

Cardiac interoception in Anorexia Nervosa: A resting-state heartbeat-evoked potential study

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Abstract

Objective: A deficit in interoception - the ability to perceive, interpret and integrate afferent signals about the physiological state of the body - has been shown in Anorexia Nervosa (AN), and linked to altered hunger sensations, body dysmorphia, and abnormal emotional awareness.

The present high-density electroencephalography (hdEEG) study aims to assess cardiac interoception in AN and to investigate its neural correlates, using an objective neurophysiological measure.

Method: Heartbeat-evoked potentials (HEPs) were computed from 5 min of resting-state EEG and electrocardiogram (ECG) data and compared between individuals with AN ($N = 22$) and healthy controls (HC) ($N = 19$) with waveform, topographic, and source imaging analyses.

Results: Differences in the cortical representation of heartbeats were present between AN and HC at a time window of 332–348 ms after the ECG R-peak. Source imaging analyses revealed a right-sided hypoactivation in AN of brain regions linked to interoceptive processing, such as the anterior cingulate and orbitofrontal areas.

Conclusions: To the best of our knowledge, this is the first study using hdEEG to localise the underlying sources of HEPs in AN. Results point to altered interoceptive processing during resting-state in AN. As our participants had a short duration of illness, this might not be the consequence of prolonged starvation. Interventions targeted at interoception could provide an additional tool to facilitate recovery.

KEYWORDS

anorexia nervosa, cardiac, EEG, heartbeat-evoked potential, interoception

Highlights

- An interoceptive deficit might play a role in the pathogenesis and maintenance of Anorexia Nervosa (AN), but research on neural correlates is lacking.

Nadia Micali and Cristina Berchio are joint senior authors.

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- Individuals with AN show altered cortical representation of cardiac signals, as measured with Heartbeat-evoked potentials (HEPs).
- Hypoactivation in a right-sided interoceptive network underlies differences in cardiac signal processing observed at the scalp.

1 | INTRODUCTION

Anorexia Nervosa is a severe psychiatric disorder characterised by fear of weight gain, restriction of energy intake leading to low body-weight, and disturbed body perception (American Psychiatric Association, 2013). Despite a growing body of research, AN's aetiology is not fully understood (Treasure et al., 2020) and therapeutic approaches are still limited.

Over the last decades, there has been increasing recognition that deficits in interoception – the process by which the nervous system senses, interprets, and integrates internal bodily signals – may contribute to various mental health conditions (Khalsa et al., 2018).

Regarding AN, a possible deficit in interoception is supported by several clinical signs. First, early clinical descriptions of AN highlight difficulties in recognising inner bodily states (Bruch, 1962). Second, since the perception of emotions is closely linked to that of inner bodily states (Wiens, 2005), deficits in interoception might underlie difficulties in emotion processing (alexithymia) (Brewer et al., 2016). Moreover, body image distortion is a key symptom of AN, and interoception plays an important role in body representation (Blanke et al., 2015). Finally, recent neurobiological pathophysiology hypotheses of AN have posited the important role of the insular cortex (Nunn et al., 2011), a key region in interoception (Critchley et al., 2004).

The above-mentioned considerations hint to possible interoceptive deficits in AN. There is increasing interest in the role of interoception in the pathogenesis and maintenance of AN (Jacquemot & Park, 2020; Martin et al., 2019). However, a considerable part of current findings comes from self-report or behavioural tasks (Martin et al., 2019). Individuals with AN show abnormal scores on the Interoceptive Awareness subscale of the Eating Disorder Inventory (EDI-IA) (Jenkinson et al., 2018). However, the EDI-IA subscale only partially taps into physiological states, and likely reflects disorder-specific dysfunctional thoughts (Pollatos et al., 2008). Regarding behavioural tasks, most evidence of abnormal interoception in AN comes from the heartbeat counting task (HCT) (Pollatos et al., 2008), in which participants are instructed to count the number of heartbeats they perceive during a set time interval, without taking their pulse (Schandry, 1981). From this task, cardiac

interoceptive accuracy is computed. Interestingly, compared to healthy controls (HC), individuals with AN report lower confidence ratings about their performance in the HCT, with confidence decreasing with greater illness severity, suggesting reduced interoceptive insight (Kinnaid et al., 2020). The HCT was repeatedly criticised as a biased index of interoceptive abilities; it has been shown to rely on prior knowledge or estimates of heart rates and to be modulated by individual differences in decision threshold for reporting heartbeats (Desmedt et al., 2018). There is general agreement against this task as a measure of interoception. Objective measures of interoception that do not rely on subjective experience or prior knowledge can be helpful. The study of neural correlates of interoception in AN has been limited. Using functional magnetic resonance (fMRI), Kerr and colleagues (Kerr et al., 2016) directly looked at interoceptive attention, asking participants to focus, while in the scanner, to their heart, stomach, and bladder sensations. In this study, the authors found insular cortex dysfunction in AN when focussing their attention to heart and stomach sensations. Studying the neural processing of cardiac signals would benefit from methods with higher temporal resolution.

