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Enhanced cortical processing of cardio-afferent signals in anorexia nervosa

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HIGHLIGHTS

- Heartbeat evoked potentials were heightened in anorexia nervosa.
- There was a trend toward higher interoceptive accuracy in anorexia nervosa.
- Cardiac autonomic activation and interoceptive sensibility were unaltered.

ABSTRACT

Objective: To assess cardiac interoception in anorexia nervosa (AN) using a multidimensional approach.
Methods: We assessed the physiological dimensions of cardioception, i.e. the peripheral signal itself (heart rate, HR, and heart rate variability, HRV) and its cortical representation (heartbeat evoked potentials, HEPs), and the psychological dimensions of interoceptive accuracy (heartbeat perception) and interoceptive sensibility (confidence ratings). Electroencephalogram (EEG) and electrocardiogram (ECG) were recorded concurrently during rest and while performing a heartbeat perception task in a sample of 19 female in-patients with AN (DSM-5) and 19 healthy control women (HC).
Results: HEPs, defined as mean EEG amplitude in a time window of 455–595 ms after the R-peak of the ECG, were significantly larger in the AN than in the HC group across conditions ($p = .002$, $d = 1.06$). There was a trend toward better heartbeat perception in AN, but no group differences in HR, HRV, and confidence ratings.
Conclusions: Individuals with AN showed an interoceptive profile of heightened cortical processing, a trend toward heightened interoceptive accuracy, and unaltered cardiac autonomic activation and interoceptive sensibility.
Significance: In terms of neurobiological models of AN, enhanced cortical representations of interoceptive signals might reflect a mechanism, which promotes fasting by alleviating negative body states.

1. Introduction

Anorexia nervosa (AN) is an eating disorder (ED) characterized by severely low body weight and body image disturbance (American Psychiatric Association, 2013). High mortality rates (Arcelus et al., 2011) and unsatisfactory long-term treatment outcomes (Zipfel et al., 2000) rank it among the severest of mental disorders. One of the earliest hypotheses regarding the etiology underlying AN, was that of a fundamental deficit in body perception, comprising the perception of body shape, but also of signals from within the body, especially as relating to hunger and satiety (Bruch, 1962). This idea is also reflected in current neurobiological theories of AN, which posit a central role of the insular cortex, a key area with regard to interoceptive processing (Nunn and Frampton, 2008; Kaye et al., 2009, 2013; Nunn et al., 2011). According to these theories, a possible dysfunction in the insular cortex is linked to a range of AN symptoms, such as altered perception of hunger, satiety, and body image, but also of emotions.

It is well documented in the literature that individuals with AN experience high levels of alexithymia, that is, difficulties identifying and describing emotions (Zonnevijlle-Bendek et al., 2002; Bydlowski et al., 2005; Speranza et al., 2005). Several theories of emotion emphasize the important role, which the perception of bodily symptoms plays in the experience of emotions (James,

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1884; Schachter and Singer, 1962; Damasio, 1996). In particular, heartbeat perception has been related to emotional processing (Pollatos et al., 2005b; Herbert et al., 2007) and alexithymia (Herbert et al., 2011). Accordingly, the current study investigates cardiac interoception as a possible mechanism underlying emotion-processing deficits in AN.

Current neurobiological theories of AN rely almost exclusively on neuroimaging data and, therefore, should be complemented by electrophysiological data, which allows insights into underlying processes with high temporal resolution. This is particularly relevant for the investigation of interoceptive processes related to brief physiological events, such as heartbeats. The multi-dimensional approach adopted in the current study, including electrophysiological and self-report data, aims at extending current knowledge on *where* in the brain altered activity occurs, together with information on *how* neurophysiological alterations link to cognitive processing in AN. More detailed knowledge of cortical processes underlying altered interoception in AN is crucial for the development of specifically targeted interventions.

The perception of signals originating from internal organs is referred to as interoception or visceroception. In the theoretical framework by Garfinkel and Critchley, interoception is subdivided into the dimensions of interoceptive accuracy, sensibility, and awareness (Garfinkel and Critchley, 2013; Garfinkel et al., 2015). Interoceptive accuracy refers to behavioral measures of accuracy of the perception of bodily signals, for example, the number of counted heartbeats in relation to the number of recorded heartbeats during a given time interval. While interoceptive sensibility involves self-report measures of body perception, metacognitive interoceptive awareness is defined as the correspondence between interoceptive accuracy and interoceptive sensibility. In a recent paper by Forkmann et al. (2016) physiological states were added as a further dimension that is assumed to underlie the other three dimensions. This reflects the notion of interoception as a physiological process of signal transmission from an internal organ to the central nervous system (CNS; Vaitl, 1996). The current study was, therefore, designed to not only comprise self-report measures of interoception, but also indicators of underlying physiological processes. Such a distinction is especially important in AN, where cognitive factors are known to affect ratings of body sensations, such as hunger and satiety (Garfinkel et al., 1978; Herpertz et al., 2008).

