocha Freire, Garcia, & Nardi, 2014). Taken together, these findings suggest that there may be a deficit in prefrontal down-regulation and limbic up-regulation of negative emotion associated with depression and anxiety.

The aim of the current study was to examine the neural substrates employed during implicit processing of positively and negatively valenced facial expressions in AN and HC participants. Based on the neuroimaging findings outlined above, we hypothesised that participants with AN would have atypical pattern of reduced recruitment of lateral PFC while processing emotional faces. Further, based on previous work conducted in mood and anxiety disorders as well as behavioural work in AN, we hypothesise that participants with AN would show a pattern of activation suggestive of anomalies in emotional reactivity. Specifically, we hypothesise that relative to the HCs, participants with AN would show increased activation in the amygdala, insula, and fusiform gyri while processing the emotional facial expressions.

2. Materials and methods

2.1. Participants

Forty right-handed females participated in the study. Twenty participants had a current DSM-IV diagnosis of AN, which was confirmed using the Structured Clinical Interview for Diagnosis – Researcher
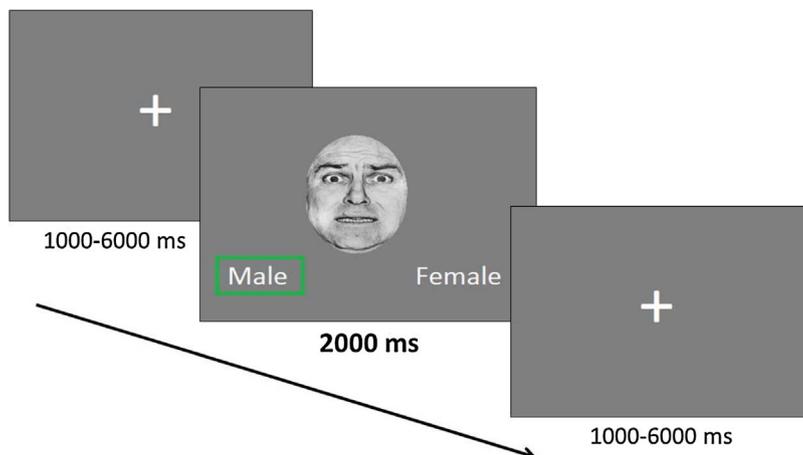
Version (Spitzer, Williams, Gibbon, & First, 1992). Fifteen participants with AN were recruited from the community through advertisements posted on eating disorder charity websites (i.e. BEAT and Succeed). The AN participants recruited from the community were not receiving psychological treatment during the time of the study. Five participants with AN were recruited from the Bethlem Royal Hospital, South London and Maudsley NHS Trust and were receiving treatment during the study. 60% of the participants with AN were taking antidepressants during the time of the study, 45% of the AN participants reported comorbid depression and 25% reported comorbid anxiety disorder. Twenty age-matched HC women of healthy weight were recruited from the community and amongst King's College London students and staff.

The exclusion criteria for all participants were a history of head trauma, hearing or visual impairment, neurological disease, MRI incompatibility, acute suicidality, and history of (or current) alcohol or drug abuse. Additionally, HC participants were screened with the Structured Clinical Interview for Diagnosis − Researcher Version (Spitzer et al., 1992) and were excluded if they had current or a history of psychiatric disorders. HC participants were also excluded if did not have BMI between 18.5 and 25.0 or were taking psychotropic medication. All participants gave a written, informed consent prior to taking part in the study and were compensated for their participation. The study was approved by a National Research Ethics Service committee (approval number: 11/LO/0373) and was conducted in accordance with the latest version of Declaration of Helsinki.

2.2. Questionnaire measures

The eating disorders examination questionnaire (EDEQ) (Fairburn & Beglin, 1994), a 36-item self-report measure, was used to assess eating restraint, eating concern, shape concern, and weight concern over the past 28 days.

The depression, anxiety, and stress scale (DASS) (Lovibond & Lovibond, 1995), a 21-item self-report measure, was used to assess depression, anxiety, and stress over the past two weeks.

