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ORIGINAL ARTICLE

Intimate stimuli result in fronto-parietal activation changes in anorexia nervosa

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Abstract

Background Intimacy is a key psychological problem in anorexia nervosa (AN). Empirical evidence, including neurobiological underpinnings, is however, scarce.

Objective In this study, we evaluated various emotional stimuli including intimate stimuli experienced in patients with AN and non-patients, as well as their cerebral response.

Methods Functional magnetic resonance imaging was conducted using stimuli with positive, neutral, negative and intimate content. Participants (14 AN patients and 14 non-patients) alternated between passive viewing and explicit emotion regulation.

Results Intimate stimuli were experienced less positively in AN patients compared to non-patients. AN patients showed decreased cerebral responses in superior parietal cortices in response to positive and intimate stimuli. Intimate stimuli led to stronger activation of the orbitofrontal cortex, and lower activation of the bilateral precuneus in AN patients. Orbitofrontal responses decreased in AN patients during explicit emotion regulation.

Conclusions These results show that intimate stimuli are of particular importance in AN patients, who show experiential differences compared to non-patients and altered activation of orbitofrontal and parietal brain structures. This supports that AN patients have difficulties with intimacy, attachment, self-referential processing and body perception.

Level of evidence Level III, case–control study.

Keywords Anorexia nervosa · Intimacy · Neuroimaging · fMRI · Emotion regulation · Orbitofrontal cortex · Precuneus

Introduction

Anorexia nervosa (AN) is a severe mental disorder with a life time prevalence of 2% in women, with only about 40% recovering [1]; recovery criteria are however subject to discussion [2]. Typically, AN occurs in a vulnerable

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developmental phase of young women, which includes profound changes of the body and the ability to enter intimate relationships. The precise etiology of AN is not known, though psychosocial and neurobiological abnormalities likely interact.

Functional brain imaging in AN has so far focused on disease-specific items (i.e., food or body) [3]. There is very little evidence with respect to neural underpinnings of general emotional stimuli, including intimacy in AN [3]. Uher et al. [4] found occipital activity differences for aversive stimuli, which they discussed as unspecific, while activations in response to disease-specific stimuli showed strong frontal differences in their study.

Before going into the pathophysiology of AN with respect to intimacy, we briefly mention some general aspects of emotion processing. Definitions and concepts of emotions are not uniform [5–8]. In principle, emotions are a set of action tendencies, physiological reactions, facial expressions and subjective feelings which evolve over time in response to internal or external stimuli of individual relevance [9–11]. Emotion theories comprise dimensional and categorical approaches [12].

Emotion processing difficulties within AN might be twofold, with increased reactivity on one hand and inability to regulate emotions on the other hand. To test the differentiation between regulatory and emotional systems, an emotion induction and regulation paradigm is useful because the limbic system involved in emotion induction and the prefrontal areas involved in emotion regulation are spatially differently located in the brain [13, 14].

Intimacy should be discerned from more basic emotions such as anger or fear. According to Yoo et al. [15] intimacy refers to the "partners' general sense of closeness with each other" and it involves "intellectual, interpersonal, affective, and physical aspects of the couple relationship", suggesting a close relation to attachment [16]. The relation of avoidant and insecure attachment styles in AN as well as difficulties with the separation-individuation process have been pointed out [17]. Intimacy is related to love, however, it is a matter of debate whether love is a specific emotion or a state that leads to various emotions [18]. Intimacy as well as love can be regarded as complex emotions (i.e., a blend of emotions related to sexual drives and attachment [16]). Developmental disturbances in AN concerning self, body and intimate relationships in AN were already characterized by H. Bruch [19]. However, there has been surprisingly little empirical evidence for disturbances of intimacy and sexual functioning in AN since [20], and only a few studies call attention to the subject [20–24].

With respect to the current study, some recent works deserve attention: our group had evaluated a set of visual intimate stimuli for the use of clinical samples (for details see below, method section and [25]). Though functional imaging has been used to study brain responses to erotic stimuli in men, few studies have done so in women. Walter et al. [26] studied 11 healthy heterosexual males and 10 heterosexual females and reported activations of the ventral striatum, hypothalamus and anterior cingulate cortex (ACC) when viewing erotic vs. non-erotic emotional visual stimuli. They did not find differences between men and women. Li et al. [27] evaluated visual erotic rewards in 38 male non-patients (NPts) and reported strong activations of the orbitofrontal cortex (OFC). Striatal and OFC activation has also been reported in studies of romantic and parental love, emphasizing that these areas are rich in oxytocin binding sites [18, 28]. Finally, Arnow et al. [29] studied a clinical sample, i.e., female participants with hypoactive sexual desire disorder, reporting increased frontal activation.