Traditionally, studies on interoception in AN have focused on interoceptive sensibility using questionnaires, such as the Eating Disorder Inventory (EDI; Garner et al., 1983). Individuals with AN score higher on the Interoceptive Awareness subscale of the EDI than healthy control persons (Garner et al., 1983), reflecting reduced interoceptive sensibility, and higher scores predicted ED symptom onset in several studies (Leon et al., 1995, 1999; Killen et al., 1996). Recent studies investigating interoceptive accuracy via heartbeat perception show interoceptive deficits in AN (Pollatos et al., 2008, 2016a), though mixed results have been obtained for bulimia nervosa and EDs in general (Klabunde et al., 2013; Eshkevari et al., 2014). Self-reports of body sensations, however, are strongly affected by cognitive factors, such as beliefs regarding calorie content (Garfinkel et al., 1978) or amount of food consumed (Herpertz et al., 2008), and dieting rules (Garfinkel, 1974). Moreover, in AN, ratings of food stimuli in the gustatory and visual domains diverge from neural activity in the insular cortex (Wagner et al., 2008; Holsen et al., 2012; Oberndorfer et al., 2013). Assuming that ratings of body sensations arise from an interplay of perception, in the sense of cortical representation of a stimulus, and cognitive processing, the cognitive processing part of the equation appears to be particularly biased in individuals with AN. This highlights the importance of assessing interoception in AN not merely via self-report, but also at the physiological level, which does not necessarily involve conscious processing of the signal.

For the assessment of the interoceptive domain of physiological states, heartbeat evoked potentials (HEPs) represent a well-established electroencephalographic (EEG) indicator. They reflect the cortical representation of afferent signals related to the cardiac cycle (Schandry et al., 1986). Importantly, HEPs may constitute an index for the functionality of brain regions that are presumed to play a major role in the etiology of AN, especially the insular cortex (Nunn and Frampton, 2008; Kaye et al., 2009, 2013; Nunn et al., 2011). HEPs are sensitive to short-term food deprivation (Schulz et al., 2015a), but they have not yet been studied in the context of long-term fasting or AN.

The consequences of long-term fasting in AN on cardiac autonomic modulation remain a matter of debate in the literature. While most studies find parasympathetic dominance, there are also studies reporting sympathetic dominance or no alterations as compared to healthy individuals (Mazurak et al., 2011). Recently, it has been suggested that patients switch from parasympathetic to sympathetic dominance with progression of the disorder (Nakai et al., 2015; Sachs et al., 2016). Considering the lack of clarity concerning alterations in cardiac autonomic regulation in AN, we selected a sample of AN patients currently in in-patient treatment, to ensure that they were not in an acute fasted state and that possible cardiovascular complications had been medically treated at the time of testing. This allows us to evaluate possible effects in cortical processing and perception of interoceptive signals independently of cardiac autonomic regulation.

In summary, the role of physiological processes for altered interoceptive processing in AN and the specificity of interoceptive domains, in which AN patients show alterations, remain unclear. In the current study, we, therefore, investigated interoceptive sensibility, interoceptive accuracy, CNS representation of interoceptive signals (as reflected by HEPs), and autonomic cardiac activation in AN. We expected (I.) interoceptive accuracy, indexed by performance in a heartbeat perception task, to be lower in individuals with AN as compared to healthy control participants (HC), as previously reported (Pollatos et al., 2008, 2016a). We further hypothesized (II.) that this difference would be reflected in altered CNS representation, with the AN group showing lower HEP amplitudes than the HC group. Furthermore, we included mean heart rate (HR) and an indicator of sympathetically mediated heart rate variability (HRV) to test for possible alterations in sympathetic cardiac modulation between groups (Hypothesis III.). Confidence ratings in the heartbeat perception task were expected to indicate reduced interoceptive sensibility in AN (Hypothesis IV.).

2. Method

2.1. Participants

Female in-patients ($n = 20$) meeting criteria for AN according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) were recruited from a psychosomatic hospital in Rosenheim, Germany (Schön Klinik Roseneck). A female HC group ($n = 20$) matched for age and socioeconomic status was recruited through posters, flyers, and mailing lists at the University of Luxembourg. Exclusion criteria for both groups were age below 18 years, past or current psychotic disorders, current substance abuse or dependence, current posttraumatic stress disorder and, in addition, for the HC group, present or past ED and current mental disorders. All participants were screened for current and past mental disorders with the Structured Clinical Interview for DSM-IV (SCID-I; First et al., 2002). AN diagnoses were additionally confirmed with the self-report screening version of the Structured Interview for Anorexic and Bulimic Syndromes (Fichter and Quadflieg, 2000) and consultation of the DSM-5 criteria. Data from two participants were excluded from the analyses due to insufficient quality of the EEG data, resulting in a final sample size of 38 participants (AN = 19, HC = 19).