2.3. Design and procedure

During a 6-min event-related functional magnetic resonance imaging (fMRI) task participants were presented with black and white images of faces (Fig. 1). The face stimuli consisted of prototypical happy (intensity: 100%), prototypical fearful (intensity: 100%), and neutral faces. The stimuli were selected from a standardised set of facial expressions (Ekman & Friesen, 1976), and consisted of ten different adults displaying each of the selected emotions (5 female and 5 male). Happy and fearful faces were used as they have previously been found to strongly capture participants' attention and produce robust activation of the amygdala, fusiform gyrus, insula, and prefrontal regions (Fusar-Poli et al., 2009;

Fig. 1. Implicit emotion processing task.
The happy, fearful, and neutral faces were presented one at a time for 2000 milliseconds (ms) during which participants identified the gender of each face. Faces were preceded by a fixation cross the presentation of which was jittered between 1000 and 6000 ms.

Lundqvist & Ohman, 2005; Williams & Mattingley, 2006). Additionally, unlike angry or disgusted faces, fearful faces are not considered to be indicative of direct threat (Hunnius, de Wit, Vrins, & von Hofsten, 2011). The neutral faces were used as a baseline comparison condition to allow investigation of neural responses to facial affect.

Twenty happy, fearful, and neutral faces were presented in a pseudo-randomised order. The faces were presented one at time for 2000 ms followed by an inter-stimulus interval (ISI) fixation cross. The ISI was varied between 1 and 6 s. To ensure participants were attending to the stimuli, they were asked to identify the gender of the faces by pressing the appropriate buttons. This is a paradigm frequently employed to investigate implicit social-emotional processing (Stuhrmann, Suslow, & Dannlowski, 2011).

2.4. Image acquisition and pre-processing

Magnetic resonance images were acquired using GE Signa 1.5 T scanner (GE Medical Systems, Milwaukee, Wisconsin) at the Centre for Neuroimaging Science, King's College London. An 8-channel headcoil was used to transmit and receive the radio frequency signal. T2* – weighted images depicting blood oxygen level dependent (BOLD) signal were acquired using an interleaved ascending acquisition order with a repetition time of 2 s with 40 ms echo time and an 80° flip angle. Whole brain coverage was acquired in 30 slices with 4 mm slice thickness and 0.4 mm slice gap. 180 T2* – weighted whole brain volumes were acquired with an in-plane resolution of 3.75 mm × 3.75 mm. Additionally, high-resolution sagittal T1–weighted structural images (MP-RAGE) were acquired with a repetition time of 8.592 ms. The echo time was 3.8 ms with an 8° flip angle. Whole brain coverage was acquired in 180 slices with an in-plane resolution of 1.25 mm × 1.25 mm, and 1.2 mm slice thickness and 1.2 mm slice gap.

Prior to analysis, the fMRI data was pre-processed using SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London) implemented in Matlab 2015b (Mathworks, Natick, Mass.). Pre-processing involved slice-timing and volume-to-volume head motion correction. The data was then co-registered to a high-resolution DARTEL template, created out of the participants T1–weighted structural images (Ashburner, 2007), and normalised to Montreal Neurological Institute (MNI) space. The data was spatially smoothed using an 8 mm FWHM three-dimensional isotropic Gaussian kernel.

2.5. Statistical analysis

2.5.1. Questionnaire and behavioural data

Questionnaire and behavioural data were analysed with Stata 14 (StataCorp. 2015, College Station, TX: StataCorp LP.). Due to skewed nature of the questionnaire data, group differences were investigated with nonparametric median Chi^2 tests. Prior to analysis, gender identification accuracy data was transformed with arcsine and square root transformation to allow further analysis under the general linear model framework. The gender identification accuracy and reaction time data were then analysed with a bootstrapped mixed model (1000 repetitions). Trial (fearful, happy, neutral) and group (AN, HC) were entered as fixed effects variables with a random intercept. Significant effects and interactions were further investigated by calculating post-hoc contrasts and pair-wise comparisons. $P < 0.05$ was considered significant.

2.5.2. Neuroimaging data

On subject level, each participant's fMRI data were analysed under the general linear model framework in SPM 8. A canonical haemodynamic response function was used to model the BOLD signal for each of the following conditions: happy faces, fearful faces, and neutral faces. The time-series was adjusted for head motion using the Friston 24-parameter model (Friston, Williams, Howard, Frackowiak, & Turner, 1996) and low-frequency drift was filtered out using high-pass filter set to 1/128s. To investigate relative activation or deactivation in response to fearful and happy facial expressions compared to neutral faces, the following contrast images were generated for each participant: fear > neutral and happy > neutral.