The HEP (HEP) was proposed as a neurophysiological measure of cardiac interoception: it is an event-related potential computed by time-locking electrophysiological data to a specific part of the electrocardiogram (ECG) cycle (Park & Blanke, 2019). The HEP was first introduced as an index of the cortical processing of cardiovascular activity (Schandry et al., 1986), and has increasingly been used as a measure of interoception (Coll et al., 2021). Heartbeat-evoked potentials have been studied in the context of heartbeat sensations, emotional feelings, and body representation, and show reduced amplitudes in certain psychiatric disorders (Park & Blanke, 2019; Terhaar et al., 2012). Only one study has focused on HEPs with electroencephalography (EEG) in AN, using a combination of resting-state and HCT in adult women with AN (Lutz et al., 2019): the authors report higher mean amplitudes in AN over frontal and central scalp regions.

However, the comparison of HEPs across studies is hindered by a lack of standardisation in preprocessing, choice of time-window, and diversity in experimental designs (Park & Blanke, 2019). There is an emerging need

to consider not only HEP amplitude but also its underlying sources. High-density EEG systems and source imaging can inform us on which brain regions are differentially active (Michel & Brunet, 2019), providing insights into spatiotemporal dynamics of cardiac signal processing in AN. To date, the underlying sources of the HEP in AN have not been investigated.

This high-density EEG study aims to expand the literature on neural correlates of interoception in AN, adding onto existing HEP evidence (Lutz et al., 2019) and complementing it with source localization, to identify which regions might show altered activity in AN. We aim to compare adolescents and young adults with AN with HC on their HEP. Heartbeat-evoked potentials are measured during resting-state to assess the spontaneous cortical processing of heartbeats, without the concurrent influence of attention, arousal, or context. Heartbeat-evoked potentials can be seen independently of conscious perception, since “afferent signals from the body continuously reach the brain and, consciously or unconsciously, the brain is continuously monitoring interoceptive information” (Shao et al., 2011). Based on the literature on dysfunctional interoception in AN (Martin et al., 2019), we expect altered cortical representation of the heartbeat in individuals with AN compared to HC, which might be reflected in differential source activations in those brain regions thought to underly the HEP.

2 | METHODS

2.1 | Sample

Twenty-two female individuals with AN and 19 sex- and age-matched HC, aged 12–20, participated in this study. Eighteen individuals with AN had restricting type AN, and four had binge/purge AN. Individuals with AN were recruited from the adolescent and adult eating disorder (ED) services of Geneva University Hospital (HUG), while HC were recruited through social media, schools, universities, and ads in local youth centres. Exclusion criteria common to all participants were: any neurological disorders; history of head trauma. Further exclusion criteria specific to HC were: any psychiatric disorders; any ED symptoms.

Information on the sample size justification can be found in the Supplementary Material.

2.2 | Instruments

Socio-demographic information (i.e.: ethnicity, handedness, parental education) was collected for all

participants. Parents (for ages <14), both parents and participants (for ages 14–18), or participants alone (ages >18) gave written informed consent.

The Strengths and Difficulties Questionnaire was administered to exclude psychopathology in HC (Muris et al., 2003): participants completed the questionnaire together with their parents (up to age 16), or alone (ages 17 and above). The Eating Disorder Examination Questionnaire (EDE-q) (Fairburn et al., 1993) was completed by all participants, to assess the presence of ED symptoms on four domains (Restraint, Eating Concern, Shape Concern, Weight concern). The State-Trait Anxiety Inventory was administered to all participants, who completed either the child version (Spielberger et al., 1973), for ages 12–16, or the adult version (Spielberger, 1983), for ages 16–20. To assess cognitive functioning, 4 sub-scales (similarities, vocabulary, matrix reasoning, block design) of the Wechsler Intelligence Scale for Children Fifth Edition [WISC-V, ages 12–16] (Wechsler, 2014) or the Wechsler Adult Intelligence Scale Fourth Edition [WAIS-IV, ages 16–20] (Wechsler, 2008) were completed by all participants.

Three individuals with AN were taking medication (selective serotonin reuptake inhibitors (SSRIs), one of whom was also taking anti-convulsants. The median time since AN's symptoms onset was 5.5 months (IQR = 3.0–9.5, range = 3–31 months).

This study was approved by the University of Geneva ethical committee and follows the principles of the Declaration of Helsinki. Approval number: CCER, PB_2017-00465 (15-221).

2.3 | Electroencephalography and electrocardiogram data acquisition

To overcome existing challenges due to the heterogeneity in experimental designs, choice of reference electrode, and time-window selection, we designed a study that: (a) is entirely based on resting-state data, that can be easily replicated, does not rely on HCT, and avoids the possible influence of experimental paradigm itself on cardiac activity; (b) does not rely on single waveform analyses, but looks at the global scalp level, with reference-free topographic analyses, and source imaging over the whole brain; (c) considers a large time window rather than choosing a-priori specific windows.

Participants sat in a comfortable chair (in a lighted Faraday cage) with their head on a chin rest and feet flat on the ground. They were instructed to relax with eyes closed during a 5-min period, during EEG and ECG recordings. The temperature in the room was around 20–22 C, with minimal noise levels. The light was turned on.

Participants were not instructed to focus on their heartbeats.

Electroencephalography data was recorded with 256-channels (EGI, Philips Electrical Geodesics, Inc.), with 1000 Hz as sampling rate, Cz as reference electrode, and channel impedances kept below 30 k Ω . ECG signals were recorded using “Physio16 boxes”, connected to the amplifier (Net Amps 400) of the EGI. ECG data were collected via two EGI-compatible electrodes, placed between the fifth and seventh rib and above the heart close to the sternum.