The present study focused on neural correlates of intimate stimuli. To discern specific reactions to intimacy, we also used positive and negative emotional stimuli for emotion induction. As our study is the first of its kind, it is largely exploratory. In this pilot study, we focused on emotion induction. Explicit emotion regulation was also evaluated, similar to a related study in borderline patients [30]. We briefly report these data, too, though they are not the focus of this pilot investigation.

We expected increased activation of prefrontal cortices, particularly the dorsolateral prefrontal cortex (DLPFC). This is because AN patients have a high inclination towards control, particularly with difficult emotions, and we expected intimacy to be a difficult emotion for them. As the OFC is relevant to reward expectations/salience [31, 32], including erotic reward [27], we expected differences of OFC activation. Furthermore, we assumed increased activation of the amygdala, due to negative emotions in AN when confronted with intimacy. We expected higher blood oxygen level-dependent (BOLD) responses of the ACC, based on its function of emotion evaluation, attentional control and response selection [3]. Additionally, we hypothesized less activation in the dorsomedial prefrontal and temporal cortices for positive non-intimate stimuli [33] and increased BOLD signals of frontal regions concerning negative emotions. The latter hypothesis was because there is often blunted affect in AN, though we are aware that Uher et al. [4] did not find such differences.

Methods and materials

Participants

Fourteen heterosexual female AN patients (two left-handed) were recruited at the Department of Psychosomatic Medicine and Psychotherapy at the University of Freiburg. All patients were in the acute phase, seeking treatment. Eleven

were diagnosed as restrictive AN, two with binge-eating/purging and one with purging-type AN. Diagnoses were made by experienced and board-certified psychiatrists and psychologists. Psychopathological data of AN patients are displayed in Table 1. AN patients typically had high scores on the disorder-specific scales (i.e., drive for thinness, bulimia and body dissatisfaction) of the Eating Disorder Inventory [34], as well as increased scores on the Beck Anxiety and Depression Inventory [35, 36]. Three AN patients took antidepressants (two were on Fluoxetine and one on Mirtazapine), one took 10 mg of Melneurin, one 2.5 mg of Olanzapin at night, and five were on hormonal contraception. Fourteen right-handed female NPts were age-matched (AN 21.4 ± 3.1 years, NPts 22.8 ± 2.9 years; $t(26) = 1.26$; $p = 0.218$). NPts were recruited by local advertisement and had overlap with the NPts concerning an functional magnetic resonance imaging (fMRI) study examining emotion regulation in borderline personality disorder [30]. NPts did not meet current diagnostic criteria for Axis I or II disorders. However, Eating Disorder Inventory and anxiety and depression scores were not available for NPts. General exclusion criteria were lifetime psychotic or bipolar disorder type-I, attention-deficit/hyperactivity disorder, dissociative identity disorder, serious and/or unstable medical illness, substance dependence. After description of the study, written informed consent was obtained. The study was approved by the Ethics Committee of the University of Freiburg.

Experimental task

To examine differences in brain activity related to emotion induction as well as explicit emotion regulation between AN patients and NPts, we used an adapted version of a classic emotion regulation paradigm [30, 37]. We measured BOLD signal changes during two experimental conditions: a traditional look condition, i.e., emotion induction, and an emotion regulation, i.e. safe condition. The look condition required participants to attend to the pictures and respond naturally without altering their emotional state [37]. During the safe condition, participants were instructed to realize themselves being safe (inspired by schema therapy theory [38]). Both conditions were presented in a pseudo-randomized order (no more than three identical conditions in a row occurred), and this order was used for all participants. Participants implemented the two strategies during the presentation of a picture, which was preceded by an instruction cue. As soon as the picture disappeared, participants assessed their emotional state at that moment using a horizontal − 100 to 100 mm visual analogue scale (Fig. 1a). The task consisted of 96 trials divided into four runs of 24 trials each.