Groups did not differ significantly in terms of age, educational level, or socioeconomic status according to the International Standard Classification of Education (ISCED-97; Organisation for Economic Co-operation and Development, 1999). As expected, the AN group had a lower body mass index (BMI) than the HC group, and higher mean scores on the subscales Drive for Thinness, Bulimia, Body Dissatisfaction, and Interoceptive Awareness of the Eating Disorder Inventory-2 (EDI-2; Garner, 1991). Furthermore, the AN group had higher mean scores on the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), the trait version of the State and Trait Anxiety Inventory (STAI; Spielberger et al., 1970) and the state version of the STAI at the beginning of the experimental session. Demographic sample characteristics are displayed in Table 1.

In the AN group 10 patients (52.6 %) were diagnosed with restrictive-type AN and 9 patients (47.4 %) with binge-eating/purging subtype. Six patients had between one and three comorbid DSM-IV diagnoses of current major depressive episode, obsessive compulsive disorder, agoraphobia or bipolar-I-disorder. Furthermore, six patients were under medication with selective serotonin reuptake inhibitors (SSRI). Onset of AN symptoms was, on average, 9.74 years (*SD* = 6.65, range 2–23) before testing. Eleven patients (57.9%) had had AN for 10 years or more and can thus be considered to have been in a state of chronic AN (Noordenbos et al., 2002). The remaining eight patients reported symptom onset between 2 and 9 years ago. The patients' age ranged from 18.8 to 37.0 years (20.6 to 35.8 years in the HC group). The current in-patient treatment had lasted for an average of 32.74 days (*SD* = 24.12, range 6–97) at the time of the EEG testing session.

2.2. Procedure

The study was approved by the national ethics review board of Luxembourg (Comité National d'Ethique de Recherche Luxembourg), the Ethics Review Panel of the University of Luxembourg, and the ethics review board of the medical faculty of the Ludwig-Maximilians-University of Munich, Germany. All participants provided written informed consent prior to data collection. Study participation took place in two sessions held on separate days. During the first session, participants were interviewed with the SCID-I and a custom-made socio-demographic interview, and completed questionnaires. In the second session, psychophysiological assessment was carried out. Stimulus presentation and response collection were run with E-Prime 2.0 (Psychology Software Tools, Sharpsburg, PA). After preparation of the EEG electrodes, participants were given insert earphones. Participants were seated in a comfortable chair in front of a laptop computer. First, a 5-minute resting-state measurement was completed. This was followed by the heartbeat perception task. The session was concluded with a second picture-viewing task, containing body images and emotional pictures. Results pertaining to the picture-viewing tasks will be reported elsewhere. Participants were asked to refrain from consuming caffeine on the day of testing. As the study took place in an in-patient setting, AN patients were required to eat regular meals and had all eaten within two hours before testing. Participants received a gift voucher as reimbursement for their participation.

2.3. Schandry heartbeat perception task

Interoceptive accuracy was assessed by a heartbeat perception task, as originally designed by Schandry (1981). After a practice trial (25 s) participants were asked to silently count their own heartbeats during fixed intervals (25 s, 35 s, 45 s, and 55 s, in random order) without explicitly feeling their pulse. The duration of each counting interval was indicated on screen by the presence of a fixation cross. After each trial, participants were asked to enter the number of heartbeats counted and to indicate how confident they felt about their result on a 9-point Likert scale from 0 (*very uncertain*) to 8 (*very certain*). Responses to the latter question were used as an indicator of interoceptive sensibility. Interoceptive accuracy and sensibility were based on the taxonomy suggested by Garfinkel and coworkers (Garfinkel and Critchley, 2013; Garfinkel et al., 2015). Interoceptive accuracy scores were calculated according to the formula:

$$1/4\ \Sigma[1 - (|\text{recorded heartbeats} - \text{counted heartbeats}|/\text{recorded heartbeats})].$$

2.4. EEG and ECG recording, data reduction, analysis

Psychophysiological data were recorded with a 64-channel actiCAP active electrode EEG-system with BrainAmp amplifiers (Brain Products, Gilching, Germany). Ag/AgCl EEG electrodes were mounted according to the 10/20-system and referenced to FCz.

Table 1

Demographic characteristics of the AN and HC groups.