2.4 | Electroencephalography and electrocardiogram preprocessing

Electroencephalography and ECG data were band-pass filtered between 1 and 40 Hz (4th order Butterworth band-pass filter), with a 50 Hz notch filter. For EEG, the initial montage of 256 channels was reduced to 204 to exclude peripheral face and neck electrodes, likely to be contaminated by muscle artefacts (Berchio et al., 2019). Raw EEG data were visually inspected, and epochs contaminated by muscle and movement artefacts were marked and excluded from further analysis.

Several methods, computational and non-computational, have been proposed to remove the cardiac field artefact (CFA), the heart's electrical field still detectable at the scalp (Dirlich et al., 1997). In a review of the methodological considerations of the HEP (Park & Blanke, 2019), the authors recommend a combination of complementary approaches to minimise the CFA. In this study, we opted for the following: (a) applying independent component analysis (ICA) to remove CFA-related components, (b) comparing ECG amplitudes (and parameters) between groups, to rule out significant differences in ECG signal strength across time (Park & Blanke, 2019), (c) restricting the time window for the analysis to exclude the R-peak and minimise CFA (see “HEP waveform”).

Infomax-based ICA was run to remove artefacts caused by eye movements as well as the CFA. The decision to remove a certain component was guided by the component's map topography and time course.

ECG R-peaks were automatically detected using the MATLAB graphical user interface R-DECO (Moeyersons et al., 2019) and confirmed by visual inspection. If ECG recordings had inverted polarity, this was adjusted with a custom script. Markers were generated at the location of each R-peak.

Electroencephalography data were segmented into epochs of -200 ms preceding to $+600$ ms following each

R-peak, and then averaged to compute individual HEPs. Heartbeat-evoked potentials were visually inspected and bad channels were interpolated using a 3D spherical spline (Perrin et al., 1987). Heartbeat-evoked potentials were re-referenced to the average reference, filtered with a spatial filter [for technical details, see (Michel & Brunet, 2019)], and down-sampled to 250 Hz. Group grand averages were computed. All preprocessing steps apart from ICA were performed on CARTOOL Software v1.3.91 (Brunet et al., 2011). Independent component analysis was performed using the EEGLAB Runica algorithm (Delorme & Makeig, 2004). The same segmentation into epochs (-200 ms - $+600$ ms around R-peak) and averaging was done for ECG data, to compute individual and group average ECG signals.

2.5 | Statistical analyses of demographic, Heartbeat-evoked potentials, and electrocardiogram data

Since some variables collected did not follow a normal distribution, sample characteristics were compared by means of Wilcoxon's rank-sum tests, with an alpha of 0.05. A flow diagram summarising the entire analysis pipeline can be found in the Supplementary Material (S. M., Figure S1).

2.6 | Analysis at the scalp level

2.6.1 | Heartbeat-evoked potential waveform

A waveform analysis of the HEP was performed to compare our findings with traditional approaches. Heartbeat-evoked potential amplitudes were compared between groups at each electrode and time point using a randomisation test. Data were normalised by mean global field power. The randomisation test is based on bootstrapping Monte Carlo methods, and no assumption about data distribution is needed (Beasley & Rodgers, 2012); for technical details, see (Brunet et al., 2011). Non-parametric statistics, such as permutation and randomisation tests, may reduce the probability of false discoveries (Maris & Oostenveld, 2007).

To exclude the R-peak related CFA, the time window was restricted to 150–600 ms post R-peak (Dirlich et al., 1997). We set the number of randomisation runs to 5000. Only effects lasting more than 20 ms consecutively were considered significant, with an alpha of 0.05. Setting a temporal constraint of a minimal period of significance indeed allows for protection against type I error, reducing

the probability that effects may have arisen by chance (Guthrie & Buchwald, 1991).

2.6.2 | Topographic analysis of Variance

Since waveform analyses are not reference-independent (Brunet et al., 2011), and the choice of reference electrode varies across HEP studies (Park & Blanke, 2019), global scalp analyses were performed. The Topographic analysis of Variance (TANOVA) is a reference-free and non-parametric randomisation test for differences in map topographies (Murray et al., 2008), which correspond to different configurations of active sources in the brain (Srebro, 1996). Since the TANOVA uses a randomisation test, it helps controlling for family-wise error rate (Maris, 2004). A between-group TANOVA was performed on the window 150–600 ms post R-peak. We set the number of randomisation runs to 5000, with an alpha of 0.05. To assess whether statistically significant group effects were consistent and stable across time, post-hoc tests were performed re-computing the TANOVA on the average signals of the corresponding time points (Koenig et al., 2011). This test was implemented in the MATLAB-based open source toolbox Randomisation Graphical User interface (Ragu) [for technical details, see (Koenig et al., 2011)].

2.7 | Analyses in the source space

To assess group differences in active brain networks, we used a linear distributed inverse solution model (i.e., low resolution brain electromagnetic tomography 'LORETA') (Pascual-Marqui et al., 1994). For each HEP, inverse solutions were calculated with a 4 shell Locally Spherical (LSMAC) Model (Spinelli et al., 2000) on 6008 gray matter voxels using the average brain template from the Montreal Neurological Institute (<https://brainweb.bic.mni.mcgill.ca/brainweb/>). The timecourse of each solution point was normalised using a z-score transformation implemented in Cartool [see (Michel & Brunet, 2019) for technical details].