Table 1 Characteristics of Anorexia nervosa patients ($n = 14$)

BAI	17.2 ± 10.2
BDI	22.6 ± 12.1
EDI—drive for thinness	72.1 ± 22.7
EDI—Bulimia	59.8 ± 21.4
EDI—body dissatisfaction	55.3 ± 12.4
BMI—current	16.1 ± 1.2
BMI—lowest life time	14.7 ± 1.6
Disease duration (years)	3.3 ± 3.9

BAI Beck Anxiety Inventory (sum), *BDI* Beck Depression Inventory (sum), *EDI* Eating Disorder Inventory (T-Scores), *BMI* body mass index (kg/m^2)

Stimuli

Visual stimuli consisted of pictures in four categories: 24 negative, 24 neutral, 24 positive and 24 intimate. The pictures were selected from the International Affective Picture System [39], and additional intimate pictures from Jacob et al. [25]. In that study, 41 heterosexual females rated and validated a set of 100 stimuli with intimate content on valance, arousal and dominance (for example, see Fig. 1b). Only pictures with a social content (i.e., one person emotionally relating to the viewer or two or more persons interacting) were selected. The pictures were randomly presented per participant and balanced across condition types. Presentation of the stimuli and recordings of behavioral responses were controlled by Presentation software (Neurobehavioral Systems Inc., Albany, CA, USA). The visual stimuli were projected via PC and projected onto a screen that was viewed via goggles.

Procedure

Prior to scanning, participants were trained on a practice task outside the scanner, to ensure correct and confident use of the emotion regulation strategy and to familiarize them with the nature of the pictures. This task was similar to the experimental task inside the scanner, but contained novel stimuli during the scan. Once completing the practice task, participants entered the scanner. The scanning session started with a resting state run (data reported separately), followed by two runs of the experiment and an anatomical scan. Next, two more emotion regulation runs and a final resting state run were acquired.

Imaging acquisition

Images were obtained on a 3 T Siemens tim-Trio Magnetom whole body scanner (Siemens Medical Systems, Erlangen, Germany) equipped with an 8-channel head coil. Participants were scanned in head-first supine position. Head movements were minimized using foam paddings.

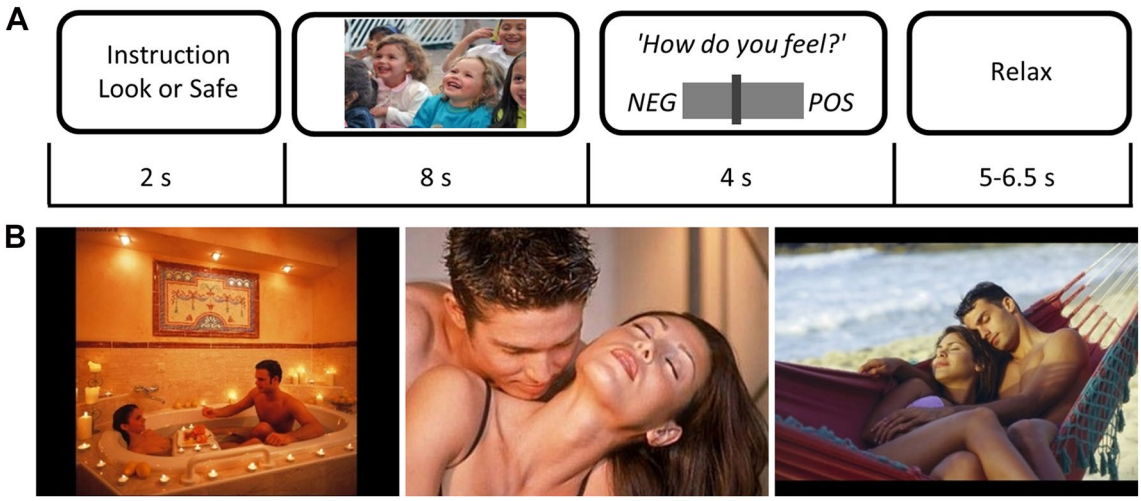

Fig. 1 Schematic overview of a single trial and examples of intimacy stimuli. **a** Schematic overview of a single trial of the task. Each 19–20.5 s trial consisted of a 2 s visual instruction to either 'look' or 'realize being safe', an 8 s presentation of the picture for carrying out the instruction, a 4 s rating period and a 5–6.5 s fixation (cross hair). During the rating period, participants indicated their emotional experience at the moment moving the pointer on the horizontal scale using a button box between negative (− 100) to positive (100). **b** Visual stimuli of intimacy (for details see [25])

Additionally, participants were instructed not to look away from the pictures or to close her eyes, and avoid moving as much as possible during scanning.