Each participant's contrast images were then entered into group level analysis, which was conducted with the Robust Regression toolbox (http://wagerlab.colorado.edu/tools) implemented in Matlab 2015b (Wager, Keller, Lacey, & Jonides, 2005). The Robust Regression toolbox uses iteratively re-weighted least squares (IRLS) to increase statistical power and reduce the impact of extreme outliers (Fritsch et al., 2015; Wager et al., 2005). We chose this method to reduce the likelihood of false findings due to presence of extreme outliers that could arise from head motion, scanner related artefacts, or individual participants who were substantially different from the rest of the sample during the time of the MRI scan.

The contrast images were first entered into region of interest (ROI) IRLS analyses to test a priori hypotheses. The WFU Pickatlas toolbox in SPM 8 was used to create the following ROI masks: bilateral amygdala, bilateral insula, bilateral fusiform gyri, and bilateral lateral PFC. To investigate group differences within these regions, group status was added as a contrast-coded covariate (1, −1: AN, HC). Thus, positive test statistic indicates greater activation in the AN group relative to the HC group and negative test statistic indicates greater activation in the HC group relative to the AN group. The ROI findings were corrected for multiple comparisons with a voxel-wise nonparametric permutation test with 10000 iterations (α < 0.05). The permutation test uses the max T distribution to generate a new corrected t-threshold each voxel must reach to be considered significant.

We, additionally, explored whether the mean activation in the significant ROIs correlated with medication status, BMI, DASS total score, duration of illness, and eating disorder psychopathology as measured by EDEQ within the AN group. The correlations were conducted by extracting mean signal change from the significant ROIs in each contrast as recommended by Vul, Harris, Winkielman, and Pashler (2009). Nonparametric Spearman's rho correlations were then conducted with Matlab 2015b and p < 0.01 was considered significant following correction for multiple comparisons.

Finally, we also conducted an exploratory whole brain analysis to investigate if significant group differences were present in any further regions outside of the a priori ROI masks. As above, the contrast images were entered into whole brain IRLS analysis with group status was added as a contrast-coded covariate (1, −1: AN, HC). The whole brain findings were corrected for multiple comparisons with voxel level False Discovery Rate (FDR) set at q < 0.05. Effect size, and lower and upper bound 99.9% confidence interval maps were generated using the EScalc toolbox implemented in Matlab 2015b (http://restfmri.net) (Gao & Zang, 2015).

3. Results

3.1. Clinical characteristics

The socio-demographic and clinical characteristics of the groups are presented in Table 1. There were no significant differences in age or years of education between the AN and HC participants. As expected the participants with AN had significantly lower BMI and reported significantly more eating disorder psychopathology, depression, anxiety, and stress than the HC participants.

3.2. Gender identification

Gender identification mean reaction times and accuracy are presented in Table 2. There was a significant difference between the groups in gender identification RTs, with the HC participants being significantly faster to identify the gender of the faces than the participants with AN.

Table 1
Demographic and clinical characteristics.

	AN (N = 20) Mean (SD)	HC (N = 20) Mean (SD)	X^2 statistic, p value
Age	28.6 (10.81)	25.75 (3.40)	$X^2 < 0$, p = 1.00
Years of education	15.95 (2.56)	16.25 (4.28)	$X^2 = 0.10$, p = 0.752
Duration of illness (years)	13.0 (10.1)	–	–
BMI	15.87 (1.70)	21.15 (2.26)	$X^2 = 27.92$, p < 0.001
EDEQ Total	4.16 (0.99)	0.57 (0.54)	$X^2 = 34.11$, p < 0.001
EDEQ Restraint	4.20 (1.35)	0.45 (0.53)	$X^2 = 26.95$, p < 0.001
EDEQ Eating concern	3.71 (1.06)	0.13 (0.18)	$X^2 = 34.11$, p < 0.001
EDEQ Shape concern	4.66 (1.15)	1.05 (0.98)	$X^2 = 26.95$, p < 0.001
EDEQ Weight concern	4.07 (1.51)	0.65 (0.70)	$X^2 = 20.63$, p < 0.001
DASS Total	70.32 (22.56)	12.30 (13.01)	$X^2 = 27.92$, p < 0.001
DASS Anxiety	17.79 (7.54)	1.80 (3.11)	$X^2 = 16.01$, p < 0.001
DASS Depression	25.47 (11.03)	2.90 (4.38)	$X^2 = 21.55$, p < 0.001
DASS Stress	27.05 (8.34)	7.60 (7.13)	$X^2 = 16.01$, p < 0.001