The time window for between-group comparison of brain networks was chosen based on the TANOVA results. To minimise type I error, we opted for a randomisation test. To compare the estimated current density between groups, a randomisation test was run on the average time window, on 116 regions of interest (ROI) from the Automated Anatomical Atlas (Tzourio-Mazoyer et al., 2002), with an alpha of 0.05, and 5000 randomisation runs. For all significant effects, identified by the

randomisation test, post-hoc *t*-tests were performed and *t* values were reported to highlight the decrease/increase in activity.

2.8 | Electrocardiogram analyses

Relevant ECG measures, such as mean HR, heart rate variability (HRV, defined as the standard deviation of R-R intervals), minimum and maximum HR were extracted for all participants and compared across groups by means of Wilcoxon's rank-sum tests.

To show that observed HEP effects are not due to differences in simultaneous ECG activity, ECG amplitudes were compared between groups across the whole time-window by means of a *t* test ($\alpha = 0.05$). To maximise the efficiency of the test in detecting between group effects, no time constraints were applied.

2.9 | Correlations

Average current density scores were extracted from the significant ROIs of the between-groups comparison and correlated with each clinical measure of interest (Body Mass Index (BMI), EDE-q subscales, STAI-trait, STAI-state). To correct for multiple comparisons, we created a correlation matrix between the ROIs and computed the effective number of independent tests, following the Meff method (Li & Ji, 2005), and applied the Sidak correction.

3 | RESULTS

3.1 | Sample characteristics

Individuals with AN had significantly lower BMI compared to HC ($p < 0.001$), as expected. They also reported significantly higher STAI-state and STAI-trait anxiety levels ($p < 0.001$) compared to HC, and higher scores on all EDE-q sub-scales (all $p_s < 0.001$). There were no significant group differences in age ($p > 0.05$). Demographic and clinical data are summarised in Table 1.

3.2 | Heartbeat-evoked potential analyses

In both groups, visual inspection of map topographies highlighted a left posterior positive polarity at around 200–280 ms post R-peak, corresponding to the rising phase of

| | HC | | AN | | <i>p</i> |
|------------------------|--------|-------|--------|-------|----------|
| | Median | IQR | Median | IQR | |
| Number of participants | 19 | | 22 | | |
| Age | 17 | 4 | 16 | 2.75 | 0.142 |
| Body mass index | 20.29 | 3.08 | 16.51 | 2.03 | <0.001 |
| Mean HR | 70.37 | 10.48 | 66.12 | 14.95 | 0.331 |
| Minimum HR | 56.98 | 12.77 | 56 | 12.28 | 0.928 |
| Maximum HR | 90.23 | 11.12 | 83.57 | 24.68 | 0.281 |
| Heart rate variability | 67.12 | 32.02 | 62.63 | 37.62 | 0.330 |
| STAI ^a | | | | | |
| State | -1.15 | 1.35 | 1.01 | 2.77 | <0.001 |
| Trait | -0.28 | 1.02 | 1.99 | 2.46 | <0.001 |
| EDE-q global | 0.43 | 0.72 | 3.49 | 2.60 | <0.001 |
| EDE-q sub-scales | | | | | |
| Restraint | 0.2 | 0.6 | 3.7 | 3.15 | <0.001 |
| Eating concern | 0.2 | 0.4 | 2.7 | 2.4 | <0.001 |
| Shape concern | 0.63 | 1.13 | 3.38 | 2.69 | <0.001 |
| Weight concern | 0.4 | 1.1 | 3.7 | 3.3 | <0.001 |

Abbreviations: AN, Anorexia Nervosa; EDE-q, eating disorder examination questionnaire; HC, Healthy controls; HR, heart rate; IQR, interquartile range; STAI, state and trait anxiety inventory.

^az-scores.

the cardiac T-peak, which evolves into a bilateral posterior positive polarity at around 280–330 ms (between T-peak and T-end). After 330 ms, while the AN group still shows a bilateral posterior positive polarity, in HC a pronounced central positivity can be seen (see, Figure 1a).

No significant group differences were observed in the number of components removed by ICA (median for AN = 13.5; median for HC = 11; *p* (Wilcoxon's rank-sum) > 0.05). The groups did not differ in the number of epochs used to compute the HEPs (mean for AN: 333.32 (SD = 64.80); mean for HC = 333.89 (SD = 65.644), *p* > 0.05).

3.2.1 | Waveform results

The non-parametric randomisation test on the waveforms revealed five clusters of significant between-group differences (see, Figure 1a, b). Post-hoc *t* tests indicated that, compared to HC, individuals with AN have higher HEP amplitude at a central cluster (268–300 ms; *n* electrodes = 9); lower HEP amplitude at a left frontal cluster (328–360 ms; *n* electrodes = 27); higher HEP amplitude at

a right occipital cluster (336–356 ms; *n* electrodes = 5); lower HEP amplitude at a left temporal cluster (384–420 ms; *n* electrodes = 11); higher HEP amplitude at a left temporal cluster (540–568 ms; *n* electrodes = 21). See Table 2 for the test statistics of each cluster. The *t* values correspond to the cluster average of maximum *t* values across time. Average HEP amplitudes for each cluster (mean across electrodes and time) are also summarised in Table 2.

3.2.2 | Topographic analysis of Variance results

The TANOVA revealed a between-group difference in map topographies at 332–348 ms (*p* < 0.05). This latency corresponds to the end phase of the ECG *T* wave. Corresponding map topographies show a bilateral posterior positive polarity in AN and a more pronounced central positive polarity in HC (Figure 1c).