	Group							
	AN (*n* = 19)		HC (*n* = 19)		Between-groups tests			
Demographics	*M*	*SD*	*M*	*SD*	*t*	*df*	*p*	*d*
Age	25.20	5.28	24.60	3.94	0.40	36	0.70	0.13
Body Mass Index	15.79	1.67	22.33	3.19	−7.92	27.17	<0.001	2.57
EDI Drive For Thinness	3.81	1.08	2.21	0.77	5.25	36	<0.001	1.70
EDI Bulimia	2.33	1.21	1.61	0.47	2.43	23.35	0.023	0.79
EDI Body Dissatisfaction	3.84	1.15	2.87	0.97	2.82	36	<0.01	0.91
EDI Interoceptive Awareness	3.38	1.15	2.12	0.57	4.27	26.20	<0.001	1.39
BDI-II	0.84	0.63	0.27	0.16	3.91	20.29	<0.01	1.27
STAI-T	2.48	0.68	1.64	0.36	4.70	27.31	<0.001	1.52
STAI-S	2.29	0.57	1.66	0.39	3.99	36	<0.001	1.29
	Mdn		*Mdn*		*U*		*P*	*r*
Educational level[a]	4		3		185		0.91	0.023
Socio-economic status[a]	5		5		176		0.91	0.025

Note. All questionnaire scores were calculated as mean values. AN = anorexia nervosa; HC = healthy control; EDI = Eating Disorder Inventory; BDI = Beck Depression Inventory-II; STAI-T = State and Trait Anxiety Inventories, Trait version; STAI-S = State and Trait Anxiety Inventories, State version.

[a] As educational level and socio-economic status are ordinally scaled, only the median is reported as descriptive statistic, and the Mann-Whitney *U* test was performed for between-groups comparisons.

Impedances were kept below 20 kΩ. Bipolar horizontal EOG (electrodes placed next to the outer canthi of both eyes) and vertical EOG (above and below the right eye), as well as ECG (Einthoven lead II configuration) were recorded with Ag/AgCl electrodes. Data were sampled at a rate of 1000 Hz. Hardware recording high-pass filters were set to 0.016 Hz. Psychophysiological data were analyzed with BrainVision Analyzer 2.

Offline, EEG data were re-referenced to linked mastoids (TP9, TP10). Then, a bandpass filter of 0.1 to 35 Hz (24 dB/octave) was applied. Eye movements and blinks were corrected with Gratton-Coles algorithm (Gratton et al., 1983). Subsequently, the data were visually inspected and remaining artifacts were excluded from further analysis. In the ECG data, R-peaks were automatically detected and manually confirmed by visual inspection. Mean HEP amplitudes were exported for a time window of 455 to 595 ms after the R-peak of the ECG to minimize effects of the cardiac field artifact (Gray et al., 2007; Schulz et al., 2013, 2015a, 2015b; Müller et al., 2015). In this time range, the HEP is generally found to be a positive deflection (Schulz et al., 2013, 2015a, 2015b; Müller et al., 2015). Mean amplitudes were derived for two additional time windows, of the same length as the HEP window (140 ms), to control for general between-group differences in electrocortical activity: an early control window from 180 to 320 ms (Schulz et al., 2015a), and a late control window from 660 to 800 ms. An earlier time frame than in Schulz et al. (2015a, 2015b) was chosen for the late control window to avoid overlap with consecutive cardiac cycles at an average HR of 74.11 (corresponding to an RR-interval of 809 ms). The 63 electrode positions were aggregated into 9 scalp sectors to test for gross effects of laterality and scalp location (Pollatos and Schandry, 2004; Shao et al., 2011; Schulz et al., 2015a). The following scalp sectors were created: left-frontal (Fp1,AF3,7,F1,3,5,7), mid-frontal (Fz), right-frontal (Fp2,AF4,8, F2,4,6,8), left-central (FC1,3,5,7,FT7,9,C1,3,5,T7,CP1,3,5,TP7), mid-central (FCz,Cz,CPz), right-central (FC2,4,6,FT8,10,C2,4,6,T8,CP2,4,6,TP8), left-parieto-occipital (P1,3,5,7, PO3,7,9,O1), mid-parieto-occipital (Pz,POz,Oz), right-parieto-occipital (P2,4,6,8, PO4,8,10,O2).

HR and HRV analyses were performed with ARTiiFACT software (Kaufmann et al., 2011). Artifacts in the interbeat-interval data were removed through linear interpolation. Spectral analysis of RR-interval series was carried out using Fast Fourier Transformation (FFT). We calculated low frequency in normalized units (LF n.u.; frequency band: 0.04 to 0.15 Hz), which is sensitive for central sympathetic activation (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996).