Echo-planar imaging (EPI) was performed to acquire T2*-weighted images, using the following imaging parameters: TR = 2000 ms, TE = 27 ms, flip angle = 90°, FoV = 192 × 192 mm, voxel size = 3 × 3 × 3 mm, and matrix = 64 × 64. Each run recorded 252 images, one volume consisted of 34 interleaved measured axial slices. The T2*-weighted images were optimized with a negative tilt of 30°, to minimize susceptibility and distortion artifacts within the amygdala and OFC [40]. High-resolution whole brain T1-weighted anatomical scans in sagittal plane were acquired, using a sequence (TR = 2200 ms, TE = 4.11 ms, flip angle = 12°, FoV 256 × 256 mm, voxel size 1 × 1 × 1 mm), involving 160 volumes.

Preprocessing

All preprocessing and statistical analyses were performed with BrainVoyager QX version 2.6 (Brain Innovation, Maastricht, The Netherlands). The first two images were discarded due to saturation effects. Preprocessing contained slice time correction with sinc interpolation, 3D motion correction for three translational and three rotational directions with trilinear/sinc interpolation, removal of low-frequency drifts by high-pass temporal filtering of 2 sines/cosines and spatial smoothing with a 6 mm full-width-at-half-maximum isotropic Gaussian kernel [41]. After preprocessing, the functional images were coregistered with the anatomical data per run, and for each run a volume-time-course was created. All anatomical scans were peeled from the skull and corrected for intensity inhomogeneity. Spatial normalization was performed using standard Talairach transformation procedures [42].

Data analyses

The applied general linear model included ten predictors: instruction, negative-look, positive-look, intimate-look, neutral-look, negative-safe, positive-safe, intimate-safe, neutral-safe and ratings. Additionally, six motion parameters were added as confound predictors.

Differences in brain activity between AN and NPts during emotion induction were the primary focus of this study. Therefore, to examine emotion induction, three whole-brain voxel-wise random effect analyses of variance (RFX ANOVA) of the following contrasts were carried out: (1) stimuli (negative-look vs. neutral-look) × group (AN vs. NPts), (2) stimuli (positive-look vs. neutral-look) × group (AN vs. NPts), and (3) stimuli (intimate-look vs. neutral-look) × group (AN vs. NPts). In addition, differences of BOLD responses during explicit emotion regulation, i.e., condition (safe vs. look) × group (AN vs. NPts) was assessed within regions that were significant during emotion induction; as well as whole brain effects of emotion regulation, i.e., condition (safe intimate vs. look intimate) × group (AN vs. NPts).

The resulting F-maps were thresholded at a significance level of $p < 0.005$ and corrected for multiple comparisons with cluster size, which seemed an adequate compromise of reducing type-I and -II errors [43]. The minimal cluster

size threshold of 12 voxels was determined with the cluster-level statistical threshold estimator plug-in implemented in BrainVoyager, yielding a corrected cluster-level of $p < 0.05$ (Monte Carlo simulation, 1000 simulations [30]). Detailed analyses of the resulting clusters were performed in SPSS version 21 (IBM Cooperation, New York), using the extracted mean cluster beta of each predictor per participant. Finally, each cluster was examined for confounding effects of medication within AN [stimulus × medication (medicated vs. unmedicated)].

Emotional state ratings were tested for an interaction of the factors group × emotion × condition (Look, Safe) in a mixed linear model using the afex package [44] under R [45], considering within and between subjects' effects, and post hoc two-sample t tests (unequal variances) with a threshold $p < 0.05$.

Results

With respect to experienced emotion ratings during the task, testing for group (AN, NPts) × stimulus category (negative, positive, intimate, neutral) × condition (look, safe) ($F(3,2598) = 0.31$; $p = 0.82$) and group × condition ($F(1,2600) = 0.85$; $p = 0.36$) revealed no significant interaction. The interactions group × stimulus category ($F(3,2393) = 8.95$; $p < 0.001$) and stimulus category × condition were significant ($F(3,2597) = 7.34$; $p < 0.001$; post hoc t tests showed that the latter was largely driven by negative stimuli, which were experienced less emotional during the safe vs. look condition. The single factor group ($F(1,26) = 7.96$; $p = 0.009$) and stimulus category ($F(3,275) = 699.08$; $p < 0.001$) were significant, while condition alone was not significant ($F(1,2598) = 2.76$; $p = 0.10$). Contrasting AN with NPts post-hoc in the look condition demonstrated significant differences of intimate ($t(22.1) = 2.48$; $p = 0.021$) and neutral stimuli ($t(18.0) = 3.31$; $p = 0.004$) with lower ratings by AN. There were no significant differences of positive ($t(25.8) = 1.41$; $p = 0.172$) and negative stimuli ($t(16.6) = 1.22$; $p = 0.239$). Results are displayed in Fig. 2.