Post-hoc tests on the average time window confirmed that the effect was stable and consistent across time points (*p* = 0.032).

TABLE 1 Demographic and clinical data of the study sample.

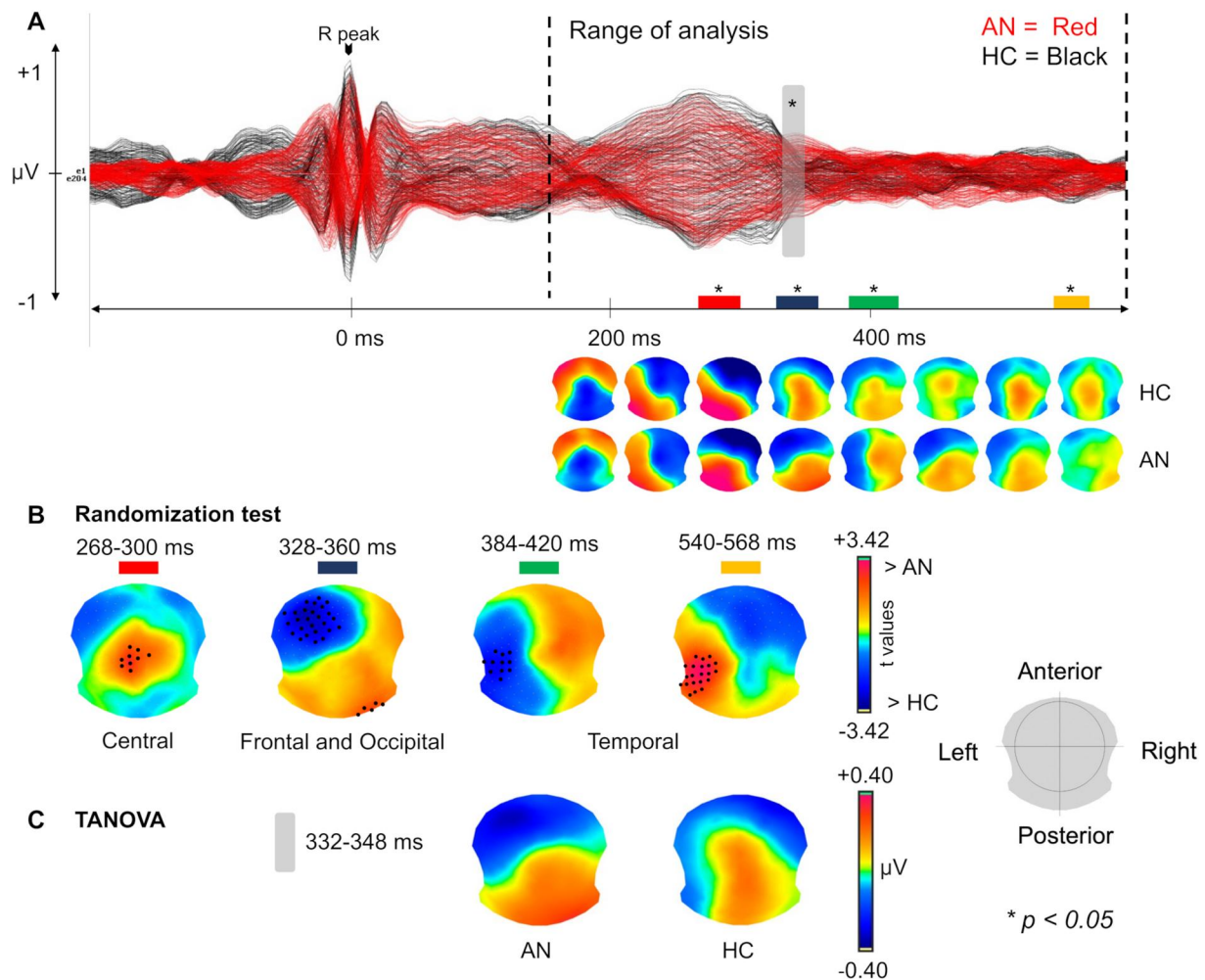


FIGURE 1 Heartbeat-evoked potential (HEP) waveforms and analyses at the scalp level. (a) Grand averages butterfly montage (204 channels). In red the grand average of the anorexia nervosa (AN) group, in black that of healthy controls (HC). The range of analysis is indicated by the black dotted lines. The grey-shaded area corresponds to the significant effect of group on electroencephalography (EEG) maps' spatial configuration. The four coloured blocks (i.e., red, blue, green, yellow) indicate the temporal windows of significant group effects of waveforms. Below, the time course of the EEG maps for both groups is shown. For all tests, significant effects are marked by asterisks (*, $p < 0.05$). (b) Each map represents significant group effects on the waveforms (randomisation test). Black dots indicate significant group effects on specific electrode locations. Post-hoc t -values are plotted to show the direction of group differences: positive t -values indicate higher HEP amplitude in the AN group, negative t -value indicate higher HEP amplitude in the HC group. (c) The EEG maps correspond to the significant effect of group on maps' spatial configuration (topographic ANOVA analysis 'TANOVA'). The grey template map shows the axial orientation of all EEG maps. [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/eat.20241)]

3.3 | Source imaging results

Source imaging analyses were run on the significant average time window from the TANOVA (332–348 ms). The randomisation test on the ROIs revealed significant group differences in the following regions: right superior frontal gyrus (dorsolateral, orbital and medial); right anterior cingulate and paracingulate gyri; right pallidum; right Heschl gyrus; right superior temporal gyrus (all $p_s < 0.05$). In all above-mentioned regions, post-hoc analyses revealed an hypo-activation in AN compared to HC (see Figure 2 and Table 3).