Statistical analyses were performed with SPSS (version 21; IBM SPSS Statistics, New York, NY, United States of America). A mixed-design 2 × 3 × 3 × 3 × 2 ANOVA was computed with the within-group variables experimental condition (rest vs. task), time window (early vs. HEP vs. late), laterality (left vs. midline vs. right), and scalp location (frontal vs. central vs. parieto-occipital), and the between-variable group (AN vs. HC). Greenhouse-Geisser correction for degrees of freedom was applied where necessary. Significant interaction effects were followed up with post hoc *t* tests. Effect sizes reported are partial eta squared for ANOVAs and Cohen's *d* for *t* tests. The significance level was set to $\alpha = 0.05$ and was Bonferroni corrected for post hoc tests. Pearson correlations were calculated to test the relationship between heartbeat perception scores and HEPs.

3. Results

3.1. Heartbeat perception and heart-rate variability

Interoceptive accuracy, as indexed by the Schandry task, showed a non-significant trend of medium effect size toward higher scores in the AN group as compared to the HC group, 0.75 ± 0.18 vs. 0.65 ± 0.19, $t(36) = 1.68$, $p = .10$, $d = 0.55$ (Hypothesis I). No significant group difference was observed in interoceptive sensibility (confidence ratings) during the Schandry task (Hypothesis IV), 4.03 ± 3.66 vs. 3.66 ± 2.09, $t(36) = 0.54$, $p = .60$, $d = 0.18$. There were no significant differences between the AN group and the HC group in mean HR (Hypothesis III), 75.77 ± 9.07 vs. 72.45 ± 7.18, $t(36) = 1.25$, $p = .22$, $d = 0.41$ or LF n.u., 58.40 ± 16.67 vs. 59.69 ± 18.04, $t(36) = -0.23$, $p = .82$, $d = 0.075$, respectively.

3.2. Heartbeat evoked potentials

Regarding differences between the AN and HC groups (Hypothesis II), the groups did not differ in electrocortical activity overall, $F(1,36) = 0.49$, $p = .49$, $\eta_p^2 = 0.013$. Yet, there was a significant Time Window × Group interaction (see Table 2 for *F*-statistics). At $\alpha' = 0.017$ significant group differences appeared in the HEP interval, $t(36) = 3.28$, $p = .002$, $d = 1.06$, but not in the early control interval, $t(36) = -1.33$, $p = .19$, $d = 0.43$, or the late control interval, $t(36) = -0.71$, $p = .48$, $d = 0.23$. In the HEP interval the AN group (0.03 ± 0.22) had higher mean amplitudes than the HC group (−0.25 ± 0.31). There was a significant three-way interaction Group × Time Window × Laterality. During the HEP time window ($\alpha' = 0.017$), the AN group had significantly higher HEP amplitudes than the HC group at midline, $t(36) = 3.90$, $p < .001$, $d = 1.27$, and right electrode sites, $t(36) = 3.03$, $p = .0045$, $d = 0.98$, but not at left electrode sites $t(36) = 1.77$, $p = .084$, $d = 0.57$. There was also a significant four-way interaction Group × Time Window × Scalp Location × Laterality. At $\alpha' = 0.0056$ the AN group had significantly higher HEP amplitudes than the control group in the mid-frontal sector, $t(36) = 3.29$, $p = .002$, $d = 1.07$, the mid-central sector,

Table 2
Significant ANOVA effects for heartbeat evoked potentials.

Effect	*F*	df_1, df_2	*p*	η_p^2	Post-hoc results for HEP time window
Time Window	4.56	2, 72	0.014	0.11	
Scalp Location	11.08	1.23, 44.29	<0.001	0.24	
Laterality	4.71	1.67, 60.06	0.017	0.12	
Time Window × Group	6.45	2, 72	0.0027	0.15	AN > HC
Time Window × Scalp Location	64.00	2.25, 80.82	<0.001	0.64	Central > parieto-occipital
Time Window × Laterality	11.50	2.58, 93.04	<0.001	0.24	Left < midline > right
Group × Time Window × Laterality	4.27	2.58, 93.04	0.010	0.11	AN > HC at midline and right locations
Time Window × Condition × Scalp Location	3.01	2.58, 92.74	0.042	0.077	Rest: central > parieto-occipital, Schandry: frontal > parieto-occipital, central > parieto-occipital
Time Window × Scalp Location × Laterality	11.44	3.90, 140.44	<0.001	0.24	Highest amplitudes at mid-central locations
Group × Time Window × Scalp Location × Laterality	12.00	3.90, 140.44	<0.001	0.25	AN > HC at mid-frontal, mid-central, and right-central locations
Time Window × Condition × Scalp Location × Laterality	2.64	5.36, 193.04	0.022	0.068	No significant post-hoc tests

Note. HEP = heartbeat evoked potential; AN = anorexia nervosa; HC = healthy control group.

$t(36) = 3.77$, $p = .001$, $d = 1.22$, and the right-central sector, $t(36) = 3.48$, $p = .001$, $d = 1.13$, but not in any other sector.