With respect to the neural underpinnings, contrasting negative vs. neutral stimuli (look condition, AN vs. NPts) did not yield any significant differences. The contrast positive vs. neutral stimuli (look condition, NPts vs. AN) showed one area identified at the superior parietal cortex (Table 2), with AN showing less activation than NPts when presented with positive stimuli.

When contrasting intimate vs. neutral stimuli (look condition, NPts vs. AN) frontal and parietal brain areas differed (Table 2). Simple effect analysis revealed stronger activation of AN, compared to NPts when presented with intimate stimuli in the right OFC, and less activation in the superior parietal cortex and bilateral precuneus (Fig. 3). Furthermore, AN showed marginally less activity in the temporoparietal cortex compared to NPts for intimate stimuli.

When lowering the threshold to a more liberal $p < 0.005$ without correction for multiple comparisons, the left OFC, right DLPFC, bilateral anterior PFC and right dorsal striatum became significant; whereas at $p < 0.05$ (uncorrected)

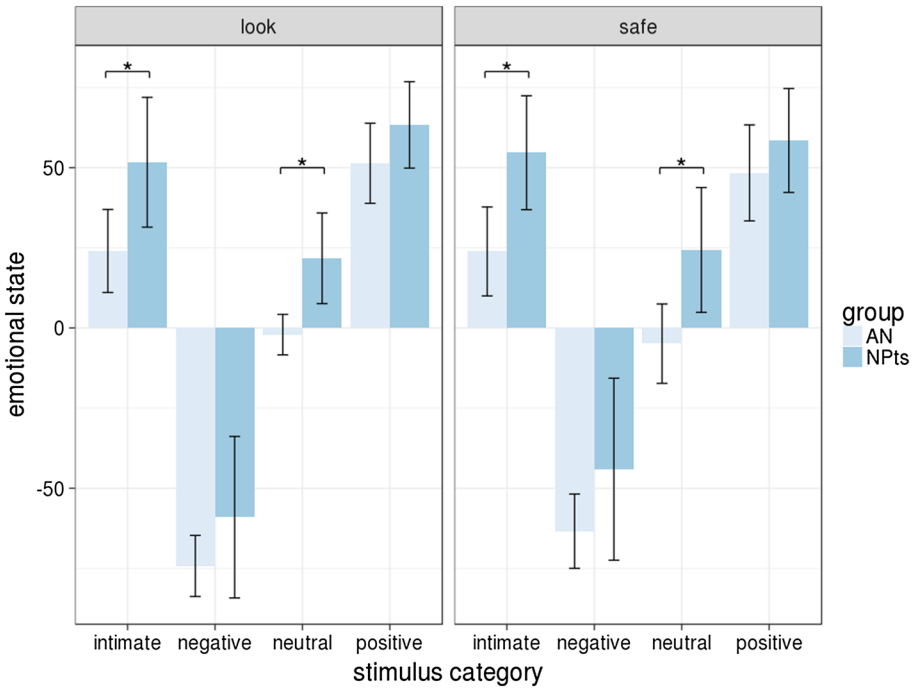

Fig. 2 Valence ratings of emotions. Average valence ratings (on a visual analogue scale) ranging from −100 (negative) to 100 (positive) of patients with anorexia nervosa (AN) and non-patients (NPts), separated for the look condition (left panel) and safe condition (right panel). Error bars are 95% confidence intervals over the mean ratings per participant. *Significant differences $p < 0.05$

Table 2 Results of whole-brain voxel-wise random effects ANOVAs of emotion induction