3.4 | Electrocardiogram analyses

Due to non-normal distributions, ECG parameters were compared with Wilcoxon's rank-sum tests. There were no significant group differences in minimum HR, maximum HR, mean HR, or HRV (all $p_s > 0.05$, see Table 1).

The between-group t test on the average ECG waveform revealed no significant differences at any of the time points (−200 - +600 ms), excluding the possibility that observed HEP effects are due to group differences in peripheral cardiac signals.

3.5 | Correlations

Average current density scores were extracted for the significant ROIs from the between-groups comparison and correlated with each clinical measures of interest (BMI, EDE-q subscales, STAI-trait, STAI-state). After correction for multiple comparison (Li & Ji, 2005), the only significant correlations were in the HC group: between the average current density of right superior frontal gyrus (medial) and STAI-state (spearman $\rho = 0.8$, $p < 0.001$) and that of right Heschl gyrus and STAI-trait (spearman $\rho = 0.7$, $p = 0.002$). No correlations survived correction for multiple comparisons in AN (for all correlations, see the Supplementary Material, and Tables S1 and S2).

4 | DISCUSSION

The current study investigated cardiac interoception with HEPs and source imaging in young individuals with AN.

TABLE 2 Heartbeat-evoked potential (HEP) amplitudes and post-hoc test results.

| Cluster | Mean amplitude | | | <i>p</i> | <i>d</i> _{cohen} |
|----------------|----------------|--------|-----------------------|----------|---------------------------|
| | AN | HC | <i>t</i> ^a | | |
| Central | 0.229 | 0.047 | 2.647 | 0.013 | 0.829 |
| Frontal | -0.241 | -0.03 | -3.089 | 0.004 | -0.967 |
| Occipital | 0.283 | 0.037 | 2.826 | 0.008 | 0.885 |
| Early temporal | -0.167 | -0.019 | -2.867 | 0.007 | -0.898 |
| Late temporal | 0.034 | -0.147 | 3.424 | 0.002 | 1.072 |

Abbreviations: AN, Anorexia Nervosa; HC, healthy controls; HEP, heartbeat-evoked potential.

^acluster average of maximum *t*-values across time.

To the best of our knowledge, this study is the first to use high-density EEG to localise the sources of HEPs in AN. Results point to differences in the cortical representation of heartbeats between AN and HC, in both HEP waveforms and topographies. Individuals with AN show a hypo-activation in several brain regions involved in interoception.

Randomisation tests on the waveforms showed that HEPs in AN differ from HC in five clusters: HEP amplitudes were higher at central, occipital and temporal electrodes, and lower at frontal and temporal electrodes (later window). Significant effects range from 268 to 420 ms following R-peak. Our results seem consistent with the spatiotemporal properties of HEPs: as reported by previous studies (Pollatos & Schandry, 2004), HEPs are predominantly observed over frontocentral brain regions at 200–500 ms following R-peak. A previous study on HEPs in AN (Lutz et al., 2019) reported increased mean HEP amplitudes (455–595 ms) in mid-frontal, mid-central, and right-central clusters. Temporally, this effect overlaps with our late temporal cluster, in which increased HEP amplitude is also seen. However, the comparison of results across the two studies is hindered by the different choice of reference (mastoid vs. average, since changing the reference will affect the shape of the waveforms at each electrode (Brunet et al., 2011)). While our data are solely based on resting-state, the data by Lutz et al. (2019) were merged across conditions (resting-state and HCT), further complicating comparisons.

Complementing waveform analyses with reference-free topographic analyses and source localization helps overcome these limitations and reduce ambiguity across studies. Group differences in map topographies were observed at 332–348 ms: this effect temporally overlaps with the frontal and largest cluster of differences in

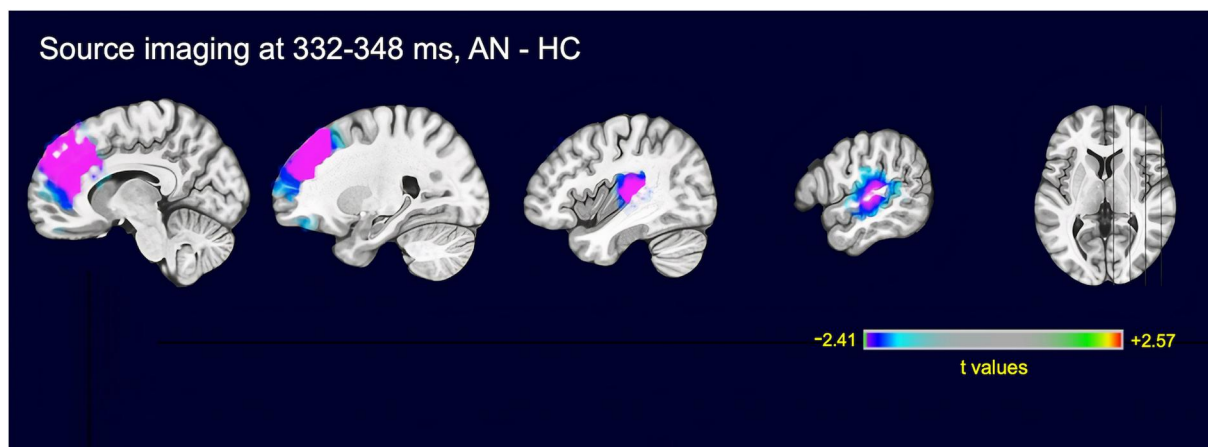


FIGURE 2 Electroencephalography (EEG) source imaging results. Brain regions showing reduced activation in anorexia nervosa (AN) relative to healthy controls (HC). To visualise the direction of the effect, the *t*-values from post-hoc *t* tests are plotted here. Negative *t*-values indicate reduced activation in the AN group compared to HC (332–348 ms). All $p_s < 0.05$. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Between-group source imaging on the ROIs, Anorexia Nervosa (AN) - healthy controls (HC) (post-hoc *t* tests; 332–348 ms).