In summary, the effect of higher mean amplitudes in the AN than in the HC group was specific to the HEP interval and localized to central scalp regions, with no difference between the conditions. Average HEP waveforms for the AN and HC groups are displayed in Fig. 1. Fig. 2 shows scalp topographies for the two groups during the HEP time window. Table 2 summarizes all statistically significant ANOVA effects. The inclusion of depression scores as covariate did not affect any of the results reported. Results of these analyses are, therefore, omitted from the current report.

3.3. Correlations

To test for the previously reported correlation between interoceptive accuracy and HEPs (Schandry et al., 1986; Montoya et al., 1993; Pollatos and Schandry, 2004), we correlated performance in the heartbeat perception task with HEP amplitudes. There were no significant correlations, neither with HEPs recorded during the HPT, Pearson's $r = 0.16$, $p = .35$, nor under resting conditions, Pearson's $r = 0.016$, $p = .92$.

4. Discussion

The goal of the current study was to investigate physiological processes underlying altered interoception in AN. We found significantly higher CNS representation of cardio-afferent signals in the AN group (Hypothesis II.) but no significant differences between groups in sympathetic cardiac modulation (Hypothesis III.). Groups did not differ significantly in interoceptive accuracy (Hypothesis I.) or interoceptive sensibility (confidence ratings; Hypothesis IV) although there was a statistical trend toward higher accuracy in AN.

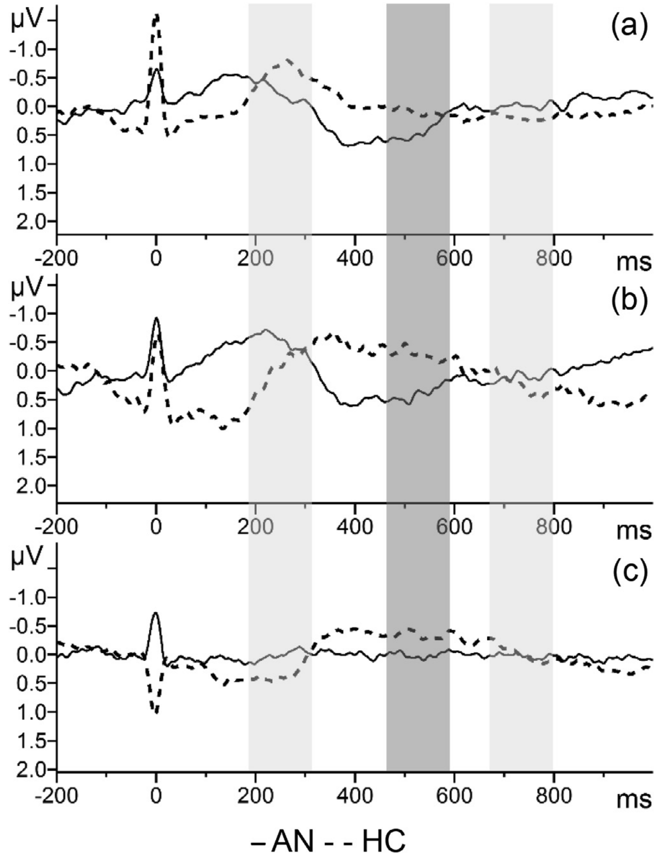

Fig. 1. Heartbeat evoked potentials (HEPs) for the anorexia nervosa (AN) and healthy control (HC) groups for the three significant clusters (a) mid-frontal, (b) mid-central, and (c) right-central. For each cluster, the signal was pooled across electrodes and conditions. The R-peak of the ECG occurred at 0 ms. The next R-peak occurred at 809 ms on average. The HEP time window is indicated by a dark grey bar (455–595 ms) and the control time windows by light grey bars (180–320 ms and 660–800 ms).

To our knowledge, this is the first study investigating higher (self-report) and lower (physiological) levels of interoceptive processing in AN concurrently. The results suggest that altered interoceptive processing in AN is not merely the result of altered cardiac functioning, as AN patients did not differ from healthy controls in HR or HRV, suggesting similar sympathetic and parasympathetic tone in both groups. These results are in line with several other studies reporting no differences between individuals with AN and HC regarding cardiac autonomic modulation at rest (Melanson et al., 2004; Murialdo et al., 2007). Systematic reviews of the literature confirm that although bradycardia and parasympathetic dominance are often found in AN, results of sympathetic dominance or no alterations as compared to HC are also common (Mazurak et al., 2011; Sachs et al., 2016). Alterations of cardiac autonomic function generally return to normal after refeeding (Rechlin et al., 1998; Mont et al., 2003). While the patients participating in our study were still underweight (BMI < 18.5), their treatment program required them to consume five meals per day, thus excluding effects of acute fasting. They were also under constant medical attention, making it likely that major complications (Casiero and Frishman, 2006) had been successfully treated before participation in the study. It could be argued, therefore, that the alterations found in higher-order interoceptive processing were not caused by alterations in peripheral physiological processes.