Functional region of interest	L/R	BA	Talairach coordinates of peak voxel			Voxels (mm^3)	*F* score	*p* value	Post hoc intimate stimuli
			x	*y*	*z*				
Negative vs. neutral stimuli, AN vs. Npts									
None									
Positive vs. neutral stimuli, AN vs. NPts									
Superior parietal cortex	R	3	32	− 29	54	1930	18.92	< 0.001	
Intimate vs. neutral stimuli, AN vs. NPts									
Orbitofrontal cortex[a]	R	47	17	28	− 9	383	15.07	0.001	0.042 AN > NPts
Temporoparietal junction	L	41	− 49	− 32	15	581	17.76	< 0.001	0.082 AN < NPts
Superior parietal cortex	R	5	29	− 38	63	473	15.18	0.001	0.015 AN < NPts
Precuneus	R	7	11	− 59	54	640	16.24	< 0.001	0.049 AN < NPts
Precuneus	L	7	− 13	− 56	57	424	14.17	0.001	0.033 AN < NPts

$p < 0.005$ and corrected for multiple comparisons with a cluster-size threshold at $p = 0.05$

[a]Region showed a relatively reduced response in AN patients compared to NPts during realizing to be safe vs. passive viewing, when presented with intimate stimuli

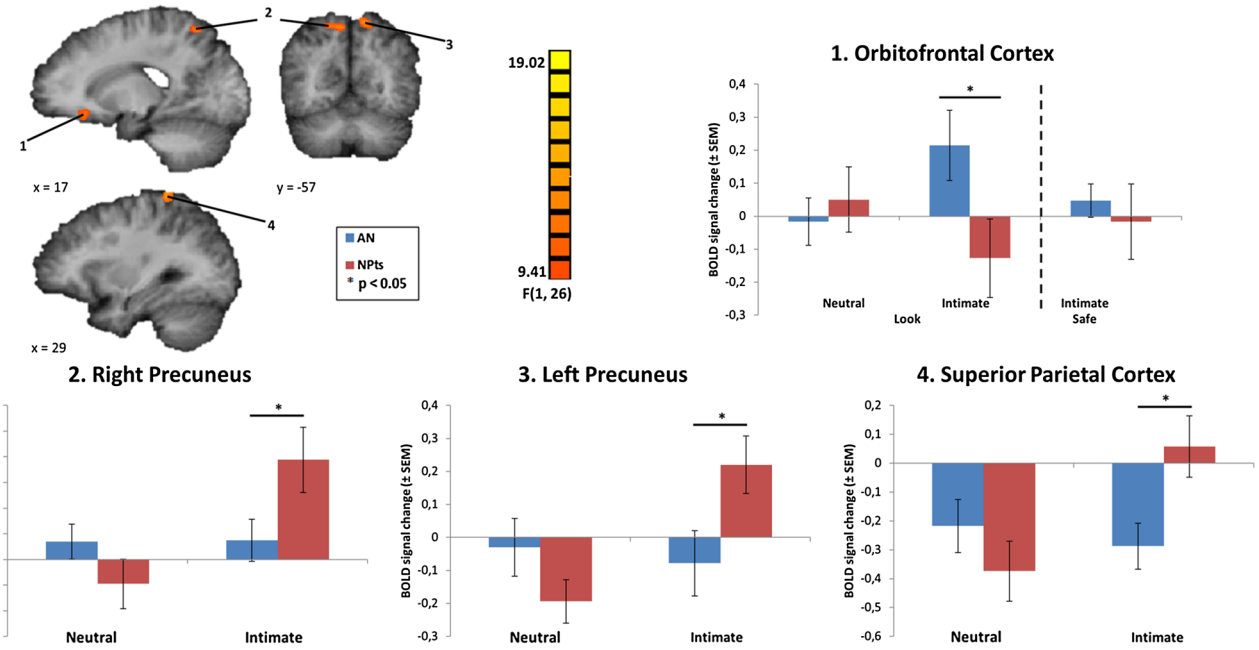

Fig. 3 Locations and bar plots of beta values of clusters resulting from whole-brain RFX ANOVA testing differences in emotion induction concerning intimate stimuli. Bar plots represent BOLD signal change in z-scores, and error bars indicate SEM. The F-map was overlaid on an average brain of all participants shown in radiological convention, cluster coordinates are reported in Talairach space

the left amygdala and bilateral dorsal ACC were significant. Simple effects exhibited a higher activation in AN compared to NPts during passive viewing of intimate stimuli in the right anterior PFC and right dorsal ACC, and at trend level in the left OFC and right DLPFC. Additionally, the dorsal striatum and amygdala showed a similar pattern in which AN and NPts respond in the opposite direction (Figure S1). During passive viewing of intimate stimuli AN showed significant higher activation in the dorsal

striatum, and NPts showed significant less activity in the amygdala.