AN = anorexia nervosa; HC = healthy comparison; BMI = body mass index; EDEQ = Eating Disorder Examination Questionnaire; DASS = Depression, Anxiety, and Stress Scale.

In gender identification accuracy, there was a significant difference between trials with all participants being significantly more accurate in the happy trials than fearful or neutral trials (Z = 2.37, p = 0.018, 95% CI [0.005, 0.05]; Z = 2.73, p = 0.006, 95% CI [0.01, 0.04]). There were no significant differences in accuracy between neutral and fearful trials across participants (Z = 0.33, p = 0.742, 95% CI [-0.02, 0.03]). There was also a significant effect of group and a significant trial x group interaction (Table 2). Post-hoc tests revealed that HC participants were significantly more accurate than the participants with AN only in the fearful trials (Z = 2.64, p = 0.008, 95% CI [0.01, 0.09]), but not in the happy (Z = −1.42, p = 0.155, 95% CI [-0.04, 0.01]) or neutral trials (Z = 1.27, p = 0.205,95% CI [-0.01,0.04]).

3.3. Regions of interest findings

3.3.1. Happy > neutral faces
The ROI findings are presented in Fig. 2 and Table 3. There was a significant difference in BOLD signal change between groups in recruitment of the right posterior insula while viewing happy > neutral faces (Fig. 2A, Table 3). Inspection of the contrast parameter estimates revealed that there was simultaneous BOLD signal increase in the right posterior insula in the AN group and BOLD signal decrease in the posterior insula in the HC group in this contrast (Fig. 2A). No further significant differences between groups were found in the amygdala, fusiform gyri, or lateral PFC in this contrast.

Additionally, within the AN group, the mean BOLD signal change in the insula ROI did not significantly correlate with medication status, duration of illness, psychopathology, or BMI in this contrast (Supplementary Table 1).

3.3.2. Fearful > neutral faces
The ROI findings revealed a significant difference between the AN and HC groups in BOLD signal change in left amygdala in response to fearful relative to neutral faces. Similarly, there was a significant difference between groups in BOLD signal change in the left VLPFC in this contrast. Inspection of the peak parameter estimates revealed that there

was a relative increase BOLD signal in the left amygdala and VLPFC in response to the fearful expressions in the HC group, but not in the AN group (Fig. 2B,C). No further significant differences between groups were found in the insula or fusiform gyri in this contrast.

Additionally, within the AN group, the mean BOLD signal change in the VLPFC or amygdala ROIs did not significantly correlate with medication status, duration of illness, psychopathology, or BMI in this contrast (Supplementary Table 1).

3.4. Whole brain findings

The exploratory whole brain analysis did not reveal any regions of significant differences in BOLD signal change between groups within the happy > neutral or fearful > neutral contrasts. The effect size maps revealed regions of activation with large effect sizes in response to fearful > neutral and happy > neutral faces in the AN > HC group contrast (Supplementary Fig. 1, Supplementary Fig. 2). However, these regions did not survive whole brain voxel level correction.

4. Discussion

The aim of the current study was to investigate anomalies in the neural substrates employed during implicit processing of positive and negative emotional facial expressions in AN. There was a significant difference between groups in the recruitment of left VLPFC and the amygdala while processing fearful facial expressions, with the HCs showing significantly increased activation in both of these regions while the participants with AN did not. Additionally, we found a significantly increased activation of the right posterior insula in the AN group relative to the HC group while viewing happy facial expressions. No group differences were found in the fusiform gyri in response to fearful or happy facial expressions. Similarly, no group differences were found in the exploratory whole brain analysis.