Our finding of stronger CNS representation of cardio-afferent signals in the AN group, as compared to the HC group, can therefore be interpreted in terms of a selective disturbance of interoceptive signal processing at the level of cortical representation. Brain regions potentially implicated in the generation of HEPs include the anterior cingulate, the right insula, the prefrontal cortex, and the left secondary somatosensory cortex (Pollatos et al., 2005a). A strong overlap becomes evident with regions, which are discussed in current neurobiological theories of AN, postulating a central role of the insular cortex, in particular (Nunn and Frampton, 2008; Kaye et al., 2009, 2013; Nunn et al., 2011). Supporting these theoretical assumptions, a neuroimaging study by Kerr et al. (2016) found heightened activation in the anterior insula during attention to one's own heartbeat in weight-restored individuals with AN. The current results suggest that heightened cardiac interoception in AN can also be demonstrated with HEPs, a measure with high temporal resolution, which is able to link cortical activity directly to the heartbeat as a brief event. This suggests the possibility that the cortical representation of cardiac stimuli might be one of the functions of the insular cortex, which is altered in AN. It has been proposed that in AN food has a negative connotation and, therefore, fasting serves as a reward (Kaye et al., 2013). In light of the present findings, one could argue that heightened cortical representation of interoceptive stimuli enhances the perception of negative physiological states associated with food intake and thereby promotes fasting as a relief from negative body states. This would also be in line with findings of altered interoceptive processing during meal and food stimulus anticipation (Oberndorfer et al., 2013; Khalsa et al., 2015).

Interestingly, heightened cortical processing was not directly translated into improved interoceptive accuracy, as we found only a non-significant trend toward better interoceptive accuracy in the AN group. This result is in contrast to previous studies, which found reduced interoceptive accuracy in AN (Pollatos et al., 2008, 2016a). It should be noted that the two studies by Pollatos and

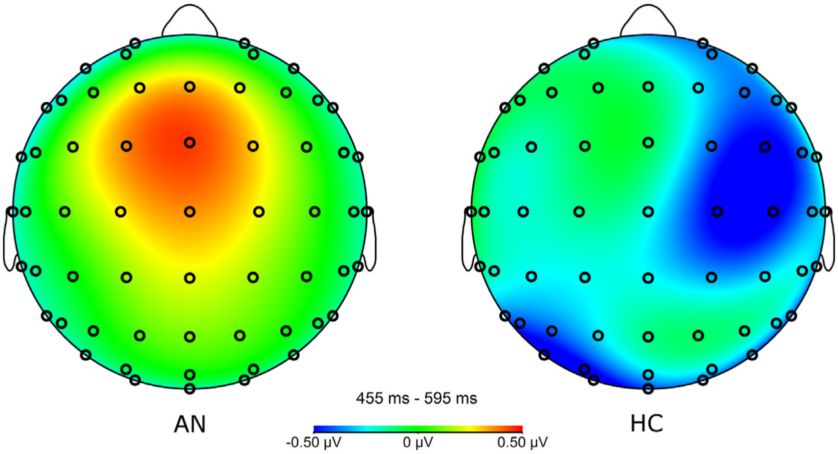

Fig. 2. Scalp topographies of heartbeat evoked potentials (HEPs) for the HEP time window, averaged across conditions. The anorexia nervosa (AN) group is shown on the left, the healthy control (HC) group on the right.

coworkers and the present study assessed AN patients, who differed in a range of characteristics: e.g., treatment modality (self-help group vs. psychosomatic hospital), duration of the current treatment (on average more than one month in the current sample), duration of the disorder, AN subtype, and possibly comorbidities (which were not reported in the other studies). It is likely that disorder characteristics and current treatment affect interoceptive performance in AN, as first results by Fischer et al. (2016) indicate that interoceptive accuracy in AN might improve with treatment.

We assessed interoceptive sensibility with confidence ratings during the heartbeat perception task. The groups did not differ on this measure. In contrast, the AN group had more disadvantageous scores on the EDI Interoceptive Awareness subscale, which may also be interpreted as a measure of interoceptive sensibility. This EDI subscale consists of items referring to the perception of hunger and satiety, as well as items on the perception of emotions (Khalsa and Lapidus, 2016). We would argue, therefore, that interoceptive sensibility is not generally altered in AN, but that alterations are limited to the interpretation of body signals linked to constructs of particular relevance to AN symptoms, such as hunger, satiety, and emotions.