| ROI | <i>t</i> | <i>p</i> | <i>d</i> _{cohen} |
|---|----------|----------|---------------------------|
| Right superior frontal gyrus (dorsolateral) | −2.409 | 0.021 | −0.754 |
| Right superior frontal gyrus (orbital part) | −2.387 | 0.022 | −0.748 |
| Right superior frontal gyrus (medial) | −2.027 | 0.049 | −0.635 |
| Right anterior cingulate and paracingulate gyri | −2.28 | 0.028 | −0.714 |
| Right pallidum | −2.181 | 0.035 | −0.683 |
| Right heschl gyrus | −2.214 | 0.033 | −0.693 |
| Right superior temporal gyrus | −2.037 | 0.048 | −0.638 |

Note: non-significant results from TANOVA (average *p* values): from 200 to 328 ms, *p* = 0.57; from 352 to 600 ms, *p* = 0.37.

Abbreviations: AN, Anorexia Nervosa; HC, healthy controls; ROI, regions of interest.

waveforms, where individuals with AN show reduced HEP amplitudes. Given that different scalp fields must be generated by different configurations of neuronal sources (Brunet et al., 2011), results from these analyses served as a basis for the estimation of the HEP sources.

In this time window (332–348 ms), individuals with AN show reduced activation in a right-sided network comprising the superior frontal gyrus (dorsolateral, medial and orbital), the anterior cingulate and paracingulate gyrus, the superior temporal gyrus, pallidum, and Heschl's gyrus.

Concerning the waveform results and the source imaging, none of the significant windows from the waveform analyses fully overlap with the significant effect of the TANOVA (i.e., 332–348 ms), used in the between-group contrast for source imaging. However, for the two time-windows that partially overlap, we found lower HEP amplitude at a left frontal cluster (328–360 ms), and higher HEP amplitude at a right occipital cluster (336–356 ms) in AN compared to HC. The lower amplitude at frontal cluster seems to suggest a reduced top-down regulatory mechanism in AN, and is overall in line with the hypo-activation at the source level. Any other differences found in the waveforms did not correspond to significant differences in map topographies, and thus were not investigated at the source level.

Concerning the hypo-activation found in AN, a subset of these regions overlaps with brain areas involved in interoceptive processing: ascending visceral afferents to the brainstem also project to more rostral regions, including the anterior cingulate cortex, the orbitofrontal and medial prefrontal cortices (Chen et al., 2021).

Most hypo-active regions in our AN sample show structural connections to the insula. The anterior insula, a region involved in cardiac interoception (Critchley et al., 2004), is connected to the anterior cingulate cortex, orbitofrontal and ventromedial prefrontal cortices, superior temporal gyrus, including Heschl's gyrus (Ghaziri

et al., 2017), and to the globus pallidus (Ghaziri et al., 2018).

However, we did not find differences in activation in the insular cortex itself. Several explanations could account for this: it is possible that the insula's role in cardiac signal processing is unaltered in the active stage of AN, and that interoceptive deficits are rather due to related cortical networks. Previous fMRI findings report functional alterations in different regions of the insula during interoceptive attention (Kerr et al., 2016). However, the HEP generates a very different signal from task-based fMRI, and it should be noted that (a) we provided no attentional instructions or stimulation, and (b) we did not choose the insula as a-priori ROI. These methodological differences could account for inconsistencies across studies. Finally, we cannot exclude that EEG source localization may have failed to adequately detect activity from the insula, located deep in the brain.

Most of the regions that are hypo-active in our sample are functionally involved in interoceptive processing. Lesion studies (Khalsa et al., 2009) and fMRI studies (Pollatos et al., 2007) show that the anterior cingulate cortex is involved in the awareness of cardiac sensations. The right superior temporal gyrus has been linked to multisensory integration, with convergent activity in this region during interoceptive and exteroceptive information processing (Salvato et al., 2020). The orbitofrontal and prefrontal cortices, together with the anterior cingulate cortex, have been proposed to play a role in the integration of interoceptive information with emotional or cognitive states (Chen et al., 2021). The ventromedial prefrontal cortex is activated during evaluation of both emotional and bodily state (Terasawa et al., 2013), and has been identified as a source of the HEP (Park et al., 2014).

Moreover, a right-hemispheric dominance of cardiac interoceptive networks was highlighted by studies on interoceptive attentiveness to heartbeats (Critchley

et al., 2004; Pollatos et al., 2007), reinforcing the possibility that the observed right-sided hypo-activation pertains to cardiac signals.