The current findings revealed reduced activation of the left amygdala in the people with AN relative to the HCs while processing fearful facial expressions. Regarding the HCs, these findings are in line with previous

Table 2
Gender identification mean reaction times and accuracy.

	Trial	AN (N = 20) Mean (SD)	HC (N = 20) Mean (SD)	X^2 statistic, p value
Reaction time (ms)	Fearful faces	934.13 (208.12)	812.78 (143.66)	Trial: $X^2 = 2.09$, p = 0.352
	Happy faces	956.15 (227.28)	827.10 (122.32)	Group: $X^2 = 64.94$, p < 0.001
	Neutral faces	951.20 (204.50)	783.80 (100.98)	Trial x Group: $X^2 = 2.11$, p = 0.348
Accuracy (%)	Fearful faces	85.50 (5.60)	89.00 (5.76)	Trial: $X^2 = 10.15$, p = 0.006
	Happy faces	89.75 (3.02)	88.75 (3.58)	Group: $X^2 = 4.10$, p = 0.043
	Neutral faces	87.13 (4.08)	88.38 (2.84)	Trial x Group: $X^2 = 10.56$, p = 0.005

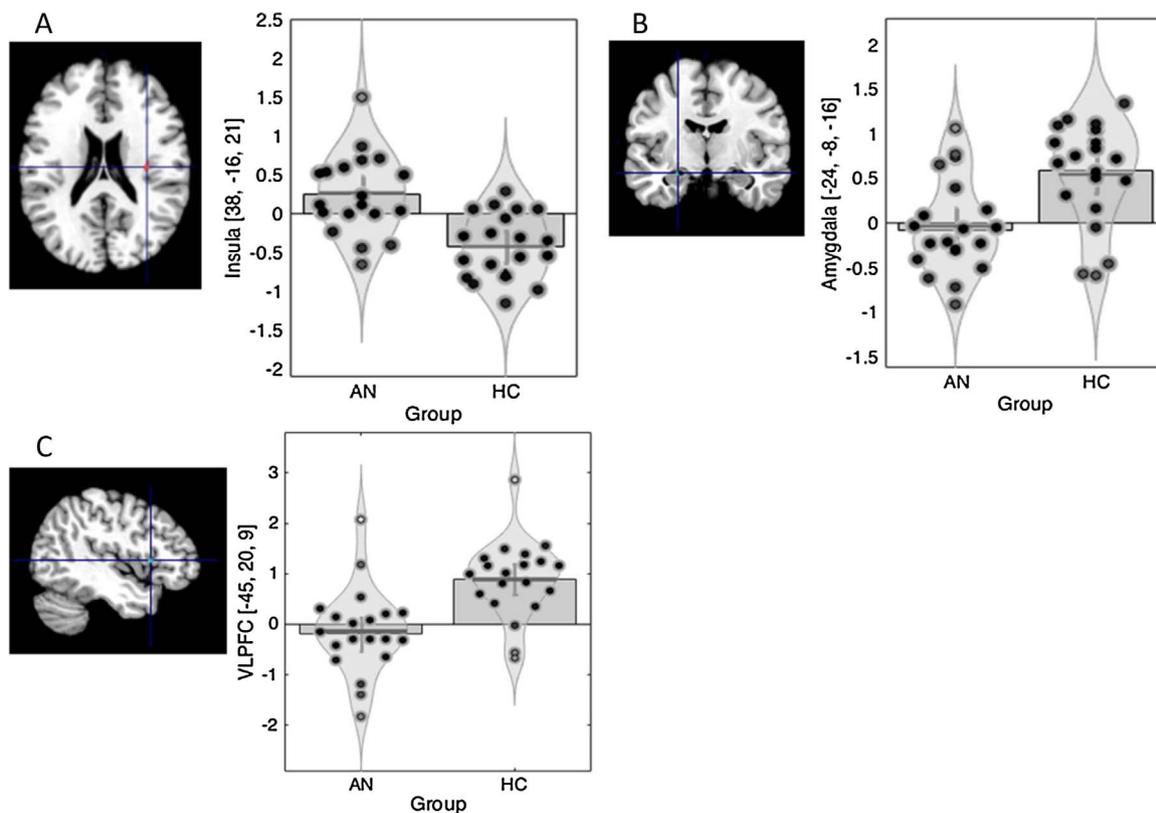AN = anorexia nervosa; HC = healthy comparison; ms = milliseconds.