The stimulus (intimate vs. neutral) × medication (medicated vs. unmedicated) interaction within AN in these clusters did not yield significant results.

When additionally investigating the effect of explicit emotion regulation (safe intimate vs. look intimate × AN vs. NPts) in the OFC, AN showed a relative reduction of BOLD response during the safe condition, whereas NPts showed a relative increase when presented with intimate pictures (Fig. 3). The same pattern was displayed in the more liberal brain areas, i.e., the DLPFC and anterior PFC (Figure S2). An additional whole-brain analysis of the effect of explicit emotion regulation when confronted with intimate pictures, i.e., condition (safe intimate vs. look intimate) × group (AN vs. NPts), showed five regions: left ventrolateral PFC, left anterior PFC, right middle temporal gyrus, left fusiform gyrus and left lateral globus pallidus. Simple effects showed BOLD differences in the same direction: AN showed a decreased activity in the safe condition compared to the look condition in all clusters, whereas NPts showed the opposite, an increased activity in the ventrolateral PFC, anterior PFC, fusiform gyrus and lateral globus pallidus. No significant condition (safe vs. look) × medication interaction within AN was observed for any of the clusters.

Discussion

To our knowledge, this is the first functional imaging study in AN to investigate emotion induction and emotion regulation of various emotional stimulus categories. In addition to positive and negative stimuli, we focused on intimate stimuli, which are assumed to be of core emotional relevance to this patient group.

Behavioral data during the look condition, i.e., emotion induction, showed that intimate stimuli as well as neutral stimuli were experienced less positively by AN patients, while there were no significant differences with respect to positive and negative stimuli. On the one hand, these results are in line with a previous study of ours [10] showing little differences between AN and NPts with respect to positive and negative stimuli, and with other studies [3]. On the other hand, it strongly supports the notion that intimate stimuli specifically are perceived differently by AN patients. A recent review on emotion generation and regulation also pointed out that interpersonal and self-worth related issues such as shame, subjugation, fear of losing autonomy and intimacy are of importance in AN as well as emotional clarity—problems often persisting in individuals recovered from AN symptoms [46]. A bias to perceive neutral stimuli more negatively has been found in other studies, too [47, 48], which, however, seems not to be disorder-specific [49]. Emotion regulation showed no differential effect between groups.

In concordance with the results of emotion experience during emotion induction, the strongest differences of cerebral activation occurred in response to intimate stimuli. The contrast of negative vs. neutral stimuli did not show any differences in BOLD responses. Interestingly, one of the first fMRI studies in eating disorders found strong frontal differences with disease-specific stimuli but also none with aversive emotional stimuli [4]. We are not aware of similar studies involving contrast positive vs. neutral emotional stimuli. Our data elicited differences in the superior parietal cortex with less BOLD responses in AN compared to NPts. We cannot readily explain these results. However, other imaging studies in AN had shown parietal activity decreases with various paradigms, and grey matter decreases have been described in this area [50–53]. This is also pointed out in a review, which reports lower activity at rest together with electrophysiological and serotonin-binding abnormalities of the bilateral parietal cortex, suggesting a more general deficiency in this area in AN [54].

In sharp contrast to positive and negative emotional stimuli, intimate stimuli induced higher BOLD responses in the right OFC and lower BOLD responses in the superior parietal cortex and bilateral precuneus in AN patients compared to NPts. The OFC is implicated in various functions including food intake, sexual desire, (erotic) reward and salience, attachment and value-guided decision-making [27, 28, 31, 32, 50, 55, 56]. Clinically, damage to this area results in maladaptive interpersonal behavior and impaired self-monitoring [57]. Since clinically AN patients show impairments in attachment, intimacy and sexuality, the greater activation in the OFC during presentation of intimate stimuli dovetails nicely. Furthermore, the OFC has reciprocal connections with the amygdala and integrates affective value of stimuli from the amygdala in context and goal-dependent manner. Similarly, the groups showed opposite patterns in the amygdala, although at lenient significance levels. This indicates more emotional involvement in AN patients when viewing intimate stimuli, which are likely of negative or conflicting nature to them.