Based on the existing literature, most regions in our hypoactive network show alterations in AN compared to HC. Individuals with AN exhibited a negative relationship between heart sensation intensity prior to the fMRI task and ventromedial prefrontal cortex activation to food stimuli, while the opposite was seen in HC (Kerr et al., 2017). Increased activity in the cingulate cortex during painful stimulation was observed (Bär et al., 2015). An increase in regional cerebral blood flow was seen in AN following treatment in cingulate, medial and right dorsolateral prefrontal cortices (Matsumoto et al., 2006), and this was accompanied by improved IA. Hypo-perfusion has also been reported in these regions in individuals with AN compared to HC (Naruo et al., 2001).

Activity in these brain areas did not correlate with clinical traits (BMI, anxiety, or ED symptoms) in AN. In HC, higher anxiety levels corresponded to higher activity in superior frontal gyrus (medial) and Heschl's gyrus. Such a correlation was not observed in AN, suggesting a dysfunctional mechanism in which anxiety fails to modulate brain activity. This result is consistent with previous evidence in a weight-restored AN sample, where no correlations were observed between insular activity and clinical measures during heart-focused attention (Kerr et al., 2016).

Overall, our study highlights a small but consistent indication of reduced cortical processing of cardiac signals in recent-onset AN. While other studies find effects in the opposite direction (Kerr et al., 2016; Lutz et al., 2019), the role of context should be considered. Arousing or anticipatory contexts might affect interoceptive processing in AN: meal anticipation was shown to alter interoceptive processing in AN, resulting in meal-related visceral illusions and exaggerated cardiorespiratory sensations (Khalsa et al., 2015). Additionally, the nature of interoceptive alterations was shown to vary during anticipation versus processing of aversive or food-related stimuli (Berner et al., 2018). Individuals with AN might process interoceptive signals to a lesser extent during neutral conditions, but to a greater extent in arousing contexts or when instructed to do so. Additionally, the lack of instructions to focus on heart sensations likely made the HEP smaller (Petzschner et al., 2019), possibly accounting for the short time-window of between-group differences. However, measuring the HEP during rest provides an indication of what happens naturally.

Our results indicate that altered central processing of cardiac sensations is already detectable in young

individuals in early stages of the illness: unlike the study by Lutz et al. (2019), where over half of the participants had been suffering from AN for 10 years or more, our sample consists of adolescents and young adults at an early phase of the disorder (<3 years), and fewer confounding from long-term effects of AN and prolonged starvation are to be expected. Moreover, the AN sample is relatively homogenous in AN diagnosis and mostly medication-free. Although our study does not shed light onto the role of interoception in the pathophysiology of AN, it could rule out that interoceptive deficits are merely the consequence of chronic starvation.

4.1 | Limitations

Our findings need to be understood in light of some limitations. Our sample size is relatively small, though comparable to that of other HEP studies in clinical samples (Lutz et al., 2019). The sample size did not allow us to distinguish between different AN subtypes (restricting type and binge-eating/purging type), in which interoceptive deficits could present differently.

Three out of 22 individuals with AN were taking prescribed medication (SSRIs): however, a previous study on patients with depression showed no effect of antidepressant medication on the HEP (Terhaar et al., 2012).

We observed that altered central processing of heartbeats is present during early-stage AN and thus is likely not the result of chronic illness: however, as we do not have data on a recovered AN sample, we cannot disentangle whether altered interoception is a state marker of AN or rather a trait marker predisposing to the illness. We only investigated cardiac interoception: as interoception is a complex construct, care should be taken in generalising our results. There is limited evidence on how well cardiac interoception generalises to other interoceptive modalities (Herbert et al., 2012), and gastrointestinal interoception might be more compromised in AN, given the gastrointestinal complications associated with the illness (Mehler & Brown, 2015).

5 | CONCLUSIONS AND FUTURE DIRECTIONS

Overall, this is the first study to use high-density EEG to identify the HEP sources in AN: results point to altered interoceptive processing during resting-state in a sample of young individuals in early-stage AN, supporting the hypothesis that interoceptive deficits might contribute to

some clinical symptoms. However, since research on the neural correlates of interoception in AN is limited, further replications are needed to confirm or refute interoceptive alterations over the course of the disorder.

Future studies should complement the HEP with different interoceptive modalities, as well as multiple measures of each modality, as previously done in healthy participants (Fittipaldi et al., 2020). More comprehensive self-report measures of interoception have been evaluated in eating disorders (Brown et al., 2017), and could provide a valuable alternative to existing measures for studies wishing to include self-report. Novel, more sensitive indices of Interoceptive Awareness have also been developed and tested successfully in multidimensional frameworks (Fittipaldi et al., 2020), and were shown to correlate with HEPs, but not in AN.

Using the same measure at different stages of treatment could inform us on treatment-related changes in interoceptive processing. Treatment-wise, attentional training, neuromodulation (Richter et al., 2021), and exposure to interoceptive sensations during meal anticipation (Khalsa & Lapidus, 2016) have been suggested as interventions. Floatation therapy has also been shown to enhance awareness of interoceptive sensations through a reduction in exteroceptive input (Feinstein et al., 2018). Existing evidence suggests that incorporating interventions targeted at improving interoceptive processing in the treatment for AN is likely to have a positive effect on its symptoms and facilitate recovery.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data are available from the corresponding author upon request.

ETHICS APPROVAL STATEMENT

This study was approved by the University of Geneva ethical committee and follows the principles of the Declaration of Helsinki. Approval number: CCER, PB_2017-00465 (15-221).

PATIENT CONSENT STATEMENT

All participants signed a written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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