Fig. 2. Regions of interest findings in AN and HC participants.
A.) Differences in signal change between the AN and HC participants in the right posterior insula in the happy > neutral contrast; B.) Differences in signal change between the AN and HC participants in the left amygdala in the fear > neutral contrast; C.) Differences in signal change between the AN and HC participants in the left VLPFC in the fear > neutral contrast. The bar plots indicate group means and the error bars represent the 95% confidence intervals for the mean. The overlaid violin plots provide an indication of the density and distribution of the data and the circles inside the violin plots indicate weighted individual data points. Black circles indicate weight of 1, white circles indicate weight of 0, and grey circles indicate reduced weights. AN = anorexia nervosa; HC = healthy comparison; VLPFC = ventrolateral prefrontal cortex.

work showing that healthy individuals show an elevated amygdala response to negative emotional facial expressions during both implicit and explicit tasks (Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006; Hung et al., 2010; Sato, Yoshikawa, Kochiyama, & Matsumura, 2004). Additionally, previous studies in AN have reported reduced recruitment of the amygdala in people who had recovered from AN relative to HC participants in an explicit facial emotion processing task (Bang et al., 2016). Thus, these findings suggest that blunted amygdala response to negative facial affect in AN may be trait-like anomaly that persist after recovery.

The current findings also showed reduced recruitment of the left VLPFC in participants with AN relative to the HCs, in response to fearful facial expressions. Increased activation of the VLPFC in healthy individuals has been found in studies where participants are presented with negative facial expression or neutral facial expressions in negative context (Kim et al., 2004; Marumo, Takizawa, Kawakubo, Onitsuka, & Kasai, 2009; Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006). In AN, reduced frontal response to emotional facial expression has been

previously reported in an EEG study, which found reduced frontal P300, while viewing negative facial expressions (Pollatos, Herbert, Schandry, & Gramann, 2008). Additionally, reduced activation of lateral and medial PFC regions has been reported in AN while viewing positive and negative social behaviour (McAdams & Smith, 2015). Such reduced PFC reactivity has also been associated with poorer general clinical outcome at 1-year follow-up (Schulte-Rüther et al., 2012). These findings highlight the importance of atypical activation of these regions in acute AN and suggest that this could contribute to illness maintenance.

A possible interpretation of these findings is that unlike in depression and anxiety disorders (Groenewold et al., 2013; Mochcovitch et al., 2014), people with acute AN may show generally blunted reactivity to negative social-emotional stimuli. This interpretation is supported by behavioural work that has found that relative to HCs, people with acute AN display less negative facial affect while viewing negative film stimuli (Davies, Schmidt, & Tchanturia, 2013; Davies et al., 2016). People with AN also tend react in an emotionally cold and detached manner to negative emotionally provoking stimuli relative to HCs (Ambwani et al.,

Table 3
Regions of interest findings in AN and HC participants.

Contrast	Peak MNI Coordinates			Contrast signal change					
	x	y	z	AN Mean (SE)	HC Mean (SE)	Max T	p value	k	ROI
Happy > Neutral	38	−16	21	0.26 (0.12)	−0.42 (0.10)	4.68	0.0001	14	Insula
Fearful > Neutral	−24	−8	−16	−0.08 (0.13)	0.60 (0.14)	−3.55	0.001	10	Amygdala
	−45	20	9	−0.19 (0.17)	0.90 (0.15)	−4.21	< 0.0001	16	VLPFC

Voxel size 1.5 mm × 1.5 mm × 1.5 mm. AN = anorexia nervosa; HC = healthy comparison; MNI = Montreal Neurological Institute; SE = standard error of the mean; k = number of voxels; ROI = region of interest; VLPFC = ventrolateral prefrontal cortex.

2015). Taken together these finding suggest that people with AN may have atypical blunted response to negative social-emotional cues.