Contrary to our expectations, we neither found a difference in HEP amplitudes between the resting and heartbeat perception conditions, nor a correlation between HEPs and heartbeat perception. Although both effects have previously been demonstrated in healthy samples (Schandry et al., 1986; Montoya et al., 1993; Pollatos and Schandry, 2004), these associations remain to be established in clinical samples. The effects were neither found in individuals with major depressive disorder (Terhaar et al., 2012), nor with depersonalization/derealization disorder (Schulz et al., 2015b). These findings further corroborate the notion that some mental disorders are accompanied by selective alterations at certain levels of interoceptive processing. Taking into account the peripheral and central physiological levels, as well as the self-report levels of interoceptive accuracy, sensibility, and awareness, mental disorders appear to show certain profiles of alterations on some, but not all interoceptive levels. This would not only account for low correlations between these levels, but would also explain diverging results between studies assessing different levels of interoception, e.g. Pollatos et al. (2008, 2016a) and the current study.

The neurobiological theory of AN by Kaye et al. (2009, 2013) has recently been translated into a novel treatment approach for AN, including psychoeducation and practical exercises based on the current knowledge regarding neurobiological alterations in AN (Hill et al., 2016). To further enhance such evidence based interventions, we suggest to adopt a multidimensional perspective, respecting the levels of processing at which alterations occur and, hence, their accessibility to conscious cognitive influence. While altered interoceptive sensibility might be amenable to cognitive interventions, alterations at basic levels of interoceptive processing might require interventions such as attentional training, or biological interventions, for example, repetitive transcranial magnetic stimulation (rTMS; Pollatos et al., 2016b). Exposure to interoceptive sensations during meal anticipation has also been proposed (Khalsa and Lapidus, 2016).

4.1. Limitations

In the current study we assessed in-patients with AN receiving treatment. Participants were not selected and showed the usual range of psychological comorbidities. Eleven patients had had AN for 10 years or more, indicating a chronification of the disorder (Noordenbos et al., 2002). Although this procedure led to a somewhat heterogeneous sample, it also resulted in increased representativeness, thereby enhancing ecological validity and generalizability to other hospitalized AN patients. We did not directly assess effects of psychoactive medication on heartbeat perception and HEPs and, therefore, cannot exclude a possible influence on the results. Yet, a previous study showed no differences in heartbeat perception or HEPs in depressed patients with or without antidepressant medication (Terhaar et al., 2012).

AN often results in cardiac complications due to malnutrition (Casiero and Frishman, 2006). This may have affected the present results, as cardiac parameters, such as HR and stroke volume, are positively correlated with heartbeat perception (Schandry et al., 1993). Although patients with AN often show bradycardia, patients in our sample had a comparable mean HR as compared to HC persons. In the present study, we included indicators of sympathetic cardiac modulation (HR and low frequency HRV), due to their relationship with effects of short-term fasting on interoception (Herbert et al., 2012a).

Although the sample size of the current study appears relatively small with 19 AN individuals and 19 HC, it is comparable to sample sizes in similar studies. Significant differences in interoceptive accuracy between individuals with or recovered from EDs have previously been reported in samples of 15 (Pollatos et al., 2016a), 28 (Pollatos et al., 2008), or nine (Klabunde et al., 2013) patients, with an effect size of Cohen's $d = 1.16$ in the study by Klabunde et al. (2013). Research on HEPs in populations with mental disorders was conducted with sample sizes of, for example, 16 (Terhaar et al., 2012), or 23 (Schulz et al., 2015b) patients, with an effect size of $\eta^2 = 0.18$ for the difference between depressed patients and HC in the study by Terhaar et al. (2012). Based on these studies it may be concluded that patients with EDs and several other mental disorders show interoceptive alterations of medium to large effect size when compared to HC. The sample size of the current study was, therefore, sufficient to detect the expected effects, based on the existing literature.

Finally, although there is a substantial correlation between cardiac and gastric interoception (Whitehead and Drescher, 1980; Herbert et al., 2012b; van Dyck et al., 2016), and the majority of previous studies on EDs is also based on cardiac interoception, it cannot be ruled out that AN individuals may primarily show an alteration in gastrointestinal interoception. Future studies should assess interoception related to multiple organ systems, as well as multisensory integration of bodily information (Riva and Dakanalis, 2018).

4.2. Conclusions

The current results suggest a profile of specific interoceptive alterations in AN, with heightened interoception at the level of CNS representation and, on the self-report level, a trend towards higher interoceptive accuracy, and unaltered interoceptive sensibility. Enhanced cortical processing of interoceptive signals might promote fasting through alleviation from negative body states. The differentiation between measurement levels clearly shows that all levels should be considered in future studies of interoception in AN. Comparing our results to those of other studies (Pollatos et al., 2008, 2016a; Fischer et al., 2016) further highlights the necessity of exploring potential alterations in the interoceptive profile of AN over the course of the disorder. In addition, we need to identify the relevance of targeting specific interoceptive alterations with specific interventions, to complement and optimize current approaches to the treatment of AN.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose.

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