The precuneus is involved in highly integrated functions such as self-referential processing, autobiographic memory, modulation of consciousness and the default mode network [58]. In response to intimate stimuli, reduced activation in the precuneus might indicate that self-reflection results in emotional distress, and therefore, is possibly being suppressed to provide avoidance behavior associated with maladaptive self-other body perception in AN patients. In agreement with the present results, previous studies showed decreased activation in the precuneus in relation to body image distortion in patients with AN [59, 60]. Additionally, this region shows significant grey matter loss in AN, and it

might particularly also be susceptible to the effects of AN in the long run [53, 61, 62]. Xu et al. [63] recently pointed to the importance of the precuneus and the medial prefrontal cortex during social evaluations in AN, including a possible predictive value.

Regarding emotion generation and regulation the DLPFC and anterior PFC were shown at uncorrected threshold, and therefore, should be interpreted with due caution. However, these areas might serve as regions of interest in future studies in this field. The DLPFC showed marginally higher activation in AN patients compared to NPts during passive viewing of intimate stimuli, which corresponds to the assumed primary control and inhibitory processing functions of this region, as we had hypothesized. Therefore, it could be speculated that AN patients already implicitly regulate their emotions when confronted with intimate stimuli without being instructed to do so. The function of the anterior PFC is not too well understood, though integrating outcomes of separate cognitive operations in the pursuit of higher goals seems likely [64]. In line with our hypothesis, AN showed higher activation of the dorsal ACC.

Importantly, the findings of the OFC and precuneus seem specific for intimate stimuli, in that emotion induction with positive and negative emotions did not elicit such differences between groups. The superior parietal cortex showed a similar response pattern to positive non-intimate emotional and intimate stimuli, which might be rather unspecific as discussed above.

The results described above pertain to the emotion elicitation portion of the task. Results of explicit conscious emotion regulation indicated a relative decrease of the BOLD responses in the prefrontal regions in AN patients. It is contrasted by NPts who showed increases of BOLD responses. We postulate that AN patients already activate emotion regulation processes on an implicit unconscious level during passive viewing of intimate stimuli—while NPts showed increased activation in these regions during explicit emotion regulation.

Several relevant limitations of this pilot study should be acknowledged. First, the number of participants is limited, only females were included and few were on medication. The latter might have been a confounding factor, but we performed additional analysis within the AN group, as adding medication as a covariate removes variance associated with group differences, and interactions of medication were not significant within any of the resulting clusters. We decided not to exclude patients on medication because requesting patients to be free of medication several weeks before scanning does not assure a normal brain state at the moment of scanning, and for some medication the washed out effect can last several months in the brain [65]. Education status was not investigated. Unfortunately, we did not investigate current or prior sexual relationships as well as attitudes towards intimacy and sexuality. This is of importance and must be addressed in future studies on this subject. Furthermore, a few had binge-eating and purging-type behavior, i.e., mixed subgroups, and two were left-handed. Eating Disorder Inventory and Beck Anxiety and Depression Inventory were not available for NPts.

However, the study should be regarded as a pilot investigation, and due to time and cost constraints we were not able to enlarge the number of participants at this time. Future studies should increase the number of subjects, exclude medication and aim for a less heterogeneous group. Second, we only assessed behavioral data during scanning, and stimuli were not rated in more depth with respect to arousal and valence. Additionally, participants should also be more thoroughly studied with respect to attachment styles. In such studies, the comparison with long-term recovered participants and longitudinal changes will greatly enhance the knowledge of this important issue.

In summary, when confronted with intimacy, heterosexual female AN patients showed increased activation of the OFC, which is associated with value-guided decisions, reward, sexuality and attachment. Additionally, decreased activation of the precuneus, which is implicated in self-referential processing and body image distortion in AN patients, was observed. Further, areas important in emotion regulation such as the DLPFC and anterior PFC, shown at more lenient thresholds, indicate increased emotion regulation in AN on an implicit level (Look condition). In this respect, the notion of various researchers that emotion regulation likely sets in early and close to the generation of emotions themselves is important [6, 11]. We assume that the issue of intimacy is of high ambivalence to AN patients, which is reflected by these strong activations, and by the AN group's lack of reduction in amygdala activation with intimacy stimuli, opposite to what was shown by NPts. Further studies need to validate this pilot data, and longitudinal studies before and after therapeutic interventions as well as the study of recovered AN women will be of great interest to further enlighten our understanding of the neurobiology of AN. It would also be of interest how patients with bulimia nervosa and obesity differ from AN.

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Compliance with ethical standards

Conflict of interest There were no potential conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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