The present study also found a significant increased activation of the right posterior insula in the AN group relative to the HCs while viewing happy facial expressions. A recent meta-analysis found increased activation of the posterior insula in people with AN relative to HC participants when processing stimuli depicting bodies using a variety of paradigms, including comparing own body to images of slim bodies (Zhu et al., 2012). Among healthy individuals, such increased activation of the bilateral posterior insula has previously been associated with perception and experience of emotions, particularly negative emotions (Duerden, Arsalidou, Lee, & Taylor, 2013; Grecucci, Giorgetta, van't Wout, Bonini, & Sanfey, 2013; Waugh et al., 2016). Furthermore, healthy individuals show increased activation of the posterior insula in response to a task involving up-regulation of others' negative intentions (Grecucci et al., 2013).

The above findings suggest that people with AN may exhibit atypical reactivity to positive social-emotional stimuli that is similar to that seen in healthy individuals in response to negative stimuli. This interpretation is supported by previous behavioural work showing that people with AN have a tendency to avoid positive emotions (Lampard, Byrne, McLean, & Fursland, 2011). Additionally, when presented with positive film clips people with AN display fewer reciprocal positive facial expressions, and report less positive subjective positive affect and more negative positive affect than HC participants (Cardi et al., 2015; Davies et al., 2011; Davies et al., 2016; Lang et al., 2016). Additionally, people with AN report greater social anhedonia and general difficulties deriving pleasure from social interactions (Tchanturia et al., 2012). Taken together, these findings suggest that people with AN may have an atypical reaction to positive social-emotional stimuli.

4.1. Clinical implications

The present findings differ from what is seen in depression and anxiety disorders, and suggest that a generally blunted response to negative and atypical response to positive social-emotional information in acute AN. When taken together with recent findings in people who have recovered from AN (Bang et al., 2016), the findings suggest that a blunted response to negatively valenced stimuli may persist after recovery. Reduced reactivity to emotional stimuli has been suggested to have negative affective and social consequences, including elevated negative mood, negative social evaluation by others, and increased isolation (Butler, Lee, & Gross, 2009; Gross, 2002; Szczurek et al., 2012). Furthermore, atypical emotional reactivity in AN also has negative impact on carers and has been associated with increased anxiety and anger in the family (Treasure et al., 2012). Thus, these social-emotional processing difficulties in AN are important targets for interventions.

4.2. Limitations

The main limitation of the current study was the relatively small sample size limiting the exploration of potential confounding effects of AN subtypes, inpatient treatment, and medication. However, we took steps to combat this by exploring the effects of eating disorder psychopathology and medication status on the present findings in post-hoc correlational analyses. Additionally, since we did not include weight restored AN participants or people recovered from AN, it is also not possible to ascertain to what extent the present findings are due to malnutrition. Therefore, future studies with larger and balanced samples are required to replicate and further explore the impact of medication on neural correlates of social-emotional processing in AN. Future, studies would also benefit from further exploring the neural correlates of social-emotional processing difficulties across age and duration of illness.

Although the present study explored the impact of self-reported

eating pathology and medication status on the findings in correlational analyses, we did not examine the impact of comorbid disorders. Previous studies have reported that people with AN report higher levels of a number of comorbidities that could impact social-emotional processing, such as autistic symptoms and alexithymia (Caglar-Nazali et al., 2014; Doris, Westwood, Mandy, & Tchanturia, 2014; Westwood et al., 2016).Future studies would benefit from investigating the impact of autistic symptoms and alexithymia on neural processes recruited during social processing in AN.

Finally, the current study only used happy and fearful facial expressions. Utilising a wider range of emotional facial expressions, including disgust, anger and sadness would be of interest. Furthermore, the current study also only used static images without context. Future studies would benefit from using more ecologically relevant designs that include dynamic facial expressions with contextual information.

5. Conclusions

The current study investigated neural mechanisms that underlie processing of fearful and happy facial expressions in AN. The ROI findings revealed decreased BOLD signal in the left amygdala and VLPFC while processing fearful facial expressions in the AN participants compared to HC. Additionally, we found a cluster in the right posterior insula with a relative increase in the BOLD signal while processing happy facial expressions in AN, but not in the HC participants. These findings go some way to support the social-emotional elements of the cognitive-interpersonal maintenance model and calls for interventions that target difficulties in social-emotional difficulties in AN.

Conflict of interest

None

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.biopsycho.2017.07.010.

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